CASE REPORT

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Mass effect: a plethora of symptoms caused by an otherwise benign transitional pituitary meningioma. Case report

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Abstract

Meningiomas are among the most commonly encountered tumors of the central nervous system, being more frequent in females. We present the case of a dyslipidemic male patient, previously diagnosed with coronary artery disease for which he previously underwent percutaneous coronary intervention with the placement of two bare metal stents on the left anterior descending artery. He was presented to the emergency department for atypical angina and a seven-day history of dizziness when switching from clino- to orthostatism, reduced visual acuity, diplopia and vomiting. Electrocardiogram (ECG), both at rest and exercise test were suggestive for myocardial ischemia. Echocardiography revealed myocardial hypokinesia in the territory of the right coronary artery and of the left descending artery, while coronarography showed insignificant intra-stent stenosis. Imaging techniques revealed a frontobasal extraneuraxial mass, creating a compressive effect on both middle cerebral arteries and on the optic chiasm as well as thickening of the dura mater adjacent to the mass. Endocrinology blood tests showed hypocortisolemia, hyperprolactinemia and low levels of free thyroxine (fT4), suggesting secondary combined pituitary hormone deficiency. The patient underwent surgery and total resection of the tumor was performed. Definite diagnosis – transitional meningioma – was obtained through histological examination and immunohistochemistry. The key feature of this case was the extra-cardiac cause of angina accompanied by ECG abnormalities in a patient with stable coronary heart disease, in whom the clinical presentation was secondary to blood pressure variations in the context of pituitary and adrenal deficiency.

Keywords: angina, blood pressure variations, pituitary hormone deficiency, meningioma.

Introduction

Meningiomas are the most common benign tumors arising from the arachnoid cap cells of the leptomeninges and accounting for 13–26% of all primary tumors of the central nervous system [1]. Their incidence was 30–40% in autopsy series [2], suggesting that almost 20% remain asymptomatic. Although meningiomas occur in a wide age range, they predominantly affect patients in the sixth and seventh decade of life, being more frequent in females, with a female to male ratio of 1.8:1 [2]. They are mostly solid tumors, and their characteristic appearance on computed tomography (CT) scan or magnetic resonance imaging (MRI) is usually sufficient to establish a correct diagnosis.

This case report aims to underline that even a benign tumor can have serious consequences, either by mass effect or other mechanisms, and the fact that when faced with a challenging range of seemingly unrelated symptoms, a physician should always strive to find and treat the cause of the disease, not just its polymorphic manifestations.

Case presentation

We report the case of M.G., a 70-year-old male who was admitted in the Department of Internal Medicine at the Emergency Clinical Hospital of Bucharest, Romania, in April 2014 (Chart No. 17249), for a history of three weeks of atypical angina and a seven days long history of dizziness during postural changes from clino- to orthostatism, reduced visual acuity, diplopia and vomiting.

His medical history was relevant for dyslipidemia and coronary artery disease for which he had undergone percutaneous coronary intervention (PCI) with the placement of two bare-metal stents (BMS) at the site of the left anterior descending (LAD) artery seven years before the current presentation, with insignificant intra-stent stenosis showing on the four-years control coronary angiogram. His pharmacological therapy thus included a beta-blocker, a statin and an antiplatelet agent (Acetyl-salicylic acid).

Given the symptoms of angina and his medical history, an electrocardiogram (ECG) exercise test was performed

in ambulatory care two weeks before current admission. The test result was positive for myocardial ischemia, showing down-sloping ST-segment depression of 0.2 mV in LAD artery territory and the patient was then referred to a heart clinic for further evaluation.

However, the occurrence of the latter symptoms urged the patient to present to the Emergency Department (ED). On clinical examination, the patient was in moderate distress, pale, with orthostatic hypotension – blood pressure (BP) values in clinostatism and orthostatism were 112/78 mmHg and 70/40 mmHg, respectively, heart rate 70 beats/min, with a regular cardiac rhythm and no heart murmurs on auscultation. On neurological examination, the patient had diplopia with no other abnormalities.

ECG showed sinus rhythm, 72 bmp, QRS axis at 30°, repolarization abnormalities suggesting anterior myocardial ischemia (Figure 1).

