Myoid differentiation and EMA expression in fibrosarcomatous dermatofibrosarcoma protuberans

O. Arican, S. Bakaris, E. Bulbuloglu and F. Ezberci

SUMMARY

Dermatofibrosarcoma protuberans (DFSP) is a relatively unusual, locally aggressive cutaneous tumor of intermediate malignancy. Fibrosarcomatous DFSP (FS-DFSP), a rare variant of DFSP, has a higher tendency for recurrence and metastasis. Recently, a small number of cases of another variant of FS-DFSB characterized by areas of myoid differentiation have been reported. We present here a 35 year-old female patient with myoid differentiation in FS-DFSP. The tumor on the left scapular region had slowly grown over six years. Examination revealed a domeshaped, firm, nontender, violaceous dermal nodule. Histologically, it was composed of a monotonous spindle cell population arranged predominantly in a storiform pattern and to a lesser extent in a fascicular fibrosarcomatous pattern with a parallel arrangement of the cells. Immunohistochemically, the tumor cells showed diffuse expression for vimentin and CD34. In the center of the tumor areas with frequent mitosis, hypercellular and negative reactive for CD34 were seen. In addition, approximately 10% of the cells were positive for epithelial membrane antigen. Myoid differentiation was found around the blood vessels. The myoid areas were positive for smooth muscle actin and negative for desmin. It is possible that the presence of hyperplastic myofibroblasts is a reactive phenomenon to the proliferation of tumor cells. We believe that this finding around blood vessels may be present in DFSP or FS-DFSP. However, when myoid areas, myoid fascicles and myoid nodules are seen in the stroma, it may be a new morphological variant of DFSP and/or FS-DFSP.

KEY WORDS

dermatofibrosarcoma protuberans, sarcomatous, myoid differentiation

Introduction

Dermatofibrosarcoma protuberans (DFSP) is a relatively unusual, locally aggressive cutaneous tumor of low-intermediate malignancy. Whether DFSP is of fibroblastic, histiocytic, or neuroectodermal origin is still a matter of controversy (1). It has been considered a distinct clinicopathological entity since Darier and Ferrand's (2) description in 1924 but its characteristic microscopic pattern was noted only in 1962 by Taylor and Helwig (3). Several histological variants of DFSP have been described including a fibrosarcomatous vari-

Table 1. Differential diagnosis of DFSP (1,4,12).

Atypical fibroxanthoma	Dermal dendrocytic hamartoma
Classic fibrosarcoma	Nodular fasciitis
Myxofibrosarcoma	Desmoplastic melanoma
Malignant fibrous histiocytoma	Diffuse neurofibroma
CD34 positive benign fibrous histiocytoma	Plexiform fibrohistiocytic tumor
Giant cell fibroblastoma	Neurolemoma
Myxoid liposarcoma	Morphea-type basal cell carcinoma
Dermatomyofibroma	Morphea
Solitary fibrous tumor	Keloid

ant (FS-DFSP), a myxoid variant, an atrophic variant, a variant resembling malignant fibrous histiocytoma, a sclerosing DFSP, a palisaded DFSP, pigmented DFSP or Bednar's tumor, a granular cell variant and a combined variant with giant cell angiofibroblastoma (4). In the relevance of diagnosis, the different variants lie mainly in avoiding pathologic misdiagnosis as all of them, except for FS-DFSP, appear to have similar clinical behavior (5). It has been suggested that FS-DFSP, a rare variant of DFSP, has a higher tendency for recurrence and metastasis (6). Recently, a small number of cases of another variant characterized by areas of myoid differentiation in FS-DFSP have been reported (5,7-13).

