Primary Amenorrhea Associated with Hyperprolactinemia in Polyglandular Autoimmune Syndrome Type II: A Case Report

Amenorreia primária associada com hiperprolactinemia em síndrome poliglandular autoimune tipo 2: relato de caso

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Rev Bras Ginecol Obstet 2018;40:425–429.

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Abstract

Polyglandular autoimmune syndrome type II (PGA-II) is a rare immunoendocrinopathy syndrome characterized by the occurrence of autoimmune Addison disease along with diabetes mellitus type 1 and/or autoimmune thyroid disease. Here, we report the case of a 23-year-old female with PGA-II who was followed up at the dermatology and endocrinology clinics of the Universidade Federal do Triângulo Mineiro, located in the state of Minas Gerais, Brazil. First, the patient presented diffuse skin hyperpigmentation, vitiligo; and in sequence, due to vomiting, appetite and weight loss, hypoglycemia, amenorrhea, and galactorrhea, the patient was then diagnosed with PGA-II. The patient also presented intense hyperprolactinemia due to primary hypothyroidism. The late diagnosis of PGA-II is frequent because the disorder is uncommon and has non-specific clinical manifestations. This report emphasizes the significance of a timely diagnosis and appropriate treatment to reduce morbidity and mortality associated with these diseases, especially Addison disease. The present study reports a rare case of a patient with PGA-II with primary amenorrhea associated with hyperprolactinemia.

Keywords

- autoimmune polyglandular syndrome
- type II
- hyperprolactinemia
- amenorrhea
- autoimmune polyendocrinopathies
- vitiligo

Resumo

A síndrome poliglandular autoimune tipo 2 (SPGA-2) é uma síndrome de imunoendocrinopatia rara caracterizada por doença de Addison autoimune associada à diabetes mellitus tipo 1 e/ou doenças tireoidianas autoimunes. Relatamos aqui o caso de uma paciente de 23 anos de idade com SPGA-2 que foi acompanhada nos ambulatórios de dermatologia e endocrinologia da Universidade Federal do Triângulo Mineiro,

received
December 8, 2017
accepted
March 6, 2018
published online
June 27, 2018

DOI https://doi.org/10.1055/s-0038-1655749.
ISSN 0100-7203.

Palavras-chave
- síndrome poliglandular autoimune tipo 2
- hiperprolactinemia
- amenorreia
- poliendocrinopatias autoimunes
- vitiligo

localizada no estado de Minas Gerais, Brasil. Primeiramente, a paciente apresentou hiperpigmentação cutânea difusa e vitiligo; posteriormente, por apresentar vômitos, hiporexia, perda ponderal, hipoglicemia, amenorreia e galactorreia, foi diagnosticada com SPGA-2. A paciente apresentou também intensa hiperprolactinemia secundária apenas ao hipotireoidismo primário. É comum o diagnóstico tardio da SPGA-2, pois a doença é rara e apresenta manifestações clínicas inespecíficas. Este relato de caso enfatiza a importância do diagnóstico e tratamento precoces com o objetivo de reduzir a morbimortalidade associada a essas doenças, especialmente à doença de Addison. O presente estudo descreve um caso raro de uma paciente com SPGA-2 com amenorreia primária associada a hiperprolactinemia.

Introduction

Polyglandular autoimmune syndromes (PGAs) are a heterogeneous group of rare diseases that fall within one of four patterns of autoimmune failure.[1–3] The most common pattern is PGA type II (PGA-II), which has greater phenotypic variability and associated diseases that manifest later in life.[1] The other types of PGA include type I, which usually consists of chronic mucocutaneous candidiasis, hypoparathyroidism and adrenal insufficiency; type III, which usually consists of thyroiditis and others autoimmune diseases, and type IV, which by definition consists of two autoimmune disorders not classified in type I, II, or III.[3] However, some authors only consider the existence of the types I and II, including types III and IV as part of PGA-II type.[4,5] Polyglandular autoimmune syndromes type II is rare, with a prevalence of 1.4 to 2.0 cases per 100,000 individuals, and affects predominantly middle-aged women.[4,6,7] The syndrome expresses an autosomal dominance pattern with incomplete penetrance and has been associated with human leukocyte antigen (HLA)-DR3 and/or HLA-DR4 haplotypes that increase genetic susceptibility.[4,7,8]

