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t(1;2)-Positive Localized Tenosynovial Giant Cell Tumor With Bone Invasion

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Abstract. *Background: Localized tenosynovial giant cell tumor (LTGCT) is one of the most common benign soft-tissue tumors of the foot. Although pressure erosion in the adjacent bone may be seen, intraosseous invasion of LTGCT is extremely rare. Recent molecular studies have identified the presence of pathognomonic translocation involving the colony stimulating factor 1 (CSF1) gene at 1p13. Case Report: We present an unusual case of LTGCT mimicking a malignant tumor on imaging. The patient was a 16-year-old woman with no history of trauma who presented with a 2-year history of a slow-growing, painless mass in the left fourth toe. Physical examination revealed a 2-cm, elastic hard, immobile, nontender mass. Plain radiograph showed a lytic lesion with a partially sclerotic rim in the proximal phalanx of the fourth toe. Computed tomography demonstrated an expansile lesion with plantar cortical destruction. Magnetic resonance imaging revealed a nodular mass with intermediate signal intensity on T1-weighted sequences and heterogeneous high signal intensity on T2-weighted sequences. The mass had intense contrast enhancement. Complete excision of the mass was performed, and the bone defect was repaired with calcium phosphate cement. Cytogenetic analysis revealed a t(1;2)(p13;q37) translocation as the sole anomaly. Fluorescence in situ hybridization demonstrated the presence of CSF1 rearrangements. Conclusion: Although extremely rare, LTGCT should be considered in the differential diagnosis of an intraosseous lesion near small joints, especially when seen in the toe.*

Localized tenosynovial giant cell tumor (LTGCT), also known as giant cell tumor of tendon sheath, is a benign neoplasm that usually occurs in young to middle-aged adults, with a female predominance (1). The worldwide estimated incidence rate of LTGCT is 39 per million person-years (2). LTGCT typically presents as a slow-growing, painless, firm mass or nodule and is more likely to occur in the forefoot. The standard first-line treatment is surgical excision. Arthroscopic excision can be successful in producing favorable functional results in some cases. A recent systematic literature review with a meta-analysis showed a low recurrence rate (7%) and a moderate complication rate (12%) in LTGCT of the foot and ankle (3).

Cytogenetic studies have indicated that 1p13 is frequently involved in TGCT (4-20). The most common translocation is t(1;2)(p13;q37) resulting in a collagen type VI alpha 3 (*COL6A3*)-colony stimulating factor 1 (*CSF1*) gene fusion (21, 22). There is no evidence to support the use of any cytogenetic or molecular biomarkers for predicting recurrence.

The etiology of bone invasion or destruction in LTGCT is unclear. The intraosseous invasion of LTGCT may mimic a primary bone tumor on imaging (23, 24). In this article, we present an unusual case of LTGCT with bone invasion, displaying a t(1;2) translocation involving *CSF1*. We also provide a literature review about the clinical features of LTGCT with bone involvement.

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Key Words: Tenosynovial giant cell tumor, cytogenetics, 1p13, 2q37, CSF1, invasion.

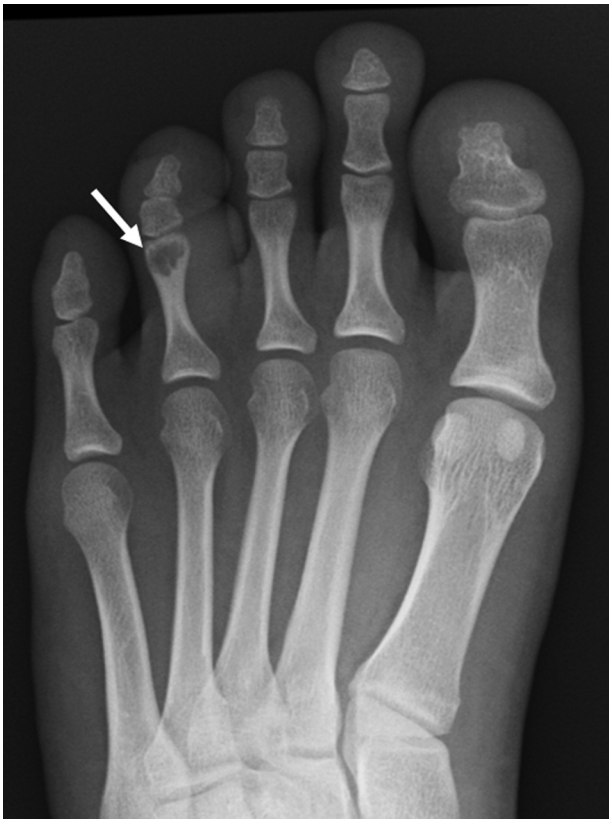

Figure 1. *Anteroposterior radiograph of the left foot demonstrates a lytic lesion with a partially sclerotic rim (arrow) in the proximal phalanx of the fourth toe.*

