EDITOR'S CHOICE

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

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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

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)

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 lymphoplasmacytoid 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 eosinophilc nucleoli (fig 1). Individual cells are separated by somewhat hyalinised collagen, containing 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

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 lentigenous melanoma, anogenital melanoma, (+) in 72% of primary versus 73% of metastatic melanoma according to Plaza *et al*[2]; (+) in 36 % of malignant melanomas according to Went *et al*[5]
- **PGP 9.5**: 10% (+) in melanoma
- **LMWCK**: focally (+) in 10%–22% of melanoma, especially metastatic lesions according to Kim *et al*[7] 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 histiogenesis. 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.

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

Continued

Table 1 Continued

Lesion	Clinical features	Histology	Immunohistochemistry
			(+) Vimentin
			(+) MSA
			(+) Focal factor XIIIa
			(+) Focal S-100
			(−) HMB-45
			(−) Mart 1/Melan A
			(−) MiTF
Granular cell tumour	Solitary painless nodule	Plump, spindle and epithelioid cells with abundant eosinophilic cytoplasm and inconspicuous bland nuclei	(+) 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	(+) Mart1/MelanA
		Perivascular accentuation	(+) MiTF
		Multinucleated giant cells	(+) S-100 in 33%
		Size <8 cm, mitotic count <1/50 HPFs, no necrosis	(+) 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 epitheliod 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 epthelioid 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

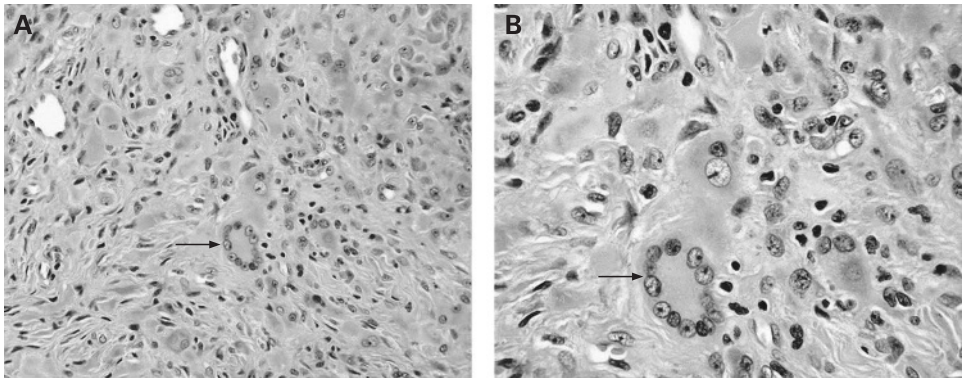

Figure 1 (A, B) Epithelioid cutaneous fibrous histiocytoma. Infiltration of the dermis with epithelioid cells that have eosinophilic cytoplasm, vesicular nuclei and small nucleoli. Inflammatory cell infiltrate and Touton-type giant cell (arrows) are also demonstrated. H&E, original magnification: ×200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

