Non-melanocytic mimics of melanoma, part II: intradermal mimics

L C B Tong, Z S Kamil, A Al Habeeb, D Ghazarian

Department of Laboratory Medicine and Pathobiology, University of Toronto and University Health Network, Toronto, Ontario, Canada

Correspondence to: Danny Ghazarian, Department of Laboratory Medicine and Pathobiology, University of Toronto, University Health Network, 200 Elizabeth Street, Department of Pathology, 11th Floor, Toronto, Ontario, Canada M5G 2C4; danny.ghazarian@uhn.on.ca

Accepted 28 October 2008
Published Online First
18 November 2008

ABSTRACT

Intradermal melanoma diagnosis poses a great deal of confusion on many occasions since it can mimic almost any tumour within the dermis. In part I, the different features of intraepidermal mimics were discussed. In this part, there is discussion of the clinical, cytomorphological and immunohistochemical features of intradermal mimics of melanoma and how to distinguish these conditions from melanoma. There is also a description of the ultrastructural features of some of these conditions that may help to distinguish melanoma from its mimics. It is hoped that this approach, together with part I of the non-melanocytic mimics of melanoma, will aid in better overall understanding of melanoma and its mimics.

Melanoma has diverse clinical and cytomorphological features. Melanoma cells have various sizes and shapes, and nuclear and cytoplasmic features, and they are arranged in different architectural patterns (box 1). Therefore, it may be difficult to differentiate melanoma from its various mimics of epithelial, mesenchymal and haematological cell line of differentiation by histology alone. For this reason, immunohistochemical stains are essential to differentiate melanoma from other tumours. This should be done with clinical and histological correlation. Furthermore, several diagnostic problems arise with desmoplastic, spindle cell, de-differentiated, recurrent and metastatic melanoma. In addition, the absence or minimal presence of the junctional component, and small size biopsies, can impose significant anxiety to pathologists. However, it should be kept in mind that the junctional component when present is a very helpful feature in distinguishing primary dermal melanoma from its intradermal mimics.

In this review, dermal non-melanocytic mimics of melanoma (box 2) are described, mainly with regard to their clinical, histological and immunohistochemical features, with an emphasis on the differentiating features.

Before discussing the different features of melanoma mimics, we want to emphasise the utility of immunohistochemistry as an essential tool in the diagnosis of melanoma.

In addition to the well-known melanocytic markers (S-100, human melanoma black (HMB)-45, Mart1/Melan A, microphthalmia transcription factor (Mitf)), other immunohistochemical markers can be useful in melanoma diagnosis (box 3).^{1–13}

In addition, some melanomas can exhibit unusual features when using immunohistochemistry (box 4).^{12–23}

BENIGN DERMAL MIMICS

Scar

Histological distinction of scar from desmoplastic melanoma can be challenging to pathologists. This problem is usually encountered when evaluating melanoma re-excision specimens for residual tumour.²⁴ Clinical and histological features of scars are outlined in table 1. This diagnostic challenge may be resolved by examining histological and immunohistochemical features. Desmoplastic melanoma (DM) is the main diagnostic mimic of scars, but it usually displays neurotropism and may demonstrate prominent nuclear atypia, and hyperchromasia. In addition, lymphocytic nodular aggregates are seen commonly in DM, compared to diffuse lymphocyte infiltrate in scar (depending on the age of the scar). While DM expresses nuclear and cytoplasmic S-100 staining patterns, myofibroblasts of scars rarely express a cytoplasmic S-100 staining pattern.^{24–25} In addition, scars may be focally positive for smooth muscle actin (SMA) (table 1); however, this feature can also be seen in some melanomas such as DM and spindle cell melanoma.

Cutaneous inflammatory pseudotumour

Inflammatory pseudotumour is a distinct, yet heterogeneous group of mesenchymal tumours composed of myofibroblasts, admixed inflammatory cells and hyalinised collagenous stroma. It occurs in various organs including the skin. Cutaneous disease clinically presents as solitary firm papules or nodules of a few millimetres to several centimetres in diameter.

Histologically, two completely different patterns can be recognised.²⁶ One pattern is characterised by poorly circumscribed spindle cell proliferation in the dermis that might extend to the subcutis. The cells are bland and may arrange focally in fascicular or storiform pattern. A heavy inflammatory cell infiltrate composed of plasma cells, lymphoplasmacytoid and small lymphocytes is distributed throughout the tumour. Thickened, hyalinised collagen bundles are usually identified. According to the authors, this pattern represents true cases of inflammatory myofibroblastic tumour (IMT) of the skin. IMT is now considered a neoplastic lesion that may have a malignant potential as it may recur or metastasise. Careful microscopic and immunohistochemical examination can confirm the diagnosis in challenging cases, as this sometimes can mimic metastatic melanoma (table 1).^{26–27} IMTs express anaplastic lymphoma kinase 1 (ALK-1) by immunohistochemistry in approximately 50% of cases. This expression is more common in younger patients and reliably predicts the presence of an

Box 1: Checklist of morphological features in the assessment of intradermal tumours (in descending order of frequency)

Size of cells

- ▶ Large cell
- ▶ Intermediate cell
- ▶ Small cell

Shape of cells

- ▶ Epithelioid
- ▶ Oval
- ▶ Spindle
- ▶ Dendritic

Cytoplasmic features

- ▶ Amphophilic
- ▶ Eosinophilic
- ▶ Plasmacytoid cell
- ▶ Histiocytic-like cell
- ▶ Rhabdoid cell
- ▶ Clear cell
- ▶ Granular cell
- ▶ Signet-ring cell
- ▶ Balloon cell
- ▶ Pseudolipoblastic cell

Nuclear features

- ▶ Hyperchromasia or vesiculation
- ▶ Prominent nucleoli
- ▶ Intranuclear inclusions
- ▶ Binucleation and multinucleation
- ▶ Lobation
- ▶ Multiple nucleoli
- ▶ Nuclear grooving and angulation
- ▶ Inconspicuous nucleoli

Architectural patterns

- ▶ Sheets
- ▶ Nested
- ▶ Fascicular
- ▶ Whorling
- ▶ Trabeculated or cord like
- ▶ Infiltrative desmoplastic
- ▶ Pseudoglandular/pseudopapillary/pseudofollicular
- ▶ Angiocentric
- ▶ Pseudorosetting

ALK gene rearrangement (which can be detected by fluorescence in-situ hybridisation).²⁷

The second pattern shows well-defined dermal, and dermal/subcutaneous nodules that are composed of a lymphoplasma-cytoid infiltrate with many plasma cells set in a background of thick, hyalinised collagen bundles. This pattern has no spindle cell component and is also known as plasma cell granuloma.²⁶

Epithelioid cutaneous fibrous histiocytoma

Epithelioid fibrous histiocytoma (EFH) is a variant of benign fibrous histiocytoma. EFH differs from benign fibrous histiocytoma in that tumour cells of the former are predominantly epithelioid. Those cells have eosinophilic cytoplasm, vesicular nuclei, and small eosinophilic nucleoli (fig 1). Individual cells are separated by somewhat hyalinised collagen, containing

Box 2: Dermal non-melanocytic mimics of melanoma

Benign mimics

- ▶ Scar (specifically with desmoplastic melanoma)
- ▶ Inflammatory pseudotumour
- ▶ Epithelioid cutaneous fibrous histiocytoma
- ▶ Cellular cutaneous fibrous histiocytoma
- ▶ Xanthogranuloma (juvenile and adult types)
- ▶ Cellular neurothekeoma
- ▶ Reticulohistiocytoma (solitary epithelioid histiocytoma)
- ▶ Granular cell tumour
- ▶ Benign perivesicular epithelioid cell tumours (PEComas)

Mimics of uncertain biological behaviour

- ▶ Primitive non-neural granular cell tumour
- ▶ Langerhans cell histiocytosis
- ▶ Atypical cellular neurothekeoma
- ▶ Borderline malignant perivesicular epithelioid cell tumours (PEComas)
- ▶ Inflammatory myofibroblastic tumour of the skin

Malignant mimics

- ▶ Primary
 - Dermatofibrosarcoma protuberans (with spindle cell melanoma)
 - Atypical fibroxanthoma
 - Malignant peripheral nerve sheath tumour
 - Cutaneous leiomyosarcoma
 - Epithelioid angiosarcoma
 - Epithelioid sarcoma
 - Spindle cell squamous cell carcinoma
 - Cutaneous malignant granular cell tumour (extremely rare)
 - Cutaneous lymphoproliferative disorders and other haematological malignancies
 - Malignant perivesicular epithelioid cell tumours (PEComas)
 - Follicular dendritic cell sarcoma
 - Anaplastic/pleomorphic Kaposi sarcoma
 - Plexiform fibrohistiocytic tumour of the skin
 - Monomorphic spindle cell synovial sarcoma
 - Postradiation sarcoma
- ▶ Metastatic
 - Breast carcinoma
 - Lung carcinoma
 - Renal carcinoma
 - Thyroid carcinoma
 - Lymphoproliferative disorders and other haematological malignancies
 - Prostate carcinoma
 - Others (such as colorectal, endometrial, ovarian and hepatocellular carcinoma)

prominent blood vessels and a sparse mononuclear inflammatory cell infiltrate.²⁸

The prominent epithelioid component of EFH mimics melanoma; therefore both histological and immunohistochemical features are needed to make the distinction (table 1).²⁸ In contrast to primary melanoma, EFH does not have junctional nests of melanocytes and is negative for melanocytic markers (table 1). We emphasise that in the absence of the junctional component or in some cases of metastatic melanoma (amelanotic), it can be challenging to distinguish these lesions from

