Solar keratosis, pterygium, and squamous cell carcinoma of the conjunctiva in Malawi

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SUMMARY The histological features of 234 conjunctival biopsies from Africans in Malawi have been re-examined. The appearances of solar keratosis, pinguecula, and pterygium are presented as part of a continuous spectrum of the same pathological process and aetiology, which may lead to carcinomatous change. The results are discussed with regard to the specific geographical distribution of such lesions found by other workers, with particular emphasis on ultraviolet radiation as the main aetiological factor.

Squamous cell carcinoma of the conjunctiva is more common in Africa than in temperate climates (Templeton, 1967; Ticho and Ben-Sira, 1970; Daoud and Osman, 1970; Maertens and Blodi, 1972). It has been suggested that these tumours arise from pre-existing lesions which are the result of prolonged exposure to ultraviolet light. These lesions are usually classified as a pinguecula or pterygium by ophthalmologists and are characterised by a wedge-shaped opaque thickening near the limbus which may extend on to the cornea from the scleral conjunctiva. Histopathologists usually describe such lesions as solar keratosis and often comment on the degree of epithelial atypicality or dysplasia. However, Cameron (1965) does not emphasise epithelial changes or a liability to carcinomatous change. With these problems in mind we have re-examined the histological features of 224 conjunctival biopsies from Africans in Malawi. The results are discussed in the light of observations from several geographical locations.

Materials and methods

Since 1968 diagnostic histopathology for all hospitals in Malawi has been undertaken by the Department of Morbid Anatomy, St. Thomas's Hospital Medical School, London. All biopsies and removed surgical specimens are fixed in 10% formalin and are then forwarded to the Central Laboratories in Blantyre. They are then dispatched in weekly batches by air to London, where they are processed and sectioned.

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During this period the number of ophthalmologists in Malawi has varied, and specialist attention is not available throughout the country. The proportion of conjunctival lesions from which biopsy specimens have been taken and sent for histological examination has also varied. The numbers of cases reported here do not therefore give any idea of the true incidence or prevalence of these conditions. They are, however, recognised as a common problem in ophthalmic practice.

All biopsy and surgical material from Malawi is coded according to the Standardised Nomenclature of Pathology. Reports coded for eye or orbit were extracted and the slides from all lesions involving the conjunctiva were reviewed. In some cases extra sections were cut and stained with elastin-Van Gieson's stain. Each biopsy was assessed for degenerative and inflammatory changes in the sub-epithelial connective tissues and for abnormalities of the squamous epithelium and melanocytes.

Results

The clinical information was limited in many of these cases, but the great majority of conjunctival biopsies had been diagnosed either as pterygium or pinguecula (Fig. 1), though the criteria for this differentiation were not constant. There were also some patients with a clinically invasive carcinoma (Fig. 2) and a few with other lesions such as papilloma.

HISTOPATHOLOGY

The main histological features and the diagnosis are shown in Tables 1 and 2; 167 lesions were reclassified as 'solar keratosis' with varying degrees of

Fig. 1 A typical precancerous lesion (pterygium) extending on to the cornea

Fig. 2 Squamous cell carcinoma with invasion of corneal tissues

epithelial abnormality, 54 as invasive carcinomas, and in 13 there was difficulty in assessing the nature of the lesion; several of these were considered to be 'microinvasive' carcinomas.

SUBEPIDERMAL CONNECTIVE TISSUES

Changes similar to those seen in the skin in senile or solar keratosis were present in 163 out of the 167 lesions which were finally classified as solar keratosis. They are characterised by fragmentation and elastotic degeneration of collagen fibres, often with accentuation of their eosinophilia and, sometimes, with foci of collagen necrosis (Fig. 3). In microinvasive carcinomas these connective tissue changes were evident in the same section in only 8 out of 13 cases and in those with frankly invasive carcinomas in 17 out of 37 cases. In the latter it was evident that there was a desmoplastic reaction to the infiltrating tumour, and this may have obscured the degenerative changes.

