Autoimmune Polyglandular Syndrome Type 2 with Alopecia Universalis and Hypoparathyroidism

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Abstract

A 46 years old female, presented with severe fatigue, hypotension and hyperpigmentation. Her basal serum cortisol level at 8 a.m. was <1.0 µg/dl which suggested a diagnosis of Addison’s disease. An association with latent autoimmune diabetes of adult and autoimmune hypothyroidism led to a diagnosis of Polyglandular Autoimmune Syndrome type II (PAS II). She also had alopecia universalis and hypoparathyroidism which are very rare in PAS type II syndrome. On treatment with hydrocortisone and fludrocortisone there was drastic improvement in the clinical features.

Introduction

When immune dysfunction affects two or more endocrine glands, in conjunction with other non-endocrine immune disorders the Polyglandular Autoimmune (PGA) syndrome should be considered.¹ There are two major subtypes of PGA syndrome. Type 1 is also called APECED (Autoimmune Polyendocrinopathy, Candidiasis and Ectodermal Dystrophy) or MEDAC

PAS type II (Multiple Endocrine Deficiency Autoimmune Candidiasis Syndrome; Carpenter syndrome) is the coexistence of adrenal insufficiency with autoimmune thyroid disease, and/or type 1 diabetes mellitus (DM). PAS type II is more common than type 1.² The other types of Autoimmune Polyglandular Syndromes are 3 and 4. Type 3 is autoimmune thyroid disease associated with other autoimmune diseases (excluding Addison’s disease and or hypoparathyroidism while Type 4 is a combination of organ-specific diseases not included in the previous groups.³

Case Report

A 46 years old female, known to have diabetes for one year presented to hospital with complaints of severe fatigue and loss of energy for 1 month. She had also noticed darkening of skin of face and hair loss for 3 months, for which she took treatment from her general practitioner, without improvement. She was already on oral hypoglycemic drugs ((combination of glimepiride and metformin, 2 mg and 500 mg) twice a day for the past one year. She also complained of circumoral tingling, numbness and muscle cramps on and off. However there was no history of carpopedal spasm on detailed enquiry. She had two healthy male children, 16 and 13 years old. She had a normal menstrual history except for the last one year when she had scanty bleeding and prolonged menstrual cycles as she was approaching menopause. Her height was 160 cms, weight 61 kg and body mass index (BMI) was 23.82 kg/m². On examination her pulse was 62/min, blood pressure was 80/60 mmHg. She had no anaemia or any obvious neck swelling. There was complete baldness as well as loss of hair in eyebrow (Figure 1), axilla and pubic region. On detailed examination there were bluish blackish patches on the tongue, (Figure 2), buccal mucous membrane, and there was bronze darkening of skin of face and knuckle (Figure 3).

Lab investigations revealed hemoglobin of 12 gm/dl (normal 12.0-15.8 gm/dl), fasting blood glucose 234 mg/dl (normal <126 mg/dl), and post-prandial blood glucose of 317 mg/dl (normal <200 mg/dl). Because of persistent hypotension the basal serum cortisol levels were sent. The basal serum cortisol level at 8 a.m. was <1.0 µg/dl (normal 5-25 µg/dl). One ampoule (250 mcg) cosyntropin was given intravenously and serum cortisol level was measured 45 minutes later. The cortisol level increased to 27 µg/dl (normal >14 µg/dl). The test was positive and indicated primary adrenal insufficiency. Her ultrasensitive TSH was 7.25µIU/mL (0.34-4.25

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µIU/mL), free T3 was 1.4 pg/ml (2.4-4.2 pg/ml) and free T4 was 0.45 ng/dl (0.7-1.24 ng/dl). Her HbA1c was 7.2 (> 6.5 % considered diabetes), serum C peptide level was 0.21 ng/dl and glutamic acid decarboxylase (GAD) antibody was positive (patients >500 IU/ml, >10 IU/ml considered positive). Her serum parathyroid hormone was 4.5 pg/ml (normal 8-51 pg/ml), serum calcium was 8 mg/dl (normal 8.7-10.2 mg/dl) and serum phosphorus was 5.8 mg/dl (normal 2.4-4.1 mg/dl). Other electrolytes were normal. Ultrasonography of abdomen, chest x ray, electrocardiogram (ECG), magnetic resonance imaging of brain (MRI) and computerized tomography (CT) of abdomen were normal. Ultrasonography of thyroid showed hypoechoic lesions and her anti-thyroid peroxidase antibody (TPO) was positive 418.7 U/L (normal 35 IU/L). In spite of oral hypoglycemic drugs which she was already taking from outside, her blood glucose levels were not controlled, hence she was shifted to premeal regular insulin, on day 1 of admission, the total insulin requirement being 46 units of regular insulin. She was also started on oral tab hydrocortisone 20 mg in the morning and 10 mg in evening. Looking at the thyroid profile she was advised 50 µgm of thyroxine after 15 days, in the morning. After starting the treatment three months later, on follow up her symptom of fatigue was much better, hypotension was corrected and there was drastic improvement in hyperpigmentation at all sites (Figures 4 and 5). In view of hypoparathyroidism she was also started on Vitamin D 60,000 U/day and elemental calcium 1 gm/day. Her repeat serum parathyroid hormone was also done on follow up to confirm hypoparathyroidism which came out to be 4 pg/ml. However, her blood glucose levels demanded further increase in insulin requirement by 12 units.

