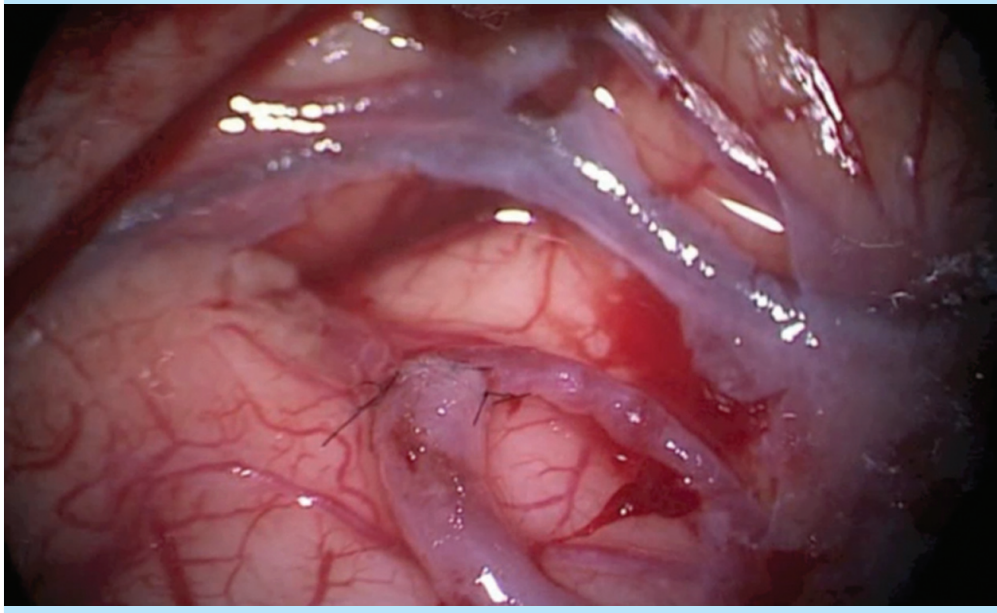
ISSN 0103-5355

Brazilian Neurosurgery

Arquivos Brasileiros de Neurocirurgia

Number 2 • Volume 40 • Pages 113–206 • June 2021



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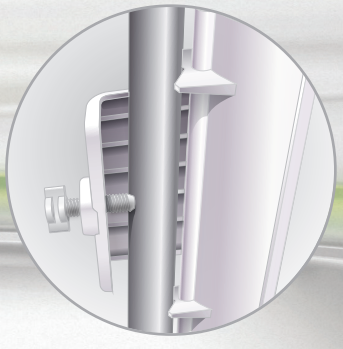

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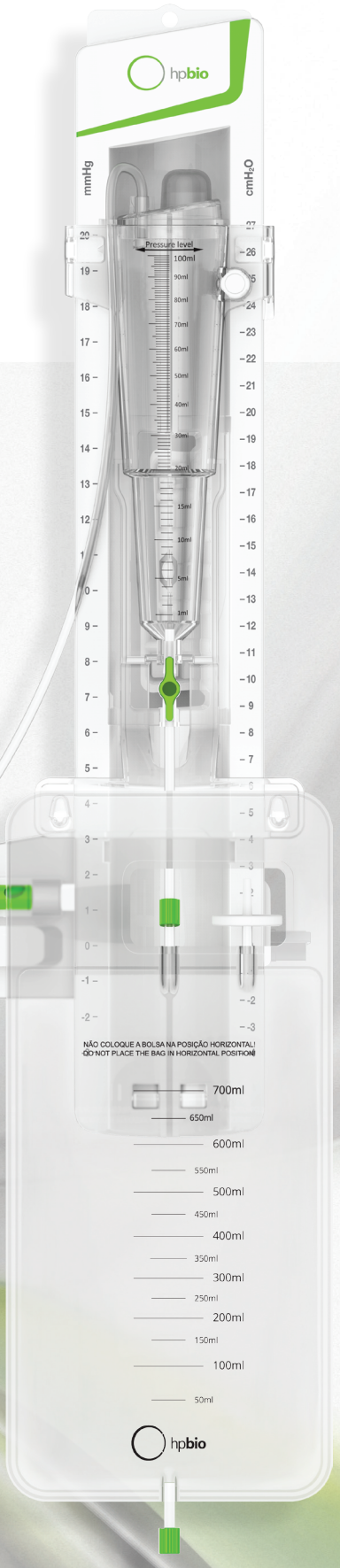

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ISSN 0103-5355

Brazilian Neurosurgery
Arquivos Brasileiros de Neurocirurgia

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Volume 40, Number 2/2021

Brazilian Neurosurgery
Arquivos Brasileiros de Neurocirurgia

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(Isolan GR, Caracante RA, Telles JPM, Rabello NN, Figueiredo EG. Superficial-Temporal-Artery-To-Middle-Cerebral-Artery Bypass in Cerebrovascular Occlusive Disease and Hemodynamic-Related Ischemia: Illustrative Case and Literature Review. Arq Bras Neurocir 2021;40(2):130–136)

 Arquivos Brasileiros de Neurocirurgia is published four times a year in March, June, September, and December by Thieme-Revinter Publicações Ltda, Rua do Matoso, 170, Rio de Janeiro, 20270-135, Brazil.

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Arquivos Brasileiros de Neurocirurgia is an official publication of the Brazilian Neurosurgery Society (Sociedade Brasileira de Neurocirurgia) and the Portuguese Language Neurosurgery Societies. It is listed in LILACS and LILACS-Express (Latin-American and Caribbean Center on Health Sciencies Information), and Latindex (Regional Cooperative Online Information System for Scholarly Journals from Latin America, the Caribbean, Spain and Portugal). Thieme Medical Publishers is a member of the CrossRef initiative.

ISSN 0103-5355

Utility of Intraoperative Ultrasound in Neurosurgery

Utilidade do ultrassom intraoperatório em neurocirurgia

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Arq Bras Neurocir 2021;40(2):e113–e119.

Abstract

Objective The purpose of the present study is to demonstrate the usefulness of intraoperative ultrasound guidance as a technique for the assessment, in real time, of tumor resection and as a navigation aid during intra-axial brain lesion removal on patients admitted in the Neurosurgical Department at the Hospital Universitario de Caracas, Caracas, Venezuela, in 2018.

Methods A total of 10 patients were enrolled, each with intra-axial brain lesions with no previous neurosurgical procedures and a mean age of 49 years old, ranging from 29 to 59 years old.

Results A male predominance was observed with 7 cases (70%) over 3 female cases (30%). Six patients had lesions in the dominant hemisphere. The frontal lobe was the most commonly affected, with 5 cases, followed by the parietal lobe, with 4 cases. After craniotomy, ultrasound evaluation was performed previously to dural opening, during tumor resection and after tumor removal. The mean tumor size in axial, coronal and sagittal views was 3.72 cm, 3.08 cm and 3.00 cm, respectively, previously to dural opening with intraoperative ultrasound. The average tumor depth was 1.73 cm from the cerebral cortex. The location and removal duration from the beginning of the approach (ultrasound usage time) was 83.60 minutes, and the average surgery duration was 201 minutes. Navigation with intraoperative ultrasound served to resect intra-axial tumors more precisely and safely. There was no postoperative complication associated with the surgery in this series of cases.

Conclusions Intraoperative ultrasound guidance for intra-axial subcortical tumor resection is a technique that serves as a surgical and anatomical orientation tool.

Keywords
- intraoperative ultrasound
- brain tumor
- glioma surgery

Resumo

Objetivo O objetivo do presente estudo é demonstrar a utilidade da orientação ultrassonográfica intraoperatória como técnica de avaliação, em tempo real, da ressecção tumoral e como auxiliar de navegação na remoção de lesão cerebral intra-axial em pacientes internados no Serviço de Neurocirurgia do Hospital Hospital Universitario de Caracas, Caracas, Venezuela, em 2018.

received
August 21, 2020
accepted
November 16, 2020
published online
February 15, 2021

DOI https://doi.org/10.1055/s-0040-1722243.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Métodos Foram incluídos 10 pacientes, cada um com lesões cerebrais intra-axiais, sem procedimentos neurocirúrgicos prévios e idade média de 49 anos, variando de 29 a 59 anos.

Resultados Foi observada predominância do sexo masculino com 7 casos (70%) sobre 3 casos do sexo feminino (30%). Seis pacientes tinham lesões no hemisfério dominante. O lobo frontal foi o mais acometido, com 5 casos, seguido do lobo parietal, com 4 casos. Após a craniotomia, a avaliação ultrassonográfica foi realizada previamente à abertura dural, durante a ressecção do tumor e após a retirada do tumor. O tamanho médio do tumor nas incidências axial, coronal e sagital foi de 3,72 cm, 3,08 cm e 3,00 cm, respectivamente, previamente à abertura dural com ultrassom intraoperatório. A profundidade média do tumor foi de 1,73 cm do córtex cerebral. O tempo de localização e remoção desde o início da abordagem (tempo de utilização do ultrassom) foi de 83,60 minutos, e o tempo médio de cirurgia foi de 201 minutos. A navegação com ultrassom intraoperatório serviu para ressecar tumores intra-axiais com mais precisão e segurança. Não houve complicações pós-operatórias associadas à cirurgia nesta série de casos.

Conclusões A orientação ultrassonográfica intraoperatória para ressecção de tumor subcortical intra-axial é uma técnica que serve como ferramenta de orientação cirúrgica e anatômica.

Palavras-chave
- ultrassom intraoperatório
- tumor cerebral
- cirurgia de glioma

Introduction

The fundamental steps in any neurosurgical procedure are: spatial orientation, correlation between the preoperative images and intraoperative findings, and determination of the exact anatomical relationships of a tumor with the surrounding normal brain tissue and adjacent vessels. These steps translate into less transgression of the brain and vessels, limiting manipulation to the lesion itself, with the objective of minimizing postsurgical neurological deficits. The real-time correlation between the information provided by preoperative images and topographic transoperative data are not offered by any of the modern neuronavigation imaging techniques. Often, the surgeon faces a normal appearing cerebral cortex and tumor of < 1 cm in diameter deep in the cortex.[1,2] Changes in the spatial position of the tumor during and after resection occur related to manipulation, cerebrospinal fluid aspiration, hemorrhage or removal itself.[3]

Intraoperative ultrasound guidance (iUS) is a tool that continues to improve over time in terms of image quality, helping distinguish between pathological and normal tissue with good accuracy and functioning as a real time topographic orientation guide, making it an interesting method to consider for routine use in neurosurgery. It can be used in any operating room, without special instrumentation or arrangements, and can be utilized without the presence of a radiologist or technician; it adds a small amount of time to the surgical procedure and the costs are considerably lower compared with neuronavigation devices and intraoperative magnetic resonance imaging (iMRI).[4]

The known applications of the intraoperative ultrasound guidance are: tumor localization, resection evaluation, identification of surrounding vessels and patency of dural sinuses, brain abscess-guided aspiration, ventriculostomy, among others; however, its use is not routinely standardized.[5]

Guided tumor resection is associated with higher global survival rates.[6–9] Intraoperative magnetic resonance imaging and neuronavigation are established and well-known techniques, but enormous implementation and maintenance costs and increased surgical duration associated with these techniques indicate that, in the meantime, it is probable that they will not reach most of the neurosurgical units around the world.[4–10]

Intraoperative ultrasound guidance is a technique with lower cost compared with the mentioned iMRI and neuronavigation. An iMRI unit value ranges between US$ 3 million to US$ 7 million depending on equipment specifications. The value of an intraoperative computed tomography (CT) scan is between US$1.5 million and US$ 3 million, also depending on equipment specifications plus maintenance fees and licenses associated. The value of an intraoperative ultrasound unit varies between US$ 25.000 and US$ 55.000.[11]

Ionizing radiation is a concern with the use of intraoperative CT scan unit that is spared with the use of iUS. Postsurgical complications regarding compression of the transductor against the cerebral cortex or infection rates related to iUS are not higher than the one associated by the procedure itself.[12]

In low-grade glioma surgery, the intraoperative differentiation between the tumor and normal cerebral tissue can be quite challenging.[13,14] The iUS might narrow this gap with the help of real time images.[3,6,15] The iUS constitutes a complementary tool to neuronavigation images, and it has been proposed for routine use in brain tumor surgery, intra and extra-axial, supra or infratentorial and in intradural spinal tumors. Intraoperative ultrasound guidance differentiates normal from pathologic tissue in 80 to 88% of the cases, and its use

increases lesion resection by 55%. Higher rates can be observed if the lesions have heterogeneous properties or cystic areas.[16,17] Intraoperative ultrasound guidance also provides vascular mapping, particularly arterial, related to the lesion and adjacent tissue, especially when utilized in cerebral arteriovenous malformations. After tumor resection, it is possible to evaluate the presence of residual lesions on the surgical field.[16]

Methods

A descriptive, case series type of study was performed.[18] From January to December 2018, 380 surgeries were performed at the Neurosurgery Service of the Hospital Universitario de Caracas, Caracas, Venezuela; of these, 50 were intracerebral tumors, 10 were excluded from family members refusing the procedure, and 30 were emergency surgeries. Other exclusion criteria were previous cranial surgery, deep brain tumors who met the criteria for the use of stereotactic guided biopsy, extra-axial brain tumors, and pregnancy, leaving a sample of 10 patients with the diagnosis of a brain tumor who met the inclusion criteria (a subcortical intra-axial brain tumor diagnosed with magnetic resonance imaging (MRI) and voluntary wish to participate in the study).

A data collection instrument was developed to gather information related to the investigation. Each case was discussed in the weekly medical grand round and was included in the prior authorization of the study by the chairman of the Neurosurgical department and attendants. The preoperative dimensions of the tumor were measure in coronal, sagittal and axial views to compare the MRI with the intraoperative ultrasound findings and to evaluate the percentage of resection.

The surgical procedures were performed in the Hospital Universitario de Caracas with the presence of the usual nursing personnel and using habitual neurosurgical instruments standard in every cranial case.

The ultrasound equipment used for all the cases was: Phillips Ultrasound model Sparq Diagnostic Ultrasound System GMDN 40761 (Phillips Ultrasound Bothell, Bothell, WA, USA). With strict aseptic and antiseptic measures, the technique was applied after an osteoplastic craniotomy of 8×8 cm minimum for the use of a linear 7 to 11 mHz transducer and a 3, 5 to 5 mHz sectorial transducer. After the craniotomy, the transducer is placed and the first ultrasound is performed, after the dural opening a second ultrasound is performed, placing the transducer directly on the brain parenchyma. The size of the tumor and the nearby vascular structures with Doppler was taken into account. The distance between the brain surface and the lesion was recorded.

The ultrasound usage, tumor resection and the entire surgical case times were recorded. The ultrasound was also used after apparent complete macroscopic resection and, if remnants of the lesion were found, they were resected if considered safe without damaging surrounding vascular structures or eloquent brain areas.

Bioethical aspects: each patient was properly informed of the procedures and signed the informed consent form. Each of the four bioethical principles was respected.[20] The present study was evaluated and approved by the bioethical committee of the Hospital Universitario de Caracas.

Statistical analysis: A database was developed with the use of the statistical analysis software IBM SPSS Statistics for Windows, Version 19 in Spanish (IBM Corp., Armonk, NY, USA). Descriptive statistical of absolute frequency was used and mode, median, mean and standard deviation with 95% confidence intervals (CIs) were registered. The statistical test utilized was the t-student for continuous variables with normal distribution following the Kolmogorov-Smirnov test. The chi-squared test was used for discrete variables. Statistical significance was considered with a $p\text{-}value < 0.05$.

Results

A total of 10 patients were included in the study, with a mean age of 49 years old, ranging from 29 to 59 years old. The male gender predominated with 7 cases (70%), and there were 3 females (30%). Six patients had the lesion in the dominant hemisphere, and the lobe most frequently affected was the frontal, with 5 cases, followed by the parietal lobe with 4 cases. In ►**Table 1**, the description of every case is displayed including gender, age, diagnosis, and location.

Table 1 Demographic characteristics

Case	Gender	Age (years old)	Diagnosis	Localization (lobe)
1	M	33	Low grade glioma	Parietal - left
2	M	46	High grade glioma (glioblastoma)	Parietal – right
3	F	53	Metastatic adenocarcinoma	Parietal – right
4	M	38	Low grade glioma	Frontal – left
5	M	59	Cavernous angioma	Parietal – right
6	M	54	Metastatic adenocarcinoma	Occipital – right
7	M	55	Metastatic adenocarcinoma	Frontal – left
8	F	38	High grade glioma (glioblastoma)	Frontal – left
9	M	56	Low grade glioma	Frontal – right
10	F	29	High grade glioma (glioblastoma)	Parietal - right

Regarding the dimensions of the tumors, it was found that, on average, in the axial, sagittal and coronal views, the sizes were 3.72, 3.08 and 3.00 cm, respectively, similar to the preoperative MRI dimensions. The tumor depth on average was 1.73 cm. The time to locate and resect the lesion with ultrasound (US) was 83.60 minutes, and the average surgical duration was 201 minutes. These dimensions had a significant central tendency measure when the t-student test was applied ($p < 0.005$) (►**Table 2**). The cases were operated by a resident of the last year of the postgraduate degree in neurosurgery; a tendency toward lowering surgical duration with each following case was observed. (►**Fig. 1**).

All patients with the diagnostic of glioblastoma (high grade glioma) had an hypoechoic US pattern. In the case of grade 2 gliomas (low grade glioma), one out of three patients had hypoechoic pattern and two patients had an isoechoic pattern. Metastatic adenocarcinomas had a hyperechoic pattern. One cavernous angioma had a hyperechoic pattern. There was not a statistically significant difference (►**Table 3**). It was possible to identify the tumor borders before the resection in all of the patients included in the present study; ►**Fig. 2** shows a case of a metastatic adenocarcinoma in which that gross total resection was made.

Discussion

The extent of tumor resection has been associated with a significant increase in life expectancy and improvement of

Table 2 Tumor characteristics and surgery duration

Variables	Mean	Standard deviation	95% Confidence interval		*p-value**
			Inferior	Superior	
Tumor dimensions (cm)					
Axial	3.72	1.92	2.34	5.09	< 0.001
Coronal	3.08	1.42	2.06	4.09	< 0.001
Sagittal	3.00	2.24	1.40	4.60	0.002
Tumor depth (cm)	1.73	1.78	0.45	3.01	0.013
Ultrasound usage time (minutes)	83.60	30.17	62.01	105.19	< 0.001
Surgery duration (minutes)	201.10	38.41	173.63	228.57	< 0.001

*T- student test.

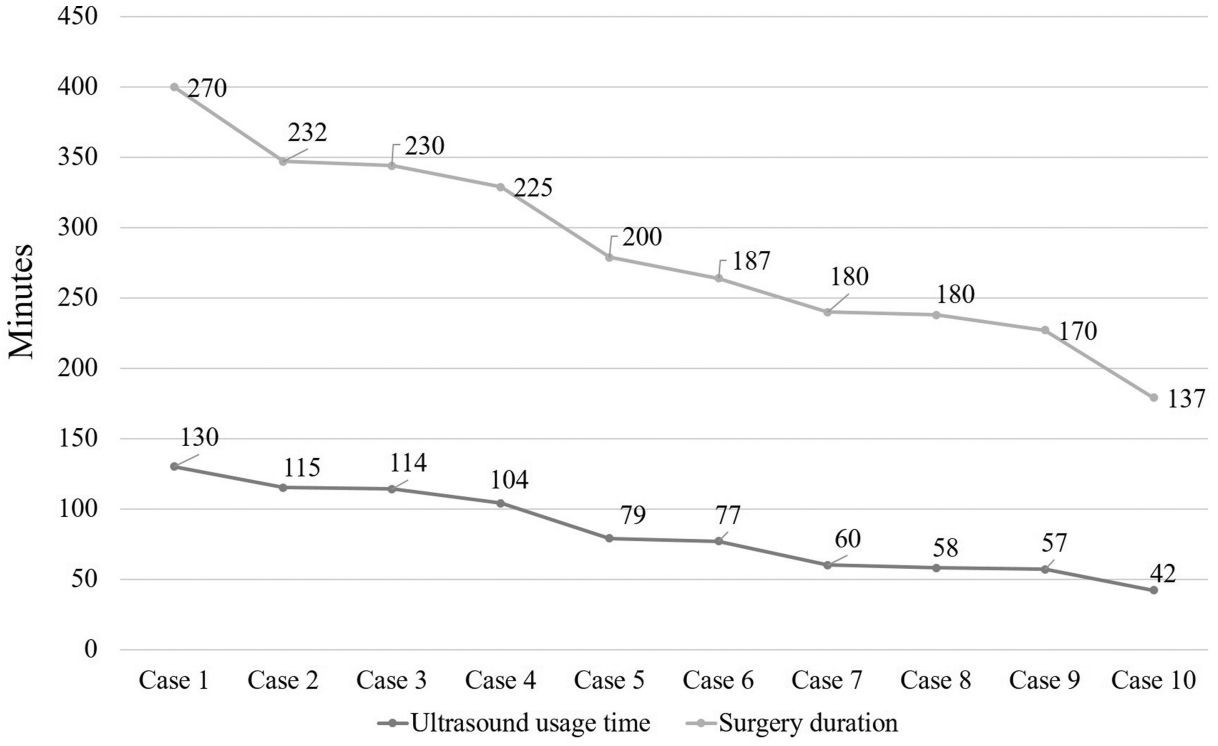

Fig. 1 Ultrasound usage time and surgery duration.

Table 3 Relation between histopathological diagnosis and ultrasound image pattern

Histopathologic Diagnosis	Ultrasound pattern						Total	
	Hypoechoic		Isoechoic		Hyperechoic			
	N	%	N	%	N	%	N	%
Glioblastoma (high grade glioma)	2	20.00	0	0.00	0	0.00	2	20.00
Grade II glioma (Low-grade glioma)	1	10.00	2	20.00	0	0.00	3	30.00
Metastatic adenocarcinoma	1	10.00	1	10.00	2	20.00	4	40.00
Cavernous angioma	0	0.00	0	0.00	1	10.00	1	10.00
Total	**4**	**40.00**	**3**	**30.00**	**3**	**30.00**	**10**	**100.00**

$p > 0.05$; not significant.

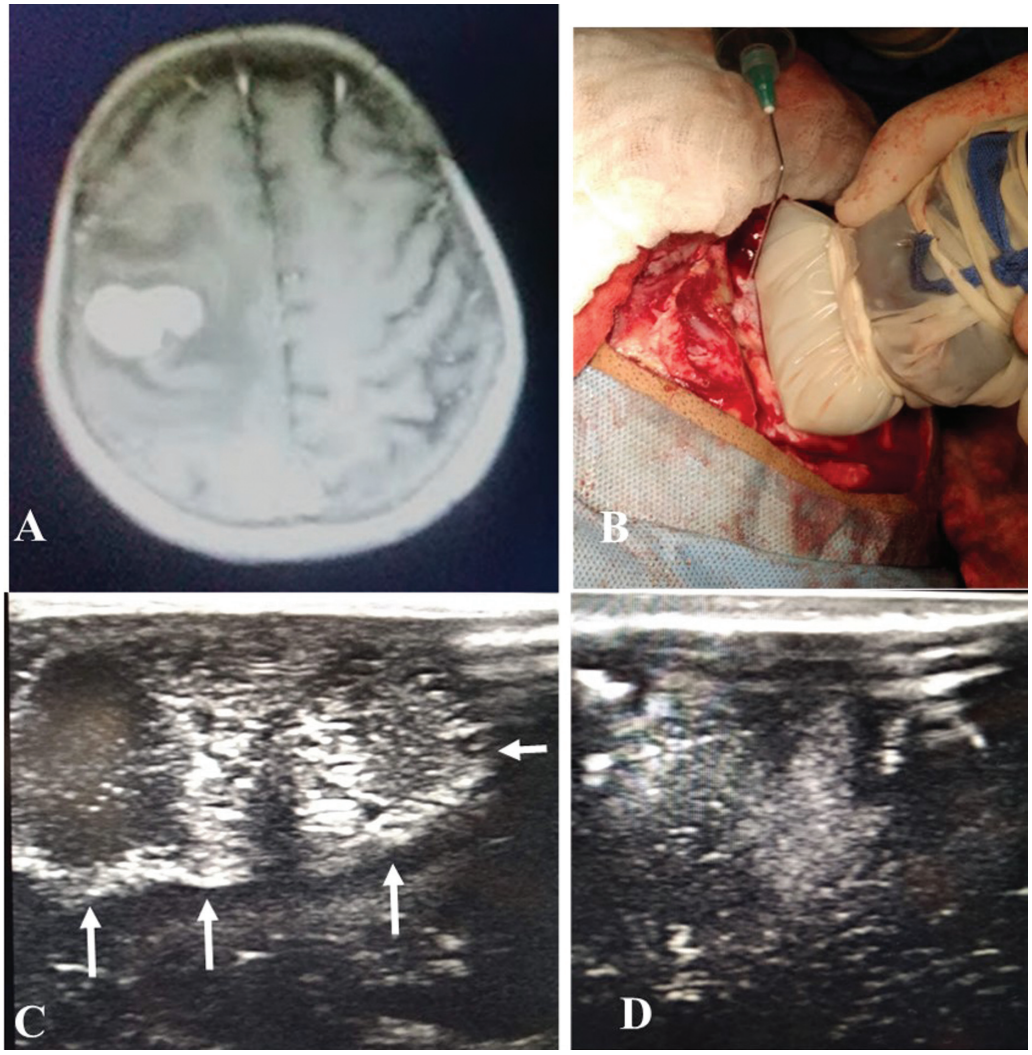

Fig. 2 Case of a metastatic adenocarcinoma in the right parietal lobe (►**Fig. 2A**), intraoperative image with the transducer placed on the dura (2B), characteristic of the image on ultrasound and delimited with arrows (2C), in the 2D image it is the area of edema after gross total resection.

neurological deficits directly related to the size of the tumor and the level of compression of the surrounding brain tissue, making it interesting that the appropriate use of the navigation technique these objectives, at limitant was that due to institutional difficulties, we do not have magnetic resonance or neuronavigator to properly compare and establish costs, we believe that other characteristics such as: cost / effectiveness, applicability, reliability, reproducibility are possible with this technique, and that training can decrease surgical time.[21,22]

We found that iUS is a very sensitive technique for a brain tumor lesion, secure and precise in the intraoperative trajectory planning toward the lesion and not time consuming compared with other techniques frequently used in our

department such as stereotactic-guided surgery and neuronavigation. These findings are similar to those of other authors.[5,21] Intraoperative ultrasound guidance is an effective tool for locating supratentorial brain tumors after the craniotomy, and also an aid for resection control in real-time.[4,5,12,15,23–26] In our case series, we were able to remove the lesions regardless of the histopathological diagnosis.

Our cases series, the iUS behavior of brain metastasis was demonstrated by a hyperechoic signal, compared with the surrounding normal brain tissue; high-grade gliomas were hypoechoic, and low grade gliomas had an isoechoic signal, which made difficult the differentiation between normal brain tissue as established by Gousias et al.[6] and Mair et al.[3] High-grade gliomas and metastasis are hyperechoic compared with the brain with sharp borders, and glioblastomas have cystic cavities hypoechoic in nature (necrosis). Low-grade gliomas are isoechoic but still distinguishable from surrounding parenchyma.

Intraoperative ultrasound guidance results in less normal brain tissue injury, identification of intralesional or adjacent vascular structures, precise location of subcortical tumors after durotomy independently of the histopathological diagnosis. It is considered a utility method, fast, easy to handle by the neurosurgeon with a short but continuous learning curve that mandates basic knowledge of ultrasonography. Its benefits justify the routine usage for subcortical, intra-axial brain lesions, regardless of the size or histopathological diagnosis.

Preoperative planning of the approach correlating radiological images with craniometric reference points or neuronavigation is mandatory as it affects the final results of the surgery. The craniotomy size should be $\sim 8 \times 8$ cm if a 7 to 11 MHz linear transducer is going to be used. It is also recommended that ultrasonographic interpretation of transoperative images should be included in formal neurosurgical residency programs, in order to stimulate future generations to compare this technique with newer and more advanced techniques to standardize its use in appropriate clinical scenarios.

Limitations related the use of iUS are reverberation in deep seated lesions,[27] not giving information of tumor location prior to craniotomy, size of craniotomy related to the size of the transducer used. The 6×2 cm linear 7 to 11 MHz transducer was utilized more frequently, giving higher resolutions and better details with a depth up to 10 cm from the cerebral surface. Regarding resection control, we found that the postsurgical cavity has to be completely hemostatic without overlying hematomas (hyperechoic), because it interferes with the evaluation of the peripheral tissue and residual tumor. Also, the usage of cottonoids or surgical patties interferes with the postresection evaluation.

There were no complications related to pressure of the transducer against the normal brain tissue measured by postsurgical physical evaluation of each patient, nor increase in surgical site infections.

Neuronavigation has an advantage related to approach and location planning prior to craniotomy or durotomy, but we found that, frequently, the problem in accessing deeply seated lesions is not related to craniotomy location, but after durotomy or corticotomy, and the limitations of this technique after cerebrospinal fluid shifts or partial resection of the tumor are widely known.[28–30]

intraoperative magnetic resonance imaging is a technique with similar results related to the assessment of tumor resection, as stated in many studies,[23–26] but at a higher cost: requiring complete rebuilding of operating rooms, training of nursing personnel and usage of special surgical instruments; besides, it is not available in our country. This type of technique has indications in resection control of tumors in the diencephalon, brain stem, trans-sphenoidal approaches, among a few others.

Recently, neuronavigation integrated with high resolution tridimensional intraoperative ultrasonography addresses both common problems during tumor resection: location before craniotomy and resection control, respectively.[30] But studies comparing these combined approaches with the use of each alone are lacking.

Conclusions

Intraoperative ultrasound guidance for intra-axial subcortical tumor resection is a technique that serves as a surgical and anatomical orientation tool, which correlates with preoperative images and intraoperative findings. We recommend using this technique routinely for intra-axial supratentorial brain tumor resection.

Sources of Financial and Material Support
The present research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interests
The authors have no conflict of interests to declare.

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Endovascular Treatment in the Subclavian Steal Syndrome: Series of 29 Patients

Tratamento endovascular na síndrome do roubo da subclávia: Série de 29 pacientes

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Arq Bras Neurocir 2021;40(2):e120–e124.

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Abstract

Subclavian steal syndrome is a group of symptoms resulting from retrograde flow in the vertebral artery, "stealing" blood from the posterior intracranial circulation and other territories, caused by stenosis or occlusion of the subclavian artery proximal to the origin of the same vertebral artery, or even of the brachiocephalic trunk. Most of the time, it is an incidental finding in patients with other conditions or cerebrovascular risk factors. We report a series of 29 patients with an angiographic diagnosis, in which 7 received treatment (all endovascular), all with symptoms directly related to this condition. Advanced age, systemic arterial hypertension, diabetes mellitus, smoking and stroke were comorbidities frequently related. Six patients improved completely after the procedure and one remained with vertigo.

Keywords
- subclavian steal syndrome
- arteriography
- left side
- angioplasty

Resumo

A síndrome do roubo de subclávia é um grupo de sintomas decorrente de fluxo retrógrado na artéria vertebral, "roubando" o sangue da circulação posterior intracraniana e de outros territórios, causado por estenose ou oclusão da artéria subclávia proximal à origem da mesma artéria vertebral, ou mesmo do tronco braquiocefálico. Na maioria das vezes, trata-se de um achado incidental em pacientes com outras condições ou fatores de risco cerebrovasculares. Relatamos uma série de 29 pacientes com diagnóstico angiográfico, em que 7 receberam o tratamento (todos via endovascular), todos com sintomas diretamente relacionados a essa condição. Idade avançada, hipertensão arterial sistêmica, diabetes mellitus, tabagismo e acidente vascular cerebral foram comorbidades frequentemente relacionadas. Seis pacientes melhoraram totalmente após o procedimento e um permaneceu com vertigens.

Palavras-chave
- síndrome do roubo de subclávia
- arteriografia
- lado esquerdo
- angioplastia

received
May 19, 2020
accepted
August 24, 2020
published online
February 15, 2021

DOI https://doi.org/10.1055/s-0040-1719000.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Introduction

Subclavian steal syndrome (SSS) occurs when there is stenosis of the subclavian artery (SA) proximal to the origin of the vertebral artery (VA), causing retrograde flow in the ipsilateral VA.[1]

Most patients are asymptomatic due to the slow progression of the disease and the development of collateral circulation.[2] The main symptoms of SSS include vertebrobasilar insufficiency and arm lameness. There are reports of cardiac ischemia in patients undergoing myocardial revascularization with mammary artery grafts.[3] Other possible symptoms include ataxia, tinnitus, syncope, visual disturbances, perioral paresthesia, alternating paresthesia, dysphagia, dysarthria, transient amnesia or headache.[4]

The diagnosis can be made with doppler ultrasound and angiotomography or angioresonance, following the investigation. However, digital subtraction arteriography (DSA) is still the gold standard for its dynamic character.[2]

Optimized drug treatment is the best initial therapy for this syndrome, with surgery reserved for refractory symptomatic cases. Percutaneous angioplasty and stent, in addition to grafts for SA bypass, are the main surgical procedures.[5]

Material and Methods

A cross-sectional and descriptive study was performed based on the analysis of the series of cases diagnosed in a referral hospital in southern Brazil, between February 2008 and February 2018.

All selected patients were diagnosed by angiography (DSA) and information was collected from the reviews of medical records. Clinical, angiographic and therapeutic characteristics of SSS were individualized and analyzed in each patient.

Results

The medical records of 38 patients with angiographic diagnosis of SSS between February 2008 and February 2018, performed by the Interventional Neuroradiology team of a public health hospital in southern Brazil, were retrospectively reviewed. Nine were excluded due to poor baseline neurological status related to other causes, considered Rankin modified scale 4 or 5, due to the difficulty in associating SSS with signs and symptoms, and also due to this severe functional disability, there would be no practical benefit of any intervention for the treatment of SSS.

Of the remaining 29, 20 were men (68.9%) and 9 women (31.1%). The average age at diagnosis was 66.0 years old (ranging from 45 to 87 years old). In relation to the side of the affected SA, there were 20 cases on the left and 9 on the right. In addition, 22 patients (75.8%) had significant stenosis or occlusions in at least one more cervical vessel, this being more frequent in males (80%) than in females (66.6%). Of the concomitantly affected vessels, the left internal carotid artery (ICA) was the most common (16 of 22 patients or 72.7% of the grand total), followed by the right ICA in 13 patients (59%), the left VA in 4 (18.8%), the right VA in 3 (13.6%), and the basilar artery with 1 patient (4.5%).

Most had some cerebrovascular risk factor: 20 out of 29 (or 68.9%) with hypertension, 58.6% smoking, 48.2% previous stroke, 41.3% dyslipidemia, 34.4% diabetes, 24.1% coronary artery disease, 20.6% peripheral obstructive arterial disease and 6.8% alcoholism.

Only 9 patients (31.1%) were symptomatic, and 20 were asymptomatic (68.9%). The most common symptoms were: syncope (33.3% or 3 out of 9), vertigo (33.9%) and episodes of low visual acuity (33.3%), followed by ataxia (22.2% or 2 out of 9) and episodes of mental confusion (11.1%).

Seven (77.7%) symptomatic patients underwent stent and balloon angioplasty of the SA. The average time from symptom onset to angioplasty was 15.2 months (ranging from 1 month to 6 years). The procedures were performed through the right femoral access, under general anesthesia and total intravenous heparinization. Normally, a peripheral guide sheath was positioned in the brachiocephalic trunk and a long stent was delivered crossing the stenosis. Although the stent produced partial opening of the vessel, a balloon catheter inflated to 10 to 13 Atm reached a definite impact of the stent and normalized the cervical and intracranial blood flow. There were no complications or related deaths in any of the procedures. In the postoperative period, we maintained the use of simvastatin 40mg and double anti-aggregation (aspirin 100mg and clopidogrel 75mg) daily. Six patients (85.7%) completely improved their symptoms, and only 1 (14.3%) maintained vertigo.

The results are shown in ►**Tables 1** and **2**.

Discussion

Subclavian steal syndrome is a rare vascular condition, resulting from a subocclusion/ stenosis of the SA or brachiocephalic artery, where blood flows from the contralateral VA to the basilar artery and goes down retrogradely through the ipsilateral VA, leading to collateral circulation in the upper limb.[6]

Contorni[1] was the first to recognize and describe this retrograde flow, in 1960, using angiography in a patient with an absent radial pulse. A year later, Reivich[7] associated this phenomenon with transient ischemic attack and, therefore, became the first to correlate it with neurological symptoms. The term "subclavian steal," however, was coined by Fisher[6] in 1961, after observing that the anomaly caused the ipsilateral SA to receive retrograde flow from the contralateral circulation at the expense of the vertebrobasilar circulation.

The prevalence of SSS in the literature is between 0.6% and 6.4%.[8] A recent large-scale prevalence analysis found 5.4% of SSS in a series of 7,881 ultrasound examinations of extracranial vessels in the neck.[9]

Our study indicates a predominance on the left side with 68.9, and the literature suggests that the left side really is the most affected, reaching 82.3% in a series.[9] The justification for predilection for the left side would be the more acute angle of the origin of the left SA, causing turbulence of flow and potential increase of atherogenesis, and consequently, stenosis / subocclusion.[5]

Regarding the prevalence of gender, studies differ mainly in the selection of patients in different studies, with different

Table 1 Main results of the patients selected in this study

Cases	29	
Gender		
	Male	20 (68,9%)
	Female	9 (31.1%)
Average age (years old)	66 (45–87)	
SSS Side		
	Left	20 (68.9%)
	Right	9 (31.1%)
Other vessels		
	Left ICA	16 (72.7%)
	Right ICA	13 (59%)
	Left VA	4 (18.8%)
	Right VA	3 (13.6%)
	BA	1 (4.5%)
Risk factors		
	Hypertension	20 (68.9%)
	Smoking	17 (58.6%)
	Previus stroke	14 (48.2%)
	Dyslipidemia	12 (41.3%)
	Diabetes	10 (34.4%)
	CAD	7 (24.1%)
	POAD	6 (20.6%)
	Alcoholism	2 (6.8%)
Symptoms		
	Yes	9 (31.1%)
	No	20 (68.9%)
Main symptoms		
	Syncope	3 (33.3%)
	Vertigo	3 (33.3%)
	Loss of Visual Acuity	3 (33.3%)
	Ataxia	2 (22.2%)
	Mental confusion	1 (11.1%)
Treated patients	7 (77.7%)	

Abbreviations: BA, basilar artery; CAD, coronary artery disease; ICA, internal carotid artery; POAD, peripheral obstructive artery disease; SSS, subclavian steal syndrome; VA, vertebral artery.

Table 2 Treated patients in the present study

	Age	SSS side	Symptoms	Time symptoms-treatment (months)	Results
A	66	Right	Vertigo + Ataxia	6	Improved
B	67	Left	Syncope	13	Improved
C	59	Right	Syncope	15	Improved
D	78	Right	Syncope + LVA	72	Improved
E	51	Left	MC + LVA	1	Improved
F	81	Left	Ataxia	2	Improved
G	73	Left	Vertigo	1	Maintened

Abbreviations: SSS, subclavian steal syndrome; LVA, low visual acuity; MC, mental confusion.

inclusion and exclusion criteria: some analyzing only symptomatic patients, others only treating patients and others all incidental diagnoses by imaging. In the present study, the high prevalence in males was found in a group with an angiographic diagnosis of the imagological subclavian steal phenomenon, not necessarily with the clinical syndrome.

Subclavian steal syndrome is most often caused by atherosclerosis, therefore it is related to cerebrovascular risk factors.[10] In our series of 29 cases, 26 had at least 1 of these factors. Other etiologies were not found in our series, but include congenital malformations, fibromuscular dysplasia, neurofibromatosis, inflammation (for example, Takayasu and other forms of arteritis), radiation exposure and mechanical causes (for example, trauma or compression syndromes).[2]

Symptoms of vertebrobasilar insufficiency, such as paroxysmal vertigo, dizziness, diplopia, ataxia, dysarthria and syncope, continue to be the main symptoms in the clinical practice.[5] In the present study, these findings corresponded to $>$ 77.7% of symptomatic patients, similar to the symptomatic patients treated in the study by Wrotniak et al., with 82%. However, asymptomatic patients still remained the majority, $>$ 70%, according to the literature as being the majority group in the presentation of SSS (which in our study was 68.9%).[9]

Doppler ultrasound with color flow images (wave amortization or monophasic changes) is the noninvasive modality of choice in the evaluation for subclavian arterial disease.[2] Angiotomography and angioresonance provide excellent anatomical resolution with accurate information on lesion morphology, length, and location. Invasive DSA is the definitive test, with images not subtracted providing anatomical mapping, while digital subtraction characterizes stenosis.[2]

A small percentage of patients with SSS really need no therapeutic intervention.[11] Asymptomatic patients should not be submitted to interventions, since they could prevent future disease with medical therapy, which includes antiplatelet drugs, such as aspirin, and a lipid-lowering statin therapy with a goal of low-density protein (LDL) cholesterol $<$ 100 mg/dL.[11] Stopping smoking, controlling the blood pressure, and glycated hemoglobin A1C rate $<$ 7% are advised[7] to reduce the morbidity and mortality risk related to atherosclerotic disease, which can lead to ischemic events in the heart and in the brain.[11]

The surgical vascular intervention options include: axillary-axillary bypass, carotid-subclavian bypass, and transposition of the SA.[12] The carotid-subclavian bypass showed low risk of mortality and small recurrence rates.[5] Law et al. found that

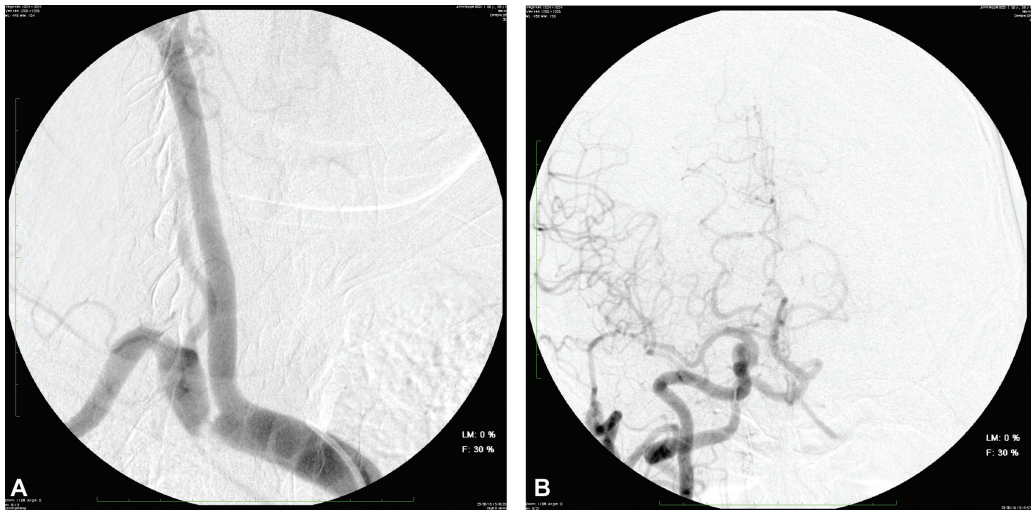

Fig. 1 (A) Right subclavian artery with suboclusive stenosis and a retrograde flow in the vertebral artery. Right anterior oblique view. (B) Right common carotid artery and filling of posterior circulation through extra-intracranial anastomosis. Anteroposterior view.

