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Pitfalls and Important Issues in the Pathologic Diagnosis of Melanocytic Tumors

Stanley W. McCarthy, MBBS, FRCPA, FFOP (RCPA), Richard A. Scolyer, BMedSci, MBBS, MD, FRCPA, FRCPath

Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Sydney, Australia
Melanoma Institute Australia, Sydney, Australia
Discipline of Pathology, The University of Sydney, NSW, Australia

ABSTRACT

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), histologic features (including architecture, cytology, and the host response), awareness of pitfalls, and judgment. Several types of nevi—such as regenerating nevi, combined nevi, acral nevi, deep penetrating nevi, and Spitz nevi—are prone to be misdiagnosed as melanoma. Melanomas often underdiagnosed include the nevoid, desmoplastic, Spitzoid, and regressed types. The type of biopsy and suboptimal processing may also significantly influence the diagnosis.

INTRODUCTION

Melanoma continues to be a major health problem in those of white, mainly Celtic, ancestry. Exposure of fair-skinned individuals to strong ultraviolet light (including sunlight), especially as a child, appears to be a significant factor in the evolution of many cutaneous melanocytic tumors. Although their incidence is increasing, mortality rates are falling except in elderly men, a group that is often reluctant to seek early medical advice.[1] As the most common malignancy in young white adults, melanoma has a disproportionate effect on the most productive years of life.[2]

Address correspondence to:
Richard A. Scolyer, BMedSci, MBBS, MD, FRCPA, FRCPath
Tissue Pathology and Diagnostic Oncology
Royal Prince Alfred Hospital
Missenden Road
Camperdown NSW 2050, Australia
Tel: (+61) 2-95157011
Fax: (+61) 2-95158405
Email: richard.scolyer@sswahs.nsw.gov.au

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PATHOLOGIC DIAGNOSIS

Accurate pathologic diagnosis of melanocytic tumors requires a suitable biopsy, assessment of many histologic criteria, awareness of potential pitfalls, relevant experience, and, in difficult cases, judicious consultation.[3–5] Correlation of a range of basic morphologic and clinical features is necessary because many of the individual features are shared by both nevi and melanomas. In the future, molecular and genetic studies may be useful adjuncts for an accurate diagnosis, particularly for a difficult lesion for which it is not possible to be certain from its histologic features whether the lesion is benign or malignant.[6–8]

The morphologic features of importance are shown in Table 1 and are discussed here.

Architectural

Good symmetry is often associated with benign behavior. Poor symmetry and irregular margins are more often found in dysplastic, traumatized, and malignant melanocytic tumors. Ulceration, vascular invasion, neurotropism, and satellites are also more frequent in melanomas but can also occasionally occur in nevi. Minor perineural invasion may be found in all types of benign nevi, so is not very helpful when diagnosing melanocytic tumors. Pagetoid epidermal invasion is very common and not usually significant in acral lesions, regenerating nevi (''pseudomelanoma''), or ''irritated'' nevi (eg, trauma, sunburn).[5,9]

Cytologic

Cytologic features may be deceptive, especially in nevoid melanomas with small cells and uniform cytology, deep penetrating nevi with nuclear pleo-

Table 1. Morphologic Features of Melanoma

Architectural
• Asymmetry
• Irregular margins
• Ulceration
• Vascular invasion
• Microsatellites
• Pagetoid epidermal invasion
Cytologic
• Nucleoli (especially if irregular and multiple)
• Deep or frequent mitoses
• Poor maturation
Host response
• Lymphocytic infiltrate
• Stromal fibrosis (especially in desmoplastic melanoma)
• Regression

morphism, and regenerating nevi with epithelioid cells. Nucleoli when irregular or frequent (average more than 2 nucleus) usually indicate dysplasia or malignancy. Mitoses when abnormal, frequent (more than 2 per mm^2), 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 postpubertal patients.

Host Response

The host response is usually cellular and/or stromal.

Cellular. Regressing tumors, benign or malignant, are usually infiltrated, at least initially, by lymphocytes. Scattered foci of lymphocytes are a common feature in desmoplastic melanoma. Benign nevi and some aggressive epithelioid melanomas lack a cellular response.

Stromal. Periretal lamellar collagen is common in dysplastic nevi 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]

Clinical features of importance

Age: Melanomas are uncommon in children just as Spitz nevi are rare in middle-age 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 age 35.[11] Females have a better prognosis than male patients with melanoma.

