Pathology of malignant skin tumours

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Abstract

The incidence of malignant skin tumours has significantly increased in recent years. In addition to establishing a diagnosis, histopathological assessment of these tumours provide vital prognostic information that often inform decisions related to onward referral, optimal treatment and follow-up care. Using the example of the three most common skin (cancers basal cell carcinoma, squamous cell carcinoma and malignant melanoma), this review outlines how the contents of the histopathology report influence patient management. Recently, unravelling the molecular pathogenesis of some of these tumours has paved the way for development of novel molecular targeted therapies. This article will familiarize the reader with these developments and also improve their overall understanding of the role of pathology in a multidisciplinary team setting towards management of cancer patients.

Keywords Diagnosis; histopathology; management; prognosis; skin cancers

Introduction

The skin is the largest organ system and is composed of two broad layers. It is surfaced by the epidermis which not only provides mechanical protection but also contains melanocytes which produce melanin. By absorbing visible and ultraviolet light, melanin reduces radiation-induced DNA damage. The epidermis is supported by a thick layer of fibro-elastic stroma called the dermis containing blood vessels and adnexal structures such as hair follicles, sebaceous and sweat glands.

The incidence of all forms of skin cancer in the UK has increased over the last 30 years. Although a malignant tumour of the skin can arise from any of the constituent cell types, those arising from the cells populating the surface epidermis (i.e. keratinocytes and melanocytes) are most frequent. The most common malignant skin tumours in much of the Western world are basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and malignant melanoma.

In this review we shall outline the pathological characteristics of the three most common malignant skin tumours with particular emphasis on aspects which influence prognosis and management.

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Basal cell carcinoma

Clinical presentation

Basal cell carcinoma is the most common malignant tumour of the skin typically, but not exclusively arising on areas exposed to sunlight. The clinical appearance is variable but the most common presentation is that of a slow growing, red-skin coloured nodule with telangiectasia which frequently ulcerates. Some tumours present as an erythematous macule/patch or an indistinct, indurated, scar-like plaque.

Histopathology

BCC derives its name from the histological similarity to normal basal (basaloid) cells of the epidermis. In addition to the diagnosis, a pathology report of a BCC provides information which has direct implication on prognosis and management. This includes *histological sub-typing* based mainly on the growth pattern into 'low-risk' and 'high-risk' variants. These individual subtypes have distinctive clinical presentations (see below). Other histologic features of clinical relevance include tumour thickness, perineural and lymphovascular invasion, margin status and whether atypical squamous differentiation is present. BCCs rarely metastasize to regional lymph nodes – usually only after many years of growth and attaining considerable size.[1]

Low-risk BCC variants

- **Nodular BCC:** This most common subtype presents as a papulonodule clinically (Figure 1a) and is characterized by variably sized solid or cystic islands of basaloid cells. These tumour nests are bordered by a palisaded row of cells at the periphery ('picket fence' appearance). Tumour islands are often separated from the surrounding myxoid stroma by a cleft like space ('retraction artefact') (Figure 1b). In line with the primitive nature of the basaloid cells, the tumour cells tend to be small, hyperchromatic, contain very scant cytoplasm and show brisk apoptosis and mitotic activity.
- **Superficial BCC:** A superficial BCC presents as an erythematous plaque with a subtle raised edge appreciated by stretching the skin (Figure 2a). Scale-crust is not a prominent feature. Histologically it comprises multiple, superficial, bud-like down growths of basaloid tumour cells arising from the under surface of the epidermis. The dermis between the superficial tumour lobules show increased vascularity and fibrosis (Figure 2b). It is sometimes difficult to pinpoint the peripheral extent of a superficial BCC histologically due to an apparently multifocal growth pattern and this explains the high local recurrence rate associated with this subtype.

