Intrasellar mass with hypopituitarism as a manifestation of sarcoidosis

Case report

J. I. Lara Capellan, M.D., L. CueLLar Olmedo, M.D., J. Martinez Martin, M.D., Ma del Mar Marin, M.D., M. Garcia Villanueva, M.D., F. Marin Zarza, M.D., and H. de la Calle Blasco, M.D.

Departments of Endocrinology, Pathology, and Neurosurgery, Hospital Ramón y Cajal, Madrid, Spain

A 45-year-old woman was admitted suffering from headache, weight loss, asthenia, pedal edema, and amenorrhea. Morphological and functional studies revealed an intrasellar mass causing hypopituitarism without diabetes insipidus. Histological examination of the tissue obtained at transsphenoidal surgery was compatible with a diagnosis of sarcoidosis. The clinical and histological features, together with the presence of cutaneous anergy and ocular lesions, led to the diagnosis of sarcoidosis. The presentation of sarcoidosis in this patient was very unusual because it was not accompanied by characteristic intrathoracic findings or by diabetes insipidus.

Key Words: granuloma □ hypophysis □ hypopituitarism □ sarcoidosis □ intrasellar lesion

Sarcoidosis uncommonly affects the central nervous system (CNS), this involvement being recorded in only 3.5% to 5% of cases; in addition, hypopituitarism presenting as the only clinical manifestation of sarcoidosis is extremely unusual. Hypopituitarism is rarely reported without diabetes insipidus. In this paper, we describe a case of CNS sarcoidosis showing hypopituitarism without diabetes insipidus.

Case Report

This 45-year-old woman was referred with a 2-year history of headache, loss of weight, asthenia, pedal edema, intolerance to low temperatures, xeroderma, amenorrhea, and progressive loss of axillary and pubic hair.

Examination. Body temperature was 36.5°C, blood pressure was 130/70 mm Hg, and the heart rate was 76 beats/min. The patient weighed 62.2 kg and showed no cardiopulmonary abnormalities. Physical examination was otherwise unremarkable, except for the scarce axillary and pubic hair.

Blood analysis was normal, including a hemogram and serum glucose, creatinine, triglycerides, cholesterol, calcium, phosphorus, serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, total bilirubin, and alkaline phosphatase studies. Total protein level was 7.24 gm/dl (albumin 46.8%, alpha-1 5.9%, alpha-2 11.8%, beta 16.7%, and gamma 18.8%). Immunoglobulin (Ig)G content was 1300 mg/dl, IgA 358 mg/dl, and IgM 221 mg/dl. Urinalysis showed no abnormalities. A hormonal survey showed triiodothyronine (T3) 90 ng/dl, thyroxine (T4) 3.3 µg/dl, and thyroid-stimulating hormone (TSH) 1.2 µU/ml. Following administration of 400 µg of thyrotropin-releasing hormone (TRH) intravenously, the TSH level reached a peak of 2.7 µU/ml at 60 minutes. The basal prolactin content was 14 ng/ml and rose to 17 ng/ml 60 minutes after an intravenous bolus of TRH. Basal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels were both less than 1.5 mIU/ml, showing no response to an intravenous bolus of LH-releasing hormone (LH-RH). Basal growth hormone (GH) level was 2.8 ng/ml. At both 0900 and 2300 hours, cortisol and adrenocorticotropic hormone (ACTH) concentrations were less than 0.5 µg/dl and 25 pg/ml, respectively. Water metabolism was normal, assessed by a water-deprivation test with exogenous antidiuretic hormone administration.

After some months of substitution therapy with T4 (100 µg/day) and hydrocortisone (30 mg/day), the hor-
monal values were as follows: T₃ 107 ng/dl, T₄ 6.5 μg/dl, and GH 3.8 ng/ml (basal level) and 8.8 ng/ml (peak level 60 minutes after intravenous administration of 400 μg TRH). Serum glucose levels after a 75-gm oral glucose tolerance test (OGTT) at 0, 30, 60, 90, and 120 minutes were 75, 123, 135, 124, and 96 mg/dl, respectively. During the OGTT, GH values were 2.9, 2.6, 2.5, 2.3, and 1.6 ng/dl, respectively.