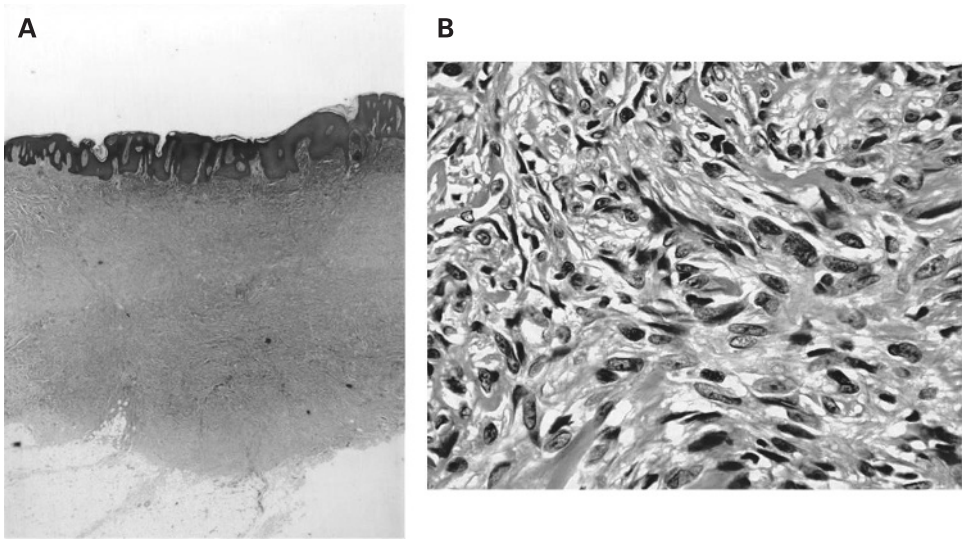

Figure 2 (A, B) Cellular cutaneous fibrous histiocytoma. Eosinophilic spindle cells with vesicular nuclei and eosinophilic nucleoli infiltrate the dermis with extension to the superficial subcutaneous fat. H&E, original magnification: ×16 (A), ×400 (B).

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. Ultrastructually, 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

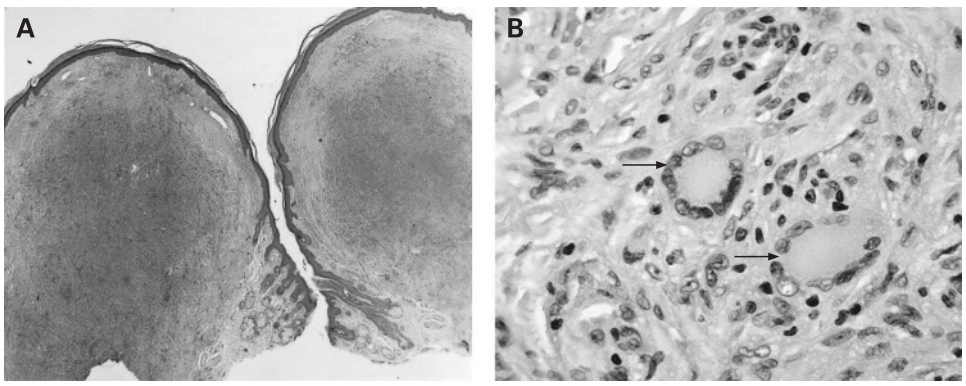

Figure 3 (A, B) Juvenile xanthogranuloma. The dermis is infiltrated by histiocytes with eosinophilic finely vacuolated cytoplasm and multinucleated giant cells of Touton type (arrows). Inflammatory infiltrates are also seen. H&E, original magnification: ×16 (A), ×400 (B).

