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ANATOMICAL PATHOLOGY

Cutaneous tumoural melanosis: a presentation of complete regression of cutaneous melanoma

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Summary

Partial regression is common in cutaneous melanoma; however, complete regression manifesting as tumoural melanosis is rare, conceptually challenging and under-reported. In this study we report on clinical, histological and molecular findings in four cases of completely regressed cutaneous melanoma with nodal or brain metastasis, followed by a comprehensive review of the literature. Our series included three women and one man with an average age of 60 years, and clinical presentation with hyper-pigmented cutaneous lesions. The main histological findings were expansile aggregates of melanophages with complete absence of malignant melanocytes on microscopic and immunohistochemical examination of the entire primary skin lesions, as well as substantial reduction in the number of junctional melanocytes in the overlying epidermis. *NRAS* mutant/*BRAF* wild type metastatic deposits were identified in three patients, with one patient having a *BRAF V600E* mutant metastatic tumour. Tumoural melanosis likely represents a partially effective immunological response to melanoma, with complete eradication of cutaneous disease and less effective systemic results. Patients with tumoural melanosis should be managed as potential completely regressed cutaneous melanoma, with comprehensive physical examination, imaging work up and close follow up.

Key words: Tumoural melanosis; nodal melanosis; regressed melanoma; *NRAS* mutations; *BRAF* mutations.

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INTRODUCTION

Partial regression is a relatively common finding in primary cutaneous melanoma, occurring in 10–50% of cases.[1] On the other hand, extensive or complete regression appears to be a rare event with an estimated incidence of 0.2%;[2,3] however, it is believed that the latter phenomenon is under-reported. Complete regression of a primary cutaneous melanoma likely accounts for the majority of metastatic melanomas with an unknown/occult primary; with the inclusion of the latter cases, it has been speculated that complete regression may occur in up to 15% of melanomas.[1] Regression in melanoma occurs as a result of host immunological response directed against tumour antigens, and is characterised histologically by a variably dense lymphocytic infiltrate in the dermis accompanied by fibrosis, vascular proliferation and melanin pigment deposition.[4] Tumoural melanosis (TM) is a histological term defined by nodular accumulation of melanin laden macrophages (melanophages) and extracellular melanin in the tissue, without melanocytes. In the skin, TM often manifests clinically as a hyper-pigmented flat or papulonodular lesion.[5]

Diagnosing completely regressed cutaneous melanoma without residual melanocytes is conceptually challenging. Although TM is highly suggestive of regressed melanoma, it is not entirely specific and melanosis may be seen with regression of a wide range of benign and malignant pigmented epithelial and melanocytic lesions. Therefore, to establish a diagnosis of melanoma with complete regression, a comprehensive clinical work up is necessary, including a skin survey, radiological imaging and additional biopsies of suspicious cutaneous and extra-cutaneous sites including potential nodal deposits. Furthermore, the histological diagnosis of a clinically suspicious lymph node may be complicated by the occurrence of TM, indicating complete regression of metastatic melanoma in a lymph node. In this study we identified a series of patients with histologically sampled completely regressed cutaneous melanoma to further elucidate the clinical, pathological and molecular features of this phenomenon.

MATERIALS AND METHODS

We interrogated the Anatomical Pathology database of PathWest Laboratory Medicine over ten years (2007–2017), including external consultation cases, using AP system software (Version 8.5.4.2). We searched the database for cases coded as malignant melanoma containing key words such as ‘complete regression’, ‘extensive regression’, ‘severe regression’, ‘tumoral melanosis’ and ‘nodal melanosis’ in the pathology report. The histology and immunohistochemical slides on potential cases were reviewed by three dermatopathologists (NMA, NTH, BAW) to confirm the diagnosis. Subsequently, further molecular, clinical and radiological data were collected, and if available, additional histological/cytological samples of suspicious nodal or visceral lesions either prior to or after the cutaneous excision were reviewed. We adopted and slightly modified the Smith and Stehlin criteria[6] for inclusion of cases (Table 1). In particular, in addition to nodal metastasis we also accepted cases with confirmed visceral metastatic spread. A skin survey must have been performed to exclude other suspicious melanocytic lesions. The location of positive nodes and their anatomical relationship with the primary

