

## CASE REPORTS

# When a disease doesn't come alone: A case report of polyglandular autoimmune syndrome type 2

## Quando uma doença não vem só: Um caso clínico de síndrome poliglandular autoimune tipo 2

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### ABSTRACT

Autoimmune polyglandular syndromes (PAS) are a complex and heterogeneous group of diseases characterized by the combination of two or more endocrine or non-endocrine organ dysfunctions.

Herein is presented the case of a 16-year-old female with a history of asthenia, prostration, and weight loss who was diagnosed with hypothyroidism and iron deficiency anemia. Two weeks after starting therapy with levothyroxine and iron, she developed an adrenal crisis with nausea and vomiting. Low cortisol, elevated adrenocorticotropic hormone, and positive antiadrenal and antithyroid peroxidase antibodies confirmed the diagnosis of autoimmune polyglandular syndrome type 2 (PAS-2). Symptoms resolved with hydrocortisone, fludrocortisone, and levothyroxine.

PAS-2 is a rare but potentially serious disorder. A high clinical suspicion is required, as most symptoms are nonspecific. Early diagnosis may prevent life-threatening complications.

**Keywords:** Addison's disease; autoimmune polyglandular syndrome type 2; Hashimoto's thyroiditis

### RESUMO

As síndromes poliglandulares autoimunes (PAS) são um grupo complexo e heterogêneo de doenças caracterizado pela combinação de duas ou mais disfunções endócrinas autoimunes.

É apresentado o caso de uma adolescente de 16 anos de idade com história de astenia, prostração e perda de peso, que foi diagnosticada com hipotireoidismo e anemia ferropénica. Duas semanas após ter iniciado tratamento com levotiroxina e ferro, desenvolveu insuficiência suprarrenal com náuseas e vômitos. Os níveis de cortisol baixo e hormona adrenocorticotrópica elevada e presença de anticorpos anti-suprarrenal e antiperoxidase tiroideia positivos confirmaram o diagnóstico de síndrome poliglandular autoimune tipo 2 (PAS-2). O tratamento com hidrocortisona, fludrocortisona e levotiroxina levou à remissão dos sintomas.

A PAS-2 é uma condição rara, sendo necessária uma elevada suspeita clínica para a mesma, dado que a maioria dos sintomas são inespecíficos. O diagnóstico precoce pode prevenir complicações potencialmente fatais.

**Palavras-chave:** doença de Addison; síndrome poliglandular autoimune tipo 2; tiroidite de Hashimoto

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## INTRODUCTION

Autoimmune polyglandular syndromes (PAS) are a group of disorders characterized by the association of endocrine and non-endocrine autoimmune features.<sup>(1)</sup> Autoimmune polyglandular syndrome type 2 (PAS-2) is the most common form of PAS. It is a rare disorder in which autoimmune adrenal insufficiency is associated with autoimmune thyroid dysfunction (Schmidt syndrome) and/or type 1 diabetes mellitus (Carpenter syndrome).<sup>(2,3)</sup>

Typically diagnosed in adulthood, it is more common in middle-aged women (20-40 years) and has an estimated prevalence of 1.4-2/100,000 inhabitants. There are few reports in pediatric patients.<sup>(2-4)</sup>

PAS-2 is associated with genetic abnormalities of human leukocyte antigen (HLA) class II alleles, which regulate antigen presentation to T cell receptors.<sup>(1,3)</sup>

The presence of adrenal insufficiency is a clinical criterion for PAS-2. Autoimmune thyroid disease is present in 70% and type 1 diabetes mellitus in 50% of patients.<sup>(5,6)</sup>

Adrenal insufficiency is the first endocrine abnormality in approximately 50% of patients, occurs concurrently with autoimmune thyroid disease or diabetes mellitus in about 20%, and after these in about 30%.<sup>(5,7)</sup>

Other endocrine disorders may be present in PAS-2, including primary hypogonadism (5-50%) and diabetes insipidus (<1%). In addition, non-endocrine disorders have been reported, although in a much smaller percentage of patients. Vitiligo, myasthenia gravis, celiac disease, pernicious anemia, immunoglobulin A (IgA) deficiency, immune thrombocytopenia purpura, Sjögren's syndrome, and rheumatoid arthritis are some examples.<sup>(8,9)</sup>

Diagnosis is often delayed, sometimes leading to multiple complications. These patients typically present with isolated endocrine dysfunction and later develop other autoimmune diseases, requiring ongoing monitoring.<sup>(2,3)</sup>

## CASE REPORT

A 16-year-old female presented to the Pediatric Emergency Department with a six-month history of asthenia and prostration. Symptoms had started after SARS-CoV-2 infection. She also had a history of nausea for the past three days, recent weight loss, and an episode of vomiting on admission.

Two weeks earlier, the girl had been started on iron (329.7 mg once daily (OD)) and levothyroxine (0.088 mg OD) after being diagnosed with iron deficiency anemia and hypothyroidism by her primary care physician, which she was currently still taking. At that time, she complained of extreme fatigue, but the physical examination was described as normal. The analytical results are shown in **Table 1**.

