Unilateral Conjunctival in situ Squamous Carcinoma with Bilateral Conjunctival Chlorpromazine-Induced Secondary Melanosis Masquerading as in situ and Invasive Melanoma

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Key Words
Conjunctival in situ squamous carcinoma · Bilateral melanosis · Chlorpromazine · Masquerade

Abstract
Purpose: To describe the clinical and histopathological features of a 61-year-old male with a history of eczema, asthma and schizophrenia on long-term chlorpromazine medication, who developed a unilateral limbal tumour in association with bilateral melanosis. Procedures: The patient was referred for a routine cataract assessment, and an incidental pink gelatinous limbal lesion was detected on the left side, associated with bilateral speckled brown conjunctival pigmentation. The limbal lesion and brown pigmentation were biopsied. The tissue was fixed in standard buffered formalin and processed to paraffin wax, and sections were stained with haematoxylin and eosin. Tissue from the pigmented area was also processed for transmission electron microscopy. Results: The biopsy from the limbal lesion showed an in situ squamous carcinoma associated with prominent numbers of intra-epithelial eosinophils. The biopsy of the pigmented area showed bilateral melanosis without atypia. The latter was attributable to an increase in melanin production rather than to melanocyte hyperplasia. Melanophages were also present in the adjacent substantia propria. These pigment changes were entirely compatible with chlorpromazine-induced secondary melanosis. The biopsy of the pigmented area showed bilateral melanosis without atypia. The latter was attributable to an increase in melanin production rather than to melanocyte hyperplasia. Melanophages were also present in the adjacent substantia propria. These pigment changes were entirely compatible with chlorpromazine-induced secondary melanosis. Conclusions: This paper highlights the first documented occurrence of in situ squamous carcinoma with bilateral chlorpromazine-induced conjunctival secondary melanosis. This clinically masqueraded as in situ melanoma/primary acquired melanosis and invasive melanoma. Bilateral melanosis is rare, has many causes and, in this case, was drug induced. This highlights the importance of
thorough history taking and illustrates that not all pigmented and amelanotic lesions are in situ melanomas, primary acquired melanosis or invasive melanomas. Lastly, atopy was a risk factor for the development of this in situ squamous carcinoma.

Introduction

Bilateral conjunctival melanosis or pigmentation due to excess melanin, caused by either increased melanogenesis or an increase in melanocytes (hyperplastic or neoplastic), is rare. The causes can be divided into local, systemic and drug-related. Local causes include racial pigmentation (the commonest cause) [1], ocular melanocytosis [2], Stevens-Johnson syndrome [3], vernal conjunctivitis [4] (both are post-inflammatory melanosis/melanin pigment incontinence-type situations) and rarely bilateral primary acquired melanosis (PAM) [5]. Systemic causes include Addison’s disease [1], Peutz-Jeghers syndrome [6, 7], Carney’s complex [8, 9], acanthosis nigricans [10, 11], xeroderma pigmentosa [12] and bilateral diffuse uveal melanocytic proliferation-associated conjunctival pigmentation [13]. Drug causes include the phenothiazine class of drugs (e.g. chlorpromazine) [14].

We describe a case of a male Caucasian with schizophrenia on long-term chlorpromazine medication, who developed a limbal lesion on the left side on a background of bilateral conjunctival melanosis. Our patient’s case was further complicated by a history of atopy, the potential role of which is also discussed.

Case Report

A 61-year-old man with a long history of eczema, asthma and schizophrenia presented with decreased vision due to cataracts. Examination confirmed the cataracts but also identified a pink gelatinous lesion at the medial left limbal and bulbar conjunctiva (fig. 1a, b), with extension onto the medial upper and lower tarsal conjunctiva (not shown). Brown speckled pigmentation was also identified over both bulbar conjunctivae (fig. 1c–e), in keeping with the initial clinical interpretation of PAM or in situ melanoma with a possible amelanotic invasive melanoma of the limbus. His facial skin was slate-grey in colour and lichenified (fig. 1a).

Further enquiry revealed that he had taken the anti-psychotic drug chlorpromazine for 27 years and had recently been commenced on procyclidine and Depixol. He was also on ranitidine and bronchodilator inhalers for his asthma.

Fig. 1. a Photograph of the left eye. Note the generalised, lichenified brown skin pigmentation in this Caucasian patient. b The abducted left eye showing the nasal gelatinous squamous carcinoma with extension onto the nasal conjunctiva. c The adducted left eye showing the patchy brown pigmentation over the temporal bulbar conjunctiva (arrows). d The adducted right eye showing the temporal bulbar conjunctival brown pigmentation (arrows). e The right eye showing brown plica pigmentations. f Haematoxylin and eosin (HE) staining of a biopsy from the left conjunctival lesion showing a thickened epithelium. g Higher-power HE of the image shown in f, confirming full-thickness squamous epithelial dysplasia indicative of in situ squamous carcinoma. h HE of the pigmented area shown in c. Note how the pigment is forming supra-nuclear caps (arrow). i HE of the stromal pigment in the same biopsy as shown in h (arrow). j HE of the same biopsy as in h, showing numerous stromal eosinophils indicative of the patient’s atopic state (eczema and asthma) (arrow). k Masson-Fontana stain confirming the presence of melanin (black signal) in mostly basal epithelial cells. l Transmission electron micrograph showing stage 4 melanosomes in a stromal macrophage lysosome (melanophage) corresponding to i. m Transmission electron micrograph; the cell on the left is a melanocyte in the epithelium, containing stage 2 and 3 melanosomes spread out in the cytoplasm (thin arrow) compared to the neighbouring epithelial cell containing stage 4 melanosomes in lysosomes (thick arrow).

