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Original Article

COL1A1-PDGFB gene fusion in dermatofibrosarcoma protuberans: a useful diagnostic tool and clinicopathological analysis

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Abstract: The PDGFB gene is found at 22q12.3-q13.1, and the COL1A1 gene is located at 17q21.3-q22.1. If the COL1A1 gene of 17q21-22 is fused with the PDGFB gene of 22q13.1, then it forms a new COL1A1-PDGFB fusion gene, one that has been found in dermatofibrosarcoma protuberans (DFSP) and lasts for many years. The expression of PDGFB loses the regulation of upstream inhibitory factors and leads to the mass production of COL1A1-PDGFB chimeric mRNA under the initiation of COL1A1 sequence, a crucial factor in the development of DFSP. In our study, we retrospectively analyzed 2 cases: case 1 is a 25-year-old student with three surgical resections in his right lumbar region. Initially, his diagnosis (from another hospital in 2009) was vascular lymphangioma. When the disease recurred after 6 years, he went to our hospital and the diagnosis was giant cell fibroblastoma (GCF). Molecular pathology (using the fluorescence in situ hybridization, FISH) showed the COL1A1-PDGFB gene fusion, presented as the fusion of 3 or more red and green signals. In 2017, the patient had another recurrence of the disease, and he underwent a third surgical resection. The other case is a 51-year-old woman who had presented with pain in her left lumbosacral, accompanied by left buttock and left thigh numbness for 3 months. The diagnosis was DFSP, which also showed COL1A1-PDGFB gene fusion. Here we review the clinicopathologic features and differential diagnosis of this rare tumor, so that it can be better recognized.

Keywords: Dermatofibrosarcoma protuberans, recurrence, COL1A1-PDGFB gene fusion, differential diagnosis

Introduction

Dermatofibrosarcoma protuberans is a rare, indolent and slow-growing aggressive neoplasm of intermediate malignancy, which originates from the dermal layer of the skin. Accounting for 1.0%-2.0% of all soft tissue sarcoma and 0.1% of all tumors [1], DFSP always presents as a low-grade soft tissue neoplasm, which grows slowly but has a high rate of recurrence, especially after an insufficient surgical excision. According to its histological classification, DFSP can be divided into many subtypes: mucoid type, fibrosarcoma type, containing giant cell fibroblastoma type, atrophic type, sclerosing, granulocytic, and pigment type [2]. Darier and Ferrand first found this tumor in 1924, describing it as "progressive and recurring dermatofibroma," and one year later, Hoffman named it dermatofibrosarcoma protuberans [3]. Giant cell fibroblastoma, which originates from the dermis, has many clinical and histological features in common with DFSP, such as slow growth, and a high rate of recurrence. It is thought that GCF was a juvenile form of DFSP, but the karyotyping of GCF revealed that it is the same balanced or unbalanced translocations and additional ring chromosomes derived from chromosomes 17,22. At the molecular level, the transformational GCF changes of the chromosome resulting in molecular rearrangements are similar to DFSP, which leads to COL1A1-PDGFB gene fusion, and all these results show that GCF and DFSP have similar histological origins [4, 5]. In addition, many diseases have close relationships with PDGFB, such as idiopathic basal ganglia calcification (IBGC), breast cancer, rectum cancer, meninges tumor, nasopharyngeal carcinoma,

Table 1. Sources of the antibodies used in the immunohistochemistry analysis

Source	Antibody
CD34	Monoclonal, clone QBEnd/10
S-100	Monoclonal, clone 4C4.9
Bcl-2	Monoclonal, clone 8C8
CD99	Monoclonal, clone 9C01
Vimentin	Monoclonal, clone V9
SMA	Monoclonal, clone 1A4
Desmin	Monoclonal, clone D33
CK	Monoclonal, clone AE1/AE3
EMA	Monoclonal, clone E29
Calponin	Monoclonal, clone E29
Ki-67	Monoclonal, clone MIB-1

All antibodies were obtained from Maixin Biotech, Inc. (Fuzhou, China), and were ready to use.

infant hemangioma, retinopathy of prematurity, and so on.

Materials and methods

We studied 2 cases at the First Affiliated Hospital of Bengbu Medical College from September 2014 to December 2017. One case is a 25-year-old student who presented with a painless tumor in his right lumbar nine years ago and experienced two recurrences. The other case is a woman who presented with a 3-month-history of pain in her left lumbosacral accompanied by numbness in her left buttock and thigh. H&E-stained sections (4 μm thickness) were reexamined to evaluate the tumor's histological features and immunohistochemistry was performed with the Envision technique. Antibody details are given in **Table 1**. Clinical demographics and follow up data were obtained from medical records and from referring physicians.

