The t(1;10)(p22;q24) TGFBR3/MGEA5 Translocation in Pleomorphic Hyalinizing Angiectatic Tumor, Myxoinflammatory Fibroblastic Sarcoma, and Hemosiderotic Fibrolipomatous Tumor

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Context.—Pleomorphic hyalinizing angiectatic tumor (PHAT) of soft parts, hemosiderotic fibrolipomatous tumor (HFLT), and myxoinflammatory fibroblastic sarcoma (MIFS) are 3 distinct entities of low-grade spindle cell mesenchymal neoplasm. These tumors have similar clinical presentations and partially overlapping but distinctive pathologic features. A recurrent translocation, t(1;10)(p22;q24), has been detected in a subset of PHAT, HFLT, MIFS, and HFLT/MIFS hybrid cases. Translocation t(1;10)(p22;q24) involves transforming growth factor β receptor 3 (TGFBR3) and meningioma-expressed antigen 5 (MGEA5) genes on chromosomes 1p22 and 10q24, respectively. However, the percentage of translocation in PHAT, HFLT, and MIFS varies significantly among different studies. The relationship among these tumors has been a controversial topic among experts.

Objective.—To discuss the diagnostic and functional significance of translocation t(1;10)(p22;q24) TGFBR3/MGEA5 rearrangement in HFLT, PHAT, and MIFS.

Data Sources.—PubMed was used for this study.

Conclusions.—Diagnosis of HFLT, PHAT, and MIFS is challenging because of a lack of unique morphologic, immunophenotypic, molecular, and cytogenetic markers. The recurrent t(1;10)(p22;q24) translocation and/or TGFBR3/MGEA5 rearrangement was reported in 55 patients, with a relatively even distribution among HFLT, PHAT, and MIFS (17 HFLT, 15 MIFS, 13 MIFS/HFLT, and 10 PHAT). This indicates that current morphology-based diagnostic criteria do not identify reliably the subset of soft tissue tumor with t(1;10) translocation. Genetic heterogeneity of these tumors is supported by the recent detection of a mutually exclusive, second recurrent genetic change, t(7;17) TOM1L2-BRAF translocation or BRAF amplification, in a subset of MIFS.

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The classification of soft tissue tumors has changed through the years. The changes include descriptions of new entities, redefinitions of old entities, incorporation of newly identified genetic changes, and other things. At the end of the last century, several groups described 3 new types of soft tissue tumors with similar clinical presentations: pleomorphic hyalinizing angiectatic tumor of soft parts (PHAT) in 1996, myxoinflammatory fibroblastic sarcoma (MIFS) in 1998, and hemosiderotic fibrolipomatous tumor (HFLT) in 2000. These tumors are listed as separate entities in the recently published WHO Classification of Tumors of Soft Tissue and Bone. A common recurrent genetic change, t(1;10)(p22;q24) translocation, was detected in a subset of HFLT, MIFS, HFLT/MIFS hybrid, and PHAT. Fluorescence in situ hybridization (FISH) demonstrated the break points within the genomic loci of transforming growth factor-β receptor 3 (TGFBR3) on chromosome 1p22 and meningioma-expressed antigen 5 (MGEA5) on chromosome 10q24. However, the percentages of this translocation in PHAT, HFLT, and MIFS vary significantly among different studies. The relationship between these tumors has been a controversial topic among experts in the field.

To help understand the significance of t(1;10)(p22;q24) translocation in HFLT, MIFS, and PHAT, we reviewed the clinicopathologic features of these tumors and the current views on their relationship. We then summarized all published cases with t(1;10)(p22–31;q22–25) translocation and/or TGFBR3/MGEA5 rearrangement detected by conventional karyotyping and FISH, respectively. Finally, we discussed the potential molecular mechanism of TGFBR3/MGEA5 rearrangement in the tumorigenesis of these lesions.
**Clinicopathologic Features of PHAT, HFLT, and MIFS, and Their Potential Relationship**

**Pleomorphic Hyalinizing Angiectatic Tumors of Soft Parts**

PHAT is defined as a rare, locally aggressive tumor consisting of spindled and pleomorphic cells, clusters of ectatic, fibrin-lined vessels, and inflammatory cells. It was originally reported in 1996 as a low-grade, slow-growing mesenchymal tumor resembling schwannoma because of several common features, such as unusual vasculature, intranuclear cytoplasmic inclusions, absence of mitosis, and mast cell abundance. Fewer than 100 cases have been reported to date; the largest series included 41 cases.

