

Multiple primary dermatofibrosarcoma protuberans tumors in a single patient with chromosomal microarray analysis: A case report and review

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Abstract

Dermatofibrosarcoma protuberans (DFSP) is a cutaneous sarcoma with a high propensity for local invasion and recurrence. Although it is a rare event, the occurrence of multiple tumors in a single patient raises a diagnostic dilemma, as metastatic disease should be differentiated from multiple primary malignant events. In more than 90% of DFSP, a pathogenic t(17;22) translocation leads to the expression of COL1A1::PDGFB fusion transcripts. Karyotype analysis, fluorescence in situ hybridization, and RT-PCR can be useful ancillary studies in detecting this characteristic rearrangement, and sequencing of the fusion transcript can be used to support a clonal origin in metastatic and multifocal disease. However, previous reports have demonstrated variable sensitivity of these assays, in part due to the high sequence variability of the COL1A1::PDGFB fusion. Here, we report a patient who developed two distinct DFSP tumors over the course of 7 years. Chromosomal microarray analysis identified distinctive genomic alterations in the two tumors, supporting the occurrence of multiple primary malignant events.

KEYWORDS

array-based CGH, dermatofibrosarcoma protuberans, multiple primary

1 | INTRODUCTION

Dermatofibrosarcoma protuberans (DFSP) is the most common cutaneous sarcoma, thought to be of fibroblastic differentiation.¹ DFSP most often presents as a slow-growing, multinodular, cutaneous mass in middle-aged adults.¹ This tumor is composed of minimally pleomorphic spindle cells that diffusely infiltrate the subcutaneous fat. Although metastasis is rare, DFSP is locally aggressive, and tumors are typically several centimeters in size at the time of diagnosis.^{2,3}

Excision with wide margins or Mohs micrographic surgery has been advocated to achieve local control.^{4,5} Approximately 15% of DFSPs occur on the head and neck, and the approach to positive surgical margins is important in sites of functional importance, including re-excision or adjuvant radiation therapy.⁵ Moreover, DFSP can undergo fibrosarcomatous transformation in 3%–20% of cases, with associated higher rates of metastasis and local recurrence.⁶

The well-characterized molecular features of DFSP include a pathogenic t(17;22)(q22;q13) translocation, leading to the expression

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of *COL1A1::PDGFB* fusion transcripts in approximately 96% of tumors.^{1,7,8} The secreted fusion product is thought to drive autocrine and paracrine activation of the PDGFB signaling pathway, which is mitogenic in fibroblasts.² Accordingly, the overexpression of *PDGFB* transcripts, as measured by RNA chromogenic in situ hybridization, is highly sensitive and specific for DFSP.⁹ Of the approximately 4% of DFSPs that are negative for *COL1A1::PDGFB* fusions, most will have gene rearrangements involving *PDGFD*.^{7,8,10} Imatinib mesylate, which targets the PDGFB receptor, produces an objective response in more than half of patients, although complete responses are uncommon and eventual progression occurs after a median of 1.7 years.^{11,12}

The occurrence of multiple DFSPs in a single patient raises a diagnostic dilemma, as differentiating metastatic disease from multiple independent tumors will influence management. The occurrence of multiple DFSPs may be sporadic,^{13,14} associated with pregnancy,¹⁵ or occurring in the setting of hereditary cancer syndromes, including Li-Fraumeni and Lynch syndromes, as well as in adenosine deaminase-deficient severe combined immune deficiency (ADA-SCID).^{16–19} In several reports, sequencing or PCR analysis of the *COL1A1::PDGFB* fusion has proven useful.^{20,21} For example, in eight patients with ADA-SCID and multiple DFSPs, *COL1A1::PDGFB* sequencing found that individual tumors displayed distinct t(17;22) breakpoints, arguing for multiple primary malignant events in each patient.¹⁹ Conversely, the finding of identical breakpoints in tumors from different locations may suggest either cutaneous metastasis or a single oncogenic event, such as a somatic mutation during development, leading to multiple primary tumors.²² Although there is also the possibility of coincidental similarity in which unrelated tumors show identical fusion transcripts, the high variability of breakpoint positions in *COL1A1* makes this relatively improbable.²³

We report the case of a 48-year-old male who developed two DFSP tumors over 7 years. Chromosomal microarray analysis identified distinctive patterns of copy number variations in the two tumors, supporting multiple primary malignant events in this patient.

