EDITOR'S CHOICE

Spindle cell melanocytic lesions—part I: an approach to compound naevoidal pattern lesions with spindle cell morphology and Spitzoid pattern lesions

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ABSTRACT

Melanocytic lesions show great morphological diversity in their architecture and the cytomorphological appearance of their composite cells. Whereas functional melanocytes reveal a dendritic cytomorphology and territorial isolation, lesional naevomelanocytes and melanoma cells typically show epithelioid, spindled or mixed cytomorphologies and a range of architectural arrangements. Spindling is common to melanocytic lesions, and may be either a characteristic feature or a divergent appearance. The presence of spindle cells may mask the melanocytic nature of a lesion, and is often disconcerting, either because of its infrequent appearance in a particular lesion or its interpretation as a dedifferentiated phenotype. Spindle cell melanocytic lesions follow the full spectrum of potential biological outcomes, and difficulty may be experienced judging the nature of a lesion because of a lack of consistently reliable features to predict biological behaviour. Over time, recognition of numerous histomorphological features that may portend a more aggressive lesion have been identified. However, the translation of these features into a diagnostic entity requires a gestalt approach. Although most spindle cell melanocytic lesions can reliably be resolved with this standard approach, problem areas do exist and cause no end of grief to the surgical pathologist or dermatopathologist. In this review, the authors present their algorithmic approach to spindle cell melanocytic lesions and discuss each entity in turn, in order to (1) model a systematic approach to such lesions, and (2) provide familiarity with those melanocytic lesions that either typically or occasionally display a spindled cytomorphology.

INTRODUCTION

Melanocytic lesions of the skin can be a notorious challenge for the pathologist.[1–5] This is due in part to the lack of consistent and reliable features differentiating benign from malignant melanocytic proliferations, but also to the great morphological variability that melanocytes can exhibit.[6 7] The former point is illustrated by the vast array of features that a pathologist must evaluate when confronted with a melanocytic entity, features that, when considered on their own, exhibit limited diagnostic utility. The general approach to diagnosing a melanocytic lesion is through a gestalt impression which incorporates: clinical parameters; architectural parameters including size, silhouette, pattern of growth and degree of maturation; cytological parameters including cytomorphology, extent of atypia and mitotic activity; and often ancillary studies as well. The morphological variability of melanocytic lesions is exhibited by both architectural and cytological variations.[6 8] Particular difficulty arises when melanocytes express cytomorphological features that create uncertainty about the cell of origin, as may be seen with spindled melanocytic lesions.[7 9] This difficulty is compounded when the architectural features most typical of melanocytic lesions are poorly developed or absent. This architectural and cytomorphological variability of melanocytes, in addition to the diagnostic challenges of differentiating benign from malignant lesions, accounts for the vast array of terms applied to melanocytic lesions—a list that can be intimidating. Numerous publications discuss selected challenges and pitfalls that may be encountered in the diagnosis of specific melanocytic entities.[10–21] This review will focus specifically on spindle cell melanocytic lesions, with itemisation of those melanocytic entities that characteristically or occasionally show a spindled cytomorphology, with particular reference to diagnostically challenging situations and pitfalls. We also provide the algorithmic approach to these lesions that we use. The review is structured according to this approach. Part I deals with our algorithmic approach to spindle cell melanocytic lesions and includes their initial categorisation into compound naevoidal pattern lesions, Spitzoid lesions, intradermal proliferations and horizontally oriented lesions.[21a] Part I further covers the compound naevoidal pattern lesions and the Spitzoid lesions. Part II continues with a discussion of intradermal melanocytic proliferations, horizontally oriented lesions and combined lesions.

Before embarking upon the hefty task of cataloguing a list of cutaneous spindle cell lesions, it is worthwhile attempting a definition for the widely used but fairly loosely defined 'spindle cell'. The term is one that is quite malleable to the needs of the pathologist and as such is rather freely used in cytological description of cellular morphology (figure 1). Perhaps, in its purest sense, spindling refers to cells with elongated fusiform nuclei. Such cells are best appreciated when they are present in a fascicular arrangement, imparting a streaming quality to the lesion. Fusiform spindled cells may be further qualified as: having rounded ends or being 'cigar-shaped' (eg, leiomyoma, many spindle cell melanomas); showing waviness or being 'comma-shaped' (eg, neuroma, neurofibroma, neuroidal naevus); or with tapered ends (eg, myofibroblasts, nodular fasciitis). Intermediate forms can also be seen and may appear blunted (eg, dermatofibroma,

desmoplastic melanoma). Spindle cells may also vary in their thickness, appearing either plump (leiomyoma, melanoma) or thin (neurofibroma, fibromatosis, common blue naevi). Oval nuclei also impart a vague spindled quality, and many lesions with oval nuclei are classically listed as spindle cell lesions (eg, perineurioma, desmoplastic naevi, cellular blue naevi). The overall pattern of arrangement or other formations may offer further histogenetic clues (slit-like spaces in Kaposi sarcoma; storiform pattern in dermatofibrosarcoma protuberans; herringbone pattern in fibrosarcoma or malignant peripheral nerve sheath tumour (MPNST); palisading in neural lesions), as may other characteristic features (presence of nucleoli (eg, nodular fasciitis, melanoma), intranuclear inclusions (melanocytic lesions), subnuclear vacuoles (smooth muscle)). Spindle cells also encompass lesions with intermediate epithelioid and spindled morphologies, as may often be seen in histiocytic disorders such as Langerhans cell histiocytosis, dermatofibromas and atypical fibroxanthomas. Many melanocytic lesions offer further examples, such as frequent desmoplastic melanomas and Spitz naevi. Cellular–stromal interactions may further impart a spindling phenotype either by direct compressive effects or through chemical interaction.[22–24] In general, interstitial infiltrating lesions may take on an oval or spindled morphology due to partial distortion as they infiltrate between collagen bundles. Given the standard option of describing a cell as either spindled or epithelioid, other cytomorphologies such as dendritic or stellate may thus also fall under the somewhat inappropriate label of spindled, including the common blue naevus, fibrous papules and dendritic cell tumours, particularly when the finer details may not be well appreciated on light microscopy. Finally, most epithelioid tumours also have spindle cell variants (and vice versa) (eg, epithelioid sarcoma, carcinoma). Clearly, the task of outlining spindle cell lesions becomes a laborious one when, by convention and practice, the term spindle cell: (1) encompasses a range of differing cytomorphologies; (2) may arise by nature of the histogenetic origin of the lesion, the nature of the lesional cells or the effects of the surrounding stroma; or (3) may be applied in intermediate, admixed or even inappropriate settings to satisfy convention or simplicity. Nevertheless, in this article, we try to consider all the possible applications of the term spindle cell to melanocytic lesions, but also try to put the term in appropriate context with respect to finer cytomorphological descriptions that offer diagnostic utility. After all, even though a neuroidal naevus, a cellular blue naevus and a pigmented spindle cell naevus of Reed are all spindle cell melanocytic lesions, they can still be distinguished from each other on the basis of cytomorphology alone.

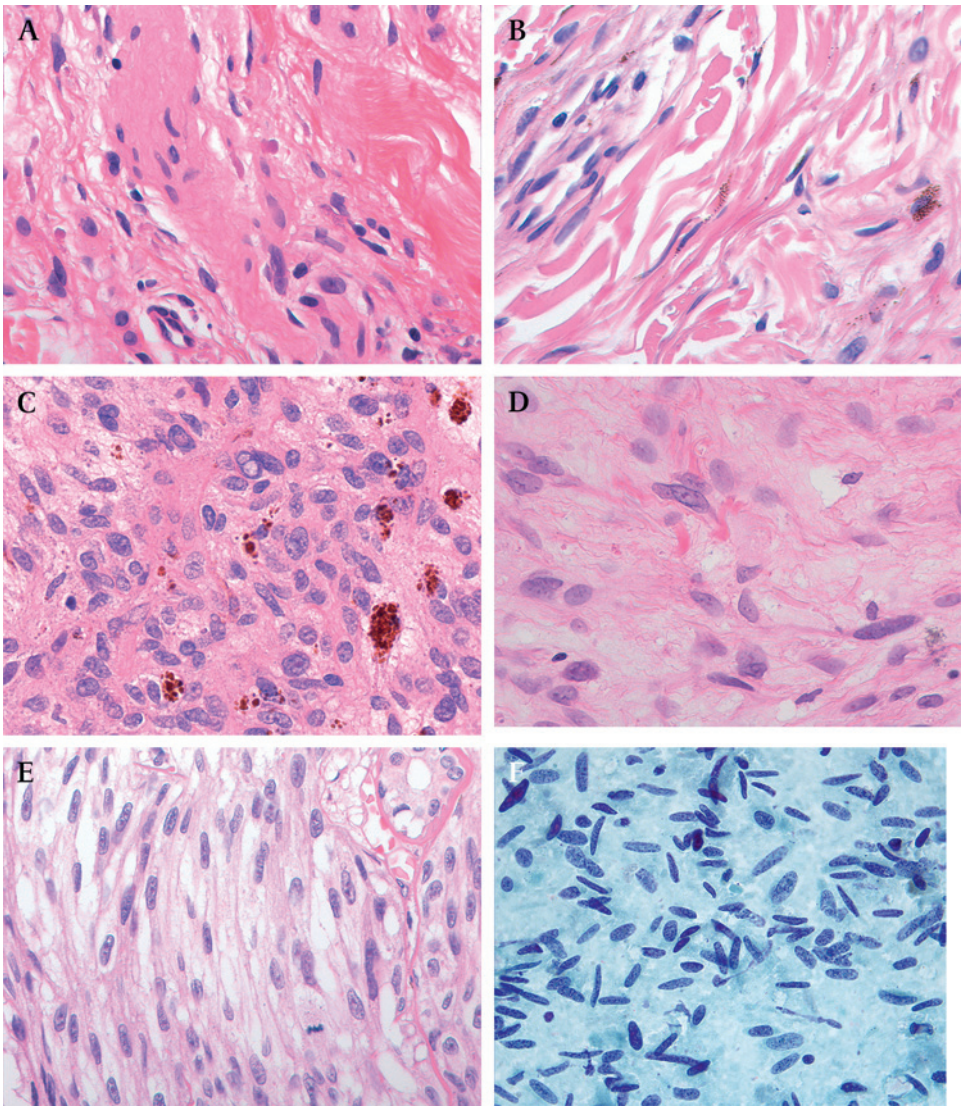

Figure 1 Examples from the morphological spectrum of 'spindle cells' (all images: H&E; 600×). (A) Wavy or 'comma-shaped' (neuroidal) spindle cells from the tactoid bodies of a neuroidal naevus (56-year-old woman; shoulder). (B) Slender bipolar spindle cells from a common blue naevus. Oval-shaped melanocytes can also be seen towards the upper left (63-year-old woman; shoulder). (C) Blunted oval spindle cells from a satellitic nodule of a plaque-type cellular blue naevus (50-year-old woman; abdomen). (D) Plump 'histiocytoid' spindle cells from a desmoplastic melanoma (54-year-old man; forehead). Spitzoid lesions also typically show a spindle cell component that varies from histiocytoid to fusiform with additional characteristic Spitzoid features (figure 5B). (E) Fusiform spindle cells from a spindle cell melanoma (79-year-old man; lower back). Prominent nucleoli, high-grade nuclear atypia, mitotic activity and clear cytoplasm are noted as additional features in this case. (F) Cytological preparation of a metastatic spindle cell melanoma. Elongated fusiform cells with high-grade cytological features are noted in this aspirate (78-year-old man; subcutaneous submandibular mass). (Image courtesy of Dr William Geddie).

ALGORITHMIC APPROACH TO MELANOCYTIC SPINDLE CELL TUMOURS (FIGURE 2)

Establishing the histogenetic origin of a cutaneous spindle cell lesion: histopathological assessment, ancillary testing and clinical correlation

When first confronted with a spindle cell tumour of the skin, the first step is to classify the histogenetic origin of the lesional cells before proceeding with further diagnostic categorisation. Although for many cell types, a spindled morphology often equates with a lack of differentiation or metaplastic differentiation (eg, epithelia), for other cell types, spindling represents the appropriate differentiated morphology of the cells (eg, peripheral nerve sheath, smooth muscle, fibroblasts/myofibroblasts). Evaluating the histomorphological features of spindled tumours is an essential step in establishing the histogenetic origin of many spindled lesions. Although non-melanocytic spindled lesions are not the focus of this review, an approach to cutaneous spindle cell melanocytic lesions cannot proceed without consideration of the potential non-melanocytic mimics that often arise in the differential diagnosis; therefore we have listed some useful clinical, histological and immunohistochemical features of non-melanocytic spindle cell lesions in table 1. Suffice it to say that for certain non-melanocytic spindle cell tumours, histomorphology alone is generally sufficient for confident diagnosis, whereas, in others, ancillary methods (usually immunohistochemistry) are required in the diagnostic work-up. The reader is also referred to other excellent publications for consideration of non-melanocytic cutaneous spindle cell lesions.[25–32] For melanocytes, spindling is a common and, even occasionally, a definitive feature in certain types of melanocytic lesions (eg, blue naevi, Spitz naevi, melanoma). Spindling in melanocytes does not necessarily reflect a lack of differentiation, and, in fact, the epithelioid morphology of naevomelanocytes seen in most common melanocytic naevi reflects a deviation from the functional dendritic morphology of intraepidermal melanocytes.[21 33] Even nesting, the characteristic organisational pattern of melanocytic lesions, represents a deviation from the isolated and territorial behaviour of functional melanocytes. Furthermore, type C ('Schwannian') melanocytes represent a maturation phenomenon that may occasionally be seen in aged melanocytic naevi ('neuroidal naevi', 'naevi with neurotisation').[34] Alternatively, high-grade melanomas often take on a spindled morphology, reflecting a metaplastic or dedifferentiation phenomenon.[6 9 31 35 36] Nonetheless, in most cases of spindle cell melanocytic lesions, melanocytic differentiation may be determined/inferred through evaluation of the histomorphological features of the lesion (box 1), whereas in others further ancillary testing is required (table 2).[6 21 26 37–54]

Assessing the biological potential of melanocytic spindle cell tumours

Having optimally established the histogenetic origin of a lesion through clinical parameters and histomorphology with or without ancillary studies, the next step in the algorithmic

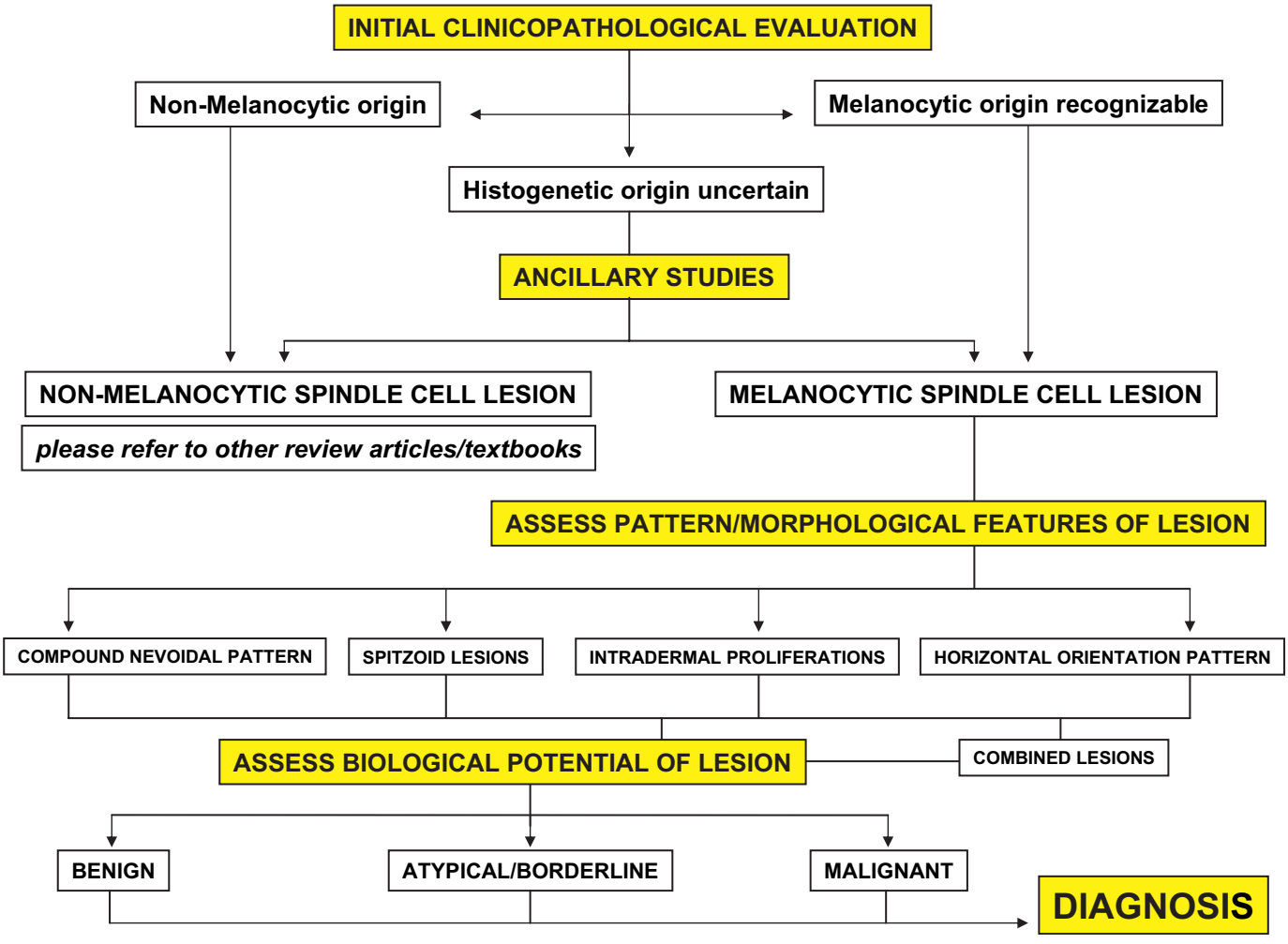

Figure 2 Algorithmic approach to a cutaneous spindle cell lesion.

