

Dermatofibrosarcoma Protuberans: A Study of Clinical, Pathologic, Genetic, and Therapeutic Features in Korean Patients

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Received: January 28, 2014

Revised: May 23, 2014

Accepted: May 28, 2014

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The authors have no financial conflicts of interest.

Purpose: Dermatofibrosarcoma protuberans (DFSP) carries a translocation resulting in the collagen type I alpha 1 (*COL1A1*)-platelet-derived growth factor beta (*PDGFB*) fusion gene, which is responsible for *PDGFB* activation. The purpose of this study is to evaluate the clinicopathological, genetic, and therapeutic features of DFSP in Korean patients. **Materials and Methods:** Clinicopathological features of 37 patients with DFSP were reviewed. Multiplex reverse transcriptase-polymerase chain reaction (PCR) was carried out in 16 patients using formalin-fixed, paraffin-embedded tissues and specific primers for *COL1A1* and *PDGFB*. **Results:** The mean age of 37 patients was 37.4 years old. The most common tumor location was the trunk. All patients were treated primarily with surgery: 34 (91.7%) cases with Mohs micrographic surgery (MMS) and 3 (8.3%) cases with wide local excision. The median follow-up time was 33.7 months. Two patients, one in each treatment group, demonstrated local recurrence during the follow-up period. The *COL1A1-PDGFB* fusion gene was expressed in 14 (87.5%) cases, demonstrated by reverse transcriptase PCR analysis. No association was found among the different *COL1A1-PDGFB* fusion transcripts, the various histological subtypes and clinical features. **Conclusion:** Our results support the effectiveness of MMS in treating DFSP. The *COL1A1-PDGFB* fusion transcript was observed in 87.5% of patients. Therefore, *COL1A1-PDGFB* is a useful and accurate tool in diagnosing DFSP in Koreans.

Key Words: Dermatofibrosarcoma protuberans, collagen type I alpha 1-platelet-derived growth factor beta, histological subtype, Mohs micrographic surgery

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INTRODUCTION

Dermatofibrosarcoma protuberans (DFSP) is a sarcomatous tumor of the cutaneous tissue first described by Taylor in 1890.¹ It is an uncommon infiltrative dermal and subcutaneous tumor characterized by progressive local growth of CD34+

spindle cells with a highly infiltrative pattern.² Surgical excision is the main treatment modality; however, local recurrence rates after conservative surgical resection have been reported to be 26% to 60%.^{3,4} Although wide local excision (WLE) has been shown to further reduce the recurrence rate to 0% to 30%,^{2,7} several reports indicate that Mohs micrographic surgery (MMS) results in a lower overall recurrence rate (0–8%) compared with WLE.^{7,8}

Cytogenetically, DFSP carries a rearrangement of chromosomes 17 and 22, which results in formation of the collagen type I alpha 1 (*COL1A1*)-platelet-derived growth factor beta (*PDGFB*) fusion gene.⁹ This gene codes for a fusion protein that overlaps functionally with the mature form of *PDGFB*.¹⁰ It activates *PDGFB* receptor (PDGFR), and thus accelerates DFSP growth through an autocrine-paracrine loop. Based on this knowledge, imatinib mesylate has been used to treat patients with inoperable DFSP, and has shown impressive clinical results.⁹ We previously reported 11 patients with DFSP who were successfully treated by MMS,⁸ and the purpose of our present study is to evaluate the clinicopathological, genetic (*COL1A1-PDGFB*), and therapeutic features of DFSP in 37 Korean patients.

MATERIALS AND METHODS

Case selection and clinicopathological data

All cases of DFSP included in the pathological database of Yonsei University Health System in Seoul, Korea from 1997 to 2012 were reviewed. Informed consent was obtained in accordance with the ethical committee procedures of the institution (IRB No. 4-2011-0659). The following clinical data were recorded: age, gender, tumor location, tumor size (centimeters), tumor type (primary or recurrent), surgical treatment by WLE or MMS, number of micrographic stages, type of surgical repair (primary closure, graft, or flap), local recurrence, distant metastasis, and follow-up period (months). Patients with both primary and recurrent lesions were included. Primary disease was defined as the presence of tumor without previous treatment or recent tumor excision with histologically positive margins. Recurrent disease was defined as that occurring within or juxtaposed to the previous surgical excision site ≥ 6 months after the initial excision. Histological confirmation of DFSP was done before WLE or MMS in all patients, and all tumors were stained for CD34. Patients were contacted to evaluate the surgical sites for recurrence. Data on recur-

rence and any subsequent procedures were collected and compiled.

