0021-972X/04/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 89(2):574–580

doi: 10.1210/jc.2003-030395

CLINICAL CASE SEMINAR

Tumors Metastatic to the Pituitary Gland: Case Report and Literature Review

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Tumors metastatic to the pituitary gland are an unusual complication of systemic cancer typically seen in elderly patients with diffuse malignant disease. Breast and lung are the commonest sites of the primary tumor, whereas diabetes insipidus is the most frequent symptom at presentation. Their rarity and usually indolent course, as well as the lack of specific clinical and radiological features, impede their differentiation from other more common sellar area lesions, particularly when history of malignancy is absent. Management of these patients may also be very difficult because the prognosis depends on the course of the primary neoplasm. A 68-yr-old man, with no history of malignancy, presented with recent onset of hypopituitarism, mild diabetes insipidus, headaches, left oculomotor nerve palsy, and progressive bilateral deterioration of visual acuity and visual fields. Magnetic resonance imaging revealed a large sellar mass compressing the optic chiasm and invading the left cavernous sinus, whereas a prolactin elevation at 438.6 ng/ml (19.73 nmol/liter) was noted. Decompression of the sellar region was attempted, and pathology disclosed a metastatic hepatocellular carcinoma. On postoperative investigation, primary liver tumor was identified and confirmed by biopsy. The patient improved transiently but died 3 months after diagnosis because of deterioration of the liver disease. The relevant literature is reviewed in light of this unusual case, illustrating the problems in the diagnosis and management of patients with metastasis to the pituitary. (*J Clin Endocrinol Metab* 89: 574–580, 2004)

IN 1857, L. BENJAMIN first described a case of metastasis to the pituitary (MP) gland in an autopsy of a patient with disseminated melanoma (1). Since then, a number of surgical and autopsy series and sporadic case reports have described metastatic tumors to the pituitary. MP is an infrequent clinical problem reported in 0.14–28.1% of all brain metastases in autopsy series (1–3). However, during the last few decades, MPs have been noted with increasing frequency, reflecting the improvement in survival rates of patients with cancer and the use of more sensitive imaging techniques (4, 5).

Breast and lung cancer are the most common primary neoplasms metastasizing to the pituitary. Most often they are part of a generalized metastatic spread, usually associated with five or more additional metastatic sites, especially osseous (1–10). Typically, they affect elderly patients in the sixth or seventh decade of life (6, 11), with no clear sex predominance. Nevertheless, MP may be the first manifestation of an occult primary tumor or the only site of metastasis (2, 4, 5, 12, 13) and may very occasionally occur in early adulthood (2, 14).

Abbreviations: CT, Computer tomography; HCC, hepatocellular carcinoma; MP, metastasis to the pituitary; MRI, magnetic resonance imaging; PRL, prolactin; T1WI, T1-weighted image(s); T2WI, T2-weighted image(s); TSS, transsphenoidal surgery.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

Since early studies, most authors underscore the prevalence of diabetes insipidus in MPs (2, 10, 15–17), reported at 100% in some series (2, 10), whereas symptomatic anterior pituitary failure and cranial nerve deficits have been less frequently described at presentation (15–17). This has been attributed to a trend of metastasis to the posterior lobe and infundibulum. Prolactin (PRL) elevation at levels less than 200 ng/ml (9.0 nmol/liter), consistent with stalk compression, is not uncommon in MPs (13) and usually rules out the presence of a PRL-secreting tumor.

Antemortem diagnosis is difficult because the majority of MPs are clinically silent and too small to cause radiological changes (7, 18). But even when symptomatic, metastatic tumors cannot be reliably distinguished from primary sellar tumors on the basis of clinical and radiographic presentation (6, 7, 12, 15). In fact, they may mimic a pituitary adenoma (1, 4, 7, 15, 16) or a variety of sellar area lesions, benign or malignant (tumor, granuloma, abscess, cyst, aneurysm, trauma, apoplexy), confusing the diagnosis, especially when clinical evidence of malignancy is absent (4, 8, 13, 19–22). In cancer patients, the differentiation between metastasis and benign lesion is essential for the therapeutic plan, to avoid unnecessary operations in severely compromised patients (4, 9). Local therapy aiming at symptom relief may be beneficial; however, prognosis is determined by the primary tumor.

Here, we present a case of MP in which the absence of known malignant background and high PRL levels confused

the diagnosis. Incidence, pathogenesis, diagnosis, and management of patients with MP are described.

