Abstract. Diffuse-type tenosynovial giant cell tumor (TSGCT) is a locally aggressive neoplasm that primarily affects the synovium and tendon sheath in young adults. Rearrangement of chromosome band 1p13 is now considered a characteristic genetic feature of TSGCT, with the most frequent chromosomal alteration t(1;2)(p13;q37). Here, we describe a unique cytogenetic finding of diffuse-type TSGCT arising in the ankle of an 18-year-old woman. Magnetic resonance imaging demonstrated an ill-defined juxta-articular mass with decreased signal intensity on both T1- and T2-weighted images. Contrast-enhanced T1-weighted images showed intense enhancement of the mass. Open complete resection was performed. Histologically, the tumor was composed of mononuclear cells admixed with multinucleated osteoclast-like giant cells, foam cells, siderophages and inflammatory cells. Cytogenetic analysis revealed a reciprocal translocation involving chromosomes 1 and 17, concomitant with a few other numerical and structural alterations. In addition, trisomy 5 as the sole anomaly was identified in two metaphase cells. To the best of our knowledge, this is the first report of this neoplasm with t(1;17)(p13;p13).

Tenosynovial giant cell tumor (TSGCT) has been divided into two main subtypes with different clinical features and biological behavior (1). The localized type, also known as giant cell tumor of tendon sheath, typically presents as a well-circumscribed soft tissue mass in the fingers. The local recurrence rate is 4% to 30% but these recurrences are cured by re-excision (1). Diffuse-type TSGCT, often referred to as pigmented villonodular synovitis, is defined as a poorly-circumscribed, infiltrative soft tissue mass that usually occurs in large joints. This potentially aggressive lesion recurs in 18% to 50% of cases, occasionally necessitating radical surgery (1).

To date, clonal chromosomal aberrations have been described in 18 localized and 28 diffuse TSGCTs (2-16). The short arm of chromosome 1, in particular 1p11-13, is frequently involved in TSGCTs. Several chromosomal segments have been recognized as translocation partners to 1p11-13, and the most preferred rearrangement is t(1;2)(p11-13;q35-37). Further molecular analyses of this translocation have led to the identification of a novel collagen type VI alpha3 (COL6A3)-colony stimulating factor 1 (CSF1) fusion gene (17, 18). In addition, another possible cytogenetic subgroup might be characterized by translocations involving 16q24 (4, 9, 13, 14). Trisomy for chromosome 5 or 7, usually as the sole anomaly, has been detected only in the diffuse type. In this article, we report a new case of diffuse-type TSGCT with a t(1;17) translocation and trisomy 5. We also review the cytogenetic and molecular genetic characteristics of TSGCT.

Case Report

An 18-year-old woman presented with a 6-month history of a slowly-growing, painless mass in the lateral aspect of the left ankle. There was no history of antecedent trauma. Physical examination revealed a 5-cm, elastic soft, poor mobile, non-tender mass. Neurological and vascular examinations were unremarkable. Laboratory values were within the normal ranges. Plain radiographs showed soft tissue swelling without calcification or cortical bone erosion. Magnetic resonance imaging revealed an ill-defined juxta-articular mass. The mass exhibited intermediate signal intensity on T1-weighted images (Figure 1A) and predominantly low signal intensity on T2-weighted images (Figure 1B). Contrast-enhanced T1-weighted images demonstrated intense enhancement of the mass (Figure 1C).

The patient underwent a core needle biopsy and the pathological diagnosis was diffuse-type TSGCT. Open complete resection was performed. Histologically, the tumor
was composed of mononuclear cells admixed with multinucleated osteoclast-like giant cells, foam cells, siderophages and inflammatory cells (Figure 2A and B). Atypical mitoses and nuclear atypia were not present. These findings confirmed the diagnosis of diffuse-type TSGCT. The postoperative course was uneventful, and the patient is doing well without local recurrence two months after surgery.

Cytogenetic Analysis

A representative fresh tissue sample was obtained from the surgical resection. Standard culture and harvest procedures were performed as described previously (19). Karyotypic descriptions were expressed according to the International System for Human Cytogenetic Nomenclature 2009 (20). Twenty metaphase cells were analyzed. Cytogenetic analysis revealed a 1;17 translocation among other clonal abnormalities in six metaphase cells (Figure 3). In addition, trisomy 5 as the sole anomaly was detected in two metaphase cells (Figure 4). The karyotype was as follows: 45,X,X,t(1;17)(p13;p13),add(13)(p11.2),-15,-22,+mar1[6]/47,XX,+5[2]/46,XX[12].

Discussion

Most TSGCTs display simple karyotypes characterized by one or few chromosomal rearrangements or numerical alterations (21). Cytogenetic data have shown that 1p11-13 is frequently involved in structural aberrations (2-16). Although the most common translocation partner of chromosome 1 is 2q35-37, others include 1q21, 3q21, 5q22-31, 8q21-22, 9q32, 11q11-12, 12q24, 19p12 and 22q12 (4, 9, 10, 12, 14). Recently, West et al. identified CSF1 as the gene at the 1p13 breakpoint (17). Moreover, CSF1 was found to be fused to COL6A3 at 2q37 in a subset of TSGCTs (17, 18). Most recently, Panagopoulos et al. demonstrated a novel CSF1-S100 calcium binding protein A10 (S100A10) fusion gene in a diffuse-type TSGCT with t(1;1)(q21;p11) (16). In this fusion gene, the part of CSF1 coding for the CSF1 protein was fused to exon 3 of S100A10.

In the current case, we identified a novel t(1;17)(p13;p13) translocation among other clonal abnormalities. The ubiquitin specific peptidase 6 (USP6) gene is located on 17p13 and is involved in diverse cellular processes such as intracellular trafficking, protein turnover, inflammatory signaling and cell transformation (22). Interestingly, USP6 rearrangements and USP6 fusion genes have been identified in aneurysmal bone cyst (23) and nodular fasciitis (24). Both lesions tend to occur in younger patients and histologically show the occasional presence of multinucleated osteoclast-like giant cells. We suggest that USP6 is a possible candidate as a fusion partner for CSF1.

Gains of chromosome 5 or 7 have been detected only in the diffuse-type TSGCT (1). In the current case, we identified trisomy 5 as the sole anomaly in two metaphase cells. However, the pathobiological significance of trisomy 5 remains unclear. On the other hand, a previous comparative genomic hybridization study did not show any gain of chromosome 5 (12). The apparent discrepancy may be explained by the insensitivity of comparative genomic hybridization to reveal changes that are present in fewer than 50% of the cells.

Recent in situ hybridization studies demonstrated CSF1 receptor (CSF1R) RNA and protein expression in TSGCTs (17, 25). CSF1R is a transmembrane tyrosine kinase receptor, and a protein tyrosine kinase inhibitor, imatinib, is likely to be an effective therapeutic agent in diseases where
CSF1R is implicated (26). Blay et al. initially reported a case of recurrent diffuse-type TSGCT showing a complete response after imatinib therapy (27). More recently, Cassier et al. reported that the overall response rate with imatinib 400 mg daily in patients with locally advanced/metastatic TSGCTs was 19% (28). Moreover, the overall symptomatic response rate was 73%. These results suggest that the use of targeted-inhibitors of CSF1R such as imatinib may be a good therapeutic option in the treatment strategy of locally advanced, metastatic, or recurrent TSGCTs.

In summary, we herein reported a case of diffuse-type TSGCT with a novel reciprocal translocation between chromosomal regions 1p and 17p. Further studies are req to elucidate the significance of this peculiar translocation in the pathogenesis of TSGCT.

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References