Polyglandular autoimmune syndromes type II (, or Schmidt syndrome, is characterized by the occurrence of Addison disease (100% of cases) along with diabetes mellitus type 1 and/or autoimmune thyroid disease.[5,7,9,10] In addition, PGA-II can be associated with less frequent manifestations (4–11% of cases), such as vitiligo, gastritis, hypogonadism, hepatitis, and alopecia areata. Rare autoimmune conditions (frequency $< 1\%$) include myasthenia gravis, rheumatoid arthritis, and Sjögren syndrome.[8] The most frequent clinical combinations of PGA-II are Addison disease and Hashimoto thyroiditis.[7]

The treatment for PGA-II involves therapeutic measures that target the pathology of the autoimmunities as they appear separately, and prognosis been related to the recognition of adrenal insufficiency, which is primarily responsible for significant morbidity and mortality.[8]

The aim of the present study is to report a rare case of a 23-year-old female patient with PGA-II with primary amenorrhea associated with hyperprolactinemia.

Case Presentation

A 23-year-old female patient had been attending the dermatology clinic of Universidade Federal do Triângulo Mineiro for vitiligo and diffuse skin hyperpigmentation. When the patient presented with asthenia, nausea, vomiting, loss of appetite, lethargy, progressive weight loss ($\sim$ 10 kg in 6 months), chronic intestinal constipation, and primary amenorrhea associated with galactorrhea, she was referred to the endocrinology clinic. Patient history obtained from her relatives revealed that she was diagnosed with neuropsychomotor development delay in her childhood and had been recently hospitalized for hypoglycemia (23 mg/dl). Upon initial physical examination, the patient had a height of 155.6 cm, weight of 38 kg (IMC = 15.8 kg/m^2), diffuse skin hyperpigmentation with vitiligoid hypopigmented strains (face, back, and limbs), and arterial hypotension (90/60 mm Hg). The pubertal development of secondary sex characteristics was at Tanner stage 4 with galactorrhea in the mammary expression (►**Fig. 1**).

The laboratory tests revealed autoimmune hypothyroidism with positive anti-thyroid autoantibodies and primary hypocortisolism with an autoimmune etiology characterized by high concentrations of adrenocorticotropic hormone (ACTH) and decreased levels of cortisol associated with the positivity of anti-21 hydroxylase. The tests also revealed hyponatremia and hyperkalemia (►**Table 1**), which confirmed the diagnosis of PGA-II. In addition, the patient presented with high concentrations of prolactin (365.3 ng/ml), but magnetic resonance imaging of the sella turcica showed only discreet pituitary hyperplasia without tumor mass. Despite neuropsychomotor development delay, the patient did not use drugs that could contribute to hyperprolactinemia.

The patient was administered a daily dose of prednisone (7.5 mg), 9-α -fludrocortisone (0.1 mg), and levothyroxine (50 µg). She showed significant improvement in her initial symptoms with weight gain, increased blood pressure, resolution of galactorrhea, and diffuse skin lightening (►**Fig. 2**). In addition, the thyroid function was stabilized, and hydroelectrolyte disturbances were corrected. Two months after the initiation of levothyroxine therapy, the prolactin concentrations normalized (8.13 ng/ml).

