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Tenosynovial giant cell tumor

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Abstract: Tenosynovial Giant Cell Tumor (TGCT) is a group of typically benign lesions arising from the synovium of joints, bursae and tendon sheaths. Depending on their growth pattern and clinical course, they are divided into localized and diffuse types. It is predominantly caused by a mutation in the stromal cells of the synovial membrane leading to overexpression of the colony stimulating factor 1 that recruits CSF1R-expressing cells of the mononuclear phagocyte lineage into the tumor mass. The lesions contain mainly histiocyte-like and synovial cells accompanied by varying numbers of multinucleated giant cells, mononuclear cells, foam cells, inflammatory cells and hemosiderin deposits. The gold standard for detecting and monitoring the disease is MRI, where the characteristic hemosiderin accumulation can be best appreciated, but it is a histological examination that is most conclusive. The main treatment is surgical resection of all pathological tissue, but radio- and chemotherapy are also viable options for certain groups of patients.

Keywords: pigmented villonodular synovitis, PVNS, tenosynovial giant cell tumor, epidemiology, diagnosis, treatment.

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Introduction

According to the newest, 2020 5th edition of the WHO Classification of Tumours tenosynovial giant cell tumors (TGCT) are a group of typically benign lesions sharing the same pathogenesis and histological features. It derives from the synovium of joints, tendon sheaths and bursae and is characterized by synovial hyperplasia and hemosiderin deposition. These tumors fall into two subtypes — localized-type TGCT (formerly giant cell tumor of tendon sheath/nodular tenosynovitis) and diffuse-type TCGT (formerly pigmented villonodular sclerosis/tenosynovitis/fibrous xanthoma of synovium) according to their growth pattern (localized and diffuse) and location (intra- and extra-articular) with varying clinical courses and symptoms [1]. The previously uncertain nature of the disease has resulted in some confusion across publications with regard to the terminology referring to this group of lesions. The other names in use include nodular or diffuse pigmented villonodular tenosynovitis, xanthogranuloma, benign synovioma and fibrous histiocytoma of tendon sheath or synovium [2].

Pathology

TGCT are neoplasms characterized histologically by proliferation of synovial cells, although only a small percentage of the cells (2–16%) in the tumor mass actually carry the neoplastic mutation, most of them being non neoplastic reactive cells which gave rise to a variety of theories regarding its etiology. Chromosomal abnormalities discovered in TGCT include trisomy for chromosomes 5 and 7 and structural aberrations of 1p11-13. The most commonly observed mechanism is the translocation of the short arm of chromosome 1p11-13, where at the 1p13 breakpoint the Colony Stimulating Factor 1 (CSF1) gene is located, to chromosome 2q37 region containing the collagen 6A3 promoter element. These genetic rearrangements in TGCT lead to a local overexpression or a longer lifetime of the CSF1 mRNA. The CSF1 acts through its receptor on CSF1R-expressing cells of the mononuclear phagocyte lineage leading to the second messenger activation of tyrosine kinase Src and deregulated osteoclastogenesis. By overexpressing the CSF1 tumor cells attract an inflammatory infiltration containing mononuclear and multinuclear osteoclast-giant cells. This implies that only the stromal cells carry the neoplastic mutation and that the osteoclasts recruited to the tumor mass are a reactive component. This unique phenomenon among mesenchymal tumors is called “the landscape effect” [3–7].

