

Tenosynovial Giant Cell Tumor Involving Quadriceps Muscle – A Case Report of Two Cases

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Learning Point of the Article:

Tenosynovial GCT though a rare occurrence, should have a high index of suspicion, hence should be diagnosed radiologically and to be treated surgically with close clinical and radiological follow-up for recurrence.

Abstract

Introduction: Tenosynovial giant cell tumors (TS-GCTs) are benign soft-tissue tumors that arise from the synovium of joints, bursae, and tendon sheath. They are classified into two major forms – localized and diffuse types with varied clinical presentation and treatment protocol.

Case Report: A 38-year-old gentleman presented with complaints of left thigh swelling and pain since 18 months. He underwent aspiration and a surgical procedure elsewhere without much improvement. Diagnosis was confirmed on magnetic resonance imaging (MRI). Surgical resection was done and specimen was correlated histopathologically. Another 15-year-old boy presented with complaints of right knee pain and swelling since 5 months. MRI was done which showed knee effusion with synovial thickening for which aspiration was done and started on antibiotics but symptoms persisted. Hence, surgical resection and biopsy was done which was confirmed to be TS-GCT. Both patients regained full knee movements postoperatively and were uneventful.

Conclusion: The mainstay of treatment of TS-GCT diffuse type is complete open surgical resection with role of adjuvant radiotherapy/chemotherapy being controversial.

Keywords: Tenosynovial giant cell tumor, tenosynovial-giant cell tumor of knee, diffuse type, open biopsy, magnetic resonance imaging, wide resection, radiotherapy, chemotherapy.

Introduction

Tenosynovial giant cell tumors (TS-GCT), also known as pigmented villo-nodular synovitis (PVNS), are primary soft-tissue tumors that arise from the synovium of joints, bursae, and tendon sheath. They are benign (non-cancerous), do not metastasize, and are locally aggressive. Giant cell tumor of soft tissues was initially classified under “malignant giant cell tumor of soft parts” [1] eventually reclassified as “giant cell tumor of low

malignant potential” as they lack cytological atypia, even in the presence of increased mitotic activity and vascular invasion [2]. They are clinically and histologically similar to giant cell tumor (GCT) of bone [3]. A category of “pigmented villo-nodular synovitis, bursitis, and tenosynovitis” was proposed to group together lesions previously known under different names according to location [4]. Most authors favored a non-tumoral reactive etiology, as an implication of inconspicuous

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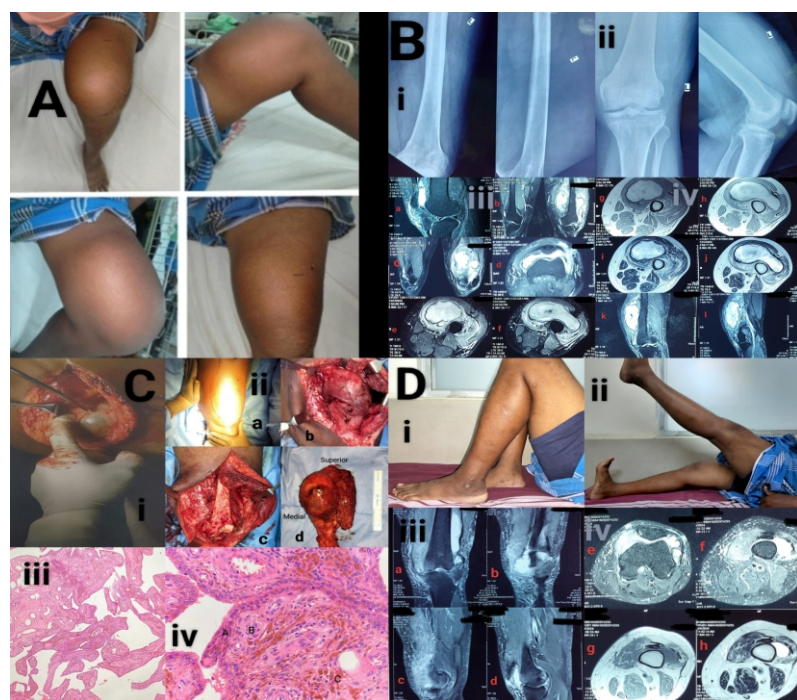