During the initial investigation, a pelvic ultrasound was conducted to determine the presence of autoimmune oophoritis, but no changes in the uterus or ovaries were detected. The gonadotrophic axis evaluation was compatible with hypogonadotropic hypogonadism, characterized by decreased concentration of estradiol associated with inappropriately normal

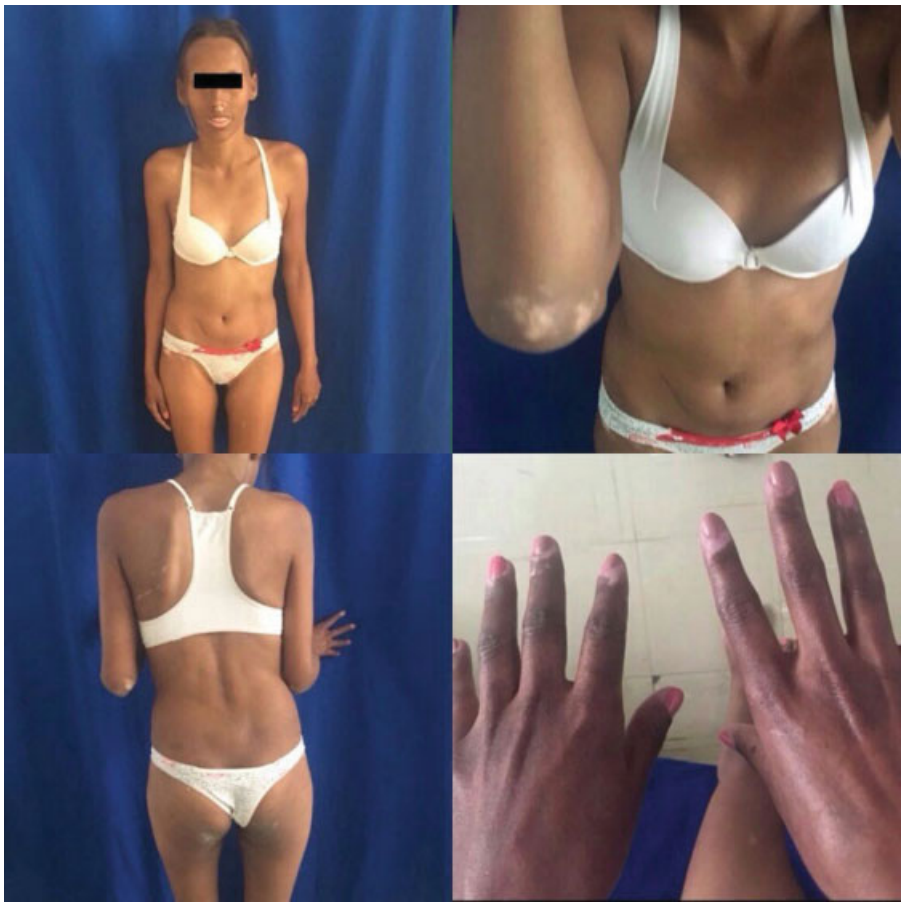

Fig. 1 Diffuse skin hyperpigmentation, vitiligoid stains (face, back, buttocks, and limbs) and nutritional status of the patient upon admission.

Table 1 Laboratory test obtained at the admission and after two months of treatment

Laboratory tests	Before treatment	2 months after treatment
TSH	64.82 mUI/L	1.69 mUI/L
Free T4	0.913 ng/dL	1.59 ng/dL
Anti-TPO	252.3 UI/mL	—
Anti-TG	131.1 UI/mL	—
Basal Cortisol	0.10 ug/dL	—
Anti-21 hydroxylase	20.5 U/ml	—
Sodium	130 mmol/L	135 mmol/L
Potassium	6.67 mmol/L	4.26 mmol/L
Blood Glucose	77.5 mg/dL	84.1 mg/dL
Prolactin	365.3 ng/mL	8.13 ng/ml
DHEAS	0.88 ug/dL	—
Hemoglobin	11.4 g/dL	15.5 g/dL
ACTH (pg/mL)	above 1,250 pg/mL	—
FSH	3.6 mUI/mL	10.11 mUI/mL
LH	2.8 mUI/mL	12.39 mUI/mL
Estradiol	15.35 pg/mL	24.04 pg/mL

Abbreviations: ACTH, adrenocorticotropic hormone; Anti-TG, anti-thyroglobulin; Anti-TPO, antithyroperoxidase; Free T4, thyroxine free; FSH, follicle stimulating hormone; LH, luteinizing hormone. DHEAS, dehydroepiandrosterone sulfate; TSH, thyroid-stimulating hormone.

