Aggressive pituitary lesion with a remarkably high Ki-67

Lesão pituitária agressiva com Ki-67 notavelmente elevado

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SUMMARY

The uncommon aggressive pituitary tumors are named carcinomas when metastases are detected, either in the central nervous system and/or systemically. Some cases are associated with hormonal overproduction, but most are diagnosed because of local symptoms. These neoplasias are generally refractory to current treatments. A 51 year-old woman presented sudden onset of headache, left arm paresis and left facial hypoesthesia. Computed tomography scan and magnetic resonance imaging revealed a pituitary tumor invading the left sphenoidal and cavernous sinuses. Laboratory data excluded hormonal hypersecretion. The patient underwent transsphenoidal surgery and histological findings showed a neoplasia with Ki-67 estimated at 75%. Medical imaging excluded both a primary occult tumor and central nervous system or systemic dissemination. Three weeks postoperatively, neurological condition worsened, with new onset of ataxia, bilateral ptosis, ophthalmoplegia and an increase in the size of the lesion, leading to surgical intervention by craniotomy, followed by only a few sessions of radiotherapy, because of severe disease progression. Patient died nearly 2 months after the initial manifestations. This case illustrates the aggressiveness of some pituitary lesions, the limited efficacy of current treatment modalities such as surgery or radiotherapy and the pitfalls of the current pituitary tumors classification. To our knowledge, this case corresponds to one of the most aggressive pituitary neoplasms reported so far, with a very high Ki-67 index (75%) and short survival (2 months). Ki-67 index could be of prognostic value in pituitary tumors. Pituitary tumors World Health Organization (WHO) classification could be revisited. Arq Bras Endocrinol Metab. 2014;58(6):656-60

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SUMÁRIO

Os raros tumores pituitários agressivos são chamados carcinomas quando são detectadas metástases, sejam sistêmicas e/ou em sistema nervoso central. Alguns casos estão associados com superprodução de hormônio, mas a maioria é diagnosticada em função dos sintomas locais. Essas neoplasias são geralmente refratárias aos tratamentos atuais. Uma mulher com 51 anos de idade apresentou dor de cabeça de início súbito, paralisia de braço esquerdo e hipoestesia facial esquerda. A tomografia e a ressonância magnética revelaram um tumor pituitário invadindo os seios esfenoidal e cavernoso esquerdos. Os dados laboratoriais excluíram hipersecreção hormonal. A paciente foi submetida à cirurgia transesfenoidal, e os achados histológicos mostraram uma neoplasia com Ki-67 estimado em 75%. As imagens excluíram tanto um tumor oculto primário quanto disseminação sistêmica ou do sistema nervoso central. Três semanas após a cirurgia, a condição neurológica apresentou piora com início de ataxia, ptose bilateral, oftalmoplegia e aumento do tamanho da lesão, levando à intervenção cirúrgica por craniotomia, seguida por apenas algumas sessões de radioterapia devido à progressão grave da doença. A paciente veio a óbito depois de quase dois meses das manifestações iniciais. O caso ilustra a agressividade de algumas lesões pituitárias, a eficácia limitada das modalidades atuais de tratamento, como a cirurgia ou a radioterapia, e as limitações da classificação atual de tumores pituitários. Até onde sabemos, esse caso corresponde a uma das neoplasias pituitárias mais agressivas descritas até hoje, com um nível muito alto de Ki-67 (75%) e sobrevida curta (2 meses). O nível de Ki-67 pode ser de valor prognóstico em tumores pituitários. A classificação da Organização Mundial da Saúde (OMS) para tumores pituitários deveria ser revisitada. Arq Bras Endocrinol Metab. 2014;58(6):656-60

INTRODUCTION

Pituitary tumors account for approximately 15% of all intracranial neoplasms (1,2). The majority is benign, non-invasive and asymptomatic. Some are detected incidentally by imaging exams; others are functioning-tumors generating hormonal syndromes (decreasing ordered: prolactin; ACTH; GH; TSH; LH), whereas others are suspected due to local mass symptoms. Hypopituitarism can also occur in some cases, particularly in larger tumors (3).

