Primary de-differentiated, trans-differentiated and undifferentiated melanomas: overview of the clinicopathological, immunohistochemical and molecular spectrum

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Abstract

Primary cutaneous and mucosal melanoma shows a wide histological spectrum. The correct diagnosis depends upon the demonstration of melanocytic differentiation by recognition of an associated *in-situ* component or immunohistochemical evidence of a melanocytic phenotype using conventional melanocytic markers, such as S-100, SOX10, Melan-A and HMB-45. Exceptionally, melanomas lose their melanocytic phenotype, at least focally, and show differentiation towards other lineages. Review of the literature shows that de- and trans-differentiation in melanoma is rare but probably under-recognised and under-/span>reported. These often large and frequently ulcerated tumours affect adults and show a wide anatomical distribution, including mucosal sites, although there is a predilection for sun-damaged skin of the head and neck. Histologically, the tumours are biphasic and contain a pre-existing conventional melanoma. The de-differentiated component closely resembles atypical fibroxanthoma, both morphologically and immunohistochemically. Trans-differentiated melanoma may show rhabdomyosarcomatous or spindle cell carcinomatous features. Undifferentiated melanomas are similar tumours in which the conventional melanoma component is absent. Their diagnosis depends entirely upon the clinical context and identification of a classical melanoma driver gene mutation, i.e. *BRAF* V600E. The diagnosis of these rare and unusual tumours is challenging, and requires thorough tumour sampling and recognition of the background of a pre-existing but often focal conventional melanoma together with molecular analysis.

Introduction

Melanoma shows a wide morphological spectrum and its histopathological subtypes may be related to different patterns of sun exposure and distinct underlying molecular characteristics, and may show variable clinical behaviour. Rare melanomas may show at least focal loss of melanocytic differentiation with differentiation towards other lineages. This is a poorly understood phenomenon, documented in the literature mainly as case reports and short case series, but it is probably under-recognised and under-reported. These tumours have been variably referred to as 'de-differentiated melanoma', 'metaplastic melanoma', 'melanoma with heterologous elements', 'trans-differentiated melanoma' or 'melanoma with divergent differentiation'. The documented histopathological spectrum is broad and includes most commonly fibroblastic/myofibroblastic, rhabdomyosarcomatous and osteocartilaginous differentiation, while Schwannian, perineurial, smooth muscle, ganglionic and ganglioneuroblastic, neuroendocrine, epithelial and angiosarcomatous differentiation patterns are rare observations.[1,2]

In this paper, we apply the term 'de-differentiated melanoma' to biphasic tumours composed of a background of a conventional melanoma with additional morphologically and immunohistochemically distinct areas characterised by immunohistochemical loss of expression of all conventional melanocytic markers (S-100, SOX10, Melan-A and HMB-45) and no further specific line of differentiation on morphology and immunohistochemistry. The term 'trans-differentiated melanoma' is used for biphasic tumours composed of a background of a conventional melanoma and additional areas lacking morphological and immunohistochemical evidence of melanocytic differentiation, but showing heterologous elements on morphology and/or immunohistochemistry. Using this strict definition, tumours with osteocartilaginous, neural, ganglionic and ganglioneuroblastic differentiation cannot be regarded as truly showing de-/trans-differentiation due to their retained expression of S-100 and SOX10. More recently, and due to our expanding knowledge of the molecular mechanisms involved in the formation of melanocytic tumours, so-called 'undifferentiated melanoma' has been increasingly recognised (Table 1).[3,4] These entirely de-/trans-differentiated tumours lack a

morphologically and immunohistochemically recognisable background of conventional melanoma, but the molecular identification of mutations in typical melanoma driver genes, such as *BRAF*^{V600E}, for example, is at least supportive of this rare diagnosis.[4] Careful clinical and pathological correlation is, however, necessary in these tumours, as *BRAF* mutations have also been described in other tumours which may primarily involve the skin or as metastatic deposits.[5]

