

# Conjunctival intra-epithelial neoplasia occurring in young patients with asthma

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## Abstract

**Background** Conjunctival intra-epithelial neoplasia (CIN) typically occurs in elderly individuals. A number of aetiological factors are implicated in CIN, including life-long exposure to ultra-violet light and immunodeficiency states, particularly HIV infection. Asthma is a common condition affecting more than 3.5 million individuals in the UK, and is associated with atopy in approximately 70% of cases. In this paper we describe CIN occurring in young patients with asthma.

**Methods** Retrospective case series: A review of our ocular oncology database helped to identify 11 patients <55 years of age and presenting with CIN. Of these, seven (64%) were noted to have co-existent asthma.

**Results** Seven patients were included in the study (six male and one female). Mean age at presentation was 44 years (range 36–54 years). Five patients showed unilateral disease, whereas two showed bilateral. Five patients showed local recurrence; however, there were no cases of metastasis.

**Conclusion** The occurrence of CIN, particularly bilateral CIN, in younger immunocompetent individuals is very unusual, and the presence of asthma in 64% of our patient cohort suggests that atopic asthma may be a further aetiological factor involved in the development of this rare neoplasm.

*Eye* (2010) 24, 1182–1185; doi:10.1038/eye.2009.296; published online 4 December 2009

**Keywords:** conjunctiva; neoplasia; asthma

dysplasias of the conjunctival epithelium with no invasion of the basement membrane. It may be graded in severity from mild to severe or carcinoma *in situ*. The term ocular surface squamous neoplasia (OSSN) includes both pre-invasive disease (CIN) and invasive disease (squamous carcinoma). OSSN is rare in temperate climates,<sup>1</sup> but increases in frequency at places closer to the equator.<sup>2</sup> Lifelong exposure to ultraviolet light is therefore considered to be the major aetiological factor in the development of OSSN. However, a number of other factors have also been implicated, including immunodeficiency states such as HIV<sup>3</sup> and iatrogenic immunosuppression post-organ transplantation,<sup>4</sup> human papilloma virus (HPV) infection,<sup>5</sup> as well as atopic eczema.<sup>6</sup> OSSN typically affects elderly individuals with a mean age in excess of 60 years.<sup>7</sup> In this paper, we describe an apparent association between asthma and CIN occurring in young and middle-aged adults.

## Materials and methods

Between 1998 and 2008, 11 patients aged <55 years were seen at the ocular oncology clinic in Sheffield with a diagnosis of CIN. Of these, three were from sub-Saharan Africa, one was HIV positive and a further seven patients suffered from asthma. We retrospectively reviewed the records of this cohort of asthmatic patients, documenting their age, gender, laterality, treatments, and clinical outcomes.

## Results

Seven patients were included in the study, six male and one female. Mean age at presentation was 43 years (range 36–54 years). Mean follow-up was for 38 months (range 6–120 months).

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Received: 4 June 2009  
 Accepted in revised form: 27 October 2009  
 Published online: 4 December 2009

## Introduction

The term conjunctival intra-epithelial neoplasia (CIN) encompasses a range of squamous

**Table 1** Patient demographics and treatments performed

Patient	Age at presentation	Gender	Laterality	Treatment	Number of recurrences	Follow-up (months)	Human papilloma virus expression
1	36	Male	Left	Ex, cryo, MMC	3	120	Yes (types 16 and 18)
2	40	Male	Bilateral	Ex, cryo, MMC	2	72 (died of pulmonary complications)	Not tested as predeceased
3	45	Male	Right	Ex, MMC	0	10	No consent for testing
4	36	Female	Right	Ex, cryo, MMC, PDT	3	46	No
5	39	Male	Bilateral	Ex, cryo, MMC,	1	15	No
6	54	Male	Right	Ex, cryo, MMC	1	12	Yes (type 16)
7	49	Male	Right	In, MMC	0	6	Yes (type 16)

Abbreviations: cryo, cryotherapy; Ex, excision; In, incisional biopsy; MMC, mitomycin C 0.02%; PDT, photodynamic therapy.

