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Case report Free Access

Recurrent diffuse tenosynovial giant cell tumour of knee joint with emphasis on treatment trends: a case report

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Abstract

Introduction: Tenosynovial giant cell tumor is a benign lesion that frequently recurs locally. The recurrence rate is quite high for diffuse tenosynovial giant cells. Complete surgical excision remains the standard of treatment, yet radiotherapy can be delivered in cases of recurrence. Here we present a case of recurrent diffuse tenosynovial giant cell treated with Image Guided-Intensity modulated radiotherapy. The case report also highlights and discusses other potential treatment options available or under investigation.

Case presentation: A 32-year-old female presented to us as a recurrent case of Diffuse tenosynovial giant cell tumor (DTGCT). She was offered above-knee amputation, which she refused. The role of systemic therapy was explored. She was taken for Image-guided; intensity-modulated radiotherapy (IG-IMRT).

Discussion: DTGCT shows a widespread morphological spectrum. Though Surgery remains the standard of care, Post op radiotherapy can be delivered in incomplete synovectomy or recurrence cases. The potential use of agents targeting CSF1/ CSF1R in D-TGCT has been explored.

Conclusion: Post operative radiotherapy with advanced External beam radiation therapy techniques IG-IMRT, after surgery produced acceptable functional status and excellent local control with few side effects. Our patient post radiotherapy phase was uneventful. His 6-month evaluation was suggestive of no recurrence.

Keywords: Tenosynovial giant cell tumor, Surgery, Radiotherapy

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Introduction

Tenosynovial giant cell tumor is a soft tissue tumor classified by WHO into localised-type (L-TGCT) and diffuse-type (D-TGCT). L- TGCT is more common than D-TGCT. Most patients present with complaints of swelling around the joints and restriction of movements associated with pain (1). MRI helps establish D-TGCT diagnosis. It also serves as a choice to assess residual D-TGCT after synovectomy and for postoperative follow-up. The standard treatment of choice is surgery, but an adjuvant radiotherapy option can be considered in recurrent cases or as a post-operative adjuvant in residual cases. Recurrences can reach as high as upto 60% for D-TGCT, whereas they are as low as 4 % in case of L-TGCT. Microscopic characteristics include lipid-rich macrophages, large cells, hemosiderin deposits, and fibrous stroma. Due to its locally aggressive character, PVNS can cause osteoarthritis and joint destruction if left untreated. Image-guided approach (IGRT) Intensity-modulated radiation treatment has shown notable clinical benefits, including improved response and less toxicity to the surrounding normal tissues (2,3). For D-TGCT, the potential use of agents targeting CSF1/ CSF1R in D-TGCT has been explored (4,5). Here we present a recurrent case of D-TGCT in a middle-aged female who under adjuvant radiotherapy using Image guidance. Here we report a case of recurrent Diffuse tenosynovial giant cell tumor post multiple surgeries, treated with advanced radiotherapy technique. Other possible treatment options that are available or being investigated are also highlighted and discussed in the case report.

Case presentation

A 32-year-old female presented initially in 2015 elsewhere with swelling in the anterior aspect of her left knee with no history of trauma. She underwent surgery and the post-operative histopathological report was suggestive of Villonodular Synovitis. MRI of the left knee revealed extensive mass like synovial thickening within the suprapatellar fossa, paracondylar region, popliteal fossa and intrameniscal surface with cortical erosion of fibula, distal femur and proximal tibia. Features were suggestive of a giant cell tumor. Synovial Biopsy of my left knee was in favor of a Benign Giant Cell Tumor-rich lesion. She was offered open arthrotomy with synovectomy of her left knee with exploration of posteromedial knee in view of varicose veins. She continued her follow-up with a local practitioner. Now she has presented to us after nine years with a suspected recurrence. The MRI outside was suggestive of an ill-defined mass like synovial proliferation in the patella femoral and tibia femoral joints, which appears hypointense on T1 and hyperintense on T2/STIR images. The findings represent features of pigmented villonodular synovitis or diffused synovial Giant Cell tumor. She underwent core biopsy from swelling of her knee. Histopathological impressions revealed Epithelioid neoplasm. Immunohistochemistry (IHC) was performed for final confirmation. The lesion was weak positive for Pan CK, focal positive of p16, Desmin and p63 and showed diffuse positivity for CD68 (Figure 1).