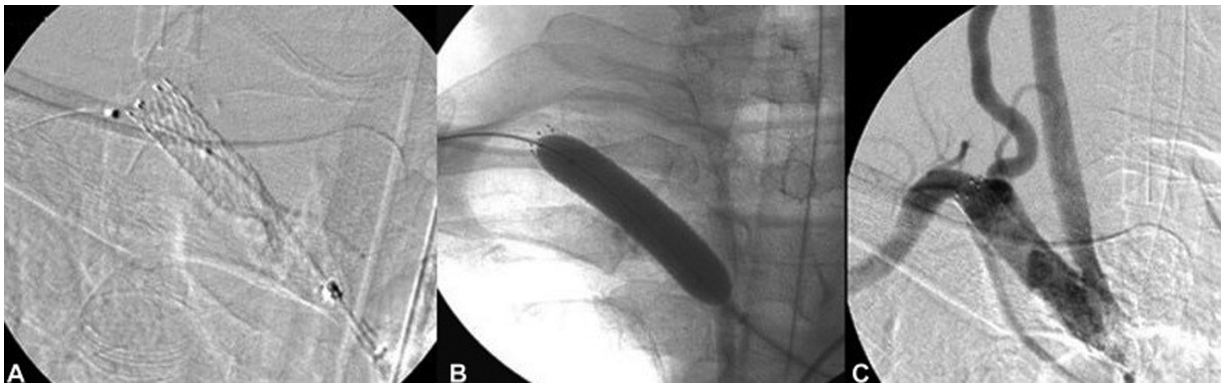

Fig. 2 Angioplasty. (A) Delivered and opened stent covering the entire stenosis. (B) Inflating the balloon. (C) Satisfactory final result.

transpositions have the highest long-term 5-year patency rate (100%), followed by PTFE (95%) and Dacron grafts (84%), and saphenous vein grafts have the lowest patency rate (65%).[17] Percutaneous transluminal angioplasty (PTA) has a high rate of patency for subclavian stenosis or occlusion, the latter with a lower rate.[13] Percutaneous transluminal angioplasty (PTA) has a high rate of patency for subclavian stenosis or occlusion, the latter with a lower rate. Percutaneous transluminal angioplasty has a high rate of good outcome and a low incidence of recurrence, especially in proximal stenosis.[14–16] It is minimally invasive and, therefore, has lower rates of complications; stenting has been considered safe when compared with the surgical vascular intervention.[16] In a series of 110 patients treated by PTA with a follow-up of almost 3 years, patients with SA stenosis and occlusion had patency rates of 93 and 65%, respectively.[14] Risks related to PTA are stroke, arterial rupture, stent migration and reocclusion.[16] Patients who already had an occlusion presented with a high rate of reocclusion (35–50%).[15,16] A regular follow-up for at least 2 years post-PTA is recommended.[16] None of the studies reviewed in the present article clarify how long a patient with total occlusion is still submitted to an intervention with angioplasty (►**Figs. 1** and **2**).

Conclusion

Prospective randomized studies are needed to elucidate the fact that several papers analyze subclavian PTA in stenosis and occlusion, but they do not mention whether or not they have clinical and/or angiographic criteria for SSS.

Conflict of Interests

The authors have no conflict of interests to declare.

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Epidemiological Study of Patients with Spinal Cord Injury Treated in POLEM, a Specialized Clinic in São Paulo State – Brazil

Estudo epidemiológico de pacientes com lesão medular tratados na POLEM, clínica especializada no estado de São Paulo – Brasil

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Arq Bras Neurocir 2021;40(2):e125–e129.

Abstract

Objective To analyze the epidemiological profile of patients with spinal cord injury treated at POLEM – Associação de Apoio às Pessoas com Lesão Medular (Association for Supporting People with Spinal Cord Injury).

Method The population studied comprised 113 patients with spinal cord injury, of traumatic or nontraumatic etiology, and the data obtained were compared with those of other institutions.

Results Of the 113 patients, 70.8% were male and 29.2% female. Traumatic lesions were responsible for 54% of the patients, and nontraumatic for 46%. Of the patients with traumatic injury, 90.2% were male, the main cause being traffic accidents. In nontraumatic lesions, women were the most affected, 51.9%; and dysraphism and myelitis were the main causes (31% and 21%, respectively).

Conclusion The results showed an important incidence of spinal cord injury due to trauma, mainly affecting young individuals of productive age and low educational level, representing high economic and social costs. The data found in the present study are similar to those of other studies performed in our country.

Keywords
- spinal cord injury
- epidemiology
- causes
- rehabilitation

Resumo

Objetivos Analisar o perfil epidemiológico dos pacientes com lesão medular atendidos na POLEM – Associação de Apoio às Pessoas com Lesão Medular.

Método A população estudada compreendeu 113 pacientes com lesão medular, de etiologia traumática ou não, e os dados obtidos foram comparados com os de outras instituições.

received
March 19, 2020
accepted
September 4, 2020
published online
February 15, 2021

DOI https://doi.org/10.1055/s-0040-1719009.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Resultados Dos 113 pacientes, 70,8% eram do sexo masculino e 29,2% do sexo feminino. As lesões traumáticas foram responsáveis por 54% dos pacientes, e as não traumáticas por 46%. Dos pacientes com lesão traumática, 90,2% eram do sexo masculino, sendo a principal causa os acidentes de trânsito. Nas lesões não traumáticas, as mulheres foram as mais acometidas, 51,9%; e o disrafismo e as mielites foram as principais causas (31% e 21%, respectivamente).

Conclusão Pelos dados obtidos, mostrou-se a incidência importante de lesão medular por trauma, acometendo principalmente indivíduos jovens, em idade produtiva e com baixo nível de escolaridade, representando elevados custos econômico e social. Os dados encontrados no presente estudo são semelhantes a outros realizados em nosso país.

Palavras-chave
- lesão medular
- epidemiologia
- causas
- reabilitacão

Introduction

Spinal cord injury (SCI) is one of the most devastating lesions that can compromise people's health. Besides physical incapacity, it causes serious psychological, financial and social losses.

As an aggravating factor, care with people with spinal cord injury, in addition to treatment in the acute phase, requires continuous multidisciplinary care, without which the patient will not be better recovered. All this entails enormous expenses. In Canada, according to Krueger et al., the lifetime treatment cost of a person with incomplete paraplegia is around CAD $ 1.47 million, while for a person with complete quadriplegia the cost is around CAD $ 3.03 million. This estimate includes the costs of the various complications that occur. The annual expense for treating people with spinal cord injury in Canada reaches CAD $ 2.67 billion.[1] Most studies show a high male/female ratio, especially in traumatic lesions, with a high incidence in young individuals, ~ 30 years old. Traffic accidents are the main etiological agent.[1]

We try to show the causes of spinal cord injury and its level, stratified according to gender, age when the injury occurred, time elapsed between the onset of illness and the start of treatment, socioeconomic situation, nutritional status of the patients, function of the bladder and bowel.

Studies on the epidemiology of spinal cord injury in Brazil and even in South America are rare.[2,3] Data on the prevalence and treatment costs are also uncertain. With the present study, we try to show the main causes and nuances of this disease in our association and make a comparison with other works performed both in Brazil and in other countries.

It is intended mainly, together with other published works, to provide subsidies for the establishment of strategies for prevention and treatment, reducing the suffering of people and expenses arising from this serious illness.

Methods

The records of 113 patients suitable for the start of rehabilitation activities at POLEM were analyzed and reviewed. All of the patients had a clinical diagnosis of spinal cord injury. The data that will be included in the present study were obtained from clinical records, both from active patients still in the process of rehabilitation, and from patients who no longer participate in the activities in the association.

The charts analyzed include the initial evaluations of the therapeutic segments, and the anamneses of the physiotherapy, neurology, occupational therapy, nutrition, psychology (patient and caregiver), nursing, and social services sectors were reviewed.

The variables analyzed in the present study were: gender, types of injury (traumatic or nontraumatic), etiology and level of injury, age when injured, age at the start of rehabilitation, time interval between the onset of lesions and early rehabilitation, schooling, marital status, whether or not they have any type of health plan, use of assistive technology, receipt of benefits, caregivers, body mass index (BMI), bowel functioning and bladder catheterization.

The collected data was typed in spreadsheets of the Microsoft Excel application in Windows 7 (Microsoft Corporation, Redmond, WA, USA), in the form of double entry for the verification of typos. The descriptive analysis was performed and presented in absolute and relative frequency distribution tables (percentage).

Results

Out of the total number of 113 assisted patients, 80 (70.8%) were male and 33 (29.2%) were female, a ratio of 2.42:1. Of these, 61 (54%) suffered traumatic injuries and 52 (46%) had nontraumatic lesions, with a ratio of 1.17:1.

Among the traumatic lesions, 55 (90.2%) of the patients were male and 6 (9.8%) were female, the ratio was 9.16:1.

In the nontraumatic lesions, unlike the traumatic lesions, the predominance was female, 27 (51.9%), while in males there were 25 (48, 1%), ratio 1.08:1.

Among the traumatic injuries, traffic accident stood out with 33 patients, 15 by car accident, 13 by motorcycle accident, and 5 by trampling. In traffic accidents, 7 patients had between 11 and 20 years old, 4 male and 3 female. In the age group of 21 to 40 years old, there were 30 men and no women. Between 41 and 60 years old, there were 3 male patients and no female patients. Among the traumatic injuries, the injuries due to fall of height, injury by firearm projectile, diving in shallow water and trauma by load should be highlighted. See ►**Table 1**.

Table 1 Traumatic Etiology

Traumatic Etiology	Absolute number	%
Automobile accident	15	25
Motorcycle accident	13	21
Fall of height	11	18
Firearm Injury (FAI)	8	13
Trampling by car	5	8
Trauma by load	6	10
Shallow water diving	3	5
Total	61	100

Table 2 Nontraumatic Etiology

Nontraumatic Etiology	Absolute number	%
Spinal cord Disraphism	16	31
Myelitis	11	21
Tumoral	10	19
Cervical spondylotic myelopathy	4	8
Vascular disease	3	6
Amyotrophic lateral sclerosis	2	4
Multiple sclerosis	2	4
Siyringomyelia	2	4
Could not report	2	4
Total	52	100

Among nontraumatic lesions, dysraphism is the main cause, followed by myelitis. See ►**Table 2**.

Regarding the level of the lesion, the thoracic region was the most affected, followed by the cervical region and finally the lumbar region. See ►**Table 3**

The mean age for incidence of the lesion (traumatic or nontraumatic) was 38 years and 3 months old, ranging from 1 day old (congenital lesion) to 75 years old. The time interval between the incidence of the lesion and the beginning of rehabilitation in the association was 6 years and 5 months, ranging from 1 month old to 43 years and 3 months old.

Regarding marital status, 47 individuals (4 1.6%) were married and 45 (39.8%) were single. Widows accounted for 6 (5.3%), divorced for 7, (6, 2%) and 8 (7.0%) lived in a stable union.

Of those assisted, 42 (37.2%) had health care plans and 61 (53.9%) were users of the Brazilian Unified Health System (SUS, in the Portuguese acronym). In 10 charts we did not find such information.

Among the beneficiaries, 107 (94.7%) used one or more types of assistive technology, and the most common were: wheelchair, shower chair, long tutors with pelvic belt, special mattress and others. See ►**Table 5**.

Out of the patients treated, 40 (35.3%) were in retirement, 27 (23.9%) were sick, and 13 (11.5%) were under Continuous Benefit Payment (BPC, in the Portuguese acronym). In 33 records, there was no reference to the receipt of benefits.

In the charts analyzed, 98 patients (86.7%) received caregiver assistance and 10 (8.8%) did not receive it, and in 5 (4.4%) medical records no information was found in this regard.

Bladder emptying data show that 20 patients (17.7%) had urinary incontinence, 48 (42.5%) had intermittent clear

Table 3 Injury Level

Injury Level	Absolute number	%
Thoracic	57	50
Cervical	37	33
Low back	19	17
Total	113	100

Table 4 Level of schooling

Level of schooling	Absolute number	%
Did not complete elementary school	54	47.7
Completed high school	28	24.7
Completed higher education	7	6.2
Did not complete high school	6	5.3
Completed elementary school	5	4.4
Attended nursery school	3	2.7
Illiterate	3	2.7
Attended technical education	2	1.8
Not old enough to attend school	2	1.8
Did not complete higher education	1	0.9
Attended special education	1	0.9
No information found	1	0.9
Total	113	100

Table 5 Type of assistive technology

Type of technology	Absolute number	%
Wheelchair	90	80
Shower chair	52	46
Tutor long with pelvic belt	9	8
Gutters	21	19
Walker	13	11
Egg Box Mattress	14	12
Others *	46	41

* others: long tutor without pelvic belt (1 patient), board transfer,[2] bracing for shaving,[1] bracing for the computer,[1] hand orthosis,[4] splint to handle[4] abdominal strap,[1] compression stocking,[4] positioning roller,[1] cervical collar,[1] Putti vest,[1] Canadian crutches[5] axillary crutches,[1] common cane,[2] 4-point cane,[2] water mattress,[2] air mattress,[3] hospital bed,[7] water seat,[4] air seat,[3] gel seat,[1] vehicular adaptation.[1]

catheterization, 38 (33.6%) had spontaneous urination, 2 (1.8%) underwent cystostomy, and in 5 medical records (4.4%) we did not obtain data.

Regarding nutritional status, of the 113 patients evaluated, 30 (26.5%) were eutrophic, 21 (18.6%) were preobese or overweight. The same number of 5 patients (4.4%) for grade III and grade I low weight was found. There were 3 patients with grade II low weight (2.7%).

The variables for classification of BMI were: grade I obesity, 7 patients (6.2%), grade II, 2 patients (1.8%), grade III, 1 patient (0.9%). In 39 (34.5%) of the patients, the BMI was not evaluated.

Regarding intestinal function, it was found that 30 (26.5%) had constipation and that 60 (53.1%) didn't, and 23 patients (20.4%) were not evaluated.

Discussion

In the present study, the data show a significant prevalence of spinal cord injury in men, which is in agreement with data found globally.[2] This number is due to the high incidence of trauma as a cause in males. Of note among the traumatic causes are traffic accidents as the main responsible for SCI, and the main site of injury is the thoracic spine, followed by the cervical spine.

In the literature found in national journals, however, there is divergence in the data, some differing mainly in the cause and location of the trauma.

An epidemiological study performed at the Lar Escola São Francisco, in the city of São Paulo, state of São Paulo, Brazil, with 171 patients seen from 1999 to 2001, showed that 107 (62.6%) were male and 64 (37.4%) were female. The mean age of those attended was 35.4 years old, ranging from 1 to 78 years old. These data are similar to those found in the present study. There was a discrepancy in the causes, because in 53 (30.1%) it was due to firearm injury (FAI), 30 (17.5%) due to falls, 23 (13.4%) due to tumor, and 15 (8.8%) due to traffic accident.[3]

Work done by Botelho et al. at the Hospital Mandaqui in São Paulo, where 95 patients with medullar spinal trauma were attended, 82 (86.3%) were male and 13 (13.7%) were female, a ratio of 6.3:1, numbers close to those shown in the present study. Regarding the etiology, the main ones were: falls, 31 patients (32.6%), automotive accident ($n = 22$; 23%), dive in shallow water ($n = 14$; 14.7%), and FAI (5.2%).[4] These data are different from those found in POLEM.

In the Physiotherapy Outpatient Clinic of the Universidade de Ciências Médicas da Paraíba, a survey of 59 patients showed that 55 (93.22%) were male and 6 (6.77%) were female. The mean age was 34 years old and the thoracic segment was the most affected ($n = 30$; 50.84%), followed by the cervical segment ($n = 24$; 40.67%) and by the lumbar segment ($n = 5$; 8.47%). Among the causes, FAI was the main one, with 27 patients (45.76%), followed by car accident, with 12 (20.33%) patients.[5] In the Disability Service Center (DAC, in the Portuguese acronym) of the Universidade de Passo Fundo, out of the 49 patients attended, 40 (81.6%) were male and 9 (18.4%) were female. The thoracic level was the most affected (77.5%), and the main causes were falls (36.7%), traffic accidents (32.7%) and FAIs (24.5%).[6]

In the masters dissertation of Noronha, in June 2008, she evaluated 156 patients with spinal cord injury. The main causes were 37 patients (23.7%), 32 due to FAI (20.5%), and 31 due to car accident (19.9%). There was a predominance of lesions in the thoracic level (45.8%), followed by the cervical level (43.2%).[7]

Another study, performed by Brito et al., comprised 87 patients, 71 (81.6%) male and 16 (18.4%) female, with a mean age of 33.9 years old. The most affected level was the thoracic, with 33 patients (37.9%), followed by the cervical, with 23 patients (26.4%), numbers close to those shown in the present study. Regarding the etiology, falls occurred in 37 patients (42.6%), followed by car accident in 21 (24.2%), motorcycle accident in 15 (17.2%) and FAI in 11 (12.6%).[8]

A study performed at the Neurological Physiotherapy Outpatient Clinic of the Hospital Universitário Regional do Norte do Paraná, with 25 patients with complete SCI, showed that 20 (80%) were male and 5 (20%) were female, with a mean age of 34, 6 years old. Regarding the etiology, 50% were victims of car accident, 20.8% were victims of FAI, 12.5% were whitewash and 8.3% were due to surgical procedures.

Custódio et al., in a retrospective survey with a sample of 208 patients, showed that 164 (78.85%) were male and 44 (25.15%) were female. Traffic accidents corresponded to 44.70% of the cases, motorcycle accidents to 56 patients (26.92%), automobile accident to 37 patients (17.78%), FAI to 30 patients (14.42%), fall to 13.94%, tumor to 7.69%, diving in shallow water to 5.76%, myelopathy due to stenosis to 2.88% and myelitis to 3.36%. The most affected level was the thoracic (54.8%), followed by the cervical (35.1%) and the lumbar (10.1%).[10]

In underdeveloped or developing countries, the percentage of SCI due to traumatic causes, mainly due to traffic accidents, is considerably high. In developed countries, this index has fallen, and the number of people with nontraumatic SCI has increased. But, even in these countries, there are disparate numbers. In Ontario, Canada, the main cause of traumatic SCI is fall from height. And in the states of Alabama and Mississippi, USA, the injury by violence is the main cause. Sports and recreational injury is the leading cause in the British Columbia, Canada (17.9%), in Utah (15.7%), USA, being the lowest in Mississippi (3.5%).

Among the nontraumatic causes, there is also a great variation in the data found. In the present study, dysraphism and myelitis are the main causes, being that dysraphism showed a superior number to the ones found in the international studies.

It was also observed in the present study that the mean age for the incidence of the lesion was 35 years and 3 months old, and the time interval between the beginning of the SCI and the start of the rehabilitation center suitable 6 years 5 months, which is compatible with data found in other studies conducted in Brazil.[3,7,10]

Another important fact is the low level of schooling among the patients, coinciding with data from the Brazilian

Institute of Geography and Statistics (IBGE, in the Portuguese acronym) Demographic Census, conducted in 2010, which indicates that there are 45.6 million Brazilians with at least 1 type of disability. Out of this total, 6.7% have complete higher education and 61% have no education or incomplete fundamental level.

Among nontraumatic causes, there is also great variation in statistics. In a study conducted in Okayama, Japan, the incidence of nontraumatic spinal cord injury is 20 per 1 million people and degenerative spinal disease accounts for 59% of the cases. Tumors account for 19% of the cases.[2]

In South Asia, only India has epidemiological data in three studies on the causes of SCI. High rates of bone-marrow tuberculosis were found in Bangalore (26%), Karnataka (25%) and Kashmir (38%). But tumors also have a high incidence, 29% in Bangalore and 27% in Karnataka.[2]

In Western Europe, data from 8 countries are reported: Denmark, France, Germany, Israel, Italy, The Netherlands, Scotland and Spain. The median incidence of nontraumatic spinal cord injury was 6 per 1 million people per year. We found high tumor rates (25%) and degenerative spine disease (32%) on average. Dysraphism was found in 5% in Spain and Italy and in 2% in Denmark. Myelitis was the cause in 7% of the cases in Israel, 14% in Denmark, and 23% in Italy.[2]

In Turkey, studies in Ankara showed that tumors (29%) and degenerative diseases of the spine (29%) were the main causes. In Istanbul, tumors and degenerative diseases of the spine were responsible for 22% and 25%, respectively. Inflammatory diseases were responsible for 23% of the cases in Ankara and of 20% in Istanbul. Dysraphism was the cause in 6% of the cases.

In the USA, a retrospective 5-year study points to spinal stenosis and tumors as the main causes of SCI, with 54% and 26%, respectively. Myelitis accounted for 5% of patients treated.[11] See **table 4**.

Conclusion

It was demonstrated in the present study that trauma represents the main cause of SCI affecting patients treated by POLEM, with the thoracic spine being the most affected. Out of the population studied, the highest incidence occurs in the young population, in working age, with a large majority of families with low educational level, representing a high economic and social cost. Based on the present study and on several others, preventive measures should be traced to decrease the incidence of this disease, which is a real tragedy.

Authors' Contributions

To perform this work, all authors contributed to the data collection and their individualization in the area of action, literature, discussion, review, approval and drafting the final version of the results. Lopes J. E. A.: article intellectual concept and study design; Simões I. L. K.: confection of graphics and tables, typing.

Conflict of Interests

The authors have no conflict of interests to declare.

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Superficial-Temporal-Artery-To-Middle-Cerebral-Artery Bypass in Cerebrovascular Occlusive Disease and Hemodynamic-Related Ischemia: Illustrative Case and Literature Review

Bypass STA-MCA para doença cerebrovascular oclusiva e isquemia hemodinâmica: Caso ilustrativo e revisão da literatura

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Arq Bras Neurocir 2021;40(2):e130–e136.

Abstract

Stroke is the third most common cause of death worldwide. About 10% to 15% of strokes related to the territory of the carotid artery are associated with its complete occlusion. There is an important subgroup of patients with cerebrovascular occlusive diseases who might benefit from an external-carotid-to-internal-carotid bypass. In the present study, we report a case of a 53-year-old male patient with stenosis of the M2 branch of the middle cerebral artery (MCA), with a history of ~ 20 episodes of transient ischemic accidents (TIA)s, in whom an anastomosis of the M4 branch of the superficial temporal artery-MCA was performed. The patient was discharged in three days, and in the two years of follow-up, they were no more TIAs. We also conducted a review of the literature on cerebrovascular occlusive disease and extracranial-intracranial bypass surgery. New methods to evaluate cerebral hemodynamics made it possible to classify a new subgroup of patients with symptomatic cerebrovascular disease and documented cerebrovascular compromise in whom the drug therapy fails, who can benefit from the extracranial-intracranial bypass. Our case report illustrates the advantages of revascularization in these selected patients.

Keywords

- extracranial-intracranial bypass
- middle cerebral artery
- superficial temporal artery
- microvascular anastomosis
- cerebrovascular occlusive disease

Resumo

Acidentes vasculares cerebrais (AVC) são a terceira causa de mortalidade mundialmente. Entre 10 e 15% dos AVCs relacionados à artéria carótida estão associados com sua oclusão completa. Há um subgrupo importante de pacientes com doenças cerebrovasculares oclusivas que podem se beneficiar de um by-pass carótida-externa-carótida-interna. Neste

received
July 22, 2020
accepted
September 25, 2020
published online
January 18, 2021

DOI https://doi.org/10.1055/s-0040-1721335.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

estudo, reportamos o caso de um homem de 53 anos com estenose do ramo M2 da artéria cerebral média, com história de 20 acidentes isquêmicos transitórios (AIT), que foi tratado com anastomose de M4 com a artéria temporal superficial. O paciente foi de alta no terceiro dia pós-operatório e, em dois anos de follow-up, não houve mais AITs. Também conduzimos uma revisão da literatura sobre doença cerebrovascular oclusiva e by-pass intra-extracraniano. Novos métodos para avaliar a hemodinâmica cerebral tornaram possível a classificação de um novo subgrupo de pacientes com doença cerebrovascular sintomática em quem a terapia medicamentosa falhou, que podem se beneficiar de um by-pass intra-extracraniano. Nosso relato de caso ilustra as vantagens de revascularização em pacientes selecionados.

Introduction

Stroke is the second most common cause of death around the world, according to World Health Organization (WHO).[1] About 10% to 15% of strokes related to the territory of the carotid artery (CA) are associated with complete CA occlusion, which means, in the United States, an estimated 61 thousand patients with first-ever strokes, and 19 thousand patients every year with transient ischemic accidents (TIAs) associated with complete CA occlusion.[2] With the advent of different diagnostic imaging methodologies that enable the study of cerebral hemodynamics, an important subgroup of patients has emerged. This cluster is composed of subjects in maximal medical therapy with hemodynamic compromise and symptomatic cerebrovascular occlusion disease ipsilateral to the occlusion. This group might benefit from external-CA-to-internal-CA bypass since their annual risk of stroke is $\sim$ 10% to 14% against 4% to 6% in those with preserved cerebral vasomotor reactivity.[3,4] The present article aims to discuss the surgical approach in these cases through an illustrative case and a short review of the literature.

Illustrative Case

A 53-year old male was found to have a stenosis of the M2 segment of the middle cerebral artery (MCA) on cerebral angiography. His past medical history accounted for $\sim$ 20 episodes of TIAs with right-sided facial-brachial hemiparesis and aphasia events. He also had controlled diabetes and hypertension, and was in dual-platelet anti-aggregation therapy. An anamostosis of the M4 branch of the superficial temporal artery (STA) was performed to increase the blood flow in the MCA territory. The patient was discharged in three days, and, in the two-year follow-up, there were no more TIAs. ►**Fig. 1** shows the pre- and postoperative arteriographies.

Surgical Technique

Under general anesthesia and intraoperative monitoring with an electroencephalogram and somatosensory evoked potentials, the patient is put in the supine position, with the head tilted to contralaterally to the craniotomy and fixed with the Mayfield three-point head holder. For patients with restriction of lateral neck rotation, a rolled blanket is put under the ipsilateral shoulder. The Doppler examination helps locate the branches of the STA on the scalp. Unless angiography or magnetic resonance angiography (MRA) shows a larger frontal branch, the posterior branch is chosen. The frontal branch must be used in cases of atresia of the parietal branch, previous craniotomy with a lesion to the parietal branch, or anterior-branch dominance.

An incision is made along the delineated course of the greater branch of the STA, extending from the preauricular region superiorly and then curved anteriorly. If the anterior branch is chosen, the surgeon must consider the fact that fibers of the superior division of the facial nerve can be crossing the region, and that this branch is anterior to the hairline. An

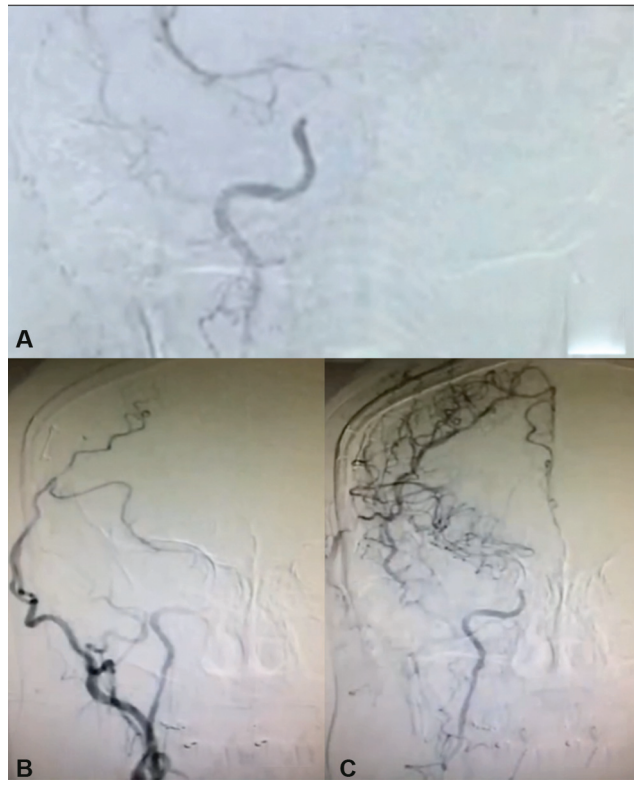

Fig. 1 Pre- and postoperative arteriography. (**A**) Preoperative arteriography showing significant occlusion of the internal carotid artery. (**B and C**) Postoperative arteriography showing significant reperfusion from the superficial temporal artery-middle cerebral artery (STA-MCA) bypass.

option in such cases is direct dissection over the artery or "from the underside of the scalp flap distally".[5]

After choosing the branch, the incision is deepened under magnification into the subcutaneous layer, where the STA branches run. Most commonly, the posterior branch is identified and followed to its origin using sharp dissection under microscope magnification. It is crucial to preserve the tissue adjacent to the vessel, except for the site used in the anastomosis (including the tip in which the adventitia is dissected) (►**Fig. 2A**).

Craniotomy is started by cutting the temporalis muscle, dissecting it with Bovie electrocautery, and fixing it with retractors. Following the exposure of the underlying bone, two burr holes are made, and the craniotomy is performed using a drill. Afterward, the dura is opened in a curvilinear fashion and tacked around the margins of the craniotomy to avoid postoperative epidural hematoma. The cortical branch of the MCA is chosen based mainly on the size of the vessel ($\geq$ 1.5 mm is ideal). To facilitate the procedure, the site of anastomosis must be located far from the borders of the craniotomy, and the vessel must be oriented tangentially.

After establishing the cortical branch that will be used, attention is redirected to the STA. The tip of the artery is dissected and cut in a sharp fashion (►**Fig. 2B**). The surrounding fascia of the adventitia is stripped out only on the border side of the anastomosis. It is not recommended to dissect all of the vessel's extension because it is not helpful, and there is an increased risk of injury. A small microclip is placed proximally to the stump of the artery, which is then directed down into the level of the isolated cortical branch.

The anastomosis site of the STA is cut at a 45° angle. The proximal clip is removed to check the free flow through the end of the vessel. Then, an arteriotomy is performed on the cortical branch using sharp microscissors. The edges of both sides of the anastomosis are marked with a marking pen to highlight the lumen. At this moment, the lumen of the STA must be inspected to observe the conditions of its margins.

Temporary clips are placed proximal and distal to the site of the anastomosis in the cortical vessel, which receives an incision with the same length as that of the STA diameter. Under further magnification using the microscope, the anastomosis is performed using 10–0 sutures, with approximately 6 interrupted sutures in an end-to-side fashion preceded by anchoring sutures. To reduce injury to the endothelium of the vessel, the suture is passed through the recipient vessel from the inside out (►**Fig. 2C**). Subsequently, the hemostatic clips are removed from both the proximal and distal aspects of the cortical vessels, and then the ones in the superficial temporal artery are also removed. A small piece of absorbable hemostat is wrapped around the anastomosis site (►**Fig. 2D**). At this stage, papaverine is applied at the suture line for hemostasis (►**Fig. 3**).

The Doppler is used to confirm the patency of the STA branch, which must pulse along with the rest of the anastomosis. Currently, we are using the cut flow index for evaluation.

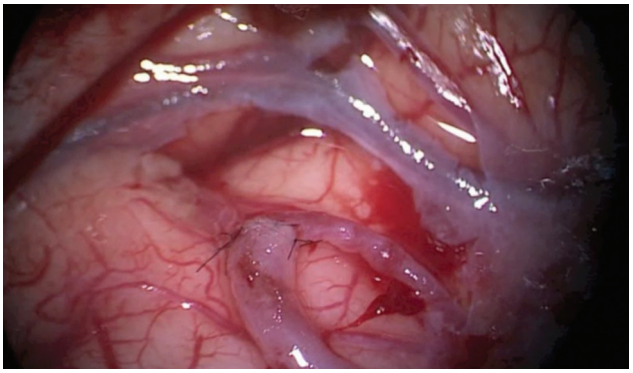

Fig. 3 Final aspect of the anastomosis: STA-MCA bypass.

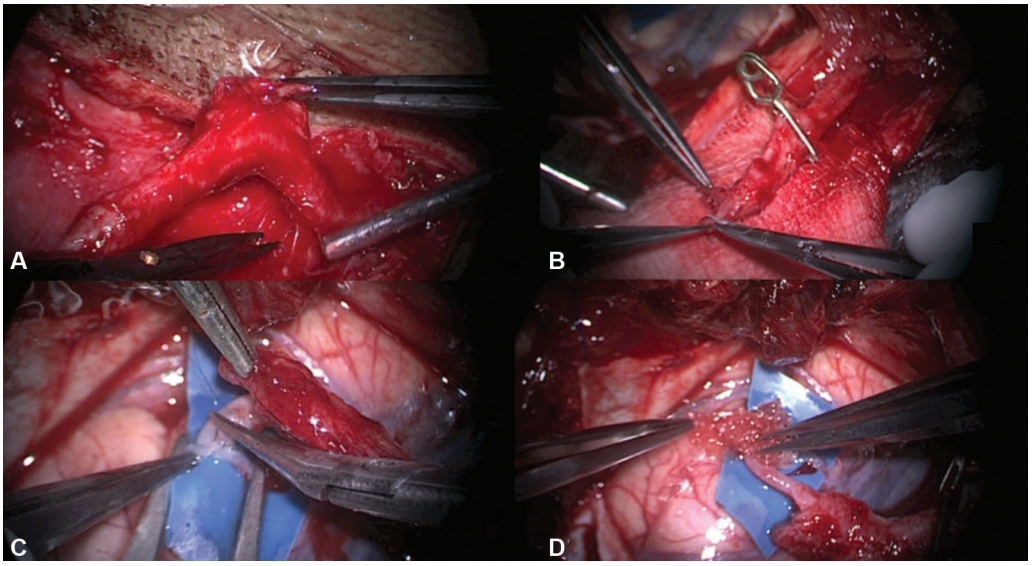

Fig. 2 Bypass preparation. (**A**) Dissection and preparation of the donor vessel, the STA. (**B**) Temporary clip placed in the STA. The vessel is then dissected and cut in a sharp fashion. The surrounding fascia of the adventitia is stripped out only in the border side of the anastomosis. (**C**) The anastomosis is performed using 10–0 sutures with around 6 interrupted sutures in an end-to-side fashion preceded by anchoring sutures. To reduce injury to the vessel's endothelium, the suture is passed through the recipient vessel from the inside out. (**D**) A small piece of absorbable hemostat is wrapped around the anastomosis site. At this stage, papaverine is applied at the suture line for hemostasis.

Closure begins by approximating the dura and applying Gelfoam (Upjohn, Kalamazoo, MI, US) to the epidural space. The bone flap is trimmed to allow a window for the entrance of the STA into the intracranial cavity. The bone is placed in position and held in place using miniplates. The temporal muscle is then approximated loosely without constriction around the pedicle of the STA. To optimize flow through the anastomosis, the unused branch of the STA is ligated. The scalp is closed using 2–0 Vicryl (Ethicon, Somerville, NJ, US) in an interrupted inverted fashion, approximating the subcutaneous tissue to the galea.

Literature Review

Historical Background

Nicholls et al.[6] concluded that unilateral CA occlusions are mainly associated with cases of ipsilateral strokes (25%) and ipsilateral TIAs (16%). Cote et al.[7] reported that, over 34 months, patients with occlusion of the internal carotid artery (ICA) with no or mild neurological deficit have an overall stroke risk of 15% – similar to that of patients suffering from TIAs or minor strokes –, and 63% of these strokes were ipsilateral to the occlusion. In patients with CA occlusion and contralateral stenosis, Hammacher et al.[8] documented a rate of stroke of 33% to 40% per year. For those patients with symptomatic CA occlusion confirmed angiographically, a 5.9% yearly risk of ipsilateral stroke was described by Hankey and Warlow.[9]

Professor M. Gazi Yaşargil,[10] a pioneer in cerebrovascular anastomosis, started to perform this procedure in dogs, and later published his results on human patients.[11,12] The technique was widely propagated, but there was no proof of the procedure's efficacy in preventing new strokes.

In the 1980s, the EC/IC Bypass Study Group[13] also failed to confirm whether the surgery was effective in preventing ischemic events in patients with atherosclerotic arterial disease in the CA or MCA territory. After that, extracranial-intracranial (EC-IC) bypass has been restricted for cases of moyamoya disease and patients who need ICA occlusion due to an unclipplable aneurysm or skull-base tumor.

Nonetheless, at the time when both studies were conducted, there was no physiological knowledge or a reliable and proven method to identify crucial hemodynamic factors that would enable the stratification of patients according to the risk of new ischemic events,[2,14–16] thus detecting a subgroup of patients that could benefit from the revascularization procedure.

Grubb Jr. et al.,[17] in the St Louis Carotid Occlusion Study (STLCOS), established that such subgroups could be identified through indirect assessments based on the brain's compensatory mechanisms regarding progressive reductions in cerebral-perfusion pressure (CPP). In the same study,[17] the authors also concluded that those patients with symptomatic CA occlusion and stage-II hemodynamic failure (decreased cerebral blood flow [CBF] with increased oxygen extraction fraction [OEF]) who were medically treated were at a higher risk for subsequent stroke.

Current Perspective

It is currently well known that a decreased CBF is generally unhelpful to detect the risk of future stroke because it cannot distinguish whether the cause of this reduction is an occlusive event or a compensatory physiological response due to reduced metabolic demands.[17]

On the other hand, the accuracy increases if activated studies are used, which means obtaining an initial measurement at rest and another after provision of a cerebral vasodilatory stimulus (with acetazolamide, hypercapnia, or physiological tasks). A reduced responsiveness of the CBF to these stimuli means that the capacity for compensatory vasodilation is exceeded, and there is an impaired cerebral vasomotor reactivity to the diminished CPP.

There are different methods to measure the cerebrovascular reactivity (CVR) indices, and thus estimate the risk of stroke, such as xenon computed tomography (XeCT) with and without acetazolamide,[18] positron-emission tomography (PET),[19,20] and transcranial Doppler flowmetry,[21] which is much less sensitive than XeCT.[22]

In subsequent series, Nussbaum and Erickson[23] were able to show improvement in patients with symptomatic cerebrovascular disease refractory to medical treatment submitted to EC-IC bypass surgery, and Charbel et al.[5] reported that careful attention to the technique could result in consistent success.

Recent Advances

Two recent multicentric randomized trials tried to validate the use of EC-IC anastomosis: the Carotid Occlusion Surgery Study (COSS),[29] in the United States, and the Japanese Extracranial to Intracranial Bypass Trial (JET).[30] The latter tested patients with XeCT, PET, or single-photon emission computed tomography (SPECT), while the former tested with PET.

The COSS was halted due to futility. The perioperative ipsilateral stroke rates were higher in the surgical group compared with the medical group. Moreover, the study concluded that the surgical treatment, in the selected patients, was not of clinical benefit. Still, later publications[24] showed that in two years the surgical group achieved high rates of bypass graft patency, improved cerebral hemodynamics, and much lower rates of recurrent ipsilateral ischemic stroke after the second postoperative day compared with medical group.[25] In a subsequent paper, the authors concluded that the majority of ischemic strokes that occurred in the postoperative period were not related to the bypass grafting but to hemodynamic fragility of the study population.[26]

The COSS was received with some criticism, primarily related to: 1) the unexpected low rate of stroke in the medical group[27,28]; 2) its semiquantitative method to measure the OEF ratio, which was different from the quantitative method applied in the STLCOS[27,29–31]; and 3) its clinical selection criteria, which included patients with a single ischemic event or those relatively neurologically stable.[27,28,32]

Nearly all of the ctiticismswere addressed by Powers et. al.[33] Still, as Esposito et al.[32] highlight that there are factors regarding the perioperative stroke rates that should have been debated, such as the lack of an established perioperative protocol for the COSS, or the recruitment requirements of the other health professionals involved in the study.

Table 1 Studies evaluating extracranial-intracranial bypass

Study	Year	N° of patients	Hemodynamic cerebral ischemia eligibility criteria	Surgical group	Medical group	Primary end points per group	Primary end points	Remarks
EC/IC Bypass Study[13]	1985	1.377	—	663	714	Postrandomization occurrences of fatal and nonfatal stroke	Medical: 205 (29%) Surgical: 205 (31%)	1. The surgical group presented fatal and nonfatal stroke events earlier 2. Bypass patency rate of 96% 3. Lack of hemodynamic selection criteria
JET[34]	2006	196	3D quantitative blood-flow measurement in active study with acetazolamide	98	98	Major stroke or death in the two-year period after surgery	Medical: 14 (14,3%) Surgical: 5 (5,1%)	1. Able to show statistically significant benefit for the surgical group 2. No events in the first 30 postoperative days
COSS[29]	2011	195	Hemispheric OEF ratio in semiquantitative measurement	97	98	All cases of stroke and death within 30 days postoperatively, plus ipsilateral hemispheric stroke within 2 years	Medical: 20 (22,7%) Surgical: 20 (21%)	1.High rates of graft patency (98%) 2. OEF ratio improvement 3. On the surgical group, 14 of 20 events were ipsilateral stroke within 30 days postoperatively. Of these 14, 12 occurred in the first 2 days
CMOSS[31]	—	330*	CTP showing misery perfusion	165*	165*	Strokes or deaths occurring between randomization and the 30-day postoperative time point, plus ipsilateral ischemic stroke within 2 years postrandomization	—	1. Not published yet

Abbreviation: 3D, three-dimensional; COSS, Carotid Occlusion Surgery Study; CMOSS, Carotid and Middle Cerebral Artery Occlusion Surgery Study; CTP, computed tomography perfusion technique; EC/IC, extracranial-intracranial; JET, Japanese EC-IC Bypass Trial; OEF, oxygen extraction fraction.
Note: *Numbers proposed in the study design.

In contrast, the JET Study,[34] in a second interim analysis, affirmed that the surgically-treated group presented a lower incidence of stroke recurrence compared with those who had only been submitted to medical therapy. Nevertheless, in the published Kaplan-Meier curve, there were no deaths within the first month in the surgical group – which seems unlikely to occur, given that the perioperative morbidity and mortality rate was of 12% in the EC-IC Bypass Trial, and of 15% in the COSS.[25,32,35]

Later, a multicentric prospective cohort, the JET-2 Study,[30] compared a total of 132 enrolled patients with symptomatic cerebrovascular occlusive disease and mild-to-moderate hemodynamic impairment with the medical arm group of the JET Study. The objective was to determine the real threshold of CBF and CVR for subsequent ischemic events only among the medically-treated patients. The authors found that patients with rest CBF $>$ 80% or CVR $>$ 10% present a lower risk, and they thus concluded that this population is unlikely to benefit from the EC-IC bypass surgery.

Due to all the controversial results and doubts surrounding the latest studies, there are still questions concerning this subject. Therefore, another trial[31] is being conducted in China under registration code NCT01758614. All the aforementioned trials were synthesized in ►**Table 1**.

Assessing Bypass Function

Regarding the technique, there are several ways to assess bypass function transoperatively, such as observing the pulsations within the donor vessel subsequently to the anastomosis, intraoperative microvascular Doppler sonography, and intraoperative angiography. The observation is inaccurate, for it is highly subjective. The Doppler enables us to properly evaluate the site of anastomosis. However, the intraoperative angiography assessment of graft patency can increase the success of the EC-IC bypass not only because it enables physicians to assess the site of anastomosis but also the extent of reperfusion from the bypass.

Yanaka et al.[36] assessed the intraoperative angiography method in 42 STA-MCA bypass procedures. The imaging findings prompted two additional procedures, and there were no complications. However, there was no systematic comparison with an ultrasonography method.

