Tenosynovial giant cell tumour: current concepts review and recent developments focusing on pathogenesis and treatment-directed classification

Fatima B Aboo,* **Marule P Kgagudi**

Division of Orthopaedic Surgery, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Corresponding author: fatimabibiaboo30@gmail.com

Citation: Aboo FB, Kgagudi PM. Tenosynovial giant cell tumour: current concepts review and recent developments focusing on pathogenesis and treatment-directed classification. SA Orthop J. 2025;24(2):90-93. http://dx.doi.org/10.17159/2309-8309/2025/v24n2a6

Editor: Prof. Nando Ferreira, Stellenbosch University, Cape Town, South Africa

Received: May 2024

Accepted: July 2024

Published: May 2025

Funding: No funding was received for this study.

Conflict of interest: The authors declare they have no conflicts of interest that are directly or indirectly related to the research.

Abstract

Tenosynovial giant cell tumour (TSGCT) is a benign, aggressive tumour arising from joint synovia, bursae and tendon sheaths. The majority of cases are localised, presenting with a localised lesion of the synovium, with 10% of presentations being of a diffuse-type synovial involvement. These can be associated with severe morbidity and a risk for malignant transformation. Recent developments in the pathogenesis originating from inflammatory and potentially neoplastic sources have highlighted the involvement of various chromosomal abnormalities, including chromosomes 1, 3, 5, trisomy 7, and trisomy 5. Additionally, the overexpression of colony-stimulating factor 1 (CSF-1) and the recruitment of its receptor (CSF-1R) on immune cells, osteoclasts and giant cells have emerged as significant factors. These developments suggest that biologic agents hold great promise as a future treatment modality, particularly for cases associated with severe morbidity. Tyrosine kinase inhibitors, particularly pexidartinib, a CSF-1R antagonist, and imatinib are further discussed in some detail. Finally, we explore the role of arthroscopic synovectomy and a recently developed treatment-directed classification for TSGCT in the localised type as a standalone procedure. The diffuse types require combination with other approaches.

The key concepts are as follows:

- Information regarding TSGCT is sparse.
- TSGCTs can be diffuse, which is associated with severe morbidity.
- New insight regarding the involvement of chromosomal involvement and the over-expression of CSF-1 has directed the use of biologics such as tyrosine kinase inhibitors for severe cases.
- A useful and practical treatment-directed classification of TSGCT has recently been developed.

Level of evidence: 5

Keywords: tenosynovial giant cell tumour, classification, pathogenesis, tyrosine kinase inhibitor, colony stimulating factor-1

Introduction

Tenosynovial giant cell tumour (TSGCT) is a group of benign aggressive tumours arising from joint synovia, bursae and tendon sheaths.[1,2] The worldwide incidence is noted at 10 per million persons/year for the localised type of TSGCT and 4 per million persons/year for the diffuse TSGCT (dTSGCT) type. Approximately 90% of TSGCT are localised, characterised by a single lesion that is well circumscribed on the affected synovium. The residual 10% of TSGCT is diffuse and can affect one compartment or the entire synovium of a given joint.[3] The latter presents mainly in large joints (> 5 cm in size), with the knee joint carrying the largest burden of presentation.[2] Gender predilection is controversial but recent studies have revealed a predilection towards female patients.[3] The median age at presentation is 47 years, with the bulk of patients being primarily treated with open surgery.[3] TSGCT is rare and not life-threatening; therefore, clinical evidence and research are sparse, and most previous studies focused on uncommon tumour locations as case reports and/or on the various treatment options for TSGCT, making the treatment of the knee TSGCT controversial.[2,7] This paper is thus aimed at a comprehensive review of the current literature regarding TSGCTs and recent developments, especially regarding the pathogenesis, treatment-directed classification and novel treatment options.

