A Clinical, Histologic, and Molecular Study of 9 Cases of Congenital Dermatofibrosarcoma Protuberans

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BACKGROUND: The diagnosis of dermatofibrosarcoma protuberans (DFSP) in childhood is often difficult because of the deceptive appearance of the lesions. Little is known about congenital DFSP, the frequency of which is probably underestimated because the initial lesion may pass unnoticed.

OBSERVATIONS: We studied 9 DFSP congenital cases (8 plaques and 1 nodule) initially suspected to be benign lesions. The first biopsies or excisions were performed after a delay of 5½ months to 15 years. All cases were CD34+. Histologic patterns were similar to the DFSP adult classic pattern in 4 cases. One case was a Bednar tumor. The histologic diagnosis of the 4 remaining cases was difficult. The collagen, type I, α 1–platelet-derived growth factor β fusion gene (COL1A1-PDGFB) was detected by means of reverse transcriptase–polymerase chain reaction or fluorescence in situ hybridization.

CONCLUSIONS: All cases of congenital DFSP were difficult to identify clinically. The diagnosis was suspected by means of histologic and immunohistochemical evaluation and was confirmed using molecular analyses. This study illustrates the difficulties and pitfalls of the recognition of congenital DFSP and emphasizes the value of immunohistochemical study with anti-CD34 and complementary molecular analysis for all cutaneous spindle cell tumors and plaques in neonates and infants.

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DERMATOFIBROSARCOMA protuberans (DFSP) is a cutaneous tumor of low-grade malignancy that has long been considered to affect adults almost exclusively. Adult DFSP is usually described as a firm infiltrative protuberant nodule. The histologic pattern of DFSP classically shows dermal and subcutaneous CD34+ spindle-shaped tumor cells arranged in a storiform pattern. Adult DFSP cells show the presence of supernumerary ring chromosomes made up of sequences from chromosomes 17 and 22 that contain the abnormal fusion gene collagen, type I, α 1–platelet-derived growth factor β (COL1A1-PDGFB). The detection of COL1A1-PDGFB in giant cell fibroblastosas (GCFs) and Bednar tumors (BTs) demonstrated that DFSP, GCF, and BT share a similar genetic origin and that GCF and BT are morphologic variants of DFSP rather than distinct entities. The treatment of choice for patients affected by DFSP or variant tumors (GCF and BT) is surgical excision, by means of Mohs microscopic surgery whenever possible, to ensure tumor-free margins. Pharmacologic therapy using the tyrosine kinase inhibitor imatinib mesylate is currently under evaluation.

In contrast to adult DFSP, little is known about DFSP in children. In particular, information about congenital cases is scarce, with only 29 reported. The frequency of DFSP at birth and in childhood is probably underestimated because a significant proportion of patients diagnosed as young adults had an earlier onset. Pediatric DFSP can mimic morphea, atrophic plaques, angiomias, or neurofibromas. Of the 6 congenital cases described by Weinstein et al, none were initially recognized as DFSP. Indeed, these apparently innocuous lesions may be neglected for a long time. On presentation, diagnosis is mainly based on the histopathologic evaluation of a biopsy sample or a limited local excision. In cases of small and superficial biopsy samples, pediatric DFSP may be confused with benign neoplasms, such as neurofibroma, fibromatosis, or fibrous hamartoma of infancy. Conversely, it may also mimic histologically aggressive malignant tumors, such as congenital fibrosarcoma.

Even in the case of an unequivocal DFSP histologic pattern, the decision to
perform surgery with appropriate margins in infants and young children is always difficult to make because of its potentially mutilating consequences. However, recent results of the use of imatinib mesylate in an 18-month-old girl with a large congenital DFSP are encouraging and may open the way to preoperative treatments to reduce the tumor size. Adult and pediatric DFSP share the same molecular anomaly. The COL1A1-PDGFB fusion gene has been detected in 15 of the 16 pediatric cases that have been studied at the molecular level.12,13,20–26 Our group previously showed the utility of the COL1A1-PDGFB fusion gene detection by means of multiplex reverse transcriptase–polymerase chain reaction (RT-PCR) in fixed paraffin-embedded tissues. Herein, we also performed fluorescence in situ hybridization (FISH) detection of the COL1A1-PDGFB fusion gene in tumor sections. We used FISH and RT-PCR analyses to confirm the diagnosis of DFSP in 9 congenital cases. Most cases were difficult to identify by means of clinical evaluation alone; therefore, the diagnosis was made by histologic evaluation completed by means of molecular and FISH analyses.