2 | CASE REPORT

A 48-year-old male presented to the dermatology clinic with a 6-year history of a “scar” on his left forehead, which slowly became more prominent. On examination, an ill-defined plaque containing multiple nodules and measuring 9 × 8 cm was present on the left forehead and scalp (Figure 1). After biopsy, pathologic examination showed a storiform-patterned spindle cell proliferation with “honeycombing” infiltration of the subcutaneous fat and extension into the skeletal muscle (Figure 2A, B), without evidence of fibrosarcomatous degeneration. By immunohistochemistry, the spindle cells were positive for CD34 and negative for S100, SOX10, and Factor XIIIa, supporting the diagnosis of DFSP. Definitive wide local excision with 1–2 cm margins was performed, with margins free on pathologic examination. He did well with no evidence of local recurrence. Seven years later, the patient returned to the clinic for follow-up, and a 1-month history of a



FIGURE 1 Primary dermatofibrosarcoma protuberans (DFSP) tumor on the scalp. (A) DFSP tumor with an ill-defined plaque containing multiple nodules, measuring 9 × 8 cm, which was present on the left forehead and scalp.

growth on his right shoulder was noted. A 1.1-cm pink plaque was biopsied, again revealing an infiltrative storiform spindle cell population (Figure 2C,D), without fibrosarcomatous changes. The tumor cells were positive for CD34 and negative for S100 and SOX-10 by immunohistochemistry. *PDGFB* RNA in situ hybridization was performed, which showed overexpression of *PDGFB*, supporting the diagnosis of DFSP (not shown). A CT scan of the chest, abdomen, and pelvis with contrast was negative for metastases or lymphadenopathy. Excision was performed with 2 cm margins, achieving histopathologic clearance.

Using single nucleotide polymorphism (SNP) microarray analysis, each tumor specimen was examined for copy number variations (Figure 3A–C). The tumor on the forehead revealed an area of complex copy gain of chromosome 17, including a 30 Mb high-level copy number gain followed by a 2 Mb lower-level copy gain, together spanning from 17q21.33 (at the site of the *COL1A1* gene) to 17q25.3, consistent with a *COL1A1* breakpoint (Figure 3B). Chromosome 22 showed a 19.4 Mb copy number gain spanning 22q21.1 to 22q13.1 (ending at the site of the *PDGFB* gene) and 11.5 Mb loss involving 22q13.1 to 22q13.3, consistent with a *PDGFB* breakpoint (Figure 3C). Gains of chromosome 3 and 18 were also noted. The second tumor, from the shoulder, harbored a 31 Mb copy number gain from 17q21.33 to 17q25.3 and a 23.5 Mb copy number gain from 22q13.1 to q13.3 segments, involving the *COL1A1* and *PDGFB* genes, respectively (Figure 3B,C). The tumor from the shoulder displayed different patterning and amplitude of copy number gains on chromosomes 17 and 22, and lacked the copy number loss at 22q13 observed in the tumor from the forehead. Furthermore, the tumor from the shoulder lacked gains of chromosomes 3 and 18, instead displaying a gain of chromosome 11 not observed in the first tumor (Figure 3). The results did not allow for the 1-kb resolution required to determine the precise intronic positions of the breakpoints in the *COL1A1* and *PDGFB* genes in either case.