High-risk BCC variants

- **Infiltrative/morphoeic BCC:** This subtype typically presents as a scar like area of induration (Figure 3a). Microscopically, infiltrative BCC shows thin, infiltrative, linear strands of basaloid cells which lack the circumscription of the low-risk subtypes (Figure 3b). Some infiltrative BCCs showing prominent sclerotic stroma with fibroblastic proliferation are often referred to as the morphoeic type. Perineural, lymphovascular invasion and local recurrences are common.

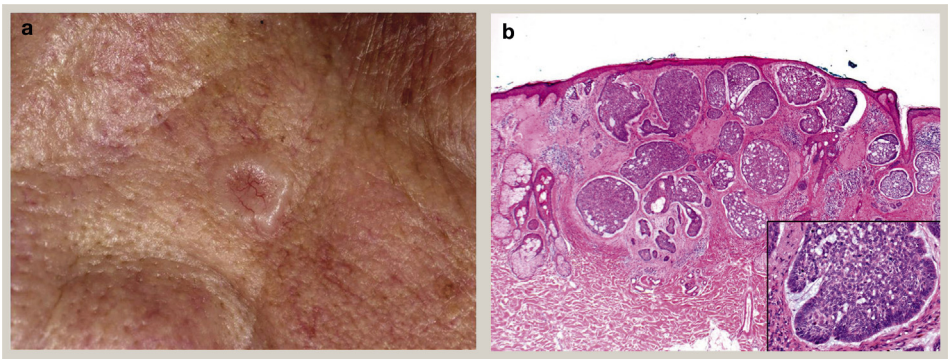

Figure 1 Nodular BCC. (**a**) Pale nodule with raised, rolled borders and telangiectasia. (**b**) Circumscribed tumour composed of multiple nodular aggregates of basaloid cells extending into the dermis. Peripheral palisading of the tumour cells and stromal retraction spaces are seen on higher magnification (inset).

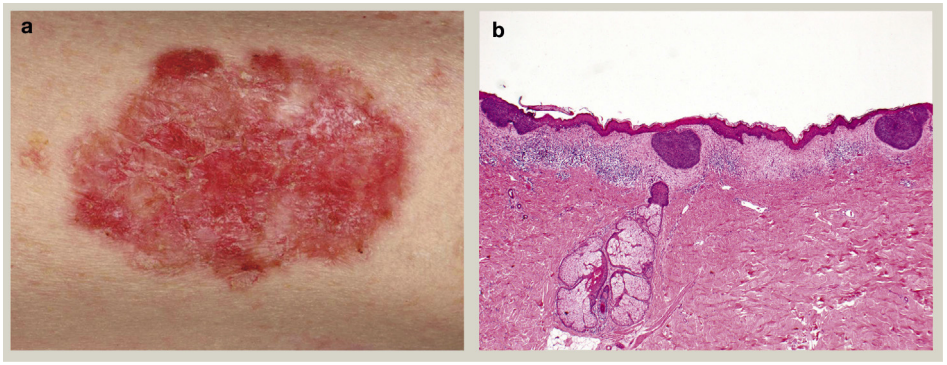

Figure 2 Superficial BCC. (**a**) Well-defined slightly raised erythematous plaque with adherent scale. (**b**) Three discrete nests of basaloid tumour cells adherent to the epidermal undersurface.

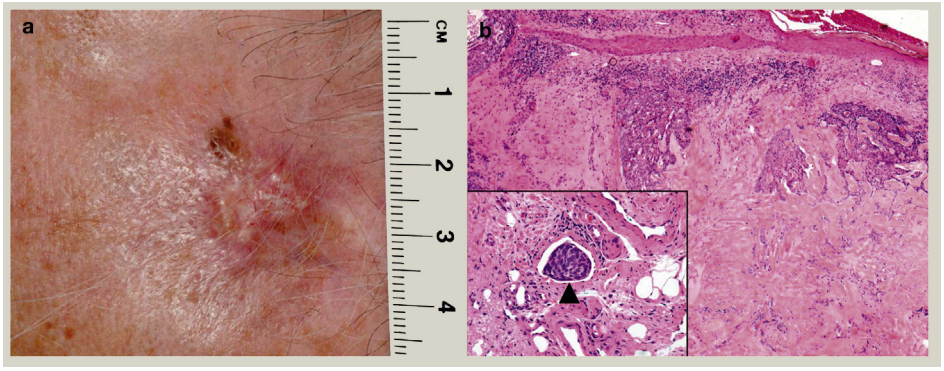

Figure 3 Infiltrative BCC. (**a**) Poorly defined pale indurated plaque with scar-like areas. (**b**) Infiltrative tumour composed of irregular strands of epithelial cells amidst sclerotic stroma. The inset shows a focus of lymphovascular invasion seen towards the periphery.

