A 54 year old man was referred to the department of neurosurgery for frontal headache and vomiting. The patient was known in the department because of previous multiple surgery for a locally invasive pituitary prolactinoma (eight years, three years, and one year previously). The neurological examination revealed a frontal mass, which adhered to the dura, suggesting a meningioma. One year later, a left temporal metastasis was removed. Three months later, the patient died, with spinal metastases, of massive lung embolism. Histology revealed a progression of adenohypophyseal prolactinoma on neuroendocrine carcinoma, with an increase in proliferating indexes and modification of hormone production. This study documents a 10 year history of a rare prolactin producing pituitary carcinoma, which metastasised via liquoral flow.

Recently 10% of pituitary adenomas grow by expansion and displacement of adjacent structures and demonstrate gross invasion: such behaviour is considered to be benign.1 Distant metastases, either cerebrospinal fluid borne or haematogenous, are generally accepted as the true diagnostic hallmark of carcinoma.2 The disruption of vascular barriers after surgical intervention is an important factor in the intracranial or extracranial spread of tumour cells,3–5 similar to the systemic spread of gliomas.3 A considerable proportion of carcinomas may develop from adenomas: progressive malignant transformation might result in a gradual increase in resistance to agonist drugs.5 The time interval between the diagnosis of primary pituitary tumours and the development of metastases is very variable, and can be as much as 25 years,6 with an average period of seven years. The major predictive index of recurrence or malignant outcome of a pituitary tumour is the proliferation rate, using anti-proliferating cell nuclear antigen (PCNA) and MIB1 antibodies.5

“The disruption of vascular barriers after surgical intervention is an important factor in the intracranial or extracranial spread of tumour cells”

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Plasma concentrations of prolactin (PRL), cortisol, and growth hormone (GH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone</td>
<td>1986</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>PRL [ng/ml]</td>
<td>35.5</td>
</tr>
<tr>
<td>Cortisol [µg/ml]</td>
<td>43.4</td>
</tr>
<tr>
<td>GH [ng/ml]</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Figure 1 (A) Magnetic resonance T1 weighted axial image shows an enlarged sella, filled by the tumour, with enhancement and right suprasellar extension, infiltrating the cavernous sinus and right optic nerve. (B) Computed tomography scan shows a right frontal lesion, with adhesion to the dura.
We report the case of a 45 year old man who complained of headaches and a visual field deficit, which were associated with hyperprolactinaemia and hypercortisolaemia (table 1). A computed tomography (CT) scan showed a large pituitary mass, extending above the diaphragm sellae and involving the suprasellar region, which was removed by the trans-sphenoidal approach.

Five and seven years later, CT scans showed two separate tumoral regrowths, with infiltration into the right cavernous sinus, which were treated by craniotomy and trans-sphenoidal resection, respectively; however, magnetic resonance imaging (MRI) showed that the tumour enclosed the right internal carotid artery (fig 1A), so that the patient was treated with radiotherapy and Sandostatin.

Nine years after the first operation, a CT scan revealed a right frontal hyperdense lesion adhering to the dura, suggesting a meningioma (fig 1B), which was surgically removed by frontal craniotomy. Sandostatin treatment was stopped.

Postmortem examination confirmed the massive pulmonary embolism and no lesions were seen outside the central nervous system. Upon en block removal of the bony sella, while material oozed from the region of the cavernous sinus, and embedded the right carotid artery. Two roundish soft masses, 2 cm in diameter, were found in the ventral grey horn of the cervical cord, beneath the spinal arachnoid.

Histological examination of surgical specimens from the three pituitary resections showed sheets of medium sized, monomorphic cells (fig 2A). The nuclei had a fine chromatin pattern and occasional small nucleoli. Mitotic figures were strikingly rare (1/20 high power frames). Over 90% of cells showed a dot-like pattern of immunocytochemical reactivity for prolactin (PRL) in the primary tumour (table 1). The histological picture of the frontal and temporal masses and of postmortem specimens revealed solid nests and trabeculae of pleomorphic epithelial cells with abundant granular, cosinophilic cytoplasm and hyperchromatic nuclei, with open chromatin, a coarsely granular pattern, and evident eosinophilic nucleoli (fig 2B). Binucleated and multinucleated cells were seen frequently. The mitotic rate ranged from five to 25/10 high power frames, with many atypical figures (fig 2B, inset). Immunohistochemistry showed a mixed population of adrenocorticotropic (ACTH) (fig 3) and PRL positive cells, globular positivity for cytokeratin, and a raised MIB1 (from 1.53% to 6.25%) and PCNA (from 22.7% to 78%) positive fraction of proliferating cells (table 2).

Ultrastructural studies, performed on retrieved specimens from paraffin wax blocks of the pituitary tumour and on glutaraldehyde fixed tissue from the frontal and temporal tumours, showed that the first specimen (1986) was made up of cells that contained densely packed, regularly shaped granules with two different diameters—one up to 300 nm (containing growth hormone (GH)) and the other over 300 nm (containing PRL)—and frequent fibrous bodies (fig 4A). These features pointed to a mixed secretion. The specimens from the frontal and temporal metastases contained sparsely granulated (300 nm) neoplastic cells (fig 4B).

Abbreviations: ACTH, adrenocorticotropic; CT, computed tomography; GH, growth hormone; MRI, magnetic resonance imaging; PCNA, proliferating cell nuclear antigen; PRL, prolactin.
The presence of frontal, temporal, and spinal metastases confirmed the malignant behaviour of the tumours, even if extensive and repeated surgical procedures may have allowed neoplastic dissemination in the cerebrospinal fluid.

We have found reports of 33 PRL carcinomas with well documented metastases (Table 3). All but eight patients died with (n = 10) or as a result of (n = 9) disease, with a mean survival time of 2.4 years (excluding deaths from intercurrent causes, as occurred in our case, or of postoperative failure). Only five patients are alive with disease and three are alive and well, although the follow up time is too short to be significant.

Our case documented the hormonal shift from a mixed PRL-GH adenoma to a PRL-GH-ACTH carcinoma: the tumour started out as a prolactinoma, associated with high cortisol values, and progressed into a mixed ACTH-PRL-GH producing carcinoma. To our knowledge, in malignant pituitary tumours...
this hormonal shift has never been described, although mixed adenomas can contain cells with PRL-GH and ACTH granules."

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REFERENCES
Progression on metastatic neuroendocrine carcinoma from a recurrent prolactinoma: a case report

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