Figure 1: Case 1 A- presenting clinical images. B- presenting radiological images (i) X-ray left femur, (ii) X-ray left knee (frontal and lateral projections), and (iii and iv) magnetic resonance imaging (MRI) left thigh with knee. (a) sagittal PDFS image; (b and c) coronal PDFS images; (d, e, f) axial PDFS images; (g and h) axial T1w images; (I and j) axial T2w images; and (k and l) sagittal T1w images). C- (i) Intraoperative image during initial excision biopsy procedure, (ii) intraoperative clinical images (a) marking incision, (b) exposure, (c) intact femur bone post-tumor excision, and (d) resected tenosynovial giant cell tumor mass lesion of size 13 × 8 cm, (iii) Histopathological examination (HPE) (200 × H and E): Section showing synovial tissue arranged in villous architecture showing synovial hyperplasia (iv) HPE (400 × H and E): Section showing synovial tissue with synovial hyperplasia (A) with subepithelium showing mononuclear cells (B) and hemosiderin laden macrophages (C). D- (i and ii) 8th month post-operative clinical follow-up and checking for active knee range of movements; (iii and iv) post-operative 8 months follow-up MRI thigh (a and b) coronal T1w images; (c and d) sagittal T1w images; (e and f) axial PDFS images; and (g and h) axial T2w images.

microtrauma and associated lipid disorder [5], while some suggesting a tumoral process, with tumorous proliferation of fibroblasts and histiocytes [6].

Tenosynovial giant cell tumors (TGCT) has a slight female preponderance (female: male = 2:1) and affects a relatively younger age group mainly between 30 and 50 years, although it can occur at any age [7, 8]. They are classified into two major forms – localized and diffuse. Diffuse type TS-GCT (D-TS-GCT) intra-articular forms are likely to spread diffusely, developing a multi-compartmental growth pattern involving at least two contiguous intra-articular synovial recesses. D-TS-GCT extra-articular growth pattern mainly occur secondary to intra-articular extension through trans-capsular fenestrations [9].

Extensive en bloc surgery, as practiced for other malignant tumors, is not indicated. Resection may be total or subtotal,

depending on the disease's history (primary or recurrent), clinical expression, diffuse or localized, nodular nature, extension, location, and progression [10]. For localized type TS-GCT (L-TS-GCT), either arthroscopic resection or open surgery yields good tumor control. Treatment of diffuse forms is more difficult especially in the knee with high local recurrence rate of 27.7% [11]. The primary aim in treating intra-articular D-TS-GCT is to remove all abnormal synovium, thus preventing local recurrence and ultimately reducing risk of arthritis whereas in extra-articular D-TS-GCT, it is necessary to prevent the destruction of the affected tendon or bursa. While D-TS-GCT exhibits neoplastic features with clonal cytogenetic abnormalities, it shares many characteristics with inflammation related to rheumatoid arthritis (RA). D-TS-GCT is likely situated in an intermediate state between inflammatory and neoplastic process [12]. Hence, non-specific anti-inflammatory drugs were used initially without much success and later on switching over to colony-stimulating factor 1 (CSF1) receptor blocking agents which are expected to show promising results in near future. Patients are to be closely followed up for clinical recurrence as it is the inherent nature of this tumor. Two patients of two different age groups presenting with this rare clinical condition and management strategy followed are being discussed in this article.

Case Reports

Case 1 (Fig. 1)

A 38-year-old male presented with complaints of the left thigh swelling and pain since 18 months. The initial fluid aspiration followed by excision biopsy procedure was done elsewhere 2 months back without much improvement. Intraoperative photo revealed a grayish-white globular mass over lateral aspect of distal thigh which was histopathologically reported as TS-GCT. Patient presented to us with a large soft ill-defined swelling over distal thigh with a lateral healed surgical scar. Knee range of movements (ROM) were terminally restricted without neurovascular deficit. X-ray showed enlarged soft-tissue shadow over distal femur extending up to patella without any bony changes. Magnetic resonance imaging (MRI) showed diffuse frond like T1/T2 hypointense synovial thickening in knee joint with large thick-walled hemorrhagic collection in vastus medialis and intermedius with possible sequestered synovium within.