- **Micronodular BCC:** The micronodular variant resembles nodular BCC, but has much smaller tumour nodules (<0.15 mm in diameter) and is less circumscribed. These micronodules infiltrate widely into the dermis and often extend into the subcutaneous fat.

Summary of pathology related management issues[2]

- *High-risk* histological subtypes (infiltrative/morphoeic, micronodular), histological features of aggression (perineural and/or vascular invasion) and involved/close surgical margins are associated with a higher risk of recurrence and usually require excision with *wider surgical margins*, *Moh's micrographic surgery* and/or *radiotherapy*.
- *Low-risk* histological subtypes without adverse histological features can be treated using *surgical destructive techniques* like curettage and cautery, cryosurgery and carbon dioxide laser ablation.

- *Small superficial BCCs* can be effectively treated non-surgically with topical immunotherapy using *imiquimod* or by *photodynamic therapy*.

Squamous cell carcinoma

Clinical presentation

Squamous cell carcinoma is the second most common skin cancer presenting as a rapidly growing indurated nodule, or non-healing ulcer in sun-exposed skin (Figure 4a). The anatomical location influences prognosis with tumours arising on the ear, hair-bearing lip and non-sun-exposed sites associated with poor outcome.

Histopathology

Being a malignant tumour arising from keratinizing cells of the epidermis, a SCC shows nests of malignant epithelial cells with variable keratin production which invade into the dermis or deeper structures (Figure 4b). Some of the prognostic determinants which a SCC histopathology report routinely provides include:

Grade: the degree of keratinization and the severity of the cytological changes form the basis of tumour grading (degree of differentiation) in a SCC. Accordingly the tumour is categorized as *well, moderate or poorly differentiated* based on the area showing the poorest differentiation. A well-differentiated tumour has cells which show easily recognizable keratin production, resemblance to normal keratinocytes and the degree of atypia is mild. In contrast, a poorly differentiated tumour may not be recognizable as an SCC at all due to the lack of keratinization and often requires ancillary tests like immunohistochemistry to establish the diagnosis. Poor differentiation is an indication for upstaging a tumour in some of the pathological staging schemes.

Histological subtype: the following three SCC subtypes are known to be associated with an increased risk of local recurrence and distant metastasis justifying their inclusion under the 'high-risk variant' category. Unfortunately they cannot be distinguished from standard SCC on clinical grounds.

- *Acantholytic SCC* has a distinctive histological appearance that result from a loss of cohesion (acantholysis) between tumour cells.
- *Desmoplastic SCC* is characterized by cords and trabeculae of oval to spindle shaped epithelial cells that infiltrate a desmoplastic stroma. Perineural invasion is frequently seen.
- *Spindle cell SCC* is a rare variant with deceptively bland spindle tumour cells and prominent, reactive stroma which can be histologically mistaken for a benign lesion such as a scar.

In addition to the above aggressive histological subtypes, SCCs arising in conjunction with squamous cell carcinoma in-situ (SCCIS) or immunosuppression are associated with a poor prognosis. Most authorities currently regard keratoacanthoma as a variant of well differentiated SCC with a propensity for spontaneous self-healing.

