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Review

Dermatofibrosarcoma protuberans with fibrosarcomatous transformation: our experience, molecular evaluation of selected cases, and short literature review

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Abstract

Dermatofibrosarcoma protuberans with fibrosarcomatous transformation (DFSP-FS) is a higher grade tumor arising from dermatofibrosarcoma protuberans (DFSP). Recent literature highlights its impact on recurrence rates, metastatic rates, and survival. In this article, we aim to describe our experience with 13 cases of DFSP-FS in terms of pathologic findings, molecular alterations, clinical outcomes, management, and also perform a short recent literature review.

Introduction

Dermatofibrosarcoma protuberans (DFSP) is a superficial low-grade sarcoma displaying a monomorphic spindle cell proliferation with characteristic storiform architecture. DFSP arises in the trunk and extremities of young to middle-aged adults in the form of a slow-growing nodule or plaque.

The tumor involves the dermis and subcutaneous tissue and infiltrates along fibrous septae in a honeycomb pattern. The cells display mild atypia and are speculated to be of fibroblastic nature. Mitotic activity is low with less than five mitoses per 10 high-power fields (HPF) in most cases. Tumor cells are diffusely immunoreactive for CD34, whereas keratin, S100, factor XIIIa, and muscle markers are negative. Smooth muscle actin is often positive in myoid nodules for which several theories postulate they may represent myofibroblastic differentiation, prominent myointimal proliferation of vessels, or entrapped arrector pili muscle bundles.[1] Myoid nodules are more frequently seen in DFSP-FS, although they have been observed in DFSP.[1] Despite presence of melanin pigment in the variant Bednar tumor, this neoplasm is not believed to be of neuroectodermal/Schwannian origin. Other morphological variants such as giant

cell fibroblastoma (juvenile variant of DFSP), sclerosing, atrophic, myxoid, and even granular cell have been described.[2,3] DFSP harbors a characteristic chromosomal translocation t(17;22) resulting in the *COL1A1-PDGFβ* fusion gene in 85–90% of cases.[4] This rearrangement is usually seen in the form of supernumerary ring or marker chromosomes that contain sequences of chromosomes 17 and 22.[4]

Fibrosarcomatous transformation (DFSP-FS) occurs in a minority of cases and is defined as an abrupt or gradual change from storiform to fascicular or herringbone architecture, high mitotic activity (usually ≥ 5 mitoses/HPF), and moderate nuclear atypia. Cases with severe pleomorphism are very uncommon and have been described.[5] CD34 expression is usually lost or weak, and PDGFβ rearrangements are still encountered by fluorescence in situ hybridization (FISH) studies. DFSP-FS has been associated with increased rates of recurrence or metastasis. Nevertheless, some authors argue that these conclusions are made in cases with suboptimal resection, variable therapy selection, and limited follow-up.[6] Wide local excision with at least 2 cm margins is the gold standard of treatment with selected patients receiving chemotherapy or radiation.[2,6]

In this article, we sought to describe our experience with 13 cases of DFSP-FS and execute a short literature review.

Materials and methods

Slides of 13 DFSP-FS spanning from 2002 to 2017 were retrieved from the University of Pittsburgh Medical Center archives for review after approval by the Institutional Review Board. Fibrosarcomatous transformation was defined as a tumor with ≥ 5 mitoses/10 HPF with moderate atypia, demonstrating loss of storiform architecture to fascicular or herringbone growth. Specimens were evaluated for percentage of fibrosarcoma, margin status, mitotic rate, and CD34 positivity. CD34 was measured semiquantitatively as 0 = negative, 1+ = weak, 2+ = moderate, and 3+ = strong staining. Eight DFSP-FS cases with available tissue, including metastatic tumors, were analyzed for *PDGFβ* gene alterations by FISH with the *PDGFβ* dual color break apart probe (ZytoLight, Germany), hybridizing to the 22q13.1 chromosomal region. Classical G-band karyotyping was performed on the metastatic deposit of case 1 at the time of resection. Tumor location, size, recurrence, and metastasis intervals were retrieved from pathology reports. The cancer registry provided vital status and data of treatment protocols utilized.

Results

There were eight females and five males with age ranging from 15 to 78 years (Table 1). Common tumor locations included: trunk (n = 6, abdomen and back); lower extremities (n = 5, ankle, thigh, and knee); and head and neck (n = 2, chin and neck). Tumor size ranged from 2 to 22 cm (median 5.5 cm).