All patients were treated by one of the two surgeons. Patients were treated by WLE or standard MMS using the fresh frozen tissue technique. WLE was performed with a 2-cm margin. For MMS, the visible border of each lesion was demarcated, and a 5-mm margin was drawn around each lesion's clinical edge. In cases of recurrence, scars were removed en bloc with the recurrent tumor before the MMS layer was excised to identify any residual tumor around the scar tissue. Afterwards, the tissue sections were placed in cassettes and submitted with the MMS map for pathological examination. If any evidence of tumor was seen within the specimen, further tissue removal was performed. Additional 5-mm-thick layer of tissue was removed after careful mapping of the positive margin, and this layer was pathologically examined as described above. This process was repeated until all margins were cleared. All sections were embedded in paraffin wax for later confirmation by haematoxylin and eosin (H&E) staining, and CD34 staining was also used in suspicious cases. For all patients, the central bulk of the tumor was sent to the pathology laboratory to have permanent sections taken to confirm the diagnosis of DFSP. All patients underwent primary reconstruction by the two surgeons.

Immunohistochemistry

Immunohistochemistry was performed on paraffin-embedded archival tissue with antibodies against CD34 (1:50; BioGenex, San Ramon, CA, USA), p53 (1:50; Dako, Carpinteria, CA, USA), and Ki-67 (1:50; Dako, Carpinteria, CA, USA). Appropriate positive and negative controls were run in parallel. Immunostaining was evaluated separately by two authors. Quantification of the immunohistochemistry marker CD34 was based on the percentage of immunoreactive cells as follows: high ($\geq 50\%$) or low ($< 50\%$). The immunohistochemical quantification of nuclear markers was evaluated as follows: positive ($> 5\%$ immunoreactive nuclei) or negative ($< 5\%$).

Identification of *COL1A1-PDGFB* fusion transcripts

Total RNA was extracted from formalin-fixed, paraffin-embedded tissue blocks using an RNeasy Mini Kit (QIAGEN, Hilden, Germany) and reverse-transcribed using a Superscript Preamplification System (Gibco-BRL, Gaithersburg, MD, USA). To detect the expression of the *PDGFB* gene, first-strand cDNA was amplified with the AGexpdgf3 and

AGexpdgf4 primers according to the methods of Greco, et al.¹⁰ To detect the presence of *COL1A1-PDGFB* fusion transcripts, polymerase chain reaction (PCR) was carried out using 17 *COL1A1* forward primers and a specific *PDGFB* reverse primer, as presented in Table 1. Seventeen *COL1A1* forward primers were designed for *COL1A1* exons 5, 8, 11, 15, 17, 20, 23, 26, 27, 32, 35, 38, 40, 42, 44, 46, and 49, and these primers were considered sufficient to span the various breakpoints within the region encoding the alpha-helical domain of the *COL1A1* polypeptide. The PCR products were directly sequenced using an Applied Biosystems 373A automated DNA sequencer to identify the breakpoints.

Statistical analysis

Associations between the clinical, histopathological, and genetic aspects were assessed using a χ^2 test and Fisher's exact test. The significance level was set at 5%. All tests were performed using a statistical software package (SPSS, Version 18.0, SPSS Inc., Chicago, IL, USA).

Table 1. Primers for *COL1A1* and *PDGFB*

Primer set	Exon	Sequence 5' to 3'
<i>COL1A1</i> (forward)		
1	5	GCCGAGATGGCATCCCTGG
2	8	CCCTGGTGAGCCTGGCGA
3	11	TCAGGGTGCTCGAGGATTGC
4	15	GGTCTCGTGAAATGATGG
5	17	AAGGTCCCCAGGGTGTGCG
6	20	AACCTGGTGCTCCTGGCAGC
7	23	AAGCTGGTCTCCCGGTGAAGC
8	26	AAGGCTGGAGAGCGAGGTGTTT
9	27	TGCTGGCAAAGATGGAGAGG
10	32	TAGAACGTGGTGCAGCTGGTCTTC
11	35	TCCCACTGGAGCTCGTGG
12	38	TGCTCCTGGAGCCAAAGGTGC
13	40	TGCTGGCGAGAAAGGATCCCCTG
14	42	AAGTCCCTCTGGAGCAAGT
15	43	TGGCAAGAGTGGTATCGTGG
16	46	TGGCTTCTCTGGCTCCAGGG
17	49	ACCTCAAGAGAAGGCTCACGATGG
<i>PDGFB</i> (reverse)		
1	2	ATCAAAGGAGCGGATCGAGTGGTC

COL1A1, collagen type I alpha 1; *PDGFB*, platelet-derived growth factor beta.