As in BCC, tumour attributes like thickness, diameter, anatomical level of invasion, perineural and lymphovascular invasion and margin status affect clinical behaviour and are routinely recorded in a histopathology report of cutaneous SCC.[3]

Summary of pathology related management issues[4]

- Well-differentiated tumours up to 4 mm in thickness and 20 mm in diameter (*low-risk tumours*) can be adequately treated by excision with a *surgical margin of 4 mm* provided they do not have any site or immunological status related adverse clinical features. These patients do not generally require routine follow-up after surgery.
- Moderate to poorly differentiated tumours, tumours >4 mm thickness and >20 mm diameter, aggressive histological subtypes (acantholytic, desmoplastic, spindle), tumours arising from SCCIS, tumours with perineural and/or lymphovascular invasion (*high-risk tumours*) usually require a *wider margin of 6 mm or more* for adequate surgical clearance. *Mohs' micrographic surgery* could be considered for such tumours especially where wide surgical margins are difficult to achieve without significant cosmetic or functional impairment.
- *Fine needle aspiration cytology and/or lymph node biopsies* should be considered in patients presenting with *enlarged regional lymph nodes.* Histologically proven node positive SCC is usually managed by regional lymph node dissection. The role of sentinel lymph node biopsy in management of high risk SCCs is yet to be determined.[5]

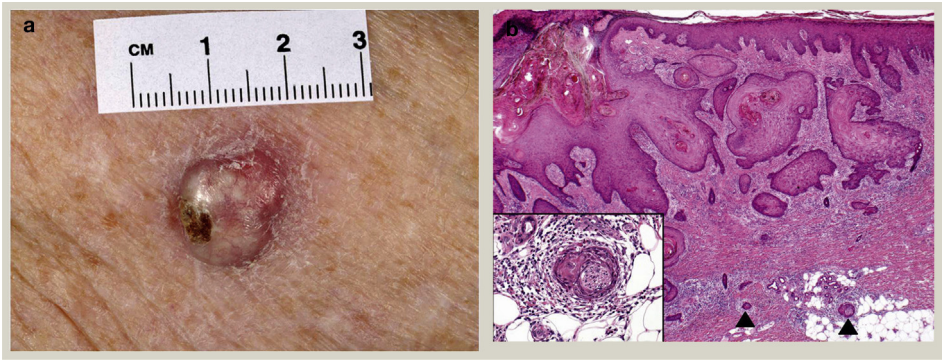

Figure 4 SCC. (**a**) Well-defined pale indurated nodule with eroded areas. (**b**) Well-differentiated SCC typically showing an invasive tumour with prominent keratin production and two areas of perineural invasion at its periphery (arrow-heads and inset).

Malignant melanoma

Clinical presentation

Melanomas generally present as **A**symmetrical, irregularly **B**ordered, pigmented lesions with **C**olour variegation usually measuring 6 mm or more in **D**iameter (Figure 5a). Recent changes in the appearance of a pre-existing mole such as enlargement, itching, pain and bleeding or development of a new pigmented lesion during adulthood are useful clinical warning signs. In melanoma, the distribution of lesion, rather than the histological appearance is related to the subtype and is discussed further in the following section.

Although most melanomas develop de novo, some 10–15% of tumours arise in a familial setting (dysplastic naevus syndrome). Importantly, if suspected these patients should be referred to genetics for further investigation. As with other skin cancers, ultraviolet radiation plays an important role in its pathogenesis. Other risk factors that have been linked with melanomas include skin colour, tendency to burn and tan poorly, large number of freckles (indicating previous excess solar exposure) and naevi, and immunosuppression amongst others.

Histopathology

Histologically, a malignant melanoma is characterized by proliferation of melanocytes initially within the epidermis and demonstrating horizontal spread *(radial growth phase)*. The tumour is either purely intra-epidermal (malignant melanoma in situ) or shows limited invasion into the upper dermis (microinvasion). This is followed by a mitotically active/expansile invasive growth phase whereby the tumour invades vertically into the dermis *(vertical growth phase)* (Figure 5b). Radial growth phase tumours have survival rates approaching 100%. Progression to the vertical growth phase heralds the emergence of a clonal population of cells which are capable of metastasis. The anatomical level of invasion is conventionally expressed in Clark levels (level I: intra-epidermal, level II/III: papillary dermis, IV: reticular dermis; V: fat).[6]

Histological subtypes

Malignant melanomas have been traditionally divided into the following four subtypes. Although the prognostic significance of these subtypes is debatable, they continue to be used since individual subtypes have good clinicopathological concordance.