CHANGES IN THE SQUAMOUS EPITHELIUM

Some abnormality of the epithelium was present in all but one of the 167 lesions. These were graded according to the degree of abnormality (Table 1).

HYPERPLASIA AND MILD DYSPLASIA

In this group of 126 cases the squamous epithelium was of normal thickness or only slightly hyperplastic

Table 1 Histological findings in non-invasive lesions (solar keratosis)

Epithelium	Connective tissue	
	Normal	Degeneration
Normal	0	1
Hyperplasia or mild dysplasia	0	126
Moderate dysplasia	3	16
Marked dysplasia or carcinoma <i>in situ</i>	1	20
Total	167	

Table 2 Histological findings in doubtful or microinvasive and infiltrating carcinomas

	Connective tissue	
	Reactive	Degenerative
Doubtful or microinvasive	5	8
Infiltrating	37	17
Total	67

Fig. 3 Solar keratosis with minimal epithelial abnormality and marked solar degeneration of subepithelial connective tissues. Haematoxylin and Van Gieson ($\times 77$)

Fig. 4 Solar keratosis with connective tissue degeneration and mild epithelial dysplasia. Haematoxylin and eosin ($\times 240$)

due to acanthosis. There was a variable keratinisation of the superficial cells, often associated with some abnormality of cell maturation and minor degrees of cell atypia or loss of polarity, which did not exceed a quarter of the total epithelial thickness (Fig. 4). In some biopsies there was spongiosis of the epithelium associated with subepithelial oedema or chronic inflammatory cell infiltration. The clinical and pathological features of this group correspond closely to the definition of pterygia (Cameron, 1965), though some ophthalmologists would refer to a number of the lesions as pingueculae (Ticho and Ben-Sira, 1970).

MODERATE DYSPLASIA

This group of 19 cases was characterised by distinct abnormalities of epithelial maturation, with loss of cellular polarity, the presence of abnormal cells with an increased nuclear-cytoplasmic ratio, dyskeratosis of focal cells, and a variable keratinisation (Fig. 5). The abnormal cells did not, however, extend to the surface and usually occupied less than three-quarters

of the total thickness of the epithelium. Rete ridges were not a feature and the basal layer was unbreached. The features in some biopsies were leucoplakic in pattern.

MARKED DYSPLASIA AND CARCINOMA IN SITU

All the lesions in this group of 21 cases showed marked disturbances of cell maturation, polarity, and nuclear size; and mitoses, often abnormal, were seen (Fig. 6). In some specimens large and atypical nuclei as found in Bowen's disease of the skin were seen, and all showed whole-thickness abnormality, though keratinisation was a variable feature. Occasionally cells were arranged in whorls, giving the appearance of a cell nest. The basal layer of cells, though abnormal, was intact and sometimes showed ridging.

MICROINVASIVE CARCINOMA

In 13 biopsies the possibility of early carcinomatous change was considered. In some there were clear-cut small foci of invasion (Fig. 7). In others the basal layer was irregular, and assessment of early infiltration was obscured by oedema and inflammation.

Fig. 5 Solar keratosis with moderate epithelial dysplasia more evident on the right of the picture. Haematoxylin and eosin ($\times 250$)

INFILTRATING SQUAMOUS CELL CARCINOMA

All cases in this group of 37 cases showed frank invasion (Fig. 8), and in many there was extensive destruction of the eye, with a fungating and ulcerated lesion. Some tumours were very well differentiated,

Fig. 6 Carcinoma in situ of conjunctiva. Haematoxylin and eosin ($\times 200$)

with much keratinisation, but a few were poorly differentiated.

CHANGES IN PIGMENT CELLS

A feature of many of these lesions was an abnormal proliferation of melanocytes. These cells contain pigment arranged in long dendritic processes extending between the squamous epithelial cells (Fig. 9) and were often seen throughout the lesion. Pigment was also often present in the squamous cells. The proportion of melanocytes to squamous epithelial cells was estimated in each biopsy and given an arbitrary score. The scores were averaged for each group as shown in Table 3. Melanocytic hyperplasia was maximum in lesions with severe dysplasia and was also often present in infiltrating carcinomas.

