Granular cell dermatofibroma: A potential diagnostic pitfall

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Abstract

Dermatofibroma, also known as "fibrous histiocytoma", is one of the most common cutaneous soft-tissue tumours. Many variants of dermatofibromas have been described and knowledge of these variations is important to avoid a misdiagnosis of a possibly more aggressive tumour. Histological features of different variants can coexist in the same lesion, but typical common fibrous histiocytoma features are generally found, at least focally, in all cases. However, when cellular changes make up the majority of the lesion, the histopathological diagnosis can become more complex and requires immunohistochemical investigations for a correct nosographic classification. We report on the case of a cutaneous fibrous histiocytoma, "granular cell" variant, found on the left leg of a 74-year-old woman.

Introduction

Dermatofibroma is a commonly occurring cutaneous lesion usually centred within the dermis. Dermatofibromas are referred to as benign fibrous histiocytomas of the skin, or superficial/cutaneous benign fibrous histiocytomas, or common fibrous histiocytoma. These mesenchymal cell lesions of the dermis clinically are firm sub-cutaneous nodules which occur on the extremities in the vast majority of cases, and which may or may not be associated with overlying skin changes.[1,2] The pathological diagnosis is easy with a typical anamnestic background or a clear pathologic feature. However, many variants of dermatofibromas have been described,[2] and knowledge of these variations is important to avoid a misdiagnosis of a possibly more aggressive tumour. The main histologic variants are: aneurysmal, hemosiderotic, cellular, epithelioid, atypical, lipidized, clear cell, palisading, atrophic, keloidal, granular cell, myxoid, lichenoid, balloon cell and signet-ring cell variants.[2-4] Histological features of different variants can coexist in the same lesion,[3] but typical common fibrous histiocytoma features are generally found, at least focally, in all cases.[1,3] The features of the variants may represent the predominant component of the lesion, making the identification of the histiocytoma harder.[4] Furthermore, some variants have distinct clinical presentations and biological behaviour, with different incidences of local recurrence and, in rare and controversial cases, metastasis, making correct diagnosis even more important.[4,5]

Case report

A 74-year-old woman came to the attention of the Plastic Surgery Unit of the University Hospital of Bari with a dark-brown papule of her left leg appeared one year before and slowly increased in size (Figure 1). She did not complain pain or previous injuries in the region. A severe venous insufficiency of her legs was noticeable, with a superficial hypertrophic and congested venous capillary network.

No other pathologies were referred. The lesion was excised under local anaesthesia and the residual loss of substance repaired with local flaps. At clinical examination a dark brown ovalar ulcerated papule with a 30 mm of diameter was detected on the anterior middle third of the left leg. The lesion was retrieved in skin excision measuring 30×20×12 mm. No follow-up data are available. The lesion was fixed to the surrounding soft tissues, showing not well-defined margins. No macroscopic lymphadenopathies were found in the draining lymphatic fields. The tissue was formalin-fixed and paraffin-embedded, and 5-µm-thick sections were obtained for haematoxylin and eosin (H&E) staining and immunohistochemical studies.

Antibodies used included CD68 (Dako Denmark A/S, PG-M1, dilution 1:50), S-100 protein (Dako Denmark A/S, polyclonal, dilution 1:5000), CD34 antibody (AbcamEP373Y dilution 1:2500), Melan-A (Dako Denmark A/S, monoclonal, M7196, dilution 1:50), CD10 (Dako Denmark A/S, monoclonal, IS648, dilution 1:500), Ki-67 (Abcam, SP6, dilution 1:200).

The lesion occupied the derma and consisted of a variable admixture of fibroblast-like cells and histocytes (Figure 2A). The latter were organized in large sheets and showed in more than 85% of the lesion a large eosinophilic cytoplasm filled of granules or microvacuoles (Figure 2B). The interposed collagenous stroma was loose and rich in blood vessels. An inflammatory, predominantly lymphocytic, infiltrate and globular collagen bundles were present in peripheral areas. The neoplasia presented defined margins with a pseudo capsule. The overlying epidermis was atrophic, with basal hyperpigmentation and melanin disposal. The lesion showed no mitotic activity. Immunohistochemically, the cells expressed diffusely CD-68 (Figure 2C); S-100 protein was expressed only in Langerhans cells, but it was negative in the cells of interest (Figure 2D); CD34, Melan-A and CD10 expression were negative. The fraction of neoplastic proliferation, assessed by Ki-67, was <1%.