Chest x-ray films and tomography showed a normal cardiac silhouette with clear lungs and no mediastinal adenopathy. Electrocardiography was normal. Tomography of the sella turcica showed an enlarged sella with fine dorsal erosions. Computerized tomography (CT) of this region disclosed an enlarged pituitary gland showing contrast enhancement and a slight suprasellar extension. Ocular perimetry revealed a central scotoma on the left eye, but no other pathological findings.

Operation. A diagnosis of pituitary tumor associated with panhypopituitarism was made. The patient underwent transsphenoidal surgery; a hard white-yellowish mass, very close to the dura, was totally excised.

Pathological Findings. The tissue obtained during surgery was fixed with 10% formalin, embedded with paraffin, and sections 5 μm thick were made. This material was prepared with hematoxylin and eosin, Masson trichrome, methenamine-silver, Ziehl-Neelsen, periodic acid-Schiff, and Wilder stains. Immunohistochemical studies were also performed with peroxidase-antiperoxidase in order to detect pituitary hormones (GH, LH, prolactin, ACTH, FSH, and TSH). All histological sections were obtained from the adenohypophysis and most of the tissue contained basically epithelioid cells and showed a chronic inflammatory reaction with numerous small and mid-sized granulomas. Some sections presented isolated multinucleated Langhans giant cells without asteroid or Schaumann bodies (Fig. 1). A peripheral lymphocytic rim surrounded these granulomas which showed well-defined borders with reticulin fibers (Fig. 2). As much as 30% of all granulomas showed small central foci of fibrinoid necrosis. No tuberculous bacilli, fungi, or other pathogenic agents were observed with special histological techniques. Pituitary parenchyma between granulomas showed diffuse lymphoplasmocytic infiltration with isolated eosinophils. Immunoperoxidase techniques showed a great number of GH-positive cells in these regions; prolactin-positive cells were also present in a lesser amount, as well as TSH- and FSH-positive cells. No ACTH- or LH-positive cells were identified. The histological diagnosis was chronic granulomatous hypophysitis.

Ancillary Studies. Ancillary studies included sputum and urine screening for tuberculous bacilli and a survey of cellular immunity (Mantoux, Candida, streptokinase, and streptodornase testing); these studies showed no abnormalities. Lung spirometry and diffusion capacity tests were normal. No pathological lung uptake was seen with 67Ga studies. A transbronchial biopsy performed with a fiberoptic bronchoscope was normal. Rapid plasma reagent and fluorescein treponema antibody tests and serological tests for Brucella were also negative. Pituitary, thyroglobulin, microsomal, ovarian, and adrenal antibodies were negative. The ophthalmological examination revealed senile macular degeneration of the right eye and sheathing of the inferior temporal artery of the left. The lower part of the left optic papilla was blurred. This optic lesion showed hyperfluorescence after administration of angiofluorescein, consistent with the presence of an ocular granuloma (Fig. 3).

Postoperative Course. The patient was prescribed hormone substitution therapy with 100 μg/day T₄ and 30 mg/day hydrocortisone and discharged. After 6 months, her clinical status was stabilized and her headache, asthenia, somnolence, and low-temperature intolerance had disappeared. Blood pressure was 140/80
Hypopituitarism in sarcoidosis

FIG. 3. Ophthalmoscopic view showing retinal inflammation at the inferior temporal border of the left eye (fluorescein angiography).

mm Hg and body temperature was 37°C. Blood chemistry and urinalysis showed no abnormalities. The T₁ level was 84 ng/dl and the T₄ content 7.4 µg/dl; the basal TSH concentration was less than 0.89 µU/ml and failed to increase with TRH administration. The basal prolactin level was 5.6 ng/ml with a maximum response of 7.1 ng/ml 30 minutes after delivery of an intravenous bolus of TRH. Basal GH level was less than 0.6 ng/ml, with no response after an intravenous bolus of TRH. The gonadotrophin level failed to rise with LH-RH stimulation. The ocular inflammatory lesions at the optic nerve as well as other local inflammatory signs had disappeared.