- *Lentigo maligna melanoma* develops on the face and other sun-exposed areas of elderly people. Microscopically, there is invasive melanoma arising in conjunction with a proliferation of atypical melanocytes along the basal layer of the epidermis (a precursor lesion commonly referred to as lentigo maligna).
- *Superficial spreading melanoma* can involve any part of the body but most commonly affects the back of men and lower extremities of women. Microscopically, this subtype is characterized by upward migration of atypical melanocytes across all levels of the epidermis (pagetoid spread).
- *Nodular melanoma* presents as a nodule or polypoid ulcerated mass often lacking the clinically useful clues for malignancy like asymmetry, border irregularity or colour variegation. Microscopically the lesion comprises a solitary expansile nodule of malignant melanocytes with no adjacent intraepidermal component of atypical melanocytic proliferation.
- *Acral lentiginous melanoma* is the most common subtype in blacks and Asians, presenting as pigmented plaques or nodules on the palmar, plantar and subungual skin. Histologically, this variant often shows prominent epidermal hyperplasia, contiguous proliferation of atypical melanocytes in the epidermis with pagetoid spread and often a spindle cell morphology of the invasive component.

One histological subtype which has a distinct survival advantage is desmoplastic malignant melanoma. This unusual variant often presents as a vague amelanotic plaque and can be equally difficult to diagnose histologically because of its superficial resemblance to a scar. Pure desmoplastic melanoma has a better prognosis than other subtypes and has a very low risk of lymph node metastasis, albeit with a significant tendency for local recurrence.

Like other malignant tumours of the skin, several elements of a melanoma histopathology report play a crucial role in patient management through determining the necessary tumour (T) stage. The TNM staging system of malignant melanoma currently used worldwide is the 7th edition American Joint Committee on Cancer (AJCC) staging (Table 1).[7] Tumour thickness, ulceration and mitotic index are the three cardinal histologic variables which determine the T stage in the AJCC staging system (Figure 5c).

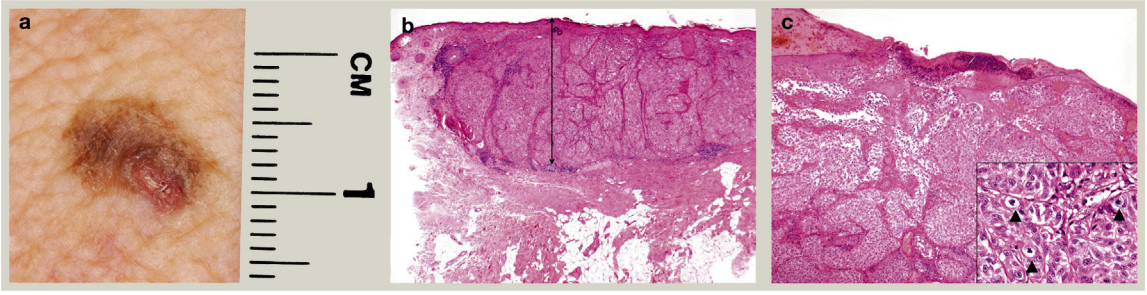

Figure 5 Malignant melanoma. (**a**) A flat asymmetrical, irregular, variegated pigmented lesion of lentigo maligna which had recently developed nodularity heralding progression to invasive tumour (lentigo maligna melanoma). (**b**) A biopsy confirms the diagnosis of a vertical growth phase lentigo maligna melanoma with a Breslow thickness of 1.8 mm (plane of measurement indicated by the vertical line). Areas of malignant melanoma in situ can be seen towards the left. (**c**) Microscopy of an example of nodular melanoma showing the two other staging determinants – ulceration and mitotic activity (arrow-heads in inset).