Therefore, until a large clinical study compares, in long-term follow-up, both methods and proves superior results for angiography, we do not recommend such a procedure, because, while sonography is a rapid, noninvasive, sensitive, and easily performed method, cerebral angiography is a time-consuming, invasive procedure with cost-benefit limitations. Microvascular Doppler sonography, however, does not distinguish between a poor and a robust flow in the anastomosis.

Currently, a quick and straightforward method to predict graft success after EC-IC bypass is the cut flow index, through which a quantitative assessment of graft patency may be performed. This approach was a significant predictor of bypass patency in 51 review retrospective cases of EC-IC anastomosis.[37] Although our rates of patency had an excellent correlation with the Doppler sonography, we must consider that the cut flow index is a very reasonable method, and we have recently started to use it.

Concerning flap necrosis, Katsuta et al.[38] studied the relationship between cutaneous necrosis after STA-MCA bypass and surgical methods or risk factors. The authors found that postoperative necrosis and arteriosclerosis obliterans were related. In a univariate analysis, smoking was a statistically significant risk factor – but not in a multivariate analysis. All seven patients with necrosis were treated with the flap method. They concluded that: 1) arteriosclerosis obliterans in the lower extremities is probably the best predictor of postoperative cutaneous necrosis; 2) the cut-down method may be preferable in patients with arteriosclerosis obliterans or smokers. In the Katsuta et al.[38] series, one patient developed scalp necrosis.

Finally, microsurgical laboratory training is paramount. A technically-perfected microanastomosis begins in the microsurgical laboratory. The neurosurgeon who wishes to perform this procedure must understand that this is the first and most crucial step for the future outcome of their patients. The continuous exercises in vessels of the placenta and later in vessels of rats will indicate essential aspects to pay attention to, such as unwilling suture of the anterior and posterior wall of the vessel, traumatic lesion of the vessel that can be avoided by careful manipulation of the adventitia, asymmetry of the suture's borders, inappropriate tension of the suture, and others.[39] The surgeon will become apt only with hard training in the laboratory. Professor Yaşargil[10] recommended training anastomosis in the laboratory for at least three months.

Conclusion

The exact parameters to indicate the STA-MCA bypass in cerebrovascular occlusive disease have not been established yet. First, because the population addressed in the recent trials seems to be comprised of patients with a more stable neurological condition. Second, because these studies point to different results. Lastly, they were criticized due to possible methodological flaws. Therefore, there is still controversy about the indications and benefits of EC-IC bypass surgery, which could be elucidated by ongoing trials. As illustrated by our case, selected patients could significantly benefit from this approach

Conflict of Interests

The authors have no conflict of interests to declare.

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Can Routine Blood Biochemistry Parameters be Predictive Prognostic Marker(s) in Operated Patients with Meningioma WHO Grade 1?

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Arq Bras Neurocir 2021;40(2):e137–e145.

Abstract

Background Today, there is a need for new and independent additional advanced markers that can predict the prognosis of meningioma patients, postoperatively. The present study aimed to find out postoperative short-term prognostic markers in patients with meningioma using their demographic data and routine blood biochemistry findings evaluated preoperatively.

Methods The Glasgow Coma Scale (GCS), and Glasgow Outcome Scale (GOS) scores of the patients were recorded. Additionally, preoperatively obtained serum glucose, C-reactive protein (CRP), sodium, potassium, creatinine, blood urea nitrogen, aspartate aminotransferase (AST), alanine aminotransferase, and hemoglobin level values, platelet, leukocyte, neutrophil, lymphocyte, eosinophil, basophil, and monocyte count results, erythrocyte sedimentation rate (ESR), neutrophil-lymphocyte ratio, platelet-lymphocyte ratio (PLR) and lymphocyte-monocyte ratio (LMR) values were evaluated.

Results In the present study, 23 operated patients with meningioma World Health Organization (WHO) grade 1 (17 females, 6 males) were included. Correlation test results revealed that the GCS score, platelet count, and serum potassium level values could directly predict the short-term prognosis of these patients. Additionally, these test results suggested that the lymphocyte, monocyte, and eosinophil count values, PLR, LMR, ESR, serum glucose, CRP, and AST level values could be indirect markers in predicting the short-term prognosis. However, likelihood ratio test results revealed that only monocyte count value, LMR value, and serum CRP level value could be the markers for prediction of the short-term prognosis.

Conclusion At the end of the present study, it was concluded that the monocyte count value, LMR value, and serum CRP level value could be the best markers in predicting the short-term prognosis of the operated meningioma patients.

Keywords
- biochemistry
- biomarker
- meningioma
- prognosis

received
August 8, 2020
accepted
November 16, 2020
published online
January 18, 2021

DOI https://doi.org/10.1055/s-0040-1722246.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Introduction

It has been shown that many immunological agents produced in tumor tissue in many types of cancer can stimulate the bone marrow to increase myelopoiesis and subsequently lead to an increase in circulating granulocytes.[1] Most tumors have been reported to be highly infiltrated by immune cells, including macrophages, neutrophils, and lymphocytes.[2] This systemic inflammation is a product of circulating immune cells and cytokines.[3] To be able to classify and predict survival, there has recently been a great deal of research on molecular markers derived from genetic and epigenetic studies on tumor tissue.[4]

Meningiomas, slow-growing brain tumors, can be still treated with total resection surgery. However, the prognosis of the patients with benign meningioma treated surgically has been reported to be worse than in the general population.[5] Previous reports in the literature have stated that interleukin-6 (IL-6) plays a role in meningioma cell proliferation and growth, and even meningioma cells produce and secrete this cytokine. Additionally, IL-6 mRNA and protein expression have been reported to be positively correlated with peritumoral edema around the meningioma.[6,7] Unfortunately, most of these markers were investigated in the tumor tissue and, therefore, it is considered to exist still a need for new additional independent biomarkers that can be inexpensive, noninvasive and easily applicable in any medical laboratory for prediction of prognosis in patients with meningioma, preoperatively.[8] The present study aimed to find out the postoperative short-term prognostic markers in patients with meningioma by using demographic, neurological status, and routine blood biochemistry findings, evaluated preoperatively.

Materials and Methods

Patient Groups

Approval for the present retrospective single-center study was granted by the Clinical Studies Local Ethics Committee (approval date: April 29th, 2020, and approval number: 2020.04.06).

A retrospective evaluation was made of patients with solitary intracranial tumors who were admitted to the Neurosurgery Clinic between January 2015 and April 2020. Then, operated patients whose histopathological diagnosis was typical meningioma World Health Organization (WHO) grade 1 were included in the present study. To investigate the effects of the age of the patients on the data of the patients, the patients were divided into two groups according to age, as follows:

- ADULT group (consisted of $<$ 65-year-old patients, $n = 13$)
- ELDERLY group (consisted of $\geq$ 65-year-old patients, $n = 10$)

Moreover, to investigate the effects of gender on the data of the patients, the patients were divided into two groups according to gender.

- FEMALE group ($n = 17$)
- MALE group ($n = 6$)

Patients with atypical or malignant meningioma, patients with other types of intracranial tumors such as glioblastoma, patients treated with recurrence of intracranial tumors, patients treated with radiosurgery, patients with multiple intracranial meningiomas, and pediatric patients ($<$ 16 years old) were excluded from the present study.

Methods

Age, gender, and routine blood biochemistry results of all participants were recorded. Additionally, the Glasgow Coma Scale (GCS) scores, duration of stay in hospital, and Glasgow Outcome Scale (GOS) scores of the patients were recorded. In the present study, the consciousness level and neurological condition of the patients at admission to the hospital were determined using the GCS.[9] The short-term prognosis was determined based on the neurological condition of the patient at discharge from the hospital after surgical treatment. This neurological condition was considered using the GOS, which was accepted in the literature as a scale to demonstrate the short-term prognosis of any patient.[10] Because the present study was planned to determine mainly the short-term prognosis of the patients after surgical treatment, the long-term follow-up findings of the patients was not included in the present study.

Biochemical Analysis

Venous blood samples collected preoperatively from the patients with meningioma were examined in the biochemistry laboratory. Serum glucose (reference interval 4.11–6.05 mmol/L), C-reactive protein (CRP) (reference interval 1.5–50.00 mg/L), creatinine (reference interval 74.26–109.62 µmol/L), blood urea nitrogen (BUN) (reference interval 6.07–15.35 mmol/L), aspartate aminotransferase (AST) (reference interval 0.08–0.67 µkat/L) and alanine aminotransferase (ALT) (reference interval 0.08–0.68 µkat/L) levels were measured using the immunoturbidimetric method.[11] Serum sodium (reference 136–146 mmol/L) and potassium (reference interval 3.5–5.1 mmol/L) level values were determined with the ion-selective electrode (ISE) method.[12] All parameters were studied on an analyzer (COBAS c501, Roche Diagnostics, Basel, Switzerland) using their original commercial kits (Roche, Basel, Switzerland).

Blood hemoglobin level values (reference interval 100.00–180.00 g/L) and platelet (reference interval 150.00–500.00 ^109/L), leukocyte (reference interval 4.40–11.30 ^109/L), neutrophil (reference interval 1.10–9.60 ^109/L), lymphocyte (reference interval 500–6,000/uL), eosinophil (reference interval 0.50–6.00 ^109/L), eosinophil (reference interval 0–1.00 ^109/L), basophil (reference interval 0–0.30 ^109/L) and monocyte (reference interval 0.10–1.40 ^109/L) count results were determined using an analyzer (Mindray BC-6800, Shenzen, China). The erythrocyte sedimentation rate (ESR) value (reference range $<$ 20 mm/hour) was measured using an automated system (ESR 40, Sistat Diagnostics, Ankara, Turkey). The neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), and systemic inflammation response index (SIRI) were also calculated as defined in the literature.[11–13]

Statistical Analysis

Parametric data were expressed as mean $\pm$ standard deviation (SD), and to find out the differences between the study groups,

these data were analyzed using the independent samples t-test ($p < 0.05$). Nonparametric data were expressed as median (minimum-maximum), and to find out the differences between the study groups, these data were analyzed using the Mann Whitney U-test ($p < 0.05$). Categorical data were expressed as number (%), and to find out the differences between the study groups, they were analyzed using the Pearson chi-squared test ($p < 0.05$).

To determine which parameters could relate to the prognosis of the patients, the correlations between the study parameters and GOS scores were analyzed using the Spearman rho correlation test ($p < 0.05$). To identify the best marker(s) in predicting the short-term prognosis, the likelihood-ratio test was applied to the variables that were found in a relationship with the prognosis ($p < 0.05$).

Results

The study group comprised 23 patients (17 females, 6 males) with a mean age of 61.39 ± 12.06 years old, the median GCS score was 15 points (10 points in 1 patient, 15 points in 22 patients), and the median GOS score was 5 points. One patient died due to massive thromboembolism, and one patient died after acute massive bleeding in the postoperative surgical field (►**Fig. 1**). One patient with a GOS score of 3 points had dementia. One of the two patients with a GOS score of 4 points had left hemiplegia, postoperatively (►**Fig. 2**), and the other one had right hemiparesis, postoperatively (►**Table 1**).

On the other hand, when the patients were divided into two groups according to age, it was seen that serum CRP level value ($Z = -1.243$, $p = 0.035$) and the duration of stay in hospital ($Z = -2.099$, $p = 0.036$) were found to be higher in patients of the ELDERLY group. However, the serum CRP levels of both groups were observed in the laboratorial normal reference range (►**Table 2**).

Additionally, when the patients were divided into two groups according to gender, it was observed that hemoglobin level values ($t = -3.864$, $p = 0.001$), serum creatinine level values ($t = -3.386$, $p = 0.003$), and ESR values ($t = 3.909$, $p = 0.001$) were found to be different between female and male patients. It was argued that hemoglobin and serum creatinine levels were higher in male patients, whereas ESR levels were lower. However, except for the ESR values, the serum hemoglobin and serum creatinine levels were observed in the laboratorial normal reference range in both groups (►**Table 3**).

The results of the Spearman rho correlation test, applied to all parameters of all patients, revealed that there was a positive correlation between age and serum CRP level values ($r = 0.424$, $p = 0.044$), and between age and duration of stay in hospital ($r = 0.547$, $p = 0.007$). A positive correlation was observed between gender and hemoglobin level ($r = 0.627$, $p = 0.001$), and between gender and serum creatinine level ($r = 0.538$, $p = 0.008$). The GCS scores correlated positively with the GOS scores ($r = 0.529$, $p = 0.009$), basophil count values ($r = 0.466$, $p = 0.025$), and platelet count values ($r = 0.467$, $p = 0.018$). A positive correlation was found between GOS scores and platelet count values ($r = 0.511$, $p = 0.013$), between the GOS scores and serum potassium level values ($r = 0.508$, $p = 0.013$), and between hemoglobin and serum creatinine level values ($r = 0.560$, $p = 0.005$). The leukocyte count values correlated positively with the neutrophil count values ($r = 0.958$, $p < 0.001$), NLR values ($r = 0.619$, $p = 0.002$), and serum creatinine level values

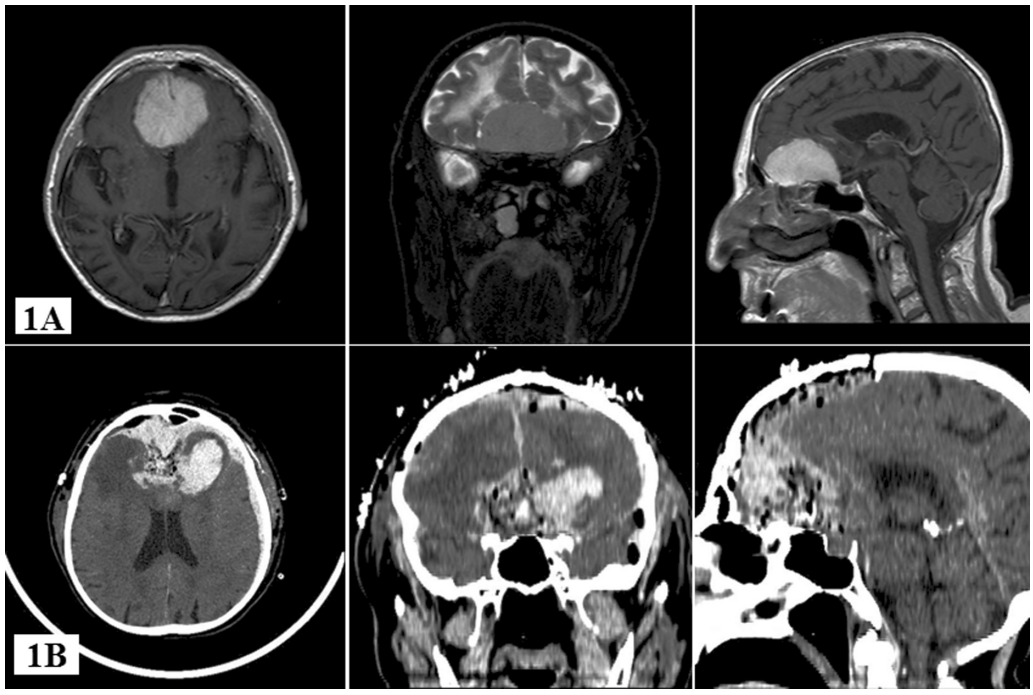

Fig. 1 Preoperative magnetic resonance imaging (MRI) with gadolinium T1-weighted images show the giant olfactory groove meningioma of the patient who died during the stay in the hospital (**1A**); and early postoperative computed tomography images show that the tumor was totally removed, but postoperative acute massive blood filled in the surgical field (**1B**).

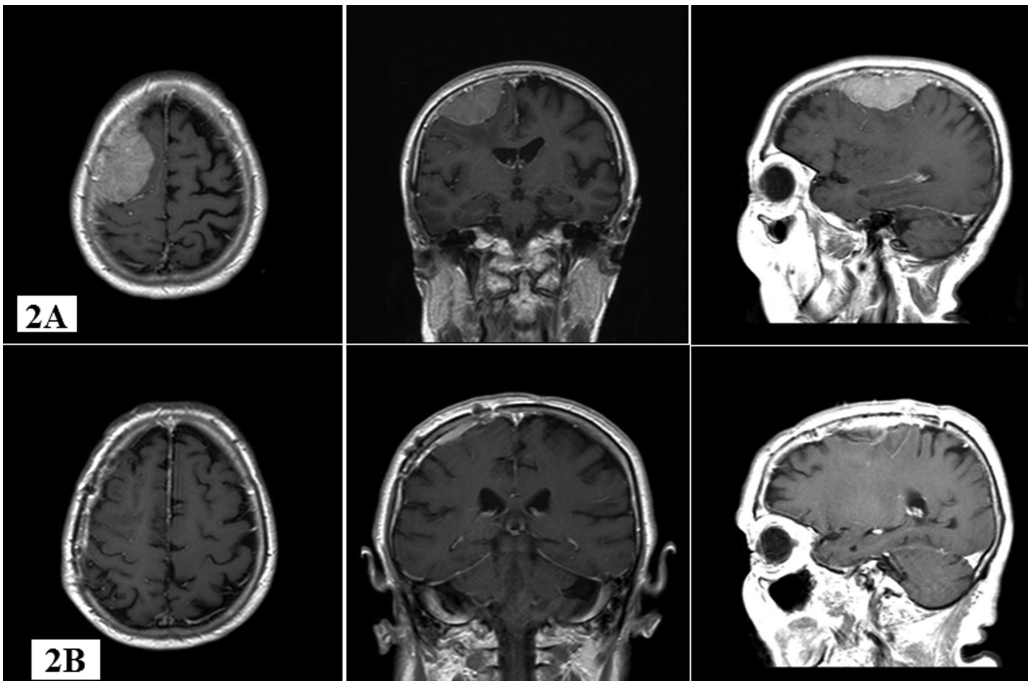

Fig. 2 Preoperative magnetic resonance imaging (MRI) with gadolinium T1-weighted images show the parasagittal meningioma of the patient whose Glasgow Outcome Score was 5 points (**2A**), and early postoperative images show that the tumor was totally removed (**2B**).

($r = 0.445$, $p = 0.033$). The neutrophil count values correlated positively with the NLR values ($r = 0.776$, $p < 0.001$), serum creatinine level values ($r = 0.531$, $p = 0.009$), and serum BUN level values ($r = 0.428$, $p = 0.042$). A positive correlation was found between the lymphocyte and monocyte count values ($r = 0.533$, $p = 0.009$), between the LMR and SIRI values ($r = 0.825$, $p < 0.001$), between LMR and serum sodium values ($r = 0.532$, $p = 0.009$), between LMR and serum AST values ($r = 0.532$, $p = 0.010$), between eosinophil count and basophil count values ($r = 0.542$, $p = 0.008$), between basophil count and platelet count values ($r = 0.417$, $p = 0.048$), between NLR and serum BUN level values ($r = 0.455$, $p = 0.029$), between NLR and serum creatinine level values ($r = 0.545$, $p = 0.007$), between PLR and serum AST level values ($r = 0.451$, $p = 0.031$), between PLR and ESR values ($r = 0.426$, $p = 0.043$), between serum glucose level values and duration of stay in hospital ($r = 0.462$, $p = 0.027$) and between serum CRP level values and duration of stay in hospital ($r = 0.591$, $p = 0.003$).

On the other hand, a negative correlation was determined between age and GCS score values ($r = -0.452$, $p = 0.030$), between age and serum potassium level values ($r = -0.450$, $p = 0.031$), between gender and ESR values ($r = -0.650$, $p = 0.001$), between hemoglobin level values and ESR values ($r = -0.571$, $p = 0.004$), between lymphocyte count values and NLR values ($r = -0.679$, $p < 0.001$), between lymphocyte count values and PLR values ($r = -0.900$, $p < 0.001$) and between eosinophil count values and PLR values ($r = -0.422$, $p = 0.045$).

Although the monocyte count values, LMR values, and CRP level values did not correlate with the GOS score values, the likelihood-ratio test results revealed that monocyte count value ($X^2 = 10.595$, $p = 0.014$), LMR value ($X^2 = 8.682$, $p = 0.034$), and serum CRP level value ($X^2 = 8.028$, $p = 0.045$) could be the best parameters for prediction of the short-term prognosis of these patients.

Discussion

In the literature, it has been suggested that serum CRP levels, which reflect the systemic response to inflammation, are related to progression of the cancer, and elevated CRP levels may be associated with poor prognosis.[8,13–16] In those studies, it has been concluded that the CRP level may be a biomarker for many cancer types.[17,18] However, in their literature review, Heikkilä et al. found no strong evidence for a causal role of serum CRP level in malignancy.[19] On the other hand, Bunevicius et al. reported in their study that there may be a relationship between high CRP concentration and shorter survival in meningioma patients, and at the end of this study, they suggested that meningioma patients presenting with high CRP levels could be considered with a high risk of complications.[6]

Additionally, it is suggested that a higher number of circulating neutrophils, monocytes, or platelets may be associated with increased tumor progression and poor survival in many types of cancer.[20–24] Moreover, Liang et al. discussed in their article that meningiomas are infiltrated with lymphocytes, macrophages, mast cells, monocytes, and microglia. They suggested that monocytes can directly stimulate tumor cell growth producing various proinflammatory cytokines such as tumor necrosis factor, IL-6, and IL-1. Tumor-associated macrophages can also increase tumor progression, and the number of circulating monocytes may reflect the formation or presence of tumor-associated macrophages. On the other hand, lymphocytes can migrate into the tumor to create a defense barrier

Table 1 Demographic and laboratory findings of the patients

Variable		Mean ± SD/Median (min-max)/N (%)
Age (years old)		61.39 ± 12.06
Gender	Female	17 (39.5%)
	Male	6 (14.0%)
Glasgow Coma Scale score		15 (10–15)
Duration of stay in hospital (days)		10 (6–51)
Glasgow Outcome Scale score		5 (1–5)
Hemoglobin level (g/L)		133.30 ± 2.01
Leukocyte count (^10^9/L)		9.09 ± 3569.83
Neutrophil count (^10^9/L)		6.44 ± 3611.59
Lymphocyte count (^10^9/L)		2.07 ± 1126.40
Monocyte count (^10^9/L)		0.42 ± 195.10
Eosinophil count (^10^9/L)		0.14 ± 116.52
Basophil count (^10^9/L)		0.04 ± 40.70
Platelet count (^10^9/L)		262.13 ± 68194.44
Systemic inflammation response index		0.75 (0.37–17.89)
Neutrophil to lymphocyte ratio		2.56 (1.10–33.14)
Platelet to lymphocyte ratio		126.33 (33.17–454.55)
Lymphocyte to monocyte ratio		5.32 (0.69–22)
Glucose (mmol/L)		6.05 (4.44–15.26)
Sodium (mmol/L)		141 (138–148)
Potassium (mmol/L)		4.48 ± 0.56
Creatinin (μmol/L)		63.65 ± 0.17
Blood urea nitrogen (mmol/L)		10.97 ± 8.65
Aspartate aminotransferase (μkat/L)		0.31 ± 6.66
Alanin aminotransferase (μkat/L)		0.32 (0.12–1.50)
C-reactive protein (mg/L)		26.70 (6.90–830.00)
Erythrocyte sedimentation rate (mm/hour)		20.13 ± 11.82

Abbreviations: max, maximum; min, minimum; N, number of patients; SD, standard deviation.

against tumor cell invasion. Therefore, low lymphocyte count in peripheral blood can cause weak defenses against tumors. At the end of their study, they demonstrated that a low LMR was associated with high tumor grade.[13,25]

In the present study, all data of the patients revealed that most of the patients were female patients < 65 years old. The inflammatory cell count results were found to be within normal intervals. The serum glucose levels were at the upper limit of normal laboratory values and the creatinine levels were at the lower limit of normal laboratory values in all patients. On the other hand, ESR values (20.13 ± 11.82 mm/hour) were at the upper limit of normal, as described by Strojnik et al.,[8] whereas the serum CRP levels (26.70 mg/L) were found within the normal reference interval (►**Table 1**).

When the patients were divided into two groups as "adult" and "elderly" patients, it was seen that the elderly patients (age > 65 years old) stayed longer in the hospital, and that their serum CRP level values were slightly higher than those of adult patients, but within a normal laboratory reference range (►**Table 2**). On the other hand, when the patients were divided into two groups according to gender, hemoglobin level values of the female patients were lower than those of male patients, but within a normal laboratory reference range, whereas their ESR values were higher than the values of male patients (►**Table 3**).

The results of the Spearman rho correlation test results performed on the data of all revealed that if the age of the patients increased, the GCS scores might be low, and serum potassium values might be measured at the lower limit of normal laboratory values. Additionally, in these patients, the duration of stay in the hospital might be longer, and CRP values might be at the upper limit of normal laboratory values. On the other hand, if the GCS scores of the patients were high, it was considered that GOS scores, basophil, eosinophil, and platelet count values could also be high. Moreover, if the platelet count and serum potassium level values were found at the upper limit of normal laboratory values, it was thought that these patients would have higher GOS scores. Briefly, it was assumed, according to the correlation test results, that the GCS scores and GOS scores of elderly patients may be lower than those of adult patients. Therefore, it was thought that elderly patients with meningioma may have a worse neurological condition on admission to the hospital, and that they would have a poor prognosis during the discharge from the hospital, postoperatively. In conclusion, it was considered that GCS score, platelet count, and serum potassium level values could predict directly the short-term prognosis of meningioma patients. In addition, it was argued that age, serum CRP level values, duration of stay in the hospital, eosinophil, and basophil count values could indirectly predict the short-term prognosis of these patients.

Additionally, the correlation test results revealed that if the platelet and basophil count values were high, these patients could have high GCS scores, and, indirectly, they could have high GOS scores and high eosinophil count values. On the other hand, the PLR values correlated positively with the serum AST and ESR values and correlated negatively with eosinophil and lymphocyte count values. Serum AST level values were positively correlated with LMR and SIRI values. The lymphocyte count values were positively correlated with monocyte count values. Therefore, if any of the lymphocyte, eosinophil, or monocyte count values were low, it was predicted that the PLR value and, therefore, LMR, SIRI, ESR, and serum AST level

Table 2 Demographic findings and laboratory results of the ADULT and ELDERLY groups

		ADULT ($n = 13$)	ELDERLY ($n = 10$)		
Variable		**Mean ± SD/Median (min-max)/N (%)**	**Mean ± SD/Median (min-max)/N (%)**	***t*/Z/X^2**	***p-value***
Age (years old)		53.38 ± 8.27	71.80 ± 7.14	–	–
Gender	Female	11 (47.8%)	6 (26.1%)	1.776‡	0.183
	Male	2 (8.7%)	4 (17.4%)		
Glasgow Coma Scale		15 (15–15)	15 (10–15)	−1.649†	0.099
Duration of hospital stay (days)		8 (6–31)	11.5 (8–51)	−2.099†	**0.036**
Glasgow Outcome Scale		5 (1–5)	5 (1–5)	−1.677†	0.094
Hemoglobin level (g/L)		129.50 ± 2.12	138.30 ± 1.83	−1.039*	0.311
Leukocyte count (^10^9/L)		8.62 ± 3900.58	9.70 ± 3182.18	−0.714*	0.483
Neutrophil count (^10^9/L)		5.94 ± 3488	7.09 ± 3849.61	−0.751*	0.461
Lymphocyte count (^10^9/L)		2.10 ± 1178.65	2.02 ± 1115.91	0.162*	0.873
Monocyte count (^10^9/L)		0.42 ± 212.88	0.42 ± 180.62	0.001*	0.999
Eosinophil count (^10^9/L)		0.15 ± 111.50	0.13 ± 127.82	0.416*	0.682
Basophil count (^10^9/L)		0.03 ± 14.62	0.05 ± 59.37	−1.147*	0.264
Platelet count (^10^9/L)		271.30 ± 71870.69	250.20 ± 64813.92	0.728*	0.475
Systemic inflammation response index		0.71 (0.37–6.14)	1.20 (0.57–17.89)	−1.116†	0.264
Neutrophil to lymphocyte ratio		1.81 (1.29–18.61)	2.69 (1.10–33.14)	−0.992†	0.321
Platelet to lymphocyte ratio		126.33 (52.93–454.55)	130.74 (33.17–383.78)	0.000†	1.000
Lymphocyte to monocyte ratio		6.13 (2.15–22)	4.98 (0.69–12.42)	−0.434†	0.664
Glucose (mmol/L)		5.72 (4.44–15.26)	6.66 (5.05–9.44)	−0.901†	0.367
Sodium (mmol/L)		141 (136–148)	142 (138–144)	−0.438†	0.661
Potassium (mmol/L)		4.57 ± 0.62	4.36 ± 0.47	0.892*	0.382
Creatinin (µmol/L)		62.76 ± 0.17	65.42 ± 0.17	−0.305*	0.763
Blood urea nitrogen (mmol/L)		10.51 ± 7.58	11.57 ± 10.02	−0.808*	0.428
Aspartate aminotransferase (µkat/L)		0.32 ± 7.30	0.30 ± 6.05	0.326*	0.748
Alanin aminotransferase (µkat/L)		0.35 (0.22–1.50)	0.28 (0.12–0.45)	−1.243†	0.214
C-reactive protein (mg/L)		20.20 (6.90–64.80)	43.90 (11.10–830.00)	−2.109†	**0.035**
Erythrocyte sedimentation rate (mm/hour)		23.31 ± 11.70	16.00 ± 11.20	1.512*	0.145

Abbreviations: max, maximum; min, minimum; N, number of patients; SD, standard deviation.
*t value (Independent Samples t-test).
†Z value (Mann-Whiney U test).
‡X^2 value (Pearson'Chi-squared test). $p < 0.05$.

values might be measured high, and, therefore, the short-term prognosis of the patient might be worse, as described before by Liang et al.[25] Thus, it was thought that the lymphocyte, monocyte, and eosinophil count values, PLR, LMR, SIRI, ESR, and serum AST level values might affect the short-term prognosis, indirectly. With these findings, it could be concluded that these parameters could be indirect markers in predicting the short-term prognosis of operated meningioma patients.[24,26] Moreover, it was found that the patients who had high serum glucose and/or CRP values might have a longer hospital stay, so these patients might be in the older age group and therefore their short-term prognosis might be poor. Thus, it was argued that serum CRP and glucose level values could be indirect markers in predicting short-term prognosis. However, neither ESR nor CRP level values were correlated with any inflammatory cell count result, and the study results suggested that meningioma could not produce any cellular inflammatory response.

Although the GOS scores correlated directly with the GSC scores, platelet count values, and serum potassium level values, the likelihood-ratio test results demonstrated that monocyte count values, LMR values, and serum CRP level values could be the best parameters in predicting the short-term prognosis of meningioma patients, as described before by Bunevicius et al., Szkandera et al., and

Table 3 Demographic findings and laboratory results of the FEMALE and MALE groups

	FEMALE ($n = 17$)	MALE ($n = 6$)		
Variable	Mean ± SD/Median (min-max)/N (%)	Mean ± SD/Median (min-max)/N (%)	*t*/Z	*p-value*
Age (years old)	60.18 ± 13.07	64.83 ± 8.56	−0.807*	0.429
Glasgow Coma Scale	15 (10–15)	15 (15–15)	−0.859†	0.390
Duration of hospital stay (days)	9 (6–31)	11.50 (8–51)	−1.061†	0.289
Glasgow Outcome Scale	5 (1–5)	5 (1–5)	−0.194†	0.846
Hemoglobin level (g/L)	125.80 ± 1.58	154.70 ± 1.51	−3.864*	**0.001**
Leukocyte count (^10^9/L)	9.51 ± 3971.25	7.89 ± 1812.71	0.952*	0.352
Neutrophil count (^10^9/L)	6.77 ± 4063.86	5.50 ± 1763.23	0.734*	0.471
Lymphocyte count (^10^9/L)	2.19 ± 1193.82	1.74 ± 918.25	0.834*	0.414
Monocyte count (^10^9/L)	0.43 ± 189.13	0.39 ± 227.86	0.374*	0.712
Eosinophil count (^10^9/L)	0.11 ± 100.03	0.21 ± 138.71	−1.864*	0.076
Basophil count (^10^9/L)	0.04 ± 44.64	0.04 ± 30.13	0.090*	0.929
Platelet count (^10^9/L)	264 ± 77170.26	257 ± 36875.01	0.216*	0.831
Systemic inflammation response index	0.71 (0.37–17.89)	1.02 (0.37–1.90)	−1.116†	0.264
Neutrophil to lymphocyte ratio	1.81 (1.10–33.14)	2.73 (1.72–18.61)	−0.980†	0.327
Platelet to lymphocyte ratio	123.67 (33.17–383.78)	140.44 (103.57–454.55)	−0.560†	0.575
Lymphocyte to monocyte ratio	4.43 (2.89–22)	6.13 (0.69–12.42)	−0.350†	0.726
Glucose (mmol/L)	6.05 (4.44–15.26)	5.61 (5.05–8.71)	−0.772†	0.440
Sodium (mmol/L)	141 (136–148)	140 (138–144)	−0.248†	0.805
Potassium (mmol/L)	4.43 ± 0.63	4.6 ± 04.28	−0.780*	0.444
Creatinin (μmol/L)	58.34 ± 0.13	78.68 ± 0.16	−3.368*	**0.003**
Blood urea nitrogen (mmol/L)	10.66 ± 9.51	11.84 ± 5.45	−0.797*	0.434
Aspartate aminotransferase (μkat/L)	0.30 ± 7.51	0.34 ± 3.15	−0.708*	0.487
Alanin aminotransferase (μkat/L)	0.27 (0.12–1.50)	0.42 (0.35–0.45)	−1.754†	0.079
C-reactive protein (mg/L)	26.90 (7.70–830.00)	25.30 (6.90–63.40)	−0.280†	0.779
Erythrocyte sedimentation rate (mm/hour)	24.59 ± 10.46	7.50 ± 2.43	3.909*	**0.001**

Abbreviations: max, maximum; min, minimum; N, number of patients; SD, standard deviation.
*t value (Independent Samples t-test).
†Z value (Mann-Whiney U test). $p < 0.05$.

Liang et al.[6,25] This finding could be interpreted as meaning that low-grade meningioma could not produce a cellular inflammatory response, but this tumor could trigger a systemic immune response, including the Th2 immune profile, and the level of this response could affect and modulate the number of circulating monocytes and lymphocytes.[25,27] Furthermore, the results of the present study revealed that a low LMR value could predict poor prognosis in operated meningioma patients, as described before in the literature.[23,25]

In conclusion, the findings of the present study are compatible with the literature and support the information reported in the literature. However, it was recognized that in order to strongly validate the findings of the present study and to reliably predict the short-term prognosis of the operated meningioma patients, these parameters should be evaluated in a larger patient population.

Limitations

There were some limitations in the present study. First, the present study was a retrospective single-center study and, therefore, the number of patients included in the present study was low. Furthermore, the defined aims of the present study precluded adding the long-term follow-up information of patients in the present study. However, the results of the present study were very interesting. Therefore, it can be recommended that the results obtained from the present study are confirmed by further studies of larger patient groups with long-term follow-up information. Second, Kataki et al. reported that meningiomas can trigger a systemic immune response and that cell-mediated immunity shifts toward the Th2 immune profile through changes in apoptosis and necrosis.[27] However, the present study results could not explore those immune responses due to its retrospective properties. Third, the comparison results of the

preoperative and postoperative blood biochemistry findings of the patients could be included in the present study. However, because it has been well known that surgical procedures would cause dramatic changes on the blood biochemistry results; therefore, the postoperative blood biochemistry findings were not included in the present study. Finally, the radiological images and detailed histopathological evaluation reports of the patients were not evaluated and not included in the present study, because the present study aimed to define the markers for predicting the short-term prognosis in patients with meningioma using their data, obtained preoperatively.

Conclusion

At the end of the present study, correlation test results demonstrated that GCS score, platelet count value, and serum potassium level values could be predictive markers of short-term prognosis in operated meningioma patients. Additionally, these test results suggested that the lymphocyte, monocyte, and eosinophil count results, as well as PLR, ESR, serum glucose, CRP, and AST level values could predict indirectly the short-term prognosis of these patients. However, regression test results revealed surprisingly that monocyte count value, LMR value, and serum CRP level value could be the "best parameters" for prediction of the short-term prognosis. Therefore, it was recognized that all these parameters should be retested in a larger patient population for the prediction of short-term prognosis.

Financial Disclosure Statements

The authors declare that they have not engaged in any financial relationship with any company whose product might be affected by the research described or with any company that makes or markets a competing product.

Informed Consent

Since the present study had a retrospective character, the patients were informed that their information could be used in the study on the condition of protecting their personal information, and consent was obtained, so no additional consent was obtained.

Conflict of Interests

The authors have no conflict of interests to declare.

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Higher Concentration of *Taenia* Antigens in the CSF is Related to Slight Ventricle Enlargement and Periventricular Neuronal Decrease in Young Rats

Maior concentração de antígenos de Taenia está associada a ligeiro aumento de ventrículos e redução de neurônios periventriculares em ratos jovens

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Arq Bras Neurocir 2021;40(2):e146–e151.

Abstract

Purpose Experimental models might help understand the pathophysiology of neurocysticercosis-associated hydrocephalus. The present study aimed to compare the extent of hydrocephalus and tissue damage in rats with subarachnoid inoculation of different concentrations of *Taenia crassiceps* cyst proteins.

Methods Sixty young rats were divided into two groups: low- and high-concentration groups. The animals in the low concentration group received 0.02 ml of 2.4 mg/ml *T. crassiceps* cyst proteins while those in the high concentration group received 0.02 ml of 11.6 mg/ml *T. crassiceps* cyst proteins. The animals underwent magnetic resonance imaging at 1, 3, and 6 months postinoculation to assess the ventricle volume. Morphological assessment was performed at the end of the observation period.

Results Repeated measures of ventricle volumes at 1, 3, and 6 months showed progressive enlargement of the ventricles. At 1 and 3 months, we observed no differences in ventricle volumes between the 2 groups. However, at 6 months, the ventricles were larger in the high concentration group (median = 3.86 mm^3, range: 2.37–12.68) compared with the low concentration group (median = 2.00 mm^3, range: 0.37–11.57), $p = 0.003$. The morphological assessment revealed a few

Keywords
- neurocysticercosis
- hydrocephalus
- neurons
- experimental model

received
July 3, 2020
accepted
August 24, 2020
published online
November 26, 2020

DOI https://doi.org/10.1055/s-0040-1718997.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

inflammatory features in both groups. However, the density of oligodendrocytes and neurons within the periventricular region was lower in the high concentration group (5.18 versus 9.72 for oligodendrocytes and 15.69 versus 21.00 for neurons; $p < 0.001$ for both).

Conclusion Our results suggest that, in rats, a higher concentration of *T. crassiceps* cyst proteins in the subarachnoid space could induce ventricle enlargement and reduce the number of neurons within the periventricular area.

Resumo

Objetivo Modelos experimentais podem ajudar a entender a fisiopatologia da hidrocefalia associada à neurocisticercose. O presente estudo teve como objetivo comparar a extensão da hidrocefalia e dano tecidual em ratos com inoculação subaracnóidea de diferentes concentrações de proteínas de cistos de *Taenia crassiceps*.

Métodos Sessenta ratos jovens foram divididos em dois grupos: grupos de baixa e alta concentração. Os animais do grupo de baixa concentração receberam 0,02 ml de proteínas de cisto de *T. crassiceps* (2,4 mg/ml), enquanto os do grupo de alta concentração receberam 0,02 ml de proteínas de cisto de *T. crassiceps* (11,6 mg/ml). Os animais foram submetidos à ressonância magnética 1, 3 e 6 meses após a inoculação para avaliar o volume do ventrículo. A avaliação morfológica foi realizada no final do período de observação.

Resultados Medidas repetidas dos volumes ventriculares aos 1, 3 e 6 meses mostraram aumento progressivo dos ventrículos. Após 1 e 3 meses, não observamos diferenças nos volumes ventriculares entre os 2 grupos. No entanto, aos 6 meses, os ventrículos foram maiores no grupo de alta concentração (mediana = 3,86 mm^3, variação: 2,37–12,68) em comparação com o grupo de baixa concentração (mediana = 2,00 mm^3, variação: 0,37–11,57; $p = 0,003$). A avaliação morfológica revelou algumas características inflamatórias nos dois grupos. No entanto, a densidade de oligodendrócitos e neurônios na região periventricular foi menor no grupo de alta concentração (5,18 *versus* 9,72 para oligodendrócitos e 15,69 *versus* 21,00 para neurônios; $p < 0,001$ para ambos).

Conclusão Nossos resultados sugerem que, em ratos, uma maior concentração de proteínas do cisto de *T. crassiceps* no espaço subaracnóideo poderia induzir o aumento do ventrículo e reduzir o número de neurônios na área periventricular.

Palavras-chave
- neurocisticercose
- hidrocefalia
- neurônios
- modelo experimental

Introduction

Neurocysticercosis (NC) is a common parasitic infection of the central nervous system (CNS) prevalent in Latin America, Sub-Saharan Africa, and Southeast Asia. Despite having a possibility of eradication, the disease remains endemic in communities with poor sanitary conditions and has reemerged in developed countries because of migratory flows.[1–3]

The course of the disease is dependent upon the number of parasites, their stage of development, distribution within the brain, the subarachnoid space and the ventricles, and parasite-host interaction.[4] In the extraparenchymal form of the disease, the cysts of the tapeworm *Taenia solium* lodge in the cerebrospinal fluid (CSF) compartments and may cause meningitis, vasculitis, hydrocephalus, and raised intracranial pressure.[5,6] Hydrocephalus is one of the most devastating complications related to extraparenchymal NC. The high rate of infections and malfunctions of the ventricular shunts used to release hydrocephalus in patients with NC are the leading causes of the considerably high mortality in these patients.[7] Neurocysticercosis-associated hydrocephalus may occur due to obstruction caused by the presence of cysts at the narrow point of the CSF flow pathway within the brain ventricles, or due to inflammation within the subarachnoid cisterns.[8–10]

The pathophysiology of NC-induced hydrocephalus and the therapeutic options for the treatment of this condition are well-studied. However, the heterogeneity of the disease among different populations and age groups, mainly concerning the clinical presentation and the response to medical treatment, is poorly understood.[11] Experimental animal models of NC-induced hydrocephalus might help to address some of these issues.

Recently, we have developed a rat model of NC-induced hydrocephalus by cisternal inoculation of *Taenia crassiceps* cysts. In this model, we observed obstructive and inflammatory features that confirmed the successful induction of hydrocephalus.[12] However, the role of inflammation in NC-induced hydrocephalus is not yet studied. Since in clinical

practice, it is common to find patients with NC-related hydrocephalus without viable cysts, it might be possible that the degenerating cysts induce hydrocephalus. The present study aimed to assess whether cisternal inoculation of *T. crassiceps* cyst antigens in different concentrations could induce hydrocephalus and tissue damage of different severities.

Methods

Experimental Animals

Sixty male Wistar rats *(Rattus norvegicus)* aged 6 weeks were used in the present study. The animals were handled according to the current guidelines for the care and use of laboratory animals, and the local institutional review board approved the study project. The animals were kept under adequate sanitary conditions with food and water available *ad libitum*, in a room with a 12 h light/dark cycle under controlled temperature (21°C).

The animals were randomly divided into 2 groups: low (n = 30) and high concentration (n = 30) *T. crassiceps* antigens inoculation groups. The animals underwent magnetic resonance imaging (MRI) at 1, 3, and 6 months after the inoculation. After the 3rd MRI, the animals were euthanized and the brains were collected for histological assessment.

