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Case Report

Unusual Course of an Aggressive Pituitary Prolactinoma: Case Report and Review of the Literature

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Brain tumor · Dopamine agonist · Prolactinoma · Pituitary carcinoma · Radiotherapy

Abstract
Pituitary carcinomas are rare tumors with heterogeneous behaviors. Their carcinogenesis is still unknown. Consequently, treatment is multimodal and not standardized. Dopamine (DA) agonists are used as first-line treatments, while radiotherapy and surgery may be used for local control of invasive tumors. We describe the case of a 35-year-old male who presented with an invasive prolactinoma, managed initially with a transsphenoidal resection, postsurgical radiotherapy and DA agonists. The patient posteriorly presented a sole metastatic lesion to the lumbar spine that was later managed with local radiotherapy. Due to pituitary recurrence of the lesion, multiple surgical resections were needed until further treatment was declined. The clinical course in this patient was unusual. He lived for 13 years after initial diagnosis, with a very invasive tumor without systemic chemotherapy. Radiotherapy is used in pituitary tumors in which surgery fails; we hypothesize that it contributed to the malignant transformation and the late resistance to DA agonists in our patient. Several biomarkers in tumoral tissue have been evaluated regarding their association with malignancy and aggressive behaviors,

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although more studies are still needed. Therapeutic strategies are limited, without evidence on the impact on overall survival and prognosis. Risk factors associated with early malignancy in pituitary prolactinomas include recurrent behavior, increase in prolactin levels with a stable sellar mass, and secondary development of DA agonist resistance. However, there are still no conclusive answers as to whether physicians should rigorously follow up these patients or provide direct therapy with aggressive approaches.

Introduction

Prolactinomas are the most common type of pituitary adenomas; they have a high recurrence rate after surgical removal and a low probability of presenting malignant behavior. Most metastases are intracranial [1]. As such, pituitary carcinomas are tumors whose prevalence is around 0.1–0.2% of all pituitary tumors, of which approximately 40–60% are prolactinomas [2, 3]. They show a higher prevalence in men. Most pituitary tumors are well differentiated and benign with indolent behavior; within the spectrum of the disease one can observe recurrent, invasive, highly proliferative, and metastatic lesions with little response to standard therapy [4]. The diagnostic criteria for pituitary carcinomas are controversial, but the diagnosis is established with the confirmation of metastasis. Likewise, there are no biomarkers to predict which sellar adenoma may present malignant transformation. Studies have shown that this malignant transformation is generally seen late into the disease, approximately 10–22 years after initial diagnosis [5]. While survival after the appearance of metastases can be very short, on certain occasions survival is prolonged many years without any clear explanation. Treatment therapies are diverse, including pharmacologic therapy with dopaminergic and somatostatin analogues, surgery, radiotherapy, stereotactic radiosurgery, and systemic chemotherapy.

Case Report

A 35-year-old male presented in early 1994 with headaches, decreased libido, impaired vision, and gynecomastia. A computed tomography (CT) scan of the sella turcica revealed a pituitary macroadenoma with suprasellar extension and invasion of the left sinus cavernosus and sphenoid sinus with prolactin levels of 2,750 ng/mL (reference value: <25 ng/mL) (online suppl. material; see www.karger.com/doi/10.1159/000499702 for all online suppl. material).

Subsequently, the patient began treatment with bromocriptine 2.5 mg/day and underwent a transsphenoidal adenomectomy in April 1994 (Fig. 1), with a significant tumor burden after surgery. Postoperatively the patient began hormone replacement therapy with prednisone, testosterone, and levothyroxine. Due to the tumor burden with invasion into adjacent structures, a transfrontal craniotomy was performed in November 1994, and 8 months later the patient received 50 Gy of sellar radiotherapy. During follow-up, the patient presented a normal campimetry, prolactin levels of 88 ng/mL, and symptomatic improvement.