Pathogenesis

Although previously thought of as having an inflammatory aetiology due to the presence of proliferative cells, TSGCTs can follow a traumatic event and/or abnormal lipid metabolism.[4] TSGCT has been recently described by immunologists as an intermediary between rheumatoid arthritis (RA) and synovial sarcoma, with clinical manifestations (joint swelling, destruction), histopathological lesions (synovitis, hyperplasia, joint cartilage

destruction) and chromosomal aberrations similar to those seen in inflammatory arthritides.[5] A correlation between chromosome 1q11-13 and TSGCTs, as well as an association with aneuploidy, trisomy 7, trisomy 5, and chromosomal derangements on chromosomes 1, 3 and 5, have been noted in the literature.[6-9] Novel insight also suggests TSCGT to be induced by a molecular pathway involving colony-stimulating factor 1 (CSF-1). There has been an overexpression of CSF-1 in synovial cells, and the recruitment of CSF-1 receptor (CSF-1R) on macrophages, giant cells and osteoclasts, resulting in synovial hyperplasia. A neoplastic origin was also postulated, with the diffuse TSGCT supporting this theory due more to its invasiveness, high rate of recurrence, malignant transformation and metastasis.[10]

Histopathology

Histopathology is diagnostic of TSGCT with microscopy often revealing mononuclear cells (including histiocytes), macrophages with extensive haemosiderin stores, and multinucleated osteoclast-type giant cells and a predominance of $CD68^{+}$ cells.[5] However, giant cells can be absent in 20% of the cases of diffuse TSGCT cases, making diagnosis challenging.[11,12] Another challenge is distinguishing between the diffuse and localised subtype of TSGCT histologically. However, the localised subtype can be characterised by multinucleated giant cells and haemosiderin deposits, while the diffuse subtype presents as an infiltrative mass with variable cellularity and cleft-like, pseudoglandular, alveolar or cystic spaces.[13] Additional histopathological features may include diffuse expansive sheets of cells with infiltrative borders and variable cellularity.[12]

Macroscopically, both types are similar, presenting either pedunculated in most cases or rarely sessile.[12] Pleomorphism with atypical mitosis and extensive necrosis on a histological sample of TSGCT is highly suggestive of a malignant transformation.[13]

Moreover, histopathology also plays a pivotal role in distinguishing between the potential differential diagnoses. Synovial chondromatosis is distinguished by the presence of multiple round bodies, resembling a cobblestone/sandstorm appearance with calcifications, while a lipoma is characterised by villous proliferation of the synovium and replacement of subsynovial connective tissue by mature fat cells. Haemarthrosis with haemosiderin deposits may be considered as a differential; however, the lack of foam cells and a clear clinical history makes it easy to distinguish between the two.[14]

Common locations for the localised TSGCT subtype include volar aspects of fingers, feet and the knee, whereas dTSGCTs often affect larger joints such as the hip and the knee.[15] History includes trivial trauma followed by discomfort and repeated joint swelling. All latter symptoms can mimic a meniscal tear or haemophilic bleed in male patients, among many other conditions.[15,16] The onset of symptoms is insidious, with the median time from the onset of symptoms to definitive diagnosis approximately 18 months.[15,17] Late presentation can be debilitating, especially with dTSGCT, with complications such as decreased range of motion, joint deformity, degenerative articular changes, and secondary osteoarthritis.[15]

Radiological features

Due to the nonspecific clinical picture, imaging plays a key role when it comes to diagnosis. Radiographic imaging usually reveals soft tissue swelling, bony erosions, and some periosteal reactions.[16] Ultrasonography typically reveals a soft mass related to the tendon sheath, usually hypoechoic irregular synovial thickening along with heterogeneous joint effusion, and is hypervascular on colour or power Doppler imaging.[15,16] CT scans, on the other hand, may demonstrate synovial thickening with slightly higher attenuation than muscle due to haemosiderin deposits with low attenuation effusions. Another modality of note is the F-fluorodeoxyglucose positron emission tomography/computed tomography (F-FDG-PET/CT) that combines positron emission tomography (PET) and computed tomography (CT), which take advantage of the hyperglycometabolism of malignant tumours for detection, staging, recurrence and metastasis.[16,17] On the F-FDG-PET/CT scan, TSGCT has shown to be exceptionally hypermetabolic, imitating musculoskeletal metastases.[16,17]

However, MRI is the gold-standard imaging modality, assisting with diagnosis, staging and follow-up evaluation. Localised forms tend to show a well-circumscribed lesion demarcated with a low signal intensity capsule due to fibrosis or haemosiderin.[15,16] dTSGCT show heterogeneous signal intensities with the T1-weighted imaging (T1-WI) showing a hypointense signal, whereas fluid-sensitive sequences reveal a hyperintense signal with foci of low signal intensity corresponding to haemosiderin in the tumour. This finding is expressed as low signal intensity on T1-WI and fluid-sensitive sequences.[16,17] Haemorrhage is an important imaging hallmark for dTSGCT.[15-17] These changes can be noted on the MRI image (*Figure 1*).

