Primary Undifferentiated/Dedifferentiated Cutaneous Melanomas

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Diagnosing cutaneous melanoma is usually straightforward based on these malignancies' histopathological and immunohistochemical features. Nevertheless, melanomas can imitate various other neoplasms, sometimes lacking the expression of conventional melanocytic markers and expressing non-melanocytic ones.

cutaneous melanoma | dedifferentiated melanoma | undifferentiated melanoma

1. Introduction

Cutaneous melanoma is an aggressive malignancy responsible for most deaths caused by skin cancers. However, melanoma is a heterogeneous disease with widely variable clinical, histopathological, immunohistochemical, and molecular features, all of which influence treatment and prognosis. [1]. Cutaneous melanomas can undergo divergent transformation, displaying immunohistochemical and ultrastructural features of other cell lineages such as epithelial cells, fibroblasts, nervous cells, osteocartilaginous cells, smooth muscle, or rhabdomyoblasts [2]. In this respect, Agaimy et al. define undifferentiated melanomas (UM) as melanomas lacking characteristic histopathological and immunohistochemical features (such as S100, MelanA, HMB45, SOX10, and MITF) and dedifferentiated/transdifferentiated melanomas (DM) as melanomas lacking these characteristics but displaying non-melanocytic ones [3]. These tumors are usually present as biphasic neoplasms with conventional melanoma components and heterologous components resembling other malignancies [2]. Divergent differentiation is a well-described phenomenon in metastatic settings [3][4][5][6][7][8][9]. Phenotype switching in metastatic melanomas is a form of cancer cell plasticity and is considered an adaptative mechanism for promoting invasion and resistance to therapy [10][11][12][13]. On the contrary, primary cutaneous melanomas displaying divergent differentiation are sporadic and poorly described in the scientific literature [3][14][15][16][17][18]. Consequently, diagnosing dedifferentiated primary cutaneous melanomas represents a serious challenge, requiring extensive histopathological and immunohistochemical analysis as these dedifferentiated tumors may also present small areas of conventional melanoma [15][17][18]. Furthermore, molecular analysis may help establish the diagnosis by revealing characteristic melanoma mutations [18].

2. General Characteristics of Undifferentiated/Dedifferentiated Melanomas

The terms “undifferentiated melanoma”, “dedifferentiated melanoma”, and “transdifferentiated melanoma” have been inconsistently used to describe melanomas that lack a melanocytic phenotype, at least partially, and may acquire differentiation towards other cell lineages. Undifferentiated melanomas are defined as completely lacking conventional histopathological and immunohistochemical melanocytic differentiation (negative for the five commonly used melanoma markers—MelanA, MiTF, HMB45, S100, and SOX10) and displaying a “vimentin-only” phenotype [19][20][21]. Dedifferentiated/transdifferentiated melanomas are biphasic tumors that show a transition between conventional melanoma components and undifferentiated areas with histopathological and immunohistochemical features of other cell lineages [19][20]. The dedifferentiated component most often resembles atypical fibroxanthoma/undifferentiated pleomorphic sarcoma. Still, it can also bear features of various other entities such as carcinomas, leiomyosarcoma, rhabdomyosarcoma, ganglioneuroblastic tumors, other sarcomas, and spindle cell neoplasms [19][20][22].

These tumors are most often encountered in metastatic lesions following systemic dissemination and divergent transformation of a conventional melanoma [21] and are exceptionally rare in primary settings, either mucosal or cutaneous [19]. Undifferentiated and dedifferentiated primary cutaneous melanomas show a preference for highly sun-damaged skin, such as the head and neck, in elderly individuals and often present as large, ulcerated nodules or plaques [19]. They also tend to have a slight predilection for male patients [19][21][23].

Undifferentiated/dedifferentiated melanomas are usually deeply invasive with a Breslow thickness over 4 mm and display a conventional area that can be either in situ or invasive of various subtypes (superficial spreading, nodular, lentigo maligna, acral lentiginous, or desmoplastic) as well as an undifferentiated/dedifferentiated component that usually represents over 50% of the tumor. The transition between the two components is typically abrupt [19]. Such cases represent important diagnostic challenges, particularly those lacking conventional components such as small biopsy specimens.

While the correct diagnosis of primary cutaneous undifferentiated/dedifferentiated melanoma is crucial to provide the best therapeutic options, the prognosis of these patients does not seem significantly different from a conventional melanoma when adjusted for tumor thickness [24]. Nevertheless, divergent differentiation is most often encountered in metastatic settings, and it seems to be associated with resistance to targeted and immune therapy [25].