Pituitary carcinomas are rare conditions, accounting only 0.1 to 0.2% of all pituitary tumors (4,5). Pituitary carcinoma is defined by the presence of craniospinal and/or systemic metastases (6,7). There is no gender preference and mean of age at diagnosis is 44 years (4). Most pituitary carcinomas develop from invasive relapsing or previously operated or irradiated invasive adenomas (8,9). Type and grade of invasiveness do not represent a criteria for malignancy, although when prominent increase its probability (4,10). For some, proliferation indexes particularly Ki-67, have important prognostic value and should be considered as diagnostic criteria (10-12). Pituitary metastatic disease, typically from breast or lung cancer, accounts for 1 to 2% of sellar masses and its differential diagnosis with pituitary tumors is challenging as they often mimic them clinically, imagiologically and histologically (13,14).

We present a rare case of pituitary neoplasm with extremely aggressive behavior, illustrating the pitfalls and difficulties in the classification and management of these entities.

CASE REPORT

A Caucasian 51 year-old woman, non-smoker, with irrelevant past medical history, not taking any medication, was asymptomatic until February 2012, when she reported sudden onset of intense headache associated with left arm paresis and left facial hypoesthesia. Neurological examination identified a minor left arm paresis, left facial hypoesthesia and slight left upper-lid ptosis; no visual impairment or other neurological defects were observed. Computed tomography (CT) scan and magnetic resonance imaging (MRI) documented a pituitary mass invading the sphenoidal and left cavernous sinuses, and the pituitary stalk was centered (Figure 1). Laboratory data was significant for mild hyponatremia (130 mmol/L), high creatine kinase (1,188 u/L), central hypothyroidism (TSH = 0.05 uUI/mL [0.34-5.60]; free-T4 = 0.51 ng/dL [0.61-1.12]) and adrenal insufficiency (ACTH not measured but serum cortisol = 1.5 ug/dL [6.7 - 22.6]). Serum prolactin was 27.9 ng/mL (2.74-19.64); GH was 0.447 ng/mL (0.01-3.607) and beta-hCG < 0.5 mUI/mL (< 0.5-2.9). LH and FSH were not measured.

The patient was submitted to transsphenoidal surgery. A tumor with a soft consistence and necrotic component of the pituitary apoplexy type was found and partially resected. Clinical improvement was observed after surgery, particularly on the intensity of the headaches, but the third left cranial nerve palsy persisted. Patient was discharged under replacement therapy with levothyroxine and hydrocortisone.

Histological findings revealed a monotonous hypercellular population of cohesive small round cells, with large nuclei and prominent nucleoli. Numerous mitotic and apoptotic figures were seen, as well as diffuse necrotic areas. Ki-67 index was estimated at 75%. Immunohistochemistry was positive for AE1/AE3 cytokeratines, nuclear p53 protein, cyclin D1 and focally positive for synaptophysin, chromogranin, neuron-specific enolase, CD 56 and epithelial membrane antigen. There was no immunoreactivity for pituitary hormones, melanoma markers (S-100, HMB45, MelanA), cytokeratines 7, 8, 18, 19, 20, thyroid transcription factor-1, CD38, CD45, CD30, CD117, vimentin and desmin (Figure 2). Fluorescence *In Situ* Hybridization (FISH) molecular analysis was performed for c-MYC and EWS genes showing normal c-MYC and EWS gene copies in 98% and 91% of the nuclei, respectively, with no rearrangements.