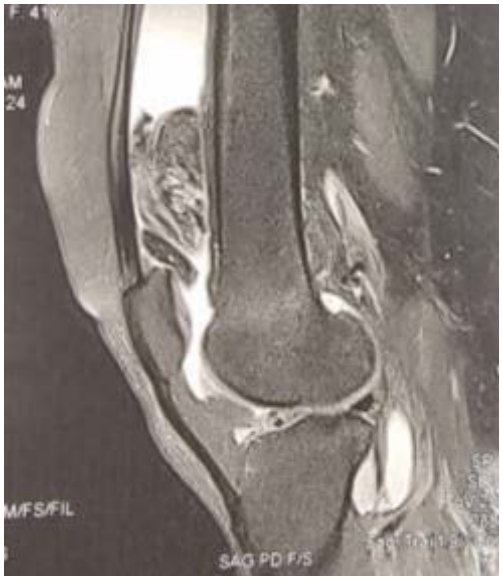

Figure 1. T2 image of a large suprapatellar TSGCT lesion

Table I: Treatment-directed classification

Type	Description	Treatment recommendation
Type 1a	Localised intra-articular	Arthroscopic resection
Type 1b	Localised extra-articular	Open resection
Type 2a	Diffuse, intra-articular with normal bone	Open resection
Type 2b	Diffuse, intra-articular with bone destruction	Open resection and arthroplasty reconstruction
Type 3	Diffuse, across the synovium	Open resection, adjuvant therapy ± amputation

Treatment

Although there is a lack of consensus regarding treatment, conservative management, surveillance, synovectomy, surgery and radiotherapy are all accepted options.[18] A treatment-directed classification system has been advocated of late (*Table I*). TSGCT

of the knee has a variable presentation which guides surgical management. One of three presentations is possible, namely, a type 1-localised, type 2-diffuse intra-articular, or type 3 diffuse across the synovium.[19] Types 1 and 2 are further subdivided into subtypes a and b based on the extent of the condition with the knee.[19] The dreaded type 3 subtypes require resection and adjuvant therapy and/or amputation for a subset of patients.[19] Some authors have strongly recommended a combined approach to minimise recurrence in diffuse lesions, with the anterior compartment treated arthroscopically and the posterior compartment by open surgery. However, posterior to the knee is a technically challenging surgery, which can be prone to complications.[19]Complications are uncommon but recurrence is the most concerning and likely to develop. However, most studies demonstrated a positive surgical outcome for pain and functional improvement.[19]

Radiosynovectomy ablation with radioisotopes can be used as an adjunct to aid synovial ablation, while radiotherapy application is now obsolete.[20] The benefits of external beam radiotherapy (EBRT) in the postoperative setting after incomplete resection to reduce the risk of local recurrence, or for treatment of recurrences, are controversial. However, a meta-analysis in 2015 of 35 observational studies found that the rate of local recurrence of diffuse TSGCT in the knee was reduced with perioperative EBRT (from 36.9% to 12.0%) with radiation doses of 20–50 Gy in 15–25 fraction within six to eight weeks of surgery.[21,22]

Biologics are showing promising potential for treatment should they satisfy safety regulations.[18]

TSGCT being described as an intermediary between RA and synovial sarcoma, as described above, has led to the development and research of novel systemic targeted therapies such as monoclonal antibodies or tyrosine kinase inhibitors.[20] The first drug that is FDA approved is pexidartinib, a CSF-1R antagonist for use in cases associated with severe morbidity or functional limitations without improvement despite surgical intervention. The ENLIVEN study showed a risk of liver injury but also a higher objective response rate for pexidartinib compared with the placebo.[20] Imatinib has also shown some efficacy in cases with locally advanced, recurrent or metastatic dTSGCT in an international multi-institutional retrospective study in 2019.[20] Furthermore, other molecules that target synoviocytes are being studied for potential applicability. To the latter, intra-articular zinc and cadmium, both with their pro-apoptotic properties, could decrease inflammation and limit joint synovial destruction minus the harmful toxicity of other treatments; however, more research is still required.[23,24] PUMA, a pro-apoptotic gene combined with a new adenovirus-baculovirus complex vector has shown promising results in inducing synoviocyte inflammation reduction and destruction in laboratory studies, but safety for such therapies for human prescription still needs validation.[25]

