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CASE REPORT

Metastatic renal cell carcinoma to the pituitary presenting with hyperprolactinemia

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ABSTRACT. Metastases to the pituitary gland from systemic cancers is a rare phenomenon and usually occurs in patients with disseminated disease. The neurohypophysis is the most commonly involved site, and diabetes insipidus is the most common presentation in these patients. Breast and lung cancer are the most common cancers metastasizing to the pituitary. Involvement of the pituitary by renal cell carcinoma (RCC) is exceedingly rare. Mild-to-moderate degree of hyperprolactinemia is a rare presentation of pituitary metastases. We report the case of a woman with metastatic RCC to the pituitary presenting an unusually high degree of hyperprolactinemia.
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INTRODUCTION

Metastases to the pituitary from systemic cancers is a rare phenomenon and usually occurs in patients with widely disseminated disease (1). The majority of systemic cancers involve the posterior pituitary (due to its systemic blood supply), making diabetes insipidus (DI) the major manifestation in these patients (2). Amongst the systemic cancers that metastasize to the pituitary, breast cancer is most common in women and lung cancer in men (3). Renal cell carcinoma (RCC) with metastasis to the pituitary is extremely rare. Hyperprolactinemia is a rare manifestation of pituitary metastasis and if encountered, it is generally mild. We report the case of a woman with metastatic RCC to the pituitary masquerading as a macroprolactinoma.

CASE REPORT

A 77-yr-old woman was referred to the endocrine clinic in October 2001 for the evaluation of a pituitary mass. The patient was asymptomatic until April 2001, when she developed blurred vision without headache or diplopia. Her poor vision was attributed to cataract. Over the next 4 months she underwent bilateral cataract surgery without any improvement in her vision. Furthermore, she developed intermittent diplopia. In August 2001, she underwent visual field testing that showed bitemporal hemianopsia. Magnetic resonance imaging (MRI) of the pituitary gland was performed and revealed a 2x2 cm pituitary mass with suprasellar extension compressing the optic chiasm and invading cavernous sinuses bilaterally (Fig. 1).

The patient reported a several month history of reduced appetite, weight loss, and fatigue. She denied a history of galactorrhea, polyuria or polydipsia or nocturia. She was on no medication. Her past history was significant for breast cancer diagnosed in 1987 for which she underwent left mastectomy. She did not receive chemotherapy or radiation. In February 2001, she had been diagnosed with RCC for which she had undergone left nephrectomy. She was considered cured from both these cancers, as chest, abdomen and pelvis computed tomography (CT) had shown no evidence of metastatic disease 2 weeks prior to the diagnosis of the sellar mass. She had undergone menopause at the age of 50 and never received estrogen therapy. Her family history was significant for brain cancer (unknown type) in two brothers, one dying at the age of 17 and the other the age of 68.

Her physical examination revealed right ptosis. Visual fields on direct confrontation confirmed bitemporal hemianopsia. The rest of her examination was normal, with the exception of evident kyphosis.

Key-words: Pituitary, prolactin, metastasis.

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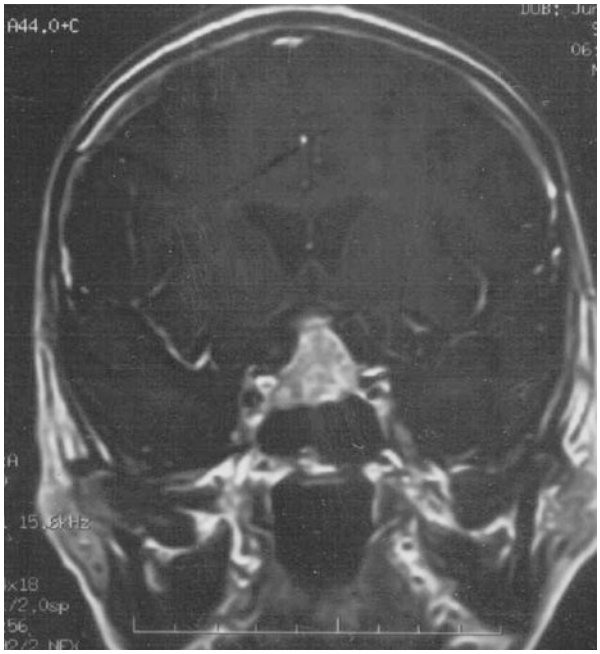

Fig. 1 - *Coronal view of gadolinium-enhanced magnetic resonance imaging of the sellar mass.*