The patient remained asymptomatic for 5 years with concurrent bromocriptine treatment. Posteriorly, prolactin was gradually increased until reaching 1,800 ng/mL, and by the time the patient received bromocriptine 45 mg/day. Due to the lack of tumor response it was changed to cabergoline 1 mg/week with a greater increase in prolactin. The patient restarted therapy with bromocriptine at a dose of 40 mg/day. In early 2000, a sella turcica magnetic

resonance imaging (MRI) scan showed a 15-mm-diameter mass in the right sphenoidal sinus, without any therapeutic change. Less than a year later, the patient reported lumbar pain, and an MRI scan showed a hypointense lesion in L1; a biopsy confirmed prolactinoma metastasis (Fig. 2, 3). Spinal radiotherapy was administered with overall symptomatic improvement. The patient began treatment with rosiglitazone at a dose of 12 mg/day due to its hypothesized antitumoral activity.

In October 2003, the patient presented with a giant mucocele that compromised the sphenoid sinus and required surgical resection. Additionally, four transsphenoidal adenomectomies were needed in the consecutive years 2002, 2003, 2004, and 2005 due to recurrence of the sellar lesion with invasion to the carotid artery and with prolactin levels averaging 1,000 ng/mL (Fig. 4). The pathology reports of the 2002 and 2003 resections were concordant with a highly densely granulated lactotroph adenoma and showed negativity for other pituitary hormones. Nonetheless, the consequent reports of the 2004 and 2005 resections showed a scarce quantity of neurosecretory granules, both with very similar histopathological findings. Furthermore, the Ki-67 index changed from 15 to 10% between the 2004 and 2005 resections.

In March 2006, an MRI scan showed great local compromise with extension to the bilateral sinus cavernosus, orbital vertex, prepontine cistern, sphenoid sinus, and suprasellar region. At the time, the patient suffered from total paralysis of the VI bilateral cranial nerve and amaurosis of the right eye. Due to intolerance to bromocriptine, the dose was lowered to 25 mg/day and he remained still with hormonal replacement therapy. The patient then declined any further treatment and passed away in March 2007.

Discussion

The therapeutic goals in malignant prolactinoma are: (1) prevention of tumor recurrence with gain of progression-free survival; (2) to mitigate the clinical consequences of excessive prolactin secretion; (3) preservation of residual pituitary function; (4) reduction of symptoms; and (5) improvement in quality of life. This means, restoring gonadal and sexual function-associated hyperprolactinemia and reducing the tumoral mass effect to improve visual defects and paralysis of the cranial nerves [1]. Pharmacologic treatment of these tumors with dopamine (DA) agonists usually decreases both their size and their hormonal secretion. Transsphenoidal surgery is considered the second therapeutic option in cases where DA agonists fail, or initially for very aggressive tumors. Radiotherapy is used to prevent regrowth of the primary tumor after surgical resection, and it is rarely used as a first therapeutic option. The lack of efficacy of standard therapies and the resistance to DA agonist is still not well understood [6].

Radiotherapy has been interrogated as a causal factor for the development of cancer, through DNA damage via alteration of the p53 pathway [5]. While some authors have reported cases of aggressive adenomas that improved clinically after radiotherapy, some have reported cases of fibrosarcomatous transformation many years after or even after no exposure to radiotherapy at all [5–7]. However, they have been shown to arise from bland tissues or adjacent meninges and not from pituitary tissue itself [6, 7]. While we believe radiotherapy could have been implicated in the process of malignant transformation of our patient, we cannot say up to what point it had an effect, especially since the patient presented a highly proliferative lesion from its initial diagnosis. Patients who receive radiotherapy do tend to have bigger lesions, which are more invasive, more functional, and with higher metastatic potential.

Therefore, there is the possibility that our patient's malignant transformation might have been due to innate characteristics and not secondary to radiotherapy.