Case Report

A 68-yr-old male presented with a 2-month history of headaches, weakness, fatigue, anorexia, and somnolence. When questioned, he also stated a decrease in shaving frequency and a mild polyuria. One month before admission, he developed gradual left palpebral ptosis, diplopia, and progressive deterioration of vision. A cranial computer tomography (CT) scan showed an isodense tumor around the optic chiasm, with inhomogeneous enhancement in contrast images. Subsequent magnetic resonance imaging (MRI) demonstrated a 2.9 × 1.8-cm sellar mass, which infiltrated the clivus, depressed the floor of the sella turcica, and extended into the left part of the sphenoid sinus. The tumor invaded the left cavernous sinus, encasing the internal carotid artery, which was laterally displaced. It also extended into the suprasellar cistern, compressing the optic chiasm and the floor of the third ventricle. Precontrast T1-weighted images (T1WI) showed an inhomogeneous high signal intensity tumor, isointense on T2-weighted images (T2WI) (Fig. 1). After gadolinium infusion, contrast and dynamic MRIs revealed rapid inhomogeneous enhancement and signal of flow void within the tumor, suggesting hypervascularity. Findings in the rest of the brain were unremarkable. Cerebral angiography depicted a suprasellar tumor blush with moderate vascularization not compatible with aneurysm, whereas the carotid arteries appeared dilated.

The patient was admitted initially to the Neurosurgical Department. On admission, he was treated with atenolol and nifedipine because of a 10-yr history of hypertension that had recently subsided. He was a heavy smoker and a former alcohol abuser. There was no history of malignancy. On physical examination, blood pressure was 140/90 mm Hg and 105/65 mm Hg at recumbent and standing positions, respectively. Achilles tendon reflexes were blunted. The skin was pale, atrophic, and dry. Fine wrinkles were present around the eyes. The axillary and pubic hair was scant, and the testes were small (8–10 ml) and soft. Neither galactorrhea nor gynecomastia was present. On ophthalmological examination, a left oculomotor nerve palsy and severe impairment of visual acuity and visual fields were confirmed. On perimetry testing, the right eye retained only central vision (finger counting at 2 m), whereas the left eye was nearly anoptic (perception of light).

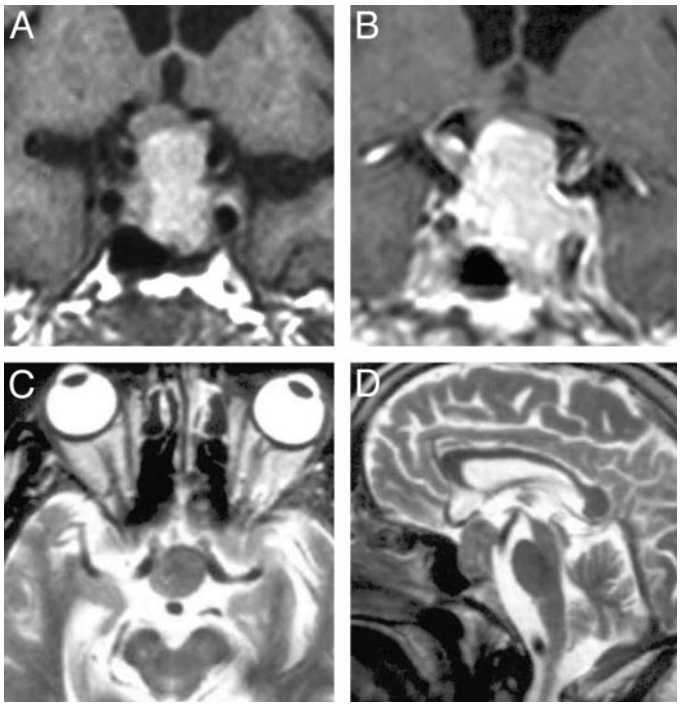

FIG. 1. A, Precontrast coronal MRI T1WI. B, Enhanced coronal T1WI. C, Axial T2WI. D, Sagittal T2WI showing pituitary mass with suprasellar extension and invasion of the left cavernous and sphenoid sinuses.

Routine laboratory tests showed a mild elevation of serum aspartate aminotransferase to 73 IU/liter (normal level, <37) and alanine aminotransferase to 46 IU/liter (normal level, <40). Basal endocrinological work-up showed corticotroph, gonadotroph, and somatotroph cell insufficiency, with normal levels of thyroid hormones (Table 1). Serum PRL was elevated at 438.6 ng/ml (19.73 nmol/liter) [normal level, <12.3 ng/ml (< 0.55 nmol/liter)], consistent with prolactinoma. Nevertheless, before the results of the endocrinological tests were available, the patient was subjected to an immediate decompressive transsphenoidal surgery (TSS), mainly in view of his increasing neurological deficits. On macroscopic exploration, the tumor was solid and fibrous, hemorrhagic, with rich vascularization, and infiltrated the sella turcica. Osseous infiltrations and intense hemorrhage inhibited the complete resection of the tumor.

