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A dermatofibrosarcoma protuberans-like tumor with COL1A1 copy number gain in the absence of t(17;22)

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Abstract

A 57 year-old woman presented with a three year history of a progressive firm plaque on the right cheek. Skin biopsies revealed a bland, storiform, spindle cell proliferation involving the deep dermis and subcutaneous fat. By immunohistochemistry the tumor cells were diffusely positive for CD34 and caldesmon with multifocal reactivity for EMA and focal, weak staining for SMA. Retinoblastoma protein expression was not detectable in tumor cells by immunohistochemistry. An interphase FISH analysis for *PDGFB* gene rearrangement was negative. A SNP-array study detected 1) a gain of chromosome segment 17q21.33-q25.3 which overlapped the entire *COL1A1* gene with a breakpoint at 17q21.33, approximately 250 Kb centromeric to the 3' end of *COL1A1* gene, 2) several segmental gains on chromosome 11 and 3) an *RBI* gene locus with normal copy number and allele frequency. While the current case resembles DFSP, it is unique in that it demonstrates a copy number gain of chromosome 17q in the absence of fusion of *COL1A1* and *PDGFB* genes and an unusual immunohistochemical staining profile. The morphologic and molecular findings suggest a novel molecular variant of DFSP not detectable with standard FISH for *PDGFB* rearrangement. This variant appears to respond to imatinib after 9 months of follow-up.

Keywords

COL1A1; (CNG) copy number gain; dermatofibrosarcoma protuberans

INTRODUCTION

Dermatofibrosarcoma protuberans (DFSP) was first described by Darier and Ferrand in 1924 (1) and is considered to be a low to intermediate grade fibrohistiocytic neoplasm (2). It

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presents most commonly in young to middle-aged adults as a plaque-like or nodular mass of the trunk or proximal extremities, and less commonly in the head and neck region (3, 4). Clinically, DFSP is characterized by locally aggressive growth with a high propensity for local recurrence (5). Microscopically, the tumor consists of a population of uniform bland spindled cells with a prominent storiform growth pattern, extending along and expanding connective tissue septa and infiltrating and entrapping adipose tissue (3).

The major cytogenetic and molecular features of DFSP have been characterized. Most adult tumors demonstrate supernumerary ring chromosomes containing sequences from chromosomes 17 and 22 and less commonly from chromosome 8 (6–13). The linear translocation derivative t(17;22)(q22;q13) is another characteristic cytogenetic finding that is more commonly encountered in the pediatric setting (14). The mechanism responsible for the oncogenic potential of these alterations is secondary to the fusion of exon 2 of platelet-derived growth factor B-chain gene (*PDGFB*) to one of several possible exons of the collagen type 1 $\alpha 1$ gene (*COL1A1*). The chimeric *COL1A1-PDGFB* consists of 5' *COL1A1* and almost the entire coding sequence of *PDGFB*, and is under the regulation of the strong promoter from *COL1A1*. As such, the fusion results in increased PDGFB production, activation of PDGF receptor β (PDGFRB) and cell proliferation (15, 16). The activation of PDGFRB forms the basis for using targeted therapy with imatinib mesylate (17, 18).

Not all DFSPs exhibit the classic cytogenetic findings; it is estimated that 8% of cases are fusion-negative, potentially harboring cryptic rearrangements of the *COL1A1* and *PDGFB* genes. Alternatively, unrelated genetic abnormalities may be responsible for driving tumorigenesis in this subset of tumors (3). Herein, we report a tumor with DFSP-like morphology and unusual immunohistochemical and molecular findings, likely representing a novel molecular variant of DFSP.

CASE REPORT

A 57 year-old previously healthy woman presented with a three year history of a progressively enlarging, firm 5 × 4 cm plaque of the right cheek (Figure 1). Two skin biopsies were performed and revealed a bland, storiform, spindle cell proliferation involving the deep dermis with extension into and expansion of the fibrous septations of adipose tissue in a honeycomb fashion. A fascicular growth pattern was not identified. The tumor cellularity was uniformly low and mitoses were scarce. The tumor was diffusely positive for CD34 and was negative for S100. A diagnosis of atypical spindle cell neoplasm most consistent with low-grade sarcoma resembling DFSP was rendered. Computed tomography (CT) and magnetic resonance imaging (MRI) of the head and neck revealed an enhancing right cheek mass involving the subcutaneous tissue without extension into skeletal muscle or bone. Regional lymphadenopathy was not identified.