## METHODS

Local ethical guidelines were followed for this study. The 9 tumor specimens suspected of being congenital DFSP were referred for molecular analysis to the Laboratory of Solid Tumors Genetics between November 1, 2001, and August 31, 2004. Case 3 was from the Pathology Department of Gustave Roussy Institute, and the other 8 cases were from the Pathology Department of Necker-Enfants Malades Hospital.

### HISTOLOGIC AND IMMUNOHISTOCHEMICAL EVALUATION

Tissues were fixed in 10% buffered formalin and paraffin embedded. Five-micrometer sections were stained with hematoxylin-eosin. Immunohistochemical analysis was performed using antibodies against CD34 (QBEnd; Immunotech, Marseille, France) (dilution 1:2000), polyclonal S100 protein (Dako, Glostrup, Denmark) (dilution 1:800), and smooth muscle actin (1A4; Dako) (dilution 1:300). Immunostaining was performed according to the streptavidin-biotin-peroxidase method.

### RNA EXTRACTION AND RT-PCR

RNA extractions, RT-PCR, cloning, and sequencing for detection of the fusion gene COL1A1-PDGFB were performed as previously described.12,27 Samples fixed in Bouin fluid were first rinsed in a saturated solution of lithium carbonate and in Tris-EDTA (20mM Tris hydrochloride, pH 8.0; 20mM EDTA, pH 8.0). The amount and quality of the extracted RNA was suitable in 5 cases, including 4 formalin-fixed samples and 1 cultured cell sample. In 4 cases (3 formalin- and 1 Bouin fluid-fixed samples), the RNA was too degraded to be analyzed.

## CYTOGENETIC AND FISH ANALYSES

Conventional cytogenetic analysis was performed for cases 1, 3, and 6 according to standard procedures of chromosomal preparations.29 For each case, 15 to 25 metaphase cells were analyzed. The bacterial artificial chromosome (BAC) clones RP11-93L18, RP11-893F2, RP11-959K5, and RP11-642F17 used as probes to detect the COL1A1-PDGFB fusion gene in the FISH experiments have been as described by Craver et al.21 (Table 1).

The FISH analysis was performed on fixed cell suspensions for cases 1, 3, and 6; on frozen tissue sections for case 1; and on formalin-fixed, paraffin-embedded tissue sections for cases 4, 5, and 7. Five-micrometer-thick sections from frozen or formalin-fixed, paraffin-embedded tissues on glass slides were treated for deproteinization as described by Coindre et al.30 If at least 1 or 2 green fluorescent signals and 1 or 2 red fluorescent signals per cell could not be seen in at least 80% of cells, the result was considered to be noninterpretable (failure of the hybridization generally due to inappropriate deproteinization conditions). For each analyzed nucleus, we evaluated the presence or absence of at least 1 yellow (or closely juxtaposed red-green) signal, resulting from fusion of the red and green fluorescent signals corresponding to the COL1A1 and PDGFB loci.

## RESULTS

### CLINICAL FINDINGS

Clinical data from the 9 patients are given in Table 2. There were 6 girls and 3 boys. The first biopsies or excisions were performed at ages varying from 5½ months to 15 years. Four lesions were located on the trunk. Other locations were the head, foot, buttock, and thigh. In 8 cases, the lesions were described as plaques, whereas 1 lesion was a subcutaneous lump (case 8). In all cases except 1, the lesion was larger than 4 cm. The clinical evolution of the lesions consisted of very slow enlargement in cases 3, 5, and 6 and the appearance of nodules in cases 4, 6, and 7. All the tumors except 1 (case 6) were

