

# Ectopic macroprolactinoma mimicking a chordoma: a case report

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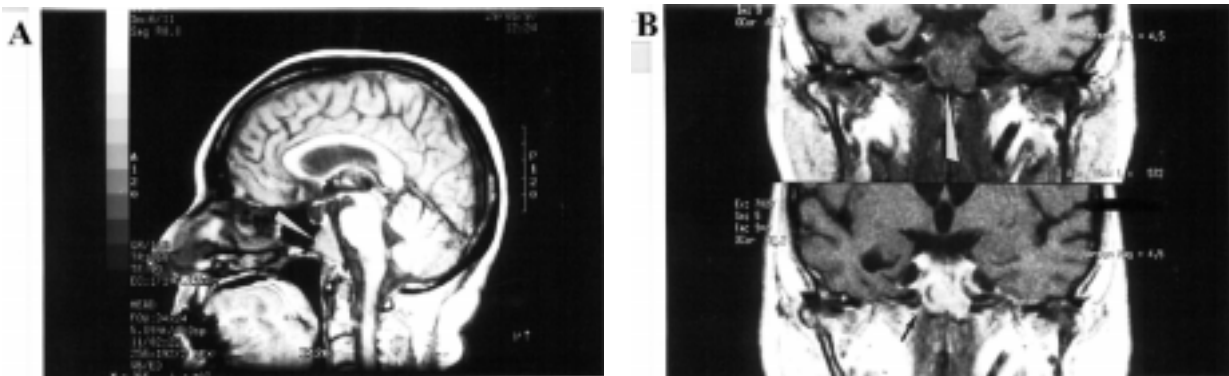
## Introduction

A tumoral mass at the clivus is uncommon and its differential diagnosis presents a challenge, since many different tumours may result in a similar radiological image. A chordoma is the most common of these tumours and represents 40% of all cases. Less common, in decreasing order of frequency, are meningiomas, astrocytoma, germinal cell tumours, lymphoma, metastases and, finally, pituitary adenoma (Wong *et al.* 1995). The last type of tumour is rarely found in this localisation and is called an ectopic pituitary adenoma, as almost all pituitary adenomas are detected in the sella turcica, where they originate from, and in the immediate suprasellar and parasellar region. Outside of these sites, pituitary adenomas can be detected as a result of extensive invasion of nearby structures, metastasis of a pituitary carcinoma, or an ectopic localisation. The majority of these ectopic

primary adenomas are situated outside the blood-brain barrier and mostly in the sphenoid sinus (Tovi *et al.* 1990). An intact pituitary gland supports the diagnosis of ectopic pituitary tumour, although cases of ectopic pituitary tumour have been reported with involvement of the intrasellar pituitary. In this article, we present an unusual intracranial ectopic pituitary adenoma located in the clivus and mimicking a chordoma.

## Case report

An 80-year-old female patient was admitted complaining of transient amnesia for two hours. At the time of admission there was retrograde amnesia, but the patient was satisfactorily orientated. The medical history included a myocardial infarction, auto-immune hypothyroidism (substituted with levothyroxine), resection of a polyp from the bladder and depression. The clinical neurological



**Figure 1** (A) MRI: overall view. Sagittal section showing mass at the clivus (arrow): status at diagnosis. (B) MRI: transverse section through the pituitary region. The tumour mass at the clivus prior to (top) and following uptake of contrast medium (bottom) is indicated by the arrows. Status after 10 weeks of treatment with cabergoline: 30% reduction in the volume of the adenoma.

**Table 1** Hormonal investigation of the patient

Hormone	Hormone levels	
	Patient	Reference values
Free thyroxine (pmol/l)	14	11–23
TSH(μU/ml)	1.2	0.3–3.5
LH (mIU/ml)	7.4	18.7–87 (postmenopausal)
FSH (mIU/ml)	34	25.8–180 (postmenopausal)
Prolactin (μIU/ml)	53420	<500 (men and postmenopausal women)
Cortisol (ng/ml) (morning)	134	53–203
ACTH (pg/ml)	12	10–60
IGF-I (ng/ml)	180	100–300

TSH, thyrotrophin; ACTH, adrenocorticotrophin; IGF-I, insulin-like growth factor-I.

examination detected no motor deficiencies, no sight problems, and there was no vomiting. The patient complained of a minor headache.