PHATs mainly occur in adults of both sexes during their fifth or sixth decade of life (range, 10–86 years). Tumor sizes range from 0.3 to 19.7 cm. The tumors frequently involve the subcutis of lower extremities, such as feet, ankles, and legs. Occasionally the tumor cells may extend to nearby skeletal muscle or superficial dermis with entrapment of skin adnexa. There are case reports of PHAT occurring at other body sites, such as the back, chest wall, buccal mucosa, breast, forearm, buttock, hilum of kidney, renal parenchyma, palpebra, and pelvic retroperitoneum. It is not clear whether these lesions represent real PHATs at sites other than extremities or tumors with PHAT-like changes. Imaging studies showed that PHAT is a heterogeneous subcutaneous or intramuscular lesion with ill-defined margins.

Grossly, tumors may be encapsulated, and they have partially infiltrative margins, which may contribute to frequent local recurrences (more than 30%). The cut surface is usually lobulated and usually tan-yellow to brown, depending on the degree and duration of hemorrhage. Although most tumors are solid, marked cystic degeneration has also been reported. There is a broad range of morphologic variations among PHATs. The minimal morphologic features of PHATs include: (1) ectatic hyalinizing blood vessels; (2) pleomorphic stromal cells; (3) no necrosis and rare or no mitotic figures (<1 of 50 high-power fields); (4) variable inflammatory infiltrate, mainly mast cells (eosinophils, lymphocytes, plasma cells, or a mixture can be present); and (5) infiltrative border with marked resemblance to HFLT (described as early PHAT). The blood vessels are thin-walled and ectatic, and frequently arise in clusters with intravascular thrombi. The vessel walls and surroundings are lined with different amounts of amorphous material, consistent with fibrin or collagen. The sizes of the vessels range from small (about 2–3 times the size of a small artery) to very large (grossly identified). The relative volume of the ectatic vessels may occupy up to 50% of the tumor. Fresh hemorrhage and hemosiderin deposits, including intracellular hemosiderin, reflecting prior hemorrhage, are common. The neoplastic cells include bland spindled to oval fibroblastic cells in bundles or sheets, and scattered large pleomorphic cells with nuclear pseudo-inclusion, low nuclear to cytoplasmic ratios, and moderate to abundant eosinophilic cytoplasm. Some cases may have MIFS-like features, such as myxoid stroma or ganglion-like cells with prominent nuclei similar to Reed-Sternberg-like cells. Both spindle and pleomorphic tumor cells are consistently positive for vimentin, with varied expression of CD34, factor XIIIa, VEGF, and CD99, but are negative for S100 protein, cytokeratin, desmin, epithelial membrane antigen, smooth muscle actin, HMB-45, MyoD1, p63, and CD31 (determined by immunohistochemistry). Tu-

mor cells have low proliferative indices, which are determined by either Ki-67 positivity (1%–3%) or percentage of S-phase cells, measured via immunohistochemistry or flow cytometry, respectively. Most Ki-67+ cells are large and pleomorphic. Focal high-grade sarcomas, with features similar to myxofibrosarcoma, have been reported in several cases, especially recurrences. Distant metastasis of PHAT has not been reported.

The Mayo Clinic group identified by FISH the t(1;10) TGFBR3/MGEA5 translocation as the only recurrent genetic change in PHAT with a relatively high frequency (8 of 12 cases; 67%). However, this translocation was not detected in several PHAT cases tested by other groups. A single case report of PHAT/HFLT showed a complex karyotype 45,XX,der(1)t(1;3)(p31;q12),−3,der(10)t(1;10)(p31;q25)[11]/46,XX[4]. However, FISH was not performed to confirm that the translocation t(1;10)(p31;q25), which is different from the typical t(1;10)(p22;q24), occurred within the genomic loci of TGFBR3 and MGEA5.

**Hemosiderotic Fibrolipomatous Tumor**

HFLT is defined as an unencapsulated, locally aggressive neoplasm composed of adipocytes and hemosiderin-laden spindle cells, focally prominent hemosiderin-laden macrophages, and scattered chronic inflammatory cells. In 2000, 10 cases of HFLT were described as heavily pigmented spindle cell proliferations within circumscribed benign lipomatous lesions, mainly occurring on the ankles of older women. HFLT was initially considered to be reactive, because of a prior history of trauma in most patients. In 2004, a HFLT-like component, initially named early PHAT, was reported in the periphery of all PHAT cases in which the periphery was evaluable. In 2006, Brown and Fletcher reported 13 cases of HFLT, and they specifically noted that PHAT-like lesions were not found in any cases. The authors proposed it to be a neoplastic process because of a consistent morphology and high frequency of local recurrences.