Since the previous biopsy reports and slides were available, after

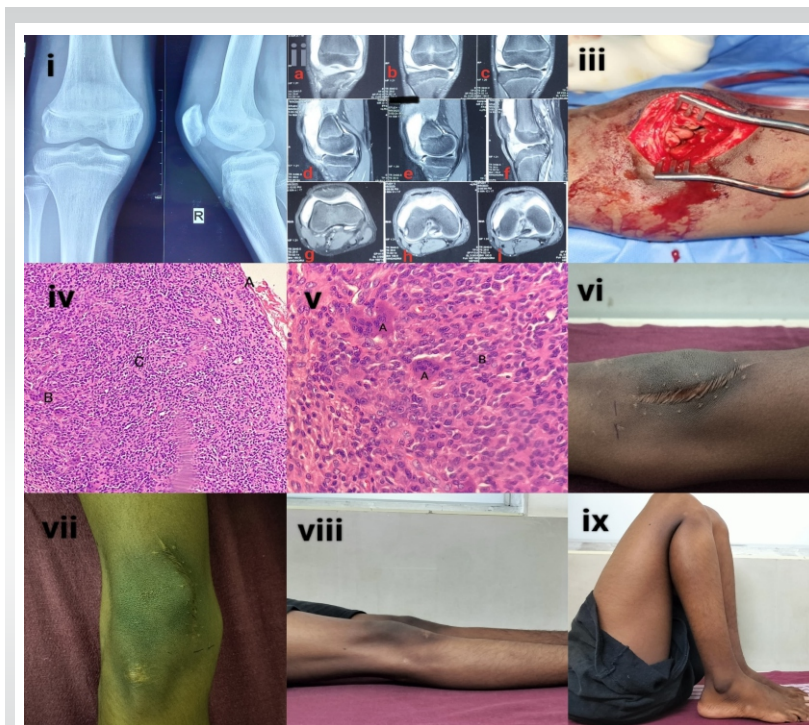


Figure 2: Case 2 (i) X-ray right knee (frontal and lateral projection), (ii) magnetic resonance imaging right knee- (a, b, c) coronal T2w images; (d, e, f) sagittal T2w images; (g, h, i) axial T2w images), (iii) intraoperative clinical image, (iv) histopathological examination (HPE) (200× H and E) synovial epithelial tissue (A) with underlying neoplasm with sheets of osteoclastic multinucleated giant cells (B) and mononuclear cells (C), (v) HPE (400× H and E) mononuclear cells (B) intermixed with osteoclastic multinucleated giant cells (A). (vi, vii, viii, ix) 1 year post-operative follow-up and checking for active knee range of movements.

discussion with the surgical oncologist, it was decided to perform marginal/wide excision of the lesion. The tumor was exposed by an anteromedial longitudinal incision. Predominantly marginal excision of tumor was done without disturbing the tumor capsule as femoral artery was close to the tumor medially. Vasti and rectus were preserved to whatever extent possible. The tumor which was extending into the joint anteriorly was excised in-Toto along with the visible synovium. There was a debate as to whether radiotherapy and chemotherapy were required for this patient but they were not given for the patient after reviewing the available literature [11,13-16]. Histopathological examination (HPE) was done showed and confirmed features suggestive of TS-GCT. He was advised to continue his professional activities after 3 months of surgery. At 8 months follow-up, his knee flexion was 110° with no extensor lag and MRI thigh showed no recurrent/residual lesion with only mild-moderate knee joint effusion. His Musculoskeletal Tumor Society (MSTS) score (total score = 30) improved from pre-operative value of 10 to score of 18 at 3rd post-operative month and 29 at 1 year follow-up.

