CONJUNCTIVAL INVOLVEMENT IN MALIGNANCY-ASSOCIATED ACANTHOSIS NIGRICANS

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SUMMARY

Acanthosis nigricans classically presents with pigmented skin lesions over the neck, groin and axillae. It may involve the mucosal surfaces, particularly the oral mucosa. Conjunctival involvement is very rare, especially in the variety associated with malignancy. We report a case of acanthosis nigricans associated with squamous cell carcinoma of the bronchus where bilateral papillary conjunctivitis, progressing to hypertrophic papillary conjunctival and lid margin lesions, was the presenting feature. Topical treatment with corticosteroid and artificial tear drops resulted in the partial improvement of the ocular symptoms.

Acanthosis nigricans is a rare skin disorder of unknown aetiology which was independently described by Pollitzer[1] and Janovsky.[2] It is characterised by the development of localised, pigmented, hyperkeratotic lesions on the neck, face, groin, antecubital and popliteal fossae, umbilicus and axillae. The lesions may be generalised and profound.[3] Velvety overgrowth of the skin at the flexures may be accompanied by filiform growths around the face, mouth and the tongue. Roughness of the palmar and plantar skin can occur (tripe palms) and strongly suggests the presence of an underlying malignancy.[4] The main histological features of acanthosis nigricans are hyperkeratosis, papillomatosis, acanthosis and areas of apparent epidermal atrophy. Mucosal lesions tend to involve the mouth and usually occur in the malignant variety of the disease. Conjunctival involvement is very rare.[5] It may take the form of marked conjunctivitis with diffuse papillary hypertrophy. The palpebral conjunctiva may or may not be pigmented.[6,7] We report a case of malignant acanthosis nigricans presenting with bilateral papillary conjunctivitis as the first feature.

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Eye (1993) 7, 648–651

CASE REPORT

A 74-year-old man, a retired scrap metal worker, was referred by his general practitioner. He had a 3 month history of red and gritty eyes. He smoked 15 cigarettes a day and had not suffered from any eye, skin or allergic problems in the past. On examination, he was found to have diffuse conjunctival hyperaemia with fine papillary changes in both lid margins and conjunctiva. There was early lower lid medial ectropion in both eyes. The visual acuity was 6/6 in each eye. The cornea, anterior chamber and intraocular pressures were normal. A diagnosis of chronic blepharoconjunctivitis was made and the patient was treated with lid hygiene and chloramphenicol ointment.

Four months later, he presented with an exacerbation of his symptoms. On examination, marked conjunctival papillary hypertrophy was noted nasally on the bulbar conjunctiva and lid margins. There was also partial loss of eyebrows (Figs. 1, 2 and 3). The lower lid medial ectropion had progressed and was causing epiphora in the right eye. He was treated with prednisolone 0.5% eye drops, hydrocortisone 1% eye ointment and artificial tear drops. In the meantime, the patient presented to the general phys-

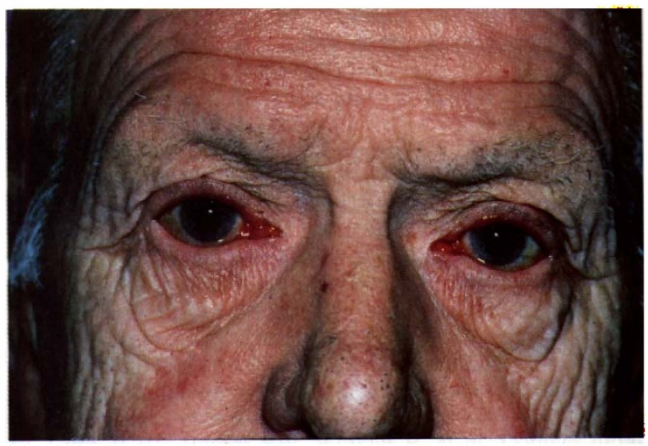

Fig. 1. *Acanthosis nigricans involving the lid margins causing mild ectropion and tearing. There is no loss of eyebrows.*