Her initial laboratory evaluation was as follows: sodium=141 meq/l (135-148), potassium=4.5 meq/l (3.5-5.0), creatinine=1.3 mg/dl (0.5-1.2), TSH=1.96 uIU/ml (0.5-4.5), free T4=0.4 ng/dl (0.7-1.6), LH=<0.2 mIU/ml (14-62), FSH=<0.3 mIU/ml (25-160), IGF-1=66 ng/ml (71-290), cortisol=4.7 ug/dl (drawn at 11 am) (6-26), PRL=210 ng/ml (0-18) (confirmed after serum dilution). PRL was assayed by a two site monoclonal antibody immunoenzymometric assay (AIA-PACK PRL on the Tosoh AIA NexIA) (Tosoh Biosciences, Inc., S. San Francisco, CA).
The differential diagnosis included macroprolactinoma, non-secreting pituitary tumor, or sellar mass of other nature. The possibility of metastatic disease was considered unlikely due to lack of symptoms of diabetes insipidus and no evidence of metastatic disease elsewhere. She was started on hydrocortisone (10 mg in am and 5 mg in pm) and levothyroxine (75 mcg/d) with dramatic improvement of her constitutional symptoms. Although an 11 AM serum cortisol of 4.7 ug/dl is not diagnostic of adrenal insufficiency, because of the high likelihood of adrenal insufficiency (sellar mass and failure of the other pituitary hormones), and of the clinical response to hydrocortisone therapy, no dynamic evaluation of her adrenal function was deemed necessary. The decision was made to send the patient in for pituitary surgery. The day before surgery, serum PRL was confirmed to be elevated at 186 ng/ml. On 10/23/01, the patient underwent transphenoidal resection of the mass. The tumor was highly vascular and the patient required intraoperative blood transfusion. Debulking of the tumor was performed, however, complete excision was deemed impossible due to the degree of invasiveness. Pathology showed metastatic RCC (Fig. 2). Immunostaining for PRL was negative.
In May 2002, a repeat MRI of the brain showed a slight increase in the suprasellar mass along with new metastatic lesions in the left lateral ventricle (1.4x1.2x1 cm) and in the left temporal bone (2.5x1.5 cm) near the left orbit. PRL remained elevated at 148.3 ng/ml. A CT scan of the body showed three 1 cm nodules in the lungs and one lesion in the spleen, consistent with metastatic disease. She underwent stereotatic radiosurgery in July 2002 receiving 3000 cGy in 6 fractions to the sella. In August 2002, she received

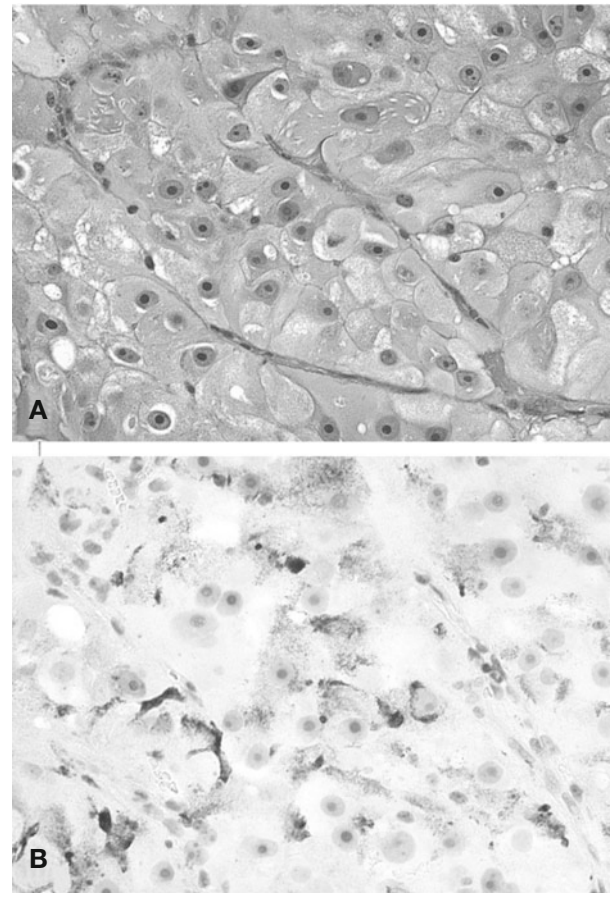

Fig. 2 - *Renal cell carcinoma (RCC) metastatic to the anterior pituitary. Typical of renal cell carcinoma, the tumor cells have prominent nucleoli, abundant granular cytoplasm and a nested growth pattern (A). The tumor cells are immunoreactive for RCC (B) but not PRL (not shown).*

2400 cGy to her left temporal lesion in 12 fractions. In November 2002, repeat MRI showed stabilization of her cerebral lesions. However, the splenic lesion had increased in size. Her condition worsened and she subsequently died due to metastatic brain disease.