Table 1 Non-melanocytic spindle cell tumours of the skin

Select spindle cell tumours	Clinical features	Characteristic morphological features	Immunophenotype (excluding vimentin) and cytogenetics
Epithelial lesions			
Spindled squamous cell carcinoma	Sun-damaged skin; commonly ulcerated	Epidermal connection/origin; look for adjacent epithelial dysplasia; look for better differentiated foci with keratinisation or intercellular junctions	p63; basal keratins; AE1/AE3 ±
Metastatic sarcomatoid carcinoma	History of carcinoma; other metastases	Lesion centred within dermis ± vascular space invasion; destructive growth; high-grade cytology and malignant features (mitoses, necrosis)	Keratins; other markers depending on the site of origin
Mesenchymal lesions			
Fibrous			
Fibrous papulae (angiofibroma)	Small, skin-coloured to slightly pigmented papules; most common on face/nose; may be multiple on penis; multiple facial angiofibromas associated with tuberous sclerosis	Slight elevation of epidermis which commonly shows melanocytic hyperplasia; dermis reveals fibrosis with prominent perifollicular accentuation as well as mild vascular proliferation; scattered stromal stellate cells ± spindle cells	Factor XIIIa
Fibromatosis	Male > female	Uniform infiltrative proliferation of bland slender spindle cells with negligible mitotic activity embedded in a fibrous stroma	β-Catenin in variable proportion of cells; actins ±
Fibrous hamartoma of infancy	Age, 0–4; males; axilla and proximal extremities	Organoid pattern of adipose tissue, fibrous trabeculae and loosely arranged spindle/stellate cells within a myxoid stroma	Actins ±; CD34 ± in spindle cells
Infantile digital fibromatosis	Age, 0–3; digital location	Poorly circumscribed, uniform proliferation of slender spindle cells in a fibrous stroma; characteristic intracytoplasmic eosinophilic inclusions	Actins
Myofibroma/myofibromatosis	Children or adults	Multinodular and biphasic pattern of dark cellular spindle cells areas interposed with lighter areas composed of plump myoid cells with abundant eosinophilic cytoplasm	Actins (weaker staining in dark areas)
Fibrosarcoma	Originate from soft tissue; radiation history; hypoglycaemia is rare complication	Densely cellular proliferation of uniform spindle cells with variable cytological atypia and mitotic activity, often forming a herring-bone pattern within a variably fibrotic stroma ± necrosis ('classic fibrosarcoma'); sometimes admixed fibrous and myxoid areas ± giant hyalinising rosettes ('low-grade fibromyxoid sarcoma'); or prominently multinodular myxoid pattern with curvilinear vascular channels ('myxofibrosarcoma')	Scattered cells showing positivity for actins/desmin is acceptable (referred to by some as 'myofibrosarcoma') LGFMS reveals a recurrent t(7;16)(q34;p11) *translocation resulting in a* FUS-CREB3L2 *chimaeric gene*
Adipocytic			
Spindle cell lipoma	Location: upper back, neck; Male > female	Circumscribed lesion composed of variable proportions of adipose tissue and bland spindle cell areas which contain 'ropey' collagen, variably fibrous and myxoid stroma, and abundant mast cells; may find admixed pleomorphic cells ('pleomorphic lipoma')	*CD34, bcl-2±; loss of 16q, 13q material*
Well-differentiated liposarcoma	Adults; rare cases occur superficial to fasciae	May enter the differential of a spindle cell tumour when comprised predominantly of fibrous areas with atypical stromal cells (ie, sclerosing variant), when there is smooth muscle differentiation (ie, lipoleiomyosarcoma) or when high-grade spindle cell transformation occurs ('dedifferentiated liposarcoma'); generally some adipocytic component ± lipoblasts	MDM2 and CDK4 expression in adipocytes and stromal cells

Continued

Table 1 Continued

Select spindle cell tumours	Clinical features	Characteristic morphological features	Immunophenotype (excluding vimentin) and cytogenetics
Myxoid liposarcoma	Preference for lower extremity	Multinodular proliferation of small round-ovoid cells within a myxoid matrix with prominent 'chicken-wire' vasculature; admixed lipoblasts; variable cellular small round cell component	t(12;16)(q13;p11) translocation resulting in a *FUS—CHOP* chimaeric gene
Muscle			
Leiomyoma	May be multiple/grouped; may be painful	May arise from erector pili muscle (piloleiomyoma), from blood vessels (angioleiomyoma) or from smooth musle bundles present in genital site (genital leiomyoma); appear as relatively well-circumscribed nodules composed of intersecting fascicles of plump fusiform ('cigar-shaped') nuclei often showing subnuclear vacuoles	SMA, desmin, calponin, h-caldesmon
Leiomyosarcoma	May demonstrate rapid enlargement or ulceration	As per leiomyoma with variable loss of recognisable differentiation and malignant features: cytological atypia often with extreme pleomorphism; mitotic activity ± atypical mitoses; often necrosis	SMA, desmin, calponin, h-caldesmon
Rhabdomyosarcoma (spindle cell variant)	Age: affects children	Fascicles of uniform fusiform spindle cells with prominent nucleoli and eosinophilic cytoplasm which may reveal cross-striations or scattered rhabdomyoblasts	Desmin, MSA, myoglobin, myoD1, myogenin
Vascular			
Spindle cell haemangioma	Location: typically distal extremities; often multinodular	Admixture of cellular spindle cells areas and vascular/cavernous spaces often lined by hobnailed endothelial cells; may be seen to originate from a large calibre vessel; negligible atypia and mitotic activity	Actin; vascular markers variably positive (CD34 often negative)
Kaposi sarcoma	HIV/immunocompromised; elderly	Variably dense (depending on stage), infiltrating proliferation of atypical and mitotically active spindle cells forming slit-like vascular spaces; extravasated RBCs; associated plasma cell infiltrate; eosinophilic globules	CD31, CD34, D2-40, FLI-1, HHV8
Kaposiform haemangioendothelioma	Age: birth—teenage years; thrombocytopenia (Kasabach—Merritt phenomenon); ill-defined violaceous plaque	Irregular nodules composed of Kaposi-like spindle cell areas, capillary haemangioma-like vascular areas and glomeruloid structures; presence of hyaline globules and haemosiderin	CD31, CD34, D2-40, FLI-1
Angiosarcoma, high-grade (spindle cell)	Sun exposure (eg, scalp in elderly); lymphoedema (ie, Stewart—Treves syndrome); post-radiation (eg, breast cancer); arising de novo in soft tissues	High-grade spindle cells are cellular highly atypical tumours which may show a number of cytomorphologies, commonly spindle cell; look for residual lower-grade areas showing evident vascular spaces lined by crowded, hyperchromatic and mitotically active endothelial cells	CD31, CD34, D2-40, FLI-1; variable loss of one or more markers when poorly differentiated
Other			
Myxoma	Association with Carney's complex	Circumscribed, lobulated lesion composed of small spindled to stellate cells embedded in a prominent myxoid stroma, often with prominent vascularity ('angiomyxoma')	SMA

Continued

Table 1 Continued

Select spindle cell tumours	Clinical features	Characteristic morphological features	Immunophenotype (excluding vimentin) and cytogenetics
Solitary fibrous tumour/haemangiopericytoma	Enlarging painless mass originating from soft tissue; hypoglycaemia in 5%	Circumscribed mass with biphasic pattern: (1) cellular areas composed of fusiform-spindled cells embedded in a fibrous stroma, and arranged in short fascicles or in a patternless manner; and (2) paucicellular myxoid or hyalinised areas; variably prominent staghorn HPC-like vessels; increased mitoses, necrosis or atypia suggest an atypical or malignant solitary fibrous tumour	- CD34, CD99, bcl2, SMA ±, EMA ±
Synovial sarcoma, monophasic variant	Age: adolescents/young adults; site: para-articular regions, mainly thigh/knee; deep-seated palpable mass ± pain	Cellular fascicular arrangement of relatively uniform fusiform spindle cells with high-grade features including numerous mitoses; stroma may be fibrous, hyalinised or myxoid; extensive sampling/careful examination may reveal the epithelioid/glandular component	Keratins, EMA, TLE1, CD99 ±; multiple variants of the t(X;18) translocation forming the *SYT—SSX* chimaeric gene
Epithelioid sarcoma, spindle cell ('fibroma-like') variant	Age: adolescents/young adults; site: distal extremities, mainly hand/wrist; slow-growing and painless; ulceration	Superficial or deep nodules composed of epithelioid and/or plump spindled cells with variable atypia often simulating a loose palisading/necrobiotic granulomatous reaction; superficial lesions typically ulcerate the surface; diagnosis often requires diagnostic consideration, clinical correlation and a diligent search for malignant features in the lesion	Co-expression of vimentin and keratin; EMA; CD34 ±
Metastatic sarcomas	Evidence of primary/metastatic disease	Depends on histogenetic origin of primary lesion, but often highly pleomorphic; deep dermal-based or subcutaneous-based lesions with evidence of vascular space invasion	Depends on primary lesion
Neural lesions			
Neuroma			
Traumatic	Sites of trauma/amputation (often digits); often painful	Variably sized irregular proliferation of mature nerves, commonly with background evidence of tissue injury (fibrosis, inflammation)	S100 (Schwann cells); EMA (perineurial cells); NF (axons)
Palisaded encapsulated neuroma	Face; adults; small dome-shaped papules; may be polypoid	Small, often multilobulated but well-circumscribed proliferation of fascicles of mature nerves; cellular palisading often appreciable; no true encapsulation	S100 (Schwann cells); EMA (perineurial cells); NF (axons)
Neurofibroma and variants	Rubbery nodules or polyps; multiple, diffuse or plexiform type associated with neurofibromatosis	Haphazard arrangement of all elements of a nerve embedded in a mucinous stroma with numerous admixed mast cells; generally well-circumscribed but non-encapsulated; slender wavy spindle cells; scattered collagen fibres reminiscent of 'shredded carrots'; many variants including plexiform, pigmented, deep and diffuse types	S100 (Schwann cells); NF (axons)
Schwannoma and variants	Deep-seated nodule; common to flexor aspects of extremities	Encapsulated nodule composed purely of Schwann cells without other elements of peripheral nerves; biphasic appearance with cellular (Antoni A) and myxoid paucicellular areas (Antoni B); slender wavy spindled cells with palisading that may form palisaded structures called Verocay bodies; thick-walled hyalinised vessels; variants include cellular, ancient, plexiform and melanotic	S100 diffusely and strongly positive
Perineurioma	Nodule usually present in subcutis	Well-circumscribed proliferation of fine spindle cells arranged in short intersecting fascicles embedded in a fibrous stroma; sclerosis may be prominent ('sclerosing perineurioma')	EMA

Continued

Table 1 Continued

Select spindle cell tumours	Clinical features	Characteristic morphological features	Immunophenotype (excluding vimentin) and cytogenetics
Neurothekeoma			
Nerve sheath myxoma	Young—middle-aged adults; female>male; head, neck and upper extremities preferred locations; skin-coloured rubbery nodules	Well-circumscribed paucicellular tumour composed of discrete lobules separated by fibrous septae; lobules composed of slender spindle cells embedded in a prominent myxoid stroma; atypical variant exists which shows higher-grade cytological features, mitotic activity, and greater cellularity	S100, collagen IV
Cellular neurothekeoma	Young adults; female>male; head, neck and upper extremities preferred locations	Cellular, infiltrative tumour composed of epithelioid or spindled cells arranged in a nested or fascicular pattern growing between dermal structures in a non-destructive manner; cells reveal prominent cytoplasm, nucleoli, ± focal atypia and/or moderate mitotic activity; stroma often fibrotic, hyalinised or occasionally myxoid	PGP9.5, CD10, MiTF±, SMA ±
Cutaneous meningioma	Dermal/subcutaneous nodule	Infiltrative dermal or subcutaneous nodule composed of epithelioid and/or spindled cells in a whorled pattern; calcifications may be present; atypia and mitotic rate are variable	Coexpression of vimentin and EMA; PR ±
Granular cell tumour	Uncommon solitary or occasionally multiple nodular lesions; preferentially affects tongue; more common in African-Americans especially when multiple	Infiltrative dermal or subcutaneous lesion (often subtle) comprised of bland epithelioid cells with small bland nuclei and abundant granular eosinophilic cytoplasm +/− larger intracytoplasmic eosinophilic bodies (cytoplasm is PAS +); often there is overlying pseudoepitheliomatous hyperplasia; spindling is an uncommon cytomorphology that may portend an atypical or malignant granular cell tumour - look for necrosis, cytological atypia, prominent nucleoli, increased mitotic rate (> 2 per 10hpf), increased nuclear: cytoplasmic ratio and pleomorphism of lesional cells	S-100, NSE, myelin basic protein +/−, Leu-7 +/−; EM shows pleomorphic lysosomes and may show evidence of neural differentiation (eg, myelin residues, neuritic processes)
Merkel cell carcinoma	Elderly; sun-exposed sites	Destructive, infiltrative and high-grade malignant tumour with necrosis, high mitotic rate, occasional surface ulceration; may see pagetoid spread; spindled morphology may be seen in rare cases; nuclei show 'salt and pepper' chromatin and lack nucleoli; minimal cytoplasm	CK20, LMWK, EMA and other keratins (often in a paranuclear dot-like pattern); synaptophysin; chromogranin; NSE
MPNST	Adults, associated with NF1 (patients may be younger) especially arising from plexiform neurofibromas	Deep-seated infiltrative tumour (rarely involves skin) composed of fascicles of uniform, mitotically active fusiform spindle cells often with a prominent 'herring-bone' pattern; variable atypia ± necrosis; stroma may be myxoid; heterologous differentiation; look for precursor lesion or areas with better neural features (eg, wavy nuclei, palisading nuclei)	S100 (half show focal/weak positivity; half are entirely negative); Leu-7 and myelin basic protein may be positive in a minority of cases
Fibrohistiocytic lesions			
Dermatofibroma	Common; dimple sign; often hyperpigmented	Interstitial dermal-based nodule comprising plump spindled cells (classically) with cellular densities ranging from inconspicuous to densely cellular lesions with mitotic activity ('cellular dermatofibroma'); collagen trapping; epidermal hyperplasia with tabling and basal layer hyperpigmentation and/or hyperplasia	Factor XIIIa; usually scattered cells stain for actins, CD68, S100 and CD34 as well