Family history: Melanomas are common in some families and first-degree relatives.

Site: Sun-exposed areas are more likely to develop nevi and melanomas in white patients. Desmoplastic melanomas most commonly involve the head and neck region and are frequently associated with lentigo maligna.[12] They may be subtle clinically and histologically, and hence may not be diagnosed until they are at an advanced clinical stage.[9]

History of lesion: A lesion of long duration that 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 nevi.

THE BIOPSY

An excisional biopsy is preferred wherever possible.[1,3,5] 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 (eg, Breslow thickness, mitotic rate).[13] Smaller specimens also may not be representative of the lesion and usually lack the edges and bases of the lesions needed to assist diagnostic interpretation.[3,4]

In the subsequent excision specimen it may be impossible to allocate atypical features such as cellular pleomorphism, mitoses, and epidermal invasion to either malignancy or regeneration. A recent study highlighted that histopathologic misdiagnosis is more common for melanomas that have been assessed with punch and shave biopsy than with excision biopsy.[14] Adverse outcomes resulting from misdiagnosis were more commonly associated with punch biopsy than with shave and excision biopsy (odds ratio, 16.6; $P < .001$). 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 posttraumatic fibrosis in compound nevi often has some overlying variable epidermal thickening.

NEVI PRONE TO MISDIAGNOSIS

Regenerating nevi are among those often misdiagnosed (Table 2). They often regenerate after incomplete removal (punch, shave, curette, incision, other trauma). Some nevi, especially compound melanocytic nevi of small congenital type and dysplastic compound nevi, display features often associated with melanoma and are sometimes termed *pseudomelanoma*. These features include Pagetoid spread of melanocytes, cytologic atypia, dermal mitoses, and HMB45 positivity.[15]

Postexcisional junctional melanocytic hyperplasia at the edge of an excision scar may show some atypia and a tendency to epidermal invasion that is sugges-

Table 2. Nevi Prone to Misdiagnosis

Regenerating nevus
''Irritated'' nevus
Postexcisional junctional hyperplasia
Cellular/hyperplastic nodule in congenital nevus
Combined nevus
Ancient nevus
Spitz nevus
Dysplastic nevus
Nevus in pregnancy
Genital nevus
Blue nevi
Dendritic
Cellular
Deep penetrating
Epithelioid
Acral nevi
Balloon and clear cell nevi
Neurotized nevus
Desmoplastic nevus
Halo nevus

tive of in situ malignancy. Irritated melanocytic nevi may show epidermal invasion, but the offending melanocytes tend to have small nuclei. Causes of irritation may be physical (eg, rubbing or scratching, topical agents, or strong sunburn).

Dysplastic nevi have variable lentiginous hyperplasia, periretal lamellar collagen, architectural disorder, and cytologic atypia (Figure 1). The cytologic 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 nevi (the most common nevi in whites) with mild to moderate cytologic atypia are stable or grow very slowly and rarely progress to malignancy. Dysplastic nevi are regarded as intermediate lesions of tumor progression between nevi and melanoma. They show S-phase ploidy and intermediate levels of genetic instability.

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

Dermal and compound nevi 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 nevi are often mistaken clinically and histologically for melanoma because of their biclonal (occasionally triclonal) nature and variability or change in color or shape.[16,17] Frequent problems are combinations of common nevus (common acquired, congenital, or dysplastic) associated with pigmented blue nevus (common blue, cellular blue, or deep penetrating) (Figure 2) or Spitz nevus (conventional, regressing, or desmoplastic).[17] The blue nevus or Spitz nevus component may dominate the lesion and show an occasional mitosis. So-called ancient nevi may represent a combined nevus with a regressing or degenerating Spitzoid component.

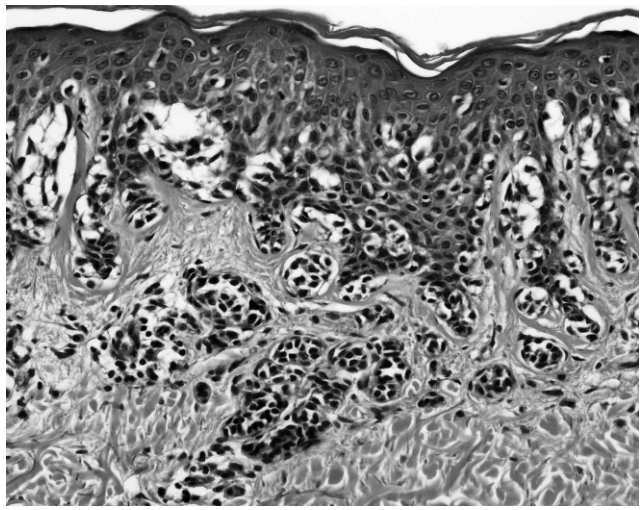

Figure 1. Dysplastic compound nevus. Note lentiginous and nested melanocytic proliferation and periretal lamellar collagen.

