

## Colonisation of basal cell carcinoma and actinic keratosis by malignant melanoma *in situ* in a patient with xeroderma pigmentosum variant

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### Abstract

Although malignant melanoma (MM) and both basal cell carcinoma (BCC) and actinic keratosis (AK) are sun-induced lesions, the co-existence of these entities at the same anatomical site (collision tumour) is exceedingly rare. We report the case of a 54-year-old woman with a known history of xeroderma pigmentosum variant (XPV) who presented with 2 separate skin lesions over the middle and upper right forearm, respectively. The clinical impression was that of BCCs or squamous cell lesions. On histological examination, both specimens showed features of melanoma *in situ* (MIS). In the first lesion, MIS merged with and colonised a superficial and focally invasive BCC. In the second lesion, MIS merged with an AK. No separate invasive nests of malignant melanoma were seen in either specimen. The atypical melanocytes were highlighted by Melan-A and HMB-45 immunostaining, whereas the epithelial cells in both the BCC and AK stained with the pancytokeratin MNF-116. The patient had a previous history of multiple MMs and non-melanomatous skin cancers and finally developed widespread metastatic malignant melanoma, which proved fatal. The rare and interesting phenomenon of collision tumours may pose diagnostic difficulties. To our knowledge, this is the first reported simultaneous presentation of cytologically malignant collision tumours in a patient with XPV.

### Introduction

The co-existence of two or more histologically distinct neoplasms arising from different cell lines resulting in a single cutaneous lesion, so-called collision or combined lesion, is relatively rare but well-described in the literature. In a review of 40,000 cutaneous lesions, Boyd and Rapini<sup>1</sup> found only 69 collision lesions. All of these were described as the contiguous type where individual lesional components are juxtaposed but separated by  $\geq 1$  mm with no transition. Intermingled collision lesions (intimate mixing of the individual

tumour cells) are less frequent.<sup>2</sup> Most often, the collision is between basal cell carcinoma (BCC) and benign naevus; BCC and seborrhoeic keratosis (SK) or SK and benign naevus.<sup>1</sup> The collision of cytologically malignant neoplasms is much less common, case reports most often describing collision of BCC and malignant melanoma (MM).<sup>2-6</sup>

Xeroderma pigmentosum variant (XPV) was first described by Ernest G. Jung in 1970 as a disease with a similar phenotype to xeroderma pigmentosum (XP) but which lacks the genetic defects of nucleotide excision repair that are characteristic of XP.<sup>7</sup> In comparison with XP, the ultraviolet-induced cutaneous neoplasms in XPV occur at a later age and XPV usually has a more favourable prognosis.<sup>8</sup>

We report a rare case of two simultaneous, cytologically malignant collision lesions in a patient with XPV. Although there are occasional reports in the literature of collision lesions in patients with XP,<sup>9,10</sup> this is, to our knowledge, the first reported case of simultaneous collision lesions in a patient with XPV.

### Case Report

A 54-year-old white female XPV patient under regular Dermatology review and who frequently attended a combined Plastic Surgery and Dermatology Clinic developed two new cutaneous lesions on the right middle and upper forearm. Both were clinically suspected as squamous cell lesions or BCCs and she proceeded to excision biopsies. Macroscopically, both lesions were elevated and keratotic, with maximum diameters of 2 cm (middle forearm) and 1.3 cm (upper forearm).

#### Lesion 1 (middle right forearm)

Histological sections showed sun-damaged skin with overlying hyperkeratosis. Multifocal, superficial BCC was identified, with a single focus of early invasive BCC. The BCC was readily diagnosed on hematoxylin and eosin sections alone. The BCC was partly colonised by small clusters and individually dispersed atypical melanocytes with abundant pale cytoplasm, large, vesicular nuclei and prominent nucleoli (Figure 1A,B). Atypical melanocytes also lay wider to the BCC. None of the melanocytes had a dendritic appearance. Immunohistochemistry with pancytokeratin MNF-116 highlighted the BCC component and spared the atypical melanocytes. S100, Melan-A and HMB-45 stained the atypical melanocytes only (Figure 1C,D). Atypical melanocytes were seen colonising the small area of invasive BCC, but separate, frankly invasive MM was not present.

The lesion was classified as a collision tumour (intermingled type) of BCC and

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melanoma *in situ* (MIS). The lesion was completely excised.