The patients with HFLT were mainly female (female to male ratio > 2:1) and in the fifth or sixth decade of life (ranging from 8 months to 74 years). The tumors involved lower distal extremities (ankles and feet) in more than 80% of patients. Cases involving other parts of the body, such as knees, thighs, hands, and cheeks, have been reported. Tumors grew up to 19 cm, and nearly half of the patients had a history of local trauma or vasculopathy. Magnetic resonance imaging studies usually show ill-defined, infiltrative subcutaneous lesions with heterogeneous signals suggesting mixed fatty and fibrous tissues.

Grossly, HFLT involves subcutaneous tissue with a circumscribed appearance. The cut surface of the tumor appears tan to yellow, and gelatinous or fatty lipoma-like. Microscopically, most tumors have at least partially infiltrative edges. This may contribute to the frequent local recurrences or residual disease (more than one-third) due to marginal/intraslesional excision. Three main components are identified with variable proportions in different cases: bland to slightly pleomorphic spindle cells, mature adipocytes, and hemosiderin pigments. The fatty component, comprising adipocytes of the same size, predominated in most cases. The adipocytes are divided into multiple lobules by fibrous septa containing bland spindle cells with vesicular nuclei and indistinct nuclei with slight atypia. Nuclear inclusions are not identified. Hemosiderin pigments are predominantly present in macrophages within spindle...
cell components. Most tumors contain scattered osteoclast-like giant cells. Scattered inflammatory cells and/or focal myxoid changes of the stroma may be seen in some cases. Mitoses are generally rare. The spindle cells are positive for vimentin, calponin, CD34, and occasionally CD68 (KP-1) or lysozyme, and are negative for caldesmon, S100 protein, smooth muscle actin, and desmin. Until the present, only 1 patient, initially receiving a diagnosis of HFLT, died of metastatic high-grade sarcoma after several recurrences.41

The recurrent cytogenetic changes in HFLT include the t(1;10) TGFBR3/MGEA5 rearrangement and amplification of VGLL3 locus on 3p12.1.7–9,32,41,42 It is notable that the detection rates of the TGFBR3/MGEA5 translocation vary significantly among different studies.

**Myxoinflammatory Fibroblastic Sarcoma**

MIFS is defined as a locally aggressive fibroblastic neoplasm that occurs primarily in distal extremities and is characterized by epithelioidfibroblasts with macronucleoli interspersed with a prominent mixed inflammatory infiltrate consisting of epithelioid fibroblasts with macronucleoli.6 In 1998, nearly concomitantly, interspersed with a prominent mixed inflammatory infiltrate characterized by epithelioid fibroblasts with macronucleoli neoplasm that occurs primarily in distal extremities and is thought with respect to the relationship between PHAT, HFLT, and MIFS are considered 3 different entities. Currently, there are 2 main schools of thought with respect to the relationship between PHAT, HFLT, and MIFS. The main issue of debate is whether MIFS is related or not to HFLT and/or PHAT.

Based on their extensive experience with PHAT, Boland and Folpe47 proposed that HFLT is the early stage of PHAT, whereas MIFS is not related to either HFLT or PHAT. The authors argue that the myxoid sarcoma component in the hybrid HFLT/MIFS cases does not have the classical morphologic features of MIFS and can only be called MIFS-like because the tumors do not have hyalinized zones and “Reed-Sternberg-like” or “virocyte-like” cells, even though they contain myxoid matrix, pleomorphic cells, pseudolipoblasts, and a mixed inflammatory cell infiltrate. In addition, classical cases of MIFS rarely seem to contain HFLT-like areas. The very low percentage of TGFBR3/MGEA5 rearrangements in classical MIFS in their prospective studies (3 of 37) and in another study (0 of 3) further supports the authors’ notion.8,9,45 Personally, we find it difficult and subjective to define the difference between classical MIFS and MIFS-like tumors, because of the nonspecificity of these morphologic features. Other experts do not deem hyalinized stroma to be a critical feature for MIFS, in contrast to the Mayo Clinic group. On the other hand, a significantly high rate of TGFBR3/MGEA5 rearrangement in MIFS was reported by 2 separate groups using FISH (7 of 9 cases; 77%).7,32,45 Half (6 of 12) of the t(1;10) translocation cases containing soft tissue tumor by conventional karyotyping were diagnosed as MIFS based on current standards.7,32,46,43

