

Case Report

Highly Aggressive and Radiation-Resistant, “Atypical” and Silent Pituitary Corticotrophic Carcinoma: A Case Report and Review of the Literature

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Keywords

Pituitary adenoma · Endocrine · Radiotherapy · Cushing’s disease · Temozolomide

Abstract

Background: Pituitary tumors typically remain silent unless interaction with nearby structures occurs. Rare subsets of pituitary tumors display aggressive phenotypes: highly mitotic, locally invasive, metastatic, chemotherapy and radiation resistant, etc. Disease progression and response to therapy is ill-defined in these subtypes, and their true prognostic potential is debated. Thus, identifying tumor characteristics with prognostic value and efficacious treatment options remains a challenge in aggressive pituitary tumors. **Case Presentation:** A 45-year-old female presented with a nonfunctioning corticotrophic pituitary macroadenoma with

biomarkers suggestive of an “atypical” subtype: Ki-67 of 8–12%, increased mitosis, and locally invasive. Despite resections and radiation, growth continued, eventually affecting her vision. Although histologically ACTH positive, the patient remained clinically asymptomatic. Twelve months later, an episode of Cushing’s disease-induced psychosis prompted a PET-CT scan, identifying sites of metastasis. Temozolomide was added to her medical regimen, and her metastatic liver lesions and bony metastases were treated with radiofrequency ablation and stereotactic body radiation therapy, respectively. Systemic treatment resulted in a drop in her ACTH levels, with her most recent scans/labs at 12 months following RFA suggesting remission.

Conclusions: This is a unique presentation of a pituitary tumor, displaying characteristics of both clinically silent corticotrophic and “atypical” macroadenoma subtypes. Although initially ACTH positive while clinically silent, the patient’s disease ultimately recurred metastatically with manifestations of Cushing’s disease and psychosis. With the addition of temozolomide to her treatment plan, her primary and metastatic sites have responded favorably to radiation therapy. Thus, the addition of temozolomide may be beneficial in the treatment of aggressive pituitary tumors.

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Background

Pituitary tumors are relatively common, with an estimated annual incidence of approximately 1–4 cases per 100,000 individuals [1–5]. Estimates from post-mortem studies suggest prevalence rates may be as high as 20% with a majority remaining clinically silent and going undiagnosed [6, 7]. This occult nature is due to the incredibly slow growth rate of most pituitary tumors, which also contributes to their favorable prognoses. Approximately one third of pituitary adenomas are nonfunctioning pituitary adenomas (NFPAs) that do not secrete a pituitary hormone although they may be positive immunohistochemically for hormone markers. These indolent tumors often take years to present clinically when symptoms are exhibited as a result of mass effect on adjacent structures such as the optic apparatus, the normal pituitary gland or stalk, or cranial nerves traversing the cavernous sinus. Further, outside of rare exceptions, pituitary tumors respond well to treatment that typically includes surgical excision with or without adjuvant radiation. Despite their indolent nature these tumors (particularly NFPAs) often demonstrate regrowth with surgery alone. Studies assessing the long-term results of surgery alone as a definitive treatment for NFPAs demonstrated the recurrence rate to be as high as 45–75% within a 10-year follow-up post-operatively [8–11]. Thus, radiation therapy (RT) was commonly offered as adjuvant therapy after subtotal resection or tumor recurrence. Both stereotactic radiosurgery and conventional fractionated radiation therapy can provide high local control, commonly higher than 85%, in a 10-year period in these situations. Further, RT alone or surgery combined with RT at the first instance of tumor regrowth had the lowest rate of additional recurrence (12.5 and 12.7%) with a median follow-up of 5.9 years (range 0.4–37.7 years), while second surgery alone showed 36.2% progression, demonstrating the challenge of achieving a gross tumor resection in regrowth situations and highlighting these tumors are highly sensitive to radiation therapy [11]. Importantly, despite relatively common regrowth, these tumors often remain a local concern as they rarely metastasize.

However, a growing accumulation of case reports and studies reveal a small subset of pituitary tumors that are fast growing, highly invasive, resistant to radiation and chemotherapy, and readily metastasize [12–14]. From the limited descriptions in the literature, these aggressive tumors appear to share some similarities including high Ki-67 expression ($\geq 3\%$), high

nuclear expression of p53, increased mitosis, and a locally invasive phenotype [12, 13, 15]. These tumors have been classified as “atypical adenomas” and are only upgraded from an adenoma to carcinoma upon metastasis [14]. These tumors are more “aggressive” than usual, with hallmarks of clinical relevant tumor regrowth despite the use of optimal standard therapies. Invasiveness alone or tumor size at presentation is not synonymous with pituitary tumor aggressiveness [16–18]. Prognosis of pituitary carcinomas is very poor with approximately 66% mortality within one year of diagnosis [19].

