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Review

Diffuse-type tenosynovial giant cell tumour: Current treatment concepts and future perspectives

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Abstract At present, the optimal treatment strategy in patients with diffuse-type tenosynovial giant cell tumour (D-TGCT) is unclear. The purpose of this review was to describe current treatment options, and to highlight recent developments in the knowledge of the molecular pathogenesis of D-TGCT as well as related therapeutic implications. Epidemiology, clinical features, and the pathogenesis of D-TGCT and the most widely used treatment modalities are described. D-TGCT is a benign clonal neoplastic proliferation arising from the synovium. Patients are often symptomatic and require multiple surgical procedures during their lifetime. Currently, surgery is the main treatment for patients with D-TGCT, with relapse rates ranging from 14% to 55%. Radiosynovectomy and external beam radiotherapy have been used in combination with surgical excision or as single modalities. The finding that D-TGCT cells overexpress colony-stimulating factor 1 (CSF1), resulting in recruitment of CSF1 receptor (CSF1R)-bearing macrophages that are polyclonal and make up the bulk of the tumour, has led to clinical trials with CSF1R inhibitors. These inhibitors include small molecules such as imatinib, nilotinib, PLX3397, and the monoclonal antibody RG7155. In conclusion, D-TGCT impairs patients' quality of life significantly. The evidence that the pathogenetic loop of D-TGCT can be inhibited could potentially change the therapeutic armamentarium for this condition. Clinical trials of agents that target D-TGCT are currently ongoing. In the meantime, international registries should be activated in order to provide useful information on this relatively rare tumour.

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1. Background

The term tenosynovial giant cell tumour (TGCT) refers to a family of proliferative and inflammatory diseases of benign course arising from the synovium of joint, bursae, and tendon sheaths. The lesion can either present as a single nodule (localised form: L-TGCT), or as multiple nodules (diffuse-type: D-TGCT) along a synovial layer or tendon sheath [1–6]. While previously these tumour types were classified as pigmented villonodular synovitis or giant cell tumour of the tendon sheath, in the most recent version of the World Health Organisation classification, TGCT has been suggested to replace both designations [5].

While surgery is the mainstay of treatment for TGCT, failure is frequent, with local relapse rates of up to 50% [2,7–9]. Furthermore, repetitive surgical treatment can lead to substantial morbidity to the impacted joints and impaired quality of life. Various forms of radiation therapy have been applied in an attempt to reduce the risk of local recurrence and as an alternative to surgery, although these strategies have not been rigorously tested in large, prospective clinical studies [10,11]. Historically, conventional chemotherapeutic agents have not been proven effective in TGCT, but new drugs are under investigation for this indication, with promising preliminary results [12–15].

This paper will review treatments currently applied for D-TGCT and will discuss emerging therapeutic options that are currently under investigation.

2. Epidemiology, clinical features, and pathogenesis of TGCT

The annual incidence rate for TGCT has been estimated at 1.8 cases per million people in the United States [16], and TGCT is equally frequent in males and females. Diagnosis usually occurs between 20 and 50 years of age [5].

D-TGCT most frequently involves the knee, hip and ankle joints. Patients generally present with pain, tenderness, swelling, or limitation of motion, and haemorrhagic joint effusions are common. At diagnosis, the symptoms are usually of relatively long duration, often spanning several years.

Radiographically, most tumours present as poorly-defined periarticular masses, frequently associated with degenerative joint disease and cystic lesions in the adjacent bone [17]. By magnetic resonance imaging, giant cell tumours typically show decreased signal intensity in both T1- and T2-weighted images (Fig. 1) [18].

For many years, the pathogenesis of TGCT has been poorly understood, with a number of sources hypothesised as contributing to its development, including neoplastic, inflammatory, traumatic, metabolic, and viral pathways [19]. More recently, TGCT was found to be a clonal neoplastic process associated with specific genetic changes, frequently due to a specific translocation: t(1;2) CSF1:COL6A3. There is also typically a reactive component with proliferation and recruitment of colony-stimulating factor 1 receptor (CSF1R)-expressing cells including macrophages, giant cells, and osteoclasts, in what is known as the 'paracrine landscape effect.'[6].

3. Current treatment strategies

There are several treatment options available for D-TGCT, although they have varying success rates and associated morbidity. While surgical excision is currently considered the principal treatment for D-TGCT [2], there is no consensus about the most

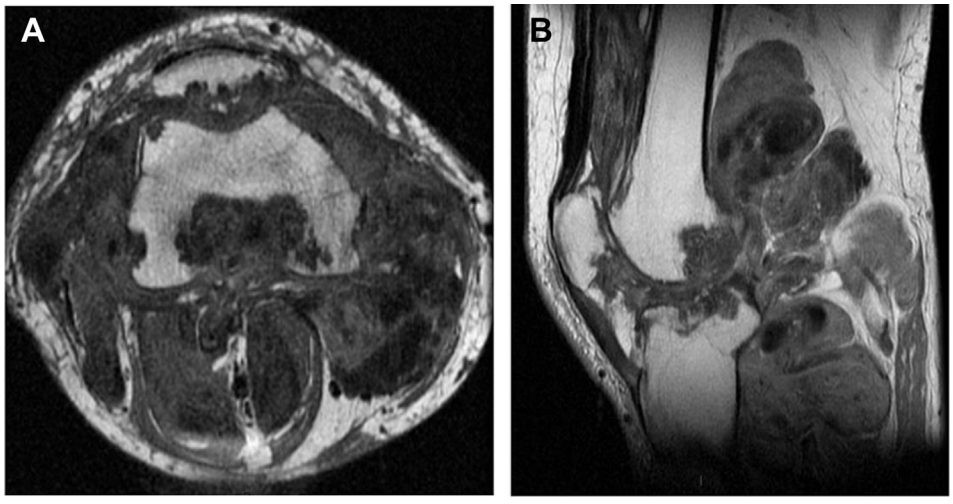

Fig. 1. T1-weighted axial (A) and T2-weighed sagittal (B) MRI-scan showing extensive D-TGCT of the knee with a large extraarticular component and bone erosion. MRI, magnetic resonance imaging; D-TGCT, diffuse-type tenosynovial giant cell tumour.