Summary

TSGCT is a rare benign tumour that presents in a heterogeneous manner and can be associated with morbidity in terms of the diffuse type and late presentation cases. The pathological classification type at presentation can guide the surgical treatment option for each patient. The common (localised) type is usually addressed with arthroscopic synovectomy, while the diffuse types are likely to necessitate a combined approach and a need for adjuvant synovial ablation to minimise complications and recurrence. Moreover, further understanding of the pathogenesis and the role of the CSF-1 and the chromosomal involvements have been key in terms of directing management with biologics, namely pexidartinib and imatinib, which are FDA approved. These novel treatments have the potential to assist, especially in cases that have severe morbidity, provided they satisfy testing and safety regulations in the long term.

Ethics statement

The authors declare that this submission is in accordance with the principles laid down by the Responsible Research Publication Position Statements as developed at the 2nd World Conference on Research Integrity in Singapore, 2010. Ethics approval was not obtained (review article).

Declaration

The authors declare authorship of this article and that they have followed sound scientific research practice. This research is original and does not transgress plagiarism policies.

Author contributions

FBA: contributed towards the first draft and literature review; read and approved the final manuscript
MPK: contributed towards the clinical information, images, ethics approval as well as supervising and editing the drafts; read and approved the final manuscript

ORCID

Aboo KB https://orcid.org/0000-0003-1295-9019
Kgagudi MP https://orcid.org/0000-0002-0078-3995