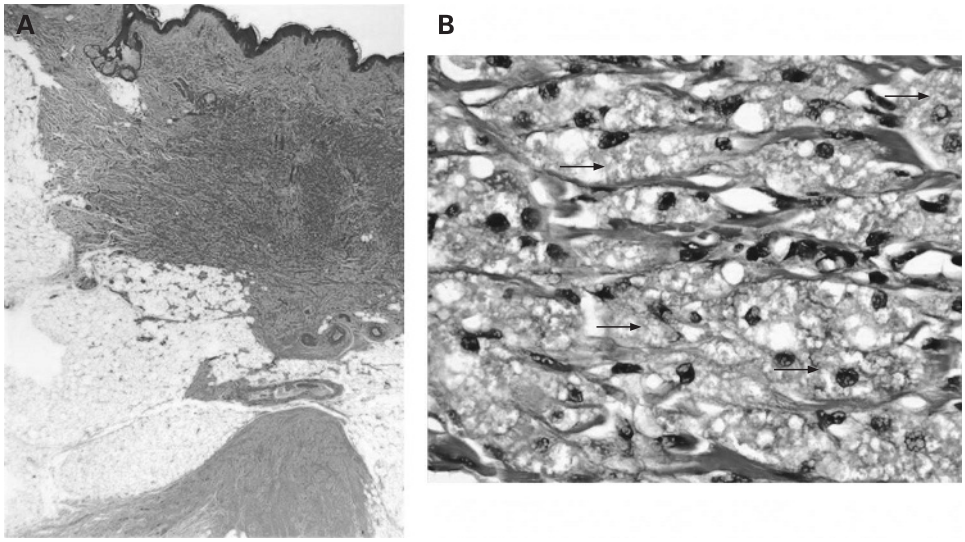

Figure 4 (A, B) Cutaneous granular cell tumour. The dermis and the subcutaneous tissue illustrate infiltration with plump, spindle and epithelioid cells with abundant granular cytoplasm (arrows) and inconspicuous bland nuclei. H&E, original magnification: ×16 (A), ×400 (B).

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 amophophilic 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

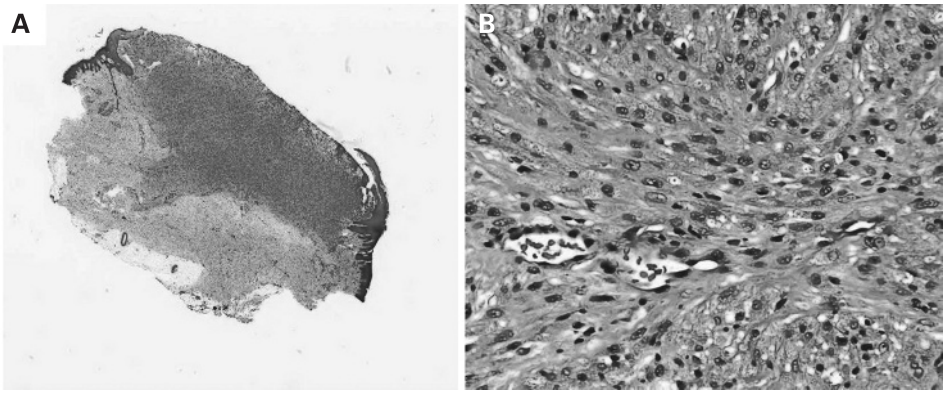

Figure 5 (A, B) Primitive non-neural granular cell tumour. Infiltration of the dermis with a well-circumscribed proliferation of spindle to polygonal cells with prominent granular cytoplasm. The nuclei are pleomorphic and some of them demonstrate prominent nucleoli. H&E, original magnification: ×16 (A), ×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	Cells with prominent granular cytoplasm	(+) Vimentin
	Female predominance	Nuclei with prominent eosinophilic nucleoli	(+) CD10
		Nuclear pleomorphism	(+) PGP 9.5
		Mild mitotic activity	(+) NKI-C3
			(+) CD 68
			(−) S-100
			(−) HMB-45
			(−) CD34
			(−) Desmin
			(−) SMA
			(−) Mart1/MelanA
Langerhans cell histiocytosis*	Scaly, crusted papules or plaques	Aggregates of Langerhans cells in the epidermis characterised by abundant blue–grey cytoplasm, indented oval nuclei with a central groove	(+) S-100,
	Affects children mainly	Little or no cytological atypia	(+) CD1a
		Dermal infiltrate of Langerhans cells that form sheets with accentuation below the epidermis; absence of melanin pigment, and presence of eosinophils	(+) Langerin (CD207)
			(−) HMB-45
			Mart 1/Melan A (−)
Inflammatory myofibroblastic tumour of the skin	Solitary firm papules and nodules	Bland spindle cells in dermis and subcutaneous fat	(+) SMA, vimentin, CD68 in spindle cells
		Heavy admixed inflammatory infiltrate	(+) ALK-1
		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]