De-/trans-differentiation in melanoma is a phenomenon most frequently observed in metastatic melanoma deposits.[3,4] In contrast, this manuscript mainly focuses upon de-/trans-differentiation in primary melanoma, which appears to be a particularly rare phenomenon, with only 27 cases reported in the literature to date (Table 2).[3,4,6–13] Primary de-/trans-differentiated melanomas mainly affect the skin, but rare examples have also been reported on non-cutaneous mucosal sites.[4,9]

Clinical presentation

Primary de-/trans-differentiated melanomas present as large and frequently ulcerated nodules and plaques, often measuring multiple centimetres in diameter.[6–8,12,13] They affect a wide range of anatomical sites, but appear to be most common on sun-damaged skin of the head and neck with a predilection for elderly men with a median age of 75 years (mean = 73 years; range = 42–90) and a male to female ratio of 1.7:1.[3,4,6–13] The disease rarely affects mucosal sites, including the respiratory, gastrointestinal and gynaecological tracts.

HISTOLOGICAL FINDINGS

Primary cutaneous and mucosal de- and trans-differentiated melanomas are large, asymmetrical and deeply invasive tumours with pushing, rather than infiltrative, deep margins with extension into anatomical levels IV or V, with a Breslow thickness ranging from 4 to 80 mm (median = 8; mean = 13 mm) (Figure 1A,B). The tumours are frequently ulcerated (79%) and display brisk mitotic activity, ranging from 3 to 40 mitoses/mm^2 (median = 12; mean = 15 mitoses/mm^2) (Figure 2A). In addition, lymphovascular (31%) and perineural (19%) invasion may be present (Table 2).[7,9,11,13]

De-/trans-differentiated melanomas are characterised by a biphasic growth pattern with a background of a conventional melanoma in addition to the de-/trans-differentiated component, while undifferentiated melanoma lacks the conventional melanoma component (Figure 2B). The conventional melanoma may be entirely *in situ* or invasive and spans the spectrum of melanoma subtypes, including superficial spreading, nodular, lentigo maligna, desmoplastic, acral lentiginous, mucosal and spindle cell melanoma (Figure 3A–F). Many de-/trans-differentiated melanomas (22%) have been reported in association with desmoplastic melanoma (Figure 4A–F).[4,8,13]

The de-/trans-differentiated component typically accounts for more than 50% of the tumour and its transition from the conventional component is abrupt, rather than gradual. The most commonly observed finding is de-differentiation followed by rhabdomyosarcomatous trans-differentiation. Morphologically, the de-differentiated component is reminiscent of atypical fibroxanthoma (AFX) or pleomorphic dermal sarcoma (PDS). It is composed of sheets of pleomorphic epithelioid or intersecting fascicles of spindled cells with variably abundant eosinophilic cytoplasm containing vesicular nuclei with prominent and multiple eosinophilic nucleoli (Figure 5A–C). Multinucleated tumour cells are often admixed. Mitotic activity is brisk and includes atypical forms, but tumour necrosis is rare. Uncommon examples show blood-filled intratumoral spaces and interspersed osteoclast-like multinucleated giant cells, analogous to pseudioangiomatous AFX/PDS (Figure 5D,E).

Rhabdomyosarcomatous trans-differentiated is characterised by a sheet-like growth of large polygonal to spindled cells with abundant brightly eosinophilic cytoplasm containing pleomorphic vesicular nuclei with prominent nucleoli (Figure 6A). Distinct rhabdoid cells with fibrillar cytoplasm may also be observed (Figure 6B). Occasionally, the tumour cells show marked nuclear pleomorphism with brisk and atypical mitotic activity, resembling pleomorphic rhabdomyosarcoma (Figure 6C,D).

Epithelial trans-differentiated is less commonly encountered and can be confirmed immunohistochemically by the presence of cytokeratin expression. Morphologically, the tumours are composed of intersecting fascicles of pleomorphic spindle cells with moderate

amounts of cytoplasm, vesicular nuclei and prominent eosinophilic nucleoli (Figure 7A,B). Mitotic activity is frequent and atypical and tumour necrosis may be present (Figure 7C). The findings are reminiscent of spindle cell cutaneous squamous cell carcinoma.

