NON-PIGMENTED INTRA-EPITHELIAL MELANOMA OF CORNEA*

BY

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PRECANCEROUS melanosis of the surface epithelium is histologically analogous to Bowen's disease (intra-epithelial epithelioma) in that both are forms of carcinoma *in situ*, which sooner or later invade the subepithelial tissue, giving rise to typical malignant melanoma on the one hand and epidermoid carcinoma on the other. It has therefore been suggested by Ashton (1957a) that the term "intra-epithelial melanoma" would be more appropriate than "precancerous melanosis" and this name has been adopted throughout the present report.

Malignant melanoma, as a primary or secondary lesion, is exceedingly rare in the cornea. Von Hippel (1928) was able to collect only ten cases, and since that time seven more have been added to the literature (Castroviejo and Castroviejo, 1931; Reese, 1943; Rossi, 1951, 1952; Lister, 1951; Ashton, 1951; Davies and Bailey, 1954; François, Gildemyn, and Rabaey, 1956). Some of these malignant tumours apparently arose from pre-existing naevi, but in only one case was the lesion described as having derived from an intra-epithelial melanoma (François and others, 1956), although the histological description of the case of Castroviejo and Castroviejo (1931) suggests that this lesion may also have had a similar origin.

The case reported here showed an intra-epithelial melanoma of one half of the cornea, which merged imperceptibly with similar changes at the limbus. A malignant melanoma was present at the limbus on the opposite side, but this was quite distinct from the corneal lesion, being separated from it by healthy corneal epithelium. The case is unique in that the lesions were completely non-pigmented.

Case Report

A married woman, aged 64, was first seen in March, 1953, complaining of persistent discomfort for some months in the left eye, which before this time had been completely normal.

Examination.—The left eye was irritable with a number of superficial punctate infiltrations confined to the lateral half of the cornea. The right eye was normal.

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Diagnosis.—The condition was thought to be a superficial punctate keratitis, and various treatments were adopted during the next few months, all without benefit.

Progress.—By October, 1953, the corneal infiltrations had increased in size and number, a marginal pannus had developed corresponding to the affected area of the cornea, and a small protuberant mass was seen at one point on the limbus. There was no glandular enlargement.

Operation.—The possibility of a neoplasm was now considered for the first time. The exuberant tissue at the limbus was removed and submitted for pathological examination and reported as a malignant melanoma. In November, 1953, the left eye was excised, care being taken to remove a wide area of conjunctiva corresponding to the lesion.

Result.—Up to December, 1956, there had been no local recurrence and the patient remains in good health.

Histology

(1) *Limbal Biopsy.*—Section shows a nodule of tissue covered on one side by a thin layer of epithelium. The subepithelial tissues are packed with malignant melanotic cells arranged in whorls, sheets, and columns (Fig. 1).

FIG. 1.—Limbal biopsy, showing subepithelial tissues densely infiltrated by malignant melanotic cells. Note the small clusters of malignant cells in the deeper layers of the covering epithelium. Haematoxylin and eosin. $\times 120$.

There is no pigmentation, and the predominant cell, which is of the spindle type, is markedly pleomorphic (Fig. 2, opposite). A few clusters of cells lie within the deeper epithelial layers resembling those seen in intra-epithelial melanomata.

(2) *Whole Eye.*—Section of the eye shows a healed biopsy scar at the limbus on the temporal side with a few malignant spindle cells lying in the surrounding stroma. At the limbus on the opposite side and extending into the bulbar conjunctiva there is an extensive cellular proliferation within the deeper layers of the epithelium (Fig. 3, opposite).

There is considerable cellular pleomorphism, cytoplasmic vacuolation, and some pyknosis; many of the cells are grouped into small nests or clusters (Fig. 4, opposite).

Agglomerations of cells are bulging into the underlying limbal stroma, but as yet have not broken away from the main mass and the lesion is apparently still in the precancerous intra-epithelial phase.

FIG. 2.—Limbal biopsy. High-power view of Fig. 1, showing typical clusters of non-pigmented malignant cells. Haematoxylin and eosin. $\times 390$.

FIG. 3.—Limbal portion of whole eye-section, showing cellular intra-epithelial proliferation. The cornea is on the left. Haematoxylin and eosin. $\times 120$.

FIG. 4.—High-power view of a cluster of proliferating intra-epithelial cells seen in Fig. 3. Haematoxylin and eosin. $\times 360$.

Within the basal layers of the corneal epithelium, on this same side, extending as far as the centre of the cornea and merging with the limbal lesion, there is a continuous collection of tumour cells separated from the substantia propria by an intact Bowman's membrane (Figs 5 and 6). The cells are rather more pleomorphic than those of the limbal precancerous lesion, having no clear cytoplasmic spaces or nest-like arrangements and thus suggesting early malignancy, although in the absence of subepithelial invasion it is difficult to be certain of this change. As in the limbal biopsy there is complete absence of pigmentation.