T. crassiceps Antigens Preparation

T. crassiceps cysts were maintained by subsequent inoculations in the peritoneal cavity of mice, where the cysts reproduce by gemmulation.[13] The cysts were aseptically removed from the peritoneal cavity of mice and collected in beakers for immediate preparation of the antigenic suspensions. For the low concentration group, the cysts were resuspended in 100 ml of saline and for the high concentration group no diluent solution was added. The cysts suspension was sonicated with 60% amplitude at 10°C until a homogenous suspension was obtained. The resulting suspensions were centrifuged at 0°C and 180 Hz for 5 minutes and the supernatant was collected. The concentration of the protein in the suspensions was determined by the Bradford method. The protein concentration in the low concentration group was 2.4 mg/ml, and in the high concentration group, it was 11.6 mg/ml.

Inoculations

The rats were anesthetized with an intraperitoneal injection of 0.1 ml/kg mixture of ketamine (100 mg/ml) and xylazine (20 mg/ml). A 1-cm long skin incision was made at the occipitocervical junction, followed by blunt dissection pf planes until reaching the skull, the posterior arc of the first vertebra, and the atlanto-occipital membrane. Next, 0.02 ml of the cyst suspension was injected with a 25-G needle between the occipital bone and the first vertebrae, through the atlanto-occipital membrane towards the cisterna magna. The skin was sutured with a 4.0 mononylon suture.

Magnetic resonance imaging

Magnetic resonance imaging was performed using a Vet-MR 0.25 T equipment (Esaote, Santo André, SP, Brazil). For MRI examination, the animals were anesthetized with 0.5 ml/kg of the aforementioned mixture of xylazine and ketamine. The image acquisition protocol consisted of T2-weighted echo gradient acquisitions (slice thickness: 0.6 mm, echo time: 5 ms, repetition time: 10 ms) which provided a good visualization of the dilated ventricles, as previously described.[12] Ventricle volume was determined using ITK-SNAP version 3.0.0 software (GNU General Public License, Philadelphia, PA, USA) with a manual segmentation of the ventricles frame-by-frame. The investigator was blinded to the animal groups.

Morphological Assessment

After the 3rd MRI (6 months postinoculation), the animals were euthanized with an overdose of xylazine and ketamine. The animals were transcardially perfused with saline to wash out blood vessel contents, followed by 10% buffered formalin for tissue fixation. The brains were dissected out of the skull and cut in the coronal plane at the level of the optic chiasm. The samples were fixed in formalin overnight and then were dehydrated by transferring the tissue through solutions of increasing alcohol concentrations. Following this, the tissues were diafanized in xylene and embedded in paraffin. The blocks were sectioned into 5 µm thick sections and the sections were stained with hematoxylin-eosin. The morphological assessment was carried out using a morphometric approach using stereological point-counting, by which a uniform grid is plotted over the image and the points crossing the lines are counted.[14] The morphometric approach considered the mean number of neurons, oligodendrocytes, astrocytes, vessels, inflammatory cells, and lymphocytes in the periventricular and ependymal regions.

Statistical Analysis

The distribution of data was assessed with the Shapiro-Wilk test. Differences between the groups were assessed using the Student t-test or the Mann-Whitney test. Differences in repeated measures within the same groups were assessed using the paired t-test and the Wilcoxon test. The Fisher exact test was used to compare frequencies. Differences were considered significant for p-value < 0.05. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp, Armonk, NY, USA).

Results

The periprocedural mortality was 9 and 19 in the low and high concentration groups, respectively. Among the remaining 21 rats in the low concentration group, 4 died during the follow-up and 1 after the 3rd MRI. In the high concentration group, from the 11 remaining animals, 3 died during the follow-up period. Thus, imaging and histological assessment were performed on the remaining 16 rats in the low concentration group and 8 in the high concentration group.

Slight enlargement of the brain ventricles was observed in both groups postinoculation; the increase was more evident and significant in the high concentration group (►**Fig 1**), mainly at 6 months postinoculation. In the low concentration group, a significant increase was observed between 1 and 3 months postinoculation (medians 1.78 mm^3 and 2.15 mm^3,

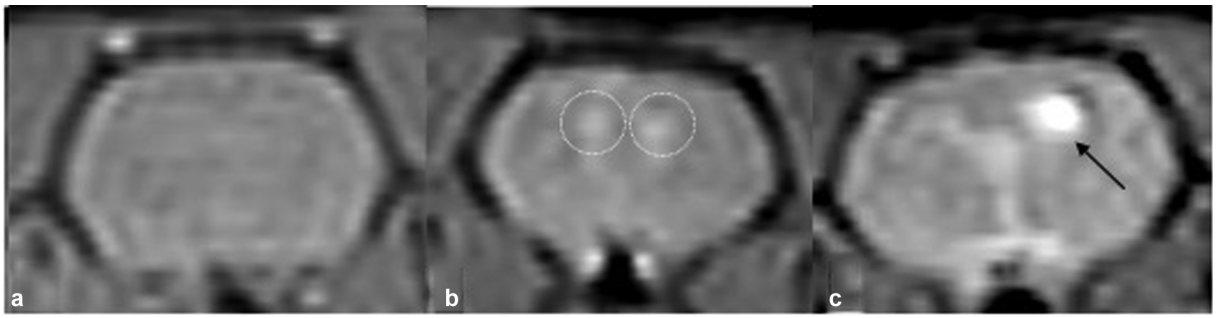

Fig. 1 Coronal magnetic resonance images (a) in the low-concentration group the ventricles cannot be visualized; (b) slight enlargement of the ventricles (dashed circles) in the high-concentration group; (c) an evident ventricle enlargement (arrow) from the high-concentration group.

Table 1 Ventricle volumes (mm^3) in the low- and high-concentration groups at 1, 3, and 6 months postinoculation

Month	Group	Average	Standard deviation	Median	Range	*p-value*
1	Low	1.67	0.85	1.78†	0.30–2.82	0.180*
	High	2.64	2.25	2.04‡	1.04–8.08	
3	Low	2.62	2.79	2.15†	0.22–12.83	0.397*
	High	3.16	3.58	1.89‡	0.45–11.20	
6	Low	2.63	2.52	2.00†	0.37–11.57	0.003*
	High	5.26	3.35	3.86‡	2.37–12.68	

†Wilcoxon test for repeated measures. In the low-concentration group, ventricle volumes were different at 1 and 3 months ($p = 0.032$), but not at 3 and 6 months ($p = 0.984$).
‡Wilcoxon test for repeated measures. In the high-concentration group, ventricle volumes were not different at 1 and 3 months ($p = 0.646$),but were different at 3 and 6 months ($p < 0.05$).
*Mann-Whitney test for independent samples. The ventricle volumes were not different between the two groups at 1 and 3 months, but were different at 6 months.

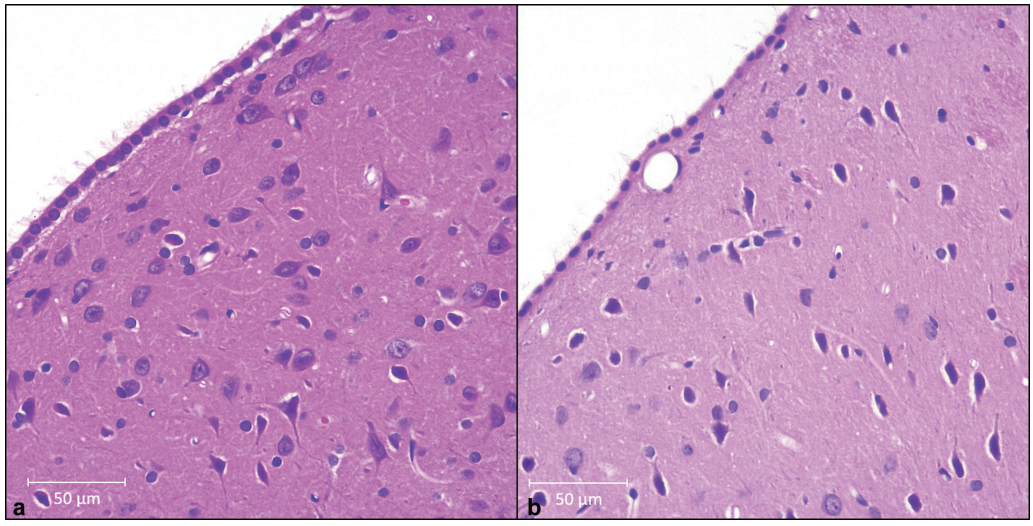

Fig. 2 Hematoxylin and Eosin staining of the brain sections depicting differences in neuronal density (a) the low-concentration group has a higher neuronal density compared to (b) the high-concentration group.

respectively), while in the high concentration group, a significant increase was observed between 3 and 6 months postinoculation (medians 1.89 mm^3 and 3.86 mm^3, respectively) (►**Table 1**). In the 1 and 3 months postinoculation follow-ups, the volumes of the ventricles were not different between the 2 groups ($p = 0.180$ and 0.397, respectively). However, a significant difference in the ventricle volume was observed between the 2 groups at 6 months postinoculation (medians 2.00 versus 3.86 mm^3; $p = 0.003$).

Morphological assessment revealed a few lymphocytes and new vessels in both groups. The ependymal lining was normal in both groups. The mean oligodendrocytes density was 9.72 and 5.18 in the low and high concentration groups, respectively ($p < 0.001$). Similarly, within the

periventricular area, a significant difference in the neuronal density was observed between the 2 groups (21.00 versus 15.69, low versus high concentration group, $p < 0.001$, ►**Figure 2**). Conversely, there was no significant difference in astrocyte density between the two groups (2.89 versus 2.74, low versus high concentration group, $p = 0.73$).

Discussion

Neurocysticercosis is a preventable, but an embarrassingly neglected infectious disease still prevalent in nondeveloped countries. It remains endemic in several countries in Latin America, sub-Saharan Africa, and Southeast Asia.[15] Experimental animal models of neurocysticercosis are a valuable tool to study the characteristics of inflammation and the basic mechanisms underlying the heterogeneous relationship between the parasite and the host.[16]

In a previous study, we observed that, in rats, cisternal inoculation of antigenic suspension of *T. crassiceps* cysts induced a slight increase in the ventricle volume, without any signs of inflammation. We speculated that it was due to the low concentration of the inoculated proteins and that the inoculation of a higher concentration of antigens could induce a more intense inflammatory response, and more evident hydrocephalus.[17] Herein, we observed that the animals who received a higher concentration of *T. crassiceps* cyst proteins had a significantly higher ventricle volume than those who received a low concentration of cyst proteins at 6 months postinoculation, confirming the previous hypothesis. In our experimental model, the induction of hydrocephalus at 6 month postinoculation is dependent on the presence of living cysts.[17] The live *T. crassiceps* cysts might continuously recruit the inflammatory cells and obstruct the narrow passages within the ventricles; thus, a combination of inflammation and mechanical obstruction may lead to hydrocephalus.[17] In contrast, the antigenic suspension form of *T. crassiceps* cysts may evoke a transient inflammatory response that may cause slight enlargement of the lateral ventricles without obvious hydrocephalus. It might be possible that inoculating the animals with even a higher concentration of cyst proteins may lead to hydrocephalus; however, further studies are required to prove this other hypothesis.

Another possible explanation is that this slight ventricle enlargement is due to a brain atrophy caused by the inflammation evoked by the response against the parasite. Actually, the intraperitoneal inoculation of *T. crassiceps* is able to impair the learning performance of mice, which is accompanied by hippocampal sclerosis. Apoptosis of hippocampal cells may be related to a breakdown of the blood-brain barrier determined by the presence of circulating *T. crassiceps* metacestode factor.[18]

Clinically, it has been well-documented that dead cysts may cause arachnoiditis, ependymitis, and hydrocephalus,[19] which is one of the reasons for using corticosteroids to control inflammation during the antiparasitic treatment.[20] A few studies have cautioned about the risk associated with intraoperative rupture of *T. solium* cysts, which may lead to ventriculitis[21,22]; however, recent studies downplayed these risks.[23–25] In the surgical management of hydatid cysts, the rupture of the cyst may worsen inflammation and lead to the seeding of infection.[26,27]

In the present study, inoculation of the animals with a higher concentration of *T. crassiceps* cyst antigens failed to induce remarkable ependymitis and hydrocephalus. A possible explanation is that inoculation does not mimic the natural degeneration of cysts observed in humans. Further studies on cyst degeneration using antiparasitic drugs are required to conclusively prove this. Another possibility is the obvious differences between the parasites (*T. solium* versus *T. crassiceps*) and the hosts (human versus rat).

We observed no significant difference in the number of inflammatory cells between the two groups. Moreover, the number of lymphocytes was low in both groups. Since the histopathological assessment was performed at 6 months after the inoculation, the possibility of a transitory and self-limited inflammation that followed the inoculation within the first few days cannot be ruled out.

Interestingly, we observed reduced oligodendrocytes and neuronal density in the periventricular area of animals from the high-concentration group, which may explain the neuropsychological changes observed in patients with neurocysticercosis. The association between dementia and neurocysticercosis was demonstrated a few years ago; patients with neurocysticercosis may present changes in working and episodic verbal memory, executive functions, naming, verbal fluency, constructive praxis, and visuospatial orientation.[28–30] Recently, another group with interest in experimental models of neurocysticercosis showed increased demyelination and hippocampal disorganization following intraventricular inoculation of *T. crassiceps* cysts.[31] However, these animals also presented ventricle enlargement, which might have caused the observed morphological changes.[32,33] In the present study, despite the low volume of the ventricles, the animals with a higher concentration of cyst antigens presented a reduced neuronal density. Further studies are required to investigate the link between neuroinflammation and neurodegeneration, as well as between neurocysticercosis and mesial temporal sclerosis, which has been extensively demonstrated in clinical studies.[34–36] Besides, a recent clinical study has shown an interesting correlation between anti-brain protein autoantibodies and the levels of secreted *T. solium* glycoprotein HP-10, suggesting that the level of stimulation of the autoantibody response may be a function of the number of viable parasites.[37] This information adds evidence to the link between neurocysticercosis and neuroinflammation.

Finally, the present study has limitations. First of all, we did not use a control group without interventions. However, in our experience with previous experiments, we found that the inoculation of saline leads to no change on MRI and histologic assessments. Second, we could not precise the extent of inflammation soon after the inoculations because histologic assessments were done only at the end of the experiments. It is possible that the animals with larger ventricles and more histologic impairments had a more exacerbate initial inflammatory response, but we cannot be certain of this point.

In conclusion, we found that inoculation of a higher concentration of *T. crassiceps* antigens in the subarachnoid space of rats leads to a more remarkable ventricle enlargement and a significant reduction in the neuronal density within the periventricular area.

Conflict of Interests

The authors have no conflict of interests to declare.

Acknowledgment

We thank Dr Agnès Fleury (UNAM) for her comments on this manuscript.

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Anastomosis Patterns between the Median and Ulnar Nerves in the Upper Limbs

Padrões de anastomose entre os nervos mediano e ulnar nos membros superiores

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Arq Bras Neurocir 2021;40(2):e152–e158.

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Abstract

There are four types of anastomoses between the median and ulnar nerves in the upper limbs. It consists of crossings of axons that produce changes in the innervation of the upper limbs, mainly in the intrinsic muscles of the hand. The forearm has two anatomical changes – Martin-Gruber: branch originating close to the median nerve joining distally to the ulnar nerve; and Marinacci: branch originating close to the ulnar nerve and distally joining the median nerve. The hand also has two types of anastomoses, which are more common, and sometimes considered a normal anatomical pattern – Berrettini: Connection between the common digital nerves of the ulnar and median nerves; and Riche-Cannieu: anastomosis between the recurrent branch of the median nerve and the deep branch of the ulnar nerve. Due to these connection patterns, musculoskeletal disorders and neuropathies can be misinterpreted, and nerve injuries during surgery may occur, without the knowledge of these anastomoses. Therefore, knowledge of them is essential for the clinical practice. The purpose of the present review is to provide important information about each type of anastomosis of the median and ulnar nerves in the forearm and hand.

Keywords
- Martin Gruber
- Marinacci
- Berrettini
- Riche-Cannieu
- median nerve
- ulnar nerve
- anastomosis

Resumo

Existem quatro tipos de anastomoses entre os nervos mediano e ulnar nos membros superiores. Elas consistem em cruzamentos de axônios que produzem mudanças na inervação dos membros superiores, principalmente na musculatura intrínseca da mão. O antebraço apresenta duas variações anatômicas – Martin-Gruber: ramo que se origina proximalmente ao nervo mediano e se une distalmente ao nervo ulnar; e Marinacci: ramo que se origina proximalmente ao nervo ulnar e se une distalmente ao nervo mediano. A mão apresenta também dois tipos de anastomoses, mais comuns, por vezes considerados padrão anatômico normal – Berrettini: conexão entre os nervos digitais comuns dos nervos ulnar e mediano; e Riche-Cannieu: anastomose entre o ramo recorrente do nervo mediano e o ramo profundo do nervo ulnar. Devido a esses

Palavras-chave
- Martin-Gruber
- Marinacci
- Berrettini
- Riche-Cannieu
- nervo mediano
- nervo ulnar
- anastomoses

received
July 13, 2020
accepted
November 16, 2020
published online
March 29, 2021

DOI https://doi.org/10.1055/s-0041-1724044.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

padrões de conexões, distúrbios musculoesqueléticos e neuropatias podem ser mal interpretadas, e lesões nervosas durante as cirurgias podem ocorrer, sem o conhecimento dessas anastomoses. Portanto, o conhecimento delas é fundamental para a prática clínica. O objetivo desta revisão é fornecer informações importantes acerca de cada tipo de anastomose dos nervos mediano e ulnar no antebraço e na mão.

Introduction

Anastomoses between the median and ulnar nerves can be found in the upper limbs. They consist of crossings of axons that can produce variations in the innervation of the muscles in the upper limbs, mainly the motor part of the intrinsic muscles of the hand.[1,2] Basically, four types of anastomoses can be found between the median and ulnar nerves in the upper limbs: two connections in the forearm (Martin-Gruber and Marinacci) and two connections in the hand (Berrettini and Riche-Cannieu).

The median nerve originates from the roots of C5 to T1 of the brachial plexus. It does not innervate any muscle in the arm. In the forearm, it is responsible for the innervation of the flexor and pronator muscles, except for the flexor carpi ulnaris muscle and half of the flexor digitorum profundus III and IV, which are innervated by the ulnar nerve. In the hand, the median nerve innervates lumbrical muscles I and II, the opponens pollicis muscle, the abductor pollicis brevis muscle, and the flexor pollicis brevis muscle. In the elbow, the median nerve branches into the anterior interosseous nerve, which is a purely motor nerve that innervates the flexor digitorum I and II, the flexor pollicis longus, and the pronator quadratus muscle.[3]

The ulnar nerve originates from the roots of C8 and T1. It also does not innervate any muscle in the arm. As previously reported,[3] in the forearm region, it innervates the flexor ulnaris carpi muscles and half of the flexor digitorum profundus III and IV. In the hand, it innervates the adductor pollicis, interosseous muscles, lumbrical muscles III and IV, the hypotenary musculature, the palmaris brevis muscle and the deep part of the flexor pollicis brevis muscle.

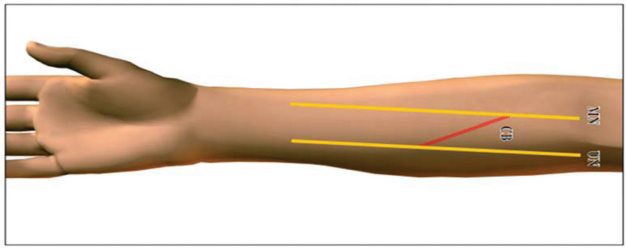

Fig. 1 Three-dimensional ilustration showing the Martin-Gruber anastomosis. Abbreviations: CB, communicating branch; MN, median nerve; UN, ulnar nerve. Source: Duran JTC, Arquez HF. Anastomosis between median and ulnar nerve in forearm and hand. Journal of c = Chemical and Pharmaceutical Research, 2016,8(8):675–680.[58]

The knowledge of the different patterns of anastomoses between the median and ulnar nerves in the forearm and hand is important to recognize the clinical manifestations in peripheral nerves and musculoskeletal disorders, as well as to plan surgical approaches and understand their prognosis.[4–7]

Martin-Gruber Anastomosis

The anastomosis in the forearm, in which the anastomotic branch originates proximally to the median nerve and joins distally to the ulnar nerve, is known as the median-ulnar anastomosis, or Martin-Gruber anastomosis (►**Figs. 1–3**).

In 1763, Martin,[8] a Swedish anatomist, was the first to consider the possibility of a connection between the fascicles of the median and ulnar nerves in the forearm. In the following century, in 1870, Gruber[9] dissected 250 forearms and found 38 connections (15.2%); since then, the median-ulnar anastomosis became known as the Martin-Gruber anastomosis.

This anastomosis can occur between the branches intended for the flexor digitorum profundus, directly from the median nerve to the ulnar nerve, between the anterior interosseous nerve and the ulnar nerve, or by combinations between these types of anastomoses.[10]

The reported incidence of the Martin-Gruber anastomosis in the literature ranges from 10.5% to 23%.[1,9,11–13] In a meta-analysis of 41 studies conducted by Roy et al.,[14] the prevalence found was of 19.5%.

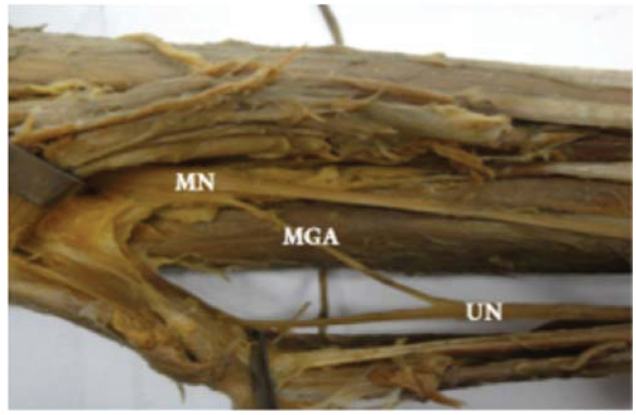

Fig. 2 Dissection of the forearm showing the Martin-Gruber anastomosis (median-ulnar). The anastomosis originates from the anterior interosseous nerve. Abbreviations: MGA, Martin-Gruber anastomosis; MN, median nerve; UN, ulnar nerve. Source: Felippe et al.[29]

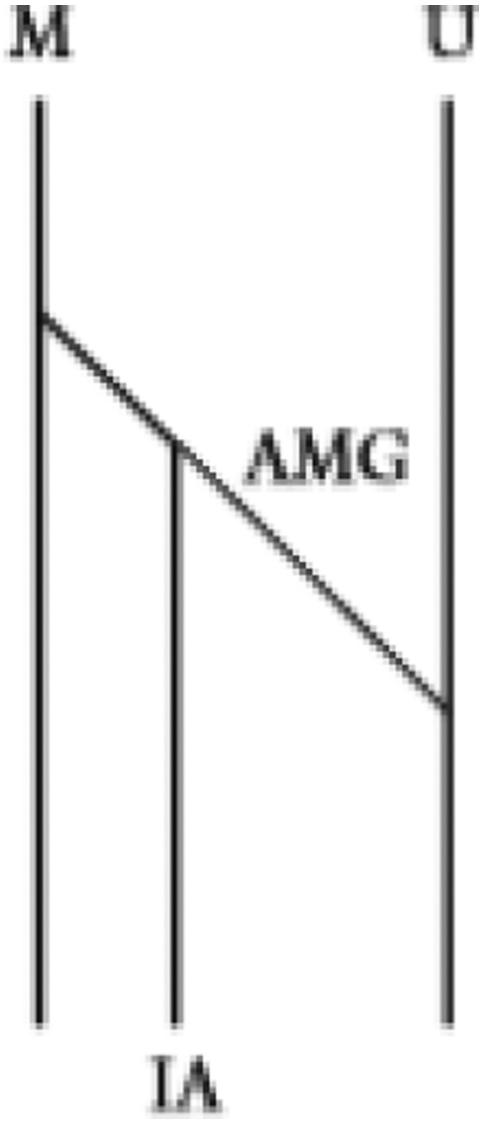

Fig. 3 Schematic representation of the Martin-Gruber anastomosis. Abbreviations: AMG, Martin-Gruber anastomosis; IA, anterior interosseous nerve; M, median nerve; U, ulnar nerve. Source: Felippe et al.[29]

The Martin-Gruber anastomosis can be divided into six subtypes – type I: oblique anastomotic branch between the anterior interosseous nerve and the ulnar nerve; type II: double anastomosis between the anterior interosseous nerve and the ulnar nerve; type III: anastomosis between the median nerve and the ulnar nerve; type IV: anastomosis between the branches of the median and ulnar nerves that follow to the flexor digitorum profundus muscle; type V: intramuscular anastomosis; and type VI: anastomosis between the median nerve branch that leads to the flexor digitorum superficialis muscle and the ulnar nerve.[15]

In about 56.5% of the Martin-Gruber anastomoses discovered, the proximal anastomotic branch originates from the anterior interosseous nerve.[9] Taams[13] suggested that the Martin-Gruber anastomosis occurs more frequently in the right forearm than in the left forearm, and is only bilateral in 10% to 40% of the cases. Gruber[9] further suggested that it would be more common to find only one anastomotic branch than two.

The Martin-Gruber anastomosis is observed mainly in the upper portion of the forearm, in the plane between the epitrochlear muscles and the flexor digitorum profundus muscle.[16,17] Srinivasan and Rhodes[18] congenitally examined abnormal fetuses (fetuses with trisomy 21) and found the Martin-Gruber anastomosis on both forearms of every fetus. Crutchfield and Gutmann[19] and Piza-Katzer[20] found a communication between the median nerve and the ulnar nerve in family members of people who showed this anomalous connection, and suggested that it is a hereditary trait, probably autosomal dominant.

The recognition of the Martin-Gruber anastomosis is important for the correct diagnosis of neuropathies, and traumatic and compressive injuries of the peripheral nerves. For example, a patient may have compression of the median nerve in the wrist through the flexor retinaculum of the hand (carpal tunnel syndrome) with preservation of the clinical symptoms and atypical electromyographic findings in the tenar musculature, or, inversely, they may have symptoms of carpal tunnel syndrome without compression of the median nerve observed by the negative Tinel and Phalen tests, due to compression of the ulnar nerve in the elbow.[21]

Brandsma et al.[22] described the cases of five patients with complete lesion to the ulnar nerve in the elbow and injury to the median nerve in the wrist, due to leprosy neuropathy, who mainteined good function of the first dorsal interosseous muscle and flexor pollicis brevis muscle. He attributed these findings to the presence of the Martin-Gruber anastomosis, which was later confirmed by studies of nerve conduction, reinforcing its clinical importance.

Marinacci Anastomosis

Another type of anastomosis can occur between the median nerve and the ulnar nerve in the forearm. The anastomotic branch originates proximally to the ulnar nerve and joins distally to the median nerve, and it is called an ulnar-median anastomosis, reverse Martin-Gruber anastomosis, or Marinacci anastomosis. It is composed mainly of motor fibers.[23] (►**Figs. 4–6**).

In 1964, Marinacci[24] reported the case of a patient who suffered trauma to the median nerve in the forearm, but preserved the muscles of the hand innervated by the median nerve, despite denervation of the flexors muscles of the

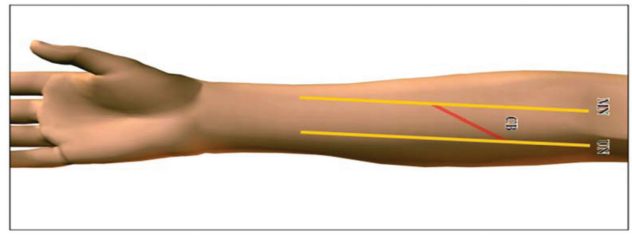

Fig. 4 Three-dimensional ilustration showing the Marinacci anastomosis. Abbreviations: CB, anastomotic branch; MN, median nerve; UN, ulnar nerve. Source: Duran JTC, Arquez HF. Anastomosis between median and ulnar nerve in forearm and hand. Journal of Chemical and Pharmaceutical Research, 2016,8(8):675–680.[58]

Fig. 5 Dissection of the forearm showing the Marinacci anastomosis (ulnar-median). The branch of the ulnar nerve gives rise to the anastomotic branch. Abbreviations: MA, Marinacci anastomosis; MN, median nerve; UN, ulnar nerve. Source: Felippe et al.[29]

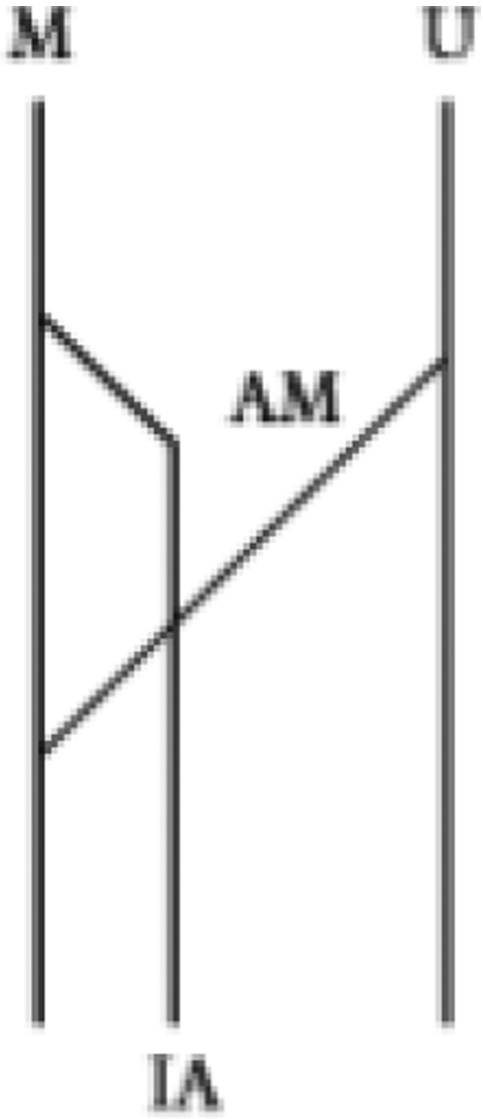

Fig. 6 Schematic representation of the Marinacci anastomosis. Abbreviations: AM, Marinacci anastomosis; IA, anterior interosseous nerve; M, median nerve; U, ulnar nerve... Source: Felippe et al.[29]

forearm. The reported frequency of Marinacci anastomosis is very low. In many studies[29], this type of anastomosis was not found, and it is considered by many authors an anatomical anomaly.

The occurrence of Martin-Gruber or Marinacci anastomoses can be understood by the fact that the median and ulnar nerves develop from a similar embryonic region.[25] There are reports of a high incidence of peripheral-nerve connections in monkeys, which indicates a phylogenetic basis.[1,26]

Regarding the Marinacci anastomosis, there are no studies on the incidence in cadavers, but its incidence in electroneuromyography studies was of 5% according to Rosen[27] and of 16.7% according to Golovchinsky[28]. Felippe et. al[29] demontrated a dissection cadaver that presented a rare case of Marinacci anastomosis: the anastomotic branch originated proximally to the ulnar nerve, and was inserted into the anterior interosseous nerve, located on the right side; it was a single anastomotic branch measuring 7.4 cm in length.[27–29]

Sraj et al.[30] published a case report of a patient who, despite presenting typical symptoms of carpal tunnel syndrome, did not manifest any of the clinical signs of median nerve compression. The patient presented evidence of compression of the ulnar nerve in the elbow, and by testing the ulnar nerve, the authors found that the patient had the symptoms of carpal tunnel syndrome. Another case reported by Sraj et al have also reported a patient with a median nerve injury to the elbow[30], without clinical repercussion in the thenar muscles, such as the abdutor pollicis brevis muscle, innervated by the median nerve. No changes were observed in the hand muscles, despite the denervation of the flexor muscles of the forearm.[29]

Berrettini Anastomosis

Communications between the median nerve and the ulnar nerve can occur with great frequency in the wrist and hand, and the anastomosis between the deep branch of the ulnar nerve and the recurrent branch of the median nerve in the tenar eminence is known as the Riche-Cannieu anastomosis. Communication between common digital nerves that emerge from the median nerve and the ulnar nerve on the surface of the palm is known as Berrettini anastomosis or ramus communicans cum nervi ulnari in anatomical terminology[4,31] (►**Figs. 7** and **8**).

Variations of the Berrettini anastomosis exist, and communications between the fourth common digital ulnar nerve and the third common digital median nerve may explain the variations in digital sensory innervation. The anastomotic branch originates most commonly from the fourth common digital nerve of the ulnar nerve, communicating distally to the third common digital nerve of the median nerve.[32] Its incidence varies drastically, between 4% and 94%, which is why some anatomists consider the Berrettini anastomosis a normal anatomical structure, and not an anatomical variation; however, this discussion is quite controversial.[5,32–34]

In 1991, Meals and Calkins[35] gave notoriety to the term Berrettini anastomosis in honor of Pietro Berrettini Cortonensi, a famous artist known for his painting of Santa Cecilia,

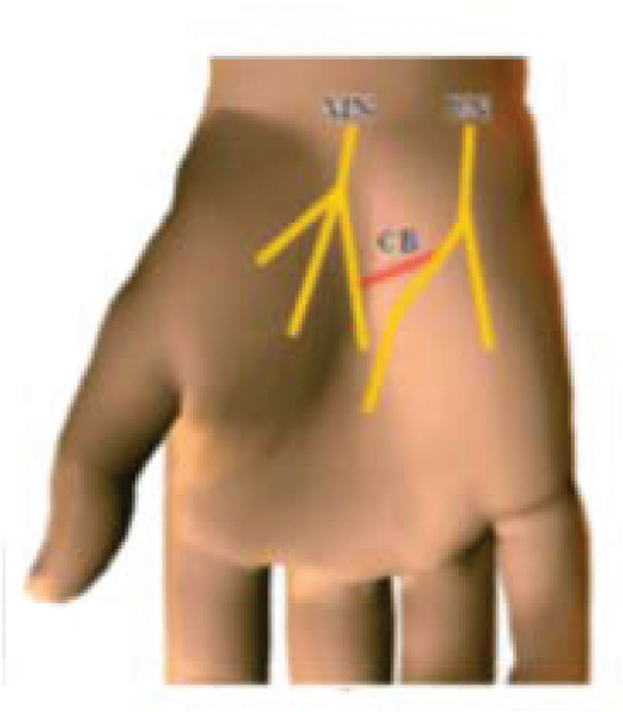

Fig. 7 Three-dimensional ilustration showing the Berrettini anastomosis in the palm of the hand. Abbreviations: CB: anastomotic branch; MN: median nerve; UN: ulnar nerve. Source: Duran JTC, Arquez HF. Anastomosis between median and ulnar nerve in forearm and hand. Journal of Chemical and Pharmaceutical Research, 2016,8 (8):675–680.[58]

who illustrated the occurrence of superficial communication between the ulnar and median nerves, in the engravings ofthe book *Tabulae Anatomicae*,[37] published in 1741.[35–37]

Berrettini's anastomosis is believed to be purely sensitive, and an injury to it results in reduced sensitivity in the region between the third and fourth fingers.[38]

Rollins and Meals[39] described the loss of sensory innervation caused by traumatic injury to the Berrettini anastomosi:, their patient reported symptoms of paresthesia in the area between the middle and ring fingers.

Fig. 8 Anatomical piece of a dissected palm. The black arrow indicates the communicating branch between the ulnar and the median nerves. Personal record provided by Dr. Marcelo Medeiros Felippe.

Loukas et al.[5] reported that there were no differences observed in the morphometric or topographic parameters according to the thnicity, age or gender of the individual.

Some anatomy books do not mention the presence of this anastomotic branch, but some atlases illustrate it as a communicating branch or anastomotic branch.[18,36,39–42] Rollins and Meals[39] paid attention to the fact that the presence of the Berrettini anastomosis can cause changes in the pattern of innervation of the fingers, according to the lesion and its topography, such as the persistence of sensitivity in the ulnar edge of the middle finger or in the radial edge of the ring finger in lesions to the median and ulnar nerves in the region of the wrist. The anastomosis is located in the middle palmar region, at a point of intersection between an axial line of the fourth finger and the Kaplan cardinal line.[43]

The Berrettini anastomosis is important because injuries can occur in the volar surface on the hand. This is due to the fact that surgeons who deal with carpal tunnel syndrome are working superficially in the area of the Berrettini anastomosis, which is why knowledge of it is extremely important.[5]

Riche-Cannue Anastomosis

The Riche-Cannieu anastomosis is located between the ulnar and median nerves in the hand. It consists of a communication between the recurrent branch of the median nerve and the deep branch of the ulnar nerve in the tenar region, and it can alter the motor innervation of the hand[44] (►**Figs. 9** and **10**). Both motor and sensitive fibers may be involved, with the possibility of three types of clinical presentation: the hand totally innervated by the ulnar nerve; motor fibers only from the ulnar nerve; or the hand with normal innervation by the median nerve, partially supplied by the ulnar

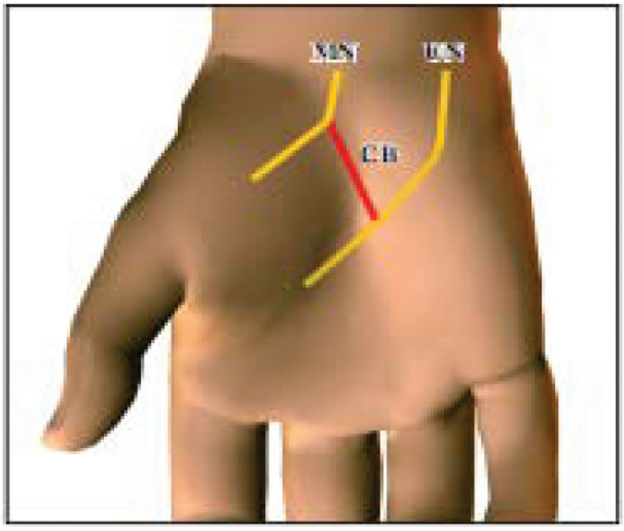

Fig. 9 Three-dimensional ilustration showing the Riche- Cannieu anastomosis in the tenar region of the palm. Abbreviations: CB, anastomotic branch; MN, median nerve; UN, ulnar nerve.. Source: Duran JTC, Arquez HF. Anastomosis between median and ulnar nerve in forearm and hand. Journal of Chemical and Pharmaceutical Research, 2016,8(8):675–680.[58]

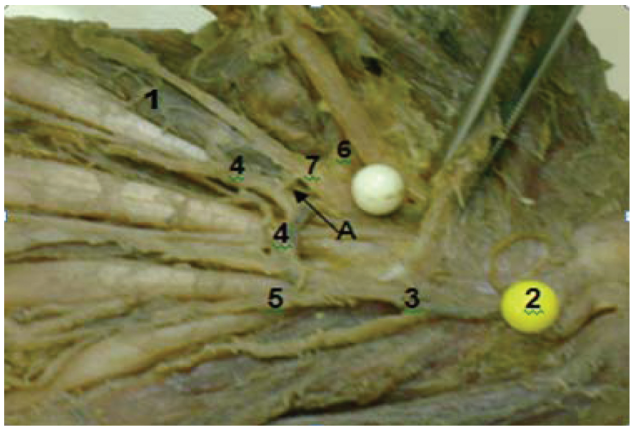

Fig. 10 Dissected palm of the hand showing the Riche-Cannieu anastomosis. Numbers: 1, first lumbrical muscle; 2, ulnar nerve; 3, trunk of the ulnar nerve; 4, deep branch of the ulnar nerve; 5, common digital palmar nerve of the ulnar nerve; 6, recurrent branch of the median nerve; 7, common palmar digital nerve of the median nerve. Personal record provided by Dr. Marcelo Medeiros Felippe.

nerve.[45] It was first described by Cannieu in 1894, who reported an anastomosis between the recurrent branch of the median nerve and the ulnar nerve in 03 out of 20 anatomical pieces that he dissected.[38] Later, in 1897, Riche[46] found anastomoses in 3 out of 12 anatomical specimens.

The incidence is quite controversial in the literature, with studies showing different prevalence rates. Studies on anatomical dissection describe the following incidences: Cannieu[47]–7%; Bölükbaşi[48]–0%; Riche[46]–13%; Yang[49]–50%; Souza[50]–50%; Harness[51]–77%; and Caetano[52]–100%. In an electrophysiological study,[38] the incidence found was of 83.3%. According to Boland et al.,[53] there is a family tendency for autosomal dominant inheritance.

The location of the Riche-Cannieu anastomosis would be at the intersection of a line perpendicular to the midpoint of the proximal flexor crease of the first finger and the axial line of the second finger.[43]

There are three types of connections described: type I: between the deep branch of the ulnar nerve and the recurrent branch of the median nerve for the two heads of the flexor pollicis brevis muscle; type II: between the deep branch of the ulnar nerve and the branch of the median nerve, within the muscular body of the transverse head of the adductor pollicis; type III: communication between these two nerves within the lumbrical muscle body.[46]

Regarding the clinical repercussion, the presence of this anastomosis can cause a risk of injury during surgical procedures, and also hinder the interpretation of electrophysiological studies in the diagnosis of neuropathies. Carpal tunnel syndrome, in particular, has been associated with exacerbated or decreased symptoms in the presence of these anastomoses.[52,54] It can generate an "ulnar-hand" phenomenon in some cases, in which the muscles in the tenar eminence only present innervation from the ulnar nerve, with no contribution from the median nerve.[55]

In an electroneuromyographic study,[56] it caused difficulty in interpreting the results, especially in the evaluation of the lesions to the median nerve, the opponens pollicis muscle, amd the abductor pollicis brevis muscle.

These anastomoses can cause confusion in the diagnosis of lesions: complete lesion to the median nerve, in a situation in which the Riche-Cannieu anastomosis exists, can be interpreted as a partial nerve injury, for example. In cases of injury to the ulnar nerve, the presence of signs of denervation of the muscles innervated by the median nerve (the opponens pollicis muscle and the abductor pollicis brevis muscle) may lead to the suspicion of of brachial plexus injury (C8-T1).[56,57]

Conclusion

Anastomoses between the median and ulnar nerves in the forearm and hand can cause confusion in the diagnosis of conditions affecting the nerve that supplies the intrinsic muscles of the hand. Crossing axons can innervate the intrinsic muscles supplied by the ulnar nerve, the median nerve, or both. This explains the cases in which nerve damage in the forearm does not cause changes in the muscles of the hand. The symptoms of carpal tunnel syndrome may be incomplete or exacerbated due to the existence of these anastomoses, which alter the innervation of the upper limb. Or a traumatic nerve injury at the level of the forearm may be mistakenly interpreted as a partial injury in the median nerve or ulnar nerve, and importance should also be given to its topography to prevent injuries to the anastomotic branches in upper-limb surgical procedures. Therefore, knowledge of these anastomoses is important, given their impact on the surgical treatment in the forearm and hand, to avoid iatrogenic injuries and prevent complications in surgeries, as well as in the clinical and electromyographic diagnosis of partial and total injuries to the median and ulnar nerves.

Conflict of Interests

The authors have no conflict of interests to declare.

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Huge Sellar Plasmacytoma as Differential Diagnosis of Invasive Pituitary Adenoma: A Case Report

Plasmocitoma selar enorme como diagnóstico diferencial de adenoma hipofisário invasivo: um relato de caso

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Arq Bras Neurocir 2021;40(2):e159–e161.