The patient denied symptoms such as fever, abdominal pain, anorexia, alopecia, headache, dizziness, bowel dysfunction, polydipsia, or desire to lose weight. She had menarche at the age

of 13 with regular catamenia lasting about five days. No significant medical history or regular medications were reported. Family history was positive for thyroid disease, with a grandmother having Hashimoto's thyroiditis. Other autoimmune diseases were denied.

Vital signs revealed a temperature of 37°C, heart rate of 109 beats per minute, and blood pressure of 99/58 mmHg (percentile <50<sup>th</sup>), and the girl was eupneic, with an oxygen saturation (SpO<sub>2</sub>) of 99% (fraction of inspired oxygen [FiO<sub>2</sub>] 21%). Capillary blood glucose was 100 mg/dL. At that time, her height was 1.59 m (15<sup>th</sup>-50<sup>th</sup> percentile of World Health Organization [WHO] growth charts), her weight was 40.5 kg (loss of approximately 3.5 kg, representing an 8% weight loss in 2 weeks), and her body mass index was 16.1 kg/m<sup>2</sup> (3<sup>rd</sup> percentile of WHO growth charts).

On physical examination on admission, the patient had an emaciated appearance and cold extremities with capillary reperfusion time <2 seconds. She also presented with cutaneous and mucosal hyperpigmentation (**Figures 1, 2, and 3**). There were no other oral or cutaneous lesions such as candidiasis. The thyroid was not palpable. No other abnormalities were noted.

Laboratory results showed improvement in anemia and a decrease in serum thyroid-stimulating hormone (TSH) levels (**Table 1**). Urea and plasma osmolality were slightly elevated. Na<sup>+</sup> was low, PO<sub>4</sub><sup>3-</sup> was high, and venous blood gas showed metabolic acidosis. The remaining results were normal. Ultrasound showed an enlarged and hypoechoic thyroid gland with irregular contours compatible with thyroiditis. Abdominal ultrasound was normal. Hydroelectrolyte and acid-base imbalances improved with intravenous (i.v.) fluids.

Autoimmune Addison's disease related to Hashimoto's thyroiditis associated with PAS-2 was suspected. Treatment with hydrocortisone (i.v. bolus) was initiated and the patient was transferred to a level III hospital for further management.

Subsequent laboratory results showed low cortisol, elevated adrenocorticotropic hormone, and positive anti-adrenal and antithyroid peroxidase antibodies, confirming the diagnosis (**Table 1**). IA2 and anti-parietal cell antibodies were also positive. Other antibodies were negative. Renin was elevated and aldosterone was slightly low.

During hospitalization, the girl received hydrocortisone (50 mg i.v. every 6 hours [Q6H] for 24 hours [h]), followed by 30 mg i.v. Q6H for 24 h, 20 mg i.v. Q8H for 24 h, and 20 mg per os (PO) Q8H for 24 h. Fludrocortisone (0.1 mg PO OD) was started after 24 h of treatment, and levothyroxine (0.088 mg id) was maintained.

She was discharged after four days of therapy with levothyroxine (0.088 mg id), hydrocortisone (10 mg os Q8H), and fludrocortisone (0.1 mg PO OD).

One month after discharge, the hyperpigmentation had resolved, and the girl had a weight gain of 9 kg. She currently maintains regular follow-up.

**Table 1** - Laboratory results two weeks before admission and on admission

	2 weeks before admission	On admission	Normal range
Hb (g/dL)	10.8	12.8	12-15
MCHC (g/dL)	31.7	34.1	32-36
MCV (fL)	72.7	74.2	81-97
Ferritin (ng/mL)	6		15-200
Glucose (mg/dL)	75	90	74-106
Urea (mg/dL)		54	19-49
Creatinine (mg/dL)	0.62	0.6	0.5-1.2
Na <sup>+</sup> (mEq/L)		130	135-145
K <sup>+</sup> (mEq/L)		4.7	3.5-5.0
PO <sub>4</sub> <sup>3-</sup> (mg/dL)		6.1	2.8-4.1
Ca <sup>2+</sup> (mEq/dL)		4.9	4.2-5.1
Total protein (g/dL)		7.8	6.6-8.7
Albumin (g/dL)		4.6	3.5-5.0
GGT (U/L)	7	5.0	0.0-38.0
GPT (U/L)	18	25	3-31
GOT (U/L)	32	35	3-31
<b>Venous blood gas</b>			
pH		7.31	
HCO <sub>3</sub> <sup>-</sup> (mmol/L)		21.7	
pCO <sub>2</sub> (mmHg)		43	
Plasma osmolarity (mOsm/L)		297.4	275-295
TSH (mU/L)	20.26	11.05	0.55-4.78
Free T4 (ng/mL)	0.76		0.9-1.8
Vit B12 (pg/mL)		426	179-1130
Folic acid (ng/mL)		16.8	1-20
Cortisol (pg/mL)		<0.5	
ACTH (pg/mL)		1004.1	4.7-48.8
Antithyroid peroxidase antibodies (U/mL)		3340.1	<60
Anti-thyroglobulin antibodies (U/mL)		<1.3	0.0-4.5
IA2 antibodies (U/mL)		38.74	positive ≥28.000
Anti-insulin antibodies (U/mL)		8.717	positive ≥20.000
Anti-GAD antibodies (U/mL)		5.819	positive ≥17.000
Anti-islet cell antibodies		Negative	
Anti-tissue transglutaminase IgA (AU/mL)		0.40	0.00-10.00
Anti-tissue transglutaminase IgG (GU/mL)		0.60	0.00-10.00
Anti-parietal cells antibodies (U/mL)		87	<10
Anti-adrenal antibodies		Positive	
Renin (uU/mL)		294.7	4.4-46.1
Aldosterone (pg/mL)		40.9	41.0-323.0