Breslow thickness

Tumour thickness (Breslow thickness) is the single most important independent prognostic factor in malignant melanoma. This is normally assessed microscopically by measuring in millimetres the distance between the surface of the granular layer of the overlying epidermis (or the ulcer in an ulcerated tumour) to the deepest tumour cells in the dermis. The current AJCC system uses 1, 2 and 4 mm as the numeric breakpoints for tumour (T) staging purpose. Often the terms thin, intermediate thickness and thick melanoma are used to denote tumours <1 mm, 1–4 mm and >4 mm in thickness.

TNM staging of cutaneous malignant melanoma (AJCC 7th edition)

Stage	Descriptor	
Primary tumour (T)	**Breslow thickness (mm)**	**Ulceration status/mitoses**
T1	≤1.0	a. Without ulceration and mitosis <1/mm^2 b. With ulceration or mitoses ≥1/mm^2.
T2	1.01–2.0	a. Without ulceration b. With ulceration
T3	2.01–4.0	a. Without ulceration b. With ulceration
T4	>4.0	a. Without ulceration b. With ulceration
Nodes (N)	**Number of positive nodes**	**Nodal metastatic burden**
N1	1	a. Micrometastasis[a] b. Macrometastasis[b]
N2	2–3	a. Micrometastasis[a] b. Macrometastasis[b] c. In-transit metastasis/satellites without metastatic nodes
N3	4 or more	In-transit metastasis/satellites with metastatic nodes
Distant metastasis (M)	**Site**	**Serum lactate dehydrogenase (LDH)**
M1a	Distant skin, subcutaneous or nodal metastasis	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastasis	Normal
	Any distant metastasis	Elevated

[a] Micrometastases are diagnosed on sentinel lymph node biopsy. They occur in the setting of no clinical abnormality.
[b] Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.

Table 1

The relationship between Breslow thickness and survival is not absolute. On rare occasions, thin melanomas develop metastases and likewise thick melanomas appear to be a biologically heterogeneous group with varying survival rates.

Ulceration

Ulceration of the tumour surface is an independent negative prognostic factor for clinically localized primary cutaneous melanoma and forms a key part of the T staging.

Mitotic index

Mitotic index has been found to be more useful than ulceration as an independent prognostic parameter particularly in thin melanomas. Like ulceration, presence of mitotic activity in the dermal component characterizes a pT1b tumour.

In addition to Breslow thickness, ulceration and mitotic index which are key determinants for tumour staging, several other histological features are routinely recorded in the pathology report. This includes regression, tumour infiltrating lymphocytes, Clark level, growth phase, microscopic satellites, cytomorphology of the tumour cells and lymphovacular/perineural infiltration.

Sentinel lymph node biopsy

Sentinel lymph node biopsy (SLNB) was developed as a means of identifying the first lymph node draining the site harbouring the melanoma. SLNB provides important prognostic information with minimal morbidity and helps in identifying a subset of clinically node negative patients who might benefit from immediate completion lymphadenectomy. Whether the technique improves survival in melanoma has been a matter of intense debate in the past although latest studies seem to indicate that SLNB does prolong disease free survival in melanoma patients.[8] Pathological handling of SLNB specimens vary between centres but generally involve study of multiple sections and use of immunohistochemistry (Figure 6). Indications for SLNB include a Breslow thickness >1 mm although the procedure is increasingly offered to patients with thinner tumours which show dermal mitoses.