Case report

A 35-year old female presented with a 2.0 x 1.5 x 1.0 cm, ill-defined dermal and subcutaneous mass on the left scapular region. The tumor had slowly grown over six years. No pain, no change in color, and no history of trauma to that area were mentioned. Her family history was noncontributory. Examination revealed a domeshaped, firm, and violaceous dermal nodule. The overlying epidermis, to which the lesion was fixed, was smooth and the nodule moved freely over deeper structures. An excisional biopsy was performed. The surgical specimen was fixed in 10% buffered-formalin, embedded in paraffin, and the sections were stained with hematoxylin-eosin. For immunohistochemistry, the sections were stained with antibodies against vimentin, desmin, CD34, alpha-smooth muscle actin, S-100 protein, cytokeratin, and epithelial membrane antigen (EMA) using the avidin-biotin peroxidase complex technique. Appropriate controls were used. Histologically, it was composed of a monotonous spindle cell population arranged predominantly in a storiform pattern and to a lesser extent in a fascicular fibrosarcomatous pattern with a parallel arrangement of the cells (Figure 1). An infiltration of the adipose tissue and rare tumor giant cells were seen. Mitoses were 1-2 per high power field, nuclear atypia was low. Immunohistochemically, the tumor cells showed diffuse expression for vimentin and CD34 and negative reaction for S-100 protein, cytokeratin. In the center of the tumor areas with frequent mitosis, hypercellular and negative reactive for CD34 were seen. These areas were evaluated as a fibrosarcomatous pattern of DFSP and accounted for 10%< of the lesion (Figure 2). In addition, approximately 10% of the cells were positive for EMA and they s were more numerous in deeper parts (Figure 3). Myoid differentiations were found around the blood vessels. Myoid areas composed of cells with bright eosinophilic cytoplasm and plump oval nuclei were observed around the blood vessels. The myoid areas were positive for smooth muscle actin, and negative for desmin (Figure 4). On the basis of the clinical, histopathologic, and immunohistochemical findings, a diagnosis of DFSP was made. As the patient had undergone an excisional biopsy, a second surgical excision with surgical margins of at least 3.5 cm was carried out. There were no tumor cells in the surgical margins of the tumor. At the time of diagnosis, cranial, chest and abdominal CT scans did not show any suspected metastatic foci and lymph nodes were normal. There has been no sign of recurrence and metastasis in 32 months of follow-up.

Discussion

The age distribution for DFSP ranges from 6 to 87 years of age but most commonly occurs during early- to mid-adult life. Males are more frequently affected than females (14). The tumor is usually painless, and often a long-standing solitary multinodular mass presents most commonly on the trunk, followed by the proximal extremities, chest and the head and neck (1). The pathogenesis of DFSP is not clearly understood. Recent genetic research has been able to show chromosomal translocations or ring chromosomes, which occur in DFSP

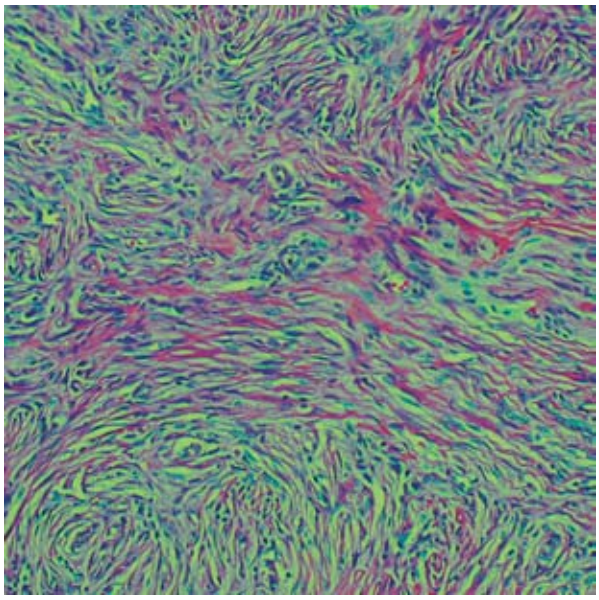

Figure 1. A storiform pattern of dermatofibrosarcoma protuberans (DFSP), (HEx20).

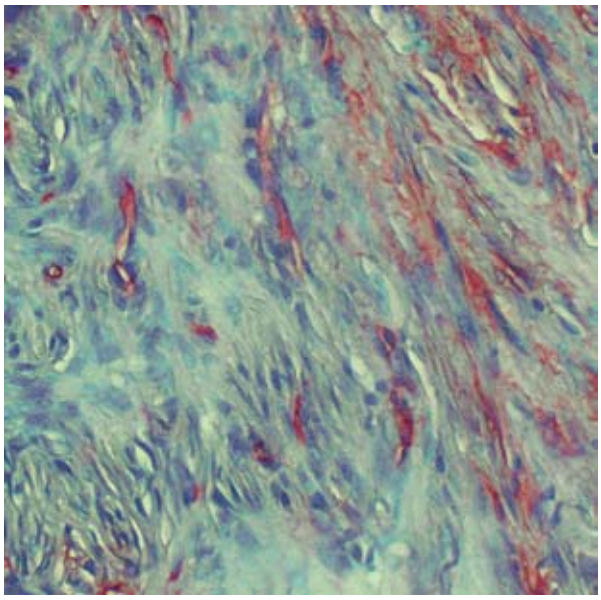

Figure 2. Low-medium magnification showing the transition between DFSP and fibrosarcomatous tumor areas. Note the marked diminution of CD34 immunostain in fibrosarcomatous portion of the tumor; streptovidin-biotin amplified complex (ABCx20).