My approach

Box 3: Other immunohistochemical markers that can be expressed in melanoma

- ▶ **CD99:** (+) in 10–60% of melanomas
- ▶ **Bcl-2:** 60% (+) in primary melanoma, 76% (+) in metastatic melanoma
- ▶ **CEA:** 42% (+) in primary melanoma, 36% (+) in metastatic melanoma
- ▶ **EMA:** 19% (+) in primary melanoma, 23% (+) in metastatic melanoma
- ▶ **CD56:** 50% (+) in cases of spindle cell, desmoplastic melanoma; dedifferentiated and metastatic melanoma may express CD56
- ▶ **CD10:** 61–69% in metastatic melanomas, 21.4% in primary melanomas
- ▶ **SMA, MSA:** 32% (+) in spindle cell and desmoplastic melanomas
- ▶ **CD68:** (+) in 50 % of nodular malignant melanoma; CD68 is (+) in 86 % of primary and metastatic melanoma according to Pernick *et al*⁶
- ▶ **CD117 (C-kit):** mucosal/oral melanoma, acral lentiginous melanoma, anogenital melanoma, (+) in 72% of primary versus 73% of metastatic melanoma according to Plaza *et al*⁷; (+) in 36 % of malignant melanomas according to Went *et al*⁸
- ▶ **PGP 9.5:** 10% (+) in melanoma
- ▶ **LMWCK:** focally (+) in 10%–22% of melanoma, especially metastatic lesions according to Kim *et al*⁹ and Ben-Izhak *et al*⁸
- ▶ **Vimentin:** almost always (+) in melanoma, 94–100% of primary versus 98–100% of metastatic melanoma
- ▶ **Tyrosinase:** (+) in 30 % of primary melanoma, 25% of metastatic melanoma

Abbreviations: CEA, carcinoembryonic antigen; EMA, epithelial membrane antigen; LMWCK, low molecular weight cytokeratin; MSA, muscle specific actin; PGP, P glycoprotein; SMA, smooth muscle actin.

melanoma on histology alone, and hence clinicopathological correlation and immunohistochemistry are critical in achieving the correct diagnosis.

Cellular cutaneous fibrous histiocytoma

Cellular fibrous histiocytoma is another variant of benign fibrous histiocytoma. It is more cellular than the usual benign fibrous histiocytoma. Distinctive histological features include fascicular growth pattern, predominance of eosinophilic spindle cells with tapering nuclei, moderate mitotic rate (mean three per 10 high-power fields (HPFs)), and in some cases extension into the superficial subcutaneous fat (fig 2).²⁹ In small skin biopsies or specimens without an epidermal component, the presence of moderate mitotic rate and eosinophilic spindle cells may make it difficult to distinguish between cellular fibrous histiocytoma and melanoma, and adjunct immunohistochemical studies are helpful to make the distinction (table 1).

Xanthogranuloma (juvenile and adult types)

Xanthogranuloma is a benign dermal lesion of histiocytic differentiation and is seen in children and adults. It presents as solitary or multiple cutaneous lesions.³⁰ These lesions extend from superficial papillary to mid or deep reticular dermis, and they are composed of one or more of the three cell types:

Box 4: Unusual immunohistochemical profiles of some melanomas

Melanomas that can be S-100 (+), HMB-45 (–), Mart1/MelanA (–), MiTF (–)

- ▶ Desmoplastic/spindle cell melanoma (usually only S-100 (+)) up to 100%
- ▶ Dedifferentiated melanoma (metastatic)
- ▶ Unusual variants of melanoma such as signet cell and rhabdoid phenotypes

Melanomas that can be S-100 (–)

- ▶ Ocular melanoma, HMB-45 (+), Mart1/MelanA (+)
- ▶ Sinonasal melanoma, HMB-45 (+)

Abbreviations: HMB, human melanoma black; MiTF, microphthalmia transcription factor (nuclear stain).

mononuclear cells, multinucleated cells with or without Touton features, and spindle cells (fig 3).³¹ In contrast to melanoma, xanthogranuloma does not have a junctional component or express melanocytic markers (table 1). Touton-type giant cells, if present, can also help to differentiate xanthogranuloma from melanoma.

Cellular neurothekeoma

Cellular neurothekeoma is a plexiform dermal lesion with an uncertain histogenesis. The lesions are usually located in the dermis, but they may also involve the subcutaneous tissue. According to two large studies, cellular neurothekeomas have common features including (1) lobulated or micronodular architecture composed of nests and bundles of epithelioid and spindled cells, (2) cells with eosinophilic cytoplasm often separated by dense hyaline collagen, (3) occasional osteoclastic giant cells, and (4) mild cytological atypia and pleomorphism.^{32–33}

Atypical histological features, including pleomorphism, infiltration of subcutis and a high mitotic rate (atypical cellular neurothekeoma), can make the differentiation from melanoma difficult. In contrast to melanoma, cellular neurothekeoma lacks junctional nests of melanocytic cells. In addition, the majority of cellular neurothekeomas express diffuse positivity with NKI-C3 and are negative for melanocytic markers (table 1).

Several immunohistochemical markers have been proposed as useful markers to aid in diagnosis of neurothekeoma (table 1).^{33–37}

Reticulohistiocytoma (solitary epithelioid histiocytoma)

Solitary epithelioid histiocytoma (SEH) is the newly proposed name for reticulohistiocytoma.³⁸ It is located in the superficial dermis to deep dermis and is composed of large epithelioid histiocytes with lymphocytes and neutrophils. The histiocytes have densely eosinophilic cytoplasm with distinct nucleoli and mild nuclear atypia. There is mild mitotic activity (0–4 mitoses per 10 HPFs). Common immunohistochemical markers for SEH are listed in table 1.

SEH shares some morphological features with melanoma, including growth along the dermal–epidermal junction, tumour cells with eosinophilic cytoplasm, distinct nucleoli and nuclear atypia. In contrast to melanoma, SEH does not stain with melanoma markers, but it may have focal reactivity for S-100 protein (in entrapped dendritic cells).

Table 1 Benign non-melanocytic mimics of intradermal melanoma

Lesion	Clinical features	Histology	Immunohistochemistry
Scar	Previous trauma or iatrogenic procedures	Scattered spindle cells Mild cytological atypia Might be mitotically active (depending on the age of the scar)	Occasionally focally S-100 (+) fibroblasts (cytoplasmic pattern) (+) SMA focally (-) HMB-45 (-) Mart1/Melan A (-) MiTF
Inflammatory pseudotumour	Solitary papules and nodules	Mature plasma cells, lymphocytes Bland-looking spindle cells arranged in fascicular pattern	(+) SMA, vimentin, CD68, PGM-1 in spindle cells (+) ALK-1 in IMT (-) S-100, HMB-45, Mart1/MelanA, MiTF
Epithelioid cutaneous fibrous histiocytoma	Middle-aged adults No gender preference	Predominant epithelioid cells, separated by hyalinised collagen (keloidal type) Multinucleated giant cells	(+) FXIIIa (+) Diffuse CD10 (+) Focal S-100 dendritic cells (±) Stromelysin-II (+) CD68 (granular pattern) (-) CD34 (-) S-100 (-) HMB-45 (-) Mart1/Melan A (-) MiTF (+) Factor XIIIa
Cellular cutaneous fibrous histiocytoma	Young or middle-aged adults Male predominance Head and neck, extremities	Eosinophilic spindle cells in fascicular pattern Moderate mitotic rate	(+) HMGA1, HMGA2 (+) Diffuse CD10 (+) CD68 (granular pattern) (±) Stromelysin-II (-) S-100 (-) HMB-45, (-) Mart1/Melan A (-) MiTF (+) Vimentin
Xanthogranuloma (adult and juvenile types)	Head and neck	Multinucleated giant cells Touton giant cells Spindle cells Chronic inflammatory cells.	(+) CD 68 (+) α-1 Antitrypsin, α-1 antichymotrypsin (+) CD10 (+) Factor XIIIa (-) S-100 (dendritic cells can be focally positive) (-) CD1a (-) HMB-45 (-) Mart1/Melan A (-) MiTF (+) NKI-C3 (non-specific)
Cellular neurothekeoma	Female predominance in twenties Head and neck, upper extremities	Epithelioid and spindled cells arranged in fascicles and nodular aggregates Pleomorphism Low mitotic rate	(+) Leu-7 (CD57) (+) NSE (+) MiTF (+) MMP-II (+) PGP 9.5 (+) CD10 (+) CD68 (+) Vimentin (+) SMA (+) Focal factor XIIIa (-) S-100 (-) HMB-45 (-) Mart1/MelanA (+) CD163
Reticulohistiocytoma (solitary epithelioid histiocytoma)	Young adults Male predominance	Histiocytes with ground-glass cytoplasm Lymphocytes and neutrophils Mild mitotic activity	(+) CD68 (+) Variably α-1 antitrypsin (+) Lysozyme

Continued

Table 1 Continued

Lesion	Clinical features	Histology	Immunohistochemistry
Granular cell tumour	Solitary painless nodule	Plump, spindle and epithelioid cells with abundant eosinophilic cytoplasm and inconspicuous bland nuclei	(+) Vimentin (+) MSA (+) Focal factor XIIIa (+) Focal S-100 (-) HMB-45 (-) Mart 1/Melan A (-) MiTF (+) S-100
	Twice as common in women as in men	Cells mainly in the superficial dermis with varying degree of epidermal extension	(+) Calretinin (+) Inhibin (+) CD68 (-) Mart 1/Melan A (-) HMB-45 (-) MiTF
PEComa	Depends on type and site of PEComa	Clear or eosinophilic spindle-epithelioid cells	(+) HMB-45
		Fascicular, nested, sheet-like patterns Perivascular accentuation Multinucleated giant cells Size <8 cm, mitotic count <1/50 HPFs, no necrosis	(+) Mart1/MelanA (+) MiTF (+) S-100 in 33% (+) SMA, MSA (+) Desmin (+) Cyclin D1 (+) Vimentin (+) Pan-cytokeratin

ALK-1, anaplastic lymphoma kinase-1; HMB, human melanoma black; HPF, high-power field; MiTF, microphthalmia transcription factor; MMP, matrix metalloproteinase; HHV, human herpesvirus; HMGA, high mobility group A; MSA, muscle specific actin; PGP, P glycoprotein; NSE, neuron-specific enolase; PEComa, perivascular epithelioid cell tumour; SMA, smooth muscle actin.

Granular cell tumour

Granular cell tumour (GCT) is a tumour of nerve sheath origin, so called because of the coarse cytoplasmic granularity (illustrated better by periodic acid–Schiff stain) that is typically found among its constituent cells.