The Intertwined Relationship Between PHAT, HFLT, and MIFS

In the current World Health Organization classification, PHAT, HFLT, and MIFS are considered 3 different entities. However, because of their similar clinical presentation, overlapping morphologic features, and shared cytogenetic change of t(1;10) translocation, their relationship has been debated, with controversial opinions being held among different experts. Currently, there are 2 main schools of thought with respect to the relationship between PHAT, HFLT, and MIFS. The main issue of debate is whether MIFS is related or not to HFLT and/or PHAT.
The other view is that these tumors (HFLT, MIFS, and PHAT) likely represent different morphologic manifestations of a single genetic entity. Morphologic overlapping is manifested at several levels. The neoplastic cells in these tumors are likely derived from a similar population of mesenchymal origin. The tumor cells are bland spindle, rounded, or epithelioid. They present singly, in clusters or sheets. The tumor cells have a similar immunophenotype. Vimentin is always positive. CD34 is positive in most cases. Other lineage markers are always negative, including keratin, S100, smooth muscle actin, desmin, etc. Necrosis of tumor cells is not identified in general. Mitoses are rare, which is consistent with the slow growth of the tumor mass. The edges of all tumors are infiltrative, which contributes to frequent local recurrences. One feature to distinguish these tumors is the presence of either pleomorphic cells in PHAT, or virocyte-like or Reed-Sternberg-like large pleomorphic cells and/or pseudolipoblasts in MIFS. Tumor cells in HFLT show minimal pleomorphism and atypia. However, pleomorphic cells in some cases of PHAT were morphologically compatible with the pseudolipoblasts or virocyte-like cells or Reed-Sternberg-like cells in MIFS.\textsuperscript{12,20,30,51}

The stroma components of these tumors demonstrate large variation. HFLT is characterized by prominent mature adipocytes and marked hemosiderin deposition. PHAT has angiectatic, hyalinizing vasculature. Inflammatory infiltration and myxoid stroma are essential for MIFS. However, as described in their definition, both PHAT and HFLT have angiectatic, hyalinizing vasculature. MIFS has myxoid stroma. Hybrid tumors with mixed features of MIFS/HFLT are reported. All PHAT cases show HFLT-like changes at the periphery (early PHAT). Necrosis and/or mitosis may prompt consideration of high-grade sarcoma.

The presence of hybrid lesions with features of 2 or more tumors provides additional evidence to place these tumors under the same umbrella. Hybrid MIFS/HFLT tumors exhibit the synchronous or metachronous presence of HFLT and MIFS.\textsuperscript{7,32,41,52,53} All PHAT cases have HFLT-like lesions at the periphery of the tumors.\textsuperscript{8–10} Several experts propose that PHATs may merely be MIFS associated with angiectatic-hyalinized vessels because of their morphologic similarities.\textsuperscript{44,54} We recently diagnosed a slowly growing subcutaneous mass on the ankle of a 56-year-old woman as PHAT (Figure 2, A through D). HFLT-like (Figure 2, E) and MIFS-like (Figure 2, F through H) lesions were identified in different areas of this case. Rearrangement of TGFBR3/MGEA5 was confirmed by FISH (data not shown).

Translocation of t(1;10) TGFBR3 and/or MGEA5 lends further support to consider HFLT, PHAT, and MIFS as a single entity. However, t(7;17) TOM1L2-BRAF translocation or BRAF amplification was detected in a subset of MIFS cases recently.\textsuperscript{46} These 2 recurrent genetic changes are mutually exclusive in the few cases tested despite the similar morphology of the tumors. Therefore, these tumors (HFLT, MIFS, and PHAT) have a heterogeneous genetic background. To facilitate further understanding of the role of t(1;10) in these tumors, we summarized all published cases carrying this translocation.