DISCUSSION

The pituitary gland is a relatively rare site for secondary metastases from systemic cancer (1). The majority of these metastases occur in patients with widely disseminated disease and are often discovered only at autopsy. In 1857, Benjamin reported the first such case in a patient with widely disseminated disease (4). In addition to causing hypopituitarism, the majority of systemic cancers also involve the posterior pituitary, making diabetes insipidus (DI) a prominent clinical manifestation in these patients (2). This has been attributed to the systemic blood supply of the neurohypophysis through the hypophysial arteries (compared to protected portal circulation of the anterior pituitary) (2). The adenohypophysis, if involved, is usually by direct extension of metastases from the neurohypophysis.

Amongst the systemic cancers that metastasize to the pituitary, breast cancer is most common in women and lung cancer in men (3). RCC metastases to the pituitary are extremely rare. In 1981, Anniko et al reported the first case (5). Since then, only a handful of patients with pituitary metastases from RCC have been described in the literature (6). As patients with pituitary metastases often have widespread metastatic disease, it is possible that some of the symptoms due to hypopituitarism may simply be attributed to the systemic disease without aggressively pursuing the evaluation of pituitary hormones. This means that the prevalence of pituitary dysfunction secondary to metastases may be even higher than commonly thought.

Pituitary metastases from RCC tend to behave differently from other metastatic lesions, as they usually target the adenohypophysis, resulting in panhypopituitarism (7). Pathological specimen in our patient did not show any normal pituitary tissue. However, the elevated PRL seems to indicate that some normal tissue was preserved. This observation leads us to speculate that in our patient the main cause of hypopituitarism was compression of the pituitary stalk.

In clinical practice it is important to differentiate pituitary adenomas from metastatic tumors. Findings consistent with bony destruction of the sella, clinoids or clivus, rapid growth of the tumor on serial imaging, sclerotic margins of the sella strongly suggest metastases. Recent reports have suggested that MRI may be able to differentiate between pituitary adenomas and RCC metastases. Due to hypervascularity of RCC, MRI shows intra-tumoral flow voids (a finding almost never seen in pituitary adenomas) (8). This finding was not present in our patient. Similarly, cerebral angiography may reveal tumor blush filling the sella (8).

It is commonly accepted that stalk compression can cause PRL levels up to 150 ng/ml (9). Hyperprolactinemia (secondary to compression of the infundibulum) is considered to be a rare manifestation of metastatic cancers to the pituitary. When hyperprolactinemia is present, it is usually mild (50-54 ng/ml) (10). The highest PRL levels in pituitary metastasis reported in the literature were 149 ng/ml in a case of colon cancer, and 123 ng/ml in a case of breast cancer (11, 12). Hyperprolactinemia (99 ng/ml) secondary to RCC metastases to the pituitary has been described only in one previous case presenting with DI and bitemporal hemianopsia 4 yr after the resection of the primary tumor (13).

Macroprolactinemia is a relatively common condition in which large PRL molecules (big- big PRL) accumulate in the plasma of some individuals causing a mistaken diagnosis of hyperprolactinemia (14). This condition is relatively frequent, and it has been reported to be responsible for up to 24% of hyperprolactinemias (15). Although we did not check the serum of our patient for big-big PRL, we believe that this is an unlikely explanation of her hyperprolactinemia since the highest PRL level reported in macroprolactinemia is 110 ng/ml (15) and the average is 42.3 ng/ml (14).

There have been reports of systemic cancers metastasizing to existing pituitary adenomas (16). Although most of the pituitary tumors were non-secreting adenomas, there are at least two case reports in the literature in which the systemic cancer metastasized to an existing prolactinoma (17, 18). However, in our case, pathology showed no evidence of a concurrent pituitary adenoma. Finally, there has been a report of RCC with ectopic production of PRL (19), however, the negative staining of the tumor for PRL ruled out this possibility.

In summary, we report a case of metastatic RCC to the pituitary masquerading as a macroprolactinoma. To the best of our knowledge, this is the highest level of PRL ever reported due to stalk compression by a RCC metastasis. This case shows that pituitary metastases may be the initial manifestation of a recurrence of a malignancy considered to be cured, that panhypopituitarism (in the absence of clinical DI) may be a rare manifestation of pituitary metastases (particularly RCC), and that PRL level above 200 ng/ml can be seen in patients with pituitary metastasis.

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