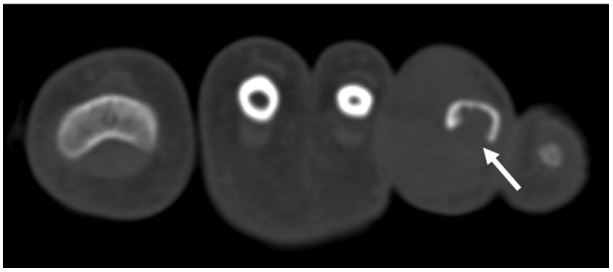

Figure 2. *Axial computed tomography scan reveals an iso-attenuated mass with plantar cortical destruction (arrow) in the left fourth toe. The different toes are intact.*

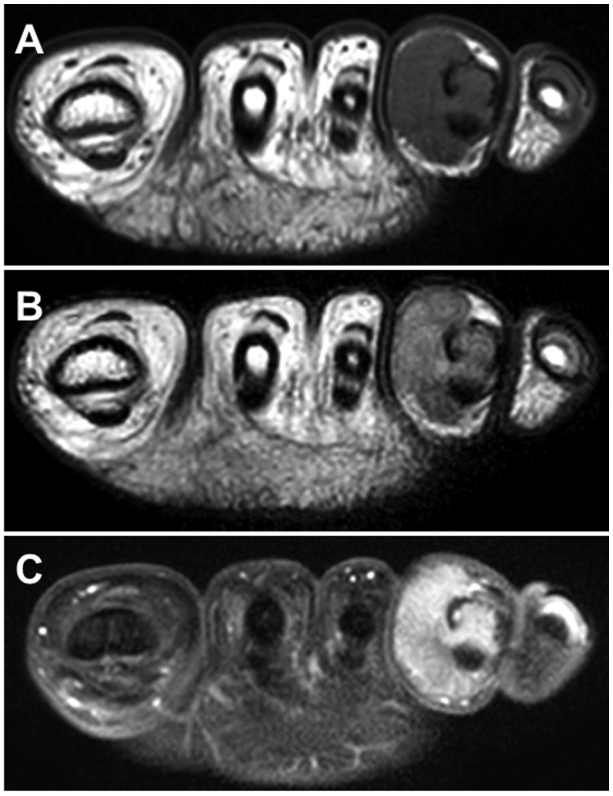

Figure 3. *Axial magnetic resonance images of localized tenosynovial giant cell tumor involving the left fourth toe. The mass shows intermediate signal intensity on T1-weighted image (A) and heterogeneous high signal intensity on T2-weighted image (B). Contrast-enhanced fat-suppressed T1-weighted image (C) demonstrates intense enhancement throughout the mass.*

Case Report

A 16-year-old woman presented with a 2-year history of a slow-growing, painless mass in the left fourth toe. Physical examination revealed a 2-cm, elastic hard, immobile, nontender mass. Neurologic and vascular examinations were unremarkable. Laboratory values were within the normal ranges. Plain radiograph showed a lytic lesion with a partially sclerotic rim in the proximal phalanx of the fourth toe (Figure 1). Computed tomography (CT) demonstrated an expansile lesion with plantar cortical destruction (Figure 2). Magnetic resonance imaging (MRI) revealed a nodular mass with intermediate signal intensity on T1-weighted sequences (Figure 3A) and heterogeneous high signal intensity on T2-weighted sequences (Figure 3B). Contrast-enhanced fat-suppressed T1-weighted sequences (Figure 3C) demonstrated intense enhancement of the mass. Integrated positron emission tomography/CT images showed mild fluorodeoxyglucose uptake in the lesion, with a maximum standardized uptake value of 3.88.

The patient underwent an open biopsy, and the pathological diagnosis was LTGCT. Complete excision of the mass was performed, and the bone defect was repaired with calcium phosphate cement. Histologically, the tumor consisted of a mixture of small histiocyte-like cells, larger

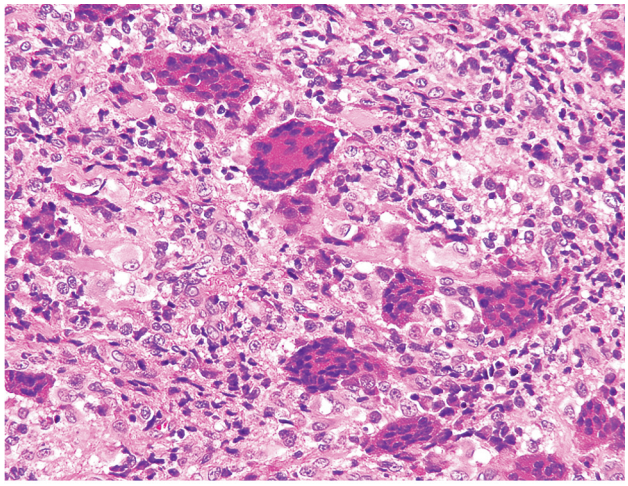

Figure 4. *Histological finding of localized tenosynovial giant cell tumor. The tumor consists of small histiocyte-like cells, larger epithelioid cells and multinucleated osteoclast-like giant cells (hematoxylin and eosin staining, original magnification ×100).*