<table>
<thead>
<tr>
<th>Probe</th>
<th>Chromosomal Location</th>
<th>Gene (PCR)</th>
<th>GenBank Accession No.</th>
<th>Database</th>
<th>Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP11-893F2</td>
<td>17q21.33</td>
<td>COL1A1 exon 27 (+), COL1A1 exon 49 (+)</td>
<td>AC015909</td>
<td>RMC</td>
<td>RMC</td>
</tr>
<tr>
<td>RP11-93L18</td>
<td>17q21.33</td>
<td>COL1A1 exon 27 (+), COL1A1 exon 49 (+)</td>
<td>AG21716, AG312713</td>
<td>May 2004 UCSC database release</td>
<td>BPRC-CHORI</td>
</tr>
<tr>
<td>RP11-959K5</td>
<td>22q13.1</td>
<td>PDGFB exon 1 (+), PDGFB exon 6 (+)</td>
<td>AG667333, AG712722</td>
<td>June 2002 UCSC database release</td>
<td>BPRC-CHORI</td>
</tr>
<tr>
<td>RP11-642F17</td>
<td>22q13.1</td>
<td>PDGFB exon 1 (+), PDGFB exon 6 (+)</td>
<td>AG497780, AG049372</td>
<td>May 2004 UCSC database release</td>
<td>BPRC-CHORI</td>
</tr>
</tbody>
</table>

Abbreviations: BAC, bacterial artificial chromosome; BPRC-CHORI, BACPAC Resources Center–Children’s Hospital Oakland Research Institute (http://bacpac.chori.org/); COL1A1-PDGFB, collagen, type I, α1–platelet-derived growth factor β polypeptide; FISH, fluorescence in situ hybridization; PCR, polymerase chain reaction; RMC, Resources for Molecular Cytogenetics, University of Bari, Italy (http://www.biologia.uniba.it/rmc); UCSC, University of California Santa Cruz (http://genome.ucsc.edu/index.html).
surgically treated by means of limited or wide excision. Tumors with positive margins were subjected to reexcision (cases 4, 7, and 8). Case 3 was the only case of the series suspected to be DFSP at the first clinical examination (at 11 years old). A hypopigmented plaque was present already at birth, but medical counseling was sought only after considerable enlargement at 11 years old (Figure 1). Clinical diagnoses in the other cases were difficult and erratic, probably because the lesions were examined at a young patient age, when they still did not have a fully typical appearance. Case 5, a very small bluish plaque remained difficult to characterize DFSP. In cases manifesting as plaques, benign lesions such as tufted hemangioma, angioma, fibrous hamartoma of infancy, infantile fibromatosis, congenital cutaneous aplasia, mastocytoma, and sacrococcygeal teratoma were initially suspected (Table 2). In case 3, a very small bluish plaque remained difficult to characterize clinically. For the erthyematosus and infiltrating plaque of case 2, no precise clinical diagnosis was established. In cases 7 and 8, which had the appearance of an erthyematosus macule and a subcutaneous bluish lump, respectively, a fibrosarcoma was proposed among the possible diagnoses.

