An Unusual Pituitary Pathology

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Nonadenomatous lesions of the pituitary represent a small part of the intrasellar processes. However, when encountered, they may present a diagnostic difficulty (1).

Most of them are discovered because of the tumoral syndrome, due to the compression of the pituitary and the surrounding structures, and may lead to hypopituitarism, diabetes insipidus, secondary hyperprolactinemia, visual field disturbances, and oculomotor abnormalities. None of these signs are fairly specific of these lesions, and, with the exception of diabetes insipidus which is more rare, they could very often be seen in pituitary adenomas. In some cases however, these tumors may be incidentalomas, provoking no pituitary or ocular dysfunction.

Making a more precise diagnosis on the basis of biological, hormonal, and radiological examinations is of primary importance, as it may lead to a less aggressive, although very efficient, medical therapy in some cases.

The case history we are presenting here shows the difficulties encountered in the diagnosis of these unusual pituitary processes and highlights the potential interest of recently developed techniques in the endocrinological exploration of these patients.

Case Report

A 54-yr-old menopausal woman of Caucasian origin was admitted to the hospital complaining of extreme weakness, headache, and vomiting. The patient had no previous medical history and was taking no medication. At clinical examination, she presented with signs of hypopituitarism and a mild diabetes insipidus. The basic laboratory tests showed an inflammatory syndrome, with a rise of sedimentation rate to 81 mm/h, fibrinogen to 8 g/L, but normal white blood cell count. Endocrine tests at admission showed a complete anterior pituitary deficiency, with undetectable gonadotropin and TSH values for a low estradiol and free T3-T4, low insulin-like growth factor I, and no stimulation of GH and cortisol by insulin tolerance test.

Pituitary computed tomography scan and magnetic resonance imaging (MRI) examinations were performed (Fig. 1), showing an endosellar mass and a thickening of the pituitary stalk. There were no intrasellar calcifications. The clinical history and the radiological imaging were not in favor of a pituitary adenoma. Diabetes insipidus is rare even in nonfunctioning adenomas. Moreover, a pituitary stalk involvement by an intrasellar adenoma is very rare.

These examinations suggested that this lesion belongs probably to other types of sellar lesions, which are listed in Table 1.

Because of the nonavailability of gadolinium at that time, contrast images were not performed. However, the T1 and T2 weighted images were not in favor of a cystic lesion nor of a craniopharyngioma. Other diagnoses like intrasellar hematoma, melanoma, lipoma, vascular (2) or bony tumor were unlikely because of the lack of the MRI signal modifications usually found in these lesions. Moreover, the very high sedimentation rate could not be explained by these lesions. An inflammatory lesion or a secondary tumor were therefore considered, and a general screening was started to better determine the diagnosis.

Pituitary abscesses (3) usually appear in a context of septicemia, which was not found in our patient. These could be associated with a purulent central nervous system fluid and, in some cases, a rise in white blood cells, none of which were present.

Tuberculosis skin test was negative, and body fluid cultures for bacteria and mycobacteria were sterile. Moreover, radiological examinations did not show any primary tuberculous lesion. Syphilitic serology (VDRL and TPHA) was negative. All autoimmunity markers, including antineutrophil cytoplasmic antibodies, were normal. Screening for a primary neoplasia, including chest X-ray and computed tomography, gastroscopy, abdominal echotomography, gynecological examination, and mammography, did not unveil any tumorous lesion. For all these reasons, an abscess, or a tuberculous (4, 5), syphilitic, or metastatic (6) lesion seemed to be unlikely.

A pituitary localization of a lymphoma or a plasmocytoma was very unlikely, as this sole localization has rarely been described (7).

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Langerhans-cell histiocytosis usually shows the involvement of other organs and does not cause a rise in sedimentation rate (10). However, a unique pituitary localization is possible, and the definite diagnosis may only be given by a biopsy of the lesion (11). Granular cell tumors are usually asymptomatic (12). Neurosarcoidosis is a rare diagnosis (5% of all sarcoidosis cases), but a possible diagnosis for our case (13, 14). Laboratory tests showed, however, normal angiotensin-converting enzyme values that, without excluding this disease, gave another argument against it. Wegener’s granulomatosis (15, 16) was possible too, despite the lack of involvement of other organs and the presence of normal ANCA. Because of the lack of definite arguments, an inflammatory pituitary granuloma was considered the most likely diagnosis.

