CASE REPORT

A rare association of polyglandular syndrome type 2 with other autoimmune conditions

Lucas Miranda Capóssoli, João Carlos Ramos-Dias

Abstract: Autoimmune polyglandular syndrome (APS) is defined as a heterogeneous group of polyendocrine diseases, which can be classified into type I and II (APS-2). APS-2 is a rare polygenic condition represented by the presence of primary autoimmune adrenal insufficiency, associated with type 1 diabetes mellitus and/or autoimmune thyroid disease. The coexistence of these three diseases, present in 10% of APS-2 cases, is called Carpenter syndrome. In APS-2, other complications can coexist that make this condition even more uncommon. In this report, we present a very rare case of a 41-year-old woman with APS-2 and the classic triad of autoimmune diseases that characterize this morbidity, associated with other autoimmune conditions, namely: vitiligo, autoimmune panniculitis, Sjögren's syndrome, autoimmune gastritis and celiac disease. Together, all alterations present in our patient represent less than 1% of the population with APS-2. Thus, we remember that certain signs and symptoms present in the same patient may be part of a set of different autoimmune diseases that coexist with each other.
Keywords: Autoimmune polyglandular syndrome Type 2, Autoimmune diseases, Type 1 Diabetes mellitus, Addison's disease, Autoimmune thyroiditis.

INTRODUCTION

Autoimmune polyglandular syndrome (APS) can be defined as a heterogeneous group of polyendocrine diseases, where there is a concomitant occurrence of at least two endocrine gland deficiencies due to autoimmune mechanisms, and can be classified into type I (APS-1) and II (APS-2)[1,2].

APS-1, also known as juvenile APS, Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED) or Whitaker Syndrome, is a monogenic autosomal recessive manifestation defined by the presence of chronic mucocutaneous candidiasis, hypoparathyroidism and autoimmune primary adrenal insufficiency (APAI)[1,3,4]. It originates from dysfunctions in the *AIRE* gene (autoimmune regulator) and although rare, it generally appears in childhood and in females[1,3,4].

In relation to APS-2, this is a polygenic condition represented by the presence of APAI, associated with type 1 diabetes mellitus (T1DM) and/or autoimmune thyroid disease[1,5]. The coexistence of these three diseases, present in 10% of APS-2 cases, is called Carpenter syndrome[1,5,6]. Although rare, APS-2 is the most prevalent form of APS, being present in 1.4 to 2 individuals/100 thousand inhabitants, in addition to being more prevalent in adult women (3:1) and in the second to fourth decades of life[1,2,5,6]. Its pathophysiology is complex, but despite being polygenic, haplotypes of the human leukocyte antigen (*HLA*) deserve to be highlighted, such as *DQ* and *DR*[1,4,5,6,7]. Other less frequent complications (4-11% of cases) may coexist in APS-2, such as vitiligo, hypergonadotropic hypogonadism, celiac disease, alopecia, autoimmune gastritis, as well as other rare manifestations (<1%), such as Sjögren's Syndrome, *Myas-*

Pontifical Catholic University of São Paulo, Faculty of Medical and Health Sciences Sorocaba. Sorocaba, (SP), Brazil.

https://doi.org/10.11606/issn.2176-7262.rmrp.2024.214223

thenia Gravis and rheumatoid arthritis[6,8]. Early diagnosis of APS-2 is important to avoid future morbidity and mortality, and encompasses clinical, laboratory findings (including hormonal and antibody levels against target organs) and images, being individualized for each pathology[1,2,5,6]. Treatment consists of isolated therapies for each disease and replacement of various hormonal deficiencies[1,4,5,6].

We report an extremely rare case of a woman with APS-2 with the classic triad of autoimmune diseases that characterize this morbidity, associated with other autoimmune conditions. Approval by the Research Ethics Committee (REC) is registered under number 5,945,897.

