A Case Report: Addison's Disease in a Patient with Hypothyroidism and Vitiligo, A Suspected Case of Autoimmune Polyendocrine Syndrome Type 2

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ABSTRACT:

Addison's disease, or primary adrenal insufficiency, is characterized by diffused hyperpigmentation, weight loss, and low blood pressure. The diagnosis of this condition is based on laboratory tests with low serum cortisol and high serum adrenocorticotropic hormone. In terms of management, diagnostic workups and treatment of specific causes, as well as hormone replacement therapy, should be considered. We reported a case of a 41-year-old Thai female with a gradual onset of generalized darkening of the skin, accompanied by other autoimmune presentations, including autoimmune thyroiditis and vitiligo. The aforementioned findings have led to suspicion of autoimmune polyendocrine syndrome type 2.

Key words: Addison's disease, Autoimmune polyendocrine syndrome, Autoimmune polyglandular syndrome

Introduction

Addison's disease is a rare endocrine disease that is caused by the destruction of the adrenal glands, resulting in adrenal insufficiency. Common clinical presentations include weight loss, muscle weakness, fatigue, and low blood pressure[1]. Hyperpigmentation is a characteristic feature that distinguishes Addison's disease from other forms of adrenal insufficiency. Various etiologies have been described, and the most common is an autoimmune response[2]. Autoimmune polyendocrine syndrome (APS) is an immune-mediated condition that affects multiple endocrine organs, such as adrenal glands. The coexistence of Addison's disease with autoimmune thyroiditis and/or type 1 diabetes mellitus is referred to APS type 2, which is more prevalent than APS type 1[3].

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Case report

A 41-year-old female with a history of Hashimoto's thyroiditis and vitiligo visited the Institute of Dermatology due to progressive darkening of the skin. She was previously diagnosed with vitiligo at the age of 30. Depigmented patches had emerged on the upper chest, palms, and soles of her hands and feet. At the age of 39, there were progressive darkening of the skin, starting from her face and spreading to the rest of the body, with marked hyperpigmentation present on her areola, palmar creases, and knuckles. None of these hyperpigmented lesions were found in the vitiligo-affected areas. Additionally, she experienced fatigue and weight loss. No headaches, blurred vision, loss of consciousness, or altered bowel habits were observed. Her underlying medical condition was Hashimoto's thyroiditis, and levothyroxine was regularly prescribed. Physical examination revealed diffused hyperpigmentation on the face, trunk, extremities, and palmar crease (Figure 1). Multiple depigmented, non-scaly patches were noted over her chest wall, dorsum of both hands, and palms (Figure 1). The oral mucosa, hair, and nails were unremarkable. Histopathology of hyperpigmented lesion on right palmar crease revealed epidermal hypermelanization and mild superficial perivascular lymphocytic infiltration (Figures 2A, 2B).