Blue nevi variants cause special problems. ''Dendritic'' blue nevi (Figure 3) and sclerosing cellular blue nevi may have an infiltrative pattern similar to desmoplastic melanomas, but the latter often have some junctional change, are almost invariably nonpigmented, and are negative with HMB45.[18]

Deep penetrating nevi frequently show moderate nuclear pleomorphism, abut nerves, and have an occasional dermal mitosis (Figure 4). 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.[18]

Epithelioid blue nevi (as in Carney syndrome) and other so-called pigmented epithelioid melanocytomas are also low-grade melanocytic tumors that apparently frequently involve regional lymph nodes, yet paradoxically appear to have a favorable prognosis.[19] These nevi 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 nevi may be confused with their malignant counterparts. The nevi usually have bland nuclei and lack mitoses.

Neurotized and desmoplastic common nevi can be confused with desmoplastic melanoma especially

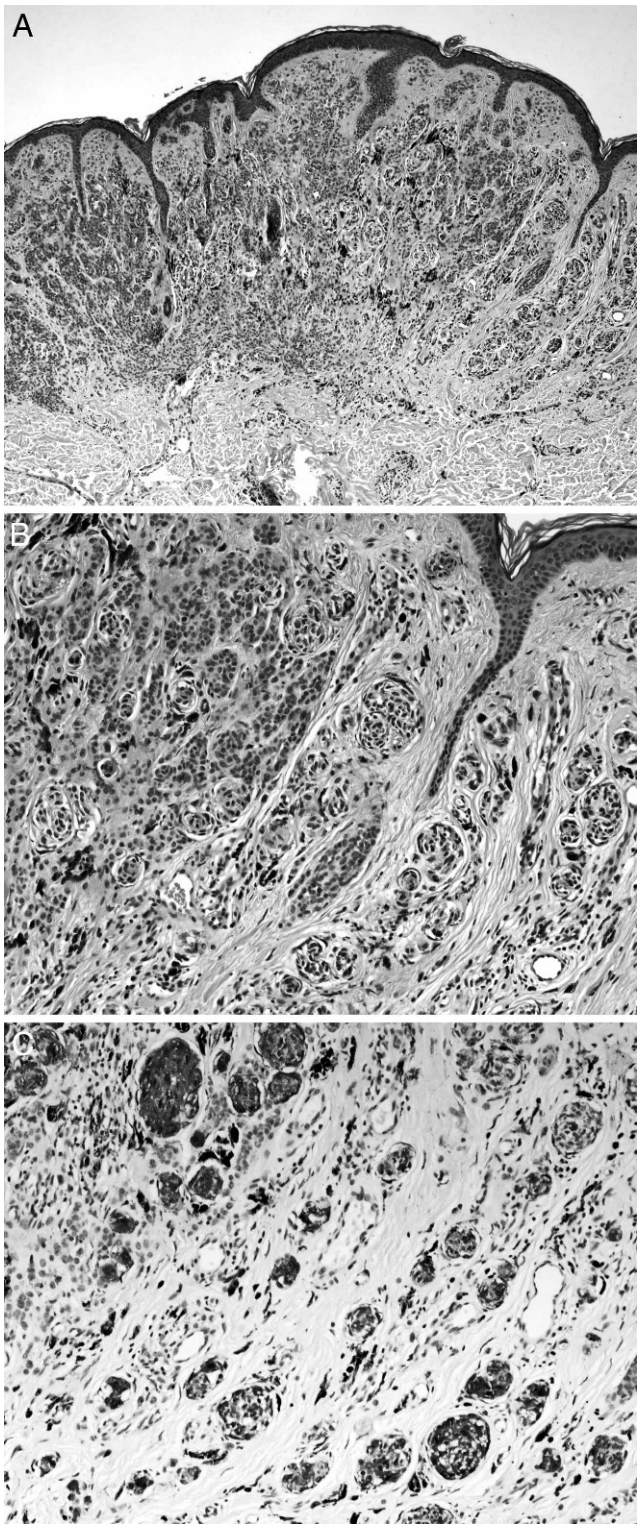

Figure 2. A and B, Combined nevus with dermal nevus and deep penetrating nevus components. C, Many of the deep penetrating nevus cells are lightly pigmented and positive for HMB45.