Annealing temperature: 65.7°C.

Table 2. Clinicopathologic Characteristics of 37 DFSP Patients

Clinicopathologic variables	Number of patients (%)
Total cases	37
Follow-up months	
Mean (range)	33 (6–79)
Age (yrs)	
Mean (range)	37.4 (3–74)
Gender	
Male/female	19 (51.3)/18 (48.6)
Location	
Head and neck	4 (10.8)
Upper extremity	8 (21.6)
Lower extremity	9 (24.3)
Trunk	16 (43.2)
Size (pre-op)	
Median size (cm ² , range)	6.2 (1.2–44.2)
Size (post-op)	
Median size (cm ² , range)	19.6 (2.5–122.7)
Histology	
Conventional	28 (75.7)
Fibrosarcomatous	5 (13.5)
Myxoid	2 (5.4)
Giant cell fibroblastoma	2 (5.4)
Primary/recurred	
Primary (<i>de novo</i>) tumor	24 (64.9)
Recurred tumor	13 (35.1)
Surgical Method	
MMS	34 (91.9)
WLE	3 (8.1)
Mohs layer	
1	11 (32.4)
2	19 (54.9)
3	3 (8.8)
4	1 (2.9)
Repair	
Primary closure	23 (62.2)
Flap	9 (24.3)
Graft	3 (8.1)
Secondary intention	2 (5.4)
Subcutaneous infiltration of tumor	
Yes	19 (51.4)
No	18 (48.6)
Muscle infiltration of tumor	
Yes	8 (21.6)
No	29 (78.4)
Recurrence	
Yes	2 (5.4)
No	35 (94.6)

MMS, Mohs micrographic surgery; WLE, wide local excision; DFSP, dermatofibrosarcoma protuberans.

RESULTS

Clinicopathological findings

In total, 37 cases of DFSP were reviewed. The clinicopathological features are summarized in Table 2. The mean age at diagnosis was 37.4 years, and the ratio of males to females was 1.1:1. The most common tumor location was the trunk (43.2%), followed by the extremities and the head and neck. Of the 37 cases analysed, 24 cases (64.9%) were *de novo* neoplasms and 13 (35.1%) were recurred cases. All the recurred cases were previously treated by simple excision or WLE. The median preoperative tumor size was 6.2 cm². All patients were treated primarily by surgery: 34 (91.9%) cases by MMS and 3 (8.1%) by WLE. One patient with recurred DFSP was treated with imatinib mesylate as a neoadjuvant therapy before MMS, because of multiple recurrences and the location of the tumor, which was on the finger web.¹¹ Imatinib 400 mg twice a day for 3 months followed by reduced dose, 400 mg once a day for 2 months, was prescribed. MMS was performed after reduction of tumor size with Imatinib treatment. For those tumors that were treated with MMS, a mean of 1.8 Mohs stages were required. The median postsurgical defect size was 19.6 cm². Postsurgical defects were reconstructed by primary closure in 23 cases (62.2%), covered by flaps in 9 cases (24.3%), grafts in 3 cases (8.1%), and secondary intention healing in 2 cases (5.4%). None of our patients were treated with radiotherapy after surgery. The mean follow-up period was 33 months (range 6–79), and 2 patients (1 MMS and 1 WLE) demonstrated local recurrence during follow-up. None of the patients showed distant metastasis. Of the 34 cases of DFSP treated by MMS, 1 case recurred. The permanent pathological slides and CD34 stain of the MMS specimens of this patient were reviewed afterwards, which

showed positive margins.