Table 1 DFSP-FS data and vital status

DFSP-FS case	Age/sex	Tumor location	Tumor size (cm)	% of fibrosarcoma	Mitoses/10 HPF	CD34	Primary resection margin status	Recurrence	Metastasis	PDGFβ FISH alterations	Vital status
1	26/M	Ankle	8.4	100%	52	0–2+	-	Yes, at 20 months	Yes, at 11 months to groin	+ in both tumor and metastatis	AWOD at 42 months
2	27/M	Thigh	2.7	10%	5	1+	-	No	No	+	AWOD at 25 months
3	38/F	Abdomen	5.5	80%	12	1+	+, re-excision negative	No	No	+	AWOD at 2 years
4	52/M	Thigh	22.0	90%	28	2–3+	-	No	No	+	AWOD at 14 months
5	74/F	Thigh	6.5	85%	9	0–1+	+ followed by radiation	No	No	+	AWOD at 10 months
6	73/F	Back	7.2	UNK	15	0–1+	+, re-excision negative	Yes, at 38 months	No	+	AWOD at 7 years
7	47/M	Abdomen	2.0	30%	7	1–3+	+, re-excision negative	No	No	ND	AWOD at 3 years
8	45/F	Chin	3.5	30%	10	ND	+, re-excision negative	No	No	ND	AWOD at 39 months
9	38/F	Abdomen	9.5	50%	10	0–3+	-	UNK	UNK	ND	Alive
10	15/F	Neck	9.0	60%	8	2–3+	+, UNK if re-excision or radiation was done	No	No	ND	AWOD at 16 years
11	24/M	Back	5.0	60%	10	0–2+	+, followed by radiation	No	No	+	AWOD at 23 months
12	79/F	Knee	2.1	95%	27	0–1+	+ followed by radiation	No	No	Monosomy ch22	AWOD at 16 months
13	65/F	Abdomen	5.0	75%	23	0–2+	+, UNK if re-excision or radiation was done	No	No	ND	AWOD at 4 years

DFSP-FS, dermatofibrosarcoma protuberans-fibrosarcomatous; AWOD, alive without disease; ND, not done; UNK, unknown; HPF, high-power fields.

Nine (9/13, 69%) cases had positive margins, three (3/13, 23%) had negative margins <2.0 cm, and one case (1/13, 7.6%, case 1) had negative margins ≥2.0 cm (Fig. 1). Histologically, most tumors presented at least focal conventional DFSP consisting of a bland spindle cell proliferation, storiform architecture, and CD34 positivity. All cases displayed significant increased mitotic activity of ≥5/10 HPF up to 52/10 HPF. Eleven of 12 DFSP-FS were at least focally positive for CD34 with variable intensity. The fibrosarcomatous component comprised ≥75% in seven tumors, 50–74% in three tumors, 49–25% in two tumors, and ≥24% in one tumor.

Adjuvant chemotherapy or radiation was additionally utilized in five patients (Table 2). Case 1 metastasized to the groin at 11 months and recurred at the original site at 20 months despite wide excision and chemotherapy (one cycle of doxorubicin plus ifosfamide after resection and two cycles after metastasis) (Fig. 2a–f). Case 6 involved the margins of the primary excision and was re-excised with negative margins. However, the tumor eventually recurred at 38 months (Fig. 3a–d). Twelve patients are currently alive and disease free with a follow-up of 10 months to 16 years. One patient is alive, but tumor status remains unknown.

PDGFβ alterations were present in eight DFSP-FS and one metastatic deposit by FISH analysis (Fig. 4a). The *PDGFβ* gene rearrangements and/or copy number gains were present in 7/8 cases. Case 12 showed apparent monosomy of chromosome 22 (Fig. 4b). Cytogenetic studies were also performed in the metastatic tumor in case 1, confirming t(17;22) with gains in 1p22, trisomies 7, 8, 17, 22, and the presence of a marker chromosome (Fig. 5).