Histologically, the cells are plump, spindle and epithelioid, with abundant eosinophilic cytoplasm and inconspicuous bland nuclei (fig 4). These cells are mainly found in the superficial dermis with varying degrees of epidermal extension.³⁹ The growth pattern can be that of short fascicles, nested or lentiginous arrangement. Accordingly these tumours can be easily confused with melanocytic lesions. Immunohistochemistry plays important role in differentiating GCT, especially from metastatic melanoma that lacks the junctional component (table 1; also see fig 5).^{39 40} Ultrastructural studies have shown the cytoplasmic granules of GCT to be secondary lysosomes, and they should be differentiated from melanosomes or premelanosomes.

Perivascular epithelioid cell tumours

The perivascular epithelioid cell tumour (PEComa) is a distinctive group of tumours arising from the perivascular epithelioid cell. PEComas apply to angiomyolipomas of the kidney and liver, clear cell sugar tumours, lymphangioleiomyomatosis of the lung, and tumours of the soft tissue and viscera with spindled or epithelioid morphology and myomelanocytic differentiation. Histologically, PEComas can present with circumscribed or infiltrative patterns with clear to lightly eosinophilic spindle or epithelioid cells, which arrange in nested, fascicular, and occasionally sheet-like pattern. Most often, PEComas arrange in a radial fashion around blood vessels. Prominent intrinsic vasculature ranging from delicately arborising capillaries to thicker, often hyalinised arterioles and small arteries is another feature of this tumour. Multinucleated giant cells may also be present. The perivascular accentuation of tumour and the intimate association with vessel walls is a

Figure 1 (A, B) Epithelioid cutaneous fibrous histiocytoma. Infiltration of the dermis with epithelioid cells that have eosinophilic cytoplasm, vesicular nuclei and small nucleoli. Inflammatory cell infiltrate and Touton-type giant cell (arrows) are also demonstrated. H&E, original magnification: ×200 (A), ×400 (B).

Figure 2 (A, B) Cellular cutaneous fibrous histiocytoma. Eosinophilic spindle cells with vesicular nuclei and eosinophilic nucleoli infiltrate the dermis with extension to the superficial subcutaneous fat. H&E, original magnification: $\times 16$ (A), $\times 400$ (B).

useful clue to the diagnosis. Because of the rarity of these tumours, there has been no definite classification as to whether these tumours are benign, or may carry a risk of aggressive behaviour. Flope *et al* suggested criteria for malignancy including a size of >8.0 cm, mitotic count of >1 per 50 HPFs and necrosis.⁴¹ Accordingly, benign, uncertain malignant potential and malignant categories are based on zero, one and two of these criteria, respectively. Secondary features suggesting aggressive behaviour include infiltrative edges, cellularity and nuclear pleomorphism.⁴² Given these morphological features plus immunohistochemical features (tables 1 and 3),^{41 42} PEComas can closely mimic melanoma and can be differentiated based on S-100 negativity; however, up to 33% of PEComas express S-100 protein as well. Important clues to the diagnosis of PEComa in this context include perivascular accentuation of tumour cells, negative history of melanoma, visceral location of tumour, actin positivity, and absence of the t(12:22) translocation.⁴²

INTRADERMAL MIMICS OF UNCERTAIN BIOLOGICAL BEHAVIOUR

Primitive non-neural granular cell tumour (also known as atypical polypoid granular cell tumour)

Primitive non-neural granular cell tumour (PNGCT) is a disease of uncertain biological behaviour, with unknown line of differentiation. Le Boit *et al* first described it as “primitive polypoid granular cell tumour” in 1991.⁴³ PNGCT is histologically, immunophenotypically and ultrastructurally different

from conventional granular cell tumour.^{44–46} Histologically, PNGCTs are well-circumscribed dermal lesions with overlying epithelial hyperplasia and they consist of tumour cells that are elongated spindle-shaped to round or polygonal cells with prominent granular cell change (fig 5). The nuclei can be hyperchromatic or vesicular and have prominent eosinophilic nucleoli, and they can demonstrate pleomorphism, and increased mitotic count. Immunohistochemically, common markers are outlined in table 2. Ultrastructurally, there are primitive cells with large secondary lysosomes.⁴⁴ Most importantly, PNGCT is a diagnosis of exclusion.

Primitive non-neural granular cell tumour and melanoma, particularly metastatic melanoma with granular cell changes share common features including cytological pleomorphism, hyperchromatic nuclei with prominent nucleoli. Therefore, it is of utmost importance to carefully differentiate PNGCT from metastatic melanoma since both of these lesions usually do not have a junctional component. Accordingly, immunohistochemistry is crucial to make that distinction (table 2). Ultrastructurally, PNGCT does not contain any melanosomes or premelanosomes.⁴⁴

Langerhans cell histiocytosis

Skin involvement is frequent in both acute and chronic Langerhans cell histiocytosis (LCH); however, it has been reported only rarely in patients as the sole manifestation of the disease. It usually affects children, but can present in all

Figure 3 (A, B) Juvenile xanthogranuloma. The dermis is infiltrated by histiocytes with eosinophilic finely vacuolated cytoplasm and multinucleated giant cells of Touton type (arrows). Inflammatory infiltrates are also seen. H&E, original magnification: $\times 16$ (A), $\times 400$ (B).

Figure 4 (A, B) Cutaneous granular cell tumour. The dermis and the subcutaneous tissue illustrate infiltration with plump, spindle and epithelioid cells with abundant granular cytoplasm (arrows) and inconspicuous bland nuclei. H&E, original magnification: $\times 16$ (A), $\times 400$ (B).

ages. Clinically, it presents as scaly, crusted papules or plaques with the scalp, face and genital areas as the most commonly involved locations.

Confusion with primary melanoma only occurs when there is prominent infiltration of the epidermis by Langerhans cells (LCs), especially when examining small biopsies. Microscopic features of LCs along with immunohistochemistry help to separate this condition from melanoma. On histology, there are aggregates of LCs seen in the epidermis, and these are characterised by abundant blue-grey cytoplasm, indented oval nuclei with a central groove, and little or no cytological atypia. Eosinophils are often present. In addition, the absence of melanin pigment is another helpful feature in LCH. Immunohistochemically, LCs are positive for S-100, CD1a, langerin (CD207) but negative for other melanocytic markers (table 2).^{47–50} Ultrastructurally, the presence of rod-shaped or rocket-shaped granules (Birbeck granules, LC granules) is the diagnostic hallmark of LCs.

Inflammatory myofibroblastic tumour of the skin

Inflammatory myofibroblastic tumour (IMT) of the skin is characterised by poorly circumscribed spindle cell proliferation in the dermis that might extend to the subcutis. The cells are bland and may arrange focally in fascicular pattern. A heavy inflammatory cell infiltrate composed of plasma cells, lymphoplasmacytoid, and small lymphocytes is distributed throughout

the tumour. In addition, thickened, hyalinised collagen bundles are usually identified. The myofibroblasts are spindle to polygonal with single, double or multiple nuclei, and prominent eosinophilic nucleoli. Thus, it may be confused with melanoma; however, careful microscopic examination and adjunct immunohistochemistry usually confirm the diagnosis (table 2).²⁶

MALIGNANT DERMAL MIMICS

Dermatofibrosarcoma protuberans

Dermatofibrosarcoma protuberans (DFSP) is a cutaneous fibrous neoplasm of intermediate malignancy that can mimic melanoma. Pigmented DFSP (Bednar tumour) is a rare variant that can also be confused with melanoma due to the presence of pigmented cells.

Histologically, DFSP is composed of monotonous spindle-shaped cells arranged in a storiform pattern (fig 6). These cells have amorphophilic or eosinophilic cytoplasm with poorly defined cell borders. The mitotic count is low, <5 per 10 HPFs.^{51–52} Bednar tumour also contains $<5\%$ pigmented cells with round to oval vesicular nuclei. The spindle-shaped cells are positive for vimentin, CD34, and focally for CD10, while the pigmented cells in Bednar tumour are positive for S-100.

It is essential to differentiate DFSP and its pigmented variant from spindle cell melanoma because these lesions may share common histological and immunohistochemical features, including spindle-shaped cells, and pigmented cells that are

Figure 5 (A, B) Primitive non-neural granular cell tumour. Infiltration of the dermis with a well-circumscribed proliferation of spindle to polygonal cells with prominent granular cytoplasm. The nuclei are pleomorphic and some of them demonstrate prominent nucleoli. H&E, original magnification: $\times 16$ (A), $\times 400$ (B).

Table 2 Intradermal mimics of uncertain biological behaviour

Lesion	Clinical features	Histology	Immunohistochemistry
Primitive non-neural granular cell tumour	Young to middle-aged adults Female predominance	Cells with prominent granular cytoplasm Nuclei with prominent eosinophilic nucleoli Nuclear pleomorphism Mild mitotic activity	(+) Vimentin (+) CD10 (+) PGP 9.5 (+) NKI-C3 (+) CD 68 (-) S-100 (-) HMB-45 (-) CD34 (-) Desmin (-) SMA (-) Mart1/MelanA (+) S-100,
Langerhans cell histiocytosis*	Scaly, crusted papules or plaques Affects children mainly	Aggregates of Langerhans cells in the epidermis characterised by abundant blue-grey cytoplasm, indented oval nuclei with a central groove Little or no cytological atypia Dermal infiltrate of Langerhans cells that form sheets with accentuation below the epidermis; absence of melanin pigment, and presence of eosinophils	(+) CD1a (+) Langerin (CD207) (-) HMB-45 Mart 1/Melan A (-) (+) SMA, vimentin, CD68 in spindle cells (+) ALK-1 (-) S-100, HMB-45, Mart1/MelanA, MiTF
Inflammatory myofibroblastic tumour of the skin	Solitary firm papules and nodules	Bland spindle cells in dermis and subcutaneous fat Heavy admixed inflammatory infiltrate Hyalinised collagenous stroma	(-) S-100, HMB-45, Mart1/MelanA, MiTF

*The ultrastructural hallmark of Langerhans cells is the rod-shaped or rocket-shaped granules (Birbeck granules, Langerhans cell granules), which may be needed to establish the diagnosis of Langerhans cell histiocytosis.
ALK-1, anaplastic lymphoma kinase-1; HMB, human melanoma black; MiTF, microphthalmia transcription factor; PGP, P glycoprotein; SMA, smooth muscle actin.

positive for S-100. The differences include the storiform architecture of spindle-shaped cells, which are almost always positive for CD34, and negativity for other melanocytic markers (table 3) in DFSP and its pigmented variant. Furthermore,

ultrastructural studies of Bednar tumour, although rarely carried out in daily practice, may be helpful because the pigmented cells contain mature melanin granules, but no premelanosomes.⁵¹

Figure 6 (A–D) Dermatofibrosarcoma protuberans. Spindle cells with eosinophilic cytoplasm infiltrating the dermis and the subcutaneous fat (arrowheads) in a storiform pattern (S). One mitotic figure is illustrated (arrow). H&E, original magnification: ×16 (A), ×100 (B), ×400 (C), ×400 (D).

