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BRIEF COMMUNICATION

SNP array and FISH findings in two pleomorphic hyalinizing angiectatic tumors

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Pleomorphic hyalinizing angiectatic tumor (PHAT) is a rare soft tissue tumor of intermediate malignancy and uncertain cellular origin and lineage of differentiation. Although PHAT is still poorly characterized at the genetic level, there is a potential genetic overlap with two other soft tissue tumors: myxoinflammatory fibroblastic sarcoma (MIFS) and hemosiderotic fibrolipomatous tumor (HFLT); MIFS and HFLT share a characteristic t(1;10)(p22;q24) with breakpoints in the *TGFBR3* locus on chromosome 1 and near the *MGEA5* locus on chromosome 10. Recently, a PHAT with a similar t(1;10) was reported, suggesting a genetic link between MIFS/HFLT and PHAT. To ascertain whether PHAT is also associated with this translocation, two cases were subjected to single nucleotide polymorphism (SNP) array and fluorescence in situ hybridization analyses. Neither PHAT showed a t(1;10) or other types of rearrangement of the *TGFBR3* or *MGEA5* loci. Both tumors showed imbalances in the SNP array analysis, but none was shared. Thus, the results indicate that PHAT is genetically distinguishable from MIFS and HFLT, but further studies are needed to identify the salient genetic pathways involved in PHAT development.

Keywords Pleomorphic hyalinizing angiectatic tumor, PHAT, SNP array, FISH

Pleomorphic hyalinizing angiectatic tumor (PHAT) is a locally recurrent but non-metastasizing tumor of soft parts of undetermined cellular origin and lineage of differentiation. It typically arises in the subcutaneous soft tissue of adults and shows no gender predilection. Microscopically, it is characterized by small clusters of ectatic, fibrin-lined, thin-walled blood vessels surrounded by a mitotically inactive, atypical spindled stroma. The cells contain polymorphic nuclei, and the stroma contains large areas of hyalinization and variable inflammatory infiltrate (1,2). Recent studies have shown a possible morphologic and genetic overlap with two other soft tissue tumor types: myxoinflammatory fibroblastic sarcoma (MIFS) and hemosiderotic fibrolipomatous tumor (HFLT). In the latter two tumors, a recurrent t(1;10)(p22;q24) has been reported (3,4). The breakpoints in chromosome arm 1p map to the *TGFBR3* gene, and the breakpoints in 10q are located in or near the *MGEA5* locus. Often, the translocation is unbalanced, with only the der(10)t(1;10) being present (3,4). In both balanced and unbalanced translocations, the 3′ region of *TGFBR3*, which is transcribed from centromere to telomere, is translocated to chromosome 10, at or near the 3′ region of *MGEA5*, which is transcribed from telomere to centromere; thus, the transcriptional orientation of the two genes makes a functional fusion gene an unlikely outcome of the translocation. Instead, transcriptional deregulation of the *FGF8* gene, located downstream of *MGEA5* on chromosome 10, has been associated with the translocation (3). In addition to the t(1;10), MIFS and HFLT share frequent amplification of proximal 3p, including the *VGLL3* gene, which is highly expressed when amplified (3,4); however, amplification of 3p has also been detected in other tumor types (5).

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To our knowledge, there are cytogenetic data on only one PHAT, which showed the karyotype 45,XX,der(1)t(1;3)(p31;q12),-3,der(10)t(1;10)(p31;q25) and includes an unbalanced t(1;10) that is very similar to the one reported in MIFS and HFLT (6). Here, we report two cases of PHAT that were investigated for genetic alterations using single nucleotide polymorphism (SNP) array and fluorescence in situ hybridization (FISH) analyses for rearrangement of the *TGFBR3* and *MGEA5* loci.

