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CASE REPORT

An Endocrine Puzzle: A Case Report of Autoimmune Polyglandular Syndrome Type 2

Um Quebra-Cabeça Endócrino: Relato de Caso de Síndrome Poliglandular Autoimune Tipo 2

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ABSTRACT: Autoimmune polyglandular syndrome type 2 is an autoimmune endocrine condition characterized by Addison's disease (autoimmune primary adrenal insufficiency) associated with autoimmune thyroid disease and/or type 1 diabetes. Additionally, it may be associated with other autoimmune conditions. It presents a diagnostic challenge, leads to increased morbidity and mortality, and reduces quality of life. We present the clinical case of a 31-year-old man diagnosed with type 1 diabetes and vitiligo since childhood. During outpatient follow-up, around the age of 30, he developed clinical and laboratory criteria for Addison's disease and seronegative hypothyroidism. The case highlights the need for screening for autoantibodies in patients with autoimmune endocrinopathies, due to the increased risk of new autoimmune conditions.

KEYWORDS: Autoimmune polyglandular syndrome type 2; Addison Disease; Diabetes Mellitus, Type 1; Thyroiditis

RESUMO: A síndrome poliglandular autoimune tipo 2 é uma condição endócrina autoimune caracterizada por Doença de Addison (insuficiência adrenal primária autoimune) associada a doença tireoidiana autoimune e/ou diabetes tipo 1. Além disso, pode estar associada a outras condições autoimunes. Apresenta um desafio diagnóstico, gera aumento da morbimortalidade e redução da qualidade de vida. Apresentamos o caso clínico de um homem de 31 anos com diagnóstico de diabetes tipo 1 e vitiligo desde a infância. Durante o seguimento ambulatorial, por volta dos 30 anos, evoluiu com critérios clínicos e laboratoriais de doença de Addison e hipotireoidismo soronegativo. O caso reforça a necessidade de rastreamento de autoanticorpos em pacientes com endocrinopatias autoimunes, devido ao risco aumentado de novas condições autoimunes.

DESCRITORES: Síndrome Poliglandular Autoimune Tipo II; Doença de Addison; Diabetes Mellitus Tipo I; Tireoidite

INTRODUCTION

Autoimmune Polyglandular Syndrome Type 2 (APS Type 2) is an autoimmune endocrine disorder characterized by the dysfunction of multiple glands (adrenal, thyroid, pancreas). First described in 1926, its understanding has evolved to recognize it as a complex, polygenic condition resulting from a loss of immunological tolerance.[1–3] Although rare, with an estimated prevalence between 1:10,000 and 1:20,000 in the general population, its importance lies in the risk of potentially fatal crises, especially those related to adrenal insufficiency.[2,4,5]

APS Type 2 requires the obligatory presence of Addison's disease (autoimmune primary adrenal insufficiency), associated with autoimmune thyroid disease (such as Hashimoto's Thyroiditis or Graves' disease), which is present in 69-82% of patients, and/or type 1 diabetes mellitus (T1DM), present in 30-52% of cases.[1,3,4] The most common combination is Addison's disease with autoimmune thyroid disease, which is known as Schmidt's Syndrome.[1] The clinical presentation is usually variable, with an insidious onset and slow progression. In addition to the main endocrinopathies, the syndrome can be associated with other autoimmune conditions, such as hyperparathyroidism, vitiligo, autoimmune gastritis with vitamin B12 deficiency, chronic autoimmune hepatitis, alopecia, myasthenia gravis, rheumatoid arthritis, Sjögren's syndrome, celiac disease, and hypergonadotropic hypogonadism.[2–4,6]

The pathophysiology of APS Type 2 involves a complex interaction between genetic and environmental factors. There is a strong association with specific Human Leukocyte Antigen (HLA-DR3 and/or HLA-DR4) haplotypes, as well as non-HLA genes like CTLA-4 and PTPN22. The disease is more common in women,

with a 3:1 ratio compared to men, and its incidence is highest between the second and fifth decades of life.[1,7]

CASE PRESENTATION

We present the case of a 31-year-old male patient, E.P., with type 1 diabetes mellitus since the age of 10, admitted to Hospital Universitário Evangélico Mackenzie with abdominal pain, weight loss, nausea, vomiting, hyperglycemia, and positive ketonemia (>3 mmol/L). With no fever or signs of infection, he had irregular insulin use, constituting diabetic ketoacidosis secondary to poor adherence to the therapeutic treatment. He was already being followed by primary care and an endocrinologist. There were a history of vitiligo and a family history of diabetes mellitus, vitiligo, and pheochromocytoma. During hospitalization, he achieved glycemic stabilization with intensive insulin therapy. Infectious screening exams revealed no changes, allowing for hospital discharge with referral for outpatient follow-up.

In outpatient follow-up, chronic hyperglycemia persisted, and he already presented complications such as paresthesia in hands and feet, reduced visual acuity, and impaired renal function. Extreme glycemic variability, low adherence to carbohydrate counting, and irregular use of insulin in fixed doses were observed, with repeated elevations of glycated hemoglobin.

Tests for thyroid dysfunction were requested: anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) antibodies, both negative, but with elevated TSH and reduced free T4, establishing the diagnosis of seronegative hypothyroidism.

After a few months, he was readmitted to the hospital with fatigue, postural hypotension, tachycardia, and cutaneous hyperpigmentation in areas of vitiligo. Serum cortisol at 8 a.m. was 3.6 ng/dL (reference range: 5–25 ng/dL), confirming primary adrenal insufficiency.