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Discussion

Benign fibrous histiocytoma is considered as one of the most common benign tumours of the skin, with a very low recurrence rate ranging from 3% to 5%.[5]

Our data are in agree with Literature because dermatofibromas occur in people of all ages, although more commonly from the ages of the 20s to 40s, and develop more frequently in females than males, with as high as a 2:1 female to male predominance according to some reports. Aloi *et al*.[4] assert the benign nature of these lesions because in literature it was described a possible spontaneous regression and relapses of them.

The etiology is unknown, but some Authors[3] recognize a possible etiopathogenetic cause to the local reaction of histiocytes after a local traumatic injury or an insect bite.[5] Dermatofibroma is clinically asymptomatic and painless. Macroscopically it is described as roundish or ovoidal, firm dermal nodule, usually of less than 10 mm in diameter. It often shows a characteristic central white, scar-like patch on dermatoscopic examination.[1,5]

Dermatofibroma with granular cells was described the first time in 1991 by LeBoit and Barr.[3] The cellular morphology of the lesion shows a large cytoplasm replete with coarse eosinophilic granules. These last are due to an increased number of secondary lysosomes and maintain the same histiocytes cellular lineage.[5] Different theories have been proposed to explain the mechanisms underlying lysosomal aggregation within the cytoplasm of these cells.[5,6] It would appear that this process is caused by the dysfunction of a lysosomal enzyme or a lysosomal-associated protein involved in enzyme activation, rather than enzymatic targeting or lysosomal biogenesis.[5]

These cytoplasmic changes are a constant features of granular cell tumours. However, cellular granularity can be observed in numerous cutaneous benign neoplasm and needs differential diagnosis elements. It is very important to consider the morphology and the immunohistochemical evaluation which, sometimes, can be decisive for the right diagnosis. Changes to granular cells can represent 30% to 90% of the whole tumour mass and it represents, as well as our case, a great challenge for the pathologist.

Our case presented a hard diagnosis because the tumour mass was made up of more than 85% of granular cells. Morphology of lesions could be a great help in differential diagnosis by comparing with the benign granular cell tumour (GCT), which differs (GCDF) for the different histogenesis: in fact, an immunohistochemical study with antibodies against the S-100 protein was strongly and diffusely positive in benign granular cell tumour, but negative in GCDF, conversely CD68 will be positive in GCDF and almost totally negative in GCT.[6-8]

Differential diagnosis with granular cell malignancy is less apparently complex, since it has evident mitosis and cytological atypia, which could lead to the suspicion that it may be a malignant entity distinct from GCDF.

Primary polypoid granular cell tumour (PPGCT) may represent another lesion that must be correctly discriminated against by

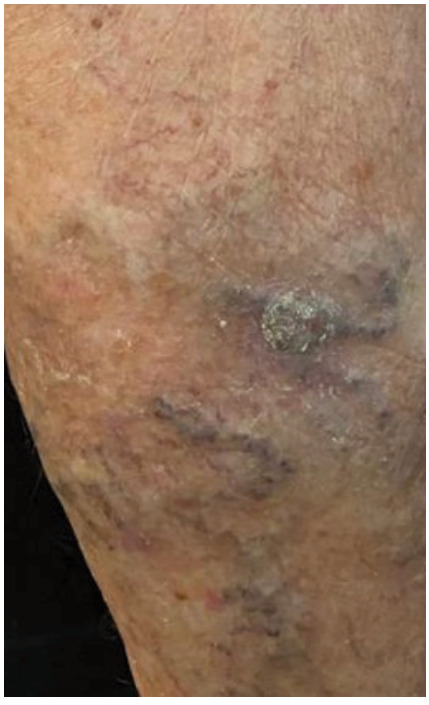

Figure 1. A dark-brown papule of the left leg appeared one year before and slowly increased in size.

