Autoimmune Polyglandular Syndrome type 2

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SUMMARY

Autoimmune polyglandular syndrome type 2 (APS 2) is defined by the presence of Addison's disease (AD) associated with autoimmune thyroid disease and/or Type 1 diabetes mellitus (T1DM). It is a rare disease, affecting about 1.4-2 cases/100,000 inhabitants. Its less frequent clinical presentation is the combination of AD, Graves' disease, and T1DM. We present the case of a 42-year-old woman with a history of total thyroidectomy due to Graves' disease, type 2 diabetes mellitus, and hypertension, who sought the ED due to asthenia, dizziness, nausea, and vomiting. She reported having stopped antihypertensive therapy due to hypotension and presented a glycemic record with frequent hypoglycemia. On physical examination, she had cutaneous hyperpigmentation. She had no leukocytosis, anemia, hypoglycemia, hyponatremia or hyperkalemia, and a negative PCR. Serum cortisol <0.5 ug/dl (4,3-22,4), urine free cortisol 9 ug/24h (28-214), ACTH 1384 pg/mL (4,7-48,8), aldosterone and renin in erect position of 0 pg/ml (41-323) and 430.7 uUI/ml (4.4-46.1) respectively. Quantiferon TB was negative; computerized axial tomography of the adrenals showed no infiltrations, hemorrhage, or masses. The 21-hydroxylase antibody assay was positive. B12 vitamin was normal, anti-GAD antibodies were positive, anti-insulin, anti-IA2, and anti-transglutaminase antibodies were all negative. The patient started insulin therapy and treatment for AD with prednisolone and fludrocortisone with good clinical response. This case aims to alert to the need for high clinical suspicion in the diagnosis of AD. Since this is a rare autoimmune disease, it is important to screen for other autoimmune diseases in order to exclude APS.

KEYWORDS: *Polyendocrinopathies, Autoimmune. Addison's Disease. Diabetes Mellitus, Type 1. Thyroid Diseases*

INTRODUCTION

Autoimmune polyglandular syndromes are a rare group of polyendocrine conditions that included multiple glandular deficiencies associated with other autoimmune diseases[1], such as hypergonadotropic hypogonadism, vitiligo, chronic atrophic gastritis, pernicious anemia, chronic autoimmune hepatitis, and celiac disease. Autoimmune polyendocrine syndrome type 2 (APS II) is defined by the presence of Addison's disease (AD) associated with autoimmune thyroid disease and/or diabetes mellitus (DM) type 1[2]. It is a rare condition, affecting approximately 1.4-2 cases/100,000 inhabitants[3]. Its least frequent clinical presentation is the combination of Graves' disease and diabetes mellitus type 1. We present a case of APS II with the complete triad.

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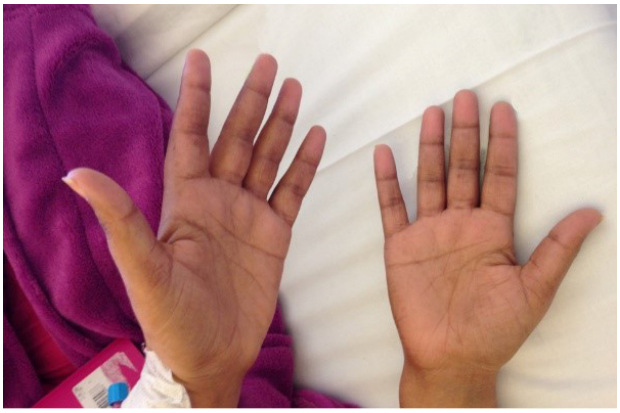
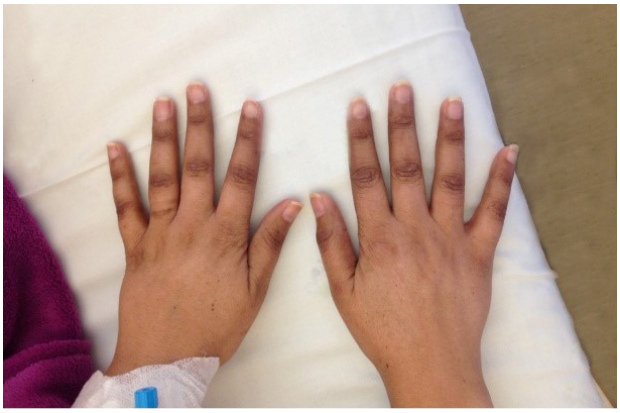
CLINICAL CASE