A specimen measuring 2 × 2 × 1 cm and consisting of multiple pieces of hard white tissue was submitted for histological examination. Histology showed a malignant neoplasm with sinusoidal-trabecular focally tubular pattern infiltrating the pituitary parenchyma (Fig. 2). The neoplastic cells showed mild atypia of their nucleus with prominent nucleolus. In many cells, the cytoplasm was clear, with vacuoles of different size, occasional round hyaline globules, and rare bile deposits. In a proportion of cells, a periodic acid-Schiff-positive granular cytoplasmic reaction was seen. Differential diagnosis included chordoma and metastatic carcinoma of renal, hepatic, or lung origin. The immunophenotype of the tumor was hepatocyte positive, α-fetoprotein and cytokeratin 8 and 18 focally positive, and cytokeratin 20 negative. Immunohistochemical analysis for pituitary hormones (ACTH, GH, PRL, β-TSH, β-FSH, β-LH, and α-subunit) showed negative results. The proliferation index using the Ki-67 antibody was estimated at 7%. All the above findings, taken together, were consistent with the diagnosis of metastatic well-differentiated hepatocellular carcinoma (HCC) of the hepatocytoid cytological variant.

Postoperatively, the patient was mildly disorientated. Consciousness, weakness, and anorexia were significantly improved with hydrocortisone substitution. Headaches remitted, but there was no substantial restoration of the visual fields or the ophthalmoplegia. He was eventually transferred to the Department of Endocrinology, Diabetes and Metabolism, where the investigation showed no change of the endocrine environment. PRL decreased to 307.0/321.7 ng/ml (13.81/14.47 nmol/

TABLE 1. Basal endocrinological evaluation

Hormone	Level measured	Normal levels
T_3	111 ng/dl (1.7 nmol/liter)	60–200 ng/dl (0.9–3.0 nmol/liter)
T_4	7.1 μg/dl (91.4 nmol/liter)	6.4–15.5 μg/dl (82.4–200.0 nmol/liter)
TSH	0.12 mIU/liter (0.12 mIU/liter)	0.3–4.0 mIU/liter (0.3–4.0 mIU/liter)
FSH	<0.7 mIU/ml (<3.15 IU/liter)	1.6–17.8 mIU/ml (7.2–80.1 IU/liter)
LH	<0.3 mIU/ml (<2.7 IU/liter)	1.6–17.8 mIU/ml (14.4–160.2 IU/liter)
Testosterone	<14 ng/dl (<0.48 nmol/liter)	270–1070 ng/dl (9.4–37.1 nmol/liter)
ACTH	2.9 pg/ml (0.64 pmol/liter)	9–52 pg/ml (2.0–11.0 pmol/liter)
Cortisol	2.3 μg/dl (63.4 nmol/liter)	5–25 μg/dl (138–690 nmol/liter)
GH	0.6 ng/ml (27.9 pmol/liter)	<5.0 ng/ml (<232.5 pmol/liter)
IGF-I	<30 ng/ml (<30 μg/liter)	71–290 ng/ml (71–290 μg/liter)
PRL	438.6 ng/ml (19.73 nmol/liter)	<12.3 ng/ml (<0.55 nmol/liter)

T_3, [conversion factor (CF), 0.0154]; T_4, (CF, 12.87); TSH, (CF, 1.0); FSH, (CF, 4.5); LH, (CF, 9.0); testosterone (CF, 0.0347); ACTH, (CF, 0.22); cortisol (CF, 27.59); GH, (CF, 46.5); IGF-I (CF, 1.0); PRL (CF, 0.045).