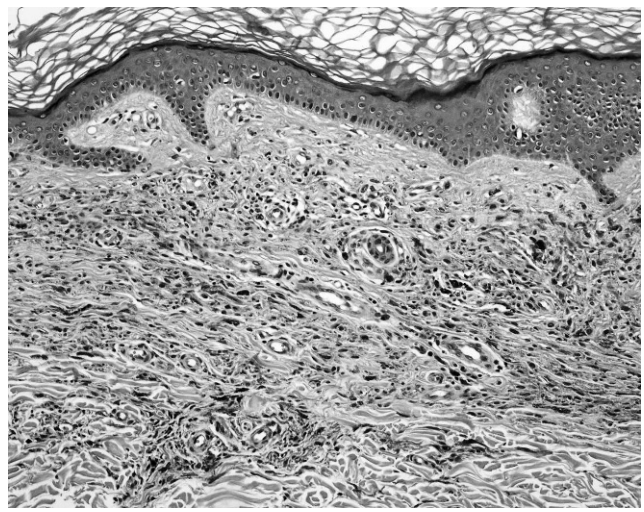

Figure 3. Conventional (dendritic) blue nevus.

of ''pure type.'' The nevi, however, lack atypical junctional changes, dermal mitoses, and scattered clusters of lymphocytes.

''Halo'' or regressing nevi may present with alarming color change, with a ''darkening'' center and pale periphery, especially in children (Figure 5). Most of these atypical compound nevi 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. Although they are most frequent in children, they also occur in middle-age and old age groups.

Acral nevi and genital nevi resemble dysplastic nevi elsewhere in the skin. Focal Pagetoid epidermal invasion, especially in the acral nevi, is alone not an indication of malignancy. Tables 3 and 4 contain further information on acral nevi.

Spitz nevus and Spitzoid tumors are a common problem and share many of the histologic features of melanoma (Table 5).[6,11,20] Those with atypical features cause the most concern, and many are of uncertain biologic behavior (Table 6).[21]

AN APPROACH TO ATYPICAL CASES

The following approach may be taken in situations of atypical cases in which it is difficult to be certain whether they are benign or malignant:

- Complete excision is probably mandatory.
- Avoid overdiagnosis to prevent excessive treatment and possible medicolegal action.
- Give a preferred diagnosis, acknowledging the degree of uncertainty.
- Seek further opinions.

The safest course is to manage the lesion as a melanoma (ie, wide excision with or without sentinel lymph node biopsy).[22] However, wide local excision

