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Grand Rounds

A 26-year-old man with ocular complications after adverse reaction to phenytoin

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History

A 26-year-old black man was admitted to the Burn Unit of Hamilton General Hospital, Ontario, following an adverse drug reaction to phenytoin. He was diagnosed with toxic epidermal necrolysis (TEN) and Ophthalmology was consulted to assess for ocular complications (Figure 1). The Score of Toxic Epidermal Necrosis (SCORTEN) for this patient was 2 (SCORTEN is a validated severity-of-illness score that is predictive of mortality; scores range from 0–7, with 2 corresponding to a 12.1% mortality rate), because he was <40 years of age, had no associated malignancy, had a heart rate of >120 beats/minute, no electrolyte abnormalities (blood urea nitrogen, serum glucose, or serum bicarbonate), and a detached body surface of >10%.[1] He had no comorbidities. His medical history was remarkable for epilepsy. The patient had 85% of his body covered in a thin vesicular slightly blistering rash. His systemic involvement included oral and orbital edema and ulceration of his lips, oral mucosa, scrotum, glans, and upper right chest.

Examination

Visual acuity was counting fingers bilaterally. The visual acuity testing in each eye individually was limited secondary to painful mucosal and epidermal involvement precluding an accurate verbal or written response to conventional testing. Pupils were equal and reactive to light, with no relative afferent pupillary defect. Extraocular motility was minimally restricted; however, there was evidence of significant bilateral symblephara (Figure 2). Anterior segment examination with a portable slit-lamp revealed a small epithelial defect on the left cornea. There was significant conjunctival hyperemia and chemosis without conjunctival ulcerations. Intraocular pressure and fundus examination were within normal limits in each eye.

Ancillary Testing

No ancillary testing was performed.

Treatment

Intravenous immunoglobulin (IVIG) treatment was initiated systemically. Cyclosporine A was initiated topically to act as an immunomodulator to decrease swelling and allow for tear production. Frequent preservative-free artificial tears were also added to hydrate the ocular surface and flush away inflammatory mediators. As our patient had ocular surface adhesions, daily lysis, sweeping of the fornix using a glass rod, and debridement of the loosened epithelium was performed to decrease late complications. In addition, a steeply curved acrylic scleral shell was placed to prevent further symblephara formation.[2]

The patient was followed closely for complete resolution of ocular surface damage and continued to remain asymptomatic of long-term sequelae at the 3 months' follow-up, with a visual acuity of 20/30 in each eye at last follow-up.[3]

Differential Diagnosis

Toxis epidermal necrolysis (TEN), a very rare and potentially fatal skin disorder, is a severe form of Stevens-Johnson syndrome (SJS).[4] It is usually triggered by immunological reaction caused by drugs taken for the first time.[2] It was suspected in this patient because he lacked an infection source and symptoms occurred after

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Figure 1. Epidermal sloughing and hemorrhagic crusting of oral mucosa.

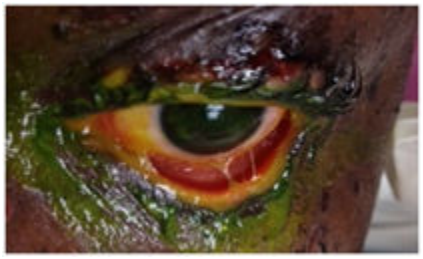

Figure 2. Presence of symblephara and significant conjunctival hyperemia.

recent change to one of the well-recognized causative agents (phenytoin).

Ocular cicatricial pemphigoid often presents with an insidious onset of redness, dryness, and foreign body sensation. It usually occurs in patients older than 55 years of age and is characterized by remission and exacerbations. Presentation often includes symblephara (inferior greater than superior) and foreshortening of the inferior fornix.

Staphylococcal scalded skin syndrome is caused by an exfoliative toxin produced by roughly 5% of *Staphylococcus aureus*. These toxins can lead to a red rash and separation of the epidermis with diffuse sheetlike desquamation.

Toxic shock syndrome is a potentially fatal illness caused by enterotoxin type B produced by *Staphylococcus aureus*. Patients demonstrate presence of an infection and systemic symptoms.

Phototoxic skin reaction refers to the development of cutaneous disease as a result of the combined effects of a chemical and light. Typically, they appear as an exaggerated sunburn response, but only on sun-exposed areas of the body.

Numerous other conditions may present in a similar fashion, including trachoma, cicatricial conjunctivitis secondary to chronic topical medications (especially pilocarpine, phospholine iodide and antiviral agents), chemical burn, and radiation treatment. In addition to the entities mentioned above, the possibility of a malignant process (eg, conjunctival intraepithelial neoplasia and squamous cell carcinoma) should always be considered, particularly in older patients with risk factors.

Diagnosis and Discussion

TEN is usually triggered by immunological reaction, with incidence rate of 0.4–1.2 cases per million persons and mortality rates in the range of 25%–35%.[4,5] It is most commonly caused by drugs taken for the first time (usually anticonvulsants and antibiotics).[2] It was suspected in this patient, because symptoms occurred after recent change to one of the well-recognized causative agents (phenytoin) in the absence of an infection or history of specific medical conditions to support an alternative etiology.

Incidence of ocular involvement during the acute phase is between 50% and 88%[4,6] and chronic complications have been noted in up to 35% of survivors.[2] An inflammatory reaction involving the ocular surface destroys goblet cells and results in decreased secretion of mucin, which impairs tear distribution and stability. Frank scarring of the bulbar and forniceal conjunctivae can lead to symblepharon or ankyloblepharon, which cause inadequate blinking/closure and affect ocular motility. Loss of the normal glandular structures of the ocular surface and eyelids leads to severe dry eye problems and vision loss.[2]

The optimal acute ocular therapeutic regimen for TEN remains a topic for continued debate. Various interventions have been proposed, including intravenous methylprednisolone, topical steroids, and immunomodulator as well as a “Triple TEN” acute ocular management protocol, which comprises administration of triamcinolone into each of the fornices, insertion of a scleral shell spacer, and placement of amniotic membrane tissue over the corneal and limbal regions.[7]

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