Histology

TGCT diagnosis can be solely based on clinical symptoms and radiological findings, however, the only way to do it conclusively is through histological examination. The localized-type TGCT and the more clinically aggressive diffuse-type TGCT are morphologically similar, both composed of mononuclear and multinucleated cells, CD68 and CD163 (histiocytic markers) positive associated in varying proportions with spumous, chronic inflammatory and multinuclear cells. Nevertheless, the diagnosis is mostly made on the basis of the H-E–stained tissue without using immunohistochemical stains [3, 8, 9]. Localized-type TGCT is very similar to the individual lobules of diffuse-type TGCT but in general it contains less hemosiderin and more extracellular collagen than the latter [10]. Histologically there is an extensive cellular polymorphism among tumors and within the tumor mass. Variation in the number of osteoclast-type giant cells, mononuclear cells, foamy macrophages, the amount of hemosiderin, sclerosis, and the degree of stromal hyalinization are responsible for a wide morphologic spectrum [11]. Histologically, localized forms of TGCT are characterized by circumscribed, multinodular masses surrounded by dense collagen pseudo capsules consisting of cellular and hypocellular areas. The cellular area is composed of round or polygonal cells that blend with hypocellular collagenized zones. Most cells in the cellular areas possess the characteristics of histiocytes and synovial cells accompanied by various amounts of hemosiderin. Xanthoma cells and mononuclear foam cells occur frequently. Hypocellular areas consist of fibroblasts within a fibrous or homogenized stroma. The characteristic multinucleated giant cells are found scattered randomly throughout both cellular and fibrous areas and resemble normal osteoclasts [12]. In contradiction to the well-delineated localized-type TGCT, diffuse-type TGCT has a papillary character and shows a diffuse infiltrative growth pattern along the synovium with cleftlike spaces and discohesive zones. The multinucleated giant cells are less conspicuous and not as uniformly dispersed in diffuse-type TGCT and are rarely seen in highly cellular areas. In fact they may be absent in up to 20% of cases. Repetitive episodes of hemarthrosis are the cause of hemosiderin accumulation what is best seen in intra-articular diffuse-type TGCT where trauma of the villi and repetitive episodes of hemarthrosis occur most easily because of the limited joint volume and mobility but it may be not so prominent in the extra-articular locations [11]. The overall histologic appearance of the diffuse variant may raise suspicions of a malignant tumor like rhabdomyosarcoma, synovial sarcoma, or epithelioid sarcoma. The correlation between the histologic features and the imaging findings is essential to increase the likelihood of a correct diagnosis [8]. Although very uncommon there are cases of malignant TGCT reported in the literature showing its aggressive nature and significant risk of mortality. According to Bertoni *et al.* (1997), the most important histologic features of malignancy include (a) a nodular, solid infiltrative pattern of the

lesion; (b) large, plump, round or oval cells with deep eosinophilic cytoplasm and indistinct borders; (c) large nuclei with prominent nucleoli; and (d) necrotic areas. Atypical mitoses are occasionally seen [9]. The criteria for histologically malignant PVNS have also been developed at the US Armed Forces Institute of Pathology (AFIP); according to these guidelines, malignant PVNS must have at least five of the following eight features: diffuse pleomorphism, prominent nucleoli, high nuclear to cytoplasmic ratio, mitotic activity greater than 10 per 10 high-power fields, necrosis, discohesion of tumor cells, paucity of giant cells, and a diffuse growth pattern [8].

Macroscopic appearance

De Saint Aubain Somerhausen *et al.* 2000 describes 38 cases of diffuse-type tenosynovial giant cell tumor lesions which are poorly circumscribed with infiltrative margins, ranging in size from 1.7 to 13 cm (mean 5.4 cm, median 4.3 cm). A distinctive villous architecture was described in two cases whereas a markedly multinodular appearance was noted in eight cases. The sections were described as soft, friable, or rubbery, yellowish to brownish with occasional white, fibrous-looking areas. Isolated cases of cystic degeneration and necrosis were observed [11]. Localized type-TGCT are described by Recep Bedir *et al.* 2014 and Masahiro Ushijima *et al.* 1986 as firm, lobular and nodular masses with well-defined borders. The cut surfaces were gray-white mottled with brown or yellow tinge, depending on the amount of hemosiderin or foam cells in the tumors. A distinction was made between localized type TGCT of the digits and that of larger joints. For the digits, the tumors were spherical or ovate and ranged in size from 0.8 cm to 3.0 cm at the greatest diameter, with an average size of 1.1 cm. For the large joints, the tumors consisted of a single nodule and tended to be larger and more irregular in shape than the digit tumors, ranging in size from 1.0 cm to 6.0 cm at the greatest diameter, with an average size of 2.0 cm [12, 13].