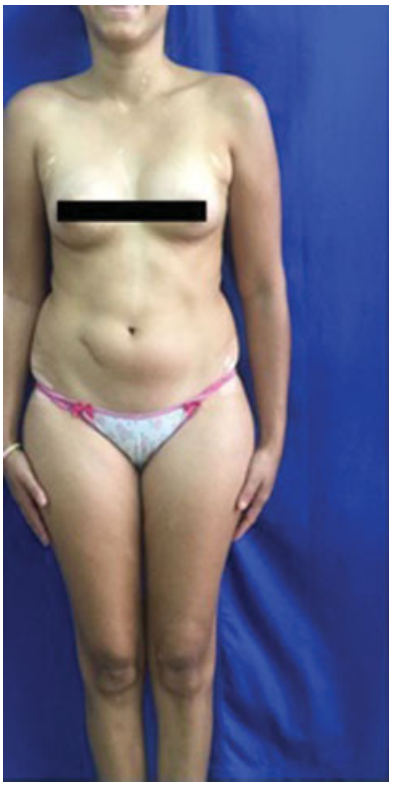

Fig. 2 The patient after 5 months of treatment, with evidence of diffuse skin lightening and weight gain.

concentrations of FSH and LH (►**Table 1**). Other autoantibodies were also dosed for screening of autoimmune diseases (anti-glutamic acid decarboxylase-65, anti-islet cells, antitissue transglutaminase antibodies, parietal cell and anti-intrinsic factor antibodies), which were negative. The patient presented with menarche 3 months after the initiation of treatment, which confirmed that amenorrhea was secondary to hyperprolactinemia.

Discussion

The present case of PGA-II in a 23-year-old patient is rare because of the presence of primary amenorrhea associated with hyperprolactinemia at a level consistent with concentrations found commonly in prolactinomas (365.3 ng/mL), which resulted in the delay of diagnosis. According to Michel et al (2014), the frequent late diagnosis of PGA-II is the result of the nonspecific nature of the symptoms of adrenal insufficiency (Addison disease) and Hashimoto thyroiditis.[11–14] Autoimmune adrenal insufficiency slowly progresses and gradually impairs the adrenal cortex glands, leading to glucocorticoid, mineralocorticoid, and adrenal androgen deficiencies. Skin hyperpigmentation, resulting from the continuous stimulation of pituitary corticotrophs, is the most common sign of adrenal insufficiency and aids in the diagnosis of PGA-II. In the present case, the observed skin hyperpigmentation associated with vitiligo compelled the patient to seek dermatological consultation, where the patient's symptoms led to the eventual PGA-II diagnosis by the endocrinology department. Skin hyperpigmentation results from cross-reactivity between high concentrations of ACTH as a result of a lack of cortisol feedback and melanocortin 1 receptor in the keratinocytes. Diffuse skin darkening may be more prominent in the palm lines, oral mucosa, edge of the lips, and around scars and nipples. Approximately 50% of patients with Addison disease develop another autoimmune disorder throughout their lifetime; therefore, patients with autoimmune diseases should undergo active surveillance for the detection of other autoimmune diseases.[11]