References

1. Verspoor FGM,Hannink G. Systemic treatment of tenosynovial giant cell tumours in context. Lancet. 2019;394(10197):446-48. https://doi.org/10.1016/s0140-6736(19)30947-x
2. Gouin F, Noailles T. Localized and diffuse forms of tenosynovial giant cell tumor (formerly giant cell tumor of the tendon sheath and pigmented villonodular synovitis). Orthop Traumatol-Sur. 2017;103(1):S91-S97. https://doi.org/10.1016/j.otsr.2016.11.002
3. Mastboom MJL, Verspoor FGM, Verschoor AJ, et al. Higher incidence rates than previously known in tenosynovial giant cell tumors. Acta Orthop. 2017;88(6):688-94. https://doi.org/10.1080/17453674.2017.1361126
4. Ottaviani S, Ayral X, Dougados M, Gossec L. Pigmented villonodular synovitis: a retrospective single-center study of 122 cases and review of the literature. Semin Arthritis Rheum. 2011;40(6):539-46. https://doi.org/10.1016/j.semarthrit.2010.07.005
5. Nilsson MA, Höglund M, Panagopoulos I, et al. Molecular cytogenetic mapping of recurrent chromosomal breakpoints in tenosynovial giant cell tumors. Virchows Archiv. 2002;441(5):475-80. https://doi.org/10.1007/s00428-002-0640-y
6. Rowlands CG, Roland B, Hwang WS, Sevick RJ. Diffuse-variant tenosynovial giant cell tumor: A rare and aggressive lesion. Hum Pathol. 1994;25(4):423-25. https://doi.org/10.1016/0046-8177(94)90154-6
7. Perk, C, Labs K, Zippel H, Buttgereit F. Localized pigmented villonodular synovitis of the knee joint: neoplasm or reactive granuloma? A review of 18 cases. Rheumatol. 2000;39(2):172-78. https://doi.org/10.1093/rheumatology/39.2.172
8. West RB, Rubin BP, Miller MA, et al. (2006). A landscape effect in tenosynovial giant-cell tumor from activation of CSF1 expression by a translocation in a minority of tumor cells. Proceedings of the National Academy of Sciences of the United States of America [online]. 2006;103(3):690-95. https://doi.org/10.1073/pnas.0507321103
9. Cupp JS, Miller MG, Montgomery K, et al. Translocation and expression of CSF1 in pigmented villonodular synovitis, tenosynovial giant cell tumor, rheumatoid arthritis and other reactive synovitides. Am J Surg Pathol. 2007;31(6):970-76. https://doi.org/10.1097/pas.0b013e31802b86f8
10. Al Farii H, Zhou S, Turcotte R. The surgical outcome and recurrence rate of tenosynovial giant cell tumor in the elbow: a literature review. J Shoulder Elbow Surg. 2019;28(9):1835-40. https://doi.org/10.1016/j.jse.2019.05.007
11. Murphey MD, Rhee JS, Lewis R, et al. Pigmented villonodular synovitis: radiologic-pathologic correlation. Radiographics. 2008;28(5):1493-518. https://doi.org/10.1148/rg.285085134
12. Xie G, Jiang N, Liang C, et al. Pigmented villonodular synovitis: a retrospective multicenter study of 237 cases. PLoS ONE [online]. 2015;10(3):e0121451. https://doi.org/10.1371/journal.pone.0121451
13. Somerhausen NDSA, Fletcher CD.. Diffuse-type giant cell tumor: clinicopathologic and immunohistochemical analysis of 50 cases with extraarticular disease. Am J Surg Pathol. 2000;24(4):479-92.
14. Spierenburg G, Ballesteros, CS, Stoel BC, et al. MRI of diffuse-type tenosynovial giant cell tumour in the knee: a guide for diagnosis and treatment response assessment. Insights into Imaging. 2023;14(1). https://doi.org/10.1186/s13244-023-01367-z
15. 1Wan JMC, Magarelli N, Peh WCG, et al. Imaging of giant cell tumour of the tendon sheath. La radiologia medica. 2010:115(1):141-51. https://doi.org/10.1007/s11547-010-0515-2
16. Chang JS, Higgins JP, Kosy JD, Theodoropoulos J. Systematic arthroscopic treatment of diffuse pigmented villonodular synovitis in the knee. Arthrosc Tech. 2017;6(5):e1547–e1551. https://doi.org/10.1016/j.eats.2017.06.029
17. Broski SM, Murdoch NM, Skinner JA, Wenger DE. Pigmented villonodular synovitis. Clin Nucl Med. 2016;41(1):e24-e31. https://doi.org/10.1097/rlu.0000000000000893
18. Zheng K, Yu X, Hu Y, et al. A new simple and practical clinical classification for tenosynovial giant cell tumors of the knee. Orthop Surg. 2021;14(2):290-97. https://doi.org/10.1111/os.13179

19. Robert M, Farese H, Miossec P. Update on tenosynovial giant cell tumor, an inflammatory arthritis with neoplastic features. Front Immunol. 2022;13. https://doi.org/10.3389/fimmu.2022.820046
20. Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. Lancet (London, England), [online]. 2019;394(10197):478-87. https://doi.org/10.1016/S0140-6736(19)30764-0
21. Mollon B, Lee A, Busse JW, et al. The effect of surgical synovectomy and radiotherapy on the rate of recurrence of pigmented villonodular synovitis of the knee. Bone Jt J. 2015;97-B(4):550-57. https://doi.org/10.1302/0301-620x.97b4.34907
22. Verspoor FGM, Mastboom MJL, Hannink G, et al. Long-term efficacy of imatinib mesylate in patients with advanced tenosynovial giant cell tumor. Sci Rep [online]. 2019;9(1):14551. https://doi.org/10.1038/s41598-019-51211-y
23. Bonaventura P, Courbon G, Lamboux A, et al. Protective effect of low dose intra-articular cadmium on inflammation and joint destruction in arthritis. Sci Rep. 2017;7(1). https://doi.org/10.1038/s41598-017-02611-5
24. Gounder MM, Thomas DM, Tap WD. Locally Aggressive Connective Tissue Tumors. J Clin Oncol. 2018;36(2):202-209. https://doi.org/10.1200/jco.2017.75.8482
25. Hong S-S, Marotte H, Courbon G, et al. PUMA gene delivery to synoviocytes reduces inflammation and degeneration of arthritic joints. Nat Commun. 2017;8(1). https://doi.org/10.1038/s41467-017-00142-1