Epidemiology

Most publications are based on the data from a single study conducted in one US county in 1980, wherein the annual incidence rate (IR) amounted to 9.2 cases per million person-years for localized-type TGCT and 1.8 cases for the diffused-type TGCT [14]. However, as reported more recently these statistics are undervalued due to the increasing awareness of the disease and constantly improving diagnostic methods. Two nationwide studies reveal significantly higher IR than was reported before. A registry-based Cohort Study in Denmark points to the fact that the incidence rate per million person-years for the localized-type TGCT and the diffuse-type TGCT adds up to 30.3 and 8.4, respectively [15]. In the nationwide study conducted in The Netherlands, on the grounds of anatomical site, localized-type TGCT is divided into

two groups, one affecting digits defined as localization distal to metacarpal or metatarsal bones and the other localized-extremity TGCT is defined as all sites near joints proximal and including metacarpal and metatarsal joints. The Incidence Rate is estimated at 34 per million person-years for TGCT in digits, 11 in localized-extremity and 5 in diffuse-type [16]. The bulk of the new cases are diagnosed in the age category 40–59 [15, 16]. Although rare, children are also diagnosed with TGCT [8, 17]. The youngest case of the TGCT incidence ever reported was a 6-months-old [17]. According to different studies there is a female predominance in localized-type TGCT incidence accounting for approximately 61% [15]. However, gender distribution of diffuse-type TGCT varies from 51% to 69% in favour of women [15, 18].

Location

Localized-type TGCT is the second most common soft-tissue mass of the hand. The sites most frequently affected by localized-type TGCT are the digits (up to 85% of cases), with the flexor zones predominating. The digit most commonly associated with the condition is the index finger [1, 8, 16, 19]. However, as a site the knee joint is mainly involved and at the same time the one most affected by D-TGCT, 64% of cases in the latter location are of the diffuse-type TGCT and 46% of the localized-type TGCT [16]. The less common locations of the diffuse-type are ankle, hip and shoulder, while for the localized-type wrists, foot and ankle, although any joint can be affected, including the temporomandibular joint, the sacroiliac joint and spinal inter-apophyseal joints [8, 16, 17]. The vast majority of cases are limited to a single joint, nonetheless, the diseases can be polyarticular or multifocal, which is diagnosed almost exclusively in children [20]. Regarding gender there is no significant difference in terms of localisation [16].

Clinical presentation

The course of the disease is chronic, slowly progressive, with no distinctive clinical manifestation and the median duration of symptoms till diagnosis varied from 10 months to 3 years, although it may be shorter e.g. due to torsion [14, 21, 22]. The reported symptoms differed among the patients and were related to the type of disease, intra- or extra-articular location and the affected joint [8, 22]. The initial clinical manifestation of the intra-articular type mostly involved pain and swelling which may not be seen in all locations such as the hip, where the leading symptom is pain with reduced swelling sensation [8, 21]. Far less frequently would the patient complain about a limited range of motion, joint locking during movement, extra-articular mass, increased warmth of the surrounding skin, joint instability or as it is in the case of the knee about pseudo-meniscal signs [21–24]. The extra-articular form was mostly con-

nected with palpable mass and pain and significantly less with swelling or joint dysfunction [8, 22]. The TGCT in digits may rarely be related to sensory disturbances [25]. Some of the patients had no initial clinical manifestation and the diagnosis was made on the grounds of unrelated causes or as preparation for prosthetic arthroplasty [21–23].

Radiographic features

Plain radiography

Conventional radiography is typically used as an initial diagnostic method, but may not reveal any abnormalities [8]. The first and most frequently seen signs include periarticular soft tissue swelling and well-circumscribed lobulated synovial masses of high density on the grounds of hemosiderin accumulation [24, 26]. In the course of the disease, bone erosion may be visible, which appears as subchondral, cyst-like lesions with well-defined sclerotic margins, usually on both sides of the joints, in non-weight-bearing regions [8, 22, 24]. The prevalence of the osseous manifestation is higher in joints with limited capacity such as the hip (up to 90% of cases), the elbow or the ankle, which enables an outward growth of lesions. While bone erosion is seen only in 25% of cases in the more capacious knee joint with the capsule allowing mass to expand outside the joint space into the adjacent bursal regions [8, 27]. It all leads to the enlargement of the suprapatellar pouch and local osseous changes in the patello-femoral joint [24]. Calcifications and periosteal reaction are a rare finding and the width of joint space as well as the normal bone mineralisation usually stay preserved [8, 26]. Arthrography, which is rarely used to diagnose the disease, may reveal a filling defect caused by multiple lobulated masses [8, 24, 27].