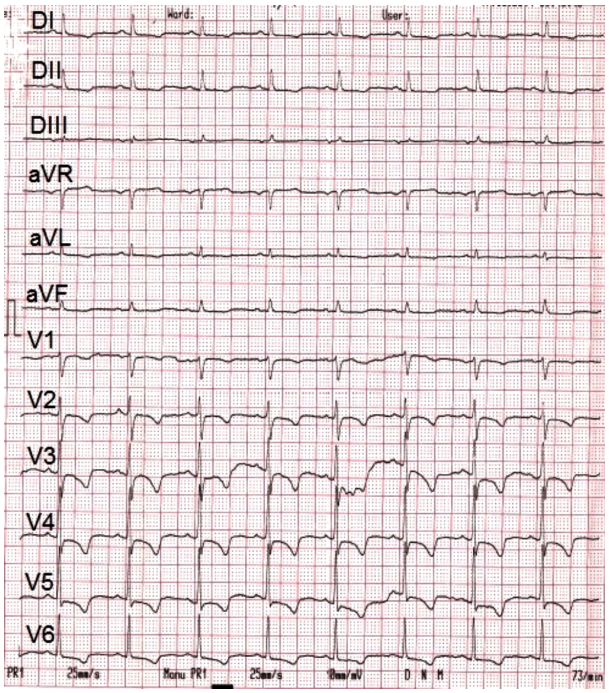

Figure 1 – ***ECG aspect on admission revealing sinus rhythm, 73 beats/min, QRS axis at 30°, repolarization abnormality suggesting anterior myocardial ischemia.***

Chest X-ray and abdominal ultrasound were unremarkable. The patient was not diabetic and laboratory tests showed normal glucose levels.

Echocardiography revealed myocardial hypokinesia in the territory of the right coronary artery (RCA) and the LAD artery, but without systolic dysfunction (left ventricle ejection fraction of ~50%), mild diastolic dysfunction, septal bulge and no significant valvular heart diseases.

In order to rule out a new coronary artery lesion, emergency coronarography was performed and showed minor changes compared to the previous examination: lipid infiltration within the LAD artery, in-stent neointimal hyperplasia creating a 40–50% stenosis of the proximal segment of LAD artery, atherosclerotic plaques creating a 50–60% stenosis of the medium segments of RCA and left circumflex artery.

Given the recent history of dizziness when switching from clino- to orthostatism, a cerebrovascular cause was suspected. Carotid ultrasonography revealed diffuse carotid atheromatosis with atherosclerotic plaques creating a stenosis of maximum 45% of both common carotid arteries, without hemodynamic impact.

Taking in consideration the new-onset diplopia, a head CT was performed (Figure 2) showing a 35/33 mm solid suprasellar tumor creating a compressive effect at the origin of both middle cerebral arteries and the optic chiasm, also with the bilateral enlargement of the supratentorial subarachnoid spaces.

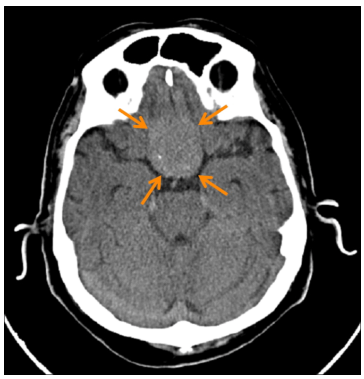

Figure 2 – ***CT aspect of a 35/33 mm solid suprasellar tumor, creating a compressive effect at the origin of both middle cerebral arteries and the optic chiasm.***

Afterwards, a head MRI (Figure 3) revealed a frontobasal extraneuraxial mass, measuring 31/37/20 mm, intensely gadolinophilic, flanked by the ethmoid and sphenoid bones, extending to the optic chiasm and incorporating the supracavernous segments of the internal cerebral arteries. Also, thickening of the dura mater adjacent to the mass ("dural tail sign") was observed (Figure 4). The pituitary stalk was posteriorly displaced by the tumor.

