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Case Report

Pituitary carcinomas: Rare and challenging

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ABSTRACT

Background: Pituitary carcinomas (PCs) are defined as adenohypophyseal tumors with metastatic activity within and outside the boundaries of the central nervous system (CNS). The condition is rare and therefore seldom reported; most lesions are hormone producing and have a tendency for complex evolution. As such, the management of PCs remains difficult. We present an illustrative case of PC with a brief review of the recent medical literature.

Case Description: A 58-year-old patient was diagnosed with prolactinoma in 2005. The ensuing biochemical and radiological evolution proved contentious; local tumor control was never fully achieved despite multimodal management including pharmacological treatment, repeated resections, and radiotherapy. In late 2017, the patient developed metastatic lesions within the confinements of the CNS requiring further surgical interventions, high-dose radiation, and systemic treatment.

Conclusion: As it was the case in our patient, PCs require tailored, multimodal treatments according to the degree of infiltration, site of invasion, and hormone status. Further studies are necessary to understand the mechanisms promoting "extra-sellar" activity, particularly at distant sites; the identification of biomarkers exposing the risk of PC remains a crucial aspect of diagnostics, prevention and future customized therapies.

Keywords: Adenoma, Central nervous system, Metastatic activity, Pituitary carcinoma

INTRODUCTION

Pituitary carcinomas (PCs) are rare malignant neoplasms, accounting for approximately 0.12% of adenohypophyseal tumors and 6% of local invasive adenomas.[10,16,19] According to the World Health Organization, PCs are composed of adenohypophyseal cells with craniospinal or systemic metastatic activity.[8,10,20] These lesions often arise from previously resected and/or irradiated infiltrating adenomas;[4] yet, there are no histological criteria enabling differentiation of local invasive adenomas from those with carcinogenic potential.[8] Malignant activity is usually slow and topographically wide; furthermore, around 20% of these tumors remain biochemically nonfunctional.[19] Consequently, patients may remain asymptomatic for a longer period of time before the initial diagnosis. In addition to this, PCs have a tendency for complex evolution. Due to these factors mentioned, the management of PCs remains challenging, yet of the utmost

importance to those few affected.[18] Here, we present an illustrative case of PC with contentious evolution, reviewing the latest developments in the fields of diagnosis and treatment.

CASE DESCRIPTION

We present a case of a previously healthy, 58-year-old male patient, who developed bitemporal hemianopsia in the first few months of 2005. The ensuing radiological assessment revealed a 22 mm × 20 mm × 15 mm pituitary mass with chiasmatic/bilateral optic nerve upward dislocation [Figure 1]; the complementary endocrine screening showed evidence of a growing prolactinoma (March 2005). Subsequent management proved complicated despite the use of pharmacological treatment, repeated surgical interventions, and the access to high-dose radiation therapy schedules. Metastatic activity was reported almost 12 years after initial diagnosis [Figures 2-4 and Table 1], remaining largely unresponsive to multimodal treatment. Despite this entangled evolution, the patient presented with symptoms of mild–moderate fatigue (Karnofsky Performance Status (KPS) 70-80) at the last follow-up (13 years after diagnosis), mostly due to ongoing antiepileptic treatment, uncontrolled prolactin levels, and chemotherapy. Table 1 describes key timeline points relevant to this case.

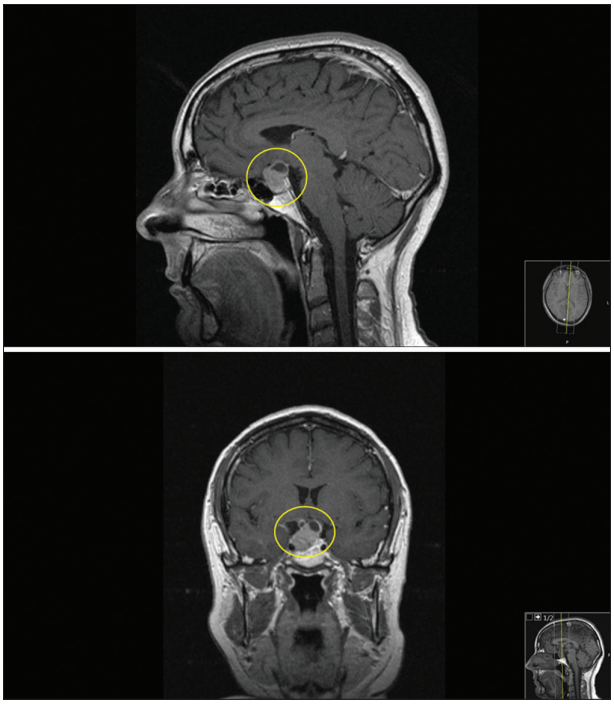

Figure 1: Top: Contrast-enhanced T1-weighted sagittal cross-sectional magnetic resonance imaging at initial diagnosis (2005). Bottom: Same study, coronal cross-section. Evidence of a 22 mm × 20 mm × 15 mm prolactinoma with chiasm/bilateral optic nerve upward dislocation.