Sonographic features

The sonographic features of TGCT are nonspecific. In the diffuse intra-articular type there are such elements seen as heterogeneous echogenic masses, joint effusion, hypoechoic thickened synovium with nodular or villous appearance and in some cases underlying bone erosion. The projection of the localized intra-articular type is similar to the diffuse-type, but with a solitary mass. As regards the extra-articular location, an examination reveals a hypoechoic, well circumscribed mass arising from the tendon sheath, which is not moving with the tendon during a dynamic examination. Doppler Imaging usually exposes increased blood flow in all of the TGCT types in question [8] (Fig. 1).

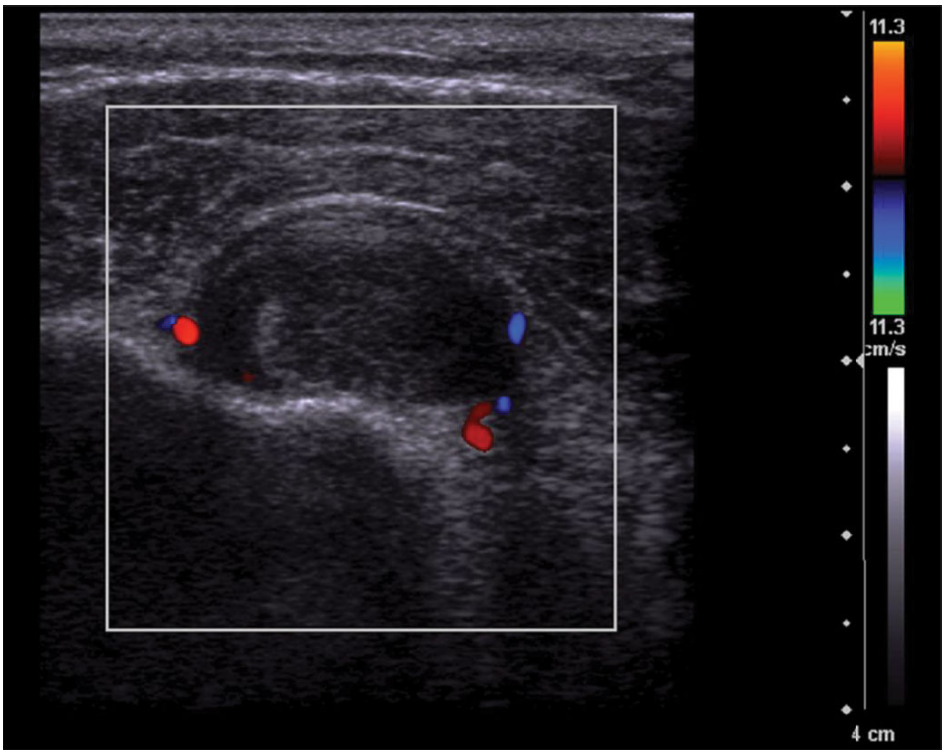

Fig. 1. Doppler ultrasound image — tenosynovial giant cell tumor of the knee.

CT

Regarding the diffuse type, a CT reveals a synovial mass of slightly higher radiodensity than that of the surrounding muscle, ranging from 55 to 75 Hounsfield Units (HU), which results from hemosiderin deposits [8, 28]. However the extent of the disease is better appreciated on MRI than on CT, due to the higher contrast resolution. Bone erosion and subchondral cysts with thin sclerotic edges can be seen in bones on both sides of the joint. As for the localized form of TGCT, CT scans are unspecific typically with a mass of similar attenuation to that of the adjacent muscle and less frequently of higher attenuation [8]. The contrast enhancement of the lesion is indistinctive and variable [26]. Arteriography may demonstrate prominent neovascularity and mild arteriovenous shunting [8]. More recently positron emission tomography-computed tomography (PET-CT) scans have also been used to study TGCT as well as to assess the therapeutic effects with the systemic modality of treatment chosen [29]. On fluorine 18 fluorodeoxyglucose (18F-FDG) PET-CT, TGCT can be displayed as a focal avid lesion, which can resemble metastatic disease [30].