### Table 2. Clinical and Histologic Data From 9 Congenital Lesions

<table>
<thead>
<tr>
<th>Case No./Patient Sex</th>
<th>Lesion Location</th>
<th>Initial Size, cm</th>
<th>Initial Clinical Aspect</th>
<th>Clinical Diagnosis</th>
<th>Histologic Diagnosis (Type of Sample; Age)</th>
<th>CD34 Labeling</th>
<th>Clinical Evolution/Treatment; Margin Size/Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F Buttock</td>
<td>8</td>
<td>Angiomatosus firm plaque</td>
<td>Tufted hemangioma vs infantile myofibromatosis</td>
<td>DFSP (B and E; 5.5 mo)</td>
<td>+ (B and E)</td>
<td>Wide E; no recurrence after 7 mo</td>
<td></td>
</tr>
<tr>
<td>2/F Lumbar</td>
<td>10 × 6</td>
<td>Erythematous and infiltrating invasive plaque</td>
<td>Difficult to characterize</td>
<td>DFSP (B and E; 3 y)</td>
<td>+ (B and E)</td>
<td>Wide E at 3 y</td>
<td></td>
</tr>
<tr>
<td>3/M Lumbar</td>
<td>NA</td>
<td>Hypopigmented plaque</td>
<td>DFSP</td>
<td>DFSP (B; 11 y and E; 12 y)</td>
<td>+ (B and E)</td>
<td>Size increasing up to 4 cm; wide E at 12 y</td>
<td></td>
</tr>
<tr>
<td>4/F Occipital</td>
<td>2 × 6</td>
<td>Pinkish fibrous plaque</td>
<td>Congenital cutaneous aplasia vs fibrous hamartoma vs infantile fibromatosis</td>
<td>Fibrous hamartoma vs infantile fibromatosis (B; 2 y)</td>
<td>DFSP (B; 7 y)</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>5/F Foot</td>
<td>&lt;0.5</td>
<td>Small bluish plaque</td>
<td>Difficult to characterize</td>
<td>DFSP (B; 10 y)</td>
<td>+</td>
<td>After a trauma, apparition of a painful depressed plaque; size increasing up to 5 × 5 cm; E at 10 y</td>
<td></td>
</tr>
<tr>
<td>6/F Thigh</td>
<td>10</td>
<td>Large angiomatosus plaque</td>
<td>Angioma</td>
<td>Suggestion of DFSP (B; 3 y)</td>
<td>Some cells +</td>
<td>Size increasing, apparition of nodules from 3 to 11 y; no treatment*</td>
<td></td>
</tr>
<tr>
<td>7/F Trunk</td>
<td>4 × 1</td>
<td>Erythematous macula</td>
<td>Fibromatosis vs xanthomatous hamartoma vs congenital cutaneous aplasia vs infantile fibrosarcoma</td>
<td>Desmoid fibromatosis vs DFSP (B; 15 y and E; 15 y)</td>
<td>DFSP (2 y later†)</td>
<td>+† Rapid evolution into fibromatosic plaque with nodules; E at 15 y, complementary E 6 mo later</td>
<td></td>
</tr>
<tr>
<td>8/M Thorax</td>
<td>4.5 × 2</td>
<td>Hypodermic bluish lump</td>
<td>Fibrosarcoma vs angioma vs mastocytoma</td>
<td>DFSP (E; 3 y)</td>
<td>+†</td>
<td>Nodules at 2 y; E, 1.2 cm, at 3 y; complementary E, 3 cm</td>
<td></td>
</tr>
<tr>
<td>9/M Sacrum</td>
<td>8</td>
<td>Plaque</td>
<td>Sacrococcygeal teratoma</td>
<td>BT (E; 10 mo)</td>
<td>+</td>
<td>Limited E; no recurrence after 6 mo</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** B, biopsy; BT, Bednar tumor; DFSP, dermatofibrosarcoma protuberans; E, excision; NA, not available; ND, not done.

*A wide excision was recommended but was refused by the patient’s family.

†CD34 labeling was performed retrospectively when the antibody became commercially available.

### HISTOLOGIC AND MOLECULAR FINDINGS

**DFSP With Classic Histologic Patterns**

Cases 3, 5, 7, and 8 had histologic features similar to the adult classic pattern of DFSP (Table 2). The epidermis was normal or slightly thinned. The dermis and the subcutaneous fat showed a dense, poorly circumscribed, monomorphous cell proliferative mass arranged in interwoven fascicles with a typical “honeycomb” pattern (Figure 1). Proliferating cells were CD34+, PDGFB negative, SMA negative, and spindle shaped and did not show any atypia. Necrotic, fibrosarcomatous, and mitotic areas were absent. Case 7 was initially diagnosed as a desmoid fibromatosis because at the time of excision DFSP was not yet considered to be a tumor that affects children; moreover, anti–CD34 antibody was not available. The diagnosis was later revised to DFSP on the basis of the CD34+ labeling and the COL1A1-PDGFβ fusion gene detected by means of FISH. Case 9 presented as typical CD34+ DFSP containing pigmented neoplastic cells and was diagnosed as a BT. The COL1A1-PDGFβ fusion gene was
detected by FISH or RT-PCR in cases 3, 5, and 7 (Table 3 and Figure 1). The fusion genes identified by means of RT-PCR in cases 3 and 5 involved COL1A1 exons 46 and 48, respectively (Table 3), and merged FISH signals corresponding to the collagen, type I, α 1-platelet-derived growth factor β (COL1A1-PDGFB) fusion gene on the 2 abnormal chromosomes 22. The individual green and red signals correspond to COL1A1 on the 2 normal chromosomes 17 and PDGFB on the normal chromosome 22. 

