Pathological diagnosis of melanocytic tumours: clues and pitfalls
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In Australia and many other countries, melanoma is a major public health problem particularly in those individuals of Celtic ancestry. Other races are not immune, especially when acral and mucosal sites are taken into account. Accurate diagnosis requires the balancing of clinical data (including patient age and sex, family history, the anatomic site of the lesion, the history of the lesion and other factors such as a history of trauma, sunburn or pregnancy), histological features (including architecture, cytology and the host response), awareness of pitfalls and judgment. Several types of naevi are prone to be misdiagnosed as melanoma such as regenerating naevi, combined naevi, acral naevi, deep penetrating naevi and Spitz naevi. Melanomas often underdiagnosed include naevoid melanomas, desmoplastic melanomas, Spitzoid melanomas and regressed melanomas. The type of biopsy and suboptimal processing may also significantly influence the diagnosis.

PATHOLOGICAL DIAGNOSIS
Accurate pathological diagnosis of melanocytic tumours requires a suitable biopsy, assessment of many histological criteria, an awareness of potential pitfalls, relevant experience and, in difficult cases, judicious consultation1-5. Correlation of a range of basic morphological and clinical features is necessary because many of the individual features are shared by both naevi and melanomas. In the future, molecular and genetic studies may be useful adjuncts for an accurate diagnosis, particularly for difficult lesion for which it is not possible to be certain from its histological features whether the lesion is benign or malignant6 7 8.

Morphological features of importance (Table 1):
Architectural:
Good symmetry is often associated with benign behaviour.
Poor symmetry and irregular margins are more often found in dysplastic, traumatised and malignant melanocytic tumours.
Ulceration, vascular invasion, neurotropism and satellites are also more frequent in melanomas but can also occasionally occur in naevi. Minor perineural invasion may be found in all types of benign naevi so is not very helpful when diagnosing melanocytic tumours.
Pagetoid epidermal invasion is very common and not usually significant in acral lesions, regenerating naevi (“pseudomelanoma”) or “irritated” naevi (trauma, sunburn etc.) 5 9.
Cytological:
Cytological features may be deceptive especially in naevoid melanomas with small cells and uniform cytology, deep penetrating naevi with nuclear pleomorphism and regenerating naevi with epithelioid cells. Nucleoli when irregular or frequent (average > 2 nucleus) usually indicate dysplasia or malignancy. Mitoses when abnormal, frequent (>2/mm²) or deep in the lesion are always of concern and should be regarded as being of at least ‘uncertain malignant potential’ especially when occurring in post pubertal patients.

Host response:
This is usually cellular and/or stromal. Cellular: Regressing tumours, benign or malignant, are usually infiltrated, at least initially, by lymphocytes. Scattered foci of lymphocytes are a common feature in desmoplastic melanoma. Benign naevi and some aggressive epithelioid melanomas lack a cellular response. Stromal: Periretal lamellar collagen is common in dysplastic naevi and may be very thick in severe forms. Fibrosis is variable in desmoplastic melanoma. Pure forms (100% desmoplastic) appear to have a better prognosis and less frequent nodal metastases 10.

Table 1: Morphological Features of Melanoma
Architectural
- Asymmetry
- Irregular margins
- Ulceration
- Vascular invasion
- Microsatellites
- Pagetoid epidermal invasion
Cytological
- Nucleoli (especially if irregular and multiple)
- Deep or frequent mitoses
- Poor maturation
Host response
- Lymphocytic infiltrate
- Stromal fibrosis (especially in desmoplastic melanoma)
- Regression

Clinical features of importance:
Age: Melanomas are uncommon in children just as Spitz naevi are rare in middle and older age groups. Vulval melanoma is rare below the age of 40 years.

Sex: Melanomas with Spitzoid features appear to be more common in young males but the reverse is probably true after 35.11 Females have a better prognosis than male melanoma patients.

Family history: Melanomas are common in some families and first degree relatives.
Site: Sun-exposed areas are more likely to develop naevi and melanomas in Caucasian patients. Desmoplastic melanomas most commonly involve the head and neck region and are frequently associated with lentigo maligna. They may be subtle clinically and histologically and hence may not be diagnosed until they are at an advanced clinical stage.