Atypical fibroxanthoma including the deep nodular variant (pleomorphic undifferentiated sarcoma of skin)

Atypical fibroxanthoma is a cutaneous pleomorphic undifferentiated sarcoma, which typically occurs on sun-damaged actinic skin of head and neck of the elderly. It is a relatively well-circumscribed dermal tumour with a collarette of epithelium around the tumour in some cases. The tumour is composed of a haphazard arrangement of pleomorphic, spindled and epithelioid cells (fig 7A), some of which are multinucleated. There are numerous typical and atypical mitoses (fig 7B). The deep nodular variant may have perineural invasion and sometimes necrosis; thus it can be confused with melanoma. Some pathologists designate this variant as malignant fibrous histiocytoma.

Of note, pigmented atypical fibroxanthoma, a rare variant, makes the distinction between atypical fibroxanthoma and melanoma difficult. Pigmented tumour cells contain haemosiderin, which can be confirmed by Prussian iron stain. The hypothesis is that the neoplastic cells can ingest and degrade erythrocytes from intratumoral haemorrhage.⁵² The difficulty is that melanoma and pigmented atypical fibroxanthoma have significant cellular atypia, multinucleated cells and increased mitotic activity. However, pigmented atypical fibroxanthoma lacks junctional component, although it can be ulcerated, in which case this feature is not of great help in making the distinction. Immunohistochemistry may help in making the correct diagnosis (table 3).

It is important to emphasise that atypical fibroxanthoma, both conventional and pigmented, is a diagnosis of exclusion. CD10 is a recently proposed marker of atypical fibroxanthoma. However, this is a non-specific marker and can also be expressed in melanoma mainly, the metastatic melanomas.⁵³

Malignant peripheral nerve sheath tumour

Malignant peripheral nerve sheath tumour (MPNST) is a malignant soft tissue tumour. According to the current World Health Organization classification, it arises from “peripheral nerve or showing nerve sheath differentiation with the exception of tumours originating from the epineurium or the peripheral nerve vasculature”. Approximately 50% of cases are associated with neurofibromatosis-1.

MPNST is a mimic of other spindle cell tumours particularly desmoplastic melanoma. Histologically, MPNST has a fasciculated growth pattern composed of tightly packed, hyperchromatic spindle cells with faintly eosinophilic cytoplasm. Currently, all available immunohistochemical markers are not specific for MPNST. S-100 is expressed in less than half of MPNST⁵⁴ and is usually focally, weakly positive as compared with a strong and diffuse positivity in most melanoma cases. Nestin, an intermediate filament protein that is expressed in neuroectodermal stem cells, has recently been reported to be diffusely and strongly positive in the majority of MPNST.⁵⁴

The epithelioid variant of MPNST also mimics melanoma. It accounts for 5–17% of MPNSTs, and it occurs more superficially.⁵⁵ It can assume one of three forms: glands, rosettes or primitive neuroepithelium, or cells with a polygonal shape.⁵⁶ Epithelioid MPNST shows more uniform S-100 positivity than the conventional form. In contrast to most primary melanomas, MPNST lacks a junctional component and does not express other melanocytic markers (table 3).

It is important not to miss the so called MPNST-like metastatic melanoma, in which this lesion looks morphologically similar to MPNST, and the distinction between the two

entities requires careful and close clinicopathological and immunohistochemical correlation.

Cutaneous leiomyosarcoma

Primary cutaneous superficial leiomyosarcoma is rare compared with the deep subcutaneous or secondary leiomyosarcoma. Histologically, cutaneous leiomyosarcoma is composed of interlacing fascicles of elongated spindle-shaped cells with eosinophilic cytoplasm (fig 9), eccentric vacuoles and blunt-ended nuclei. The cells are pleomorphic with nuclear atypia. Kaddu *et al* identified two architectural patterns, diffuse and nodular, from a study of 19 cutaneous leiomyosarcoma.⁵⁷ Mitoses (fig 8), high cellularity and significant nuclear atypia, which are present in the majority of cutaneous leiomyosarcomas,^{57–59} may also be present in melanoma. In contrast to melanoma, cutaneous leiomyosarcomas do not have junctional melanocytes; however, this is only true for primary melanoma, as metastatic and some primary melanomas lack the junctional component. In such cases, adjunct immunohistochemical markers are helpful as leiomyosarcomas are negative for melanocytic markers (table 3).

Epithelioid angiosarcoma

Epithelioid angiosarcoma, a rare variant of angiosarcoma, is a malignant tumour of vascular endothelial cells. Histologically, these lesions can cause confusion with carcinoma and melanoma, as they consist of large epithelioid cells with abundant eosinophilic cytoplasm and irregular atypical nuclei and large nucleoli. Mitotic figures are usually prominent (fig 9).

These lesions can have cells such as macrophages with S-100 immunoreactivity, and this can further complicate the problem. In contrast to melanoma, epithelioid angiosarcoma is usually negative for more specific melanocytic markers and positive for endothelial markers (table 3).^{60–62} In difficult cases, electron microscopy can be done to reveal some Weibel–Palade bodies.

Epithelioid sarcoma

Epithelioid sarcoma is a malignant mesenchymal tumour displaying multidirectional differentiation that is predominately epithelial.^{61–63–64} Some features of the morphology of epithelioid sarcoma may mimic melanoma. The tumour is composed of uniform polygonal cells arranged in nodular aggregates that merge peripherally into spindle cells without demarcation. There is central necrosis similar to granuloma annulare and ulceration. The cells are minimally pleomorphic, with deeply eosinophilic cytoplasm (fig 10). The presence of pleomorphic polygonal cells and occasional mitoses is similar to melanoma.

Some features that differentiate epithelioid sarcomas and melanoma include clinical features, morphology and immunohistophenotype. The distal extremity location, younger age group, nodular aggregates of polygonal and spindled-shaped cells and negativity for melanocytic markers (table 3) are common features of epithelioid sarcoma.

Spindle cell squamous cell carcinoma

Spindle cell squamous cell carcinoma (SCSCC) is a variant of squamous cell carcinoma. Histologically, these tumours consist of spindled pleomorphic cells that infiltrate the dermis. They are arranged in single units or cohesive nests and lack keratinisation. On many occasions, the tumour is entirely composed of spindle cells that make it very difficult to distinguish from other spindle cell lesions, including spindle cell melanoma and desmoplastic melanoma. Therefore, immunohistochemistry

Table 3 Primary malignant non-melanocytic mimics of intradermal melanoma

Lesion	Clinical features	Histology	Immunohistochemistry
DFSP	Young to middle-aged adults	Spindle-shaped cells in storiform pattern	(+) Vimentin (spindled)
	Trunk	Pigmented cells (Bednar tumour)	(+) CD34 (spindled)
		Low mitotic rate	(+) CD 10 (focal)
		Minimal cytological atypia	(+) Focal S-100 (pigmented)
Atypical fibroxanthoma (pleomorphic undifferentiated sarcoma of skin)			(+) Apolipoprotein D
			(-) HMB-45
			(-) Mart1/MelanA
			(-) MiTF
	Male predominance	Well-circumscribed lesion	(+) Vimentin
	Head and neck	Haphazard arrangement	(+) CD68
		Pleomorphic, spindled and epithelioid cells	(+) Lysozyme
		Numerous mitoses including atypical	(+) α -1 Antichymotrypsin
		Multinucleated giant cells	(+) Focal factor XIIIa
			(+) MSA or SMA
Malignant PNST			(+) CD10 (diffuse)
			(-) S-100
			(-) Keratin
			(-) Desmin
			(-) Mart1/MelanA
			(-) MiTF
	Buttocks and thighs	Fasciculated pattern of hyperchromatic spindle cells	(+) Focal S100 (subset)
	Rare in other skin locations		(+) NSE
			(+) Leu 7
			(+) Myelin
Cutaneous leiomyosarcoma			(+) p53
			(+) HMGA2
			(-) Neurofilament
			(-) HMB-45
			(-) Mart1/Melan A
			(-) MiTF
	Adults in their 60s	Fascicles of spindle-shaped cells with eccentric vacuole	(+) Desmin
	Male predominance	Pleomorphism	(+) Caldesmon
	Hair-bearing skin of lower extremities	Nuclear atypia	(+) Vimentin
		Mitoses	(+) SMA
Epithelioid angiosarcoma			(+) MSA
			(+) S-100 (rare subset)
			(-) Mart1/Melan A
			(-) HMB-45
			(-) MiTF
	Elderly	Large epithelioid tumour cells	(+) CD31
	May bleed spontaneously	Hobnail pattern	(+) CD34
	Scalp and neck	Irregular nuclei	(+) Focal SMA
		Mitoses, including atypical ones	(+) Factor VIII-RA
		Vascular channels	(+) S-100 (rare subset)
Epithelioid sarcoma		Extravasated red blood cells	(+) LMWCK (Cam5.2)
			(+) Pankeratin (AE1/AE3)
			(+) Cytokeratin 7
			(-) HMB-45
			(-) Mart 1/Melan A
			(-) MiTF
	Young adult	Polygonal tumour cells in nodular aggregates with spindle cells in periphery	(+) Cytokeratin
	Male	Pleomorphism	(+) Vimentin
	Distal extremities	Occasional mitoses	(+) EMA
		Central necrosis	(+) CD34 (subset)
			(-) S-100
			(-) HMB-45
			(-) Mart1/Melan A