Pituitary metastization from an occult tumor or systemic secondary lesions from pituitary tumor were ruled out by several complementary exams which included mammography; breast, pelvic and thyroid ultrasound; whole-body CT scan and ^{18}F-Fluorodeoxyglucose Po-

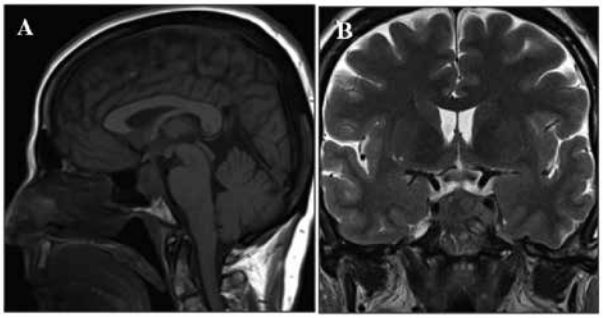

Figure 1. Magnetic resonance imaging at presentation: sagittal (**A**) and coronal (**B**) views.

sitron Emission Tomography (^{18}F-FDG-PET). Serum tumoral markers were within normal values (Carcinoembryonic Antigen; Carcinoma Antigens 15.3/19.9; CYFRA 21.1; chromogranin A, calcitonin). An Ear-Nose-Throat specialist biopsied a non-suspicious prominence in the posterior wall of cavum, which was negative for neoplasia.

Three weeks postoperatively headaches recurred associated with vomiting and neurological complaints (ataxic gait, ophthalmoplegia and bilateral ptosis); no visual field defects were present and fundoscopy was normal. Postoperatively, hypopituitarism persisted with undetectable ACTH, TSH, LH, GH and low IGF-1. CT scan at that time, showed a pituitary mass with supra-sellar and lateral extension, touching the optic chiasm and involving the left cavernous sinus and temporal lobe; no compressive effect in the brain stem or anomalies in the cerebral parenchyma were detected. Angio-MRI demonstrated a reduction in internal carotids caliber but maintained patency (Figure 3).

The patient was reoperated by frontal craniotomy with subtotal resection of the neoplasia. Intraoperatively, the tumor involved the optic nerves and infiltrated diffusely the adjacent structures. Histological findings were similar to the previous one and were consistent with undifferentiated small cell carcinoma (Figure 2). Postoperatively CT scan and MRI showed significant increase of the sellar mass, with prepontine extension and extensive invasion of the left orbit (Figures 4 and 5). Radiotherapy was initiated but discontinued after a few sessions because of severe disease progression. Rapid clinical deterioration did not allow palliative chemotherapy and the patient died a few days later, approximately 2 months after the initial manifestations.