With regard to pharmacologic therapy, DA agonists such as cabergoline and bromocriptine are considered first-class agents – particularly cabergoline, which has been shown to be more potent than bromocriptine in controlling tumoral growth in benign prolactinomas [8]. However, in our patient, the change to cabergoline concurred with an increase in prolactin levels as well as tumoral growth. Now, DA agonist resistance is defined as a lack of prolactin normalization or a failure to reduce prolactin by >50%, a lack of tumor shrinkage >50%, or both. It can also be defined as a failure to induce ovulation in women, or a failure to reduce symptoms or to normalize prolactin despite a cabergoline dose of ≥2 mg/week. Even so, tumor shrinkage is not directly considered a parameter confirming DA resistance, mainly due to restricted information in the literature. Accordingly, primary resistance in these tumors has been shown to occur in approximately 10% of microprolactinomas and approximately 11–18% of macroprolactinomas [2, 9]. Of these tumors, approximately 10–20% are resistant to cabergoline and 25–30% to bromocriptine [10].

However, secondary resistance following an initial response, as with our patient, is very rare, and hitherto has only been described in 5 previous cases, with our patient's being the sixth [8]. Likewise, the possibility that our patient was receiving subtherapeutic doses of cabergoline is stated. Given the novelty of cabergoline at the moment the patient received this treatment, he only received a maximum of 1 mg weekly. Now, higher doses of cabergoline up to 1 mg twice weekly and higher are being used in cases were the tumoral response is minimal. In contrast, our patient had an adequate response to bromocriptine for the most part of his treatment while receiving very high doses up to 45 mg/day and presenting only minimal adverse effects.

Nonetheless, it is known that during malignant tumor transformation, dysregulations of cell proliferation, cell differentiation, and alterations in intracellular signal transduction pathways take place, which in turn may affect dopamine receptor D_2 (D2R) expression. This might explain the secondary cabergoline resistance in our patient. As such, studies on in vitro cell preparations have shown that D2R is reduced in resistant prolactinomas but presents normal pharmacological affinity, while others have found that these receptors have diminished affinity to specific DA agonists such as cabergoline [10, 11]. Other studies have shown malignant prolactinomas with absence of the protein D2R in spite of having the *D2R* gene, raising the possibility that resistance may be due to posttranscriptional conformational changes [12].

Recent studies have shown associations of pharmacologically resistant prolactinomas with ESM1 microvessel density, the TGF-β/Smad signaling pathway, the *MIR-93* gene, and levels of the PRDM2 protein-coding gene [2, 12, 13]. Additionally, new case reports have shown effective responses in all pituitary carcinoma subtypes treated with temozolomide (TMZ). There is a concern, however, regarding how long treatment with TMZ should be continued. While studies have shown treatment periods of 6–9 months, some have shown long-term responses up to 24 months [12, 14]. The concern arises primarily because alkylating agents such as TMZ are associated with an increased risk of secondary malignancy, particularly hematological disorders [4]. Although the risk is relatively small, it could be relevant for patients with refractory carcinomas, who may receive long-term TMZ treatment.

Similarly, systemic chemotherapy based on lomustine/fluorouracil-5 has shown minimal collateral effects, and studies have indicated that the therapy may slow disease progression in patients with highly recurrent and aggressive tumors, but with little tumoral diminution [4, 9, 14]. Likewise, therapeutic strategies using pasireotide have been proposed, as a synergic interaction between DA and somatostatin analogues has been documented. Somatostatin

receptors (SSTRs) are also expressed in prolactinomas, particularly SSTR5 [3]. However, even with pasireotide's high affinity to 4 of 5 SSTRs, studies that analyzed tumoral response to pasireotide have been inconclusive, highlighting the fact that the presence of SSTRs in these tumors does not necessarily ensure its pharmacological response [11, 15]. On a different set of ideas, the use of PPAR-γ agonists such as rosiglitazone has been shown to inhibit tumoral cell growth. Nonetheless, studies have revealed a lack of PPAR-γ receptor expression in normal pituitary tissue [16].