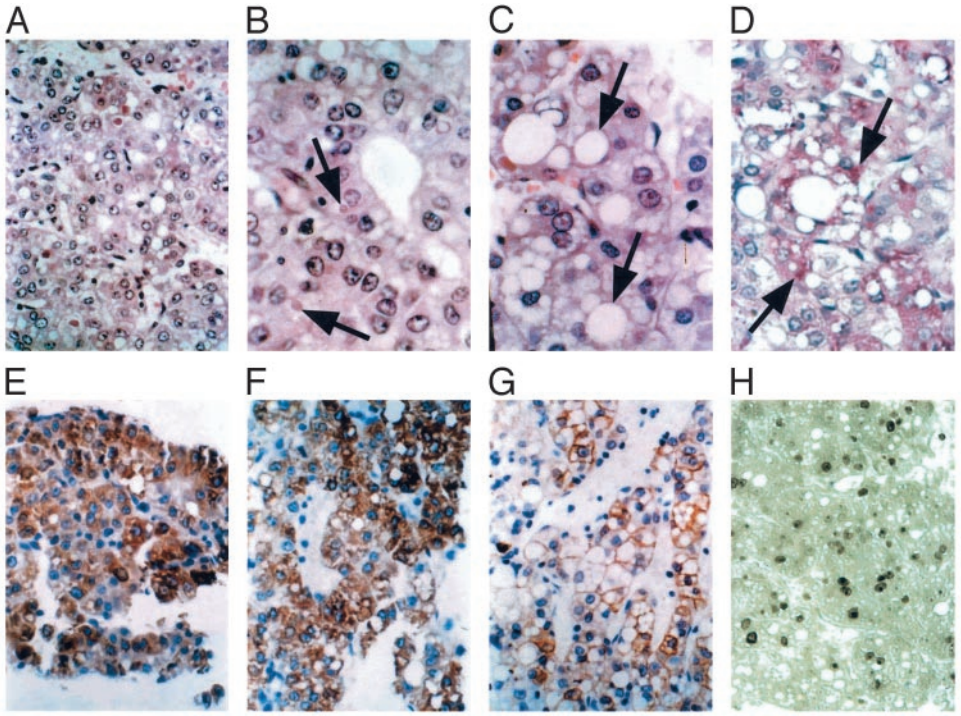

FIG. 2. Carcinoma cells from pituitary tumor in sinusoidal pattern (A). Presence of round hyaline globules (B, arrows) and large vacuoles (C, arrows). Note glycogen granules (D, arrows). Immunoreactivity for hepatocyte antibody (E), α-fetoprotein (F), and cytokeratins 8 and 18 (G). Magnification: A, ×40 (hematoxylin-eosin stain); B and C, ×100 (hematoxylin-eosin stain); D, ×100 (periodic acid-Schiff stain); E, ×40 (avidin-biotin complex); F and G, ×100 (avidin-biotin complex); H, ×80 (Ki-67 nuclear stain).

liter) after surgical decompression and was reduced to 2.1 ng/ml (0.09 nmol/liter) within 1 wk, becoming undetectable 1 wk later, under a low-dose dopamine agonist treatment (cabergoline, 1 mg/wk for 2 wk). Low urine osmolality levels (198–354 mosm/kg; normal range, 700-1400) after an overnight water deprivation, along with normal plasma osmolality (277–288 mosm/kg; normal range, 280–295), suggested mild diabetes insipidus. Desmopressin treatment was not given because the daily urine volumes did not exceed 4.0 liters.

The postoperative routine laboratory tests showed a progressive deterioration of liver enzymes. Aspartate aminotransferase increased to 125 IU/liter, alanine aminotransferase to 140 IU/liter, and alkaline phospatase to 153 IU/liter (normal range, 39–117). α-Fetoprotein also gradually increased to 3485.9 ng/ml (3485.9 μg/liter) [normal level, <15 ng/ml (<15 μg/liter)]. Liver ultrasonography disclosed two masses, 3 cm each, and parenchymal inhomogeneity, compatible with diffuse liver disease. The abdominal CT scan additionally depicted an enlargement of the head of the pancreas and the right adrenal, as well as infiltration of regional abdomen lymph nodes. Exploration with thoracic CT scan and bone scintiscan was negative. The diagnosis of HCC was eventually confirmed by a fine-needle aspiration biopsy taken from one of the liver masses.

A sequential pituitary MRI, undertaken 1 month after surgery, was largely unchanged. Adjuvant radiation therapy to the sellar region was recommended. The patient was discharged to start radiotherapy as an outpatient, but he was lost to follow-up. He died 3 months later because of deterioration of the liver disease. An autopsy was not performed.

Discussion

The pituitary gland is an uncommon site for metastasis. In surgical series, it is detected in less than 1% of patients subjected to TSS for sellar or parasellar tumors (Table 2). In

autopsy series, latent MPs are revealed in approximately 5% of patients with known malignancy (Table 2), but in about two thirds of those, the pituitary is macroscopically normal (18). In breast cancer patients, the incidence is significantly higher. The latter may be explained by the hypothesis that the PRL-rich environment of the pituitary enhances the proliferation of breast tumor cells (5).

