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Review article

Localized and diffuse forms of tenosynovial giant cell tumor (formerly giant cell tumor of the tendon sheath and pigmented villonodular synovitis)

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ABSTRACT

Tenosynovial giant cell tumor (TSGCT) is a rare benign tumor arising from joint synovia, bursae and tendon sheaths. Their variable clinical presentation is related to variations in site and progression. Localized forms are most frequent in the hands, and diffuse forms in the knee. MRI is necessary and sometimes sufficient for diagnosis. Treatment strategy is guided by progression, symptomatology, location and diathesis. Optimally complete resection is the principle of first-line treatment. Radiation therapy is effective and targeted therapies are promising; both should especially be considered in case of relapse.

1. Introduction

Tenosynovial giant cell tumor (TSGCT) or giant cell tumor of the tendon sheath is a family of lesions usually involving the joint synovia, bursae and tendon sheath. It may be intra- or extra-articular, and is classified by clinical presentation and biological behavior as localized or diffuse; the latter is more aggressive, and is also known as villonodular synovitis [1].

While any location is possible, localized forms mainly involve the digits and wrist (85% of cases); foot and ankle, knee, hip or other joint locations are more rare. Diffuse forms mainly involve the large joints: knee, hip, ankle and elbow. Localized forms are systematically benign; diffuse forms are more aggressive and destructive, and may exceptionally include a malignant component.

This great diversity of anatomic and clinical presentations and biological behaviors underlies the difficulty of therapeutic management. The present review details the main points for understanding these lesions and guiding treatment, which is not presently standardized.

2. Is TSGCT a tumoral process or a reactive lesion?

In 1941, Jaffe et al. [2] proposed a category of "pigmented villonodular synovitis, bursitis and tenosynovitis" to group together lesions previously known under different names according to location. This fuzziness in nosology prolonged the uncertainty as to whether TSGCT is a tumoral entity or not. In 1968, according to the review by Byers et al. [3], most authors favored a non-tumoral reactive etiology, with models based on iterative intra-articular blood injection, or a possible implication of iterative microtrauma and associated lipid disorder.

In 1984, Rao and Vigorita [4] suggested a tumoral process, with tumoral proliferation of fibroblasts and histiocytes. This was borne out by findings of aneuploid cells in certain TSGCTs and chromosomal findings of clonal abnormalities, mainly involving chromosome-1 deletion [5].

Finally, the consensual etiopathogenesis was proposed by West et al. [6]: there is a "landscape effect of tenosynovial giant cell tumor" caused by translocation of a small number of cells. TSGCT and the more aggressive pigmented villonodular synovitis or tenosynovitis (now categorized as localized and diffuse TSGCT, respectively) are essentially the same, comprising mono- and multinuclear cells; translocation involving locus 1p 13 is found in most TSGCTs, in a small proportion of cells (2–16%) with hyperexpression of CFS1. These tumor cells recruit macrophages bearing CFS1R receptor, differentiate into multinuclear cells and create the aggressive multinuclear "landscape" of TSGCT.

This biological understanding opens the way, as in other mesenchymal tumors [gastrointestinal stromal tumor (GIST), Darier-Ferrand disease] for successful targeted therapies.

These abnormalities underpin the rationale for medical management of TSGCT, to which we shall return in the section dealing with treatment.

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3. When and how to diagnose TSGCT

TSGCT is a rare pathology (incidence, 1/1,800,000) affecting young subjects [7]:

- 4th and 5th decades for the more frequent localized form;
- and a little earlier (< 40 years) for the diffuse form.

It may even so occur at any age, although rare in children.

Nodular forms are more frequent in females (2:1), whereas female predominance is slight in diffuse forms.

Clinical presentation is relatively nonspecific, but TSGCT should be considered in the absence of evidence for any other synovial pathology.

Localized forms predominate in the digits (85%), near to the synovial sheaths or interphalangeal joints, and more often on the palmar than the dorsal side. Other locations comprise wrist, foot and ankle, knee and, very rarely, hip or elbow [8]. The intra-articular localized form are mostly frequent in the knee.

Diffuse forms are mainly intra-articular, in the knee (75% of cases), hip, ankle or shoulder, although all synovial joints may be involved: temporomandibular, spinal inter-apophyseal joints, etc. Involvement is usually of a single-joint or single locus; rare multifocal cases have been reported, generally bilateral concerning the same joint (knee or ankle) or multifocal forms reported especially in children [9,10].

Extra-synovial soft-tissue forms mainly concern the knee, thigh or foot, in periarticular tissue although intramuscular and subcutaneous forms also exist.

Interview reveals trauma in half of cases, although causality is unclear. Symptom progression is slow; intervals between first signs and diagnosis are long: 10 months to 3 years. However, acute forms have been reported, related to torsion and necrosis of a pediculated nodule.