Ten cases of conjunctival papilloma were seen during the period of investigation and none showed precancerous changes. There was no evidence to support the idea that carcinoma of the conjunctiva arises in pre-existing benign lesions of the papillomatous type (Goldberg *et al.*, 1963).

Discussion**NOMENCLATURE AND PATHOLOGY**

In an earlier paper from Malawi, Ticho and Ben-Sira (1970) described the clinical and pathological features of lesions in the bulbar conjunctiva close to the limbus occurring in the African population. They described 3 clinical groups:

(1) Pinguecula (25 cases). These are localised yellowish-white swellings without keratinisation. On histological examination, there is subepithelial

Fig. 7 Microinvasive carcinoma. The arrow indicates an area where the epithelium is invading connective tissues. Haematoxylin and eosin ($\times 210$)

Fig. 8 Invasive squamous cell carcinoma. Haematoxylin and eosin ($\times 190$)

Fig. 9 Melanocytic hyperplasia with dendritic processes extending between squamous cells in a patient with carcinoma *in situ*. Fontana's silver technique ($\times 180$)

stromal degeneration, with minimal epithelial change apart from acanthosis.

(2) Elevated white glistening lesions surrounded by pigment. These showed 3 histological subgroups: simple epidermalisation with hyperkeratosis and rete peg formation (22 cases); leucoplakia with more advanced dyskeratosis (36 cases); and Bowen's type of precancerous change (12 cases).

Table 3 Melanocytic hyperplasia in solar keratosis and in carcinoma of the conjunctiva

Epithelium	Melanocytes
Normal	2.0
Mild dysplasia	4.1
Moderate dysplasia	4.4
Severe dysplasia	5.4
Carcinoma <i>in situ</i>	2.5
Well differentiated carcinoma	3.1
Moderately differentiated carcinoma	2.2
Poorly differentiated carcinoma	—

(3) Fleishy protruding lesions of an invasive nature, often pink or red and papillomatous or cauliflower in shape (8 cases), which were all invasive squamous cell carcinomas.

Martens and Blodi (1972) described epibulbar lesions in Africans from Zaire. They differentiated pingueculae which are elevated, whitish lesions at or near the limbus from pterygia, which they describe as soft elevations with a smooth surface surrounded by blood vessels and fixed to the limbus. Hogan and Zimmerman (1966) suggest that when there is nuclear atypicity and dyskeratosis in either a pterygium or a pinguecula the additional term 'active keratosis' may be used. Sevel and Sealy (1969) identified 3 major groups: pterygia, defined as 'a degenerative and hyperplastic process in which there is encroachment of the bulbar conjunctiva onto the cornea' (this category loosely included pingueculae); carcinoma *in situ* (which is equated with Bowen's disease); and invasive carcinoma. The criteria were based solely on the histopathological appearance, and they found no absolute correlation with the clinical features.

All these lesions have features which are seen in damage by solar irradiation, and the covering of the eye is 1 site in an African which is not protected from this effect by pigmentation. It has been observed that carcinomas of the conjunctiva arise more frequently on the medial aspect of the conjunctiva in the interpalpebral fissure. This localisation may be related to the mechanism of sunlight-induced blepharospasm (Sevel and Sealy, 1969).

Our findings suggest that the lesions, which are nearly all associated with solar damage to sub-epithelial connective tissues, represent a continuous spectrum of epithelial abnormality from slight acanthosis and hyperkeratosis through mild and moderate dysplasia to severe dysplasia and carcinoma *in situ*. Inevitably in a biological phenomenon there is some variation in the type and degree of

response, and this can account for patterns labelled as epidermalisation, leucoplakia, or Bowen's disease. Similar histological variations occur in precancerous lesions of the skin and cervix, and it is not possible to demonstrate an absolute correlation between the histopathological abnormality and the biological potential of the lesion. In reporting the histology of these lesions we suggest that the term 'solar keratosis' be used and qualified by the degree of epithelial abnormality as mild, moderate, or severe dysplasia, or carcinoma *in situ*.