The patient was treated by hormonal replacement therapy (0.1 mg tyroxine and 25 mg hydrocortisone daily). She was then discharged from the hospital and referred to our institution to discuss the indications for a pituitary biopsy. She was retested for infectious and autoimmunity markers. The screening for a primary tumor was continued by an examination of the upper respiratory tract. A granulomatous lesion of the cavum was found and biopsied.

First histological examination

Histological examination of the cavum biopsy showed an ill-defined granulomatous inflammation with the presence of epithelioid cells, giant plurinucleated cells, and small areas of nonspecific necrosis. On the basis of histology alone, a diagnosis of either Wegener’s granulomatosis or tuberculosis was first proposed.

Several special stains were then performed. The orcein staining demonstrated some vascular modifications in medium-sized arteries that may accompany Wegener’s granulomatosis. No organisms were seen on Zielh-Neelsen stains.

**TABLE 1.** Some of the nonadenomatous pituitary tumors already described in the literature (1)

<table>
<thead>
<tr>
<th>Noninflammatory tumors</th>
<th>Inflammatory tumors</th>
<th>Cysts</th>
<th>Others</th>
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</thead>
<tbody>
<tr>
<td>Granulous cell</td>
<td>Abscess</td>
<td>Rathke</td>
<td>Hamartomas</td>
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<tr>
<td>Craniohypophyngioma</td>
<td>Sarcoïdosis</td>
<td>Arachnoid</td>
<td>Ganglioneuros</td>
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<tr>
<td>Chordoma</td>
<td>Lymphocytic hypophysitis</td>
<td>Epidermoid</td>
<td>Accessory salivary glands</td>
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<tr>
<td>Metastatic</td>
<td>Giant cell granuloma</td>
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<tr>
<td>Meningioma</td>
<td>Histiocytosis</td>
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<td>Sarcoma</td>
<td>Wegener</td>
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<td>Melanoma</td>
<td>Tuberculosis</td>
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<td>Lymphoma</td>
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<td>Plasmocytoma</td>
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<td>Glioma</td>
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<td>Schwannoma</td>
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<td>Germinal cell</td>
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<td>Vascular</td>
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<td>Bony</td>
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<td>Lipoma</td>
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of the tissue. On the basis of these results, the diagnosis of Wegener’s granulomatosis was preferred.

Clinical course

The patient was therefore treated with corticosteroids (prednisolone). She was then lost for follow-up. Two months later she again presented to the hospital. She was still under corticosteroids and complained of the reappearance of headache and vomiting. Clinical examination showed the presence of cavernous and chiasmatic syndromes. At MRI examination, the lesion showed an increase in size with a suprasellar extension, a chiasmatic compression, and a lateral extension in the cavernous sinuses (Fig. 2). Contrast images showed a peripheral shell with a necrotic center. There was no meningial involvement.

The patient underwent a pituitary surgery by a transsphe- noidal approach. The neurosurgeon (A.S.) proceeded to a large debulking of the tumor, relieving the chiasmatic compression. Tissue samples were sent to the pathology department.

Second histological examination

The histological aspect was quite similar to that described for the cavum. At low magnification, the normal pituitary
tissue was replaced by an extensive inflammation. At higher magnification, granulomatous features were observed with the presence of epithelioid cells and giant plurinucleated cells (Fig. 3). Focal areas of necrosis were also present but did not exhibit the typical aspect of caseation. As in the previous sample, no acid-fast bacilli were detected by the Zhiel staining. A diagnosis of granulomatous hypophysitis was proposed and probably related, because of the history of the patient, to a Wegener’s granulomatosis.

Clinical course

On the basis of clinical suspicion, the worsening of the symptoms under corticoids, and the fact that pathological examination could not exclude an infectious etiology, the patient was empirically treated by antituberculosis thri-therapy. Three months after the beginning of this treatment, there were a tremendous improvement in the clinical conditions and a complete disappearance of the inflammatory syndrome. To definitely determine wheter the patient had a mycobacterial infection, a detection of Mycobacterium tuberculosis DNA by the polymerase chain reaction (PCR) technique was performed in the pathology departement.

