Pituitary carcinoma recurrent to the lumbar intradural extramedullary space: Case report

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Context: Pituitary tumors are rare, and pituitary carcinomas are rarer still. Prognosis is poor, with less than 50% of patients surviving past 1 year after diagnosis. In this case of spinal metastasis from an adrenocorticotrophic hormone-secreting pituitary carcinoma, the intradural extramedullary metastases recurred in the same lumbar area 6 years apart.

Findings: Fourteen years prior to presentation in our clinic, a 48-year-old woman was diagnosed with pituitary adenoma which was treated with resection followed by radiation. Eight years later, an intradural extramedullary spinal drop metastasis at L2–L3 was again treated with resection and radiation. Three years later, magnetic resonance imaging (MRI) revealed a mass encasing the right carotid artery, which was treated for 1 year with chemotherapy using temozolomide (Temodar). Three years later, MRI showed intradural extramedullary metastases at the L3–L4 intervertebral disc space and behind the L3 vertebral body; treatment was again resection followed by radiation. Back pain and weakness resolved after surgery and her neurological examination returned to baseline. There was no evidence of recurrence 1 year after surgery.

Conclusion/clinical relevance: In this unusual case, this pituitary carcinoma metastasized twice in 6 years to virtually the same intradural extramedullary lumbar region. Surgical resection of these masses aided in relieving neurological symptoms and prolonging life.

Keywords: Pituitary carcinoma; Metastases, Neoplasm; Spinal cord neoplasms, Intradural-extramedullary, L2–L3; Pituitary adenoma, ACTH-secreting; Disc, Intervertebral, L3–L4

Introduction

Pituitary carcinomas, as opposed to pituitary adenomas, are defined by metastases that are craniospinal or systemic.^{1,2} Pituitary carcinomas can also transform from invasive adenomas through surgery or radiotherapy.³ While radiotherapy and surgery have been the treatments of choice for these rare lesions, prognosis is poor.¹ We report a patient who not only developed a pituitary carcinoma with lumbar spinal drop metastases, but who also had recurrent intradural extramedullary tumors in virtually the same location several years later.

Case summary

A 61-year-old woman with a history of an adrenocorticotrophic hormone (ACTH)-producing pituitary carcinoma presented with severe back pain and pain radiating from her lower extremities. She was diagnosed

with a pituitary adenoma 14 years earlier when she presented with heavy menstrual bleeding, headache, blurred vision, and left eye droop. After a debulking resection followed by radiation therapy, she did well for 8 years, at which time she presented with back and leg pain, shingles, and Cushing's disease. Magnetic resonance imaging (MRI) revealed an intradural extramedullary tumor at L2–L3, which was resected. The lesion was an ACTH-producing tumor with the same histological appearance as her prior adenoma. Due to its metastasis, the classification of the pituitary tumor was changed from an adenoma to a carcinoma. Symptoms of Cushing's disease subsided with radiation therapy. She has used a cane since the surgery and has a mild foot drop.

Three years later she presented with blurred vision and MRI revealed a new mass measuring 1.7 cm in diameter encasing the right cavernous carotid artery. This central nervous system recurrence with cranial nerve palsy and blurred vision resolved with Temodar (temozolomide), which she took for 1 year. Two years

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later, she presented with severe back pain radiating to her lower extremities, as well as weakness when she walked. Neurological examination revealed muscle strength 4+/5 of her left lower extremity in dorsi and plantar flexion. Lumbar MRI showed several compression fractures and a mass at L3 that was $1.5 \times 1.8 \times 1.1$ cm at the

L3–L4 intervertebral disc space (Figs. 1A–C). After L3 lumbar laminectomy with partial extension at the previous laminectomized L2 space, pathology confirmed the tumor was the recurrent ACTH-immunoreactive neuroendocrine neoplasm (Figs. 2A–C). Post-operatively, the patient's back pain resolved and her neurological

Figure 1 (A) Sagittal T1 fast-spin-echo (FSE) image shows intradural tumor at L3–L4. (B) T1 weighted sagittal MRI shows intradural mass at L3–L4. There is a compression fracture at T12 and L3. Clumping of nerve roots suggest arachnoiditis consistent with previous surgery. There is also diffuse replacement of the bone marrow at L1–L2 secondary to previous radiation therapy. (C) T2-weighted axial MRI shows intradural tumor filling half the spinal canal.

Figure 2 (A) Hematoxylin and eosin-stained histology section of the L3 intradural tumor. The tumor is composed of loosely cohesive cells arranged in sheets with focal papillary architecture. The nuclei are uniform, round to oval, and show delicate ‘salt and pepper’ chromatin that is characteristic of neuroendocrine cells. The nuclei are eccentrically placed within granular eosinophilic cytoplasm. (B) Hematoxylin and eosin-stained histology section of the L3 intradural tumor. A higher magnification image of the tumor highlights the monomorphic round nuclei with small pinpoint nucleoli. In the upper left corner of the photomicrograph a pseudorosette is seen. (C) Immunohistochemical stain ACTH. The tumor cells are immunoreactive with ACTH. This stain shows granular cytoplasmic positivity, highlighting the adrenocorticotrophic hormone secretory granules.

examination returned to baseline. There was no evidence of recurrence 1 year after surgery.