Continued

Table 1 Continued

Select spindle cell tumours	Clinical features	Characteristic morphological features	Immunophenotype (excluding vimentin) and cytogenetics
Spindle cell xanthogranuloma	Nodules on head and neck of young adults	Circumscribed dermal proliferation of primarily spindled cells with histiocytic features including vacuolated or foamy cytoplasm and reniform nuclei; collagenous stroma; look for giant cells including Touton forms and xanthomatous areas (typically rare)	CD68; lysozyme; factor XIIIa ±; SMA ±
Plexiform fibrohistiocytic tumour	Children and young adults; Extremities	Plexiform pattern lesion composed of two areas: (1) fibroblastic spindle cell areas arranged in sweeping fascicles; and (2) interspersed epithelioid granuloma-like areas with osteoclast-like giant cells	SMA in spindle cells; CD68 in epithelioid cells
DFSP	Young to middle age; trunk and proximal extremities; indurated plaque/multinodular mass	Infiltrative cellular proliferation of uniform bland spindle cells arranged in a short fascicular and storiform pattern within a fibrous or occasionally myxoid stroma; honeycomb infiltration of subcutaneous tissue; low mitotic rate; may be pigmented ('Bednar tumour') or show fibrosarcomatous degeneration	CD34; recurrent t(17;22) (q22;q13.1) translocation resulting in a *COL1A—PDGF-*βchimaeric gene
AFX/undifferentiated pleomorphic sarcoma	Sun-exposed site of elderly patients; often ulcerated; occasional history of radiation	Expansile dermal nodule composed of a pleomorphic cellular proliferation of highly atypical and mitotically active cells in a variable stroma (often fibrous); multinucleated giant cells; pure spindle cell variant exists; background evidence of solar injury	Variably positive for CD68, SMA, CD10, stromylesin-3; entrapped S100 and factor XIIIa-positive cells
Haematogenous			
Mastocytosis	Young or old; Darier's sign; may blister; cutaneous and systemic forms; histamine-related systemic symptoms	Diffuse or perivascular dermal infiltrate of atypical mast cells (often spindled); metachromatic granular cytoplasm; multilobated mast cells	Tryptase, CD117; c-kit mutations by PCR
Dendritic cell sarcomas			
Langerhans cell histiocytosis/sarcoma	Children; male>female; single or multiorgan disease	Diffuse dermal infiltration of oval cells with grooved nuclei and often epidermotropism; cells are generally not spindled; admixed inflammatory cells especially eosinophils	S100, CD1a; Birbeck granules on electron microscopy
Follicular dendritic cell sarcoma	Age: variable but mainly adults; skin rarely affected; slow-growing painless mass	Fascicular, whorling or storiform pattern of fusiform or oval spindle cells often with admixed epithelioid areas; cells show histiocytoid nuclear features (grooves, nucleoli, convolutions, multinucleation); prominent admixed lymphocytic component; atypia and mitotic rate variable but often low	CD21, CD35, CD23; variable positivity for S100 and CD68; desmosomal junctions and elongated cytoplasmic processes with electron microscopy
Interdigitating dendritic cell sarcoma	Age: variable but mainly adults; skin rarely affected; slow-growing painless mass	Fascicular, whorling or storiform pattern of fusiform or oval spindle cells often with admixed epithelioid areas; cells show histiocytoid nuclear features (grooves, nucleoli, convolutions, multinucleation); prominent admixed lymphocytic component; atypia and mitotic rate variable but often low	S100, CD68; admixed cells are T-cells (CD3+); interdigitating cytoplasmic processes on electron microscopy
Sarcomatoid lymphoma	Variable	Rare cytomorphological pattern of lymphomas (usually anaplastic large cell lymphomas or other T-cell lymphomas but reported cases of B-cell lymphomas as well); elongated hyperchromatic cells usually of high grade; may have myxoid stroma	Variable immunophenotype depending on underlying lymphoma subtype (CD30 and EMA; CD45 and CD3; CD45 and CD20)

Continued

Table 1 Continued

Select spindle cell tumours	Clinical features	Characteristic morphological features	Immunophenotype (excluding vimentin) and cytogenetics
Intermediate/reactive lesions			
Scar	History of trauma; may be skin-coloured or hyperpigmented	Circumscribed growth of variably cellular fibrous tissue arranged parallel to the surface with admixed vertically oriented vessels and loss of adnexal structures; overlying flattened epidermis with loss of rete pegs and basal layer hyperpigmentation ± melanocytic hyperplasia; mild atypia or occasional mitoses acceptable; stroma matures from slightly myxoid to sclerotic; keloidal collagen fibres often admixed or prominent	Actin ± (myofibroblastic differentiation); scattered S100-positive cells (entrapped Langerhans cells)
Nodular fasciitis	Young patients; preferred location is upper arm; recent onset and rapid growth; history of trauma ±	Zonal pattern of a spindle cell proliferation with a myxoid centre and a cellular/hyalinised fibrous periphery; cells are plump, tapered, with prominent nucleoli suggestive of myofibroblasts; patternless arrangement of cells ('tissue culture' pattern); mitotic activity variable; prominent admixed inflammatory component; micro-haemorrhages, haemosiderin, microcysts	Actins
Inflammatory myofibroblastic tumour	Children—young adults; rarely cutaneous; may have systemic symptoms (fever, malaise, anaemia, raised ESR)	Infiltrative lesion composed of spindle cells with minimal or low-grade atypia, collagen fibres, myxoid stroma, and admixed inflammatory cells including numerous eosinophils and plasma cells; architecture varies and includes nodular-fasciitis-like, fascicular/storiform and paucicellular/hyalinised; dense cellularity, high mitotic counts with atypical forms and necrosis portend a more aggressive course	Actins; ALK1 ±; keratins ±
Lesions expressing specific melanocytic markers			
PEComa, spindle cell variant ('clear cell myomelanocytic tumour')	Any age but mainly young adults; female>male; only rarely associated with tuberous sclerosis (strong association with angiomyolipoma)	Circumscribed masses with subtly infiltrative borders; typically epithelioid cells that are clear to faintly eosinophilic arranged in a nested, sheet-like or fascicular pattern; spindle cell morphology not uncommon; radial arrangement of cells around blood vessels; larger lesions with mitoses, high-grade atypia and necrosis should be interpreted as malignant PEComas	SMA, HMB-45, Melan-A, MiTF ±, desmin ±; S100 usually negative but occasionally positive
Clear cell sarcoma	Age: 20—40; site: lower extremity > upper extremity; slow-growing mass arising from aponeuroses	Multinodular mass comprising nests of uniform spindled cells with clear to lightly eosinophilic cytoplasm and prominent nucleoli; may have epithelioid areas; nests are separated by fibrous trabeculae; melanin often detectable (may require Fontana—Masson stain); multinucleated tumour, giant cells common	S100, HMB-45, Melan-A, MiTF; recurrent t(12;22)(q13;q12) producing a *ATF1—EWS* chimaeric gene

Lists diagnostic clinical, histopathological and immunohistochemical/molecular features of select non-melanocytic spindle cell cutaneous lesions (please refer to table 4 for a list of spindle cell melanocytic tumours). The most relevant spindle cell tumours that arise in the differential diagnosis of melanocytic spindle cell lesions are highlighted in bold. As vimentin may be positive in nearly any spindle cell tumour, its pattern of staining is not listed unless of particular relevance.
AFX, atypical fibroxanthoma; DFSP, dermatofibrosarcoma protuberans; EM, electron microscopy; EMA, epithelial membrane antigen; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; hpf, high power fields; LGMS, low-grade fibromyxoid sarcoma; LMWK, low molecular weight keratin; MiTF, microphthalmia transcription factor; MPNST, malignant peripheral nerve sheath tumour; MSA, muscle specific actin; NF, neurofilament; NF1, neurofibromatosis, type 1; NSE, neuron specific enolase; PEComa, perivascular epithelioid cell tumour; RBC, red blood cell; SMA, smooth muscle actin.

Box 1 Histomorphological features suggestive of melanocytic differentiation in a spindle cell lesion

Cytomorphological features suggestive of melanocytic differentiation
- Melanin pigmentation
  - consider other pigments: haemosiderin, exogenous pigment, lipofuscin
  - consider melanin production in non-melanocytic lesions
  - consider melanin incontinence in non-melanocytic lesions
- Intranuclear cytoplasmic inclusions
- Multinucleation
- Nucleoli (typically prominent in melanoma)
- Cytoplasm variable in terms of quantity and character

Architectural features suggestive of melanocytic differentiation
- Epidermal component
  - Junctional location
    - Nested pattern
    - Lentiginous pattern
  - Pagetoid pattern
- Dermal component
  - Nested pattern
  - Congenital pattern (including growth along adnexal and neurovascular structures; herniation of melanocytic nests into dilated lymphovascular structures)
  - Other patterns may also be seen (diffuse, trabecular, pseudovascular)
  - Evidence of dermal maturation
- Stromal response may be evident
  - Lymphocytic infiltrate/reaction
  - Dermal fibrosis
  - Presence of melanophages
  - Other regressive features (irregular scattering of lesional cells, vascular proliferation)

Other features consistent with a melanocytic lesion
- Look for background/admixed clear-cut melanocytic lesion
- Presence of solar elastosis (for certain entities)
- Macroscopic 'gross' features (pigmentation, ABCD criteria)
- Lack of features to suggest non-melanocytic origin (table 1)
- Histochemical staining
  - Fontana–Masson or Schmorl staining for melanin pigment
  - Melanin bleach
  - DOPA reaction to demonstrate tyrosinase activity
- Immunohistochemical phenotype (table 2)
- Ultrastructural demonstration of melanosomes/pre-melanosomes

approach to a spindle cell melanocytic lesion is to assess the lesion's biological/malignant potential. Classic pathological tenets teach us that such potential generally correlates very closely with cytological atypia/anaplasia (ie, cytological features) and invasive/destructive growth (ie, architectural features). Unfortunately, in the realm of melanocytic lesions, this approach may be misleading in a number of settings. For instance, Spitz naevi and naevoid melanomas are two examples where the degree of cytological atypia fails to reflect the true biological potential of the lesion. Spitz naevi, deep penetrating naevi and cellular blue naevi are examples of benign spindle cell melanocytic lesions that typically show infiltrative patterns that disguise their benign nature. Desmoplastic melanomas on the other hand are infiltrative lesions with full malignant potential. Furthermore, invasion is a difficult concept to appreciate in melanocytic lesions because precursor melanocytic cells/melanoblasts migrate from the neural crest through the dermis to reach their ultimate 'supposed' epidermal location (as well as other sites of normal melanocyte migration).[21 55 56] Hamartomatous malmigration may occur, resulting in a variety of dermal or combined lesions. Furthermore, naevic aggregates that have successfully completed upward migration through the dermis into the epidermis still undergo a normal maturation pattern of 'falling off' from their initial intraepidermal location with descent into the dermis. Thus there are no reliable tissue barriers available to evaluate definitive invasive growth. Rather, through the determination of malignant cytological and architectural features, a melanoma is considered 'invasive' (or perhaps more accurately, capable of local invasive behaviour and distant spread), once it is present within the dermis and thus potentially accessible to nerves, lymphatics and other vascular spaces. This, of course, presumes a junctional origin for melanoma; however, rare examples of completely intradermal melanomas are known (eg, malignant blue naevus, malignancy arising within the dermal component of a congenital naevus, primary dermal melanoma). Thus, in many respects, determination of the biological/malignant potential of a melanocytic lesion must rely on other evaluated features.

Owing to the high clinical detectability of cutaneous melanocytic lesions, their relative commonality, and their general ease of excision, there has accumulated a general wealth of experience that has permitted the correlation of histopathological features with biological behaviour. Unfortunately, no single feature (except in extreme cases) allows reliable discrimination of benignancy from malignancy. Rather, a gestalt impression is formed by weighing the relative value of numerous clinical and histopathological features with or without immunohistochemical features in order to predict the biological behaviour (and thus achieve a diagnosis) of a given lesion. It is this generalised understanding of the correlation between a host of histopathological features and biological outcomes that outlines the standard approach to melanocytic lesions (table 3). However, owing to the significant morphological variability of melanocytic lesions, there exist numerous examples of lesions that violate these generalised rules (eg, deep expansile cellular nodules in cellular blue naevi; cytological atypia and pagetoid activity in Spitz naevi), and so, phenotypic categories are created that permit a more precise assessment of the biological potential associated with each histological feature. It is with this objective that an initial pattern approach offers clinical value.

Architectural patterns of melanocytic spindle cell lesions

Recognising that a dogmatic cytomorphological and generalised architectural approach applied universally to spindle cell melanocytic lesions may be misleading, an architectural patterns approach may be used to categorise melanocytic lesions into specific recognised patterns for which generalised rules may be applied in a more reliable manner in order to qualitatively assess the biological potential of a given lesion. Four general architectural families can be defined (figure 3):

A. Compound naevoidal pattern
B. Spitzoid lesions
C. Intradermal proliferations
D. Horizontal orientation pattern

Assessment of biological potential follows somewhat differently for lesions in each pattern category. Ultimately it is the clinicopathological experience with different lesions that guides thresholds for diagnostic terminology. Each category will be discussed further in the following section with a focus on highlighting the features that allow most precise assessment of biological potential. Table 3 lists the features that should be

evaluated when a melanocytic lesion is encountered and states in a general way the impact that each has upon the estimated biological potential of the lesion. Of course, consideration must be given to the lesion being dealt with before applying relative weight to the findings (eg, pagetoid spread is of significant concern in a Clark's naevus but a well-established finding in benign acral naevi; perineural location of lesional cells may be seen in blue naevi but is otherwise generally indicative of malignancy).

Reaching a diagnosis

Outside of a few well-recognised melanocytic entities, the pathological diagnosis of melanocytic lesions is daunting for many. This is, in part, due to the great array of diagnostic terms available. The long list of existing melanocytic lesions reflects two aspects of melanocyte pathobiology:

1. The cytomorphological and architectural diversity of melanocytic lesions
2. The difficulty in recognising universally reliable histomorphological features to accurately reflect the biological potential of melanocytic lesions.

The first point reflects the traditional morphologist's view, in which diagnostic entities are defined by their histomorphological appearance (eg, neuroidal naevus, desmoplastic naevus, pigmented spindle cell naevus). The second point reflects the utilitarian need to communicate in a diagnostic term the clinical potential of a lesion (eg, naevi of special sites, atypical Spitz tumour, melanoma). Despite this great range of lesional names in melanocytic pathology, it should be remembered that the ultimate aim of diagnosis is to guide clinical management of a lesion, and so should reflect the biological potential of the lesion. Ultimately, this means that, despite the terminology used, a lesion fundamentally falls into one of three categories:

1. Benign—essentially no risk of aggressive/malignant biological potential (eg, compound naevus)
2. Atypical/borderline
   a. Atypical lesions—lesions that are overall consistent with a benign lesion but which display unsettling atypical features that may portend a more aggressive course (eg, atypical blue naevus, common or cellular)
   b. Lesions of uncertain biological potential—lesions that generally behave in a benign manner but with exceptions common enough to warrant conservative management (eg, cutaneous neurocristic hamartoma), or rare lesions for which the natural history is not confidently known (eg, plaque-type cellular blue naevi with satellitic nodules)
   c. Borderline lesions—lesions with pathological features that overlap with those of malignant entities to the point that assurance that the lesion is not in fact its malignant mimic cannot be reliably made (eg, Clark's naevus with high-grade atypia; junctional Clark's naevus bordering on melanoma in situ)
3. Malignant—malignant biological behaviour is predicted (or a significant risk to progress to such for in situ lesions) (eg, nodular melanoma)

In making diagnoses, one should thus concern oneself with the application of diagnostic terminology that relays precise transmission of the lesion's histogenetic origin and its risk of aggressive/malignant biological behaviour, thus facilitating appropriate clinical management decisions. Often melanocytic lesions may not fall neatly into any predefined category, and a descriptive diagnosis or qualifying statement may best accomplish this task. On occasion, we do find it acceptable to use the term 'melanocytic lesion of undetermined malignant potential' (MELTUMP) for lesions that exhibit features that raise concern about their biological potential, and also fail to satisfactorily show clinical, architectural and cytomorphological features to define them as an established entity. Such a diagnosis should not be ashamedly felt as a failing of the pathologist's diagnostic ability, but rather the final deduction that the biological potential of the lesion in question simply cannot be accurately predicted on the basis of clinical, histological and cytological data with or without other ancillary information, despite a diligent attempt to do so. In addition, there should be no better diagnostic term to reflect the histology of the lesion in a way that still communicates its uncertain biological potential (eg, atypical Spitz naevus, atypical cellular blue naevus, Clark's naevus with high-grade features). On such occasions, a comment is warranted to more precisely describe the pathological difficulty, estimate the biological risk of the lesion, and provide management recommendations. Nevertheless, optimal communication is best achieved when terminology is well defined and strongly established, and so, when possible, the most established and simplest diagnostic terms should be used. Thus, whenever possible, we do avoid terms, such as MELTUMP, that do not effectively communicate a lesion's biological potential or its architectural pattern. Towards this end, we begin our discussion of the most established and useful diagnostic entities within the spindle cell melanocytic spectrum (table 4) with a focus on the diagnostic features and potential pitfalls.