Continued

Table 3 Continued

Lesion	Clinical features	Histology	Immunohistochemistry
Spindle cell squamous cell carcinoma	Elderly men Sun-exposed skin Head and neck Upper extremities Upper back and chest	Spindled pleomorphic tumour cells No keratinisation May show desmosomal junctions	(–) MiTF (+) 34βE12 (+) AE1/AE3 (+) Cytokeratin 5/6 (+) P63 (nuclear) (–) S-100 (–) HMB-45 (–) Mart1/MelanA (–) MiTF
Cutaneous malignant granular cell tumour	Rarely seen in children Larger than their benign counterparts	Necrosis Spindling Vesicular nuclei with large nucleoli Increased mitotic activity >2/10 HPF High N/C ratio Pleomorphism	(+) S-100 (+) Calretinin (+) Inhibin (–) HMB-45 (–) Mart1/MelanA (–) MiTF
Cutaneous lymphoproliferative disorders and other haematological malignancies	Can affect any age	Large pleomorphic mononuclear cells	(+) LCA (CD45) Depending on type of lymphoma: B cell markers T cell markers Blast markers Myeloma markers (CD138) (–) S-100 (–) HMB-45 (–) Mart1/MelanA
Merkel cell carcinoma	Head and neck and extremities of older adults Solitary rapidly growing hard nodule	Small monomorphic basophilic cells with round to oval shaped nuclei and scanty cytoplasm Nuclei have finely granular dispersed chromatin and small inconspicuous nucleoli Tumour cells mainly occupy the dermis, but pagetoid spread of the tumour cells into the epidermis can be seen	(+) CK20 and LMWCK typical dot-like paranuclear or cytoplasmic staining (+) Variably for CD56, CD57, EMA, chromogranin and synaptophysin (–) S-100 (–) HMB-45 (–) Vimentin (–) Mart 1/Melan A (–) MiTF
Malignant PEComa	Depends on type and site of PEComa	Clear or eosinophilic spindle-epithelioid cells Fascicular, nested, sheet-like patterns Perivascular accentuation Multinucleated giant cells >8 cm in size, >1 mitotic figure/50 HPFs, necrosis	(+) HMB-45 (+) Mart1/MelanA (+) MiTF (+) S-100 in 18% (+) SMA, MSA (+) Desmin (+) Cyclin D1 (+) Vimentin (+) Pan-cytokeratin (+) CD21
Follicular dendritic cell sarcoma	Mostly affect adults Intranodal or extranodal painless mass	Spindle to ovoid cells arranged in storiform or fascicular pattern Oval nuclei, distinct nucleoli, delicate nuclear membrane Indistinct cell border Fibrillary cytoplasm	(+) CD35 (+) CD23 (+) Desmoplakin (+) EMA (+) Vimentin (+) S-100 in 35% (+) CD68 in 11% (+) Clusterin (+) Fascin (+) Podoplanin (–) HMB-45 (–) Mart1/MelanA

Continued

Table 3 Continued

Lesion	Clinical features	Histology	Immunohistochemistry
Anaplastic/pleomorphic Kaposi sarcoma	HIV setting	Spindle to epithelioid cells arranged in solid sheets and fascicles Pleomorphic nuclei with prominent nucleoli Atypical mitoses Extravasated red blood cells	(-) MiTF (-) Cytokeratin (-) CD30 (-) CD3 (-) CD79a (-) CD34 (-) CD1a (+) CD34
			(+) D2-40
			(+) CD31 (patchy)
			(+) HHV-8 latency-associated nuclear antigen-1 (+) VEGFR-3 (+) Podoplanin (-) S-100 (-) HMB-45 (-) Mart1/MelanA (-) MiTF
Plexiform fibrohistiocytic tumour of the skin	Young patients Female predominance Trunk, extremity, face	Plexiform pattern Spindled and histiocytoid cells Osteoclast-type giant cells Cellular pleomorphism, mitotic activity, vascular invasion (may sometimes look like non-necrotising granulomas)	(+) CD68 (+) SMA (+) PGP 9.5 (+) S-100A6
			(+) MiTF (+) CD57 (-) HMB-45 (-) Mart1/MelanA
			(+) EMA, HMWCK, LMWCK
			(+) Type IV collagen, CD57, rarely S-100 (+) CD99, CD56, neurofilaments (-) Chromogranin, synaptophysin
Monomorphic spindle synovial sarcoma	Adolescents, young adults Lower extremities	Spindle and epithelioid cells High nuclear/cytoplasmic ratio Variable mitotic rate	(-) HMB-45, Mart1/MelanA, MiTF (+) Vimentin, other mesenchymal markers S-100 could be positive (-) HMB-45, Mart1/MelanA
Post-radiation sarcomas including rhabdomyosarcomas	Post-radiotherapy	Spindle cells Cellular atypia High mitotic rate	

DFSP, dermatofibrosarcoma protuberans; EMA, epithelial membrane antigen; HMB, human melanoma black; HMWCK, high molecular weight cytokeratin; LMWCK, low molecular weight cytokeratin; MiTF, microphthalmia transcription factor; MSA, muscle specific actin; NSE, neuron-specific enolase; PEComa, perivascular epithelioid cell tumour; PGP, P glycoprotein; PNST, peripheral nerve sheath tumour; SMA, smooth muscle actin; VEGFR, vascular endothelial growth factor receptor.

(table 3) can help reach a diagnosis. Recently, p63 was identified as marker for SCSCC.⁶⁵ Demonstration of desmosomal junctions can be a useful diagnostic criteria, but in many cases these are not visible on the conventional H&E slides.

Cutaneous malignant granular cell tumour

Malignant granular cell tumours (GCT) are rare tumours that make up less than 2% of all granular cell tumours.⁶⁶ These tumours tend to be larger than their benign counterparts and

Figure 7 (A, B) Atypical fibroxanthoma. Pleomorphic epithelioid and spindle cells infiltrating the dermis. Two atypical mitotic figures are demonstrated (arrows). H&E, original magnification: ×16 (A), ×400 (B).

Figure 8 (A, B) Cutaneous leiomyosarcoma. The dermis is infiltrated with pleomorphic spindle cells, some with cigar-shaped nuclei and eosinophilic cytoplasm. Mitotic figures can also be seen (arrow). H&E, original magnification: $\times 16$ (A), $\times 400$ (B).

are rarely seen in children. Histologically, malignant GCTs are similar to benign GCTs, but they have a constellation of histological features that favour malignancy. These features include nuclear atypia with prominent nucleoli, nuclear pleomorphism, increased nuclear/cytoplasmic ratio, increased mitotic activity (>2 per 10 HPFs), spindling and necrosis. Tumours that have three or more of these criteria are considered malignant with an increased risk for metastasis.³⁹ However, lack of these criteria does not exclude malignancy. Distinction from melanoma in most cases can be confirmed by immunohistochemistry (table 3).

Cutaneous lymphoproliferative disorders and other haematological malignancies

Primary cutaneous lymphoma and other haematological malignancies are challenging to diagnose because they have various histological manifestations. They can mimic melanoma because the former may include large pleomorphic mononuclear cells that may be confused with atypical melanocytes. An ancillary immunohistochemical panel includes B cell marker, T cell markers, blast markers, myeloma markers (table 3), and specific genetic translocations, plus melanocytic markers can help reach a diagnosis. Discussion of each subtype of cutaneous lymphoma is beyond the scope of this review. Often, diagnosis can be achieved after correlation of clinical, histological and immunohistochemical features. Special attention should be given to the

CD30-positive lymphoproliferative disorders, as these may be confused with melanoma.

Merkel cell carcinoma

Merkel cell carcinoma (MCC) is a primary neuroendocrine carcinoma of the skin that mainly involves the head and neck and extremities (mainly dorsum of the hands) of older adults, and it presents clinically as a solitary rapidly growing hard nodule. Microscopically, MCC is one of the small, round, blue cell tumours that is often characterised by nested or trabecular pattern of growth, high mitotic rate and frequent single-cell necrosis, and sometimes zonal necrosis. One of its histological differential diagnoses includes melanoma (small cell variant). However, histological correlation with the clinical data and immunohistochemistry can help rule out melanoma. Histologically, MCC consists of small monomorphic basophilic tumour cells with round to oval shaped nuclei and scanty cytoplasm. The nuclei have finely granular dispersed chromatin and small inconspicuous nucleoli. The tumour cells mainly occupy the dermis and may extend into the subcutaneous fat; however, pagetoid spread of the tumour cells into the epidermis, although rare, can occur and has been reported.⁶⁷ A dense lymphocytic infiltrate is characteristically present within and surrounding area of the tumour.

Immunohistochemical features are usually helpful to aid the diagnosis (table 3).^{68–69} Electron microscopy demonstrates the

Figure 9 (A, B) Epithelioid angiosarcoma. Infiltration of the dermis with large epithelioid cells (arrows) with abundant eosinophilic cytoplasm and prominent eosinophilic nucleoli. One mitotic figure is demonstrated (arrowhead). H&E, original magnification: $\times 16$ (A), $\times 400$ (B).

Figure 10 (A, B) Epithelioid sarcoma. The dermis is infiltrated with pleomorphic epithelioid cells (arrows) with abundant eosinophilic cytoplasm and inconspicuous nucleoli. H&E, original magnification: $\times 200$ (A), $\times 400$ (B).

neuroendocrine nature of MCC cells by showing dense core neurosecretory granules, paranuclear aggregates of intermediate-sized filaments, complex intercellular junctions and cytoplasmic spinous processes.

Follicular dendritic cell sarcoma

Follicular dendritic cell sarcoma (FDCS) is an uncommon neoplasm of adulthood and can affect patients over a wide age range. It can arise in nodal and extranodal sites including skin.