**CLINICOPATHOLOGIC FEATURES OF SOFT TISSUE TUMORS WITH t(1;10) TRANSLOCATION AND/OR TGFBR3/MGEA5 REARRANGEMENT**

Translocation t(1;10)(p22–31;q22–25) was first reported in 1995 for a case of grade 1 myxoid malignant fibrous histiocytoma\textsuperscript{49} prior to a formal description of PHAT, HFLT, and MIFS. Based on current standards, the best classification for the case is MIFS. In 2001, the translocation t(1;10)(p22;q24) was reported in a case of MIFS, and FISH confirmed that the break point was distal to G0T1 gene on chromosome 10q24 and proximal to BCL10 gene on 1p22.\textsuperscript{48} In 2008, t(1;10)(p22;q24) was reported in a case of HFLT.\textsuperscript{41} In 2009, 4 cases of MIFS and 1 case of HFLT were found to have t(1;10)(p22;q24) in PHAT, MIFS, and HFLT—Liu, Sukov, & Ro
Figure 2. A case of pleomorphic hyalinizing angiectatic tumor (PHAT) from the right ankle of a 58-year-old woman shows morphologic features of classical PHAT (A through D) with areas compatible with hemosiderotic fibrolipomatous tumor (HFLT; E) and myxoinflammatory fibroblastic sarcoma (MIFS; F through H). A, Low-power image showing neoplastic spindle cell proliferation intermixed with mature adipose tissue, areas of myxoid stroma, angiectatic vessels with thrombi, and hemosiderin deposits. B, Bland neoplastic spindle cell proliferation in interlacing fascicles. A thrombus (arrow) is visible in a small arteriole. C, Extensive perivascular hyalinizing material consistent with collagen within a cluster of angiectatic vessels with thrombi. D, A large pleomorphic cell, hemorrhage, and prominent hemosiderin (including intracytoplasmic) deposition with scattered t(1;10)(p22;q24) in PHAT, MIFS, and HFLT—Liu, Sukov, & Ro
Table 1. Summary of Reported Soft Tissue Tumor Cases With t(1;10) Translocation

<table>
<thead>
<tr>
<th>No.</th>
<th>Karyotype</th>
<th>Diagnosis</th>
<th>Age, y/ Sex</th>
<th>Site</th>
<th>Follow-up, mo</th>
<th>Source, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46,X,-X,add(1)(q21 or q32);t(1;10)(p22;q22),+14[2]/46,XX,add(1)(p11)[2]/46,XX[5]</td>
<td>MIFS</td>
<td>43/F</td>
<td>Dorsal foot</td>
<td>9/NED/R0</td>
<td>Szymanska et al,49 1995</td>
</tr>
<tr>
<td>2</td>
<td>39–44,XX,der(1)[t(1;10)(p22;q24)] [8],del(1)[p22][2],–3,del(1)[p11][4],der(10)[t(1;10)(p22;q24)],–13,–13[5],add(14)[p11][3],der(13:14)(q10)[10][2],–16[3],add(16)[q24][5],–18[5],–21[9],–22[6],andder(22)[t(3:22)p11][6]</td>
<td>MIFS</td>
<td>53/F</td>
<td>Dorsal foot</td>
<td>NA</td>
<td>Lambert et al,44 2001</td>
</tr>
<tr>
<td>3</td>
<td>46,XX,t(1;10)[p31;q25][4]/45,XX,1,der(3)[t(1;10)[1;10];3][q12;p13],der(10)[t(1;10)[p31;q25]] [11]/46,XX[5]</td>
<td>HFLT</td>
<td>35/F</td>
<td>Dorsal foot</td>
<td>NA</td>
<td>Wettach et al,42 2008</td>
</tr>
<tr>
<td>4+</td>
<td>43–46,XX,add(1)[q21],der(1)[t(1;10)[p22][q24]],t(3)x1–2,add(1)[p16],add(6)[p25],der(10)[t(1;10)(p22;q24)],–17,–21</td>
<td>MIFS</td>
<td>41/F</td>
<td>Dorsal foot</td>
<td>128/NED/R3</td>
<td>Hallor et al,7 2009</td>
</tr>
<tr>
<td>5</td>
<td>41–42,XX,del(1)[q11];–2,der(3)[t(3;10)[p21];q],–9,add(10)[t(24),del(10)[q22],der(12)[add(12)<a href="t(1;10)%5Bt(1;10)(p22);q22">t(11)</a>,add(14)[q32],add(16)[p11],–17,add(21)[p11],–22,–22</td>
<td>MIFS</td>
<td>45/M</td>
<td>Lower leg</td>
<td>84/AWD/R1</td>
<td>Hallor et al,7 2009</td>
</tr>
<tr>
<td>6</td>
<td>Second recurrence: 45,X,t(X;7)[p22][12],–1,der(3)[t(1;3)[q25];q27][del(3)[p21][p23],der(10)[t(1;10)(p22;q24),–13,–r;91,XXX,t(X;7),–1,der(3)[t(1;3)[del(3),der(10)[t(1;10),–13,–r]+</td>
<td>MIFS</td>
<td>38/F</td>
<td>Dorsal foot</td>
<td>260/AWD/R7</td>
<td>Hallor et al,7 2009</td>
</tr>
<tr>
<td>7</td>
<td>Fourth recurrence: 45,X,t(X;7),–1,der(3)[t(3;1;3)[del(3),der(10)[t(1;10),–13,–r]+</td>
<td>MIFS</td>
<td>83/M</td>
<td>Lower leg</td>
<td>15/DOC/R0</td>
<td>Hallor et al,7 2009</td>
</tr>
<tr>
<td>8+</td>
<td>61,XY,–X,–Y,+1,1(t(1;10)[p22];q24),–2,–3,–4,–5,–7,–8,–9,add(9)[p22],–10,add(11)[p15],–15,–18,–21,–mar,DMIN</td>
<td>MIFS</td>
<td>40/F</td>
<td>Dorsal foot</td>
<td>71/AWD</td>
<td>Hallor et al,7 2009</td>
</tr>
<tr>
<td>9+</td>
<td>45,X,add(1)[p21],der(3)[t(21)[p25];q21][ins(3)[p25];q21],t(8;14)[q33][t(10)[t(1;10)(p22;q24)] ,der(10)[t(1;10)(p22;q24)],–1+</td>
<td>HFLT</td>
<td>40/F</td>
<td>Ankle</td>
<td>8/NED/R0</td>
<td>Antonescu et al,52 2011; and Elco et al,53 2010</td>
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<tr>
<td>10+</td>
<td>45,X,add(1)[p22],add(3)[t(15)[p21];q26],der(10)[t(1;10)[p22];q24],–1+</td>
<td>MIFS/HFLT</td>
<td>32/F</td>
<td>Foot</td>
<td>NA</td>
<td>Antonescu et al,52 2011</td>
</tr>
<tr>
<td>11+</td>
<td>46,X,add(1)[p22],add(3)[p11],der(10)[t(1;10)[p22];q24][24]/46,XX,add(1)[p21],add(3)[p21],der(10)[t(1;10)[2]/45,XX,add(1)[p13],–3,add(3)[p21],der(10)[t(1;10)[1]/46,XX,del(1)[q11],add(1)[p13],der(3)[t(3;1)[q11][p13],der(10)[t(1;10)][1]</td>
<td>MIFS/HFLT</td>
<td>44/F</td>
<td>Foot</td>
<td>NA</td>
<td>Antonescu et al,52 2011</td>
</tr>
<tr>
<td>12</td>
<td>45,XX,del(1)[t(1;3)[p31][q12],–3,der(10)[t(1;10)[1;25][q11][46,XX][4]</td>
<td>PHAT</td>
<td>37/F</td>
<td>Dorsal foot</td>
<td>&gt;60/??/R1</td>
<td>Wei et al,14 2012</td>
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</table>