CASE REPORT

Woman, 41 years old, white, artisan, in a stable union, from the interior of São Paulo. She was referred to the Pediatric Endocrinology service when she was 4 years old after a coma episode, to continue the treatment of T1DM. During her follow-up, she had several hospitalizations due to diabetic decompensation, stemming from poor metabolic control. In addition to diabetes, several other autoimmune pathologies were diagnosed throughout her life. The chronology of the appearance of these diseases is shown in table 1.

Table 1. Chronology of the age of onset and diagnosis of the autoimmune diseases presented by the patient, with their respective clinical and laboratory characteristics.

Chronological age (years)	Diagnosed pathology	Clinical-laboratory characteristics
4	Type 1 diabetes mellitus	Diabetic ketoacidosis
18	Chronic lymphocytic thyroiditis (Hashimoto's thyroiditis)	- Dry skin, infiltrated facies, goiter, edema in the lower limbs - TSH[1] = 37.2 mIU/mL (VR: 0.35-4.940 mIU/mL) - fT4[2] = 0.6 ng/dL (VR: 0.7-1.8 ng/dL) - Positive anti-TPO[3] and anti-thyroglobulin antibodies
	Vitiligo	Hypochromic lesions on hands and face
	Autoimmune panniculitis	- Inflammatory processes in the skin - Areas of atrophy and skin hardening, in areas no longer used for insulin application

25	Sjögren's syndrome	- Dryness of eyes and mouth - Positive Anti-RO and Anti-La
27	Autoimmune primary adrenal insufficiency (APAI) [4]	- Asthenia and hypoglycemia, with laboratory confirmation after ITT[5]: cortisol peak = 12.8 µg/dL (expected>18µg/dL)
	Autoimmune gastritis	- Nausea, vomiting, diarrhea and epigastric pain - Anemia, vitamin B12 deficiency, hypergastrinemia - UGE[6] (with biopsy)
	Celiac disease	Diarrhea and a lot of flatulence with a foul odor related to pasta, bread, milk

[1]TSH = Thyroid stimulating hormone; [2]fT4 = Free thyroxine; [3]TPO = Thyroid peroxidase; [4]APAI = Autoimmune primary adrenal insufficiency; [5]ITT = Insulin tolerance test; [6]UGE = Upper gastrointestinal endoscopy.

In addition to the diseases mentioned above, the patient currently has the following comorbidities: arterial hypertension (under treatment since the age of 17); diabetic nephropathy diagnosed at 17 years of age, with macroscopic proteinuria (449 mg/24 hours, RV: above 300 mg/24 hours = macroproteinuria); bilateral non-proliferative diabetic retinopathy (evidenced on funduscopy at age 20); dyslipidemia; convulsive crises (slow and wide waves of right parietal projection in electroencephalography); diabetic sensory peripheral neuropathy.

Regarding obstetric history, in 2001, at the age of 19, the patient became pregnant, presenting several complications during the gestation period, such as pre-eclampsia, hypoglycemia, ketonuria and

furunculosis. The birth was cesarean section, at 27 weeks and 5 days, and the baby survived. In 2003, she experienced a spontaneous miscarriage at 4 and a half weeks of pregnancy. And in 2007 she had her last pregnancy with a birth at 32 gestational weeks, and this baby also survived.

Currently, the patient is clinically stable, with occasional episodes of hypoglycemia and receiving specific treatment for her various illnesses. Upon physical examination, at her last consultation, she was in good general condition, conscious, oriented, hydrated, acyanotic, anicteric, without edema, weighing 74.9 kg, height 159 cm, and body mass index compatible with overweight (29.6 kg/m^2). Waist circumference was 110 cm, heart rate was 86 bpm and blood pressure was 136/88 mmHg. The hypochromic spots of vitiligo are located on the face, hands, feet, genital region and thighs. According to the staging proposed by Kidney Disease: Improving Global Outcomes (KDIGO), diabetic kidney disease is in stage G2 A1.