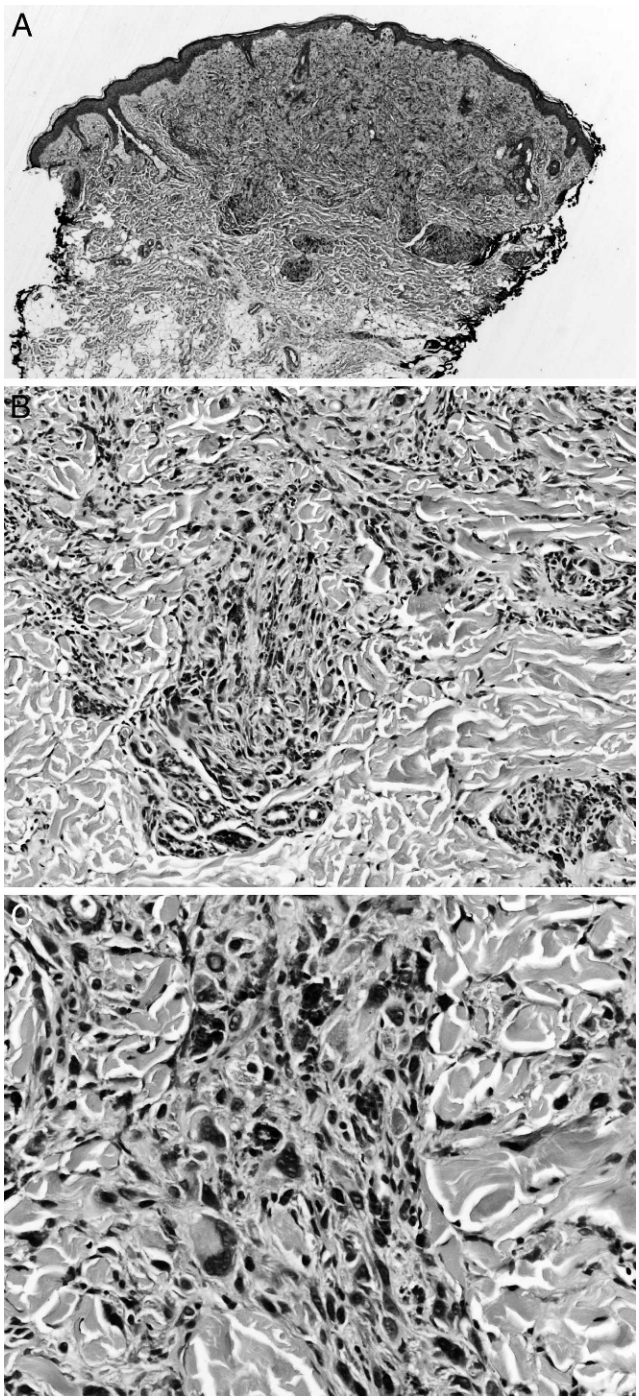

Figure 4. Deep penetrating nevus. A, Note ''V''-shaped architecture. B and C, The cells shows moderate nuclear variation and occasional intranuclear pseudoinclusions.

may not be appropriate if there is likely to be unacceptable cosmetic disfigurement, and any comorbidity and multiple draining node fields may be relative contraindications to sentinel lymph node biopsy.[13,23] When there is uncertainty about whether a melanocytic tumor is benign or malignant, the pathologist should document in his/her report the thickness of the tumor (and other important features of the tumor such as its mitotic rate and ulcerative state). This information may be used 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 lists a group of melanomas that may make diagnosis a challenge. They are discussed here.

Nevoid Melanomas

Nevoid melanomas (Figure 6) mimic a benign nevus. 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.[15] Large and spindle cell types are called Spitzoid or Spitz nevuslike melanoma. A probable indolent variant resembling a dermal nevus develops on the lower limb of elderly women.

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

Desmoplastic Melanoma

Desmoplastic melanomas (Figure 7) may be difficult to detect clinically as they are usually nonpigmented and may resemble a scar, a dermatofibroma, a basal cell carcinoma, or a poorly healing pyogenic granuloma.[9] Histologically they may be confused with immature scars (which may also have S-100−positive spindle cells and foci of lymphocytes), desmoplastic nevi (usually symmetrical and lacking atypia, mitoses, and lymphocytic foci), desmoplastic Spitz nevi (plump cells and associated epidermal thickening), sclerosing cellular blue nevus (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.