MRI

MRI is the most essential of all medical imaging methods and allows for the diagnosis, assessment of the extent of the disease and treatment planning [31, 32]. The preoperative MRI not only detects the disease but also corresponds to the postoperative findings in up to 67% of cases [33]. The correct preoperative assessment is crucial to detect, if the lesion is extra-articular in extent and what tissues surrounding the joint are affected. Misdiagnosis can lead to incomplete resection and more frequent recurrences [8, 22]. The localized-type TGCT is a well-circumscribed nodular lesion in the synovial lining of bursa, joint or tendon sheath, while the diffuse-type is described as a multinodular lesion affecting a larger portion or multiple compartments of the synovial lining. The names intra- and extra-articular indicate the location inside or outside the synovial lining of the joint, respectively [1]. However, there are cases of TGCT occurring concomitantly in both locations. In different MRI modalities, areas of signal intensity corresponding to histological composition of the tissue can be distinguished. In the diffuse-type proliferated synovium has a heterogeneous appearance on T2WI with areas of high-signal intensity due to inflammation and equal or higher intensity to that of the surrounding muscles on T1WI [8, 24, 27, 34, 35]. The appearance of localized-type TGCT is isointense compared to the surrounding muscles on T1WI and predominantly hyperintense on T2WI [32] (Fig. 2, 3). In addition, for both types of TGCT, T1WI and T2WI show areas of intermediate to low signal intensity depicting hemosiderin deposits [24, 32]. The blooming artifact can be appreciated on the gradient-echo images, which presents itself as areas of low-intensity larger than their original size that are caused by iron in hemosiderin deposits [8, 27]. Within the mass there are also regions of signal intensity consistent with fat, which results from the presence of lipid laden macrophages [24]. There is prominent heterogeneous enhancement of TGCT with Gadolinium, being the effect of marked vascularity [8, 27, 32]. The coexisting joint effusion appears as high-signal intensity on T2WI [34]. On MRI, bone involvement can be appreciated as erosion and the forming of subchondral cysts, observed in the late phase of the disease and more frequently in the diffuse-type than in the localized-type. In some cases the vast bone erosion can mimic the marrow invasion. Joint space narrowing can be visible in the course of the disease [8]. Muscle/tendon tissue, ligament or neurovascular structures can be affected, which is defined as clear involvement or encagement >180° of those structures [36]. In some cases MRI shows features of recurrence prior to the appearance of clinical symptoms, and is therefore used in the monitoring of TGCT [31, 33].

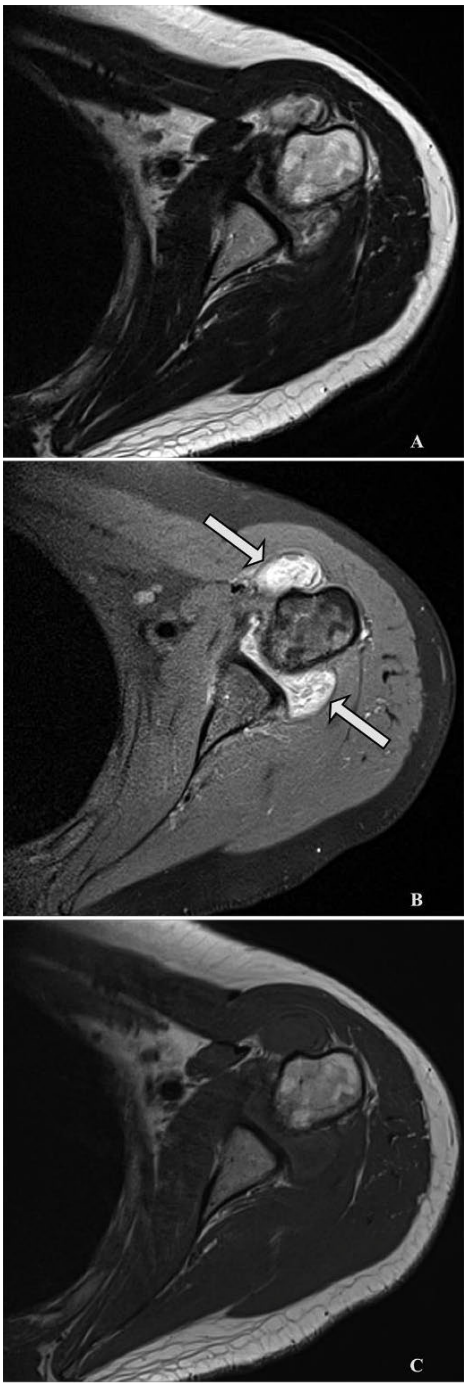

Fig. 2. Axial T2-weighted (**A**), Fat-Suppressed T2-weighted (**B**) and T1-weighted (**C**) MR images of tenosynovial giant cell tumor of the glenohumeral joint (arrows).

