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CLINICAL CASE SEMINAR

Extensive Inflammatory Pseudotumor of the Pituitary

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A 40-yr-old female presented with an extensive lesion of the sellar area and the sphenoid sinus, spreading to the optic nerves and associated with pachymeningitis. Histological findings were consistent with an inflammatory pseudotumor, and steroid treatment allowed the disappearance of all the lesions.

Inflammatory pseudotumors of the pituitary are very rare. This case appears unique with regard to the extension of the lesions and the dramatic response to medical treatment. The differential diagnosis of inflammatory lesions of the pituitary is difficult. It relies mainly on histological analysis and includes sarcoidosis, Wegener’s granulomatosis, histiocytosis (Langerhans, Rosai-Dorfman, and Erdheim-Chester diseases) and lymphocytic hypophysitis. (J Clin Endocrinol Metab 86: 4603–4610, 2001)

Despite the accuracy of current diagnostic tools, nonadenomatous lesions of the pituitary still create diagnostic challenges to the endocrinologist. The most frequent lesions that may be encountered are Wegener’s granulomatosis, Langerhans histiocytosis, sarcoidosis, lymphocytic and granulomatous hypophysitis, and bacterial and parasitic infections. These may be of autoimmune origin and may represent the first manifestation of a systemic disease. Their precise identification is crucial to determine the most appropriate treatment, which is usually nonaggressive medical therapy.

We present the case of an extensive inflammatory pituitary lesion, spreading to the sphenoid sinus, meninges, and frontal lobes. In the light of clinical and laboratory results, the diagnosis of inflammatory pseudotumor (Ip) was made. Corticosteroid treatment caused marked clinical, biochemical, and imaging improvement. The case in this report is unique with regard to extension of the lesion and its response to therapy.

Case Report

A 40-yr-old African woman presented several times with frontal headaches at the out-patient clinic between April and December 1996. The clinical and laboratory findings, electroencephalogram, and computed tomography scan of the brain were normal. In December 1996, the intensity of the headaches increased, and she complained of rapidly losing sight in her left eye. The patient also complained of lack of menses for 3 months and severe asthenia for 2 wk. Her previous history included pulmonary tuberculosis in 1993 and the delivery of a healthy baby in 1995.

Clinical examination revealed mild fever, left exophthalmos, and amaurosis. Brain magnetic resonance imaging (MRI; Fig. 1, A and B) showed that the sphenoid sinus was filled with T2 hyperintense material. Contrast enhancement demonstrated that the lesion involved the pituitary, the area of the optic chiasma, and nerves, mainly on the left side. Pachymeningitis was observed in front of the sphenoidal jugum, at the level of the cranial base dura and of the falx cerebri. Examination of the cerebrospinal fluid (CSF) revealed a moderately increased protein concentration (636 mg/liter; normal, 150–450), normal glycorrhachia and chlorine levels, and abnormal cell count (no red cells and 62 white cells/mm³; mainly lymphocytes). Laboratory tests showed a normal white blood cell count, an increased erythrocyte sedimentation rate (85 mm/h; upper limit, 10), and increased C-reactive protein (12 mg/liter; upper limit, 6).

Taking into account her past medical history, the diagnosis of a central nervous system tuberculosis was considered first, but the CSF abnormalities were not in favor of mycobacterial infection. Iv antibacterial and antifungal treatment was started. CSF, sputum, urine, and gastric fluid cultures were all negative for bacteria, fungi, and parasites, including acid test bacilli. The PCR for Mycobacterium tuberculosis performed on gastric fluid was also negative. Chest x-ray was normal. These results did not support the diagnosis of an infection, including mycobacterial meningoencephalitis.