SPINDLE CELL MELANOCYTIC LESIONS

Compound naevoidal pattern lesions (figure 4)

The first architectural pattern is the 'compound naevoidal pattern', which exhibits underlying architectural features reminiscent of an ordinary naevocellular naevus, prototypically with both a junctional and an intradermal component (see box 2 for notable pitfalls). This is the most common melanocytic pattern encountered. Naevoidal pattern lesions are generally circumscribed and symmetric compound melanocytic lesions. They tend to present as macules or papules, but may also be dome-shaped, papillomatous or occasionally polypoid. Benign naevoidal lesions show organised growth that is often nested and lacking confluence or irregularity in pattern. Junctional shouldering should not be prominent. With age, compound naevoidal lesions tend to mature via descent into the dermis, and some lesions may thus lack an appreciable junctional component. Such lesions still maintain the remaining naevoidal features, and so are still considered consistent with an overall 'naevoidal' pattern, albeit intradermal rather than compound. Malignant lesions may preserve a naevoidal appearance, but generally show superimposed features of concern to varying degrees (eg, large size, dense confluent growth, deep expansile growth, pagetoid spread, dermal mitoses). Papillomatous or verruciform epidermal changes occasionally accompany both benign and malignant 'naevoidal' lesions. Cytomorphology may

Box 2 Notable challenges/pitfalls in the evaluation of naevoidal pattern spindle cell melanocytic lesions

Atypical spindle cell proliferation in a congenital naevus versus spindle cell melanoma arising within a congenital naevus.
Naevi of special sites exhibiting pseudomelanomatous features versus melanoma arising in special sites.
Diagnosis of naevoid melanoma with spindle cell morphology.
Spindle cell melanoma versus other spindle cell lesions.

Table 2 Immunohistochemical features of spindle cell melanocytic lesions

IHC stain	Description	Staining in spindle cell/desmoplastic melanomas	Staining in other spindle cell melanocytic lesions	Other lesions in the diagnosis of a spindle cell melanocytic lesion that may stain positively
S100	Acidic calcium-binding protein homodimer or heterodimer formed of three subunits ($\alpha\alpha$, $\alpha\beta$, $\beta\beta$); shows cytoplasmic and nuclear staining	Very high sensitivity (98.7%); moderate specificity	Highly sensitive for all melanocytic lesions	Neural lesions (neuroma, neurofibroma, schwannoma, classic neurothekeoma, MPNST) Langerhans cell histiocytosis/sarcoma Langerhans cell or S100+ dendritic component in other lesions (AFX, DF, scar, LMS) Interdigitating dendritic cell sarcoma Some epithelial lesions (eg, myoepithelial, adnexal lesions)
Melan-A/Mart-1	Protein component of the premelanosomal membrane Shows cytoplasmic staining	Low sensitivity (21.6%);very high specificity	Stratified pattern of staining with increased expression in junctional zone and superficial dermis Diffuse positivity in blue naevi, and occasionally in Spitz naevi	PEComa and related tumours Clear cell sarcoma Adrenocortical tumours Non-melanocytic tumours with melanin production
HMB-45	Premelanosomal glycoprotein gp100 Shows cytoplasmic staining	Low sensitivity (17.6%); very high specificity	Stratified pattern of staining with increased expression in junctional zone and superficial dermis Diffuse positivity in blue naevi, and occasionally in Spitz naevi	PEComa and related tumours Clear cell sarcoma Non-melanocytic tumours with melanin production
Tyrosinase	Melanosomal enzyme required for melanin synthesis Shows cytoplasmic staining	Low sensitivity (26.4%); very high specificity	Stratified pattern of staining with increased expression in junctional zone and superficial dermis Diffuse positivity in blue naevi, and occasionally in Spitz naevi	PEComa and related tumours Clear cell sarcoma Non-melanocytic tumours with melanin production
MiTF	Transcription factor expressed by melanocytes and critical for melanocyte development and expression of tyrosinase Shows nuclear staining	Low sensitivity (15.5%); moderate–high specificity	Sensitive stain for most melanocytic tumours May have slightly higher sensitivity for desmoplastic melanoma than other melanocytic specific markers	PEComa and related tumours Clear cell sarcoma Non-melanocytic tumours with melanin production Cellular neurothekeomas and rare expression in other neural lesions (NF, schwannoma) May be expressed by DF, AFX, smooth muscle neoplasms, and rare carcinomas
Other IHC stains that typically show positive staining in melanomas but which lack validated utility in the routine evaluation of melanocytic lesions	Vimentin – highly sensitive but completely non-specific especially in spindled forms NKI/C3 – another high-sensitivity but low-specificity antibody (lower sensitivity in desmoplastic melanoma) p75 – only low–moderate sensitivity and specificity for melanoma but has been advocated as a potentially useful marker in the diagnosis of desmoplastic melanoma CD117 (c-kit) – growth factor receptor crucial for melanocyte migration and development expressed in many melanocytic lesions including melanoma and Spitz naevi MIB-1/Ki67 – increased proliferative fraction (ie, > 10%) suggests a malignant process (although overlap exists, an unequivocally increased proliferative fraction (ie, > 20%), particularly when there is no decrease with depth of the lesion, strongly suggests melanoma) Cyclin D1 – another proliferation marker that may show increased expression in melanomas (and Spitz naevi) compared with other benign melanocytic lesions WT-1 – expression may suggest melanoma over benign melanocytic proliferations (other than Spitz naevi); expressed in desmoplastic melanoma Nestin – a stem cell marker of neural crest-derived cells that may be preserved in a proportion/majority of melanomas			
Other IHC stains that may show misleading positive staining in rare cases of melanoma	CD34 (also reported positivity in blue naevi and related lesions) Cytokeratins, epithelial membrane antigen Desmin CD68 CD10 CD56 CD57			

AFX, atypical fibroxanthoma; DF, dermatofibroma, IHC, immunohistochemistry; LMS, leiomyosarcoma; MiTF, microphthalmia transcription factor; MPNST, malignant peripheral nerve sheath tumour; NF, neurofibroma; PEComa, perivascular epithelioid cell tumour.

Table 3 General approach to melanocytic lesions: evaluation of clinical and pathological features

Histopathological feature	Favours benign	Favours malignant
Clinical		
Age	Children/young adult (<30 years)	Adults/elderly (≥30 years)
Gender/location	M=F; any location	M, trunk; F, trunk/lower extremities
Colour	Uniform brown	Variegated, black
Borders/circumscription	Irregular	Regular
Size/diameter	<10 mm	>10 mm
Symmetry	Symmetrical	Asymmetrical
Evolution	Stable lesion	New, changing or ulcerated lesion; symptomatic lesion (pain/pruritus)
Architectural		
Size	<10 mm	>10 mm
Symmetry	Symmetrical	Asymmetrical
Circumscription	Well circumscribed	Poor circumscription
Regularity†	Regular	Irregular
Density of growth	Uniform, non-dense	Dense, sheet-like or confluent growth
Pagetoid ascent of cells	Absent	*Present
Architectural maturation‡	Present	Absent
Epidermal reaction	Characteristic of certain lesions	Ulceration or 'consumption of epidermis'
Cytological		
Nuclear size	Small (less than keratinocyte)	Large (larger than keratinocyte)
Nuclear/cytoplasmic ratio	Low	High
Chromasia	Hypo/normochromatic	Hyperchromatic
Pleomorphism	Absent	Present
Nuclear membranes§	Regular: thin and uniform	Irregular: non-uniform thickenings, abnormal nuclear shapes
Nucleoli	Absent—variable/small	Present—macronucleoli, multiple nucleoli
Chromatin	Fine/dispersed	Coarse
Cellular cohesion	Cohesive	Dyscohesive
Pigmentation	Coarse melanin granules	Fine dusty melanin, amelanotic
Cytological maturation‡	Present	Absent¶
Stromal		
Lymphocytic infiltrate	Absent—Mild	Present (often 'brisk')
Plasma cells**	Absent	May be present
Regressive features††	Absent	May be present (partial or complete)
Solar elastosis	Absent or incidental	Supportive in certain lesions (desmoplastic melanoma, lentigo maligna, lentigo maligna melanoma)
Immunohistochemical‡‡		
Proliferative index (Ki67, MIB-1)	Negligible (<5%)	Increased (>15%)
Immunophenotypic maturation (HMB-45, proliferative index)‡	Stratified staining pattern with loss of dermal expression with descent	Diffuse positivity
Other		
Mitotic activity	Negligible; none in deep dermis	Increased numbers, deep dermal forms, clustering atypical forms, mitoses in pagetoid cells
Perineural invasion	Absent	May be present
Angiolymphatic invasion	Absent	May be present
Necrosis	Absent	May be present

*Benign exceptions exist—please see text.
†Regularity of growth refers to a nested (or occasionally diffuse) pattern that shows uniformity in size and shape of nests, and which does not reveal destructive growth or large expansile nodules.
‡Maturation may be evident in three ways: architectural—diminishment of nesting pattern with decrease in nest size; cytological—decrease in size of melanocytes with loss of cytoplasm and nucleoli; immunophenotypic—loss of activated melanocytic markers (HMB-45, decreased proliferative index).
§Intranuclear cytoplasmic inclusions are a common feature of melanocytes both benign and malignant and offer no discriminating value in terms of biological potential; however, other nuclear membrane irregularities are suggestive of an atypical/malignant lesion (eg, nuclear membrane thickenings, nuclear snouts/indentations/grooves).
¶Do not mistake a residual dermal naevic component as evidence of maturation.
**Plasma cells may accompany foci of scarring or concurrent inflammatory conditions.
††Regressive features include: fibrosis, mononuclear inflammatory infiltrate, vascular proliferation, presence of melanophages, and a scattered distribution of any remaining dermal component (ie, in partial regression).
‡‡See also table 2.

vary from bland and quiescent to overtly malignant. Distinguishing benign from malignant lesions exhibiting this pattern is generally not challenging, with the notable exception of naevoid melanoma, which is often a challenging diagnosis that may be revealed when there are subtle or pronounced deviations from the standard naevoidal architecture or bland cytomorphology in an otherwise naevoidal pattern lesion. In certain cases, the diagnosis may only be made in retrospect following clinically evident malignant behaviour of a lesion. The spindle cell melanocytic lesions characterised by a compound naevoidal pattern are discussed in turn as follows:

1. Neuroidal naevus/melanocytic naevus with neurotisation
2. Congenital naevus with spindle cell component
3. Naevi of special sites

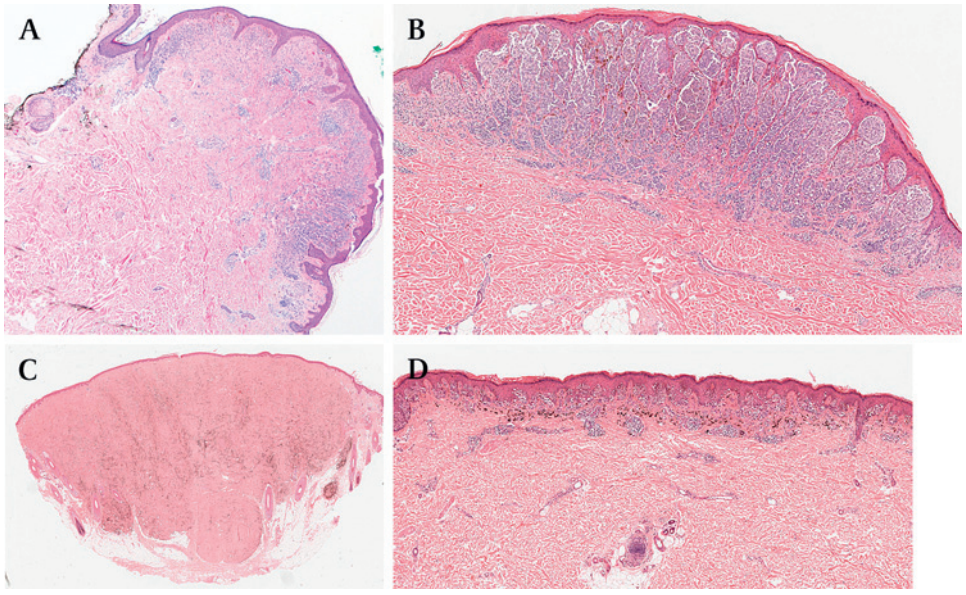

Figure 3 Architectural patterns of spindle cell melanocytic lesions. (A) Compound naevoidal pattern (H&E; 30×). Observe the well-circumscribed and symmetrical compound architecture of this compound naevus with partial dermal desmoplasia (49-year-old man; abdomen). The lesion is dome-shaped and shows prominent nesting and an organised appearance. Oval-type spindle melanocytes can be seen in the desmoplastic areas on higher power. The nature of the lesion is otherwise readily apparent from the surrounding type A naevocellular melanocytes. (B) Spitzoid pattern (H&E; 50×). Spitzoid lesions are characterised by both architectural features and cytological features (table 6 and figure 6). This atypical compound Spitz tumour (50-year-old woman; upper back) shows the typical Spitzoid silhouette including small size, sharp circumscription and prominent symmetry. Epidermal hyperplasia and retraction artifacts around large, vertically oriented junctional nests are also readily apparent. Partial dermal maturation may also be seen at low power. Concern regarding this lesion was raised because of its prominent epithelioid cell component and increased mitotic activity, including mitoses at the deep front of the lesion. (C) Intradermal pattern (H&E; 10×). This common blue naevus (67-year-old woman; posterior neck) shows an infiltrative melanocytic lesion confined to the dermis with prominent melanophages. The background dermis is fibrotic. The lesion is rather prominent, large and deeply infiltrative with a bulging margin, which is generally more in keeping with a cellular blue naevus; however, cellular areas were not noted to warrant a diagnosis of cellular blue naevus. This represents one typical pattern of intradermal melanocytic proliferations. A second pattern is the presence of nodular intradermal aggregates of spindled melanocytes in confluent nests or fascicles, as may be seen in metastatic melanoma or melanocytoma. (D) Horizontally oriented pattern (H&E; 20×). Prominent junctional/radial growth is characteristic of a number of melanocytic lesions, and such lesions may show spindle cell morphology, as seen in this compound Clark's naevus (33-year-old man; thigh). The junctional nests show architectural disruption compatible with a Clark's naevus. The prominent stromal reaction is also consistent. Higher-power examination revealed mild non-uniform cytological atypia. Occasional melanocytic lesions may exhibit an apparent horizontal orientation either due to the thinness of the dermal component or possibly as a result of its disruption.