DFSP With Peculiar Histologic Features

Cases 1, 2, 4, and 6 had some histologic features evocative of DFSP but also presented unusual features that made the diagnosis difficult. However, infiltration and immunohistochemical patterns as well as molecular data confirmed the diagnosis of DFSP. In cases 1, 2, and 4, histologic examination of early biopsy samples showed loose, dermal, monomorphic, spindle-shaped cell proliferation, sparing adnexal structures and extending to the upper subcutis (Figure 2 and Figure 4). In the subcutis, cell proliferation was arranged in interstitial bundles and was associated with interspersed mature fat. Tumor cells occasionally showed a vacuolated lipoblastlike light cytoplasm.

Cellular density was very low, without nuclear atypia, mitoses, or storiform pattern. There were always moderately dilated blood vessels, with thick hyaline walls. All the cases were CD34+, PS100 negative, and SMA negative. Initial diagnoses of fibrous hamartoma of infancy, angiomma, and lipoblastoma were often discussed before the results of the immunohistochemical study were known. Diagnosis of DFSP was established using RT-PCR and FISH analyses (fusion of the COL1A1 exon 32 with the PDGFB exon 2) for case 4 (Figure 2). For cases 1 and 2, the COL1A1-PDGFB fusion gene was detected by means of FISH analysis (RT-PCR could not be performed because of lack of good-quality RNA). Case 6 showed a combination of typical CD34+ spindle cells and dermal plump cells packed in small nodules surrounding numerous capillaries that did not express CD34 (Figure 3). No COL1A1-PDGFB fusion gene was detected by means of RT-PCR and FISH, and the tumor karyotype did not show any chromosomal abnormality (Figure 3).
We report a series of 9 congenital lesions that illustrate the difficulties and pitfalls of the recognition and diagnosis of childhood DFSP and highlight the benefit of immunohistochemical and molecular investigations. The most frequent anatomical locations in this series were the trunk (4 of 9 cases) and the proximal extremities (2 of 9 cases). This is consistent with locations previously reported in most congenital DFSP. The trunk and proximal extremities are also the most frequent sites for adult DFSP. However, as stressed by Weinstein et al, a clinical suggestion of congenital DFSP should not be ruled out because of a lower limb or head location, and pediatric DFSP may occur frequently in distal acral locations. All the lesions except 1 had a nonnodular clinical appearance, which was described. They were depicted using various terms, such as erythematous, pinkish, bluish, hypopigmented, angiomatous, depressed, atrophic, fibrous, infiltrated, or firm plaques, or as erythematous macules.

We noticed a significant delay (5 1/2 months to 15 years) between onset of the lesion and proper diagnosis. In some cases it was due to the innocuous appearance of the plaque, which did not prompt the parents to seek medical advice or the physician to perform a biopsy. In other cases, the delay was caused by an erroneous initial histologic diagnosis. This was the case for biopsies performed before 1995, which is before anti-CD34 labeling, which is now a powerful diagnostic tool for distinguishing DFSP from other tumors. In most cases, the initial clinical diagnoses were more often directed toward nonneoplastic or benign lesions, such as congenital cutaneous aplasia, hematoma, infantile fibromatositis, myofibromatosis, hamartoma, hemangioma, tufted angioma, mastocytoma, and teratoma.

In most cases, diagnoses were made on the basis of classic histologic and immunohistochemical features. Histologic recognition was particularly difficult because of the very small size of the skin biopsy samples, which usually ranged from 2 to 3 mm. These tiny biopsy samples did not allow a proper overview of the various aspects of the tumor. In particular, they were sometimes too superficial to include the "honeycomb" pattern and the high cellular density of the hypodermal infiltration. Moreover, the histologic patterns were sometimes misleading.