Histopathological findings

H&E-stained slides were reviewed. The tumors were categorized histologically as conventional DFSP versus special variants: giant cell fibroblastoma (GCF, combination of spindle cell patterns with myxoid areas, multinucleated giant cells, and distinctive sinusoid-like spaces), myxoid (DFSP with >50% myxoid stromal changes), or the presence of areas with high-grade fibrosarcomatous changes (DFSP-FS) in at least 5% of the lesion. The high-grade fibrosarcomatous areas could be recognized by fascicular, herringbone growth patterns at low power and unusually increased cellularity and cytologic atypia.¹² Conventional DFSP (28 cases, 75.7%) was the most common histologic type in our study. In 5 cases (13.5%), storiform pattern was admixed with high-grade cellular areas to form a herringbone appearance which is consistent with DFSP-FS. There were 2 cases (5.4%) of myxoid DFSP and 2 cases (5.4%) of GCF. In 19 cases (51.4%), tumors showed tentacle-like projections into the underlying subcutaneous tissue, resulting in a honeycomb appearance. In 8 cases (21.6%), the tumor showed muscle infiltration. Compared with conventional DFSP, DFSP-FS showed significant subcutaneous ($p<0.05$) and muscle infiltrations ($p<0.001$). The histologic subtype of the 2 patients who showed recurrence in our study was DFSP-FS. The recurrence rate of DFSP-FS was significantly higher compared to other types of DFSP ($p=0.015$).

Immunohistochemistry

All of the tumors expressed CD34. In our study, all DFSP-FS demonstrated high CD34 expression. However, there was no significant difference in CD34 expression compared with conventional DFSP. Ki-67 and p53 were expressed in 27.3% and 24.2% of cases, respectively, and were more

Table 3. Immunohistochemical Findings of Conventional DFSP and DFSP-FS

	n (%)	DFSP (%)	DFSP-FS (%)	<i>p</i> value
CD34				NS
Low	12 (36.4)	12 (42.9)	0 (0)	
High	21 (63.6)	16 (58.1)	5 (100)	
Ki-67				0.003
Negative	24 (72.7)	24 (85.7)	0 (0)	
Positive	9 (27.3)	4 (14.3)	5 (100)	
p53				0.023
Negative	25 (75.8)	24 (85.7)	1 (20)	
Positive	8 (24.2)	4 (14.3)	4 (80)	

DFSP, dermatofibrosarcoma protuberans; DFSP-FS, dermatofibrosarcoma protuberans-fibrosarcomatous variant.

CD34, high (≥50%) or low (<50%) according to percentage of immunoreactive cells; Ki-67 and p53, positive (>5% immunoreactive nuclei) or negative (<5%).

prevalent in DFSP-FS than in conventional DFSP (Table 3). All 5 cases of DFSP-FS showed positive immunostaining for Ki-67, compared with 14.3% positivity in conventional DFSP ($p=0.003$). For p53, 80% of the cases in DFSP-FS stained positive, compared with 14.3% in conventional DFSP ($p=0.023$).

Analysis of the COL1A1-PDGFB fusion transcripts

In 16 of 37 cases, reverse transcriptase-PCR analysis was performed. Only 16 cases out of 37 contained human RNA of sufficient quality/quantity for PCR amplification. The COL1A1-PDGFB fusion gene was expressed in 14 (87.5%) cases. Sequencing analysis of the different fusion types revealed a high variety of combinations among several exons of CO-

L1A1 (from exon 5 to exon 49) and exon 2 of PDGFB. The COL1A1 breakpoints occurred at the following exons: 25 (two cases), 29 (two cases), 32 (two cases), 34 (five cases), 43 (one case), and 45 (two cases). No association was found among the different COL1A1-PDGFB fusion transcripts, histological subtypes and clinical features. A schematic representation of our findings is depicted in Fig. 1.

DISCUSSION

Since DFSP is an uncommon tumor, it has not been well-studied in Asia, and there are few reports in the literature.^{8,13-15} Therefore, we analysed the clinical, pathological, and ge-

