JOURNAL OF NEUROSURGERY:
Case Lessons

J Neurosurg Case Lessons 5(3): CASE22363, 2023
DOI: 10.3171/CASE22363

Natural history of pituitary carcinoma with metastasis to the cervical spine: illustrative case

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BACKGROUND Pituitary carcinoma is a rare tumor of the adenohypophysis with noncontiguous craniospinal dissemination and/or systemic metastases. Given the rarity of this malignancy, there is limited knowledge and consensus regarding its natural history, prognosis, and optimal treatment.

OBSERVATIONS The authors present the case of a 46-year-old woman initially treated with invasive prolactin-secreting pituitary macroadenoma who developed metastatic disease of the cervical spine 6 years later. The patient presented with acutely worsening compressive cervical myelopathy and required posterior cervical decompression, tumor resection, and instrumented arthrodesis for posterolateral fusion.

LESSONS This case underscores the importance of long-term monitoring of hormone levels and having a high clinical suspicion for metastatic disease to the spine in patients presenting with acute myelopathy or radiculopathy in the setting of previously treated invasive secreting pituitary adenoma.

https://thejns.org/doi/abs/10.3171/CASE22363

KEYWORDS cervical myelopathy; intradural extramedullary mass; pituitary carcinoma; prolactinoma; spinal metastases; spine tumor

Pituitary carcinoma (PCa) is defined as a malignant tumor of the adenohypophysis with concomitant noncontiguous craniospinal dissemination and/or systemic metastases. PCas represent only 0.1%–0.2% of all surgically treated adenohypophysial neoplasms, and they are indistinguishable radiologically and histopathologically from other types of pituitary adenomas.[1–4] Most PCas derive from invasive functional macroadenomas (most often secreting adrenocorticotrophic hormone or prolactin)[2,5,6] and are associated with particularly high 1- and 5-year mortality rates of 43%–44% and 71.4%, respectively.[1,7–9]

Given the rarity of PCa and the relative paucity of literature on the topic—fewer than 200 combined case reports and small case series in the English literature—there remains limited knowledge and consensus regarding the natural history, prognosis, and optimal management of this challenging disease.[3,10,11] Accordingly, each novel case encountered warrants reporting to improve our collective understanding of the presentation, natural history, behavioral heterogeneity, and response of these lesions to different treatment modalities. The purpose of this article is to highlight the importance of continued monitoring of pituitary hormone levels in patients with invasive secreting pituitary adenomas after surgery as well as the need to have a high level of clinical suspicion for metastatic disease to the spine in these patients who re-present years later with new-onset myelopathy or radiculopathy.

Illustrative Case

History and Examination

A 46-year-old woman with a past medical history of smoking, hypothyroidism, rheumatoid arthritis, and osteoporosis presented to an outside hospital after worsening peripheral vision led to a motor vehicle accident. Imaging revealed a large sellar/suprasellar mass abutting the bilateral internal carotid arteries and displacing the optic chiasm superiorly. The patient endorsed approximately 4 years of amenorrhea, but she denied any history of galactorrhea. She was managed medically with cabergoline

ABBREVIATIONS HPF = high-power field; MRI = magnetic resonance imaging; PCa = pituitary carcinoma.
INCLUDE WHEN CITING Published January 16, 2023; DOI: 10.3171/CASE22363.
SUBMITTED August 25, 2022. **ACCEPTED** October 19, 2022.

(prolactin 3,258 ng/mL, normal 2.8–26.0 ng/mL) and initially had a good response to dopamine agonist therapy (Fig. 1).

After several years, the patient's prolactin level rebounded. Imaging revealed interval growth and extension into the hypothalamus (Fig. 2A and B). The patient underwent a transsphenoidal subtotal resection at an outside facility, with pathological analysis confirming invasive prolactin-secreting pituitary macroadenoma with mildly increased mitotic rate (1/10 per high-power field [HPF]) and mildly increased Ki-67 proliferative index of 4%–8%. Despite her initial transsphenoidal resection, her prolactin remained elevated (4,223 ng/mL), and subsequent imaging showed disease progression (Fig. 2C and D). She was then referred to our institution. Formal ophthalmological visual field testing was performed, which revealed a significant right-sided temporal field deficit and a less severe left-sided temporal field deficit (Fig. 3).