Abstract

Sellar plasmacytomas are rare tumors arising from plasma cells. They are often misdiagnosed as adenomas. We report the case of a 63-year-old woman with headache, cranial nerve III palsy and decreased visual acuity. Imaging revealed an extensive lesion centered on the clivus, extending to the cavernous sinus bilaterally and into the sphenoid sinus. The hormonal tests were compatible with panhypopituitarism and mild hyperprolactinemia. The first hypothesis was invasive pituitary adenoma. Partial resection was achieved, and the immunohistochemical evaluation was compatible with plasmacytoma. After a few weeks, she developed lumbar and hip pain, and the imaging confirming osteolytic lesions. The final diagnosis was multiple myeloma.

Keywords
- sellar plasmacytoma
- multiple myeloma
- parasellar mass
- differential diagnosis

Resumo

Plasmacitomas selares são tumores raros originados de células plasmáticas. Freqüentemente são diagnosticados erroneamente como adenomas. Relatamos o caso de uma mulher de 63 anos com cefaleia paralisia dos nervos cranianos III e diminuição da acuidade visual. A imagem revelou uma lesão extensa centrada no clivus estendendo-se para o seio cavernoso bilateralmente e para o seio esfenoidal. Os testes hormonais foram compatíveis com pan-hipopituitarismo e hiperprolactinemia leve. A primeira hipótese era adenoma hipofisário invasivo. Foi realizada ressecção parcial e a avaliação imunoistoquímica compatível com plasmocitoma. Após algumas semanas ela desenvolveu dor lombar e no quadril e a imagem confirmando lesões osteolíticas. O diagnóstico final foi mieloma múltiplo.

Palavras-chave
- plasmacitoma selar
- mieloma múltiplo
- massa parasselar
- diagnóstico diferencial

received
July 6, 2020
accepted
March 9, 2021
published online
August 3, 2021

DOI https://doi.org/10.1055/s-0041-1731062.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Introduction

Plasmacytomas of the sellar region were first reported in 1970 by postmortem pathologic diagnosis, an observation that predates a case from 1977 that was previously attributed as the first.[1] They are rare tumors localized on the sellar region arising from plasma cells.[2] It is believed that the entity originates from the surrounding mucosa of the sellar region and clivus, which can be locally aggressive.[3] Plasmacytomas are often misdiagnosed as adenomas due to the rarity of this disease and the limited clinical experience of entity in this location. The pathological study shows distinct plasmacytoid features, including prominent nucleoli. Another differential diagnosis is chordoma. We report the case of a patient diagnosed with sellar plasmacytoma and associated hypopituitarism followed by the discovery of multiple myeloma.

Case Report

A 63-year-old female with well-controlled hypertension presented with a 5-month frontal headache and 3-month impaired visual acuity, worse in the left eye. The admission neurological exam was notable for a slowly reactive left pupil and left CN III palsy, with ptosis. Computed tomography (CT) imaging demonstrated homogeneous expansive lesion with epicenter in the clivus, invading the sphenoid sinuses and with erosion of dorsum sellae and anterior clinoids bilaterally (►**Fig. 1D**). Selar magnetic resonance imaging (MRI) revealed a $4.6 \times 4.6 \times 3$ cm homogeneously contrast enhancing lesion. There was extension into the bilateral cavernous sinuses, surrounding the cavernous carotid artery bilaterally, and into the sphenoidal sinus, sellar region, optic canal, and superior orbital fissures (►**Figs. 1A**, **1B** and **1C**). Endocrine evaluation demonstrated mild hyperprolactinemia [43.78 ng/dl (5.18–26.53 ng/dl)], hypocortisolemia (3.4 ug/dl [3.7–19.4 ug/dl]) and low T4 level (0.57 ng/dl [0.7–1.8 ng/dl]) characterizing panhypopituitarism. We found no evidence of renal insufficiency, anemia, bone pain, or hypercalcemia. The patient was diagnosed presumptively with a nonfunctioning pituitary macroadenoma and underwent endoscopic endonasal transsphenoidal approach for resection of the lesion. However, because of clinically important hemorrhage, the procedure was aborted after resection of ~ 30% of the mass. After the surgery, there was mild improvement in visual acuity. Three weeks after hospital discharge, the patient presented atraumatic lumbar and hip pain. She underwent a hip MRI that found multiple heterogeneous osteolytic lesions affecting the pelvic bones and proximal femurs, as well as hip joint effusion. Immunoglobulin electrophoresis revealed monoclonal IgA/Kappa peak. The final surgical pathology evaluation of sellar mass confirmed immunopositive expression for Kappa light chain (CD138 and Kappa positives) consistent with plasmacytoma (►**Fig. 2C** and **2D**). It was negative for Lambda chain, chromogranin, and CAM 5.2. The bone marrow biopsy showed no obvious finding of plasma cell proliferation.

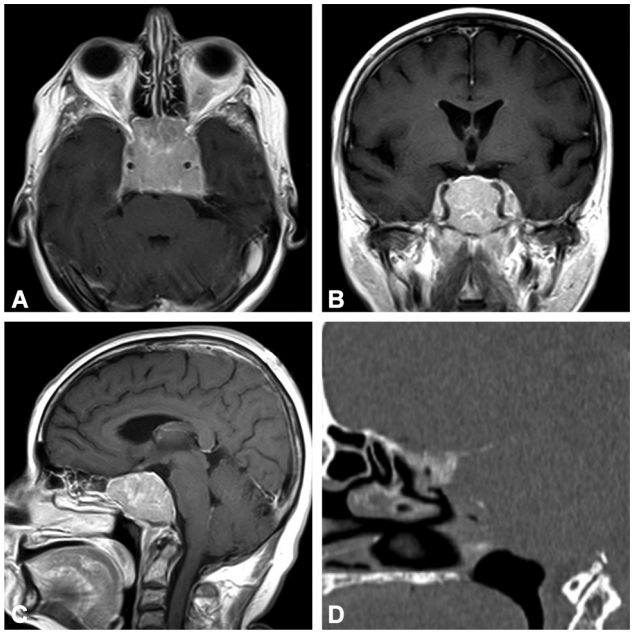

Fig. 1 Contrast-enhanced magnetic resonance imaging scan showing a homogeneously enhanced lesion centered in the clivus, with extension into the sphenoid sinus and bilateral cavernous sinus (**A**, **B** e **C**). Computed tomography scan showing the destroyed clivus and the invaded sphenoid sinus (**D**).

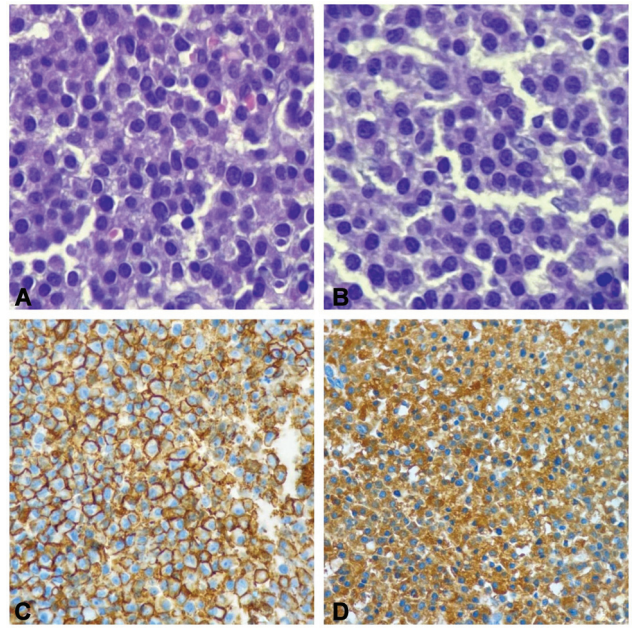

Fig. 2 Pathological study revealing proliferation of plasmacytoid cells with abundant basophilic cytoplasm, perinuclear hof, round eccentric nuclei, "clock face" chromatin and indiscernible nucleoli (**A and B**). The immunohistochemical study revealed tumor cells positive to CD138 (**C**) and kappa chain (**D**).

Discussion

The most prevalent sellar/parasellar tumor is pituitary adenoma, which presents more often with visual field deficits than cranial neuropathies. Another condition that should be considered for differentiation is chordoma.[3] Lee et al.,[2] after reviewing 70 cases of sellar plasmacytoma (including 65

cases reported from literature), found the following results: slight predominance in male subjects (57% males vs 43% females), median age of 59 years old, and hyperprolactinemia in 38% of the patients (median level 36.7 ng/mL). The majority of the patients presented with mass effect symptoms, including headaches in 70%, cranial nerve palsies in 65%, and visual disturbances in ~ 80%. DiDomenico and Ampie et al.,[1] in a review of 31 cases (including a new described), found a predominance in male subjects (55% vs 45%), and median age of 61 years old. The cranial nerve more affected is the abducens.[1] The case reported was a woman, slightly older, with clinical presentation similar to that described in the literature. The endocrinological pattern differed, as it describes hypopituitarism in only ~ 15% of cases. Our case presented with panhypopituitarism and hyperprolactinemia, the last due to stalk effect. It is unusual to find well preserved anterior pituitary function in cases of pituitary adenoma with extensive sellar fossa and clivus destruction.[3] The size of the tumor also differed from the studies reviewed. The mean was 3.4 cm (ranging from 0.9–-3.9 cm, n: 12),[1] while the tumor described was 4.6 cm in its greatest extent. To all the references, sellar plasmacytoma have a greater propensity for cavernous sinus invasion and erosion of the parasellar bone, including the cranial nerve foramina.[1] Light microscopy examination might not always be helpful in the differential diagnosis of a parasellar mass, because the features of poorly differentiated plasma cells sometimes resemble the profile of an atypical pituitary adenoma, and immunohistochemical staining is required for definitive diagnosis of a plasmacytoma,[3] as it happened in our case. Nearly half of the patients in their study initially presented with sellar plasmacytomas and ultimately had a subsequent diagnosis of multiple myeloma at full work-up or on follow-up.[1] J. Lee et al.,[2] however, found only 37% of the patients diagnosed concurrently with myeloma on presentation of the parasellar plasmacytoma. Our case developed other symptoms that suggested the diagnosis of multiple myeloma just a few weeks after the procedure of partial resection of the sellar mass, even before the immune histopathological diagnosis.

Conclusion

Despite being rare, plasmacytoma should be considered as a possible diagnosis of sellar mass. It is found mainly in men, presenting with headache, diplopia, visual deficit, CN palsy (e.g., CN VI), imaging with cavernous sinus invasion and erosion of the parasellar bone. Increased awareness of this rare tumor and its clinical features can help clinicians to develop an appreciation for the importance of accurately diagnosing and effectively managing patients with sellar/parasellar plasmacytomas.

Highlights

- Sellar plasmacytoma should be considered as differential diagnosis of sellar masses.
- Sellar plasmacytoma is more common in elderly men.
- The most common symptoms are headache and diplopia, due to cranial neuropathies.
- Sellar plasmacytoma can present before diagnosis of multiple myeloma.

Conflict of Interests

The authors declare that there is no conflict of interests.

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Multiple Brain Abscesses Secondary to Odontogenic Infection: A Clinical Case Report

Abscessos cerebrais múltiplos secundários à infecção odontogênica: Um relato de caso clínico

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Arq Bras Neurocir 2021;40(2):e162–e166.

Abstract

Introduction Cerebral abscess is a suppurative infection of the cerebral parenchyma, which may occur due to contiguity, hematogenous dissemination of distant foci, secondary to open traumatic brain injuries, or be idiopathic.

Clinical Case A 63-year-old male patient sought assistance due to a severe headache in the frontal region associated with chills and lack of appetite that started four days before. Clinical examination of the patient showed no significant changes. Imaging and laboratory tests on admission showed only nonspecific changes, such as leukocytes 18,540, platelets 517,000, and c-reactive protein 2,0. In such case, magnetic resonance imaging (MRI) of the skull was performed with contrast, showing the presence of expansive lesions compatible with multiple brain abscesses in the right parieto-occipital region.

Discussion After excluding the main focus of hematogenous dissemination and in view of the identification of the agent *Streptococcus intermedius* by means of secretion culture collected through a surgical method, the hypothesis of abscess due to contiguous dental pyogenic foci was pointed out.

Conclusion Dental evaluation showed multiple foci of infection with periodontitis and dental abscess, which were treated along with the use of antibiotics directed to the etiologic agent.

Keywords
- cerebral abscess
- dental infection
- Streptoccocus intermedius

Resumo

Abcesso cerebral é uma infecção supurativa do parênquima cerebral, podendo ocorrer por contiguidade, disseminação hematogênica de foco a distância, secundário a traumas cranioencefálicos abertos ou ser idiopático. Caso clínico: Paciente do sexo masculino, 63 anos, procura atendimento devido a queixa de cefaleia intensa com início há quatro dias. Exame de imagem realizado evidencia lesãos expansivas

received
September 2, 2020
accepted
November 16, 2020
published online
March 29, 2021

DOI https://doi.org/10.1055/s-0040-1722242.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Palavras-chave
- abcesso cerebral
- infecção odontológica
- Streptoccocus intermedius

compatíveis com abscessos cerebrais múltiplos na região parieto-occipital a direita. Discussão: Após a exclusão dos principais focos de disseminação hematogênica e diante da identificação do agente Streptococcus intermedius por meio de cultura de secreção coletado por método cirúrgico, foi levantada a hipótese de abscesso por contiguidade de foco piogênico dentário. A avaliação odontológica evidenciou múltiplos focos infecciosos com periodontite e abscesso dentário, que foram tratados conjuntamente com o uso de antibiótico direcionado para o agente etiológico.

Introduction

Cerebral abscess is a suppurative infection that affects the cerebral parenchyma.[1] It is the second most common purulent infection in the immunocompetent central nervous system (CNS), followed only by bacterial meningitis.[2] Parenchyma involvement can occur due to contiguous infection mechanisms (between 40 and 50% of cases), hematogenous dissemination of distant focus (25% of cases), secondary to open traumatic brain injuries (10% of cases) or idiopathic (15% of cases).[3,4]

In most cases, the etiologic agent is of bacterial origin; however, it should be noted that these can also occur via other microorganisms, such as protozoa or fungi.[5] The microbiological agent involved in the genesis of the abscess depends on how it is inoculated into the brain tissue. Furthermore, abscesses that occur due to contiguous infection are usually caused by infections in nearby regions, such as otitis, mastoiditis, sinusitis, periodontal disease, among others.[6–8] Among the most common pathogens are: *Staphylococcus aureus*, *Streptococcus sp, Haemophylos influenzae*, *Bacteroides* and *Peptostreptococcus*.[4,6]

Abscesses related to dental infections typically have polymicrobial derivation, highlighting the *streptococci, staphylococci species, Actinomyces sp, Actinobacillus sp, Fusobacterium sp.*[9] Secondary spreads to otitis, mastoiditis or sinusitis are more related to streptococcal (especially *Streptococcus pneumoniae*), *Enterobacteriaceae, S. aureus* and some anaerobes such as *Prevotella sp., Bacteroides sp.*[1] Abscesses caused by otitis and/or mastoiditis have a greater coefficient of temporal lobe and cerebellum infection, while the secondary to rhinosinusitis or periodontal infection most commonly affect the frontal lobe.[2,4,10] In addition, abscesses originating from hematogenous dissemination are usually multiple and tend to affect, predominantly, regions irrigated by the middle brain (posterior frontal lobe and parietal lobe).[2,3,10]

In relation to the most common focus of hematogenous dissemination, it could be mentioned: infective endocarditis, cardiac alterations such as tetralogy of Fallot, patent foramen ovale, cyanotic heart disease; lung abscess or bronchiectasis.[2,3,10] The foci of the spread of infectious endocarditis are often related to *S. Aureus*, species of streptococcus and bacteria of the HACEK group (*Haemophilus spp, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens and Kingella kingae*).[1] Infections of pulmonary dissemination focus or heart diseases that involve formation of arteriovenous shunts are generally polymicrobial, and involve streptococcus, anaerobic species (*Actinomyces sp., Prevotella sp., Bacteroides sp., Fusobacterium sp*), *staphylococci* and *Enterobacteriaceae*[1,10].

Infections linked to neurosurgical procedures due to nosocomial infections have *Meticycline-resistant S. Aureus* as its main cause, but other species such as propionibacterium and coagulase-negative staphylococcus may also be involved.[4,10] In trauma-related abscesses, it is known that *Cranioencephalic S. Aureus* is the main agent.[4,11]

Objective

To report a clinical case to identify the etiology and other cause and effect relationships involved in the genesis of a rare case of brain abscess.

To analyze the diagnostic approach performed and correlate it with the main current diagnostic protocols.

Clinical Case Report

Anamnesis

A 63-year-old male patient sought assistance due to complaints of low back pain and severe headache. He reported that 4 days before he presented with severe headache in the frontal region, associated with chills and lack of appetite. He sought care at the local Emergency Unit, where he received symptomatic medication, resulting in partial improvement of symptoms. He also reported that 24 hours before he noticed the onset of pain in the lumbar region, of the prick type, associated with paresis in the lower limbs and partial paresthesia in sporadic moments.

General physical examination did not show any particularity and, at the neurological examination, he was bedridden, with no signs of meningeal irritation, with muscle strength and reduced tactile sensitivity in the left lower limb.

Laboratory admission tests were requested, namely: Leukocytes 18,540 without deviation presence of rods, platelets 517,000, urea 54, creatinine 0.9, sodium 140, potassium 4.5, lactate 17.20, ionic calcium 1.2, magnesium 2, 3, c-reactive protein 2, urine test unchanged. Simple chest radiographs did not show any significant changes. In such case, magnetic resonance imaging (MRI) of the skull was performed with contrast (►**Fig. 1**).

After referral to blood cultures and echocardiography, to rule out possible foci of hematogenous dissemination, no

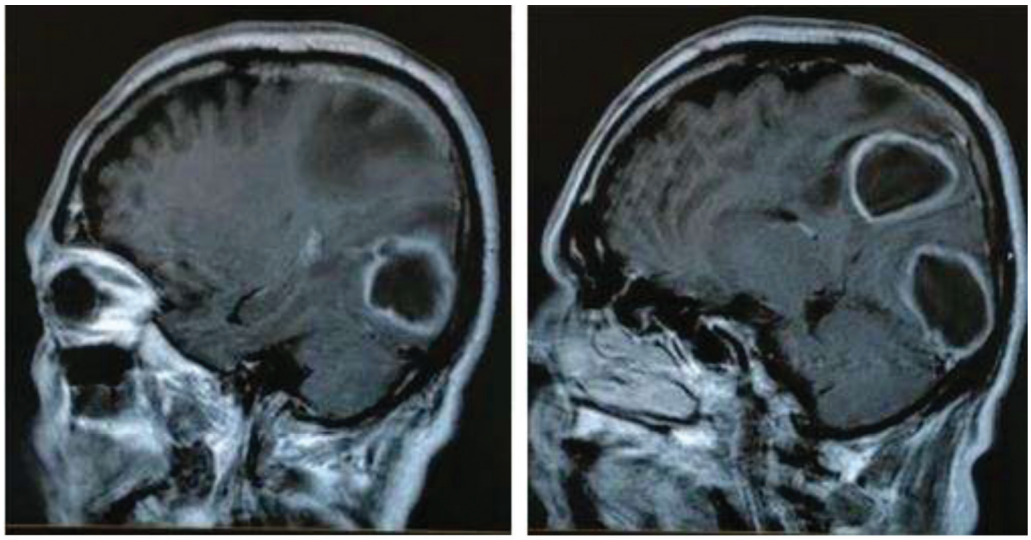

Fig. 1 Shows the magnetic resonance of the skull, performed with the patient under discussion, showing expansive lesions compatible with multiple brain abscesses. **Source**: The authors (2020).

underlying changes were demonstrated. Then, antibiotic therapy with ceftriaxone and metronidazole was started.

Seven days after admission, the patient showed an evolution with a lower level of consciousness, requiring orotracheal intubation and urgent surgery. Therefore, craniotomy was performed to remove cystic lesions, with the collection of material for culture. Six days after the surgery, the secretion culture followed, positive for *Streptococcus intermedius*. In view of the identified etiologic agent, an oral and maxillofacial surgeon evaluation was requested, since the existence of signs of gingivitis with severe periodontitis and dental abscess in two teeth was confirmed, associated with mucositis in the soft structures. Finally, the region was cleaned, in addition to maintaining the use of intravenous antibiotics for 21 days.

Discussion

When facing a patient with a headache complaint, the first step is to identify whether this is a primary or secondary disorder.[12] Primary headaches refer to chronic and continuous disorders of a dysfunctional nature, not involving anatomical or structural changes,[13] while secondary headaches are symptoms of an underlying, neurological or systemic disease (meningitis, brain tumor, among others).[14]

The main premonitory for identifying a secondary headache is the presence of alarm signs: change in the pattern of pre-existing headache, progressive intensity headache, sudden onset, associated focal neurological deficit, decreased level of consciousness, seizure, systemic manifestations (fever, toxemia, immunodepression, skin rash), beginning after 50 years of age.[12,14] It is evident that, in the face of a headache with alarm signs, it is necessary to use imaging exams for better diagnostic clarification, with computed tomography (CT) being the exam of choice.[12]

The patient presented several alarming signs that indicated it was a secondary headache: sudden onset, progressive intensity, onset after 50 years of age, focal neurological deficit (reduced strength in the left lower limb), signs of toxemia with fever and chills. As for the other clinical manifestations, here we show all three classic manifestations of brain abscesses: headache, fever and focal neurological deficit.

Initially, a CT scan of the skull was performed. However, it became necessary to perform an MRI to better assess the lesion. This last examination showed multiple brain abscesses in the parieto-occipital region. As reviewed, multiple abscesses are more common in hematogenous foci, and tend to occur in the middle cerebral artery supply region, predominating in the posterior region of the frontal lobe and in the anterior region of the parietal lobe. Foci of hematogenous dissemination to the occipital lobe may occur, but are less common.

Under suspicion of hematogenous dissemination, it is mandatory to find the primary focus. The most common focus of hematogenous dissemination are endocarditis, cardiovascular malformations and pyogenic lung infections. The complete absence of pulmonary symptomatology, associated with an admission-free X-ray of the chest, practically rules out the latter form of dissemination, resting the hypotheses in the probable cardiac focus. The echocardiogram is the exam of choice for the assessment of endocarditis or cardiac structural changes. In this case, the echocardiogram showed no changes, making it necessary to investigate further to find the primary focus of the infection.

While the specific agent is not identified, the guidelines indicate the beginning of empirical antibiotic therapy. Third and fourth cephalosporins generation are the first choice for coverage of gram positive and gram negative germs, while the combination with metronidazole provides adequate coverage against anaerobic germs. It is a given fact that the choice of antibiotic therapy in this case, performed with ceftriaxone and metronidazole, was appropriate.

After surgical removal and material collection, the culture showed the etiologic agent involved in the infection of

the parenchyma: *S. intermedius*. This agent is a highly positive, facultative anaerobic bacterium that is part of the commensal flora of the oropharynx and gastrointestinal tract. Their involvement in polymicrobial and suppurative infections is common.[15] Faced with an infection by a common agent in the oral mucosa, the hypotheses now fall on a probable odontogenic spread.

The evaluation of the oral health team showed multiple foci of oral infection, with the presence of severe periodontitis and dental abscess. Periodontitis is a chronic inflammatory process of bacterial etiology, which affects a dental structure (connective tissue, periodontal fiber and bones).[16,17] The most common etiological agents associated with periodontitis are *Aggregatibacter actinomycetamcomitans* and *Porphyromonas gingivalis* species.[16]

Streptococcus is the group of bacteria most related to oral diseases.[18] Some species such as *Streptoccocus mutans* are related to the occurrence of dental caries, while *S. Intermedius* and *Streptoccocus constellatus* usually colonize dental biofilm in patients with untreated chronic periodontitis.[18,19] The colonization of previous periodontal foci by bacteria of the species *S. Intermedius* and *S. constellatus* exacerbate the initial infectious process, which can trigger tooth loss and pyogenic complications such as brain abscess, liver abscess and bacteremia.[19–21] Despite being part of the normal flora of the oropharyngeal, genitourinary and gastrointestinal tracts, evidence of reports of involvement of these species in purulent infections such as brain and liver abscesses, as well as the occurrence of bacteremia caused by *S. Intermedius* after dental manipulation, even without the presence of an infectious process active gingival.[20–22]

The finding of a common bacterium of the oral flora in the culture of the abscess, associated with several foci of dental infection liable to spread, reinforces the hypothesis that this abscess was caused by contiguous infection from these multiple odontogenic foci.

Final Considerations

The reported case was a rare case of cerebral abscess secondary to odontogenic infection. In agreement with the literature, abscesses caused by the spread of contiguous foci tend to be single abscesses, keeping a close relationship between the dissemination focus and the location of the abscess formation. Furthermore, this type of case affects the frontal lobe, and rarely causes multiple abscesses.

We can conclude from the consultation of the literature and the report of the case presented that it is not common for odontogenic infections to complicate with the formation of abscesses in the parieto-occipital region, even more so with multiple involvement. The immediate treatment of the abscess and its source with multidisciplinary care allows the full recovery of the patient.

Conflict of Interests

The authors have no conflict of interests to declare.

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Meningeal Carcinomatosis for Prostate Adenocarcinoma Mimicking Chronic Subdural Hematoma: Case Report and Literature Review

Carcinomatose meníngea de adenocarcinoma de próstata mimetizando hematoma subdural crônico: Relato de caso e revisão da literatura

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Arq Bras Neurocir 2021;40(2):e167–e173.

Abstract

Introduction Cerebral metastases are the most common cancer of the central nervous system (CNS). Meningeal infiltration by neoplasms that did not originate in the CNS is a rare fact that is present in 0.02% of the autopsies.

Epidemiologically, the radiological presentation mimicking a subdural hematoma is even more uncommon. We report a case of meningeal carcinomatosis by an adenocarcinoma of the prostate mimicking a chronic subdural hematoma.

Case Report A 60-year-old male patient was diagnosed with prostate cancer in 2011. He underwent radical resection of the prostate, as well as adjuvant hormonal therapy and chemotherapy.

Five years later, the patient presented peripheral facial paralysis that evolved with vomiting and mental confusion. Tomography and magnetic resonance imaging scans confirmed the subdural collection.

At surgery, the dura was infiltrated by friable material of difficult hemostasis. The anatomicopathological examination showed atypical epithelial cells. The immunohistochemistry was positive for prostate-specific antigen (PSA) and other key markers, and it was conclusive for meningeal carcinomatosis by a prostate adenocarcinoma.

Discussion Meningeal carcinomatosis presents clinically with headache, motor deficits, vomiting, changes in consciousness and seizures.

The two most discussed mechanisms of neoplastic infiltration are the hematogenous route and retrograde drainage by the vertebral venous plexus.

Keywords
- subdural hematoma
- metastasis
- adenocarcinoma
- prostate

received
February 21, 2020
accepted
April 22, 2020
published online
March 29, 2021

DOI https://doi.org/10.1055/s-0040-1713092.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Conclusion Variable clinical presentations may occur in dural metastases; however, the radiological presentation as subdural hematoma is rare. There are few descriptions of cases like this one in the literature.
To support the diagnosis, the previous medical history is as important as the complementary exams and the radiological findings, because the symptoms are common at the neurological emergency. To our knowledge, this is the first report of a prostate neoplasm mimicking chronic subdural hematoma in Brazil.

Resumo

Introdução Metástases cerebrais são o tipo mais comum de câncer do sistema nervoso central (SNC). A infiltração meníngea por neoplasias não originárias do SNC é fato raro, estando presente em 0.02% das autópsias.
Epidemiologicamente, a apresentação radiológica mimetizando hematoma subdural é ainda mais incomum. Nós relatamos um caso de carcinomatose meníngea por adenocarcinoma de próstata mimetizando hematoma subdural crônico.
Relato de Caso Homem de 60 anos foi diagnosticado com câncer de próstata em 2011. O paciente foi submetido a prostatectomia radical, bem como a quimioterapia e terapia hormonal adjuvante.
Cinco anos depois, ele apresentou paralisia facial periférica, que evoluiu com vômitos e confusão mental. Tomografia e ressonância magnética confirmaram coleção subdural. Na cirurgia, a dura-máter encontrava-se infiltrada por material de difícil hemostasia. O exame anatomopatológico descreveu células epiteliais atípicas. A imunohistoquímica foi positiva para antígeno prostático específico (APE) e outros marcadores-chave, sendo conclusiva para carcinomatose meníngea por adenocarcinoma de próstata.
Discussão Clinicamente, esses pacientes apresentam-se com cefaleia, déficit motor, vômitos, alterações do nível de consciência e convulsões.
Os dois mecanismos mais prováveis de infiltração neoplásica são a rota hematogênica e a drenagem retrógrada pelo plexo venoso vertebral.
Conclusão Várias apresentações clínicas podem ocorrer em metástases durais; no entanto, mimetizar hematoma subdural é fato raro. Existem poucas descrições de casos como este na literatura.
Para dar apoio ao diagnóstico, o histórico médico prévio, bem como os exames complementares e os achados radiológicos são importantes porque os sintomas são comuns na emergência neurológica. Pelo que sabemos, este é o primeiro relato de neoplasia de próstata mimetizando hematoma subdural crônico no Brasil.

Palavras-chave
- hematoma subdural
- metástase
- adenocarcinoma
- próstata

Introduction

Brain metastases (BM) are the most common type of cancer of the central nervous system (CNS), and are more common in the sixth decade of life. In total, 40% of cancer patients developing metastases have BM, with ~ 200 thousand new cases per year in the United States.[1] The ratio of BM to primary brain cancer is of up to 10:1 cases.[1]

Metastatic meningeal infiltrations are uncommon, occurring in 8% to 9% of the cases in primary extracranial neoplasms. They behave primarily as meningeal expansive lesions usually mimicking meningiomas.[1]

Brain metastases presenting clinically and radiologically mimicking chronic subdural hematomas are very rare,[2–4] and are present in only 0.02% of autopsies of patients with suspicion of metastatic infiltrations of the meninges.

In the present paper, we report a case of prostate adenocarcinoma that presented as meningeal carcinomatosis, with clinical and radiological aspects of a chronic subdural hematoma, and we perform an extensive literature review.

Case Report

A 60-year-old male patient with previous history of hypertension and diabetes was diagnosed with prostate cancer in 2011 was submitted to radical prostatectomy followed by hormonal therapy and adjuvant chemotherapy. He kept the follow-up with the urologist and oncologist, with the disease under control.

In January 2016, he presented a sudden right peripheral face palsy that was managed as Bell palsy. In March 2016, he underwent a skull imaging exam due to hearing loss and

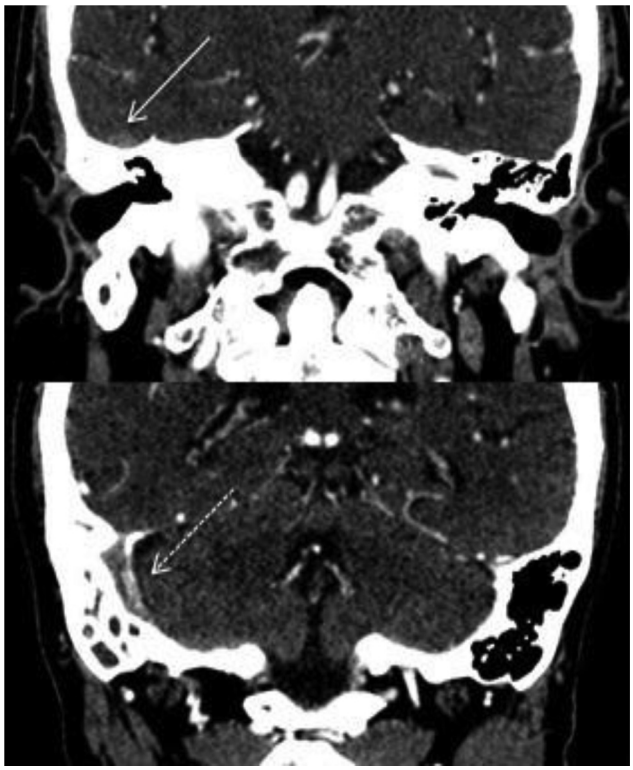

Fig. 1 Computed tomography scan of multislice contrasted skull (March 2016) - atrophy of the right mastoid, with signs of thrombosis of the sigmoid sinus (lower arrow).

auricular pain. The computed tomography (CT) scan revealed mastoid infiltration in the right side, and he was diagnosed with chronic mastoiditis and initiated antibiotic therapy.

The condition evolved during the antibiotic therapy with the patient presenting headaches of moderate intensity, dizziness, as well as some episodes of falls and small cranial traumas. Twenty days after the antibiotic therapy began, he developed vomiting and mental confusion. At this moment, he was admitted to our service for a neurological evaluation.

Upon admission, he presented a Glasgow Coma Scale (GCS) score of 14 (OR [Ocular Response], VR [Verbal Response], MR [Motor Response]), a right peripheral facial palsy (House-Brackmann 3), and a left incomplete hemiparesis grade 4+.

The patient underwent a CT scan that showed right fronto-parieto-occipital subdural hypodensity, slight meningeal enhancement, signs of mastoid atrophy, and thrombosis of the adjacent sigmoid sinus (►**Fig. 1**).

At that moment, we first thought about chronic subdural hematoma because of the history of falls and mild repetitive small cranial traumas or subdural empyema, because of the previous diagnosis of mastoiditis.

The patient underwent a magnetic resonance imaging (MRI) scan that confirmed the subdural collection but without restriction in the diffusion sequence, making the diagnosis of subdural empyema less probable (►**Fig. 2**).

Because of the dural enhancement, we chose to treat the subdural collection by a small craniotomy in April 2016. During the surgery, the subdural collection was yellowish in color, and the dura mater was infiltrated by friable neoplastic material of difficult hemostasis.

Drainage of the collection and incomplete resection of the dural lesion were performed. In the postoperative period, the patient evolved with improvement of the mental confusion and left motor deficit.

The histopathological analysis of the infiltrated meninges demonstrated atypical epithelial cells, suggesting an epithelioid carcinoma (►**Fig. 3**). The immunohistochemistry was positive for the prostate-specific antigen (PSA), cytokeratin AE1/AE3, epithelial membrane antigen (EMA) and androgen receptor antigens, being conclusive for meningeal carcinomatosis by a primary acinar prostate adenocarcinoma, Gleason grade 5. (►**Figs. 4** and **5**).

The involvement of the temporal bone, initially managed as mastoiditis, revealed a neoplastic infiltration of the adenocarcinoma.

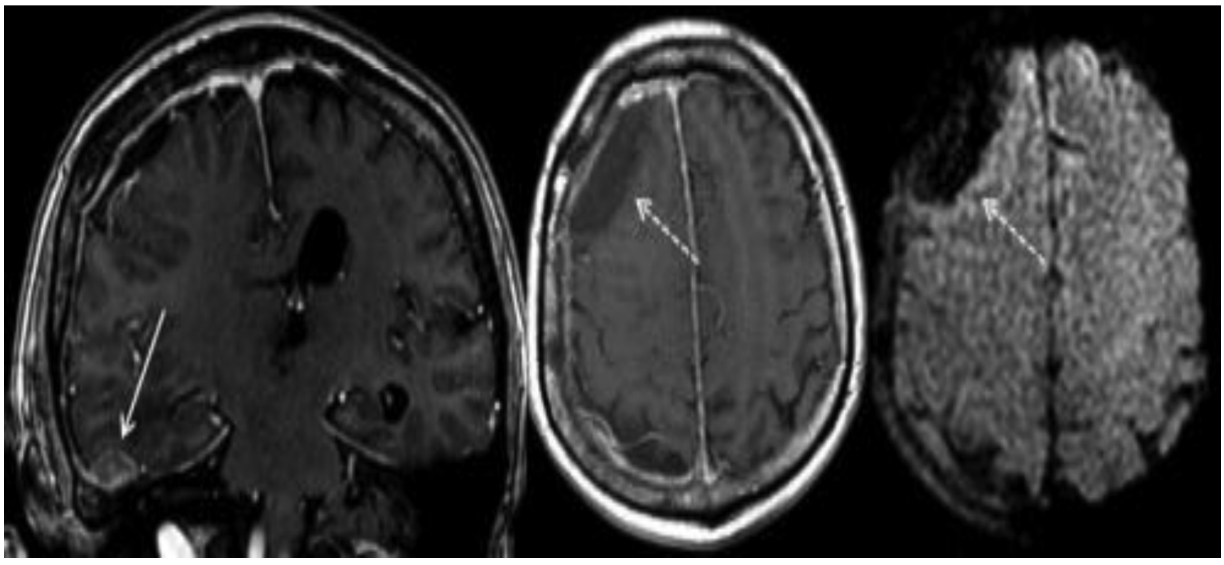

Fig. 2 Magnetic resonance imaging scan of contrasted skull (April 2016) - weighted sequence in T1 in the coronal plane showing dural enhancement adjacent to the temporal bone. The T1 and diffusion-weighted imaging sequences in axial cuts show subdural collection without diffusion restriction.

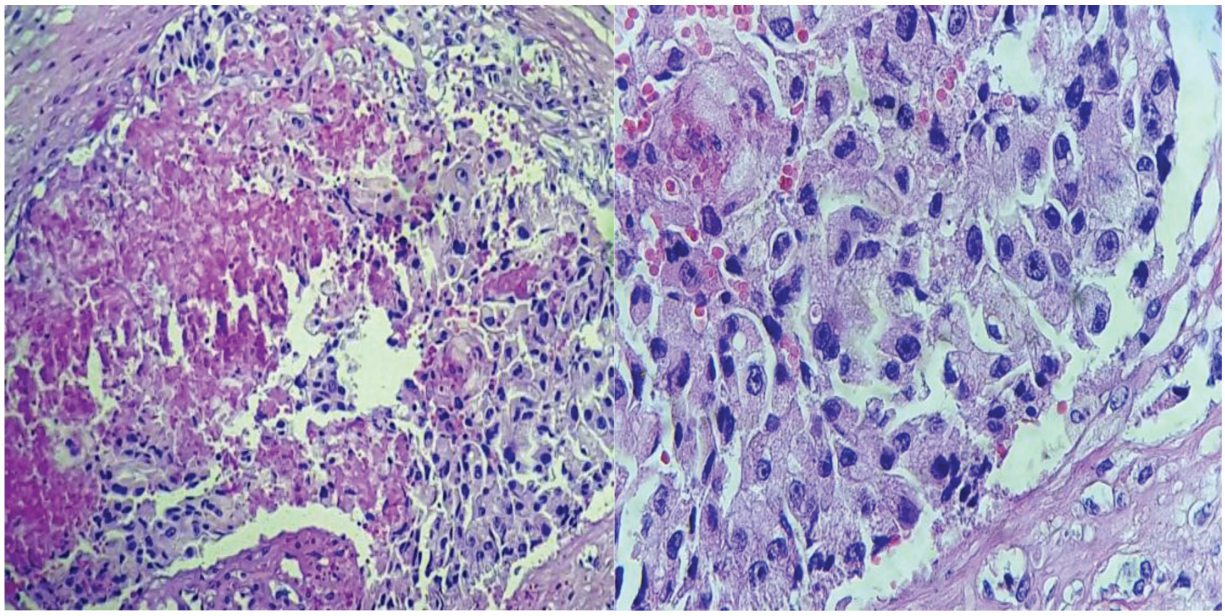

Fig. 3 10x magnification: histological sections show extensive meningeal infiltration by malignant epithelial neoplasia with solid block layout and marked comedonecrosis. 40x magnification: cellular details with pleomorphic nuclei are observed.

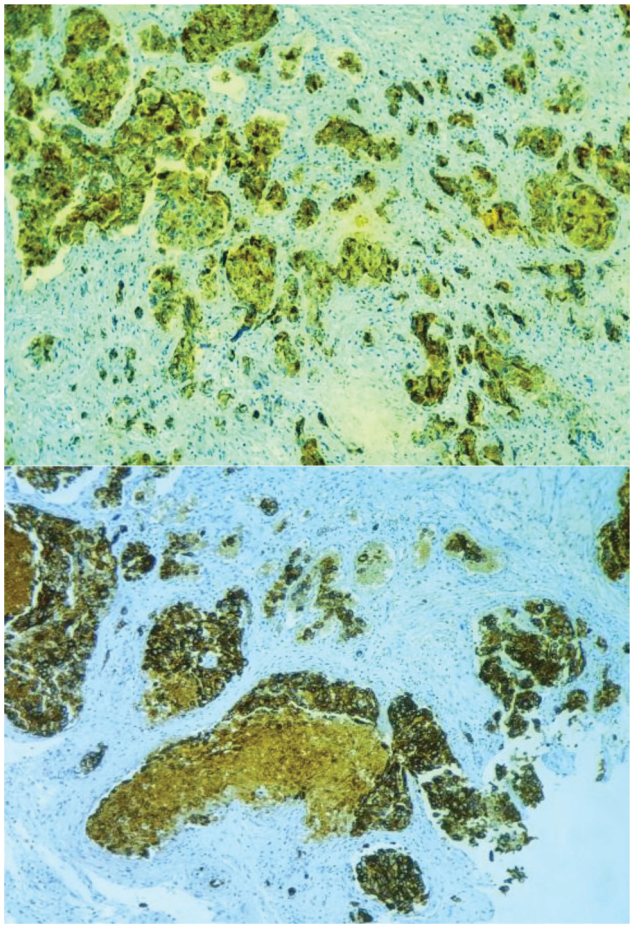

Fig. 4 Cytokeratin AE1/AE3, clone E1/AE3, strong and diffuse positivity in injured cells. Prostate-specific antigen (PSA) /clone 28a4, strong and diffuse positivity in injured cells.

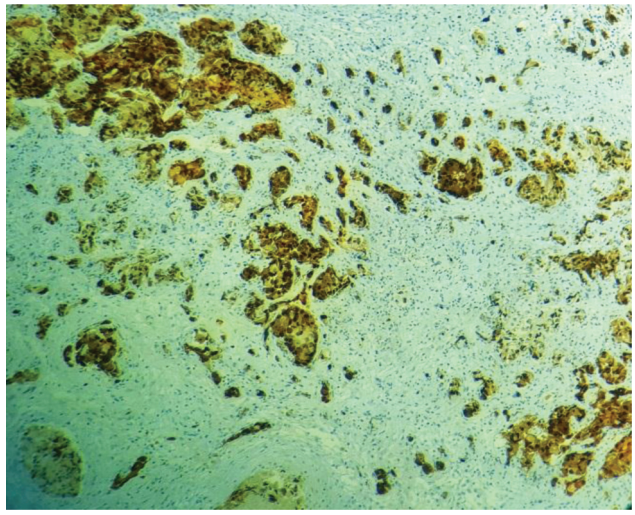

Fig. 5 Androgen receptor, clone AR441, strong and diffuse positivity in injured cells.

The patient was submitted to an Ommaya catheter for intrathecal chemotherapy. The procedure was uneventful. He was discharged at the end of May and died in July 2016 due to clinical complications.

