

Ocular surface squamous neoplasia in an immunosuppressed patient with atopic keratoconjunctivitis

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Abstract We describe a patient with severe atopic dermatitis and keratoconjunctivitis, who was prescribed both systemic and topical ciclosporin and who developed ocular surface squamous neoplasia (OSSN). To provide additional information on the incidence of the association between topical ciclosporin use and OSSN, we counted the total prescriptions for topical ciclosporin issued in our hospital between 2003 and 2006 (804 patients) and, for the same period, we reviewed the records of patients with OSSN for a history of treatment with ciclosporin or a history of atopy. No other case of OSSN in a patient with a history of topical ciclosporin use was identified, which makes it difficult to implicate topical ciclosporin as the causative factor.

Keywords Ocular surface squamous neoplasia · Ciclosporin · Atopic keratoconjunctivitis

Introduction

There are a small number of reports of ocular surface squamous neoplasia (OSSN) in patients with atopic

keratoconjunctivitis (AKC) treated with topical ciclosporin [1, 2]. However, the magnitude of this risk has not been defined. We describe a patient with severe atopic dermatitis and AKC prescribed both systemic and topical ciclosporin who developed OSSN. To provide additional information on the incidence of this association we counted the total prescriptions for topical ciclosporin issued in our hospital between 2003 and 2006 and, for the same period, we reviewed the records of patients with OSSN for a history of treatment with ciclosporin or a history of atopy.

Case study

A 56-year-old female with AKC, who had used regular topical nedocromil and prednisolone 0.3 %, developed papillomatous lesions on the lower tarsal conjunctiva of the right eye. Two years previously she had been prescribed a 2-month course of topical ciclosporin 2 % drops twice daily, and she had been taking oral ciclosporin (4 mg/kg) for several years. The oral ciclosporin had been prescribed by her dermatologist to control her atopic dermatitis which was severe and generalised. An excisional biopsy confirmed that these conjunctival lesions were benign. Systemic ciclosporin has a number of potential side effects including nephrotoxicity, and toxicity screening was carried out by the patient's dermatologist. Due to concern about the link between systemic ciclosporin and epithelial tumours, her dermatologist changed her

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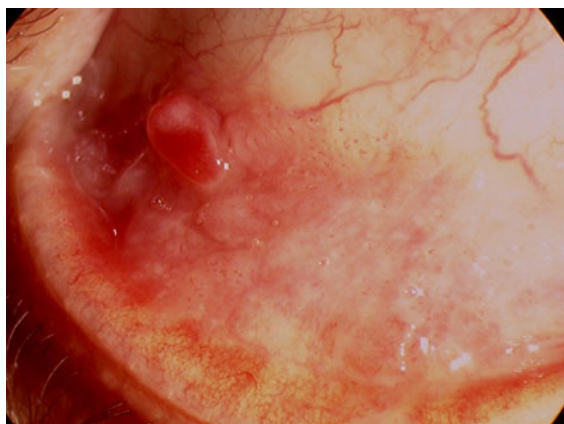


Fig. 1 Slit-lamp photographs of the bulbar conjunctiva of the right eye prior to the biopsy which first confirmed CIN3

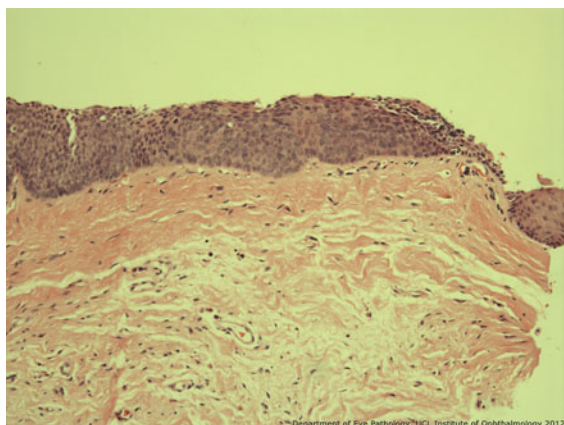


Fig. 2 Photomicrograph of a cross-section of the conjunctiva showing CIN3. The epithelium is thicker than normal (acanthosis) and the full thickness of the epithelium is replaced by atypical, pleomorphic epithelial cells. Image is courtesy of Dr. Caroline Thaug, UCL Institute of Ophthalmology, London

systemic immunosuppression treatment to azathioprine and continued to perform toxicity screening. She restarted topical ciclosporin 2 % BD in both eyes for another year, after which time there were again extensive papillomatous changes in the lower fornix and bulbar conjunctiva (Fig. 1). Topical and systemic immunosuppression was stopped, and a second biopsy showed CIN3 (Fig. 2). Topical mitomycin C 0.04 % QDS for two cycles gave a good initial response. Three years later a recurrence was treated with three more cycles of mitomycin C. Cryotherapy was used to treat three more recurrences over the next 2 years, and a

recent recurrence, 6 years from diagnosis, was treated with three cycles of mitomycin C.

Discussion

The major risk factors for development of OSSN are ultraviolet light, infection with human papilloma virus types 16 and 18 and immunodeficiency. Atopy has also been proposed as a risk factor, with one case series in which six of the ten patients with conjunctival intraepithelial neoplasia (CIN) had atopic dermatitis [1], a second case series of seven cases in seven patients with AKC in which the size of the sample population was not given [2] and a further case series of CIN in young patients with asthma [3].

There is an association between squamous cell carcinoma of the skin and the use of topical or systemic immunosuppression with calcineurin inhibitors such as ciclosporin and tacrolimus [4, 5]. However, we are aware of only four other cases of conjunctival squamous cell carcinoma reported in patients treated with systemic calcineurin inhibitors, all of whom were organ transplant recipients with no reported history of allergic eye disease [6–8].

Topical ciclosporin can be a useful steroid-sparing agent in AKC. There is concern based on animal models and case reports about a possible link between topical tacrolimus and the development of skin malignancy. However, the magnitude of this risk is debated and many dermatologists continue to prescribe it, preferring its “unknown risk” profile to the known risk profile of topical steroid use [9]. It is also not known if there is a risk solely associated with the use of topical ciclosporin. Bohringer et al. [10] used topical ciclosporin in 76 patients with ocular surface inflammation for a mean duration of 5.9 years and found no clinical or cytological evidence of malignant epithelial transformation in any patient. In the 4 years 2003–2006, topical ciclosporin was prescribed for 804 patients with ocular surface inflammatory conditions at our hospital (201 patients per annum), of whom 120 (15 %) received six or more prescriptions. We also identified 20 cases of CIN diagnosed between 2003 and 2006 (five cases per annum). Although none had been prescribed topical ciclosporin, several had a history of systemic immunosuppression, and one other patient had severe atopic dermatitis.

In conclusion, we report a case of OSSN that developed in an area of prior conjunctival papilloma. The patient was atopic and on systemic immunosuppression and had also used topical and systemic cyclosporin. The presence of multiple risk factors for the development of OSSN in this case makes it difficult to implicate topical cyclosporin as the causative factor. In the subsequent 4 years there were no other cases of OSSN in patients using topical cyclosporine who were seen at our institution despite a large number of prescriptions for topical cyclosporin.

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