Angiosarcomatous[2] or adenocarcinomatous[14] trans-differentiated tumours are rare findings that have only been reported in metastatic melanoma deposits, but not in primary cutaneous tumours.

Immunohistochemical features

By definition, the de-/trans- and undifferentiated components show loss of expression of all conventional melanocytic markers, such as S-100, SOX10, Melan-A and HMB-45 in contrast to the adjacent conventional melanoma component, if present (Figure 3B,C,E). De-differentiated areas show expression of CD10, CD68 and SMA, similar to AFX/PDS (Figure 5F). The trans-differentiated tumours are further characterised by expression of lineage-specific markers, often in keeping with the morphological pattern. Expression of desmin, myogenin and MyoD1 may be seen seen in areas of rhabdomyosarcomatous trans-differentiated tumours (Figure 6E,F), while cytokeratin but not p40 or p63 expression is seen in tumours with heterologous epithelial trans-differentiation (Figure 7D).

MOLECULAR FINDINGS

Although the conventional and de-/trans-differentiated melanoma components are clearly morphologically and immunohistochemically distinct, they usually share the same mutational and copy-number alteration profiles, further confirming the concept of true de-/trans-differentiation in melanoma and refuting previous hypotheses of a possible collision tumour.[3,8,12,13] In keeping with the predilection for sun-damaged skin of elderly patients and a predominance of desmoplastic melanoma, *NF1* was found to be the most frequently mutated gene.[8,13] Like other *NF1*-mutated melanomas,[15,16] these tumours have a high mutation burden, are enriched for *TP53* mutations and lack *BRAF* p.V600E or *NRAS* p.Q61 mutations.[13]. Hot-spot mutations in the *BRAF* and *NRAS* genes have been described in de-/trans-differentiated

melanomas arising in conventional nodular (*BRAF* or *NRAS* mutated)[4,13] or superficial spreading (*NRAS*-mutated) melanoma.[12] In the absence of a conventional melanoma component, the diagnosis of undifferentiated melanoma is more difficult to establish and relies solely upon the molecular demonstration of mutations typically associated with melanoma, including *BRAF* p.V600E or *NRAS* p.Q61 mutations.[4] Immunohistochemistry for BRAFV600E and NRASQ61R correlates well with the presence of *BRAF* p.V600E and *NRAS* p.Q61 mutations in melanoma and can be used as a surrogate marker.[17–19] Although no data are currently available for primary de-, trans- and undifferentiated melanomas, NRASQ61R immunohistochemistry has been found to be useful in the setting of a metastatic undifferentiated melanoma.[20]

Clinical behaviour and outcome

Given the rarity of these tumours, it is difficult to make definitive statements on clincal behaviour and outcome. Although these tumours usually exhibit poor prognostic factors, including an increased tumour thickness, ulceration and brisk mitotic activity,[21] their clinical behaviour does not appear to be more aggressive than conventional melanoma when adjusted for tumour thickness. Nodal metastasis and distant metastasis are encountered in 64 and 50% of cases, respectively.[3,4,9–13] The sentinel lymph node positivity rate is 60% and the mortality rate is 20%.[3,6–13] Importantly, the prognosis of primary cutaneous de-/trans-differentiated melanoma appears to be closely related to the conventional melanoma, with a better prognosis for tumours arising in a desmoplastic melanoma.[22]

DIFFERENTIAL DIAGNOSIS

The diagnosis of de-/trans-differentiated melanoma is notoriously challenging, as the de-/trans-differentiated component may be dominant. Thorough sampling and recognition of the conventional melanoma is therefore of particular importance for accurate diagnosis, with emphasis on the identification of an often subtle *in-situ* component and immunohistochemical work-up for conventional markers of melanocytic differentiation. The diagnosis of

undifferentiated melanoma in the absence of a recognisable conventional melanoma component is entirely dependent upon appropriate molecular analysis with the identification of well-established melanoma driver gene mutations.

The differential diagnosis of these tumours is dictated by the morphological and immunohistochemical features of the de-/trans-differentiation aspect of the tumour. The clinical setting is often not helpful diagnostically, as de-/trans-differentiated melanoma and tumours in the differential diagnosis frequently both arise on sun-damaged skin of elderly patients.