DISCUSSION

General aspects

Hypophyseal tumors account for 15% of all intracranial tumors;[14] 35%–40% are locally invasive, whereas only 0.1%–0.2% are found to develop to PC.[14,15,17] To the best of our knowledge, <200 cases of PC have been described to date. The time interval between initial diagnosis and metastatic

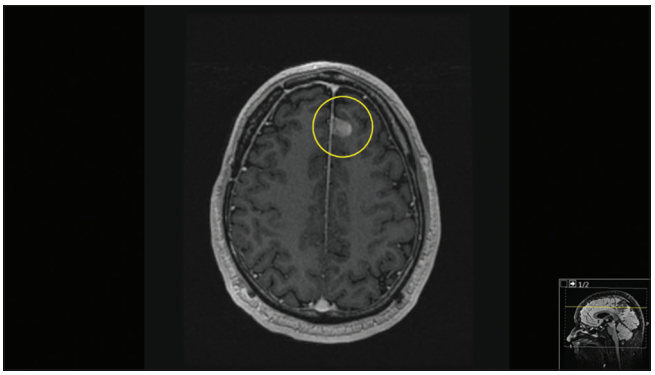

Figure 2: Follow-up contrast-enhanced T1-weighted axial cross-sectional magnetic resonance imaging (November 2017) showing a 10-mm left-sided frontal lesion within the anterior limits of the falx cerebri: Suspected metastatic lesion (pituitary carcinoma).

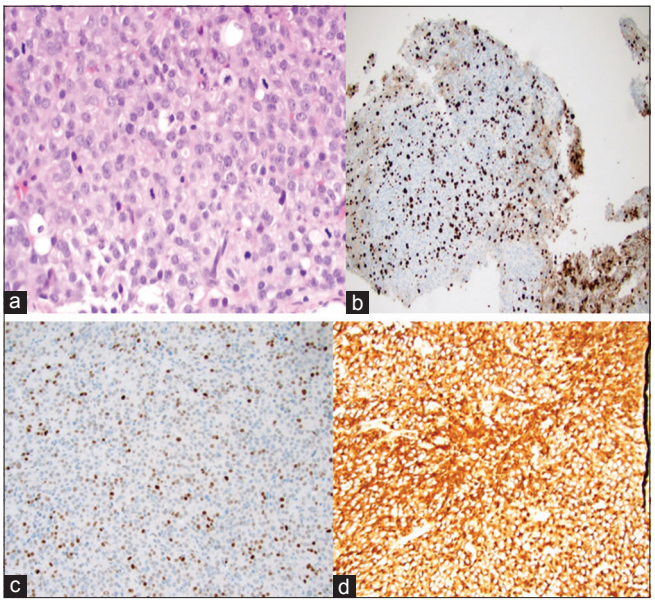

Figure 3: (×400). Microscopic reassessment of samples from second metastasectomy (November 2017) for the purpose of this article (a) H&E staining: high mitotic activity in a population of large cells with atypical nuclei and prominent nucleoli. (b) KI67: high proliferation (35%). (c) Overexpression of P53 limited to a few tumor cells (anti-p53 antibody). (d) Diffuse Immunostaining for prolactin. Of note, thyroid stimulating hormone, growth hormone, adrenocorticotropic hormone, CK-AE1AE3 proved negative. Samples from the first metastasectomy were not made available for reanalysis.

Table 1: Key timeline relevant to this case.