The laboratory tests were normal. A brain CT showed a tumoral process at the height of the clivus, with destruction of surrounding bone structure. MRI depicted a contrast captivating, slightly unhomogeneous mass, with a cystic component on the right and some invasion at the bottom of the sphenoid sinus. The lesion did not extend posteriorly and showed enhancement with gadolinium. At the level of the pituitary gland, a partially empty sella was described (Fig. 1A,B). The initial differential diagnosis consisted of a chordoma or, less likely, a primary brain tumour, a haematological tumour or a metastasis.

Tumour markers (Carcino-embryonic antigen, α-foetoprotein) were negative. To exclude hormonal deficiencies in view of the empty sella turcica, an hormonal investigation was carried out, revealing a surprisingly high prolactin level (Table 1). Subsequently a short Synacthen test (250 μg i.v.) was carried out, showing normal increasing cortisol levels. Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were unusually low. All other pituitary hormones were within normal limits.

A mass at the level of the clivus, combined with very high prolactin levels, suggested the diagnosis of an ectopic macroprolactinoma. Because of the headache, possibly due to this tumour, the patient was treated with the long-acting dopamine agonist, cabergoline, in a dose of 2×0.5 mg weekly. Prolactin levels dropped from 53 420 mIU/ml to 3752 mIU/ml in four weeks and to 224 mIU/ml in eight weeks (normal value: <500 mIU/ml). The treatment was well tolerated by the patient and complaints of headache subsided, but subsequently hot flushes occurred with the normalisation of the prolactin levels, due to the increasing levels of LH and FSH.

A control MRI after 10 weeks illustrated a 30% reduction in the volume of the adenoma. The dose of cabergoline was reduced after six months to 0.5 mg weekly, with the continuation of normal prolactin levels.

## Discussion

Pituitary tumours account for 15% of all intracranial tumours in adults (Laine *et al.* 1990). An ectopic pituitary tumour was first described by Erdheim in 1909. Ectopic pituitary tumours are rare and, to our knowledge, a total of 33 cases have been reported in publications. The age of patients varies between 6 and 71 years; the majority are men (Matsumura *et al.* 1990), although prolactinoma is more frequent in women (Delgrange *et al.* 1996).

Most ectopic pituitary tumours have a location outside the blood-brain barrier, with a preference for the sphenoidal sinus (68%). Other extracranial locations are the nasal cavities, the nasopharynx and the temporal bones. Intracranial locations consist of the suprasellar region, the clivus (as in our patient), parasellar and in the sella turcica, but outside the pituitary capsule. Only eight ectopic pituitary adenomas at the clivus have previously been described in publications (Ortiz-Suarez & Erickson 1975, Lloyd *et al.* 1986, Shenker *et al.* 1986, Anand *et al.* 1993, Mount *et al.* 1993, Arnesen & Scheithauer 1994, Kikuchi *et al.* 1994, Wong *et al.* 1995). There were three different hormonal diagnoses: one of Cushing's disease, three of non-functional adenomas and four of prolactinomas.

To our knowledge, there are eleven published cases of ectopic macroprolactinoma out of the total number of thirty-three ectopic pituitary tumours (Table 2). Considering all ectopic pituitary adenomas, five were found to have Cushing's disease, four acromegaly and the others were either plurihormonal or non-functional ectopic pituitary tumours.

In our case, apart from the high level of prolactin, the patient had normal levels of LH and FSH, which is unusual for a woman of this age. The underlying mechanism is a decreased gonadotrophin releasing hormone (GnRH) secretion in the hypothalamus and in hypophyseal portal blood as a result of chronic hyperprolactinaemia. That high prolactin suppresses GnRH even if secreted ectopically and with no direct contact