Complementary biological evaluation

Protein electrophoresis was normal. Carcinoembryonic antigen and human immunodeficiency virus antibodies in the blood were negative. Immunological tests (rheumatoid factor, antinuclear antibodies, C3 and C4 levels, antineutro-

Abbreviations: CSF, Cerebrospinal fluid; Ip, inflammatory pseudotumor; Lh, lymphocytic hypophysitis; MRI, magnetic resonance imaging.
phil antibodies, angiotensin-converting enzyme) were normal. Endocrinological tests revealed pituitary insufficiency with low gonadotropins levels [LH, 2.4 IU/liter (normal, 1–20); FSH, 2.9 IU/liter (normal, 2–17.4)] and low E2 levels (12 ng/liter; normal, 30–200). TSH was not elevated (0.69 mIU/liter; normal, 0.2–5.2) in the presence of a decreased free T3 (1 ng/liter; normal, 1.5–3.1) and free T4 (3.8 ng/liter; normal, 7–17) concentrations. Blood PRL levels were increased (104 μg/liter; normal, 2.2–24), and basal GH was low (<0.06 μg/liter). Low T3 and T4 and normal basal TSH were in favor of secondary hypothyroidism. This was confirmed by the TRH test, which showed no TSH response (maximum value, 2.5 mIU/liter after 30 min). Evaluation of adrenocortical function provided inconclusive results.

Clinical course

Treatment with oral l-T4 and cortisone markedly improved the asthenia. As the lesion displayed inflammatory features at MRI, in January we started corticosteroid treatment (250 mg methylprednisolone, iv, on d 1 and 2 and 125 mg, iv, on d 3 and 4). Two weeks later, the patient improved her general condition, the exophthalmos and fever disappeared, the headaches decreased in intensity, left visual acuity improved, and periodic menses reappeared. Laboratory tests also improved (erythrocyte sedimentation rate, 29 mm/h; PRL, 29 μg/liter). CSF biochemistry and cell count were normalized, and MRI showed a shrinkage of the sellar mass. MRI with gadolinium enhancement revealed that the lesion persisted in the pituitary, left optic nerve, and frontal meninges. The dramatic response to corticosteroids suggested an inflammatory process and led to a transsphenoidal biopsy of the lesion.

Histological examination

Biopsies were fixed in 10% buffered formalin and stained with hematoxylin and eosin, periodic acid-Schiff reaction, and Ziehl-Neelsen stain to exclude fungi and tubercular bacilli infection, respectively. Paraffin-embedded sections were dewaxed in xylene, rehydrated through a graded series of decreased concentrations of ethanol, heated in a microwave oven in citrate buffer (0.1 mol/liter; pH 6.0) for antigen retrieval, and incubated for 2 h with several primary antibodies.

The immunohistochemical study relied on the avidin-biotin-peroxidase complex method (ABC, Vector Laboratories, Inc., Foster City, CA), using monoclonal antibodies, including those for vimentin (DAKO Corp., Glostrup, Denmark; 1:800 dilution), desmin (DAKO Corp.; 1:200), actin (muscle; DAKO Corp.; 1:400), CD68 (DAKO Corp.; 1:200), CD1a (Novocastra, Newcastle, UK; 1:20), and S100 (DAKO Corp.; 1:1,000), and polyclonal antibodies for κ and λ lgs chains (DAKO Corp.; 1:40,000). After rinsing, the endogenous peroxidase was blocked with 1% hydrogen peroxide. Parallel sections were incubated with irrelevant normal mouse or rabbit serum as a negative control.

Two main elements could be identified: spindle-shaped cells mixed with collagen deposits and clusters of inflammatory cells (mainly lymphocytes and plasma cells mixed with some neutrophils; Fig. 2). Inflammatory cells were predominant superficially, whereas fibrous areas and bone destruction were observed in depth (Figs. 3 and 4, A–C). Few blood vessels were identified in the center of the lesion. The peripheral area was not clearly delimited, and sinus epithelium presented with ulcerative lesions. Neither granulomas nor necrosis were seen. Reactions using periodic acid-Schiff and Ziehl-Neelsen stains were negative.

Immunohistochemical examination revealed an intensive positive cytoplasmic reaction of plasma cells for κ (Fig. 2).
5A) and λ (Fig. 5B) light chains. Among fibrous areas, spindle-shaped cells were strongly positive for antivimentin (Fig. 6A) and antiactin (Fig. 6B) and weakly positive for antidesmin (Fig. 7), whereas S100 protein (Fig. 8A) and CD1a (Fig. 8B) were negative.