Timeline	Treatment	Outcome
March–May 2005	Bromocriptine mesylate presurgery	No biochemical or clinical response
June–July 2005	Cabergoline treatment due to further increase in Prolactin	Minor visual improvement the following 10 months. MRI unchanged, no substantial decrease in levels of prolactin
May 2006	First transsphenoidal hypophysectomy	Histology reported as benign prolactinoma (Ki67 – 2%, low mitoses)*. Further visual improvement and decrease of prolactin (to 137 μg from 1500 μg presurgery)
August 2006	Bromocriptine mesylate reinstated (Adjuvantic)	Prolactin elevation to 423 μg. MRI: tumor regrowth in the sella and around the hypophyseal stalk
April 2007	Second transsphenoidal surgery	Histology reported as benign prolactinoma (Ki67 – 4%, low mitoses)*. Rapid decrease of prolactin levels (from >400 to 150 μg); hormonal substitution with cortisol, testosterone, and thyroxine required (postsurgery)
September–December 2007	• MRI: 8-mm tumor next to the hypophyseal stalk (Lesion 1) + 10-mm lesion within the left cavernous sinus (lesion 2). Levels of prolactin unchanged • Lesions 1 and 2 treated with GKRS (20 Gy and 26 Gy, respectively) • Bromocriptine disrupted and cabergoline reinstated	Prolactin dropping to 120–140 μg post GKRS. Stable biochemical and radiological evolution under 2008
October 2009	Lesion 2 retreated with GKRS (20 Gy) due to MRI-confirmed relapse and gradual increase in prolactin levels during the course of 2009 (up to 222 μg)	Stable biochemical and radiological evolution under 2010 and most of 2011
October 2011–February 2013	Sequential chemotherapy (lomustine followed by TMZ) due to recurrence of L1 and L2	No response to chemotherapy, further tumor growth
March–April 2013	First transcranial tumor resection followed by prophylactic proton beam radiation to the surgical cavity	Histology confirms relapsing prolactinoma (Ki67 – 17%, increasing number of mitoses)*. Stable biochemical and radiological evolution up to November 2017
November 2017	Second transcranial tumor resection due to 10-mm left-sided frontal lesion within the confinements of the falx	PC histologically confirmed according to (i) available medical notes and (ii) reanalysis of the previously collected samples [Figures 2 and 3]**
January–May 2018	• Follow-up MRI [Figure 4]: 4–5 mm right-sided frontobasal metastasis (Lesion 3) + 6–7 mm lesion within the limits of the chiasm (Lesion 4) • Lesion 3 treated with GKRS (25 Gy); Lesion 4 not treated due to potential post-GKRS visual impairment • Prophylactic radiation to the surgical region in the falx (LINAC, 30Gy in 5 fractions)	Gradual increase in levels of prolactin despite despite radiotherapy (up to 12800 μg, April 2018)
June–September 2018	Treatment with somatostatin analog	MRI-confirmed tumor growth in the sella; prolactin-levels up to 22080 μg despite treatment
October 2018	Started chemotherapy carboplatin/Taxol	Outcome not reported

*Data based on previous medical notes; further immunohistochemical data could not be found. **Immunohistochemical reanalysis for the purpose of this case report. PC: Pituitary carcinoma, MRI: Magnetic resonance imaging, GKRS: Gamma knife radiosurgery, LINAC: Linear accelerator, TMZ: Temozolomide

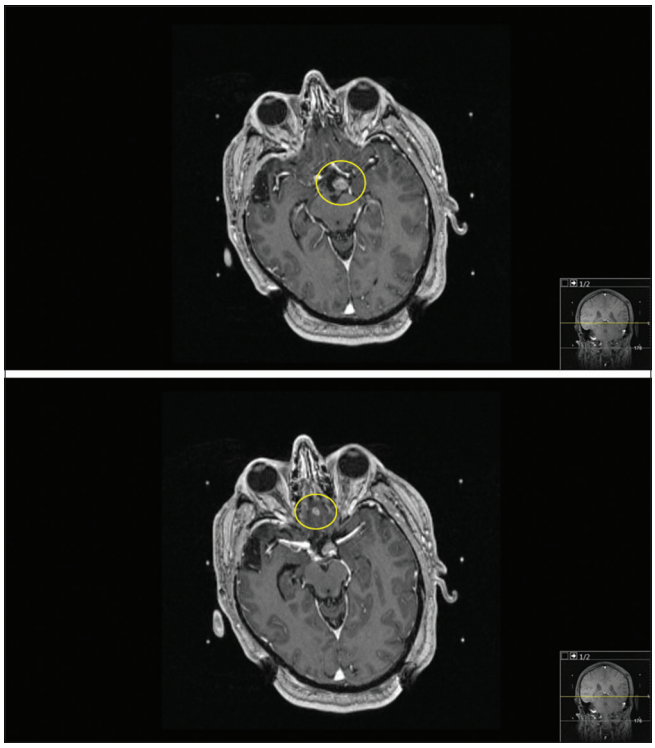

Figure 4: Top: Follow-up contrast-enhanced T1-weighted axial cross-sectional magnetic resonance imaging (January 2018): new metastatic lesion within the limits of the chiasm. Bottom: the same study exposing a concurrent frontobasal metastasis.

activity has been reported to range from 0.3 to 18 years (mean = 6.6 years/median = 5.0 years).[15] As demonstrated in our case description, prognosis remains poor[9] and <50% of PC patients survive the 1st year of metastatic disease.