Abbreviations: AWD, alive with disease; DOC, dead of other causes; HFLT, hemosiderotic fibrolipomatous tumor; MIFS, myxoinflammatory fibroblastic sarcoma; NED, no evidence of disease; PHAT, pleomorphic hyalinizing angiectatic tumor; NA, not available; R, recurrence; 60/??/R1, the disease outcome for this patient was not documented in the literature.

* TGFBR3/MGEA5 rearrangement was confirmed by fluorescence in situ hybridization.

contain the same translocation.7 It is notable that in this study, 3 cases of MIFS were initially diagnosed as myxofibrosarcoma, 1 as myxoid malignant fibrous histiocytoma, whereas HFLT was originally diagnosed as dermatofibrosarcoma protuberans. To date, the t(1;10)(p22–31;q22–25) translocation has been detected by conventional cytogenetic karyotyping in a total of 12 cases (Table 1). The patients ranged from 32 to 83 years of age (median, 41.5). Female patients predominated, with a female to male ratio of 10:2. The tumors were located in the lower extremities: feet (8), ankles (2), and lower legs (2). The diagnoses of the tumors were MIFS (6), HFLT (3), mixed inflammatory cells. E, HFLT-like area showing fibrin-lined angiectatic vessels with thrombi adjacent to mixed spindle cells and mature adipose tissue with hemosiderin deposit. F, MIFS-like area showing scattered large pleomorphic cells and bland spindle cells floating in myxoid stroma, and scattered inflammatory cells. G, A Reed-Sternberg-like binuclear cell with prominent eosinophilic nuclei. H, A pseudolipoblast with hyperchromatic, irregular nucleus surrounded by myxoid cytoplasm. Two mature lymphocytes are seen inside the cell, consistent with emperipolesis (hematoxylin-eosin, original magnifications ×40 [A], ×100 [B, C, and E], ×400 [D, G, and H], and ×200 [F]).
Abbreviations: rMGEA5

rMGEA5 contained an HFLT-like component, but none of the HFLT translocation (Table 1). Morphologically, all PHAT cases stratified complex karyotypes in all tumors with t(1;10) discussed earlier, conventional cytogenetic studies demonstrated complex karyotypes in all tumors with t(1;10) translocation (Table 1). Morphologically, all PHAT cases contained an HFLT-like component, but none of the HFLT cases had areas resembling classical PHAT. Two cases of hybrid HFLT/MIFS were initially diagnosed as HFLT and recurred as MIFS. Follow-up information was available for only a few patients (Table 1); more than 60% of the patients had persistent or relapsed disease. Local recurrences were detected in all patients who were monitored for more than 5 years. One patient progressed from HFLT to MIFS, and died of extensive metastases. One PHAT case had focal high-grade myxoid sarcoma with necrosis and increased mitosis, although no follow-up data were available. There was no clinical or morphologic difference between these cases of HFLT, MIFS, hybrid HFLT/MIFS, and PHATs, with or without rearrangement.