through a fusion of the chromosome regions 17q22 and 22q13 (15). The classic histologic features of DFSP include a monotonous storiform (mat-like) growth pattern of uniform and cytologically bland tumor cells with hyperchromatic and spindle-shaped nuclei and a characteristic honeycomb pattern of infiltration into subcutaneous fat (1,13). CD34, known as the human hematopoietic progenitor cell antigen, may be accepted as the most valuable and highly specific immunohistochemical marker for the diagnosis of DFSP (1,16). The histopathological differentiation of DFSP from other tumors is shown in Table 1. Complete removal of all tumors in each patient is a major challenge in the treatment of DFSP (17). Distant metastasis is rare (<5%), but if surgical resections are performed with inadequate margins, local recurrence rates can be 33-60% (17,18). Most lo-

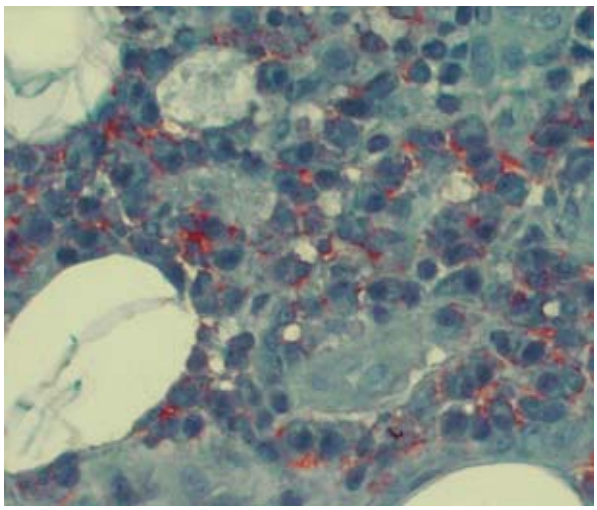

Figure 3. In deeper parts there is positive immunostaining for epithelial membrane antigen (EMA), (ABCx20).

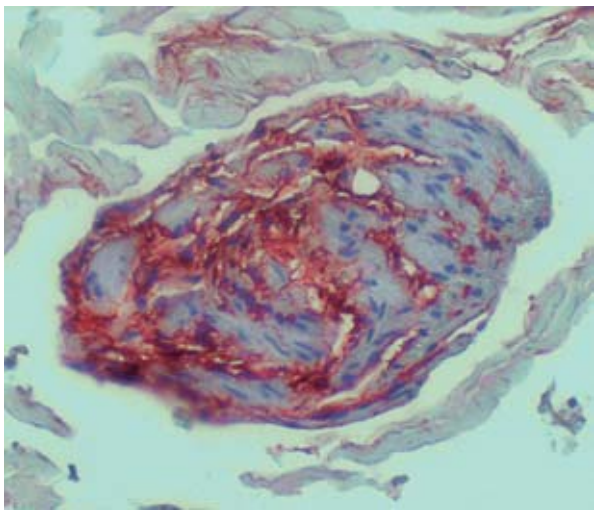

Figure 4. Smooth actin immunostaining showing myoid nodule centered around small vessels within DFSP, (ABCx20).

cal recurrences of DFSP (50-75%) are noted within 3 years of excision (1).