Common histological features include a storiform or fascicular array of spindle, ovoid or polygonal cells with oval nuclei, delicate nuclear membrane, vesicular or granular chromatin, distinct nucleoli, indistinct cell borders, and slightly eosinophilic, fibrillary cytoplasm (fig 11). Occasional pseudonuclear inclusions may be seen. Small lymphocytes are scattered throughout the tumour. Additionally, occasional binucleated and multinucleated tumour cells (fig 11) may be present. The tumour cells sometimes form sheets, circular whorls, follicle-like structures, trabeculae or pseudovascular spaces.

FDCS differential diagnoses consist of spindle cell lesions, including melanoma. FDCS can be usually differentiated from melanoma by morphology; however, immunohistochemistry is needed to confirm the diagnosis in challenging cases (table 3).^{70 71}

Anaplastic/pleomorphic kaposi sarcoma

Kaposi sarcoma (KS) is an endothelial cell neoplasm often occurring in the setting of HIV infection. Histologically, KS may range from dermal subtle vascular proliferation to sheets and fascicles of atypical spindle cells with scattered slit-like spaces. The anaplastic/pleomorphic variant can show solid sheets of epithelioid cells that can form irregular vascular spaces, with or without areas of necrosis. The nuclei are pleomorphic with

variably prominent nucleoli, and numerous mitoses, including atypical forms. Hence, this lesion can mimic melanoma and the distinction between them can be achieved with careful histological and immunohistochemical examination in conjunction with clinical history (table 7).⁷² We emphasise here that clinical history is crucial in diagnosis.

Plexiform fibrohistiocytic tumour of the skin

Plexiform fibrohistiocytic tumour (PFHT) of the skin is a distinct entity of low-grade malignant or borderline malignant potential that affects mostly young adults but can occur in a wide age range.⁷³ These tumours can be morphologically classified into three groups: fibroblastic, histiocytic (often with osteoclast-type giant cells) and mixed. These tumours usually exhibit a plexiform and infiltrative arrangement of cells at the dermal/subcutaneous junction. In addition, PFHT usually lacks atypia. However, cellular atypia, pleomorphism and atypical mitoses can be seen. Osteoclast-type giant cells are often present in PFHT, particularly in the histiocytic subtype, especially in areas of haemorrhage. Stromal hyalinisation and occasional myxoid changes may also be seen.

Additional features of PFHT may include the presence of microfat, adnexal sparing and metaplastic bone changes. Distinguishing PFHT from melanoma can be achieved by histology and immunohistochemistry (table 3).⁷³ PFHTs can also mimic granulomatous inflammation of the skin.

Monomorphic spindle synovial sarcoma

Synovial sarcoma is a well-defined soft tissue sarcoma with monomorphic and biphasic histological subtypes. The tumour is more prevalent in adolescents and young adults, and occurs predominantly in the lower extremities. Skin is an unusual location for synovial sarcoma, but it has been reported in the

Figure 11 (A, B) Follicular dendritic cell sarcoma. The dermis is infiltrated with a storiform array of spindle, ovoid or polygonal cells with oval nuclei, delicate nuclear membrane, distinct nucleoli, indistinct cell borders, and slightly eosinophilic, fibrillary cytoplasm. Multinucleated giant cells are also illustrated (arrows). H&E, original magnification: $\times 16$ (A), $\times 400$ (B).

Table 4 Metastatic mimics

Metastatic mimic	Common site	Histology	Immunohistochemistry
Lung	Anywhere (especially chest wall and abdomen)	Adenocarcinoma: intracytoplasmic mucin, lymphovascular invasion Squamous cell: focal keratinisation and necrosis Small cell: neuroendocrine features	Adenocarcinoma CK7+/CK20– (+) TTF-1 (+) CEA Squamous cell carcinoma (+) HMWCK (+) CK5/6 (+) p63 Small cell carcinoma CK7+/CK20– (±) TTF-1 (+) Synaptophysin (+) Chromogranin (+) CD56 Melanocytic markers (–) S-100 (–) HMB-45 (–) Mart1/Melan A (–) MiTF
Breast	Chest wall Scalp	Ductal: glands and comedo necrosis Lobular: single-row files of tumour cells	CK7+/CK20– ER+/PR+ (+) AR in apocrine lesions (+) GCDFP (+) CEA (–) S-100 (–) HMB-45 (–) Mart1/MelanA (–) MiTF
Renal	Anywhere (especially head and neck)	Abundant clear cytoplasm Vascular stroma	CK7–/CK20– (+) Vimentin (+) CD10 (+) EMA (+) RCC antigen (–) S-100 (–) HMB-45 (–) Mart1/MelanA (–) MiTF
Prostate	Genital region, anterior thigh	Gland formation Hyperchromatic pleomorphic nuclei	CK7–/CK20– (+) PSA (+) PAP (–) S-100 (–) HMB-45 (–) Mart1/MelanA (–) MiTF
Thyroid	Head and neck (especially scalp)	Looks similar to primary thyroid carcinoma Medullary carcinoma may be Congo red positive related to the amyloid deposits.	Papillary and follicular CK7+/CK20– (+) TTF-1 (+) Thyroglobulin Medullary (+) Synaptophysin (+) Chromogranin (+) CD56 Melanocytic markers (–) S-100 (–) HMB-45 (–) Mart1/MelanA (–) MiTF

AR, androgen receptor; CEA, carcinoembryonic antigen; CK, cytokeratin; EMA, epithelial membrane antigen; ER, oestrogen receptor; GCDFP, gross cystic disease fluid protein; PR, progesterone receptor; HMB, human melanoma black; HMWCK, high molecular weight cytokeratin; MiTF, microphthalmia transcription factor; PAP, peroxidase-antiperoxidase; PSA, prostate specific antigen; RCC, renal cell carcinoma; TTF-1, antithyroid transcription factor antibody.

literature. The biphasic histological variant is rarely a diagnostic dilemma. However, monomorphic spindle cell variant poses difficulty and its most important differential diagnoses include fibrosarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumours, primitive neuroectodermal tumours⁷⁴ and melanoma.

Histologically, the tumour is composed of nodular mass usually centred in the deep dermis with extension into the papillary dermis and subcutis. The cells are round to spindle shape arranged in fascicular or solid pattern, with minimal cytoplasm, darkly stained nuclei and variable mitotic rate. Distinct glandular and stromal elements may be present. Additional features include wiry collagen, and necrosis. This variant of synovial sarcoma can be sometimes mistaken for melanoma; however histological and immunohistochemical examinations usually make the distinction (table 3).^{74 75} Detection of the synovial sarcoma-associated t(X;18) by either cytogenetic or molecular genetic methods may be necessary to confirm the diagnosis of synovial sarcoma in difficult cases.⁷⁴

Post-radiation sarcomas including rhabdomyosarcomas

Post-radiation sarcomas are well-recognised long-term complications of radiotherapy. Such sarcomas have been reported in the soft tissues and skin. Cutaneous angiosarcoma is a well-known example and probably the commonest of such complications. These sarcomas can mimic melanoma histologically and thus clinicopathological correlation with adjunct immunohistochemistry is required to confirm the diagnosis (table 3). An example of such mimic also includes rhabdomyosarcomatous differentiation, which can be mistaken with rhabdoid variant of melanoma.

METASTATIC MIMICS

Time of development

The majority of cutaneous metastases occur after the diagnosis of the internal malignancy. A minority of cutaneous metastasis represents first presentation of malignancy. Clinical information and morphological features usually help to make the diagnosis and ancillary studies such as immunohistochemical features are useful when one of the above is not available.⁷⁶

Figure 12 (A, B) Metastatic medullary thyroid carcinoma to the skin. The dermis is infiltrated with sheets of slightly atypical spindle/oval cells with eosinophilic cytoplasm, hyperchromatic nuclei and inconspicuous nucleoli. A mitotic figure is demonstrated (arrow). H&E, original magnification: $\times 16$ (A), $\times 200$ (B).

Clinical history, including radiological studies and morphological analyses of previous biopsy, is also helpful.

Site of primary tumour

According to Krathen's meta-analysis, the overall incidence of cutaneous metastases is 5.3% (1080/20 380).⁷⁷ Breast carcinoma is the most common primary tumour with cutaneous metastases in women, while lung carcinoma is the most common primary with cutaneous metastases in men. Breast carcinoma has the highest incidence of cutaneous metastasis (24%) while prostate carcinoma has the lowest incidence (0.7%). The incidence of lung, colorectal, renal, ovarian and bladder carcinoma cutaneous metastases is similar and ranges between 3% and 4%.

Prognostic aspects

Cutaneous metastases represents grim prognosis; approximately two-thirds of the patients died within the first 6 months of diagnosis.^{76 77}

Lung carcinoma

Cutaneous metastases from lung carcinoma represent approximately 1–5 % of all lung carcinomas.^{78 79} Cutaneous metastases of adenocarcinoma, squamous cell carcinoma and small cell carcinoma of lung resemble their primary (table 4). Cutaneous metastases of lung carcinoma resemble melanoma because both lesions can be composed of large epithelioid cells without any glandular formation. The common features of lung cutaneous metastases include focal keratinisation in squamous cell carcinoma, intracytoplasmic mucin and gland-formation in adenocarcinoma, and neuroendocrine features in small cell carcinoma. In addition to clinicopathological correlation, an immunohistochemical panel can help to confirm the diagnosis (table 4).

Breast carcinoma

Breast cutaneous metastases resemble the primary tumour. Cutaneous metastasis of invasive ductal adenocarcinoma can demonstrate glandular structures and may show comedo necrosis, while cutaneous metastases of invasive lobular carcinoma often show single-row filing of tumour cells.

Take-home messages

- ▶ Non-melanocytic intradermal mimics of melanoma can be separated into primary and metastatic lesions; primary dermal mimics are more common than metastatic mimics.
- ▶ It should be kept in mind that it is crucial to differentiate intradermal mimics from metastatic melanoma or primary melanoma that does not have a junctional component since morphological features can be very similar in these lesions. Therefore, immunohistochemistry is a critical tool in reaching a diagnosis.
- ▶ The most common primary of cutaneous metastases is breast carcinoma followed by lung and renal carcinoma.
- ▶ Melanomas can present with rare malignant phenotypes including rhabdoid, signet ring, balloon or granular cell morphologies. Also they may have neural, muscular, cartilaginous and osseous differentiation. Hence they should be differentiated from their mimics by proper history and immunohistochemistry.