The presence of TNFα was also assessed (1). Immunohistological techniques used New Gushine (red coloring). Epithelium as well as some of the stromal cells were stained in red (Fig. 9, A and B). Some of these appeared to be typical plasma cells (Fig. 9C).

**Diagnosis**

Frequent pituitary pathologies, such as adenomas and craniopharyngiomas, were easily ruled out on the basis of histological characteristics of the excised material. The inflammatory origin of the lesion was likely, but its further identification proved difficult. Its differential diagnosis shall be considered in the discussion. Taking into account the histological features, the marked response to corticosteroid treatment and the lack of evidence for any autoimmune disease, the diagnosis of an IP involving the sphenoid sinus, sellar area, optic chiasma, optic nerves, and meninges was made.

**Clinical course**

Treatment with oral corticosteroids was started and was maintained for 10 months. Six months after the end of treat-
ment, the patient remained free of clinical symptoms. Control MRI was normal (Fig. 10, A and B), and substitutive thyroid treatment could be discontinued. \( T_3, T_4, \) PRL, and dehydroepiandrosterone sulfate levels were normal. A TRH test showed a normal basal TSH (1.6 mIU/liter) with a normal increase in serum TSH concentrations (peak, 7.8 mIU/liter after 15 min). Eight months after the end of treatment, the patient presented with epilepsy. Brain MRI showed bilateral isolated frontal pachymeningitis. CSF showed the presence of inflammatory cells, and the erythrocyte sedimentation rate was increased. Corticosteroids were introduced for 2 months, and azathioprine (100 mg Imuran/d; Glaxo Wellcome Inc., Temple Hill, UK) was given as a long-term treatment. Control MRI showed no abnormalities.

Seven months after the withdrawal of corticosteroids, the patient became psychotic. Brain MRI demonstrated bilateral frontal pachymeningitis with extensive bilateral frontal lobe edema (Fig. 11). This second relapse was treated with a new course of corticosteroids and oral methotrexate (7.5 mg/wk). Azathioprine medication was replaced by oral methotrexate (7.5 mg/wk). Once again, corticosteroids produced a complete disappearance of the lesions after 4 wk (Fig. 12). Eighteen months later, the patient reported no specific complaints.

**Discussion**

Nonadenomatous lesions of the pituitary consist of a heterogeneous group of infectious, neoplastic, and immunological diseases (2). Sophisticated diagnostic procedures are often necessary to provide an accurate diagnosis, which, in the case of infectious or inflammatory etiology, may lead to a nonaggressive and efficient medical therapy. In our case the clinical and laboratory findings were not specific enough to allow a definite diagnosis. MRI only ruled out a possible pituitary adenoma. Considering the past medical history of the patient, central nervous system tuberculosis appeared to be a putative diagnosis (3), but additional tests excluded this possibility. Primary or metastatic tumors of nonpituitary origin were unlikely according to the lack of neoplastic cells in the biopsy material. Solitary plasmocytoma of the sphenoid sinus involving the pituitary fossa (4) has been reported, but this diagnosis was ruled out because plasma cells were polyclonal for the\( \kappa \) and \( \lambda \) light chains. Pituitary histiocytosis were also considered. Langerhans histiocytosis was described in the sellar area, but the selective adenohypophyseal insufficiency and the lack of cells expressing S100 protein or CD1a caused the rejection of this hypothesis (2).

Rosai-Dorfman disease is a rare histoproliferative disease affecting the lymph nodes. In approximately 43% of cases, extranodal sites may be involved (5). Central nervous system
manifestations of the disease are rare and most of the time are dura-based, resembling meningiomas (6). Yet, one case of an isolated intraparenchymal cerebral lesion without dural attachment (6) and another of pituitary tumor (7) have been reported. Microscopically, the lesion consists of proliferative histiocytes exhibiting the characteristic cytoplasmic staining against S100 (5). Although the clinical characteristics of the lesion observed in our patient could suggest a Rosai-Dorfman disease, the histological pattern and especially the lack of cells expressing S100 made this diagnosis unlikely.