Neoplasms from almost every tissue have been reported to metastasize to the pituitary (2, 9); however, breast and lung cancer account for approximately two thirds of MPs (Table 3), being the commonest cause among women and men, respectively. Of note is that in approximately 3% of cases the primary tumor remains undetected despite intensive investigation (Table 3). Liver tumors rarely metastasize to the pituitary. We are aware of only one detailed publication by Aung *et al.* (23), who described two patients with occult HCC metastatic to the pituitary and the skull base. Both presented with cranial nerve palsy, headaches, weight loss, and mild hyperprolactinemia [18–24 ng/ml (0.81–1.08 nmol/liter)], whereas one of them also presented with hypogonadism. Previously, McCormick *et al.* (3), reviewing 220 MPs, mentioned another case, as did Morita *et al.* (5) in their surgical series of 36 cases. That makes four published cases of primary liver tumor with MP in a total of 380 MPs reviewed (1.1%).

Symptoms from MPs are reported in 2.5–18.2% of cases (3, 4, 9, 13, 15, 16, 24), mostly because they occur in end stage cancer patients and do not have the time to become evident (12, 25). In addition, systemic complications of malignancy, including nonspecific symptoms (weakness, vomiting, weight loss) and central nervous system involvement, may mask anterior pituitary deficiency (5). Thus, the majority of cases have been accidentally revealed during an autopsy or after a palliative hypophysectomy in patients with metastatic breast cancer (1, 3, 4).

Metastatic deposits can reach the sella via several routes (5, 8, 9): 1) direct hematogenous spread to the pituitary parenchyma or diaphragma sellae; 2) spread from a hypothalamo-hypophyseal or infundibulum metastasis through the portal vessels; 3) extension from juxtasellar and skull base metastasis; and 4) meningeal spread through the suprasellar cistern. McCormick *et al.* (3), reviewing location of MP in 201 cases, found an involvement of the posterior lobe either alone or in combination with the anterior lobe in 84.6%, whereas only the anterior lobe was affected in 15.4%. The predilection for metastasis to the posterior lobe is mainly attributed to the lack of direct arterial blood supply of the anterior lobe (1–3, 5, 8, 10, 12, 15, 16, 18, 25, 26). The posterior lobe is supplied by the hypophyseal arteries, whereas the anterior is nourished by the portal vessels system and secondarily by the lower infundibular stem, which partly arises from the posterior lobe. Another contributing factor is that the posterior lobe has a larger area of contact with the adjacent dura (1, 18). Metastatic deposits in the anterior lobe are usually the result of contiguous spread from the posterior lobe (25). The anterior lobe seems to be susceptible to ischemic infarcts and is associated with a larger metastatic lesion of the posterior lobe (18, 25). However, extensive destruction of the anterior lobe leading to clinically evident anterior pituitary insufficiency is not common (16, 18).

The most common symptom seems to be diabetes insipidus (2, 10, 15–17), reflecting a predominance of metastasis to the posterior lobe. McCormick *et al.* (3), in their review of 40 symptomatic cases, noted diabetes insipidus in 70%, whereas only 15% had one or more anterior pituitary deficiencies. However, recent studies using more sensitive imaging techniques and endocrinological tests, allowing earlier and more accurate diagnosis, have increased the incidence of anterior lobe involvement (5, 15, 27), as shown in Table 4. During the course of the disease, most patients will develop diabetes insipidus (2), after invasion of the infundibulum or hypothalamus. Occasionally, diabetes insipidus is transient, because regeneration of neurohypophyseal fibers may occur, or intermittent (11). Corticotroph cell insufficiency may obliterate the presence of diabetes insipidus until corticosteroid treatment is instituted. In the series by Morita *et al.* (5), hypothyroidism and hypoadrenalism were the most frequent types of symptomatic hypopituitarism, with hypogonadism following next. Nevertheless, in exceptional cases, MPs may present with a hyperfunctional syndrome. Cushing's syndrome and acromegaly have been reported in cases of metastasis to a preexisting corticotroph or somatotroph cell adenoma (20, 28), as well as in exceptional cases of metastasis originating from primary tumors with ectopic ACTH or GH secretion (26, 29). Syndrome of inappropriate antidiuretic hormone secretion has also been described. Ectopic antidiuretic hormone secretion by the primary tumor was confirmed in one case (30), whereas the mechanism re-

TABLE 2. Incidence of pituitary metastases in large series

Series of	%	n
TSS for sellar lesions	1.0	30/3044
Palliative hypophysectomy for breast cancer	10.3	25/243
Autopsy for breast cancer	17.6	174/989
Autopsy for all systemic cancer	5.1	307/6049

Data are from Refs. 3, 9, 10, 15, 17, 18, and 27.