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Table 1 Clinicopathological criteria for including cases in this study

Clinicopathological criteria
1. History and/or clinical evidence of a pigmented lesion situated in an area drained by tumour-involved lymph nodes or histological/cytological evidence of distant metastasis (including visceral metastasis).
2. Absence of any other primary lesion identifiable by history or physical examination (including skin, ophthalmological and mucosal sites) that could represent the original lesion of melanoma.
3. Presence of atypical pigmented or depigmented change in the skin at the site of the presumed primary lesion, with all or a majority of the typical histological features associated with regression found on biopsy (attenuated epidermis, dermal melanophages, lymphocytic or chronic inflammatory infiltrate, reactive vascular proliferation, and fibrosis).
4. Absence of any direct or indirect prior treatment to account for regressive changes in the suspected primary cutaneous lesion.
5. Histological and immunohistochemical absence of malignant melanoma cells in excision (step-serial sections of the entire primary site are important to confirm the absence of small residual foci of malignant cells).

cutaneous lesion was evaluated. In addition, all cases were further assessed to ensure that patients did not undergo any prior treatment that could potentially cause regression, such as immunotherapy.[7] All included patients gave informed consent.

RESULTS

After application of strict inclusion and exclusion criteria, we identified four cases of completely regressed cutaneous melanoma with proven metastatic disease out of the total 5138 cases of cutaneous melanoma identified in our archives, representing an incidence of 0.07%. The clinicopathological findings are summarised in Table 2.

There were three women and one man with an average age of 60 years (range 46–69). The primary lesions showed an average clinical size of 11.5 mm (range 6–15 mm). Two patients (Cases 1 and 2) presented initially with suspicious hyperpigmented cutaneous lesions, and incisional and excisional biopsies, respectively, showed TM with expansile aggregates and nodular sheets of melanophages within the mid to deep dermis and extensive extracellular melanin (Fig. 1,2). One showed areas of necrosis (Case 1). There was no evidence of perineural or lymphovascular invasion. No atypical dermal or junctional melanocytes were identified on haematoxylin and eosin (H&E) stained sections or by immunohistochemistry for melanocytic markers including SOX10 and Melan-A. Both lesions showed a significant reduction in melanocytes within the overlying epidermis (Fig. 3). Further radiological investigations in Patients 1 and 2 revealed 18F-fluorodeoxyglucose positron emission tomography (PET) avid lymph nodes suspicious for metastasis, and subsequent fine needle aspiration (FNA) cytology and core biopsy confirmed deposits of metastatic melanoma. Patient 1 proceeded to have wide local excision of her cutaneous lesion, which again showed large areas of TM with other features of regression and a complete absence of atypical melanocytes. Regional nodal clearance was performed in both patients and showed viable tumour deposits of metastatic melanoma in both, with additional areas of tumoural melanosis in one patient (Case 1) (Fig. 4).

Table 2 Summary of patients' demographics, clinicopathological presentations, molecular findings and follow up information