While the simultaneous diagnosis of hypothyroidism and autoimmune adrenal insufficiency is expected in patients with PGA-II, there are few reports of this occurrence in the literature. Gouveia et al (2010)[1] described the chronological sequence of PGA-II pathology onset, with Hashimoto thyroiditis commonly appearing simultaneously with or subsequently to adrenal gland disease. In the present case, the patient was diagnosed with the two diseases simultaneously, despite the presentation of amenorrhea, which could have led to an earlier diagnosis. Menstrual disorders, such as primary amenorrhea, can be associated with many systemic diseases; however, reports have indicated that in primary hypothyroidism, the increase of the thyrotropin-releasing hormone (TRH) stimulates not only the pituitary thyrotrophs, but also, to a lesser extent, the lactotrophs. In addition, in this disease, the pituitary cells have reduced sensitivity to the inhibitory effects of dopamine. Consequently, a small to moderate increase in the levels of prolactin is common in primary hypothyroidism.[13] In the present case, the hyperprolactinemia was much more pronounced than expected, which led to the magnetic resonance imaging of the sella turcica to detect prolactinoma. However, 2 months after the initiation of levothyroxine for the treatment of hypothyroidism, the prolactin levels normalized (8.13 ng/mL) without the use of specific medications for hyperprolactinemia. This outcome confirms the causal relationship between hypothyroidism and hyperprolactinemia.

Although rare, there are reports in the literature of prominent hyperprolactinemia secondary to primary hypothyroidism. Ansari et al (2016)[13] reported a case of PGA-II with very high concentrations of prolactin (3,234 mIU/L) that were secondary to primary hypothyroidism. Numerous similar clinical cases have also been published, but with reportedly lower prolactin levels (below 100 ng/ml).[14,15] Vitiligo is relatively common (prevalence of 0.5–2.0% of the general population), but its pathogenesis is not fully understood. Autoimmunity as an etiological cause has been suggested because of the frequent association with other autoimmune diseases, with autoimmune thyroid disease present in 14 to 34% of vitiligo cases. In other diseases of autoimmune etiology, such as diabetes mellitus, adrenal insufficiency, systemic lupus erythematosus, alopecia areata, pernicious anemia, and myasthenia gravis, vitiligo has been associated with varying frequencies.[16] In addition, other factors that corroborate the hypothesis of the autoimmunity pathogenesis of vitiligo are the presence of anti-melanocyte antibodies and a favorable response to immunosuppressive therapy.[17] Thus, clinically

evident autoimmune diseases, such as vitiligo, can be considered clinical markers of the disease in its manifested form (not yet diagnosed) or latent form (only with positive autoantibodies), which may develop over time.[7]

Conclusion

The present clinical case emphasizes the need for earlier clinical recognition of PGA-II and possible autoimmune disease associations. Clinical markers, such as vitiligo, skin hyperpigmentation, and amenorrhea associated with galactorrhea, may aid in the earlier diagnosis of PGA-II. Although rare, the PGAs directly affect the quality of life and survival of diagnosed patients. The present case highlights the need for standardized protocols for the diagnosis and treatment of autoimmune diseases, which will reduce the morbidity and mortality associated with these syndromes. As a follow-up proposal for PGA-II patients, the authors suggest regular visits every 6 months to follow-up the already diagnosed diseases as well as for screening of other autoimmune conditions that may arise and that were described in this article as more commonly associated with PGA-II. In addition, the physicians should be alert at each visit to detect any signs and symptoms of suspected autoimmunity, with early referral of the patient for appropriate investigation and treatment.

Conflicts of Interest

The authors declare that there are no conflicts of interest in relation to the publication of this article.

Acknowledgments

The authors thank Universidade Federal do Triângulo Mineiro (UFTM, in the Portuguese acronym) and Hospital de Clínicas of UFTM for the relevant contribution in the development of this case report. There was no financial support for this case report.