TABLE 3. Origin of primary tumor metastatic to the pituitary in 380 cases

Tumor origin	n	%	Tumor origin	n	%	Tumor origin	n	%
Breast	151	39.7	Pancreas	5	1.3	Larynx	2	0.5
Lung	90	23.7	Pharynx	5	1.3	Germ cell tumor	2	0.5
Gastrointestinal	24	6.3	Endometrium	5	1.3	Ovary	2	0.5
Colon	9		Leukemia	5	1.3	Retroperitoneum	1	0.3
Stomach	7		Urinary bladder	4	1.1	Bile duct	1	0.3
Ileum	1		Uterine cervix	4	1.1	Squamous cell	1	0.3
Prostate	19	5.0	Liver	4	1.1	Lymphosarcoma	1	0.3
Unknown	12	3.1	Multiple myeloma	3	0.8	Penis	1	0.3
Kidney	10	2.6	Paranasal sinus	3	0.8	Thymus	1	0.3
Melanoma/skin	9	2.4	Oral cavity	3	0.8	Nasal cavities	1	0.3
Thyroid	8	2.1	Lymphoma	2	0.5	Salivary glands	1	0.3

Data are from Refs. 2, 3, 5, 7, 9, 10, 13, 14, 18–26, 30, 35, and 37–51.

TABLE 4. Clinical presentation of 190 symptomatic pituitary metastases

Symptom/finding	n	%	Symptom/finding	n	%
Diabetes insipidus	86	45.2	Cognitive/psychiatric deficit	5	2.6
Cranial nerve II deficit	53	27.9	SIADH	3	1.5
Anterior pituitary insufficiency (partial or total)	45	23.6	Cerebral hemorrhage	3	1.5
			Cranial nerve V dysfunction	3	1.5
Cranial nerve III, IV, VI palsy	41	21.6	Seizures	2	1.0
Headaches/postocular pain	30	15.8	Amenorrhea/galactorrhoea	2	1.0
Fatigue/general malaise	15	7.9	Decreased libido	2	1.0
Hyperprolactinemia	12	6.3	Cushing's syndrome	2	1.0
Pituitary apoplexy	9	4.7	Acromegaly	2	1.0
Nausea/vomiting	7	3.7	CSWS	1	0.5
Anorexia/weight loss	6	3.1	Orthostatic hypotension	1	0.5
Altered consciousness	5	2.6	Tumor increase on dopamine agonist	1	0.5

Data are from Refs. 2, 3, 5, 7, 9, 10, 13, 14, 18–26, 30, 35, and 37–51; SIADH, Syndrome of inappropriate antidiuretic hormone; CSWS, cerebral salt wasting syndrome.

mains obscure in other cases (13). Bilateral hemianopsia is the most common type of visual field impairment (1, 2). Infiltration of the adjacent cavernous sinus usually induces cranial nerve III palsy, or less frequently, nerve IV palsy. Compression of nerve VI is relatively uncommon because it is well sheltered within the cavernous sinus (6, 8). Facial numbness due to cranial nerve V dysfunction is also rare. Tumor extension to the septum pellucidum or the frontal lobes may result in cognitive deficit or psychiatric symptoms and in anosmia if cranial nerve I is affected. Stretching of the diaphragma sellae or ventricular distention can give rise to headaches or intracranial hypertension.

Hyperprolactinemia was encountered in 6.3% of MPs reviewed (Table 4) and was always attributed to stalk compression, with the exception of three cases that proved to be a metastasis to a preexisting prolactinoma (7, 20, 28). All three cases concerned women on bromocriptine therapy by the time MP emerged. The degree of hyperprolactinemia is important for the differential diagnosis because PRL levels above 200 ng/ml (9.0 nmol/liter) are generally considered as indicative of a prolactinoma (11, 31), with a few exceptions (32, 33). The highest PRL level reported in MPs, due to stalk compression, is 149.2 ng/ml (6.71 nmol/liter) (25). In our case, the high PRL levels and the presence of clinical findings of long-standing hypogonadism were strongly suggestive of a prolactinoma; however, this was not confirmed because immunohistochemical analysis was completely negative for PRL and no adenomatous tissue was found in the examined tumor fragment. Nevertheless, the infiltration of a preexisting prolactinoma by metastatic deposits cannot be totally excluded because a significant portion of the tumor was not resected and an autopsy was not performed. In contrast, nor can hyperprolactinemia due to stalk section effect be excluded, considering that PRL levels up to 662 ng/ml (29.79 nmol/liter) have been described in cases of nonfunctioning pituitary adenomas (33). Furthermore, the fact that a nearly 30% decrease of PRL levels was noted immediately after the decompression surgery supports pituitary stalk compression as the most likely explanation for our patient's hyperprolactinemia. Gernez-Lestradet *et al.* (34) encountered a similar diagnostic dilemma in a patient with a sellar tumor and PRL levels of 500 ng/ml (22.5 nmol/liter). Their patient was subjected to a TSS because of neurological dysfunction, and histology was initially consistent with prolactinoma; however, on reexamination after an occult lung cancer was found, MP was confirmed and immunohistochemistry was negative for PRL. Regarding metastasis to a pituitary adenoma, it is noteworthy that although tumor-to-tumor metastasis is extremely rare (7), 18 published cases were found in the literature (7, 8, 13, 20, 28, 35). In 13 of the cases, the host tumor was a nonfunctioning adenoma, whereas the remaining five cases concerned PRL-, ACTH-, and GH-secreting adenomas.