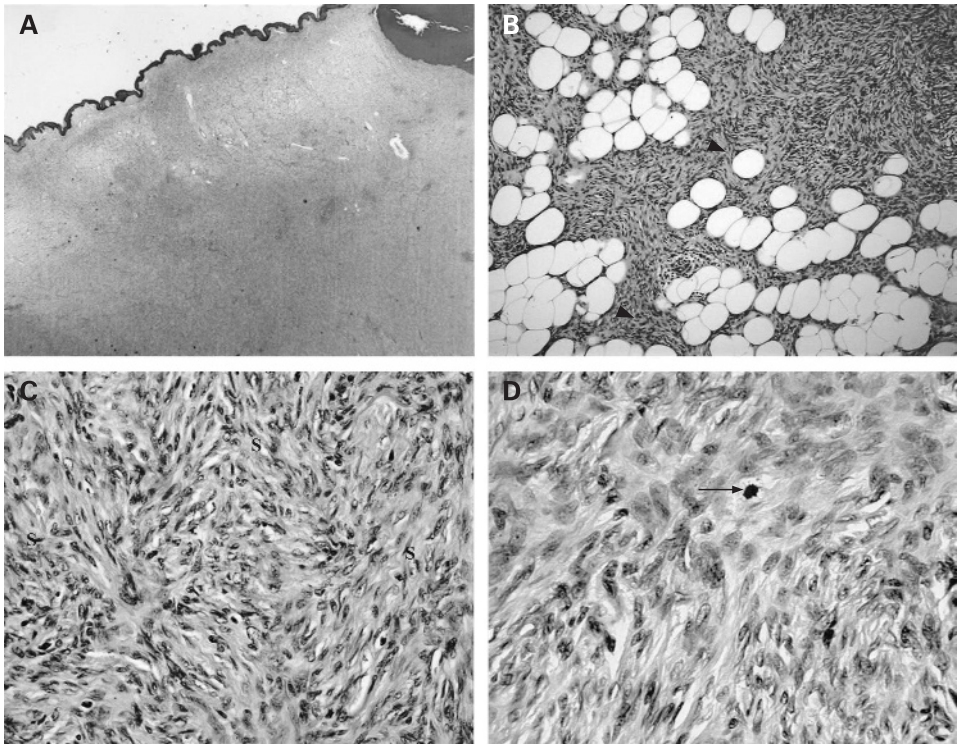

Figure 6 (A–D) Dermatofibrosarcoma protuberans. Spindle cells with eosinophilic cytoplasm infiltrating the dermis and the subcutaneous fat (arrowheads) in a storiform pattern (S). One mitotic figure is illustrated (arrow). H&E, original magnification: ×16 (A), ×100 (B), ×400 (C), ×400 (D).

