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Case study

# Malignant tenosynovial giant cell tumor with *CDKN2A/B* genomic alteration: a histological, immunohistochemical, and molecular study☆

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**Summary** Diffuse-type tenosynovial giant cell tumor (D-T TSGCT) is regarded as a benign but locally aggressive neoplasm with significant recurrent potential. We report a case of malignant D-T TSGCT with pleural metastases arising in the left knee in a 57-year-old man. The tumor demonstrated atypical features, including a solid infiltrative pattern with spindling of the tumor cells, nuclear pleomorphism with prominent nucleoli, and markedly increased mitotic activity (>20 mitoses/10 high-power fields). The immunoprofile demonstrated clusterin+, D2-40+, CD68+, p63+, MDM2+, and p16+ tumor. The next-generation sequencing–based assay demonstrated loss of the *CDKN2A/B* gene. Pleural metastases with identical histologic and immunohistochemical features were identified 2 years later after primary tumor resection. To the best of our knowledge, this is the first reported case of D-T TSGCT with *CDKN2A/B* genomic alteration, MDM2 expression, and p16 loss. Clinicians and pathologists should be aware of the morphologic variability and the metastatic propensity of this entity.


## 1. Introduction

Diffuse-type tenosynovial giant cell tumor (D-T TSGCT), also known as *pigmented villonodular tenosynovitis*, is a locally aggressive neoplasm composed of synovial-like mononuclear cells admixed with multinucleate giant cells, foam cells, siderophages, and inflammatory cells [1,2]. The tumor may be intra-articular or extra-articular and predominantly arises in tendon sheaths and in the synovia of large joints [1]. Malignant D-T TSGCT is exceedingly rare [1-7]. Malignant TSGCT is defined by the coexistence of a benign giant cell tumor with overtly malignant areas or by recurrence of a typical giant cell tumor as a sarcoma [1].

Benign D-T TSGCTs have recently been characterized by the discovery of *COL6A3-CSF1* gene fusion derived from a recurrent chromosomal translocation, t(1;2)(p13;q37) [8-10]. The cytogenetic and molecular genetic features of malignant D-T TSGCT are largely unknown [11]. Therefore, it is instrumental to identify critical molecular alterations implicated in the malignant transformation of benign lesions.

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We describe the clinicopathological and immunohistochemical findings, as well as the molecular alterations, of a malignant D-T TSGCT with bilateral pleural metastases.

### 1.1. Clinical history

A 57-year-old man presented with a left knee mass. Magnetic resonance imaging (MRI) demonstrated a large, heterogeneous mass (4.6 × 2.2 × 1.7 cm) within the anterior lateral joint extending along the synovial surface of the left knee (Fig. 1A). The mass demonstrated avid fluorodeoxyglucose uptake on positron-emission tomography–computed-tomography (PET-CT) imaging (Fig. 1A, inset). The patient has had 2 prior excisions of a D-T TSGCT at an outside institution, which rapidly recurred, requiring a second excision, which rapidly recurred as well. The tumor progressed despite 2 rounds of chemotherapy. The patient was advised to consider a left above-knee amputation for local control. Two years after surgery, he developed shortness of breath and was found to have a large left pleural effusion with numerous pleural nodules (Fig. 1B).

## 2. Materials and methods

### 2.1. Histology

Representative/extensive tissue sections from the surgical specimens were fixed in 10% buffered formalin and embedded in paraffin. For routine microscopy, 4-$\mu$m–thick sections were stained with hematoxylin-eosin.

### 2.2. Immunohistochemistry

Immunohistochemical staining was performed using an automated immunostainer (BenchMark; Ventana, Tucson, AZ) and Ultraview universal indirect biotin-free DAB detection kit. The following antibodies were used: Ki-67, p53, p63, CD117, p16, clusterin, S100, desmin, and D2-40 (prediluted, mouse monoclonal; Ventana); CD68, CD117, D2-40, CD34, and cytokeratin AE1/AE3 (prediluted, mouse monoclonal; Dako, Carpinteria, CA); smooth muscle actin (prediluted, mouse monoclonal; Cell Marque, Rocklin, CA); MDM2 (1:20, mouse monoclonal; Invitrogen, Carlsbad, CA). A positive nuclear,