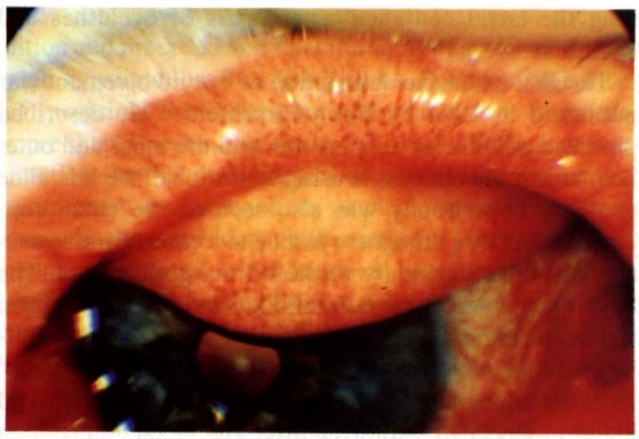

Fig. 2. *Papillae in the upper tarsal conjunctiva.*

ician with unexplained weight loss, change of bowel habit, and loss of axillary and pubic hair. He had a pigmented, hyperkeratotic rash affecting his axillae, abdomen, groin and thighs (Fig. 4) associated with dystrophic nail changes (Fig. 5). A provisional diagnosis of acanthosis nigricans was made.

A diamond-shaped medial conjunctivoplasty was performed in order to correct the ectropion. The excised conjunctiva was examined microscopically. Histological examination showed marked acanthosis and papillomatosis characteristic of acanthosis nigricans (Fig. 6). Biopsy of the skin lesions also confirmed the diagnosis of skin acanthosis nigricans. Investigation for a possible underlying malignancy followed. Results of routine haematological tests, blood glucose measurement, thyroid function test, chest radiograph, abdominal ultrasound, upper and lower gastrointestinal endoscopy, and barium studies were normal. The biochemical profile revealed evidence of mild hyperparathyroidism with raised calcium and lowered phosphate levels. Ectopic parathyroid hormone secretion secondary to bronchial carcinoma was suspected. A CT scan of the thorax showed the possible presence of a small opacity in the anterior segment of the right upper lobe. However, bronchoscopic examination did not confirm the CT findings.

Two months later, the patient presented with increased soreness of the eyes. He was treated with topical corticosteroid and artificial tear drops. The ocular symptoms improved over the ensuing 4 months with partial resolution of conjunctival hypertrophy. The predominant feature at this time was now chronic arthralgia. The patient's general condition remained stable for a further 2 years until he presented to the general practitioner with an episode of haemoptysis. Bronchoscopy showed a tumour situated between the left upper and lower lobe bronchi. Histological examination confirmed a squamous cell carcinoma of the bronchus.

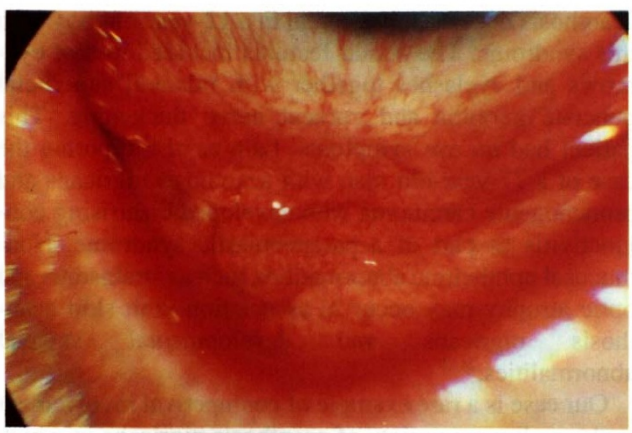

Fig. 3. *Gross conjunctival hypertrophy in the lower fornix.*

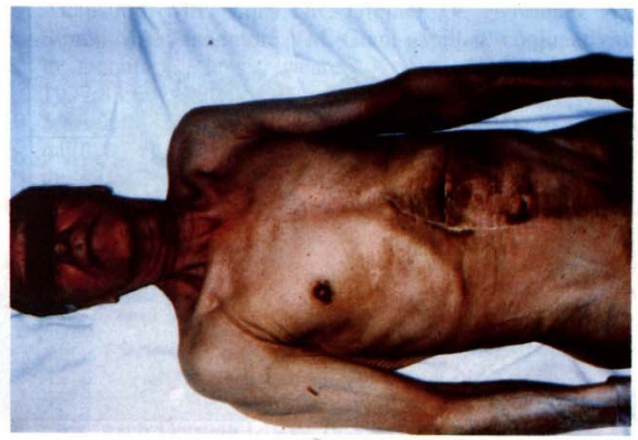

Fig. 4. *Acanthosis nigricans of the skin, particularly affecting the neck, nipples and the abdominal wall.*

In summary, a 74-year-old male smoker presented to the eye department with papillary conjunctivitis as the first manifestation of acanthosis nigricans. An underlying squamous cell carcinoma of the bronchus was discovered 3 years after the initial presentation.

