JAMA Dermatology Clinicopathological Challenge

Recurrent Oral Mucosal Ulcerations and Gingival Edema

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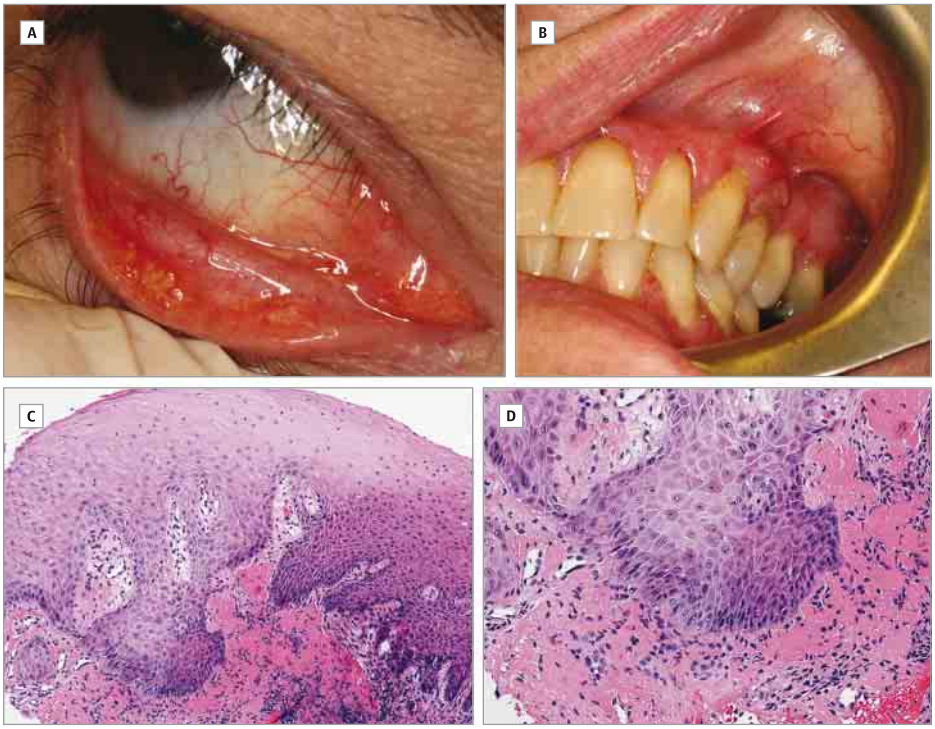

A, Pseudomembranous masses affecting conjunctival mucosa of the left eye consistent with ligneous conjunctivitis. B, Edema with rolled margins and nodular ulceration of the left maxillary gingiva. C and D, Punch biopsy specimen from the maxillary gingiva showing aggregates of relatively amorphous, eosinophilic material beneath the epithelium and around blood vessels (C, hematoxylin-eosin, original magnification ×100; D, hematoxylin-eosin, original magnification ×200).

A white woman in her 50s presented for evaluation of recurrent gingival ulcers of 8 years' duration. She reported that at the time of initial onset, multiple painful ulcers had appeared on the anterior maxillary gingiva. She stated that the lesions had resolved spontaneously without treatment but recurred 8 years later as swelling and ulceration of the maxillary and mandibular gingiva. She denied involvement of cutaneous surfaces and reported a history of ligneous conjunctivitis since childhood (**Figure**, A). Her medical history was significant for hypothyroidism, seizures, and functional heart murmur. Medications included levothyroxine sodium, mometasone furoate, levocetirizine, and benzonatate. Review of systems was significant for easy bruising and prolonged bleeding. Intraoral examination revealed generalized mild edema with rolled margins of the maxillary and mandibular gingiva accompanied by nodular ulceration of the left maxillary gingiva (Figure, B). Biopsy specimens were obtained from the gingival ulcer (Figure, C and D) and buccal mucosa for routine histological and direct immunofluorescence analysis, respectively. Also obtained were a complete blood cell count with differential and comprehensive metabolic panel; no abnormal findings were identified.

WHAT IS THE DIAGNOSIS?