We present a 42-year-old woman, who was emigrated from France between age 19 and 36, with a history of total thyroidectomy due to Graves' disease 11 years ago, DM type 2 with four years of evolution and hypertension, who sought the DE due to a continued condition, with three months of evolution, asthenia, weight loss (12 kg in three months), dizziness, abdominal pain predominantly in the right quadrants, nausea, and vomiting. She reported having suspended anti-hypertension therapy due to hypotension and presented a glycemic record with frequent hypoglycemia. Other medical history included dyslipidemia, asthma, and repeated urinary tract infections (ITUs). She was medicated with 100 mg sitagliptin, 5 mg folic acid, 0.1 mg levothyroxine, 10 mg atorvastatin, 320 µg budesonide+formoterol + 9 µg SOS. She had complementary diagnostic exams from a DE context, from 1.5 months before, due to a similar clinical scenario: analytical assay with slight microcytic anemia, negative CRP (Table 1), abdominal/pelvic/kidney/bladder ultrasound and combur without abnormalities. She was discharged with an indication for symptomatic treatment and an iron kinetics analysis, video colonoscopy, and outpatient EGD. The iron kinetics and video colonoscopy showed no abnormalities. The EGD was still pending completion. Upon physical examination at DE, TA was 104/77 mmHg, without orthostatic hypotension, FC: 83/min, no fever, discolored mucosa, with skin hyperpigmentation (Figures 1A and 1B); the rest of the exam showed no other abnormalities. After suspected suprarenal insufficiency, the examination proceeded. Analytically, there was no leukocytosis, anemia, hypoglycemia, hyponatremia, or hyperkalemia, and CRP was negative. Morning serum cortisol <0.5 ug/dl (4.3-22.4), free cortisol in urine 9 ug/24h (28-214), ACTH 1384 pg/mL (4.7-48.8), aldosterone and renin in an upright position of 0 pg/mL (41-323) and 430.7 IU/mL (4.4-46.1), respectively (Table 1). An additional study was conducted to investigate the cause of primary suprarenal insufficiency. Negative Quantiferon TB, suprarenal computed axial tomography without infiltrations, hemorrhage, or masses. Results for 21-hydroxylase antibodies were positive. After the autoimmune cause was confirmed and with a previous history of autoimmune thyroid disease, the investigation continued with normal vitamin B 12, positive anti-GAD, and negative anti-insulin, anti-IA2, anti-transglutaminase. In this context,

TABLE 1. ANALYTICAL STUDY.

Test	Results 1.5 months before	Results in hospitalization	Reference values
Leukocytes	4.8x10^9/L	5.0x10^9/L	4.5 – 11.50
Hemoglobin	11.4 g/dL	13.4 g/dL	12 – 15
Glucose	171 mg/dL	154 mg/dL	74 - 106
Sodium	134 mEq/L	136 mEq/L	136 - 145
Potassium	4.3 mEq/L	4.7 mEq/L	3.4 – 4.4
CRP	0.09 mg/dL	1 mg/dL	<0.50
AST	56 UI/L		3 – 31
ALT	61 UI/L		3 – 31
Urea	26 mg/dL	47 mg/dL	16 – 42
Creatinine clearance	0.5 mg/dL	0.7 mg/dL	0.5 – 1.2
Urinary cortisol		9 ug/24h	28-214
Morning serum cortisol		<0.5 ug/dl	4.3-22.4
ACTH		1.384 pg/mL	4.7-48.8
Renin		430.7 UI/mL	4.4-46.1
Aldosterone		0 pg/mL	41-323





FIGURES 1A AND 1B. SKIN HYPERPIGMENTATION.

the patient started insulin therapy and targeted treatment to AD with hydrocortisone and fludrocortisone, with good clinical response, maintaining a follow-up in external consultations.

DISCUSSION

There are three types of APS, of which SPGA2 is the most common and most frequent in women between the third and fourth decades of life.

Our patient was a middle-aged woman, precisely at the peak of APS II incidence. The coexistence of Graves' disease, DM type 1, and AD is in line with the APS II diagnosis.

