Bilateral yellow plaques on the upper eyelids

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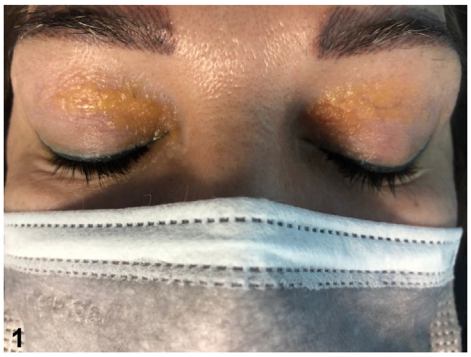
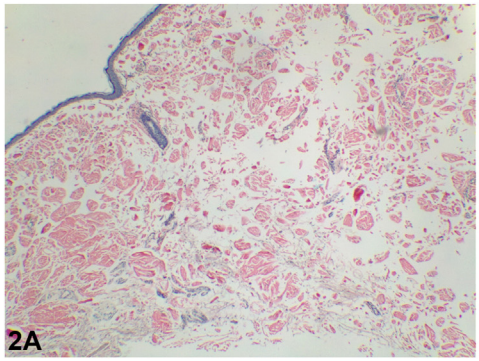
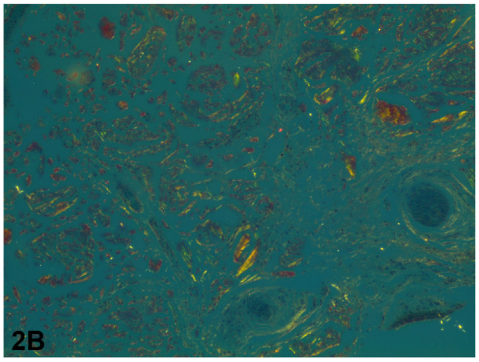
Key words: amyloidosis; skin; eyelids.







CASE PRESENTATION

A 49-year-old normolipemic woman presented with a 5-year history of intermittently pruritic, yellow-colored lesions over both upper eyelids. Her past medical history was notable for voice hoarseness 3 years ago, which had extensively been worked up, leading to no specific etiology. On examination, a 1.5 × 2 cm waxy plaque involving each upper eyelid was noted (Fig 1). No associated petechial/purpuric lesions were observed, and the general physical examination was otherwise unremarkable. The histopathological examination is shown in Fig 2, *A* and *B*.

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Question 1: Considering the clinical and histopathologic images, what is the most likely diagnosis?

A. Xanthelasma

B. Amyloidosis

C. Necrobiotic xanthogranuloma

D. Lipoid proteinosis

E. Sarcoidosis

Answers:

A. Xanthelasma — Incorrect. Xanthelasma usually presents as yellowish papules, plaques, or nodules symmetrically distributed on the medial side of the upper eyelids. Under the microscope, foam cells (ie, fat deposit-laden histiocytes) are seen primarily within the upper reticular dermis or in perivascular and periadnexal areas.[1] The rarity of cutaneous amyloidosis cases resembling a xanthelasma will make the diagnostic approach challenging, especially when lipid profile is normal. Although authors would not see it practical to biopsy every xanthelasma-appearing lesion even when lipid profile returns normal, starting with a comprehensive medical history and physical examination which is followed by further laboratory testing, if deemed necessary, would seem appropriate. Nonetheless, to find a more evidence-based approach, further studies are needed to investigate the prevalence of cutaneous amyloidosis in patients with preliminary diagnosis of xanthelasma.

B. Amyloidosis — Correct. Generally, skin lesions include shiny, waxy papules with a translucent appearance resembling a vesicle or bulla, predominantly around mucocutaneous junctions, including the orbits, nares, lips, and genitals. Also, deposition of amyloid will cause vessel wall fragility leading to the development of purpuric lesions following minor trauma or valsalva maneuver. Pink extracellular amorphous deposits staining positive for Congo red with apple-green birefringence under polarized microscopy are typically detected (Fig 2, *A* and *B*).[2] Patients with amyloidosis may present with hoarseness which is thought to be due to the deposition of abnormal protein in the larynx and trachea. Although not confirmed with the biopsy, patient was found to have vocal cord thickening during laryngoscopy which can best be explained by systemic amyloid deposition.[3]

