

the background of numerous plasma cells and foamy histiocytes. Lipid laden vacuoles were also seen (Fig 1F). Thus, a diagnosis of xanthogranulomatous lesion was made. Immunohistochemistry revealed positivity for CD3, CD20, CD68 (histiocyte specific), CD138, and CD134 (blood vessel specific). CD1a, CD30, CD15, and Latent Membrane Protein were negative. Liver and renal function tests results were within normal limits. Enzyme-linked immunosorbent assay results for human immunodeficiency virus, hepatitis B surface antigen, hepatitis C antigen were negative. A diagnostic endoscopy of the nasal cavity was normal. Positron emission tomography confirmed the absence of any systemic involvement. The patient was diagnosed as having adult-onset asthma and periocular xanthogranuloma (AAPOX). He was prescribed oral prednisolone, 1 mg/kg per day, and advised slow taper for a 3-month period. He was also prescribed prism glasses to alleviate his double vision. A telephone conversation 45 months later revealed that he is continuing to take low-dose oral steroids (10 mg/d) under the care of a local physician and is symptom free (Fig 1G). The patient has been advised to undergo regular systemic evaluation.

Xanthogranulomatous diseases are a group of non-Langerhans cell histiocytosis characterized histopathologically by the presence of Touton giant cells, lymphocytes, plasma cells, and histiocytes. Areas of fibrosis or necrosis may also be seen.¹ It may involve the orbit and the adnexa in the following forms: (1) adult-onset xanthogranuloma, (2) AAPOX, (3) necrobiotic xanthogranuloma, or (4) Erdheim-Chester disease.

Diseases with predominantly xanthomatized histiocytes form a major part of the non-Langerhans histiocytosis and are of unknown origin.² Histopathologic and immunohistochemical analysis along with systemic investigations are imperative for accurate diagnosis.¹

AAPOX is associated with late-onset asthma with bilateral anterior orbital or preseptal lesions (the overlying skin typically displaying a yellowish tint). Simultaneous involvement of conjunctiva along with the skin and orbit has also been reported.³ Associated lymphadenopathy and paraproteinemia indicate an underlying disorder of B-cell proliferation. Our patient did not have any systemic involvement. Because of the rarity of this disease, the management guidelines are not yet well defined.

It is mandatory to perform a thorough search for systemic involvement and to rule out Erdheim-Chester disease, which involves multiple organs and has a devastating course and response to treatment. Fluorodeoxyglucose positron emission tomography and computed tomography are useful as an initial investigation and as a follow-up tool.⁴ Treatment options for AAPOX comprise systemic steroids, immunosuppressants, and surgery. When the lesions are confined to the anterior orbit, surgery or debulking alone has been successful in a few cases.^{1,2,5–8} Intralesional steroid injections may be useful in isolated preseptal or anterior orbital involvement but come with the inherent risk of central retinal artery occlusion, ophthalmic artery occlusion, glaucoma, eyelid necrosis, and subcutaneous fat atrophy.⁹ Systemic steroids are

preferred when there is an associated immune system disorder, asthma, or systemic involvement. Oral steroids with cyclophosphamide pulses are useful.^{7,8}

Cyclophosphamide, methotrexate, and azathioprine have been used as steroid-sparing agents and also in refractory cases.^{2,7,8} Radiotherapy has been used in combination with immunosuppressive treatment for cicatricial changes.^{1,5}

The xanthogranulomatous group of diseases has characteristic presentation patterns. To the best of our knowledge, intraocular involvement has been reported with rarity in the medical literature. It was found in 1 patient described by Sivak-Callcott et al.¹ in 2006 and then in a case series of AAPOX by Kiratli et al.¹⁰ These patients responded to debulking followed by long-term oral steroid therapy.¹⁰ Our patient had extensive bilateral orbital involvement without typical skin changes. Hence, we conclude that AAPOX may present without any skin discoloration and can have orbital involvement that threatens vision. Systemic involvement may or may not be present. According to the current literature, systemic steroids are the mainstay of treatment. Immunosuppressive agents are suggested in refractory cases.

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Impact of supervised epinephrine autoinjector administration during food challenges on parent confidence



Rapid administration of intramuscular epinephrine is the first-line treatment for anaphylaxis. Patients are prescribed an epinephrine autoinjector (EAI), which may be self- or caregiver administered,

depending on the patient's age. However, carrying the EAI does not guarantee its use. Reasons for EAI underuse include failure to recognize anaphylaxis symptoms and lack of confidence. Psychological factors may drive parent hesitation of EAI use, such as fear of hurting their child.^{1,2} In addition to optimizing intrinsic factors, such as the size, shape, and color of the device, methods using video technology or large-scale educational programs have been

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implemented to promote EAI use, with modest success.^{3–6} Anaphylaxis is a potential outcome of physician-supervised oral food challenges and therefore presents an ideal opportunity for real-world EAI training. To our knowledge, this is the first study of EAI training during actual episodes of anaphylaxis. This study describes the effect of supervised EAI administration on parent confidence.

This study was approved by The University of British Columbia/Children's and Women's Health Centre of British Columbia Research Ethics Board. Children aged 2 to 17 years undergoing supervised oral food challenges at the British Columbia Children's Hospital Allergy Clinic were enrolled from January 2014 to October 2015. Consenting children agreed to administer the EAI under supervision if anaphylaxis occurred during the oral food challenge. Anaphylaxis was defined by the World Allergy Organization criteria.⁷

A prechallenge questionnaire validated by pediatric allergists and a biostatistician examined demographic and clinical characteristics and baseline confidence in 4 domains: (1) confidence in ability to *recognize* a severe allergic reaction, (2) confidence in EAI *administration*, (3) perceived technical *knowledge* of EAI technique, and (4) perceived *skill* in EAI use. An identical postchallenge questionnaire was completed by the operator of the EAI (parent or patient). Confidence levels were evaluated on a 5-point scale (1 indicating not very confident and 5 indicating very confident). Parents and patients provided written feedback on their experience, and practitioners evaluated participant knowledge and technique on a similar 5-point scale (1 indicating very poor and 5 indicating excellent). Data were recorded in Microsoft Excel 2011 (Microsoft Corp, Redmond, Washington). Statistical analyses were performed using R version 3.2.2. The Mann-Whitney test, Spearman correlation, and Kruskal-Wallis 1-way analysis of variance were used to measure associations between demographic and clinical characteristics and confidence. The Wilcoxon signed-rank test compared confidence before and after the challenge.