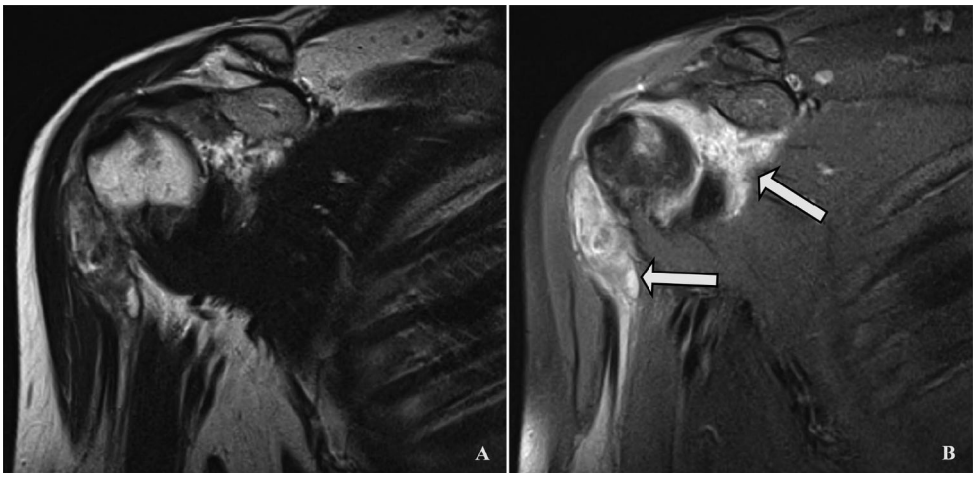

Fig. 3. Coronal T2-weighted (**A**), Fat-Suppressed T2-weighted (**B**) MR images of tenosynovial giant cell tumor of the glenohumeral joint of the same patient (arrows).

Treatment

Surgical treatment

Resection is the first line of treatment in TGCT. The best form of surgery is still debatable and depends on the tumor's site and location. Also in use are radiosynovectomy, external beam radiotherapy, chemotherapy and tyrosine-kinase inhibitors alongside surgery or as single modalities. The progression of the disease tends to be slow, therefore urgent treatment is usually not necessary [22]. It is crucial to differentiate the limited from the diffuse forms of the disease as it changes the treatment strategy. The localized-type TGCT has a ten-year recurrence risk of up to 9.8% and lifetime recurrence risk up to 15% [15]. For the localized-type TGCT, a simple surgical excision as a sole treatment is normally sufficient to cure it. It can be diagnosed during surgery [23]. Its location and structure mostly enables a total resection. If technically possible and the lesion is accessible, arthroscopy is the prefered method. Arthroscopic excision allows the minimisation of both recurrence and morbidity compared with open excision [37]. As for diffuse-type TGCT the optimal treatment strategy is unclear. Surgery aiming for a total resection of the pathological tissue is the main treatment option. A complete synovectomy is typically recommended. However, it is often difficult to obtain a complete resection due to the tumor's diffuse growth pattern, complex joint anatomy and the demanding surgical techniques involved. The diffuse form is particularly troublesome due to its frequent recurrences. It has a high local recurrence rate regardless of the applied treatment strategy and over time it becomes increasingly difficult to cure. Recurrence rates of TGCT increase with time

[22, 38]. The 10-year risk of recurrence is 19.1% while the lifetime risk of recurrence reaches 55% [15]. Patients often undergo multiple surgeries which may result in partial loss of function of the affected joint (even secondary arthrosis and the need for joint replacement). This in turn leads to a decline in their quality of life compared to the general population [38]. If the recurrence of the tumor is observed after resection, subsequent surgery seems to be less effective. Therefore, the initial treatment must focus on preventing recurrence, minimising morbidity and achieving the best possible outcome in terms of functionality and quality of life [18, 31, 39, 40]. The type of surgery depends on the form of TGCT, the tissues involved and the joint affected. For the knee, neither open surgery nor arthroscopy has been conclusively proved to be a better treatment option. While the former enables easier resection, it comes with a greater risk of knee stiffness, a longer hospital stay and an extended rehabilitation period. The latter offers only partial resection and has a higher risk of recurrence but provides better functional outcomes. Some reports claim that a combined method of open posterior and arthroscopic anterior synovectomy is a viable approach to diffuse TGCT of the knee. This method allows good visibility of the operated area and easy access to the pathological intra- and extra-articular tissue making it easier to achieve complete resection. It displays a low recurrence rate and a low postoperative complication profile as well as excellent functional outcomes [31, 39, 41].