Discussion

The first case of non-traumatic subdural hematoma secondary to metastatic invasion was described by Westenhoefer,[5] who reported a case of stomach carcinoma.[5,6] Meningeal carcinomatosis presenting as chronic subdural hematoma is present only in 0.02% of the autopsies performed in patients with suspicion of meningeal metastatic infiltration.[3]

Table 1 Cases of prostate adenocarcinoma presenting as subdural collection described in the literature

Study	Age	Clinical findings	Aspect of the extra-axial collection on tomography	Preoperative skull resonance findings	Surgery	Surgical findings	Histopathological infiltrate	Outcome
Bucci and Farhat[11]	62	Headache and mental confusion; trauma: no	Isodense extraxial collection	Not performed	Craniotomy for s ubdural collection	Slim hematoma membrane	On the hematoma membrane	Death 4 days postoperatively
Bucci and Farhat[11]	63	Confusion and weakness in the limbs;trauma: no	Hypodense extraxial collection	Not performed	Craniotomy for s ubdural collection	Subdural hematoma with membrane	On the hematoma membrane	Not Reported
Cheng et al[12]	72	Headache and hemiparesis; trauma: no	Hypodense extraxial collection	Not performed	Hematoma surgery (not specified)	Dural invasion by yellow mass; without hematoma	On the dural membrane	Death 4 months postoperatively
Dols et al[13]	54	Headache and facial palsy; trauma: no	Isodense extraxial collection	Extense dural involvement	Not performed	–	–	Death after 3 days of hospitalization
Dorsi et al[10]	71	Headache; trauma: yes	Hypodense extraxial collection	Extense dural involvement	Craniotomy, tumoral resection and collection drainage	Dural nodular invasion associated with yellow subdural collection	On the dural membrane	Not reported
Dorsi et al [10]	72	Mental confusion; trauma: no	Hypodense extraxial collection	Nodular dural involvement	Trepanning and collection drainage	Hematoma	On the hematoma membrane	Death 7 days postoperatively
Meara et al[14]	62	Behavioral change; trauma: no	Hypodense and nodular extraxial collection	Not performed	Trepanning and collection drainage	Subdural hematoma and dural invasion	On the dural membrane	Death 4 days postoperatively
Patil et al[15]	71	Headache; trauma: yes	Isodense and hypodense collection	Not performed	Trepanning converted into craniotomy and tumoral biopsy	Diffuse Subdural Tumor in Plaque	In subdural tumor	Death 25 months postoperatively
Yu et al[16]	62	Convulsive crisis; trauma: no	Bilateral isodense extraxial collection	Difuse dural involvement with nodular areas	Not performed	–	–	Not reported
N'Dri Oka et al[17]	60	Headache, mental confusion, and hemiparesis; trauma: no	Hypodense and multilobular collection in crescent	Not performed	Craniotomiy for acute subdural hematoma	Subdural yellowish tumor	On the subdural membrane	Not reported
Tomlin and Alleyne[18]	61	Headache and mental confusion; trauma: yes	Isodense extraxial collection	Not performed	Trepanning converted into c raniotomy for tumoral biopsy	Subdural and difuse dural involvement	On the subdural and dural membranes	Death 3 months postoperatively
Nzoukou et al[7]	65	Mental confusion and weakness in the limbs;trauma: yes	Bilateral extraxial multinodular hyperdense collection	Not performed	Trepanning converted into craniotomy	Difuse dural involvement by yellow ish tumor	In the subdural, dural and bone membranes	Death 5 months postoperatively
Present study	60	Headache, mental confusion, and hemiparesis; trauma: yes	Hypodense colllection	Subdural collection, without diffusion restriction	Craniotomy for subdural collection	Subdural citrine collection and dura matter infiltrated by crumb cloth	Meningeal infiltration by epithelial cells.	Death 3 months postoperatively

The most common primary histological types involve prostate adenocarcinoma, followed by breast, lung and gastric adenocarcinomas.[7,8] The two most discussed mechanisms of neoplastic infiltration are the hematogenous pathway and retrograde drainage by the vertebral venous plexus.[7]

Clinically, these patients may progress with headache in 40% of the cases. Other possible symptoms are motor deficits, vomiting, changes in consciousness, and, more rarely, seizures.[1]

The complementary exams are key parts of the diagnostic search.[9] The MRI of the skull in diffusion-weighted imaging (DWI) was of great importance in the description of the case herein reported by reducing the possibility of empyema, since there was an initial suspicion that the patient was a carrier of chronic mastoiditis. In some cases, meningeal infiltration is evident in the preoperative period, which is extremely important for surgical planning.

There are few reported cases of prostatic adenocarcinomas mimicking clinical pictures of chronic subdural hematomas. As to the pathophysiology of this process, some authors consider it is secondary to obstruction of the intradural vein by the tumor, with increased pressure on the capillaries and extravasation of the blood into the subdural space.[6] More modern studies add other mechanisms such as rupture of the fragile neovascular microvasculature of the tumors, and hemorrhagic effusion of the lesions by angiodesmoplastic reaction.[8]

In a literature review,[10] cases of meningeal carcinomatosis due to prostate adenocarcinoma were found presenting or mimicking a chronic subdural hematoma. These cases are described in ►**Table 1.–**[7,10–18]

Regarding these cases, when the surgical and histopathological findings were observed, six cases were defined as presenting only meningeal invasion, with no evidence of subdural collection.

With the inclusion of the case herein described, the mean age of presentation is 64 years,[2] with headache and mental confusion being the most reported clinical signs. History of trauma was present in 38.4% of the descriptions. The mean time between the diagnosis of the primary site and the discovery of meningeal carcinomatosis ranges from 3 months to 7 years, a fact that is compatible with the clinical case herein presented. The surgical techniques employed in the described cases varied from trepanation with lavage of the cavity with an isotonic solution to craniotomy.

The surgical approach is indicated for oncological diagnosis and when there is clinical symptomatology established by the mass effect of the collection. Care should be taken in the precise hemostasis of pachimeninges infiltrated by neoplastic cells due to the increased risk of hemorrhage in the dural space in the postoperative period.[19]

Conclusion

Variable clinical presentations may occur in dural metastases; however, clinical and radiological presentations as chronic subdural hematoma are very rare. There are few descriptions of cases like this in the literature.

Due to the difficulty in performing surgery due to tissue friability, the operative procedures must be succinct, with drainage of the blood collection when present and biopsy of the pachimeninges for the diagnosis by histopathological and immunohistochemical studies to better determine the primary site of the neoplasia in these patients and for a therapeutic definition.

To support the diagnosis, the previous medical history is as important as the complementary exams and the pathology studies because the symptoms are common in the neurological emergency. To our knowledge, this is the first report of prostate cancer mimicking a chronic subdural hematoma in Brazil.

Conflict of Interests

The authors have no conflict of interests to declare.

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Extracerebral Pterional Metastasis from Malignant Meningioma: A Case Report

Metástase pterional extracerebral de meningioma maligno: Relato de caso

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Arq Bras Neurocir 2021;40(2):e174–e178.

Abstract

Anaplastic or malignant meningiomas that are classified as World Health Organization (WHO) grade III account for less than 1% of all meningiomas diagnosed. Despite the aggressive course, distant metastases are a rarity, occurring in only 0.1% to 0.2% of cases. We report the case of a 56-year-old woman who presented with parasagittal benign meningioma that underwent malignant transformation along with metastasis into the right orbitosphenoid region. The clinical, radiological, and histopathological aspects are highlighted, with an emphasis on the natural history of meningiomas.

Keywords
- atypical meningioma
- malignant meningioma
- metastasis

Resumo

Meningiomas anaplásicos ou malignos classificados como grau III da Organização Mundial da Saúde (OMS) representam menos de 1% de todos os meningiomas diagnosticados. Apesar do curso agressivo, as metástases à distância são raras, ocorrendo em apenas 0,1% a 0,2% dos casos. Relatamos o caso de uma mulher de 56 anos que apresentou meningioma benigno parassagital que sofreu transformação maligna e metástase para a região orbito esfenoidal direita. São destacados os aspectos clínicos, radiológicos e histopatológicos, com destaque para a história natural dos meningiomas.

Palavras-chave
- meningioma atípico
- meningioma maligno
- metástase

Introduction

Meningiomas are primary neoplasms that affect the central nervous system (CNS) of adults and can be found wherever there is arachnoid membrane. They have an estimated incidence of 4 to 6 cases per 100,000 people per year, and an approximate prevalence of 97.5 per 100,000 inhabitants in the United States.[1,2] They are classified by the World Health Organization (WHO) according to tumor differentiation and mitotic activity into 3 types: benign (WHO grade I), atypical (WHO grade II), and anaplastic or malignant (WHO grade III).[3] Most cases are of the first type, often resulting from deletions in chromosome 22q12, leading to the inactivation of the neurofibromin 2 (NF2) gene, which is also called merlin or schwannomin. This is clinically manifested by a long-term oligosymptomatic course and uniform histology that is devoid

received
July 9, 2020
accepted
November 16, 2020
published online
February 15, 2021

DOI https://doi.org/10.1055/s-0040-1722247.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

of atypia and mitosis, respecting the limits of the neuropil. The other two less common types of meningioma are associated with a mosaic of chromosomal losses at 1p, 6q, 10 and 14q, and amplification at 17q23. This results in polymorphic histology: atypia, mitoses, and a more aggressive behavior affecting the neurovascular structures and invasion of nervous tissue.[4,5] Similar to astrocytomas, the malignant forms (grade III) may be primary ('de novo'), when they appear with this phenotype, or secondary, when they result from transformation of a lower histological grade meningioma. Regardless of their origin,

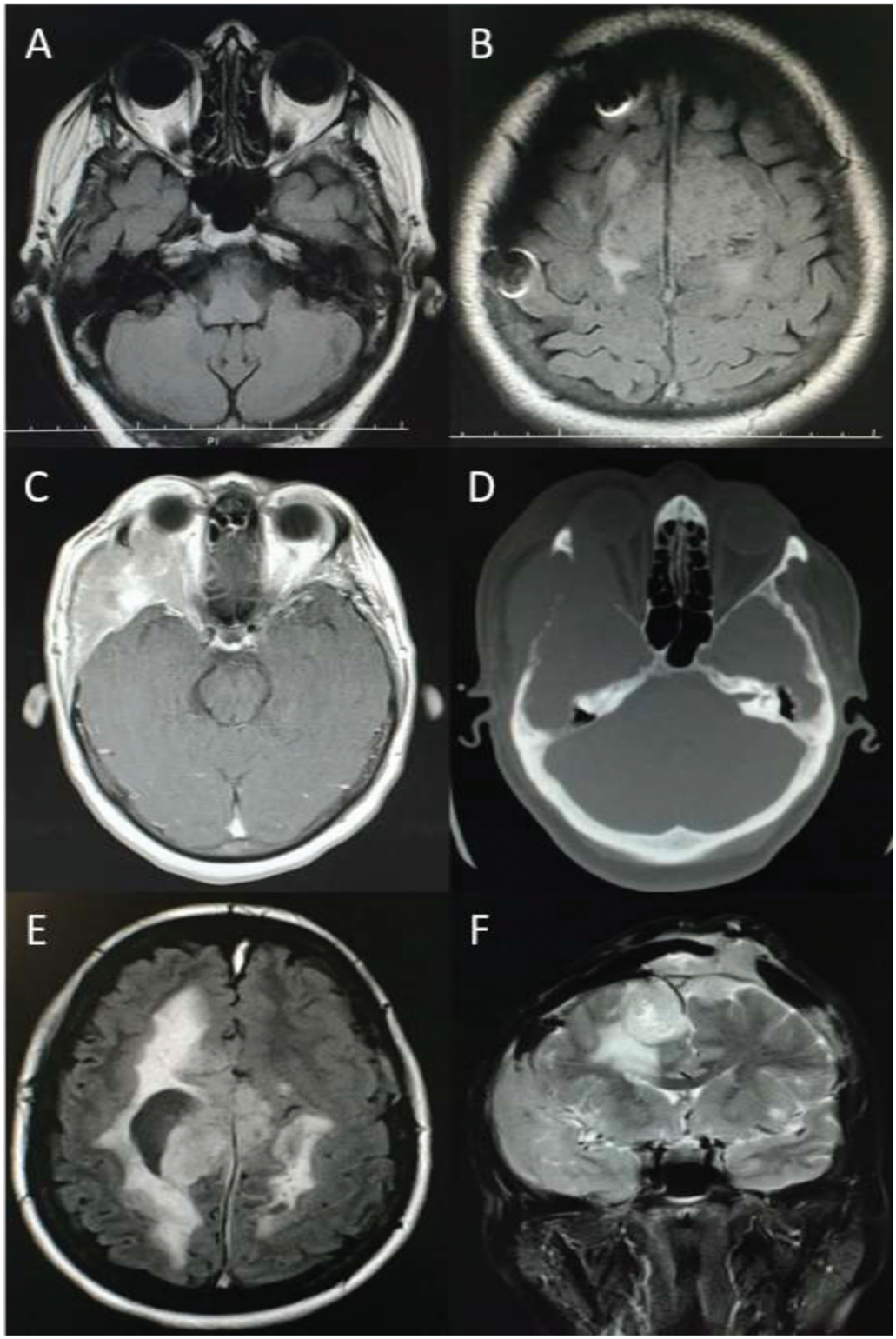

Fig. 1 Magnetic resonance imaging (MRI) scan 8 months after the first surgery (2012) (**A, B**). In 2015, the patient underwent an MRI scan that showed a large orbitotemporal mass (**C**) and a computed tomography (CT) scan of the skull with temporal osteolysis (**D**). Magnetic resonance imaging scan of the skull demonstrating cystic solid neoplasia with edema and sagittal sinus invasion (**E,F**). Radiological findings indicate the malignant transformation that the tumor underwent (**C-F**).

grade-III meningiomas always indicate a very severe disease, with recurrence rates close to 95%, and an average survival limited to 1.5 years.[6,7] This adverse scenario results from the difficulty of performing total exeresis of these tumors due to infiltration of eloquent structures and invasion of neural tissue combined with very high cell proliferation kinetics.[8,9] With regard to the treatment of this class of tumors, surgical resection continues to be the best option in most cases in which the clinical condition and characteristics of the neoplasm enable an operative intervention, followed by adjuvant radiotherapy. To date, there is controversy about the efficacy of chemotherapeutic agents with conflicting results; therefore, this method is not used routinely.[10]

Case Report

JAS, a 56-year-old woman, began to suffer from generalized seizures in 2012, and was diagnosed with an expansive lesion in the bilateral frontal (parasagittal) region, which was larger on the right side. The patient underwent surgical treatment due to the involvement of cortical veins and the partially patent superior sagittal sinus. The only treatment to which the patient was submitted was surgery; she did not undergo any other treatments, such as chemotherapy and/or radiotherapy. Partial resection of the neoplasm (Simpson 3) was chosen, with the histopathology confirming that it was fibroblastic meningioma of WHO grade I. The patient was followed up on a regular basis, periodically underwent magnetic resonance imaging scans, showed apparent residual disease stability, and asymptomatic clinical course until July 2015. At this point, she started complaining of right retroocular pain, accompanied by ophthalmoplegia and low visual acuity on the same side (►**Fig. 1**). In the following weeks, the lesion became apparent under the skin of the right orbital and temporal areas. There was an increase in volume of the frontal region surrounding the previously-operated site, gradual worsening, and episodes of seizures accompanied by sensory alteration. The imaging showed a large expansive lesion occupying the right pterional region, with extensive osteolysis of the temporal bone, zygoma, and orbital wall (►**Fig. 1**). There was also a significant change in the shape and volume of the frontal residual mass, which had multilobulation, signs of invasion of subcutaneous tissue and the superior sagittal sinus, formation of cystic cavity, and perilesional edema. Due to the systemic (Karnofsky 30) and neurological (Glasgow 11) involvement, we chose to perform diagnostic macrobiopsy (Simpson 5). The histopathological analysis confirmed the progression of the initial tumor to a WHO grade-III malignant meningioma with highly positive immunohistochemistry for epithelial membrane antigen (EMA), weakly positive for progesterone receptor, and high proliferative index (K_i-67 expression; 20% to 30%) (►**Fig. 2**). Two weeks after the biopsy, the patient succumbed to the disease.

Discussion

About 90% of the meningiomas diagnosed in the clinical practice correspond to the benign form (WHO grade I). The remaining are atypical meningiomas (WHO grade II), which account for 5% to 7% of the cases, and malignant meningiomas (WHO grade III), which are rare, appearing in less than 3% of patients.[11,12] In prognostic terms, almost 80% of the patients with benign meningiomas survive for 10 years after the diagnosis, while only 40% of people with malignant meningiomas survive the disease for a decade, corresponding to a 5-year mortality rate of 70%.[13,14]

Metastasis is one of the classic signs of aggressiveness and malignancy in a neoplasm,[15,16] so it is logical to expect the tumor to spread almost exclusively in cases of atypical and anaplastic meningiomas. However, there are several reports on the occurrence of metastasis in benign meningiomas (WHO grade I).[17,18] A recent systematic review[19] of distant metastasis of meningiomas published in 2013 identified only 115 cases; 34% of them originated from benign meningiomas, while the remainder were atypical (21%) and malignant (40%) meningiomas, most often appearing almost five years after the first surgery.

It is likely that the intriguing proportion observed among the three groups, in which a surprisingly high number of metastasis from benign meningiomas is noted, may express an analytical or aggregation bias, since most (90%) cases diagnosed in the clinical practice are of WHO grade I on the histological examination. However, considering that this retrospective study[19] included histological criteria prior to the current WHO classification of CNS tumors,[3] in addition to the existence of a somewhat poorly -defined class of benign meningiomas containing atypias,[20] the high number of metastases found in 'benign' meningiomas warns that this complication is not negligible. It occurs more often than expected, leading to the need to reassess the more conservative management in these cases.[21]

In the case presented here, it appears that the metastasis came from the parasagittal tumor, originally a WHO grade-I fibroblastic meningioma, which progressed to malignant transformation, rapidly increasing in volume with the invasion of local structures, particularly cortical veins tributary to the superior sagittal sinus. Since intracranial veins are devoid of valves,[22] it is likely that invasion/occlusion of the superior sagittal sinus caused a reversal in centrifugal venous drainage from the cerebral cortex to the jugular veins. This led to the direction of the blood flow to the venous group through the great anastomotic Trolard vein or even the Labbé vein, a possible way in which metastasis could reach the pterional region from the frontal region.[23]

Unlike the original benign tissue, devoid of atypia or signs of anaplasia, the tumor sample collected from the progression/metastasis stage revealed several signs of atypia, such as increased cell population, prominent nucleoli, cell stratification, and altered nucleus-cytoplasm relationship, with foci of mitosis. Such morphological features were further complemented by immunohistochemistry, which not only confirmed the meningeal nature of the neoplasm (staining the cells strongly by the epithelial membrane antigen, poor progesterone receptor labeling, cytokeratin negativity), but also marked proliferative kinetics expressed by a high proliferative index (K_i-67 expression), quantified between 20% and 30%.[24]

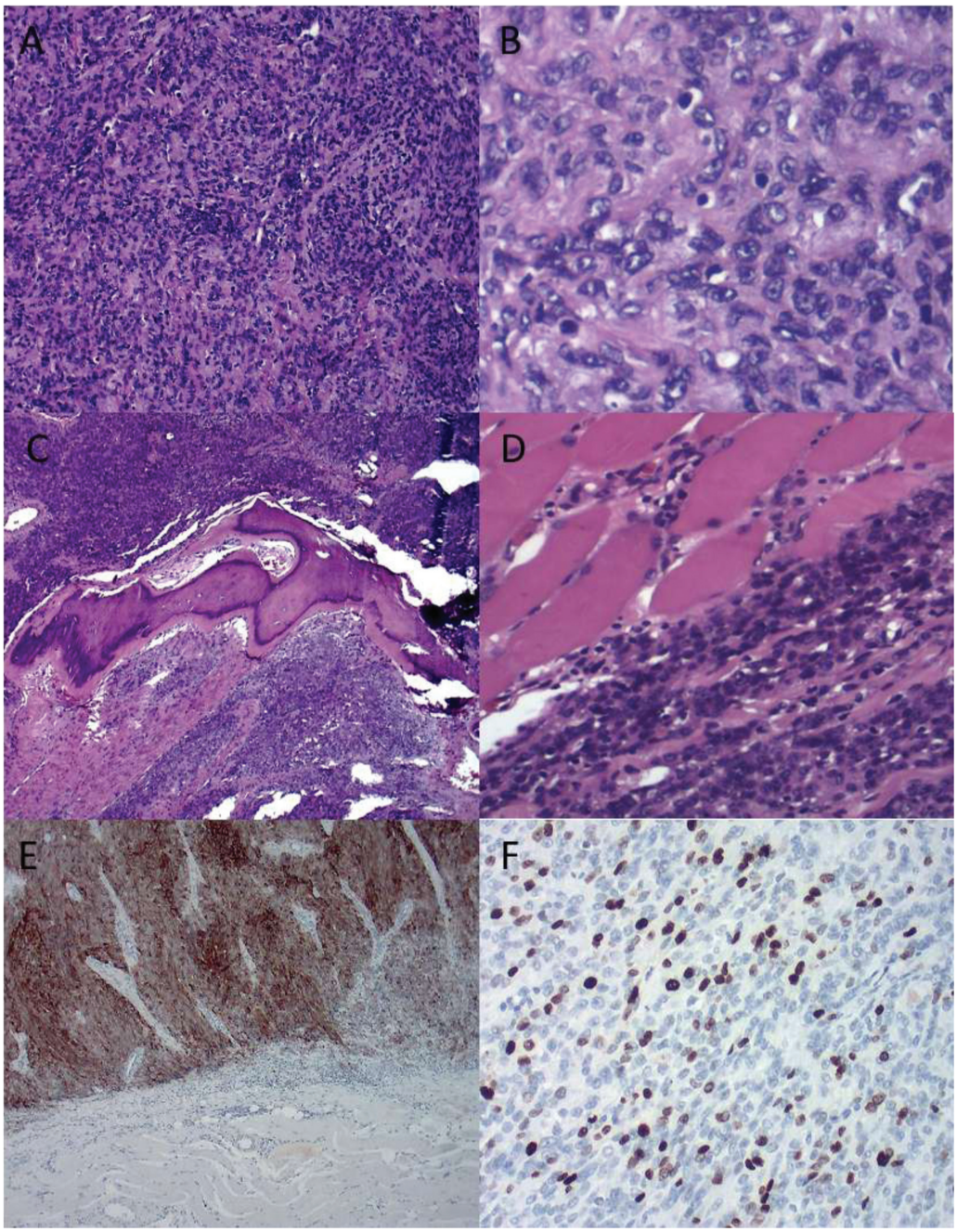

Fig. 2 (**A**,**B**) Cellular polymorphism with atypias and mitoses. (**C**) Bone infiltration. (**D**) Invasion of the temporal muscle. (**E**,**F**) Histopathological examination with positive result for epithelial membrane antigen (EMA) and high K_i-67 (20–30%) expression respectively.

Finally, the transformation of a benign meningioma into a malignant meningioma raises the question of whether this process could be part of the natural history of meningiomas in general; does a grade-I benign form gradually evolve to the grade-III malignant type through an intermediary grade-II atypical stage, as seen in secondary glioblastomas, or does it merely 'jump' directly, from benign to malignant grade III, without any intermediary stage? In any case, perhaps it will be more reasonable to adopt a less conservative approach when facing benign meningiomas.

Conclusion

Metastasis of meningiomas are rarely seen in the neurological practice. When they occur, they represent an additional problem that indicates a poor prognosis that may progress rapidly, as in the case presented here, to an advanced and fatal disease. The evolution from a typical or atypical meningioma to a malignant meningioma is an important aspect of the report herein presented, as it warns of this possibility in the natural history of the disease. This suggests that some of these low-grade lesions are

only an evolutionary stage, and that by mechanisms not yet fully understood they may develop malignancy. The possibility of malignancy of benign meningiomas confirms the general idea that the surgical treatment should aim, whenever possible, for the complete removal of all meningeal tumor with safety margins, as provided in Grade I of the Simpson classification.[25]

Conflict of Interests

The authors have no conflict of interests to declare.

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Non-fatal Bihemispheric Penetrating Brain Injury from a Crossbow Arrow with Good Clinical Outcome: Case Report

Lesão cerebral penetrante bi-hemisférica não fatal por flecha de besta com bom desfecho clínico: Relato de caso

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Arq Bras Neurocir 2021;40(2):e179–e182.

Abstract

Crossbow injuries to the head have seldom been reported in the literature, and they represent a unique type of penetrating brain injury (PBI) in which a low-velocity arrow results in an intracranial fragment larger than most high-velocity projectiles, usually with a lethal outcome. We present the case of a 34-year-old man who attempted suicide with a self-inflicted cranial injury from a crossbow arrow, with a right parietal point of entry and a palpable subcutaneous tip in the left parietal region. The emergency team reported a Glasgow coma scale (GCS) score of 15, and the patient was brought sedated and intubated. Computed tomography (CT) imaging scans showed that the arrow crossed both parietal lobes, with mild subarachnoid hemorrhage and small cerebral contusions adjacent to its intracranial path. Careful retrograde removal of the penetrating arrow was performed in the CT suite, followed by an immediate CT scan, which excluded procedure-related complications. The patient woke up easily and was discharged 3 days later with mild left hand apraxia and no other neurologic deficits. To the best of our knowledge, there are no similar case reports describing both good clinical outcome and rapid discharge after a bihemispheric PBI. Individualizing the management of each patient is therefore crucial to achieve the best possible outcome as PBI cases still represent a major challenge to practicing neurosurgeons worldwide.

Keywords
- Craniocerebral Trauma
- penetrating brain injury
- foreign bodies
- posttraumatic subarachnoid hemorrhage

Resumo

As lesões cranianas causadas por bestas raramente foram relatadas na literatura, e representam um tipo único de lesão cerebral penetrante (LCP), na qual uma flecha de baixa velocidade resulta em um fragmento intracraniano maior do que a maioria dos projéteis de alta velocidade, geralmente com um resultado letal. Apresentamos o caso de um homem de 34 anos que tentou suicídio com lesão craniana autoinfligida por uma

received
May 11, 2020
accepted
September 4, 2020
published online
February 15, 2021

DOI https://doi.org/10.1055/s-0040-1719008.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

flecha de besta, com um ponto de entrada parietal direito e uma ponta subcutânea palpável na região parietal esquerda. A equipe de emergência relatou uma pontuação na escala de coma de Glasgow (ECG) de 15, e o paciente foi levado sedado e intubado. A tomografia computorizada (TC) mostrou que a seta cruzava ambos os lobos parietais, com ligeira hemorragia subaracnoideia e pequenas contusões cerebrais adjacentes ao seu trajeto intracraniano. Foi realizada remoção retrógrada cuidadosa da flecha penetrante na sala de TC, seguida de TC imediata, que excluiu complicações relacionadas ao procedimento. O paciente acordou facilmente e recebeu alta 3 dias depois com apraxia leve da mão esquerda e sem outros défices neurológicos. Do que sabemos, não há relatos de casos semelhantes que descrevam bom resultado clínico e alta rápida após LCP bihemisférica. Individualizar o tratamento de cada paciente é, portanto, crucial para alcançar o melhor resultado possível, pois os casos de LCP ainda representam um grande desafio para neurocirurgiões praticantes em todo o mundo.

Palavras-chave
- trauma craniocerebral
- lesão encefálica penetrante
- corpos estranhos
- hemorragia subaracnoideia pós-traumática

Introduction

Penetrating brain injury (PBI) refers to a type of traumatic brain injury in which a foreign object penetrates the skull and injures the brain. It is less common than blunt head trauma, accounting for only 10% of all head injuries, although its consequences are generally worse.[1,2]

Most cases of PBI are caused by gunshot bullets. Knives, arrows, spears, rocks, screwdrivers, chopsticks and other sharp objects have also been reported.[1]

Crossbow injuries represent a unique type of PBI in which a low-velocity foreign body (arrow) results in an intracranial fragment larger than high-velocity gunshot bullets.[3] There are very few reports in the literature regarding this type of PBI, each one requiring singular assessment and management.

The present report describes the rare case of a non-fatal self-inflicted head injury from a crossbow arrow which penetrated both parietal lobes, resulting in mild neurologic impairment after the successful removal of the arrow.

Case Report

A 34 year-old Portuguese man with a history of major depression attempted suicide with a self-inflicted head injury from a crossbow arrow.

The emergency team was called and reported the presence of a PBI from a crossbow arrow with a right parietal point of entry. The tip of the arrow was palpable right under the skin of the left parietal region, with no exit wound. A Glasgow coma scale (GCS) score of 15 was reported, and the patient only complained of right upper limb paresthesia, with no evidence of hemorrhage on the spot. Sedation, endotracheal intubation and connection to a ventilatory prosthesis were performed, and the patient was transferred to the emergency department of our hospital.

In the emergency department, continuous infusion of propofol was started, and a full laboratory work-up was performed, showing mild normocytic anemia (hemoglobin 12,6 mg/dl), neutrophilic leukocytosis (12×10^9/L leukocytes with 89% of neutrophils) and elevated C-reactive protein (3,2 mg/dl), with no sign of drug intoxication or coagulation-related disorders. The chest radiography and the electrocardiogram were also normal. The patient was taken to the computed tomography (CT) suite, (►**Fig. 1a**) and underwent a CT imaging scan of the brain, which documented sulcal subarachnoid hemorrhage (SAH), mainly on the left parieto-occipital region, as well as cerebral contusions along the intracranial path of the crossbow arrow (►**Fig. 1b**). Bone-window imaging assessment confirmed the aforementioned path of the arrow (►**Fig. 1c**), and a three-dimensional (3D) reconstruction of the skull surprisingly showed three calvarial defects in the right parietal region confirming three different suicide attempts, of which only one represented a PBI (►**Fig. 1d**).

Given the long intracranial course of the object, involving multiple brain compartments, we preferred to remove the penetrating arrow in the CT suite, as it would be possible to immediately locate any possible source of hemorrhage during the procedure. The arrow was therefore removed manually along the respective penetrating route. A new CT scan of the brain showed no evidence of procedure-related complications.

The patient was subsequently transferred to the intensive care unit. After propofol withdrawal and extubation, the patient woke up easily, with mild left-hand apraxia and no other neurologic deficits. Antibiotic prophylaxis with intravenous amoxicillin-clavulanate was introduced due to the increased risk of infection. A control CT scan was performed the day following the removal of the crossbow arrow, demonstrating the expected decrease in attenuation of the aforementioned hemorrhagic lesions, with slight increase in the area of the surrounding edema (►**Fig. 2a**).

Finally, the patient was transferred to the Department of Neurosurgery. After a final clinical assessment, he was discharged and remained under follow-up appointments. A control CT scan performed three weeks later showed complete resolution of the sulcal SAH and cerebral contusions (►**Fig. 2b**).

Discussion

Crossbow injuries to the head have rarely been reported in the literature, and most of them had a fatal outcome and happened in developing countries as a result of robberies,

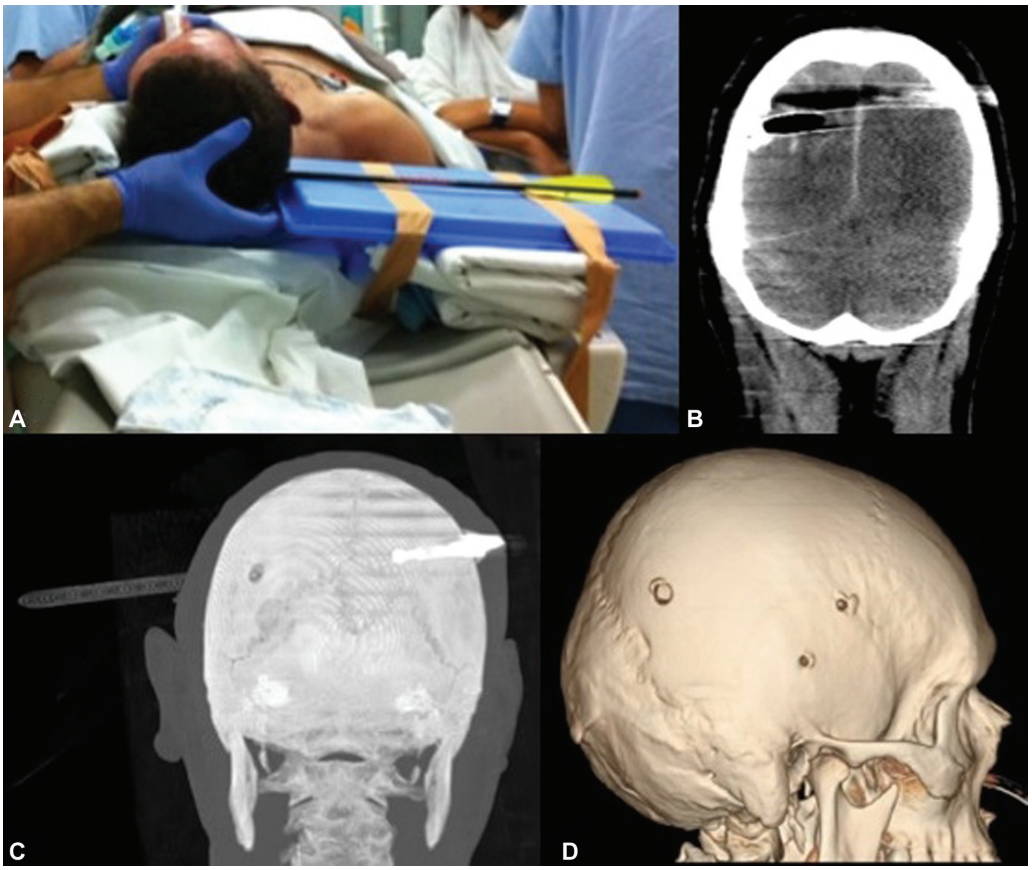

Fig. 1 (**A**) Photograph of the patient in the CT suite with the crossbow arrow entering the right parietal calvaria. (**B**) The CT imaging scan showing mild sulcal SAH and cerebral contusions along the intracranial path of the arrow, with multiple artifacts from metallic hardware. (**C**) Bone window CT scan demonstrating a subcutaneous arrow tip in the left parietal region. (**D**) 3D reconstruction of the skull showing three calvarial defects in the right parietal region, confirming a total of three suicide attempts.

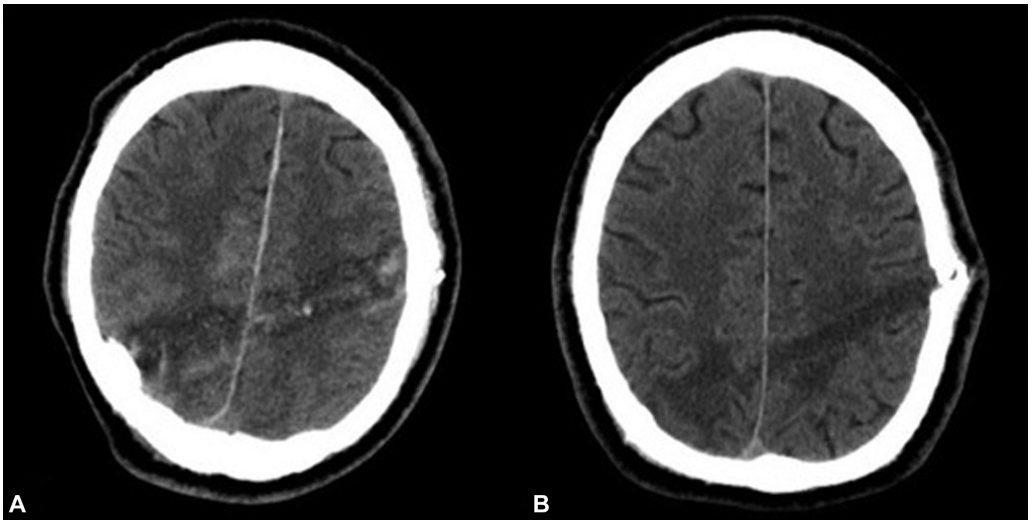

Fig. 2 (**A**) Control CT scan performed the day following the removal of the crossbow arrow, demonstrating the expected decrease in attenuation of the sulcal SAH and cerebral contusions, with a slight increase in the area of the surrounding edema. (**B**) Control CT scan performed 3 weeks later, showing complete resolution of the aforementioned hemorrhagic lesions.

communal clashes, disputes between farmers and cattle herdsmen, and cattle theft.[4]

Despite having a relative low-velocity (as fast as 58 m/sec) compared with firearm projectiles, the sharpness and propulsion force of the crossbow may be enough to enable penetrating injuries of the skull at short range.[5] In these cases, the consequences of the PBI depend on multiple factors, including the size of the penetrating object, the energy and speed of entry, the intracranial path, changes in intracranial pressure, and associated injuries.[1,6] Since the tip of the arrow and its shaft have the same diameter, the injury is generally limited to the tissues directly crossed by the blade, and may be non-fatal.[1,5]

In the case herein reported, the crossbow arrow penetrated the right parietal calvaria and crossed both parietal lobes, with a palpable subcutaneous tip in the left parietal region. Given the absence of neurologic deficits at the initial assessment, the intracranial path of the arrow and the report of mild sulcal SAH and small cerebral contusions adjacent to its shaft on CT imaging, we regarded the possibility of major vessel damage as less likely to have occurred. Nonetheless, the rate of vascular complications after TBIs can range from 5% to 40%, and it mostly corresponds to traumatic aneurysms, arteriovenous fistulas, SAH, vasospasm and venous thrombosis. Special attention must be payed to traumatic aneurysms, which may present in a delayed fashion (typically two to three weeks after the injury). Therefore, follow-up CT-angiography and digital subtraction angiography should be performed at least four weeks after the incident.[7]

The management strategy of the intracranial foreign body was another major challenge. First, most case reports of cranial crossbow and other low-velocity injuries describe removal in the operating room, enabling hemostasis, debridement of necrotic tissues, and closure.[3] Given the long intracranial trajectory of the arrow, and since vascular injury is sometimes only revealed with the removal of the foreign body, we decided to remove retrogradely the arrow in the CT suite, as it would enable the prompt recognition of a possible source of hemorrhage. In addition, the patient presented with a small skin injury with healthy edges, with no need for wound debridement. Kulwin et al.[3] suggest that the removal of arrows and similar low-velocity large penetrating projectiles should occur in a radiologic setting due to increased patient safety and optimized healthcare costs. Nevertheless, the operating room was put on notice for possible emergency surgery in case of severe procedure-related hemorrhage. Secondly, most case reports describe anterograde removal of the penetrating arrow to avoid further damage from the razor-sharp blades.[1] Considering that no exit wound was found, we performed a careful retrograde removal followed by immediate CT imaging scans to exclude procedure-related damages.

Infectious complications of arrow-induced cranial injuries are not uncommon (occurring in as many as 15% of all PBI cases), and include meningitis, ventriculitis and cerebral abscess due to contaminated foreign objects, skin, hair and bone fragments. *Staphylococcus aureus* is the most frequently reported infectious agent, although gram-negative bacteria may also be implicated.[6] Prophylactic parenteral broad-spectrum antibiotics should be administered as soon as possible in all PBI cases. Based on this principle, we started intravenous amoxicillin-clavulanate, and no infectious complications were registered.

Cerebrospinal fluid (CSF) leaks may also develop in PBI patients due to possible dural tears; CSF leaks can present through the entry or exit sites of the penetrating object, as well as through the ear or nose when mastoid air cells or paranasal sinuses have been violated respectively. Temporary CSF diversion through a ventricular catheter or lumbar drain is generally performed when CSF leaks do not stop spontaneously. Surgical correction (either by direct closure of dural defects, or by using grafting materials) is recommended for refractory cases.[8]

Finally, 30% to 50% of PBI patients develop posttraumatic epilepsy, mainly because of cerebral scarring. In $\sim$ 10% of the cases, seizures will develop within the first 7 days after the trauma, and in 80%, during the first 2 years.[6] Aarabi et al.[9] reported significant differences in late-onset epilepsy in PBI patients according to the admission GCS score. Since our patient was admitted with a GCS score of 15, no antiseizure drugs were introduced.

Conclusion

Crossbow injuries to the skull are rare and usually have a fatal outcome.[5] Our case report is unique, as the patient survived a total of three suicide attempts from a self-inflicted crossbow, one of which crossed both cerebral hemispheres. Furthermore, the patient was discharged three days after the trauma, with mild left hand apraxia and no other neurologic deficits. To the best of our knowledge, there are no other case reports describing simultaneously a good clinical outcome and rapid discharge after a bihemispheric PBI.

We also described our experience with the removal of the penetrating arrow in the CT suite, discussed its advantages, and reviewed some of the most frequent complications of PBI.

Our case report reinforces the need to individualize the management of each PBI patient to achieve the best possible outcome. Further research in trauma is needed, as PBI cases still represent a significant challenge to neurosurgeons worldwide.

Conflict of Interests

The authors have no conflict of interests to declare.

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Intradural Spinal Arachnoid Cyst in a Pediatric Patient: A Case Report

Cisto aracnoide espinhal intradural em paciente pediátrico: um relato de caso

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Arq Bras Neurocir 2021;40(2):e183–e185.

Abstract

The present case reports a 13-year-old patient with an intradural arachnoid cyst, which manifested itself with a sudden loss of strength and sensitivity in the lower and upper limbs and a severe pain in the cervical and thoracic region. On examination, a lesion displayed as an intradural hematoma; however, a laminotomy was performed and it was realized that the lesion was an arachnoid spinal cyst of the cervical-dorsal spine.

Keywords
- arachnoid cyst
- laminotomy
- spine
- pediatrics

Resumo

O presente trabalho relata o caso de um paciente de 13 anos que apresentou um cisto aracnoide intradural espinhal, que se manifestou com uma perda súbita de força e sensibilidade nos membros inferiores e superiores, bem como uma forte dor nas regiões cervical e torácica. Ao exame, a lesão apresentou-se como um hematoma intradural; todavia, ao ser realizada a laminectomia, tratava-se de um cisto aracnoide espinhal da coluna vertebral cérvico-dorsal à direita.

Palavras-chaves
- cisto aracnoide
- laminectomia
- coluna vertebral
- pediatria

Introduction

Spinal arachnoid cysts are uncommon, and intradural cysts are even less common, although the pediatric population is more likely to have an intradural cyst compared with the general population.[1–3] The intradural cyst consists of an arachnoid bag filled with cerebrospinal fluid, which consists in a benign lesion that is entirely in the dural space.[4,5] The course of the spinal arachnoid cyst is not fully understood, and many authors create theories to explain the pathophysiology.[3]

received
August 6, 2020
accepted
November 17, 2020
published online
January 18, 2021

DOI https://doi.org/10.1055/s-0040-1722241.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

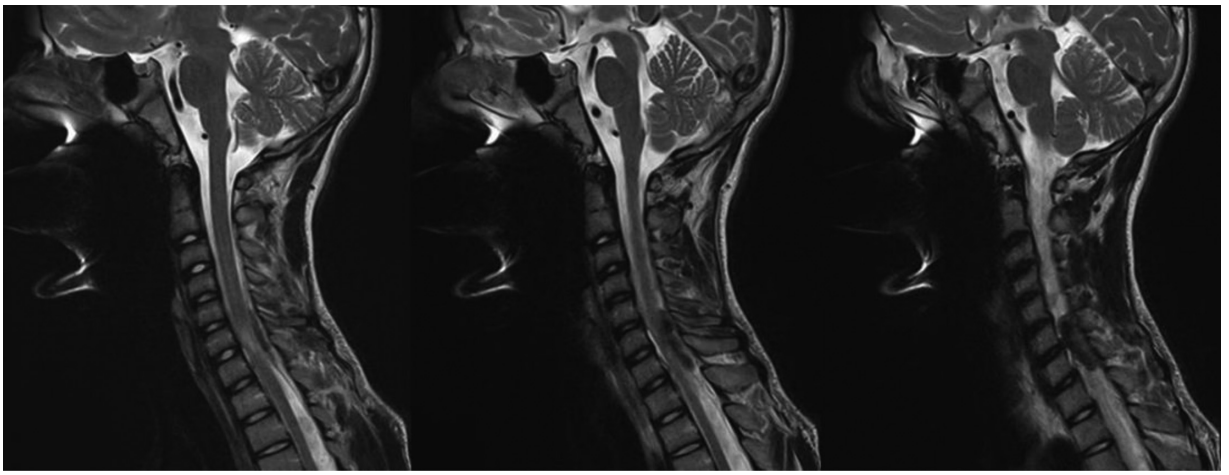

Fig. 1 Sagittal T2 section shows a lesion in high signal intensity at the right posterolateral level of C6 to D1.

