Cytarabine-Induced Keratoconjunctivitis: A Common Complication of High Dose Therapy for Acute Myeloid Leukemia

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ABSTRACT: Here we describe a case of cytarabine ocular toxicity in a patient with acute myeloid leukemia. Keratoconjunctivitis is a well-described side effect in the hematology/oncology literature. Prophylactic topical steroids are typically initiated, with variable efficacy.

I. Case History

- Patient demographics: 61 year old Caucasian male
- Chief complaint: ocular pain and light sensitivity OD developing over the last 3-4 hours
- Ocular history: remote history of LASIK surgery OU, recent symptomatic PVD OS (3 months ago)
- Medical history: Acute Myeloid Leukemia (AML) diagnosed 7/1/16, Type 2 DM, hypertension, hyperlipidemia
- Medications: Insulin, glucagon, aspirin 81 mg, acylovir, lisinopril, metoprolol, clonidine, levofloxacin, posaconazole, ondansetron, prochlorperazine, tramadol
- Other salient information: Patient has been treated for AML with induction using cytarabine/daunorubicin. Remission was achieved and patient was readmitted for consolidation treatment on 8/14/16 with high-dose cytarabine. As a part of treatment protocol, the patient was prophylactically started on topical prednisolone 1% suspension 2 drops OU every 4 hours (round-the-clock) on days 1-8 of the treatment cycle. Topical prednisolone was discontinued 2 days before presentation.

II. Pertinent findings

- Clinical: superior sectoral bulbar injection with few scattered petechial hemorrhages along superior limbus OD at initial presentation. Re-evaluation 36 hours later revealed evidence of corneal epithelial microcysts OU.
- Laboratory studies: Automated CBC with differential showed pancytopenia and blasts, and bone marrow studies were consistent with AML
- Radiology studies: Head CT on 7/21/16 and 8/19/16 displayed no cytarabine-related cerebral edema
- Bone marrow biopsies:
  - 7/4/16: 78% CD34+ blasts (demonstrating acute myeloid leukemia)
  - 7/22/16 (after first course of cytarabine induction): 2% myeloblasts
  - 8/4/16: 1.8% myeloblasts

III. Differential diagnosis

- Primary/leading: cytarabine-induced keratoconjunctivitis with sectoral episcleritis and localized subconjunctival hemorrhages OD
• **Others:**
  - Subconjunctival hemorrhage secondary to thrombocytopenia
  - Infectious keratitis/conjunctivitis/uveitis given patient is immunocompromised
  - Herpes Simplex Viral Keratoconjunctivitis (patient is on prophylactic acyclovir)
  - Fungal Keratitis: commonly *Candida albicans* if immunocompromised, patient is on prophylactic antifungals

**IV. Diagnosis and discussion:**

• **Elaborate on the condition:** Cytarabine (cytosine arabinoside) is an antineoplastic agent commonly used in the treatment of acute myeloid leukemia. Cytarabine has the ability to penetrate body fluids, including the blood-brain barrier, and has been found in the aqueous humor and tears (Bubalo). This distribution increases the risk of ocular toxicity, which frequently occurs with high-dose cytarabine (HiDAC) and is most strongly associated with the duration of dosing (Bubalo). In fact, the majority of patients whose regimens are at least six to eight days experience eye problems (Higa et al.). Ocular findings include bilateral corneal epithelial microcysts (typically more central), conjunctival hyperemia, fine corneal opacities, severe blepharospasm, and moderate conjunctival inflammation (Bubalo). Systemic side effects include leukopenia, thrombocytopenia, nausea, vomiting, central nervous system and cerebellar toxicity (Bishop).

• **Expound on unique features:** This patient was prophylactically placed on topical prednisolone 1% during his course of treatment with cytarabine. Onset of symptoms occurred two days after the topical corticosteroids were discontinued.

**V. Treatment, management**

• **Treatment and response to treatment:** Patient was re-started on topical prednisolone 1% suspension 2 drops OU every 4 hours. At follow up visit 36 hours later the patient was no longer symptomatic, and sectoral injection had resolved, however corneal microcysts were noted OU. Topical prednisolone was continued with a reduced dosage of 1 drop OU every 4 hours while awake. The patient had not had a dilated fundus exam since his diagnosis of AML, so 3 days later this was performed bedside and revealed scattered peripheral blot hemorrhages, likely due to the patient’s pancytopenic status. A decrease in corneal microcysts was also noted at this exam, and topical prednisolone taper was initiated. Recommendations were made to the hematology-oncology service to initiate on days 1-8 of subsequent chemo cycles: (1) fluorometholone 0.1% 1 gtt QID OU while awake with taper; (2) preservative-free carboxymethylcellulose 0.5% 2 gtt QID OU while awake; and (3) fluorometholone ung QHS OU.

• **Refer to research where appropriate:**
  - Topical corticosteroids are commonly used for prophylaxis of keratoconjunctivitis in patients undergoing treatment with cytarabine at doses of 1000 mg/m² or greater, with a recommended dosing of 2 drops every 4-6 hours continued 48 hours after the last dose of cytarabine (Bubalo). The incidence of keratoconjunctivitis in patients treated with topical corticosteroids is reduced from 85-92% to 8-16% (Takehiko Mori et al.). This
is thought to be due to a combination of decreased DNA replication in corneal cells by corticosteroids and dilution of the concentration of cytarabine in the tears (Bubalo).

- Mori et al. showed that frequent eye rinse with sterile saline can also be effective in reducing the incidence and severity of keratoconjunctivitis. A small study by Higa et al. concluded that topical corticosteroids are not significantly better than artificial tears in prevention of ocular toxicity.

- There is no standard protocol in prophylactic treatment of cytarabine-induced keratoconjunctivitis; studies have employed the use of a variety of topical steroids including betamethasone, dexamethasone, and prednisolone (Bubalo).

- The incidence and severity of conjunctivitis has also been reduced with the addition of topical NSAIDs to corticosteroids (Matteucci et al.).

- **Bibliography:**


**VI. Conclusion**
Clinical pearls, take away points: The ocular toxicity of cytarabine has been well established in the literature for over 30 years. However, this seems to be familiar mainly to hematologists and oncologists, and has not been mentioned in ophthalmic literature in the last few decades. Current oncology protocols suggest patients undergoing treatment with high-dose cytarabine may benefit most from prophylactic treatment with a topical corticosteroid and eye rinse, although more research done on this topic from an ophthalmic perspective may reveal effective treatments that are safer and more comfortable for the patient. There is no consensus on which topical corticosteroid is most appropriate; given the absence of uveitis in these patients, a less-penetrating topical steroid such as fluorometholone may be sufficient for keratoconjunctivitis prophylaxis while minimizing side effects, such as IOP elevation and cataract formation. Frequent preservative-free artificial tears may be an important adjuvant to topical corticosteroids.