Lymphoid Hypophysitis in a Patient With Lymphoid Thyroiditis, Lymphoid Adrenalitis, and Idiopathic Retroperitoneal Fibrosis

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- We describe the autopsy findings in a 24-year-old woman with a clinical picture of pituitary and adrenal insufficiency which had its onset shortly after a normal pregnancy and delivery of a normal infant, two years before the mother’s death. There were heavy lymphocytic infiltrations of the adeno-hypophysis, thyroid, and adrenals as well as diffuse retroperitoneal fibrosis with numerous peri-vascular lymphocytic infiltrates. It is concluded that lymphoid hypophysitis probably represents the hypophysial counterpart of other endocrine autoimmune disorders and that immune mechanisms may also play a role in the pathogenesis of the so-called idiopathic retroperitoneal fibrosis.


Lymphoid hypophysitis is a rare condition that appears to be closely related to pregnancy and was found to be associated with “other” autoimmune disorders in four of the 12 cases reported, to our knowledge, in the literature.1-3

Idiopathic retroperitoneal fibrosis is, on the other hand, an uncommon disease of questionable autoimmune pathogenesis that can occur either alone or in association with several established immunopathologic conditions.4-6

The aim of this case report is to describe the clinicopathologic findings of a unique association of lymphoid hypophysitis with lymphoid thyroiditis, lymphoid adrenalitis, and idiopathic retroperitoneal fibrosis.

REPORT OF A CASE

A 24-year-old woman, gravida 1, para 1, was admitted to the Emergency Department of Hospital São João, Porto, Portugal, in June 1980 with hypoglycemic coma. She recovered after treatment and was then transferred to the Department of Medicine.

Two years before admission and after an uneventful pregnancy she had an eutopic delivery. Some days later she began experiencing asthenia, anorexia, weight loss, and sporadic biparietal headaches. Following delivery she developed agalactia and amenorrhea that continued until her death. She also complained of hair loss and experienced two episodes of unconsciousness which caused her admission in “peripheral” hospitals for short periods with clinical improvement but without diagnosis.

On admission the physical examination showed a pale and very badly nourished patient (40 kg) with normal hairy distribution. Her blood pressure was 80/75 mm Hg; pulse rate, 60 beats per minute and regular; temperature, 36.5 °C; funduscopia, normal; and liver and spleen, within normal limits. There were no adenopathies and the thyroid gland was not palpable. The neurologic examination did not disclose any abnormalities and an electrocardiogram showed low-voltage complexes. The results of laboratory studies showed persistent hypoglycemia, 40 to 86 mg/dL; normocytic normochromic anemia with a hemoglobin level of 8.8 to 11.0 g/dL; and an elevated erythrocyte sedimentation rate of 55 to 60 mm/hr. The study of complement revealed the following: total hemolytic activity, 49 for CH50 units (normal, 33 to 50 for CH50 units); C3, 72 mg/dL (normal, 80 to 140 mg/dL); and C4, 56 mg/dL (normal, 20 to 50 mg/dL). The immunoelectrophoresis of the serum showed an increased quantity of IgG and slightly increased IgM. Coombs’ test was negative. The search for antinuclear antibodies and lupus erythematosus cells yielded negative results.

Thyroid studies showed the following: serum thyroxine, 9.5 μg/100 mL (normal, 4.5 to 12 μg/100 mL); and serum triiodothyronine, 50 ng/100 mL (normal, 50 to 200 ng/100 mL). The study of adrenal metabolites in urine revealed the following: 17-ketosteroids, 1.0 mg/24 hours (normal, 10 ± 3 mg/24 hours); Silber-Porter chromogens, 1.0 mg/24 hours (normal, 4.1 ± 1.8 mg/24 hours); total 17-hydroxysteroids, 1.0 mg/24 hours (normal, 8 to 15 mg/24 hours); and a urinary creatinine of 700 mg/24 hours. After stimulation with adrenocorticotropic hormone the 24-hour urine...
contained the following: 17-ketosteroids, 6.9 mg; Silber-Porter chromogens, 5.0 mg; and total 17-hydroxysteroids, 11 mg. The results of other laboratory examinations were normal. Skull roentgenograms showed a normal pituitary sella.

During hospitalization the patient had several episodes of obturation and precoma from which she recovered with the administration of intravenous dextrose. On the 58th hospital day the patient became comatose with signs of decerebration and died a few hours later. The post-mortem study was requested with the tentative clinical diagnosis of “pituitary and adrenal insufficiency.”

PATHOLOGIC FINDINGS

The autopsy was performed 42 hours after death and revealed an edematous brain (1,430 g) with moderate tonsillar hernias. The size and shape of the hypophysis was normal. The thyroid gland was small (8 g), whitish, and hard. The heart was small (160 g) and there was some blood-stained fluid (100 mL) in the pericardial sac. The lungs were edematous (630 g and 690 g, respectively) and there were bilateral pleural effusions (200 mL and 100 mL on the right and left sides, respectively). There was a fibrotic retroperitoneal mass about 4 cm in thickness that involved the iliac vessels of both sides as well as the left ureter. The left kidney was hydronephrotic and atrophic (45 g) while the right kidney was voluminous (235 g) and had a normal shape. The adrenals were very small and had extremely thin cortices. No abnormalities were found in the digestive tract, liver, pancreas, spleen, or ovaries.