Discussion

DFSP-FS has been regarded as a more aggressive tumor with a higher risk for recurrence and metastasis.[7,8] A recent meta-analysis which included 1422 DFSP and 225 cases of DFSP-FS showed that DFSP-FS had a higher recurrence rate of 29.8% compared to 13.7% of DFSP.[7] Metastasis (14.4% vs. 1.1%) and mortality (14.7% vs. 0.8%) rates were equally increased.[7] In our cohort, the recurrence rate was 15.4% and the metastatic rate 7.7%, both less than the values in the meta-analysis but limited because of the small number of cases studied. It is important to note that case 1 metastasized even though margins were ≥2.0 cm from tumor and one cycle of chemotherapy was given post surgery. Unfortunately, the chemotherapy in this case was discontinued early because of intolerance. The presence of additional chromosome aberrations is consistent with tumor progression in this case. Also, case 6 recurred 38 months later despite documented negative margins. The subtle pattern of infiltration and sampling errors contribute to this phenomenon. In addition, location of tumors in difficult regions may not be amenable to wide excision. Nevertheless, mortality rates compared to other high-grade sarcomas are lower, and patients have a

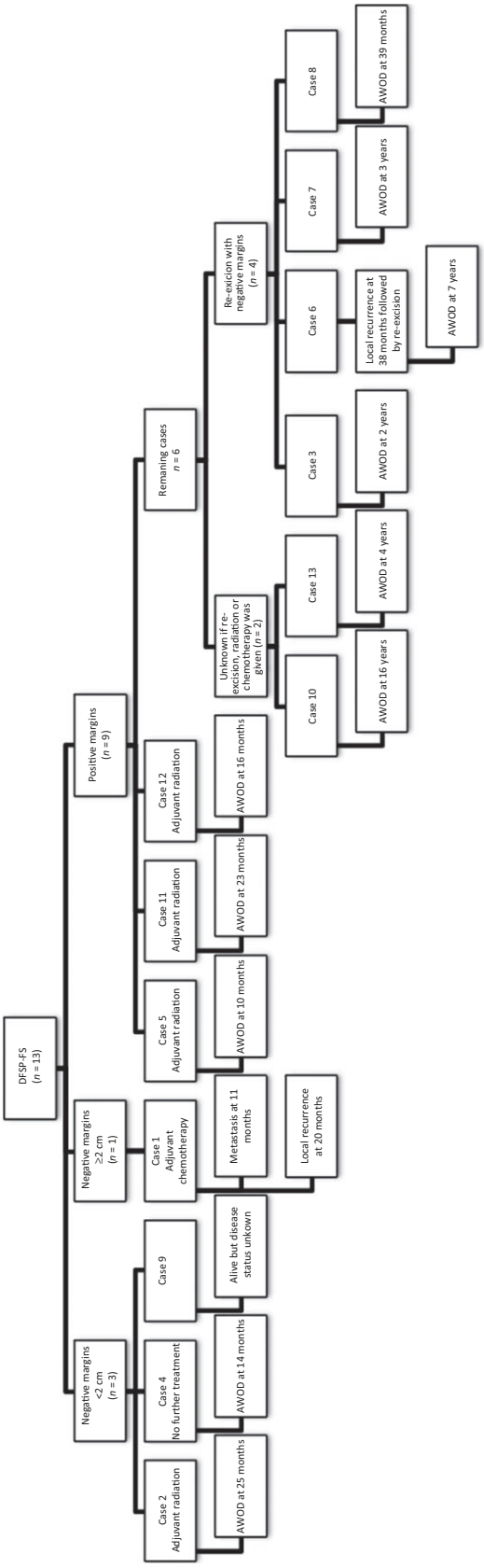

Figure 1 Results flowchart

Table 2 Specific treatment protocols

Case	Additional treatment	Comments
1	Adjuvant chemotherapy 1 cycle of adriamycin and ifosfamide after first resection 2 cycles of adriamycin and ifosfamide after resection of metastasis	Discontinued after poor tolerance and compliance
2	Adjuvant radiation 60 Gy in 30 fractions using a 12 MeV beam	Given due to close margins
5	Adjuvant radiation 66 Gy in 33 fractions using a 6 MV beam	Given due to positive margins
11	Adjuvant radiation 55 Gy in 20 fractions using a 6 MV beam	Given due to positive margins
12	Adjuvant radiation 40 Gy in 10 fractions using a 9 MeV beam	Given due to positive margins