3. Histological, Immunohistochemical, and Molecular Features of Primary Cutaneous Undifferentiated/Dedifferentiated Melanomas

Since primary cutaneous melanomas with divergent differentiation are rare, most articles discussing these lesions are case reports. However, in 2021, Ferreira et al. published a more extensive series of 11 cases [23]. They included tumors displaying a biphasic appearance with conventional melanoma areas and dedifferentiated areas lacking expression of S100, SOX10, MelanA, and HMB45. These patients were primarily elderly, with a mean age of 76, and had a slight but insignificant male predilection. The most affected sites were sun-exposed areas such as

the head and neck, followed by the extremities. In most cases (7), the dedifferentiated component was represented by atypical fibroxanthoma, while two others displayed rhabdomyosarcomatous differentiation with positive expression of desmin, myogenin, and MyoD1, and the remaining two cases displayed epithelial differentiation with positive expression of AE1/AE3 and MNF116. The diagnosis of atypical fibroxanthoma is one of exclusion as no immunohistochemical marker is entirely specific for this neoplasm, and extensive tests should be performed to rule out other entities. DNA sequencing was performed on seven cases to further evaluate these neoplasms, all of which displayed genetic mutations frequently encountered in melanomas. *NF1* mutations were noted in five cases, with four presenting this mutation in both the conventional and the dedifferentiated components. The fifth case displayed this mutation in the dedifferentiated component, while the conventional component was unavailable for analysis due to insufficient material. One case displayed an *NRAS* mutation in both components, and one showed a *BRAF* p.V600E mutation in the dedifferentiated area. Finally, non-p.V600E *BRAF* mutations were found in three of the cases, which also had *NF1* mutations [23].

Even rarer than melanomas with atypical fibroxanthoma features are rhabdoid melanoma. Rhabdoid melanomas are often encountered in metastatic sites and are exceptionally rare as primary cutaneous melanomas [26]. Rhabdoid melanomas are defined as melanomas exhibiting large pleomorphic cells with abundant eosinophilic cytoplasm with hyaline inclusions and eccentric nuclei [27]. It must be noted that the term “rhabdoid” describes a morphological feature as these areas not only usually lack conventional melanocytic markers but most often also lack muscle-specific markers, thus failing to exhibit true rhabdomyosarcomatous differentiation [26][27][28]. Such cases may still be challenging to diagnose as they are usually amelanotic and clinically atypical for a melanocytic lesion. Therefore, a comprehensive histopathological examination is required to spot small areas resembling melanoma [27][29]. Cases displaying true rhabdomyosarcomatous differentiation express one or more markers such as desmin, actin, MyoD1, and myogenin while failing to express conventional melanocytic markers in the dedifferentiated area [26][29][30][31][32].

Primary cutaneous melanomas can rarely present osteoid and chondroid areas, sometimes expressing bone-specific markers such as SATB2. Nevertheless, this expression is usually weaker than in osteosarcomas [33]. These tumors tend to occur on acral skin, but various other locations, such as the sun-exposed skin of the face, have been reported [34][35][36]. Local traumatism may trigger these lesions, as various authors have reported a history of trauma at the site of osteo-chondroid melanomas [35]. In this respect, Ali et al. presented the case of a 26-year-old female with melanoma on her index finger with a biphasic neoplasm composed of conventional melanoma and areas of osseous differentiation positive for SATB2 [34].

Cutaneous melanomas can display angiomatoid features in even rarer instances than those discussed above. Fonda-Pascual et al. described such a case, whereby they reported a nodular melanoma arising on the scalp of a 63-year-old woman. The tumor showed an area of tubular structures filled with erythrocytes [37]. However, the immunohistochemical tests were negative for CD31 and D2-40 and positive for S100, SOX9, and HMB45. Further genetic tests revealed a *BRAF* V600E mutation. Ambrogio et al. also reported a case of an 87-year-old man with a cutaneous melanoma displaying pseudo-angiomatous features [38]. This tumor expressed S100, MelanA, and

HMB45 in the differentiated component but not in the area with pseudo-vascular spaces. However, this area lacked expression of vascular markers, and SOX10 was positive in both components.

Apart from the aforementioned dedifferentiated melanomas, a few other rarer possibilities have been cited in the literature, including melanomas expressing macrophage and vascular markers and other markers such as keratins, FLI-1, CEA, calretinin, PAX8, and PAX2 [39]. Aberrant expression of these markers, sometimes associated with the loss of various melanocytic markers, may pose significant diagnostic challenges. Therefore, comprehensive immunohistochemical analysis and molecular studies may be required to establish a diagnosis.

Finally, desmoplastic melanomas represent particular entities as they may appear deceivingly bland and usually lack expression of melanocytic markers such as HMB45, MelanA, tyrosinase, and PRAME but generally express S100 and SOX10 [39][40]. Nevertheless, cases of desmoplastic melanomas lacking all conventional melanocytic markers, including S100 and SOX10, have been described [39][41].

4. Conclusions

Undifferentiated/dedifferentiated primary cutaneous melanomas are sporadic and may be difficult to diagnose due to their unusual histopathological and immuno-histochemical characteristics. Clinical presentations may be useful as this type of tumor most often affects elderly males and occurs on the sun-exposed skin of the head and neck followed by the extremities. However, extensive immunohistochemical analysis is mandatory in such cases as most of them fail to express HMB45 and MelanA but may have retained expression, at least focally, of S100, SOX10, and PRAME. Nevertheless, none of these markers are entirely specific for melanomas, and further molecular analysis may be required to detect mutations associated with melanomas. Additionally, detecting genetic mutations in dedifferentiated melanomas helps diagnose these lesions, evaluate the prognosis, and identify the best therapeutic approach.

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