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Schmidt's Disease: A Case Report

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ABSTRACT

The Polyglandular autoimmune syndromes (PGA) consists of immune dysfunction affecting two or more endocrine glands and other non-endocrine organs. There are PGA I, PGA II and PGA III. The second type involves dysfunction of the adrenal gland, namely Addison's disease plus either autoimmune thyroiditis or type I Diabetes Mellitus. We report the case of a 21 year old female known to have Hashimoto disease who has presented with generalized fatigue and abdominal pain induced by an adrenal insufficiency onset. She was diagnosed with PGA II and treated with hydrocortisone and levothyroxine to which her condition quickly responded and eventually improved.

Keywords: *Polyglandular Autoimmune Syndromes, Schmidt's Disease, Endocrine Glands, Diabetes Mellitus*

Introduction

Immune dysregulation leads to a cluster of endocrine abnormalities, which manifest discreetly in subjects as autoimmune polyglandular syndromes (PGA) (Sperling *et al*., 2000). The discreet patterns of manifestation allows anticipation of other associated hormonal discrepancies as well as the adequate treatment of each. The diagnosis of each type is dependent on the diagnosis of each of the diseases associated with it. Although an important diagnostic tool, the presence of autoantibodies is not indicative of organ damage. There are three major entities: PGA I, PGA II and PGA III (Sperling *et al*., 2000; Hansen *et al*., 2014). While PGA I features mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency, the latter is a feature of PGA II along with thyroid autoimmunity and type I diabetes mellitus. PGA III consists only of thyroid autoimmunity and type I diabetes mellitus. PGA II, also known as Schmidt's syndrome, is more common than PGA I and usually manifests, although very rare, in middle-aged women. The prevalence of Schmidt's disease is 1.3-2.0 per 100,000 population (Sonthalia *et al*., 2013). The autoimmune thyroid disease in PGA II can manifest as thyroiditis or Grave's disease. Hence, both hypo- and hyperthyroidism can be features of PGA II. We report the case of 21 years-old woman known to have Hashimoto disease, who was received at the emergency department for severe abdominal

pain, vomiting and fatigue secondary to an adrenal insufficiency onset and was diagnosed with PGA II.

Case Presentation

We present the case of a 21-years old woman who was referred by the endocrinology clinic to the emergency department for severe generalized fatigue, vomiting and abdominal pain. No clue of dyspnea, headache, fever and dizziness was evident. The patient reported progressing face, hands, lips and tongue hyperpigmentation that has started one and half month before presentation and was still progressing.

The patient detailed that her chief complaint goes back to about 18 months prior to presentation. She reported 3 episodes of syncope. The patient was diagnosed previously with Hashimoto hypothyroidism to which she had been taking 25 mcg of thyroxin daily. Otherwise, she denied any other medical conditions or surgical interventions.

Upon physical exam, the patient seemed pale, anicteric, moderately emaciated with clear lungs and scaphoid abdomen with mild pain on deep palpation. Melanodermia was evident on her lips, tongue and hands (Fig. 1, 2 and 3). Otherwise, physical exam was normal.

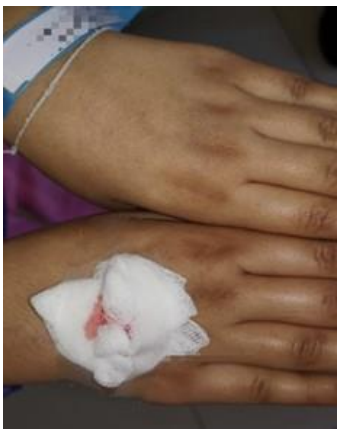

Figure 1: Hyperpigmentation of the hands.

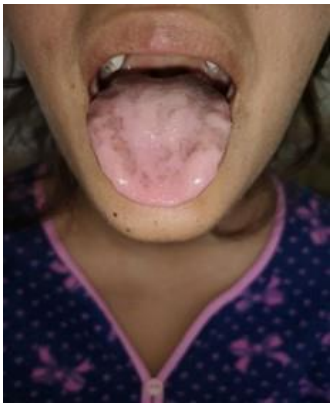

Figure 2: Hyperpigmentation of the tongue.

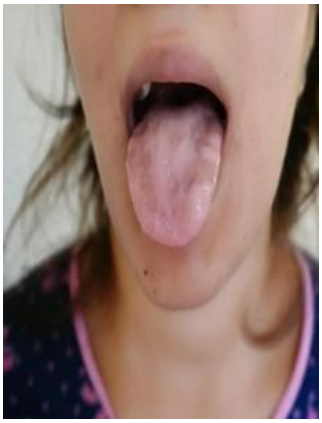

Figure 3: Hyperpigmentation of the lips and tongue.

Laboratory workup included a complete blood count and differential, blood electrolytes measurement, thyroid and adrenal function test, and autoimmune antibodies titer measurement. The results along with the normal range of each are evident in Table 1. The patient presented with symptoms of adrenal insufficiency. This is demonstrated as well through the laboratory findings of anemia (HB 10.3 g/dl) and leukocytosis (WBC 14280/ mm3), which are related to adrenal insufficiency and crisis.

A Ct scan of the abdomen and pelvis was done using IV contrast and revealed normal findings with no adrenal pathology. A pituitary and brain MRI were also done and revealed normal findings. Chest x-ray was normal with no evidence of pleural effusion or pulmonary edema.