Operative and Postoperative Courses

The patient underwent repeat surgical resection of her invasive prolactin-secreting pituitary macroadenoma via a microscope-assisted transnasal transsphenoidal approach. Residual tumor was noted on post-operative imaging (Fig. 2E and F). Five months later, she underwent 5 weeks of fractionated external beam radiotherapy to the residual tumor (total dose 45 Gy). The cabergoline therapy was discontinued because of questionable efficacy at this point in her treatment. After reresection and adjuvant radiation, subsequent imaging showed disease regression, and her prolactin level decreased to 227.9 ng/mL and stabilized at approximately 200 ng/mL for a couple of years (Fig. 1).

Two years later, the patient's prolactin level began to increase. She reported neck and shoulder pain and bilateral hand numbness. Imaging showed further regression of her intracranial disease, but magnetic resonance imaging (MRI) of the cervical spine with and without contrast disclosed an intradural extramedullary mass spanning C2–4 of the cervical spine. She was initially managed conservatively with close follow-up, but she re-presented with acute cervical myelopathy and progression of the cervical lesion (Fig. 2G and H). She underwent a far lateral approach for C2–5 laminectomies, resection of the intradural extramedullary lesion at C3, and C2–5 instrumented arthrodesis for posterolateral spinal fusion. The tumor was purple in color and soft in consistency. Cabergoline was restarted at twice her initial dose after surgery. On postoperative day 4, she became unresponsive and had pulseless electrical activity on an electrocardiogram; she died shortly thereafter. Her death was attributed to a cardiac arrhythmia in the setting of nonobstructive coronary artery disease. Autopsy revealed 90% left anterior descending artery and 60% right coronary artery stenosis.

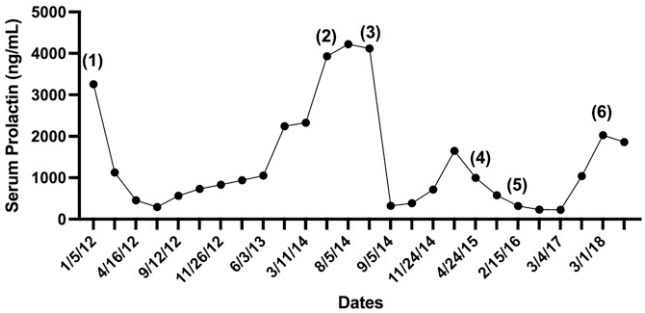

FIG. 1. Measured serum prolactin levels (ng/mL) throughout the patient's diagnosis with atypical pituitary prolactinoma, treatment, and recurrence as pituitary carcinoma with cervical spine metastasis. The annotated measurements were taken at the following clinically significant time points: (*1*) initial presentation and initiation of cabergoline, (*2*) initial transnasal transsphenoidal resection at outside hospital, (*3*) repeat transnasal transsphenoidal resection at our institution, (*4*) initiation of fractionated radiation, (*5*) completion of radiation therapy, and (*6*) discovery of cervical metastasis after presenting with acute cervical myelopathy.

Histopathology

The pathological diagnosis after the second transnasal resection was atypical pituitary adenoma with increased nuclear atypia, occasional single-cell necrosis, avid prolactin staining, mildly increased mitoses (1/10 per HPF), MIB-1 of 25%, and mildly increased Ki-67 of 4%–8%.

The cervical lesion had sheets of cells in a nesting pattern with moderate eosinophilic granular cytoplasm, large round nuclei, stippled chromatin, increased mitoses (1/8 per HPF), no necrosis, positive p53 staining in 10% of tumor nuclei, MIB-1 of 30%, and avid staining for prolactin and synaptophysin. Thus, the diagnosis was consistent with a prolactin-secreting PCa (Fig. 4).

Discussion

Observations

We report a case of a patient with invasive pituitary prolactinoma who was treated with transsphenoidal resection of a pituitary tumor, dopamine agonist therapy, and adjuvant radiotherapy and who re-presented 6 years later with a compressive intradural extramedullary PCa metastasis of the cervical spine. PCa with metastatic spread to the spine represents an exceptionally rare disease entity with only a few case reports describing its presentation, natural history, and treatment.[12–26] Nearly 90% of these tumors arise from invasive secreting pituitary macroadenomas; in very rare instances, they can arise de novo from normal adenohypophysis.[8,27,28] However, there remain no reliable predictors of which pituitary tumors will ultimately metastasize to become PCas.[29] Moreover, the average latency period of 6.6 years from diagnosis of pituitary adenoma to presentation with PCa and the variation of latency periods for different adenoma types further complicate early recognition and treatment of this disease.[5,30]

