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Fat Necrosis with an Associated Lymphocytic Infiltrate Represents a Histopathologic Clue that Distinguishes Cellular Dermatofibroma from Dermatofibrosarcoma Protuberans

Short running title: Fat Necrosis: A clue to diagnosis

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Abstract: (170/200 words)

Background: Cellular dermatofibromas (CDFs) and dermatofibrosarcoma protuberans (DFSP) can be challenging to differentiate from one another. Morphologically, both entities commonly extend into the subcutis, exhibit high cellularity with limited cytologic atypia and have a mixed fascicular-to-storiform growth pattern. We sought to evaluate the significance of fat necrosis with an associated lymphocytic infiltrate as a histopathologic clue for distinguishing CDFs from DFSP.

Methods: We identified cases in our pathology database with a primary diagnosis of CDF or DFSP. Punch or excisional biopsy specimens with extension into the subcutis were selected. Previously biopsied lesions and specimens that did not interact with the subcutis were excluded. Histopathologic features were evaluated in hematoxylin and eosin stained sections.

Results: Fat necrosis with lymphocytic infiltrate was present in 20/20 cases of CDF. None of the 20 DFSP cases had fat necrosis with lymphocytic infiltrate although 4/20 had fat necrosis alone.

Conclusions: Fat necrosis with associated lymphocytic response can aid in the distinction between CDF and DFSP.

Introduction:

Dermatofibromas (DFs) are common benign dermal proliferations of fibroblasts and histiocytes. Characteristic histopathologic features include sparing of the papillary dermis, epidermal hyperplasia with basilar hyperpigmentation, entrapment of peripheral collagen bundles, and an admixed chronic inflammatory infiltrate. Of the many variants of DFs, cellular dermatofibromas (CDFs) are relatively uncommon, accounting for approximately 5-10% of dermatofibromas.[1,2] In comparison to conventional DFs, CDFs tend to be larger in size and have a higher recurrence rate that ranges from 10-26%.[1,3] Histopathologic features differentiating CDFs from conventional DFs include: increased cellularity, frequent extension into the subcutis, increased mitotic rate, and a fascicular-to-storiform growth pattern.[1] These features overlap with characteristics of dermatofibroma sarcoma protuberans (DFSP) and can create a diagnostic dilemma.

DFSPs are low-grade, locally aggressive cutaneous sarcomas comprised of monotonous spindle cells. The cells are characteristically arranged in a storiform pattern with neoplastic cells infiltrating subcutaneous tissue and encasing individual adipocytes resulting in a honeycomb appearance. DFSPs are considered neoplasms of intermediate potential with a high rate of local recurrence of up to 50%.[4] However, metastasis is an uncommon event, which usually occurs in the setting of fibrosarcomatous transformation.[5]

Immunohistochemical stains and molecular studies can aid in distinguishing CDFs from DFSPs. CD34 positivity occurs in approximately 90% of DFSPs but is also present in up to 25% of CDFs. [3,6] However, CD34 positivity in CDFs is limited to the periphery as compared to the diffuse pattern of staining in DFSPs. Also, in contrast to CDFs, immunohistochemistry of DFSP shows an absence of CD163 and factor XIIIa, [3, 7] although factor XIIIa positivity in dermal dendrocytes can confound interpretation. In diagnostically challenging cases, ancillary molecular tests can be exploited and the presence of COL1A1-PDGFB fusions in DFSPs by can aid in distinguishing DFSPs from CDFs.

We have frequently observed fat necrosis with an associated lymphocytic infiltrate in CDFs and sought to evaluate this as histopathologic clue for distinguishing CDFs from DFSPs, in conjunction with other histopathologic features.

Materials and Methods:

With approval from University of Michigan Institutional Review Board, cases of CDF and DFSP were identified through a retrospective search of a University of Michigan Department of Pathology database for the period between 2008 and 2017. Punch or excisional biopsy specimens with extension into the subcutis were selected. Previously biopsied lesions and specimens that did not interact with the subcutis were excluded. The diagnosis was confirmed using hematoxylin and eosin-stained sections of paraffin-embedded formalin-fixed tissue of each case and previously performed immunohistochemical stains. Histopathologic features of each case were evaluated, including the presence of peripheral collagen trapping, honeycombing, chronic inflammation (including lymphocytes or plasma cells within the lesion),

floret-like giant cells, epidermal hyperplasia, grenz zone, and fat necrosis with associated lymphocytic infiltrate.

Results:

We identified 40 cases, of which 20 were CDFs and 20 were DFSPs. Clinical characteristics of the cohort are summarized in Table 1. CDF patients were younger than DFSP patients, with mean ages of 34 and 49 respectively (Table 1). CDFs and DFSPs were commonly located on the trunk or the lower limb/limb girdle; each affected equal proportions of men and women.

CDFs and DFSPs differed in a number of histopathologic features (Table 2; Figure 1). Fat necrosis with associated lymphocytic infiltrate was seen in all cases of CDF (20/20) and none of the cases of DFSP (0/20). The lymphocytic infiltrate was consistently observed in areas of fat necrosis and was present at the junction of the dermis and subcutis, often with perivascular accentuation Although fat necrosis was seen in 4/20 cases of DFSP, these cases showed a pseudomembranous type of fat necrosis without any associated lymphocytic infiltrate. However, pseudomembranous fat necrosis does not seem to be specific for DFSP, as this pattern was also observed in many cases of CDF. Honeycombing was more common in DFSP (17/20 vs. 2/20 with CDF). Peripheral collagen trapping occurred in 14/20 cases of DFSP and all cases of CDF (Table 2; Figure 2). The presence of floret-like giant cells, Grenz zone, epidermal hyperplasia, or hemosiderin-laden macrophages also did not distinguish between CDF and DFSP.