Out of all pituitary tumors, 3–15% are considered atypical pituitary adenomas, and only 0.1–0.2% are frank pituitary carcinomas defined by the presence of craniospinal and/or systemic metastasis [19, 20]. Due to the paucity of cases, our current understanding of this unique subpopulation of pituitary neoplasms is very limited. Thus, the accumulation of relevant reports is critical for expanding our knowledge on this rare disease.

Herein, we present the case of a 45-year-old female who was initially diagnosed with a nonfunctioning, pituitary macroadenoma with a Ki-67 of 8–12%, nuclear pleomorphism, and prominent nucleoli. Despite resections and radiation, her tumor continued to grow and invade local tissues. Upon encroachment of the oculomotor nerve, the patient began to experience ptosis. Further clinical signs, such as progressive weight gain and a psychotic episode requiring hospital admission, led to the identification of liver and C1 metastases. Biopsy of the liver confirmed pituitary origin, which was ACTH-positive. Radiofrequency ablation (RFA) and stereotactic body radiation therapy (SBRT) were used to locally treat her liver and bone metastases, respectively. The patient was systemically treated with cabergoline and temozolomide. Since starting systemic treatment eight months ago, her cortisol levels have been properly maintained and her malignancy has remained stable. Furthermore, she has experienced an improvement in her diplopia.

Case Presentation

In August 2013, our 45-year-old female patient underwent a gross total resection of a 2.5 cm non-functioning pituitary adenoma with degenerative changes and recent hemorrhage, at an outside institute. Pathologic examination revealed small sheets of pleomorphic cells with positive staining for synaptophysin, chromogranin, CAM5.2, and AE1/AE3. She was subsequently followed regularly until March 2014, when repeat imaging showed her tumor had recurred in the sella turcica with asymptomatic invasion into the left cavernous sinus. The patient underwent a debulking resection of the sellar component of the tumor. Upon pathologic review, the recurrence specimen was found to now stain positively for ACTH as well as contain some atypical features including nuclear pleomorphism, large nucleoli, mitotic figures, and Ki-67 staining of 8–12%. Although lacking p53 nuclear expression, the tumor’s increased mitosis, Ki-67, and invasive phenotype led to the classification of atypical pituitary adenoma [20]. She remained without Cushingoid symptoms at that time. She tolerated the surgical resection well and subsequently underwent postoperative CyberKnife radiation to a dose of 25 Gy given in 5 fractions to the residual mass completed in June 2014. On radiographic follow-up, a small amount of residual disease was observed in the left cavernous sinus. Over the next year and a half, the adenoma demonstrated slow, but persistent progression, and the patient began complaining of issues in her left eye concerning for CN III, IV, and VI palsies including lid ptosis and difficulty with left eye abduction and adduction. The diplopia progressed to persistent double vision, which was compounded by intermittent severe headaches causing nausea and vomiting.

Due to her clinical and symptomatic progression, she established care with our institution in December 2015 to discuss repeat irradiation for her recurrent pituitary macroadenoma and undergo a full endocrine evaluation. At that time, her salivary cortisol levels were found to be approximately four times the upper limit of normal though she remained clinically asymptomatic. She initiated treatment with pasireotide 0.6 mg/mL subcutaneously twice a day and cabergoline 0.5 mg twice a week for this clinically-silent, ACTH-secreting pituitary adenoma with the intent to slowly titrate up her cabergoline dose to 2 mg twice a week. Repeat brain MRI two months later showed disease progression with her soft-tissue mass measuring $3.0 \times 1.9 \times 2.1$ cm compared to $1.7 \times 2.0 \times 2.7$ previously. The MRI also revealed persistent left cavernous sinus involvement with vascular encasement of the left internal carotid artery and newly-identified possible mild abutment of the left optic nerve. Of note, the patient's ACTH was stably elevated with cortisol levels maintained within normal range at this time.

