Metastasising Pituitary Neuroendocrinal Tumour with Peptide Secretion

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Abstract
A 26-year-old male presented with prolactin-secreting invasive pituitary macroadenoma, which was partially excised with right pterional craniotomy. Post-operative computerized tomography revealed persistence of the tumour and hence he was started on oral bromocriptine therapy. His therapeutic compliance was poor. Seven years later he presented with further increase in size of the pituitary macroadenoma with hepatic and gastric metastasis. Upper gastrointestinal endoscopic biopsy of the metastatic lesions and immunohistochemical staining diagnosed it as a neuroendocrinal tumour with peptide secretion. He was initially treated with oral bromocriptine alone and later along with octreotide.

INTRODUCTION
Prolactinomas are the commonest hormone secreting tumours of the pituitary and represent 25% of surgically removed pituitary adenomas.1 Therapy is aimed at reducing the size of the adenoma and functioning of the gland. Medical therapy with dopaminergic agonist agents provides excellent results.2 Surgical decompression is required for macroadenomas with invasive and compressive symptoms. Rarely pituitary tumours exhibit metastatic behaviour. Initially they present as adenomas and later by virtue of the metastasis they are diagnosed as carcinomas.

CASE REPORT
A 26-year-old male presented with blurring and narrowing of visual fields since two months and unilateral left sided headache for 5 years. Ophthalmic examination revealed right sided temporal hemianopia, left sided inferior temporal field defect. Ocular movements were normal in both eyes. Fundus examination revealed pallor of both the optic discs. There was no other neurological deficit. Serum prolactin (Prl) was 850 ng/ml and the other circulating pituitary hormones were normal. A computerized tomographic (CT) scan of the brain revealed right sided temporal hemianopia, left sided inferior temporal field defect. Ocular movements were normal in both eyes. Fundus examination revealed pallor of both the optic discs. There was no other neurological deficit. Serum prolactin (Prl) was 850 ng/ml and the other circulating pituitary hormones were normal. A computerized tomographic (CT) scan of the brain revealed pituitary macroadenoma with suprasellar extensions and compression of the optic chiasma. The patient was diagnosed to have prolactin-secreting macroadenoma.

The lesion was partially excised by right pterional craniotomy and the post-operative period was uneventful. His visual field returned to normal following surgery. Histopathology revealed a chromophobe adenoma. Post-operative contrast enhanced CT scan showed a residual enhancing tumour in the pituitary fossa. His post-operative serum Prl was 364 ng/ml and he was treated with oral bromocriptine 10 mg/day. After a month, serum Prl decreased to 219 ng/ml. The dose of bromocriptine was increased to 20 mg/day. He was advised radiotherapy but was lost to follow-up.

Seven years later, the patient presented with fullness of abdomen, nausea, and epigastric pain with easy fatiguability. Clinical examination revealed tenderness in the right hypochondrium, bitemporal hemianopia and pallor of both the optic discs. His liver function tests and chest radiograph were normal. The serum prolactin was 387 ng/ml. Ultrasound (US) abdomen revealed multiple hypoechoic lymph nodes or ascites. Contrast enhanced CT scan of the abdomen revealed accentuation of the multiple hypoechoic areas in the liver and multiple gastric mucosal polypoidal masses. Upper gastrointestinal (GI) endoscopy revealed multiple diffuse mucosal polyps confined to fundus and proximal body of the stomach, first and second part of the duodenum (Fig. 1). Which were subjected to endoscopic punch biopsy. Colonoscopy was unremarkable. Magnetic resonance (MRI) imaging of the sellar and parasellar regions confirmed the recurrence of pituitary macroadenoma. Biopsy from the polypoidal masses (Fig. 2) revealed polypoidal hyperplasia, lymphoplasmacytic infiltration in the lamina propria and small nodular aggregates of mildly amphophilic cells with uniform round nuclei arranged in microacinar, cribriform and trabecular patterns. Immunohistochemistry (IHC) exhibited positivity...
to Prl, growth hormone (GH), neuron-specific enolase (NSE), synaptophysin, chromogranin, and S-100 protein and was negative for adrenocorticotrophic hormone (ACTH). The serum prolactin was 533 ng/ml. He was started on oral bromocriptine 20 mg/day with a plan to initiate radiotherapy. Additional therapy with subcutaneous octreotide (Sandostatin) (300 mg/day) was initiated together with oral bromocriptine. After six weeks of bromocriptine and octreotide, the serum prolactin decreased to (136 ng/ml) but there was no change in GH. The upper GI endoscopy and repeat biopsy from the polypoidal mass revealed similar features as before. Because of poor compliance of the patient radiotherapy of the tumour could not be instituted.

**DISCUSSION**

Malignant prolactinomas with intracranial and extracranial metastasis are very rare. Initially they present as adenomas. Genetic mutations ras and P53 as late events account for their malignant transformation. In about 32% of patients with prolactin secreting macroadenomas initial normalization of prolactin has been reported and in 25% of the patients normalization of prolactin occur on long term follow up after surgery. Even with radiotherapy prolactin normalizes in only 20-30% of patients within 5-15 years. In 40% of cases bromocriptine therapy reduces the tumour size to less than 50% in macroadenomas.

Usually pituitary neoplasm exhibit varying degrees of positivity for pituitary tropic hormones by IHC. But the positivity by NSE, chromogranin, synaptophysin, S-100 protein apart from GH and Prl reflect that the tumour is mostly neuroendocrine in nature rather than a simple pituitary neoplasm. This patient presented with hepatic and upper GI metastasis seven years after the initial presentation. To the best of our knowledge there has been no such report of a neuroendoctrine tumour of pituitary with peptide secretion manifesting with hepatic and gastric metastasis, treated with bromocriptine and octreotide from the published literature.

Malignant prolactinoma with hepatic metastasis and prolactin producing hypophyseal carcinoma with hepatic metastasis have been reported. Various forms of therapy have been tried, and the mortality has been due to pulmonary thromboembolism. Because of GH and Prl positivity of the metastatic deposit we tried octreotide therapy along with bromocriptine. There was no appreciable decrease either in the size of the pituitary tumour or gastric polypoidal mass with either bromocriptine or bromocriptine plus octreotide. Bromocriptine alone reduces the serum Prl by turning off the intracellular Prl - synthesizing machinery within 6-8 weeks of therapy. In this patient there was a decline in prolactin but not its normalisation perhaps due to smaller dose. Octreotide is effective only if the tumour cells express somatostatin receptors (subtype 2 and 5). Poor differentiation of the tumour can explain the non-responsiveness to therapy with octreotide. Longer duration of therapy with higher doses of bromocriptine along with irradiation of the primary pituitary lesion would have been beneficial. Poor compliance of the patient did not permit us to follow up therapy.

**REFERENCES**