FIG. 5.—Tumour cell proliferation within deeper layers of corneal epithelium separated from substantia propria by an intact Bowman's membrane. Haematoxylin and eosin. $\times 120$.

FIG. 6.—High-power view of Fig. 5, showing intra-epithelial cellular proliferation of the cornea. Haematoxylin and eosin. $\times 380$.

Discussion

Malignant melanomata of the outer eye usually arise from either a pre-existing naevus or from an intraepithelial melanoma, and the distinction can frequently be made on the clinical history alone. A pre-existing naevus, for instance, will have been noted from childhood, whereas intra-epithelial melanoma is a disease of the fourth and fifth decades and arises in a previously healthy epithelium. Furthermore, a conjunctival intra-epithelial melanoma is characteristically diffuse, and, by the time malignant change has developed, may have spread to involve the whole of the bulbar and palpebral conjunctiva together with the caruncle and adjacent skin of the lids (Greer, 1954).

The histological picture of intra-epithelial melanoma is now well known and, except for the absence of pigmentation, our description is typical of the condition. The history and histological picture of this case leave no doubt that the whole neoplastic process began as an intra-epithelial melanoma of the conjunctiva. This condition, even if widespread, rarely extends onto the cornea, and it is surprising that this feature has not attracted more attention. The reason for this corneal immunity is unknown, although of course there are elsewhere in the body other examples of freedom from direct spread by a neoplasm. Blondis (1946) believes that at the limbus there is a physiological barrier which breaks down in disease to permit the migration of melanocytes into the cornea.

The possibility that some of the reported cases of primary melanomas of the cornea have in fact arisen from the limbus, cannot be completely excluded. Even in the well described case of Davies and Bailey (1954) doubt must be cast upon the corneal origin as the authors describe the basal cell proliferation extending to the region of the limbus. A more certain case of a corneal primary was that of Blanquinque (1892), who described a "melanosarcoma" in a woman aged 60. The patient had noted a red spot near the centre of the cornea 20 years earlier, and this remained quiescent for 11 years, gradually increased in size for 9 years, and at the time of excision had extended to 1 mm. beyond the limbus. Reese (1951) published a photograph of a corneal melanoma and stated that serial sections showed no limbal invasion.

The origin of true primary corneal epithelial melanomas, if they exist, is not apparent. Reese (1951) believes that they arise either from the Schwann cells of the corneal nerves or from the basal cells of the epithelium, thus embracing two opposing theories of the histogenesis of melanomata—a neural and an epidermal origin.

Recent work, however, has proved that melanogenesis takes place exclusively within the cytoplasm of the dendritic cells (Billingham, 1948, 1949; Billingham and Medawar, 1948, 1950, 1953), which pass under a variety of names, *i.e.* melanocytes, melanoblasts, and Langerhans' cells. They lie between and beneath the basal cells of the epidermis, and according to

Billingham (1948) have a neural origin. It follows, therefore, that if benign and malignant melanomata arise from these dendritic cells, as is now widely believed (Cappell, 1951; Lewis, 1954; Lloyd, 1954; Evans, 1956), they also must have a neural and not an epidermal origin.

Dendritic cells have not been found within the normal corneal epithelium, but Redslob (1922), using a silver stain and the "dopa" reaction, showed that "melanoblasts" are present in the epithelium of injured corneae. He was unable to obtain a specimen of a normal human cornea but found no evidence of "melanoblasts" in the normal corneae of rabbits, and this has recently been confirmed (Michaelson, 1952). Redslob (1922) found melanoblasts in one apparently normal cornea but on deeper section he was disappointed to find evidence of an old injury. He concluded that the presence of vascularization was necessary to bring melanoblasts into the cornea.

Ashton (1957b) is not convinced that this is the complete explanation. He suggests that the melanocytes may be carried into the cornea from the limbus (where they can be demonstrated in normal eyes) by the epithelial slide that follows corneal injury. As is well known, this sliding movement may be extensive, with migration of epithelial pigment and goblet cells for some considerable distance into the cornea (Duke-Elder, 1954). It is therefore likely that injury is the predisposing cause of corneal melanomata which appear to be primary, and since there was no evidence of trauma in this case the corneal lesion is considered to be an extension from the limbal intra-epithelial melanoma.

The other feature of interest is the complete absence of pigmentation. Lloyd (1954) states that Fontana's silver stain will demonstrate the presence of melanin granules in most non-pigmented melanomata; but on the tissues from the patient here reported the technique gave negative results. Amelanotic melanomata have been reported elsewhere in the body recently by Andrews (1950), Bhende (1952), and Hecht (1953). Malignant melanomata of the choroid are occasionally non-pigmented, but within the conjunctiva and cornea lack of pigmentation must be exceedingly rare.

This feature frequently makes the diagnosis of such lesions extremely difficult, both clinically and histologically, especially if the cellular pattern is unusual as occurred in the case of Hecht (1953). It was fortunate that the histological picture in our case was so typical that the absence of pigmentation caused no confusion.

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