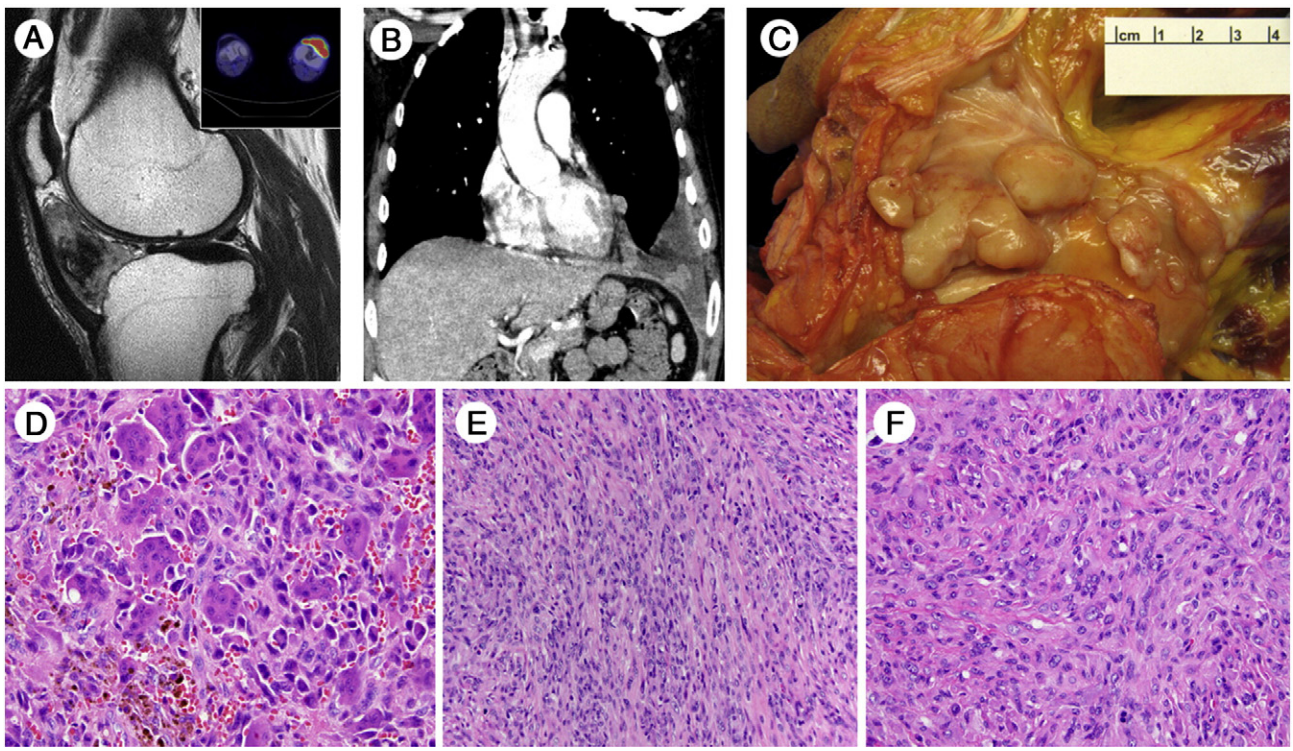


**Fig. 1** Malignant diffuse-type tenosynovial giant cell tumor. A, MRI proton density sequence demonstrates a large, heterogeneous mass within the anterior lateral joint extending along the synovial surface of the left knee. The mass demonstrates avid fluorodeoxyglucose uptake on PET-CT imaging (inset). B, Coronal CT scan demonstrates a left pleural effusion with enhancing pleural metastases. C, Note multiple yellow-tan nodules involving synovial tissue and muscle tendon. D, Note synovial-like mononuclear cells admixed with multinucleate osteoclastlike giant cells and siderophages. E, Note solid growth pattern, spindle cell morphology, and absence of multinucleate osteoclastlike giant cells and siderophages in area with sarcomatoid dedifferentiation. F, Note large, plump, round or oval tumor cells with eosinophilic cytoplasm in area with sarcomatoid dedifferentiation. A, Proton density MRI sequence, left knee; PET-CT scan, inset. B, CT scan, chest. C, Left knee mass, gross. D, Hematoxylin and eosin, original magnification ×200 (D), ×100 (E), ×200 (F).