With a lack of disease control with medical management, the patient elected for a repeat course of radiation therapy. In February 2016, the patient underwent a stereotactic radiosurgery (SRS) delivering a single fraction of 14 Gy using a head frame-based technique. Follow-up MRI one month after repeat SRS demonstrated the tumor had only a minimal increase in size, thought to likely represent pseudoprogression given the previously fast growth rate of the neoplasm that now appeared to be relatively stable post-irradiation. Repeat MRI three months later was unchanged and still demonstrated the pituitary adenoma extending into Meckel's cave, partially compressing the internal carotid, and abutting the left optic nerve. A five-month follow-up MRI showed the bulk of the disease to remain unchanged, however, a small, but obvious, enhancement in the oculomotor nerve concerning for progression was identified. Review of the SRS radiation treatment plan confirmed only low dose exposure to CN-III, not favoring but also not ruling out radiation-induced neuritis due to her previous history of fractionated SRS. Disease progression was high on differential. Due to the slow rate of growth and location in question, observation was deemed most appropriate over further treatment intervention. At the seven-month post-radiation follow-up, ACTH levels were found to have increased from 155 to 269 (norm. 0–46 pg/mL) over the month prior, but the salivary and urine cortisol levels remained within normal ranges. Repeat MRI imaging at seven, ten, and fourteen months after SRS all demonstrated a stable, large pituitary lesion with CN-III enhancement and elevated, but stable ACTH levels at seven and ten months after SRS.

However, starting at twelve months post-radiation, her ACTH levels began to steadily increase each month, reaching 667 in June 2017. Following this rise in ACTH, the patient's cortisol levels began to rise despite taking 2 mg of cabergoline twice weekly. These endocrine abnormalities resulted in noticeable weight changes as well as an episode of psychosis secondary to Cushing's with acute anxiety and paranoia prompting hospital admission. On this admission, her ACTH and urine cortisol levels had spiked to 677 pg/mL (norm. 0–46 pg/mL) and 279 µg/dL (norm. ≤45 µg/dL) respectively, despite continued treatment, although serum cortisol levels remained relatively stable at 23.2 mcg/dL (norm. ≤10 mcg/dL). Repeat MRI revealed only mild primary tumor progression with a tumor size of $2.9 \times 1.8 \times 2.6$ increased from $2.7 \times 1.7 \times 2.6$ in April 2017 and $2.6 \times 2 \times 1.7$ in December 2016. A multi-disciplinary, neuro-oncology tumor board suggested the use of PET-CT to identify a potential extra-pituitary source as an explanation for this atypical disease presentation. The board also recommended temozolomide (150 mg/m² nightly for five consecutive nights) in an attempt to slow any new growth or invasion and added ketoconazole (500 mg BID) to her on going cabergoline treatment to manage her Cushing's disease. The PET-CT confirmed the presence of an FDG-avid pituitary mass with additional lesions in the liver and left occipital condyle-lateral C1 vertebra with associated bony destruction as well as potential involvement of the left adrenal

gland. Biopsy of a liver lesion confirmed metastatic pituitary corticotroph carcinoma. In July 2017, the patient underwent RFA to her liver lesions and SRS (16 Gy in 1 fraction) to her C1 lesion.

One week after receiving RFA and the same day as undergoing SRS, the patient’s ACTH levels had dropped dramatically to 188 (down from 677 measured three weeks prior) and displayed a decreasing trend with monthly levels measured at 128, 86, 78, 59, and 53 pg/mL. Serum cortisol levels have returned to normal ranges with a nadir of 2.9 mcg/dL (norm. ≤ 10 mcg/dL) four months following her RFA and SRS treatments and have remained stable since. It should be noted that ACTH did display suppression after dexamethasone administration, <12 pg/mL suppression. Monthly repeat imaging (both CT and MRI) for three consecutive months following RFA and SRS showed the three ablated hepatic lesions had decreased in size, while the vertebral and pituitary masses had remained stable. No other areas concerning for disease have been identified, and per these findings, three-month imaging intervals were initiated. Her most recent scan (14 months following RFA/spine SRS) showed decreasing size in the both the primary and metastatic sites.

Since receiving her most recent RFA and SRS treatment, fourteen months have passed, and the patient has finished her eleventh cycle of temozolomide (150 mg/mm² given over 5 consecutive days every 4 weeks) and pasireotide 0.6 mg/mL subcutaneously twice a day. All diagnostic scans and lab tests suggest her disease is in remission. Moreover, function has begun to be restored in the patient’s eye movement, and her diplopia has become less severe.