Cutaneous metastases of breast carcinoma resemble melanoma because both lesions may have atypical pleomorphic epithelioid tumour cells (table 4). Ancillary immunohistochemical stains are helpful when histological features are equivocal (table 4).

Renal carcinoma

Cutaneous metastasis affects about 3–6% of patients with renal cell carcinoma (RCC).⁷⁷ Histologically, cutaneous metastasis of RCC is similar to the primary tumour (table 4). The lesion is located in the dermis, with some lesions extending into the subcutis. Cutaneous metastases of RCC resemble melanoma because both lesions show atypical epithelioid cells and have the tendency for lymphovascular invasion.⁸⁰ However, cutaneous metastases of RCC consist of cells with prominent clear cell change and vascular stroma, in contrast to melanomas that consist of atypical melanocytes and often have junctional component. An adjunct immunohistochemical panel is an essential tool for diagnosis (table 4).

Thyroid carcinoma and other endocrine tumour metastases to the skin

Cutaneous metastases from thyroid carcinoma are rare. There is no consensus on which type of thyroid neoplasm has the highest incidence of cutaneous metastases.^{81–82} The cutaneous lesion presents as flesh-coloured nodules that may be pruritic and ulcerate.⁸³ Histologically, the cutaneous metastases vary according to the primary type of thyroid carcinoma. Cutaneous metastases of papillary thyroid carcinoma show enlarged nuclei, intranuclear inclusions and nuclear grooves. Medullary thyroid carcinoma can also metastasise to the skin (figure 12). Immunohistochemical features are often useful (table 4). Most of the metastases are in the head and neck region.

Adrenocortical carcinoma cutaneous metastasis may mimic melanoma. Immunohistochemically, they are MelanA positive, but HMB-45 negative.

Pheochromocytoma cutaneous metastasis can be S-100 positive, likewise melanoma; however, they are HMB-45 and MelanA negative. Another endocrine malignancy that can metastasise to the skin and mimic melanoma morphologically is parathyroid carcinoma, which is immunoreactive to parathyroid hormone and negative for S-100, HMB-45, and Mart1/MelanA.

Prostate carcinoma

The incidence of cutaneous metastases from prostate carcinoma is less than 1%.⁷⁷ Clinically, they present as nodules, red macules and papules, or tumours with an angiomatous appearance.⁸⁴ Histologically, the tumour cells are gland forming, epithelial or anaplastic. Cutaneous metastases of prostate carcinoma resemble melanoma because both lesions consist of pleomorphic, hyperchromatic cells with atypical nuclei. However, the former have usual features such as gland formation. Along with clinicopathological correlation, immunohistochemistry analyses are helpful ancillary tests (table 4).

Competing interests: None.

REFERENCES

1. **Monteagudo C**, Calduch L, Navarro S, *et al*. CD99 immunoreactivity in atypical fibroxanthoma: a common feature of diagnostic value. *Am J Clin Pathol* 2002;**117**:126–31.
2. **Plaza JA**, Suster D, Perez-Montiel D. Expression of immunohistochemical markers in primary and metastatic malignant melanoma: a comparative study in 70 patients using a tissue microarray technique. *Appl Immunohistochem Mol Morphol* 2007;**15**:421–5.
3. **Huttenbach Y**, Prieto VG, Reed JA. Desmoplastic and spindle cell melanomas express protein markers of the neural crest but not of later committed stages of Schwann cell differentiation. *J Cutan Pathol* 2002;**29**:562–8.
4. **Kanitakis J**, Narvaez D, Claudy A. Differential expression of the CD10 antigen (neutral endopeptidase) in primary versus metastatic malignant melanomas of the skin. *Melanoma Res* 2002;**12**:241–4.
5. **Went PT**, Dirnhofer S, Bundi M, *et al*. Prevalence of KIT expression in human tumors. *J Clin Oncol* 2004;**22**:4514–22.
6. **Pernick NL**, DaSilva M, Gangi MD, *et al*. "Histiocytic markers" in melanoma. *Mod Pathol* 1999;**12**:1072–7.
7. **Kim YC**, Lee MG, Choe SW, *et al*. Acral lentiginous melanoma: an immunohistochemical study of 20 cases. *Int J Dermatol* 2003;**42**:123–9.
8. **Ben-Izhak O**, Stark P, Levy R, *et al*. Epithelial markers in malignant melanoma. A study of primary lesions and their metastases. *Am J Dermatopathol* 1994;**16**:241–6.
9. **Wilkinson AE**, Glasgow MA, Hiatt KM. Immunoreactivity of CD99 in invasive malignant melanoma. *J Cutan Pathol* 2006;**33**:663–6.
10. **Leader M**, Collins M, Patel J, *et al*. Vimentin: an evaluation of its role as a tumour marker. *Histopathology* 1987;**11**:63–72.
11. **Miettinen M**, Franssila K. Immunohistochemical spectrum of malignant melanoma. The common presence of keratins. *Lab Invest* 1989;**61**:623–8.
12. **Margo CM**, Crowson AN, Mihm MC. Unusual variants of malignant melanoma. *Mod Pathol* 2006;**19**(Suppl 2):S41–70.
13. **Longacre TA**, Egbert BM, Rouse RV. Desmoplastic and spindle-cell malignant melanoma. An immunohistochemical study. *Am J Surg Pathol* 1996;**20**:1489–500.
14. **Anstey A**, Cerio R, Ramnarain N, *et al*. Desmoplastic malignant melanoma. An immunocytochemical study of 25 cases. *Am J Dermatopathol* 1994;**16**:14–22.
15. **Kay PA**, Pinheiro AD, Lohse CM, *et al*. Desmoplastic melanoma of the head and neck: histopathologic and immunohistochemical study of 28 cases. *Int J Surg Pathol* 2004;**12**:17–24.
16. **Nakagawa H**, Imakado S, Nogita T, *et al*. Osteosarcomatous changes in malignant melanoma. Immunohistochemical and ultrastructural studies of a case. *Am J Dermatopathol* 1990;**12**:162–8.
17. **Sheibani K**, Battifora H. Signet-ring cell melanoma. A rare morphologic variant of malignant melanoma. *Am J Surg Pathol* 1988;**12**:28–34.
18. **Rütten A**, Huschka U, Requena C, *et al*. Primary cutaneous signet-ring cell melanoma: a clinico-pathologic and immunohistochemical study of two cases. *Am J Dermatopathol* 2003;**25**:418–22.
19. **Breier F**, Feldmann R, Fellenz C, *et al*. Primary invasive signet-ring cell melanoma. *J Cutan Pathol* 1999;**26**:533–6.
20. **Gavino AC**, Gillies EM. Metastatic rhabdoid melanoma: report of a case with a comparative review of the literature. *J Cutan Pathol* 2008;**35**:337–42.
21. **Borek BT**, McKee PH, Freeman JA, *et al*. Primary malignant melanoma with rhabdoid features: a histologic and immunocytochemical study of three cases. *Am J Dermatopathol* 1998;**20**:123–7.
22. **Aisner DL**, Maker A, Rosenberg SA, *et al*. Loss of S100 antigenicity in metastatic melanoma. *Hum Pathol* 2005;**36**:1016–9.
23. **Dauer EH**, Lewis JE, Rohlinger AL, *et al*. Sinonasal melanoma: a clinicopathologic review of 61 cases. *Otolaryngol Head Neck Surg* 2008;**138**:347–52.
24. **Chorny JA**, Barr RJ. S100-positive spindle cells in scars: a diagnostic pitfall in the re-excision of desmoplastic melanoma. *Am J Dermatopathol* 2002;**24**:309–312.
25. **Robson A**, Allen P, Hollowood K. S100 expression in cutaneous scars: a potential diagnostic pitfall in the diagnosis of desmoplastic melanoma. *Histopathology* 2001;**38**:135–40.
26. **El-Shabrawi-Caelen L**, Kerl K, Cerroni L, *et al*. Cutaneous inflammatory pseudotumor – a spectrum of various diseases? *J Cutan Pathol* 2004;**31**:605–11.
27. **Gleason BC**, Hornick JL. Inflammatory myofibroblastic tumors: where are we now? *J Clin Pathol* 2008;**61**:428–37.