During the first two decades of the patient's life, age and gender do not play an important role in the incidence of the cyst.[1] However, most of the reported cases are single cysts and occur commonly at the level of the thoracic spinal cord, located more often dorsally to the neural elements.[4,6–8]

Case Report

A 13-year-old male patient arrived at the emergency care unit complaining of sudden back pain in the cervical and thoracic region. At nightfall on the same day, the patient developed severe pain and progressive loss of strength in the legs, resulting in difficulty in walking, followed by loss of sensation, initially in the right lower limb and then in the left lower limb. He was medicated with intravenous symptomatic drugs, however he continued without any improvement in pain. After the patient was forwarded to the hospital, the computed tomography (CT) scan of the cervical and thoracic spine suggested that he had an injury at the C5-C6level, with a slightly increased density in the vertebral canal. On physical examination, he had hemiplegia in his right lower limb and weak movement in his left lower limb, with an asymmetric degree of strength (worse on the right). He also had a tingling sensation and decreased bilateral tactile and thermoalgesic sensitivity down to the level of the nipples, strength grade 3 on the right upper limb and grade 2 on the left upper limb. Trauma, as well as similar episodes and symptoms, were denied previously. The patient did not use continuous medications, had never undergone surgery or previous hospitalizations. After performing cervical and dorsal spine magnetic resonance imaging (MRI) (►**Fig. 1**) with weighted sequences in T1 and T2 in the axial and sagittal planes, an expansive lesion was observed in the right posterolateral portion of the spinal canal in an epidural situation, in the C6, C7 and D1 segment, measuring $\sim 3.2 \times 1.3$ cm (largest craniocaudal diameter), hyposignal in the T2-weighted sequence and slightly in hypersignal in T1, compatible with the diagnostic hypothesis of hematoma. This injury had a compressive effect, with alteration in the signal intensity of the adjacent spinal cord (edema). The laminotomy procedure of the C7-D2 segment was performed (►**Fig. 2**), and when entering the arachnoid membrane there

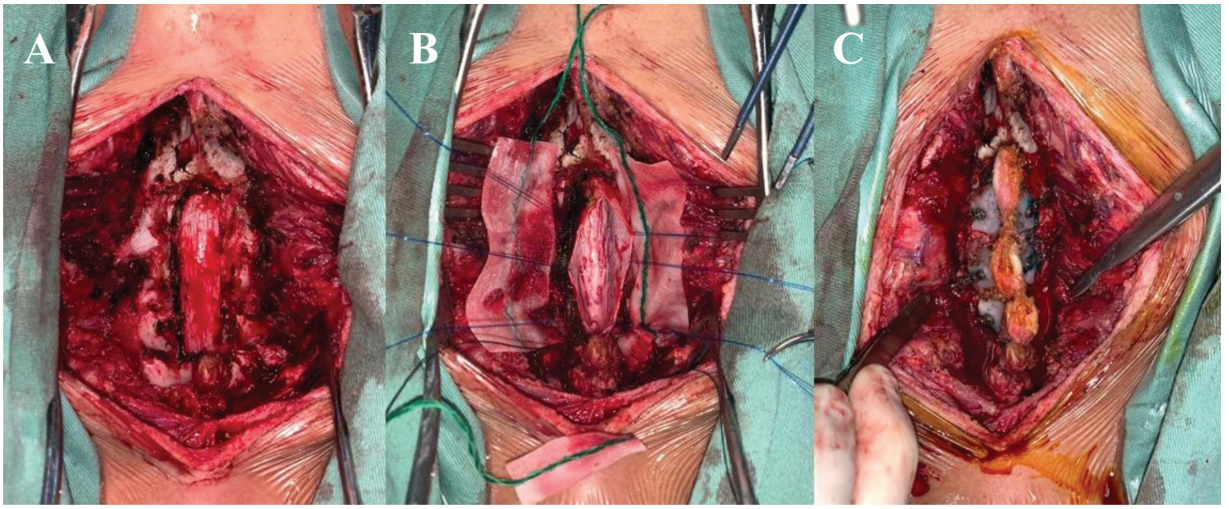

Fig. 2 (A) Bulging of dural bag at C5-D1. (B). Exposure of the spinal cord with the rightmost arachnoid space, after communication and resection of the cyst. C. Final design after laminotomy with microplates at C5-D1.

was a large spillage of cerebrospinal fluid under high pressure. It was observed that the lesions consisted of a cystic intradural arachnoid lesion and the resection was performed. The anatomopathological result indicated a tiny fragment of connective tissue, apparently derived from the arachnoid, in continuity with some red blood cells. In the postsurgical period, the patient continually improved the pain, the strength and the sensitivity.

Discussion

Arachnoid cysts are often attributed to congenital defects, therefore being defined as the main origin by the authors.[1,5,9] Although their etiology is inconsistent, it is believed that some of these cysts are derived from trauma, hemorrhage, anesthetic procedures and secondary to inflammation, such as meningitis and aranoiditis.[10] Despite these cysts being frequently asymptomatic, they eventually are able to produce symptoms when they compress the spinal cord and/or nerve roots, both suddenly and in a progressive manner.[8] They are able to cause pain, weakness, sensory changes, and gait disorders.[11] Large cysts located in the lumbar spine can also lead to loss of bladder and/or intestine control and cramps.[4]

In cases of symptomatic injuries, surgical treatment must occur and is usually performed by simple fenestration or limited laminotomy. The purpose of surgery is neural decompression and prevention of cyst replenishment. Therefore, the cyst is completely dried out and the communication with the arachnoid space is closed, repairing the dural failure.[11–13] If left untreated, spinal cysts would cause permanent severe neurological damage. In the case of asymptomatic individuals, is indicated the constant monitoring of the cyst.

Neurological deficits from arachnoid cysts are treatable. Surgical intervention shows excellent postoperative results. Most patients present complete or significant recovery, and many remain stable, even when symptoms have been present for a long time.[1,14,15]

About the negative findings from this pathology, the most invasive opening in repeated laminectomies is related to complications such as kyphoscoliosis.[2] The patient may also develop syringomyelia and slow progressive myelopathy.[6,8,11]

Conclusion

Arachnoid cysts of the spine are lesions of uncertain etiology and may not have the characteristics of a cerebrospinal fluid sign on MRI and simulate other pathologies. What is clearly known is that cysts that cause compression of the spinal cord and surrounding nerves cause significant neurological deficits in the patient. Therefore, it is essential to perform a surgical procedure as soon as possible to obtain the best possible result for the condition, which is complete neurological recovery.

Conflict of Interests

The authors have no conflict of interests to declare.

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Pleomorphic Xanthoastrocytoma with Oligodendroglioma-Like Areas with Negative 1p19q Co-Deletion

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Arq Bras Neurocir 2021;40(2):e186–e189.

Abstract

The most common mixed glioma encountered in routine surgical practice is oligoastrocytoma (OA); however, its is currently considered a vanishing entity. The 2016 classification of the World Health Organization (WHO) discourages the diagnosis of tumors as mixed glioma. The recommendations are that diffuse gliomas, including those with mixed or ambiguous histological features, should be subjected to molecular testing. Dual-genotype OAs are not yet a distinct entity or variant in the classification. We report a case of mixed glioma: a pleomorphic xanthoastrocytoma (PXA) mixed with an oligodendroglioma. The immunohistochemistry (IHC) pattern of isocitrate dehydrogenase 1 (IDH1) negativity with retained nuclear expression of the alpha-thalassemia x-linked intellectual disability syndrome (ATRX) protein, and 1p19q co-deletion negativity in both the components enabled its identification as a mixed glioma rather than a collision tumor. To the best of our knowledge, the case herein presented is the fourth case of PXA with oligodendroglioma. Out of the other three reported cases, only one was of a collision tumor with a dual genotype, and the other two showed similar molecular signatures in both components. The present article discusses the histological, immunohistochemical and molecular features of the aforementioned case.

Keywords
- pleomorphic xanthoastrocytoma
- mixed glioma
- composite glioma
- oligodendroglioma
- 1p19q

Introduction

Pleomorphic xanthoastrocytoma (PXA) is uncommon, and it represents less than 1% of all brain tumors.[1] Tumors have heterogeneous histological appearance, including spindle cells, lipidized cells, giant cells, eosinophilic granular bodies, and perivascular lymphocytes. The variant forms in which PXA exhibits a mixed histologic pattern have been described, and they include ganglioglioma (GG), dysembryoplastic neuroepithelial tumor (DNET), oligodendroglioma, diffuse astrocytoma (DA), and epithelioid glioneuronal tumor (EGT).[2–8] Perry et al.[4] were the first to describe an oligodendroglioma with PXA, in which the oligodendroglioma component comprised 90% of the tumor, but 1p19q co-deletion was negative. They concluded that PXA represented the astrocytic component of oligoastrocytoma (OA). After a decade, Hattab et al.[5] described a collision tumor with genetically distinct areas of PXA and oligodendroglioma. Murakami et al.[6] reported a case of oligodendroglioma with a PXA-like microlesion with similar molecular signature. The case herein presented is the fourth case of composite PXA and oligodendroglioma with negativity of 1p19q co-deletion in both components.

received
August 13, 2020
accepted
November 16, 2020
published online
January 18, 2021

DOI https://doi.org/10.1055/s-0040-1722245.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Case History

A 31-year-old man presented with a 15-year history of seizures. The frequency of the seizures was of ~ 6 to 7 episodes a month, which were followed by loss of consciousness and right-hand automatism. He was on antiepileptic medications. A contrast-enhanced magnetic resonance inaging (MRI) scan of the brain revealed an intra-axial multi-loculated subcortical solid cystic mass lesion in the right temporal lobe with expansion of the temporal lobe and effacement of the adjacent sulci. The solid portion of the lesion was iso-hypointense on T1, slightly hyperintense on T2, and showed enhancement on post contrast. Internal blooming areas were observed within the lesion. The cystic component was hypointense on T1 and hyperintense on T2 and on fluid-attenuated inversion recovery (FLAIR images). A midline shift of 4 mm toward the left side was observed. The findings were suggestive of a low-grade glioma – LGG/PXA. The patient underwent right temporal craniotomy and decompression of the mass.

A biopsy of superficial and deep tissues was performed. Sections of the deep-tissue biopsy showed two different and intermingled morphologies. There were nodules of round monomorphic cells (oligodendroglial areas) mixed with other lesions, showing spindle to lipidized cells, with highly pleomorphic cells, including binucleated and multinucleated cells and perivascular lymphocytic infiltrate (PXA). No mitosis or necrosis were observed (►**Fig. 1a**). The superficial-tissue biopsy showed a mainly normal brain parenchyma with a tiny focus of tumor with round monomorphic cells with clear

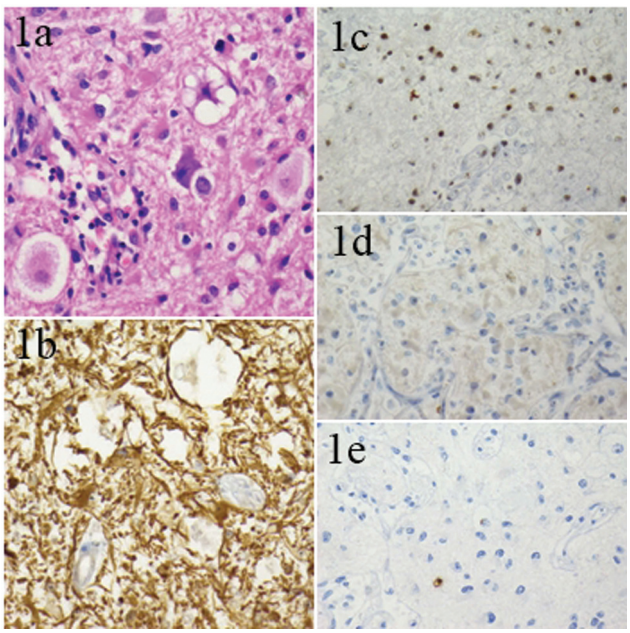

Fig. 1 Pleomorphic xanthoastrocytoma (PXA) with spindle to lipidized and highly pleomorphic cells, eosinophilic granular bodies, and perivascular lymphocytic infiltrate (**a**); strongly positive glial fibrillary acidic protein (GFAP) (**b**); retained nuclear expression of the alpha-thalassemia x-linked intellectual disability syndrome ATRX protein (**c**); no expression of isocitrate dehydrogenase 1 (IDH1) (**D**); the MIB E3 ubiquitin protein ligase 1 (MIB-1) labeling index is < 1% (**E**); a: hematoxylin and eosin (H&E); b: GFAP; c: ATRX; d: IDH1; e: Ki67. Original magnification (a-e): 40 X.

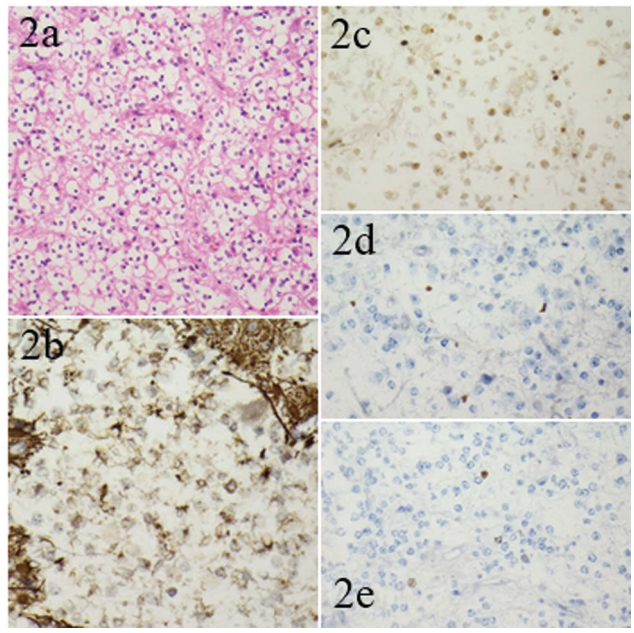

Fig. 2 Oligodendroglial areas with round monomorphic cells with clear cytoplasm arranged in a honeycomb pattern (**a**); GFAP negative (**b**); retained nuclear expression of ATRX (**c**); no expression of IDH1 (**d**); the MIB-1 labeling index is < 1% (**e**); a: H&E; b: GFAP; c: ATRX; d: IDH1; e: Ki67. Original magnification (b-e): 40 X; a: 20X.

cytoplasm arranged in a honeycomb pattern (►**Fig. 2a**). A delicate chicken-wire network of branching capillaries was noted. No mitosis, necrosis, or endothelial proliferation were observed. The glial fibrillary acidic protein (GFAP) (GA-5) was positive in the PXA component, but negative in the oligodendroglial component (►**Fig. 1b**&**2b**). The alpha-thalassemia x-linked intellectual disability syndrome ATRX (BSB-108) protein was retained in both components (►**Fig. 1c**&**2c**). The level of p53 (DO7) was of 2% in both the components, and isocitrate dehydrogenase 1 (IDH-1) (H09) was negative in both components (►**Fig. 1d**&**2d**). The level of KI-67 (SP6) was of 1% in both the components (►**Fig. 1e**&**2e**), and synaptophysin (Snp88) and CD34 (QBEnd/10) were positive in the PXA component. Co-deletion of 1p19q (by dual-color fluorescence in situ hybridization [FISH] using Vysis LSI 1p36/1q25 and 19q13/19p13) was performed, and it was negative in both components. The features were compatible with mixed glioma (PXA with oligodendroglioma- like areas, World Health Organization [WHO] grade II). As residual disease was observed on the postoperative scan, the patient was advised to undergo radiotherapy (RT).

Discussion

The PXA is an astrocytic tumor thought to originate from subpial astrocytes or their precursors. First described in 1973, it was only formally incorporated in the WHO classification in 1993, and it frequently occurs within the first 3 decades of life with the symptom of seizures. Most of these tumors are located in the superficial cerebral cortex, commonly in the temporal and parietal lobes, and present as a complex cystic lesion with associated mural nodules. Isocitrate dehydrogenase mutation

is usually absent, and ATRX expression is retained. Over 2/3 of these have B-Raf proto-oncogene, serine/threonine kinase (BRAF) mutations.[8] The rate of mutations in p53 is of up to 25%. Complete surgical resection and radiotherapy (RT) are the components of the standard care in cases of PXA. This treatment has a good prognosis, with a recurrence-free survival rate of 70.9% at 5 years. Oligodendroglioma originates from oligodendrocytes or from glial precursor cells. However, the dominance of the oncogenic signaling over the cell of origin determines the of the gliomaphenotype.[1] Oligodendrogliomas most commonly occur in the frontal lobe, with a peak incidence in fifth and sixth decades of life. These are diffusely infiltrating gliomas with IDH1 or IDH2 mutation, 1p19q co-deletion, and telomerase reverse transcriptase (TERT) promoter mutation. Mutations in the ATRX or tumor protein p53 (TP53) are not observed. The GFAP labels minigemistocytes and gliofibrillary oligodendrocytes, whereas the classic oligodendroglioma cells exhibit minimal or negative GFAP expression. The 5-year survival rate approaches 79.5%. Although less aggressive, oligodendrogliomas remain incurable, despite the treatment with RT and chemotherapy.

The histopathological diagnosis of mixed/composite glioma is based on the presence of two morphologically distinct glial tumors either diffusely mixed or separated, although the latter is rare.[5] If these components are genetically distinct, they are termed collision tumors. The 4 commonly used molecular parameters to categorize diffuse gliomas are absence/presence of IDH mutations, 1p/19q co-deletion, TP53 mutation and ATRX loss. Sahm et al.[9] re-evaluated 43 cases of OA using these 4 paramaters, and reclassified 31 as typical oligodendrogliomas and 11 as DA. Only 1 case had partial 1p19q loss, with IDH1 mutation, ATRX loss, and p53 expression.[9]

Four cases of composite PXA/oligodendroglioma have been reported in the literature, and are summarized in ►**Table 1**. The ages of the partients ranged from 18 to 48 years. Two of the tumors were located in the temporal lobe, and the other two, in the parieto-occipital and frontal lobes. The case herein presented is similar to the case described by Perry et al.[4] because both were 1p19q co-deletion negative favoring that oligodendroglial component may be arising from PXA; however in the case reported by Perry et al.,[4] PXA the formed a minor component, and in the case reported here it was a predominant component. Moreover, the negative expression of IDH1 in the oligodendroglial component suggests that it may arising from the PXA. The case described by Murakami et al.[6] had oligodendroglioma as the predominant component with its classical molecular signature, suggesting that the PXA-like microlesion arose from the oligodendroglioma.

Yamada et al.[7] described a case of combined PXA/infiltrating astrocytoma in which both components showed IDH R132H mutation, but BRAF V600E mutation was only observed in the PXA component and concluded it as intratumoral heterogeneity and clonal evolution. Dual-genotype OAs are also assumed to arise from an IDH-mutant cell of origin, which later, during tumorigenesis develops morphologically distinct subpopulations of tumor cells with astrocytic and oligodendroglial genotypes.[1] Aisner et al.[8]

Table 1 Comparison of reported cases of composite pleomorphic xanthoastrocytoma/oligodendroglioma

Case reports	Age/ Gender	Clinical features	Location	Predominant component/ WHO Grade	Immunohistochemistry			Molecular studies					Terminology
					p53	IDH1	ATRX	1p19q	IDH1	BRAF	p53	EGFR	TERT	
Perry et al., 2001[4]	18/F	Headache, visual disturbance	Parieto-occipital	Oligodendroglioma (90%)/Grade II	NA	NA	NA	N	NA	NA	NA	NA	NA	PXA represents the astrocytic component of OA
					Both components			Both components						
Hattab et al., 2011[5]	25/F	Headache	Left temporal	PXA (80%)/Grade III	< 10%	NA	NA	N = PXA; P = oligodendroglioma	NA	NA	N	N	NA	Collision tumor
Murakami et al, 2020[6]	48/M	Seizures	Left frontal	Oligodendroglioma (> 90%)/Grade II	< 10%	P	R	P	P	N	NA	NA	P	Monoclonal origin, PXA microlesion arising from oligodendroglioma
					Both components			Both components						
Present case	31/M	Seizures	Right temporal	PXA (70%)/Grade II	2%	N	R	N	NA	NA	NA	NA	NA	Monoclonal origin, oligodendroglioma-like areas arising from PXA?
					Both components			Both components						

Abbreviations: ATRX, alpha-thalassemia x-linked intellectual disability syndrome; BRAF, B-Raf proto-oncogene, serine/threonine kinase; EGFR, epidermal growth factor receptor; IDH, isocitrate dehydrogenase; F, female; M, male; N, negative; NA, not available; OA, oligoastrocytoma; P, positive; PXA, pleomorphic xanthoastrocytoma; R, retained; TERT, telomerase reverse transcriptase; WHO, World Health Organization.

described three cases of composite pleomorphic xanthoastrocytoma-epithelioid glioneuronal tumor (PXA-EGT) and found BRAF mutation in both components, which suggests a common origin.

To conclude, the histogenesis of combined PXA and oligodendroglioma is unknown. All composite gliomas should be subjected to molecular studies in order to enhance our understanding about their tumorigenesis. The case herein reported suggests that PXA can change its morphology to oligodendroglioma. An integrated approach can provide further insights into gliomagenesis.

Contribution of the Authors

1 Deepa Goel - data analysis, manuscript preparation, manuscript editing.
2 - literature search, manuscript review.
3 - manuscript review.
Guarantor - Dr. Deepa Goel.

Conflict of Interests

The authors have no conflict of interest to declare.

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Co-Occurrence of Pineal-Region and Pituitary-Stalk Hemangioblastomas in a Patient Presenting with Von Hippel-Lindau Disease – A Case Report

Ocorrência simultânea de hemangioblastomas na região pineal e na haste hipofisária em paciente com doença de Von Hippel-Lindau – Relato de Caso

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Arq Bras Neurocir 2021;40(2):e190–e194.

Abstract

Introduction Hemangioblastomas of the pineal region or pituitary stalk are extremely rare. Only two cases of hemangioblastomas involving the pineal region have been reported, and four involving the pituitary stalk. The purpose of the present manuscript is to describe an unusual case of supposed hemangioblastoma found concomitantly in the pineal region and pituitary stalk of a patient diagnosed with Von Hippel-Lindau (VHL) disease.

Case Report A 35-year-old female patient with a previous diagnosis of VHL complaining of occipital headaches and balance disturbances for three weeks, who previously had a cerebellar hemangioblastoma resected. The visual characteristics of the tumor suggested a friable vascular lesion with a reddish-brown surface, and an incisional biopsy was performed. The tumor consisted of a dense vascular network surrounded by fibrous stroma abundant in reticulin and composed by both fusiform and dispersed xanthomatous cells; the immunohistochemistry was immunopositive for neuron-specific enolase and immunonegative for epithelial membranous antigen. The patient

Keywords
- tumor
- von hippel-lindau
- hemangioblastoma

received
June 12, 2020
accepted
August 24, 2020
published online
November 26, 2020

DOI https://doi.org/10.1055/s-0040-1718999.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

has been monitored closely for 2 years, and the supratentorial masses have not presented any volume alteration.

Conclusion This rare association must be taken into account in patients with VHL disease, or at least be suspected in patients who present a thickening of the pituitary stalk and a pineal-region mass. We believe a biopsy of our asymptomatic patient could have been dangerous due to inherent complications like intraoperative bleeding. We recommend close observation of asymptomatic lesions with MRIs every six months or until the lesions become symptomatic. If the pineal-region tumor does become symptomatic, gross resection via a transcallosal approach would be ideal.

Resumo

Introdução Hemangioblastomas da região pineal ou da haste hipofisária são raros. Apenas 2 casos foram reportados para a pineal e 4, para a haste hipofisária. O objetivo deste artigo é relatar um caso incomum de supostos hemangioblastomas encontrados concomitantemente na pineal e na haste hipofisária em paciente com Doença de Von Hippel-Lindau (VHL).

Relato de Caso Mulher de 35 anos, com diagnóstico de VHL e histórico de ressecção de hemangioblastoma cerebelar, apresentou cefaleia occipital e queixas relacionadas ao equilíbrio por 3 semanas. As características visuais do tumor sugeriam lesão vascular friável com superfície vermelho-amarronzada, sendo realizada biópsia incisional. O tumor consistia de rede vascular densa rodeada de estroma fibrótico abundante em reticulina e composto de células xantomatosas. Imunohistoquímica positive para enolase específica de neurônios (NSE) e negative para antígeno membranoso epitelial (EMA). Paciente monitorada por 2 anos, sem alteração nas massas.

Conclusão Essa associação rara deve ser suspeitada em pacientes com VHL, na presença de espessamento da haste hipofisária e massa pineal. Acreditamos que uma biópsia, para a paciente assintomática, seria perigosa devido a complicações inerentes como hemorragia intra-operatória. Recomendamos observação de lesões assintomáticas com RM a cada 6 meses ou até que as lesões se tornem sintomáticas. Caso o tumor da região pineal se torne sintomático, ressecção macroscópica por via transcalosa seria ideal.

Palavras-chave
- tumor
- Von Hippel-Lindau
- hemangioblastoma

Introduction

Hemangioblastomas are hypervascular tumors that correspond to approximately 2% of all primary central nervous system (CNS) neoplasms. According to the World Health Organization (Grade I), this pathological entity is composed of benign, non-metastasizing tumors, and is found mainly in the cerebellum and spinal cord. Although their origin is unknown, hemangioblastomas may occur sporadically or in association with Von Hippel-Lindau (VHL) disease in 20% to 38% of the cases.[1–14]

Hemangioblastomas that affect the pineal region or the pituitary stalk are extremely rare. To the best of our knowledge, there have only been two case reports of hemangioblastomas involving the pineal region, while hemangioblastomas on the pituitary stalk have been reported in four cases. Besides, there is only a single report of VHL patients with hemangioblastoma in the pineal region in concurrence with pituitary hemangioblastoma.[12–14]

Thus, the purpose of the present manuscript was to describe an unusual case of supposed hemangioblastoma found concomitantly in the pineal region and pituitary stalk of a patient diagnosed with hemangioblastosis. Given its unusual location, one must classify this lesion under a distinct diagnosis of VHL disease in patients with masses in the pineal region and pituitary stalk.

Case Report

A 35-year-old female patient with a previous diagnosis of VHL was referred to a neurology reference service. She had been complaining of occipital headaches and balance disturbances for three weeks. The patient reported that she had undergone a posterior fossa surgical intervention in order to resect a cerebellar hemangioblastoma during the previous year in another institution. She reported a close relative also diagnosed with VHL, although the patient herself had no known abdominal tumors or retinal hemangiomas.

A physical examination detected a segmental loss of pain and temperature with intact proprioception in the upper limbs, as well as mild tetraparesis with hyperreflexia, clonus,

and a bilateral Babinski sign. The lower cranial nerves were intact. The pupils presented no sign of pseudo-Argyll Robertson. Both the direct and consensual pupilar reflexes were preserved. A complete ophthalmological examination with fundoscopy presented no abnormalities.

The results of a magnetic resonance imaging scan performed in the emergency room indicated T1-weighted brightly enhancing masses in the pineal region and the pituitary stalk— with the absence of hydrocephalus. Moreover, there was also a large and brightly enhancing mass in the posterior fossa, syringomyelia, small lesions in the caudal portion of the cerebellum, and a cluster of hemangioblastomas in the area postrema of the medulla. There were no clinical or laboratory endocrinological alterations suggesting a functional pituitary tumor. Complete blood and cerebrospinal fluid investigations did not yield any results indicating a distinct diagnosis of other pineal-region tumors. The supratentorial lesions were closely monitored since the patient had no symptoms related to them. The posterior-fossa lesion was resected via a suboccipital approach, and the syringomyelic cavity was drained, resulting in a significant improvement of the symptoms.

During the transoperative approach, the visual characteristics of the tumor suggested a friable vascular lesion with a reddish-brown surface. An incisional biopsy was performed, followed by an uneventful wound closure.

Sections for a microscopic examination were taken at thicknesses of 3 µm, and they were stained with hematoxylin and eosin (H&E). The tumor mass consisted of a dense vascular network surrounded by fibrous stroma abundant in reticulin and composed by both fusiform and dispersed xanthomatous cells (►**Figure 1**). An immunohistochemistry analysis was performed, and the tumor was immunopositive for neuron-specific enolase (NSE) and immunonegative for epithelial membranous antigen (EMA). Based on both the microscopic and immunohistochemical analyses, the diagnosis of hemangioblastoma was established.

After the diagnosis, the patient has been monitored closely for 2 years, and the supratentorial masses have not presented any volume alteration (►**Figure 2**).

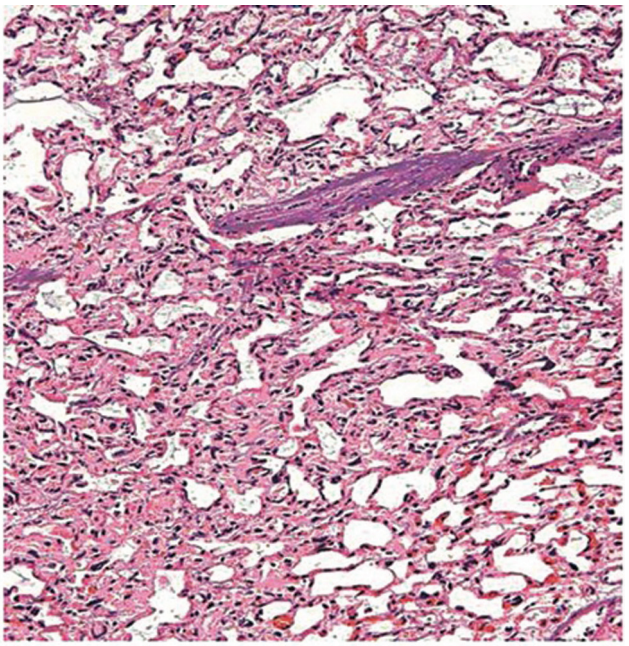

Fig. 1 Histological features of the hemangioblastoma demonstrating an intensive vascular network surrounded by fibrous connective tissue.

Discussion

Nearly 25% of hemangioblastomas are associated with VHL disease.[2,13] The tumor grows slowly and is frequently associated with cerebellar cysts or a syrinx in the brain stem or spinal cord. Von Hippel-Lindau disease is an autosomal-dominant neoplasia syndrome caused by a germline mutation or deletion of the VHL tumor suppressor gene that lies in the short arm of chromosome 3 (p25.3). This disease has a prevalence of approximately 1 in 39,000 persons. The clinical criteria for VHL disease are those established by Melmon and Rosen.[8] According to these criteria, for a patient to be diagnosed with VHL disease, they need at least two central nervous system (CNS) or retinal hemangioblastomas (present case), or one hemangioblastoma associated with renal carcinoma, pheochromocytoma, pancreatic cyst, or papillary cystadenoma of the epididymis.

In the absence of family history, the presence of a single hemangioblastoma or another manifestation of VHL disease can confirm the diagnosis. A sample of peripheric blood is enough to confirm the presence of the VHL gene mutation. The overall risk of finding VHL germline mutations ranges from 4% to 14% in patients with a single CNS hemangioblastoma without other clinical criteria for VHL disease. Patients with VHL disease affected with CNS hemangioblastomas typically develop symptoms early in life (average age of manifestation: approximately 33 years).[12,15]

Whereas sporadic hemangioblastomas are nearly always solitary, cerebellar hemangioblastomas in patients with VHL disease are often multiple and associated with additional retinal, brainstem, spinal cord, or lumbosacral nerve root hemangioblastomas.[7,11,16] The presence of a synchronous pituitary lesion neither supports nor discredits the potential diagnosis of hemangioblastoma in the case presented, given the several alternatives of differential diagnoses. This co-occurrence of a pineal region hemangioblastoma with a pituitary hemangioblastoma in patients with VHL is very rare. As reported by the sole study[17] reporting such a case, very similar histopathological analyses between both lesions were found, as well as the concomitant radiological enhancement after an injection of gadolinium.

Tumors in the pineal region correspond to around 1% of CNS neoplasms. A wide variety of tumors can affect this region, the most common being germ-cell tumors, gliomas, and pineal-cell tumors.[5] Despite being powerful diagnostic tools, the MRI and computed tomography (CT) are both low in sensitivity and specificity when it comes to the differential diagnosis of pineal-region masses. The diagnostic accuracy increases with the measurement of serum or cerebrospinal fluid alpha fetoprotein (AFP), human chorionic gonadotrophin (HCG), and

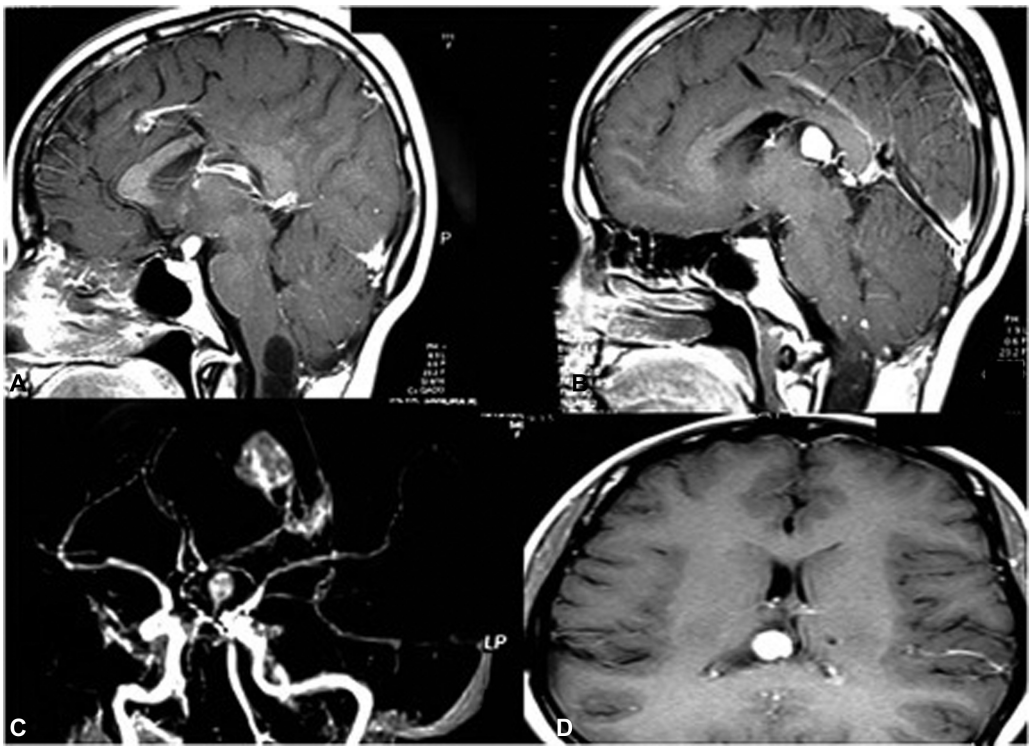

Fig. 2. (**A**) Sagittal T1 gadolinium-enhanced MRI showing a brightly enhancing mass in the pituitary stalk. (**B**) Sagittal T1 gadolinium-enhanced MRI showing a brightly enhancing mass in the pineal region and a cluster of hemangioblastomas in the area postrema of the medulla. (**C**) Magnetic resonance angiography demonstrating a vascular tumor in the suprasellar region and pineal region. (**D**) Axial gadolinium-enhanced MRI showing a brightly enhancing mass in the pineal region.

carcinoembryonic antigen (CEA). If the HCG is positive, one must consider either choriocarcinoma, mixed germ-cell tumor with choriocarcinomatous elements, or a mixed germ-cell tumor with syncytiotrophoblastic giant cells. A positive AFP may point to endodermal sinus tumor or mixed germ-cell tumors with endodermal sinus tumor. Germinoma, embryonal carcinoma, mature teratoma, immature teratoma, mixed germ-cell tumors, pineocytoma, and pineoblastoma should be taken into account when the HCG and AFP are negative.[5]

The pituitary stalk region can harbor tumors (pituitary-stalk tumors, PSTs) or other infiltrative processes, such as histiocytosis, sarcoidosis, infections or autoimmune diseases.[3,18,19] Central diabetes insipidus with isolated PST can result from various lesions. In one study,[16] a precise etiology was recognizable at the first manifestation of symptoms in 4 out of 26 patients (15% of the cases): these 4 patients had Langerhans histiocytosis. Germinoma should be suspected in all patients with Diabetes Insipidus (DI) and PST, even when neurological and ophthalmological symptoms are absent. From anatomical findings, the primary site of germinomas in the hypothalamic-neurohypophyseal axis seems to range from the posterior lobe of the pituitary gland to the stalk.[20] A PST with an identical aspect has also been reported in adult patients with idiopathic DI who do not present with germinoma, Langerhans histiocytosis, sarcoidosis, or infectious granuloma.[6] There have been four cases of pituitary stalk hemangioblastoma,[17] with only one being surgically treatable.[11]

Conclusion

This rare association must be taken into account in patients with VHL disease, or at least be suspected in patients who present a thickening of the pituitary stalk and a pineal-region mass. We believe a biopsy of our asymptomatic patient could have been dangerous due to inherent complications like intraoperative bleeding. We recommend close observation of these asymptomatic lesions with a series of MRIs every six months or until one of the lesions becomes symptomatic. If the pineal-region tumor does become symptomatic, we believe that a gross resection via a transcallosal approach would be ideal.

Conflict of Interests

The authors have no conflict of interests to declare.

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Multifocal Pseudotumorous Form of Neuroparacoccidioidomycosis in an Immunocompetent Patient: A Clinicopathological Review Based on a Case Report

Neuroparacoccidioidomicose multifocal de forma pseudotumoral em paciente imunocompetente: Uma revisão clinicopatológica baseada em um relato de caso

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Arq Bras Neurocir 2021;40(2):e195–e199.

Abstract

Neuroparacoccidiodimycosis (NPDM) is an uncommon granulomatous disease, which more frequently affects immunocompromised male patients over 30 years of age in the course of chronic lung disease. *Paracoccidioides brasiliensis* (PB) is an endemic fungus in Brazil, and grows as thick-walled yeast (with round to oval bodies) measuring 10 µm to 60 µm in diameter. Neuroparacoccidiodimycosi may develop many years after transmission and/or primary lung involvement. The authors describe a case of NPDM affecting a male patient, 52 years of age, farmer, heavy smoker, with clinical complaint of headache, asthenia, seizures, and prostration in the previous nine months. Upon physical examination, the patient presented regular general condition, without other relevant physical alterations. Computed tomography (CT) showed multiple bilateral pulmonary nodules associated to enlargement of the mediastinal lymph node. Magnetic resonance imaging (MRI) and CT scans of the central nervous system showed

Keywords

- paracoccidiodomycosis
- south american blastomycosis
- paracoccidioides brasiliensis
- central nervous system
- mycosis
- pathology

received
January 7, 2020
accepted
August 24, 2020
published online
November 26, 2020

DOI https://doi.org/10.1055/s-0040-1719005.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

six heterogeneous nodular lesions compromising the frontal and parietal lobes, the largest one measuring 3.8 × 3.2 × 3.2 cm. The hypothesis of a neoplastic process compromising the lung and brain was considered. A biopsy of the mediastinal lymph node showed epithelioid granulomas, which exhibited round, thin-walled fungal structures in Grocott silver stain. The stereotactic biopsy of the frontal lesion was constituted by necrotic tissue admixed with some round to oval, thin-walled fungi measuring 10 µm to 60 µm, compatible with PB (identified on Grocott silver stain/confirmed in culture). The diagnosis of NPDM was then established. The employed therapeutic regimen was intravenous amphotericin B, itraconazole, and sulfamethoxazole-trimetropin. After ninety days of clinical follow-up, no episodes of seizures/neurological deficits were identified, and a marked decrease in the number and size of the lung and brain lesions were found.

Resumo

A neuroparacoccidiodimicose (NPDM) é uma doença granulomatosa incomum, que acomete mais freqüentemente pacientes imunocomprometidos do sexo masculino com mais de 30 anos, no curso de doença pulmonar crônica. *Paracoccidioides brasiliensis* (PB) é um fungo endêmico no Brasil e cresce como levedura de parede espessa (com corpos arredondados a ovais) medindo 10–60 µm de diâmetro. A NPDM pode se desenvolver muitos anos após a transmissão e / ou envolvimento pulmonar primário. Os autores descrevem um caso de NPDM em paciente masculino, 52 anos, agricultor, tabagista pesado, com queixa clínica de cefaleia, astenia, convulsões e prostração nos últimos nove meses. Ao exame físico, o paciente apresentava estado geral regular, sem outras alterações físicas relevantes. A tomografia computadorizada (TC) mostrou múltiplos nódulos pulmonares bilaterais associados a linfonodomegalia mediastinal. A TC / ressonância magnética do sistema nervoso central revelou seis lesões nodulares heterogêneas comprometendo os lobos frontal e parietal, a maior delas medindo 3,8x3,2x3,2 cm. Foi considerada a hipótese do processo neoplásico comprometendo pulmão e cérebro. A biópsia de linfonodo mediastinal mostrou granulomas epitelioides, que exibiam estruturas fúngicas arredondadas e de paredes finas na coloração pela prata de Grocott. A biópsia estereotáxica da lesão frontal era constituída por tecido necrótico entremeado por algumas estruturas fúngicas redondas a ovais e de parede fina, medindo 10–60 µm, compatível com PB (identificado na coloração de prata Grocott / confirmado em cultura). O diagnóstico de NPDM foi então estabelecido. O esquema terapêutico empregado foi anfotericina B intravenosa, itraconazol e sulfametoxazol-trimetropina. Após 90 dias de acompanhamento clínico, nenhum episódio de convulsão / déficit neurológico foi identificado, e uma diminuição acentuada no número e tamanho das lesões pulmonares e cerebrais foi encontrada.

Palavras-chave
- paracoccidio-domicose
- *blastomicose da América do Sul*
- paracoccidioides brasiliensis
- sistema nervoso Central
- Micose
- patologia

Introduction

Central nervous system (CNS) mycoses have assumed greater importance as the number of immunocompromised patients has increased over the past few decades.[1–3] Fungal infections in the CNS have also been increasing, because of the growing use of complex surgical procedures, invasive medical devices, and long-term broad-spectrum antibiotics. Considerable progress has been made in our understanding of fungal pathobiology, in special due to the sequencing of fungal genomes and the employment of animal models to determine the different components of fungal virulence.[1–3] The epidemiology of CNS fungal disease is variable in the literature. Relevant epidemiological data come from the databse of the Transplant-Associated Infection Surveillance Network.[4] Many CNS mycoses are preceded by lung infections, and fungi reach the CNS via the hematogenous route. The risk factors that lower host resistance include neutropenia, hematological malignancy, steroids, diabetes mellitus, systemic lupus, renal failure, and impaired cell-mediated immunity.[1,2,4]

Paracoccidiodomycosis (PDM), or South American blastomycosis, is caused by *Paracoccidioides brasiliensis* (PB). The fungi grow as thick-walled yeast with round to oval bodies, which are 10 µm to 20 µm in diameter and give rise to single or

multiple thin-necked buds.[1,5,6] These fungi probably live in the vegetation or soil. Usually, PDM is a granulomatous disease that initially compromises the lungs and the oral mucosa, and then spreads to the lymph nodes, the adrenal glands, and, rarely, to the CNS.[1,3,5,6] Herein, the authors present a case of neuroparacoccidioidomycosis (NPDM) affecting an immunocompetent male patient, and discuss the pathological and clinical data of this uncommon cerebral mycosis.