Lessons

Treatment options for PCa span a wide gamut and include hormonal agents, surgical debulking or resection, fractionated radiotherapy or stereotactic radiosurgery, and chemotherapy/targeted therapies.[9,31] However, given our current inability to predict which secreting pituitary adenomas will ultimately metastasize to become PCa, treatment can be significantly delayed and therefore rendered less effective with conventional therapeutic modalities. This case exemplifies the importance of continued long-term monitoring of hormones in patients with secreting pituitary adenomas, because a progressive increase in secreted hormone levels is likely to represent local and/or systemic disease recurrence/progression. Despite much progress during the last decade in the treatment of PCa for which conventional treatment modalities have failed, mechanistic underpinnings and long-term response and outcomes remain unclear.

This case demonstrates that suspicion for metastatic spinal disease must remain high in patients with a history of invasive secreting pituitary adenomas who re-present years later with signs of myelopathy or radiculopathy. Given the lack of quality evidence guiding the treatment of PCa, especially metastatic disease of the spine, further studies are warranted.

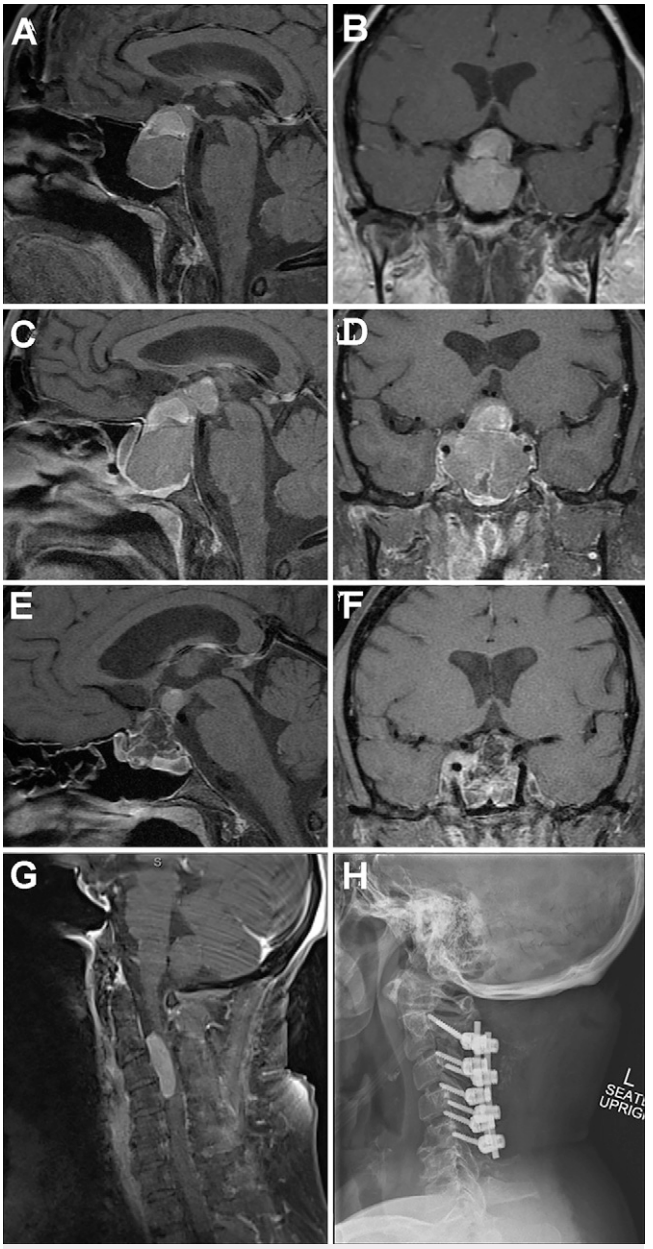

FIG. 2. A and B: Preoperative MRI. Sagittal (A) and coronal (B) T1-weighted pituitary MRI with contrast shows sellar and suprasellar solid and cystic mass (2.3 × 2.8 × 4.0 cm) with hypothalamic indentation, superior displacement of the optic chiasm, and surrounding vasogenic edema. **C–F:** MRI of the pituitary gland. Sagittal (C) and coronal (D) T1-weighted pituitary MRI scans with contrast obtained after initial resection show blood products and fluid levels within the sellar mass, increased mass effect along the hypothalamus with partial effacement of the third ventricle, and bilateral cavernous sinus invasion with partial encasement of bilateral internal carotid arteries. Sagittal (E) and coronal (F) T1-weighted pituitary MRI scans with contrast obtained after repeat resection of invasive prolactin-secreting pituitary macroadenoma with fat and fascia graft packing in the sphenoid sinus and sella turcica. There is a small amount of residual enhancing tumor along the hypothalamus and at the floor of the third ventricle and incomplete encasement of the right internal carotid artery without narrowing.