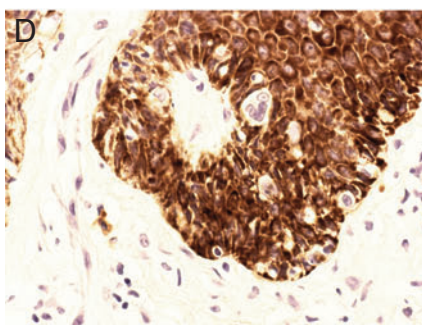
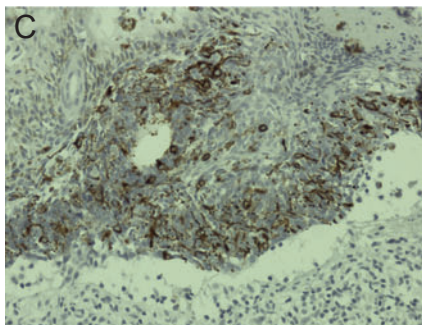
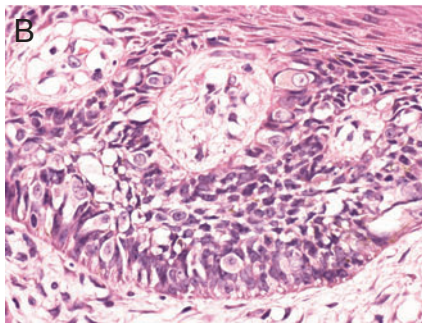
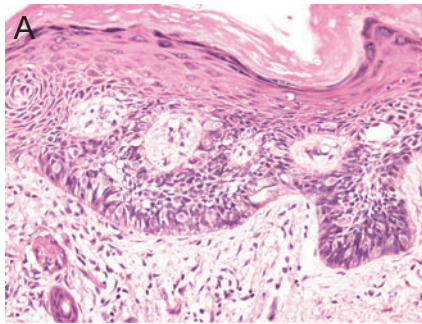
#### Lesion 2 (upper right forearm)

Histological sections showed sun-damaged skin with overlying parakeratosis. The epidermis was acanthotic and included several foci of keratinocyte dis-cohesion. The lesional keratinocytes were enlarged with pale cytoplasm, hyperchromatic nuclei and some prominent nucleoli. In areas, atypical keratinocytes extended through the full thickness of the epidermis. Occasional binucleate keratinocytes were also noted. No invasive component was seen. These features, in isolation, were diagnostic of AK. In addition, there were large atypical melanocytes within the epidermis that were both individually dispersed and arranged in small clusters. Focally, these atypical melanocytes extended through the full epidermal depth. In areas, atypical melanocytes merged with and colonised the actinic keratosis (AK) (Figure 2A,B). Immunohistochemistry with pancytokeratin MNF-116 highlighted nearly all of the epidermis with sparing of the atypical melanocytes. The atypical melanocytes were highlighted with Melan-A, S100 and HMB-45 (Figure 2C). No invasive melanoma component was identified.

This lesion was classified as a collision lesion (intermingled type) of AK and MIS. The AK component was excised but MIS was incompletely excised at one peripheral margin.

Three further cutaneous lesions were removed at the same surgical appointment – a Clark level 4 nodular MM from the lower right forearm, and two superficial spreading MMs of Clark levels 2 and 3 from the back and left calf

respectively. The patient had a past medical history of multiple other solar-related cutaneous neoplasms including BCCs, MMs and squamous cell carcinomas (SCC) over the preceding 30 years. This history reflects the greater propensity to UV-induced cutaneous neoplasms that is characteristic of XPV.



**Figure 1. Superficial basal cell carcinoma (BCC) colonised by atypical melanocytes: A) x20; B) x40. C) Melan-A highlighting melanocytes colonising BCC x20; D) MNf-116 staining of superficial BCC with sparing of atypical melanocytes x40.**

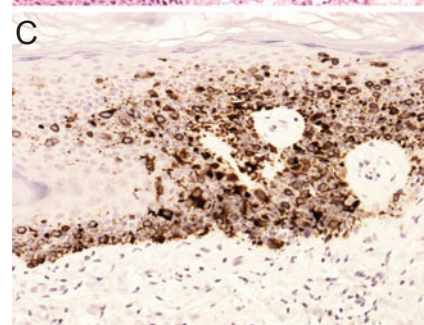
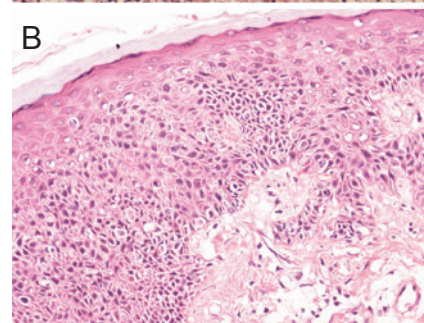
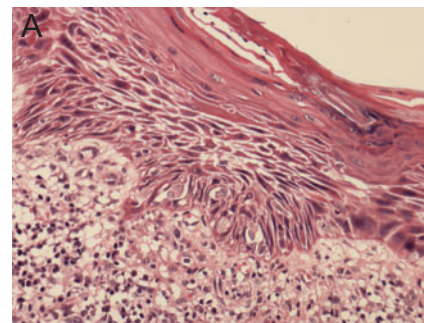
## Follow up

One year after excision of the collision lesions, the patient developed metastatic malignant melanoma to the lung and subsequently to the pelvis, which proved fatal.

