Unusual Allergic Reaction to Intralesional Bleomycin in Periocular Haemangioma

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ABSTRACT

Capillary haemangiomas are the most common periocular tumours among children. Most of them resolve spontaneously. The most common indication for intervention is visual impairment. Intralesional bleomycin injections have been used successfully to treat periocular haemangiomas resistant to conventional treatment modalities. In the literature, the most commonly reported side effects of intralesional bleomycin are local skin reactions like erythema, swelling, and pigmentation. Here, we report a highly unusual case of a severe allergic reaction to the fourth dose of intralesional bleomycin injection in a periocular haemangioma in a 7-year child. The clinical features and subsequent management of the patient are also discussed.

Key Words: *Anaphylaxis, Intralesional bleomycin, Periocular haemangioma.*

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INTRODUCTION

Capillary haemangiomas, benign tumours arising from the vascular endothelium, are the most common periocular tumours found in children. Typically manifesting in the first few months of life, their natural course is a rapid proliferative phase followed by stabilisation and then involution which classically occurs in a centrifugal pattern.[1]

The most common indication for intervention is the risk of amblyopia which can be either sensory deprivation amblyopia or anisometropic amblyopia. Other indications include exposure keratopathy from significant proptosis and optic nerve compression, both of which are more likely to occur in deep orbital haemangiomas.[2]

The conventional management of periocular haemangioma includes systemic and intralesional steroids, topical and systemic non-selective beta-blockers, subcutaneous interferon-alpha injections, laser therapy, radiotherapy, and surgical excision. Various studies have reported the successful use of intralesional bleomycin injections for capillary haemangiomas both as first-line management and as the last resort where other modalities have failed.[1]

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Here, we report an interesting case of a fatal allergic reaction witnessed in a pediatric haemangioma that was treated with systemic beta-blockers and intralesional bleomycin injections.

CASE REPORT

Institutional Review Board (IRB) approval as well as oral and written consent were taken from the guardian of the patient for publication of images and report.

A 7-year child presented to a tertiary care hospital in September 2022 with a lesion on his right lower eyelid. It was first noticed at the age of 9 months, and progressive increase in the size was noticed thereafter. A physical examination disclosed a raised dark purple mass in the right lower eyelid. It had a spongy consistency on palpation and did not blanch with pressure. The mass was compromising the palpebral fissure, turning it into a horizontal slit (Figure 1). However, the uncorrected visual acuity in the right eye was 6/6. The anterior and posterior segment examinations were unremarkable. A complete systemic examination revealed no other abnormalities.

An MRI of the face and orbit revealed a poorly defined abnormal signal intensity lesion measuring approximately 4.0 × 3.2 × 2.5 cm (TS×CC×AP) in the pre- and infraorbital soft tissues. It appeared isointense on T1, heterogeneously hyperintense on T2 weighted imaging (WI) and showed heterogeneous post-contrast enhancement. Inferiorly, it showed extension into the premaxillary soft tissues. Medially, it was reaching up to the right nasal ala. Multiple tortuous, low-intensity voids were seen within the lesion. Posteriorly, it appeared inseparable from the anteroinferior margin of the right globe and showed infraorbital extension along the orbital floor, appearing inseparable from the right inferior rectus muscle.

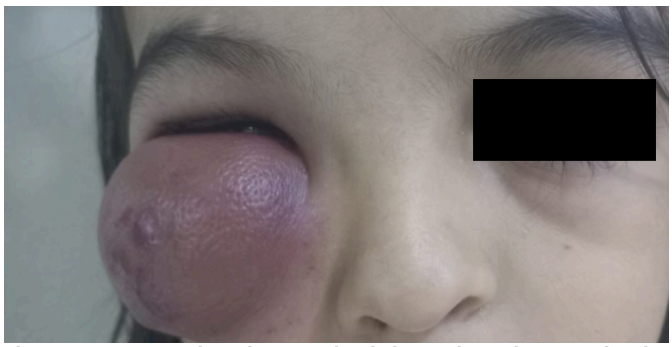

Figure 1: Preoperative photograph of the patient shows periocular haemangioma compromising the palpebral fissure of the right eye.

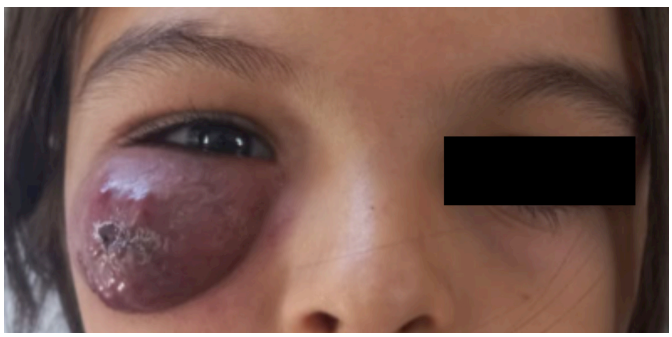

Figure 2: Postoperative photograph of the patient after three doses of intralesional bleomycin shows significant reduction in size of the lesion of the right lower eyelid.

CT carotid angiography revealed evidence of an arteriovenous malformation involving the right periorbital soft tissues, predominantly supplied by superficial temporal and maxillary branches of the external carotid artery. The venous drainage was predominantly in the internal jugular vein with the prominence of its tributaries on the right side. Vascular congestion was seen in the right orbit and on the right half of the face.

