# Diffuse blistering rash with ocular involvement

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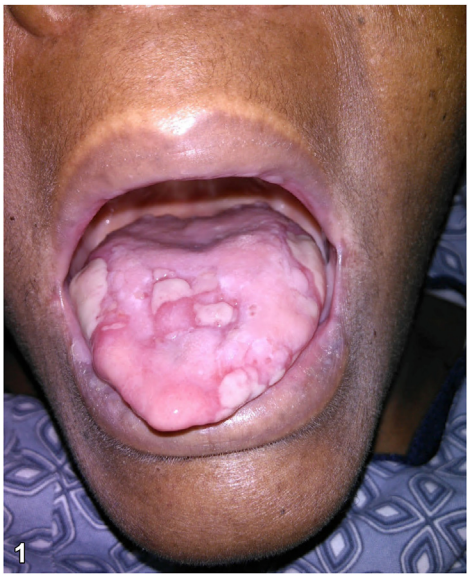


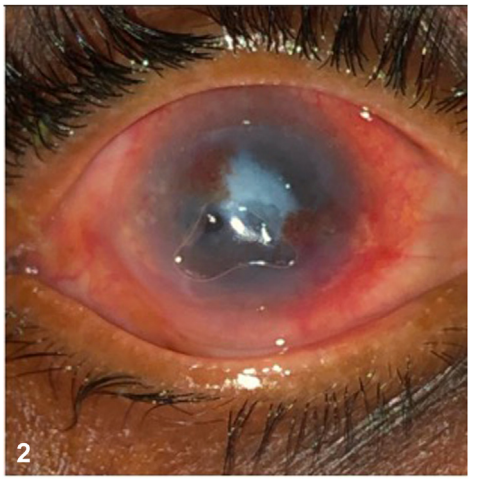


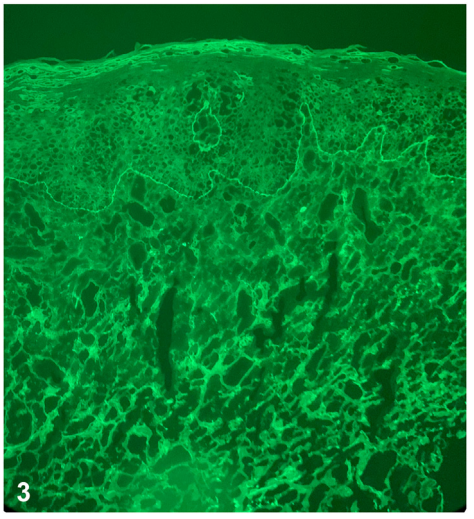


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A 45-year-old woman with a 4-year history of a blistering eruption presented with eye pain and decreased vision for 4 months. Her only medication, lisinopril, had been started 5 years earlier. Examination revealed hypopigmented scars on the trunk and extremities, oral erosions and vesicles (Fig 1), bilateral symblepharon, and right corneal neovascularization and ulceration (Fig 2). Histopathology demonstrated a subepidermal blister with neutrophils. Direct immunofluorescence demonstrated IgA in a linear pattern along the basement membrane zone (Fig 3); IgG, Immunoglobulin M, fibrinogen, and C3 were negative. Serology was negative for anti−NC16a-BP180, anti-BP230, anti−collagen VII, antinuclear antibodies, and circulating anti−basement membrane zone antibodies.

**Question 1: What is the most likely diagnosis?**

**A.** Bullous pemphigoid

**B.** Linear IgA disease (LAD)

**C.** Pemphigus vulgaris

**D.** Mucous membrane pemphigoid

**E.** Bullous systemic lupus erythematosus

**Answers:**

**A.** Bullous pemphigoid − Incorrect. Bullous pemphigoid is characterized by large, tense subepidermal blisters. Significant mucosal involvement is uncommon. Direct immunofluorescence shows linear deposits of C3 and IgG along the basement membrane.

**B.** LAD − Correct. LAD presents with a wide distribution of vesicles and bullae, with up to 50% of patients experiencing mucosal disease.[1,2] Ocular involvement is rare but, if present, can lead to scarring, corneal ulceration, and blindness. Immunofluorescence with the linear deposition of IgA at the basement membrane zone is the gold standard for diagnosis.

**C.** Pemphigus vulgaris − Incorrect. Pemphigus vulgaris is characterized by painful, flaccid intraepidermal blisters, commonly on the oral mucosa. Cutaneous involvement typically spares the palms and soles. Direct immunofluorescence shows the intercellular deposition of IgG.