**Table 2** Cases of ectopic pituitary adenoma reported in the literature

Case	Reference	Sex/age (years)	Localisation	Endocrine activity
1	Erdheim (1909)	M/53	Sphenoid sinus	Acromegaly
2	Kepes & Fritzlen (1964)	M/40	Sphenoid sinus	—
3	Oritz-Suarez & Erickson (1975)	F/15	Clivus	Cushing
4	Chessin <i>et al.</i> (1976)	F/64	Nasopharynx	—
5	Rothman <i>et al.</i> (1976)	M/15	Suprasellar	— but hypopituitarism postoperative
6	Borit & Blanshard (1979)	F/62	Sphenoid sinus	— but MEN type 1
7	Bonner <i>et al.</i> (1979)	F/23	Parasellar	Cushing/Nelson
8	Rasmussen & Lindholm (1979)	M/36	Nasal cavity	—
9	Rasmussen & Lindholm (1979)	M/54	Sphenoid sinus	—
10	Rasmussen & Lindholm (1979)	M/27	Below sphenoid wing	Acromegaly
11	Rasmussen & Lindholm (1979)	M/36	Petrous temporal bone	—
12	Corenblum <i>et al.</i> (1980)	*	Sphenoid sinus	Acromegaly
13	Kammer & George (1981)	F/51	Sphenoid sinus	Cushing
14	Warner <i>et al.</i> (1982)	M/59	Sphenoid sinus	Acromegaly/prolactinoma
15	Matsushita <i>et al.</i> (1984)	F/40	Sphenoid sinus	Prolactinoma
16	Burch <i>et al.</i> (1985)	F/43	Sphenoid sinus	Cushing
17	Shenker <i>et al.</i> (1986)	M/49	Sphenoid sinus/clivus	Prolactinoma/primary hyperparathyroidism, chronic renal failure
18	Lloyd <i>et al.</i> (1986)	M/49	Sphenoid sinus/clivus	Prolactinoma
19	Lloyd <i>et al.</i> (1986)	F/49	Sphenoid sinus	Plurihormonal adenoma
20	Neilson & de Gadarevian (1987)	M/6	Temporal lobe (left)	—
21	Scheingart <i>et al.</i> (1987)	M/49	Sphenoid sinus	Cushing
22	Heitzmann <i>et al.</i> (1989)	F/17	Sphenoid sinus	Prolactinoma
23	Heitzmann <i>et al.</i> (1989)	M/'old'	Sphenoid sinus	Prolactinoma
24	Kleinschmidt-DeMasters <i>et al.</i> (1990)	M/47	Third ventricle	Gonadotrophic adenoma
25	Matsumura (1990)	M/71	Suprasellar	Corticotrophic adenoma
26	Kamphorst <i>et al.</i> (1992)	M/58	Parasellar	Prolactinoma
27	Mount <i>et al.</i> (1993)	M/71	Clivus	Prolactinoma
28	Anand <i>et al.</i> (1993)	F/58	Clivus	Corticotrophic adenoma No activity Prolactinoma
29	Arnesen & Scheithauer (1994)	M/40	Clivus	Prolactinoma
30	Kikuchi <i>et al.</i> (1994)	M/*	Sphenoid sinus/clivus	—
31	Hattori <i>et al.</i> (1994)	*	Sphenoid sinus	Prolactinoma
32	Hattori <i>et al.</i> (1994)	*	Sphenoid sinus	Prolactinoma
33	Wong <i>et al.</i> (1995)	M/67	Clivus	—

\*, not known.

between the hypothalamus and the ectopic prolactinoma, is illustrated in the present case. This has also been found in rat studies where prolactin-secreting cells were transplanted outside the pituitary (Smith & Bartke 1987, Koike *et al.* 1991).

Ectopic pituitary tissue usually follows the tract of Rathke's pouch and has also been observed in post-mortem investigations in normal persons (Hori 1985). These remnants of the embryonic tissue can develop hypertrophy and hormonal activity even when the pituitary is normal. In some cases ectopic tissue hypertrophy may be the result of a reduction in size of the normal pituitary gland following pituitary surgery, or in

the presence of an empty sella turcica with compensatory increase in activity of the ectopic cells (McGrath 1970). In these cases the differential diagnosis can be made between hypertrophy of the remnants and a true ectopic pituitary adenoma. The prolactin levels in our patient were so high that they cannot be explained by hypertrophy and, therefore, a true adenoma is most likely.