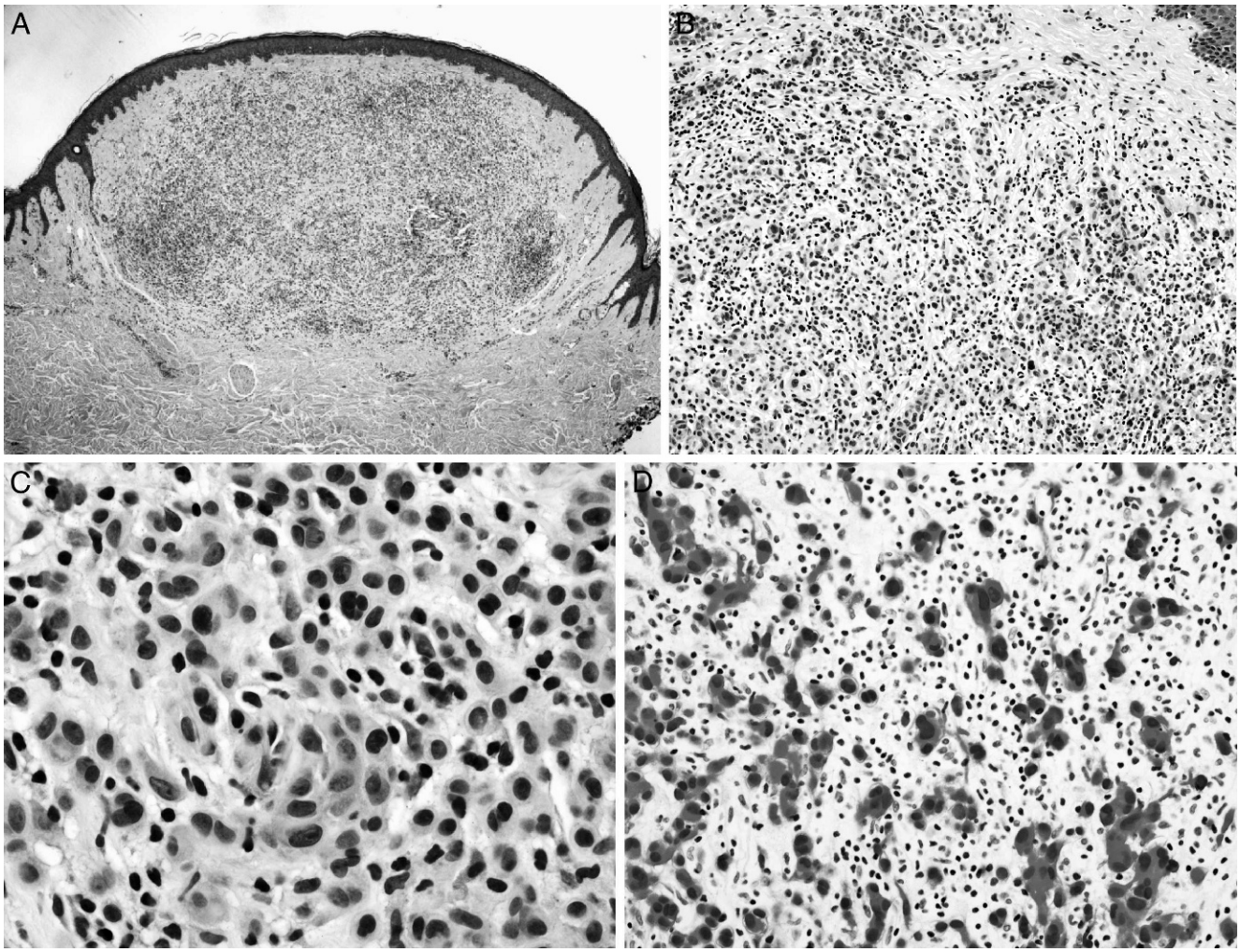

Figure 5. A–D, Regressing (''halo'') intradermal Spitz nevus. B and C, The plump epithelioid melanocytes have eosinophilic glassy cytoplasm and are dispersed among an infiltrate of small lymphocytes. D, The melanocytes show strong positivity (nuclear and cytoplasmic) for S-100 protein in contrast to the interspersed small lymphocytes.

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, and (3) a subepidermal band of angiofibroplasia (often up to 0.8 mm thick), which may variably contain a few lymphocytes, melanophages, and an occasional melanocyte. Capillaries are usually slightly increased.

Table 3. Nevi of Acral Skin

Histopathologic Features That Can Cause Concern
Suprabasilar melanocytes (''Pagetoid spread'') (observed in 30%–79% of cases)
Atypical size, shape, location of junctional nests
A subset (acral lentiginous nevi) show
Predominantly lentiginous growth
Poor circumscription
Asymmetry
Small biopsies

Table 4. Acral Nevi v Acral Melanoma

Features Favoring Melanoma
Severe cytologic atypia
Lymphocytes abutting junctional zone
Marked architectural disorder
Increased density of melanocytes
Excessive Pagetoid spread
Poor maturation
Expansile growth
Dermal mitoses and lymphocytes

Table 5. Features of Spitz Nevi

Diameter usually <6 mm
Symmetrical
Diffuse epidermal hyperplasia
Hypergranulosis
Terminal nests
Uniformity of cells and nests across lesion
Kamino bodies
Subepidermal clefts
Telangiectatic vessels
Nested and single cell Pagetoid spread
''Maturation'' and often merging with dermal collagen
Spindle/epithelioid cells
Mitotic figures $\leq 2/mm^2$
Absent deep or abnormal mitoses

Table 6. Atypical Features for Spitz Nevus

Diameter >10 mm
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 cytologic atypia
Irregular or multiple nucleoli
Dermal mitoses $>2/mm^2$
Deep mitoses
Abnormal mitoses

MELANOMA PATHOLOGY REPORT

The pathology report should include all factors that affect accurate diagnosis, management, and prognosis.[13,24] Currently the most important prognostic factors are tumor thickness (Breslow), dermal mitotic rate (which also influences the rate of sentinel lymph node positivity), and ulceration.[1,25–32] Other factors are Clark level, site (trunk worse than extremities), age, and gender (males worse than females). The synoptic report currently used by the