FIG. 2. (*continued*) →

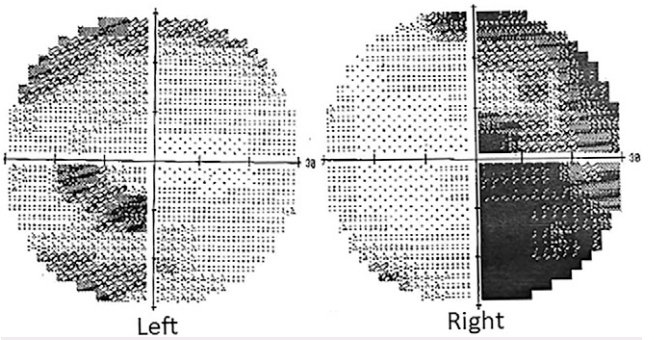

FIG. 3. Preoperative automated perimetry visual field testing shows right temporal hemianopsia and mild left-sided visual field defect.

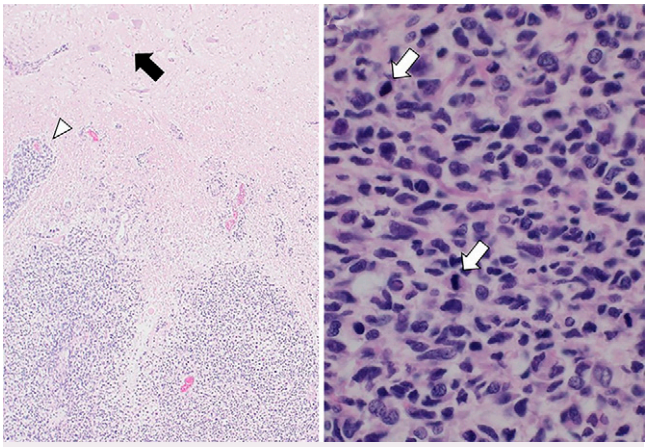

FIG. 4. Histopathological sections of the tumor infiltrating the cervical cord stained with hematoxylin and eosin. **Left:** Hypercellular tumor is seen infiltrating the lateral cord along Virchow-Robin spaces (*white arrowhead*). Anterior horn motor neurons are seen in the upper half of the image (*black arrow*). Magnification ×20. **Right:** The tumor is hypercellular and composed of cells with enlarged, irregular, hyperchromatic nuclei and a small amount of eosinophilic cytoplasm. Magnification ×600. Numerous mitotic figures (*white arrows*) are seen.

Acknowledgments

We thank Joshua A. Sonnen, MD, for providing the pathological description and Kristin Kraus, MSc, for her assistance with preparation of this paper.

FIG. 2. G and H: Imaging showing progression of the cervical lesion. G: Sagittal T1-weighted MRI of cervical spine with contrast shows a 3.6-cm intradural extramedullary ventrally located mass from C2–3 levels with severe spinal canal stenosis at C2–3 and C3–4 levels. H: Lateral plain radiograph obtained after cervical mass resection with C3–6 laminectomies and C2–5 posterior spinal fusion. Hardware is intact, and there is unchanged cervical spine alignment.

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Disclosures

Dr. Sherrod reported grants from AO Spine Foundation outside the submitted work. Dr. Dailey reported personal fees from Zimmer Biomet and personal fees from AO North America outside the submitted work. No other disclosures were reported.

Author Contributions

Conception and design: Couldwell, Gamboa, Wilkerson, Kundu. Acquisition of data: Couldwell, Gamboa, Wilkerson, Kundu, Dailey. Analysis and interpretation of data: Couldwell, Gamboa, Wilkerson, Kundu, Sherrod. Drafting the article: Couldwell, Gamboa, Wilkerson, Kundu, Sherrod. Critically revising the article: Couldwell, Gamboa, Sherrod, Dailey. Reviewed submitted version of manuscript: Couldwell, Gamboa, Sherrod, Dailey. Statistical analysis: Gamboa. Administrative/technical/material support: Gamboa. Study supervision: Couldwell, Gamboa, Dailey.

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