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Addisonian Pigmentation of the Oral Mucosa

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Cutaneous pigmentation is a hallmark of Addison disease. When present, the hyperpigmentation generally localizes to sun-exposed surfaces. This case highlights a less well-recognized cutaneous feature that is pathognomonic for the disease: oral mucous membrane hyperpigmentation. We describe this unique type of discoloration in detail and contrast it with other forms of oral pigmentation.

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Case Report

A 9-year-old girl presented with a 4-month history of painless black patches on the tongue and gingiva. The patches had persisted despite treatment with oral fluconazole, which had been prescribed empirically for presumed oral candidiasis. Results of a physical examination revealed scattered, asymptomatic, bluish-black macules on the dorsal surface of the tongue, the mucosal surface of the lower lip, and the hard palate (Figure). No cervical lymphadenopathy was noted. The patient's medical history was notable for a recent diagnosis of primary adrenal insufficiency and Addison disease.

Significant laboratory evaluation results included findings consistent with primary adrenal insufficiency: a nocturnal plasma cortisol level of 0.3 $\mu\text{g}/\text{dL}$ (reference range, 2–10 $\mu\text{g}/\text{dL}$) and a corticotropin level of 1300 pg/mL (reference range, 9–52 pg/mL).

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Free thyroxine and thyrotropin levels were within reference range.

Comment

Addison disease, a chronic primary insufficiency of the adrenal glands, results in both glucocorticoid and mineralocorticoid deficiency. Historically, tuberculosis accounted for most cases of Addison disease.¹ Autoimmune destruction of the adrenal glands, also known as *autoimmune adrenalitis*, is now the most common cause of Addison disease in both children and adults.^{2,3} Autoimmune destruction of other endocrine tissues can occur concurrently. These polyglandular autoimmune syndromes are associated with hypoparathyroidism, pernicious anemia, and chronic mucocutaneous candidiasis (type 1); diabetes mellitus (type 2); or thyroiditis (type 3).⁴ Type 3, however, consists of an autoimmune thyroiditis syndrome in the absence of Addison disease.⁵ Although most children (75%) presenting with isolated Addison disease are boys,⁶ type 1 autoimmune polyglandular syndrome occurs equally in boys and girls.² Other causes of Addison disease in children include trauma and adrenocortical hemorrhage, which is most commonly associated with meningococcemia.⁴

Most of the symptoms arising from primary adrenal insufficiency result in cortisol deficiency. Symptoms include fatigue, weakness, orthostasis, nausea, vomiting, weight loss, and anorexia. Common presenting symptoms seen in children include hypoglycemia, gastrointestinal disturbances, and progressive peripheral weakness. Hyperpigmentation of the skin and mucosal surfaces, the most specific sign of Addison disease, occurs in up to 92% of patients.⁷ This dyspigmentation may precede other manifestations by up to 10 years.⁸

Pigmentation of the oral mucosa is considered pathognomonic for Addison disease. This distinctive finding can aid in distinguishing Addison

disease from other endocrinopathies that also may present with hyperpigmentation, such as hyperthyroidism.⁹ The oral hyperpigmented macules of Addison disease can be found diffusely on the tongue, gingiva, buccal mucosa, and hard palate. The macules tend to be blue-black or brown and can be spotty or streaked in configuration. The pattern of pigmentation is usually patchy and can occasionally alternate with leukodermic patterns.

The hyperpigmentation of Addison disease tends to produce a generalized bronze appearance that is more easily detectable in fair-skinned children. In dark-skinned children, a similar increase in color may be mistaken for a tan. Hyperpigmentation occurs most prominently at the flexures, sites of pressure and friction, palmar and plantar creases, and sun-exposed areas. It also may result in intensification of normally pigmented areas such as the genitalia and areolae mammae.⁶ Scars also can exhibit hyperpigmentation, which only appears in scars acquired after the onset of the disease. Coexistence of pigmented and uncolored scars may aid in the precise dating of the destructive process found in the adrenals.⁸ Paradoxically, vitiligo also may be seen in patients with Addison disease and may occur concurrently with hyperpigmentation. Pigmentation of the vaginal mucosae and conjunctivae also are frequently observed in affected patients.¹

Hyperpigmentation associated with Addison disease presumably occurs secondary to overproduction of the pro-opiomelanocortin byproduct β -lipotropin, which is secreted in excess amounts concomitantly with corticotrophin from the pituitary gland because of the lack of feedback inhibition seen in adrenal insufficiency states.¹⁰ Other conditions that lead to increased corticotrophin production also may present with similar cutaneous hyperpigmentation, as seen in adrenoleukodystrophy (Siemerling-Creutzfeldt disease),¹¹

familial adrenocorticotropin unresponsiveness syndrome (familial glucocorticoid deficiency),¹² thymic carcinoids,¹³ and paraneoplastic corticotrophin production in the setting of underlying malignancy¹⁴; however, oral pigmentation has not been specifically reported in these cases.

Adequate hormone replacement therapy typically results in a decrease in the degree of cutaneous pigmentation, though oral pigmentation persists indefinitely.¹⁵ In this particular case, the patient's



Pigmentation of the tongue (A) and lower lip (B) in Addison disease.

oral pigmentation did show modest improvement with good hormonal control; however, when the patient was noncompliant with hormonal therapy, her pigmentation worsened clinically. In some affected younger children, the skin color may eventually return to normal with therapy.

Differential Diagnosis

Diagnoses that may mimic the oral pigmentation of Addison disease include: oral "black tongue" candidiasis, ethnic pigmentation, and reactions to certain drugs. Black hairy tongue and black tongue candidiasis are disorders believed to be caused by *Candida albicans* and occasionally *Aspergillus* species. These conditions are associated with long-term use of antibiotics. Characterized by dense, black, bluish-black, or brown "matted" areas of the dorsal surface of the tongue, black tongue candidiasis can be successfully eliminated by discontinuation or minimization of antibiotics, gentle brushing of the tongue surface, and use of an oral antifungal agent.¹⁶

The most common pattern of ethnic or racial pigmentation is a band of pigment at the junction of attached and alveolar mucosa. In contrast to Addison disease, pigmentation on the tongue of those with skin of color is typically localized to the tips of isolated groups of filiform papillae.¹⁷ Such pigmentation, usually found only in persons with dark skin, also can be found as isolated pigmented patches in 5% of Caucasians.

Drug-induced pigmentation can range from brown (seen with oral contraceptives, cytotoxic agents, and some anticonvulsants) to yellow or blue-black (as seen with the antimalarial drugs quinacrine, chloroquine, and hydroxychloroquine).¹⁸ Long-term use of minocycline has been associated with a blue-gray staining of the tongue, gingival margins, palate, and pretibial surfaces.

Patchy blue-black hyperpigmentation of the oral mucosa should cause suspicion of Addison disease, particularly if appropriate systemic signs are noted and if no other explanatory factors, such as concomitant candidiasis, ethnic background, or drugs, are associated.

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