Table 7. Melanomas Prone to Cause Diagnostic Problems

- Nevoid
- Spitzoid
- Desmoplastic
- Regressed

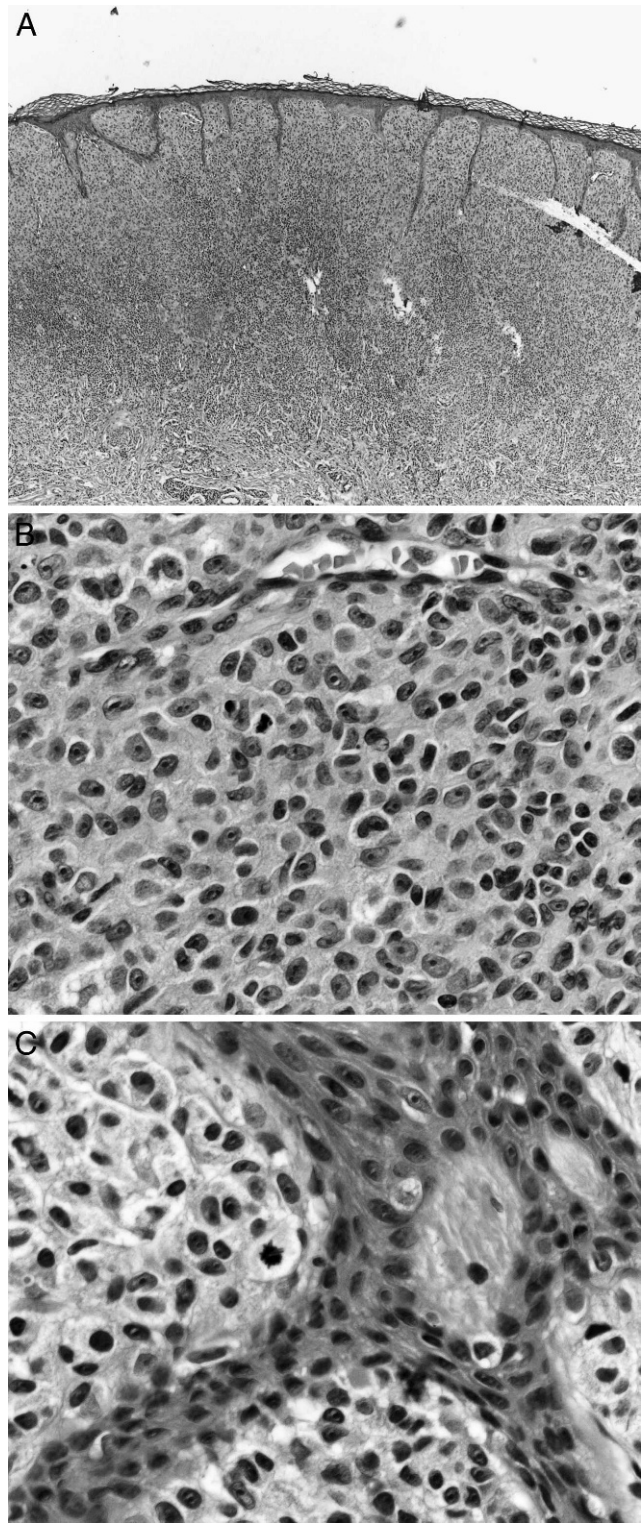

Figure 6. Nevoid melanoma. Note the thin, elongated rete ridges of the epidermis (A) associated with expanded dermal papillae containing nevoid melanocytes of intermediate size (B). On high power (C), the cells show nucleoli and occasional mitoses.

