Primary antiphospholipid syndrome and panhypopituitarism: a unique presentation

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ABSTRACT

Lymphocytic hypophysitis (LH) has been described previously in systemic lupus erythematosus (1.3%), Sjögren’s syndrome (0.8%). Lymphocytic hypophysitis (LH) is rarely associated with rheumatic diseases, although three cases of pituitary disease associated with antiphospholipid syndrome (APS) have been described. Here, we report a possible association between APS and LH for the first time. A 34-yr-old woman with primary APS presented with polyuria, polydipsia, hypernatremia and impaired vision. Her hormone profile was compatible with panhypopituitarism, and sellar magnetic resonance imaging (MRI) depicted a normal pituitary gland with a thickened and displaced stalk and infundibulum portion. Hormone replacement was started, and the patient experienced a good clinical evolution.

Keywords: Panhypopituitarism; Lymphocytic hypophysitis; Hypophysitis; Antiphospholipid syndrome

INTRODUCTION

Antiphospholipid syndrome (APS), or Hughes’ syndrome, was first described twenty-five years ago in patients with systemic lupus erythematosus (SLE) who presented recurrent vascular thrombosis and obstetric morbidities in association with antiphospholipid antibodies. Subsequently, the description of similar clinical findings in patients without an underlying autoimmune disease has led to the consideration of primary antiphospholipid syndrome (PAPS) as a new clinical pathology.

APS is now considered a systemic disease that, in addition to the classic episodes of deep venous thrombosis and stroke, may affect almost all body organs and systems. Involvement of the heart, placenta, blood, kidneys and endocrine system is increasingly being described.

In recent years, endocrine complications in patients with APS or antiphospholipid antibodies have been recognized. The adrenal glands, thyroid, parathyroid, ovaries, testes and pituitary are involved in this syndrome. In the literature, only three patients with pituitary dysfunction and primary APS have been described, and none of these patients had been diagnosed with suspected lymphocytic hypophysitis (LH).

Therefore, the objective of this study was to describe one patient with PAPS that was associated with panhypopituitarism, which was probably due to LH.

CASE REPORT

In 1994, a 34-year-old Caucasian woman presented with erythematosus nodules compatible with erythema nodoso in her lower limbs that were associated with paresthesia and urinary and fecal retention. Diagnosis was compatible with transverse myelitis. Serologies for infectious disease, antinuclear, anti-dsDNA, anti-Sm, anti-Ro/SS-A, anti-La/SS-B and anti-U1RNP antibodies were negative. The treatment of choice was prednisone 60 mg/day for 2 months, which was then slowly decreased until stopped. The patient recovered all neurological functions except for urinary retention. In 1998, she had episodes of fever, headache, polyuria, polydipsia, hypernatremia, temporal hemianopsia and secondary amenorrhea. Hormonal evaluation was con-
consistent with diabetes insipidus (serum Na 161 mEq/L and serum Osm 322 mOsm/kg H₂O) and panhypopituitarism: undetectable serum estradiol and gonadotrophins; serum cortisol 1.9 mcg/dL (normal value: 7-31 mcg/dL); ACTH < 17 pg/mL (normal value: <60 pg/mL); free T4 0.5 ng/dL (normal value: 1.5-3.5 ng/dL); TSH 0.43 mcU/mL (normal value: 0.5-4.2 mcU/mL); PRL 13.7 ng/mL (normal value: 2.5-14.5 ng/mL); GH 0.1 ng/mL (normal value: <5.0 ng/mL); and IGF-I 93 ng/mL (normal value: 84-277 ng/mL).

MRI showed a normal pituitary gland with a thickened and displaced stalk and infundibulum (Figure 1). Serologies for HIV, syphilis, hepatitis B and C and toxoplasmosis were negative. Thorax x-ray, tuberculin test and calcium levels were also negative or normal. Screening for tumors was negative. LH was suspected due to the hormonal deficiency that was disproportionate to the pituitary lesion and the MRI findings in a young female with a previous autoimmune disease. The patient was treated with an immunosuppressive dose of prednisone (20 mg/day that was then tapered to 5 mg/day) for eight years with no recovery of pituitary function despite the fact that stalk resumed its normal appearance Figure 2). Her weight was 65 kg. The patient was on levothyroxine 100 mcg/day, estrogen 0.625 mg/day, progesterone 10 mg/day and intranasal of artificial arginine-vasopressin hormone (DDAVP), which improved her symptoms despite persistent amenorrhea.