DISCUSSION

Papillary conjunctivitis classically occurs in conditions with an underlying hypersensitivity mechanism. It is often associated with hay fever, perennial allergic conjunctivitis, vernal disease, chronic irritation (as seen in keratoconjunctivitis sicca), contact lens wear, ocular prosthesis, corneal and conjunctival sutures, topical medications, and infections such as molluscum contagiosum and chlamydial eye disease. Systemic diseases such as

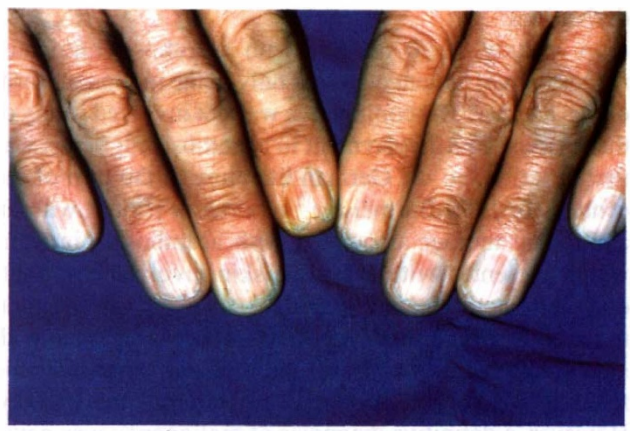

Fig. 5. *Dystrophic nail changes associated with acanthosis nigricans.*

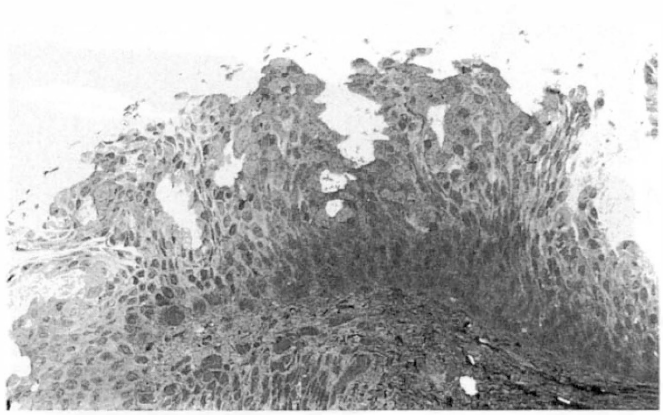

Fig. 6. *Histology of conjunctiva showing acanthosis and papillomatosis.*

amyloidosis or sarcoidosis can cause a similar clinical picture.[8] In some of these cases the condition may take the form of conjunctivitis with giant papillae.[9,10] Papillary conjunctivitis may also be associated with acanthosis nigricans.[11–13]

Various forms of acanthosis nigricans have been described.[14] A hereditary type, which is transmitted as an autosomal dominant trait, presents during childhood and is usually benign and not associated with systemic disease. In another variety, also known as pseudoacanthosis nigricans, the condition occurs in adults and is associated with endocrine disease, particularly hyperinsulinaemia, diabetes mellitus, thyroid disease, obesity and rarely pituitary tumours.[15,16] The type of acanthosis nigricans which affects older patients is strongly associated with malignancy of internal organs, in particular adenocarcinoma of the gastrointestinal tract. Approximately 85% of adult patients with non-hormone-related acanthosis nigricans have an abdominal tumour; gastric carcinoma accounts for 60% of these malignancies. Hepatic, oesophageal, bronchial and breast tumours are the next most common association. Non-epithelial tumours such as sarcomas, Hodgkin's disease and other lymphomas are rarely associated with acanthosis nigricans. Drug-induced acanthosis nigricans can be caused by corticosteroids, oestrogens, nicotinic acid and hydantoin derivatives.[3]

In a study of 90 patients with acanthosis nigricans, mucosal involvement occurred only in the malignant form of the disease.[5] The conjunctiva was not involved in any of these cases. Eye involvement in acanthosis nigricans was first described in the German literature at the turn of the century. In 1899 Burmeister[13] reported a patient with an abdominal tumour associated with acanthosis nigricans which presented with extensive skin involvement, bilateral conjunctivitis and papillary changes in the oral mucosa. In 1901 Little[17] reported a 60-year-old man with skin acanthosis nigricans, weight loss, and other systemic features possibly indicative of an internal malignancy. However, a definitive diagnosis of malignancy was never confirmed. The ocular features included foreign body sensation, semi-purulent discharge, papillary lesions involving the tarsal conjunctiva, and loss of eyelashes and eyebrows.