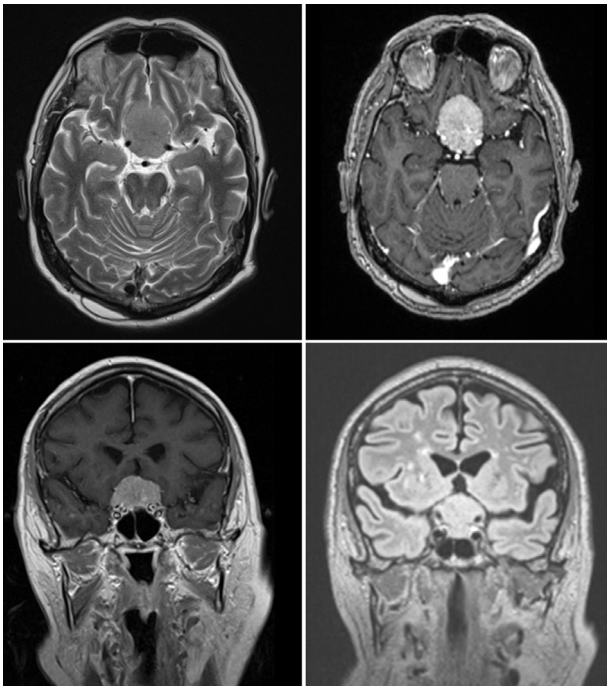

Figure 3 – ***MRI aspect revealing a frontobasal extraneuraxial mass, measuring 31/37/20 mm, intensely gadolinophilic, flanked by the ethmoid and sphenoid bones, extending to the optic chiasm and incorporating the supracavernous segments of the internal cerebral arteries.***

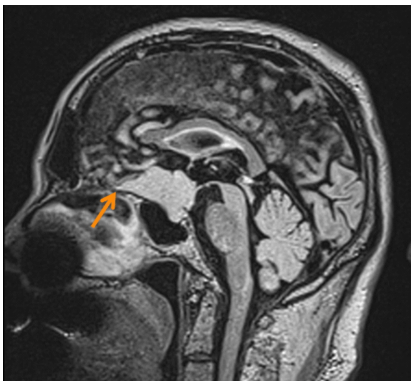

Figure 4 – ***MRI aspect revealing thickening of the dura mater adjacent to the mass ("dural tail sign").***

Hormone testing revealed low levels of serum cortisol: 2.14 µg/dL (normal values: 10–20 µg/dL), low levels of free thyroxine (fT4): 6.7 pmol/L (normal values: 10.6–22.7 pmol/L) and moderate high levels of prolactin: 897 µIU/mL (normal values: 98–456 µIU/mL), which led to the diagnosis of secondary combined pituitary hormone deficiency and hyperprolactinemia, thus hormonal treatment with Prednisone and Levothyroxine was initiated.

In this setting, considering that the imaging tests suggested an extraneuraxial tumor, the decision was to proceed to surgery, which would also allow biopsy and histological diagnosis. Therefore, the patient was transferred to the Department of Neurosurgery at the "Bagdasar–Arseni" Emergency Clinical Hospital, Bucharest (Chart No. 15085). After thorough preoperative planning, the tumor was totally removed by using a subfrontal approach. The tumor was sent for histological assessment.

From the macroscopic point of view, the tumor had white-gray color and elastic-soft consistency, while histologically [Hematoxylin–Eosin (HE)-stained sections] (Figures 5 and 6), the tumor consisted of cells arranged in whorls with hyalinized and calcified centers ("psammoma bodies"). The immunohistochemical tests showed immunoreactivity to epithelial membrane antigen (EMA) (E29, Lab Vision®, 1:50 – Figure 7), Ki-67 (MIB1, Immunologic®, 1:500 – Figure 8), progesterone receptor (PR) (rabbit anti-human, Dako®, 1:100 – Figure 9) and vimentin (VIM 3B4, Dako®, 1:400 – Figure 10). The pathological examination established the diagnosis of transitional pituitary meningioma.

The postoperative evolution was uneventful. Significant clinical improvement was observed after surgical therapy. The head CT after three months from surgery revealed the absence of a recurrent tumor (Figure 11). Afterwards, the disease-free status of the patient was confirmed during a three-year follow-up (last check-up in April 2017).

