Pituitary carcinoma with a single metastasis causing cervical spinal cord compression

Case report


Division of Medical Sciences, The Cancer Centre, and Department of Neurosurgery, Queen Elizabeth Hospital, Edgbaston, Birmingham, England

Pituitary carcinomas are rare, with fewer than 100 cases having been reported in the English-language literature. The diagnosis of pituitary carcinoma requires the demonstration of cerebrospinal and/or systemic metastases rather than local invasion. The lesion carries a poor prognosis; fewer than 50% of patients survive beyond 1 year after diagnosis. In this report the authors describe the case of a 68-year-old man who had undergone transphenoidal debulking surgery and pituitary radiotherapy 4 years earlier for a pituitary adenoma. He presented with cervical cord compression due to a single metastasis from pituitary carcinoma. The authors discuss the management of this entity and review the literature for current opinion on the pathogenesis of these tumors, factors resulting in malignant transformation, and the reliability of markers that predict future malignant behavior. Evidence for the various treatment modalities is also appraised.

KEY WORDS • pituitary carcinoma • radiotherapy • pathogenesis • management

Case Report

History and Examination. This 68-year-old man initially presented in 1995 with reduced visual acuity and bitemporal hemianopia. Early investigations suggested anterior ischemic optic neuropathy, but the patient was then lost to follow up. In 1996 he was referred to a specialist pituitary clinic, having presented again with worsening visual field loss, lethargy, and impotence. Initial endocrine investigations revealed the following values (normal ranges are listed in parentheses): thyroxine 12.5 pmol/L (9–20 pmol/L), thyroid-stimulating hormone less than 0.1 mU/L (0.4–5.5 mU/L), luteinizing-hormone 0.5 IU/L (1–8 IU/L), follicle-stimulating hormone 0.5 IU/L (2–11 IU/L), prolactin 2741 mU/L (40–360 mU/L), testosterone 2.6 nmol/L (8–29 nmol/L), and short synacthen test: cortisol 36 nmol/L at baseline and 147 nmol/L after 30 minutes. Magnetic resonance imaging of the pituitary demonstrated a cystic dumbbell-shaped pituitary tumor that compressed the optic chiasm (Fig. 1 left). The clinical presentation, hormone profile, and radiographic findings suggested a clinically nonfunctioning pituitary adenoma with elevated prolactin concentration due to pituitary stalk compression (hypothalamic–pituitary disconnection).

Management. The patient underwent transphenoidal surgery to debulk the tumor (Fig. 1 right), resulting in significant improvement of his visual fields. Histological evaluation showed findings consistent with a pituitary adenoma (Fig. 2 upper) with immunostaining for prolactin (Fig. 2 lower). Postoperatively, he was followed up according to local protocol but in 1998, MR imaging revealed that the residual tumor had enlarged. Further surgery was not performed at this time, but the patient underwent fractionated external-beam radiotherapy to treat the pituitary fossa (45 Gy in 25 fractions during a 5-week period).

In November 2000 he was admitted to a different center with a 2-month history of severe neck pain and arm and leg weakness; he was unable to walk or lift his arms. In addition he had lost urinary and bowel sphincter func-
tion and exhibited upper motor neuron signs in all four limbs. The diagnosis of cervical spinal cord compression was confirmed on MR imaging, which demonstrated an intradural, extramedullary mass between C2–4 (Fig. 3). Following cervical laminectomy, the lesion was macroscopically excised when it was found to be noncontiguous with the adjacent spinal cord. He made an excellent neurological recovery. Histological examination showed medium-sized round cells arranged in sheets with scattered mitoses and immunostaining for chromogranin A, synaptophysin, and neuron-specific enolase, as well as prolactin (Figs. 4 upper and center). The proliferative index measured using MIB-1, an antibody against Ki-67, was approximately 10% (Fig. 4 lower). There was no evidence of a further primary tumor or metastatic disease outside the cervical region. The patient underwent radical radiotherapy to treat the cervical and upper thoracic spine (50 Gy in 30 fractions during a 6-week period).

Nine months after the cervical spine surgery, he experienced rapidly failing vision (Fig. 5) and MR imaging documented expansion of the pituitary tumor, which compressed the optic chiasm (Fig. 6). His vision improved after a transcranial debulking procedure. Histological evaluation again showed a prolactin-staining neuroendocrine tumor, which was similar in appearance to the lesion removed at the time of the initial transsphenoidal resection in 1996. Review of histological data concerning the pituitary tumor excised in 1996 revealed no features predictive of malignancy. The MIB-1 proliferative index was approximately 1% (Fig. 7), but both pituitary and cervical tumors stained for prolactin. Serum prolactin measured following transcranial debulking surgery was 1538 mU/L. In light of the recurrent and apparent aggressive nature of the tumor, he was placed on dopamine agonist therapy (cabergoline) in the hopes that it would confer a possible antiproliferative effect. Despite high-dose dopamine agonist therapy (1 mg cabergoline five times weekly), serum prolactin concentrations remained greater than 1000 mU/L. An MR imaging study performed in April 2002 revealed a small pituitary

FIG. 1. Left: Pituitary MR image obtained at initial presentation in 1996 revealing cystic dumbbell-shaped pituitary tumor compressing the optic chiasm. Right: Pituitary MR image obtained after transsphenoidal surgery to debulk the lesion.