Erdheim-Chester disease is a rare non-Langerhans cells histiocytosis affecting multiple organ systems (8). Symmetric sclerosis of the long bones is usually reported, but the central nervous system (8) and sinus (9) can also be affected. Among patients with central nervous system involvement, the most frequent manifestations are diabetes insipidus, cerebellar syndromes, orbital lesions, and extra-axial masses involving the dura (8). Histologically, Erdheim-Chester disease is characterized by plasma cell infiltration, mixed with lymphocytes, large histiocytes with foamy cytoplasm, and Touton giant cells. Histiocytes express CD68, occasionally S100, and never CD1a. This pattern was not observed in our patient.

Sarcoidosis is known to involve the central nervous system in about 10% of cases. Sellar localization is the most frequent one and may be complicated by aseptic meningitis and cranial nerve palsies (10). Yet, primary sinus localization is uncommon, and extensive cerebral lobes edema is not mentioned. The normal blood angiotensin-converting enzyme values were not in favor of this diagnosis. Sarcoidosis may show similar histological abnormalities in pituitary compared with lymph nodes (11), granulomas (which may be less delimited in pituitary), concentric fibrosis, and T cell infiltrate around granulomas. None of these elements was observed in the lesion. For these reasons, the diagnosis of sarcoidosis was rejected.

Wegener’s granulomatosis was not compatible with the histological abnormalities cited above, especially as no vasculitis was reported. Extensive cerebral lobe edema was also not suggestive of Wegener’s granulomatosis.

Necrotizing infundibulo-hypophysitis has been described in two patients (12) presenting with an unusual form of lymphocytic hypophysitis (Lh), as diabetes insipidus was the main endocrinological abnormality, and necrosis was highly present at histological analysis. Our patient did not present either of these characteristic elements. It should also be stressed that necrotizing infundibulo-hypophysitis as well as the usual form of Lh may extend to the hypothalamus or the chiasmatic area, but never involves the meninges or the cerebral lobes (12, 13).

The histological pattern of the biopsy specimen was not specific, but the demonstration of polyclonal plasma cells and lymphocytes surrounded by fibrous tissue rich of myofibroblastic spindle cells allowed us to consider the diagnosis of an Ip. The latter is mainly one of exclusion, as there are no pathognomonic features or specific tests to confirm it (14). This possibility was supported by the fact that the lesion appeared radiologically extensive and contrast enhancing (15), and it was remarkably responsive to corticosteroids (16).

The term Ip is not unanimously accepted by all pathologists. However, considering the lack of histological consensus, in this article we shall continue to use it. Ip are rare and were described for the first time in their orbital localization (17) and later in lungs (18), upper respiratory tracts (19), head and neck (14, 15), gastrointestinal (20) and urinary tracts (21), as well as central nervous system (22). The term Ip represents inflammatory lesions with a broad spectrum of histological features, varying from a predominance of inflammatory cells
mixed with some fibrous tissue to extensive fibrous lesions trapping some inflammatory cells (14). These two main aspects are respectively referred to as plasma cell granulomas and fibrous Ip (14, 15) and can be part of the multiple fibrosclerosis syndrome. The latter was described as any association of retroperitoneal fibrosis, mediastinal fibrosis, sclerosing cholangitis, Riedel’s thyroiditis, and fibrosing pseudotumor of the orbit (23). A possible association between these different entities and testicular fibrosis as well as fibrous proliferation of the sellar and parasellar area (24) was suggested. Hypertrophic intracranial pachymeningitis was also considered to be part of the syndrome of multiple fibrosclerosis (14, 25).

The etiology of Ip remains obscure. An autoimmune hypothesis is thought to be the most likely, supported by the association of Ip with type I diabetes mellitus, rheumatoid arthritis, and systemic lupus erythematosus and by the therapeutic response to immunosuppressive drugs (14).
The treatment of Ip is controversial. Many researchers agree that accessible lesions should be first treated surgically (14, 19). When surgery cannot be performed or is incomplete, corticosteroids may be administered, with a greater efficacy in pure inflammatory lesions than in fibrous lesions (26). In patients not responding to corticosteroid treatment or when surgery cannot be performed, radiotherapy can be helpful (19). Otherwise, immunosuppressive drugs [cyclosporine (27), methotrexate (28), azathioprine (14), or cyclophosphamide (29)] can be used. Despite all of these treatments, a relapse rate of 37% has been reported (30).