Case 2 (Fig. 2)

A 15-year-old male presented with complaints of right knee pain

and swelling since 5 months. X-ray had no bony abnormality. Symptoms did not subside following conservative management; hence, MRI was done which showed significant knee joint effusion with synovial thickening – probably inflammatory etiology for which aspiration was done and started on antibiotics but symptoms persisted. The patient underwent right knee subtotal synovectomy and open biopsy. Intraoperative specimen showed multiple intra-articular grayish-white soft-tissue nodules. HPE was done showed features suggestive of TS-GCT. The patient obtained full knee ROM with no extensor lag and was back to his regular scholastic and sports activities by 3rd post-operative month. One year post-operative follow-up was uneventful. His MSTS score (total score = 30) improved from pre-operative value of 16 to score of 26 at 3rd post-operative month and 30 at 1 year follow-up.

Discussion

TS-GCT and the more aggressive PVNS (now categorized as localized and diffuse type TS-GCT, respectively as per World Health Organization classification of soft tissue and bone tumors) are essentially the same. There was no clear cut distinction identified between the two subtypes histopathologically; hence, diagnosis can be made only

Table 1: Checklists on follow-up MRI following various types of treatment [19]

Modality of treatment	Checklist
Surgical excision	➤ Local recurrence
	➤ Early development of OA
Radiotherapy	➤ Local recurrence
	➤ Skin necrosis
	➤ Malignant transformation
CSF1-receptor inhibitors	➤ Semi-quantitative tumor volume change
	➤ Decrease in SI along synovium
	➤ Reduction in capsular distension and joint effusion as well as increase in hemosiderin deposition.
CSF1: Colony-stimulating factor 1, OA:Osteoarthritis, SI: Signal Intensity, MRI: Magnetic resonance imaging	

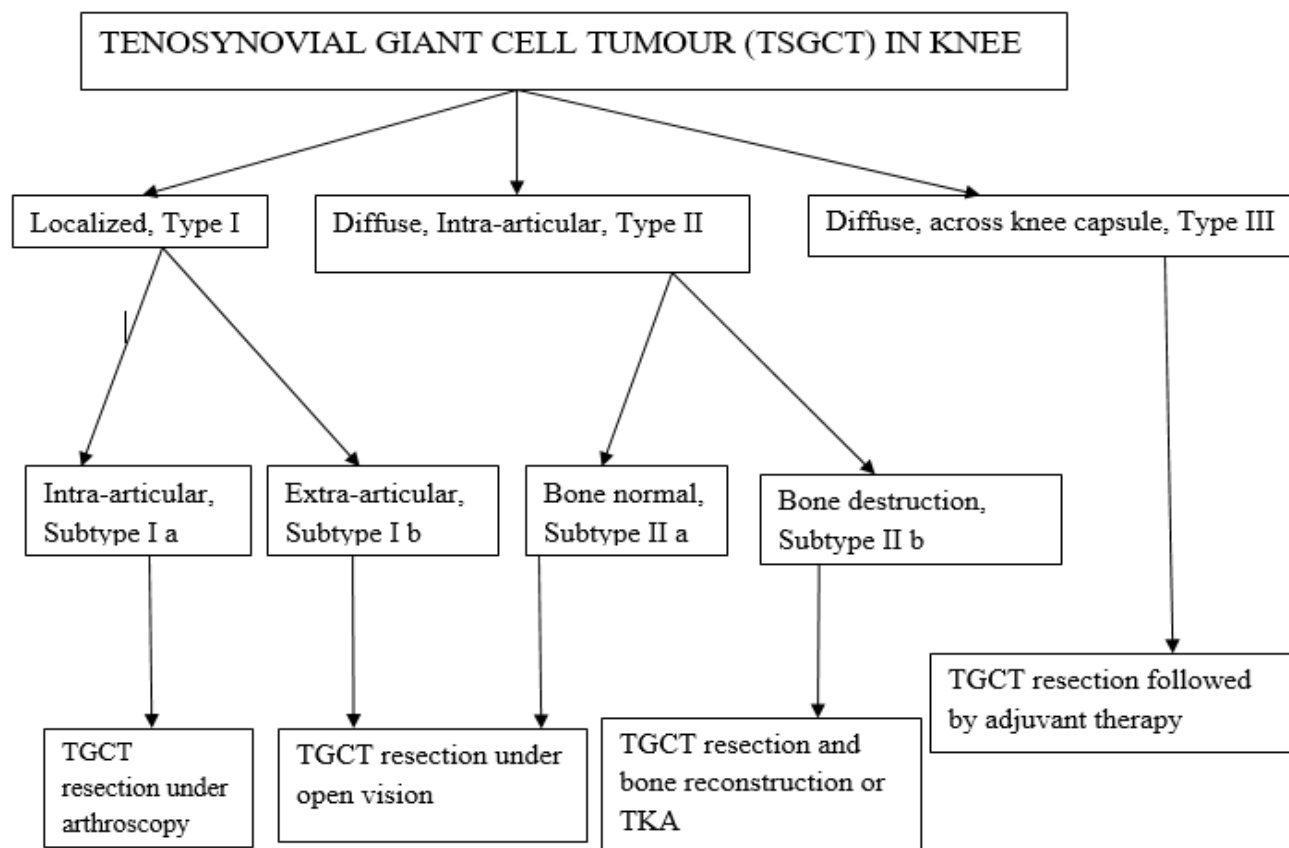
Table 2: Comparison between localized and diffuse types of TS-GCT