Approximately 50% of patients with suprarenal insufficiency have other autoimmune diseases associated with it, and thyroid disease is the most frequent of them — however, only 1% of patients with autoimmune thyroid disease suprarenal insufficiency[4,5].

Suprarenal insufficiency is the first manifestation in 50% of cases. It appears simultaneously with diabetes mellitus or autoimmune thyroid disease in 20% of cases, and after these pathologies in approximately 30% [6,7].

In this case, the first manifestation was the thyroid disease, with adrenal insufficiency emerging 11 years later.

Since this was a patient with a history of recurrent UTIs, complaints of abdominal pain, nausea, and vomiting, in the first approach at the DE exams were conducted in order to exclude acute pathologies, such as UTIs, acute cholecystitis/cholangitis, renal colic, and adnexal pathology.

Since there was a nonspecific and continued clinical presentation of anorexia with weight loss, nausea, and vomiting associated with mild microcytic anemia, an outpatient examination was conducted in order to exclude gastrointestinal pathologies, in particular, neoplastic disease.

The early diagnosis of AD significantly reduces the morbidity and mortality of the disease. However, since the clinical presentation can by inaccurate and nonspecific, in most cases, the diagnosis is delayed. The concept of APS consists in the fact that a patient with autoimmune disease has a higher probability of developing a new autoimmune disease than the general population. It is described that the circulating autoantibodies associated with a particular type of disease may be present months to years prior to its development[5]. Thus, after the diagnosis of an autoimmune disease, it is crucial to screen for other associated pathologies. In this patient, the fact that she was emigrated without a medical follow-up may have influenced her medical guidance and the late diagnosis of Lada DM and AD.

CONCLUSION

This case report aims to alert to a rare entity (AD), with a not very specific clinical presentation, that requires a high degree of suspicion to reach an early diagnosis, reinforcing the idea that it is necessary to make the appropriate screening for other associated autoimmune diseases.

Contribution of the authors

All authors contributed equally to the development of this work.

RESUMO

A síndrome poliglandular autoimune tipo 2 (SPGA2) é definida pela presença de doença de Addison (DA) associada à doença tiroideia autoimune e/ou diabetes mellitus tipo 1 (DMT1). Trata-se de uma doença rara, afetando cerca de 1,4-2 casos/100.000 habitantes. A apresentação clínica menos frequente é a combinação de DA, doença de Graves e DMT1.

Apresenta-se mulher de 42 anos, com antecedentes de tiroidectomia total por doença de Graves, diabetes mellitus tipo 2 e hipertensão, que recorre ao SU por quadro arrastado de astenia, emagrecimento, tonturas, náuseas e vômitos. Referia ter suspendido terapêutica anti-hipertensora por hipotensão e apresentava registro glicêmico com hipoglicemias frequentes. Ao exame físico, salientava hiperpigmentação cutânea. Analiticamente sem leucocitose, anemia, hipoglicemia, hiponatremia ou hipercaliemia, PCR negativa. Cortisol sérico matinal <0,5 ug/dl (4,3-22,4), cortisol livre na urina 9 ug/24h (28-214), ACTH 1.384 pg/mL (4,7-48,8), aldosterona e renina em posição ereta de 0 pg/mL (41-323) e 430,7 uUI/mL (4,4-46,1), respectivamente. Realizado estudo complementar para averiguar causa de insuficiência suprarrenal primária. Quantiferon TB negativo, tomografia axial computadorizada das suprarrenais sem infiltrações, hemorragia ou massas. Anticorpos anti-21-hidroxilase positivos. Foi aprofundada a investigação com vitamina B12 normal, anti-GAD positivo, anti-insulina, anti-IA2, antitransglutaminase, negativos. Nesse contexto, a doente iniciou insulinoterapia e tratamento dirigido para a DA com prednisolona e fludrocortisona, com boa resposta clínica.

Este caso tem como objetivo alertar para a necessidade de elevada suspeição clínica no diagnóstico de DA. Sendo esta uma doença autoimune rara, é importante rastrear outras doenças autoimunes no sentido de excluir SPGA.

PALAVRAS-CHAVE: *Poliendocrinopatias autoimunes. Doença de Addison. Diabetes mellitus tipo 1. Doenças da glândula tireoide.*

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