The microinvasive and infiltrating carcinomas showed a variable degree of squamous differentiation. However, whereas the classical type of carcinoma *in situ* could be envisaged as the predecessor of a poorly differentiated tumour, the preinvasive histology of a well differentiated tumour remains uncertain.

Proliferation of dendritic melanocytes among the atypical squamous epithelial cells was a common finding, particularly in moderate and severe dysplasias, and sometimes this feature had led to a clinical diagnosis of cellular naevus or malignant melanoma. No cases of malignant melanoma of the conjunctiva were seen during the period under review. Some focal pigmentation may be seen in normal African conjunctivae, and it seems possible that the melanocytic hyperplasia represents a protective response.

Most authors suggest that these various lesions, whatever terminology is used, represent different stages of a process resulting in some patients in the development of an invasive carcinoma. The high frequency of solar keratosis (pterygia) of the conjunctiva in Africans is associated with a high incidence of squamous cell carcinoma, which suggests that they are precancerous. Zimmerman (1964) emphasised that carcinoma rarely arose in the epithelium overlying pterygia or pingueculae. However, solar keratosis of the skin does not invariably lead to invasive carcinoma, nor are dysplastic lesions in other sites, such as the cervix, always progressive.

EPIDEMIOLOGY AND AETIOLOGICAL FACTORS

The higher frequency of these lesions in Africans living in the tropics may be accounted for by increased exposure to ultraviolet light, though, as Maertens and Blodi (1972) point out, the humidity is often high and ultraviolet rays are readily absorbed in a humid atmosphere. Cameron (1965) found a good correlation between latitude and pterygium rates:

Pterygium rate	Latitude
Low (0-1.9%)	40°
Moderate (2-4.9%)	35°-40°
High (5-10%)	30°-35°
Very high (10% or more)	30°-equator

He held the view that the incidence of pterygium is highest in areas where the sun is at an angle of 80° or more for the larger part of the year. Thus, in such areas, the populations are exposed to ultraviolet rays of wavelength from 3200 Å to 2900 Å (320 to 290 nm). In areas where the wavelengths are in the band below 2900 Å the prevalence of pterygium is relatively low, and this is correlated with the oblique angle at which the rays fall.

The prevalence of pterygia in countries between the Equator and the 30th parallel such as North India and Pakistan, Mexico, the Central American States, and the West Indies agrees well with the expected rates. Similarly, most of Europe, Asia, and Canada, which lie north of the 40th parallel, have a low rate. There are some parts of the world (mainly islands) where the pterygium rate is about 20% or more, e.g., Hawaii, Samoa, Marshall Islands, Aitutaki, and Aruba. This may be due to reflection of ultraviolet light from the sea.

However, Parthasarathy and Gupta (1967) do not think Cameron's theory can explain the wide variation in the prevalence rates in different states of rural India. Pterygium is common in the states of Maharashtra, Andhra, and Pradesh, but Madras, and especially Kerala, which are nearer the Equator, have a lower incidence. Moreover, there are other discrepancies between the theoretical world distribution based on latitude (Cameron, 1965) and the actual distribution. Thus Rasanayagam (1973) reports that the prevalence of pterygium in West Malaysia is 7.4% whereas the expected theoretical prevalence for an area between 0° and 4° N should be over 10%. Other exceptions to the relationship with latitude are found in Borneo, Java, and New Guinea, whose actual pterygium rates are lower than expected, with some parts of New Guinea under 5%. However, in the mainland area of New Guinea the prevalence of pterygium is higher in the coastal lowlands and lowland savanna than in the lowland rain forest (Vines, 1970). Sivasubramaniam (1970) also has figures for Ceylon which do not agree with Cameron's hypothesis. Ceylon lies between 6° and 10° N latitude, and according to Cameron the theoretical expected rate for pterygium in Ceylon should be more than 10%. However, Sivasubramaniam found a prevalence of only 0.7%. He postulated that the thick and luscious vegetation carpeting the whole land, the absence of deserts, the fanning of the land by 2 monsoons, which bring rain-bearing clouds to the central hills rising to a height of 9000 ft (2700 m) above sea level are all mitigating factors. The ample cloud cover and vegetation cut down the ultraviolet radiation.