**POTENTIAL MOLECULAR MECHANISM OF t(1;10) TRANSLOCATION-MEDIATED TUMORIGENESIS**

Although t(1;10) TGFB3/MGEA5 rearrangement is a recurrent cytogenetic change in HFLT, MIFS, and PHAT, the functional significance of t(1;10) in these tumors was only explored in the initial study. One unique feature of this translocation is the assumption that an oncogenic chimera TGFB3/MGEA5 protein is not formed because the 3’ sequences from TGFB3 and MGEA5 are juxtaposed in opposite directions on the der(10)t(1;10) chromosome. Because, using genome-wide microarray analysis and real-time quantitative polymerase chain reaction, the mRNA levels of TGFB3 and MGEA5 in 3 tumor specimens (2 MIFS and 1 HFLT) with t(1;10) were similar to those in 2 control tumor specimens (1 MIFS and 1 pleomorphic sarcoma with prominent inflammation) without translocation and the controls, the authors excluded a direct role for both TGFB3 and MGEA5 in the formation of these tumors. Instead, they proposed that upregulation of FGF8 and/or NPM3, genes downstream of MGEA5 on chromosome 10, potentially contributed to the tumorigenesis. To date, no follow-up studies have been performed to confirm their hypothesis.

The unbalanced translocation causes heterozygosity of TGFB3 and MGEA5, which theoretically should reduce full-length mRNA and protein expression by half. A change of less than 2-fold is expected for the mRNA levels of both TGFB3 and MGEA5 between tumors with and without translocation because of contaminating stroma cells and inflammatory cells. This minor difference is generally not considered significant by microarray analysis or real-time quantitative polymerase chain reaction. In addition, these assays do not distinguish truncated or short gene transcripts from full-length products. Therefore, the evidence presented in the initial study was not convincing enough to rule out a direct role for TGFB3 and MGEA5 in tumor formation.

**Table 2. Summary of Fluorescence In Situ Hybridization Studies on Hemosiderotic Fibrolipomatous Tumor (HFLT), Pleomorphic Hyalinizing Angiectatic Tumor (PHAT), Myxoinflammatory Fibroblastic Sarcoma (MIFS), and Mixed HFLT/MIFS**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. (%)</th>
<th>F:M</th>
<th>rTGFB3, No. (%)</th>
<th>rMGEA5, No. (%)</th>
<th>rTGFB3/MGEA5, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIFS</td>
<td>10 (20.8)</td>
<td>5:3</td>
<td>0 (0)</td>
<td>4 (40)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>HFLT</td>
<td>16 (33.3)</td>
<td>10:2*</td>
<td>1 (6.3)</td>
<td>1 (6.3)</td>
<td>14 (87.5)</td>
</tr>
<tr>
<td>HFLT/MIFS</td>
<td>13 (27.1)</td>
<td>8:5</td>
<td>3 (23.1)</td>
<td>0</td>
<td>10 (76.9)</td>
</tr>
<tr>
<td>PHAT</td>
<td>9 (18.8)</td>
<td>5:4</td>
<td>1 (11.1)</td>
<td>2 (22.2)</td>
<td>6 (66.7)</td>
</tr>
<tr>
<td>Total</td>
<td>48 (100)</td>
<td>32:12</td>
<td>5 (10.4)</td>
<td>7 (14.6)</td>
<td>36 (75)</td>
</tr>
</tbody>
</table>

Abbreviations: rMGEA5, rearranged MGEA5 only; rTGFB3, rearranged TGFB3 only; rTGFB3/MGEA5, both TGFB3 and MGEA5 are rearranged.

*a The accurate number of female and male patients cannot be determined from the literature. Among the 16 patients, 10 of them are female.
Both 1p22 and 10q24 regions have been found as nonrandom sites of deletion and translocation in a variety of human neoplasms, such as lymphoma and leukemia, melanoma, mesothelioma, carcinoma, leiomyosarcoma, and others.55–57 However, to date, the recurrent translocation of t(1;10) TGFBR3/MGEA5 has only been detected in HFLT, MIFS, and PHAT, implicating a disease-specific or even pathognomonic role. Both genes have been involved in the development and progression of multiple tumors.58–66 TGFBR3 is considered to be a tumor suppressor gene. Therefore, loss of 1 copy of each gene may have additive effects in promoting tumor formation. Alternatively, short isoforms or truncated gene products of TGFBR3 and/or MGEA5 with tumorigenic function cannot be ruled out completely.