(For figure see next pages.)
Biopsies from the left conjunctival mass unexpectedly showed an in situ squamous carcinoma (fig. 1f, g). In the same biopsy, there was increased melanin pigmentation of the non-dysplastic epithelium with eosinophils and melanophages in the substantia propria (fig. 1h–j). The pigment formed supra-nuclear caps and was positive for Masson-Fontana (fig. 1k); transmission electron microscopy confirmed normal melanosomes. These were present in squamous epithelial cells, intra-epithelial melanocytes and stromal macrophages (fig. 1l, m). Immunohistochemistry with Melan A showed no increase in intra-epithelial melanocyte numbers. It was concluded that the pigment was secondary to the long-term use of chlorpromazine, a drug well recognized to cause conjunctival and skin pigmentation [14]. This refuted the initial clinical interpretation of PAM of neoplastic type.
The in situ squamous carcinoma was treated with a combination of cryotherapy as well as intra-lesional and topical interferon. Unfortunately, the disease did not respond and progressed to cover most of the left bulbar conjunctiva. The patient has now been started on topical 5FU, with early promising results.

Discussion

This case report has covered the following three important points: (1) squamous carcinoma masquerading clinically as melanoma; (2) the differential diagnosis of bilateral conjunctival melanosis, and (3) the role of atopy in conjunctival squamous cell carcinoma.

The bilateral melanosis was clinically thought to be PAM (implying a neoplastic proliferation of melanocytes), and, by inference, the amelanotic pink limbal lesion was thought to be an invasive melanoma. PAM is usually a unilateral condition but can be bilateral in 13% of cases [5]. In this case, the conjunctival pigmentation was secondary to chlorpromazine medication, and the limbal lesion was an in situ squamous carcinoma. Cameron [14] described the largest series of ocular melanosis secondary to chlorpromazine use in 1967 and noted that those patients with conjunctival pigmentation usually had the heaviest skin pigmentation induced by the drug. The conjunctival pigmentation comprised limbal inter-palpebral brown triangular areas of even distribution, resembling the brown pigmentation of conjunctival naevi. Other findings included corneal and lens pigmentation. The mechanism of the hyperpigmentation is thought to be secondary to stimulating melanogenesis with or without drug complexes binding to the melanosomes and is dose dependent. Another commonly used drug known to cause conjunctival pigmentation is minocycline [15], a tetracycline derivative. Minocycline, when used as a long-term therapy in doses of >100 mg/day, has been shown to cause discolouration of the skin, nails, bulbar conjunctiva, oral mucosa, teeth, bones and thyroid gland. It is thought that the pigment is either a drug metabolite-protein complex chelated with calcium or insoluble minocycline-melanin complexes within macrophages of the epidermis. Epinephrine-containing eye drops blacken the conjunctiva, eyelid margins and caruncle but are not commonly used in today’s practise. A detailed history and examination of a patient may also reveal a rare diagnosis of alkaptonuria, which is a disorder of the phenylalanine/tyrosine metabolism of homogentisic acid oxidase, resulting in an accumulation of homogentisic acid in connective tissues, where it is oxidised into a darkly pigmented melanin-like product [16]. The pigment usually develops by the fourth decade of life, and 70% of cases develop ocular changes. These consist of blue-black discolouration of the inter-palpebral sclera just anterior to the insertions of the horizontal rectus muscles. The peripheral cornea may also develop fine brown deposits in the Bowman’s layer and the anterior stroma in the inter-palpebral region. Alkaptonuria is a multi-system disease, and a detailed history may reveal associated systemic problems [16].

In our case, the patient also had an in situ squamous carcinoma and a history of atopy. Atopy is thought to be a risk factor for squamous carcinoma development. Heinz et al. [17] reported patients with conjunctival squamous cell carcinoma who had atopic eczema and postulated that aberrant T-cell function found in atopic conditions might be a factor in causing malignant transformation of the ocular surface. Rundle et al. [18] reported 7 cases of in situ squamous carcinoma with asthma. In 5 cases, the disease recurred and in 2 cases, the in situ squamous carcinoma was bilateral. Most of these cases contained high-risk HPV DNA and occurred on unexposed conjunctiva (medial inferior bulbar, covered by the lower lid), which raised the possibility of chronic irritation (rubbing?) being a possible factor in neoplastic transformation of the conjunctival squamous epithelium [18]. The presence of eosinophils in the cases published by Rundle et al. [18] and in the biopsies from our case is salient, as they are involved in the ‘itch’ cycle, leading to eye rubbing with possible neoplastic transformation
of the squamous epithelium as alluded to. Allergic eye rubbing can also cause pigmentary changes (e.g. vernal conjunctivitis [4]), accentuating the pigment-inducing effects of chlorpromazine as already discussed.

This patient’s course was characterised by a progression of the neoplasia despite standard treatment. We have observed that other patients with atopy have an identical clinical course. This may be related to atopy-induced dysfunctional immune system. Recently, it has been shown that a drop in mucosal immunity is associated with reactivation of latent HPV infection [19].

In conclusion, this case has a clinically documented in situ squamous carcinoma masquerading as melanoma. Secondly, not all inter-palpebral conjunctival pigmentations in Caucasians are neoplastic PAM, and a careful history may reveal a rare iatrogenic cause, as in this case. Thirdly, this case has documented in situ squamous carcinoma on a backdrop of atopy and discussed the role of atopy in its pathogenesis.

Disclosure Statement
The authors declare that there are no conflicts of interest.

References