Nearly all observers have found that there is a higher incidence in men than women and an in-

creasing incidence in age from 20 to 50 years. In North Malaysia a study was conducted on Malays, Indians, and Chinese. In the former 2 groups the sex ratio was 3:1 male:female, but in the Chinese the male preponderance was less (10:7, male:female). This might be due to the Chinese women leading a more active outdoor life. The incidence in fishermen is much higher than in the general population, and that in Chinese fishermen is more than in Malays (Rasanayagam, 1973). It is interesting and perhaps not wholly surprising that in Ceylon two of the high incidence areas are coastal, and here the occupation of the populace is fishing. However, two other coastal areas (Jaffra and Bathirla) where fishing is the livelihood show a low incidence of pterygium (Sivasubramaniam, 1970).

There is a little evidence for ethnic variations in the prevalence rates of pterygia. Ash (1950) reported a higher incidence in blacks than whites in America. Ida Mann (1962) in her surveys of whites, full bloods, and coloured people in West Australia emphasised that there is a much higher prevalence among the full bloods and coloured people than in the whites. She has deduced from the physical characteristics and sagas and legends of the aborigines (= original Australians) that they have come from the Dravonian Hill tribes in South India. Indeed, the Dravonian races of South and East India are noted for their high incidence of pterygium. In the study in West Malaysia the highest racial prevalence is found in the Chinese. The majority of Indians in Malaysia are immigrants from South India, and this group had a lower prevalence than other ethnic groups (Rasanayagam, 1973). This might be due to the inclusion of Ceylonese in the Indian group, which would tally with the low incidence of pterygium found in Ceylon by Sivasubramaniam (1970).

Youngson (1972) reviewed 5000 Arabs in Jerusalem of whom 460 (9.2%) had true pterygium; 298 patients had unilateral pterygia, of which 183 were in the left eye and 115 in the right eye, a significant difference. An ingenious theory was postulated by Batten (1972), who considers that this may be due to shading of the right eye with the right hand. An unusual feature of Youngson's study was the observation that the lesions regressed in old age.

Some workers, including Scarpa (1880), Gerundo (1951), and Friede (1949), believed that chronic bacterial or catarrhal conjunctivitis initiates the progress. Stellwag-Carion (1880) suggested that pterygium may develop from an ulcer caused by herpes virus. Poncet (1880) thought that 'vibrions' were responsible and claimed to have seen spores in the tissue of the pterygium head. Other workers have suggested that trauma, vitamin A deficiency, or the installation of native medicines may play a

role. There is no good epidemiological evidence to support any of these as major factors in the pathogenesis of such lesions. Elliot (1966) suggested that ultraviolet light caused drying of the tear film and that this was followed by pterygium. Goldberg and David (1976) carried out a study to investigate the correlation between the occurrence of pterygia and the 'dry eye', but were unable to demonstrate a significant difference between patients with pterygium and controls. This study fails to support the hypothesis of Mackie (1971) and Paton (1975), who suggest that there is a primary abnormality of the tear film which predisposes to pterygium formation.

Conclusions

Although there are some unexplained features, the overall epidemiological findings and the pathology of the lesions suggest that ultraviolet radiation is the major factor in the development of solar keratosis (pterygium) and, in consequence, the high incidence of squamous cell carcinoma of the conjunctiva in the tropics. Other cofactors, some of which have been discussed, may enhance the process. While latitude is the most important factor determining the exposure to ultraviolet light, many geographical factors such as cloud, altitude, and vegetation will influence the dose to the conjunctiva. Such factors may explain some of the variable frequencies in the tropics.

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