	Case no.			
	1	2	3	4
Age	60	69	45	65
Sex	F	F	F	M
Primary site	Right calf	Left ankle	Scalp	Left back
Metastatic site	Right inguinal LN	Left groin LN	Brain	Left scapular subcutaneous LN
Clinical	Hyperpigmented plaque	Hyperpigmented plaque	Hyperpigmented plaque	Hyperpigmented macule
Maximum diameter	15 mm	10 mm	15 mm	6 mm
First presentation	Primary cutaneous lesion	Primary cutaneous lesion	Brain metastases with brain mass effect and haemorrhage	Subcutaneous LN metastasis
Radiology	PET avid right inguinal and external iliac LNs	PET avid groin LNs	CT and MRI showed metastatic deposits in brain	None performed
Histopathology				
Primary lesion	TM with surrounding areas of fibrosis, focal necrosis and epidermal attenuation	TM with surrounding areas of fibrosis and attenuation of epidermis	Multiple nodules of TM with surrounding areas of fibrosis, and remnants of an adjacent benign naevus	Patches of dermal TM and fibrosis with epidermal attenuation
Metastatic lesion	Sheets of viable MM cells in inguinal LN with areas of TM	Sheets of viable MM cells in a groin LN	Cerebral parenchyma infiltrated by sheets of viable MM cells	Sheets of viable MM cells with tumour necrosis and TM in a subcutaneous LN
Molecular studies	*NRAS (c.182A > G, p.Gln61Arg)*; *BRAF WT*	*NRAS (c.181-182delinsAG, p.Gln61Arg) and MET (c.2962C > T, p.Arg988Cys)*; *BRAF WT*	*BRAF (c.1799T > A, p.Val600Glu)*	*NRAS (c.35G > A; p.Gly12Asp)*; *BRAF WT*
Follow up	Alive after 22 months	Alive after 6 months	Deceased after 32 months	Alive after 6 months

CT, computed tomography; LN, lymph node; MM, malignant melanoma; MRI, magnetic resonance imaging; PET, positron emission tomography; TM, tumoural melanosis; WT, wild type.

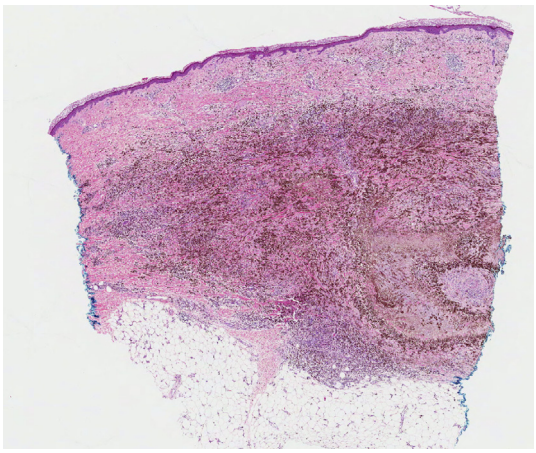

Fig. 1 Low power microscopy of the completely regressed cutaneous melanoma in Case 1 shows a nodular aggregate of melanophages with areas of necrosis and inflammation in the dermis with attenuation of the overlying epidermis (H&E).

Patient 3 was a fit and healthy woman who presented to the Emergency Department with sudden onset altered consciousness, vomiting, confusion and speech difficulties. Brain imaging showed a large parenchymal haemorrhage with multiple scattered haemorrhagic lesions showing significant mass effect, consistent with haemorrhagic metastases. She was urgently transferred to the neurosurgical unit and a craniotomy for decompression and resection of the haemorrhagic tumour was performed. Histopathological and immunohistochemical examination demonstrated metastatic melanoma. Further history and examination revealed a suspicious hyperpigmented scalp plaque. On excision there were intradermal expansile collections of heavily pigmented melanophages. This area of tumoural melanosis was surrounded by residual portions of a naevus, characterised by cytologically bland melanocytes arranged as both nests and single cells showing maturation with depth (Fig. 5). No atypical melanocytes were present.