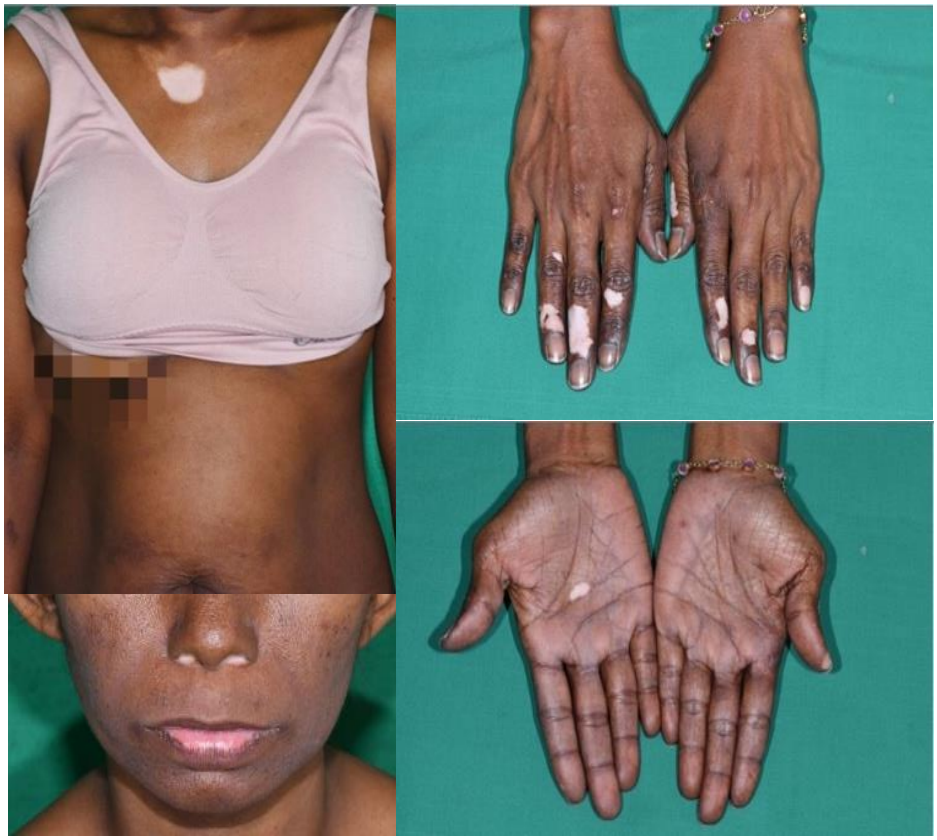

Figure 1 Diffused hyperpigmentation on the face, trunk, extremities, and palmar crease and multiple depigmented, non-scaly patches on her chest wall, dorsum of both hands, and palms

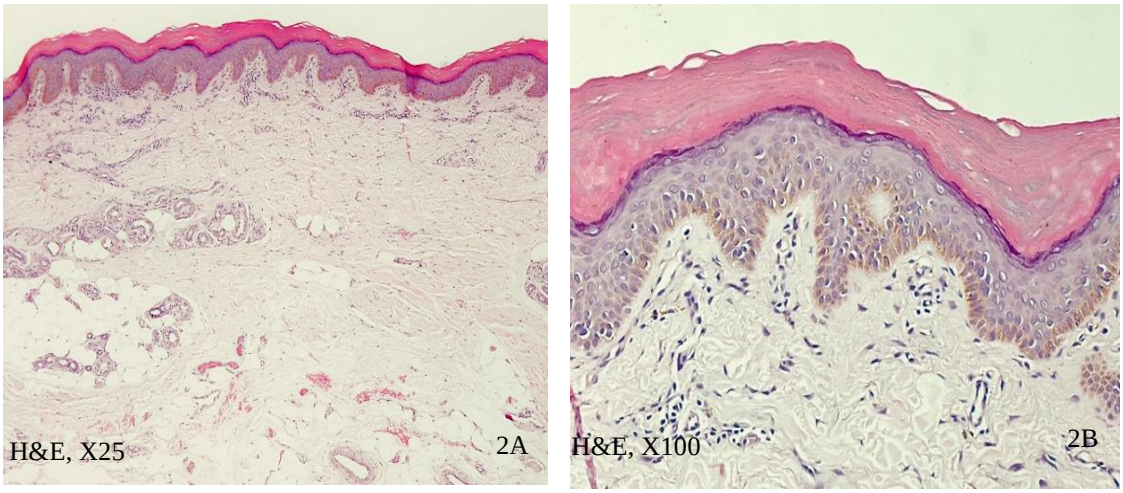

Figure 2A A sparse superficial perivascular lymphocytic infiltration
Figure 2B Hypermelanization of basal layer of epidermis

Her laboratory tests showed a normal complete blood count. Blood chemistry parameters including renal function tests, liver function tests, and serum electrolytes were normal. Endocrinology study revealed a low morning cortisol at 0.5 ug/dL (reference range 3.7-19.4 ug/dL), while adrenocorticotropic hormone (ACTH) was markedly elevated at 2123 pg/mL (reference range 4.7-48.8 pg/mL). Evaluations for cobalamin (vitamin B12) and folate deficiencies were unremarkable.

Discussion

Addison's disease (AD), or primary adrenal insufficiency, is a rare endocrine disease that was first described in 1855 by Thomas Addison.[1] The estimated prevalence is 0.6 per 100,000 population[2]. Various etiologies of Addison's disease have been reported. The most common cause is an autoimmune response. Other possible causes include tuberculosis infection, congenital adrenal hyperplasia/ adrenoleukodystrophy, and gland metastasis invasion[1-2]. Adrenal gland destruction reduces cortisol production, resulting in a feedback signal to the hypothalamic-pituitary axis and an increase in plasma ACTH and melanocyte stimulating hormone (MSH)[4]. Hyperpigmentation distinguishes AD from other forms of adrenal insufficiency. The insidious nature and non-specific symptoms of AD often lead to delays in diagnosis.