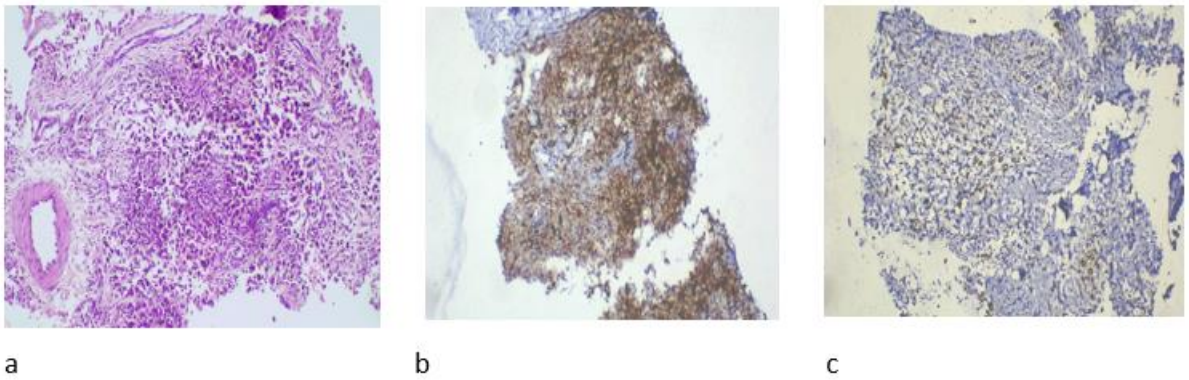

Figure 1. a: high power view showing epithelioid cells and spindle cells along with congested vessels, b: Immunohistochemistry showing diffuse positivity for CD68, c: Immunohistochemistry showing focal positivity for desmin.

The lesion was negative for S100, HMB 45, Melan A, CD34, CD138, CD45, SAT B2 and MDM2. The final impression with the above IHC was favorable for diffuse tenosynovial Giant Cell Tumor. She was offered above-knee amputation, which she refused. The role of systemic therapy was explored. She agreed to radiotherapy. She was taken for Image-guided; intensity modulated radiotherapy (IG-IMRT). She tolerated well without any significant side effects. Her 6 months evaluation was suggestive of no recurrence. She is doing well and has been kept on follow up. To reduce the incidence of lower limb edema, elastic stocking and regular lower limb physiotherapy has been reinforced. She is planned for repeat the imaging after 6 months.

Discussion

Diffuse tenosynovial giant cell tumor, formerly known as pigmented villonodular synovitis, is a rare benign mesenchymal tumor which has its origin from tendon sheaths or synovial bursa or synovial tissue of large joints. Knee is the most common joint affected (2). The 2020 WHO Classification defines it as a locally aggressive neoplasm which rarely metastasizes. (6) With female predilection, it affects the young population and is common at ages 40 and 50 years.

MRI T1 weighted, T2 weighted or Fluid restricted sequences help to detect residual DTGCT post synovectomy. A modification of RECIST (m-RECIST) can be applied for higher accuracy.

For the detection of hemosiderin associated with tumor bleeding, a gradient-echo sequence can be useful. Intravenous gadolinium contrast is useful for post-synovectomy follow-up and for detecting tumors. Bleeding is a common feature of D-TGCT imaging, and it is typically identified as blooming on gradient echo images. The severity of D-TGCT is determined by a number of criteria, including muscle/tendinous, ligament, neurovascular, cartilage invasion and cortical bone erosion.

Suspicious DTGCT should be confirmed with the help of image-guided biopsy. Core biopsy, generally performed under local anesthesia as either CT-guided or USG-guided, can obtain a representative sample. DTGCT shows a widespread morphological spectrum. D-TGCT may present as synovial thickening, is characterized as frond-like with villous or nodular shape. Villous pattern is often exhibited when intra-articular, whereas tumors show infiltrative margins with multinodular growth when extra articular. Diffuse-type TGCT (D-TGCT) consists mostly of mononuclear cells with few multinucleated giant cells, foamy histiocytes and hemosiderin deposition. Immunohistochemistry in TGCT reveals expression of clusterin in the large mononuclear cell. Immunohistochemistry shows clusterin expression, desmin positivity in mononuclear cells and CD68, CD 163 and CD 45 positivity in smaller histiocyte-like cells.

Excision of diseased synovium is the preferred choice. Performing complete resection is challenging. Mostly open surgical excision along with synovectomy or arthroscopic excision is the modality adopted. Though adequate synovectomy may not be sufficient, relapses have been seen as high as in 44% of cases, with many occurring within 5 years or within 2 years. Results of 40 patients' arthroscopic excision of PVNS were evaluated in retrospective research by Jain et al. This clinical series found that arthroscopic excision works effectively for both diffuse and localized PVNS, as well as for recurrences. Keyhani et al. employed the Lysholm score and the International Knee Documentation Committee (IKDC) score throughout a 5-year follow-up. Heijden et al.'s retrospective examination of 30 patients found that open synovectomy was superior to arthroscopic synovectomy in terms of quality of life and functional outcome for TGCT knees.

Studies have shown that post-operative radiotherapy can be offered in incomplete synovectomy patients, those who refuse surgery or in inoperable patients. With the advancement of image guidance, the side effects related to conventional traditional techniques like two-dimensional conformal radiotherapy (2D-CRT) or three-dimensional conformal radiotherapy (3DCRT) are significantly lower. Outcomes, on the other hand, in terms of clinical response, are better with low toxicity to normal tissues documented (2,3). Postoperative adjuvant external irradiation is currently a crucial treatment for patients with D-TGCT as numerous publications have demonstrated, and it can greatly enhance local control (7, 8). The dosage for postoperative radiation, however, is up for debate. As

of right now, the majority of researchers think that the 36Gy total dose is safe and effective because it is less than the long-term threshold of joint fibrosis.