History of lesion: A lesion of long duration which has changed in size or color, become itchy, or bled easily should always be investigated. Any trauma, previous biopsy, sunburn or topical agent may induce regenerative features that simulate malignancy.

Pregnancy: May induce frequent mitoses in otherwise banal naevi.

THE BIOPSY
An excisional biopsy is preferred wherever possible. Lesser specimens (punch, shave, curettings) may be distorted and may not permit adequate assessment of the vital parameters needed by the clinician for definitive treatment e.g. Breslow thickness, mitotic rate. Smaller specimens may also not be representative of the lesion and usually lack the edges and bases of the lesions needed to assist diagnostic interpretation. In the subsequent excision specimen it may be impossible to allocate atypical features – cellular pleomorphism, mitoses and epidermal invasion to either malignancy or regeneration. A recent study highlighted that histopathological misdiagnosis is more common for melanomas that have been assessed with punch and shave biopsy than with excision biopsy. Adverse outcomes due to misdiagnosis were more commonly associated with punch biopsy than with shave and excision biopsy (odds ratio 16.6, p<0.001). The use of punch and shave biopsy also leads to increased microstaging inaccuracy. It is often difficult to separate traumatic fibrosis from regression fibrosis. The latter is more often associated with epidermal atrophy whereas post-traumatic fibrosis in compound naevi often has some overlying variable epidermal thickening.

NAEVI PRONE TO MISDIAGNOSIS (Table 2)

Table 2: Naevi Prone to Misdiagnosis

- Regenerating nevus
- “Irritated” naevus
- Post-excisional junctional hyperplasia
- Cellular/hyperplastic nodule in congenital naevus
- Combined naevus
- Ancient naevus
- Spitz naevus
- Dysplastic naevus
- Naevus in pregnancy
- Genital naevus

- Blue naevi
  - Dendritic
  - Cellular
  - Deep penetrating
  - Epithelioid
- Acral naevi
  - Balloon and Clear cell naevi
- Neurotized naevus
- Desmoplastic naevus
- Halo naevus
Regenerating Naevi. Naevi often regenerate after incomplete removal (punch, shave, curette, incision, other trauma). Some naevi, especially compound melanocytic naevi of small congenital type and dysplastic compound naevi, display features often associated with melanoma and are sometimes termed “pseudomelanoma”. These features include Pagetoid spread of melanocytes, cytological atypia, dermal mitoses and HMB45 positivity.\(^{14}\)

Post-excisional junctional melanocytic hyperplasia at the edge of an excision scar may show some atypia and a tendency to epidermal invasion suggestive of in situ malignancy.

“Irritated” melanocytic naevi may show epidermal invasion but the offending melanocytes tend to have small nuclei. Causes of irritation may be physical e.g. rubbing or scratching, topical agents or strong sunburn.

Dysplastic naevi have variable lentiginous hyperplasia, periretal lamellar collagen, architectural disorder and cytological atypia. The cytological atypia may be mild, moderate or severe. Severe atypia or moderate atypia associated with irritative or Spitzoid changes may readily be mistaken for malignancy. The vast majority of dysplastic naevi (the commonest naevi in Caucasians) with mild to moderate cytological atypia are stable or grow very slowly and rarely progress to malignancy. Dysplastic naevi are regarded as intermediate lesions of tumour progression between naevi and melanoma. They show S-phase ploidy and intermediate levels of genetic unstability.

Cellular/hyperplastic nodules in congenital naevi may have mitoses but they are not abnormal. The nodules usually have pushing margins and merge with the adjacent banal component of the naevus.

Naevi in pregnancy. Dermal and compound naevi of small congenital type in pregnancy may show increased numbers of normal-looking mitoses in the otherwise banal dermal nevomelanocytes and appear to be without clinical significance.

Combined naevi are often mistaken clinically and histologically for melanoma because of their biclonal (occasionally triclonal) nature and variability or change in color or shape.\(^{15}\)\(^{16}\) Frequent problems are combinations of common naevus (common acquired, congenital or dysplastic) associated with pigmented blue naevus (common blue, cellular blue or deep penetrating) or Spitz naevus (conventional, regressing or desmoplastic)\(^{16}\). The blue naevus or Spitz naevus component may dominate the lesion and show an occasional mitosis. So-called “ancient naevi” may represent a combined naevus with a regressing or degenerating Spitzoid component.