In 1951, first case of metastasizing DFSP containing areas that were histologically indistinguishable from fibrosarcoma was reported, and following a number of case reports and some case series, FS-DFSP was specified as a separate condition (13). Besides a female predominance in FS-DFSP (19), there are no remarkable differences in either age of patients or anatomic localization of the tumor between classical DFSP and FS-DFSP (13,20). In addition, the extension of fibrosarcomatous areas needed for diagnosis of FS-DFSP is not clearly defined (9). Mentzel et al. used the term FS-DFSP when fibrosarcomatous areas accounted for at least 5% of the whole lesion (13). Fibrosarcomatous change is characterized as mitotically active cellular areas composed of spindle cells arranged in a clearly fasicular, often herringbone-like growth pattern (13). The tumor cells in the fibrosarcomatous areas of FS-DFSP show less or no CD34 staining contrary to classical form (4). Mentzel et al. described that loss of CD34 immunopositivity may be in keeping with tumor progression to CD34-negative fibrosarcoma (13). Wang et al. found that DFSP and fibrosarcomatous areas in FS-DFSP have showed similar gene fusion (15). In patients with FS-DFSP, local recurrence rates are 73-89% and distant metastasis rates are 14-63% (19,21). Mentzel et al. (15) and Bowne et al. (22) showed that FS-DFSP represents a form of tumor progression associated with aggressive biologic behavior, a shorter prerecurrence interval and a significantly poorer prognosis when compared with classical DFSP.

Myoid differentiation in DFSP and FS-DFSP seems to be a very rare phenomenon. Recently there have been several reports and approximately 30 cases of FS-DFSP, in medical literature (5,7-13). Calonje and Fletcher reported the myoid areas as being distributed randomly in the tumor without any consistent relation to hair follicles or blood vessel walls, and this they interpret as myoid differentiation of neoplastic cells of DFSP (5). O'Connell and Trotter studied two cases of FS-DFSP and reached the same conclusion (8). However, Diaz-Cascajo briefly introduced two independent cases containing myoid areas, and commented that serial sections of tumors revealed a close relationship between myoid areas and the wall of intraneoplastic blood vessels (9). Sanz-Trelles et al declared that origin of myomatous areas could be a hyperplasia of the vascular muscle cells or a proliferation of the pericytes with differentiation towards smooth muscle cells (12). Morimitsu et al (10) and Wang et al (11) suggested that the myoid areas are likely to be related to hyperplasia of myofibroblast in stroma rather than myofibroblastic differentiation of tumor cells. Oliveirea-Soares et al (7) and Mentzel et al (13) agreed that myoid differentiation is a variant of DFSP and FS-DFSP in their case series. On the other hand, a recent report of myoid differentiation in a metastasis of FS-DFSP by Ohtani et al (23) suggested that this differentiation may be neoplastic as well. They observed actin-positive myoid cells arranged in sporadic tumor cells or fascicle-forming cells in pulmonary metastasis of FS-DFSP. These cells may be a neoplastic appearance different from that of entrapped perivascular smooth muscle cells, and they lacked any relationship to the vessels.

The histogenesis of FS-DFSP remains controversial. Wrotnowski et al believe that fibrosarcomatous areas represent the development of a second neoplasm separate and distinct from surrounding DFSP (24). Grouls and Hienz consider the neoplasm to represent a transition between DFSP and fibrosarcoma (25). Diaz-Cascajo et al (19) and Ding et al (26) believe that FS-DFSP represents a peculiar variant of DFSP able to undergo progression to a higher malignant neoplasm. We agree with the latter conclusion because DFSP and fibrosarcomatous areas show similar gene fusion but FS-DFSP behaves more aggressively than does the classical form.

In our case, approximately 10% of the cells were positive for EMA. Zamecnik et al observed an expression of EMA, one of the markers for perineural cell differentiation, in DFSP. These authors believe that perineural and myoid cell differentiations do not exclude one another in DFSP (27). Myoid differentiation was described as a new morphologic variant of what is usually FS-DFSP and sometimes DFSP. In our case, we found myoid differentiation seen around blood vessels as have some other authors (9,12). It is possible that the presence of hyperplastic myofibroblasts is a reactive phenomenon to the proliferation of tumor cells. We believe that this finding may be found in DFSP or FS-DFSP. But some authors showed that myoid areas, myoid fascicles and myoid nodules were observed as being irregular and patternless in stroma (5,8,10,11). We believe that when these findings are found in the stroma, it may be a new morphological variant of DFSP and/or FS-DFSP. Myoid differentiation in DFSP or FS-DFSP and their clinical prognosis should be investigated further in large case series.

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AUTHORS' ADDRESSES

Ozer Arican MD, Department of Dermatology, Kahramanmaras Sutcu Imam Medical Faculty, Alpaslan Turkes Bulv, Baskose Apt 6/12, Kahramanmaras TR 46000, Turkey
Corresponding author, e-mail: ozerari@gmail.com
Sevgi Bakaris MD, Department of Pathology, same address
Ertan Bulbuloglu MD, Department of Surgery, same address
Fikret Ezberci MD, same address