A. Amyloidosis

B. Systemic sclerosis

C. Hypoplasminogenemia

D. Lipoid proteinosis

Diagnosis

C. Hypoplasminogenemia

Microscopic Findings and Clinical Course

Histologic sections showed epithelial acanthosis and spongiosis with ulceration, granulation tissue, and a mixed inflammatory infiltrate. Amorphous, eosinophilic deposits were noted in a subepithelial and perivascular distribution. A trichrome stain highlighted the substance with a red color, suggesting that they were fibrinoid deposits and thus ruling out scleroderma. An amyloid stain and direct immunofluorescence analysis had negative results. Due to the limited clinical presentation, lipoid proteinosis was not given much scrutiny. Thus, based on the cumulative findings, a diagnosis of hypoplasminogenemia was considered. This was confirmed by laboratory testing, which revealed a plasma plasminogen level of 52% (reference range, 78%-130%). The patient was prescribed fluocinonide gel, 0.05%, twice daily to the affected gingiva and clotrimazole troches 10 mg 3 times daily for antifungal prophylaxis with marked improvement of her oral lesions.

Discussion

Hypoplasminogenemia (type 1 plasminogen deficiency; OMIM 217090) is a rare, autosomal-recessive disorder characterized by reduced levels of circulating plasminogen.[1] Plasminogen is the inactive precursor of plasmin, which is a protease that plays critical roles in intravascular and extravascular fibrinolysis, wound healing, angiogenesis, and extracellular matrix homeostasis. The plasminogen gene (*PLG*) is located on chromosome 6q26, and an array of mutations have been reported, with the K19E missense mutation being most common.[2] Patients with homozygous and compound heterozygous mutations have been described, and consanguinity is reported in up to 40% of cases.[3] There is a higher incidence in females than in males, with a reported ratio of approximately 1.5:1.

In most patients, plasminogen plasma levels are less than 50% of the reference range.[2] Severe cases may manifest during infancy or childhood, whereas milder disease may not be evident until adulthood. However, there may be little correlation between actual plasminogen levels and disease expressivity.[1] A pseudodeficiency state may develop in patients who have a qualitative defect in plasminogen (dysplasminogenemia; type 2 plasminogen deficiency). However, whereas hypoplasminogenemia is associated with an array of variably severe clinical complications, dysplasminogenemia is not associated with an overt phenotype.[1,3]

Hypoplasminogenemia is characterized by diminished wound-healing capability, with persistence of granulation tissue and accumulation of fibrin primarily within the mucous membranes.[1,2] The lesions often manifest as white-yellow or erythematous, nodular ulcerations that, over time, take on a ligneous consistency. Patients are at risk for development of lesions in conjunctival mucosa (ligneous conjunctivitis), the gingival and/or periodontal tissues (ligneous gingivitis and/or periodontitis), and less commonly in the mucosal tissues of the respiratory, gastrointestinal, and genitourinary tracts.[1,2] The mouth may be the only site of involvement, with lesions manifesting as ulcerations and gingival hyperplasia that may progress to rapid periodontal destruction and eventual tooth loss.[2-7] Blindness, congenital occlusive hydrocephalus, and Dandy Walker malformation have also been reported.[2] The skin is almost always spared. However, juvenile colloid milium has been associated with ligneous conjunctivitis and ligneous gingivitis, thereby suggesting a common etiologic link between these 2 disorders.[8]

Our patient's oral lesions resolved following treatment with topical fluocinonide, without evidence of recurrence. Notwithstanding her favorable response, management of this disorder is often challenging. Surgical excision of the ligneous lesions is not typically recommended because of risk of rapid recurrence and poor long-term outcomes.[3,4] Use of plasminogen-containing, topical thrombolytic agents may be beneficial for the ocular lesions but is less successful for lesions in other mucosal sites.[3] Systemic therapies, including heparin sodium, corticosteroids, cyclosporine, azathioprine sodium, and warfarin sodium have been used with inconsistent results.[2,3,7,9] A therapeutic goal for patients with oral involvement should include reducing gingival inflammation.[4,9] In some patients, resolution of the oral lesions occurred only after complete tooth loss.[7]

This case highlights the importance of recognizing the oral complications of a systemic disease. Hypoplasminogenemia should be included in the histologic differential diagnosis of submucosal, amorphous eosinophilic deposits.

ARTICLE INFORMATION

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Published Online: September 3, 2014. doi:10.1001/jamadermatol.2014.2115.

Conflict of Interest Disclosures: Drs Alawi, Greenberg, and Stoopler are employed by the University of Pennsylvania. Dr Stoopler receives an honorarium from WebMD for providing expert viewpoints and royalties from the American Dental Association. No other disclosures are reported.

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