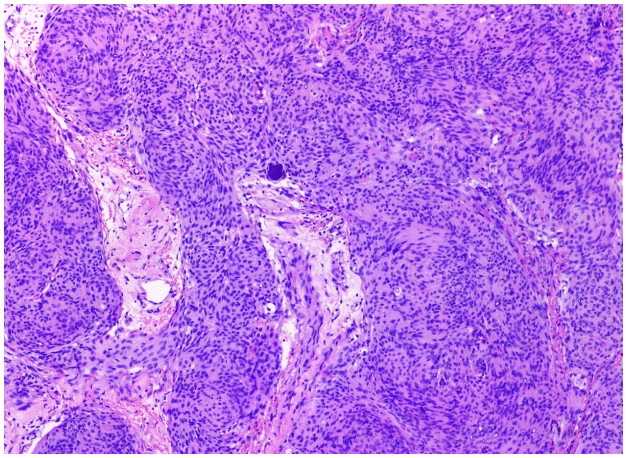

Figure 5 – ***The tumor cells are uniform and forming lobules partly demarcated by collagenous septa with rare psammoma bodies (HE staining, ×100).***

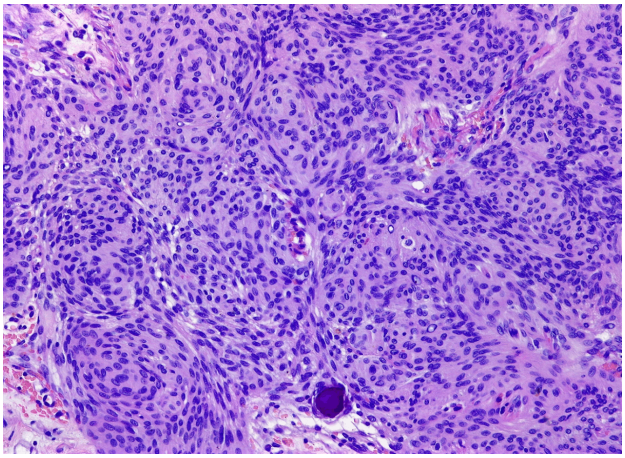

Figure 6 – ***The eosinophilic cytoplasm is abundant. The indistinct cellular margins have a syncytial appearance. The nuclei are oval, with delicate chromatin and some are optically clear (HE staining, ×200).***

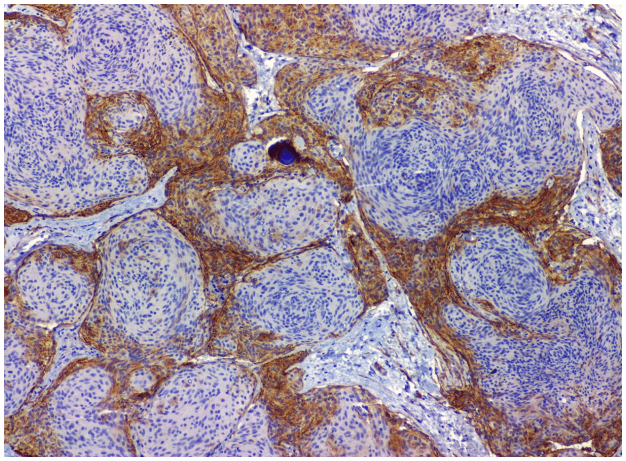

Figure 7 – ***Positive zonal staining for EMA immunohistochemistry (×100) in tumor cells.***

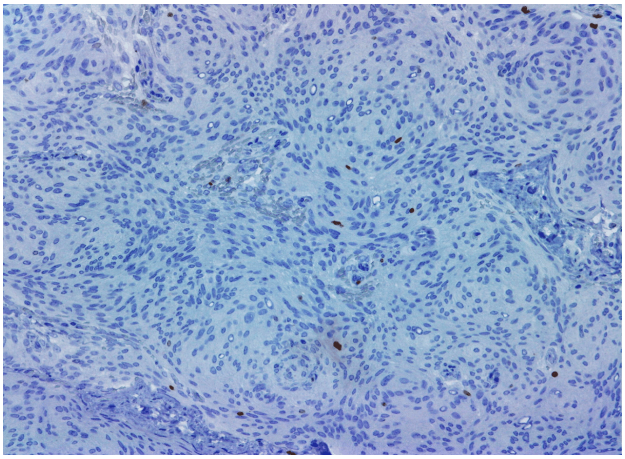

Figure 8 – ***Positive staining for Ki-67 immunohistochemistry (×200) revealing a low Ki-67 index (2–3%).***