Features	Localized-type (L-TS-GCT)	Diffuse-type (D-TS-GCT)
Incidence [7, 8]	45/MPY	5/MPY; extra-articular form constitutes only 5–15% of all D-TS-GCTs
Nature of tumor	More common, indolent and benign	Less common, but more destructive and locally aggressive
Location [7, 23]	Synovium of joint/bursae/tendon sheath; usually affects small joints	Usually affects large joints; Mono-articular mainly intra-articular often extending extra-articularly
Most common sites [7, 23]	Digits and wrist (85%), foot (15%), ankle and knee	Peri-articular soft tissues involving knee (75%), hip (15%), ankle, shoulder, and elbow
Presentation	Nodules/pedunculated mass-discrete and encapsulated. Less likely to cause arthritic changes	Widespread involvement of synovium; progress to cause arthritic changes and joint degeneration
MRI [19] (commonly visualized as low SI areas)	Speckled; single nodules with circumscribed margins and peripheral hypo-intensity	Extensive and granular; multi-nodular with infiltrative margins and lack of peripheral hypo-intensity (due to lack of capsule) – Most sensitive finding
Management	Surgery (curative)	Surgery – but high risk of recurrence. Hence, chemotherapy is advised- either neoadjuvant/adjuvant (case dependent)
Recurrence rate [7, 8]	Less (<15%)	High. 50% (if intra-articular); 33–50% (if extra-articular)
MPY: Million person-years, OA: Osteoarthritis, SI: Signal intensity, MRI: Magnetic resonance imaging, TS-GCT: Tenosynovial giant cell tumor		

clinically and radiologically. TGCT subtypes share a common underlying pathogenesis, mainly related to a colony-stimulating factor-1 translocation (overexpression) involving locus 1p 13 (in 2–16% of cells), thus creating an aggressive multinuclear “landscape” of TS-GCT [17]. There are no environmental, genetic, occupational, lifestyles, demographic, or regional risk factors involved in the development of these tumors.

Imaging of D-TS-GCT constitutes conventional radiographs of knee which are usually normal, sometimes showing features of osteoarthritis and joint erosion [12]. Although ultrasound is not much useful due to low specificity, it can be used to perform image-guided biopsies. MRI is the imaging modality of choice to diagnose D-TS-GCT, to plan surgeries with adjuvant radiotherapy/chemotherapy, and to assess residual lesions and local recurrence present after synovectomy or treatment response to chemotherapy. Furthermore, cartilage invasion, cortical bone erosions, muscular/tendinous, ligament, and

neurovascular involvement were proposed as parameters that determine the severity of D-TS-GCT [17]. D-TS-GCT is more prone to bleeding (compared to L-TS-GCT); hence, hemarthrosis is a common finding expressed as low-signal intensity (SI) on both T1-weighted imaging and fluid-sensitive sequences. Hemorrhage constitutes classic D-TS-GCT imaging hallmark mostly detected as “blooming artifacts” (secondary to hemosiderin deposition) – presents as enlarged and disproportionately lower SI of blood deposits on gradient echo sequences compared to spin-echo sequences. Although pathognomonic for diagnosis, its absence does not rule out TS-GCT [18]. Common post-operative changes include skin thickening, fat stranding or inflammation in Hoffa, subcutaneous, and intramuscular edema. Diffuse synovial thickening is equivocal for D-TS-GCT residual disease within the first 6 months due to associated reactive synovitis. Growing, enhancing solid, and nodular synovial thickening should raise

Illustration 1: A comprehensive treatment protocol for the new clinical classification for tenosynovial giant cell tumor of knee [20].

suspicion of disease recurrence [12].