The main histologic lesions concerned the endocrine organs and the retroperitoneal fibrotic mass. The adenohypophysis was edematous and fibrotic and had scanty parenchymal cells and numerous lymphocytes that were dispersed throughout the gland and formed a few germinal centers (Fig 1, left and right). The thyroid gland showed a marked fibrotic lobulation and abundant lymphocytic infiltrates which frequently formed germinal centers; the thyroid follicles were strikingly reduced in number and size but there was no oncocytic transformation of the epithelial cells (Fig 2, left and right). In the adrenals there was an almost total disappearance of the cortical cells with a concurrent massive lymphocytic infiltration (Fig 3).

The retroperitoneal fibrotic tissue was mainly composed of dense, sometimes hyaline, collagen and contained foci of lymphocytes that were generally clustered around vessels and rarely formed germinal centers (Fig 4). The fibrotic tissue intimately enveloped the adventitia of the iliac vessels as well as the left ureter and the sheath of some nerves but did not invade them.

Some foci of perivenular lymphocytes were also seen in subepicardial areas of the myocardium, in salivary glands, and in the portal spaces of the liver. The ovaries were normal and had a few follicular cysts. The mammary glands were atrophic.

The electron microscopic study of...
Summary of the Findings in Patients With Lymphoid Hypophysitis

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Kidney fragments did not disclose the presence of any electron-dense deposits near glomerular basal lamina.

**COMMENT**

The present case has remarkable similarities with most of the 12 cases of lymphoid hypophysitis reported so far in the literature.

All the patients were women and in nine of them there was, like in our case, a close temporal relationship between the onset of symptoms and pregnancy (Table).

The histologic examination of the pituitary disclosed a similar picture in every case which has been referred to as anterior hypophysitis, lymphomatous hypophysitis, or lymphoid hypophysitis and is completely different from those seen in the healed postpartum pituitary necrosis or in the giant cell granuloma of the pituitary.

The hypophysitis was accompanied in four of the cases by other lymphocytic lesions (Table). Lymphoid infiltration of the hypophysitis also occurs in some cases of the so-called Schmidt's syndrome. These findings have been put forward as arguments favoring an "autoimmune" pathogenesis for lymphoid hypophysitis.

This assumption is supported by the association in the present case of lymphoid hypophysitis with lymphoid thyroiditis, lymphoid adenitis, and diffuse retroperitoneal fibrosis which was considered as "idiopathic" in the absence of any evidence pointing to a causative agent.

The etiopathogenesis of idiopathic retroperitoneal fibrosis is still a matter of controversy, but most authors tend to regard this disorder as a manifestation of a systemic autoimmune disease. In fact, idiopathic retroperitoneal fibrosis has been reportedly associated with idiopathic fibrosis of several organs including hypophysitis and thyroid, and with lesions of presumable immunologic etiopathogenesis such as systemic vasculitis, "collagen diseases," and glomerulonephritis with intra-membranous electron-dense deposits.

These findings, together with the presence of abundant lymphocytic perivascular infiltrates in the fibrotic tissue and the evidence obtained in similar lesions of the mediastinum suggest that an immunopathologic process may also be involved in the pathogenesis of the so-called idiopathic fibrosis.

The fact that idiopathic retroperitoneal fibrosis is generally found in middle-aged men whereas lymphoid hypophysitis is typically a disease of young women also contributes to increase the unlikelihood of their fortuitous coexistence in our case.

Little is known about the etiology of lymphoid hypophysitis. There is, nevertheless, enough evidence to suggest that its striking prevalence in pregnant and puerperal women is probably related to the peculiar immunologic disturbance of such periods.

The observation of a more severe experimentally induced lymphoid hypophysitis in postpartum rats than in the control group also supports the finding of a decreased adenohypophyseal function in 25% of the women who had pituitary autoantibodies in the postpartum period compared with only 4% of those with no demonstra-
ble antibodies provide additional evidence linking the hypophysitis to the aforementioned immunologic “disturbance” of pregnancy.

Such an association is further reinforced by the finding of high titers of prolactin cell antibodies in patients with hypopituitarism or hypothyroidism as well as by the demonstration of circulating antipituitary antibodies in the serum of one of the patients with lymphoid hypophysitis.

It is known that there is an increased risk of exacerbation of autoimmune disorders in the postpartum period, and both Ginsberg and Walfish and Amino et al described postpartum thyroiditis with more or less obvious signs of hyperfunction.

It is also known that in most cases of Hashimoto’s thyroiditis there are enlarged glands that may initially present as hyperfunctioning lesions. This appears to be due to the stimulator effect played by some of the “causative” antibodies.

A similar phenomenon may occur in lymphoid hypophysitis. This would explain the clinicopathologic features of those cases that were misdiagnosed either as nonfunctioning tumors or as prolactin producing adenomas as well as the fibrotic, end-stage appearance of the hypophysitis of the cases diagnosed at the time of autopsy.

In conclusion, we concur with those authors who consider that lymphoid hypophysitis associated with hypophysitis should be regarded as a distinct clinicopathologic entity that can present either as an atrophic lesion with hypopituitarism or as an exophytic lesion mimicking a pituitary tumor. There is also enough evidence to support the concept that lymphoid hypophysitis represents the hypophyseal-seal component of other autoimmune disorders, although one still cannot yet define the exact mechanism that links these disorders together as well as those which explain their relationship to the so-called immunologic “disturbance” of pregnancy.

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References