The first extensive description of eye involvement was published in 1904 by Birch-Hirschfeld.[12] He described pin-head papillae at the punctum and the inner and outer lid margins of both eyes causing distortion of the lids. Fine papillary hypertrophy was also seen on the tarsal conjunctiva and was thought to be due to a chronic inflammatory response secondary to the lid margin changes. The bulbar conjunctiva was normal. Excision of the lid margin lesions resulted in an initial reduction of the tarsal papillary reaction which recurred after a few months. Toyama[11] reported another case with papillary changes at the lid margin associated with trichiasis. The tarsal conjunctiva showed fine papillary hypertrophy just behind the posterior lid margin. The bulbar conjunctiva was slightly hyperaemic and showed a band-like pigmentation at the area of lid–globe contact. Weiss,[7] in a review of ocular involvement in acanthosis nigricans, described the lesions as trachoma-like flat papillae which arose independently within the tarsal conjunctiva and the lid margin. In a case report, Corrado[18] described hyperkeratotic papillae in the tarsal conjunctiva and the lid margins. The bulbar conjunctiva remained unaffected.

Lamba and Lal[19] have reported ocular changes, particularly in the skin of the eyelids, in a 6-year-old boy with the benign form of acanthosis nigricans. In their case, eyelid skin of both eyes was involved and in one eye non-pigmented hypertrophic changes were present in the bulbar conjunctiva. The cornea showed infiltration, vascularisation and central perforation, possibly secondary to the eyelid changes. Histological examination of the conjunctiva demonstrated marked epithelial hypertrophy with hyperkeratosis and melanin-containing cells in the basal layer.

Newman and Carsten[20] briefly reported the case of a 61-year-old man with a 16 year history of dermal acanthosis nigricans. In this case there was involvement of the periorbital area and palpebral and bulbar conjunctiva. The type of acanthosis nigricans was not specified. The association of ichthyosiform erythroderma, sensorineural deafness and keratitis has been recognised as a distinct syndrome (KID syndrome).[21] Singh[22] described a case of acanthosis nigricans of the skin in a 12-year-old boy with this syndrome. The ocular features included loss of eyebrows and eyelashes together with bilateral superficial punctate keratitis and corneal nerve thickening. This patient had no eye symptoms. Lam *et al.*[23] reported the case of a 77-year-old man with acanthosis nigricans and bronchogenic carcinoma who developed cicatrising conjunctivitis as part of a paraneoplastic syndrome. Non-mucosal ophthalmic abnormalities such as strabismus and optic atrophy may occur in association with skin acanthosis nigricans and developmental skeletal abnormalities.[24,25]

Our case is a rare example of conjunctival involvement in the malignant variety of acanthosis nigricans in which the conjunctival histological changes are documented.

The ocular involvement was the first feature of the condition and preceded non-specific signs of systemic disease such as weight loss by a few months. Despite a high index of suspicion, the underlying malignancy was diagnosed more than 3 years after the initial ophthalmological presentation. In this case, there was partial improvement of symptoms in response to topical steroids. Steroids dampen the secondary inflammatory processes which occur as a result of mechanical irritation due to the abnormality of conjunctival and lid surfaces. Lubricant tear drops were also helpful in the management of the ocular symptoms.

Acanthosis nigricans may present to the ophthalmologist with obvious lid involvement or more subtle conjunctival abnormalities. In the elderly patient it is usually part of a paraneoplastic syndrome and its occurrence signals the presence of an underlying malignancy. In these cases full systemic investigation is warranted.

The authors are grateful to Miss A. Alavi and Mr. C. K. Rostron for their comments on this paper.

Key words: Acanthosis nigricans, Conjunctiva, Eye lids, Malignancy, Paraneoplastic syndromes, Topical steroids.

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