Blue naevi variants cause special problems. “Dendritic” blue naevi and sclerosing cellular blue naevi may have an infiltrative pattern similar to desmoplastic melanomas but the latter often have some junctional change, are almost invariably non-pigmented and are negative with HMB45.\(^{17}\)
Deep penetrating naevi frequently show moderate nuclear pleomorphism, abut nerves and have an occasional dermal mitosis. Rare cases, either large or with scattered mitoses, may involve a regional or sentinel lymph node. Whether this is a “benign metastasis” or an indication of future malignant progression is controversial.\textsuperscript{17}

**Epithelioid blue naevi** (as in Carney’s syndrome) and other so-called “pigmented epithelioid melanocytomas” are also low grade melanocytic tumours that apparently frequently involve regional lymph nodes yet paradoxically appear to have a favourable prognosis\textsuperscript{18} and should probably be regarded as being of uncertain malignant potential especially those in children and young adults and when associated with pseudoepitheliomatous hyperplasia.

**Balloon and clear cell naevi** may be confused with their malignant counterparts. The naevi usually have bland nuclei and lack mitoses.

**Neurotised and desmoplastic common naevi** can be confused with desmoplastic melanoma especially of “pure type”. The naevi, however, lack atypical junctional changes, dermal mitoses and scattered clusters of lymphocytes.

‘**Halo’ or regressing naevi** may present with alarming color change, with a “darkening” centre and pale periphery, especially in children. Most of these atypical compound naevi have a dermal component of smaller darker nevomelanocytes disrupted by lymphocytes, a feature suggestive of early regression. An occasional dermal mitosis does not indicate malignancy. Though most frequent in children, they also occur in middle and old age groups.

**Acral naevi and genital naevi** resemble dysplastic naevi elsewhere in the skin. Focal Pagetoid epidermal invasion, especially in the acral naevi is alone not an indication of malignancy. See also Tables 3 and 4.

**Table 3: Naevi of Acral Skin: Histopathological Features Which Can Cause Concern**
- Suprabasilar melanocytes (“Pagetoid spread”) (30-79%)
- Atypical size, shape, location of junctional nests
- A subset (acral lentiginous naevi) show
  - Predominantly lentiginous growth
  - Poor circumscription
  - Asymmetry
- Small biopsies

**Table 4: Acral Naevi v Acral Melanoma: Features favouring melanoma**
- Severe cytological atypia
- Lymphocytes abutting junctional zone
- Marked architectural disorder
- Increased density of melanocytes
- Excessive Pagetoid spread
• Poor maturation
• Expansile growth
• Dermal mitoses and lymphocytes

Spitz naevus and Spitzoid tumours are a common problem and share many of the histological features of melanoma (Table 5)\(^6\)\(^11\)\(^19\). Those with atypical features cause most concern and many are of uncertain biological behavior (Table 6)\(^20\).

Table 5: Features of Spitz Naevi
- Diameter usually < 6mm
- Symmetrical
- Diffuse epidermal hyperplasia
- Hypergranulosis
- Terminal nests
- Uniformity of cells and nests across lesion
- Kamino bodies
- Subepidermal clefts
- Telangiectatic vessels
- Nested & single cell
- Pagetoid spread
- “Maturation” and often merging with dermal collagen
- Spindle/epithelioid cells
- Mitotic figures \(\leq 2/\text{mm}^2\)
- Absent deep or abnormal mitoses

Table 6: Atypical Features for Spitz Naevus
- Diameter >10mm
- Asymmetry
- Ulceration
- Lack of maturation
- Deep extension
- Expansile dermal nests
- Epidermal thinning
- Long thin rete ridges
- Peripheral Pagetoid epidermal invasion
- Sparse Kamino bodies (children)
- Marked cytological atypia
- Irregular or multiple nucleoli
- Dermal mitoses >2/mm\(^2\)
- Deep mitoses
- Abnormal mitoses

An Approach to Atypical Cases.
- Complete excision is probably mandatory
- Avoid overdiagnosis to avoid excessive treatment and possible medico-legal action.
- Give a preferred diagnosis acknowledging the degree of uncertainty.
- Seek further opinions.