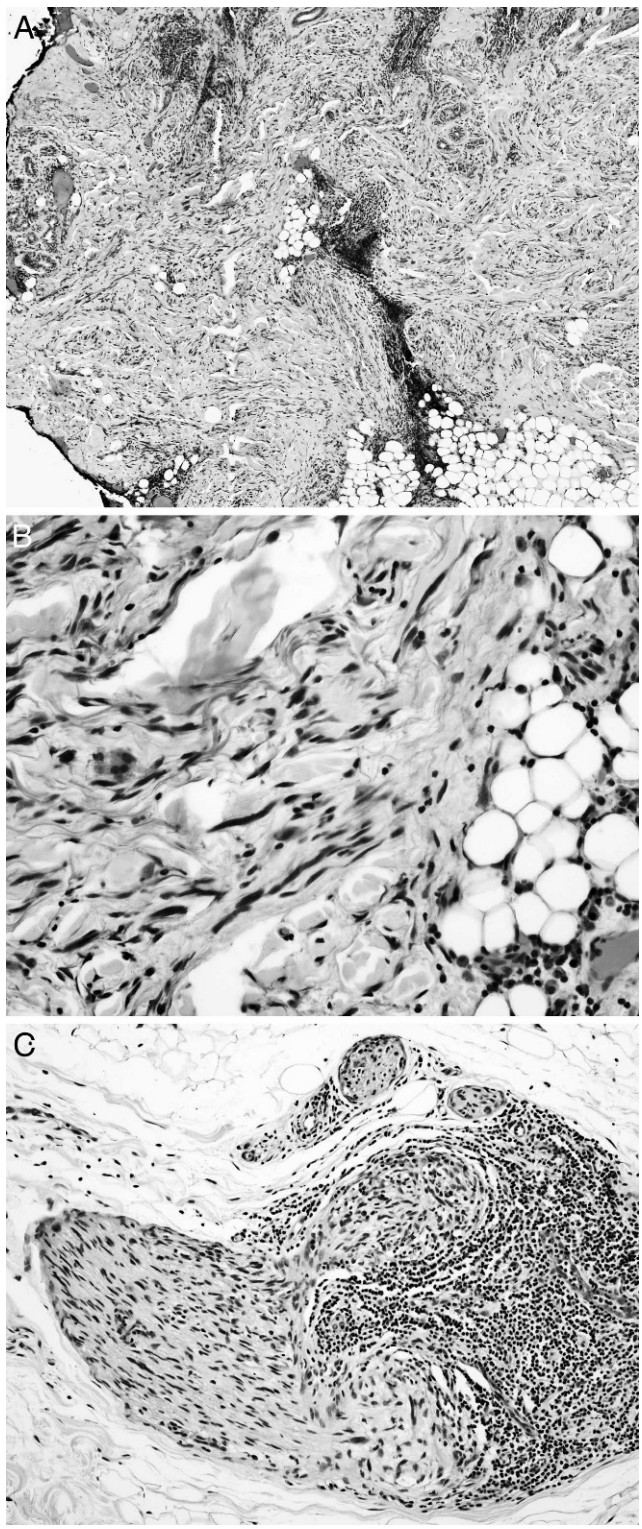

Figure 7. Desmoplastic neurotropic melanoma. A, A subtle spindle cell proliferation is present, extending to the inked surgical margin. Note the associated clusters of lymphocytes, which often represent an important clue to diagnosis. B, Some nuclei are elongated and hyperchromatic. C, The neurotropism in this case is predominantly intraneural.

Table 8. Synoptic Report for Melanoma

Specimen type: excision
Site: right anterior chest
Diagnosis: melanoma
Classification/main pattern: nodular
Thickness: Breslow 2.2 mm
Clark level: 4
Ulceration: 0.6 mm (10% of dermal invasive width)
Dermal mitoses: up to 5/mm^2
Predominant cell type(s): epithelioid
Intravascular/intralymphatic invasion: not seen
Angiotropism[32]: not seen
Neurotropism: not seen
Microsatellites: not seen
Desmoplasia (% of dermal invasive tumor): present (10%)
Features of regression:
  Early tumor infiltrating lymphocytes: focal and mild
  Intermediate: not seen
  Late (fibrosis and loss of rete ridges): not seen
Associated nevus: mild dysplastic compound nevus
Actinic/solar elastosis: moderate
Margins:
  In situ component
    Nearest peripheral: 1.5 mm
  Invasive component
    Nearest peripheral: 1.7 mm
    Deep: 2.8 mm
Comment: Tumor cells show positive staining with S-100 (+++), Melan-A (++), and HMB45 (++). Ki67 stains about 5% of tumor cells.
Summary:
  Skin right anterior chest: melanoma, Breslow thickness 2.2 mm, no ulceration, dermal mitoses up to 5/mm^2, Clark level 4

Melanoma Institute Australia (formerly known as the Sydney Melanoma Unit) is shown in Table 8.[33]

Margins of Excision

The margins of excision 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 tumors where atypical melanocytes ''trail off'' at the edges.[34] 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.

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