The findings of normal pituitary gland, normal adrenals, elevated ACTH, TSH, anti-21-hydroxylase antibodies, and anti-thyroglobulin antibodies and low cortisol and FT4 levels revealed primary adrenal insufficiency, namely Addison's disease, and affirmed a previous diagnosis of hypothyroidism. Hence, the patient was diagnosed with PGA II i.e. Schmidt's disease. She was treated initially with hydrocortisone 100 mg three times per day and the dose of levothyroxine was increased to 100 mcg per day. After 2 days of hospitalization, the patient improved and her general status was stabilized. The patient was then discharged on Hydrocortisone daily dose of 20 mg, Fludrocortisone 0.1mg/j and levothyroxine of 100 mcg and a recommendation of monthly laboratory workup for modification of the treatment regimen.

Discussion

The combination of Addison's disease with either type I diabetes mellitus or thyroid autoimmune disease is an obligation for the diagnosis of Schmidt's disease. The latter is the most common immunoendocrinopathy (Sperling *et al*., 2000). The thyroid autoimmune pathology can manifest as either hypo- or hyperthyroidism. Usually, PGA II can be observed with other endocrinopathies such as primary hypogonadism, vitiligo, rheumatoid arthritis, lupus, Sjogren and myasthenia gravis.

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The etiology of types of PGA is mainly genetic. PGA I is due to a mutation of the AIRE gene on chromosome 21, which is inherited in an autosomal recessive manner (Bello and Garla, 2022). It manifests as adrenal insufficiency, mucocutaneous candidiasis, and hypocalcaemia and hyperphosphatemia i.e. hypoparathyroidism. PGA II and III are both due to mutations in the HLA DQ/DR regions (Sperling *et al*., 2000; Bello and Garla, 2022). These regulate antigen presentation to T-cell receptors (TCRs). PGA II is a polygenic disease. Multiple genetic loci and environmental factors depart major heterogeneity to this disease. HLA and non-HLA genes can redispose to PGA II. Examples include HLA-DR3 and HLA-DR4 haplotypes and CD25-interleukin-2 receptor gene, cytotoxic T-lymphocyte protein 4 and protein tyrosine-protein phosphatase, non-receptor type 22 genes. As the diagnosis of PGA II depends on symptoms, genetic testing is mainly for evaluation of assessment of predisposition. However, family members of patients diagnosed with PGA II must be annually checked for symptoms. Diagnosed patients are essentially monitored for organ dysfunction (Husebye *et al*., 2018).

Some of the cases of PGA II appear to be sporadic in nature. Meanwhile, PGA III can be transmitted in an autosomal dominant manner with incomplete penetrance (Kahaly, 2009). Of note, other syndromes qualify as PGAs. An example is an X-linked syndrome of immunodysregulation, enteropathy and polyendocrinopathy. It is due to mutation in the FOXP3 gene. Moreover, there is an emergence of new endocrinopathies secondary to cancer immunomodulatory treatments that can lead to manifestations similar to the aforementioned PGAs.

Diagnosis of each PGA type resides in the constellation of endocrinopathies manifested in each case (Sperling *et al*., 2000; Hansen *et al*., 2014; Kahaly, 2009). Hence, the treatment is targeted through hormonal replacement therapy to compensate for the hormonal deficit depicted in each case. In this case, a hydrocortisone daily dose as well as fludrocortisone were given to compensate for the primary adrenal insufficiency and levothyroxine dose was increased to adjust for the low FT4 precipitated by the already diagnosed Hashimoto thyroiditis and the high TSH indicative of inadequate levothyroxine therapy. Key fact is the necessity of initiation of hormonal therapy for the compensation of the adrenal insufficiency before hypothyroidism. Correction of the latter initially can precipitate an adrenal crisis. This patient presented with symptoms of adrenal crisis after being on levothyroxine replacement therapy. Hence, reflection on this sequence in hormonal therapy is key for adequate management in PGA II (Freeland *et al*., 2017) [1].

Table 1: Showing the result of laboratory workup and the normal range of each parameter.

Laboratory test	Parameter	Obtained value	Normal range
Compete blood count with differential	Hemoglobin (g/dl)	10.3	11-16
	Hematocrit (%)	33.4	35-47
	Total White blood cell count (/mm^3)	14280	4000-11000
	Neutrophil (%)	67	40-65
	Basophil (%)	0	0-1
	Lymphocyte (%)	28	25-40
	Eosinophil (%)	1	1-4
	Platelets (/mm^3)	324000	350000-400000
Electrolytes	Sodium (mmol/l)	142	135-150
	Potassium (mmol/l)	4	3.5-5.5
	Chloride (mmol/l)	105	55-117
	Magnesium (mg/dl)	1.65	1.6-2.5
	Phosphorus (mg/dl)	4.71	2.7-4.8
	Calcium (mg/dl)	9.59	8.5-10.5
Thyroid function test	TSH (mIU/l)	23.65	0.27-5
	FT4 (ng/dl)	0.02	0.7-1.9
Adrenal function test	ACTH (pmol/l)	837	1.1-13.2
	Cortisol (mcg/dl)	0.387	2-3
Autoantibodies titer	Anti 21-hydroxylase antibodies (ratio)	95.4	<10
	Anti-thyroglobulin antibodies (IU/ml)	156.9	<115
	Anti-thyroid antibodies TPO antibodies	37.12	<32
	Anti-T-glutaminase IgA antibodies (UA/ml)	Negative	Pos>18
Others	Creatinine (mg/dl)	0.62	0.5-1
	Fasting blood sugar (mg/dl)	91	70-110

Consent: The patient signed consent and approved to share her images, condition, laboratory and imaging results for the purpose of medical publications. She was informed of her right to refuse to participate and share her condition and she was aware of the purpose of this publication.

Conflicts of Interest: None of the authors have any conflict of interest.

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Ethical Clearance: Retrieval, analysis and sharing of the medical file and images associated was done with previous apprehension of the ethical committee. Case reports are not required to have a written ethical committee approval. A consent signed by the patient is mandatory for data retrieval and publication.

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Web-Links

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