Many of the patients with ectopic pituitary tumours are asymptomatic and the tumour is a fortuitous finding during an investigation for other complaints or whilst a post-mortem examination is being carried out (Rasmussen & Lindholm 1979). Ectopic tumours can result in clinical symptoms when they disrupt the normal pituitary function

due to hypersecretion (e.g. amenorrhoea in ectopic prolactinoma) or when compressing nearby structures. The most frequent complaint is headache (approximately 35%), followed by visual disturbances due to chiasm compression. Epilepsy is a rare symptom, only described in cases where the temporal cortex is also affected (Lundberg *et al.* 1977). In our patient there was a simultaneous appearance of transient global amnesia and ectopic macroprolactinoma, but this was probably just a coincidence. Published articles provide one case where transient global amnesia was related to haemorrhagic prolactin-secreting pituitary adenoma (Honma & Nagao 1996). Whilst the clinical presentation is similar to that of our patient, the ectopic adenoma in our patient does not seem to have been responsible for the clinical findings, since the temporal lobe was not invaded by the tumour, and no signs of recent haemorrhage were found on the MRI or brain CT.

The diagnosis is usually based on radiological findings in addition to an endocrinological investigation. A conventional skull X-ray may be the first indication if the tumour is adjacent to the sella turcica and erosion on the bony structures is visible. Most diagnoses are based on brain CT, where the morphology, the localisation and the extension of the lesion can be seen. Using MRI, T<sub>1</sub> and T<sub>2</sub> weighed images, gadolinium enhancement and detailed images in different positions can be made to provide clues to the differential diagnosis (Laine *et al.* 1990).

In the case of an isolated mass at the clivus, the following differential diagnoses are considered: chordoma, non-Hodgkin lymphoma, metastasis, chondrosarcoma, meningioma, craniopharyngeoma, germinal cell tumour, astrocytoma, and pituitary adenoma (Wong *et al.* 1995). If both a mass at the clivus and an important hyperprolactinaemia are present, an ectopic prolactinoma or the exceedingly rare prolactin-secreting carcinoma are likely.

Pathological examination of biopsy specimens taken from ectopic pituitary tumours requires both a light microscopic and immunohistochemical examination (hormonal activity). Pituitary adenomas at the clivus can show anaplastic features, complicating the differential diagnosis since they are very rare in this localisation. The light microscopic examination reveals a clearly increased number of mitoses and nuclear pleomorphism; therefore, an additional electron microscopic or even immuno-electron microscopic investigation is necessary (Mount *et al.* 1993). The electron microscope shows, among other things, spherical secreting granules that are being removed at the lateral side of the cell, dense nucleoli, and a richly developed rough endoplasmatic reticulum indicating endocrinological activity. A pathological examination, if possible, is especially important for the differential diagnostic problems if the hormonal investigation prov-

ides no additional information, as is the case in the non-secreting ectopic pituitary adenomas.

The treatment of ectopic macroprolactinoma consists of two approaches.

### **Pharmacological treatment**

Dopamine agonists are still the corner stone of the conservative treatment of prolactinomas (Teramoto 1996). As for normal macroprolactinomas, the patient in our case reacted favourably to the new long-acting dopamine agonist (cabergoline), with a fast reduction of the prolactin levels to normal levels as well as a significant reduction in the size of the tumour. Researching the literature, we found that patients with ectopic macroprolactinoma were treated with varying rates of success: two did not respond to bromocriptine and required surgery, and two responded very well. Successful treatment suggests that dopamine receptors are also present in ectopic prolactinoma (Warner *et al.* 1982).

### **Surgical treatment**

If the patient is symptomatic and resistant to pharmacological therapy, surgery can be considered on condition that the tumour is accessible. Post-operative radiotherapy and/or pharmacological treatment can complement the treatment if the tumour has not been completely removed (Anand *et al.* 1993).

The question arises whether these tumours should be treated in patients who have no complaints. It may be medically justified to adopt a 'wait and see' attitude and to follow the tumour with MRI.

### **Conclusion**

Ectopic pituitary tumours are rare and are usually located on the trajectory of Rathke's pouch, with a preference for the sphenoid sinus. The tumour is, in very rare cases, located at the clivus. The differential diagnosis is mainly with chordoma, based on the medical imaging and the clinical presentation, and can be difficult. A complementary endocrinological investigation may therefore be useful and, in case the hormonal investigation and the iconographic documents do not lead to a clear diagnosis, biopsy of the lesion should be performed whenever possible.

The most frequent pituitary tumour is a prolactinoma. This also seems to be the case in ectopic pituitary tumours, as was the case in our patient. Treatment with cabergoline gives favourable results in the rate of reduction of the prolactin levels and the reduction in tumour size.

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