MGEA5 Gene

MGEA5 was initially identified as a novel homolog of Caenorhabditis elegans hyaluronidase, by screening a meningioma expression library.67 Gene MGEA5 was mapped to human chromosomal band 10q24.1–q24.3. It encodes 2 isoforms. The short isoform (exons 1–10) has 677 amino acids (135 kDa) and is localized in the nucleus. The full-length isoform (exons 1–16) has 916 amino acids (135 kDa) and is localized in the cytoplasm. It is the only human hyaluronidase to remove O-linked β-N-acetylglucosamine (GlcNAc) from serine or threonine in proteins (O-GlcNA-case).58,69 Numerous intracellular and extracellular proteins are modified by GlcNAc, which induces a dynamic posttranslational modification similar to phosphorylation. This permits quick functional switching without protein synthesis or degradation.

Hyaluronidase and its substrate hyaluronic acid have been suggested to play a pivotal role in tumor development and metastasis.66,70 The mRNA levels of MGEA5 are altered in several different types of carcinoma.54–61 The myxoid stroma in MIFS contains hyaluronic acid, as confirmed by special stain Alcian blue.3 Reduced expression of MGEA5 in the heterozygous tumor cells may contribute to the accumulation of hyaluronic acid in the stroma, which protects tumor cells from immune attack but also prevents tumor cells from metastasis, explaining the low rate of metastasis in these tumors. Enzymatic digestion of hyaluronic acid by the hyaluronidase produced from the remaining allele generates small fragments of angiogenic oligosaccharides, which are able to stimulate endothelial cell proliferation and neovascularization.71

TGFBR3 Gene

TGFBR3 (also called β-glycan) is 1 of the 3 cell surface receptors for TGF-β cytokine.54,72,73 The gene is located on chromosome 1p22.1. The full-length protein (93.5 kDa, 851 amino acids) comprises a large, highly glycosylated extracellular ligand–binding domain (766 amino acids), a hydrophobic transmembrane domain, and a short cytoplasmic domain (42 amino acids).54,74–76 It mainly functions as a coreceptor for TGFBR2 or inhibitin, and mediates a complicated downstream signaling network involving both SMAD-dependent and SMAD-independent pathways. Its function is highly pleiotropic and context dependent.

TGFBR3 is considered a tumor suppressor gene. Loss of TGFBR3 expression, due to loss of heterozygosity or due to transcriptional downregulation, frequently occurs during initiation, progression, or metastasis of multiple human carcinomas, hematologic malignancies, osteosarcomas, and gliomas.62–66 In contrast, restoration of TGFBR3 expression in different cancer cells inhibits tumor invasion, angiogenesis, and metastasis. Therefore, reduced expression of TGFBR3 and MGEA5, caused by t(1;10) translocation, may have additive effects in promoting local neoplastic proliferation and invasion but preventing distant metastasis.

In summary, our analysis demonstrates that t(1;10) is a recurrent translocation occurring in HFLT, MIFS, and PHAT, 3 distinctive low-grade soft tissue tumors with similar clinical presentations and overlapping pathology. A total of 55 cases with t(1;10) TGFBR3/MGEA5 rearrangement have been reported. All of the tumors occurred at the extremities, with feet as the most frequent site. There was a female predominance. A high frequency of local recurrence was found. Metastasis was observed in 1 case only. The diagnoses were 17 HFLT, 15 MIFS, 13 mixed MIFS/HFLT, and 10 PHAT, thus confirming a wide range of morphologic variation and a lack of unique features to predict the translocation. The marked differences of reported TGFBR3/MGEA5 percentages in these tumors in different studies may be attributed to the small specimen sizes and diagnostic variation among different experts. The fact that t(1;10) TGFBR3/MGEA5 rearrangement only occurred in these tumors implicates the potential functional significance of both TGFBR3 and MGEA5 in the tumorigenesis of these lesions, an idea that merits further investigation. With similar clinical presentation, clinical management, and prognosis of PHAT, HFLT, and MIFS, classification of these tumors by molecular genetic changes, such as t(1;10) TGFBR3/MGEA5 rearrangement, t(7;17) TOM1L2-BRAF translocation, or BRAF amplification, may be a better approach.

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References