**Figure 2.** Case 4. A, Pinkish plaque with 6 cm of alopecia. The lesion was firm and fibrous. B, Thin biopsy specimen of the recurrence revealed the presence of a discrete proliferation of regular spindle-shaped cells in the deep dermis. Cellular density is slight and is associated with an abundant collagen matrix (hematoxylin-eosin, original magnification x25). C, Strong and diffuse expression of CD34 by tumor cells (labeling with anti-CA34 antibody, original magnification x25). D, Fluorescence in situ hybridization analysis on formalin-fixed, paraffin-embedded sections from the biopsy sample. Arrow indicates the merged green-red signal corresponding to the collagen, type I, alpha 1-platelet-derived growth factor (COL1A1-PDGFB) fusion gene in a tumor cell nucleus (hematoxylin-eosin, original magnification x100). E, Sequence of the COL1A1-PDGFB fusion gene detected by means of reverse transcriptase-polymerase chain reaction, showing an in-frame fusion of COL1A exon 32 (bold) with PDGFB exon 2. Total RNA was extracted from the formalin-fixed, paraffin-embedded biopsy fragment.
We noted that lesions that were histologically typical of DFSP were in older children vs biopsy samples with difficult-to-interpret histologic features. Thus, the confusing histologic appearance of some of the samples may be related to the very early stage of the lesions. For example, the tissue lacked hypercellularity or a storiform pattern and instead had loosely and angiomatosus stroma, plexiform arrangements, and even lipoblastlike tumoral

Table 3. Molecular Detection of the COL1A1-PDGFB Fusion Gene by Means of RT-PCR and FISH in 9 Congenital DFSP Cases

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sample Type</th>
<th>COL1A1-PDGFB Fusion Gene</th>
<th>Sample Type</th>
<th>COL1A1-PDGFB Rearrangement</th>
<th>Final Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FP and FrT</td>
<td>RNA negative</td>
<td>FrT/B-CC/E</td>
<td>Fusion</td>
<td>DFSP</td>
</tr>
<tr>
<td>2</td>
<td>FP/E</td>
<td>RNA negative</td>
<td>FP/E</td>
<td>Fusion</td>
<td>DFSP</td>
</tr>
<tr>
<td>3</td>
<td>FT/B</td>
<td>COL1A1 exon 48–PDGFB exon 2</td>
<td>CC/B</td>
<td>Fusion</td>
<td>DFSP</td>
</tr>
<tr>
<td>4</td>
<td>FP/B</td>
<td>COL1A1 exon 32–PDGFB exon 2</td>
<td>FP/B2</td>
<td>Fusion</td>
<td>DFSP</td>
</tr>
<tr>
<td>5</td>
<td>FP</td>
<td>COL1A1 exon 46–PDGFB exon 2</td>
<td>FP/E</td>
<td>Fusion</td>
<td>DFSP</td>
</tr>
<tr>
<td>6</td>
<td>CC</td>
<td>Negative</td>
<td>DC/B2</td>
<td>Negative</td>
<td>DFSP*</td>
</tr>
<tr>
<td>7</td>
<td>FP</td>
<td>RNA negative</td>
<td>FP/B</td>
<td>Fusion</td>
<td>DFSP</td>
</tr>
<tr>
<td>8</td>
<td>BP</td>
<td>RNA negative</td>
<td>Unknown</td>
<td>ND</td>
<td>DFSP</td>
</tr>
<tr>
<td>9</td>
<td>FP</td>
<td>Negative</td>
<td>Unknown</td>
<td>ND</td>
<td>BT</td>
</tr>
</tbody>
</table>

Abbreviations: B, biopsy; B2, second biopsy; BP, Bouin fluid-fixed, paraffin-embedded; BT, Bednar tumor; CC, cultured cells; COL1A1-PDGFB, collagen, type I, α1–platelet-derived growth factor β polypeptide; DC, dissociated cells; DFSP, dermatofibrosarcoma protuberas; E, excision; FISH, fluorescence in situ hybridization; FP, formalin-fixed, paraffin-embedded; FrT, frozen tissue; FT, fresh tissue; ND, not done; RNA, insufficient amount of RNA; RT-PCR, reverse transcriptase–polymerase chain reaction.

*This case of DFSP had peculiar histologic and clinical features.
cells. CD34 immunohistochemical positivity along with PS100 and SMA negativity was a relevant and crucial element of diagnosis by means of biopsy or excision. These tests helped to eliminate improper diagnoses, such as juvenile fibromatosis, infantile fibrosarcoma, and fibrous hamartoma of infancy. However, a CD34+ spindle cell proliferation of the reticular dermis does not always indicate a DFSP because a new entity called “dermal dendrocyte hamartoma” has recently been described in infancy. This entity can be confused with DFSP and can be distinguished by the absence of COL1A1-PDGFB rearrangement. At the histologic level, 1 case of congenital plaque was a BT. To our knowledge, this is the first description of a congenital BT among the 12 cases of BT reported in children.