The de-differentiated melanoma component is clinically, histologically and immunohistochemically inseparable from AFX and PDS. AFX and PDS present as frequently ulcerated nodules and plaques with a predilection for sun-damaged skin of elderly males. They are morphologically characterised by sheets and fascicles of pleomorphic epithelioid and spindle cells with admixed multinucleated giant cells and brisk and atypical mitotic activity. While AFX appears circumscribed and nodular and is confined to the dermis, PDS are poorly circumscribed and asymmetrical with invasion of subcutis, lymphovascular invasion, perineurial infiltration or tumour necrosis. As the diagnosis of AFX and PDS is one of exclusion, the tumours do not show specific lines of differentiation with immunohistochemical negativity for melanocytic, epithelial, myogenic and endothelial cell markers. Expression of CD10, CD68 and SMA is not specific, and is shared with de-differentiated melanoma.[23] De-differentiated melanoma can be separated from AFX and PDS by identification of the conventional melanoma component. Molecular studies can also be useful in this setting. Although AFX/PDS may share with melanoma mutations in the *TP53, CDKN2A* and *RAS* (*H RAS*, *KRAS* and *NRAS*) genes, as well as in the *TERT* promoter, *BRAF* or *NF1* mutations are not encountered in AFX/PDS.[24–28]

Primary cutaneous melanoma with epithelial trans-differentiation closely resembles poorly differentiated and spindle cell/sarcomatoid/desmoplastic squamous cell carcinoma (SCC) both morphologically and immunohistochemically.[29] The identification of morphologically better differentiated SCC favours poorly differentiated or spindle cell SCC, while the presence of an additional component of conventional melanoma is

diagnostic of melanoma with epithelial trans-differentiation. Similar to AFX and PDX, SCC may carry mutations in the *TP53*, *PIK3CA*, *CDKN2A* or *RAS* (*HRAS*, *KRAS* and *NRAS)* genes and *TERT* promoter, but also in the *BRAF* (non-p.V600E) and *NF1* genes.[28,30]

Squamomelanocytic tumours enter the differential diagnosis, as they show a combined epithelial and melanocytic differentiation. In contrast to melanoma with epithelial trans-differentiation, squamomelanocytic tumours are well-circumscribed and characterised by well-differentiated squamous cell carcinoma closely associated with and colonised by a melanoma component, most commonly of lentigo maligna type.[31,32]

Primary cutaneous melanoma with divergent rhabdomyosarcomatous trans-differentiation may easily be mistaken for cutaneous rhabdomyosarcoma or malignant peripheral nerve sheath tumour (MPNST) with rhabdomyoblastic differentiation (malignant Triton tumour). All three tumours share similar morphological features and an identical immunohistochemical profile with the expression of rhabdomyogenic markers such as desmin, myogenin and MyoD1. Malignant Triton tumours are deep-seated tumours occurring in young patients and often in the setting of neurofibromatosis Type I. Compared to the.preexisting conventional melanoma component, the expression of S-100 is typically focal within the conventional MPNST component and there is no expression of second-line melanoma markers, such as Melan-A or HMB-45.[33] In addition, immunohistochemical loss of H3K27me3 expression, corresponding to loss of trimethylation at lysine 27, is supportive of a diagnosis of MPNST and is only rarely observed in spindle cell or desmoplastic melanoma.[34,35] The association with a large nerve or a background of a pre-existing neurofibroma are further findings supportive of MPNST. Although mostly characterised by a complex karyotype,[36] MPNST can share *NF1* and *CDKN2A* mutations with melanoma.[37] Rhabdomyosarcoma typically affects the paediatric patient population and only rarely presents in the skin. Rhabdomyosarcomas developing on sun-damaged skin of elderly patients are exceptional.[38] The correct diagnosis of de-/trans-differentiated relies upon careful clinicopathological correlation and identification of a pre-exisiting conventional melanoma component on histology and immunohistochemistry.