Five patients exhibited unilateral disease, whereas two were bilateral cases. None of the patients gave a history of excessive UV exposure; however, two patients (patients 6 and 7) had co-existent eczema. Further clinical details are described in Table 1. The case of one patient (patient 5) is described in detail.

#### Patient 5

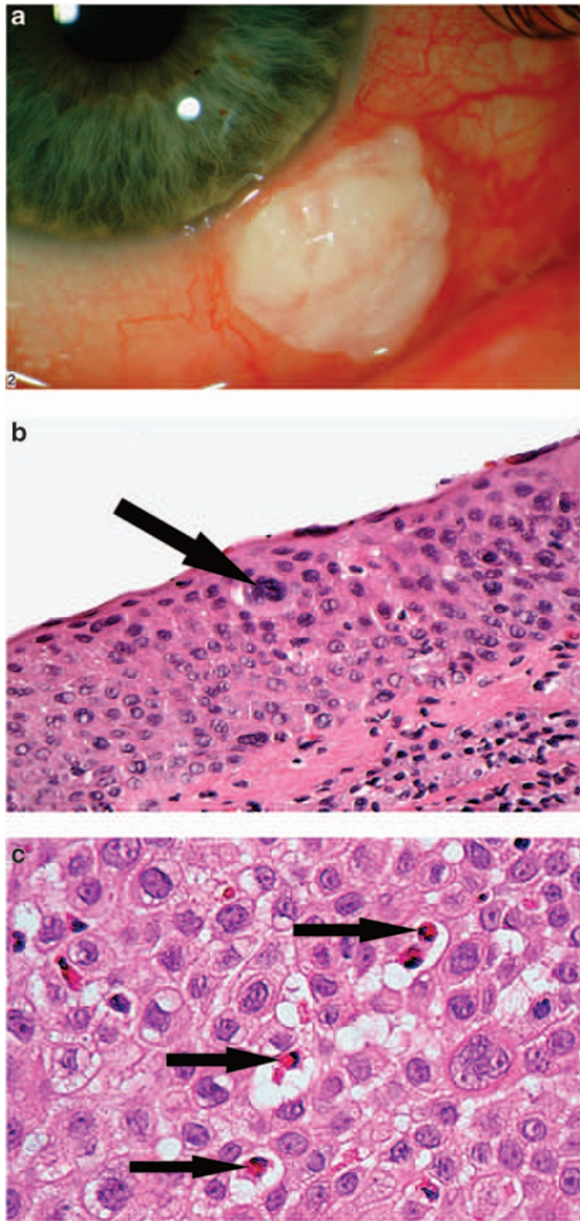
A 39-year-old man was referred in January 2008 with a leukoplakic lesion of the inferior bulbar conjunctiva of the right eye (Figure 1a). Excision biopsy with adjuvant cryotherapy revealed CIN amounting to *in-situ* squamous carcinoma (Figure 1b) with areas of conjunctival eosinophilia (Figure 1c). He was subsequently treated with four 1-week cycles of topical mitomycin C (MMC) 0.02% q.i.d. Further conjunctival map biopsies in September 2008 showed no residual disease in the right eye; however, a new lesion was noted in the left eye and excision biopsy (with adjuvant cryotherapy) confirmed CIN. He therefore received a further four cycles of MMC 0.02% in the left eye. Following this treatment, further conjunctival map biopsies demonstrated no residual disease; however, in March 2009 he developed a recurrence in the right eye, which was treated with topical interferon.