Particularly morphologic and histological markers that may suggest the malignance or aggressiveness of pituitary tumors are not clear and of little use in prolactinomas [17]. Lactotroph adenomas are histologically classified into three subtypes: sparsely granulated lactotroph adenomas, densely granulated lactotroph adenomas, and acidophilic stem cell adenomas. As such, densely granulated lactotroph adenomas are considered a rare and aggressive subtype, as was the case with our patient [18]. However, we must note the fact that the tumor our patient presented with went through considerable histopathological changes, which can be correlated with its aggressiveness. Now, some studies have described biomarkers that correlate with the tumor's aggressive behavior, including the presence of fibroblast growth factor receptor 4 (FGFR4) as well as mutations in the GH receptor and in the pituitary tumor-transforming gene (PTTG) [19]. Furthermore, associations between prolactin hypersecretion and tumor formation have been found with overexpression of the genes *HMGA2*, *HST*, and *SNAP25* [9], while underexpression of the genes *UGT2B7*, *Let7*, and *miR-493* has been found to contribute directly to adenoma formation and progression [9]. Likewise, there are associations of invasive adenomas and carcinomas with the production of collagenase type IV [9], an increase in the Ki-67 index >3%, and high immunoreactivity for p53 [9] and diminished immunoreactivity for p27.

While these findings are overwhelming, they are still of limited utility regarding the differentiation between pituitary adenomas and carcinomas, especially as some adenomas may be aggressive but not necessarily malignant. Accordingly, while the initial presentation of malignant prolactinomas may be identical to that of benign invasive prolactinomas, some authors have proposed that particular tumor behaviors may serve as indicators of malignancy or metastases. These include adenomas with multiple local recurrences, an increase in prolactin with a stable sellar mass, and the secondary development of DA agonist resistance. Correspondingly, DA agonist-resistant prolactinomas do tend to be more aggressive, invasive, and hyperangiogenic with high mitotic indexes, which further makes their management challenging [12, 17]. Now, novel molecular markers, such as the ones shown above, have been proposed as tumor invasiveness predictors that could help differentiate a benign from a malignant prolactinoma, but mostly they have shown discordant results. These studies may lead to further rigorous clinical observation, and in turn an earlier diagnosis of pituitary carcinomas, and may increase the effectiveness of treatment [2, 12].

Conclusions

The clinical course of this patient was very unusual. We chose to publish this case report a decade after the patient had passed away because, regardless of the date, this is still a very rare case. Likewise, the treatment modalities used back then for these tumors were different from those used nowadays, which serves the purpose of comparing the outcomes. Now, our patient had a very aggressive tumor, with extensive and recurrent local invasion, which then metastasized and presented secondary DA analogue resistance. Nonetheless, this patient

presented a 13-year overall survival since the initial diagnosis. We propose the possibility that radiotherapy had an influence on the malignant transformation and late resistance to DA analogues in this case. We also believe that given a different therapeutic approach, our patient might have presented a different outcome, due to the lack of novel therapies such as pasireotide at the time of the patient's disease, as well as the suboptimal cabergoline doses the patient received.

However, despite this, we still have no certainty as to what factors are implicated in patients' survival and malignant tumor transformation. The current literature is controversial and has no statistical sustainment. As such, given the small amount of reported cases and the lack of information regarding survival rates, there are no curative therapies, with treatment algorithms still being very limited. Treatment is focused mainly on palliative care, and the response to therapy is highly dependent on the biological behavior of each tumor. While some light has been shed on DA agonist resistance of malignant prolactinomas, more research is needed in order for novel therapeutic targets to become viable. In the future, new studies in different biomarkers may provide complementary biological information which, when correlated with clinical findings, could suggest a more rigorous follow-up and a more aggressive therapeutic strategy for these patients.

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Statement of Ethics

The patient's family provided written informed consent for the publication of this case report.

Disclosure Statement

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Author Contributions

Each author contributed to the treatment of the patient and diagnosis of the disease. Likewise, the first author, as well the other authors, all contributed to the writing of this manuscript, as well as to the initial retrieval and analysis of the data and the literature used for the discussion of the patient's case.