Medication in use: Insulin Glargine 24IU/day; Insulin Lispro before the three main meals, in variable doses, depending on the carbohydrate count; Levothyroxine 75mcg/day; Metformin XR 2g/day; Prednisone 5mg/day; Atorvastatin 40mg/day; Cholecalciferol 50,000IU every 15 days; Losartan 50mg/day; Furosemide 40mg/day; Pregabalin 150mg/day; Citoneurin 5 thousand IU/month; Folic acid 5mg/day; Bromopride 10mg/day and Nortriptyline 25mg/day.

DISCUSSION

Our report highlights a rare case in which there is the occurrence of Carpenter syndrome, that is, the presence of APAI, associated with T1DM and autoimmune thyroid disease. This triple association of endocrine gland deficiencies due to autoimmune mechanisms is present in the minority of people affected by APS-2; an uncommon combination of pathologies of immunological etiology, which in most cases expresses only two deficiencies[1,5,6].

The association with other autoimmune diseases makes this condition even rarer[6,7]. Thus, the event observed in the situation described shows a patient who, in addition to manifesting APS-2, also expresses a group of autoimmune complications that are quite rare in these individuals, since she presents as additional manifestations: vitiligo, autoimmune panniculitis, autoimmune gastritis, disease celiac disease and Sjogren's syndrome.

Although autoimmune diseases do not yet have an established cause, it is known that the *HLA* complex is involved in their pathogenesis. The *HLA* gene, present on chromosome *6p21* of the antigen-presenting cell, has different haplotypes, which, when altered, can generate different autoimmune phenomena in the individual. It is important to highlight that only one subtype of the modified *HLA* complex can be related to different autoimmune pathologies. The *HLA-DR* and *HLA-DQ* gene loci are responsible for the susceptibility of several autoimmune diseases, such as: T1DM, celiac disease, autoimmune thyroid disease, autoimmune primary adrenal insufficiency, vitiligo and Sjogren's Syndrome. It may be that this type of event has directly influenced the genesis of the autoimmunities present in our report[8,9,10,11,12].

Furthermore, we must highlight that this woman, in addition to several autoim-

mune diseases that manifested before the age of 30, began to present, even in her youth, several associated complications, such as high blood pressure, diabetic nephropathy, bilateral non-proliferative diabetic retinopathy, neuropathy diabetes, dyslipidemia, episodes of hypoglycemia and seizures. Therefore, it is necessary to treat and/or stabilize these various diseases and comorbidities in isolation through the use of polypharmacy. Specific drug interventions are necessary to also avoid future morbidity and mortality resulting from conditions such as cardiovascular, neurological and various tissue/organ complications.

Our patient, despite all these pathologies and comorbidities, especially T1DM, which manifested itself in early childhood, managed to have two successful pregnancies with the proposed treatment. Considering that the patient is cared for within the scope of the Public Health System, it is a great challenge for health teams to keep all of her illnesses under control, but only in this way will she be more likely to remain stable, without morbidities that significantly compromise her health-related quality of life.

CONCLUSION

We report a very rare case of APS-2 with several autoimmune diseases, present in less than 1% of this population. We remind you that health professionals responsible for monitoring any patients with autoimmune diseases must always be aware that certain signs and symptoms present in the same patient may be part of a set of different diseases that are concomitant with each other, and the recognition of this fact has direct implications not only on the quality of life, but also on the survival of these people.

REFERENCES

1. Martins MA, Carrilho FJ, Alves VA, Castilho EA, Cerri GG. Clínica Médica, volume 5: doenças endócrinas e metabólicas, doenças ósseas, doenças reumatológicas. 2. ed. Barueri: Manole; 2016. 224-31 p.