Patient 4 was an elderly man who presented to his general practitioner with a firm subcutaneous nodule over the left shoulder. Histological examination revealed a subcutaneous lymph node which was almost completely replaced by a deposit of metastatic melanoma, with areas of tumoural melanosis. Subsequent skin examination identified a 6 mm hyperpigmented macule on the left upper back, close to the prior lymph node excision, and punch excision showed a peculiar chequerboard arrangement of deeply pigmented melanophages in the dermis separated by thickened collagen bundles consistent with TM. No melanocytic proliferation

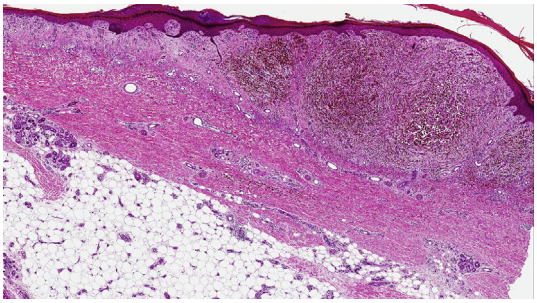

Fig. 2 An area of tumoural melanosis in Case 2, mainly located in the upper dermis (H&E).

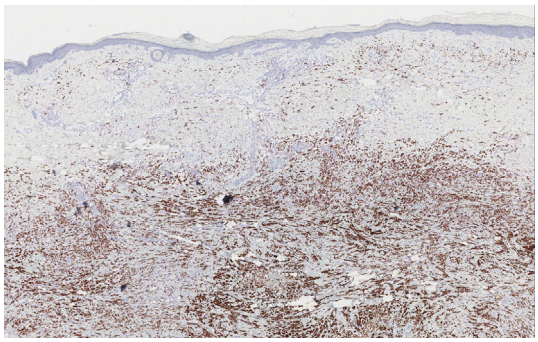

Fig. 3 Immunohistochemistry for a melanocytic marker (immunoperoxidase for SOX10 using red chromogen) highlights the absence of melanocytes in the area of tumoural melanosis as well as in the attenuated overlying epidermis in Case 1.

was identified on histological and immunohistochemical examination (Fig. 6).

Molecular testing had been performed on the metastatic tumour deposits in all cases; in two cases (Case 2 and 4) a next generation sequencing panel encompassing 26 genes (TruSight Tumour 26; Illumina, USA) including both BRAF and NRAS genes had been utilised. The tumour in Patient 1 had been tested for somatic mutations in BRAF exon 15 and NRAS exons 2 and 3 by Sanger Bidirectional Sequencing (Applied Biosystems, Australia), and the tumour in Patient 3 had been only tested for BRAF exon 15 mutations by Sanger Bidirectional Sequencing (Applied Biosystems, Australia) as well as Cobas 4800 BRAF V600 mutation assay (Roche Molecular Systems, Australia). Three cases (Cases 1, 2 and 4) showed *NRAS* mutations including *NRAS pQ61R* mutations in Cases 1 and 2 and *NRAS pG12D* mutation in Case 4; however, BRAF was wild type in these three cases (Table 2). In addition, one of these cases (Case 2) showed an additional *MET* mutation. Case 3 showed a *BRAF pV600E* mutation; this case had not been tested for *NRAS* mutations.

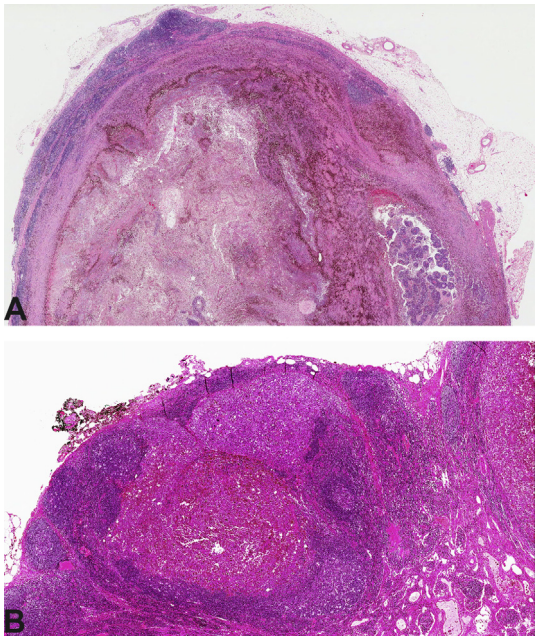

Fig. 4 (A) A histological section showing viable melanoma tumour deposit in a lymph node (right side of field) with large areas of nodal melanosis and necrosis (left side of field) in Case 1 (H&E). (B) Histological section showing melanoma metastasis in a groin lymph node in Case 2 (H&E).