In clinical terms, preoperative diagnosis of MPs is difficult. Lumbar puncture is important (16) because it may be the only preoperative examination conclusive of malignancy in cases in which meningeal spread is present. Although history or coexistence of malignancy usually leads to the diagnosis, it is of limited diagnostic value because 1.8–16% of patients with known malignancy and a sellar tumor turn out to harbor a pituitary adenoma (5, 9). Yet, absence of known neoplastic disease does not exclude the diagnosis of MP. The examination of 190 symptomatic MPs (Table 4) showed primary tumor to be latent at presentation in 83 (43.7%). Besides, in 7–57.1% of cases, pituitary is reported to be the only site of metastasis (2, 5, 15, 17, 27). However, these percentages may be considered artificially high because this type of presentation is unusual and more likely to be reported (16).

Although symptoms of MPs at presentation may resemble those of pituitary adenomas, diabetes insipidus is reported in only 1% of adenomas (5, 15), being typically a late finding (2, 25). Thus, Schubiger and Haller (17) suggested that diabetes insipidus is the most important criterion for differentiation of MP from adenomas. Presentation with hypopituitarism, headaches, or visual disturbances, is less helpful in the differential diagnosis, being described in both MPs and adenomas. Ophthalmoplegia may help more, without being pathognomonic for metastasis either (5, 15, 17). In contrast, presentation with abducens nerve palsy should always raise the suspicion for malignancy (8). The rapidity of symptom development may also contribute to the diagnosis. Consequently, a rapidly growing sellar tumor (11), especially in patients treated with dopamine agonist (7, 15), or a sudden onset of diabetes insipidus, ophthalmoplegia, and headaches in a patient over 50 yr old, as reported here, strongly suggests MP, irrespectively of history of malignancy (2, 3, 5, 6, 15).

Radiological evaluation generally has not been fruitful in distinguishing MP from adenomas (1, 3–5), unless other metastatic brain lesions coexist, a relatively uncommon occurrence, as shown in Table 5. Plain skull radiographs, conventional tomographies, and cerebral angiography provide nonspecific

TABLE 5. Radiological evaluation of 70 pituitary metastases

	Number
Plain skull radiograph	34
Sellar floor erosion	14
Sellar enlargement	10
Sellar deformity	8
Sphenoid sinus erosion	3
Sellar calcification	1
Frontal base erosion	1
Skull base metastases	1
Normal sella	10
Cerebral angiography	22
Tumor blush	14
Mass effect	5
Normal	8
Brain CT/MRI	65
Sellar enhancing mass	44
Suprasellar enhancing mass	32
Stalk enhancing/thickening	21
Sellar abnormality/enlargement	15
Cavernous sinus invasion	10
Chiasm/hypothalamus invasion	10
Loss of PL high-signal intensity	9
Dumbbell-shaped mass	8
Sphenoid sinus invasion	6
Inhomogeneous/ring tumor enhancement	5
Low-intensity signal on T2WI	2
Retrosellar enhancing mass	1
Negative	1
Other brain metastatic lesions	11

Data are from Refs. 1, 2, 4, 5–10, 12, 16–18, 20, 24–26, 28, 34, 36, and 37; PL, Posterior lobe.