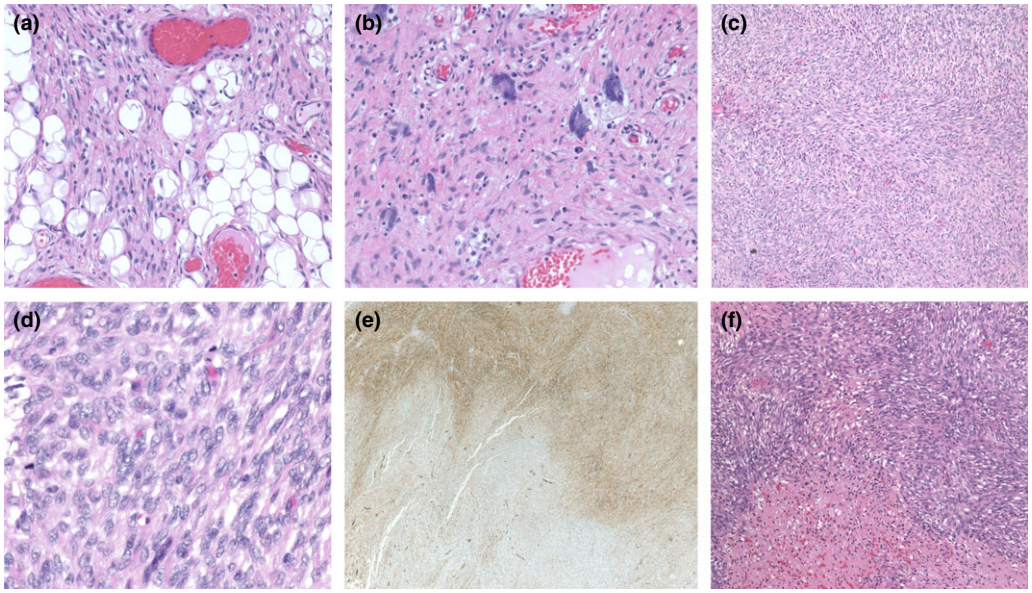

Figure 2 Case 1. Conventional DFSP was seen in the periphery of the lesion (a, H&E, ×200). Giant cell fibroblastoma-like areas were present adjacent to conventional low-grade areas (b, H&E, ×200). DFSP-FS showed a herringbone architecture (c, H&E, ×100) and increased mitotic activity (d, H&E, ×400). Patchy CD34 positivity (e, H&E, ×40). Metastasis contained only DFSP-FS (f, H&E, ×100). DFSP, dermatofibrosarcoma protuberans; FS, fibrosarcomatous

higher chance of prolonged survival. A recent large study addressed survival in patients with dermatofibrosarcoma protuberans using the national cancer database.[9] In this study, positive margins and "poorly differentiated" or "anaplastic" histology had an increased risk of mortality, whereas tumor size did not impact survival.[9] None of the patients in our small cohort died of disease. Some authors argue that the increased rates of recurrence and metastasis are caused by incomplete or marginal excision.[6,10] Goldblum *et al.* analyzed 18 cases of DFSP-FS treated with wide local excision of which only 21% (4/18) recurred and none metastasized.[6] Although not a large sample, this is a very important observation. Leaving tumor behind could account for a portion of the increased recurrence and metastatic rates but not all, as seen with case 1.

Liang *et al.* also observed that there was no significant difference in outcome based on percentage of DFSP-FS.[7] In this meta-analysis, fibrosarcomatous percentage as low as 5% was observed to result in metastases and death.[7] In another study, there was no significant difference between DFSP and DFSP-FS in the frequency of muscle or bone involvement.[11]

The initial treatment of choice remains wide local excision with 2.0 cm margins for both DFSP and DFSP-FS.[12] Mohs micrographic surgery could be used, but the current literature has not proven it is a superior treatment modality compared to wide local excision for DFSP or DFSP-FS, and it currently only holds a weak recommendation as first-line treatment as a result of the limited and low quality of evidence available.[13] Because of the infiltrative nature of this tumor, it may be difficult for the surgeon