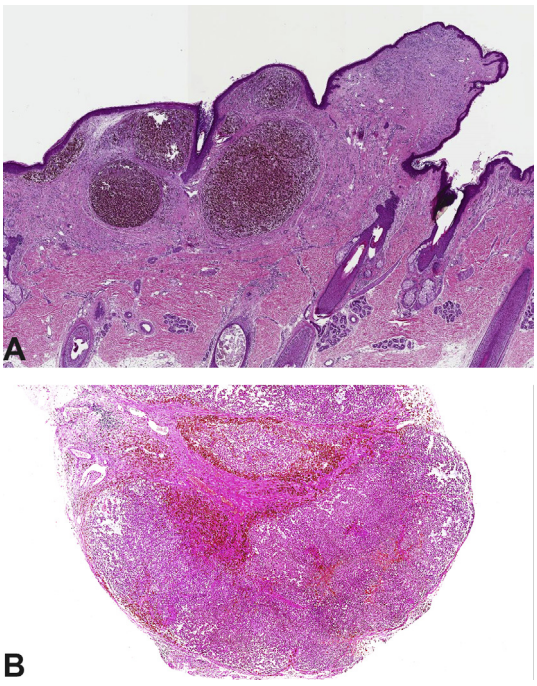

Fig. 5 (A) Tumoural melanosis in the skin of scalp in Case 3 with a co-existing polypoid intradermal naevus on the right side of field (H&E). (B) Metastatic melanoma to the brain in Case 3 (H&E).

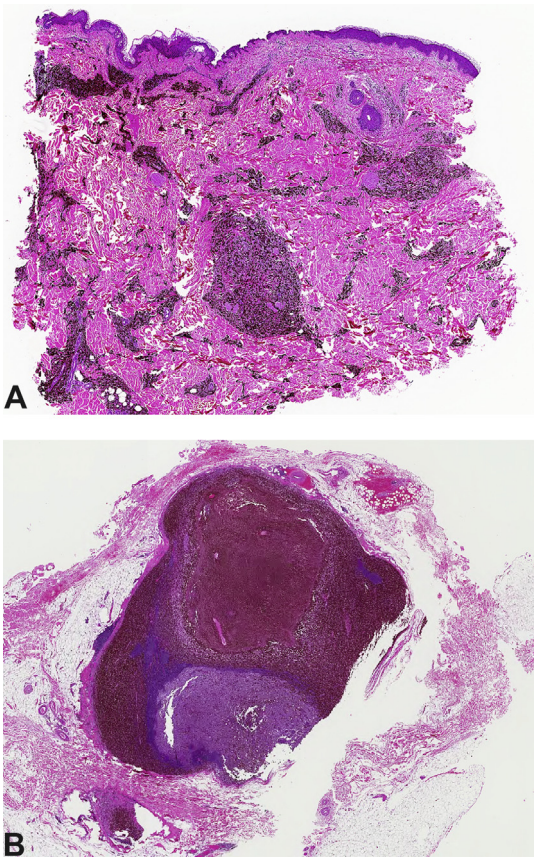

Fig. 6 (A) Tumoural melanosis in Case 4 showing a checker-board pattern in the dermis with intervening thick collagen bundles (H&E), and (B) metastatic melanoma with nodal melanosis in a regional cutaneous lymph node in this patient which clinically came to attention as a subcutaneous nodule before the primary cutaneous lesion (H&E).

On an average follow up of 21.5 months three patients were alive and free of disease; one patient (Case 3) with brain metastasis died of disease 32 months after presentation.

