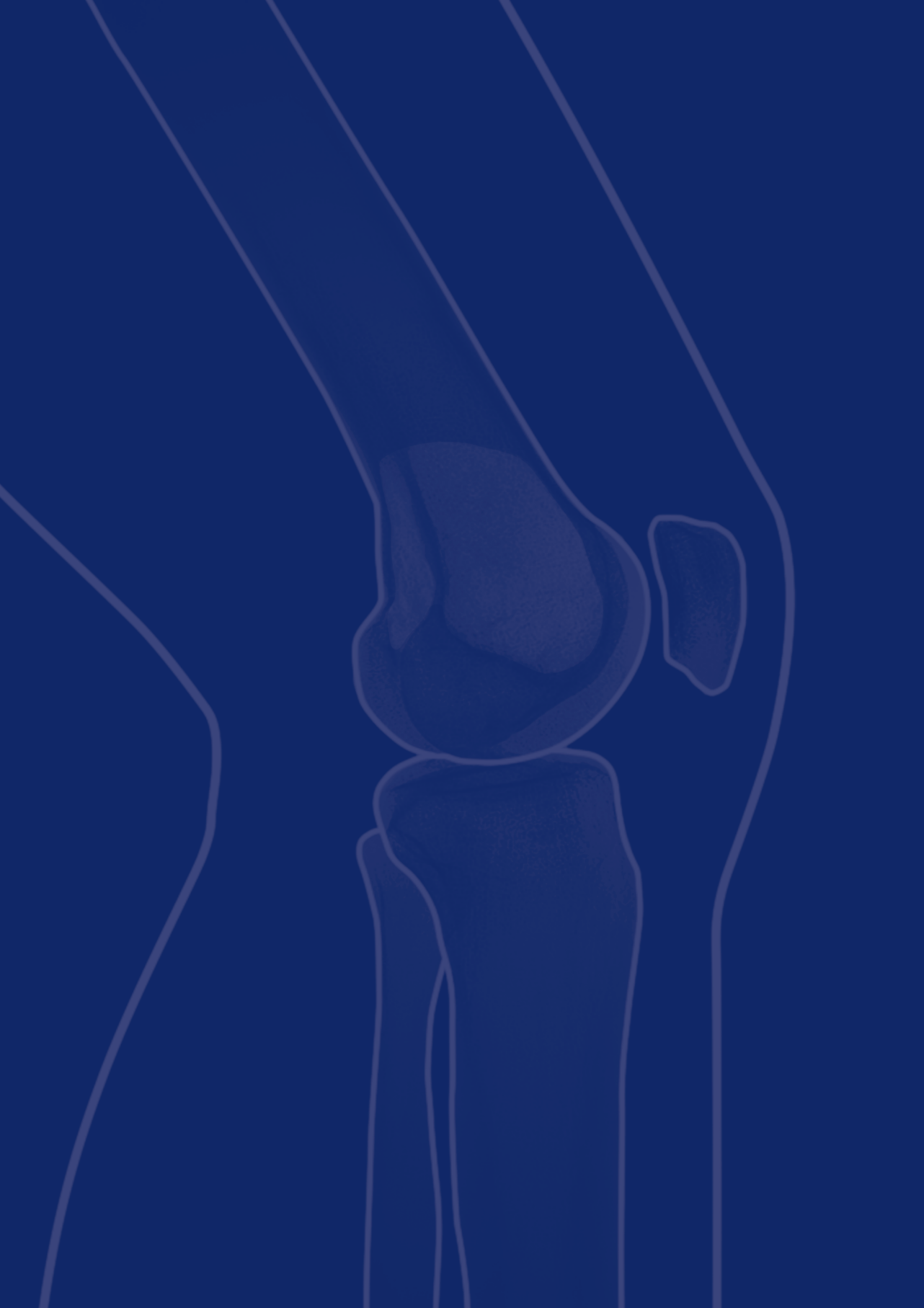
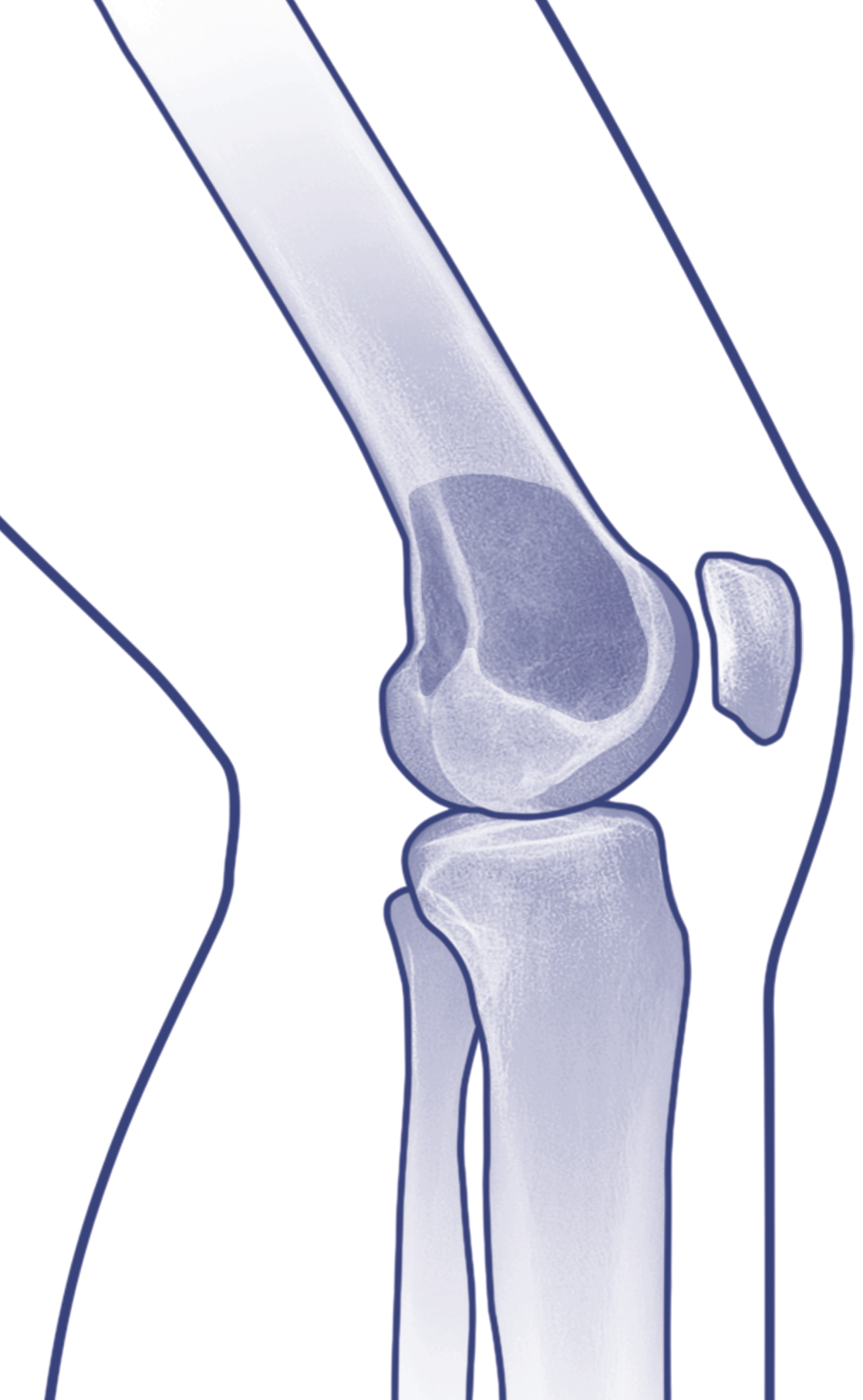