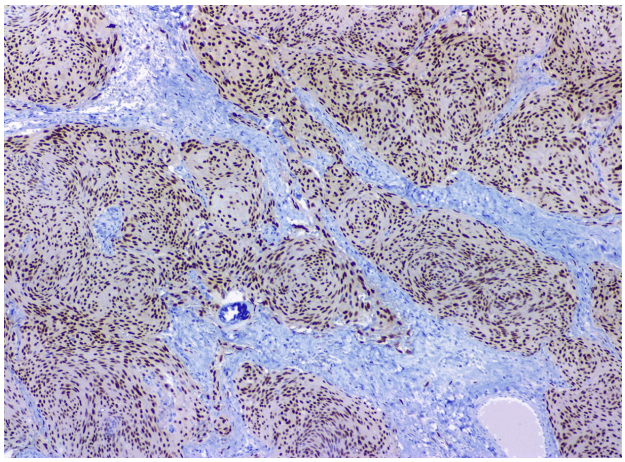

Figure 9 – *Positive diffuse staining for PR immunohistochemistry (×100) of the tumor cells nuclei.*

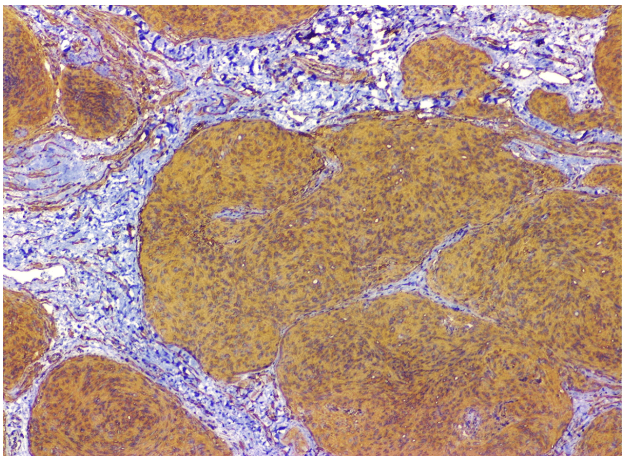

Figure 10 – *Positive diffuse cytoplasmic staining for vimentin immunohistochemistry (×100).*

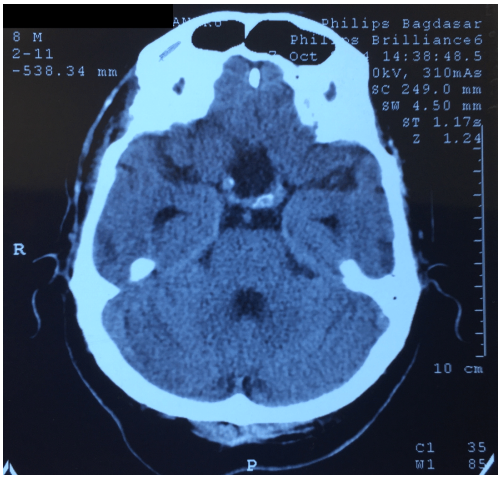

Figure 11 – *CT aspect after three months from surgery revealing the absence of a recurrent tumor.*

Discussion

In 2007, *World Health Organization* (WHO) introduced a classification of meningiomas based on histopathological criteria, which reflects their severity, proliferation potential and risk of recurrence. Approximately 90% of meningiomas are benign (WHO grade I), 5–7% are atypical (WHO grade II) and 1–3% are malignant (WHO grade III) [1]. The mechanisms involved in their molecular pathogenesis and in their malignant progression are not clear. A similar situation was noticed in case of neuroendocrine tumors [3, 4] that, in a previous study, a correlation with renal and hepatic impairment was noticed [5].

Depending on their location, meningiomas may have, more or less, a typical symptomatology: foramen magnum meningiomas may present nuchal and suboccipital pain [6]; tuberculum sellae tumors may cause progressive visual loss – "chiasmal syndrome" with ipsilateral optic atrophy and bitemporal hemianopia [7] and may extend into the optic canal and displace the anterior cerebral arteries and the pituitary stalk; cavernous sinus meningiomas associate proptosis and diplopia due to paralysis of the third and sixth cranial nerves, respectively periorbital pain and numbness due to compression of the fifth cranial nerve [8]; olfactory groove meningiomas may cause anosmia, optic atrophy, scotoma in the ipsilateral eye and papilledema in the contralateral one (Foster–Kennedy syndrome).

