Severe necrotising inflammatory skin reaction to topical 5-fluorouracil

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I report two patients who developed a severe necrotising inflammatory skin reaction with ulceration and hemorrhagic crusting during the first cycle of chemotherapy with 1% 5-Fluorouracil eye drops for Ocular surface squamous neoplasia. The skin reaction subsided on stoppage of the drops and the use of a steroid ointment. 5 fluorouracil therapy was terminated and the patients were shifted to interferon therapy subsequently.

Key words: 5-fluorouracil, inflammation, ocular surface squamous neoplasia

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Ocular surface squamous neoplasia (OSSN) can be treated with surgery or chemotherapy. Chemotherapeutic agents used for treatment include Interferon alpha 2b (IFN), Mitomycin C (MMC) and 5-Fluorouracil (5-FU). Each has its advantages and disadvantages, and currently IFN is the first choice of therapy due to its safety profile. However 5-FU is significantly cheaper, does not require refrigeration, requires a shorter treatment regimen and is as effective as IFN as a primary therapy.[1,2] In a developing country 5-FU is a viable first line therapy option in patients who are non-affording and don't have access to refrigeration. Minor reversible lid edema, itching and swelling has been reported following its use previously,[1,2]

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however no cases of severe periocular skin reaction have been reported to the best of our knowledge.

Case Reports

Case 1

A 51-year-old male patient presented with a small nodule in the right eye slowly increasing since 6 months. Clinical examination showed a gelatinous elevated mass at the nasal limbus with large feeder vessels. Systemic work up including a HIV test was negative. Based on the classical presentation and the AS-OCT findings he was started on 5-FU 1% eye drops 4 times a day for 7 days. He presented 10 days later with complaints of swelling, pain and blackening of the periocular skin. On examination there was erythema, edema and ulceration with hemorrhagic crusting around the eye [Fig. 1]. There were no signs of any systemic reaction in the patient. He was prescribed Chloramphenicol-hydrocortisone eye ointment (Chlorocol-H eye ointment, Jawa Pharma, India) twice a day for 2 weeks along with lubricant eye drops. At 2 weeks the skin lesions had fully healed leaving behind some patchy pigmentation. Since the tumor had only partially regressed he was advised to start treatment with IFN eye drops and followed up. The skin changes are reversible, except mild pigmentation as seen in the one year follow up picture [Fig. 2].

Case 2

A 55-year-old male patient presented with a superotemporal OSSN in his left eye, and was started on 5-FU drops. He presented very similarly on day 10 showing blistering with hemorrhagic crusting and ulceration of the periocular skin [Fig. 3]. He also responded well to chloramphenicol hydrocortisone eye ointment and was shifted to IFN therapy.

Discussion

5-FU was first reported as a treatment for OSSN in 1986,[3] however no major large-scale study was reported until recently when 5-FU was used as a primary therapy in OSSN.[2] After this favorable outcome report we started using 5-FU as per the recommendations of the authors, i.e. we use 1% 5-FU drops 4 times daily for a week followed by a 3 weeks of drug holiday. We repeat this cycle till complete resolution. This treatment is the first line of choice in patients who are not affording or don't have access to refrigeration facility. More recently 5-FU was also shown to have results comparable to IFN as a primary therapy for OSSN.[1]

The side effects of 5-FU drops reported in ophthalmic literature include both hyperemia and keratitis in 42% in one series[4] and pain (39%), tearing (23%), photophobia (14%), itching (4.9%), swelling (5%) and infection (2%) in the more recent series.[2]

We report two patients with primary OSSN who developed a severe necrotising inflammatory skin reaction following the first cycle of 5-FU. The reaction required us to stop further usage of 5-FU and switch the patient to IFN therapy. Mild lid edema (9.9%) is reported but there are no previous ophthalmic reports of this unusually severe inflammatory skin reaction.[1]

Dermatologists commonly use higher concentrations (2-5%) of topical 5-FU creams. In dermatologic literature mild irritant dermatitis and photosensitivity have been reported commonly, however exuberant inflammatory skin reaction has been reported when it was applied under wraps, which increase the contact time and penetration of 5-FU into the skin.[5,6] There is also an isolated case report of necrotizing cutaneous reaction to topical 5-FU in the dermatologic literature.[7] Systemic toxicity is extremely rare, and is more likely in patients with

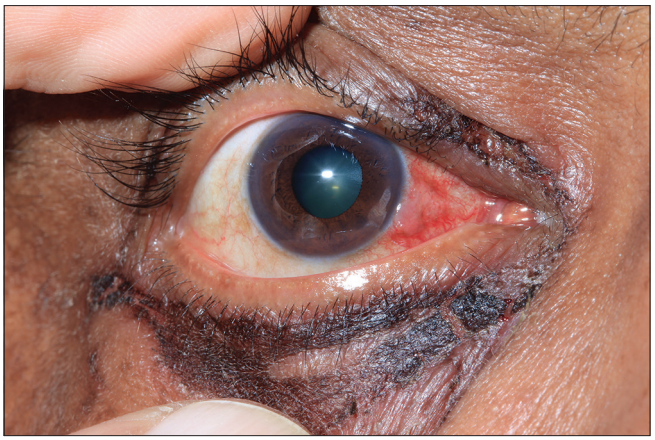

Figure 1: Case 1 - Right eye showing hemorrhagic crusting and ulceration of the periocular skin with a nasal conjunctival mass with feeder vessels

Figure 2: Case 1 - Right eye one year picture showing complete recovery of skin reaction except mild pigmentation

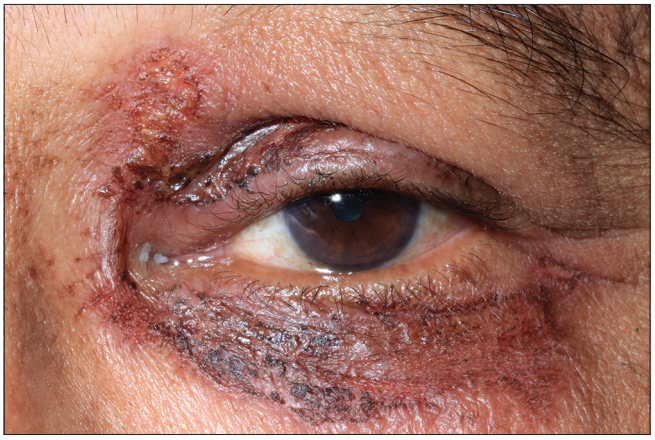

Figure 3: Case 2 - Left eye showing blistering with hemorrhagic crusting and ulceration of the periocular skin

dihydropyrimidine dehydrogenase deficiency, as a result of which they are unable to metabolize the 5-FU absorbed from the local application.[5,8] Though punctal plugging is not routinely recommended for 5-FU eye drops[2] it may be advisable to apply pressure over the medial canthus after drop instillation to minimize systemic exposure.

Our patients probably had periocular skin exposure to 5-FU from the eye drops. These drops are routinely prepared in our hospital pharmacy and an error in drug concentration is not likely. Patients are also counseled that these are anticancer drugs and should be used strictly as per prescription. We did not find any similar reports in the ophthalmic literature. We would like to advise greater caution in the usage of 5-FU for ocular surface squamous neoplasia.

Conclusion

Ophthalmologists need to be aware of the rare possibility of serious skin reactions and the rare possibility of systemic side effects even with topical use.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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