Checklists on follow-up MRI following various types of treatment [19] are shown in Table 1. Comparison between localized and D-TS-GCT is depicted in Table 2.

The differential diagnosis of extra-articular D-TS-GCT is difficult due to their rarity. Some encountered clinically and radiologically include tophaceous gout, chronic RA, synovial chondromatosis, lipoma arborescens, synovial hemangioma, hemophilic arthropathy, and hemosiderotic synovitis [19]. Our pre-operative differential diagnosis in case 1 was soft-tissue sarcoma and case 2 was chronic synovitis probably due to tubercular etiology.

It is difficult to achieve a balance between complete tumor resection and preservation of knee function. Hence, acceptable knee function can be obtained if total knee arthroplasty (TKA) is done after complete tumor resection [20]. However, the outcomes of TKA following resection of a portion of the quadriceps may be poor. TKA combined with synovectomy was considered an effective treatment for advanced TGCT with degenerative lesions [21]. However, patients with diffuse

TGCT who underwent TKA experienced more surgical complications, including stiffness and infection compared to patients with osteoarthritis who underwent TKA [13]. In all cases, pre-operative MRI extension assessment is essential to plan treatment strategy: Extension outside the joint or in posterior recess (in popliteal fossa) contraindicates isolated arthroscopic treatment [10, 11, 14]. A systematic review makes conclusions that arthroscopic excision is effective in minimizing morbidity and surgery-related complications, while an open surgical technique provides a more successful complete resection with a lower incidence of local recurrence [15].

A comprehensive treatment protocol for the new clinical classification for TGCT of the knee [20] is described in Illustration 1.

Radiation therapy (RT) is the most widely used adjuvant; RT (external and intra-articular also known as isotopic synoviorthesis) seems to reduce recurrence in D-TS-GCT, especially when synovectomy was partial [11]. External RT uses 30–50 Gy in 20 sessions [22], which is only less useful despite good disease control [10]. Intra-articular RT is not

recommended in case of bone extension or if arthroplasty is liable to be performed; it may be considered after partial synovectomy and in diffuse forms [23]. However, the synoviorthesis-surgery sequence lacks efficacy in the knee (30% recurrence) compared to other joints (9% recurrence) despite theoretic risk of malignant transformation following RT [11]. Review of literature suggests that RT (especially external) provides benefit and more clinical studies are warranted to determine its currently unknown therapeutic value.

Systemic therapy, valuable as part of a multidisciplinary approach [16] is based on developing targeted therapies and studying on the underlying molecular mechanisms of TS-GCTs. Non-specific anti-inflammatory treatment by anti-tumor necrosis factor-alpha was the first medical treatment to be described. Although surgery is the primary treatment option, emerging systemic therapies targeting CSF1-receptor are valuable. Since CSF1 gene expression was elevated in most TGCT cases, a structural blockade of CSF-1 receptor tyrosine kinase resulted in a prolonged regression in tumor volume in most patients [24, 25]. One such drug, pexidartinib provides a

novel non-surgical option to address intra-articular D-TS-GCT [16, 20], thus improving ROM, leading to its inclusion in Food and Drug Administration approved treatment protocol.

Conclusion

The mainstay of treatment of D-TS-GCT is complete open surgical resection (marginal/wide) with role of adjuvant radiotherapy and chemotherapy being controversial.

Clinical Message

TS-GCT though presenting with similar biopsy features of GCT of bone should be radiologically diagnosed and treated appropriately based on specific type. Meticulous clinico-radiological follow-up is required due to high risk of recurrence (especially D-TS-GCT) with role of adjuvant radiotherapy and chemotherapy still being controversial.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given the consent for his/ her images and other clinical information to be reported in the journal. The patient understands that his/ her names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflict of interest: Nil **Source of support:** None

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