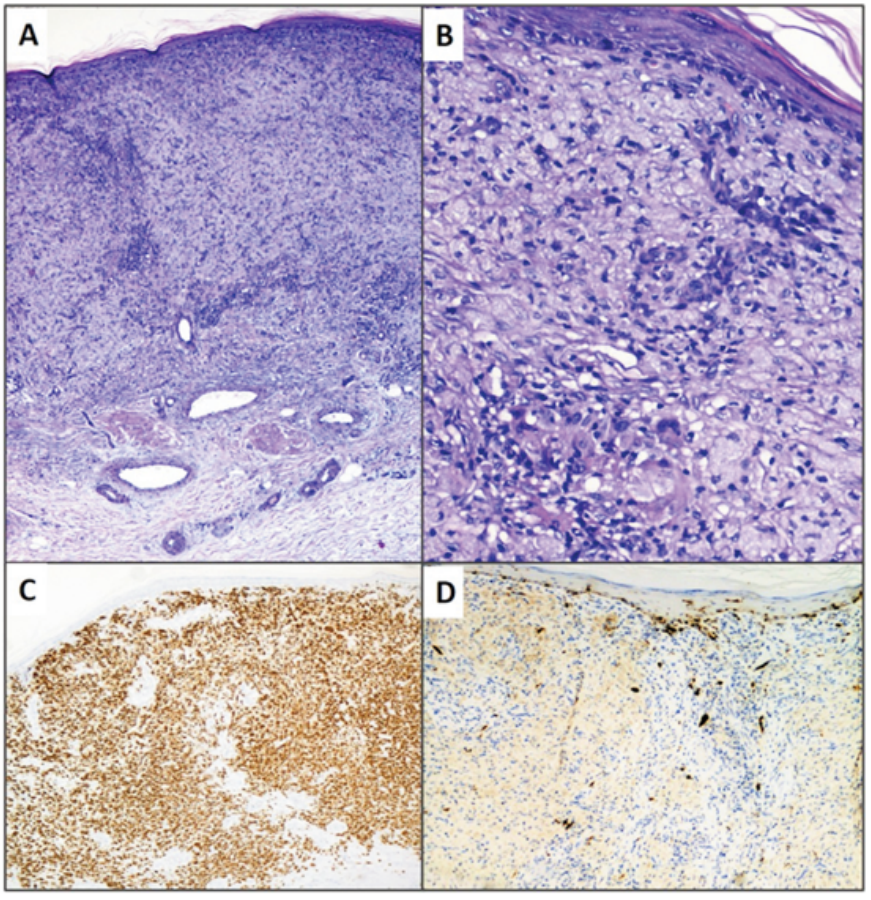

Figure 2. The lesion was composed of a variable admixture of fibroblast-like cells and histiocytes that showed in more than 90% a large eosinophilic cytoplasm filled of granules or microvacuoles (Hematoxylin-Eosin, A: original magnification 40x; B: original magnification 200x). The neoplastic cells were strongly immunoreactive for CD68 (C: original magnification 40x) and negative for S100 protein (D: original magnification 100x).

the GCDF; in more detail, PPGCT, although can morphologically simulate GCDF, differs from it due to its strong and widespread positivity to the S-100 protein, which reflects its neural derivation. On the other hand, differential diagnosis is more complex with a subtype of PPGCT, but which is not of neural derivation ("not neural").

In this case the cells that make up this tumour are largely negative to the S-100 protein and only focally they turn out to be CD68 positive. However, this should not be misleading, as it is not a fibrohistocytic-derived tumor, but the positivity to CD68 is due to the accumulation of lysosomes that characterize all neoplasms consisting, in fact, of granular cells. Therefore, the differential diagnosis can be made using the anti-NKI/C3 antibody which will intensely and homogeneously stain the cells of the non-neural PPGCT, while it will be negative in the GCDF.

Easier and more immediate is the differential diagnosis with entities such as Granular Cell Ameloblastoma (GCA) and Granular Cell Basal Cell Carcinoma (GCBCC) which have very distinct morphological characteristics, and which, even when the granular cells should represent the greatest part of the lesion, allow to detect a certain percentage of typical neoplasm that helps the pathologist to make the correct diagnosis.[9-13]

Conclusions

Granular cell changes have also been observed in other neoplasm such as schwannoma, leiomyoma and leiomyosarcoma and the Authors agree that correct morphological recognition together with the use of ancillary techniques (IHC) are sufficient to place a right one diagnosis. On the other hand, the differential diagnosis of GCDF with Granular Cell Dermatofibrosarcoma Protuberans (GCDFSP) is more complex.

It is a variant of the DFSP that undergoes granular cell changes, similarly to what we have previously described for other lesions. In this case, the morphological differential diagnosis may not be easy, although in the literature there is a greater propensity of the DFSP to invade the subcutaneous tissue more than the DF. Nevertheless, in GCDFSPs in which the granular cell component is highly represented, it is mandatory to request IHC markers such as CD34 which is positive in GCDFSP and negative in GCDF.[12-13] It is very important to recognize this entity as the clinical and biological behaviour is different compared to a typical DF.

In conclusion, granular cell dermatofibroma represents a rare histologic variant of dermatofibroma that is important to recognize because it can potentially be confused with other benign or malignant cutaneous neoplasms.

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