ACTH: Adrenocorticotropic hormone; Anti-GAD: antibodies to glutamic acid decarboxylase; GGT: gamma-glutamyl transferase; GOT: glutamic-oxaloacetic transaminase; GPT: glutamic-pyruvic transaminase; Hb: hemoglobin; HCO<sub>3</sub><sup>-</sup>: Bicarbonate; IA2: tyrosine phosphatase-related islet antigen 2; K<sup>+</sup>: Potassium; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular



**Figure 1** - Hyperpigmented upper lip



**Figure 2** - Hyperpigmented lower lip



**Figure 3** - Hyperpigmented skin on the back of the hand

## DISCUSSION

This case highlights the atypical age of onset and almost simultaneous manifestation of two endocrinopathies: adrenal insufficiency and autoimmune thyroid disease. Hypothyroidism is generally characterized by symptoms such as weight gain, muscle weakness, myalgia, cold intolerance, constipation, and menstrual irregularities. The symptoms of adrenal insufficiency are non-specific and of insidious onset. Weakness, anorexia, fasting hypoglycemia, weight loss, cutaneous and/or mucosal hyperpigmentation, salt craving, nausea, vomiting, and postural hypotension are more evident in intercurrent diseases.

In the present case, the first diagnostic approach to complaints of asthenia in a female adolescent should be to look for anemia or hypothyroidism, as these are the conditions that most commonly justify this symptom.

Two weeks after starting levothyroxine, the adolescent reported worsening symptoms. During this time, she maintained asthenia and prostration and continued to lose weight. She also began to experience nausea and vomiting. All these symptoms raised clinical suspicion of adrenal insufficiency, which was subsequently confirmed.<sup>(3,10)</sup>

It has been suggested that treatment with levothyroxine in a patient with unknown adrenal insufficiency may precipitate an adrenal crisis because it increases corticosteroid metabolism in the liver, and this may be what happened in this case.<sup>(10)</sup> Therefore, when the response to hypothyroidism therapy is not as expected, clinicians should be aware of other possible diagnoses, including PAS-2, and treat adrenal insufficiency first.

Recently, some authors have suggested that SARS-CoV-2 infection causes hyperactive immune responses and may trigger autoimmune thyroid disorders. This association was suspected in this case, as the adolescent developed symptoms after SARS-CoV-2 infection. However, further studies are required to confirm this suspicion.<sup>(8,11,12)</sup>

Once a second autoimmune disease is detected and PAS-2 is diagnosed, other autoimmune diseases should be investigated. Positive autoantibodies associated with other diseases may be detected months or years before clinical signs or symptoms arise.<sup>(3,8,10)</sup>

In this case, in addition to positive anti-adrenal and antithyroid peroxidase antibodies, anti-parietal cell and insulinoma-associated protein 2 antibodies were also detected.

Anti-parietal cell antibodies are present in 85-90% of patients with pernicious anemia, but are nonspecific for this condition, being present in other autoimmune diseases and in some healthy individuals.<sup>(13)</sup> It is acknowledged that pernicious anemia can be associated with PAS-2, but folate and B12 deficiency were excluded in this patient, and microcytic anemia was present.

Insulinoma-associated protein 2 antibodies are a type of antibody responsible for islet cell destruction in some cases of type 1 diabetes mellitus. Although weight loss and asthenia were present in this case, there were no associated blood glucose changes, polydipsia,

or polyuria. Therefore, the usefulness of these antibodies in isolation is limited.

Close and long-term follow-up of patients diagnosed with PAS-2 is recommended. In addition, it is important to educate both patients and families about the warning signs/symptoms (e.g., polyuria, polydipsia, polyphagia, etc.) so that not only can the disease be diagnosed at the earliest possible stage, but also life-threatening presentations – such as diabetic ketoacidosis or severe hypothyroidism – can be avoided.<sup>(3,8,10)</sup>

## CONCLUSION

This case report illustrates a very rare pediatric condition, PAS-2, in which autoimmune adrenal insufficiency is associated with autoimmune thyroid dysfunction and/or type 1 diabetes mellitus, requiring regular follow-up, appropriate treatment, and early detection of other, not always coexisting, pathologies. Because adrenal crisis can be life-threatening, treatment of adrenal insufficiency should be a priority.

## ACKNOWLEDGMENTS

The authors acknowledge the patient and family for their permission to publish this case report.

The authors have no potential conflicts of interest relevant to this study.

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Received for publication: 26.12.2022

Accepted in revised form: 27.09.2023