The safest course may be to manage the lesion as a melanoma\(^21\). However, wide local excision may not be appropriate if there is likely to be unacceptable cosmetic disfigurement and any co-morbidity.\(^13\)\(^22\) When there is uncertainty about whether a melanocytic tumour is benign or malignant the pathologist should document in their report the thickness of the tumour (and other important features of the tumour such as its mitotic rate and ulcerative state). This information may be utilised by the clinician to manage the patient as for a melanoma of equivalent thickness (and other prognostic parameters) if this is deemed appropriate.

**MELANOMAS PRONE TO CAUSE DIAGNOSTIC PROBLEMS** (Table 7)
Table 7: Melanomas Prone to Cause Diagnostic Problems

- Naevoid melanoma
- Spitzoid melanoma
- Desmoplastic melanoma
- Regressed melanoma

Naevoid melanomas mimic a benign naevus. Small and intermediate cell types are sometimes called “minimal deviation melanoma” (or “Lawyer’s melanoma” because they may not be diagnosed until after they have metastasized and medicolegal action may follow). Large and spindle cell types are called Spitzoid or Spitz naevus-like melanoma. A probable indolent variant resembling a dermal naevus develops on the lower limb of elderly females.

Recognition of naevoid melanomas of smaller cell types requires a high index of suspicion and recognition of subtle architectural and cytological features. Architectural features are basic symmetry, good circumscription in a nodular or verrucous pattern lacking any significant radial growth phase or epidermal invasion. Long thin rete ridges, expansile or sheet-like growth and “pseudomaturation” are common. Subtle cytological atypia is present throughout though mitoses may be sparse and only superficial. HMB45 and Ki67 staining may be helpful in some cases.

Desmoplastic melanoma.
Desmoplastic melanomas may be difficult to detect clinically as they are usually non-pigmented and may resemble a scar, a dermatofibroma, a basal cell carcinoma or a poorly healing pyogenic granuloma. Histologically they may be confused with immature scars (which may also have S-100 positive spindle cells and foci of lymphocytes), desmoplastic naevi (usually symmetrical lacking atypia, mitoses and lymphocytic foci); desmoplastic Spitz naevi (plump cells and associated epidermal thickening); sclerosing cellular blue naevus (usually HMB45 positive and have foci of melanin pigment); dermatofibroma (tapering storiform margins, epidermal thickening, absent lymphocytes) and with some soft tissue spindle cell sarcomas. Desmoplastic melanomas also often show an associated atypical junctional component (lentigo maligna / Hutchinson’s melanotic freckle) and neurotropism. Most are HMB45 and Melan A (MART-1) negative. “Pure” forms (spindle cells only) probably have a better prognosis and less frequently involve regional lymph nodes than other melanomas.

Regressed melanoma.
If the lesion is on the back or posterior shoulder a history of a previous lesion may be unavailable. Key features are:

1. Epidermal thinning with loss of rete ridges.
2. Minimal or absent atypical junctional change.
3. A subepidermal band of angiofibroplasia (often up to 0.8mm thick) which may variably contain a few lymphocytes, melanophages and an occasional melanocyte. Capillaries are usually slightly increased.

**Melanoma Pathology Report**

The report should include all factors that affect accurate diagnosis, management and prognosis. Currently the most important pathological prognostic factors for clinically localized primary melanoma are tumour thickness (Breslow), dermal mitotic rate (which also influences the rate of sentinel lymph node positivity) and ulceration. Other factors are Clark level, site (trunk worse than extremities), age and gender (males worse than females).

**Margins of Excision.**

These are important in determining further management of atypical melanocytic lesions and melanomas. The main problem is accurately assessing the margins of lentigo maligna (Hutchinson’s melanotic freckle) and some other melanocytic tumours where atypical melanocytes “trail off” at the edges. To avoid excessive excisions, a marginal excision around the clinically affected area is usually done initially for definitive diagnosis. Wider excision (as per current melanoma treatment guidelines) can then be performed once a diagnosis of melanoma has been confirmed.

# Adapted from McCarthy SW, Scolyer RA. Pitfalls and Important Issues in the Pathologic Diagnosis of Melanocytic Tumors. The Ochsner Journal 2010 (in press).

**REFERENCES**

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