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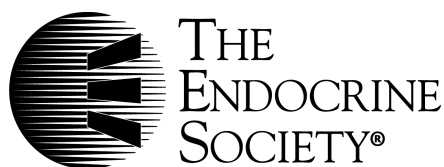
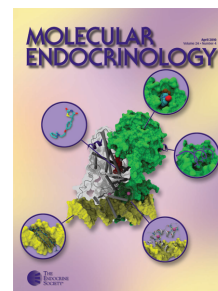
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CLINICAL CASE SEMINAR

Malignant Prolactinoma Discovered by D2 Receptor Imaging

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Malignant prolactinomas are extremely rare (1, 2). The diagnosis of these carcinomas is mainly based on the patient's medical history and the detection of metastases. Nuclear medicine offers new imaging modalities for the detection of metastases of pituitary carcinomas. These techniques may have serious consequences for subsequent investigations and therapy. The case presented here shows the clinical behavior of a malignant prolactinoma. The usefulness of dopamine D2 receptor scintigraphy for establishing the diagnosis and subsequently directing the therapeutic approach is illustrated.

Case Report

A 43-yr-old man presented with a macroprolactinoma in 1984. He was operated on by a transfrontal approach in 1984 and by two transsphenoidal approaches in 1985. Postoperatively, serum PRL levels did not normalize. The patient showed partial resistance to dopamine agonists; serum PRL levels decreased from 212 $\mu\text{g/L}$ (normal, $<20 \mu\text{g/L}$) at baseline to 57 $\mu\text{g/L}$ with bromocriptine therapy. From 1984–1991, a progressive rise in serum PRL levels was noted despite treatment with high doses of bromocriptine (55 mg/day) and thereafter quinagolide (0.8 mg/day). When he was referred to us in 1991, his serum PRL level was 757 $\mu\text{g/L}$ on quinagolide and 1575 $\mu\text{g/L}$ without treatment. Pituitary magnetic resonance imaging (MRI) showed a pituitary macroadenoma with bilateral extrasellar extension to the cavernous sinuses. Surgery was repeated using a transcranial approach. However, postoperative serum PRL values remained elevated (2181 $\mu\text{g/L}$). External pituitary irradiation was administered (total dose, 5000 rads), and treatment with cabergoline was started. From 1991–1993, a progressive decrease in PRL levels was observed (to 84 $\mu\text{g/L}$) while the patient was still being treated with cabergoline (2.0 mg every 2 days). After this period of relative efficacy of this drug, a progressive rise in serum PRL levels was observed again. The

patient was then treated four times with γ -knife radiosurgery (in 1994, 1995, 1996, and 1997). The last γ -knife treatments were less effective than the first ones (Fig. 1). The patient underwent two additional pituitary explorations in 1997 and 1998 via the transcranial route in another center, which did not reveal further tumorous tissue. He was then referred back to us. At the last hospital admission (July 1998), 2 months after the last operation and discontinuation of cabergoline treatment, serum PRL levels were much higher than previously observed (7163 $\mu\text{g/L}$). Nevertheless, MRI study did not reveal important tumor residue. Because the clinical evolution of the patient strongly suggested a malignant prolactinoma, nuclear imaging studies were performed.

