

Autoimmune polyglandular syndrome in a woman of 51 years

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Abstract. – **INTRODUCTION:** Autoimmune polyglandular syndromes (APS) are constellations of symptoms and signs of multiple glandular insufficiencies. We report a rare case of type III APS in a female patient.

CASE REPORT: A 51-year-old woman was treated with radiotherapy because of thymus hyperplasia when she was two years old; she was diagnosed with celiac disease and autoimmune hypothyroidism at 41 years old and with sicca syndrome and myasthenia gravis seronegative a few years later.

CONCLUSIONS: Our patient demonstrates a previous constellation of diseases of APS, which may be a random association but may also indicate a common immunological and genetic disturbance. The APS is an expression of a system impairment of immune tolerance to autoreactive clones, and this is necessary because the phenomena can become aggressive and expressed clinically. We suppose that the development of thymic hyperplasia or its radiotherapy in childhood may have compromise the patient's immune system.

Key Words:

Autoimmune polyglandular syndromes, Myasthenia gravis, Connective tissue disease, Fibromyalgia.

Introduction

APS is characterized by multiple endocrine gland insufficiencies that are based on autoimmune mechanisms¹. There are three main subtypes: APS type 1 (also called APECED) is characterized by autoimmune polyendocrinopathy, candidiasis, and ectodermal dystrophy; APS type 2 (Carpenter syndrome) is the coexistence of adrenal insufficiency with autoimmune thyroid disease, or type 1 diabetes mellitus; APS type 3 autoimmune thyroiditis occurs with another organ-specific autoimmune disease, type 1 diabetes mellitus, pernicious anemia, vitiligo, alopecia, celiac disease, malabsorption, sarcoidosis, Sjogren's syndrome, rheumatoid arthritis, myasthenia gravis, systemic lupus erythematosus, but not with autoimmune adrenalitis². In this article, we report a

case of a young woman with hypertension associated with several autoimmune diseases.

Case

A 51-year-old woman came to our Department because of cephalalgia suggesting arterial hypertension (blood pressure, 150/100 mmHg). When she was 2 years old, she was treated with radiotherapy because of thymus hyperplasia³. Since youth, she suffered from muscle weakness, which was exacerbated with dysphagia and rhinolalia in adulthood. At 38 years old, she underwent surgical excision of the parathyroid adenoma with the presence of thymic cells and evidenced ectopic mediastinal parathyroid. Three years later, she was diagnosed with celiac disease (tTgAb and EMA negative) and autoimmune hypothyroidism⁴ already manifest in her sister and mother and occasionally diagnosed with hepatitis HCV+ with cryoglobulinemia after an accident and thrombophilia with positive V factor Leiden for deep vein thrombosis and pulmonary thromboembolism. At 45 years old, she was diagnosed with sicca syndrome with xerophthalmia and xerostomia (parotid biopsy and Ena immunoblot negative). It was hypothesized to be mixed connective tissue disease with capillaroscopy evoking non specific autoimmune disease (Figure 1). (anti-U1RNOP negative and presence of Raynaud's phenomenon, asthenia, and pulmonary fibrosis) At 46 years old, she was diagnosed with dermatitis (orthokeratotic hyperkeratosis to skin biopsy) (Figure 2) and fibrosis of the papillary muscles evidenced on cardiac echo with color Doppler; one year later, she was diagnosed with myasthenia gravis (MG) seronegative (ab-AchR negative and nonspecific myopathic on electromyography) treated with Mestinon 60 mg with resolution of bulbar symptoms but unresolved asthenia. At 50 years old, crisis of sweating and palpitations in the movements of antireflexion, following postural orthostatic tachycardia syndrome, were diagnosed with a positive tilt test.



Figure 1. Capillaroscopy evoking nonspecific autoimmune disease.

Discussion

Among the various diagnostic hypotheses, we considered secondary hypertension, multiple endocrine neoplasia (MEN) type 1, and APS⁵. With regard to secondary hypertension, we excluded renal artery stenosis with Doppler ultrasound of the renal arteries; pheochromocytoma was excluded because of the negative result of the assay of urinary catecholamines and abdominal CT scan. Values of plasma aldosterone, renin, and cortisol were normal, and they allowed us to exclude hyperaldosteronism and Cushing's syndrome. As the patient had presented a parathyroid adenoma, we considered the possibility of the presence of MEN type 1⁶: RMN brain, abdominal CT, pituitary and pancreatic hormones in the normal range excluding pituitary adenoma, and endocrine pancreatic tumor. We suppose that the development of thymic hyperplasia or its radiotherapy in childhood may have compromise the patient's immune system⁷. The patient can be placed in a framework of autoimmune polyendocrine syndrome: in particular, in the APS type 3, autoimmune hypothyroidism is associated with various autoimmune diseases such as celiac disease,

myasthenia gravis, and Sjogren's syndrome. The exact prevalence of APS is unknown; it has been calculated that 3.5% to 4% of the total population



Figure 2. Skin biopsy highlights ta orthokeratotic hyperkeratosis, spongiosis and focal lymphocytic exocytosis.

has a complete or incomplete APS type 3. Considering that autoimmune thyroiditis is most frequently seen in patients with other autoimmune diseases (present in 10%-30% of patients), it is easy to understand why APS3 is the most important and frequent among those described to date⁸. Our patient demonstrates a previous constellation of diseases of APS 3, which may be a random association but may also indicate a common immunological and/or genetic disturbance. Epidemiologic studies have shown that genetic factors are involved in host susceptibility to autoimmune disease⁹. Indeed, the concordance rate of a particular autoimmune disease is higher in monozygotic twins in comparison to dizygotic twins. Moreover, this incidence is higher in organ-specific autoimmune disorders in comparison to non-organ-specific disorders. In organ-specific autoimmune diseases, the autoantibodies are specifically directed against antigens localized in a particular organ (Hashimoto's syndrome). In contrast, the non-organ-specific autoimmune disorders (systemic lupus erythematosus, rheumatoid arthritis, and scleroderma)¹⁰ are characterized by the presence of autoantibodies directed against ubiquitous antigens (nonspecific to a particular organ). This results in the involvement of several organs and is often characterized by the presence of specific circulating immune complexes.

The pathogenesis of autoimmune endocrine diseases involves a HLA-linked genetic susceptibility and a probable environment-induced initiating event, leading to an abnormal immune response in which both humoral and cellular mechanisms are involved. The APS is an expression of a system impairment of immune tolerance to autoreactive clones, and this is necessary because the phenomena can become aggressive and expressed clinically. Several hypotheses have been proposed to explain the mechanism of tolerance and organ-specific autoimmunity disorders; the activation of autoreactive clones CD4+ CD25+, which escaped to the central thymic tolerance and to anergia, is normally prevented by inhibitory activity waged against them by CD8+ T cells; the imbalance of the functional relationship between CD4+ and CD8+ and the alteration of regulatory T cells allows clonal expansion of autoreactive T lymphocytes¹¹.

Familiarity is an essential trait and does not refer to specific disease but to the whole complex of autoimmune diseases that can be repertate. Immunogenetic analysis has indicated haplotypes HLA DQA1 * 0301 and 0303, DQB1 * 0401 and 0405 as markers of susceptibility¹².

Conclusions

The development of thymic hyperplasia or its radiotherapy in childhood may have compromised the patient's immune system. Considering the progressive multiorgan involvement, it is appropriate to continue to follow the patient to evaluate a possible progression of the clinical case and a possible development of other systemic autoimmune diseases such as rheumatoid arthritis, scleroderma, and systemic lupus erythematosus.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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