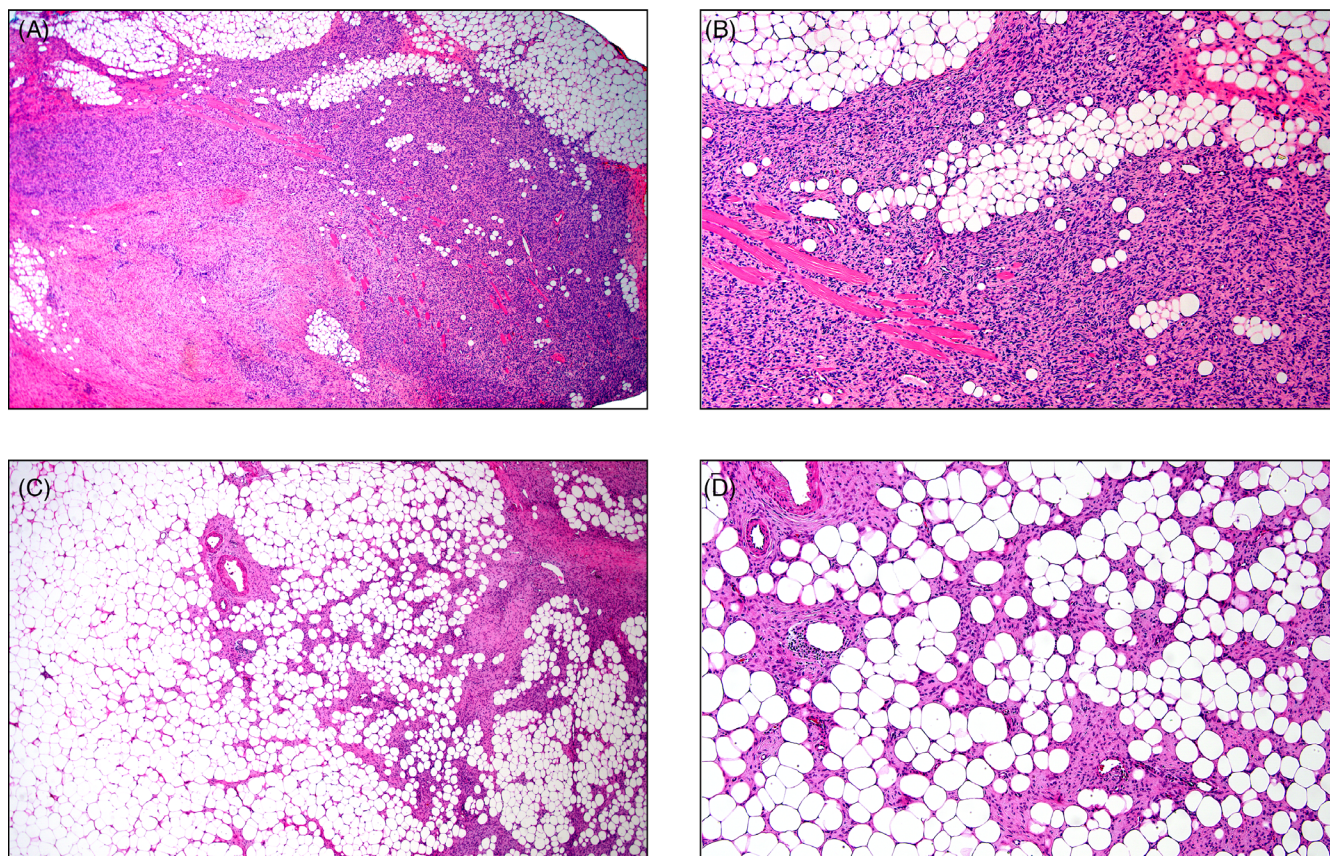


FIGURE 2 Histopathologic features of the dermatofibrosarcoma protuberans (DFSP) tumors. (A) Forehead tumor: spindle cell proliferation with storiform growth and honeycomb infiltration of adipose tissue. (B) Forehead tumor: hyperchromatic, relatively monomorphous spindled cells. (C) Shoulder tumor: spindle cell proliferation dissecting through adipose tissue. (D) Shoulder tumor: classic cytomorphology of DFSP, with relatively monomorphous spindled cells. All panels: hematoxylin and eosin stain. Magnification: $\times 40$ (A, C), $\times 100$ (B, D).

3 | DISCUSSION

The development of multiple DFSP tumors in a single patient is a rare event, although in selected populations, such as those with hereditary cancer syndromes and immunodeficiency, the risk may be higher. When multiple DFSPs do occur, the distinction between metastatic disease, a single multifocal process, or multiple independent tumors is an important question with implications for management. In previous reports, *COL1A1::PDGFB* fusion transcript sequencing or PCR analysis had proven useful in resolving this issue.^{20,21} Molecular confirmation of the *COL1A1::PDGFB* fusion may also be useful in differentiation from histologic mimics of DFSP, such as NTRK-fusion sarcomas (often with CD34+/S100+/SOX10− phenotype), which can behave in an aggressive manner.^{24–26} Here, we describe chromosomal microarray analysis as a useful ancillary study in evaluating multiple DFSPs. A chromosomal microarray is used to detect copy number variations (CNVs) within chromosomes. A CNV is a structural change in a segment of a chromosome such that the copy number of a particular segment of DNA differs from a reference genome. Small (<10 kb) CNVs may be inherited and are common in the general population, whereas larger variations are rare and more likely to be associated with disease.²⁷ Chromosomal microarrays do not specifically identify