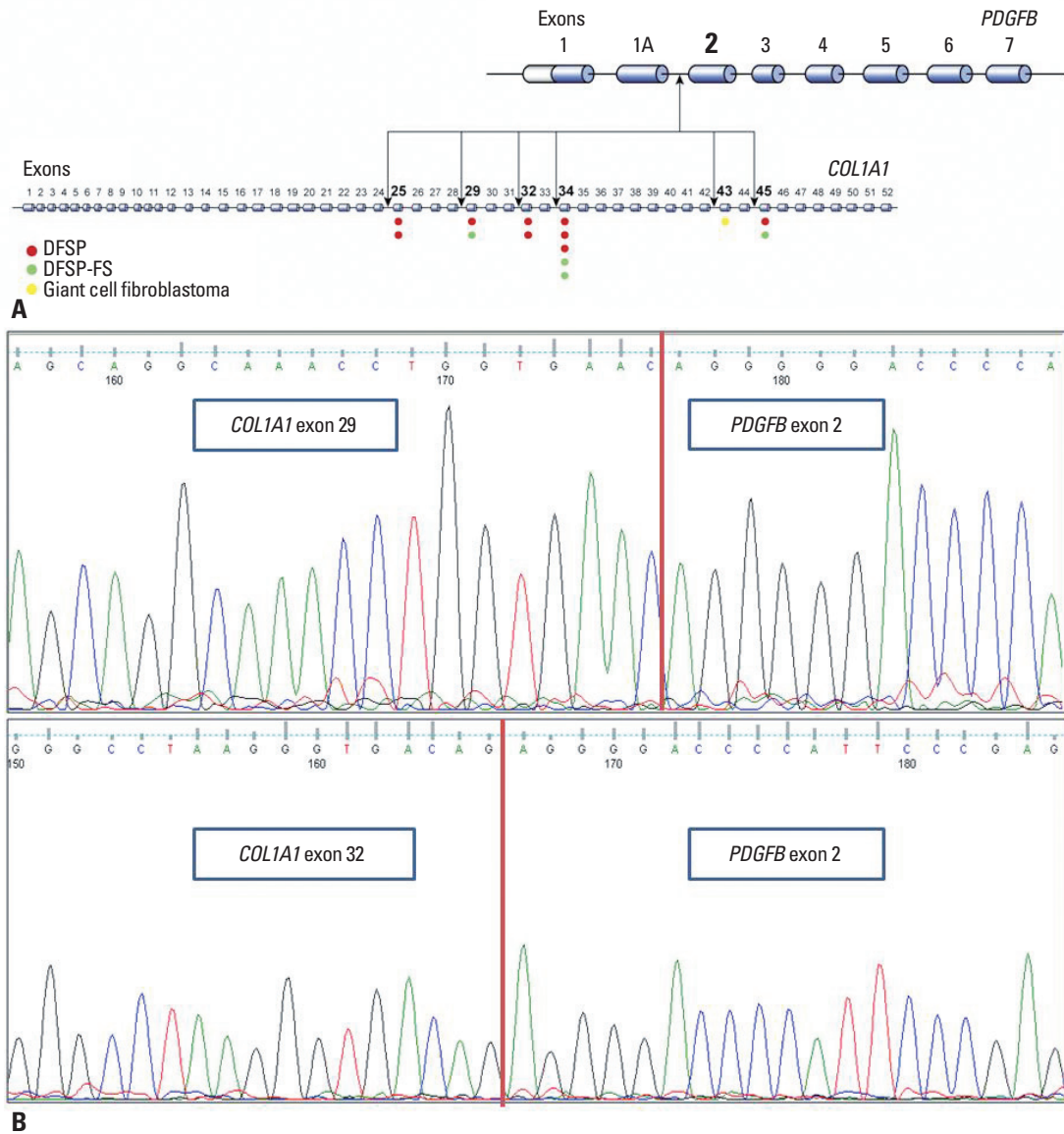


Fig. 1. (A) Schematic presentation of variable positions of collagen type I alpha 1 (*COL1A1*) breakpoints in the *COL1A1*-platelet-derived growth factor beta (*PDGFB*) fusion gene. (B) Some examples of the *COL1A1*-*PDGFB* fusion transcript. DFSP, dermatofibrosarcoma protuberans; DFSP-FS, dermatofibrosarcoma protuberans-fibrosarcomatous variant.

netic characteristics, as well as treatment and outcomes in 37 cases of DFSP in Korean patients.

DFSP is an uncommon tumor, with an overall incidence of 0.8 to 5 per million.¹⁶ It is most frequently diagnosed in people between 30 and 50 years of age, which is consistent with our results.¹⁶ It is found in similar frequencies in men and women, with only a slight male predominance.² Typically, the tumor initially presents as a slowly growing indurated plaque that can eventually transform into a violaceous to red-brown painless nodule, most commonly on the trunk or upper limbs and less often on the head and neck.⁸ Kim, et al.¹⁵ previously reported 65 cases of DFSP in Koreans, which showed similar age range and site distribution.