FIG. 2. Upper: Photomicrograph of the pituitary tumor at first presentation in 1996. H & E, original magnification × 250. Lower: Photomicrograph showing positive (brown) immunostaining for prolactin. Original magnification × 100.
remnant, and \(^{111}\)In octreotide scanning demonstrated no evidence of somatostatin binding. At the most recent follow-up examination the patient’s vision was stable.

**Discussion**

Pituitary carcinomas are rare, representing approximately 0.1 to 0.5% of all pituitary tumors.\(^4\)\(^5\)\(^12\)\(^15\) The diagnosis of pituitary carcinoma requires the demonstration of cerebrospinal metastases and/or systemic metastases and not simply evidence of local invasion, which is a common finding in cases of pituitary adenomas.\(^18\) More than 70% of these lesions are endocrinologically active,\(^12\) and it has been suggested that a significant number of those classified as clinically nonfunctioning in earlier reports actually represented prolactin-secreting tumors.\(^15\) The diagnosis carries a poor prognosis, with fewer than 50% of patients surviving beyond 1 year after identification of the lesion.\(^15\) The pathogenesis of pituitary carcinoma is unclear and there are no reliable markers that predict later malignant behavior. Most cases of pituitary carcinoma arise from macroadenomas,\(^12\) and because of their long latency period prior to metastasis (median 7 years), it is currently
believed that they arise from benign adenomas rather than appear de novo.\textsuperscript{12,15} Although what triggers this transformation remains unclear, it is likely that there is a progressive accumulation of genetic aberrations in oncogenes and/or tumor suppressor genes that changes the tumor phenotype.\textsuperscript{1} Radiation therapy and surgery have also been proposed as causes of malignant transformation and possible metastasis; however, this is unlikely because in a significant number of the reported cases of pituitary carcinoma the patients have neither undergone surgery nor radiotherapy.\textsuperscript{12,19}

The distinction between adenoma and carcinoma cannot be made on the basis of histological or ultrastructural features alone,\textsuperscript{17} but increased mitotic activity and higher labeling indices for proliferation (MIB-1 and proliferating cell nuclear antigen) have been observed in pituitary carcinomas.\textsuperscript{15} Qualitative and quantitative abnormalities of classic oncogenes (\textit{ras}, \textit{p53}, and \textit{Rb}) have also been described,\textsuperscript{10,14,20} and the authors of more recent studies suggest that metastatic deposits of pituitary carcinoma can be of distinct clonal origin from the primary tumor.\textsuperscript{2,22}

The rarity of pituitary carcinoma means that most published data exist in the form of case reports,\textsuperscript{1,6,13,16,21} which makes audit difficult; hence, there are no evidence-based standards of optimal care for these patients with this disease. Surgery is rarely curative, although repeated resection of recurrent metastases has been reported to prolong survival in some cases.\textsuperscript{15} In most cases, radiotherapy alone has a palliative effect, although radiation of central nervous system metastases may arrest growth or even induce partial regression.\textsuperscript{11,15} Experience with stereotactic radiotherapy\textsuperscript{11,15} and gamma knife surgery\textsuperscript{19} to date has been limited, and results have been variable but generally poor.
Pituitary carcinoma

Dopamine agonists have a role in the early management of prolactin-producing pituitary carcinomas, but drug resistance typically develops. A significant number of neuroendocrine tumors express somatostatin receptors, and labeled somatostatin analogs have been used to detect metastatic lesions from pituitary carcinomas. Expression of somatostatin receptors and the uptake of labeled octreotide, however, does not necessarily translate into somatostatin analog–induced tumor growth suppression; to date, the use of octreotide has been shown to have little therapeutic effect on pituitary carcinomas.

Various regimens of cytotoxic chemotherapy have been used, particularly in patients with systemic metastases, but response is at best temporary, and further research is necessary to elucidate its role in the management of pituitary carcinoma.

In summary, the case reported here displays some of the typical features associated with pituitary carcinomas. The patient initially presented with a macroadenoma, and the latency period before cervical spine metastasis developed was 4 years. Despite the poor prognosis usually associated with this diagnosis, however, 4 years after treatment he remains free from recurrence. He continues to receive high-dose cabergoline, although the persistently elevated serum prolactin level suggests a resistance to dopamine agonist therapy.

Pituitary carcinoma is rare, but an awareness of this diagnosis is important in patients with previously diagnosed pituitary adenoma who present with neurological dysfunction or other signs of disseminated malignancy. Further research is required, directed principally at identifying reliable prognostic markers for pituitary carcinoma and developing effective treatment strategies.

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References


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