rearrangements associated with gene fusions; however, CNVs with an endpoint involving the body of a gene may be consistent with a chromosomal rearrangement at that site. Notably, in many or all cases, DFSPs display aberrations (usually gains) of chromosome arms 17q and 22q, detectable by chromosomal microarray.^{28–30} In this patient, both tumors showed high copy number gains with endpoints corresponding to the *COL1A1* (located at 17q21.33) and *PDGFB* (located at 22q13.1) breakpoint regions. However, the specific CNVs differed between the two tumors, implicating different genetic events leading to the observed breakpoints of each gene. This is further supported by the differing copy number states of chromosomes 3, 11, and 18 between the tumors. These different genetic signatures imply unique genetic events leading to separate primary tumors. Fusion-driven sarcomas including DFSP can display complex clonal evolution, although the driver fusion event is conserved.³¹ Notably, increased genomic copy number of the *COL1A1::PDGFB* locus and deletion of 22q13-ter have been reported in association with fibrosarcomatous transformation of DFSP.^{32,33} In our case, the finding of two histopathologically low-risk lesions without risk factors for metastasis (e.g., fibrosarcomatous degeneration), no internal involvement by imaging, and different genetic signatures on microarray argues for the occurrence of two independent tumors.

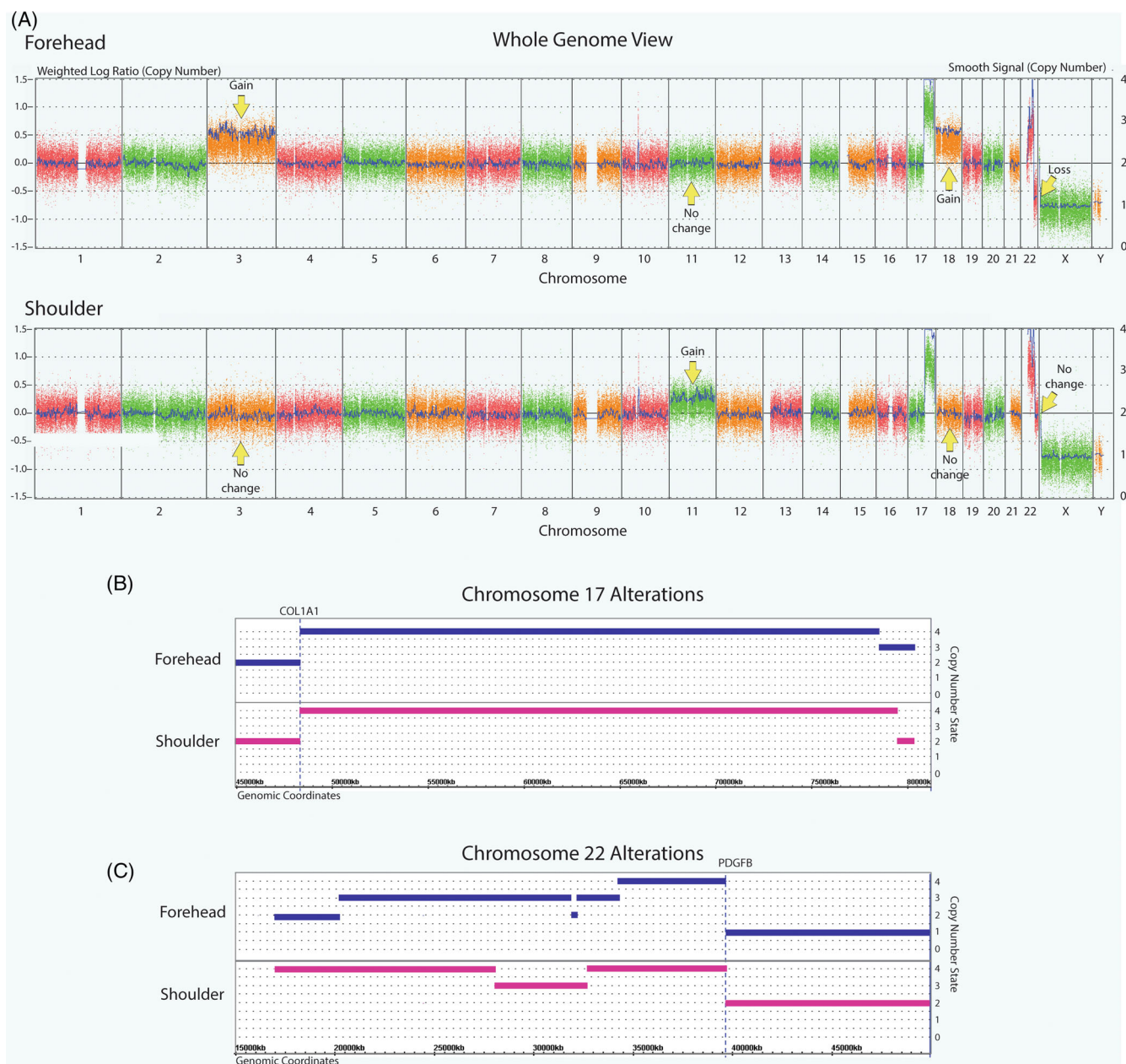


FIGURE 3 Single nucleotide polymorphism microarray analysis. (A) Whole genome comparison of dermatofibrosarcoma protuberans tumors, showing distinctive patterns of whole chromosome gains (chromosomes 3, 11, and 18) between the tumors, and a region of chromosome 22 loss in the forehead tumor that is not observed in the shoulder tumor. (B) Chromosome 17 alterations in tumor from forehead (upper blue track) and shoulder (lower pink track). Both tumors display chromosomal gains that begin at the site of COL1A1 (vertical dashed line), consistent with rearrangement of this gene, but with different endpoints. (C) Chromosome 22 alterations in tumor from forehead (upper blue track) and shoulder (lower pink track). Both tumors display chromosomal gains that end at the site of PDGFB (vertical dashed line), consistent with rearrangement of this gene, but with an additional 22q13-ter hemizygous loss in the forehead tumor that is not detected in the tumor from the shoulder.