Materials and methods

Tumors

Two cases of PHAT were investigated. Case 1 was a 58-year-old woman, who for 1 year had noticed a slowly growing tumor in her big toe. A preoperative needle biopsy was suggestive of PHAT. The 30 × 15 × 15 mm subcutaneous lesion was excised with a marginal margin. The tumor was partly encapsulated and showed infiltrative growth. The patient remains disease-free 1 year after surgery. Case 2 was a 33-year-old man with a several year history of swelling above the right knee. After trauma to this area, he noticed some increase in size and mild tenderness. A preoperative needle biopsy was suggestive of PHAT. The lesion, measuring 45 × 35 × 25 mm, was excised with a narrow margin. Macroscopically, the lesion was poorly delineated and had whitish to brownish cut surfaces. One year after surgery, there are no signs of recurrent disease. The morphology and immunophenotype of the two cases were consistent with PHAT (Figure 1, A and B).

Cytogenetic and FISH analyses

Cell culturing and chromosome banding analysis of cells from case 1 were performed as previously described (7). FISH was performed as described (8), using pools of bacterial artificial chromosome (BAC) probes for the *TGFBR3* and *MGEA5* loci to search for a potential t(1;10) and alternate rearrangements of the *TGFBR3* locus. The BAC probes were the same as those used by Antonescu et al. (4), including three probes on either side of *TGFBR3* and three probes on the telomeric side of *MGEA5*; however, due to cross hybridization of BAC probe RP11-163M2 with another chromosome when testing the probe on normal metaphase spreads, only two BAC probes were used for the centromeric side of the *TGFBR3* locus. To ensure that tumor cells were analyzed, the BAC probes were combined with a centromere-specific probe for chromosome 6 (Abbott Molecular, Des Plaines, IL) in case 2, and with a probe for the *ETV6* gene in 12p13 (Vysis LSI TEL/AML1 ES Dual Color Translocation Probe, Abbott Molecular) in case 1.

SNP array analysis

Both cases were analyzed by SNP array. The DNA was extracted from snap-frozen tumor biopsies using the DNeasy Tissue Kit, including the optional RNase A treatment (QIAGEN GmbH, Hilden, Germany). The SNP array analysis was performed using the Illumina Human Omni-Quad version 1.0 BeadChip (Illumina, San Diego, CA) as previously described (9). The positions of SNPs were according to the UCSC hg 18/NCBI Build 36 in case 1 and the UCSC hg 19/NCBI Build

Table 1 SNP array findings in two pleomorphic hyalinizing angiectatic tumors

Chromosome	Cytogenetic band	Aberration	Position of the first abnormal SNP	Position of the last abnormal SNP	Position of the last normal SNP	Position of the first normal SNP	Aberration size (Mb)[a]
Case 1[b]							
11	q14.3–22.2	HD	89,197,483	95,371,352	88,744,425	95,766,067	6.173
12	p11–13	HD	1	31,674,834	–	31,821,111	31.674
14	q11–23	Subclonal HD	18,397,682	60,652,103	–	–	42.254
14	q23–q32	HD	60,683,430	107,287,663	–	–	46.604
Case 2[c]							
1	p21.3	HD	93,297,180	99,573,733	93,181,013	100,065,568	6.276
1	p21.2	HD	100,765,696	101,622,960	100,065,568	101,767,274	0.857
1	p11–22	HD	103,916,755	121,485,163	102,546,748	141,825,659	17.568
1	p36.12	HD	21,996,848	22,054,427	21,993,170	22,068,259	0.057
6	Entire chromosome	HD	–	–	–	–	Entire chromosome
9	p22–24	HD	46,587	29,942,472	–	29,942,472	29.895
9	p21	HomD	20,178,680	22,489,243	20,176,715	22,492,584	2.310
15	q13–14	HD	32,900,295	35,391,526	32,515,849	35,698,349	2.491
15	q14–15	HD	38,161,914	45,074,519	38,123,182	45,400,358	6.912
15	q25–26	HD	87,906,904	98,285,658	87,887,951	98,430,315	10.378
16	q12.1	HD	46,402,997	51,362,257	35,278,262	51,535,063	4.959
21	Entire chromosome	HD	–	–	–	–	Entire chromosome

Abbreviations: HD, hemizygous deletion; HomD, homozygous deletion.

[a] Based on first and last abnormal SNPs.

[b] Positions according to UCSC hg18/NCBI Build 36.

[c] Positions according to UCSC hg19/NCBI Build 37.