Both evaluations were performed using the fluorescent in situ hybridization method (FISH) for molecular testing by using a dual-color dual-fusion COL1A1/PDGFB Fusion Translocation t(17;22) Probe (Anbiping, Guangzhou, China), which consists of 1 red GSP PDGFB probe and 1 green GSP COL1A1 probe. The red and green signals were fused, and it concluded as the COL1A1/PDFGB rearrangement.

This study was approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College and was conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

Results

Clinical features

Case 1: A 25-year-old student presented with a painless tumor in his right lumbar that had first been noticed nine years earlier, and there was no obvious discomfort during the whole progress of the disease. In 2009, the boy accepted his first resection in another hospital and was diagnosed with vascular lymphoma. Six years later, because of the mass recurrence, he came to our hospital, this time, and the pathological diagnosis was giant cell fibroblastoma. To confirm the diagnosis, he was recommended for molecular testing. Molecular pathology showed a tendency to PDGFB gene-related translocation. A pattern of fusion-signal was captured, and the result was recognized as giant cell fibroblastoma. Except for enlarged surgical excision, he also accepted adjuvant radiotherapy. The back ultrasound showed that in the right side of the lower back there was an incision, between the skin and fat layer, explored 5.4 cm × 4.0 cm × 2.8 cm hypoechoic, which had a clear boundary, and it seemed to have a complete envelope and an irregular liquid dark area, and the echo was uneven. In 2017, a lump was found again in the surgical incision, and then he had surgery a third time. During the operation, we found that the diameter of the tumor was about 4.0 cm, and it was located on the spine on the right erector spinae muscles superficial, and the envelope was still intact, and the texture was soft. Around the mass, there was the surgical area of the scar adhesion, the resection of the tumor was complete, around the normal tissues and the base department to the deep muscle fascia. Intraoperative frozen pathology of the surroundings and undercut margins were all negative.

Case 2: A 51-year-old woman presented in 2014 with a 3-month-history of pain in her left lumbosacral, accompanied by numbness in her left buttock and thigh. A local computed tomography (CT) scan showed that the woman had a soft tissue mass in her left lumbosacral, and the size was about 4.8 cm × 4.5 cm × 4.2 cm. The tumor was discovered in the deep fascia of the back, and the border was irregular, which damaged the L5 and S1 vertebral plates. Also,

