Addison's Disease: The Potentially Life-Threatening Tan

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Addison's disease is a potentially life-threatening endocrine disorder. The classic dermatologic sign of Addison's disease is diffuse hyperpigmentation of the skin with focal hyperpigmentation of scars, nails, and the oral mucosa. Recognition of these dermatologic manifestations in a patient with otherwise vague constitutional symptoms warrants a consideration of Addison's disease.

Primary adrenal insufficiency was first described by Thomas Addison[1] in 1855. Addison's disease is usually the result of an autoimmune adrenalitis that destroys the gland's ability to produce cortisol and mineralocorticoids.[2-4] The classic dermatologic manifestations are diffuse cutaneous hyperpigmentation associated with focal hyperpigmentation of scars and gingiva. We describe a patient with the classic dermatologic manifestations of Addison's disease and review the pathophysiology and treatment of this disease.

Case Report

A 20-year-old female presented to the dermatology clinic with a complaint of darkening scars and brown spots on her gums. During the interview, she reported that her tan had not faded over the winter. She also admitted to having an insatiable salt craving, postural dizziness, fatigue, anorexia, and constipation. Past medical history was significant for depression since 1994 or 1995, and reactive airway disease. Current medications were Paxil, Trazodone, Albuterol, and Servent metered dose inhalers. A family history of Graves disease, rheumatoid arthritis, and breast cancer was noted.

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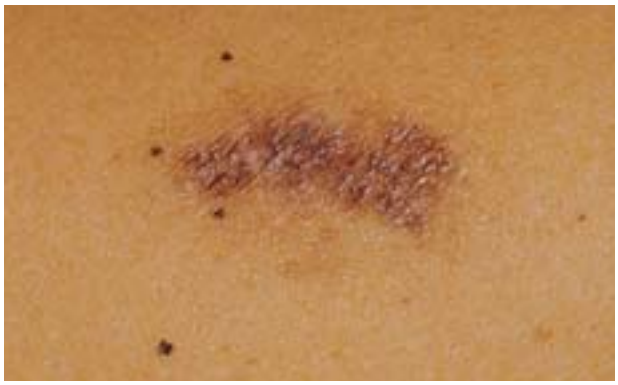

FIGURE 1. Hyperpigmented scar.

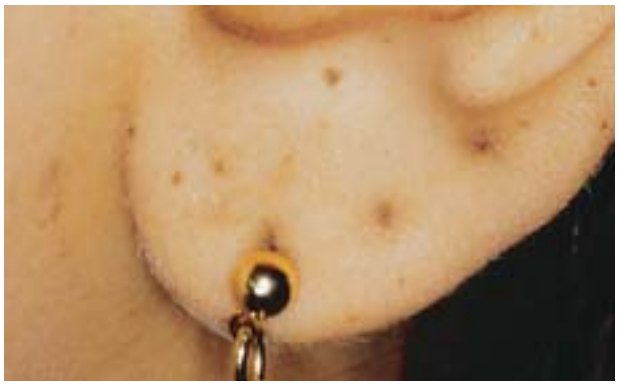

FIGURE 2. Hyperpigmented ear-piercing scars.

Physical examination revealed a very thin young woman with an extremely dark tan, hyperpigmented scars (Figure 1), including earpiercing scars (Figure 2), pigmented nail streaks, and brown macules on her gingival and buccal mucosa (Figures 3 and 4). Supine blood pressure was 108/58, with a pulse of 98. Standing blood pressure was 102/60 with a pulse of 126. Laboratory results were as follows: sodium 138, potassium 5.2, chloride 108, bicarbonate 25, blood urea nitrogen 8, creatinine 0.9, glucose 80, aspartate transaminase 38 (slightly elevated), white blood cell

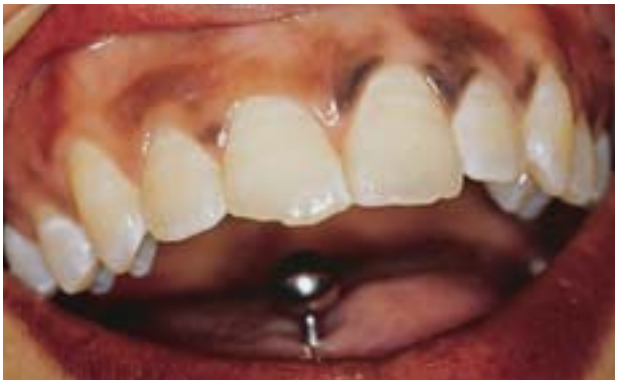

FIGURE 3. Hyperpigmented gingiva.

