Multifocal amelanotic conjunctival melanoma and acquired melanosis sine pigmento

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Abstract
Clinical and histopathological features of four cases of multifocal amelanotic malignant melanoma of the conjunctiva in association with 'acquired melanosis sine pigmento' are reported. The absence of conjunctival pigmentation in this extremely rare combination of lesions prevented early diagnosis and clinical monitoring. As a result orbital exenteration was required in three cases. This multicentric non-pigmented variety of conjunctival malignant melanoma tends to present later than pigmented forms and may require exenteration of the orbit as a primary procedure.

Malignant melanoma of the conjunctiva is uncommon but is among the most serious of ocular malignancies. The diagnosis of conjunctival melanoma is a challenge to both the ophthalmologist and pathologist. In addition the management of this neoplasm remains in dispute.

Unusually conjunctival melanomas present as pigmented lumps, which may arise spontaneously (de novo), in a pre-existent naevus, or in association with primary acquired melanosis (PAM) with atypia, a unilateral, precancerous melanocytic condition. Sometimes a combination of precursors is encountered. The degree of pigmentation of such tumours depends on the amount of melanin in the tumour cells, macrophages, or in the extracellular matrix.

There has been only one well-described case report of a recurrent multifocal pigmented malignant melanoma of the conjunctiva originating in amelanotic acquired melanosis of the conjunctiva. Griffith et al1 referred to the amelanotic precursor as 'acquired melanosis sine pigmento'. Jackobiec et al2 encountered a further four cases of multifocal conjunctival melanoma in association with amelanotic PAM, but did not mention the degree of pigmentation of the malignant melanomas.

We studied the clinical and histopathological features of four cases of multifocal amelanotic conjunctival melanoma arising in association with acquired melanosis sine pigmento.

Case reports

CASE 1
A 39-year-old plastics worker presented with a multifocal amelanotic conjunctival melanoma of his left eye in 1986. Five years earlier hot oil had been squirted into this eye by accident. Despite immediate treatment he was left with a chronically irritable eye. Two years earlier an ophthalmologist had excised a small black spot in the left inner canthal region. The histological diagnosis was then reported as 'benign cellular naevus' but subsequent review of the sections showed malignant melanoma.

On examination there were multifocal pale pink fleshy lesions involving the entire limbal area and the upper and lower palpebral conjunctiva. One small patch of pigmentation at 12 o'clock was noted. Biopsies of multiple sites showed amelanotic malignant melanoma and primary acquired melanosis with atypia. A systemic metastatic evaluation was negative. The left orbit was then exenterated using a lid splitting technique. Histological examination showed multicentric amelanotic malignant melanoma (Fig 1) with a maximum thickness of 1 mm in the superior palpebral conjunctiva. The resection margins were clear.

In 1988 needle biopsy of a left preauricular mobile swelling, which had been growing for 6 months, showed melanotic malignant melanoma. The lump was subsequently removed by partial superficial parotidectomy. A course of local radiotherapy was given to the parotid and deep cervical nodes and when the patient was last seen in 1991 no signs of local or distant metastases were noted.

CASE 2
In 1986 a 45-year-old man, who also worked in a plastics firm, presented with a 6 month history of a gradually enlarging white mass on his right cornea. On examination there was a 4x5 mm elevated amelanotic tumour (Fig 2) with a smooth surface and large feeder vessels. A mild

Figure 1  Case 1. Histology of exenteration specimen showing amelanotic malignant melanoma (arrow). Note the dark staining irregular nuclei and the complete absence of intracytoplasmic melanin pigment granules.
The corneal mass was resected using absolute alcohol to slide off the affected epithelium. Microscopic examination disclosed an amelanotic anaplastic malignant melanoma without evidence of any precursory lesion.

Seven months later superficial white deposits in the corneal epithelium and superior fornix were noted, and at follow-up no changes were observed until August 1988 when there was a 2.5 × 5 mm white multinodular tumour (Fig 3) in the palpebral conjunctiva of the right lower lid. Incisional biopsy showed an amelanotic malignant melanoma. There was no lymphadenopathy and a metastatic evaluation was negative. The right orbit was then exenterated and histological sections showed multifocal intraepithelial and subepithelial nests of amelanotic atypical S-100 positive tumour cells (Fig 4). When last seen in 1991 no signs of recurrent disease were noted.

CASE 3
A 54-year-old labourer presented with a 3 year history of intermittent redness of his left eye in June 1990. On examination there were multiple fleshy pink deposits involving the bulbar conjunctiva, the fornices, and the palpebral conjunctiva of both lids (Fig 5), and signs of chronic conjunctivitis, including large follicles and increased vascularity. Diagnostic biopsies revealed multicentric inflamed amelanotic S-100 positive malignant melanoma and areas of amelanotic primary acquired melanosis with atypia. The latter precursory condition was even detected in a biopsy of clinically unaffected conjunctiva. A systemic metastatic evaluation was negative and left orbital exenteration was performed in November 1990. When last seen in March 1991 there was no evidence of recurrence.