DFSP has a number of well-described histological variants. Most commonly, conventional DFSP demonstrates proliferation of dermal spindle cells that infiltrate into the subcutaneous fat. These proliferations are made up of monotonous cells with little pleomorphism and a low mitotic index. The spindle cells in the dermis are arranged in storiform pattern, and the infiltrating portion of the tumor is characterized as honeycomb in appearance. DFSP-FS is another variant which exhibits areas of classic low-grade DFSP with interspersed foci of significant cellular atypia and increased mitoses, and it has been estimated that 7% to 16% of tumors have areas of fibrosarcomatous change.¹⁷ Although some authors have reported that these tumors behave more aggressively and are associated with a higher frequency of recurrence and a greater risk of metastasis,^{12,17} several articles reported that the prognosis of DFSP with fibrosarcomatous transformation has a prognosis similar to that of conventional DFSP.^{18,19} In our study, 13.5% of cases were DFSP-FS. Compared with other variants, fibrosarcomatous DFSP in our study showed a higher frequency of tumor infiltration into the subcutaneous fat and muscle. Also, the recurrence rate of DFSP-FS was significantly higher compared to other types.

DFSP is characterized by the presence of a distinctive, reciprocal rearrangement of chromosomes 17 and 22 in the form of a translocation t(17;22)(q22;q13) or supernumerary ring chromosomes containing material from chromosomal regions of 17q22 and 22q13.²⁰ This rearrangement leads to the fusion of *COL1A1*, which is localized on 17q22, to the *PDGFB*, which is localized on 22q13. Confirmation of the presence of the *COL1A1-PDGFB* fusion gene is a useful tool to identify patients who may be candidates for treatment with imatinib and for the differential diagnosis of DFSP with other CD34+ tumors or CD34-DFSP. In the present study, we indeed identified *COL1A1-PDGFB* fusion transcripts in

87.5% of cases. This percentage is similar to that found by Takahira, et al.²¹ As reported by other groups,¹⁹ we did not find a significant association between the presence of different breakpoints and the histologic variants of DFSP or their clinical characteristics.

Advances in the understanding of molecular mechanisms of DFSP have resulted in the implementation of targeted therapy against DFSP based on PDGFR inhibition. Imatinib mesylate is a tyrosine kinase inhibitor rationally developed to target *BCR/ABL*, *KIT*, *FMS* (receptor for colony stimulating factor 1), *ARG* (an ABL-related gene), and *PDGFR alpha* and *beta*. It was found to be the first effective systemic therapy for DFSP. Many studies suggested the usefulness of imatinib in metastatic and locally advanced DFSP. Kérob, et al.²² reported 25 cases of unresectable DFSP treated in a phase II trial with preoperative imatinib at a dose of 600 mg daily for two months, and indicated that some DFSP patients who were initially evaluated as unresectable/metastatic or necessitating mutilating surgery had resectable tumors after imatinib therapy. Similarly, we experienced one patient who required neoadjuvant therapy with imatinib to reduce tumor size. The tumor was located at the finger web, where WLE was impossible.

Although WLE has historically been the treatment of choice for DFSP, MMS is another favorable option, as it offers the advantage of immediate microscopic examination of the entire surgical margin after excision, which allows for precise tumor mapping. The main purpose of MMS in DFSP is to minimize surgical margins, resulting in less complicated reconstruction with smaller postsurgical defects without jeopardizing the oncologic resection.^{7,23,24} A meta-analysis by Paradisi, et al.⁷ of 463 patients with DFSP treated with MMS showed recurrence in 6 cases (1.2%), confirming that the treatment of choice for DFSP is MMS.^{7,8,25} Our study also supports the use of MMS in DFSP. Thirty-four cases were successfully treated, with only one patient (2.9%) showing recurrence during follow-up. Also, the *COL1A1-PDGFB* fusion transcript was observed in 87.5% of patients; therefore, *COL1A1-PDGFB* may be a useful and accurate tool for diagnosing DFSP in Koreans.

ACKNOWLEDGEMENTS

This study was supported by the Basic Science Research Program through the National Research Foundation of Korea and funded by the Ministry of Education, Science and Tech-

nology (2011-0022376) and by 2012 14th GSK (Stiefel)/KDA Research Award.

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