**D.** Mucous membrane pemphigoid − Incorrect. Mucous membrane pemphigoid is a group of autoimmune subepithelial blistering diseases that predominantly involves the mucous membranes, with variable and minor cutaneous involvement. While deposits of multiple immunoreactants, including IgA, can be observed, most cases are characterized by the linear deposition of IgG and/or C3 along the basement membrane zone.

**E.** Bullous systemic lupus erythematosus − Incorrect. Bullous systemic lupus erythematosus presents with tense bullae in a photodistributed and flexural pattern and is always associated with systemic lupus erythematosus. Rarely, bullae precede systemic lupus erythematosus. Histopathology shows neutrophilic infiltrates in the papillary dermis and IgG at the basement membrane zone.

**Question 2: What medication is most commonly implicated in the drug-induced variant of this disease?**

**A.** Vancomycin

**B.** Phenytoin

**C.** Lamotrigine

**D.** Doxycycline

**E.** Bleomycin

**Answers:**

**A.** Vancomycin − Correct. Vancomycin has most frequently been implicated in drug-induced LAD.[2] The pathogenesis may involve drug-specific T cells that release cytokines that stimulate IgA antibody production. The disease often resolves upon the discontinuation of the drug.

**B.** Phenytoin − Incorrect. Although phenytoin is uncommonly associated with linear IgA disease, vancomycin is a more common culprit. Other cutaneous adverse effects due to phenytoin include gingival hypertrophy, drug reactions with eosinophilia and systemic symptoms, pseudolymphoma, and Stevens-Johnson syndrome.

**C.** Lamotrigine − Incorrect. Lamotrigine is associated with Stevens-Johnson syndrome, which presents 1 to 3 weeks after the exposure to the medication, with skin blistering and epidermal detachment. This patient's chronic course is unlikely to be due to Stevens-Johnson syndrome.

**D.** Doxycycline − Incorrect. Doxycycline is a tetracycline antibiotic that is associated with a phototoxic reaction, in which a patient develops a sunburn-like eruption after exposure to UV radiation.

**E.** Bleomycin − Incorrect. Bleomycin is most often associated with flagellate eruptions, which

are characterized by multiple linear erythematous and/or hyperpigmented streaks at sites of excoriation.

**Question 3: In patients without ocular disease, what is the first-line treatment for this condition?**

**A.** Itraconazole

**B.** Infliximab

**C.** Methotrexate

**D.** Dapsone

**E.** Intravenous immunoglobulin

**Answers:**

**A.** Itraconazole — Incorrect. Itraconazole is an azole antifungal medication.

**B.** Infliximab — Incorrect. Infliximab is chimeric anti—tumor necrosis factor-$\alpha$ antibody that is used for chronic inflammatory conditions, such as psoriasis and inflammatory bowel disease. Tumor necrosis factor-$\alpha$ inhibitors can also be considered for recalcitrant autoimmune blistering disorders.

**C.** Methotrexate — Incorrect. Methotrexate is a folate antagonist that competitively inhibits dihydrofolate reductase. This results in a deficiency of thymidylate and purines. DNA synthesis, repair, and cellular replication are, therefore, decreased. Methotrexate has some utility as a steroid-sparing agent for pemphigus and pemphigoid.

**D.** Dapsone — Correct. Dapsone is an antibiotic and anti-inflammatory medication that is considered the initial treatment of choice for LAD.[2] The anti-inflammatory activity of dapsone is attributed to the inhibition of neutrophil chemotaxis and myeloperoxidase, an enzyme important for respiratory burst. Importantly, prednisone, in combination with either rituximab or cyclophosphamide, should be used for patients with ocular disease. Our patient was initially treated with 50 mg dapsone daily, intravenous immunoglobulin (1 g/kg, single dose due to hospital shortage), and 375 mg/m$^2$ rituximab weekly for 4 weeks. Due to the progressive ocular and oral disease, treatment with 1 mg/kg prednisone daily, 1 g/m$^2$ pulse cyclophosphamide monthly, and 50 mg cyclophosphamide daily was initiated. Dapsone was also continued. After several months, the ocular disease stabilized and the oral disease resolved, allowing the gradual taper of the corticosteroids.

**E.** Intravenous immunoglobulin — Incorrect. Intravenous immunoglobulin has been reported as an effective treatment of LAD in patients who are nonresponsive to dapsone.

**Abbreviation used:**

LAD: linear IgA disease

**Conflicts of interest**

None disclosed.

**REFERENCES**

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