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 epineurum 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 MPNST[54] 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)
			(+) Apolipoprotein D
			(−) HMB-45
			(−) Mart1/MelanA
			(−) MiTF
Atypical fibroxanthoma (pleomorphic undifferentiated sarcoma of skin)	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
			(+) CD10 (diffuse)
			(−) S-100
			(−) Keratin
			(−) Desmin
			(−) Mart1/MelanA
			(−) MiTF
Malignant PNST	Buttocks and thighs	Fasciculated pattern of hyperchromatic spindle cells	(+) Focal S100 (subset)
	Rare in other skin locations		(+) NSE
			(+) Leu 7
			(+) Myelin
			(+) p53
			(+) HMGA2
			(−) Neurofilament
			(−) HMB-45
			(−) Mart1/Melan A
			(−) MiTF
Cutaneous leiomyosarcoma	Adults in their 60s	Fascicules of spindle-shaped cells with eccentric vacuole	(+) Desmin
	Male predominance	Pleomorphism	(+) Caldesmon
	Hair-bearing skin of lower extremities	Nuclear atypia	(+) Vimentin
		Mitoses	(+) SMA
			(+) MSA
			(+) S-100 (rare subset)
			(−) Mart1/Melan A
			(−) HMB-45
			(−) MiTF
Epithelioid angiosarcoma	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)
		Extravasated red blood cells	(+) LMWCK (Cam5.2)
			(+) Pankeratin (AE1/AE3)
			(+) Cytokeratin 7
			(−) HMB-45
			(−) Mart 1/Melan A
			(−) MiTF
Epithelioid sarcoma	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
			(−) MiTF
Spindle cell squamous cell carcinoma	Elderly men	Spindled pleomorphic tumour cells	(+) 34βE12
	Sun-exposed skin	No keratinisation	(+) AE1/AE3
	Head and neck	May show desmosomal junctions	(+) Cytokeratin 5/6
	Upper extremities		(+) P63 (nuclear)
	Upper back and chest		(−) S-100
			(−) HMB-45
			(−) Mart1/MelanA
			(−) MiTF
Cutaneous malignant granular cell tumour	Rarely seen in children	Necrosis	(+) S-100
	Larger than their benign counterparts	Spindling	(+) Calretinin
		Vesicular nuclei with large nucleoli	(+) Inhibin
		Increased mitotic activity >2/10 HPF	(−) HMB-45
		High N/C ratio	(−) Mart1/MelanA
		Pleomorphism	(−) 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	Small monomorphic basophilic cells with round to oval shaped nuclei and scanty cytoplasm	(+) CK20 and LMWCK typical dot-like paranuclear or cytoplasmic staining
	Solitary rapidly growing hard nodule	Nuclei have finely granular dispersed chromatin and small inconspicuous nucleoli	(+) Variably for CD56, CD57, EMA, chromogranin and synaptophysin
		Tumour cells mainly occupy the dermis, but pagetoid spread of the tumour cells into the epidermis can be seen	(−) 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	(+) HMB-45
		Fascicular, nested, sheet-like patterns	(+) Mart1/MelanA
		Perivascular accentuation	(+) MiTF
		Multinucleated giant cells	(+) S-100 in 18%
		>8 cm in size, >1 mitotic figure/ 50 HPFs, necrosis	(+) SMA, MSA
			(+) Desmin
			(+) Cyclin D1
			(+) Vimentin
			(+) Pan-cytokeratin
Follicular dendritic cell sarcoma	Mostly affect adults	Spindle to ovoid cells arranged in storiform or fascicular pattern	(+) CD21
	Intranodal or extranodal painless mass	Oval nuclei, distinct nucleoli, delicate nuclear membrane	(+) CD35
		Indistinct cell border	(+) CD23
		Fibrillary cytoplasm	(+) 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
			(−) MiTF
			(−) Cytokeratin
			(−) CD30
			(−) CD3
			(−) CD79a
			(−) CD34
			(−) CD1a
Anaplastic/pleomorphic Kaposi sarcoma	HIV setting	Spindle to epithelioid cells arranged in solid sheets and fascicles	(+) CD34
		Pleomorphic nuclei with prominent nucleoli	(+) D2-40
		Atypical mitoses	(+) CD31 (patchy)
		Extravasated red blood cells	(+) 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	Plexiform pattern	(+) CD68
	Female predominance	Spindled and histiocytoid cells	(+) SMA
	Trunk, extremity, face	Osteoclast-type giant cells	(+) PGP 9.5
		Cellular pleomorphism, mitotic activity, vascular invasion (may sometimes look like non-necrotising granulomas)	(+) S-100A6
			(+) MiTF
			(+) CD57
			(−) HMB-45
			(−) Mart1/MelanA
Monomorphic spindle synovial sarcoma	Adolescents, young adults	Spindle and epithelioid cells	(+) EMA, HMWCK, LMWCK
	Lower extremities	High nuclear/cytoplasmic ratio	(+) Type IV collagen, CD57, rarely S-100
		Variable mitotic rate	(+) CD99, CD56, neurofilaments
			(−) Chromogranin, synaptophysin
			(−) HMB-45, Mart1/MelanA, MiTF
Post-radiation sarcomas including rhabdomyosarcomas	Post-radiotherapy	Spindle cells	(+) Vimentin, other mesenchymal markers S-100 could be positive
		Cellular atypia	(−) HMB-45, Mart1/MelanA
		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, perivesicular 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