Our patient was immobilized with the help of VacLoc and 2 clamp orfit. A CT scan was performed 10 cm above to feet with 2. 5 mm slice thickness. MRI and CT images were fused, gross tumor volume was delineated and CTV was contoured, sparing 1 cm of normal tissue to decrease chances of lymphedema and including a whole knee joint cavity with residual disease. The MRI T2 peritumoral edema was included because of the risk of harboring microscopic extension of the tumor. The planning target volume (PTV) included the CTV with a 0.3cm isotropic margin. She was planned for 36Gy in 18 fractions @ 2 Gy per fraction. Volumetric-based inverse planning intensity-modulated radiation therapy (IMRT) is used as radiotherapy technique for generating plan. Daily setups were checked with the help of Cone beam CT (CBCT). Patients who had adjuvant radiation, particularly EBRT, had a much lower recurrence rate than those who only had surgery (8). Griffin et al in their series discussed long-term Outcome of the Treatment of High-Risk Tenosynovial Giant CellTumor/Pigmented Villonodular Synovitis with Radiotherapy and Surgery. The authors concluded that the addition of moderate-dose adjuvant radiotherapy provided excellent local control while maintaining good function with low treatment-related morbidity (9).

Organ-specific radiation-induced cancer risk estimates due to radiotherapy for benign pigmented villonodular synovitis discussed by Michalis et al used non-linear mechanistic model and differential dose-volume histograms obtained by CT-based 3D radiotherapy planning. None of the TGCT-D patients receiving EBRT had early or late radiation-related problems that were more serious than grade 2, and none of them developed any cancer induced on by radiation. Commonly documented side effects are radiation dermatitis, local pain or Lymphedema. After EBRT, patients have only sometimes had lymphedema, moderate radiation dermatitis, or local pain, according to a handful of studies.

Radiosynoviorthesis (RSO), usually with ytrrium90, is an additive treatment option (10). Yet it requires a specialized delivery system and is an invasive procedure. Systemic therapy can be offered to symptomatic patients and to those with functional impairment. CSF1 is highly expressed in all TGCT, providing the basis for targeting the CSF1R pathway expressed by macrophages (4,5). Pexidartinib is an oral selective small molecule inhibitor that targets colony stimulating factor. It is the first FDA-approved agent in symptomatic patients (11,12). The ENLIVEN study achieved its endpoint by comparing the overall response rate for pexidartinib to the placebo. As a consequence of the enclosed warning about the possibility of severe and perhaps lethal liver damage, it is only recommended and administered under a safety program called the Risk Evaluation and Mitigation Strategy, which is sponsored by the manufacturer. Multiple other agents, including Vimseltinib (an oral Tyrosine kinase inhibitor supported by the MOTION 3 study) are under investigation (Table1).

Conclusion

Post operative radiotherapy should be often considered in recurrent cases. Low morbidity, excellent local control while maintaining joint function are additional advantages. Besides IG-IMRT, Proton therapy, SBRT are promising new advancements, yet more research is needed. Currently, no recommended follow-up schedules are proposed for D-TGCT. Follow-up is generally based on new-onset symptoms with MRI of the affected joint after every 6 – 12 months. Frequent evaluation can be considered in patients needing systemic therapy. We recommend 3 monthly follow-ups in view of multiple recurrences to evaluate response and residual disease. One promising treatment strategy for TGCT is to target the CSF1/CSF1R axis. Inhibitors of CSF1/CSF1R enhance tumor response and alleviate symptoms.

Table 1. Drugs under investigation and their side effects.

Drug	M.O. A	Study	Side effects
Pexidartinib	oral selective small molecule inhibitor that targets colony stimulating factor	Tap et al (13) Phase3, double blind, placebo controlled, RCT	Primary endpoint: ORR at week 25, based on blinded central MRI 39% Pexidartinib vs 0 % placebo Side effects seen with Pexidartinib: hair color change, fatigue, AST/ALT increase
Imatinib mesylate	a tyrosine kinase inhibitor that blocks the driver mechanism of DTGCT in CSF1R	Verspoor et al (14): Retrospective cohort Locally advanced, recurrent, or metastatic diffuse TGCT in knee	Median PFS:18 months Side effects seen fatigue, edema/fluid retention, nausea, skin rash/dermatitis
Nilotinib	potent inhibition of CSF1R	Gelderblom et al (15): Phase 2 trial	Primary endpoint: proportion of pts progression free at 12wk
Emactuzumab	a humanized monoclonal antibody targeting CSF1R	Cassier et al: Phase1trial	Primary objective: evaluate safety and tolerability, determine Maximum tolerated dose or Optimal biological dose Common Adverse effects: facial edema, asthenia, pruritus

Author contribution

SA and **KG** wrote the main script, revised the script, conceptualized, and prepared figures. **SA** gathered resources

Conflict of interest

There are no Conflicts of interest.

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