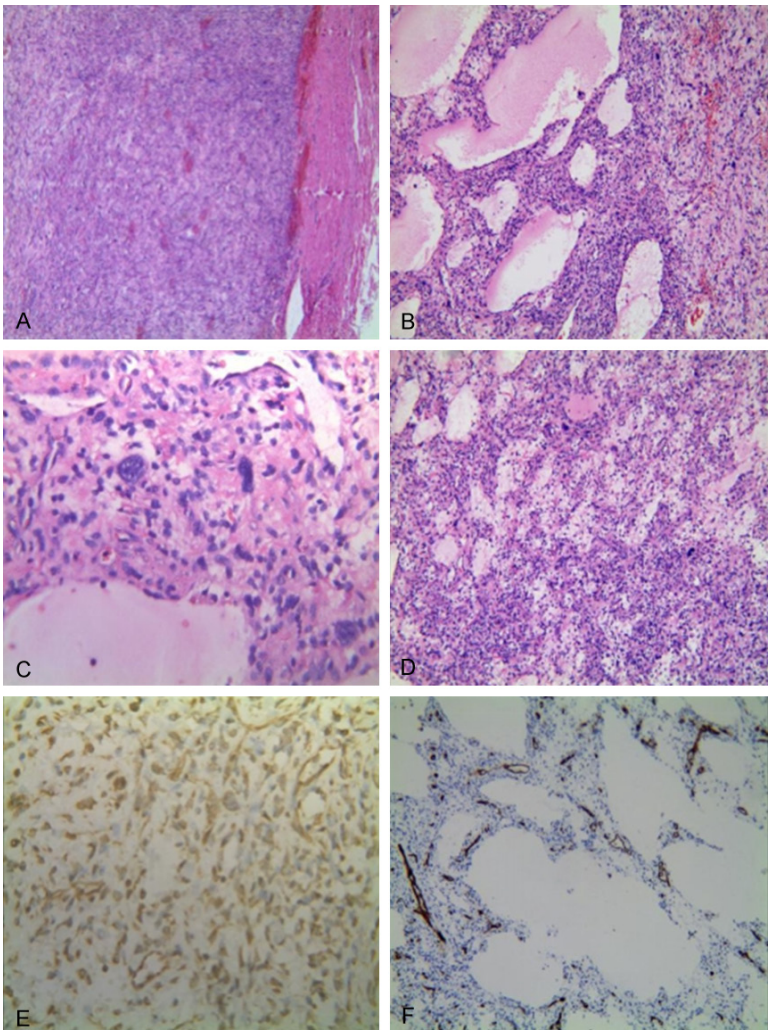

Figure 1. Histological and immunohistochemical features of case 1. A: The tumor located in the dermis layer (magnification, × 100). B: The tumors were composed of spindle cells and pseudo vascular-like cavities (magnification, × 100). C: The lining cells of cavities were large nucleus, deep-stained and distributed irregular multinuclear cells (magnification, × 400). D: The mesenchyme was rich in mucus (magnification, × 100). E: Tumor cells positive for Vim (magnification, × 400). F: CD34 stain highlighted the vascular network but not the tumor cells (magnification, × 100).

near the lumbosacral, the bone was destructed. Since she was admitted to our hospital, a history of fever, weight loss or night sweats was absent. Then she underwent a lumbosacral mass resection.

Gross and histological features

Case 1: For the first time, the boy patient's sample was described as a piece of skin tissue, about 3.0 cm long, and the diagnosis was vascular lymphangioma. In the first recurrence, he was operated on in our hospital, and the skin tissue piece was 6.0 cm × 5.5 cm × 3.0 cm, and in the cut surface one could see a 5.5 cm long nodule, and the nodule was gray-white and the texture was a little soft, locally slightly lobulated. Histologically, the boundary of the lesion was not clear, it located in the dermis layer (**Figure 1A**), and this case had infiltrated to the subcutaneous adipose layer. The tumor was composed of spindle cells and pseudo vascular-like cavities (**Figure 1B**), and the lining cells of cavities were large nuclei, with deep-stained and distributed irregular multinuclear cells (**Figure 1C**). In addition, the mesenchyme varied from mucus-like to collagen. In the previous year, the sample had a smooth surface and consisted of a 4.0 cm long nodule located in the spine on the right erector spinae muscles superficial, and the envelope was still intact, and the boundary of the lesion was not clear. Microscopically, we could see pseudo vascular-like cavities, the layer of the cavities were non-continuous spindle cells and multinuclear giant cells, and the multinuclear giant cells were of various sizes and lobulated-like. The spindle cells had an irregular arrangement like loose parallel bundles, and they were wavy, the atypia of spindle cells was obvious, and the mesenchyme was mucus-like (**Figure 1D**). Moreover, around the spindle cells there was fibrosarcoma in the local area, an indication that the tumor had the potential to progress.

Case 2: The specimen was a gray-yellow irregular soft tissue mass, the size was about 7.0 cm × 5.0 cm × 1.0 cm, in the cut surface, there was a clear boundary, the quality was slightly soft, the rest was muscle tissue, and the border of the tumor was less regular. Microscopically, the tumor appeared to be mainly located in the der-