After taking opinions from the oromaxillofacial, paediatric medicine, and interventional radiology consultants, the patient was managed by a single senior oculoplastic surgeon. The patient was started on propranolol syrup at a dose of 1 mg/kg/day and intralesional bleomycin injections under general anaesthesia (total intravenous anaesthesia with propofol only and airway was managed with effective mask ventilation) at a dose of 0.5 mg/kg (the child's weight was 22 kg) diluted in 7 ml of normal saline (roughly equivalent to the volume of the lesion) for each month. An injection was given by introducing the needle through normal skin and then advancing into the haemangioma, followed by local pressure for about 5 minutes. This management caused a significant reduction of the lesion (Figure 2). The fourth dose of intralesional bleomycin was given on 9th March at 10:00 a.m. The patient recovered from general anaesthesia uneventfully. Approximately one hour after the procedure, the patient had one episode of vomiting and a fever spike of 101°F. His Glasgow Coma Scale (GCS) was 15/15, pulse was 155 bpm, blood pressure was 90/55 mm Hg, respiratory rate was 30 per minute, oxygen saturation at room air was 98%, and fasting blood sugar was 100 mg/dl. There was periorbital and perioral edema too. After consulting the anaesthesia and paediatric departments, the patient was given IV paracetamol at a dose of 15 mg/kg in 15 minutes and IV normal saline initially in a bolus of 350 ml and then, maintenance fluid at a rate of 4 ml/kg/hour. He was catheterised, and his complete blood count (CBC), urea, creatinine, electrolytes (UCE), urine detailed report (UDR), blood cultures, urine cultures, malarial parasites (MP)/ICT, and dengue NS1, and IgM were recorded.

The patient was kept under continuous monitoring, and his propranolol syrup was stopped, but his blood pressure did not improve despite the above management. He developed three spikes of fever, with temperature going up to 102°F in the next 4 hours. The urine output was 60 ml/hour, indicating good renal perfusion. At about 9:00 p.m., his GCS dropped to 12/15 and his blood pressure dropped to 83/38 mm Hg. The patient was given a bolus of 350 ml of normal saline and was shifted to the ICU. His CBC showed a raised total leucocyte count (TLC) of 20×10^9 cells/L (90% neutrophils, 7% eosinophils, and 2% lymphocytes) as compared to 8.8×10^9 cells/L preoperatively. The UDR was unremarkable. Dengue and MP were negative. The patient was then managed as a case of anaphylactic shock, probably due to bleomycin, with septic shock as the differential diagnosis. He was given injections of pheniramine maleate (1 ml/IM), adrenaline 0.3 mg/IM (0.3 ML of 1/1000 solution), hydrocortisone 25 mg IV TDS, and ceftriaxone 1g IV OD. The patient improved dramatically with the treatment, and his blood pressures were 90/60, 100/64, and 110/70 mm Hg at 1 hour, 2 hours, and 3 hours' post-treatment, respectively. The patient was shifted to HDU for one day under observation and then to the general ward. He was shifted to oral treatment and discharged after 3 days.

DISCUSSION

Since the use of intralesional bleomycin injection for macrocystic lymphangioma and cutaneous haemangioma by Yura *et al*. and Sarihan *et al*., respectively, it has been widely adopted as a sclerotherapy for vascular malformations with impressive success rates.[3] Bleomycin is a cytotoxic and anti-tumour agent that causes oxidative damage to cellular DNA and RNA. Its sclerosing effect involves damage to the vascular endothelium and the induction of a non-specific inflammatory response thulminates in the adoption of a mesenchymal phenotype by endothelial cells.[3]

Bleomycin has emerged as a preferred sclerosing agent because of its wide availability, low cost, impressive success rates, and acceptable adverse effects profile. There was a marked improvement in the size of the lesion with intralesional bleomycin injection in our patient, which is consistent with the previous studies.[4] Although the commonly reported adverse effects after systemic bleomycin therapy are pulmonary fibrosis, hepatic toxicity, bone marrow suppression, and anaphylaxis; these are not reported with intralesional bleomycin injections, which could be due to no spill-over of bleomycin into systemic circulation after intralesional injection.[5] One study has reported raised serum alkaline phosphatase after intralesional bleomycin injection.[6] There is another case report of systemic toxicity occurring after intrapleural injection of bleomycin for malignant pleural effusion in a breast cancer patient.[7]

The most frequently reported adverse effects of intralesional bleomycin injections are local skin reactions like pain at the injection site, swelling, erythema, hyperpigmentation, superficial ulceration, and eschar formation.[8] Flagellate hyperpigmentation has been reported as a rare adverse effect of systemic bleomycin therapy in cancer patients, but it has also been reported after intralesional injections in a study.[9] One case report of an interestingly similar clinical presentation as that of the present patient, identified gelatin as a causative agent for the allergic response which was used in combination with bleomycin as a sclerosing agent.[10]

Although severe systemic allergic reactions have been reported after intravenous bleomycin therapy in cancer patients, there is no case report to date about such adverse events occurring with intralesional bleomycin injection.[10] Some of the adverse effects occurring after systemic bleomycin therapy are also rarely reported after intralesional injections. This suggests that there is at least some systemic absorption after intralesional injections in vascular malformations. Furthermore, there are reports of anaphylactic reactions to a drug occurring even after previously tolerated exposures (causing sensitisation).[11] This might explain a rare systemic toxicity occurring after the fourth dose of intralesional injection in the present patient. Further studies are required in this area for the formulation of guidelines for pre-operative laboratory investigations and the test doses of bleomycin before initiating intralesional therapy.

PATIENT'S CONSENT:
Oral and written consent were taken from the guardian of the patient for publication of images and report.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
SA: Conception, designing, and acquisition of the data.
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