4. Naevoid melanoma with spindle cell morphology
5. Nodular melanoma with a spindle cell component
6. Spindle cell melanoma

Neuroidal naevus/melanocytic naevus with neurotisation

Over time, certain melanocytic naevi may undergo a form of cytological maturation where they transform into Schwannian cells (ie, type C naevomelanocytes)[34 57] (figure 4A,B). These cells have bland wavy nuclei surrounded by a pale loose, occasionally mucinous or fibrotic stroma reminiscent of neural structures. Furthermore, the cells may be arranged in tactoid formations ('Wagner–Meissner corpuscles') further suggestive of a neural origin.[21 31] Mast cells may also be increased in these areas. Often these changes are only focal in the overall lesion with more characteristic type A or type B naevomelanocytes also present, often more superficially. Occasionally, the neurotisation may be complete or near-complete, making differentiation of the lesion from a neurofibroma difficult.[30 31] Nerve fascicle-like or even Verocay body-like structures may be observed in occasional cases.[58] Immunohistochemical staining for myelin basic protein, CD57 or glial fibrillary acid protein may be discriminating features in uncertain cases, with positivity favouring neurofibroma or possibly another neural lesion.[21 58] Pigment is rarely expressed in such lesions and S100 is non-discriminatory. More specific melanocytic markers are generally not preserved in type C naevomelanocytes, as they typically do not exhibit melanosomes or tyrosinase activity.[35] Ultrastructurally, neurotised naevic cells do not show true Schwannian differentiation because of a lack of axonal or mesaxonal structures, and may reveal the rare melanosome.[34 57 58] Overall, neuroidal naevi generally are not clinically concerning, and show an overall naevoidal pattern lacking any atypical cytological or architectural features, and so are easily recognised as benign. A junctional component to the lesion may be lacking, in contrast with the prototypical naevoidal pattern. Histopathological consideration of this form of melanocytic maturation is generally sufficient to make the diagnosis, and careful inspection for type A or B naevomelanocytic areas or a residual junctional component should be used to achieve greater certainty. Finally, there is no clinical utility in noting this phenomenon in the diagnostic report, and the lesion may be simply reported as 'compound naevus' or 'intradermal naevus'.

Congenital naevi with spindle cell component

Congenital melanocytic naevi may be evident in one of two ways: (1) clinical history of a congenital (or tardive congenital) pigmented lesion which may be stable or changing; (2) recognisable architectural features suggestive of a congenital naevus in the absence of a clinical history (ie, 'melanocytic naevus with congenital pattern'). Activated areas or proliferative nodules may account for the clinical history of a 'changing naevus', but, of course, so can the development of a melanoma arising within

Table 4 Melanocytic lesions that characteristically or occasionally show a spindle cell cytomorphology

	Lesions that characteristically or commonly show spindle cells	Lesions that occasionally show spindle cells
Naevoidal pattern	Neuroidal naevus Naevus with desmoplasia Spindle cell melanoma	Congenital naevus Naevi of special sites Naevoidal melanoma Nodular melanoma
Spitzoid lesions	Spitz naevus Atypical Spitz tumour Spitzoid melanoma Pigmented spindle cell naevus (of Reed) Atypical pigmented spindle cell naevus	
Intradermal proliferations	Dermal melanocytoses Common blue naevus (and variants) Cellular blue naevus Cellular blue naevus with Satellitic nodules Atypical blue naevus Malignant blue naevus Deep penetrating naevus Spindle cell plexiform naevus Cutaneous neurocristic hamartoma Desmoplastic naevus/desmoplastic Spitz naevus Desmoplastic/neurotropic melanoma	Melanocytoma Paraganglioma-like dermal melanocytic tumour Primary dermal melanoma Metastatic melanoma
Horizontally oriented lesions	Clark's naevus with Spitzoid morphology ('SPARK' naevus) Melanoma in situ of the solar type ('lentigo maligna') Melanoma of the solar type ('lentigo maligna melanoma')	Clark's naevus ('dysplastic' naevus) Recurrent naevus phenomenon Sclerosing naevus with pseudomelanomatous features Traumatised or treated naevi Naevi associated with inflammatory dermatoses Melanoma in situ Superficial spreading melanoma Acral lentiginous melanoma Vulvar melanoma
Mixed pattern lesions	Combined naevus	
Undefined pattern lesions		Melanocytic lesion of undetermined malignant potential ('MELTUMP')

a congenital naevus.[59 60] Architectural features that are suggestive of a congenital naevus include larger size (although congenital naevi may also be small), a diffusely infiltrative horizontal component of naevomelanocytes, a deeply penetrating component involving the lower third of the reticular dermis or even the subcutis, and prominent extension of lesional cells along adnexal and neurovascular structures.[30 31 56] Often, congenital naevi show lesional cells herniating into dilated lymphovascular spaces simulating vascular invasion. Congenital naevi also have a great capacity for heterologous morphology, including neuroidal differentiation and spindle cell morphology[31 35] (figure 4C,D). Variants of congenital naevi may be entirely spindled, may show prominent neurotisation suggestive of a neural lesion (as per the neuroidal naevus phenomenon—see above), may show blue naevus-like morphology, or may show cellular proliferative nodules or clonal areas with a spindle cell morphology.[31 59] Melanisation may be preserved in the spindle cell component of a congenital naevus, aiding histogenetic determination. Assessing the biological potential of congenital melanocytic naevi may be difficult because of the possible presence of mild cytological atypia, nucleoli, architectural irregularities and limited mitotic activity which may be seen in some cases, either diffusely within the lesion or focally within a proliferative nodule.[16 59 61] Compounding the difficulty is the potential preanalytical bias that may exist with the clinical picture of, often, a large lesion that is potentially changing and the knowledge that congenital naevi (especially giant congenital naevi) are relatively fertile ground for the development of melanoma.[61] Confound this further with the presence of a heterologous spindle cell morphology, either in part or whole, and the lesion may just be too disconcerting. Nevertheless, it should be recognised that all of these features are acceptable benign features of a congenital naevus which lacks aggressive/malignant potential. Assessment of biological potential must therefore rely on more established features of atypicality: uniform moderate—severe cytological atypia with prominent macronucleoli, confluent and irregular growth, destructive expansile or infiltrative growth including surface ulceration and necrosis, pagetoid activity (except in infants), lack of maturation, prominent dermal mitotic activity especially in the deeper portions of the lesion, etc. Proliferative nodules in congenital naevi are recognised by the relative rarity of mitoses (and the low proliferative index), evidence of maturational blending with surrounding naevic cells, and the lack of necrosis or destructive expansile growth.[16 59 61] Cytological atypia is variable but usually low grade, although significant pleomorphism can be seen. Nevertheless, the biological potential of proliferative nodules, although seemingly benign, is not fully known, and we do recommend excision of such lesions when clinically feasible. Melanoma may arise in small—medium-sized congenital naevi (as well as acquired naevi), but typically does so in the junctional component, recapitulating the pattern of a superficial spreading or nodular melanoma with overt malignant features.[30] Large congenital naevi may occasionally demonstrate malignant degeneration in the form of a dermal nodule. The malignant nature of melanomas arising within congenital naevi may be inferred from an expansile and destructive nodule, with abrupt demarcation from the surrounding lesion and often extension into the subcutaneous tissue with or without prominent tumoural necrosis, and a marked increase in mitotic activity.[59 61]

Naevi of special sites

Part of the appreciation of the biological diversity of melanocytic lesions has occurred as a result of the recognition that certain histopathologically disturbing melanocytic lesions may predictably behave in a benign manner (see figure 8 of Part II).[21a] Such clinicopathological correlation led to the recognition that benign naevi present in certain sites may exhibit histological features that normally connote an aggressive biological potential. The

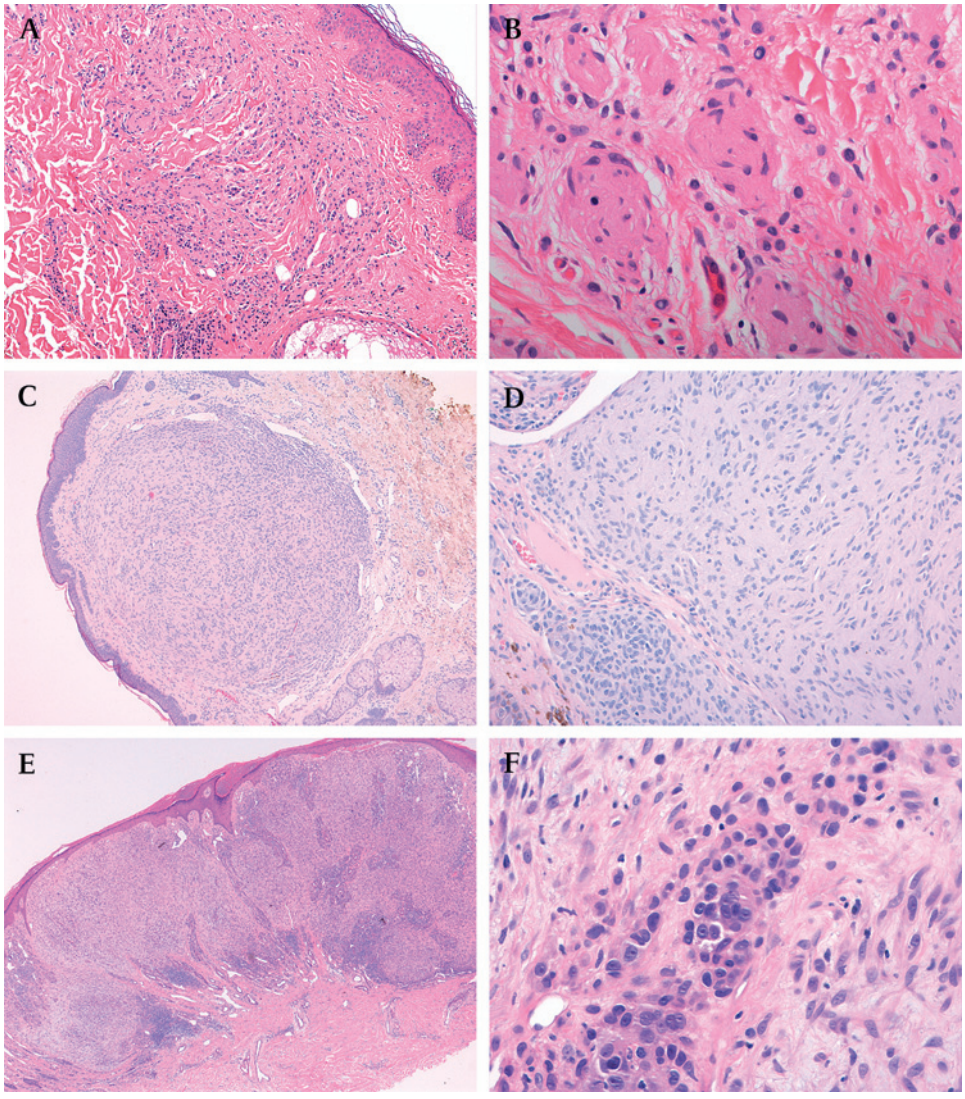

Figure 4 Compound naevoidal pattern lesions. (A) Neuroidal naevus (H&E; 100×). Observe the preservation of an overall 'naevoidal' pattern (although no junctional component is appreciated) in this lesion clinically suspected to be an intradermal naevus removed from the shoulder of a 56-year-old woman. (B) Neuroidal naevus (H&E; 400×). High-power examination highlights the neuroidal cytomorphology and the tactoid body formations. (C) Congenital naevus with spindle cell nodule (H&E; 50×). This congenital naevus removed from the back of a 22-year-old woman revealed numerous spindle cell areas including this nodule. (D) Congenital naevus with spindle cell nodule (H&E; 200×). Observe the bland cytomorphology of another spindle cell nodule and observe the more classic epithelioid naevomelanocytic nests present superficial to the nodule. (E) Naevoid melanoma with spindle cell morphology (H&E; 25×). This spindle cell melanocytic lesion presented as a changing lesion in a 45-year-old man. Notice the relative preservation of a naevoidal appearance, however, with an expansive and confluent dermal component. A prominent inflammatory reaction is also observed. (F) Naevoid melanoma with spindle cell morphology (H&E; 400×). High-power evaluation reveals the relative banal appearance of the spindled lesional cells. This focus also shows the presence of small but moderately atypical epithelioid melanocytes more recognisable as naevoid melanoma. This component was very limited and not seen in all sections. Lymphatic space invasion was also present (not shown) confirming the malignant nature of this lesion.

most classic and well defined of these special sites are acral locations[16 62–65] and the vulva.[16 62 66 67] The male genitalia, anorectal region and perineum may also be considered 'genital sites', with features akin to vulvar naevi; however, these sites are not as well studied. Other recognised special sites include the breast,[68] flexural sites[69] (ie, axilla, umbilicus, inguinal region, popliteal fossa or any other site that exists in a tissue fold such as the neck skin or abdominal folds), the ear[70 71] and scalp.[72] For most of these regions, chronic irritation of the lesion appears to be the most theoretically consistent explanation for the unusual features. Alternatively, hormonal factors have also been put forward as a possible explanation, albeit with some scepticism. The conjunctiva represents a non-cutaneous special site.[62 73 74] Spindling may be seen in naevi from special sites, and, in

Table 5 Atypical histological features characteristic of naevi from special sites

	Architectural distortion									
Special site	Irregular/confluent junctional nests	Dense dermal growth	Lentiginous growth	Pagetoid spread	Cellular dyscohesion	Cytological atypia	Dermal mitotic activity	Stromal reaction*	Spindled morphology	Major differential diagnosis
Acral	++	–	++	++	–	±	–	+	+	Acral lentiginous melanoma
Vulvar	+	++	+	±	++	++	+	++	+	Nodular melanoma
Breast	+	–	–	+	–	+	–	+	±	Superficial spreading melanoma
Flexural	+	–	–	+	±	+	–	+	±	Superficial spreading melanoma
Ear and scalp	+	–	+	+	+	+	–	+	±	Superficial spreading melanoma

*Stromal reaction pattern is usually present as papillary dermal fibroplasia (concentric, lamellar) with an inflammatory infiltrate. However, in vulvar naevi the stromal reaction may be inconspicuous or have a unique pattern showing a broad zone of eosinophilic fibrosis involving much of the dermis ± a variable inflammatory infiltrate.
–, unusual feature; ±, rare or occasional feature; +, common feature; ++, characteristic feature.

particular, is notably a feature of vulvar naevi.[62] Spindling on its own is not a feature that raises the potential risk of a lesion. Such an analysis requires evaluation of standard features with an understanding of the permissible site-related atypia (table 5).

Clinically, naevi of special sites are generally small with a banal appearance, but may occasionally show some heterogeneity in coloration, an asymmetrical profile and lack of good circumscription. Lesions tend to be stable, often over a long period of time. Spontaneous ulceration, pruritic change or a change in size or coloration may herald more ominous clinical events, warranting excision and pathological assessment. The histology of naevi removed from special sites is indistinguishable from naevi removed from other sites in most cases. However, occasional cases do show a range of architectural and histological features that deviate from the norm, features that are generally associated with melanoma (table 5). The most well recognised of these features is the possible presence of pagetoid ascension of cells. This is a well-established phenomenon in acral naevi, probably due to chronic irritation of lesions in such sites. In fact, the term 'MANIAC' (melanocytic acral naevus with intraepithelial ascent of cells) has been proposed to raise awareness of the possible occurrence of pagetoid activity in an otherwise benign acral naevus.[75] Clues as to the benign nature of the pagetoid activity in naevi from special sites are the concurrent presence of melanocytic nests undergoing transepidermal elimination, a preferential syringotropic localisation of the pagetoid activity, and the presence of pigment in the stratum corneum.[62] Pagetoid cells should be banal and should not show mitotic activity. Architecturally, naevi from special sites are small and have a symmetrical and well-circumscribed silhouette; however, this may not be appreciated depending on the completeness of excision and the sectioning of the lesion. Lesions generally show bland cytology, a lack of mitotic activity and evidence of maturation; however, irritative effects may induce changes in all three of these parameters. In cases where such features are present, they need to be interpreted within the context of the remainder of the lesion. As always, multiple dermal mitoses (especially when located deeply), high-grade cytological atypia and a complete lack of maturation are all concerning features that should trigger complete excision of a lesion. A rare mitosis or mild cytological atypia may be acceptable within an otherwise small and symmetrical lesion with no evidence of confluent growth. Vulvar naevi, however, may notably show cytological atypia, and often an alarming degree of dermal growth including occasional mitoses. Clark *et al*[76] originally described three abnormal architectural patterns of vulvar naevi: (1) the 'nested' pattern; (2) the 'dyshesive nest' pattern; and (3) the 'crowded' pattern. However, lesions often show overlapping patterns. Clinical parameters are crucial in such cases, as the threshold for diagnosing a melanoma in a young patient should be very high because of its extreme rarity. In contrast, a vulvar melanocytic lesion should be eyed suspiciously in an older patient if it has worrisome clinical or histological features. Vulvar melanomas tend to present as clinically evolving lesions in postmenopausal women, with a histological picture of a crowded lentiginous proliferation of atypical melanocytes.[66] This is in contrast with the more typical dermal proliferation and young patient age for vulvar naevi. Prominent lentiginous growth is, however, a feature that may be seen in naevi from special sites, even to the point of apparent confluence. A stromal response is also commonly encountered in naevi from special sites and includes papillary dermal fibroplasias (both lamellar and concentric), and occasionally a unique diffuse pattern of dermal fibrosis which may be confused with desmoplasia or regression.[62 66] Recognition and proper assessment of the site-related deviant cytological and architectural features, particularly when taken in the context of the patient's age and other clinical parameters, is crucial in order to avoid the systematic overcalling of biologically inert lesions biopsied from such sites. Conversely, recognition of the site-related atypia phenomenon may also lead to undercalling of truly atypical lesions.