The key feature of this case was the atypical angina accompanied by ECG abnormalities in a patient with coronary artery disease, in whom the clinical presentation was considered secondary to BP variations (especially when switching from clino- to orthostatism) in the context of both endocrine disorders and the compressive effect determined by the tumor.

Also, as a result of their mass effect, in other cases, meningiomas led to impaired secretion of pituitary hormones [9]. The presence of the "stalk syndrome" consisting of elevated prolactin, but not to such levels as seen in prolactinomas and a secretory deficit in one or more of the anterior pituitary hormones suggest either hypothalamic dysfunction or disruption of pituitary stalk [10]. Consequently, growth hormone deficiency may cause osteoporosis in adults and growth failure in children, while gonadotropin deficiency results in loss of libido or even impotence. Hypothyroidism due to thyroid-stimulating hormone deficiency and hypoadrenalism due to adrenocorticotropic hormone deficiency [11] may also develop, though being usually less severe than their primary counterparts, given the preserved mineralocorticoid secretion [12].

In clinical practice, patients with recent onset of seizures or focal neurological signs (especially in those with chronic kidney disease), possibly secondary to intracranial tumor, should undergo head MRI [13, 14]. Thus, head MRI is the best imaging technique, when gadolinium contrast is used, for the detection of meningiomas due to its ability to show the dural tail extending away from the lesion and the homogeneous enhancement of tumors [15]. Head CT scan is complementary in diagnosis showing intratumoral calcification and hyperostosis [16], while angiographic studies show the arterial supply to the meningiomas.

The macroscopic appearance is that of a globular, multiloculated mass of a gritty consistency, involving the dura mater and easily separated from the pia mater. On cut section, the tumor may be either pale and translucent or reddish-brown depending on the degree of vascularity [17].

The microscopic appearance is that of cellular areas organized in sheets with indistinguishable cytoplasmic borders, thus resembling normal arachnoidal cells.

Psammoma bodies (from the Greek word "psammos" meaning "sand") – mineralized whorls with calcium apatite and collagen [18] – constitute an additional feature of meningiomas.

Meningiomas can be clearly diagnosed by means of immunohistochemistry. These tumors are positive for EMA (in 80% of cases) and E-cadherin (a calcium-dependent cell adhesion molecule) and negative for anti-Leu 7 monoclonal antibody, which is found in schwannomas [19]. In our case, the tumor also tested positive for vimentin, progesterone receptors and Ki-67. As previous cases in the literature revealed [20], low Ki-67 expression may be correlated with the less aggressive behavior of this meningioma regarding the surrounding tissues.

Given the clinical features and histological findings, the differential diagnosis was made with other tumors such as hemangiopericytoma (positive staining for vimentin, but negative for S100), solitary fibrous tumor (positive staining for vimentin, progesterone receptors but negative for S100 and EMA), Langerhans cell histiocytosis (positive staining for S100 and negative for glial fibrillary acidic protein, but reniform nuclei), but also with other types of mengiomas (angiomatous, meningothelial, secretory, anaplastic or atypical) [1–3, 7, 21].

Surgical resection is the mainstay therapy for meningiomas. The decision on the best surgical approach is based on the result of the MRI. Thus, the type of resection differs according to tumor size, location, consistency, vascular and neural involvement, and, in the case of recurrence, prior surgical outcome.

In 1957, Simpson proposed a five-grade classification of surgical removal of meningiomas [22], which would be revised, in 1992, by Kobayashi *et al.* [23] from a microsurgical point of view and based on the extent of microscopic removal. In 1993, Kinjo *et al.* [24] included grade 0 proposing an additional 2 cm dural margin resection. The revised Simpson grading system is the most important predictive factor for meningioma recurrence correlating with extent of resection [22, 23]:

- grade I: complete microscopic removal of tumor and dural attachment with any abnormal bone;
- grade II: complete microscopic removal of tumor with diathermy coagulation of its dural attachment;
- grade IIIA: complete microscopic removal of intradural and extradural tumor without resection or coagulation of its dural attachment;
- grade IIIB: complete microscopic removal of intradural tumor without resection or coagulation of its dural attachment or of any extradural extensions;
- grade IVA: intentional subtotal removal to preserve cranial nerves or blood vessels with complete microscopic removal of dural attachment;
- grade IVB: partial removal, leaving tumor of <10% in volume;
- grade V: partial removal, leaving tumor of >10% in volume, or decompression with or without biopsy.