Molecular pathology of melanoma and clinical applications

In recent years, there has been a significant improvement in our understanding of the molecular pathways critical to the development of malignant melanoma. Additionally it is being increasingly recognized that melanomas arising in different anatomical sites tend to have different mutational abnormalities. The high frequency of BRAF mutations in melanomas arising from skin without chronic sun exposure (up to 60% of all melanomas) and KIT mutations in acral melanomas are examples of this phenomenon. It is speculated that this knowledge may lead to a biologically relevant molecular classification system of melanoma in the future.[9]

Such advances have also paved the way towards development of novel molecular targeted therapies – small molecule kinase and immune checkpoint inhibitors, which are used as monotherapy or increasingly in combination. Vemurafenib, is used to treat patients with BRAF ^{V600E} mutation positive, unresectable or metastatic melanomas with great success compared with conventional chemotherapy. Similarly imatinib, a tyrosine kinase inhibitor has the potential for use in treatment of acral

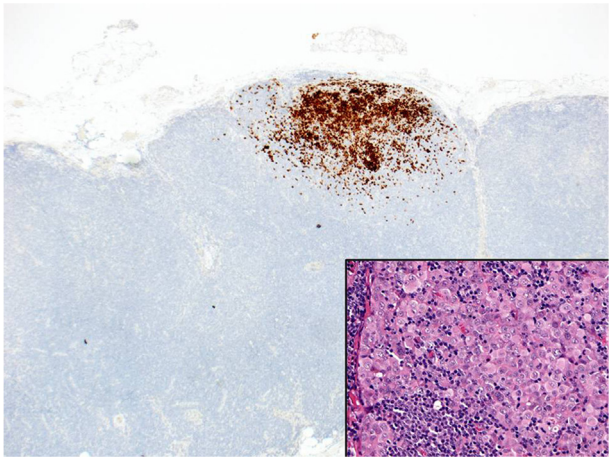

Figure 6 Sentinel lymph node biopsy. A specimen processed using standard protocol shows subcapsular and parenchymal deposits of metastatic melanoma cells on melan A (melanocyte marker) immunohistochemical staining. High power view of the corresponding field on haematoxylin eosin stained sections show cytological features of malignant melanoma (inset).

melanomas which often have KIT mutations.[10] These advances have extended the role of pathologists in assessment of melanomas and increasingly more laboratories are offering validated mutation analysis services to facilitate implementation of such novel therapeutic options.[11]

These novel targeted therapies commonly result in adverse cutaneous reactions such as morbilliform rashes and severe photosensitivity.[12] Uniquely the BRAF inhibitors can additionally result in the development of *de novo* squamoproliferative and melanocytic lesions. The squamoproliferative lesions vary in complexity from actinic keratoses, to keratoacanthomas, to squamous cell carcinomas. The melanocytic lesions may be new eruptive naevi, morphologic changes to existing naevi or rarely new primary melanomas. De novo cutaneous malignancies arising during therapy are graded and staged as described previously. In the setting of a new melanoma, mutation analysis in contrast to the original lesion is commonly BRAF ^{V600E} negative.

Summary of pathology related management issues

- The three histological features used to determine the *tumour (T) stage* in the current AJCC staging system are: *Breslow thickness, ulceration* and *mitotic index* (see table).
- Surgery is the only curative treatment for primary cutaneous melanomas. The lateral *surgical margin* is influenced by *Breslow thickness* in the following way:

Breslow thickness	Recommended excision margin
Up to 1 mm	1 cm
1.01–2 mm	1–2 cm
2.01–4 mm	2–3 cm
>4 mm	3 cm

- A *stage IB and upwards* tumour in clinically node negative patient is an indication for a *sentinel lymph node biopsy*.
- A *positive sentinel lymph node* biopsy result prompts consideration for *completion lymphadenectomy*. *Extracapsular spread* in positive lymph nodes is an indication for *adjuvant chemotherapy/radiotherapy*.
- *Novel molecular targeted therapies* based on *mutation analysis* are being increasingly used to treat patients with advanced melanomas.

Conclusion

Malignant tumours of the skin are common and their incidence is on the rise. Histopathology reports are meant not only to establish an accurate tissue diagnosis but also convey vital prognostic information about the tumour on which further management is based. It is important that clinicians who are involved in the management of such patients understand the significance of such information and recognize which tumours are likely to have a poor prognosis. It is hoped that an awareness of the clinicopathological issues related to the three common tumours discussed in this review will facilitate understanding the basis of a multidisciplinary team approach to management of malignant skin tumours in general. ◆

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