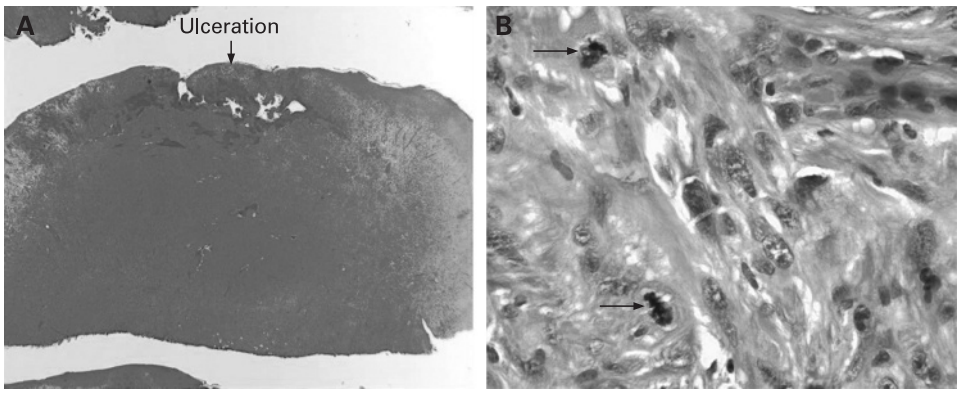

Figure 7 (A, B) Atypical fibroxanthoma. Pleomorphic epithelioid and spindle cells infiltrating the dermis. Two atypical mitotic figures are demonstrated (arrows). H&E, original magnification: ×16 (A), ×400 (B).

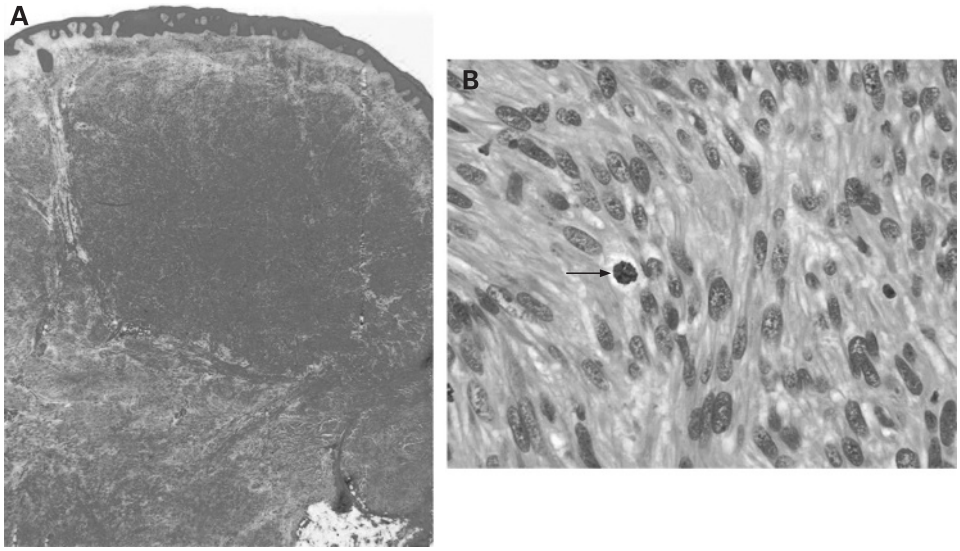

Figure 8 (A, B) Cutaneous leiomyosarcoma. The dermis is infiltrated with pleomorphic spindle cells, some with cigar-shaped nuclei and eosinophilic cytoplasm. Mitotic figures can also be seen (arrow). H&E, original magnification: ×16 (A), ×400 (B).