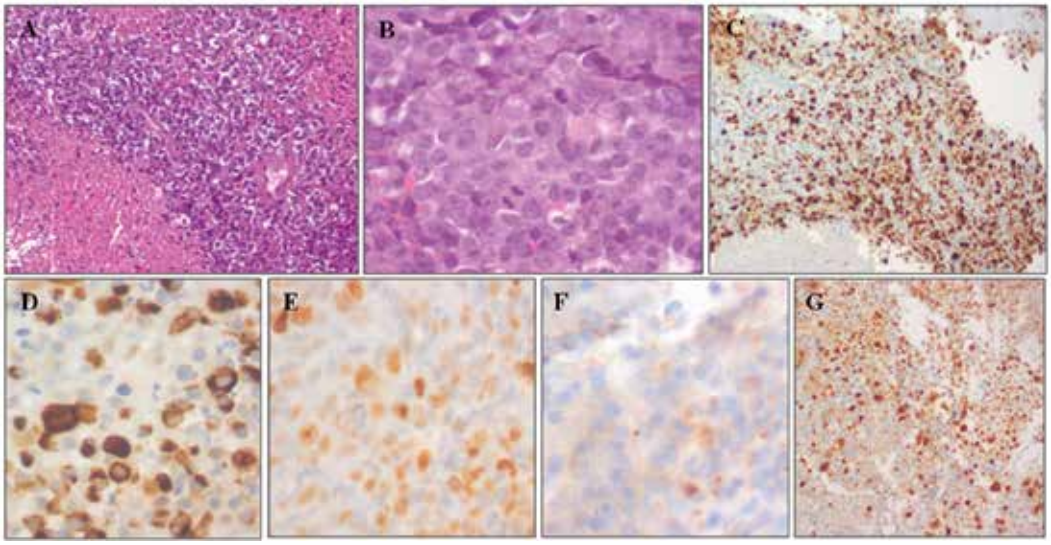

Figure 2. Pituitary carcinoma photomicrographs: **A:** hypercellular neoplasia with extensive necrotic areas (hematoxylin-eosin stain, 20x). **B:** small round cells with visible high mitotic activity (hematoxylin-eosin stain, 40x). **C:** immunohistochemistry for Ki67 protein using antibody MIB-1 quantification (20x). **D:** immunohistochemistry for AE1/AE3 cytokeratines (40x). **E:** Immunohistochemistry for p53 protein (40x). **F:** immunohistochemistry for Synaptophysin (40x). **G:** immunohistochemistry for Cyclin D1 (20x).

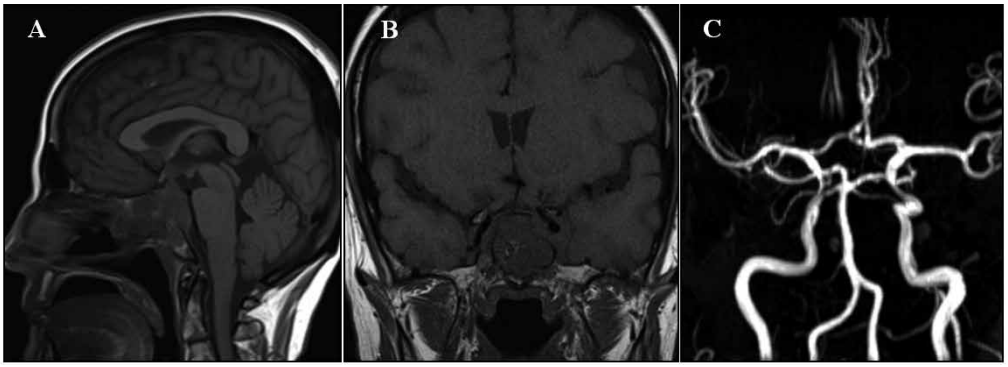

Figure 3. Follow-up magnetic resonance imaging, approximately one month after the transsphenoidal surgery (March 2012): sagittal (**A**), coronal (**B**) views and magnetic resonance angiography (**C**).

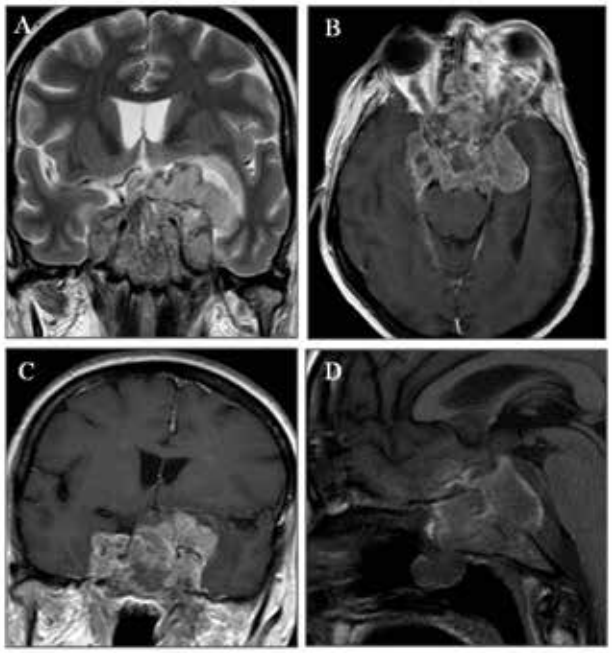

Figure 4. Follow-up magnetic resonance imaging after the second surgery and before radiotherapy, approximately 2 months after presentation (April 2012): coronal (**A,C**), axial (**B**) and sagittal (**D**) views.