The regression of the lesion and the normalization of the endocrine tests, observed in our patient after corticosteroid treatment, do not support the role of pituitary cell destruction as a cause of pituitary insufficiency. Pituitary cell compression by the inflammatory process may account for pituitary insufficiency, although the involvement of local secretion of TNF
$$\alpha$$
in its pathogenesis can be hypothesized. Indeed, it has been demonstrated in rat pituitary cell cultures that TNF
$$\alpha$$
inhibits the hormonal response of the pituitary to hypothalamic releasing factors (31). We detected large amounts of this cytokine in the biopsy sample using a monoclonal antibody. These amounts were probably underestimated because of previous corticosteroid therapy.

Several cases of Ip of the sinuses have been reported: 11 cases of maxillary tumors (15, 32–36) and 4 sphenoid tumors (37, 38–40). Only 2 of these patients suffered from pituitary insufficiency (37, 38). To the best of our knowledge, only 1 case of Ip that associates involvement of the sphenoid sinus and the sellar area together with pituitary insufficiency and cranial nerve palsies has been reported (37). However, our case is unique with regard to the marked extension of the lesion and the dramatic response to medical treatment. We found no description in the literature of total disappearance of the radiological lesions among patients presenting with pituitary insufficiency even if they received combined corticosteroid treatment and radiotherapy (37, 38). The 2 patients presenting with pituitary insufficiency remained dependent on hormonal replacement therapy (37, 38). The excellent response to corticosteroid treatment observed in our patient could be due to a limited amount of fibrosis of the lesion.

Lh may be associated with clinical and laboratory features similar to those displayed by our patient. Lh appears radiologically to be an expansive contrast-enhancing lesion of the antehypophysis (13) and the endocrinological abnormalities usually include thyroid, adrenocortical, and/or gonadal insufficiency associated with mild hyperprolactinemia (13). Circulating antibodies to PRL have been identified in some patients. The histological pattern is one of a polyclonal lymphoplasmocytic infiltration, in some cases accompanied by fibrosis. Lh shows a striking female predilection and commonly affects women during pregnancy or the puerperium (13).

Taking into account these similarities, the diagnosis of Lh had to be considered in our case. However, it was ruled out because the lesion was too extensive. Lh is more localized and is almost always limited to the sellar area. Some researchers have reported extensions to the posterior lobe or infundibulum, to the suprasellar area, to the cavernous sinuses, or to the carotid arteries (41). However, more extensive lesions have not been described, and Lh is not associated with pachymeningitis. There is only one report (42) describing an idiopathic hypertrophic cranial pachymeningitis of the cavernous sinus mimicking hypophysitis. These researchers recognized many common features between Ip and Lh, but they considered than these two pathologies represent different entities. However, this distinction may not be so clear, and there are no conclusive histological criteria in the literature that allow the differential diagnosis of Ip and Lh.

An autoimmune etiology is strongly suspected in Ip as well as in Lh. The latter is associated in 30% of cases with other immunological syndromes, such as autoimmune thyroiditis, gastric atrophy, or retroperitoneal fibrosis. Corticosteroids have been less successful in treatment of Lh; however, they have been used with lower doses than in Ip (43).
We suggest that Lh and Ip could represent two different manifestations of the same entity, with the former corresponding to a localized Ip of the antehypophysis.

In conclusion, Ip should be considered in the differential diagnosis of nonadenomatous lesions of the sellar and parasellar area. The diagnosis of these lesions is difficult. Histological, histochemical, and immunohistochemical analysis are required for diagnosis and to exclude lesions of known etiology. The distinction between inflammatory and fibrous types of Ip is crucial, as corticosteroid treatment is efficient in most cases of inflammatory-type lesions, whereas it may be ineffective in cases of Ip that harbor extensive fibrosis.

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