C. Necrobiotic xanthogranuloma — Incorrect. The usual presentation includes yellow-colored papules and nodules coalescing into indurated plaques with superficial telangiectasias, scarring, and ulceration. Histopathology demonstrates large zones of necrobiosis surrounded by well-formed, palisading lymphohistiocytic granulomas. Finding cholesterol clefts in necrobiotic areas is characteristic of necrobiotic xanthogranuloma.[4]

D. Lipoid proteinosis — Incorrect. Although hoarseness occurs in lipoid proteinosis as did in the presented case, the waxy papules of lipoid proteinosis are classically found as beaded eyelid papules on the palpebral margin. On histopathology, it can be differentiated from amyloidosis by demonstrating the Periodic acid—Schiff-positive and diastase-resistant hyaline substance.[5]

E. Sarcoidosis — Incorrect. Sarcoidosis uncommonly involves eyelid (11.5%-17%) presenting as "millet seed" nodules, ulcerated nodules, plaques, swelling, or lamellar scarring. The finding of dermal infiltrates of noncaseating, nonnecrobiotic, and nonsuppurative granulomas will be differentiating.[6]

Question 2: Which of the following is incorrect regarding this disorder?

A. Cutaneous findings found in approximately 40 percent of patients

B. Most common plasma cell dyscrasia associated with this disease is multiple myeloma

C. A large tongue (ie, macroglossia) is characteristic of this disorder

D. Periorbital purpura (raccoon eyes) is present in most patients

E. It may be directly associated with a bleeding diathesis

Answers:

A. Cutaneous findings found in approximately 40 percent of patients — Incorrect. Approximately 40 percent of patients with AL amyloidosis have cutaneous findings which may present before systemic disease providing early clues to diagnosis.[2]

B. Most common plasma cell dyscrasia associated with this disease is multiple myeloma — Incorrect. Multiple myeloma is the most common plasma cell dyscrasia, followed by Waldenstrom macroglobulinemia.[2]

C. A large tongue is characteristic of this disorder — Incorrect. Macroglossia and lateral scalloping of the tongue from impingement on the teeth is characteristic of AL amyloidosis. Amyloid

infiltration in skeletal muscle causes visible enlargement of the tongue.[2]

D. Periorbital purpura (raccoon eyes) is present in most patients — Correct. Purpura, characteristically elicited in a periorbital distribution (raccoon eyes) by a Valsalva maneuver or minor trauma, is seen only in a minority of patients but is highly characteristic of AL amyloidosis.[2]

E. It may be directly associated with a bleeding diathesis — Incorrect. Proposed mechanisms include factor X deficiency due to binding to amyloid fibrils primarily in the liver and spleen.[2]

Question 3: What complementary test would most likely explain the etiology of the skin lesions?

A. Genetic study of *ECM1* gene

B. Abdominal fat pad biopsy

C. Serum and urine protein electrophoresis

D. Lipid profile

E. No further test is required

Answers:

A. Genetic study of *ECM1* gene — Incorrect. Loss-of-function mutations in the extracellular matrix protein *ECM1* gene is used to confirm the diagnosis of lipoid proteinosis.[5]

B. Abdominal fat pad biopsy — Incorrect. In an already-diagnosed cutaneous amyloidosis case, abdominal fat pad biopsy will be redundant and will not help in delineating the etiology of the lesions.[2]

C. Serum and urine protein electrophoresis — Correct. The most common cause of systemic amyloidosis is the deposition of immunoglobulin light chains secondary to plasma cell dyscrasias in which the results of serum and urine protein electrophoresis may be abnormal. Quantitative serum-free light-chain assay will further help, when in rare occasions, as in the presented patient, the serum protein electrophoresis and urine protein electrophoresis return normal.[2]

D. Lipid profile — Incorrect. Based on the histopathological features, the diagnosis is amyloidosis and lipid profile would not be the best next step in finding the underlying causative disorder. On the contrary, dyslipidemia is seen in 50% of patients presenting with xanthelasma.[1]

E. No further test is required — Incorrect. Amyloidosis is the deposition of amyloid material with a wide range of etiologies. Therefore, conducting supplementary tests is of paramount importance in establishing the appropriate treatment plan.[2]

Conflicts of interest

None disclosed.

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