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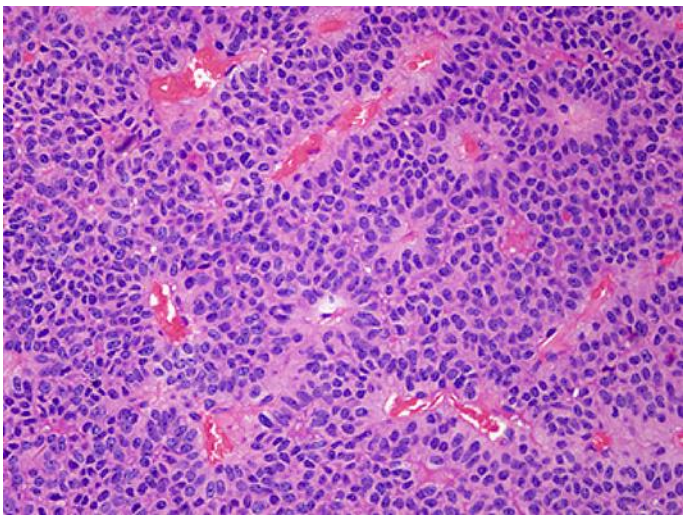

Fig. 1. H&E. ×40. Cellular proliferation with weak nuclear pleomorphism.

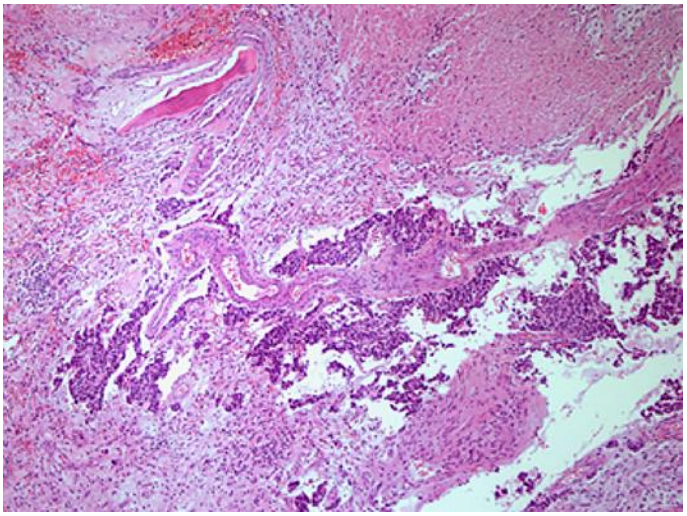

Fig. 2. H&E. ×20. Osseous infiltration by the neoplasm.

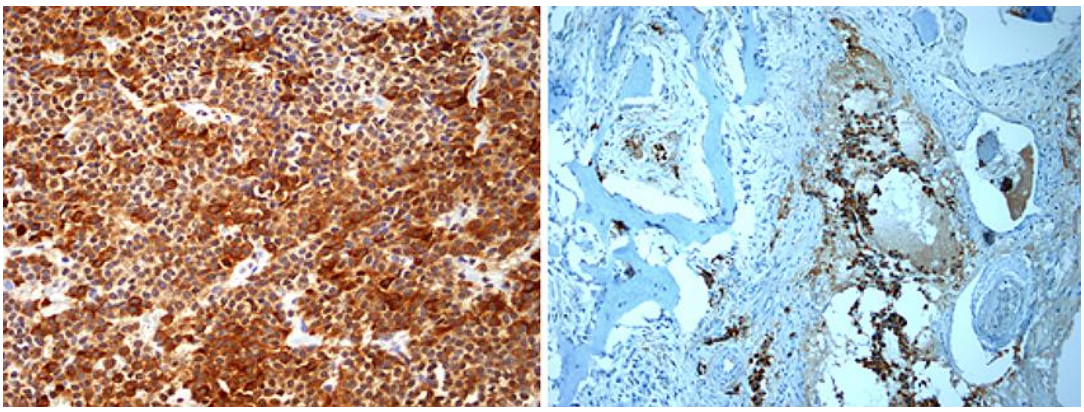

Fig. 3. Immunohistochemistry for prolactin. ×40. The image shows diffuse cytoplasmic expression and osseous infiltration by the neoplasm.

Fig. 4. Prolactin serum behavior 04/1994 to 12/2006.