Genetic investigations provide a powerful complementary tool for the diagnosis of DFSP. In this study, we performed conventional cytogenetic analysis of 3 cases. In 2 cases, the results were not informative because no chromosomal abnormality was detected. A normal karyotype may indeed represent the growth of stromal fibroblasts instead of tumor cells. In the other case, we observed an unbalanced t(17;22) translocation. This confirms that the cytogenetic hallmark of pediatric DFSP, GCF, and BT is a translocation and not a ring chromosome as in adults. It remains unresolved whether pediatric translocation derivative chromosomes undergo a transformation into ring chromosomes when the patient grows up and whether this transformation might be associated with the progression from plaque to nodular form. The presence of the COL1A1-PDGFB fusion gene specific to DFSP and variant tumors can be detected by means of RT-PCR and FISH (F.P., unpublished data, 2002-2006). We performed RT-PCR–based detection of the COL1A1-PDGFB fusion gene in 5 of the 9 lesions. The COL1A1-PDGFB fusion gene was detected in 3 cases, with breakpoints in COL1A1 exons 32, 46, and 48. These breakpoints have also been described in pediatric and adult DFSP. These data confirm the lack of a preferential COL1A1 breakpoint location correlating with the age of the patient, the histologic subtype, or any clinical particularity. In these 3 cases, the fusion gene was also detected by means of FISH analysis. The FISH analysis was also useful to identify the COL1A1-PDGFB fusion gene in 2 cases for which no RNA of sufficient quality could be obtained. In the 2 negative cases it is not known whether the negative results were because of lack of sensitivity of the RT-PCR and FISH methods or because of the absence of the COL1A1-PDGFB fusion gene. The absence of COL1A1-PDGFB may suggest a diagnosis of a lesion other than a DFSP. However, it has to be noticed that a small proportion of DFSP, estimated to be approximately 5% of cases, may contain gene rearrangements other than the classic COL1A1-PDGFB fusion. Herein, the diagnosis was finally made on the basis of the morphologic and immunohistologic pattern, although case 6 had some unusual features, such as the presence of foci of round cells.

These results in a series of congenital tumors indicate that the chromosomal rearrangements in these cases took place during pregnancy. Mechanisms of neoplasm formation in utero are still obscure. It can be hypothesized that illegitimate recombination between COL1A1 and PDGFB sequences might arise during embryogenesis or fetal development and lead to DFSP formation. To date, there are no epidemiologic data that identify any environmental or predisposing factors that may induce the development of prenatal DFSP. This warrants further investigation and could be facilitated by a systematic questionnaire about medical antecedents and maternal exposure in pediatric DFSP cases.

In conclusion, these data show that congenital forms of DFSP are often clinically misleading and that it is important to perform a biopsy on suspicious cutaneous lesions in infants. When a DFSP is histologically identified or suspected, COL1A1-PDGFB fusion gene detection will complete the investigations. From this experience, the multiplex RT-PCR analysis is useful for retrospective studies or to confirm a doubtful FISH result, but it is not the most appropriate method for routine diagnosis. In our hands, the method of choice for daily practice is FISH analysis. Fluorescence in situ hybridization on fresh or frozen samples allows better image resolution than FISH on paraffin-embedded samples; however, from a practical point of view, paraffin-embedded samples are easier to handle than frozen tissues. We recommend that a molecular analysis should be performed in any case of DFSP suspicion, preferably by means of FISH, otherwise by means of RT-PCR on paraffin-embedded samples, before performing large, often mutilating, surgical excision in infants.

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Author Contributions: Dr Pedeutour had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Maire, Fraitag, de Prost, and Pedeutour. Acquisition of data: Maire, Fraitag, Galmiche, Keslair, Ebran, Terrier-Lacombe, de Prost, and Pedeutour. Analysis and interpretation of data: Maire, Fraitag, Galmiche, and Pedeutour. Drafting of the manuscript:
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