References

1 Gouveia S, Ribeiro C, Gomes L, Carvalheiro M. Síndrome poliglandular autoimune tipo 2: caracterização clínico-laboratorial e recomendações de abordagem e seguimento. Rev Port Endocrinol Metab 2010;5:69–82
2 Gürkan E, Çetinarslan B, Güzelmansur İ, Kocabaş B. Latent polyglandular autoimmune syndrome type 2 case diagnosed during a shock manifestation. Gynecol Endocrinol 2016;32(07):521–523. Doi: 10.3109/09513590.2015.1137096
3 Gouveia S, Gomes L, Ribeiro C, Carrilho F. Rastreio de síndrome poliglandular autoimune em uma população de pacientes com diabetes melito tipo 1. Arq Bras Endocrinol Metabol 2013;57(09): 733–738. Doi: 10.1590/S0004-27302013000900010
4 Lakhotia M, Pahadia HR, Kumar H, Singh J, Tak S. A case of autoimmune polyglandular syndrome (APS) type II with hypothyroidism, hypoadrenalism and celiac disease – a rare combination. J Clin Diagn Res 2015;9(04):OD01–OD03. Doi: 10.7860/JCDR/2015/10755.5748
5 Resende E, Gómez GN, Nascimento M, et al. Precocious presentation of autoimmune polyglandular syndrome type 2 associated with an AIRE mutation. Hormones (Athens) 2015;14(02): 312–316. Doi: 10.14310/horm.2002.1513
6 Anyfantakis D, Symvoulakis EK, Vourliotaki I, Kastanakis S. Schmidt's syndrome presenting as a generalised anxiety disorder: a case report. J Med Life 2013;6(04):451–453
7 Oliveira EA, Ribeiro ES, Dantas R, Guimarães J, Geraldo P. Um caso particular de síndrome poliglandular autoimune tipo 2. Rev Port Endocrinol Metab 2013;8:100–102. Doi: 10.1016/j.rpedm.2013.06.002
8 Jose N, Kurian GP. Schimidt syndrome: an unusual cause of hypercalcaemia. J Clin Diagn Res 2016;10(05):OD21–OD22. Doi: 10.7860/JCDR/2016/16770.7783
9 Gonzalez-Perez P, Correia M, Capizzano AA, Adams HP. Isolated cortical vein thrombosis in autoimmune polyglandular syndrome type 2. Neurology 2016;86(13):1262–1263. Doi: 10.1212/WNL.0000000000002530
10 Kırmızıbekmez H, Yeşiltepe Mutlu RG, Demirkıran Urgancı N, Öner A. Autoimmune polyglandular syndrome type 2: a rare condition in childhood. J Clin Res Pediatr Endocrinol 2015;7(01):80–82. Doi: 10.4274/jcrpe.1394
11 Wang X, Ping F, Qi C, Xiao X. Delayed diagnosis with autoimmune polyglandular syndrome type 2 causing acute adrenal crisis: A case report. Medicine (Baltimore) 2016;95(42):e5062. Doi: 10.1097/MD.0000000000005062
12 Michels A, Michels N. Addison disease: early detection and treatment principles. Am Fam Physician 2014;89(07):563–568
13 Ansari MS, Almalki MH. Primary hypothiroidism with markedly high prolactin. Front Endocrinol (Lausanne) 2016;7:35. Doi: 10.3389/fendo.2016.00035
14 Goel P, Kahkasha Narang S, Gupta BK, Goel K. Evaluation of serum prolactin level in patients of subclinical and overt hypothyroidism. J Clin Diagn Res 2015;9(01):BC15–BC17. Doi: 10.7860/JCDR/2015/9982.5443
15 Moumen A, Meftah A, El Jadi H, Elmoussaoui S, Belmejdoub G. An unusual pituitary mass revealing a primary hypothyroidism!. Clin Pract 2015;5(01):733. Doi: 10.4081/cp.2015.733
16 Amerio P, Tracanna M, De Remigis P, et al. Vitiligo associated with other autoimmune diseases: polyglandular autoimmune syndrome types 3B+C and 4. Clin Exp Dermatol 2006;31(05): 746–749
17 de Jong MA, Adelman C, Gross M. Hearing loss in vitiligo: current concepts and review. Eur Arch Otorhinolaryngol 2017;274(06): 2367–2372. Doi: 10.1007/s00405-017-4452-8