2. Martins SC, Venade G, Teixeira M, Olivério J, Machado J, Marques J, et al. Autoimmune Polyglandular Syndrome type 2. Rev Assoc Med Bras [Internet]. 2019 Dec [cited 2023 Mai 30]; 65(12): 1434–7. Available from: https://doi.org/10.1590/1806-9282.65.12.1434

3. Weiler FG, Dias-da-Silva MR, Lazaretti-Castro M. Autoimmune polyendocrine syndrome type 1: case report and review of literature. Arq Bras Endocrinol Metab [Internet]. 2012 Feb [cited 2023 Mai 30]; 56(1): 54–66. Available from: https://doi.org/10.1590/S0004-27302012000100009

4. Vilar L. Endocrinologia clínica. 7. ed. Rio de Janeiro: Guanabara Koogan, 2022. 1063-68 p.

5. Singh G, Jialal I. Polyglandular Autoimmune Syndrome Type II. StatPearls [Internet]. 2023 Jan [cited 2023 Mai 30]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK525992/

6. Oliveira EA, Ribeiro ES, Dantas R, Guimarães J, Geraldo P. Um caso particular de síndrome poliglandular autoimune tipo 2. Revista Portuguesa de Endocrinologia, Diabetes e Metabolismo [Internet]. 2013 [cited 2023 Mai 30]; 8(2): 100-2. Disponível em: https://www.spedmjournal.com/section.php?id=340

7. Nascimento JL, Falcão TR, Castro AG, Cavalcante MR. Síndrome poliglandular autoimune tipo 2: relato de caso. Revista Contemporânea [Internet]. Set 2023 [cited 2023 Out 6]. Disponível em: https://ojs.revistacontemporanea.com/ojs/index.php/home/article/view/1462

8. Silva CS. Frequência dos alelos HLA-

-DQ2 e HLA-DQ8 associados com a doença celíaca em portadores de doenças autoimunes da tireoide. Universidade Federal de Pelotas [Internet]. 2019 Set [cited 2023 Nov 26]. Disponível em: https://guaiaca.ufpel.edu.br/bitstream/handle/prefix/7595/Dissertacao_Cledia_Silveira_Flores_da_Silva.pdf?sequence=1&isAllowed=y
9. Ramalho S, Nortadas R. Anticorpos na Diabetes Mellitus Tipo 1. Revista Portuguesa de Diabetes [Internet]. 2021 Fev [cited 2023 Nov 26]. Disponível em: http://www.revportdiabetes.com/wp-content/uploads/2021/07/RPD_Junho_2021_ARTIGO-DE-REVISAO_73-79.pdf
10. Neto IM, Lages AM, Melo JM. Impacto da Imunoterapia no Sistema Endócrino: Uma Revisão Sistemática. Universidade de Coimbra [Internet]. 2022 Mar [cited 2023 Nov 26]. Disponível em: https://estudogeral.uc.pt/bitstream/10316/102499/1/Tese%20de%20Mestrado%20Isabel%20Neto.pdf
11. Marchioro HZ, Castro CC, Fava VM, Sakiyama PH, Dellatorre G, Miot HA. Atualização na patogênese do vitiligo. Anais Brasileiros de Dermatologia [Internet]. 2022 Jul [cited 2023 Nov 26]. Disponível em: https://www.anaisdedermatologia.org.br/pt-atualizacao-na-patogenese-do-vitiligo-articulo-S266627522200087X
12. Barreto FV, Paula MC, Guimarães YA, Tironi TS, Carvalho DC, Peixoto BC. Manejo Estomatológico da Síndrome de Sjogren. Revista Educação e Saúde: Fundamentos e Desafios [Internet]. 2022 Ago [cited 2023 Nov 26]. Disponível em: https://uniptan.emnuvens.com.br/educacaoesaude/article/view/605/458

Indication of specific contributions from each author:

LMC- Substantial contribution to study design or data interpretation;

LMC- Participation in writing the preliminary version;

JCRD- Participation in the review and approval of the final version;

JCRD- Compliance with being responsible for the accuracy or completeness of any part of the study.

Financing: self-funded**.**

Acknowledgments: I thank my parents and sister for always supporting me. I thank the patient for her collaboration.

Corresponding Author:
Lucas Miranda Capóssoli
lucasmcapossoli@gmail.com

Received: jul 11, 2023
Approved: nov 25, 2024
Editor: Profa. Dra. Ada Clarice Gastaldi