Case Report

A male patient, 52 years of age, farmer, heavy smoker for 30 years, was referred to the hospital service with a clinical complaint of headache, asthenia, fatigue, and prostration in the previous nine months. Upon physical examination, the patient presented a regular general condition, without other relevant physical alterations. The patient's previous history did not present significant pathological processes. A conventional chest radiological study revealed a micronodular interstitial infiltrate in both lungs. A computed tomography (CT) scan of the chest showed multiple bilateral and coalescent pulmonary nodules associated to enlargement of the mediastinal lymph node (►**Fig. 1**). The patient evolved with episodes of seizures. The hypothesis of a neoplastic process compromising the lung and brain was considered. Magnetic resonance imaging (MRI) and CT scans of the CNS showed 6 heterogeneous nodular lesions, which compromised predominantly the white matter of the frontal and parietal lobes bilaterally, with surrounding areas of edema and narrowing zones of the brain grooves, and the largest one measured $3.8 \times 3.2 \times 3.2$ cm (►**Fig. 2**). The lesions were hypointense at T2, with a slight peripheral signal at T1 and diffusion restriction. On the CT/MRI scans of the abdomen, no significant alterations were observed. The patient had negative serology for HIV, hepatitis B and C, syphilis and toxoplasmosis. An analysis of the cerebrospinal fluid (CSF) did not reveal any significant data. In a biopsy of the mediastinal lymph node, we identified anthracosis and the formation of epithelioid granulomas, which exhibited small, round, thin-walled fungal structures in Grocott silver stain. A stereotactic biopsy of the frontal lesion was constituted by an amorphous, eosinophilic necrotic tissue (hematoxylin-eosin technique; ►**Fig. 3**) admixed by some round to oval, thin-walled fungal structures measuring 10 µm to 60 µm, compatible with PB (identified on Grocott silver stain and confirmed in culture; ►**Fig. 4**). The diagnosis of pulmonary PDM determining secondary involvement of the CNS was then established. The proposed therapeutic regimen was the use of intravenous amphotericin B, itraconazole, and sulfamethoxazole-trimetropin. In the first week of the pharmacological treatment, the patient developed respiratory failure, hypokalemia, and hypomagnesemia, and mechanical ventilation was started. Thirty days after this episode, the patient showed an improvement in his general clinical condition. After ninety days of clinical follow-up, no episodes of seizures or neurological deficits were identified, and a marked decrease in the number and size of the lung and brain lesions was observed.

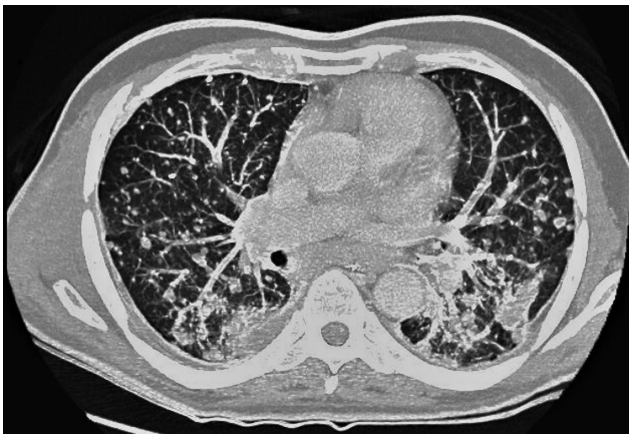

Fig. 1 Lung paracoccidioidomycosis: computed tomography scan exhibiting multiple bilateral and coalescent pulmonary nodules.

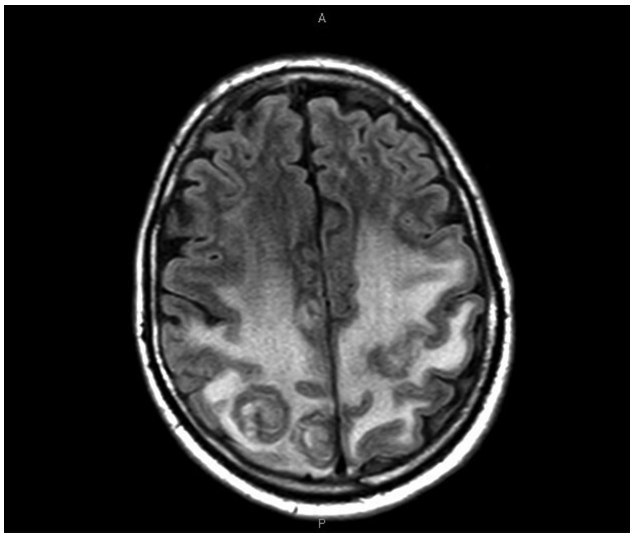

Fig. 2 Neuroparacoccidioidomycosis: magnetic resonance imaging (axial – fluid attenuated inversion recovery [FLAIR] image) scan showing two heterogeneous nodular lesions compromising the parietal lobes, with surrounding areas of edema.

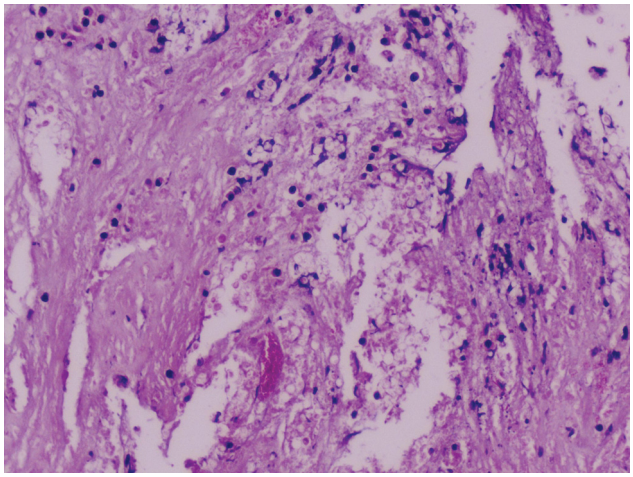

Fig. 3 Central nervous system paracoccidioidomycosis: necrotic tissue obtained by stereotactic biopsy, hematoxylin-eosin, 100X.

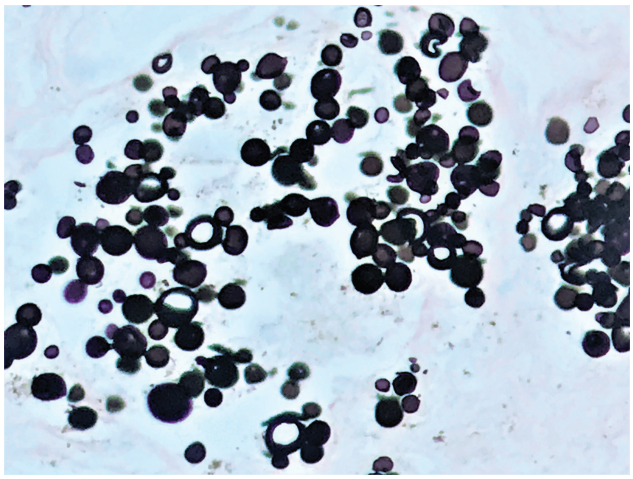

Fig. 4 Central nervous system paracoccidioidomycosis: thick-walled yeasts with round to oval bodies identified in Grocott methenamine silver stain, 200X.

Discussion

First described by Lutz in 1908, PDM is very restricted to geographic areas such as Central and South America. In Brazil, PDM is an endemic disease.[1,7–9] Most compromised patients are over 30 years of age, and males are more frequently affected. The lungs are primarily involved, and symptoms of PDM often develop many years after transmission.[1,7–9] This long latent period may be due to the fungus lying dormant in the lymph nodes. The severity of the disease is related to host immunity. Most patients present with various combinations of fever, cough, night sweats, weight loss, or chills. Pulmonary findings may be localized or may be part of a more disseminated disease.[7–11] A small number of patients remain subclinical. Acute lung infection rapidly spreads to the lymph nodes, liver and spleen. Radiological findings are unspecific, and include micronodular infiltrates, foci of consolidation, cavities, fibrosis or, infrequently, calcified nodules.[7–11] The histopathological findings range from neutrophilic microabscesses, scattered interstitial necrotizing granulomas, and consolidative granulomatous pneumonia. Progressive pulmonary disease is more common than acute/subacute lung involvement.[2,3,5,8,12] It compromises older patients who probably develop reactivation many years after transmission. Chests radiographs exhibit confluent/patchy nodular infiltrates in the mid/basal segments, usually bilateral and symmetrical. The pathological findings include lung scarring with a coarse, hobnail appearance, cavities, ulceration of the large airways, bronchiectasis, dense fibrous pleural adhesions, and pleural effusions.[2,3,5,8,12] Lung PDM can resemble and coexist with blastomycosis and tuberculosis, and a mixed piogenic and granulomatous inflammatory response is typical of the disease. Numerous organisms are usually present within giant cells.[2–4,6,8,9]

Dissemination from a primary lung disease may involve regional lymph nodes and eventually the CNS, which is usually related to the chronic form of the pulmonary disease and male patients after the third decade of life who live in rural areas. The prevalence of NPDM ranges from 4% to 15% of cases of systemic PDM.[1,4,10,12,13] Manifestations of the involvement of the CNS include headache, lethargy, raised intracranial pressure, and personality changes. Neuroparacoccidioidomycosis is most commonly associated with symptoms and signs of an expansive lesion in the brain (pseudotumorous form) or to a meningitic form.[2,3,5,8,9,12,14] On gross, the most common form of NPDM is the pseudotumorous form, which usually exhibits well-circumscribed necrotic nodules measuring from a few millimeters to several centimeters in diameter. Supratentorial lesions are predominantly found in NPDM (around 70% of the cases), and the frontal and parietal lobes are the most common locations.[2,3,5,8,9,12,14] Spinal PDM accounts for 0.6% of all cases of systemic PDM, and for 4% of the cases of NPDM.[4,5,10] The leptomeningitic form is granulomatous, predominantly basal, and may cause hydrocephalus. When it affects the dura mater, NPDM may resemble meningiomas. On microscopy, paracoccidiodomycomas (pseudotumorous form) exhibit granulomas composed of epithelioid macrophages, Langhans giant cells, necrotic central areas, and lymphocytes.[2,5,8,12,13,15] A chronic inflammatory infiltrate can be identified in the leptomeninges, and this infiltrate can extend along the Virchow-Robin space into the underlying brain tissue, especially in the hypothalamus.[2,5,8,12,13,15]

A dimorphic fungus, PB forms oval to rounds yeasts with multiple buds at 37°C in tissues and in cultures. The fungus is a white mold composed of thin septate hyphae that produce chlamydoconidia, and, when cultured, it produces < 5 µm asexual propagules known as microconidia (probably the infectious particle).[1,2,7,9,14,16] In tissue sections, the organisms are round to oval and 10 µm to 60 µm in diameter, and have thin, refractive walls. In the hematoxilin-eosin technique, their contents may be basophilic or amphophilic.[1,2,7,9,14] *P. brasiliensis* reproduces by multiple buds, which can be roughly equal or may vary in size and are linked to the parent by narrow beds. In fibrous longstanding granulomatous lesions, the yeasts may be fragmented, distorted and unevenly stained by fungal stains. Rarely, hyphae are formed in the tissues.[3,5,12,13,16] Diagnosis of lung disease can be established by sputum, bronchioalveolar lavage, and biopsies. If the submitted material is warmed with 5% potassium hydroxide (KOH), the yeasts are doubly refractive. Cell-block preparations and histological slides stained with Grocott silver stain are also sensitive techniques. In cultures, mold colonies can be obtained after incubation in Sabouraud dextrose agar supplemented with cycloheximide.[3,5,12,13] Serological tests are also useful for the presumptive diagnosis of NPDM, and these tests can be used to monitor the response to the treatment too.[2,12,13,16–19] The CSF analysis has both low sensitivity and low specificity. Gp43 and gp70 PB antigens in body fluids and in the CSF (inh-enzyme-linked immunosorbent assay [ELISA] method) can be helpful for the diagnosis of the disease. The ELISA anti-gp43 has 89% of sensitivity and 10% of specificity.[12,13,16–19] The CT/MRI scans exhibit an expansive, ring-enhancement lesion, with surrounding edema, in the pseudotumorous form of NPDM. On MRI, the pseudotumorous form can appear as hyper-, iso-, or hypointense lesions on T1 and T2-wieghted imaging.

Diffusion-weighted imaging does not normally demonstrate signal restriction.[2,5,6,13,21] In the present case, the authors report an immunocompetent, heavy smoker farmer, who developed the classic pseudotumorous form of NPDM in the course of concomitant chronic lung disease. The initially-admitted clinical hypothesis was primary lung neoplasia with secondary implants in the brain parenchyma, due previous history of smoking and the radiological data. The identification of fungal structures in the mediastinal lymph nodes and brain biopsies was fundamental to stablish the final diagnosis and correct clinical management.

Differential diagnosis includes *Coccidioides immitis* (sporangia measuring 30 µm to 60 µm and containing 1 µm to 5 µm sporangiospores – it usually occurs as meningitis), *Histoplasma capsulatum* (a dimorphic, ovoid fungi, measuring 2 µm to 5 µm), and *Cryptococcus neoformans* (yeasts measuring 4 µm to 7 µm and exhibiting a mucinous capsule).[1,2,7,12,13,19,20,22] In the presence of the pseudotumorous form of NPDM, the differential diagnosis also includes neoplasms (primary and secondary), abscesses, tuberculosis, and neurocysticercosis.[7,12,13,19,20,22–24] The therapy includes sulfonamides, amphotericin B and azoles (fluconazole, itraconazole, voriconazole).[2,3,8,11,13,14,19] Actually, the combination of oral fluconazole and trimethoprim-sulfamethoxazole for long periods (more than 12 months) is also employed in NPDM.[2,3,7,11,13,14,19]

Funding
No funding was received.

Conflict of Interests
The author have no conflict of interests to declare.

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Jugular Foramen's Paraganglioma in a Patient with Von Hippel-Lindau Disease: Case Report

Paraganglioma do forame jugular em paciente com doença de Von Hippel-Lindau: Relato de caso

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Arq Bras Neurocir 2021;40(2):e200–e206.

Abstract

Glomus jugular tumors, also known as paragangliomas (PGLs), are rare and related to several clinical syndromes described. These are located in the carotid body, the jugular glomus, the tympanic glomus and the vagal glomus. The symptoms are directly related to the site of involvement and infiltration. These lesions have slow growth, are generally benign and hypervascularized, have a peak incidence between the age of 30 to 50 years old; however, when associated with hereditary syndromes, they tend to occur a decade earlier. Several familial hereditary syndromes are associated with PGLs, including Von Hippel-Lindau disease (VHL) in $<$ 10% of the cases. The diagnosis and staging of PGLs are based on imaging and functional exams (bone window computed tomography [CT] with a "ground moth" pattern and magnetic resonance imaging (MRI) with a "salt and pepper" pattern). The cerebral angiography is a prerequisite in patients with extremely vascularized lesions, whose preoperative embolization is necessary. The histopathological finding of cell clusters called "Zellballen" is a characteristic of PGLs. Regarding the jugular foramen, the combination of two or three surgical approaches may be necessary: (1) lateral group, approaches through the mastoid; (2) posterior group, through the retrosigmoid access and its variants; and (3) anterior group, centered on the tympanic and petrous bone. In the present paper, we report a case of PGL of the jugular foramen operated on a young female patient who underwent a surgery with a diagnosis of Von Hippel-Lindau Disease (VHL) at the Neurosurgery Service of the Hospital Heliópolis, São Paulo, state of São Paulo, Brazil in 2018, by the lateral and posterior combined route.

Keywords
- glomus
- paragliomas
- von hippel-lindau

Resumo

Os tumores do glomus jugular, conhecido também como paragangliomas (PGLs), são raros e se correlacionam com várias síndromes clínicas descritas. Estes localizam-se no

received
May 11, 2020
accepted
August 24, 2020
published online
November 26, 2020

DOI https://doi.org/10.1055/s-0040-1719002.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

corpo carotídeo, na veia jugular, no ouvido médio e no corpo vagal. Os sintomas são diretamente relacionados ao sítio de envolvimento e infiltração. Essas lesões têm crescimento lento, geralmente são benignos e hipervascularizados, têm pico de incidência entre 30 e 50 anos de idade; contudo, quando associados a síndromes hereditárias, tendem a ocorrer uma década mais cedo. Várias síndromes hereditárias familiares estão associadas aos PGLs, dentre elas a Doença de Von Hippel-Lindau (VHL) em $< 10\%$ dos casos. O diagnóstico e estadiamento dos PGLs assentam-se na realização de exames imaginológicos e funcionais (tomografia computadorizada [TC] da janela óssea com padrão "traça moída" e ressonância magnética [RM] com padrão "sal e pimenta") e angiografia cerebral como pré-requisito em pacientes com lesões extremamente vascularizadas, cuja embolização pré-operatória é necessária. O achado histopatológico de aglomerados celulares denominados "Zellballen" é característico dos PGLs. Em relação ao forame jugular, a combinação de dois ou três acessos cirúrgicos pode ser necessária: (1) grupo lateral, abordagens através da mastoide; (2) grupo posterior, através do acesso retrossigmóide e suas variantes; e (3) grupo anterior, centrado no osso timpânico e petroso. No presente trabalho, relatamos um caso de PGL do forame jugular em paciente jovem do sexo feminino operada com diagnóstico de Doença de Von Hippel-Lindau (VHL) no serviço de neurocirurgia do Hospital Heliópolis, São Paulo, SP, Brasil, em 2018 por via combinada lateral e posterior.

Palavras-chave
- glomus
- parangliomas
- von hippel-lindau

Introduction

Tumors of the foramen jugular (FJ) are rare, in most cases benign, and present great difficulty in surgical treatment because of the involvement of important vascular and nervous structures.[1]

Several tumors can affect this region; among the most common are paragangliomas (PGLs) (most frequent), Schwannomas and meningiomas. Paragangliomas – also called cheemoderms, glomus tumor, chemiodectoma, glomerocytoma, tumor of the tympanic body and receptoma[2]–are benign neuroendocrine neoplasms originated from neural crest derivatives, the sympathetic and parasympathetic extra-adrenal paraganglia (glomus bodies).[3]

Malignant tumors can also affect the FJ, including metastasis (carcinomas), chondrosarcomas, and chondromas as part of the differential diagnosis of these lesions.[4]

Glomus jugular tumors are rare and commonly grouped as tumors of the skull base. The incidence of these tumors is $\sim$ 0,07 per 100,000 per year,[5] varying in some authors from 1 per 30,000.[6] These tumors arise within the JF (pars venous), with a peak incidence between the age of 30 to 50 years old;[7] however, when associated with hereditary syndromes, they tend to occur a decade earlier.[8] They become symptomatic in the 5th and 6th decades of life; women are 3 to 6 times more affected than men. These tumors grow slowly (growth rate is $\sim$1 mm per year[8]), are generally benign, hypervascularized and tend to invade the temporal bone during their growth, being diagnosed on average 5 years after the onset of symptoms. Only 1 to 5% are malignant.[5]

Symptoms are directly related to the site of involvement and infiltration. Glomus jugular tumors represent neoplastic lesions originating from the adventitia of the jugular vein, usually affected by symptoms related to the involvement of low cranial nerves, such as the vagus (X), the accessory (XI) and the hypoglossal (XII). In the variation of the tympanic glomus, the tumors are related to neuroendocrine cells along the Jacobson Nerve – the tympanic branch of the glossopharyngeal nerve that arises from its lower level – conducted by the tympanic membrane, auditory tube and mastoid region; it also carries parasympathetic preganglionic fibers from the lower salivatory nucleus that connect with the optical ganglion – it enters the tympanic cavity through the lower tympanic channel and invests in the tympanic plexus; parasympathetic fibers leave the nervous petrosus minor. A more common initial clinical presentation in $\sim$ 75% of patients is the presence of pulsatile tinnitus, followed by deafness in the conduction and vertigo. In the third anatomotopographic variant of this tumor, the vagal glomus originates from non-chromaffinous paraganglionic cells associated along the Arnold nerve – the auricular branch of the vagus nerve – or the mastoid branch – formed by a branch of the upper vagal ganglion (jugular) and an angle inferior brightness (petrous), ascension through the mastoid canal, in the lateral jugular fossa – leading to the sensitivity of the external auditory canal and the skin of the external ear. Detailed examination through otoscopy may reveal the presence of tympanic membrane invasion.

Von Hippel-Lindau (VHL) disease is a rare pathology ($\sim$ 1 in every 36.000 cases[9]), with autosomal dominant transmission and age-related penetrance ($>$ 90% until 60 years old).[10] It is caused by mutations in the tumor suppressor gene *VHL* that encodes the pVHL protein, responsible for regulating hypoxia-induced genes through ubiquitination and subsequent degradation of the α subunits of hypoxia-induced (HIF1α, HIF2 α and HIF3α). This loss of function of the protein leads to the clinical manifestation of the disease, characterized by the presence of several benign and malignant tumors,

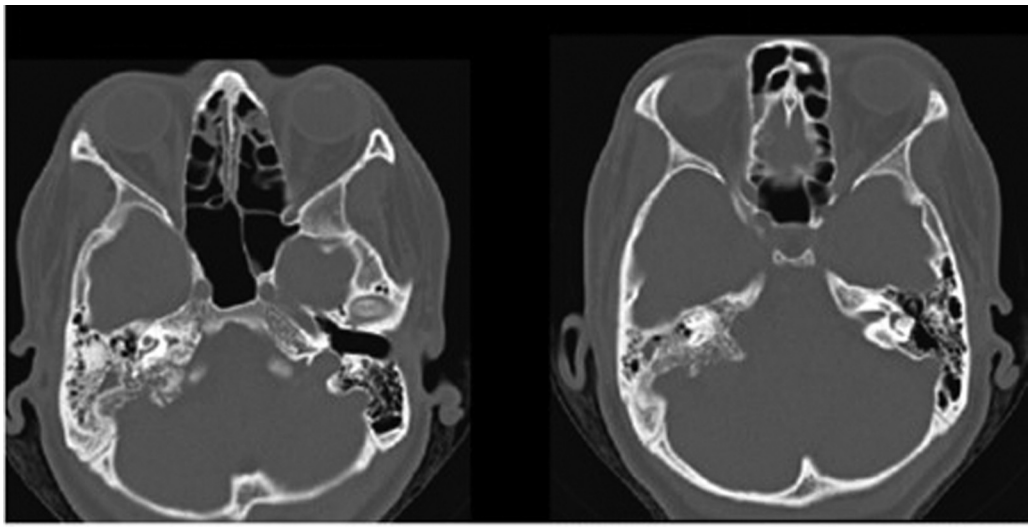

Fig. 1 Skull tomography axial sections in the bone window: parajugular portion extension and the right temporal inner ear bone with a "ground moth" pattern.

such as retinal angiomas, hemangioblastomas of the central nervous system (CNS) and renal cells carcinoma.

The authors present a case report of JF PGL operated on a patient with Von Hippel-Lindau Disease (VHL) diagnosed at the Neurosurgery Service of the Hospital Heliópolis, São Paulo, state of São Paulo, Brazil, in 2018.

Case Report

M.S., 21 years old, female, with a history of progressive hearing loss on the right side for 4 years. This symptom worsened in the previous 6 months before hospitalization, when she also started presenting subjective vertigo and right hemicranial headache, compression of mild intensity without alarm signs that denote intracranial hypertension. She was admitted to the Neurosurgery Service of the Heliópolis Hospital and after image studies a probable right glomus jugular tumor was diagnosed.

She has a history of multiple pancreatic cysts, with a familial history of Von Hippel-Lindau disease in a first-degree relative (mother), with a genetic test confirming the disease.

Submitted to a physical examination, the patient presented with anacusis on the right side. There was no change in the other components of the neurological examination. In the complementary investigation, audiometry was performed with evidence of sensorineural anacusis in the right ear. At the cranial computed tomography (CT) scan, extensive erosion of the parajugular portion and inner ear of the right temporal bone was observed with a moth-eaten pattern (►**Fig. 1**). At magnetic resonance imaging (MRI), the heterogeneous enhanced sign, like salt and pepper, was characterized in an enlarged solid / cystic lesion of $3.6 \times 3.3 \times 3.3$ cm,

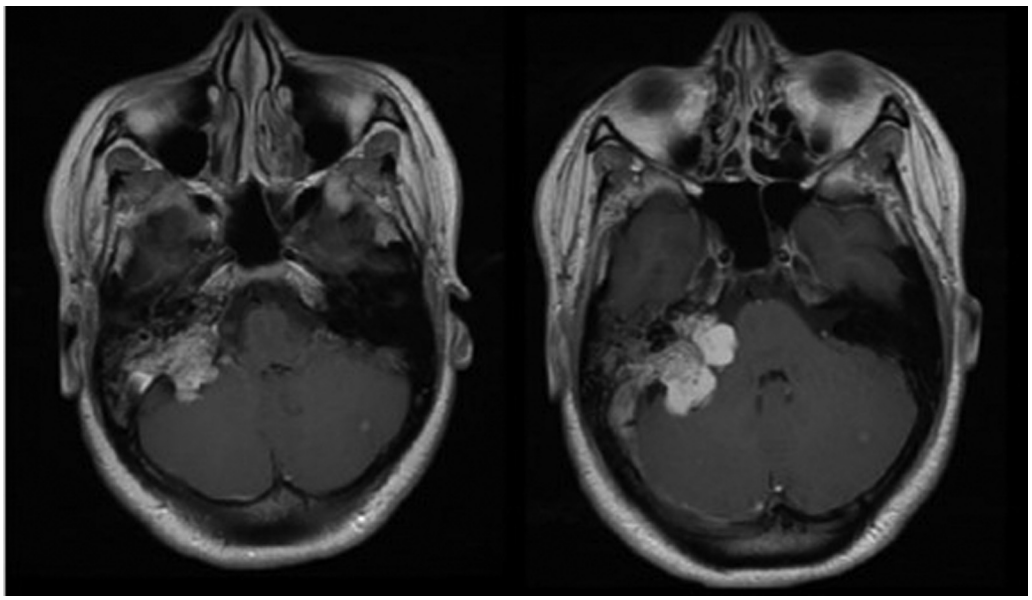

Fig. 2 Brain with contrast axial magnetic resonance imaging sections, showing a heterogeneous "salt and pepper" enhancement pattern in an expansive solid-cystic lesion.

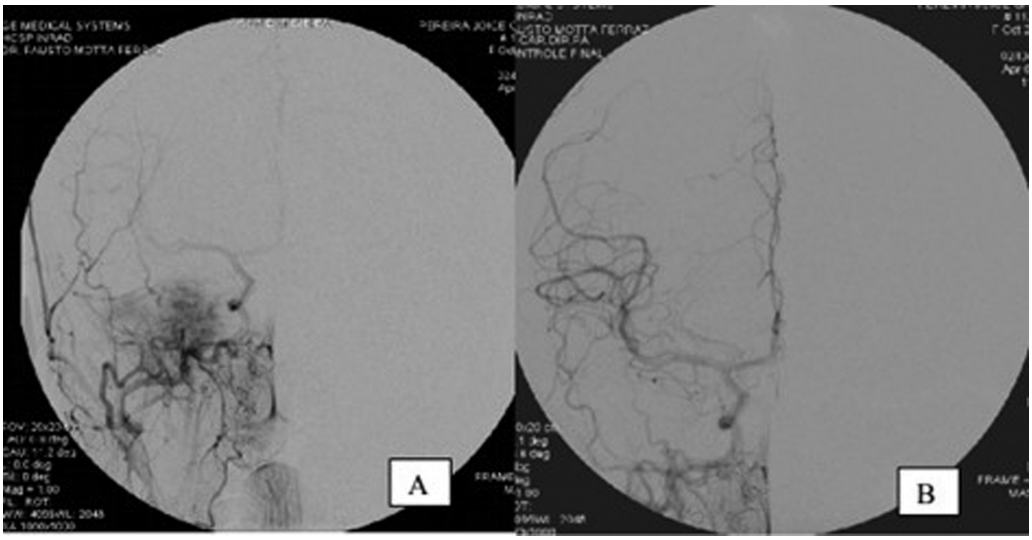

Fig. 3 Cerebral angiography in anteroposterior: A- tumor blush with tympanic branch predominant irrigation of right ascending pharyngeal artery; B- post embolization control of ascending pharyngeal artery with evident reduction in tumor vascularization.

multissepted, centered on the right jugular fossa with extension to the cistern of the cerebellopontine angle, invading the internal auditory canal, extending superiorly to the cerebellar tent, with meningeal infiltration of the middle fossa and causing compression of the middle cerebellar peduncle (►**Fig. 2**).

The most relevant laboratory tests before surgery are serum and urinary catecholamines, as well as urinary levels of vanillmandelic acid and urinary metanephrines, to determine the possibility of tumor neuroendocrine secretion. Unfortunately, preoperative values are not available.

Due to intense tumor vascularization, diagnostic cerebral angiography was performed with subsequent preoperative embolization, obtaining a satisfactory reduction in tumor vascularization; the examination revealed tumor blush with predominant irrigation of the tympanic branch of the right ascending pharyngeal artery, with contributions from the petrosal branch of the middle meningeal artery and of the stylomastoid branch of the occipital artery (►**Fig. 3**). The bulb of the right jugular vein was occluded and the cerebral venous drainage redirected to the left transverse, sigmoid and jugular sinus.

After 48 hours of embolization, microsurgical resection of the lesion was performed by the combined pre- and retrosigmoid route with intraoperative monitoring of the cranial nerves and the aid of an ultrasonic aspirator, obtaining a satisfactory excision without complications. At first, cervical dissection was performed to obtain proximal vascular control; subsequently, the presigmoid access was initiated by mastoidectomy, obtaining resection of the tumoral mastoid portion and the invasive portion in the jugular bulb. In the second stage, a lateral suboccipital craniotomy was performed for retrosigmoid access; by this route, a satisfactory resection of the lesion was obtained in the topography of the JF, which extended to the antigen-presenting cell (APC).

The histological aspect of the lesion is typical of a paraganglioma with polygonal epithelioid cells of abundant and clear cytoplasm arranged in small lobes (alveolar arrangement) called "zellbalen." The diagnosis by immunohistochemistry showed positivity for AE1-AE3, synaptophysin and protein S100.

The outcome of the patient was uneventful in the postoperative period, maintaining the neurological status and the previous right hearing loss, without any additional deficits.

Discussion

Paragangliomas (PGLs) can be sporadic or arise in the context of a familial syndrome. Currently, 40 to 60% are derived from germline mutations.[6,11] Several familial hereditary syndromes are associated with PGLs, including VHL disease. Von Hippel-Lindau disease is an autosomal dominant tumor predisposition syndrome, characterized by multiple benign and malignant tumors of the central nervous system (CNS), kidneys, pancreas, adrenal glands, and paraganglia.[12] The clinical diagnosis of VHL is defined,[13] among other criteria, by an individual with a family history in the presence of a tumor characteristic of the syndrome, such as retinal hemangioblastoma or CNS, renal clear cell carcinoma, pheochromocytoma (PCC)/paraganglioma or endolymphatic sac tumor.

In a cohort study, 109 patients were identified with VHL. The mean age at the time of VHL diagnosis was 29 years old. Family history was available in 95 patients (87%); 62 (65%) of these patients (53%) had first-degree relatives with VHL. Among these patients, 3 (3%) had paraganglioma: 2 of the inner ear and 1 along the juxtarenal aortic.[12] In a similar study from the Mayo Clinic PCC/PGL registry, 610 patients were identified with various forms and locations of PCC/PGL. From those, 81 surgical patients were included in the study, of which 19 had VHL.[14]

The patient reported in the present case had VHL disease, as she had a mother with a previous diagnosis (hemangioblastoma, pancreatic neuroendocrine tumor and positive genetic test for mutation in the *VHL* gene), in addition to presenting a CNS PGL and pancreatic cysts.

Paragangliomas have a peak incidence between the ages of 30 and 50 years old;[7] however, when associated with

hereditary syndromes, they tend to occur a decade earlier[15]; women are 3 to 6 times more affected than men and are diagnosed on average 5 years after the onset of symptoms. The PGLs (corresponding to 3% of total paragangliomas), called parasympathetic PGLs, are 50% of genetic etiology.[16] Such data are consistent with the case presented: female patient with intracranial paraganglioma, with hereditary syndrome (VHL), aged 21 years old and with symptoms lasting $\sim$ 4 years until her diagnosis.

According to Jackson et al., almost all patients will experience pulsatile tinnitus and hearing loss, either conductive or sensorineural. For Jackson et al. the hearing loss is usually conductive, but a sensorineural component may occur if the cochlea is involved. Besides that, other common symptoms include vertigo and unsteadines.[17] According to Katsuta et al. and Rothon et al.,[18,19] what we can understand is that the tumor extended to the posterior cranial fossa, through the intracranial orifice of the JF, and to the cerebellopontine angle, through the round window and the internal acoustic meatus. This pathophysiological and anatomical data of the tumor behavior is confirmed by the MRI scan, showing that the tumor has an epicenter in the right jugular fossa and extends to the ipsilateral cerebellar point, invading the internal auditory canal. This anatomical configuration, therefore, is similar to tumors of the JF (paragangliomas, schwannomas and meningiomas).

Al-Mefty et al. describes that CT, MRI, and angiographic findings were necessary diagnostic tools for PGLs. Angiographic studies were critical for assessing the appropriateness of preoperative embolization after the blood supply of the tumor had been demonstrated.[20] The typical imaging pattern of PGLs (an MRI scan with heterogeneous signal in T1 and T2 with gadolinium-enhanced in salt and pepper sign and a CT scan showing extensive erosion of the parajugular portion of the temporal bone) was the same as the one presented in this case. In the classification by Jackson et al.,[21] the tumor presented was confirmed as type II (►**Table 1**).

Digital angiography was performed in the case report patient and preoperative embolization to reduce bleeding during surgery was necessary,[5,19] being performed 48 hours before the described surgery. According to Ramina et al., preoperative embolization is very useful to reduce bleeding and surgical time. For Jackson et al., embolization, such as radiotherapy techniques, are arguably adjunctive, but should not be considered curative. For most authors, surgical treatment is considered the definitive treatment for head and neck PGLs that can offer immediate and complete tumor elimination.[17,22–24]

Table 1 Glasscock-Jackson classification for glomus tumors in the Jugular foramen

I	Tumor involving jugular bulb, middle ear and mastoid
II	Tumor extending below the internal acoustic meatus; may present intracranial extension
III	Tumor extending to the petrous apex; may present intracranial extension
IV	Tumor extending beyond the petrous apex to the infratemporal clivus or infratemporal fossa; may present intracranial extension

Source: Brain and Spine tumors – Primary and secondary. Jugular Foramen Paragangliomas. ISBN 978–1- 78984–158–9.

At immunohistochemistry,[25] a specific neuron enolase is positive in neoplastic cells, deriving from neural crest paraganglia. The S-100 protein is characteristically positive in sustaining cells, which surround the lobes of tumor cells. The 5% of K_i-67, found in this case is typical of progressive growth cells, such as PGLs. Both synaptophysin and chromogranin are associated with neurotransmitter vesicles and are positive in the cytoplasm of neoplastic cells, consistent with the neuroendocrine nature of this type of tumor. Butz JJ et al. it relates the increase in tumor size in any type of syndrome PPC/PGL with higher concentrations of catecholamines and catecholamine metabolites measured preoperatively.[12]

Intraoperative electrophysiological monitoring is essential to prevent nerve damage, to locate their trajectory inside and around the tumor and to estimate the postoperative functional prognosis.[26,27] Following the rationale exposed in the literature and seeking the integrity of the neurological function of the asymptomatic patient in relation to the other cranial nerves (except VIII), the surgery was performed with monitoring of the III to XII cranial nerves, allowing a resection guided by neurophysiology, which contributed to the excellence of the postoperative result of maintaining the function of all the cranial nerves, except the previously compromised.

Regarding access to the jugular foramen, according to Katsuta et al. and Rothon et al.,[18,19] there are three possible groups: (1) lateral group, approaches through the mastoid; (2) posterior group, approaches through the posterior cranial fossa through the retrosigmoid access and its variants; and (3) anterior group, centered on the tympanic bone. The choice of the most appropriate access requires an understanding of the nature as well as of the extent of the injury. The combination of two or three accesses may be necessary, either at different times or in a single surgical intervention.[28]

The most used surgical technique involves a mastoidectomy and access to the infratemporal fossa to resect the tumor.[17,22–24]Radical resection of large PGLs of the jugular foramen with intracranial extension is difficult, and for this reason a multidisciplinary skull base approach offers the best chance of total removal with preservation of lower cranial nerves, vessels and of the brainstem.[22]

In the case reported, a combined access was used to approach the lesion: an access from the lateral group – whose basic element is mastoidectomy – combined with an access from the posterior group (via retrosigmoid). Prior to the mastoidectomy, cervical dissection was performed to provide proximal control of the great vessels (both the internal carotid and the internal jugular vein). Immediately after the mastoidectomy, with extensive infra-labyrinthic drainage, access was allowed to the upper jugular bulb and to the tumor portion at this level.

The second stage of the surgery was a lateral suboccipital craniotomy for retrosigmoid access; according to Katsuta et al. and Rothon et al,[18,19] lesions located predominantly in the intradural space can be resected through the retrosigmoid access. This provides a broader view of the nerves entering the

JF and also has practically the same window obtained at the retrolabyrinthine route as well as the minimal mastoidectomy – with the advantage of having an obtained view in less surgical time – moreover, it exposes the cisterns of the cerebellopontine angle and the intracranial segment of the cranial nerves that cross the jugular foramen, the hypoglossal canal and the internal acoustic meatus as well.

Conclusion

Paragangliomas associated with genetic familial syndromes with VHL disease are rare entities that deserve scientific notification. This tumor resection is possible from precise clinical evaluation and preoperative exams. Complications can occur during and after the surgery and, therefore, we must be adequately prepared for their treatment. The use of embolization in the preoperative period may considerably reduce bleeding during surgery. Once again, we truly believe that experience is essential for its effective treatment.

Note

Institution where the Case Report was held: Hospital Heliópolis, São Paulo, state of São Paulo, Brazil

Conflict of Interests

The authors have no conflict of interests to declare.

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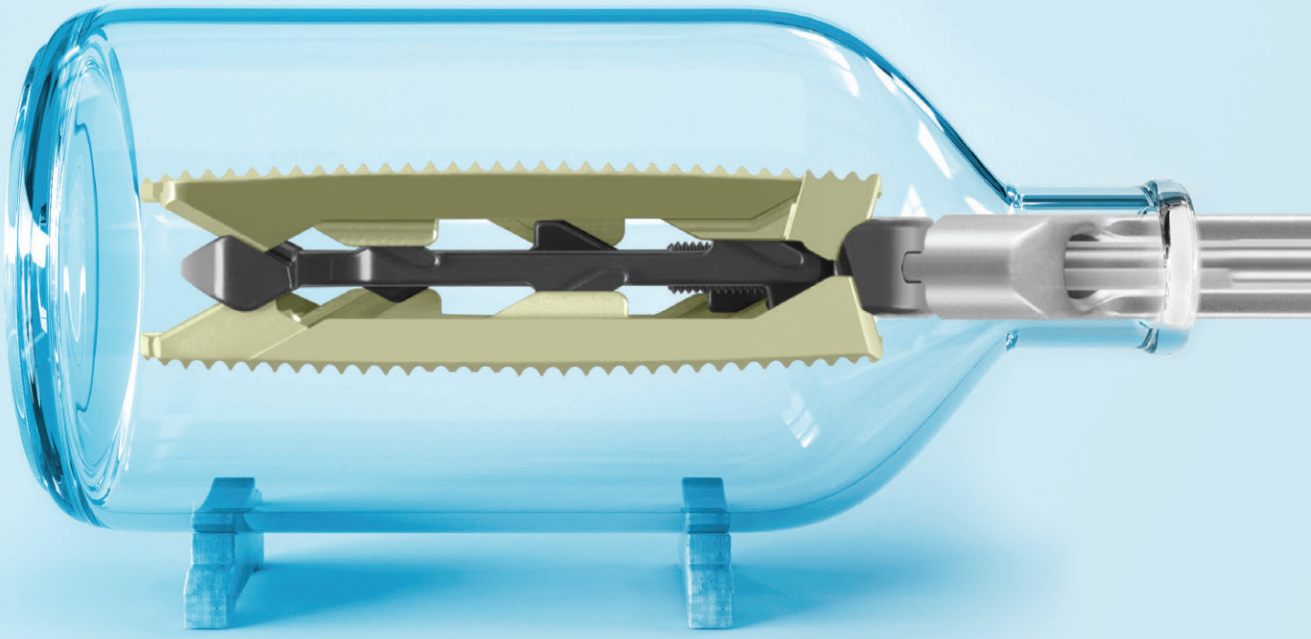

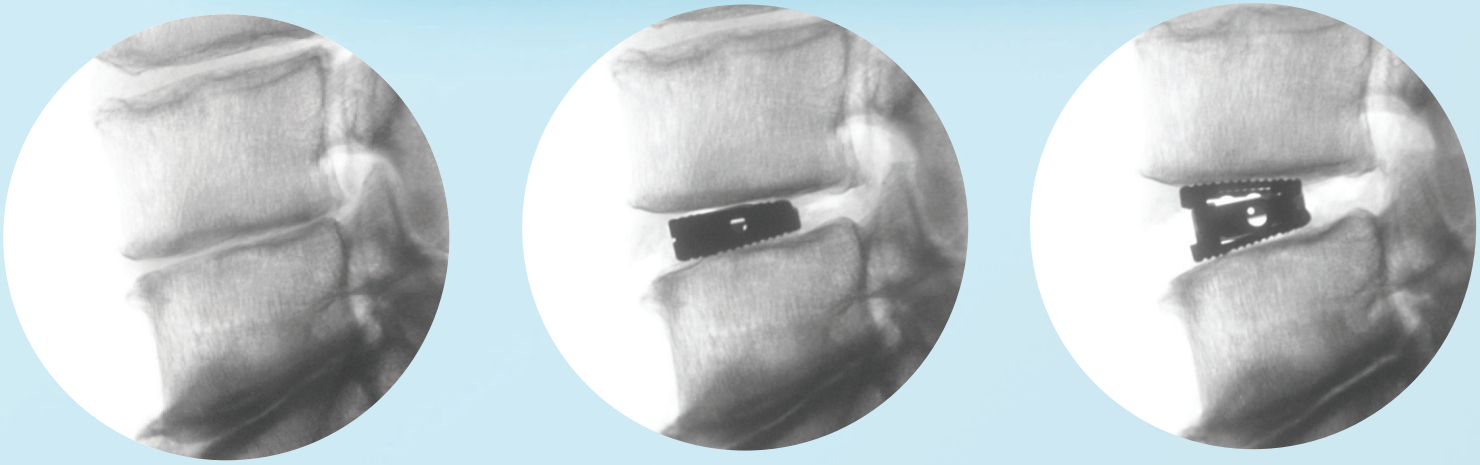

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