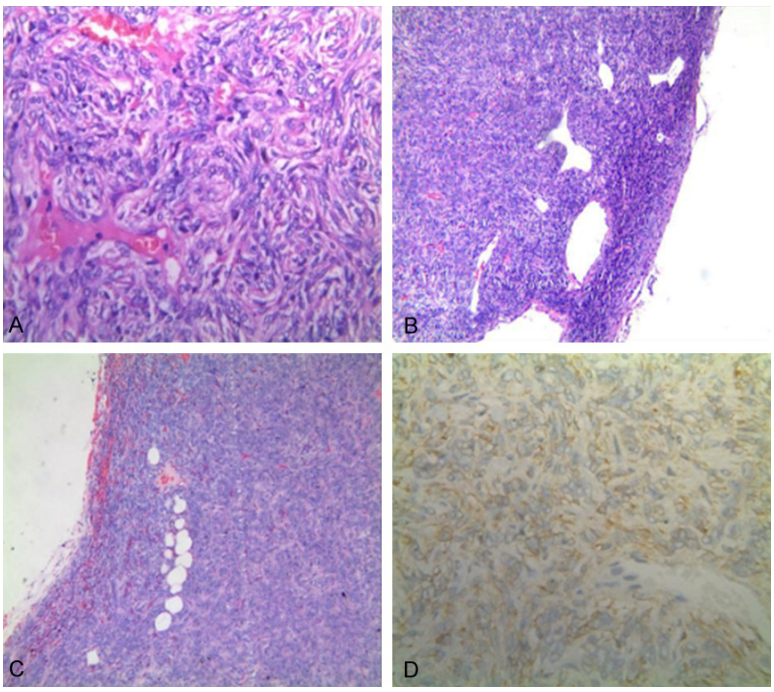

Figure 2. Histological and immunohistochemical features of case 2. A: Tumor cells were spindle cells, often characterized by storiform (magnification, × 400). B: The part of tumor tissues present the picture of hemangio-perithelioma (magnification, × 100). C: Residual fat cells in the tumor (magnification, × 100). D: Tumor cells positive for CD34 (magnification, × 400).

mis layer. In the centre of the tumor, the cells were rich, they had a storiform shape (**Figure 2A**), and part of the tumor looked like hemangioendothelioma (**Figure 2B**). The growth of those typical short spindle cells showed diffuse infiltration, and the tumor cells infiltrated into the subcutaneous adipose tissue, and interlobular infiltration grew along the fat septa. Among the tumor cells, there were a few residual fat cells (**Figure 2C**), similar to fat mother cells. The atypia of the tumor cells was not obvious, and they were characterized by low mitotic activity, occasional coagulation necrosis, and in the superficial parts and the peripheral parts the tumor cells were slender and mostly arranged irregularly.

Immunohistochemical features

Case 1: Tumor cells expressed Vim, S-100, CD-99, and bcl-2 (**Figure 1E**). Tumor cells were negative for SMA, Desmin, CK, EMA and Calponin. CD34 stain highlighted the vascular network but not the tumor cells (**Figure 1F**). Index of Ki-67 was about 40% (**Table 2**).

Case 2: Tumor cells were positive for CD34 (**Figure 2D**), CD99 and negative for others markers. Index of Ki-67 was about 5-10% (**Table 2**).

Molecular pathological alterations

The FISH of molecular cytogenetic detection of t(22q13) (PDGFB) and t(17q21) (COL1A1) was performed via the dual-color dual-fusion probe. One red and one green signal consisted of the COL1A1/PDGFB dual-color dual-fusion FISH pattern for translocation. The molecular pathology showed that they all were positive for PDGFB gene-related translocation and fusion, that is the red and the green signals were fused. In case 1, we can see that COL1A1/PDFGB was rearranged, and the cells displayed 2 fusion signals (arrow) (**Figure 3A**). In case 2, the capture shows positive cells with the COL1A1/PDGFB fusion gene, a few show 1 signal (arrow) (**Figure 3B**).

Diagnosis and differential diagnosis

Case 1: The final diagnosis was giant-cell fibroblastoma.

GCF needs to be distinguished from the typical DFSP, and it is thought that GCF is a juvenile form of DFSP, in the form of a heterozygous neoplasm, and it can be combined with pigmented or mucoid samples, but according to juvenile morbidity and repeated progress, combined with clinical behavior, histological and immunohistochemical features, molecular cytogenetic detection, making the diagnosis is not difficult.

Giant cell fibroblastoma should be distinguished with (1) Vascular tumors: Both vascular tumors and GCF have vascular-like cavities, but the lining cells of vascular tumors are mostly flat endothelial cells, rather than nuclear deep-stained multinuclear giant cells and atypia spindle cells. In addition, in addition to expressing CD34, the lining cells of vascular tumors also express endothelial markers such as CD31 and D2-40, with GCF only positive to CD34. (2) Myxoid liposarcoma: GCF often has a superficial lesion location, lacking a complex vascula-

Table 2. Immunohistochemical makers of two cases

	CD34	S-100	Bcl-2	CD99	Vim	SMA	Des	CK	EMA	Calponin	Ki-67
Case 1	-	2+	1+	1+	3+	-	-	-	-	-	40%
Case 2	1+	-	-	1+	-	-	-	-	-	-	5-10%