## Discussion

We report here two simultaneous, cytologically malignant collision lesions on the arm of a middle-aged woman with XPV: an intermingled BCC and MIS, and an intermingled AK and MIS. We believe this to be the first case report of two simultaneous, cytologically malignant collision lesions in a patient with XPV.

It has been documented that BCC can be populated by non-atypical melanocytes, which may be either peripherally located or individually scattered within the BCC component.



**Figure 2. A) Individually dispersed atypical melanocytes colonising the basal layer within actinic keratosis (AK) (x20). B) Melanoma in situ (MIS) adjacent to and merging with AK (x20). C) Melan-A staining MIS (x20).**

However, when BCCs are infiltrated with melanoma cells, the melanocytes are more densely packed and tend to form clusters.<sup>11</sup> This latter pattern was seen in both lesions from this patient. We propose that the extension of atypical melanocytes into the adjacent epidermis and beyond the limits of the BCC and AK is convincing evidence that these lesions represent collision tumours with MIS and not simply colonisation by normally-occurring melanocytes from the epidermis and hair follicles.

The pathogenesis of collision lesions is not well understood and there are several hypotheses to explain their existence. One theory describes biphasic or biphenotypic collision lesions in which it is proposed that a single cell type (pleuripotent cell) has the ability to differentiate in more than one direction, giving rise to a composite or intermingled lesion.<sup>2,5,12</sup> Another explanation is the biclonal occurrence of 2 separate but adjacent neoplasms as a result of exposure to certain carcinogenic stimuli, or as a result of paracrine factors released by one neoplasm affecting vulnerable cells in the adjacent environment.<sup>13</sup> One further possibility was given by Busam *et al.* who described a patient with recurrent melanoma of the scalp who developed multiple satellite nodules and a BCC colonised by atypical melanocytes in close proximity to the primary lesion, and regarded the collision lesion as MM that had metastasised to the BCC.<sup>14</sup>

Patients with XPV are deficient in the post replication repair mechanism as a result of a defective DNA polymerase  $\eta$  [one of the trans lesion synthesis (TLS) polymerases]. This is a low fidelity DNA polymerase that allows TLS of UV-induced DNA damage in an error-free manner.<sup>15</sup> In its absence, UV-induced lesions are bypassed by other inaccurate DNA polymerases resulting in high rates of mutagenesis and elevated cancer risk.<sup>16</sup>

In our opinion, the pathogenesis of the collision tumours in this patient is related to the marked increase in the risk of UV-induced skin neoplasms due to the reduction in DNA reparative capacity imposed by XPV. In a study of MMs developing in the general population, patients were also found to have a higher incidence of other sun-induced lesions such as BCC, SCC and AK.<sup>17</sup> With particular regard to XP, some authors favour that collision tumours are mere coincidence, arguing that, given the increased number of malignant cutaneous lesions characterising this condition, there is a strong likelihood of lesions eventually colliding. Alternatively, Stern *et al.* propose that patients with XP have precursor lesions that transform to MM. Stern's series most often found collision of MM and solar lentigo, and suggested that solar lentigo acts as a precursor lesion for MM in XP.<sup>9</sup> We do not agree with this hypothesis and believe that



there is no direct developmental pathway from solar lentigo to MM.

The presence of collision lesions poses diagnostic, therapeutic and prognostic challenges. The presence of MIS may be overlooked and the melanocytic proliferation may be dismissed as a field change of melanocyte hyperplasia. This could lead to undermanagement, especially if the MIS is not completely excised (as in the second lesion of this case report). Another important issue is the assessment of the atypical melanocytes colonising the invasive component of the BCC in this patient. Should this be considered an invasive malignant melanoma, or simply as extension of MIS cells into the invasive BCC? The therapeutic and prognostic consequences of these two alternatives are completely different. Some authors recommend considering this type of lesion as invasive MM and suggest that a Breslow thickness should be given based on the depth of immunohistochemically detected melanocytes within the BCC component.<sup>2</sup> We share other authors' view<sup>4,18</sup> that, as long as there is no separate invasive component of MM, the dermally located atypical melanocytes within invasive BCC islands should be regarded as colonisation by MIS and not as invasive MM. We do not believe that the subsequent metastases that developed in this patient came from the atypical melanocytes intermingled with the minimally invasive BCC in the first lesion. It is more likely that these metastases developed from the other truly invasive MMs that this patient had.

## Conclusions

In summary, this report describes an interesting and rare case of two simultaneous, combined, cytologically malignant cutaneous neoplasms in a woman with XPV. This represents a potential diagnostic pitfall. Awareness of this unusual association, together with the use of

appropriate immunohistochemical tests, are required to reach the correct diagnosis, and thus determine the best management.

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