Clinical characteristics

PC activity prevails in central nervous system (CNS) locations although other sites of dissemination such as the liver, bone, heart, ovaries, and lymph nodes have also been reported.[2,15] Blood-borne sella dura infiltration as well as postoperative drop metastasis and cerebrospinal fluid spreading have been described as the main pathways of CNS dissemination.[2,15,16] As many as 80%–88% of all PC tumors are hormone active, among these, prolactin (as in our case) and adrenocorticotropic hormone (ACTH) production are foremost reported, accounting for almost 50% of all PCs.[7,13] Despite its limited representation in numbers among hormonally active pituitary adenomas, ACTH-secreting PCs exhibit a preponderant rate of systemic infiltration.[7] Growth hormone (GH), luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone have also been described, yet to a less frequent extent.[11] When symptoms appear, it is often the result of an endocrine disturbance and a mass effect due to the latter-described conditions.[11] As expected, visual impairments, headaches, and hormone-related symptoms are often present;[13] yet, as previously illustrated in the present case, other symptoms may arise depending on the site and growth dynamics of the underlying metastatic activity. Ultimately, some groups have associated frequently recurring adenomas to metastatic spread.[4]

Immunohistochemistry

As is the case here, a thorough microscopic tumor evaluation from the primary and metastatic sites remains crucial in confirming diagnosis and assessing best treatment options. Histologically, PC lesions may look like typical adenomas but may also display marked pleomorphism and frequent mitoses.[2,16] In this contentious environment, some groups have reported atypical cellular morphology, higher mitotic activity (Ki-67/MIB-index), and p53 tumor suppressor gene as variables predisposing to the development of PCs.[2,4,13,17] In our case, the consecutive rise of the Ki-67 and its underlying mitotic activity at each surgery may have been indicators of the events to come [Table 1, Figure 3]. Zemmoura *et al*. identified angiogenesis, vascular invasion, gene upregulation, and allelic loss of chromosome 11 as potential factors of promalignancy in prolactinomas.[20] Metastatic development has also been associated with increased activity of Bcl-2 modulated telomerase, topoisomerase-2-α, cyclooxygenase-2, and galectin-3.[11] Other groups have theorized on the use of less common markers such as p27, Ras, the retinoblastoma gene, MEN-1, gsp, nm23, and HER2/neu; yet, their rare prevalence renders their interpretation and use difficult.[10,12] Finally, studies have focused on identifying genetic differences between invasive and noninvasive tumors. Galland *et al*. confirmed the overexpression of 4 genes common to adenomas and metastatic activity (IGFBP5, MYO5A, FLT3, and NFE2L1), in this context, being precursors of tumor cell migration. Particular interest has also been paid to MYO5A expression.[5,13]

Treatment modalities of manifest PC

The treatment of PCs remains multimodal and includes surgical resection (transsphenoidal and transcranial), linear accelerator (LINAC)- and proton-beam-based fractionated radiotherapy, single-dose GKRS, chemotherapy, immunotherapy, and the use of other pharmacological agents targeting hormone production itself.[1,2,6,9,11,15,17,18] Although treatments are customized according to metastatic deployment and biochemical status, their effects on overall disease activity remain poor, as demonstrated by the present clinical case. In recent years, positive results in several patients with PC have been reported using the alkylating agent temozolomide (TMZ).[6,10,12,14,18] Paradoxically, some studies have

highlighted a more favorable evolution of tumors with a lower immunoexpression of *O*-6-methylguanine-DNA methyltransferase (MGMT) while an intermediate-to-high MGMT expression appears to be associated with TMZ resistance.[6,10,14] In the context of glioblastoma multiforme, the methylation of the MGMT promoter is strongly associated with a better outcome when using TMZ; however, validation of the methylation status in the framework of PC remains unclear.[14] In the present case, TMZ did not prove effective although data concerning the methylation status of the tumor were unavailable. Other groups have theorized on the application of a range of alternative agents including mTOR inhibitors (rapamycin ± somatostatin analog) and R-roscovitine (CDK2/Cyclin E inhibitor) for ACTH tumors and anti-VEGF antibody treatment and EGF receptor (Erb1 and Erb2) tyrosine kinase inhibitors for dopamine-resistant prolactinomas.[3,6] Finally, promising results have been reported using isotope-labeled somatostatin analogs; however, further studies regarding their short- and long-term efficacy are warranted.

CONCLUSION

PCs are rare neoplasms with contentious metastatic evolution and require multimodal, tailored treatments. Unfortunately, despite modern medical technology, the prognosis remains poor. Although the incidence of PCs is low, further studies are necessary to understand the proliferative mechanisms leading to local invasion and metastatic activity. The identification of prognostic biomarkers for risk stratification and treatment response remains necessary in terms of prevention of PCs and future selected therapies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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