Amplification of Mycobacterium Tuberculosis DNA by PCR

Crude DNA was first extracted from the paraffin-embed- ded biopsy as previously described (17). A nested PCR was then performed on 10 μL of extracted DNA. We used a pair of primers derived from the sequence of the insertion element IS6110, which is specific for M. Tuberculosis, and situated outside of the primers proposed by Savic et al. (18). These primers were used in a first amplification step, giving an amplified DNA fragment of 559 bp (19). A second amplification was then performed on an aliquot of the first amplification product by using primers described by Savic et al. (18), delimiting a DNA fragment of 263 bp within the originally amplified DNA sequence. The first amplification was carried out using PCR Master (Boehringer Mannheim, Mannheim, Germany) in a final volume of 50 μL containing 20 pmol of each sense IS1A and antisense IS2A oligonucleotide primer. After initial denaturation of the DNA sample for 3 min at 94 C, the reaction was run for 40 cycles consisting of 30 sec at 94 C for denaturation, 2 min at 60 C for annealing, and 2 min at 72 C for extension. The second amplification was performed on 1 μL of the originally amplified DNA using the primers and PCR conditions (initial denaturation of the DNA for 13 min at 98 C followed by 40 cycles consisting of 1 min at 92 C for denaturation, 1 min at 72 C for annealing/extension) described by Savic et al. (18). The amplified product was
then electrophoresed on 2% agarose gel in Tris-Acetate-EDTA (TAE) buffer after staining with ethidium bromide. As shown in Fig. 4, the biopsy specimen of our patient was positive for M. tuberculosis DNA.

Follow-up

Antituberculosis therapy was maintained for a total of 9 months.

Clinical course

Five-year follow-up shows no signs of reappearance of the inflammatory syndrome. The patient presents no complaints under hormonal replacement therapy. Pituitary MRI shows an empty sella with no sign of tumor reappearance.

Discussion

Before the discovery of antituberculosis drug therapy, tuberculomas represented as much as 30% of the intracranial tumors in adults and 50% in children (20). The frequency is now between 0.25% and 4% in western countries (21). A unique localization in the pituitary is very rare, as meningitis are also usually involved. These cases present mainly as a secondary complication of a known tuberculosis or at least as the first manifestation of an easily diagnosed tuberculosis, with a more-or-less obvious entry point.

Moreover, the imaging findings of pituitary tuberculomas are nonspecific and may resemble other pituitary granulomas caused by a specific lesion such as syphilis, sarcoidosis, Langerhans cell histiocytosis, Wegener’s granulomatosis, and even macroadenoma or lymphocytic hypophysitis.

The diagnostic puzzle presented by our patient was associated with the unique pituitary localization, with no obvious primary infection site, until the finding of a granulomatous inflammation in the nasal cavities. The normal skin test and sterile body fluid cultures were other factors that made the diagnosis of tuberculosis less likely. The pathological examination, while not excluding a mycobacterial infection, was more in favor of a noninfectious granulomatous lesion. This diagnosis was reinforced by the clinical presentation and the complementary examinations, and led finally to corticoid therapy.

Fortunately, this treatment was not associated with any dramatic complication except for the growth of the pituitary tumor. The early and transient improvement in the complaints presented by the patient was probably related to the antinflammatory effect of the corticoids.

The pathological examination of the pituitary tissue obtained by transsphenoidal surgery did not help in refining the diagnosis, but confirmed the inflammatory nature of this tumor. The antituberculosis therapy was mainly motivated by clinical suspicion and the ineffectiveness of the corticoids. Moreover, a mycobacterial infection was never entirely excluded in any part of the history of the patient.

PCR examination was not performed earlier in the history of the patient because it was, at that time, a new technique whose usefulness was just being evaluated. The patient underwent a 9-month, 3-drug therapy, and the treatment was then discontinued. We now have a 5-yr follow-up, with no sign of recurrence of the tumor or of the clinical complaints. The patient is under a life-long hormonal replacement therapy.

The intranasal cavities are probably the site of the primary infection as no other entry points were found during the routine follow-up. It is not clear whether the mycobacterial infection of the pituitary resulted from a regional extension or from a hematogenous contamination from the cavum. A secondary extension of purulent bacterial infections has already been described from preexisting peritonsillar abscesses (22).

In conclusion, this case report illustrates the diagnosis difficulty of nonadenomatous pituitary lesions. An accurate diagnosis is important, however, because it allows the administration of an efficient medical treatment in some cases.

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