Modern neurosurgery, microsurgery and all image-guided surgery techniques have contributed to successfully resection of tumors previously considered unresectable. In our case, complete microscopic removal of the tumor was achieved (grade I), which is associated with a very low risk of only 9% for the symptoms to reappear after 10 years.

Intensity-modulated radiation therapy and stereotactic radiotherapy should be considered for recurrent or partially resected meningiomas, for patients in whom surgery is not an option because of the tumor's location or patient comorbidities. The use of chemotherapeutic agents is limited to recurrent meningiomas and only when radiotherapy cannot be applied due to minimal effect on this type of tumors [25]. In our case, no complementary therapy was necessary.

Depending on the histological grade, the recurrence rate at five years after complete removal was 3% for benign meningiomas, whereas in the case of atypical and anaplastic ones, the rate was 38% and 78%, respectively [26, 27]. In our case, the histological assessment revealed a transitional meningioma, which is a benign tumor (according to *WHO* classification) associated with a very low recurrence rate.

Given that there are no guidelines regarding a follow-up plan, this should be adapted to the individual patient depending on tumor grade, previous treatments and remaining treatment options.

Conclusions

The essential feature of this case consists of the rapid onset of symptoms specific to meningioma, given the fact that this type of tumor usually has a slow progress. Another interesting characteristic is that the patient's angina and ECG abnormalities seem to have an extra-cardiac cause, *i.e.*, the BP variations due to pituitary and adrenal deficiency, despite his long and troubled past history of coronary artery disease. Even if the transitional meningioma is a benign tumor, in this case, it could have led to heart attack and death. Therefore, early diagnosis and treatment of this disease may prevent unfortunate events.

Conflict of interests

The authors declare that they have no conflict of interests.

References

[1] Louis DN, Scheithauer BW, Budka H, von Deimling A, Kepes JJ. Meningiomas. In: Kleihues P, Cavenee WK (eds). Pathology and genetics of tumours of the nervous system. World Health Organization (WHO) Classification of Tumours, International Agency for Research on Cancer (IARC) Press, Lyon, 2000, 176–180.

[2] Rockhill J, Mrugala M, Chamberlain MC. Intracranial meningiomas: an overview of diagnosis and treatment. Neurosurg Focus, 2007, 23(4):E1.

[3] Poiană C, Neamţu MC, Avramescu ET, Carşote M, Trifănescu R, Terzea D, Neamţu OM, Dănciulescu Miulescu R. The dedifferentiation of neuroendocrine tumor metastases: myth or reality? Rom J Morphol Embryol, 2013, 54(1):201–203.

[4] Carşote M, Păun S, Neamţu MC, Avramescu ET, Iosif C, Terzea D, Constantinoiu S, Dănciulescu Miulescu R, Neamţu OM, Poiană C. The immunohistochemistry aspects in two cases of neurofibromatosis-associated abdominal tumors. Rom J Morphol Embryol, 2012, 53(2):401–405.

[5] Sinescu RD, Niculae A, Peride I, Vasilescu F, Bratu OG, Mischianu DL, Jinga M, Checheriţă IA. Uterus neuroendocrine tumor – a severe prognostic factor in a female patient with alcoholic cirrhosis undergoing chronic hemodialysis. Rom J Morphol Embryol, 2015, 56(2):601–605.

[6] Meyer FB, Ebersold MJ, Reese DF. Benign tumors of the foramen magnum. J Neurosurg, 1984, 61(1):136–142.

[7] Al-Mefty O, Smith RR. Tuberculum sellae meningiomas. In: Al-Mefty O (ed). Meningiomas. Raven Press, New York, 1991, 397–398.