Functional signs are relatively nonspecific:

- in extra-articular and tendon sheath forms, there is a very slowly progressing, painless mass that may cause skin tension in the fingers or toes, making footwear uncomfortable;
- in articular forms, there is discomfort, with repeated swelling and restricted range of motion. In the knee, there may be blockage, pseudo-meniscal symptomatology or instability [11];
- asymptomatic forms or pseudo-degenerative presentations have been diagnosed, particularly in the knee, when fitting a prosthesis or on MRI prescribed for some other reason.

Clinical examination finds a soft palpable mass in superficial locations, sometimes associated with heat and periarticular effusion or edematous swelling.

Thus, clinical examination is nonspecific but may be suggestive in:

- young adults;
- typical location, especially in a mass in the soft-tissue of the hand or foot;
- single-joint disorder with slow progression and no other sign suggestive of synovial pathology (polyarthritis, gout, incipient hemophilic arthropathy), in which case etiological assessment should be completed by biological work-up, to rule out differential diagnoses, and imaging.

Standard radiography is indispensable, and is contributive as there are bone abnormalities in 33% of diffuse forms in the knee. Bone lesions, in the form of cystic erosion, are more frequent and suggestive in the hand and hip (Fig. 1). Cysts in a non-weight-bearing region, often symmetrically on either side of the joint line or at the capsular insertion lines, without calcification, are often suggestive of articular TSGCT.

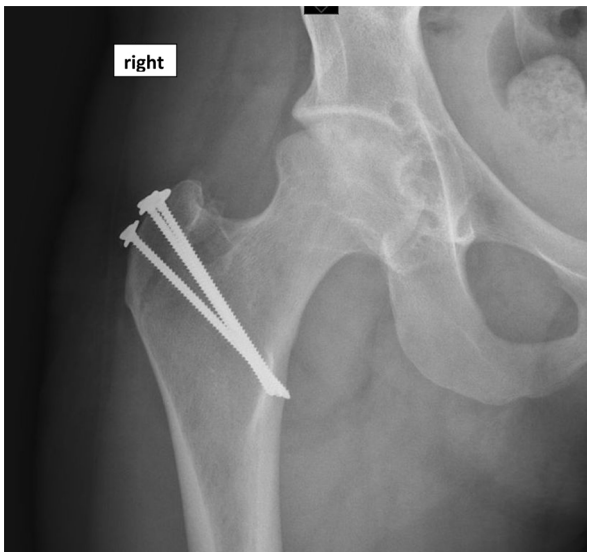

Fig. 1. Osteoarthritic progression 15 months after synovectomy of the hip with dislocation. Cysts in non-weight-bearing regions are typical of tenosynovial giant cell tumor (TSGCT) of the hip.

The most contributive examination is MRI, indispensable to diagnosis and surgical planning. Localized forms typically show as a well-delineated lesion, off-center from or else more-or-less completely enclosing the tendon in question. Diffuse forms are usually articular, showing as a soft-tissue mass with homogeneous uptake, with associated joint effusion. Fossa and extra-articular extension is often associated and should be screened for on preoperative work-up. The localized or diffuse lesion signal indicates the form of the TSGCT: variable tissue hemosiderin loading accounts for weak or intermediate signal on T1 and spin-echo T2-weighted sequences. The signal is enhanced on gadolinium injection. Gradient-echo sequences are very useful for detecting hemosiderin deposits, showing in low signal, even after injection [12] (Figs. 2 and 3).

Ultrasonography is now widely used; it does not replace MRI, but can be indicative, showing a mass of variable aspect but with suggestive location. TSGCTs appear hypervascularized on Doppler ultrasound [13], which optimally guides synovial biopsy.

Following clinical and imaging assessment, what are the differential diagnoses?

In the limbs, most lesions show different MRI characteristics: ganglion cysts, hemangioma, synovial sarcoma of the foot and nerve-sheath tumor show high T2 signal. Like TSGCT, other lesions may show intermediate T2 signal: in the foot, fibromatosis, xanthoma, Morton neuroma and certain desmoid sarcomas or tumors; location, symptomatology and clinical findings guide diagnosis, which must, however, be confirmed on specialized radiological/clinical assessment.

In periarticular, peripheral or proximal articular locations, synovial sarcoma, which is rarely intra-articular, is a difficult differential diagnosis, with high stakes. Location may be in the sheaths or bursae, like TSGCT; in 20–30% of cases, there are calcifications, which are also, although rarely, found in TSGCT. MRI typically associates a 3-fold signal: high in fluid, iso or intermediate in lipid, and low in fibrous tissue; but, although typical, this aspect is not systematic. Biopsy should be performed in case of the slightest doubt, especially in nodular forms.

In intra-articular locations, erosion and images of cysts in non-weight-bearing regions are suggestive, especially when associated with the above typical MRI aspect. Recurrent hemorrhagic synovitis

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