28. **Singh Gomez C**, Calonje E, Fletcher CD. Epithelioid benign fibrous histiocytoma of skin: clinico-pathological analysis of 20 cases of a poorly known variant. *Histopathology* 1994;**24**:123–9.
29. **Calonje E**, Mentzel T, Fletcher CD. Cellular benign fibrous histiocytoma. Clinicopathologic analysis of 74 cases of a distinctive variant of cutaneous fibrous histiocytoma with frequent recurrence. *Am J Surg Pathol* 1994;**18**:668–76.
30. **Dehner LP**. Juvenile xanthogranulomas in the first two decades of life: a clinicopathologic study of 174 cases with cutaneous and extracutaneous manifestations. *Am J Surg Pathol* 2003;**27**:579–93.
31. **Janssen D**, Harms D. Juvenile xanthogranuloma in childhood and adolescence: a clinicopathologic study of 129 patients from the kiel pediatric tumor registry. *Am J Surg Pathol* 2005;**29**:21–8.
32. **Hornick JL**, Fletcher CD. Cellular neurothekeoma: detailed characterization in a series of 133 cases. *Am J Surg Pathol* 2007;**31**:329–40.
33. **Wang AR**, May D, Bourne P, et al. PGP9.5: a marker for cellular neurothekeoma. *Am J Surg Pathol* 1999;**23**:1401–7.
34. **Campbell LK**, Thomas JR, Lamps LW, et al. Protein gene product 9.5 (PGP 9.5) is not a specific marker of neural and nerve sheath tumors: an immunohistochemical study of 95 mesenchymal neoplasms. *Mod Pathol* 2003;**16**:963–9.
35. **Sachdev R**, Sundram UN. Frequent positive staining with NKI/C3 in normal and neoplastic tissues limits its usefulness in the diagnosis of cellular neurothekeoma. *Am J Clin Pathol* 2006;**126**:554–63.
36. **Fullen DR**, Lowe L, Su LD. Antibody to S100A6 protein is a sensitive immunohistochemical marker for neurothekeoma. *J Cutan Pathol* 2003;**30**:118–22.
37. **Alkhalidi H**, Ghazarian D. Cellular neurothekeoma with a plexiform morphology: a case report with a discussion of the plexiform lesions of the skin. *J Cutan Pathol* 2007;**34**:264–9.
38. **Miettinen M**, Fetsch JF. Reticulohistiocytoma (solitary epithelioid histiocytoma): a clinicopathologic and immunohistochemical study of 44 cases. *Am J Surg Pathol* 2006;**30**:521–8.
39. **Ray S**, Jukic DM. Cutaneous granular cell tumor with epidermal involvement: a potential mimic of melanocytic neoplasia. *J Cutan Pathol* 2007;**34**:188–94.
40. **Gleason BC**, Nascimento AF. HMB-45 and Melan-A are useful markers in the differential diagnosis between granular cell tumor and malignant melanoma. *Am J Dermatopathol* 2007;**29**:22–7.
41. **Flope AL**, Mentzel T, Lehr HA, et al. Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. *Am J Surg Pathol* 2005;**29**:1558–75.
42. **Weinreb I**, Howarth D, Latta E, et al. Perivascular epithelioid cell neoplasms (PEComas): four malignant cases extending the histopathological spectrum and a description of a unique finding. *Virchows Arch* 2007;**450**:463–70.
43. **LeBoit PE**, Barr RJ, Bural S, et al. Primitive polypoid granular-cell tumor and other cutaneous granular-cell neoplasms of apparent nonneural origin. *Am J Surg Pathol* 1991;**15**:48–58.
44. **Habeeb AA**, Salama S. Primitive nonneural granular cell tumor (so-called atypical polypoid granular cell tumor). Report of 2 cases with immunohistochemical and ultrastructural correlation. *Am J Dermatopathol* 2008;**30**:156–9.
45. **Lazar AJ**, Fletcher CD. Primitive nonneural granular cell tumors of skin: clinicopathologic analysis of 13 cases. *Am J Surg Pathol* 2005;**29**:927–34.
46. **Chaudhry IH**, Calonje E. Dermal non-neural granular cell tumour (so-called primitive polypoid granular cell tumour): a distinctive entity further delineated in a clinicopathologic study of 11 cases. *Histopathology* 2005;**47**:179–85.
47. **Calonje E**. Non-melanocytic lesions mimicking melanocytic lesions. *Pathology* 2004;**36**:387–95.
48. **Punia RS**, Bagai M, Mohan H, et al. Langerhans cell histiocytosis of skin: a clinicopathologic analysis of five cases. *Indian J Dermatol Venereol Leprol* 2006;**72**:211–4.
49. **Meehan SA**, Smoller BR. Cutaneous Langerhans cell histiocytosis of the genitalia in the elderly: a report of three cases. *J Cutan Pathol* 1998;**25**:370–4.
50. **Mizumoto N**, Takashima A. CD1a and langerin: acting as more than Langerhans cell markers. *J Clin Invest* 2004.
51. **Seo IS**, Goheen M, Min KW. Bednar tumor: report of a case with immunohistochemical and ultrastructural study. *Ultrastruct Pathol* 2003;**27**:205–10.
52. **Diaz-Cascajo C**, Weyers W, Borghi S. Pigmented atypical fibroxanthoma: a tumor that may be easily mistaken for malignant melanoma. *Am J Dermatopathol* 2003;**25**:1–5.
53. **Hultgren TL**, DiMaio DJ. Immunohistochemical staining of CD10 in atypical fibroxanthomas. *J Cutan Pathol* 2007;**34**:415–9.
54. **Shimada S**, Tsuzuki T, Kuroda M, et al. Nestin expression as a new marker in malignant peripheral nerve sheath tumors. *Pathol Int* 2007;**57**:60–7.
55. **Allison KH**, Patel RM, Goldblum JR, et al. Superficial malignant peripheral nerve sheath tumor: a rare and challenging diagnosis. *Am J Clin Pathol* 2005;**124**:685–92.
56. **Laskin WB**, Weiss SW, Brattbauer GI. Epithelioid variant of malignant peripheral nerve sheath tumor (malignant epithelioid schwannoma). *Am J Surg Pathol* 1991;**15**:1136–45.
57. **Kaddu S**, Beham A, Cerroni L, et al. Cutaneous leiomyosarcoma. *Am J Surg Pathol* 1997;**21**:979–87.
58. **Choy C**, Cooper A, Kossard S. Primary cutaneous diffuse leiomyosarcoma with desmoplasia. *Australas J Dermatol* 2006;**47**:291–5.
59. **Bellezza G**, Sidoni A, Cavaliere A, et al. Primary cutaneous leiomyosarcoma: a clinicopathological and immunohistochemical study of 7 cases. *Int J Surg Pathol* 2004;**12**:39–44.
60. **Brightman LA**, Demierre MF, Byers HR, et al. Macrophage-rich epithelioid angiosarcoma mimicking malignant melanoma. *J Cutan Pathol* 2006;**33**:38–42.
61. **Fisher C**. Epithelioid sarcoma of Enzinger. *Adv Anat Pathol* 2006;**13**:141–21.
62. **Lin O**, Gerhard R, Coelho Siqueira SA, et al. Cytologic findings of epithelioid angiosarcoma of the thyroid. A case report. *Acta Cytol* 2002;**46**:767–71.
63. **Laskin WB**, Miettinen M. Epithelioid sarcoma: new insights based on extended immunohistochemical analysis. *Arch Pathol Lab Med* 2003;**127**:1161–8.
64. **Miettinen M**, Fanburg-Smith JC, Virolainen M, et al. Epithelioid sarcoma: an immunohistochemical analysis of 112 classical and variant cases and a discussion of the differential diagnosis. *Hum Pathol* 1999;**30**:934–42.
65. **Dotto JE**, Glusac EJ. p63 is a useful marker for cutaneous spindle cell squamous cell carcinoma. *J Cutan Pathol* 2006;**33**:413–7.
66. **Weiss SW**, Goldblum JR. Benign tumors of peripheral nerves. In: Weiss SW, Goldblum JR, eds. *Enzinger and Weiss's soft tissue tumors*. 5th edn. St Louis (MO): Mosby, 2008:886–7.
67. **LeBoit PE**, Crutcher WA, Shapiro PE. Pagetoid intraepidermal spread in Merkel cell (primary neuroendocrine) carcinoma of the skin. *Am J Surg Pathol* 1992;**16**:584–92.
68. **Bickle K**, Glass LF, Messina JL, et al. Merkel cell carcinoma: a clinical, histopathologic, and immunohistochemical review. *Semin Cutan Med Surg* 2004;**23**:46–53.
69. **Smith KJ**, Skelton III HG, Holland TT, et al. Neuroendocrine (Merkel cell) carcinoma with an intraepidermal component. *Am J Dermatopathol* 1993;**15**:528–33.
70. **Youens KE**, Waugh MS. Extranodal follicular dendritic cell sarcoma. *Arch Pathol Lab Med* 2008;**132**:1683–7.
71. **Chan JK**, Fletcher CD, Naylor SJ, et al. Follicular dendritic cell sarcoma. Clinicopathologic analysis of 17 cases suggesting a malignant potential higher than currently recognized. *Cancer* 1997;**79**:294–313.
72. **Craddock KJ**, Labonte S, Ghazarian D. Anaplastic Kaposi sarcoma resembling epithelioid angiosarcoma in an HIV-positive man. *Eur J Dermatol* 2008;**18**:358–9.
73. **Moosavi C**, Jha P, Fanburg-Smith JC. An update on plexiform fibrohistiocytic tumor and addition of 66 new cases from the Armed Forces Institute of Pathology, in honor of Franz M. Enzinger, MD. *Ann Diagn Pathol* 2007;**11**:313–9.
74. **Folpe AL**, Schmidt RA, Chapman D, et al. Poorly differentiated synovial sarcoma: immunohistochemical distinction from primitive neuroectodermal tumors and high-grade malignant peripheral nerve sheath tumors. *Am J Surg Pathol* 1998;**22**:673–82.
75. **Flieder DB**, Moran CA. Primary cutaneous synovial sarcoma: a case report. *Am J Dermatopathol* 1998;**20**:509–12.
76. **Azoulay S**, Adem C, Pelletier F, et al. Skin metastases from unknown origin: role of immunohistochemistry in the evaluation of cutaneous metastases of carcinoma of unknown origin. *J Cutan Pathol* 2005;**32**:561–6.
77. **Krathen RA**, Orengo IF, Rosen T. Cutaneous metastasis: a meta-analysis of data. *South Med J* 2003;**96**:164–7.
78. **D'Aniello C**, Brandi C, Grimaldi L. Cutaneous metastasis from small cell lung carcinoma. *Scand J Plast Reconstr Surg Hand Surg* 2001;**35**:103–5.
79. **Molina Garrido MJ**, Guillen Ponce C, Soto Martinez JL, et al. Cutaneous metastases of lung cancer. *Clin Transl Oncol* 2006;**8**:330–3.
80. **Mueller TJ**, Wu H, Greenberg RE, et al. Cutaneous metastases from genitourinary malignancies. *Urology* 2004;**63**:1021–6.
81. **Dahl PR**, Brodland DG, Goellner JR, et al. Thyroid carcinoma metastatic to the skin: a cutaneous manifestation of a widely disseminated malignancy. *J Am Acad Dermatol* 1997;**36**:531–7.
82. **Koller EA**, Tourtelot JB, Pak HS, et al. Papillary and follicular thyroid carcinoma metastatic to the skin: a case report and review of the literature. *Thyroid* 1998;**8**:1045–50.
83. **Alwaheeb S**, Ghazarian D, Boerner SL, et al. Cutaneous manifestations of thyroid cancer: a report of four cases and review of the literature. *J Clin Pathol* 2004;**57**:435–8.
84. **Paz-Ares L**, Olivia E, Carey RW, et al. Skin lesions in malignancy. Case 2. Skin metastases from prostate adenocarcinoma. *J Clin Oncol* 2001;**19**:2099–100.