[8] Sekhar LN, Sen CN, Jho HD, Janecka IP. Surgical treatment of intracavernous neoplasms: a four-year experience. Neurosurgery, 1989, 24(1):18–30.
[9] Schneider HJ, Aimaretti G, Kreitschmann-Andermahr I, Stalla GK, Ghigo E. Hypopituitarism. Lancet, 2007, 369(9571):1461–1470.
[10] Fernandez-Rodriguez E, Bernabeu I, Andujar-Plata P, Casanueva FF. Subclinical hypopituitarism. Best Pract Res Clin Endocrinol Metab, 2012, 26(4):461–469.
[11] Diederich S, Franzen NF, Bähr V, Oelkers W. Severe hyponatremia due to hypopituitarism with adrenal insufficiency: report on 28 cases. Eur J Endocrinol, 2003, 148(6):609–617.
[12] Toogood AA, Stewart PM. Hypopituitarism: clinical features, diagnosis, and management. Endocrinol Metab Clin North Am, 2008, 37(1):235–261, *x*.
[13] Pirici D, Ion DA, Mogoantă L, Mărgăritescu O, Pirici I, Foarfă C, Tudorică V, Panduru NM, Coconu M, Checheriţă IA. Massive cortico-subcortical ischemic stroke with a consecutive hemorrhagic event: a case report. Rom J Morphol Embryol, 2011, 52(2):699–708.
[14] Checheriţă IA, David C, Stoica L, Popescu P, Ciocâlteu A, Lascăr I. New mediators of vascular damage in dialysed patients. Rom J Morphol Embryol, 2011, 52(2):533–536.
[15] Rachinger W, Grau S, Tonn JC. Different microsurgical approaches to meningiomas of the anterior cranial base. Acta Neurochir (Wien), 2010, 152(6):931–939.
[16] Rao VJ, Lames RA, Mitra D. Imaging characteristics of common suprasellar lesions with emphasis on MRI findings. Clin Radiol, 2008, 63(8):939–947.
[17] Sindou MP, Alaywan M. Most intracranial meningiomas are not cleavable tumors: anatomic-surgical evidence and angiographic predictibility. Neurosurgery, 1998, 42(3):476–480.
[18] Wellenreuther R, Waha A, Vogel Y, Lenartz D, Schramm J, Wiestler OD, von Deimling A. Quantitative analysis of neurofibromatosis type 2 gene transcripts in meningiomas supports the concept of distinct molecular variants. Lab Invest, 1997, 77(6):601–606.
[19] Yamashima T, Tohma Y, Junkoh Y. Expression of cell adhesion molecule: epithelial-cadherin in meningiomas. Brain Tumor Pathol, 1992, 9(1):33–50.
[20] Neagu TP, Sinescu RD, Enache V, Achim SC, Ţigliş M, Mirea LE. Metastatic high-grade myxofibrosarcoma: review of a clinical case. Rom J Morphol Embryol, 2017, 58(2):603–609.
[21] Chourmouzi D, Potsi S, Moumtzouoglou A, Papadopoulou E, Drevelegas K, Zaraboukas T, Drevelegas A. Dural lesions mimicking meningiomas: a pictorial essay. World J Radiol, 2012, 4(3):75–82.
[22] Simpson D. The recurrence of intracranial meningiomas after surgical treatment. J Neurol Neurosurg Psychiatry, 1957, 20(1):22–39.
[23] Kobayashi K, Okudera H, Tanaka Y. Surgical considerations on skull base meningioma. First International Skull Base Congress, June 18, 1992, Hanover, Germany.
[24] Kinjo T, al-Mefty O, Kanaan I. Grade zero removal of supratentorial convexity meningiomas. Neurosurgery, 1993, 33(3): 394–399; discussion 399.
[25] Norden AD, Drappatz J, Wen PY. Advances in meningioma therapy. Curr Neurol Neurosci Rep, 2009, 9(3):231–240.
[26] McCarthy BJ, Davis FG, Freels S, Surawicz TS, Damek DM, Grutsch J, Menck HR, Laws ER Jr. Factors associated with survival in patients with meningioma. J Neurosurg, 1998, 88(5): 831–839.
[27] Jääskeläinen J, Haltia M, Servo A. Atypical and anaplastic meningiomas: radiology, surgery, radiotherapy, and outcome. Surg Neurol, 1986, 25(3):233–242.

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