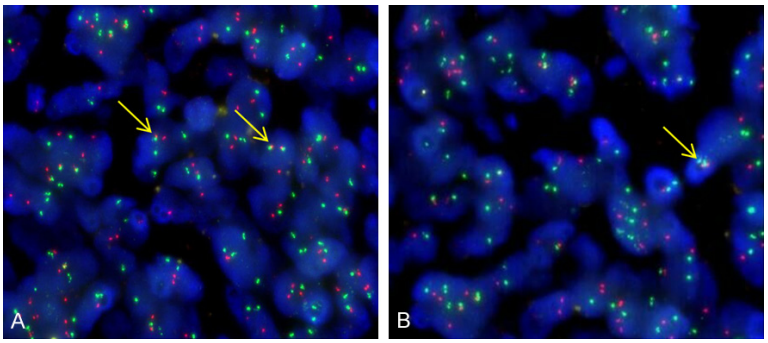

Figure 3. Molecular pathological features of 2 cases. A: In case 1, the cells display one red and one green fusion signal (yellow arrow), means COL1A1/PDFGB was rearranged. B: In case 2, the picture showing a few cells shows 1 signal, while the positive cells with the COL1A1/PDGFB fusion gene showed the red and the green fusion signals (yellow arrow).

ture as well as the arrangement of deep-stained cells along the pseudo-vascular like mother cells that completely lack fat. Myxoid liposarcoma has lighter atypia cells, with a thin plexiform vascular network, and there is no accumulation of perivascular tumor cells, and mother cells could be visible scattered around [6]. Because this case was positive for S-100, and myxoid liposarcoma also expresses S-100, there was some confusion. (3) Multiform fibroma of the skin: Occurring in the elderly, multinuclear giant cells scatter in the collagen fibers, and the tumor doesn't have sinusoidal or fissure-like pseudo vascular-like cavities, and multinuclear giant cells don't express CD34. In contrast, GCF is characterized by the lesion with an irregular distribution of fissure-like or sinusoids-like pseudo vascular cavities, and the lining cells are a layer of non-continuous spindle cells and multinuclear giant cells [6]. (4) Fibrosarcoma type protuberant cutaneous fibrosarcoma: Features of these sarcomatoid regions include high-grade, obese spindle cells that are organized in bundles rather than storiform, and mitotic activity increases in these regions, so the regions of sarcomatoid should be at least 5%-10%. Clinically, it has a high local recurrence rate and is more aggressive. On the other hand, sarcomatoid-like regions have a higher MIB-1 label index and a p53 Immunostaining positive rate.

Case 2: The final diagnosis was dermatofibrosarcoma protuberans.

The differential diagnoses included: (1) Neurofibroma: Characteristically, the tumor cells are short and slender, have no mitotic, and the cells are less abundant than DFSP. There isn't a typical storiform structure generally. Yet you could catch sight of the tactile bodies or other morphological structures suggestive of nerve differentiation [6]. Immunohistochemical techniques can also help in the differential diagnosis. DFSP tumor cells express CD34 but not S100 in contrast to all neurofibromas [7]. (2) Spindle cell lipoma: The typical spindle cell lipoma has the same size of mature adipose tissues and spindle cells, the tumor cells are distributed in the mucus-like matrix, the nuclear atypia is unobvious, and there are fewer mitotic cells. Tumor cells are often irregularly arranged in short and parallel bundles, the nuclei often appear in an obvious palisade arrangement. Unlike DFSP which is mainly in the dermis, the tumor cells are composed of CD34 positive obese spindle cells that arrange themselves in a storiform pattern and infiltrate into deep subcutaneous tissue, lacking the characteristics of old collagen [6]. (3) Benign fibrous histiocytoma: In a microscope, one sees benign fibrous histiocytoma showing that blunt round spindle cells are often mixed with inflammatory cells, hemosiderin cells, giant cells, and these cells are arranged in a short bundle and arranged randomly and not in a storiform arrangement. Subcutaneous invasions are rare, and almost no metastasis and malignancy changes have been reported unlike dermatofibrosarcoma protuberans that even has fibrosarcoma in some cases, and local recurrence can reach up to 20%-50%. Moreover, occasional cases express CD34 and focal staining. In contrast, dermatofibrosarcoma protuberans appears

such that the slim spindle cells are in a simple storiform arrangement and there are few secondary changes. Subcutaneous invasions are common and extensive, and most cases are diffuse positive for CD34 [6]. (4) Multiline undifferentiated sarcoma: Because of its characteristic manifestations, for instance, in the elderly, it is usually located in the deep muscles and exhibits rapid growth, and the storiform structure is not clear, but instead it has multinuclear, weird giant cells and small lipid droplets. Also, it has a more significant polymorphism and a lot of typical or atypical mitosis, with obvious hemorrhaging and necrosis. These are not like dermatofibrosarcoma protuberans' inert processes [6].