DISCUSSION

In this study we describe the clinicopathological features of completely regressed cutaneous melanoma (CRCM) manifesting as tumoural melanosis (TM) in four patients. This phenomenon is rare, with an identified frequency of 0.07% amongst all cutaneous melanoma cases reported over a 10-year period in our institution. The lesions presented in middle aged to older adults and involved a wide range of anatomical sites including head and neck, trunk and extremities. Cutaneous hyperpigmentation was observed at the site of the skin lesions in all patients. The main histological finding was expansile aggregates of melanophages, with absence of malignant melanocytes upon complete excision and microscopic as well as immunohistochemical examination of the entire primary cutaneous lesions. Interestingly, there was a significant reduction or complete absence of melanocytes in the epidermis overlying the skin lesions. All cases showed evidence of concurrent metastatic melanoma, confirmed by the presence of viable malignant melanoma cells, often with concurrent necrosis and melanosis, in the regional lymph nodes or brain.

The concept of CRCM manifesting as TM was introduced by Dasgupta and colleagues in 1963.[8] They reported two cases of metastatic melanoma to lymph nodes with an unknown primary, in which further investigation revealed regional pigmented skin lesions showing fibrosis and TM on histological examination. Later, Smith and Stehlin reported some additional cases and established a list of diagnostic criteria.[6] Despite characterisation of the clinical and histological features of this phenomenon, accurate identification of cases remains challenging. While not included in the Smith and Stehlin criteria, we advocate the use of immunohistochemistry with melanocytic markers such as Melan-A and SOX10 to confirm the absence of melanoma cells in putative cases of CRCM. The latter exercise is helpful to avoid missing small clusters or individual melanoma cells, which can be camouflaged within aggregates of melanophages.

A case series of CRCM by High *et al.* included four cases of their own, with an additional thirty four cases previously reported in the literature.[9] In this study the patients showed a male predominance, with a ratio of approximately 2:1, and an average age of 48 years. The lesions ranged from 4 mm to 30 mm in maximum diameter. The clinical appearances included hyper-pigmented or hypo-pigmented macules and papules to plaques. The majority of patients described an initial phase of clinical evolution with enlargement, friability and bleeding of the lesion followed by regressive alterations such as depigmentation, flattening and atrophy, occurring over 2 months to 14 years. Unifying histological findings included attenuation of the epidermis, decreased epidermal melanocytes, papillary dermal fibrosis, lymphocytic inflammatory infiltrate, telangiectasia and the presence of dermal melanophages of variable density.[9]

Regression in melanocytic neoplasms is mediated by an immunological host response manifesting as tumour infiltrating lymphocytes (TILs) which infiltrate and disrupt neoplastic cells. TILs comprise a heterogeneous population of lymphocytes including regulatory, cytotoxic, helper and

gamma/delta T-cells, natural killer cells and B cells.[10] The inflammatory infiltrate usually reduces over time as the targeted melanoma cells are gradually eliminated. Tumoural melanosis likely represents a partially effective immunological response following exposure of tumour antigens at the time of dissemination, resulting in complete destruction of the primary tumour. Neo-antigens expressed by melanoma cells, likely through activation of cell-mediated cytotoxicity of CD8+ lymphocytes, trigger a T-cell mediated apoptotic cell death.[11,12] It is notable that novel immunomodulatory agents act in a similar fashion, aiming to restore the cytotoxic function of T cells by blocking the interaction between the regulatory and cytotoxic T cells in tumour microenvironment, leading to eradication of neoplastic cells and regression.[13] In fact, TM and regressive alterations have recently been reported in patients with metastatic melanoma managed by administration of immunomodulatory drugs.[14–17] The latter therapies may induce a local tissue reaction which on histological examination is generally indistinguishable from spontaneous regression in CRCM. Identification of such prior treatment is paramount to separate spontaneously CRCM from the cases related to immunotherapy.