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

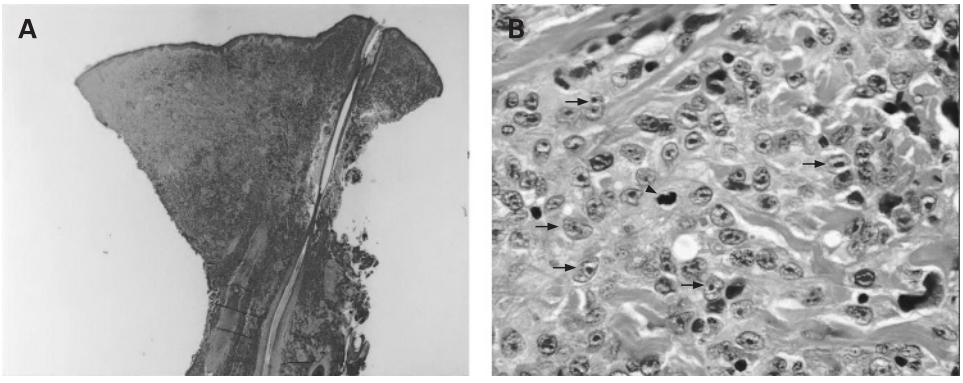

Figure 9 (A, B) Epithelioid angiosarcoma. Infiltration of the dermis with large epithelioid cells (arrows) with abundant eosinophilic cytoplasm and prominent eosinophilic nucleoli. One mitotic figure is demonstrated (arrowhead). H&E, original magnification: ×16 (A), ×400 (B).

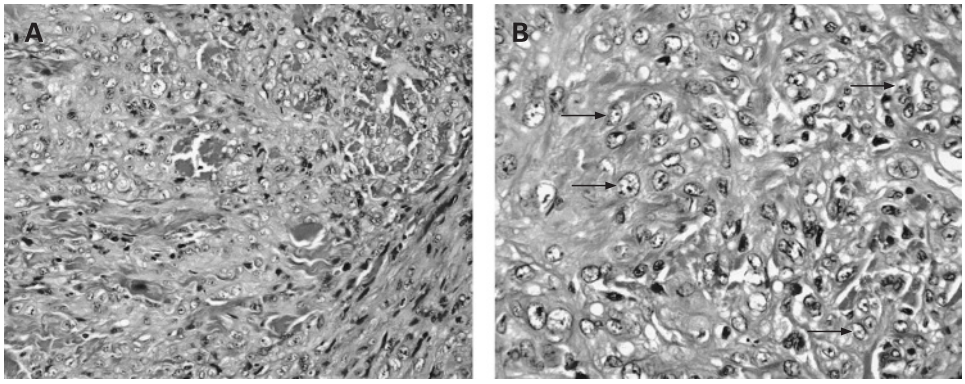

Figure 10 (A, B) Epithelioid sarcoma. The dermis is infiltrated with pleomorphic epithelioid cells (arrows) with abundant eosinophilic cytoplasm and inconspicuous nucleoli. H&E, original magnification: ×200 (A), ×400 (B).

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 conjugation 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

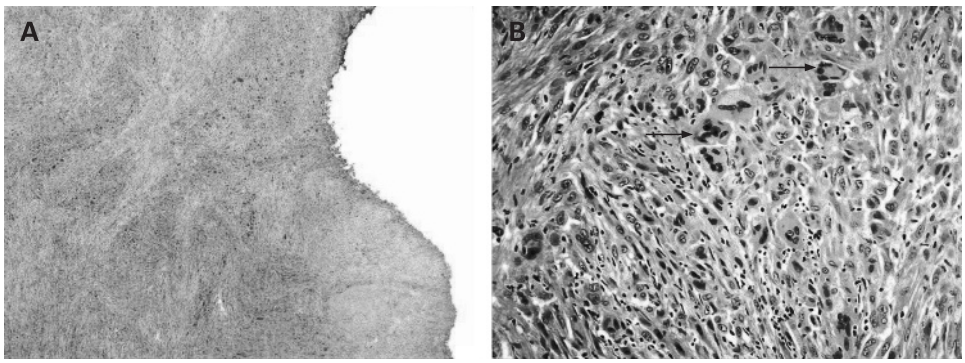

Figure 11 (A, B) Follicular dendritic cell sarcoma. The dermis is infiltrated with a storiform array of spindle, ovoid or polygonal cells with oval nuclei, delicate nuclear membrane, distinct nucleoli, indistinct cell borders, and slightly eosinophilic, fibrillary cytoplasm. Multinucleated giant cells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