Given the association of type 1 diabetes mellitus, hypothyroidism, vitiligo, and primary adrenal insufficiency, the diagnosis of autoimmune polyglandular syndrome type 2 was confirmed. After in-hospital treatment with hydrocortisone 50 mg every 6 hours, fluid and electrolyte replacement for the adrenal crisis, he continued outpatient treatment with levothyroxine and hydrocortisone at a dose of 7.5 mg, orally, distributed in a dose of 5 mg in the morning and 2.5 mg in the afternoon, with adequate clinical response and metabolic stabilization.

Despite this, poor adherence to T1DM treatment led to irregular glycemic control and progression of diabetic complications: retinopathy progressing to bilateral amaurosis, primary hypogonadism, diabetic gastroparesis, diabetic foot, and chronic renal failure on peritoneal dialysis. He had multiple hospitalizations for adrenal crisis, aggravated by poor absorption of glucocorticoids due to gastroparesis and infections related to the dialysis catheter, and episodes of diabetic ketoacidosis. In the last hospitalization, he presented with acute obstructive abdomen, evolving to death.

Table 1: Patient's laboratory chemistry analysis.

Blood Tests	Result	Unit	Normal Values
TSH	8.7	µUI/mL	0,38-5,33
Cortisol 8 a.m.	3.8	µg/dL	6,70- 22,60
Free T4	0.48	ng/dL	0,54- 1,24
Vitamin B12	918	pg/mL	200-900
Sodium	132	mEq/L	135-145
Vitamin D	48	ng/mL	30-100
Anti-TPO antibody	2,4	U/mL	<9
Testosterona	100	ng/dL	300-1000

BUN	66	mg/dL	10-50
Creatine	3.73	mg/dL	0.7-1.3
HbA1c	8.1	%	<7
PTH	437	pg/mL	12-88
C peptide	0.02	ng/ml	0.5-2
DHEA-S	139	ug/dL	18-391

DISCUSSION

APS type 2 is rare and potentially fatal if not diagnosed and treated early.[4] There are currently four main categories of autoimmune polyglandular syndromes (types 1-4), based on clinical features and inheritance patterns. APS type 2 is more common than APS type 1 but remains a rare condition.[7]

In the presented case, the patient started with type 1 diabetes and vitiligo in childhood and, about 20 years later, developed adrenal insufficiency and clinical hypothyroidism. While some endocrinopathies can emerge in close sequence, the interval between them is often years.[4,8] The clinical presentation of this case is compatible with the literature, although the diagnosis is frequently challenging.[3] The diagnosis of APS involves specific serological autoantibody tests and subsequent functional tests.[1,4] The case reinforces the need to screen for autoantibodies in patients with autoimmune endocrinopathies due to the increased risk of new associations.[1,4,8]

Primary adrenal insufficiency, or Addison's disease, results from the autoimmune destruction of the adrenal cortex. It is characterized by a deficiency of glucocorticoids and often mineralocorticoids. Symptoms include fatigue, weakness, fever, anorexia, nausea, vomiting, hyponatremia, and hyperkalemia. An adrenal crisis can lead to potentially fatal shock. Management should be immediate, without waiting for lab results, with fluid replacement and intravenous glucocorticoids.[2,5] In the described patient, complications from T1DM, such as gastroparesis and kidney failure, compromised the absorption and effectiveness of glucocorticoids, favoring the recurrence of adrenal crises.

Another relevant finding was seronegative hypothyroidism, a less common condition. This occurs in cases where antibody production takes place predominantly in the thyroid tissue itself rather than in the serum. Rare situations have been described where the thyroid tissue produces antibodies locally, identified in histological tissue after a thyroidectomy, where lymphoid cells removed directly from the gland produced anti-Tg and anti-microsomal antibodies *in vitro*.[9]

The treatment for APS type 2 is based on hormone replacement and managing complications.[3] The simultaneous management of adrenal insufficiency and T1DM is challenging because glucocorticoids raise blood glucose levels.[1,2] These patients are at a higher risk for hospitalizations, hypoglycemia, and ketoacidosis.[1] The case illustrates the complexity of managing multiple associated autoimmune endocrinopathies, especially in patients with poor therapeutic adherence and severe diabetes complications that directly impact the effectiveness of hormone replacement.

Early recognition of APS type 2 in patients with T1DM is essential to prevent adrenal crises and diabetic ketoacidosis. A timely diagnosis, combined with rigorous control of associated autoimmune diseases, can reduce complications and improve prognosis.[1,4]

CONCLUSION

Autoimmune polyglandular syndrome type 2 is a rare and multifactorial condition characterized by the progression of autoimmune endocrinopathies. The described case reinforces the importance of systematic diagnosis and endocrinological follow-up to prevent serious complications. Given the predisposition to

multiple autoimmune diseases, physicians should maintain a high index of diagnostic suspicion in patients with an isolated autoimmune disease and atypical symptoms. Screening for organ-specific autoantibodies can assist in early detection. Proper management involves hormone replacement, insulin therapy, and corticotherapy, with continuous and multidisciplinary follow-up being essential. This report contributes to the medical literature by documenting a rare combination of autoimmune diseases that started in childhood and manifested more broadly in adulthood, highlighting the need for constant clinical vigilance.

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