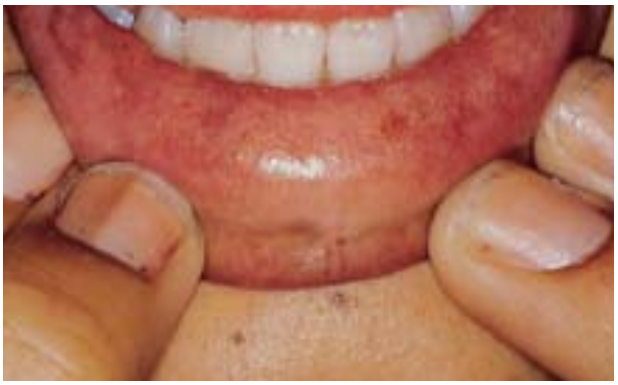

FIGURE 4. Hyperpigmented oral mucosa.

count 7,900/mm^3 with 22% eosinophils, hemoglobin 13.5 g/100 ml, hematocrit 38.3%, platelet count 272,000, and adrenocorticotropic hormone (ACTH) 1605 pg/ml (normal range, 9 to 52 pg/ml). An ACTH stimulation test revealed: baseline cortisol <0.6 µg/dl (normal range, 5 to 18 µg/dl); at 30 minutes, 0.7 µg/dl; and at 60 minutes, 0.8 mg/dl. The thyroid-stimulating hormone count was 2.2. The patient was started on hydrocortisone replacement therapy 12.5 mg in the morning and 5 mg in the evening, and Flurinef 0.05 mg daily. She was counseled to wear a medic alert bracelet, and to double or triple her hydrocortisone for minor and major illnesses.

Comments

Addison's disease, also known as primary adrenocortical insufficiency, is a disease in which insufficient amounts of mineralocorticoids and corticosteroids are produced by the adrenal glands. Patients generally present with vague symptoms such as weakness, fatigue, depression, weight loss, anorexia, nausea, vomiting, diarrhea, constipation, abdominal pain, hypotension, syncope, salt craving, vitiligo (rarely), and hyperpigmentation of the skin, scars, and mucous membranes.[3,5,6] Because of the insidious onset of the symptoms, Addison's disease may go undiagnosed until late in the course of the disease. Symptoms usually do not appear before 90% of the adrenocortical tissue has been lost. Unfortunately, Addisonian crisis, which can be fatal, may be the initial presentation of the disease. Addisionian crisis is characterized as rapidly deteriorating hypotension, shock, hypoglycemia, and hyperkalemia.

Addison's disease is caused by autoimmune adrenalitis in 60 to 70% of the cases. It is sometimes linked to the HLA-DR3 locus.[7] Other known etiologies are tuberculosis, fungal infections (histoplasmosis, coccidioidomycosis, and cryptococcosis), metastatic cancer, adrenoleukodystrophy, hemorrhages, Waterhouse-Friderichsen syndrome, sarcoidosis, and amyloidosis.[2] In autoimmune adrenalitis, complement-fixing adrenocortical autoantibodies (ACA) slowly destroy adrenocortical tissue. ACA have been shown to recognize the steroid-producing enzyme 21-hydroxylase as the autoantigen.[7,8] Recently, plasma levels of ACA and 21-hydroxylase antibodies have been shown to directly correlate with the degree of adrenal insufficiency in preclinical Addison's disease.[9] This finding may have clinical utility in monitoring disease progression and patient management.

In some cases, autoimmune destruction of glandular tissue is not limited to the adrenal gland. There are three polyglandular syndromes of which type I and II involve the adrenal glands.[10] Type I usually presents in childhood and consists of hypoparathyroidism, adrenal insufficiency, and mucocutaneous candidiasis. Type II, or Schmidt syndrome, predominantly affects women in the second and third decade. It consists of hypothyroidism and/or insulin-dependent diabetes in the presence of adrenal insufficiency.

Hyperpigmentation is a classic symptom of Addison's disease.[1,6] Normally, cells called corticotrophs in the pituitary gland produce the prohormone proopiomelanocortin, which is then cleaved to form ACTH, melanocyte-stimulating hormone (MSH), endorphin, and lipotropin. ACTH acts on the adrenal gland to maintain adequate cortisol production. There is negative feedback inhibition of ACTH by cortisol. As the adrenals fail and cortisol production becomes inadequate, there is increased production of ACTH and concomitantly MSH. The increased level of MSH stimulates melanocytes to produce more pigment, especially in sun-exposed areas, resulting in dark tans, hyperpigmented scars, and gingiva.

Treatment of Addison's disease must include replacement of both mineralocorticoids and diurnal cortisol. Patients should be directed to double or triple their hydrocortisone replacement for minor or major illnesses, and to wear a Medic Alert bracelet.

Summary

Addison's disease is often difficult to recognize. Constitutional symptoms can mimic anorexia nervosa,[11] chronic fatigue,[12] or influenza.[13] A high degree of clinical suspicion is warranted when a patient presents with complaints of constitutional symptoms, fatigue, weakness, and hypotension. An examination of the skin in these cases can be very helpful. A diffuse tan, hyperpigmentation of scars, and pigment appearing on the gingival and buccal mucosa are all signs that should alert the healthcare professional to consider primary adrenal insufficiency as the cause of the symptoms.

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