An intrasellar pituitary tumour producing metastases in liver, bone and lymph glands and demonstration of ACTH in the metastatic deposits

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Abstract. We report the history, laboratory and histological findings in a man who presented with Cushing's disease. Despite removal of the primary pituitary tumour, his disease progressed and after bilateral adrenalectomy, he became pigmented and plasma ACTH levels remained elevated. He had further pituitary surgery and radiotherapy, to relieve compression of the optic chiasma. Plasma ACTH levels remained elevated. He developed liver, bone and lymph gland metastases and after an acute paraparesis due to spinal metastases he died. Immunoperoxidase staining techniques demonstrated ACTH in the pituitary recurrence and metastases. The combination of bone, liver and lymph node metastases has not previously been reported, nor has ACTH been reported before in metastases from a primary intrasellar tumour.

Most pituitary tumours, whether they are chromophobe, eosinophil or basophil staining are benign. Some however can become large and locally invasive. Although intracranial tumours producing extracranial metastases by haematogenous spread have been reported previously, most of these cases were reported before immunocytological techniques and ACTH assay were available to study the tumour. The role of radiation in the induction of pituitary tumours in humans is uncertain, but radiation therapy might induce malignant change in pre-existing benign tumours.

Case Report

The patient presented in 1976 at the age of 58 years with hypertension. Cushing's disease was not suspected until almost 1 year later when he was noticed to have centripetal obesity, bruising and proximal weakness. His 09.00 a.m. plasma cortisol was 546 nmol/l and 10.00 p.m. plasma cortisol 552 nmol/l. The diagnosis was confirmed by a failure to suppress cortisol on dexamethasone. (Plasma cortisol after 3 days of dexamethasone 0.5 mg every 6 h was 294 nmol/l and after 3 days of dexamethasone 2 mg every 6 h was 146 nmol/l). His 09.00 a.m. plasma ACTH was 95 pg/ml. His skull X-ray showed considerable expansion of the pituitary fossa and lumbar air encephalogram revealed a mass in the sella with slight suprasellar extension. Other endocrine investigations at this time demonstrated a low plasma testosterone 1.4 nmol/l, an inadequate response of FSH and LH to gonadorelin, an inadequate response of growth hormone during hypoglycaemia and a normal plasma prolactin concentration of 400 mU/l.

He was treated with metyrapone 750 mg four times daily pending neurosurgical treatment of his tumour. At operation a soft central tumour, within its own capsule was discovered and removed. Histological studies confirmed that this was a mainly chromophobe adenoma, no basophils were seen.

Four months after his operation his plasma cortisol failed to exhibit any diurnal rhythm (535 nmol/l at midnight and 546 nmol/l at 09.00 a.m.). After low dose dexamethasone his plasma cortisol was 440 nmol/l and
after high dose dexamethasone 434 nmol/l. His plasma ACTH was 80 ng/l. He therefore underwent bilateral adrenalectomy after which cortisol was no longer present in measurable quantities and he was treated with hydrocortisone and fludrocortisone in replacement dosage.

In 1979, 12 months after his adrenalectomy he developed a left temporal and right inferotemporal visual field deficit and he was noted to be becoming increasingly pigmented. His plasma ACTH was 1333 pg/ml and plasma cortisol at the lower limit of detectability. A recurrence of his pituitary adenoma was removed surgically. The microscopic appearance had now changed showing irregular groups of mainly eosinophilic epithelial cells with occasional clusters of larger irregular cells with large dark nuclei sometimes with vacuoles and infrequently multinucleate. Post operatively, additional replacement therapy with thyroxine and testosterone esters was required. His plasma ACTH however remained elevated at 380 pg/ml. Six months later he presented again with bitemporal visual field loss, and on this occasion was treated with radiotherapy (5000 rads to the sella and suprasellar regions). Almost a year after radiotherapy, his plasma ACTH had fallen to 99 pg/ml and his visual fields became full on perimetry.

In 1982, his general condition began to deteriorate. He fell and fractured three ribs and following spinal vertebral collapse, he developed a paraparesis at D10 level. Radiology of the thoracic spine revealed that all the bones were osteoporotic, but the appearances of D10 were a little different with destruction of the pedicles. An isotope bone scan showed several areas of abnormal, increased uptake. These were in an area corresponding to D10, the sternum, around the left sacroiliac joint and the left iliac crest, lower part of the right sacroiliac joint, both femoral heads, skull vault posteriorly, the 9th and 10th ribs on the left, the 6th rib on the right, two in the shaft of the right humerus and one in the region of the pituitary fossa. The appearances were consistent with multiple metastatic deposits. He died shortly afterwards.

At post mortem there was considerable enlargement of
the pituitary fossa which measured 3 cm × 3 cm in length and width and was 2.5 cm deep. It contained a tumour mass composed of soft pink tissue with adherent blood clot. Histological study revealed a very pleomorphic haemorrhagic pituitary tumour with a narrow ring of normal pituitary glandular tissue which was quite distinct from the tumour, but separated only by an often narrow band of connective tissue. The tumour itself was composed of irregular cells varying from large giant cells often multinucleate, some vacuolated, many with hyperchromatic bizarre nuclei, to smaller cells. The irregular cytoplasm appeared to be chromophobe. The tumour cells were divided into groups by many crossing collagenous trabeculae. After fixing in formalin and sectioning no macroscopic tumour was seen elsewhere in the brain or spinal cord. A malignant tumour mass was present in the sternum extending into adjacent soft tissue. The liver was slightly enlarged with numerous metastases. Histology showed that they were well circumscribed though adjacent liver cells showed gross distortion in some places. The metastatic tumour was crossed by similar collagenous trabeculae to those seen in the pituitary tumour. The metastatic tumour cells were less pleomorphic than those of the pituitary tumour although they showed considerable variation in size and giant cells were seen. The cell cytoplasm was better defined and appeared slightly eosinophilic. Small ‘rings’ of cells were seen usually within the collagenous trabeculae. These were invaded by tumour similar to that in the liver (i.e., less pleomorphic than the tumour in the pituitary). Fibrous trabeculae were again seen and the cytoplasm was better defined and slightly eosinophilic.