Immunohistochemistry showed a diffuse pattern of CD34 staining in all cases of DFSP. Among CDF cases, 6/20 demonstrated patchy peripheral CD34 staining whereas 1/20 had weak CD34 positivity throughout with a more typical accentuation at the periphery.

Discussion:

CDFs and DSFPs share a number of clinical and histopathological features. Nevertheless, it is imperative to differentiate CDF from DFSP, which is more likely to be locally aggressive and requires wide local excision.

Clinical features such as age, sex, and lesion location have been of limited value in discriminating between CDF and DFSP.[1,3,8-11] DFSP sometimes presents as a raised plaque, but it may also present as a dermal nodule similar to CDF. Although patients who present with DFSP are older on average than those who present with CDF, both CDF and DFSP can occur in individuals of any age. Furthermore, they appear to occur equally in males and in females. DFSP may be somewhat more frequent on the trunk than CDF, but with both CDF and DFSP occurrence is commonly on an extremity and less often on the head and neck. [1,3,8-11]The clinical presentations of CDF and DFSP in our cohort are similar to those reported in previous studies and do not help to distinguish between CDFs and DSFPs.

Traditionally, CDFs and DSFPs have also been difficult to distinguish based on histopathology. CDFs are cellular proliferations of spindled cells with a fascicular-to-storiform growth pattern. They commonly extend into the subcutis, mimicking DFSP, which also has a storiform appearance. However, in the present study, we found that histopathologic features did allow CDFs to be differentiated from DFSPs (Table 2; Figure 1). In all 20 cases of CDF in our sample, we identified a lymphocytic infiltrate in association with fat necrosis whereas this finding was not observed in any of the 20 cases of DFSP. Other helpful histopathologic features in differentiating CDF from DFSP were honeycombing and chronic inflammation. Consistent with previous descriptions of CDF, floret-like giant cells, grenz zone, epidermal hyperplasia, and hemosiderin-laden macrophages did not reliably distinguish between CDF and DFSP. [1,11] Peripheral collagen trapping was present in all CDF cases in our sample but, unexpectedly, it was also present in the majority of DFSP cases.

The etiology of CDF is unclear; however, contributors to DF development have been studied and debated. Based on the presence of clonal aberrations and recurrent translocations, at least a subset of DFs are likely neoplastic.[12-14] It has also been suggested that DFs are a reactive process arising in response to inflammation or trauma.[15-16]

Fat necrosis with associated lymphocytic response has not been described previously but occurs consistently in CDF in our cohort. The absence of this finding in DFSP has important clinical implications as it may serve as an additional histopathologic clue to distinguish between CDF and DFSP.

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Table 1. Comparison of Clinical Features of CDF and DFSP

	CDF	DFSP
Mean age	34	49
Age range	10-61	27-86
Sex (M:F)	8:12	9:11
Location (%)		
Lower limb/limb girdle	8/20 (40)	7/20 (35)
Upper limb/limb girdle	5/20 (25)	1/20 (5)
Trunk	5/20 (25)	10/20 (50)
Head and neck	0/20 (0)	2/20 (10)

Table 2. Comparison of Pathologic Features of CDF and DFSP

	CDF (%)	**DFSP (%)**
Fat necrosis with lymphocytic infiltrate	20/20 (100)	0/20 (0)
Peripheral collagen trapping	20/20 (100)	14/20 (70)
Chronic inflammation	17/20 (85)	6/20 (30)
Epidermal hyperplasia	15/20 (75)	9/20(45)
Grenz zone	10/20 (50)	9/20 (45)
Hemosiderin	5/20 (25)	2/20 (20)
Floret-like giant cells	4/20 (20)	1/20 (5)
Necrosis	2/20 (10)	0/20 (0)
Honeycombing	2/20 (10)	17/20 (85)

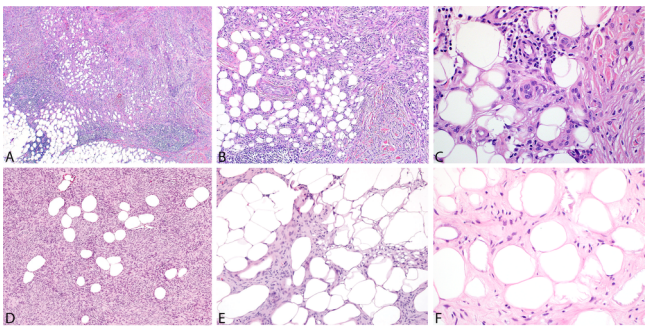
Figure legends:

Figure 1

A and B. CDF with fat necrosis and associated lymphocytic infiltrate at the junction of the dermis and subcutis with perivascular accentuation (C) (H&E, x40 and x100, x400). D. DFSP with "honeycomb" infiltration of fat without necrosis or inflammation (H&E, x100) E and F. DFSP with fat necrosis without lymphocytic infiltrate (H&E, x200) .

Figure 2

A. DFSP with peripheral collagen trapping (H&E, x200) B. CDF with peripheral collagen trapping (H&E, x200).



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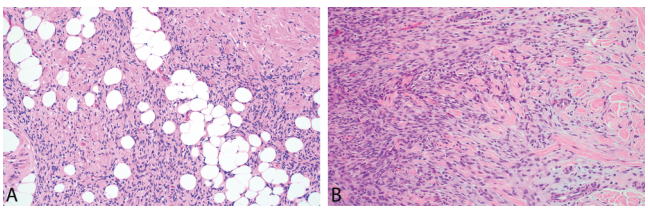

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