Discussion

Pituitary tumors are rare, and pituitary carcinomas are rarer still, representing only 0.1–0.5% of all pituitary tumors.¹ Diagnosis of pituitary carcinoma requires not just local invasion of the tumor, often noted as a pituitary adenoma, but also cerebrospinal metastases or systemic metastases.¹ Indicators such as hyper-cellularity, nuclear pleomorphism, occasional mitotic figures, necrosis, and hemorrhage are unreliable and, histologically, little difference is seen in benign, invasive adenomas, and pituitary carcinomas. In distinguishing between pituitary adenomas and carcinomas, a higher Molecular Immunology Borstel number 1 (MIB-1), higher proliferating cell nuclear antigen, higher Ki-67, and positive p53 immunoreactivity are found in pituitary carcinomas.^{1–5}

Metastasis is the key to defining a pituitary carcinoma because it shows the dissemination of the tumor. Koyama *et al.*⁶ summarized the three pathways that metastases can take from the pituitary adenoma: blood-borne, drop, and central nervous system (CNS) dissemination. With blood-borne dissemination, the tumor invades the sella dura and hematogenously creates other metastases in close dural sites. This patient had no evidence of this. Drop metastasis differs from hematogenous dissemination because it occurs along the surgical tract.^{6,7} Drop metastases are localized within or around the surgical tract and the tumor can spread when the lesion exfoliates into the sub-arachnoid space and is part of the cerebrospinal fluid.^{7,8} In carcinomas, drop metastasis can occur on its own occasionally, but surgery can enhance the likelihood.⁸ The area around the adenoma in this patient showed no metastasis from the surgical tract. After a craniotomy, cerebrospinal fluid (CSF) dissemination can occur and craniospinal metastases, as in this patient, can extend from the lesion itself to the cauda equina. In intradural extramedullary tumors, as in this patient, CSF dissemination of the metastatic tumor occurs.^{2,9} When the intradural extramedullary tumors in this patient were analyzed, and the tumor type was reclassified as pituitary carcinoma.

Prognosis is extremely poor, with less than 50% of patients surviving past 1 year after diagnosis of a pituitary carcinoma. In one rare case, a person with an ACTH-secreting pituitary carcinoma like our patient's survived more than 20 years.^{1,6} While radiotherapy and surgery have been the treatments of choice, current research shows that Temodar is effective in repressing and reducing hormone secretions, symptoms

related to tumor growth, and pituitary carcinomas size.^{10,11,12} ACTH-secreting pituitary carcinomas are the second most common endocrinologically active tumor, preceded by prolactin (PRL)-producing tumors. Other groups include growth hormone (GH)-producing tumors, thyrotrophin-stimulating hormone-producing tumors, gonadotropin-producing tumors, and non-functional tumors.^{2,5,13,14} With a median of 7 years from diagnosis of the adenoma to the metastasis, which classifies the carcinoma, ACTH-secreting tumors have the longest interval to metastasis, being almost twice as long as PRL-producing tumors.^{1,5,7} In contrast with this patient and the patient who lived more than 20 years, however, survival was shortest in patients with ACTH-secreting tumors compared with other subtypes from the time their tumor was diagnosed as a carcinoma.²

Also highlighting the rarity of this case is that PRL-producing cell carcinomas develop more often in craniospinal metastases than do ACTH-secreting pituitary carcinomas. Similar to this patient, 50% of patients with ACTH-secreting pituitary carcinomas developed active or problematic Cushing's disease, which is noted clinically, as well as by an unusual number of mitoses.² Another common development from ACTH-secreting pituitary tumors is the increased chance of hepatic mutations, which were not seen in this patient.^{2,15} Nor was it seen that the ACTH-secreting pituitary carcinoma in this patient was radiosensitive to treatment¹⁶ because of her use of Temodar.

Three previously described cases of metastases from ACTH-secreting pituitary carcinomas are summarized in Table 1.^{17–19} When comparing the previous cases to this case, the time to metastasis in this patient (and thus the diagnosis of carcinoma) was longer than that in the other three cases (8 years versus 5–6 years). The case reported by Garrao *et al.*¹⁹ showed that radiotherapy effectively reduced the size of the tumor, whereas this patient used Temodar. In the case reported by Gabrilove *et al.*¹⁸ the spinal metastases were only found post-mortem and were asymptomatic, unlike in our patient in whom the same lumbar area was affected twice in 6 years. This case and the case reported by Frost *et al.*¹⁷ show similarity in the improvement after the resection of the spinal metastases and recovery, exceeding the typical prognosis of little more than 1 year.

We present a case of a recurrent intradural extramedullary tumor from a pituitary carcinoma in the form of a low drop metastasis in the lumbar disc space. Surgery and Temodar aided in relieving the patient's symptoms, lowering her ACTH level, and prolonging her life. This patient did not develop systemic metastases like patients

Table 1 Clinical data on ACTH-secreting pituitary carcinoma cases

Reference	Age of initial adenoma diagnosis/sex	Treatment	Cushing's and/or Nelson's	Time to metastases	Presentation of metastasis	Location of metastases	Response
Gabrilove <i>et al.</i> ¹⁸ (4)	37, male	Bilateral adrenalectomy	Both Cushing's and Nelson's	5 years	Cauda equina syndrome, heart, liver, pancreas, and spinal cord	L1–L2	Death due to disease progression
Frost <i>et al.</i> ¹⁷ (3)	33, female	Resection radiotherapy	Cushing's	6 years	Cauda equina syndrome, neck pain, spinal cord	C1–C2 L5–S1	Alive at 4-year follow-up
Garrao <i>et al.</i> ¹⁹ (5)	47, female	Resection radiotherapy	Neither	5 years	Pituitary, bone (spine)	—	Death due to disease progression
Present case	48, female	Resection radiotherapy	Cushing's	8 years	Spinal cord	L2–L3	Back pain again in 2008, resolved with Temodar; then later surgery at L3–L4

with other ACTH-producing tumors, but instead developed craniospinal metastases similar to those associated with PRL-producing tumors. This case demonstrates that while intradural extramedullary metastases of pituitary carcinomas are uncommon,¹⁴ recurrence of an ACTH-immunoreactive neuroendocrine neoplasm in the same area is even rarer, though possible.

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