Imaging studies

Dopamine D2 receptor scintigraphy. Epidepride scintigraphy was performed as recently described (2). Potassium iodide (100 mg daily) was administered for 5 days, starting 24 h before radiopharmaceutical injection. [^{123}I]Epidepride was obtained from Dr. Angelberger, Österreichisches Forschungszentrum Seibersdorf GmbH (Seibersdorf, Austria), and was distributed by IDB Holland BV (Baarle-Nassau, The Netherlands). [^{123}I]Epidepride (185 megabecquerels) was administered iv, and images were obtained after 3 h. Single photon emission computed tomography images of the head were obtained using a three-headed camera (Picker 3000 xp, Picker International, Cleveland, OH) equipped with a medium energy collimator. The pulse height analyzer was centered over the energy peak (159 keV); the window width was 20%. Acquisition parameters were one scan, 36 s/frame, 120 projections, 360° rotation, 64 \times 64 matrix. Images were reconstructed using a Metz filter. Whole body images (from head to upper legs) were obtained using a two-headed camera (Prism 2000, Picker International). Acquisition time was 40 min. There was no uptake of [^{123}I]epidepride in the pituitary region. Faint uptake that could correspond to a tumor remnant was noticed close to the basal ganglia (Fig. 2). At whole body imaging, normal uptake was seen in the urinary bladder, liver, gall bladder, intestines, and lung. However, pathological uptake was seen caudal in the left thorax (pos-

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FIG. 1. Evolution of PRL levels. Quinagolide doses do not appear in the graph due to the scale used to represent the entire biological history. RxTh, Radiotherapy.

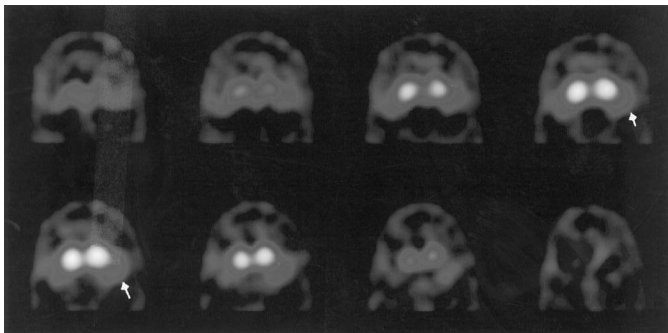
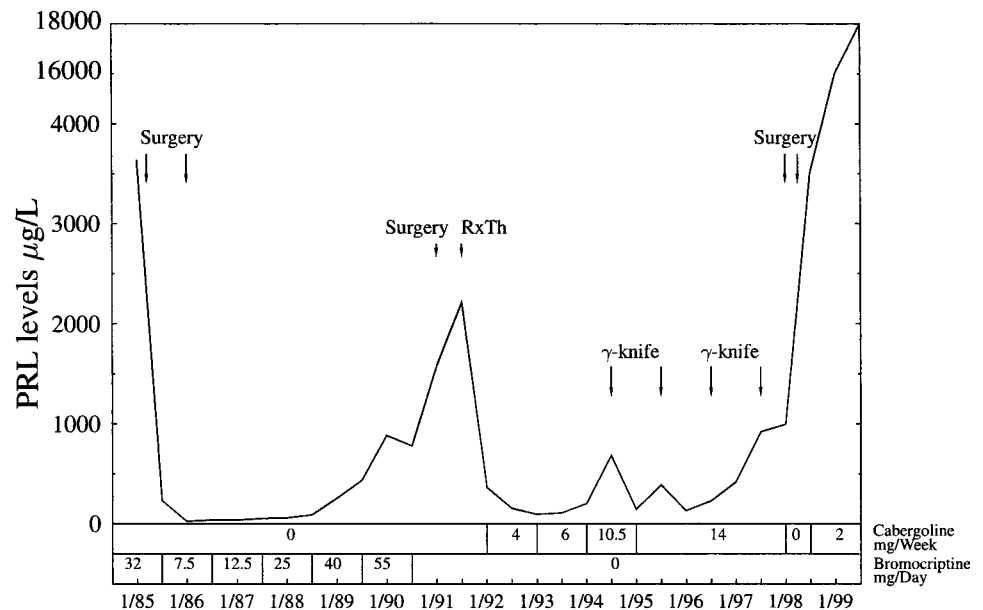


FIG. 2. Coronal slices from the sellar region during epidepride scintigraphy. Slices run from dorsal to ventral. Intense uptake in the basal ganglia and slightly increased uptake below the left basal ganglion are shown.

sibly a rib), at multiple sites in the lower thoracic and lumbar spine, and in the mediastinum and right femur (Fig. 3).