Naevoid melanoma with spindle cell morphology

Naevoid melanoma is a challenging diagnosis in melanocytic pathology. The term is relatively poorly defined, but may be used to encompasses a heterogeneous histological spectrum of malignant melanocytic lesions ranging from those histologically unrecognisable as malignant but which subsequently behave in a malignant manner[77] to those atypical melanocytic lesions composed of small (albeit atypical) 'naevoidal' melanocytes arranged in an overall pattern suggestive of a naevus but which display features that are concerning enough to warrant the label of melanoma[78–80] (figure 4E,F). Naevoid melanomas may be encountered in both young and old patients, often as a moderately sized tan nodule which may be verruciform in some cases (verruciform pseudonaevoid melanoma[81]). Although classically epithelioid in morphology, spindle cell naevoid melanomas may also be encountered.[78] Such lesions may often be recognised by the presence, albeit subtle, of cytological atypia, mitotic activity and irregular, often somewhat confluent, growth.[16 17] Commonly, the most telling feature is a large nodule with an expansile front that may reach or extend into the subcutis. In addition, there is generally no evidence of maturation. Ancillary immunohistochemical staining with HMB-45 and MIB-1 may further highlight the atypicality, increased proliferative rate, and lack of maturation of these lesions.[78 80] Needless to say, any melanocytic lesion, particularly in the setting of a new or changing lesion or one in an older patient, should be carefully scrutinised for malignant features. Although low-power examination reveals a variable degree of distortion of an underlying benign-appearing silhouette as well as a variable degree of cytological enlargement, hyperchromasia and nuclear atypia, close high-power scrutiny is generally the key to recognition and ultimate diagnosis. Evaluation of the biological potential of a naevoidal lesion should follow a standard approach to melanocytic lesions (table 3). Intradepartmental or external consultative opinions may be sought in challenging cases.

Nodular melanoma with a spindle cell component

By definition, nodular melanoma is a neoplastic proliferation of malignant melanocytes exhibiting a vertical growth phase in the absence of a horizontal growth phase.[82] A horizontal growth phase is considered to be present when the intraepidermal/junctional component of the lesion does not extend peripherally more than three adjacent rete ridges beyond the dermal component of the nodule. Such lesions probably arise from the rapid development of a melanoma into an invasive phenotype thereby avoiding a prolonged precursor horizontal growth phase. Clinically, nodular melanomas are a relatively common subtype of melanoma seen more often in older people. Lesions are characteristically rapid-growing dark nodules or polyps that commonly ulcerate and crust. Amelanotic forms are also known. Histologically, nodular melanomas preserve a compound naevoidal pattern, although, not uncommonly, ulceration obliterates the majority of the epidermal component. When preserved, the epidermis reveals an in situ component, which may reveal pagetoid activity. By definition, lesions are circumscribed (in the horizontal plane) and also generally maintain

a relatively symmetrical silhouette. The lesions are often of moderate–large size, with destructive expansile growth, dense confluence of cells, lack of dermal maturation and variable cytological atypia. Mitotic activity is generally appreciable and often high. This may further be highlighted by Ki67 or MIB-1 labelling. Spindling can be seen, and may even be the prominent cytomorphology. However, epithelioid areas are generally also present to varying extents.[8] Uniform spindling in an otherwise nodular melanoma overlaps with the generic term 'spindle cell melanoma' (see below). Spindle cell nodular melanomas are generally not difficult to diagnose. Deviant clinical, architectural and cytological features generally allow easy recognition of its malignant nature. Occasional cases may exhibit less pronounced aggressive features, but careful scrutiny usually will reveal sufficient dermal mitoses, appreciable cytological atypia or other features to permit diagnosis. In such cases, an increased proliferative fraction or immunohistochemical demonstration of a lack of maturation (eg, diffuse HMB-45 staining) may offer some assistance in diagnosis. A careful search for residual epithelioid areas, particularly in the junctional/superficial areas, helps eliminate consideration of non-melanocytic entities in challenging cases. Efforts to develop other antibodies in the diagnosis of melanoma are ongoing, with WT-1[43 47 54 83] and nestin[51–53 84] offering two potential aids in the determination of melanomas. However, the reliable utility of these antibodies has not yet been fully established.

Spindle cell melanoma

The generic term 'spindle cell melanoma' refers to a malignant melanocytic lesion with a uniform spindle cell cytomorphology. In many cases, such lesions are, in fact, nodular melanomas with complete spindled morphology. Both acral melanomas and melanomas of the solar type ('lentigo maligna melanoma') also often exhibit a spindled morphology. Both of these are generally easily recognised despite their cytomorphology on clinical and other histopathological grounds. In such cases, these terms are preferred, and we generally do not use the diagnostic term 'spindle cell melanoma' except when more precise resolution cannot be attained. The true challenge in most cases is in distinguishing such lesions from non-melanocytic spindle cell lesions (table 1). This requires careful histological scrutiny of the lesions for evidence of melanocytic differentiation (box 1) or evidence of another form of differentiation, as well as immunohistochemical confirmation (S100, other melanocytic markers, negativity for markers suggestive of other entities in the differential diagnosis). Challenging cases may arise, particularly since the more specific melanocytic immunostains are often negative in spindle cell melanomas. Multiple antibodies should be used, as occasionally MiTF or tyrosinase will show positivity despite the absence of staining with HMB-45 and Melan-A. WT-1 expression may offer some support to a presumptive diagnosis of melanoma, although its specificity is lower than that of the aforementioned stains. We do not consider S100 positivity alone to be definitive evidence of melanoma in cases that lack other evidence of melanocytic differentiation (nesting pattern, melanin production, junctional component, other immunohistochemical evidence, background melanocytic lesion). S100 positivity is also seen in neural lesions (although MPNSTs are generally only focally S100 positive and often negative). Langerhans cell lesions are also S100-positive lesions and may reveal misleading pagetoid spread.[14 85] Atypical fibroxanthomas and cellular dermatofibromas may show scattered S100-positive Langerhans cells.[29] We have also seen three cases of interdigitating dendritic sarcomas misdiagnosed as melanomas on the basis of their diffuse S100 positivity. Clinical correlation is often crucial in resolving such issues. Ultrastructural studies may also provide additional support for or against spindle cell melanoma in challenging situations (box 1).

Spitzoid lesions

The next group of recognisable spindle cell melanocytic lesions is the Spitzoid family (refer to Box 3 for notable pitfalls). The name 'Spitzoid' represents a distinct architectural and cytological pattern, which, when present in the classical form, is readily identifiable (figures 3B and 5 and table 6). Spitzoid lesions are classically well-circumscribed, symmetrical lesions that may be junctional, compound or, rarely, intradermal.[30 31 86] Compound lesions may extend deep into the dermis often in a subtly infiltrative manner, and often with discrete isolated cells or small nests present deep to the main body of the tumour ('outlier cells').[30] Spitzoid lesions by definition are composed of enlarged spindled and/or epithelioid melanocytes that typically show nucleoli and a variable degree of cytological atypia.[87 88] Multinucleation is commonly encountered in Spitzoid lesions, and nuclei characteristically show angulations and geometric forms. Cells may also fit together creating geometrical patterns. Significant eosinophilic cytoplasmic substance generally preserves a low N/C ratio in lesional cells, and may reveal a bluish tinge. Classically, Spitzoid lesions are amelanotic or hypopigmented, although hyperpigmented variants do exist. Architecturally, Spitzoid lesions may show pagetoid activity even when benign. As well, limited superficial dermal mitotic activity is permissible in benign Spitzoid lesions, although deep dermal mitoses, atypical mitoses or clustering of mitotic figures remain atypical features.[86] Spitzoid lesions are notorious for their histological overlap with melanoma, highlighted by the historic use of the outdated term 'benign juvenile melanoma' for classic Spitz naevi. The fact that Spitzoid lesions are more commonly encountered in younger populations (<20 years) compounds the need for caution in the pathological interpretation of these lesions. Fortunately, recognition of Spitzoid lesions may be aided by additional characteristic histological features including epidermal hyperplasia surrounding the junctional nests, a vertical ('raining down') orientation of junctional nests, the presence of intraepidermal eosinophilic globules ('Kamino bodies'), and artifactual stromal retraction around junctional nests ('semilunar clefts').[30 31 86 89–91] The utility of identifying Spitzoid morphology is in the recognition that certain otherwise concerning histological features may not be indicative of aggressive biological potential.

On the other hand, there are persistent concerns regarding Spitzoid lesions, in particular, the lack of pathological criteria to assuredly determine benignancy in a Spitzoid lesion.[92–98] Clinical follow-up of classic lesions in most cases reveals a benign course. Yet rare cases, particularly with the accumulation of atypical

Box 3 Notable challenges/pitfalls in the evaluation of Spitzoid melanocytic lesions

Spitz tumours versus melanoma.
Placement of Spitzoid lesions on the Spitz naevus–atypical Spitz naevus–Spitzoid melanoma spectrum.
Pigmented spindle cell naevus of Reed versus Clark's naevus.
Pigmented spindle cell naevus of Reed versus melanoma in situ/superficial spreading melanoma.

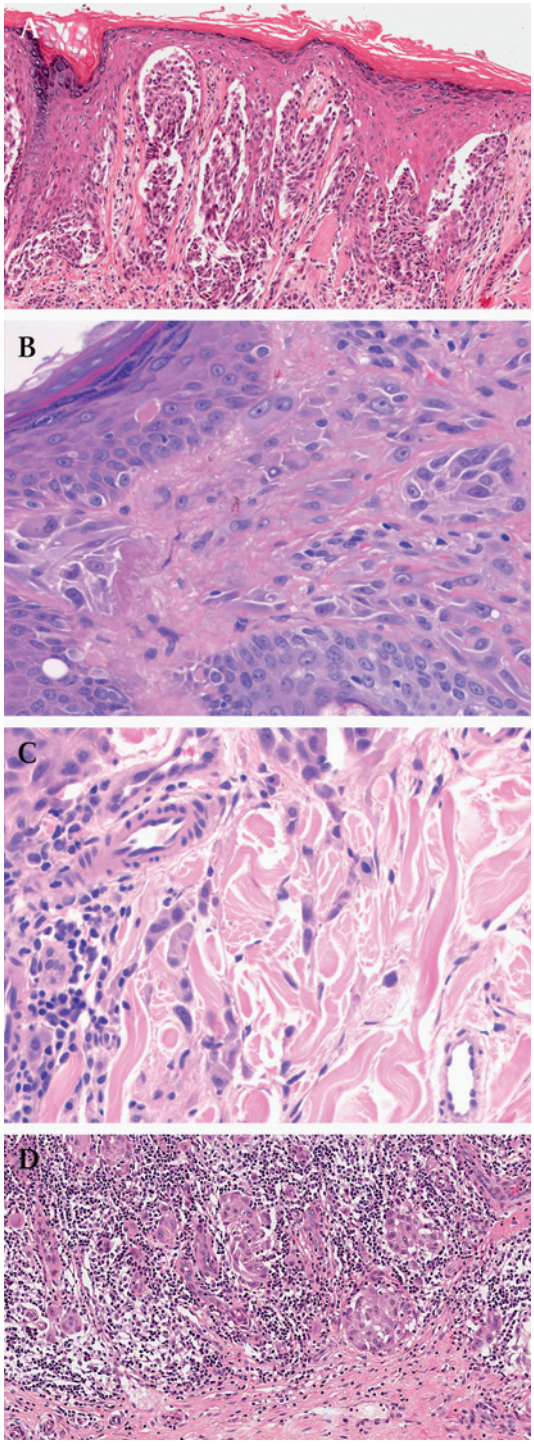

Figure 5 Histological features that characterise Spitzoid lesions. (A) Epidermal features (H&E; 200×). This compound Spitz naevus (16-year-old boy; lower back) shows epidermal hyperplasia with hypegranulosis surrounding nests of epithelioid and spindled Spitzoid melanocytes with a vertical orientation. Artifactual clefting around junctional nests ('semilunar clefting') is well appreciated. Kamino bodies and mild pagetoid activity are also present. A single junctional mitotic figure is also noted. (B) Cytological features (H&E; 400×). Classic Spitzoid cytomorphology is revealed in this compound Spitz naevus (27-year-old woman; nose). Enlarged amelanotic melanocytes with spindled, epithelioid, and intermediate cytomorphologies can be seen. The N/C ratio is low due to the presence of abundant cytoplasmic substance which displays a bluish tinge. Cytological atypia are moderate with angulated nuclei and moderate pleomorphism. Nucleoli are prominent. However, there is no significant hyperchromasia, chromatin is dispersed, and nuclear membranes are regular, consistent with a benign Spitz naevus. Multinucleation is noted in occasional cells. A small Kamino body is also noted in the epidermis. (C) Dermal architecture (H&E; 400×). The deep aspect of this compound Spitz naevus (same lesion as in (B)) reveals an infiltrative pattern with the presence of 'outlier' cells at a distance from the apparent front of the lesion. Architectural and cytological maturation of the lesional cells are apparent. (D) Atypical Spitzoid features (H&E; 200×). This atypical Spitz tumour (46-year-old woman; lower leg) showed a characteristic Spitzoid silhouette (small size, symmetry and circumscription) and cytomorphology. Concern for the lesion centred around its prominent epithelioid morphology (in an adult) and the lack of architectural or cytological maturation (note the large nests towards the deep front of the lesion). The prominent inflammation is also somewhat unusual. Sentinel lymph node biopsy was negative.

features, still have unexpected clinical outcomes, from the presence of sentinel node deposits but an otherwise benign course to disseminated metastases and death.[96 97 99–105] This uncertainty has led some to prefer usage of the term 'Spitz tumour' to 'Spitz naevi' for all except perhaps only the most classic cases of Spitz naevi.[96] As a result, Spitz naevi are ideally completely excised when it is clinically feasible.[21 92 96] This is also required since proper pathological evaluation must assess a lesion in its entirety because of the extreme importance of assessing the lesion's silhouette to identify its Spitzoid nature and form an estimate of its biological potential. Atypical lesions must be managed more conservatively. Furthermore, there has been some evolution of the concept of the Spitz naevus from a mainly paediatric melanocytic tumour, with histological features overlapping those of adult melanoma, but with an almost certain benign course when showing classical features, to a morphological entity recognised not only in children but also in adults, in which the concern for mistaken identity becomes more significant, particularly when there is partial deviation from the classical phenotype. Appropriate evaluation of Spitzoid lesions thus needs to proceed in two parallel ways (figure 6):

1. Histopathological assessment of the lesion in order to assess atypical features and thus grade the degree of atypia, placing the lesion on a poorly defined spectrum of Spitzoid lesions (ie, is it an atypical lesion?)
2. Clinical assessment of the lesion (ie, age, location, colour, size, silhouette) in order to best predict the pretest probability that the lesion is, in fact, a melanoma, regardless of histological features (ie, is it a borderline lesion?)