findings, whereas in approximately one third no sellar abnormality is displayed (Table 5). High-resolution CT and MRI are more sensitive. The CT usually shows a hyperdense or isodense mass, homogeneously or inhomogeneously enhancing (if cystic degeneration, hemorrhage, or necrosis exists) in contrast images. The MRI may demonstrate an isointense or hypointense mass on T1WI, with a usually high-intensity sign on T2WI, homogeneously enhancing postgadolinium, as well as absence of high-signal intensity of the posterior lobe on T1WI. However, neither of these findings is highly specific for MP (5, 7–9, 11–13, 15, 17, 27). Rapid increase of a sellar tumor with aggressive infiltration of adjacent tissues should raise suspicion of MP (3, 5, 6, 17, 27). Moreover, MPs usually have a rapid growth and respect the diaphragm early in their course. Therefore, a dumbbell-shaped intrasellar and suprasellar tumor, with a clear indentation at the level of the diaphragma sellae, best seen on sagittal images, is suggestive of MP (2, 11, 17, 36), although this type of presentation has also sometimes been described in benign lesions. Schubiger and Haller (17) reported that invasion of the infundibular recess by a suprasellar mass is in favor of MP, because suprasellar adenomas usually push it posteriorly. They also found in five of their seven patients a linear enhancement of the infundibulum proximal to the tumor, an unusual finding in pituitary adenomas. In our case, MP was not dumbbell shaped and showed low-signal intensity on T2WI and inhomogeneous enhancement on precontrast T1WI, probably induced by tumor hemorrhage or by protein-rich content. This is a relatively uncommon radiological presentation for MP, as it is inferred from Table 5.

In most cases, metastasis is initially suspected during surgery (4) because of the atypical appearance of the tumor, whereas the confirmation of diagnosis relies on histology (1, 4, 6). However, cases of symptomatic MPs, in which the correct diagnosis was set on autopsy or on histology review after the primary tumor was identified, have been reported (3, 23, 26, 34). Sometimes, histological features of MP and adenomas may coexist. The degree of local infiltration is not predictive of malignancy, being noted in many pituitary adenomas as well. Yet, some pituitary adenomas, especially corticotrophinomas and somatotrophinomas, can show marked nuclear pleomorphism, multinucleate tumor cells or frequent mitotic figures (20). Thus, immunohistochemical analysis of the tumor should be regarded as imperative.

Treatment, being basically palliative, depends on the symptoms and the extent of the systemic disease (3–6). In known cancer patients, a full investigation for additional metastases is mandatory. Reports of surgery of MPs indicate that the lesions tend to be firm, diffuse, invasive, vascular, and hemorrhagic; therefore, their total resection is unlikely (2, 4, 6, 10). In this setting, local radiation and/or chemotherapy are recommended as the initial course of treatment, especially in patients with widespread metastases, in combination with pituitary hormone substitution therapy (1–4, 6, 10, 16). Surgical exploration and decompression, alone or combined with radiation, is essential if clarification of diagnosis is likely to affect therapy or if suprasellar extension causes progressive deterioration in vision or pain (2–6, 13, 15, 37). Surgery and radiation are well tolerated in noncompromised patients, being associated with low morbidity and minimal complications (5, 15). As noted in our case, tumor debulging is beneficial in alleviating the local symptoms, especially headaches and visual field defect, whereas symptoms such as diplopia and those related to anterior pituitary failure remain unaffected (1, 5, 6, 15, 37). The transsphenoidal approach, completeness of resection, and aggressive treatment (surgery plus local radiation) are associated with better symptom relief but do not affect survival rates (5, 37).

Prognosis of patients with MPs is poor, not because of the location *per se* but because of the aggressiveness of the primary neoplasia (16). As in the present case, most patients die a few months after diagnosis. Mean survival length in clinical series is 6–7 months (2, 5, 10). Ntyonga-Pono *et al.* (13), reviewing 72 patients from the literature, found that only 10% of patients survived more than 1 yr after diagnosis, the longest survival being 3 yr. Patients with a single MP may have a better outcome (2, 5). Age over 65 yr at presentation, metastasis from small-cell lung carcinoma, and short duration ($<$1 yr) between initial diagnosis of cancer and pituitary invasion have been related to a poorer outcome (5).

In conclusion, we present a patient with a sellar mass, ophthalmoplegia, headaches, hypopituitarism, mild diabetes insipidus, and marked hyperprolactinemia, thought initially to represent a prolactinoma, but which on histology of the partially resected tumor proved to be a metastasis of an undiagnosed HCC. Sudden onset of diabetes insipidus, ophthalmoplegia, and headaches in a patient over 50 yr old should always raise the suspicion for MP, regardless of a history of malignancy. Although radiation or chemotherapy is the treatment of choice, a surgical approach, for obtaining histological diagnosis and alleviating symptoms, may also be considered in patients with limited metastatic disease. The

conventional limit of a PRL level of 200 ng/ml (9.0 nmol/liter), above which hyperprolactinemia is generally attributed to a prolactinoma, should always be used with caution.

Acknowledgments

Received March 6, 2003. Accepted October 27, 2003.

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