MRI. Total spine MRI was performed using T2 before gadolinium injection and T1 weighted images before and after gadolinium injection. Multiple lesions suggestive of metastases were seen along the thoracic (T1, T3, T5, T6, T7, T8, T10, and T12) and lumbar vertebrae (L1, L2, L4, and L5; Fig. 4).

Clinical follow-up

Considering the nature and the extent of the metastatic lesions, further palliative treatment was decided. Cabergoline was restarted despite its ineffectiveness in normalizing serum PRL levels. However, a significant decrease in serum PRL levels was observed again, and we hoped that this treatment might also slow down tumor progression. Local external radiotherapy was applied to the back to prevent pain and peripheral nerve palsy.

Discussion

Pituitary carcinoma is one of the traps presenting to endocrinologists. These tumors are very rare, and a review of the literature only reveals 96 cases (for 2 recent reviews, see Refs. 1 and 2), which included 28 malignant prolactinomas (1, 3–20), 25 ACTH-producing carcinomas, 12 GH-producing carcinomas, 1 TSH-producing carcinoma, and 30 gonadotropin-producing or clinically nonfunctioning carcinomas (2). At the University Hospital of Liege, this was the first pituitary carcinoma among 1200 pituitary tumors.

The distinction between carcinomas and invasive adenomas is difficult. Malignant prolactinomas do not present with distinct clinical signs that distinguish them from benign tumors. Initially, the radiological appearance may mimic that of an adenoma. Histological examination, even using tumor markers, does not allow easy differentiation between adenomas and well differentiated carcinomas. The diagnosis is usually suspected because of multiple recurrences and progressive inefficacy of treatment. However, these features can also occur in drug-resistant and aggressive adenomas. Therefore, the final diagnosis is often made after metastases have been discovered.

In the present case, the early clinical features were compatible with a recurrent adenoma. γ Knife radiotherapy was very efficient at first. The loss of efficacy of radiotherapy and radiosurgery in the later stages of the disease was attributed to either resistance or increasing aggressiveness of the tumor. However, retrospectively, this probably was the first manifestation of extracranial metastases that were not yet suspected and, therefore, not treated at that time. This hypothesis is supported by the fact that at the last two operations no tumor remnants were found in the sellar region. The persistence of increased serum PRL levels despite dopamine agonist therapy, the lack of efficacy of additional radiotherapy, and the finding of an empty sella at surgery led to the search for metastases.