A 1.4 × 1.1 × 0.6 cm incisional biopsy was performed to further define the neoplasm and revealed the aforementioned intradermal and subcutaneous spindle cell proliferation (Figure 2). An expanded battery of immunostains was performed and showed diffuse positivity with CD34 and caldesmon, multifocal reactivity for EMA and focal weak positivity for SMA.

Immunostains for desmin, S100, Sox10 and Melan-A were negative. In addition, there was loss of immunostaining for retinoblastoma (RB) protein (Figure 3). Interphase fluorescence in situ hybridization (FISH) analysis utilizing SPEC *PDGFB* break-apart probe (Zytovision) was negative for gene rearrangement. Interphase FISH analysis for copy number changes of *CDK4* (Agilent) was also negative. Single nucleotide polymorphism (SNP)-array-based DNA copy number and allelic imbalance analysis detected a gain of chromosome segment 17q21.33-q25.3 which overlapped the entire *COL1A1* gene. The breakpoint at 17q21.33 was approximately 250 Kb centromeric to the 3' end of *COL1A1* gene. Additional findings on SNP-array included segmental gains on chromosome 11, involving 11p15.4-p13, 11p13-p12 and 11p11.2-q12.1 (Figures 4 and 5). The *RBI* gene locus (13q14.2) showed a normal copy number and allele frequency.

After multidisciplinary consultations and tumor board discussions, the decision was made to initiate imatinib therapy as surgical resection was likely to result in significant functional and aesthetic morbidity. The patient was started on 400 mg of imatinib and follow-up MRI scans two months and six months later revealed a decrease in the size of the right cheek mass. The patient is clinically and radiographically responding to imatinib at nine months follow-up without side effects and continued treatment is planned (Figure 6).

DISCUSSION

The cytogenetic hallmarks of DFSP include fusions of *COL1A1* and *PDGFB* as a result of t(17;22)(q21;q13), and commonly in the setting of supernumerary ring chromosomes containing a combination of sequences derived from chromosomes 17 and 22 (6–8, 12). The *COL1A1* gene located on 17q21.33 codes for type 1 collagen, the main structural protein of connective tissue. Type 1 collagen is a heterotrimer composed of two $\alpha 1$ chains and one $\alpha 2$ chain (19). *PDGFB* is encoded by the *PDGFB* gene (22q13.1), forms homodimers or heterodimers with other PDGF polypeptide chains and binds and activates PDGFRB tyrosine kinase. PDGFB is a potent mitogen, stimulating growth, division and motility of cells, specifically cells of mesenchymal origin. (20, 21). Multiple studies have shed light on the pathobiology of the t(17;22)/*COL1A1*-*PDGFB* in DFSP, particularly in relation to the relative contributions of *COL1A1* and *PDGFB* to the transforming potential of the chimeric gene. The chimeric *COL1A1*-*PDGFB* consists of 5' *COL1A1* and all coding exons of *PDGFB* except exon1 which houses negative regulators of transcription. Therefore, the chimeric gene is under the control of the strong promoter from *COL1A1* which increases the production of PDGFB and activates PDGFRB signaling pathway in corresponding cells (12, 14, 22–24).

The variability of the fusion points between *COL1A1* and *PDGFB* is mostly due to *COL1A1* sequence size variation. The break points in *COL1A1* occur within the α -helical coding region spanning exons 7 to 47. In contrast, the fusion point in *PDGFB* appears to be highly conserved to exon 2, resulting in the synthesis of a mature PDGFB protein (12, 15, 25–30). As a result, it has been suggested that the role of *COL1A1* in the transforming activity of *COL1A1*-*PDGFB* may be limited to mediating the export of the chimeric protein product (22–24).

