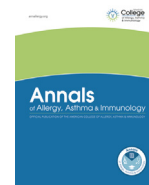




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Letter

First case of type IV hypersensitivity to periocular topotecan

Topotecan is a topoisomerase 1 inhibitor derived from the *Campotheca acuminata* plant and has been approved by the US Food and Drug Administration for ovarian, cervical, and small cell lung cancers.¹ More recently, periocular injection of topotecan with fibrin sealant has been used to treat retinoblastoma as an alternative to carboplatin.² Injection is performed in the subtenon space with a fibrin sealant to extend the duration of intraocular drug penetration in tissue, reducing the number of injections required and limiting systemic toxic effects.^{2,3} Tisseel (Baxter, Deerfield, Illinois) is a 2-component fibrin sealant derived from human pooled plasma and contains thrombin, fibrinogen, proteinase inhibitor aprotinin, and calcium chloride. All components are human derived except for bovine aprotinin.⁴ Sensitization to aprotinin has previously been described, and multiple cases of anaphylaxis during nonocular operations have been reported: a review of 124 patients indicated that 2.8% of patients reexposed to aprotinin presented with anaphylaxis.⁵ In this report, we present an 18-month-old boy with bilateral retinoblastoma who developed a type IV hypersensitivity reaction to periocular topotecan after his second exposure.

At 6 months of age, our patient was diagnosed as having stage B retinoblastoma in the right eye and stage E in the left eye.⁶ His left eye was enucleated at diagnosis, and his remaining right eye was treated with 7 cycles of systemic chemotherapy (vincristine, VP16, carboplatin). Six months later, the tumor in the right eye progressed, and the tumor board members decided to treat the recurrence with subtenon topotecan and local retinal laser photocoagulation.

Two subtenon injections were performed 6 weeks apart with the patient under general anesthesia. The topotecan was administered as per the protocol described by Mallipatna et al.² The final dose of topotecan hydrochloride (GlaxoSmithKline, Mississauga, Ontario) for each injection was 2.0 mg (0.13 mg/kg or 3.75 mg/m²). The first injection had been well tolerated. Three days after the second injection, the patient presented with worsening chemosis and subconjunctival hemorrhage. Throughout the week, the subconjunctival hemorrhage increased further and eyelid and cheek edema developed (Fig 1A). He was treated with topical 1% prednisolone acetate drops. Within 2 days his symptoms resolved. Because an allergic reaction was suspected, the patient was referred to our allergy clinic for investigation.

Skin prick tests and intradermal tests were performed with topotecan (1-mg/mL solution in sterile water) and with the fibrin sealant Tisseel (500 IU/4 mL). Skin prick test results were defined as positive if they produced a 3-mm or larger wheal 15 minutes after injection. The results of skin prick tests to topotecan, Tisseel fibrin sealant, and individual components of Tisseel, including calcium chloride, aprotinin, human fibrin glue, and thrombin, were

negative. Intradermal skin tests were then performed using sterile solutions of topotecan (1 mg/mL) and components of Tisseel (aprotinin, thrombin, human glue) to produce dilutions of 10⁻² and 10⁻³ in normal saline. An intradermal skin test result was considered positive if it was 3 mm greater than the negative control with surrounding erythema 15 minutes after injection. All intradermal skin test results were negative 15 minutes, 24 hours, and 48 hours after injection. Two controls had negative intradermal topotecan test results with these concentrations. The histamine control test result was positive.

Patch tests were then performed on the child's back, and the results interpreted after 48 hours according to the latest contact dermatitis practice parameter of the American Academy of Allergy, Asthma, and Immunology.⁷ Patch tests were initially performed to aprotinin, Tisseel, Vaseline, and 30% topotecan using Finn chambers (Smartpractice, Phoenix, Arizona). All patch test results were negative at 48 hours except for topotecan, which yielded an erythematous skin infiltration with papules and noncoalescing vesicles, considered as a strong positive reaction (2+ based on the International Contact Dermatitis Research Group nomenclature⁷). We then repeated the patch tests with lower concentrations of topotecan. The results of both patch tests with a 30% topotecan concentration and a 10% concentration were positive after 48 hours (2+ and 1+, respectively), with a negative Vaseline control (Fig 1B). The results of identical patch tests performed on a control subject were negative.

We describe the first case of confirmed type IV hypersensitivity reaction to topotecan after periocular injection of topotecan with fibrin sealant. Although multiple hypersensitivity reactions have been described to aprotinin,^{5,8} none so far have been described to periocular topotecan. Astudillo et al⁸ reported 2 cases of hypersensitivity reactions (type I and type IV) to subtenon topotecan in fibrin adhesive. However, hypersensitivity to the individual components was never tested and the culprit was never identified, even if aprotinin was suspected.⁸ Previously, only 1 case of suspected fixed drug eruption has been reported with topotecan in a 38-year-old woman treated for ovarian cystadenocarcinoma.⁹ The patient presented with an erythematous plaque on the back of her thigh after a first course of intravenous topotecan and was initially treated with antibiotics for suspicion of cellulitis. The plaque reappeared at the same location after subsequent courses of topotecan chemotherapy, and a fixed drug eruption was suspected.

Because periocular and intravitreal topotecan is currently being used to treat retinoblastoma,¹⁰ it is important to be aware of potential type IV hypersensitivity reactions to topotecan, as reported here for the first time. Clinicians should be aware of this potential complication when evaluating patients with delayed swelling and erythema of the eye after periocular injection of topotecan, and patients should be referred to the allergist for investigation.

Disclosures: Authors have nothing to disclose.

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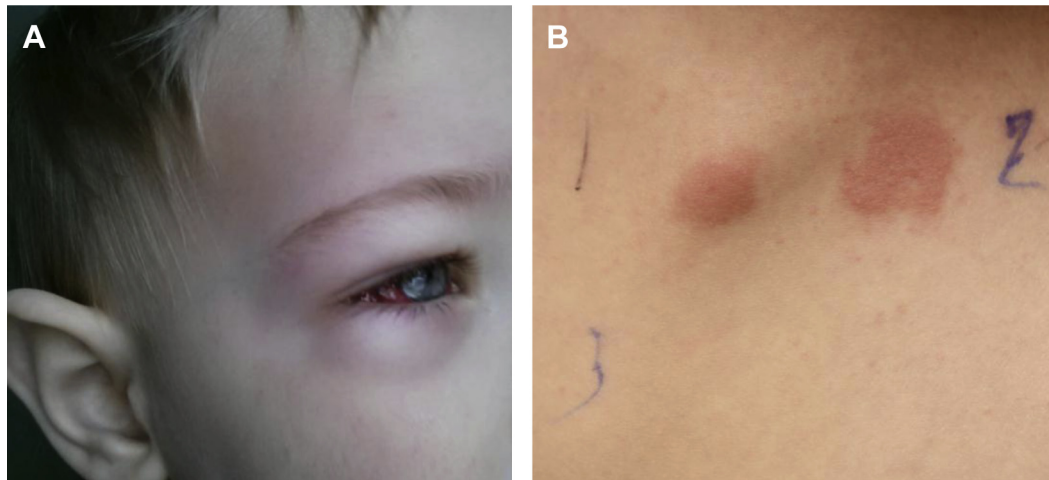


Figure 1. Clinical presentation and diagnosis of type 4 hypersensitivity to topotecan. (A), Clinical presentation of child. (B), Patch test result with 10% (1) and 30% (2) topotecan revealed an erythematous plaque after 48 hours. Control result (3) was negative.

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