Part II

Giant cell tumor of tenosynovial tissue



Chapter 9

The management of diffuse-type giant cell tumor (pigmented villonodular synovitis) and giant cell tumor of tendon sheath (nodular tenosynovitis)

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Abstract

Background Giant cell tumors of the synovium and tendon sheath can be classified into two forms: localized (giant cell tumor of the tendon sheath, GCT-TS; or nodular tenosynovitis) and diffuse (diffuse-type giant cell tumor, Dt-GCT; or pigmented villonodular synovitis, PVNS). The former principally affects the small joints. It presents as a solitary slow-growing tumor with a characteristic appearance on MRI and is treated by surgical excision. There is a significant risk of multiple recurrences with aggressive diffuse disease. A multidisciplinary approach with dedicated MRI, histological assessment and planned surgery with either adjuvant radiotherapy or systemic targeted therapy is required to improve outcomes in recurrent and refractory Dt-GCT.

Treatment Although arthroscopic synovectomy through several portals has been advocated as an alternative to arthrotomy, there is a significant risk of inadequate excision and recurrence, particularly in the posterior compartment of the knee. For local disease, partial arthroscopic synovectomy may be sufficient, at the risk of recurrence. For both local and diffuse intra-articular disease, open surgery is advised for recurrent disease. Marginal excision with focal disease will suffice, not dissimilar to the treatment of GCT-TS. For recurrent and extra-articular soft-tissue disease adjuvant therapy, including intra-articular radioactive colloid or moderate-dose external beam radiotherapy, should be considered.