Discussion and Conclusions

High Ki-67 index ($\geq 3\%$), nuclear expression of p53, increased mitotic rate, and a locally invasive phenotype are controversial markers of aggressiveness that have traditionally up-staged pituitary adenomas to an ill-defined status of “atypical.” Atypical pituitary neoplasms are thought to be more resistant to therapy and have higher rates of recurrence [21], but due to a lack of definitive evidence, this terminology was removed from WHO classification in 2017 [22]. Additionally, our patient’s tumor appeared to be one of the silent, non-functional (corticotrophic) adenoma subtypes, which immunohistologically identify as positive but do not produce elevated blood hormone levels or clinical symptoms [23]. Several reports have demonstrated that silent adenomas may be more aggressive, and in the setting of incomplete resections, progress more rapidly and with increased frequency despite multidisciplinary interventions [24–27]. Regardless of their initial state of aggressiveness, pituitary tumors that metastasize to distant locations represent a rare subtype. Because a limited number of cases have been reported in the literature, very little is known about the clinical prognosis of these pituitary tumors other than survival appears much shorter than for their less aggressive counterparts [21, 24, 26].

Furthermore, our understanding of how to treat these pituitary tumors is limited. Surgery and radiation therapy should always be considered for pituitary adenomas, and the atypical and/or silent pituitary subtypes are no exception [28, 29]. Although some reports indicate silent tumors may be more radioresistant than their functional counterparts, these findings are limited by their retrospective nature and small patient sizes yet still suggest both SRS and fractionated SRS may be of benefit [30–33]. While previous reports have illustrated that complete resection and incorporation of radiation improves outcomes, these reports are often retrospective studies that differ greatly in the surgical approach, the type and amount of radiation administered, and tumor subtype(s), making comparisons of studies and the summation

of findings difficult to interpret [16, 29, 34, 35]. The contemporary literature also suggests temozolomide may be of benefit in aggressive pituitary tumors, but there is a lack of sufficient evidence to truly support this recommendation [29]. Thus, we are greatly limited in our knowledge of treating aggressive pituitary neoplasias due to their rarity and heterogeneity: the existence of multiple subtypes, and divergent subtypes within a single tumor. The summation of small studies and case reports is critical to expanding our understanding of the clinical prognosis of locally advanced, recurring, and metastatic pituitary tumors.

Our patient’s pituitary tumor displayed several adverse characteristics suggestive of both an “atypical” and silent subtype, a combination of rare and poor prognostic subtypes that are not commonly co-observed and have rarely been reported in the literature. Despite repeated resection and two courses of radiation, her tumor continued to recur and progress, which aligns with previous reports. However, it is unclear if one phenotype predominantly contributed to her aggressive disease or if the resulting combination was worse than either alone. Furthermore, our patient’s malignancy was initially silent, but later transitioned to a functional state, a phenomenon that has been reported [36–40]. Shortly after displaying Cushing’s symptoms, metastatic disease was identified, and local control of the metastatic sites was successful using SBRT to her C1 and radiofrequency ablation for sites of liver involvement. Temozolomide was added in an attempt to systemically control her tumor. After focal and systemic treatment, our patient has demonstrated slow but consistent regression in her primary tumor, a steady decrease in her cortisol levels, as well as a nearly complete response in her metastatic sites for the past twelve months. It is unclear as to which sites, primary versus liver and bone metastasis, contributed to her Cushing’s disease, if not a combination of all of them. Although it is still early, our experience supports the addition of temozolomide in treating aggressive pituitary tumors, especially in the context of local ablative therapy for hormonal normalization and symptomatic control [29]. A clinical trial or prospective collaborative registry would better help elucidate the true benefit, if any, of adding this systemic agent to the standard localized treatment regimen of surgery and radiation therapy.

Statement of Ethics

The UNMC IRB has determined this project does not constitute human subject research as defined at 45 CFR 46.102 and 32 CFR 219.102. Therefore, it is not subject to the federal regulations.

Consent has been granted by the patient, and a signed document is available upon request.

Disclosure Statement

The authors declare that they have no competing interests.

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Author Contributions

RS, LF, and BN reviewed the patient's records and wrote the case presentation under the guidance of MB and CZ. RS, LF, BN, MB, and DO reviewed the literature and drafted the *Background, Discussion and Conclusion* sections. RS, MB, CZ, AD, and NS oversaw the clinical management of the patient. Specifically, RS, DB, and CZ managed the patient's care in the department of radiation oncology; WT oversaw the surgical management of the patient; AD evaluated and managed the patient's endocrine-related care; NS managed our patient's general medical and oncology-related care. All authors helped in the writing of the *Case Presentation* section and contributed to the final production of the case report. Collectively, all authors have read and approved the final manuscript being submitted.

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