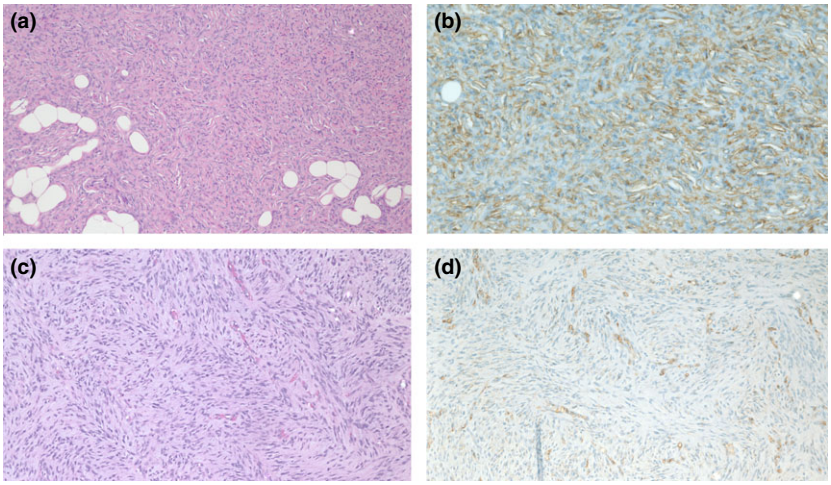

Figure 3 Case 6. Low-grade spindle cell areas with storiform pattern (a, H&E, ×100) and CD34 positivity (b, ×200). Fibrosarcomatous transformation (c, H&E, ×100) with CD34 loss (d, ×100)

to obtain a wide margin, especially in locations with proximity to critical structures. Most cases with positive or close margins at our institution receive a prompt re-excision followed by chemotherapy and/or radiation to reduce the likelihood of recurrence and metastasis. DFSP is a radioresponsive tumor that can be treated with pre- or postoperative radiation to achieve tumor reduction or local control.[14–17] Castle *et al.* published a large series of 53 cases of DFSP treated with radiation and showed that adjuvant radiotherapy should be considered in patients when surgery is not an option and on large or recurrent tumors.[17] In the same study, fibrosarcomatous transformation did not show increased risk of recurrence after treatment with surgery and radiation as compared to DFSP, supporting that radiotherapy lowers recurrence risk.[17] Thus, radiotherapy should be considered in DFSP-FS cases as previously stated by Mentzel *et al.*[8] Of note, the median dose for postoperative radiation was 60 Gy, similar to our median dose of 57.5 Gy (range, 40–60 Gy).[17] In addition for patients with metastasis or inoperable tumors, tyrosine kinase inhibitor imatinib, which works against the receptor for *PDGFβ*, has been approved as first-line treatment.[18] However, its use may be subjected to confirming the presence of the translocation or fusion protein with ancillary studies and that DFSP-FS may show limited response and resistance to treatment.[18–21] The use of other tyrosine kinase inhibitors in DFSP is at the moment very limited and needs further research.

The *PDGFβ* gene rearrangements combined with copy number gains involving chromosome 22 were present in the majority of DFSP cases in our cohort, supporting the diagnosis. DFSP tumors with monosomy 22 are rare, although they have been described previously in cases that contained a supernumerary ring or marker chromosome comprising the *COL1A1-PDGFβ* fusion gene and a single normal chromosome 22.22. However, in our patient with monosomy 22, FISH was negative for a break apart rearrangement of the *PDGFβ* gene. This finding may indicate a cryptic alteration within *PDGFβ* locus or possibly because of secondary chromosome changes such as loss of an aberrant chromosome during mitosis.