The participation rate of this study was 94% ($n = 163/173$). The median age of children was 6 years (interquartile range [IQR] = 3, 10 years), and most (57%) were male. Peanut (34%) was the most common food challenged, followed by egg (32%) and tree nuts (12%). Most parents (85%) were university educated, and 27% were health care professionals. An EpiPen was carried by 62%, Allerject/Auvi-Q was carried by 31%, and 7% carried both.

Thirty-three percent of patients perceived their child's food allergy as severe, 25% as moderate, and 20% as mild, whereas 23% indicated they did not know. One-fifth of parents had used an EAI at least once on their child or others in the family at home or in the community. Among the 129 (80%) without previous EAI experience, 82 (64%) had experienced at least one severe allergic reaction within the family; 29 (22%) had experienced 3 or more severe reactions.

The ability to recognize anaphylaxis differed, depending on perceived severity of the child's food allergy ($P < .001$). The median baseline confidence scores were as follows: recognition = 4 (IQR = 3, 4 years), administration = 3 (IQR = 3, 4), knowledge = 4 (IQR = 3, 5), and skill = 3 (IQR = 2, 4). Health care professionals were more confident than non-health care professionals in all domains ($P < .02$). Any prior EAI training was positively correlated with increased confidence in administration ($\rho = 0.23$; $P = .003$). Forty-seven participants (29%) failed the food challenge, resulting in IgE-mediated symptoms, and 18 (38%) of those had anaphylaxis and the EAI administered by either a parent (15 cases) or the patient (3 cases). Epinephrine was not needed in 29 failed challenges (62%) because these had mild reactions and did not meet World Allergy Organization criteria for anaphylaxis. Postchallenge confidence increased in all confidence domains ($P < .04$) (Fig 1). Clinician evaluation of participant technique of administering the EAI had a median score of 4 (IQR = 2, 5).

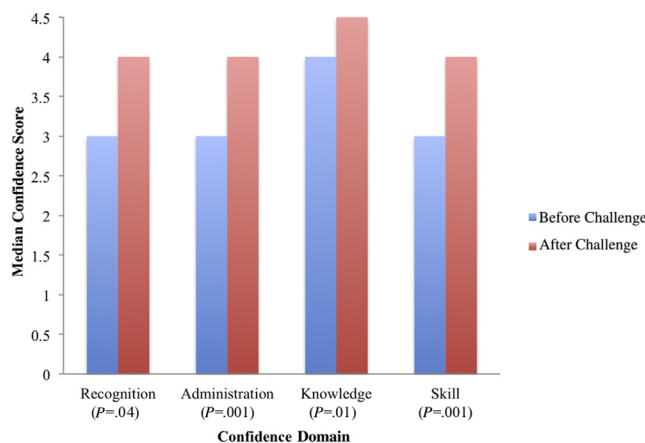


Figure 1. Prechallenge vs postchallenge mean confidence scores in various epinephrine autoinjector confidence domains ($n = 18$).

Most parents without previous EAI experience had witnessed at least 1 severe allergic reaction in their family, suggesting EAI underuse or unavailability. Although participants reported being fairly confident in recognizing anaphylaxis and had reasonable technical knowledge, confidence in EAI administration and perceived skill were suboptimal. The association between perceived severity and recognition allowed us to hypothesize that higher food allergy severity could predict greater ability to recognize a severe allergic reaction. Increased confidence in EAI administration was correlated with more training sessions. Likewise, parents who were health care professionals were more confident in all domains, suggesting that a combination of teaching and clinical experience may be important for confidence.

The rates of anaphylaxis requiring epinephrine seen in this study (11%) were consistent with those reported by other studies on the risks of oral food challenge.⁸ As predicted, using an actual life-threatening event as a learning opportunity was associated with significant increases in all confidence domains, including anaphylaxis recognition and EAI administration, knowledge, and skill. Clinicians adopted a teaching role, confirming the presence of anaphylaxis, and allowed parents to quickly appreciate symptoms evolving in real time. Specific instructions were provided to identify and correct common errors noted in previous studies, including holding the EAI backwards, placing the thumb over the needle, or forgetting to remove the safety cap.⁹ Clinicians observed that many parents were unable to recognize specific symptoms of an allergic reaction, suggesting that training sessions could be improved with incorporation of visual tools aiding identification of anaphylaxis. Several parents stated that EAI use was easier than anticipated, and many were surprised at the speed of symptom resolution. Experiencing anaphylaxis in this manner might address psychological barriers that otherwise could not be overcome by didactic teaching in the clinic. The study was limited by small numbers of failed challenges requiring epinephrine, necessitating further confirmation with a larger sample. In conclusion, supervised administration of EAI during food challenges increased confidence in recognition of anaphylaxis and knowledge of EAI use. Besides challenges, this could be applied in settings where anaphylaxis often presents (eg, emergency departments) to increase the likelihood of EAI use during subsequent episodes in the community.

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First case of type IV hypersensitivity to periocular topotecan



Topotecan is a topoisomerase 1 inhibitor derived from the *Camptotheca 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