Assessment of the clinical parameters adjusts the thresholds for translating the extent of deviation from a classical Spitz phenotype to a specific diagnosis. For example, there should be great resistance to diagnosing a Spitz naevus in an older patient because of the significant risk that the lesion is a melanoma with Spitzoid features.[86] In contrast, in a child, one should be wary before diagnosing a Spitzoid lesion with highly deviant features as a melanoma unless truly convincing malignant features are present. Needless to say, such a lesion should certainly be diagnosed in a manner that reflects its atypicality, its potential for aggressive behaviour, and the histopathological limits to ruling out a melanoma. Juvenile melanomas do certainly exist, and many tragic cases attest to the potential malignant behaviour of atypical melanocytic lesions in the paediatric population. Furthermore, it should be emphasised that the ultimate diagnosis should not be based on the pretest probability of the lesion representing a melanoma (ie, essentially the relative incidence of the lesions in the differential diagnosis) but rather the post-test probability that the lesion will behave in a biologically

Table 6 Features of Spitzoid lesions

Feature	Spitz naevus	Atypical Spitz tumour	Spitzoid melanoma
Clinical			
Age	Any age (2/3 < 20 years)	No difference	No difference
Location	Any location (extremities and trunk preferred; H&N in children)	No difference	No difference
Colour	Red–brown; occasionally pigmented	No difference	No difference
Silhouette			
a. Size	Small (most <6 mm)	Variable	Large (>10 mm)
b. Symmetry	Present	Variable	Asymmetrical
c. Circumscription	Present	Variable	Poor
Evolution/clinical course	Stable	May metastasise to regional LNs; natural history uncertain	Variable malignant course: regional LN mets but favourable outcome to widely metastatic disease and death
Architectural			
Epidermis			
Silhouette			
a. Size	Small	Variable	Large
b. Symmetry	Present (must evaluate fully excised lesion)	Variable	Asymmetrical
c. Circumscription	Present (must evaluate fully excised lesion)	Variable	Poor
Epidermal hyperplasia	Present	No difference	May be atrophic/ulcerated
Artifactual clefting	Present	No difference	Variable
Kamino bodies	May be present (~50% of cases—multiple levels increase detection)	No difference	No difference
Pagetoid spread	Often present	Variable	Prominent; present at edge of lesion or upper half of epidermis
Dermis/subcutis			
Cellular density	Variable (low–moderate)	Moderate– dense	Dense (confluent growth)
Pattern of growth	Organised, nested and interstitial growth	Variable	Confluent, destructive
Architectural maturation	Present	Variable	Absent
Deep front of lesion	Infiltrative with outlier cells	Variable	Expansile or infiltrative
Involvement of subcutis	Rare—may be minimal	Variable	May be pronounced
Stromal/inflammatory response	Variable (usually mild)	Variable	Inflammation or regression may be noted
Cytological			
Nuclear size	Moderate–large	No difference	Large
Nuclear shape	Normal–angulated	No difference	Pleomorphic
Cytoplasm	Abundant, eosinophilic 'ground-glass'	No difference	Variable
N/C ratio	Low	No difference	Variable
Multinucleation	Present	No difference	No difference
Hyperchromasia	Low–moderate	Variable	High
Nucleoli	Present (small–moderate sized)	Variable	Present (large)
Nuclear membrane	Normal	Variable	Irregular
Chromatin pattern	Dispersed	Variable	Coarse
Cytological maturation	Present	Variable	Absent
Other			
Mitotic activity	Absent–moderate (up to 6 per 10hpf); confined to junction or superficial dermis	Variable	High (often >6 per 10hpf); abnormal or deep forms
Perineural or angiolymphatic invasion	Absent	Absent	May be present
Sentinel lymph node	Negative	May be positive	May be positive
Necrosis	Absent	Absent	May be present
Immunohistochemistry			
HMB-45	Variable (typically stratified)	Variable	Variable (often diffuse)
MIB-1	Low proliferative index (<10%)	Variable (<15%)	High (>15%)
Cytogenetics	Normal or isolated gain of 11p	Intermediate–often complex aberrations	Complex chromosomal aberrations

H&N, head and neck; LN, lymph node.

aggressive manner (ie, the probability that the lesion is a melanoma or other aggressive lesion based on histopathological assessment and accounting for the pretest probability).

Efforts to resolve these issues are ongoing, with promising cytogenetic work that may allow differentiation of Spitz naevi from Spitzoid melanoma based on the extent and types of chromosomal abnormalities observed.[106–109] Spitz naevi may reveal a normal karyotype, but, not uncommonly, reveal a unique copy number increase of the small arm of chromosome 11. Melanomas tend to show complex cytogenetic anomalies including chromosomal losses of 6p, 8p, 9p and 10q, as well as copy number increases in chromosomes 1q, 6p, 7, 8q, 17q and 20q. Thus the unique nature of the 11p gain in Spitz naevi, which is not typically seen in melanoma, as well as the complex chromosomal aberrations seen in melanoma as opposed to the absent or minimal chromosomal aberrations seen in Spitz naevi (or other

naevi for that matter) offer new cytogenetic features that may be exploited to differentiate challenging cases, or even as a standard test in the work-up of Spitzoid lesions. Clearly, clinical validation is required, but such a test would be of great value in that it would allow more accurate study of the true biological basis of such lesions and a prediction of their biological potential based on their molecular make-up. Such ancillary tests are clearly enticing given the challenge inherent to predicting the biological potential of Spitzoid lesions based on morphology alone.

The spectrum of Spitzoid lesions used in our practice include:

1. Spitz naevus (and variants) (may be junctional, compound, dermal)
2. Atypical Spitz tumour (low-grade, high-grade)
3. Spitzoid melanoma/melanoma with Spitzoid morphology
4. Pigmented spindle cell naevus (of Reed) (may be junctional or compound)
   – Atypical pigmented spindle cell naevus

Spitz naevi (may be junctional, compound or intradermal)

Spitz naevi are uncommon melanocytic lesions (although often encountered in dermatopathology practice[4]), which most commonly occur on the extremities or trunk, although the head and neck region, in particular the face, is also a site of predilection in children.[52 56 110] A general rule is that one third of cases occur in children (<10 years), one third in adolescents/teenagers (10–20 years), and one third in adults (>20 years), although some studies suggest a higher proportion in adults.[111] Most appear as amelanotic/hypopigmented red or red–brown macules, papules or nodules of limited size with most <6 mm and almost all <10 mm. Rare lesions may extend up to 2 cm. Spitz naevi are usually acquired lesions that have an initial rapid growth phase, which reaches permanent stability after about 6 months.[86] Polypoid and pigmented variants do exist and are not criteria for considering the lesion atypical or for rendering an alternative diagnosis. Another clinical pattern is the agminate (multifocal) Spitz naevus. Spitz naevi may become pruritic when there is an inflammatory infiltrate, but should not ulcerate unless traumatised. Critical to the diagnosis of a Spitz naevus is its symmetry and sharp circumscription. The dermatoscopic appearance of Spitz naevi often shows a characteristic 'sun-burst' pattern.

Spitz naevi may be entirely junctional, compound (majority of cases) or intradermal. An intraepidermal pagetoid variant is also known.[86] Most lesions tend to show either a papillomatous or a dome-shaped pattern with preservation of the symmetrical and circumscribed silhouette histologically. There should be no shouldering phenomenon. Spitz naevi may grow deeply, and, in such cases, typically show an infiltrating, but non-destructive pattern of growth, often with small groups of cells or single cells isolated from the main body of the tumour at its advancing edge ('outlier cells').[30] Mild–moderate pagetoid activity is acceptable in Spitz naevi, although it should be located centrally within the lesion and should not reach the granular cell layer. True pagetoid activity must be distinguished from transepidermal elimination of melanocytic nests, however, since the latter may also be present and may extend through the stratum granulosum/corneum. Moderate mitotic activity is acceptable (up to six mitoses per 10 hpf) within otherwise classical Spitz naevi, although deep dermal mitoses, atypical mitoses, clustering of dermal mitoses, and mitoses in pagetoid cells remain features of concern. Rare cases of classical Spitz naevi in young children may reveal profuse mitotic activity.[96] We may tolerate up to 20 mitoses per 10 hpf provided that no further atypical features are appreciated and a classic silhouette is maintained, and have termed such lesions 'proliferating Spitz naevi'. The natural history of such lesions is unknown, but it is likely that they represent sampling of classic Spitz naevi during a proliferative phase of the lesion. Cytological and architectural maturation are important reassuring features in Spitz naevi, and a lack of maturation should be considered an alarming feature. In particular, a large deep dermal nest (ie, significantly larger than the more superficial nests) with an expansile border and no evidence of cytological maturation is of significant concern. The density of the cellular proliferation in Spitz naevi may vary; however, dense confluent growth, particularly if it is irregular or destructive, is an atypical feature. In addition to these characteristic cytological and architectural features, Spitz naevi classically show epidermal

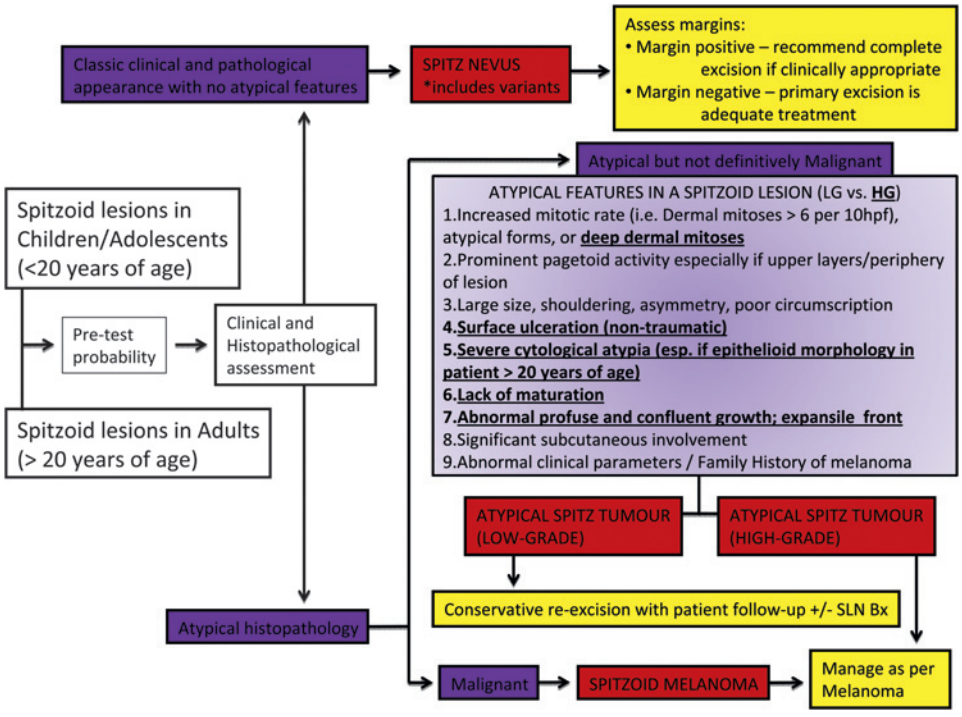

Figure 6 Algorithmic approach to the management of Spitzoid lesions. Underlined atypical features suggest a diagnosis of high-grade atypical Spitz tumour. Bx, biopsy; HG, high grade; hpf, high-power field; LG, low grade; SLN, sentinel lymph node.

hyperplasia with elongation of the rete ridges, which give a 'clutching' appearance around the junctional nests, which often contain spindled cells in a vertical orientation likened to a bunch of bananas or imparting a 'raining down' effect. Furthermore, there is typically evidence of stromal retraction around these nests, at least in part producing the so-called 'semilunar clefts'. This appearance should be contrasted with the appearance of dyscohesive melanocytic nests, which may also give the appearance of stromal separation but with an otherwise loose dyscohesive arrangement. Dyscohesion is an atypical feature and may raise concern for a melanoma. Kamino bodies[89 90] are a characteristic and fairly specific histological feature of Spitz naevi which represent amorphous PAS-positive, diastase-resistant eosinophilic globules composed of basement membrane material located at the dermo–epidermal junction.[112 113] Only rarely are they found in melanomas. Kamino bodies may be absent in Spitz naevi, especially when there is limited sampling/levels. Vascular ectasia and an inflammatory component may also be seen in Spitz naevi. Spitz naevi may be present as the following histological variants: desmoplastic (refer to part II: intradermal proliferations);[21a] pigmented (pigmented spindle cell naevus; discussed below); angiomatoid (Spitz naevus with halo phenomenon); plexiform; hyalinised; myxoid; pagetoid; as a component of a combined naevus (refer to part II: combined lesions).[21a]

Of paramount importance to the diagnosis of Spitz naevi is the presence of large spindled and/or epithelioid melanocytes with Spitzoid nuclear features (nucleoli, pleomorphism, angulated/geometric nuclei, multinucleation).[19 30 31 86–88] Hyperchromasia and coarsening of chromatin are not features of benign Spitz naevi. The cytoplasm of Spitz naevi is also characteristic because of its abundance, typical lack of pigmentation, and its glassy pale eosinophilic quality often with a bluish tinge. Spindled cells tend to predominate, and epithelioid variants should be viewed with suspicion when found in adult patients.

The classic cytological and architectural Spitzoid features are critical to the diagnosis (figure 4 and table 6), and thus light microscopy remains the 'gold standard' of diagnosis. Spitz naevi stain diffusely for S100 and generally show a stratified maturation pattern of staining with other melanocytic markers (eg, HMB-45).[92] Proliferation index markers (eg, Ki67, MIB-1) also show greater labelling towards the surface. Numerous other immunohistochemical markers (CD99,[50 92] cyclin D1,[38 45] p16,[46 92], c-kit,[49 92] bcl-2,[45] others[45 92]) have shown positive expression in Spitz naevi, but none have reproducibly been shown to differentiate benign from malignant Spitzoid lesions. Spitz naevi tend to show limited cytogenetic abnormalities in contrast with melanomas, which tend to show a multitude of changes[106–109] (discussed above). Comparative genomic hybridisation may be used to assess the cytogenetic status of lesional cells, and, if reliable discriminating cytogenetic foci are determined, routine fluorescence in situ hybridisation assays may be developed.

Atypical spitz tumour

The label 'atypical Spitz tumour' (also known as 'Spitz tumour of undetermined malignant potential' or STUMP) serves two purposes in the pathological reporting of Spitzoid lesions: (1) it highlights the significant grey zone in Spitzoid lesions in which the pathologist no longer feels comfortable promising benign biological behaviour based on clinical and pathological parameters; (2) it allows categorical placement of such lesions so that established management protocols may be followed by clinicians and for future studies on the true nature of these lesions. Compromising the latter point is the fact that this category is almost certainly a heterogeneous group of lesions, which we would ultimately wish to resolve into more appropriate diagnoses. Thus the atypical Spitz tumour category probably consists of lesions that are Spitzoid in nature as well as many lesions that are not fundamentally Spitzoid but exhibit features suggestive of a Spitzoid lesion (which, if recognised more precisely, are preferably termed 'the underlying melanocytic lesion … with Spitzoid morphology'). Furthermore, the atypical nature may be based on deviation from architectural features (eg, loss of the classic Spitzoid silhouette, lack of architectural maturation, ulceration, confluent growth with an expansile front, extension into the subcutaneous tissue), cytological features (eg, severe cytological atypia beyond the acceptable limits for Spitz naevi, increased/abnormal/deep mitoses), clinical features (eg, large size), or any combination of the above (eg, epithelioid morphology in an adult, prominent pagetoid activity in an adult). These features have mainly been discussed above (see Spitz naevus) and are also summarised in table 6. Confounding this category even further is the fact that, despite much effort, there are no reliable criteria to guide the placement of entities into this category, and, in essence, the task is largely left up to the individual thresholds tolerated by each pathologist.[96 114 115] Almost certainly, significant interobserver and potentially intraobserver variation must exist.[97] However, it is certain that no effective criteria could be put forward, as, by nature, the entity is a diagnosis by exclusion (ie, not certainly a Spitz naevus and not certainly a melanoma). This highlights the final concern about the heterogeneous population of lesions within the atypical Spitz tumour group: it contains both lesions considered in the differential diagnosis of a Spitz naevus (ie, with low-grade features or considered low risk for malignant behaviour) and lesions considered in the differential diagnosis of a melanoma (ie, with high-grade features or considered at high risk for malignant behaviour). This assessment of risk is again a gestalt of the clinical and pathological attributes of the lesion without clear defining lines of separation. Nevertheless, we do use this separation to help communicate our best estimate of malignant potential for a lesion falling in the wide gap between a Spitz naevus and a melanoma. Thus we use the terms atypical Spitz tumour (low grade) and atypical Spitz tumour (high grade). Such a division is used by other groups as well.[19 93] In general, severe cytological atypia particularly in prominently epithelioid tumours, multiple deep dermal mitoses, surface ulceration and loss of the classic Spitzoid silhouette, particularly if it is by a dense confluent proliferation that shows a bulging margin, are considered high-grade features. Clinical management may vary on the basis of this delineation in select cases (eg, Spitzoid lesion on the face of a young child). However, only a minority of cases of Spitzoid lesions should fall into the category of atypical Spitz tumour, with resolution of Spitz naevi and Spitzoid melanomas possible in most instances. Immunohistochemistry may be of some help in the evaluation of atypical Spitzoid lesions.[92] Proliferation markers such as Ki67 or MIB-1 may highlight an increased proliferation rate and/or a lack of diminished activity in the deeper components of the lesion. HMB-45 may highlight a stratified staining pattern suggestive of maturation, although diffuse staining is not incompatible with a benign compound Spitz naevus.