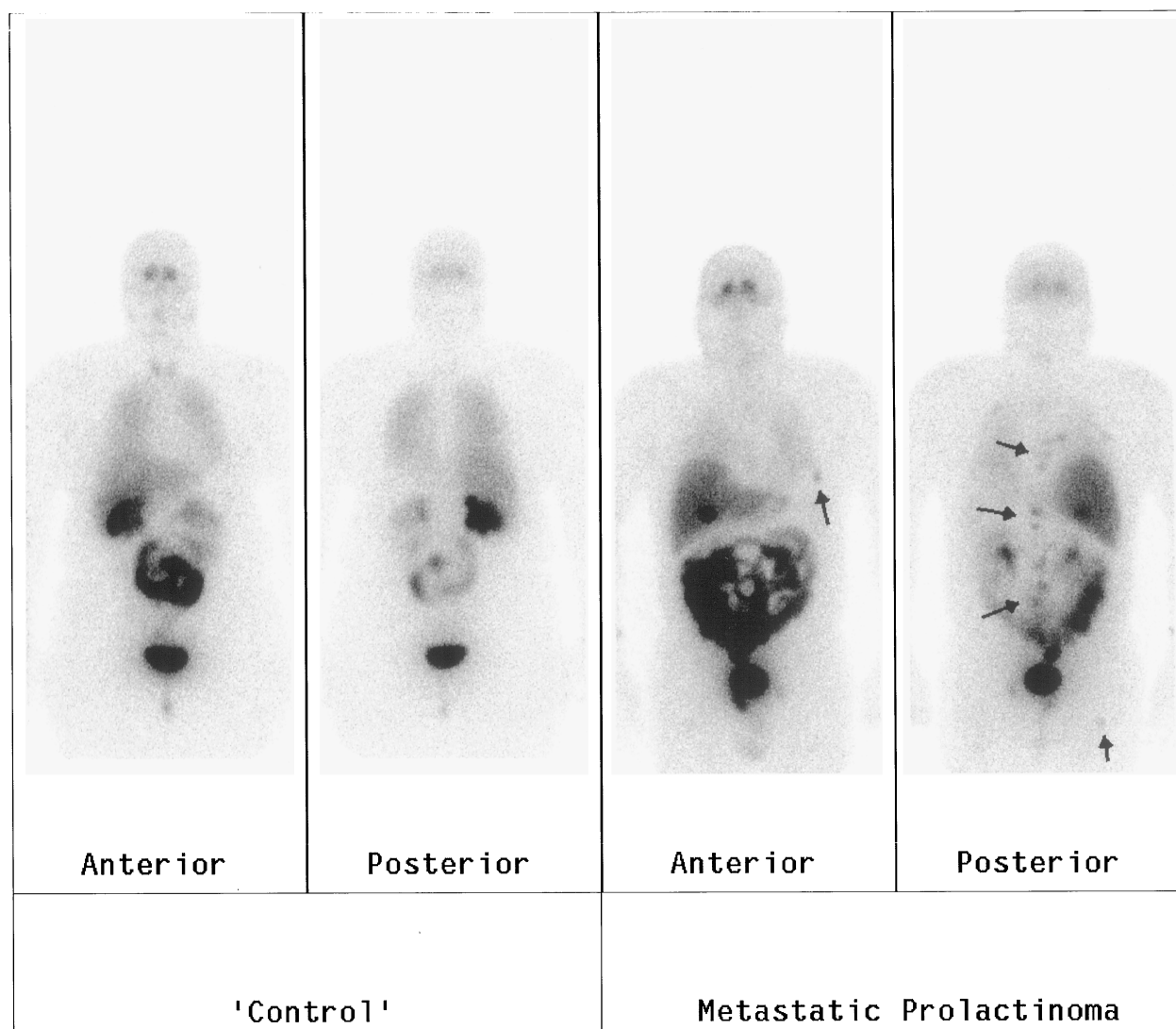


FIG. 3. Total body scintigraphy 3 h after the injection of [^{123}I]epidepride. Normal accumulation of radioactivity in the basal ganglia, thyroid, lungs, liver, bowel, and urinary bladder in a control patient (*left images* are anterior and posterior views, respectively). Pathological uptake projecting over the left anterior thorax, possibly in a rib (third image from left), and in multiple sites in the spine and right femur (*rightmost image*) in the study patient.

Malignant prolactinomas usually metastasize to the central nervous system and arachnoidal tissues. Distant metastases are rare. However, they have been reported in the skeleton in two cases (1, 3), in lymph nodes in four cases (1, 12, 18), in the lung in two cases (11, 13), and in the liver or ovaries in three cases (1, 11, 16). Some researchers suggest that metastases may have been grafted by surgery because they have been found on the surgical route in some cases (16).