Follow-up

These patients are currently alive and without any evidence of recurrence or metastasis.

Discussion

Dermatofibrosarcoma protuberans is a rare, isolated and slow-growing, aggressive neoplasm of intermediate malignancy, which originates from the dermal layer of the skin [8]. In primary cases, DFSP can on any part of the body, but the trunk is the most common location, and it was found that the tumor could occur in the chest wall [9]. Owing to its locally aggressive growth, tumor cells can extend to infiltrate adjacent structures, such as the subcutaneous tissue, muscles, tendons, and even bone structures, as in the female patient described here in our report [10]. Furthermore, DFSP has a high rate of local recurrence, and metastasis is rare, but it does occur [11]. We reported two cases of dermatofibrosarcoma protuberans. Case 1 had experienced a second recurrence, and this type was defined as a juvenile form of DFSP. Both were located in the trunk and expressed CD99 but were negative for Desmin, SMA, CK, and EMA. The tumor cells in case 2 but not case 1 expressed CD34. Thus, we determined that although DFSP expressed CD34 characteristically, it was not 100%. Histologically, the spindle cells do not have obvious atypia, the cells have low mitotic activity and occasionally have coagulation necrosis. DFSP has many subtypes, and one is DFSP which exhibits FS transformation (DFSP-FS). It is always like an invasive tumor, manifested with increased malignancy, increased recurrence and shorter intervals, and it can metastasize [12].

DFSP has a gender difference [13]. The cases in our study were one male and one female, but because of the specificity of DFSP, from magnetic resonance imaging (MRI), we can't distinguish DFSP from other soft tissue sarcomas, so it is just an accessory examination [14]. DFSP can happen in surgical scars, old burns, trauma, radiation dermatitis, vaccination sites, central venous line puncture sites and even insect bites [15]. At first, it may originally present as a skin-colored plaque with possible dark red or blue discoloration, and it is painless [16]. This neoplasm grows slowly but has a high recurrence rate, especially in an insufficient surgical excision. The cases we reported were presented as a painless tumor in the patient's right lumbar, with a 3-month-history of pain in the patient's left lumbosacral. So far, there very few cases of PDGFB gene-related translocation have been reported. PDGFB, which encodes PDGF beta chains, is a cellular homologue of the v-sis tumor gene and has a total length of 21.2 kb and contains 7 exons, wherein the exon 1 includes the coding signal sequence, exon 2, 3 has the encoding leader sequence, exon 4, 5 encodes the body of the mature protein, exon 6 encodes the COOH terminal sequence, and exon 7 is a non-coding region. COL1A1 has a total length of about 17.5 kb. 52 exons, of which exons 6 to 49 encode the α1 helical domain consisting of 338 repeating GLY-X-Y triple structure (X, Y is usually proline) composition [17]. Genetically, DFSP chromosomal structural abnormalities and gene translocation mainly include the supernumerary ring chromosome and chromosome imbalance translocation and chromosomal abnormalities. Chromosomal translocations appear to be balanced or unbalanced translocations, and the most typically unbalanced translocation is China), and (q22;q13.1), this time, der(22) increased and der(17) missing. Ring chromosomes and chromosomal unbalanced translocations can lead to rearrangement of COL1A1/PDGFB gene fusion [17]. Until Nakamura et al. found that there is a new gene rearrangement in DFSP, namely the COL1A2/PDGFB gene rearrangement fusion [18], the view of the COL1A1/PDGFB gene fusion was considered as the only specific gene of DFSP and the key factor in the

formation of DFSP. A search of the PDGFB relevant literature was conducted, and we found that many diseases have a closely relationship with PDGFB.

On all accounts, due to the particularity of DFSP and giant cell fibroblastoma, clinical symptoms and imaging manifestation are usually lacking in specificity, so it is easy to make a misdiagnosis and to miss a treatment opportunity, but at the same time, the diseases are extremely rare and have a high rate of recurrence, so we should strengthen our understanding of the diseases, taking into account the various aspects of patient information to make the correct diagnosis and to administer a timely and effective treatment. According to previous studies, CD34 and Apo D are useful immunohistochemical makers and may be very important indicators for adjuvant diagnosis [19, 20]. Combined with clinical symptoms, gross and histological features, immunohistochemical and molecular pathological analyses can aid in diagnosis. So, by detecting the PDGFB gene, we may have a better understanding about DFSP, thus leading to better treatment.

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Disclosure of conflict of interest

None.

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