Addison's disease is characterized by weight loss, muscle weakness, fatigue, and low blood pressure. The most specific sign of AD is hyperpigmentation of the skin and mucosal surfaces which occurs in 90% of patients, is due to excessive synthesis of melanin in response to elevated MSH levels[5]. The hyperpigmentation is typically accentuated on sun-exposed areas, flexural folds, and skin creases, including palmar creases or may arise on the scar. Ten percent of patients may develop vitiligo. Moreover, the disease also affects hair and nails. Some patients may develop hyperpigmented bands in the nails. Pubic and axillary hair may be scanty, particularly in female patients, due to the reduction of adrenal androgen. Gastrointestinal symptoms, including nausea, vomiting, and abdominal pain, are observed.

The differential diagnosis of acquired diffuse hyperpigmentation without indurations includes endocrinopathy (e.g. Cushing disease

and hyperthyroidism), nutritional conditions (e.g. B12 deficiency, folate deficiency), and agents (e.g. amlodipine, hydroxychloroquine, and chemotherapy). Laboratory testing aids in confirming the diagnosis. Serum cortisol and ACTH levels are the key tests that should be investigated prior to steroid replacement[6]. A low level of serum cortisol and a high level of ACTH suggest AD. Another useful confirmatory test is the ACTH stimulation test, which measures serum cortisol 30 and 60 minutes after administration of 250 µg synthetic ACTH[7]. Other laboratory findings include hyponatremia, hyperkalemia, and less commonly, hypoglycemia and hypercalcemia[8]. The histopathological findings of hyperpigmentation lesion in AD include acanthosis, hyperkeratosis, superficial perivascular lymphocytic infiltrate, basal melanin hyperpigmentation, and superficial dermal melanophages. Histopathological findings can help to confirm the disease, however the diagnosis can be made by laboratory evaluation[9]. Once the diagnosis has been confirmed, further investigations should be done to clarify the primary cause of AD.

The mutual findings of AD with other autoimmune diseases, such as vitiligo and autoimmune thyroid disease, suggests the suspicion of APS which are clusters of endocrine abnormalities due to circulating antibodies to the affected organ. APS type 1 is an autosomal recessive disease caused by an AIRE gene mutation and characterized by the development of at least two of three clinical pictures, including chronic mucocutaneous candidiasis, idiopathic hypoparathyroidism, and autoimmune AD. APS type 2 is an autoimmune disorder that is characterized by the presence of AD with autoimmune thyroid disease and/or type 1 diabetes. APS type 1 develops earlier and is more severe than APS type 2. Testing of autoantibodies may be helpful in the diagnosis, such as thyroid peroxidase antibodies in autoimmune thyroiditis, 21-hydroxylase antibodies in AD and glutamic acid decarboxylase antibodies in type 1 diabetes. The main treatment for APS is the replacement of the affected hormones[3,10].

The treatment of AD includes the replacement of glucocorticoid and mineralocorticoid hormones. Hydrocortisone at 15 - 25 mg a day is most commonly prescribed. Treatment varies depending on the primary cause, such as anti-tubercular drugs in adrenal tuberculosis. Clinical evaluation will assist physicians in detecting signs of glucocorticoid over- or under-replacement, including hypertension, weight gain, and easy bruising in the former group and weight loss and pigmentation in the latter group. The cutaneous hyperpigmentation generally resolves with cortisol replacement therapy. Two studies reported the resolution of cutaneous hyperpigmentation within 2 weeks and 2 months after starting cortisol, respectively[11-12]. Prompt treatment with intravenous steroids may be given if there is a high suspicion of adrenal crisis without confirmatory blood tests.[7] Delays in treatment may result in life-threatening adrenal crisis condition[8,13].

Since our patient presented with fatigue, weight loss, and low blood pressure, along with her diffuse hyperpigmentation, thus making her highly suspicious of having AD. The diagnosis was confirmed by blood tests, which resulted in a low cortisol level and a high ACTH level. The presence of vitiligo and Hashimoto's thyroiditis raised the possibility of an APS type 2. However, the patient passed away due to a COVID-19 infection, hence no additional laboratory testing was performed to confirm the diagnosis.

In conclusion, AD should be excluded in patients presented with acquired diffused hyperpigmentation with non-specific symptoms. In highly suspected cases, treatment with systemic corticosteroids should be initiated without a blood test to decrease the mortality rate.

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