Prolactin secreting pituitary carcinoma

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Abstract
A man with a prolactin secreting pituitary carcinoma was treated by surgery and radiotherapy. Persistent hyperprolactinaemia partially responded to oral bromocriptine for four years. Serum prolactin then rose considerably with rapid, invasive tumour recurrence. Cytoxic chemotherapy halted tumour progression for twelve months before fatal spread throughout the brain. Failure to normalise serum prolactin with bromocriptine may precede an aggressive course in patients with prolactinoma.

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Most prolactinomas are slow growing and respond rapidly to oral bromocriptine therapy with normalisation of serum prolactin levels and tumour shrinkage. Pituitary surgery and/or external irradiation are indicated in the management of prolactinomas which only partially respond to bromocriptine therapy or as part of a strategy to prevent tumour recurrence. Rarely, prolactinomas behave more aggressively and undergo malignant transformation. The role of oral bromocriptine and other therapies (surgery, radiotherapy and chemotherapy) is then unclear.

Case report
A 40 year old man presented in 1979 with headache and a left paracentral scotoma. CT scan showed a large pituitary neoplasm with suprasellar extension (figure). Preoperative endocrine assessment showed hyperprolactinaemia (serum prolactin greater than 4000 mU/L, normal range < 400 mU/L) and panhypopituitarism. Frontal craniotomy and sub-total removal of the tumour was performed with recovery of vision. Histology showed the basic architecture of a pituitary adenoma which was highly cellular and demonstrated mitotic activity. Immunohistochemistry (DAKO polyclonal antibodies) showed intense staining for prolactin, but for all other hormones was negative (ACTH, FSH, LH, GH, TSH).

Replacement therapy was started (hydrocortisone, thyroxine and sustanon 250 mgs) and radiotherapy given (4800 rads, 20 fractions, 29 days). One month after radiotherapy there was a further bilateral reduction in visual acuity. CT scan showed a large suprasellar cyst which was drained with subsequent recovery of vision (figure).

In 1980 oral bromocriptine therapy (20 mgs a day) was started to control hyperprolactinaemia (greater than 4000 mU/L). Over the next three years there was no clinical or radiological evidence of tumour recurrence although there was incomplete suppression of serum prolactin levels (500-1800 mU/L). In 1984 bromocriptine dose was increased (40 mgs a day) following a further elevation of the serum prolactin (greater than 4000 mU/L). Eight months later there was further visual disturbance. CT scan showed tumour recurrence with marked supero-lateral extension. Serum prolactin was 81 000 mU/L despite bromocriptine 40 mgs daily. Transfrontal decompression and subtotal removal of tumour produced a transient recovery but within one year there was further bilateral deterioration in visual acuity. CT scan showed another large tumour recurrence with extension towards the internal carotid bifurcation and into the middle cranial fossa (serum prolactin 19000 mU/L; bromocriptine 40 mgs daily). Further transfrontal decompression proved ineffective. Tumour histology on this occasion demonstrated a more pleomorphic tumour which was invading overlying cerebral tissue. A full course of cytotoxic chemotherapy (CCNU, procarbazine; etoposide x 4 cycles) was given with marked improvement of vision. Serial CT scans over 12 months showed no evidence of further invasive tumour spread (serum prolactin 17 000 mU/L; bromocriptine 40 mgs daily).

In 1987 there was a sudden marked elevation of serum prolactin level (greater than 42 000 mU/L). CT scan showed extensive tumour spread into the right cavernous sinus and right retro-orbital space. A combination of transfrontal decompression and further cytotoxic chemotherapy (1 cycle pre-op; 4 cycles post-op) failed to prevent further tumour progression.

There was a subsequent marked clinical deterioration with further visual loss, right sided cranial nerve involvement (3rd to 6th) and marked hyperprolactinaemia (500 000 mU/L). The patient died in 1988. At necropsy, approximately 90 cm³ of tumour tissue covered the inferior surfaces of the right frontal and temporal lobes, invaded the brain, right lateral ventricle and cerebellopontine angle, and encircled the right internal carotid artery, both optic nerves and chiasm, and the right 3rd, 5th, 7th and 8th cranial nerves. A
metastatic nodule was attached to the left vertebral artery.

**Discussion**

Pituitary carcinoma is rare and the poor correlation between histological and ultrastructural features and malignancy excludes a definitive histopathological diagnosis. Malignancy within pituitary tumours is defined by the development of local (invasive) spread and/or the presence of metastases. A literature search revealed nine other cases of prolactin secreting pituitary carcinomas. The incomplete suppression of serum prolactin levels with adequate doses of bromocriptine may indicate potential malignant behaviour in prolactinomas. Also sudden, marked elevations of serum prolactin can reflect tumour recurrence with extensive invasive spread and/or the development of metastases. Our patient illustrates both these points.

There are mixed reports of the usefulness of bromocriptine treatment in prolactin secreting pituitary carcinomas. A sustained response (suppression of serum prolactin levels, cessation of tumour growth) has been reported. However, in other patients, as in this case, there is a partial response to bromocriptine, with subsequent invasive tumour spread and/or the development of metastases after a variable latent time period (mean 7-7 years).

Surgery appears to provide only temporary palliation and there is a poor response to radiotherapy. The initial partial response to cytotoxic chemotherapy in this case has not previously been described and this combination with bromocriptine should be considered in future cases.

The natural history of prolactinoma remains poorly defined and long-term follow up with regular clinical and radiological assessment is mandatory. Incomplete suppression of serum prolactin with bromocriptine may indicate potential malignancy. A rising serum prolactin level, despite bromocriptine therapy, may indicate malignant transformation.

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