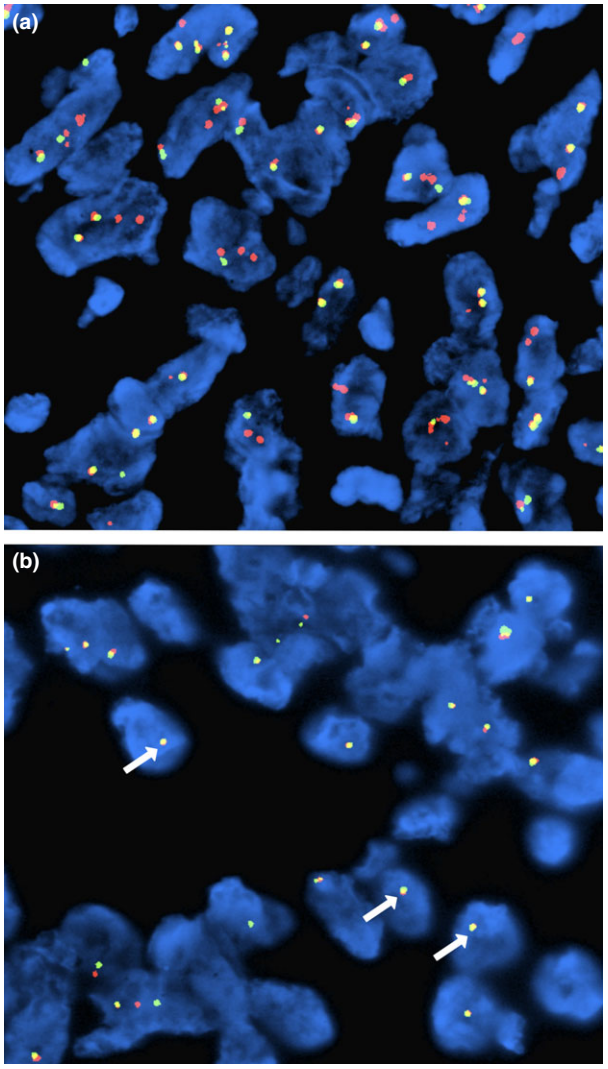

Figure 4 Case 4, *PDGFβ* break apart probe showing copy numbers alterations. (b) Case 12 showing monosomy of chromosome 22

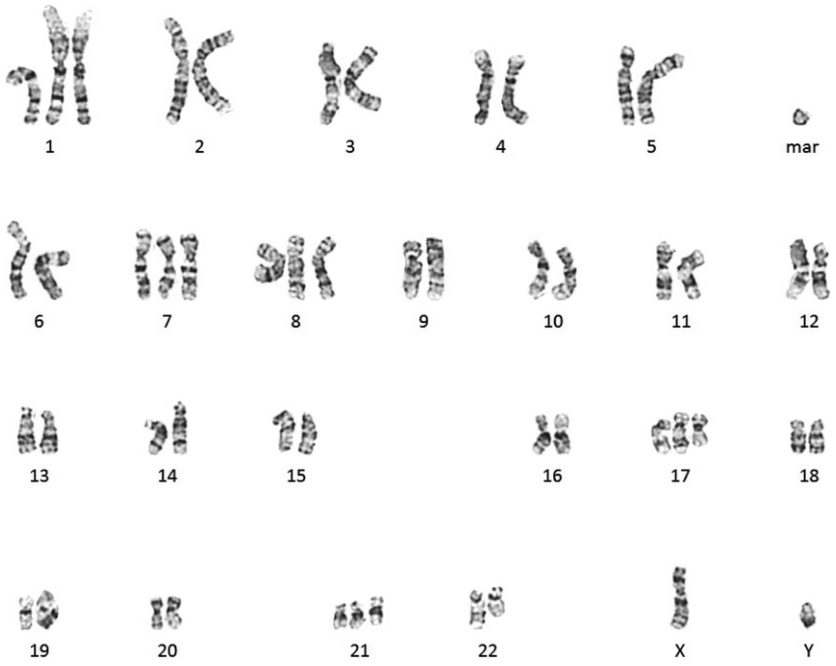

Figure 5 Abnormal karyotype observed in case 1. Cytogenetic analysis showed an extra copy of an abnormal chromosome 1 with chromatin of undetermined origin attached to the short arm, resulting in over-representation of 1q; trisomies 7, 8, 17, and 21; a translocation between the long arms of chromosomes 17 and 22, along with two normal copies of 17, resulting in trisomy 17; and a small marker chromosome. Tumor karyotype was designated as 51~53, XY,+add(1)(p22), +add(1)(p22),dup(5)(pter->p13::q13->q11.2::p11.1->qter),+del(5)(q13q33),+7,+8,+17, t(17;22)(q22;q13),+21,+mar[cp10]/46,XY[2]

In conclusion, our findings are consistent with recent evidence that fibrosarcomatous areas impact recurrence rates, metastatic rates, and survival. Wide local excision continues to be the gold standard of treatment, and additional therapy such as radiation and chemotherapeutic agents should be considered on an individualized basis. Monosomy 22 may be encountered in FISH analysis for DFSP-FS cases and may indicate a hidden *COL1A1-PDGFβ* gene rearrangement.

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