SHORT REPORT

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

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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.

Nearly 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.⁵ A considerable proportion of carcinomas may develop from adenomas³: progressive malignant transformation might result in a gradual increase in resistance to agonist drugs.^{5–6} 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”

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.

Table 1 Plasma concentrations of prolactin (PRL), cortisol, and growth hormone (GH)											
Hormone	1986				1991		1993		1995		
	13/10	14/10	17/10		2/4	12/4	4/11	15/11	29/11		
PRL (ng/ml)	35.5	S	8.9	9.2	S	10	6.3	13.1	S	12.2	1
Cortisol (µg/ml)	43.4	U			U				U		
GH (ng/ml)	0.62	R			R				R		
		G			G				G		
		E			E				E		
		R	2.67	1.36	R	0.70	0.48	0.48	R	1.28	0.1
		Y			Y				Y

Figure 2 (A) Histological picture of the first pituitary adenoma (haematoxylin and eosin; original magnification, $\times 400$) and (B) the frontal mass (haematoxylin and eosin; original magnification, $\times 400$); a mitotic figure (inset; haematoxylin and eosin; original magnification, $\times 1000$).

Figure 3 Adrenocorticotrophin reactive cells infiltrating the white matter of the spinal cord (immunoperoxidase stained; original magnification, $\times 200$).

CASE REPORT

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.

One year later, a new MRI demonstrated an expansive mass in the left temporal lobe, which was totally removed by craniotomy, and two spinal metastases. Spinal radiotherapy was started, but five months later, the patient died of massive pulmonary embolism. Necropsy was performed.

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, white 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.

Figure 4 (A) A cell with densely packed granules containing growth hormone (about 300 nm in diameter) and prolactin (larger than 300 nm). A rounded fibrous body is also visible (original magnification, $\times 15\,000$). (B) A cell with peripherally located granules only, which resemble growth hormone containing granules (original magnification, $\times 15\,000$).

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, eosinophilic 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 adrenocorticotrophin (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, adrenocorticotrophin; CT, computed tomography; GH, growth hormone; MRI, magnetic resonance imaging; PCNA, proliferating cell nuclear antigen; PRL, prolactin

Table 2 Reactivities of primary tumours, recurrences, and metastases

Hormone	Primary 1986	1° recurrence 1991	2° recurrence 1993	Frontal metastasis	Temporal metastasis	Spinal metastasis
PRL	Pos	Neg	Neg	Foc*	Foc*	Foc*
ACTH	Neg	Pos	Neg	Pos	Pos	Pos
GH	Neg	Neg	Neg	Foc*	Neg	Neg
LH	Neg	Neg	Neg	Neg	Neg	Neg
FSH	Neg	Neg	Neg	Neg	Neg	Neg
TSH	Neg	Neg	Neg	Neg	Neg	Neg
PHE5	Neg	Neg	Neg	Neg	Neg	Neg
CHRA	Pos	Pos	Pos	Pos	Nos	Pos
SY38	Pos	Pos	Pos	Pos	Pos	Pos
MIB1	1.53%	1.64%	1.20%	6.25%	6.05%	Neg
PCNA	Neg	ND	22.07%	ND	78.00%	Neg
p53	Neg	ND	Neg	Neg	4.37%	Neg
AgNOR	01:22	ND	4.51%	2.36%	ND	ND

ACTH, adrenocorticotrophin; AgNOR, argyrophilic nucleolar organiser region; Foc, focal; FSH, follicle stimulating hormone; GH, growth hormone; LH, luteinising hormone; ND, not determined; Neg, negative; PCNA, proliferating cell nuclear antigen; Pos, positive; PRL, prolactin; TSH, thyroid stimulating hormone.
*Postmortem specimen.

Table 3 Pituitary carcinomas reported in the English literature

Ist author	Age*/sex	Latency (years)	Metastases sites	Invasive adenoma	Surgery	Follow up/survival
1 Martin ⁷	31/F	5	Cerebellar vermis	Y	T,C	A&W†
2 Cohen ⁸	70/M	3	Cerebello-pontine angle	Y	No	DWD, IC/PO
3 Sang ⁹	62/M	6	Parieto-occipital	Y	C	DWD, IC
4 Gasser ³	28/M	9	Fronto-parieto-temporal	Y	C,C,C	DOD/3 years
5 Scheithauer ¹	52/F	13	Bones	Y	C,T,T	DOD/1 year
6 Landgraf ¹⁰	44/F	4	Cerebellar, spinal	Y		U
7 von Herder ¹¹	U/F	U	Spinal			U
8 Plangger ¹²	28/M	9	Fronto-parieto-temporal			U
9 Muhr ¹³	14/M	12	Cerebellar, frontal	Y	C	AWD/20 months†
10 Popovic ¹⁴	47/M	2	Anterior cranial fossa	Y	C,C,C	DWD, IC/1 week
11	56/F	12	Spinal, IV ventricle		T	DWD, IC/3 months
12 Atienza ¹⁵	34/M	4	Lung, bones	Y	C	DOD/1 year
13 Assies ¹⁶	64/M	6	Intracranial	Y		U
14 Petterson ¹⁷	40/M	9	Fronto-temporal, cerebellar	Y	C	DOD/1 year
15 Berezin ⁶	30/F	25	Intraorbital	Y	S,C	DOD/4 years
16 Kamphorst ¹⁸	45/M	13	Pons, spinal	Ectopic t.	C	DWD/IC/PO
17 Walker ⁴	32/M	9	Liver, lungs		5T,C,3T	DWD, IC/4 weeks
18	48/F	16	Bone	Y	T	DWD, IC/1 year
19	49/M	3	Lung, mediastinal	Y	C,C	DWD, IC/PO
20 Kasantikul ¹⁹	U/U‡	U	U		U	U‡
21 Long ²⁰	70/M	10	Fronto-parietal	Y	T,C,C	AWD/1 year
22 Saeger ²¹	59/M	2	Liver		T,S	DWD, IC/5 months
23 O'Brien ²²	48/M	5	Frontal		C	A&W/1 year
24 Gollard ²³	41/F	2	Cheek, pelvis		T,T,T,T	AWD/10 months
25 Rockwell ²⁴	50/M	15	Spinal	Y	T,C	AWD/21 months
26 Bayindir ²⁵	32/F	3 mos	Frontal, spinal	Y	T,C	DWD/PO
27 Pernicone ⁵	34/M	3	Bones		T	DOD/13 months
28	62/M	3	Cerebellum		C	DOD/8 years
29	54/F	1	Spinal		T	DOD/22 months
30	37/M	6	Lymph nodes		T,T	DOD/1 year
31	64/M	6	Occipital, tentorium		T	AWD/9 months
32 Popadic ²⁶	51/M	3	Spinal	Y	C,T	A&W/38 months
33 Petrossians ²⁷	43/M	14	Bones, mediastinum	Y	C,C,C,C	U
34 Our case	45/M	9	Fronto-temporal, spinal	Y	T,C,T	DWD, IC/1 year

*Age at first surgical intervention for pituitary tumour; †data reported by Popovic¹⁴; case 1: DWD/3 years; case 9: survival of 20 months; ‡data reported in an abstract.

Male to female ratio: 2.2 : 2; mean latency; 7.4 years; range, 3 months to 25 years; mean latency for only one surgery: 7.5 years; mean latency for multiple surgeries; 7.7 years.

A&W, alive and well; AWD, alive with disease; C; transfrontal craniotomy; DOD, died of disease; DWD, died with disease; IC, intercurrent causes of death; PO, postoperative death; S, surgery not specified; T, transphenoidal resection; U, unknown; Y, yes.

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.²⁸

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