Conclusion

Primary de-/trans-differentiated melanoma is rare, and occurs preferentially on sun-damaged skin of elderly men. This biphasic tumour is characterised by a conventional melanoma component (which can include any melanoma subtype, but with a preference for desmoplastic melanoma) and a de-differentiated or less commonly trans-differentiated component. In contrast, undifferentiated melanoma lacks the conventional melanoma component. De-/trans- and undifferentiated melanoma should be included in the differential diagnosis of a skin tumour arising on sun-damaged skin of elderly patients, together with atypical fibroxanthoma, pleomorphic dermal sarcoma, desmoplastic melanoma, poorly differentiated or spindle cell squamous cell carcinoma, leiomyosarcoma and rhabdomyosarcoma. The diagnostic key for de-/trans-differentiated melanoma is thorough tumour tissue sampling and the use of S100 or SOX10 immunohistochemistry to highlight the background of the conventional melanoma component, which may be *in situ* or invasive, and is frequently located in the periphery of an ulcerated tumour. The demonstration of conventional melanoma driver gene mutations (most frequently in the *NF1* but also in *BRAF* and *NRAS* genes) is of further diagnostic utility, and of particular importance in the diagnosis of undifferentiated melanoma. Although the tumours are often deeply invasive, their prognosis appears to depend upon the subtype of the conventional melanoma component, and they do not appear to be more aggressive than other melanoma subtypes when adjusted for tumour thickness.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Legends

Figure 1. De- and trans-differentiated melanomas are deeply invasive tumours extending into subcutaneous adipose tissue (**A**) and underlying fascia or galea (**B**).

Figure 2. De- and trans-differentiated melanomas are frequently ulcerated tumours (**A**) and there is often a sharp demarcation between the invasive melanoma component (left) and the de- or trans-differentiated component (right) (**B**).

Figure 3. This de-differentiated melanoma shows a nodular and polypoid growth pattern (**A**). The majority of the tumour is composed of the de-differentiated component characterised by a fascicular growth of atypical spindle cells (**B**) lacking S-100 (**C**) and SOX10 expression (**D**). A pre-existing superficial spreading melanoma is noted only in the periphery of the tumour (**E**) and is highlighted immunohistochemically by Melan-A staining (**F**).

Figure 4. This large and asymmetric tumour (**A**) contains a central nodular and cellular de-differentiated component composed of pleomorphic epithelioid tumour cells (**B**). The de-differentiated component is surrounded by a desmoplastic melanoma composed of atypical spindle cells (**C**) with invasion of underlying galea (**D**). Immunohistochemistry for S-100 (**E**) and SOX10 (**F**) highlights only the desmoplastic melanoma component, while the de-differentiated aspect is negative.

Figure 5. De-differentiated melanoma shows atypical fibroxanthoma/pleomorphic dermal sarcoma (AFX-/PDS)-like features characterised by sheet-like (**A**) or fascicular (**B**) growth patterns. There is striking nuclear pleomorphism and multinucleated tumour cells may be present (**C**). The tumours may show pseudoangiomatous features (**D**) or contain numerous osteoclast-like giant cells (**e**). No specific lines of differentiation can be demonstrated in the de-differentiated component by immunohistochemistry but, similar to AFX and PDS, there is strong and diffuse staining for CD10.

Figure 6. Trans-differentiated melanoma with rhabdomyosarcomatous features is characterised by a sheet-like proliferation of polygonal cells with brightly eosinophilic cytoplasm (**A**). Spindle cells are admixed and the cytoplasm shows a fibrillary quality (**B**). Examples reminiscent of pleomorphic rhabdomyosarcoma are characterised by pronounced nuclear pleomorphism (**C**) and atypical mitotic figures (**D**). The tumour cells express desmin (**E**), and there is nuclear staining for myogenin (**F**).

Figure 7. Trans-differentiated melanoma with epithelial features closely resembles spindle cell carcinoma. The tumour is composed of intersecting fascicles (**A**) of atypical spindle cells showing significant nuclear pleomorphism (**B**) and tumour necrosis (**C**). The tumour cells stain with AE1/3 (**D**).