In 2001, the patient presented with respiratory insufficiency due to pulmonary thromboembolism and cerebral venous thrombosis of the superior sagittal si-
nus. The investigation of thrombophilia revealed the presence of lupus anticoagulant on several occasions with 12 weeks apart. IgG and IgM anticardiolipin, antinuclear, anti-dsDNA, anti-Sm, anti-Ro/SS-A, anti-La/SS-B, anti-ribosomal P and anti-U1RNP antibodies were negative and systemic lupus diagnosis was then excluded. She denied any previous pregnancy or abortions. A diagnosis of PAPS was made (pulmonary thromboembolism and cerebral venous thrombosis plus positive lupus anticoagulant in two occasions), and anticoagulation with heparin was started, which was followed by an oral anticoagulant (dicumarol). The patient’s INR remained between 2 and 3, which is the target for venous thrombotic events. Transverse myelitis was likely a part of the APS. The patient is currently asymptomatic and has been without further complications under hormone therapy replacement and anticoagulation treatments.

DISCUSSION

This study reports, for the first time, a patient with PAPS and pituitary dysfunction (panhypopituitarism) that was probably due to lymphocytic hypophysitis.

Two important causes of hypopituitarism are prevalent in young women: Sheehan’s Syndrome and lymphocytic hypophysitis. Sheehan’s Syndrome is characterized by postpartum hypopituitarism that is secondary to pituitary necrosis after hypovolemic shock during delivery or the puerperal period. Pituitary enlargement during pregnancy increases the probability of necrosis due to vascular insufficiency mainly in patients with coagulopathy. Autoimmunity is another factor for the predisposition to ischemic necrosis. The signs and symptoms of hypopituitarism can appear during the puerperal period until thirteen years after delivery, and hormonal deficiencies can be multiple or isolated but are frequently associated with a severe growth hormone (GH) deficiency. Diabetes insipidus appears in 5% of patients with hypopituitarism. MRI shows partially empty sella. Approximately 40 years ago, the prevalence of Sheehan’s syndrome was 100-200 cases per 1,000,000 women. However, there has been a remarkable reduction in its frequency due to improved obstetric care.

Lymphocytic hypophysitis is also a rare entity with an estimated incidence of 1 per 9,000,000 cases. This disease is characterized by pituitary and/or stalk autoimmune inflammation and hypopituitarism. A definitive diagnosis depends on a pituitary histopathological analysis. Definite diagnosis can only be made through surgery or biopsy. Clinical suspicions should be raised if hypopituitarism presents with a rapid evolution of primarily a deficiency in corticotrophin that is disassociated from a pituitary gland lesion in a young female patient during the puerperal period. Symptoms of a mass, such as headache and visual loss, are very common. Diabetes insipidus appears if the posterior pituitary or stalk are involved. Sellar MRI commonly depicts a homogeneous gadolinium enhancement of the pituitary. Other autoimmune diseases can be associated with LH in 20% of patients, primarily patients with Hashimoto’s thyroiditis.

In pregnancy, an increase of approximately 30 to 100% in pituitary volume, which is caused by lactotroph hyperplasia that is secondary to estrogen stimulation, compresses the superior pituitary artery. This compression results in some ischemia during the puerperal period, which causes Sheehan’s Syndrome. In addition, the pituitary hyperplasia could be a secondary factor of LH because of the increased exposure to pituitary antigens.

In the three cases of hypopituitarism that have been described in patients with PAPS, two cases were related to thrombotic events, and one case was related to Sheehan’s Syndrome. The first case described a 62-year-old female patient with SLE who developed panhypopituitarism after a cerebral vascular event. A 48-year-old female patient with multiple thromboses secondary to PAPS was described in the second case. This patient developed weakness and obesity. Hormonal evaluation showed multiple deficiencies in the corticotrophic, thyrotrophic and gonadotrophic axes and a probable deficiency in the somatotrophic axis with normal serum prolactin. Sellar MRI was normal. The authors concluded that PAPS could have been the cause of hypopituitarism in this patient. In the third case, a 33-year-old female patient developed ACTH and prolactin deficiencies during the postpartum period. Six years later, she presented with infection and hypoglycemia. Laboratory evaluations showed thrombocytopenia secondary to PAPS. Hormonal evaluation revealed corticotrophic, gonadotrophic, tireotropic and lactotrophic deficiencies. The serum anti-pituitary antibody was negative. MRI showed a partial empty sellar region. Based on the diagnosis of postpartum hypopituitarism, the most probable etiology was Sheehan’s Syndrome. However, LH could have been associated with PAPS as it is common the associa-
tion of one autoimmune disease with another one. In this case report, the most probable cause of hypopituitarism was LH based on clinical characteristics, sellar MRI findings and the response to high doses of glucocorticoids. The serum anti-pituitary antibody assay was not available. A definitive diagnosis of lymphocytic hypophysitis depends on histopathological analysis. However, presumptive diagnosis can be based on some characteristics found in this particular case: hypopituitarism disproportionate to the grade of pituitary lesion, thickened stalk and empty sella during the follow-up. Differential diagnosis for thickened stalk is: germinoma, inflammatory diseases (histiocitose X, Wegner’s granulomatosis) and metastasis, usually do not disappear without a specific treatment.

In conclusion, this report is the first description of an association of PAPS with a presupposed LH.

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