Discussion

Granulomatous involvement of the hypothalamic-hypophyseal axis is very rare and may be an isolated finding or associated with systemic disorders such as sarcoidosis, tuberculosis, syphilis, or mycosis. Although clinical data are useful in establishing the diagnosis, morphological features combined with special histological techniques help to define the pathogenesis of the process. In our patient, the pituitary granulomas did not show caseous necrosis nor did they contain organisms. These findings, together with the clinical and laboratory data, led us to consider two diagnostic possibilities: giant-cell granuloma and sarcoidosis. Other diagnoses such as tuberculosis, syphilis, and mycosis were considered and excluded.

Giant-Cell Granuloma

The etiology of pituitary giant-cell granulomas is unknown. This process manifests as a nonsecreting tumor presenting with hypopituitarism and only rarely with diabetes insipidus. There are no specific morphological features associated with giant-cell granulomas and the possibility of a systemic disorder must always be considered. Nonetheless, some histological findings are reported more frequently in giant-cell granulomas, including the absence of caseous necrosis, ill-defined granuloma borders, and absence of a peripheral reticular fiber crown. These granulomas contain a variable number of epithelioid cells, lymphocytes, and giant cells, resembling Langhans or foreign-body cells. Old granulomas tend to become fibrotic, with very few multinucleated cells. For diagnostic purposes, it is essential to exclude granulomas in other tissues, although some authors have reported the association between pituitary giant-cell granulomas and granulomas in the adrenal glands and liver.

Sarcoidosis

Sarcoidosis is a granulomatous disease of unknown origin, characterized by bilateral hilar lymphadenopathy, lung infiltrates, and lesions of the skin, eye, and other organs, including the CNS. The CNS is affected in 3.5% to 5% of all patients with sarcoidosis. Histologically, epithelioid granulomas with a small number of giant multinucleated cells are seen; occasional asteroid and Schaumann cells are also present. Sarcoidotic granulomas are small and show a rim of reticulin and collagen fibers with incipient hyalinization. Caseous necrosis is absent, although occasionally small central foci of fibrinoid necrosis are observed.

Intrathoracic sarcoidosis is the most frequent clinical presentation (88% of cases) while isolated extrathoracic disease is quite rare (12% of cases). Although granulomatous basal meningitis is the most common neurological manifestation, hypothalamic-hypophyseal disorders may also be present. In more than 90% of all cases, this dysfunction manifests clinically as diabetes insipidus alone or with partial/total adenopituitary failure. There are very few cases of hypopituitarism without diabetes insipidus. Traditionally, hypopituitarism has been attributed to granulomatous glandular involvement. Recently, however, it has been shown that the hormonal deficit is due to hypothalamic dysfunction. On roentgenological studies the sella turcica is only very rarely enlarged, and CT occasionally shows an intra- or suprasellar mass.

Sarcoidosis affects the eye in approximately 40% of all cases, most often the anterior segment (84.7%). The posterior segment is affected more rarely (25.3%). Their manifestations consist of diffuse vitreitis, hemorrhages, neovascularization, papilledema, optic neuritis, periphlebitis, and focal granulomas. Our patient exhibited optic neuritis and an ocular granuloma.

Differential Diagnosis

Some other granulomatous diseases which can affect the pituitary gland, such as Wegener's granulomato-
pophysis should be included under the differential diagnosis of intracranial sarcoidosis. It is difficult to explain, it might be related to the effect of postoperative normalization of the GH response is compatible with the cutaneous anergy, and the presence of neoplastic agents, the cutaneous anergy, and the presence of compatible ocular lesions. We believe it is necessary to exclude sarcoidosis in any chronic disease involving granulomatous hypophysitis, searching not only for intrathoracic disease but also for extrathoracic signs. Otherwise, an erroneous diagnosis of pituitary giant-cell granuloma may be formulated.

Finally, we would like to comment on the paradoxical GH response to TRH in our patient. Although the postoperative normalization of the GH response is difficult to explain, it might be related to the effect of the local inflammatory process on the somatotrophic cells. Thus, chronic granulomatous disease of the hypophysis should be included under the differential diagnosis of pathological states associated with a paradoxical GH response to TRH.

References

Manuscript received August 10, 1989. Accepted in final form January 24, 1990.