Radiotherapy

There are two main radiotherapy (RT) methods currently used in TGCT treatment: intra-articular injection of radioactive isotopes and external beam radiotherapy. A complete resection of all pathological tissue appears to be the key to preventing recurrence, but both techniques can significantly improve the likelihood of local control and long-term function in patients with incomplete resection or progression of diffuse-type TGCT. Radiotherapy with total doses ranging from 30 to 36 Gy in 14–15 fractions over 3 weeks is considered a very safe and effective method of preventing progression or recurrence following primary surgery. The likelihood of complications after moderate-dose radiotherapy is low, however, due to the benign nature of the lesion the potential toxicity should be taken into account when choosing this treatment option [31, 37, 42, 43]. A combination of debulking surgery with intra-articular injection of yttrium90 (90Y) for extensive diffuse TGCT of major joints gives positive results, although a few cases of intra-articular 90Y treatment complications have also been observed. Out of the seven patients with d-TGCT after subtotal synovectomy of the ankle joint followed by intra-articular injection of 15 Mci (555 MBq) of 90Y, all reported pain and swelling of the joint, two developed full-thickness skin necrosis, and one a draining sinus [44, 45]. In another study, out of 40 patients with d-TGCT of the knee after operative treatment and intra- or extra-articular radiotherapy thirty-seven patients

(93%) had a good or excellent result according to the Knee Society Score clinical rating system. As regards complications in the group in question, there were four cases of advanced osteoarthritis leading to a total knee replacement and seven recurrences. Adjuvant RT can be beneficial in eradicating small foci of residual disease [31].

Chemotherapy

Limited data and still ongoing studies provide promising results of tyrosine kinase inhibitors targeting the CSF1 receptor such as imatinib, pexidartinib (PLX3397), emactuzumab (RG7155) and nilotinib. Clinical trials show that for patients with progressive or recurrent TGCT, for whom surgery cannot be considered, tyrosine kinase inhibitor therapy might be a possible treatment option. Targeting the CSF1 pathway in tenosynovial giant-cell tumors has been proved to show antitumor activity with significant tumor volume regression and good functional outcomes, but further studies are still needed to fully assess its effectiveness and safety. At therapeutic concentrations tyrosine kinase inhibitors can exhibit potential side effects including fatigue, diarrhea, anemia, hyponatremia, elevated aminotransferase levels, and neutropenia [4, 46, 47].

Differential diagnosis and conclusion

The final diagnosis of TGCT, based only on various images and modalities, is not always easy and possible, that limits the proper treatment. For this reason a differential diagnosis has to be done to exclude and limit errors. The most common conditions in such cases is the differential diagnosis include hemophilic arthropathy, synovial chondromatosis, synovial hemangioma and synovial sarcoma. MRI is very effective in distinguishing these entities. Compared with hemophilic arthropathy, both show hemosiderin deposits, but TGCT is confined to a single location and MR examination shows diffuse hemosiderin clumps, irregular synovial thickening, and distention of the synovial sac. Multiple calcified and noncalcified intra-articular bodies are typical of synovial chondromatosis. Synovial hemangioma shows a markedly hyperintense background with low-signal-intensity linear structures with possible fluid-fluid levels within the lesion in T2WI. The presence of phleboliths is suggestive of synovial hemangioma. Synovial sarcoma is associated with a characteristic triple sign in T2WI: high in fluid, iso or intermediate in lipid, and low in fibrous tissue but it doesn't always occur and can be sometimes very difficult to distinguish from TGCT. A biopsy should always be performed when exam results are even slightly inconclusive [22, 24].

Conflict of interest

None declared.

Abbreviations

CT — computed tomography
MRI — magnetic resonance imaging
TGCT — Tenosynovial giant cell tumor
WHO — World Health Organization

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