Correct Answer: D. Addison disease

Our patient ultimately developed systemic features that are characteristic of primary adrenal insufficiency or Addison disease. While lip hyperpigmentation is theoretically a common initial presenting feature of Addison disease, it is often overlooked when it presents in isolation months before the onset of systemic symptoms.[2]

Differential diagnosis. Among the differential diagnoses were pigmented contact stomatitis, mucosal melanotic macules, Peutz-Jeghers syndrome, Addison disease, and smoker's melanosis. You can reverse pigmented contact stomatitis upon removal of the allergen, which is similar to the reversible aspect of smoker's melanosis upon tobacco cessation.[3,4] Although not entirely excluded, pigmented contact stomatitis is less likely given that the patch testing was negative. The patient did not report tobacco use, which ruled out smoker's melanosis. Mucosal melanotic macules are relatively common and benign, so this was ruled out based on the clinical presentation of the case.[1] Peutz-Jeghers syndrome presents similarly but is often accompanied by gastrointestinal polyposis and increased risk of malignancy.[1]

Table 1. Selected Differential Diagnosis With Key Differentiating Characteristics

Condition	Key characteristics
Addison disease	Generalized mucocutaneous pigmentation, commonly on buccal mucosa, due to adrenal insufficiency
Pigmented contact stomatitis	Localized pigmentation in areas of contact with allergen (eg, cosmetic ingredients, oral hygiene agents); reversible upon removal of sensitizing agent
Mucosal melanotic macules	Small, well-demarcated, flat, brown to black lesions, often on the lips or buccal mucosa; benign
Peutz-Jeghers syndrome	Mucocutaneous pigmented macules (especially lips, buccal mucosa, and perioral skin), gastrointestinal polyps; hereditary
Smoker's melanosis	Pigmentation due to tobacco use, often localized and reversible

Treatment and management. According to the Endocrine Society guidelines, oral hyperpigmentation in the setting of fatigue or hypotension should prompt early hormonal evaluation to rule out adrenal insufficiency. Once a diagnosis is established, treatment includes glucocorticoid and mineralocorticoid replacement, as well as patient education on emergency hydrocortisone use and adrenal crisis.[5] Continuous monitoring is essential to ensure adequate hormone replacement and symptom control.

Outcome and follow-up. Following the Addison disease diagnosis, we initiated treatment with oral hydrocortisone (15mg in the morning and 5mg in the afternoon) and fludrocortisone (0.05 mg once daily), along with injectable stress-dose steroid. Comprehensive education on adrenal crisis prevention was offered, including training on recognizing crisis symptoms, utilizing stress dosing protocols, and performing emergency self-administration of hydrocortisone. We also screened for associated autoimmune diseases (eg, thyroid antibodies, type 1 diabetes, celiac disease). The patient was further diagnosed with Hashimoto thyroiditis and was found to have a positive autoantibody screening for Celiac disease, for which she will undergo further evaluation and treatment.

Discussion. Oral hyperpigmentation is a clinical finding with a broad differential diagnosis, encompassing physiologic, reactive, drug-induced, neoplastic, and systemic causes.[3] Among systemic conditions, Addison disease—a form of primary adrenal insufficiency—remains an essential consideration. We confirmed this patient's diagnosis based on markedly elevated ACTH levels (>2000 pg/mL), a low morning cortisol (3.3 µg/dL), and a supportive clinical presentation. Management included oral hydrocortisone and fludrocortisone, injectable stress-dose steroids, and comprehensive education on adrenal crisis prevention. Mucosal hyperpigmentation preceded systemic symptoms by several months, demonstrating that dermatologic findings may serve as an early sign of endocrine pathology.

When evaluating lip and oral mucosal hyperpigmentation in a young patient, the differential diagnosis may include mucosal melanotic macules, pigmented contact stomatitis, Peutz-Jeghers syndrome, and Addison's disease. Physiologic pigmentation is common in individuals with darker Fitzpatrick phototypes and is typically symmetric and benign.[1] Labial melanotic macules are also benign and often present as solitary, flat, brown lesion on the lower lip, occurring in approximately 3% of the general population.[3] Asymmetry, recent onset, or progression of pigmentation should raise concern for systemic causes. Pigmented contact stomatitis may arise from chronic exposure of the lips and oral mucosa to sensitizing agents, such as ingredients in certain foods, cosmetic products, or oral hygiene agents.[4] Peutz-Jeghers syndrome is a hereditary syndrome with mucocutaneous pigmentation, often described as dark spots of less than 1 mm on the lower lip and perioral lesion, in addition to gastrointestinal polyposis.[1] Other possible etiologies include Laugier-Hunziker syndrome, drug-induced pigmentation, smoker's melanosis, hyperthyroidism, and hemochromatosis.[3] Although histopathology was not required for diagnosis in this case, dermoscopic evaluation may assist in

differentiating melanotic macules from other pigmented lesions. In ambiguous cases, a biopsy may be used to exclude melanocytic neoplasms.

In Addison disease, hyperpigmentation arises from elevated ACTH levels that stimulate melanocortin-1 receptors, resulting in diffuse pigmentation, especially in sun-exposed areas and on mucous membranes.[6] Diagnosis relies on a combination of clinical suspicion, physical findings, and hormonal evaluation, underscoring the importance of early recognition in patients with oral pigmentation. With appropriate treatment, the prognosis for Addison disease is excellent; however, lifelong therapy and ongoing vigilance are required to prevent adrenal crises.

Conclusion. Early recognition and appropriate endocrine workup led to prompt diagnosis and management, reducing the risk of a potential adrenal crisis for the young patient. Since early signs can be subtle, clinicians should maintain a high level of suspicion and consider systemic causes when evaluating unexplained, progressive oral hyperpigmentation.

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