While most reports emphasize the importance of *COL1A1-PDGFB* gene fusion in the pathogenesis of DFSP, some also raise the possibility that subsets of DFSP may utilize additional drivers of tumorigenesis such as in tumors arising in the context of uncommon structural and numerical cytogenetic abnormalities (3). Mrózek et al. and Maire et al. reported a case of recurrent DFSP with a large marker chromosome showing fusion of *COL1A1* with *PDGFB* as well as segments from chromosomes 7, 8, and 21 (29, 31). Supernumerary ring chromosomes derived from chromosome 4 have also been shown to harbor *COL1A1-PDGFB* gene fusions (32). Amplified *COL1A1* and *PDGFB* sequences have been identified in DFSP with a ring chromosome 5 and a marker chromosome composed of chromosomes 12q and 22 (33). Other cytogenetic findings include supernumerary ring chromosomes composed of chromosomes 17 and 22 sequences co-occurring with trisomy 5 and 8 (6, 7) or trisomy 8 (34, 35). Trisomy of chromosomes 4, 7, 11, 12, 13, 14, 15, 16, and 18 has also been observed (14). Finally, variant translocations including t(2;17), t(X;7) and t(9;22) have been reported in DFSP, however, the investigative methods utilized in the latter reports were restricted to cytogenetic analysis and therefore, could not rule out concomitant cryptic rearrangements involving *COL1A1* and *PDGFB* genes (36–38).

The *COL1A1-PDGFB* fusion may not be the sole mediator of tumorigenesis in DFSP. A second proposed mechanism involves activation of discoidin domain receptors (DDR) I and II (22, 23). DDRs normally function as tyrosine kinase receptors and regulate several cellular functions including proliferation, migration and extracellular matrix remodeling (39). Activation of DDRs occurs after binding different types of collagen, including type I collagen (40, 41). Overexpression of DDRs 1 and 2 has been reported in certain malignancies suggesting a role in driving neoplasia (42–44). This becomes particularly relevant in DFSPs since significant quantities of collagen-like components have been identified in the extracellular matrix of DFSPs harboring the *COL1A1-PDGFB* fusion. The collagen is produced during the processing of the chimeric protein into PDGFB dimers and is predominantly composed of the N-terminal collagen fragment of the chimeric *COL1A1-PDGFB* protein (22–24).

In the current case, SNP-array detected a partial gain of chromosome 17q which overlapped the entire *COL1A1* gene. This finding is unique as it is not supportive of gene fusions as would be expected with *COL1A1-PDGFB* where the gain of 17q would start from a point within the *COL1A1* gene. Gain of *COL1A1* may therefore result in excessive production of collagen-like components thereby activating an alternative mechanism of tumorigenesis. This would also explain the patient's response to imatinib therapy as imatinib has been shown to inhibit collagen-induced DDR activation (45, 46). In addition, this tumor showed loss of RB expression despite normal copy number and allele frequency suggestive of epigenetic silencing, possible gene mutation or otherwise. Overall, the morphologic and molecular findings suggest a novel molecular variant of DFSP that is not detectable with standard FISH for *PDGFB* rearrangement. This variant appears to respond to imatinib based on nine months of follow-up.

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Figure 1. 5 cm indurated plaque of the right cheek at initial presentation. The overlying skin has a slightly irregular and nodular surface. Ink marks delineate the clinical extent of disease.

Figure 2.

Biopsy specimen revealing a dermal-based tumor ramifying through the deep dermis and extending in a honey-comb fashion into the subjacent adipose tissue (A); H&E, 20X. The infiltrate assumes an irregular and whorled pattern, is of low cellularity, expands the fibrous septa and entraps adipocytes (B); H&E, 200X. A uniform array of spindled tumor cells with slender nuclei and intercellular collagen deposition is noted. Mitotic figures were scarce (C); H&E, 400X.

Figure 3.

Immunohistochemical stains reveal diffuse, intense positivity with CD34 (A), diffuse staining with caldesmon (B) and focal weak staining with EMA (C) and SMA (D). The tumor cells were negative for desmin (E). RB is positive in endothelial cells but negative in tumor cells (F); (A–F, 400X).

Figure 4. Affymetrix OncoScan whole genome view of copy number profiling and allele frequency, demonstrating gains on chromosomes 11 and 17. *RB1* (13q14.2) shows a normal copy number and allele frequency.

Figure 5.

SNP array analysis chromosome view: a gain of chromosome 17 segment 17q21.33-q25.3 which overlaps the entire *COL1A1* gene is noted (top panel). The breakpoint at 17q21.33 is approximately 250 Kb centromeric to the 3' end of *COL1A1* gene (bottom panel).

Figure 6.
The lesion demonstrates a decrease in induration and size six months after initiation of imatinib treatment.