Scintigraphy can sometimes be very useful for demonstrating metastases and, therefore, for the confirmation of the malignant character of a tumor. Somatostatin receptor imaging has been reported to be useful for the detection of metastatic deposits in a GH-secreting carcinoma (21). The use of this technique in a case of a malignant prolactinoma may be worthwhile, because PRL-secreting cells may have somatostatin receptors. However, these cells usually possess somatostatin receptor subtype 5 (sst_5) (22), whereas [^{111}In]pentetreotide binds with high

affinity to somatostatin receptor subtype 2 (sst_2) and with only moderate to low affinity to sst_5 . Therefore, [^{123}I]epidepride, a radioisotope with high affinity for D2 receptors, was used (23). [^{123}I]Epidepride scintigraphy finally revealed areas of pathological uptake corresponding to extracranial metastases. This is the first case in the literature in which D2 receptor imaging demonstrated extracranial metastases of a pituitary carcinoma. This technique may prove useful in future difficult cases, especially when dopamine D2 receptors instead of high affinity somatostatin receptors are likely to be present in the tumor, such as prolactinomas or their malignant counterparts.

Pathological examination of malignant prolactinomas reveals only a slight degree of cytological atypia. Mitotic activity is higher, and the tumor cells are usually aneuploid. Labeling indexes for proliferation markers MIB-1 and proliferating cell nuclear antigen are higher in primary and metastatic tumors than in adenomatous cells.

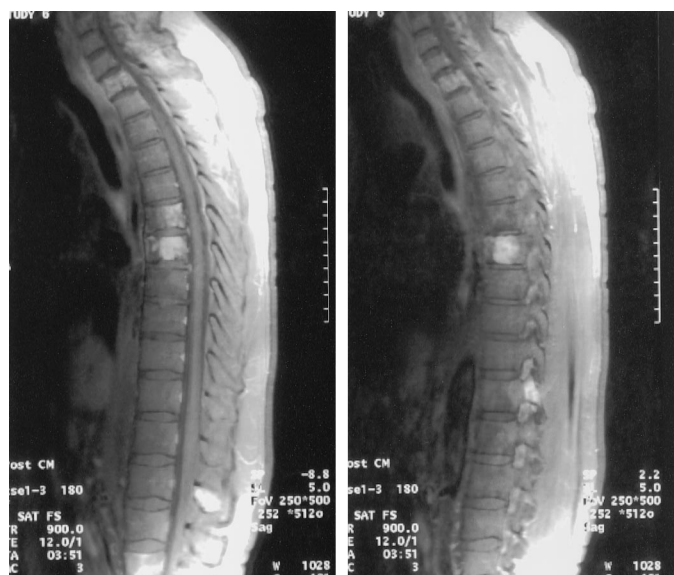


FIG. 4. Sagittal T1 spin echo sequences with gadolinium showing hyperintensities involving the body of T5 and T6, the left pedicle of T10, the T12 processus spinosus, and the body of L2 corresponding to metastases. A, Median slices (left); B, left lateral slices (right).

There is also a greater expression of p53 protein in these cells (1). Little is known about the tumorigenesis of pituitary carcinomas. Loss of retinoblastoma susceptibility gene has been demonstrated in an ACTH-secreting pituitary carcinoma (24). In another study, no mutations were detected in the p53 tumor suppressor gene or in N- or K-ras G-protooncogenes, but point mutations were identified in the H-ras gene (25).

The midterm evolution of patients presenting with PRL-secreting carcinomas is pejorative. Only 50% of the cases described in the literature showed a survival of more than 1 yr. Surgery may be useful in debulking the lesion and relieving the local compression effect. However, it cannot be repeated indefinitely despite the recurrence of the tumor. Dopamine agonists are widely used in the treatment of prolactinomas. In the case of malignant tumors, they may slightly reduce the tumor size, but without changing the final outcome. Some researchers have used cytotoxic chemotherapy with a transient improvement in the illness. The treatment consisted of different combinations of procarbazine, vincristine, etoposide, cisplatin, and lomustine. The use of tamoxifen alone has been successful in one case (16). Radiotherapy remains one of the more efficient treatments. Despite the lack of a definite cure, it can be helpful either in partly relieving the local complications of the tumor or as a palliative treatment for pain.

Note Added in Proof

The patient presented in this case died in September 1999. The last PRL level measured before his death was 45,500 $\mu\text{g/L}$.

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