#### Conclusion

CIN is a rare condition, which in temperate climates shows an incidence of 0.03 per 100 000 population,<sup>1</sup> increasing towards the equator, such that the incidence in Australia has been reported at 19 per 100 000.<sup>2</sup> Life-long exposure to ultraviolet light therefore appears to be the major risk factor in the development of CIN. The disease typically affects elderly individuals (mean age of presentation > 60 years),<sup>7</sup> although the incidence in younger patients appears to be increasing in association with immunodeficiency states, particularly HIV

infection<sup>3</sup> and iatrogenic immunosuppression following solid organ transplantation.<sup>4</sup> The role of HPV in the development of CIN is debatable,<sup>5</sup> with some authors suggesting that HPV alone, in the absence of other aetiological factors, may be incapable of causing CIN. A single study has reported CIN in association with atopic eczema,<sup>6</sup> and two of our seven patients also suffered from eczema. CIN is generally a unilateral condition, although bilateral cases have rarely been described.<sup>8</sup> Various treatment options are available, including local excision with or without adjuvant cryotherapy, topical chemotherapy with a number of agents, mainly MMC, Interferon, or 5-fluorouracil, and radiotherapy techniques such as plaque brachytherapy.<sup>5</sup> Although local recurrence is relatively common, metastasis should not occur in the absence of invasive disease.<sup>9</sup> The patients described in this study are very unusual in that not only were they relatively young and immunocompetent, they also presented with aggressive disease that was bilateral in two cases and recurrent in five.

Asthma is a common condition affecting more than 3.5 million adults and children in the United Kingdom,<sup>10</sup> and is associated with atopy in approximately 70% of cases,<sup>11</sup> which is characterised by elevated IgE levels in response to allergen presentation. The production of IgE is partly mediated by type-2 helper T lymphocytes (Th2 cells), and asthmatics (and other atopes) tend to show an exaggerated type-2 response following antigen exposure. Whereas type-2 responses predominate in neonates, they tend to decline in normal adults in favour of type-1 responses, supporting cell-mediated immunity that is particularly active against virus-infected and neoplastic cells.<sup>12</sup> This immune switch does not occur in atopes. In this series, 60% (three out of five) of the patients tested for HPV infection were found to be positive. Two of the patients so tested were found not to express HPV; however, this does not exclude HPV infection, as it can be difficult to detect HPV following incorporation of the



**Figure 1** (a) Slit-lamp photograph of the right eye of patient 5 showing a leukoplakic lesion of the bulbar conjunctiva. (b) Haematoxylin and eosin-stained section of conjunctiva showing full-thickness squamous epithelial dysplasia, amounting to *in-situ* squamous carcinoma. The arrow points to a highly atypical squamous epithelial cell in the epithelium. (c) Haematoxylin and eosin-stained section of the dysplastic epithelium shown in (b), but at a higher power. The arrows indicate eosinophils within the dysplastic epithelium, which is indicative of atopic status.

viral DNA into the host genome. Could it be that the relative deficiency of type-1 responses in asthmatics allows conjunctival neoplasia to develop, possibly mediated through HPV expression (as detected in 60%

of our patients whom we were able to test for HPV infection)?

In conclusion, we report an apparent association between asthma and CIN arising in young and middle-aged adults. Of course it may be that with such a small cohort of patients this apparent association is merely coincidental; however, the severity of disease in our patients leads us to believe otherwise. We feel that this study supports the role of atopy in the development of CIN and that clinicians should be aware that CIN occurring in association with asthma may occur at a younger age than normally expected and be more aggressive in nature.

### Summary

#### What was known before

- CIN is a rare, usually unilateral condition affecting elderly patients.
- CIN may occur at a younger age in association with immunosuppression.
- Atopic eczema has been associated with CIN.

#### What this study adds

- CIN may occur in young/middle-aged asthmatics.
- CIN in conjunction with asthma may be bilateral and resistant to treatment.

### Conflict of interest

The authors declare no conflict of interest.

### Acknowledgements

We thank Mr Andrew Bailey at the Manchester Medical Microbiology Partnership for assessing HPV status in our patients.

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