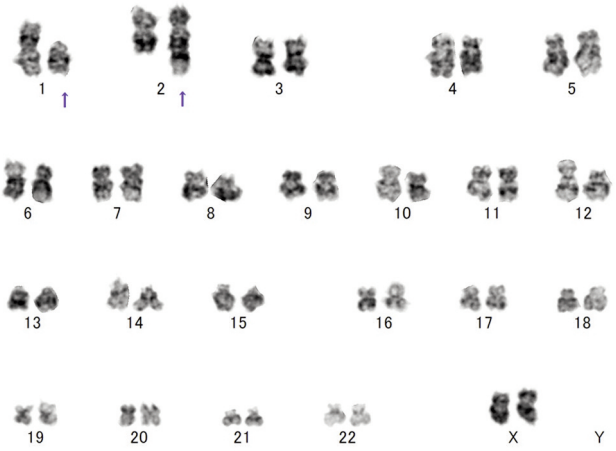

Figure 5. *A representative GTG-banded karyotype of localized tenosynovial giant cell tumor displaying a t(1;2)(p13;q37) translocation. Arrows indicate the structural chromosomal aberration.*

epithelioid cells and multinucleated osteoclast-like giant cells (Figure 4). Atypical mitoses and necrosis were not present. These findings were consistent with a diagnosis of LTGCT. There was no clinical evidence of recurrence during a follow-up period of 8 months.

Cytogenetic analysis revealed a t(1;2) translocation as the sole anomaly (Figure 5). The karyotype was as follows: 46,XX,t(1;2)(p13;p37)[3]/46,XX[17]. Fluorescence in situ hybridization (FISH) confirmed the presence of *CSF1* rearrangements.

Discussion

Radiographs of patients with LTGCT may be normal or reveal a soft tissue mass with or without osseous changes. Rare cases with intralesional calcification may be seen. Osseous changes include pressure erosion, degenerative changes, cystic changes, periosteal reaction and bone invasion or destruction (23-25). Extrinsic bone erosion is the most common radiographic osseous finding associated with LTGCT and typically demonstrates sclerotic margins (26). Lesions in the foot are more likely to produce pressure erosion in the adjacent bone. In many cases, erosive bone lesions do not require reconstruction after curettage. Degenerative or cystic changes are less common and mostly seen in large joints (23). Periosteal reaction is relatively uncommon and represents less than 10% of cases (25). Bone invasion has been described to occur in less than 5% of cases (27) and implicates the higher local recurrence rate after excision (28). The majority of cases with bone invasion have been reported in the foot/ankle (24) and hand (27, 28). Although the mechanism for bone invasion is still unclear, these findings suggest that it may be related to the location of the tumor.

The best radiologic modality to evaluate LTGCT is MRI. De Schepper *et al*. reported that there were no remarkable differences in imaging between LTGCT with and without bone involvement, except for the bone invasion itself and the more pronounced enhancement of the intraosseous component (27). In our case, MRI was helpful in delineating the presence of an extraosseous mass and the intraosseous extent of the tumor. However, the lesion demonstrated heterogeneous high signal intensity rather than low signal intensity normally associated with LTGCT on T2-weighted images.

Several chromosomal and genetic alterations have been identified in TGCT (29). TGCT is characterized by recurrent chromosomal rearrangements involving 1p13. In 2006, West *et al*. identified *CSF1* as the gene at the chromosome 1p13 breakpoint (21). *CSF1* rearrangements can be detected by FISH (30, 31), as in our case. Only a small percentage of cells (2-16%) actually have these changes, supporting a "field effect" model of tumorigenesis (21).

In the current case, we identified a t(1;2)(p13;q27) translocation as the sole anomaly. This chromosomal translocation is associated with a *CSF1-COL6A3* gene fusion. Recently, various *CSF1* fusion partners were discovered in TGCT, including S100 calcium binding protein A10 (*S100A10*), vascular cell adhesion molecule 1 (*VCAM1*), fibronectin 1 (*FN1*), cadherin 1 (*CDH1*), potassium calcium-activated channel subfamily M alpha 1 (*KCNMA1*) and

CD96 molecule (CD96) (18, 32-34). These *CSF1* fusion transcripts result in loss of *CSF1* exon 9, a negative regulator of CSF1 expression. Moreover, several studies reported the presence of Cbl proto-oncogene (*CBL*) exon 8-9 mutations in a subset of TGCTs (31, 32). However, it remains unclear whether these genomic alterations are associated with the clinical behavior of LTGCT with bone invasion.

In conclusion, we described the first case of LTGCT with bone invasion in the toe, displaying a t(1;2)(p13;p37) translocation involving *CSF1*.The diagnosis of LTGCT with bone invasion is difficult and it can mimic a primary bone tumor. Further studies are needed to better understand the correlation between certain genomic alterations and the distinct biological behavior of LTGCT.

Conflicts of Interest

The Authors declare no conflicts of interest associated with this article.

Authors' Contributions

SN performed the operation and drafted the article. JN supervised the research and assisted with writing of the article. MA and KN performed the histological evaluation. TY reviewed the article. All Authors read and approved the final article.

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