The tongue, pharynx, oesophagus, stomach, duodenum, small and large intestines and pancreas were macroscopically normal. The gall bladder was absent. The kidneys, ureters, generative organs, bladder and prostate were free from tumour. The spleen was normal. There were no enlarged lymph glands in the axillae, para aortic or inguinal regions. The thyroid gland was macroscopically normal and no residual adrenal tissue was found. The lungs were congested with areas of atelectasis and consolidation but there was no evidence of bronchial tumour. There was scarring of the parietal pleura over the site of the old rib fractures but again no tumour. There were no tumour masses in the pericardium or heart. ImmunocytoLOGY with anti ACTH and the peroxidase antiperoxidase method showed that the pituitary recurrence, liver and lymph gland metastases contained ACTH. A photomicrograph of a section of liver is shown (Fig. 1). The search for any possible primary tumour secreting ACTH or corticotrophin releasing hormone (e.g. bronchus) was negative, and it was concluded that the pituitary tumour was the primary lesion. Vertebral collapse can occur in Cushing’s disease due to osteoporosis, but here it was due to metastases.

Discussion

Metastases spread via the blood stream are an extremely rare finding in primary pituitary tumours. A search of the literature has revealed only 16 previously reported cases (Table 1). In the majority there was no evidence that the tumours were endocrinologically active. Six had Cushing’s syndrome, but evidence that the metastases actively secreted ACTH can only be based on the clinical grounds of hyperpigmentation in three cases (Cohen & Dible 1936; Forbes 1947; Salassa et al. 1959). In one further case (Kaiser et al. 1983) immunocytological investigation has shown that a parasellar tumour gave rise to metastases containing ACTH. In only one case (Myles et al. 1984) is there evidence of any other hormone activity, where, using the immunoperoxidase technique, positive staining for human growth hormone was seen in the primary tumour and metastases. Serum growth hormone was not elevated however and the patient was not clinically acromegalic.

There are no reports of patients with primary prolactinoma and metastases by haematogenous spread. There are reports however of prolactinomas giving rise to metastases in the cereboglossopharyngeal tumour (Martin et al. 1981) and spinal cord (Landgraf 1985). The metastases in these two reports were demonstrated to contain prolactin by immunofluorescent and immunohistochemical techniques, and arose presumably due to spread via the cerebrospinal fluid rather than the blood stream.

Immunohistochemical investigation has been used to demonstrate the presence of ACTH in metastases from a primary parasellar tumour (Kaiser et al. 1983), but the case we describe here is, we believe, the first in which an intrasellar pituitary tumour metastasised to bone, liver and lymph gland and in which the metastases were shown by immunohistochemistry, to contain ACTH. Plasma concentrations of ACTH were also shown to be elevated.

The rapid growth of this pituitary tumour with optic nerve involvement followed bilateral adrenalectomy. This well recognised syndrome (Nelson et al. 1958) occurs because the feedback loop of cortisol suppression on the pituitary is broken. Kaiser et al. (1983) speculated that reduction of their patient’s elevated plasma cortisol by adrenalectomy may have stimulated the tumour cells to produce more ACTH, and undergo rapid proliferation with the development of distant meta-
stases. It is therefore worthy of note that in our patient, the pituitary had undergone a pleomorphic change between his first and second cranietomies before he had any radiotherapy. It is possible that the high plasma cortisol, prior to adrenalectomy, exerted an inhibitory effect on malignant change though it is impossible to prove that the malignant change would not have occurred in any case and the adrenalectomy was merely incidental. Kaiser et al. (1983) showed in their patient that ACTH could be suppressed by supraphysiological doses of glucocorticoids. This effect is probably a direct effect on the tumour cells.

After adrenalectomy about 10% of patients develop Nelson's syndrome (Coulter 1984). Radiotherapy has been advocated to prevent this syndrome. Orth & Liddle (1971) describe in their series, 20 patients who had pituitary irradiation prior to adrenalectomy. None of these patients developed Nelson's syndrome. Moore et al. (1976) was unable to find any difference in the incidence of Nelson's syndrome; out of 100 patients subjected to adrenalectomy alone, 7 developed Nelson's syndrome and out of 20 patients who had pituitary irradiation prior to adrenalectomy, 2 developed Nelson's syndrome. The case for radiation therapy to prevent Nelson's syndrome is not proved, but in view of the pleomorphic histological changes in our patient after adrenalectomy perhaps pituitary irradiation should still be considered whenever the adrenal glands are removed as treatment for pituitary dependent Cushing's disease.

In our patient it is unlikely that radiation therapy induced the malignancy since pleomorphic changes were observed in the pituitary recurrence before radiotherapy. Although radiotherapy has been implicated in the development of fibrosarcoma (Terry et al. 1959; Newton et al. 1962) it has never been demonstrated to induce malignant change in human pituitary adenomas. Radiation in animals increases the incidence of pituitary tumours, but there is as yet no evidence of this in humans (Gold 1981).

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References


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