CASE 4
In 1987 a 46-year-old woman presented with a history of a longstanding pinguecula-like inflamed lesion in the temporal part of the left conjunctiva. Unresponsiveness to topical steroid treatment led to an excision biopsy which showed amelanotic epithelioid malignant melanoma and PAM with atypia. In the following years five nodular recurrences on multifocal sites around the limbus were excised or treated by β radiotherapy applied by a strontium-90 plaque (three doses of 800 cGy). When last seen in November 1990 there were no signs of recurrent disease.

Discussion
The absence of pigmentation in amelanotic primary acquired melanosis means that such a precursor may only be detected by biopsy and histological examination.

Jakobiec et al. observed that three out of four patients with multinodular malignant melanoma of the conjunctiva with microscopically extensive PAM sine pigmento had metastases and suggested these patients might have a worsened prognosis due to altered intrinsic biological features of the disease or problems in disease mapping. We think it is likely that amelanotic
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Figure 5 Case 3. One of multiple foci of fleshy amelanotic malignant melanoma (*) involving the chronically inflamed left upper palpebral conjunctiva.

tumours may defy early detection and reach a vertical growth phase, with the potential for metastasis. The risk of such spread is much greater if there is undetectable multifocal disease which may be undertreated by conservative management. Three of our patients with multifocal disease affecting unfavourable locations were radically treated by orbital exenteration and only one patient (case 1) had regional metastasis within 4 years of first presentation and 2 years of orbital exenteration. Although the period of follow-up has been limited, orbital exenteration in cases 2 and 3 may have prevented spread of conjunctival melanoma. The high rate of metastases in the patients reported by Jacobiec et al who were treated with a combination of cryotherapy and surgery might have been related to initial conservative management.

Conjunctival melanoma originating from an area of PAM with atypia may develop at multiple sites, which makes its management more problematic. Folberg et al found a median interval of 2.5 years between diagnosis of PAM with atypia and diagnosis of malignant melanoma. This interval enables the clinician to monitor such conditions, detect early progress to malignancy, and intervene promptly. However, when the area of acquired melanosis is amelanotic the nature of this precursor may only become apparent when frank malignant melanoma has already developed, as is illustrated above. Multiple pink or white conjunctival nodules may give rise to diagnostic difficulties. Due to late detection and the difficulty of monitoring and assessing the extent of amelanotic melanoma and PAM sine pigmento some patients with this rare combination of lesions may require orbital exenteration as a primary procedure. However even this radical surgical treatment, which has been advocated by Reese for all cases of biopsy proved invasive melanoma, may not prevent spreading of 'transit' metastases.

The absence of melanin in amelanotic melanoma and acquired melanosis sine pigmento is difficult to explain. It is of interest that in case 1 the first inner canthal lesion was pigmented, the subsequent multifocal nodules were amelanotic, and the preauricular metastasis was again pigmented. If the latter originated from the extensive amelanotic melanoma it would demonstrate the propensity of melanogenesis of at least one clone of the non-pigmented tumour cells. The production of melanin does not seem to be related to malignant potential, for melanomas with varying degrees of pigmentation have shown an ability to metastasise. The loss of the ability to make melanin may however signify a degree of dedifferentiation of tumour cells.

Jacobiec et al found that several of their patients had a pre-existent naevus by history or in their pathological material. They speculated that naevus cells may have lost a certain potential of melanogenesis during malignant transformation and proliferation thus disguising the extent of the radial growth phase. In our series, however, there was a history of a potential naevus in only one case (case 4). In our opinion the multifocal nature of the disease described in our case reports does not fit with a theory of spreading transformed naevus cells.

It is unknown whether environmental factors play a role in the aetiology of conjunctival malignant melanoma and acquired melanosis sine pigmento. The patients in both cases 1 and 2 worked in the plastics industry. The patient in case 2 had been exposed to continuous plastics fumes at work and developed an amelanotic melanoma on the cornea, which is an unusual site for such neoplasm. The rarity of this tumour, the large number of chemicals to which patients were potentially exposed, and incomplete occupational histories make it very difficult to detect possible causative agents. Although the relation between occupation and conjunctival melanoma in cases 1 and 2 may well have been coincidental, animal studies have demonstrated the propensity of certain chemicals to induce cutaneous malignant melanoma, and similar induction and development of ocular malignant melanoma has been suggested.

The purpose of this report has been to emphasise the capricious behaviour of conjunctival malignant melanoma. We have reported four cases of a previously undescribed combination of amelanotic melanoma arising in association with PAM sine pigmento. We believe that awareness of this non-pigmented variety of conjunctival melanoma is crucial for early recognition and management.

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