The prognostic significance of regression in primary melanoma is a subject of debate. The cumulative evidence suggests that complete or extensive regression involving more than 50–75% of lesional tissue is associated with an aggressive clinical course, often with concurrent metastatic disease.[18] While there are no clear guidelines, TM indicates a high probability of metastatic melanoma,[9,19] and in our view should be managed as potential CRCM, even though there are no identifiable melanoma cells in the lesion.[20] Patients presenting with TM should undergo a thorough clinical work up, including complete review of systems, comprehensive skin examination and radiological assessment, with ultrasound of regional lymph nodes and/or whole body PET scan.[21] Sentinel lymph node biopsy (SLNB) might also be considered.

The average time from the identification of a suspicious cutaneous lesion with complete regression to the development of regional nodal disease with a histological confirmation of melanoma can vary significantly. Therefore, even in the absence of detection of metastatic disease at presentation, ongoing clinical surveillance of patients with cutaneous TM is appropriate. Identifying metastases, including foci with viable tumour tissue for molecular testing for potentially targetable somatic mutations,[22] is of increasing importance for therapeutic purposes.[23]

Given the complete regression of the primary melanoma, it was only possible to test the metastatic deposits for somatic mutations. There were three cases with *NRAS* mutations/*BRAF* wild type, one of which also showed a concurrent *MET* mutation. The remaining patient was only tested for *BRAF* and showed a *BRAF pV600E* mutation. *BRAF* and *NRAS* mutations have been reported in approximately 35–50% and 10–25% of cutaneous melanomas, respectively;[24] to our knowledge there are no previous data pertaining to the mutation status of CRCM. It is interesting to observe a higher rate of *NRAS* compared to *BRAF* mutations in this series of CRCM. This raises the possibility that melanomas with *NRAS* mutation are more likely to undergo extensive spontaneous regression; however, the number of cases is too small to draw any conclusion. Previous data on metastatic melanoma of unknown primary have shown a *BRAF* mutation frequency of 49% (range 45–53%) and *NRAS* mutation frequency of 24% (range 14–32%),[25–28] similar to conventional cutaneous melanomas.

In one of our patients, remnants of a benign naevus were present adjacent to an area of TM. It seems likely that in this case the TM represents spontaneous regression in a melanoma which developed within a pre-existing naevus and it is postulated that the residual benign naevoid component lacked the tumour neoantigens which incited regression in the melanoma.

While TM is highly suggestive of a completely regressed melanoma, it is not pathognomonic. Other pigmented melanocytic and epithelial lesions including pigmented naevi, pigmented basal cell carcinoma, Bowen's disease, solar lentigo, seborrhoeic keratosis and post-inflammatory conditions have been rarely observed to induce TM.[29,30] However, the extent of melanosis is typically more limited in these cases and often a remnant of the regressing lesion is present on histological sections.

TM should also be distinguished from entities with a population of heavily pigmented melanocytes admixed with melanophages, such as pigmented epithelioid melanocytoma and pigment synthesising melanoma, in which there is an admixture of melanin-containing melanocytes often with a relatively enlarged and atypical nuclei as well as a variably dense component of melanophages and abundant extra cellular melanin pigment.[31] In such cases, immunohistochemistry for melanocytic markers such as Melan-A or SOX10 will identify the melanocytic component; however, the interpretation of staining can be difficult if brown chromogen is used, and we recommend utilising red chromogen for this purpose. Melanin bleach might also be of value in further assessment of cytological features of melanocytes which are obscured by dense melanin pigmentation.

In summary, this series adds four further cases of completely regressed primary cutaneous melanoma with tumoural melanosis, two of which showed concurrent nodal tumoural melanosis. We identified *NRAS* mutated/*BRAF* wild type tumours in three of four patients. TM likely represents a partially effective immunological response to melanoma, with local eradication of tumour cells in the skin and less effective systemic results. Awareness of this phenomenon is crucial for pathologists and clinicians, particularly in the era of efficacious systemic therapy for melanoma. All patients with TM should be managed as potential CRCM, with comprehensive physical examination, imaging work up and close follow up.

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