Table 4 Metastatic mimics

Metastatic mimic	Common site	Histology	Immunohistochemistry
Lung	Anywhere (especially chest wall and abdomen)	Adenocarcinoma: intracytoplasmic mucin, lymphovascular invasion	Adenocarcinoma
		Squamous cell: focal keratinisation and necrosis	CK7+/CK20−
		Small cell: neuroendocrine features	(+) 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	Ductal: glands and comedo necrosis	CK7+/CK20−
	Scalp	Lobular: single-row files of tumour cells	ER+/PR+
			(+) AR in apocrine lesions
			(+) GCDFP
			(+) CEA
			(−) S-100
			(−) HMB-45
			(−) Mart1/MelanA
			(−) MiTF
Renal	Anywhere (especially head and neck)	Abundant clear cytoplasm	CK7−/CK20−
		Vascular stroma	(+) Vimentin
			(+) CD10
			(+) EMA
			(+) RCC antigen
			(−) S-100
			(−) HMB-45
			(−) Mart1/MelanA
			(−) MiTF
Prostate	Genital region, anterior thigh	Gland formation	CK7−/CK20−
		Hyperchromatic pleomorphic nuclei	(+) PSA
			(+) PAP
			(−) S-100
			(−) HMB-45
			(−) Mart1/MelanA
			(−) MiTF
Thyroid	Head and neck (especially scalp)	Looks similar to primary thyroid carcinoma	Papillary and follicular
		Medullary carcinoma may be Congo red positive related to the amyloid deposits.	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 tumours[74] 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] 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.

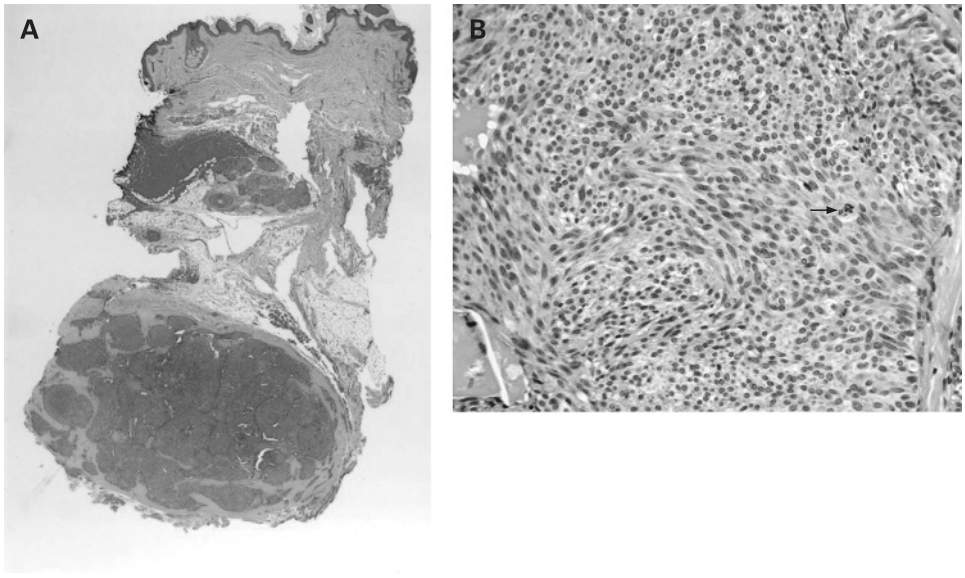

Figure 12 (A, B) Metastatic medullary thyroid carcinoma to the skin. The dermis is infiltrated with sheets of slightly atypical spindle/oval cells with eosinophilic cytoplasm, hyperchromatic nuclei and inconspicuous nucleoli. A mitotic figure is demonstrated (arrow). H&E, original magnification: ×16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

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).

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