DISCUSSION

This case report illustrates the diagnostic, therapeutic complexity and pitfalls that may characterize some pituitary lesions. In spite of the fact that a fulminant clinical course and histological findings strongly suggest a malignant diagnosis, the case did not fulfill the diagnostic criteria of pituitary carcinoma according with WHO classification (6), because there was no evidence of systemic or craniospinal metastization. However, the course of the disease was highly aggressive and rapidly progressive, despite two surgeries and radiotherapy, leading to death in approximately 2 months after the initial clinical manifestations. In addition, several histological findings (high Ki-67 proliferative index and p53 protein immunostaining) suggested a carcinoma and extensive tests excluded other differential diagnosis of primary or secondary pathology of sellar region (12-14). Nonetheless, a metastatic lesion from a primary occult tumor cannot be definitively excluded, although the negativity of ^{18}F-FDG-PET scan and the absence of other metastatic lesions makes such a diagnosis very unlikely.

As referred, craniospinal/systemic metastization were not documented which represent its inexistence or misdetection by imaging procedures. Among the exams performed to rule out primary malignancies and/or other secondary lesions, we highlight the ^{18}F-FDG-PET scan, which was negative for hypermetabolic systemic lesions eventually related with the pituitary mass of the patient. Moreover, as many authors describe, it is possible that metastatic invasive pituitary macroadenomas have silent and non-evident metastases, misleading the carcinoma diagnosis (4). In fact, autopsy studies of pituitary tumors patients revealed unknown metastases in some (4,10). On the other hand, the fatal course of these neoplasms do not allow the development of metastases, which some describe to occur in months or even years later (4,5,9). The most frequent metastatic locations includes brain (35%) and spinal cord (17%), followed by bone (14%), lymph nodes (12%), liver (10%) and lungs (6%) (9).

Pathology has a central role to the diagnosis of pituitary lesions. At present, there are no histological, immunochemical or ultrastructural markers that separate conclusively pituitary carcinoma from adenoma (15). In this case, many immunohistochemistry tests were used to exclude entities like lymphoproliferative disorder, melanoma, sarcoma, nasopharyngeal carcinoma, primitive neuroectodermal tumors, Ewing sarcoma; genetic analysis for c-MYC and EWS also contribute to rule out more convincingly lymphomas, solid tumors (like breast cancer) or central/peripheric primitive neuroectodermal tumors, respectively (16). So, at last, this case would fit pathologically the diagnosis of carcinoma of a small cell subtype from pituitary origin. ___

The protein Ki-67 is a cell proliferation marker (17) detected by the monoclonal antibody MIB-1 and is expressed as a percentage of immunopositive nuclei in the form of a Ki-67 proliferation index (18). Literature describes a mean Ki-67 for pituitary carcinomas around 12% (± 14) (4,5,9). Thapar and cols. reported a Ki-67 index of 1.37%, 4.66% and 11.91% in noninvasive adenomas, invasive adenomas and carcinomas, respectively (11). Ki-67 over 10% is already criteria to admit pituitary carcinoma for some authors (4,10,11). In our patient Ki-67 was estimated at 75%, one of the highest so far described, which predicted an unfavorable course and high probability of unsuccessful treatment, as seen.

About 90% of pituitary adenomas are operated by transsphenoidal route and a. transcranial approach is usually reserved for cases with significant suprasellar, parasellar, retrosellar and/or subfrontal tumoral extension (19). In this case, surgery as well as radiotherapy failed to control disease progression. Chemotherapy, such as temozolomide (20), was not attempted in the

patient because of low performance status and severe disease progression.

We present an exceptionally rare case of pituitary lesion that clearly illustrates the paradox and pitfalls between histological classifications and clinical behavior. This case report is a paradigm of the aggressiveness of some pituitary lesions. In our opinion, the WHO pituitary tumors classification (6) should be revisited and the criteria for pituitary carcinoma diagnosis could be revisited.

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