The use of chromosomal microarray analysis may have some advantages over other molecular techniques for evaluating DFSP, especially in cases of multiple tumors or those with uncommon gene rearrangements. The traditional techniques of karyotype, fluorescence in situ hybridization (FISH), and RT-PCR can detect the t(17;22) rearrangement in most cases. In one study, 9 out of 20 DFSP lesions were positive for COL1A1::PDGFB fusions by RT-PCR.¹⁹ Of the 11 tumors with negative or non-informative RT-PCR, 4 were confirmed to have

the characteristic fusion by FISH.¹⁹ The divergent results with RT-PCR and FISH may relate to the high sequence variability of the COL1A1::PDGFB fusions, leading to discordance with the available primer sets. In a study of 172 DFSPs, breakpoint positions were noted in 38 different exons of COL1A1, suggesting very high sequence variability.³⁴ Multiplex RT-PCR using a panel of 18 COL1A1 forward primers has high sensitivity in evaluating DFSP, but the assay is complex to perform, and amplifiable RNA cannot always be isolated.^{23,35}

Using a DNA-based SNP microarray, however, allows for the detection of chromosomal rearrangements while avoiding the dependence on a small custom primer set. In our case, a limitation of the SNP array was the lack of the fine resolution required to identify the specific introns/exons involved in the rearrangement. An additional potential limitation of the SNP array is that a truly balanced rearrangement (not associated with an adjacent CNV) would not be detected; however, previous reports suggest that most DFSPs have detectable CNVs associated with the t(17;22) rearrangement.^{28–30}

Beyond identifying copy number changes suggestive of the t(17;22) rearrangement, SNP microarrays can detect gains, deletions, or allelic imbalances affecting other chromosomes. Such additional chromosomal copy number aberrations are frequently found in DFSPs,^{28–30} although the specific chromosomes involved vary from one tumor to another. In our case, these additional CNVs provided further support that the tumors were unrelated. In addition, some copy number changes detected by SNP array may have therapeutic importance. Deletion of the *CDKN2A* locus on 9p, for example, has been detected in DFSP using SNP microarrays and, at least in small series, this loss is more common in high-grade lesions or those with fibrosarcomatous transformation.^{33,36,37} In the future, the finding of a *CDKN2A* deletion may identify lesions that are likely to respond to a CDK4 inhibitor.³⁷

Overall, our findings suggest that chromosomal microarray analysis deserves further consideration as an ancillary test in patients with multiple DFSP lesions. This technique may be a useful supplement to the traditional methods of karyotype, FISH, and RT-PCR.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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