**Discussion**

Our patient had latent autoimmune diabetes of adult (LADA), primary adrenal insufficiency, hypothyroidism and hypoparathyroidism. The evidence of LADA was a positive anti-glutamic acid decarboxylase (anti-GAD) antibody level (>500 IU/ml). In the absence of corticosteroid binding globulin deficiency, an unstimulated serum cortisol sample drawn between 6:00 and 8:00 a.m. may be useful, because a level less than 3 mcg/dl (80 nmol/l) strongly suggests adrenal insufficiency, and levels of 8 mcg per dl (221 nmol/l) or greater exclude the diagnosis of adrenal insufficiency. In our case, the basal cortisol level at 8 a.m. was 1 µg/dl (less than 3 µg/dl). Hence it was highly suggestive of adrenal insufficiency. Considering multiple endocrine affection in our patient we wanted to confirm that involvement of adrenals is primary and not secondary. The cosyntropin test works well in patients with primary adrenal insufficiency. The low-dose ACTH stimulation test (1 µg) has been shown to be more sensitive and specific than the high-dose test (250 µg), however; the high-dose test is preferred since the low-dose test has not been validated. The test has a reported specificity of 95%, with sensitivities of 97%, 57%, and 61% for primary adrenal insufficiency (250 µg cosyntropin test), secondary adrenal insufficiency (250 µg Cosyntropin test), and secondary adrenal insufficiency (1 µg Cosyntropin test), respectively. In our case very low basal cortisol
levels and failure of adrenal glands to respond appropriately to Cosynotropin was highly suggestive of primary adrenal insufficiency. Our limitation was non-availability of 21, hydroxylase antibody. Hypothyroidism was of autoimmune nature as TPO antibody was positive. So a diagnosis of PGA type II was made.

Approximately 14-20 people per million population are affected by PAS type 2. The disease is much more prevalent if subclinical forms are included. In a study of 129 patients of APS type II as far as clinical combination concern 88.4% patients had 2 main diseases (Addison’s disease and autoimmune thyroid disease), while only 11.6% of patients had the complete tri-glandular syndrome (Carpenter’s syndrome). Our patient also had all three endocrine conditions which is very rare. PGA type 2 syndrome is associated with HLA-DR3 and/or HLA-DR4 haplotypes. The pattern of inheritance is autosomal dominant with variable expressivity and a female-to-male ratio of 3-4:1, it occurs in the third or fourth decade of life. Approximately one half of patients with APS II have relatives with autoimmune disorders. However, our patient had no relatives with similar history to the best of our knowledge.

Primary adrenal insufficiency is the principle manifestation of PGA2. PGA2 can be associated with other autoimmune disorders like myasthenia gravis, primary hypogonadism, vitiligo, alopecia and serositis. Pernicious anemia also occur with increased frequency in patients with this syndrome. Our patient had alopecia universalis which is rare, and is seen in only 1 to 4% cases of autoimmune polyglandular syndrome type 2.

Hypoparathyroidism is most often isolated and idiopathic. Hypoparathyroidism in autoimmune polyendocrine syndrome type 2 is extremely rare with few isolated reports and usually presents late. Our patient also had hypoparathyroidism as evidenced by low parathyroid hormone on two occasions (day 3 of admission and on follow up) reduced calcium levels, high phosphorus level and frequent episodes of circumoral paresthesia and muscle cramps which improved after calcium and vitamin D supplements however there was no demonstrable tetany. Hypoparathyroidism in APS is most commonly associated with APS 1 observed mostly in children. Our patient had no evidence of mucocutaneous candidiasis, so she did not fit into APS type I, which is observed mostly in children.

As a rule corticoadrenal failure due to autoimmune adrenitis, both as isolated form or as component of APS syndrome, shows normal or miniscule adrenal glands bilaterally as in our case. Ultrasound technique has greatly enhanced the diagnosis of thyroid autoimmune diseases in the recent year and diffuse or multifocal hypoechoic pattern has claimed to be typical of autoimmune thyroathy, both in goitrous or in chronic atrophic thyroiditis and in Graves thyrotoxicosis.

Therapies regarding the different components of type 2 APS are similar whether they occur singly or in association with other autoimmune diseases. However it is worth remembering that thyroid hormone replacement therapy in patients with autoimmune hypothyroidism and misdiagnosed adrenal insufficiency can precipitate an adrenal failure owing to the action of thyroxine, enhancing hepatic corticosteroid metabolism. In addition, some patients with Addison’s disease show a reversible increase in thyrotropin levels, regardless of the presence of thyroid autoantibodies that is related to the loss of inhibitory effect of glucocorticoids on thyrotropin secretion. Moreover, a reduction in insulin requirement may be the first sign of Addison’s disease in patients with type I diabetes mellitus. Thus, before initiating the therapy with thyroxine or simply modifying insulin dosage, it is prudent to investigate the possible coexistence of an underlying adrenal insufficiency.

**Conclusion**

Whenever any organ-specific autoimmune disorder is diagnosed we should keep a high index of suspicion to detect other associated autoimmune disorders in order to prevent morbidity and mortality due to it. APS type 2 syndrome has variegated clinical features and associations with other diseases. Alopecia universalis can be a rare association with the disease. We have to be aware that hypoparathyroidism though generally seen in APS type 1, can be present in APS type 2 as well. Early and proper sequence of treatment of endocrine diseases will be life-saving. It is mandatory to screen patients by laboratory examination as diseases may present in subclinical forms also.

**References**