Atypical Spitz tumours in children, with or without sentinel lymph node (SLN) metastases, show almost universal survival,[114 116] with paediatric mortality from Spitzoid lesions occurring essentially only in cases in which the primary tumour is histologically clearly malignant (see Spitzoid melanoma below). This is at the centre of the debate whether or not SLN positivity is a criterion for a diagnosis of Spitzoid melanoma. Owing to the favourable outcome of paediatric patients whose

primary Spitzoid lesions are indefinite for malignancy but whose SLNs are subsequently found to contain deposits/metastases, we consider such a finding compatible with a diagnosis of atypical Spitz tumour, provided that the deposit is not highly malignant appearing and does not exhibit appreciable destructive infiltration of the lymph node. Such studies also beg the question whether or not SLN biopsies are warranted for atypical Spitz tumours, particularly because of the high rate of positivity (up to 50%).[100–102 104 105] However, until further study is carried out, we will continue to recommend SLN biopsy (in addition to complete excision with conservative margins of at least 1 cm) for cases of Spitzoid lesions equivocal for malignancy. Atypical Spitz tumours in adult patients are not as well studied, and a more guarded prognosis is warranted.

Spitzoid melanoma

The end of the Spitzoid spectrum is Spitzoid melanoma. Spitzoid melanomas share many of the general clinical features of melanoma except that they are more common in younger patients including children.[92 95 117] Spitzoid melanomas may be clinically suspected in cases of Spitzoid lesions that spontaneously ulcerate or enlarge, often with disruption of the symmetrical silhouette. Large Spitzoid lesions (ie, >10 mm) are also suspect. As opposed to the termination of the initial growth phase of Spitz naevi, Spitzoid melanomas do not attain stability but continually grow and change.[86] Overt signs of malignancy may include regional adenopathy or other evidence of metastatic disease. Occasionally, one or multiple Spitz naevi may arise near the place of a prior excision of a classic Spitz naevus, raising concern for satellitic metastases of a missed Spitzoid melanoma. However, such a phenomenon, when histologically benign, should be appreciated as satellitic Spitz naevi, akin to an agminated Spitz naevus, with no increased potential for malignant behaviour.[118] Recurrent Spitz naevi[119] may also be confused with a malignant process, and features of a recurrent naevus phenomenon should be appreciated (see part II: horizontally oriented lesions; naevi with disruption phenomena).[21a]

Histological evaluation of a Spitzoid melanoma follows as per the evaluation of any other melanocytic lesion, with attention also paid to the special features of a Spitzoid lesion (eg, presence of Kamino bodies, characteristics of the deep border, pattern of pagetoid activity) (tables 3 and 6). As previously discussed, the threshold for calling a lesion melanoma will depend on the clinical setting (ie, pretest probability). Spitzoid lesions that prompt serious consideration for a melanoma but which ultimately fall short of meeting the minimal criteria for a diagnosis of melanoma should be diagnosed as atypical Spitz tumour (high grade). Typically, a Spitzoid melanoma will exhibit an irregular pattern of growth which either disrupts or over-runs an existing organised Spitzoid silhouette or which appears completely irregular with no underlying organisation.[86 95 120] Occasionally, the disruption may occur as an expansile dermal nodule which often shows a different cytomorphology and mitotic rate compared with the background lesion. Extension of a Spitzoid lesion into the subcutaneous tissue is also an unusual feature, but not unheard of for Spitz naevi. Numerous mitoses including deep dermal forms and severe cytological atypia with macronucleoli are features favouring a Spitzoid melanoma. A clear-cut lack of architectural and cytological maturation is a more reliable feature for Spitzoid melanoma. Spitzoid melanomas should exhibit underlying characteristic Spitzoid architectural and/or cytomorphologcal features that define Spitzoid lesions in general.

Two paths generally lead a pathologist into the differential diagnosis of a Spitzoid melanoma: (1) removal of a lesion suspected to be a Spitzoid lesion (eg, red–brown nodule from the face of a child), which subsequently shows high-grade features; (2) histopathological appreciation of Spitzoid architectural and cytological features in a lesion in the absence of a suggestive clinical history (eg, often the manner in which Spitz naevi in adults come to light). In the former setting, the burden of diagnosis is typically on assessing the atypicality of the lesion (ie, placement of the lesion on the Spitzoid spectrum), and thus proceeds in a manner that identifies and grades atypical features with appreciation of what is permitted in Spitzoid lesions. In the latter setting, the burden of diagnosis is often placed on ensuring that one is dealing with a Spitzoid lesion (ie, not a melanoma with potentially misleading Spitzoid features), and so features such as pagetoid spread, cytological atypia and occasional superficial mitoses, which may be acceptable in a classic Spitzoid lesion taken from a child, may be more reflective of a malignant lesion in an adult, calling into question the true Spitzoid nature of the lesion. This is not a trivial distinction, since Spitzoid melanomas removed from children show a more favourable outcome even in the presence of SLN metastases.[114 116 117] This favourable outcome has not been noted for melanomas with Spitzoid morphology in adults. This difference in behaviour probably reflects a difference between the accurate recognition of what is probably a relatively indolent malignant tumour (Spitzoid melanoma), which overlaps significantly with lesions essentially lacking true malignant potential (atypical Spitz tumours), and a group mainly comprising fully malignant melanomas that are mistaken for Spitzoid melanomas because of suggestive histological features. For this reason, we prefer to reserve the term 'Spitzoid melanoma' for patients 20 years or under, and use the term 'melanoma with Spitzoid morphology' for older patients.

As previously mentioned, there are currently no established ancillary tests that definitively differentiate benign from malignant Spitzoid lesions. An increased proliferative index (Ki67 or MIB1 labelling) and a lack of maturation, as evidenced by diffuse HMB-45 staining, support a diagnosis of melanoma, but are not reliable[92 120 121]—a relatively low proliferative fraction (5–15%) does not exclude a melanoma, and diffuse HMB-45 staining may occasionally be seen in benign lesions. Cytogenetic demonstration of multiple chromosomal abnormalities is consistent with a diagnosis of melanoma,[106 108 109] but such testing does not have strong clinical validation and is not widespread.

Pigmented spindle cell naevus (of Reed)

A characteristic subtype of Spitz naevus is the pigmented spindle cell naevus (also known as 'pigmented spindle cell naevus of Reed' or 'Reed naevus') (figure 7). Clinically, pigmented spindle cell naevi of Reed are recognised by their deep coloration, often appearing pitch black.[32 56] Lesions are uniform in appearance, typically small (<6 mm), well-circumscribed and symmetrical. Classically, lesions occur in young adults, although children may be affected, with females affected more commonly than males. Typical location is the thigh followed by shoulder and upper arms, although lesions may be located on any skin site. Dermoscopy shows the characteristic Spitzoid sun-burst pattern. Histologically, the lesion is characteristic for its Spitzoid morphology (figure 5 and table 6), prominent pigmentation with numerous melanophages, and its horizontal orientation, often being entirely junctional, although most do reveal a limited dermal component. The benign nature of the lesion is assured through recognition of the Spitzoid nature of the lesion in conjunction with its benign silhouette (small size, sharp circumscription and good symmetry), and a lack of atypical features[30 31 122] (see below). In addition, pigmented spindle cell

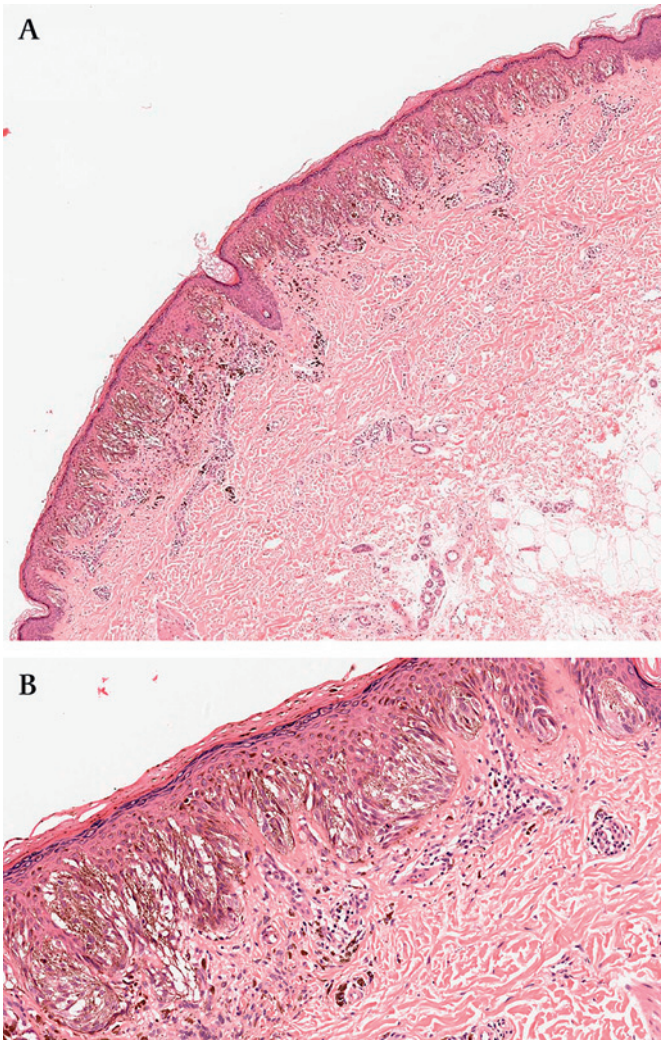

Figure 7 Junctional pigmented spindle cell naevus of Reed (36-year-old woman; forearm). (A) (H&E; 40×) Low-power examination reveals a small heavily pigmented junctional melanocytic lesion with a Spitzoid silhouette (sharp circumscription, symmetry). Epidermal hyperplasia and vertical orientation of uniform melanocytic nests are further Spitzoid features noted. There is prominent dermal pigment incontinence, but otherwise minimal stromal reaction. (B) (H&E; 200×) Prominent spindle cell morphology and vertical orientation of uniform nests is better appreciated. Although cells are enlarged with nucleoli, atypical nuclear features are otherwise not pronounced. Pigmentation is prominent. Rare mitoses are noted.

naevi reveal uniformity in the size and distribution of nests. As with any Spitzoid lesion, pigmented spindle cell naevi exhibit large nuclei with nucleoli often vertically oriented with epidermal hyperplasia and possible Kamino bodies. Occasional mitoses including rare dermal forms are acceptable. Pagetoid ascent of cells is often seen and, classically, in a nested rather than single cell pattern. Pigmented spindle cell naevi may show an apparent lack of maturation due to their thin nature. Lesions may also appear concerning because of their cellularity and typical rete bridging, although prominent fibroplasia is unusual. The major risk of misdiagnosis is with a superficial spreading melanoma/melanoma in situ or a Clark's naevus with high-grade features. The focus on the differential rests on recognition of the Spitzoid nature of the lesion, its small size and benign silhouette with a lack of shouldering, the uniformity of the lesion, and the lack of truly concerning features suggestive of melanoma outside of those permissible in Spitzoid lesions (tables 3 and 6). Our practice is to consider lesions consisting of more than a small minority of epithelioid cells with features otherwise consistent with a pigmented spindle cell naevus as a pigmented variant of a Spitz naevus, granting that this differentiation is somewhat semantic.

Atypical pigmented spindle cell naevus is a term used to raise clinical concern about the biological potential of a lesion consistent with a pigmented spindle cell naevus but which demonstrates further features that are not acceptable as strictly benign. Abnormal clinical parameters (older age, changing lesion, spontaneous ulceration), larger lesions (>1 cm), loss of the reassuring benign silhouette, severe cytological atypia, increased mitotic activity with deep dermal or atypical forms, and expansile dermal growth represent atypical features warranting some caution in the biological potential of the lesion, and a diagnosis of atypical pigmented spindle cell naevus is appropriate.[31 122] Such lesions require complete excision with conservative margins and continued patient follow-up.

CONCLUSION

In part I, we have presented our algorithmic approach to spindle cell melanocytic lesions, one which begins with the need to recognise a spindle cell lesion as melanocytic in nature. Cytological, architectural and immunohistochemical features of melanocytic lesions are discussed to facilitate such recognition. To this end, we have also included table 1, which lists diagnostic features of non-melanocytic spindle cell cutaneous lesions that may enter into the differential diagnosis of certain spindle cell melanocytic lesions. The algorithm proceeds with a categorical subdivision of spindle cell melanocytic lesions based primarily on architectural pattern. This initial step aims to provide greater acuity when proceeding with the subsequent detailed assessment of histopathological features in an effort to predict the potential biological behaviour of the lesion. A generalised

Take-home messages

- Spindling, in its many forms, is a common phenomenon (partial or complete) that may be seen in most melanocytic lesions.
- A spindle cell morphology does not necessarily connote an aggressive biological potential and must be interpreted within the context of the type of melanocytic lesion (ie, architectural pattern) as well other histopathological and clinical features.
- Spindle cell melanocytic lesions commonly show loss of melanocyte-specific immunohistochemical markers—use of multiple specific melanotic markers increases sensitivity.
- Commonly, the histogenetic origin of a spindle cell melanocytic lesion may be determined histologically by the presence of a more recognisable junctional component, by characteristic nesting, or by an admixed pigmented/epithelioid component.
- Optimal assessment of the biological capacity of spindle cell melanocytic lesions requires a gestalt impression of numerous features (clinical, histological, ancillary studies), which should proceed in a standard way but with acceptances made for lesional patterns that characteristically express certain, otherwise, concerning features.
- The pathology report should relay to the clinician information about the histogenetic nature of the lesion as well as its potential for aggressive biological behaviour in a manner that facilitates optimal management decisions.

Interactive multiple choice questions

This JCP review has an accompanying set of multiple choice questions (MCQs). To access the questions, click on BMJ Learning: Take this module on BMJ Learning from the content box at the top right and bottom left of the online article. For more information please go to: http://jcp.bmj.com/education Please note: the MCQs are hosted on BMJ Learning—the best available learning website for medical professionals from the BMJ Group. If prompted, subscribers must sign into JCP with their journal's username and password. All users must also complete a one-time registration on BMJ Learning and subsequently log in (with a BMJ Learning username and password) on every visit.

approach to grading the biological potential of melanocytic lesions is also provided. The final step is the application of diagnostic terminology. We strive to use established and communicative diagnostic terms that describe the histogenesis of the lesion, and at the same time optimally facilitating subsequent clinical management by reflecting an estimate of the biological risk posed by the lesion based on the assessment of the pathological and clinical parameters. Finally, we have begun our discussion of spindle cell melanocytic entities by covering those entities that fall under our first two categories: compound naevoidal pattern lesions and Spitzoid lesions. Continuing in part II, we proceed with a discussion of spindle cell melanocytic entities that fall under the final two categories: intradermal proliferations and horizontally oriented lesions. We also discuss combined lesions and provide summary thoughts.

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