Introduction

Giant cell-rich tumors are classified according to their site of origin, namely bone, soft tissue, synovium or tendon sheath. Those that arise from tendons and synovium are now classified into two forms: localized (nodular tenosynovitis) and diffuse (pigmented villonodular synovitis). In the World Health Organization (WHO) classification [1] the former is described as giant cell tumor of tendon sheath (GCT-TS), whereas the latter, which was first recognized and described by Jaffe, Lichtenstein and Sutro [2] in 1941 as a reactive or inflammatory disorder of the synovium of large and small joints, is described as diffuse-type giant cell tumor (Dt-GCT). The disease is mono-articular, and chromosomal aberrations are seen in both forms, suggesting a neoplastic rather than a reactive origin [3].

Giant cell tumor of tendon sheath (GCT-TS)

This local form of the disease can occur in any age group but principally affects those between 30 and 50 years of age, with a female predominance [4]. Most commonly it presents as a soft-tissue swelling in the hand or foot, adjacent to a small joint and arising from a tendon sheath or the synovial lining of a joint or bursa. It is often painless and slow growing, fixed to deep structures and abutting the bone, which can be eroded by pressure to cause scalloping [4]. In >10% of patients it arises from the synovium [5]. Solitary disease is also common in the knee and may present as an incidental finding on MRI or, more commonly, with mechanical symptoms mimicking a meniscal injury or 'loose body', which suggests a pedunculated tumor (Figure 1A). Extra-articular disease presents as a slow-growing non-painful, often palpable peri-articular mass. It is a benign condition, but may recur if incompletely excised [6].

Diffuse-type GCT (Dt-GCT)

This is a rare, usually benign proliferative tumor that develops in the synovium, with an incidence of two per 1,000,000 per year [1] in patients ≤40 years old, with an equal gender distribution. The knee is the most common site (Figure 1B); the elbow, ankle and hip are less common, and rarely the foot and temporomandibular joint may be involved. The spine may be affected, notably

the sacroiliac joints and posterior vertebral elements [7]. Characteristically there is a long history, with a delay in diagnosis. The patient often presents with an intermittently tender and painful joint. In the knee and ankle there may be recurrent swelling with spontaneous haemarthrosis. Although considered to be a benign condition, the diffuse form is more aggressive, with a high recurrence rate after surgery of 25% with intra-articular and 25% to 50% with extra-articular disease [8].

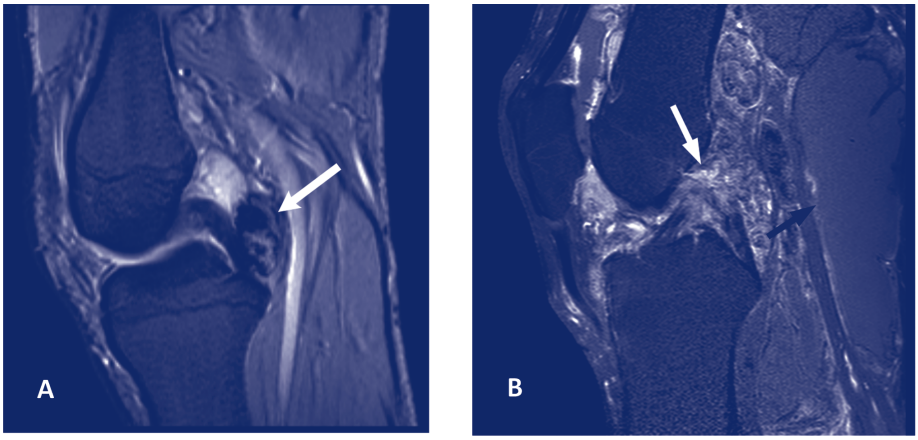

Figure 1 (A) Sagittal gradient echo MRI in a 41-year-old man with persistent pain in the right knee, showing the local form of the disease (giant cell tumor of tendon sheath, GCT-TS). MRI shows a well-defined soft-tissue mass dorsal to the posterior cruciate ligament and in close relationship to the knee capsule (white arrow). The lesion shows focal hypointense areas, owing to the 'blooming' artifact from haemosiderin. (B) Sagittal T1-weighted MRI in a 61-year-old man showing recurrence of the diffuse form of disease (Dt-GCT) (white arrow). MRI after intravenous gadolinium with fat suppression reveals an extensive proliferative synovial process of the left knee with a heterogeneous enhancement and areas of low signal intensity typical of iron deposition. Here, Dt-GCT is localized diffuse and intra-articular in relation to a large Baker's cyst (black arrow).

A review of the management of this disease is merited for a number of reasons:
The reclassification of the disease, according to the site and the tissue of origin, recognizes two distinct forms, nodular and diffuse, with the latter behaving in a more aggressive manner.
With improvements in imaging, notably MRI, a radiological and pathological diagnosis of the condition can be made, identifying the extent of disease and allowing for planned treatment and resection.
Recognition of this condition as a tumor rather than a reactive or inflammatory disorder, with a chromosome aberration identified in both the local and diffuse forms.

The need for a multidisciplinary approach to the management of diffuse disease, with selective histology and planned surgical resection to avoid the high incidence of local recurrence.
The potential use of adjuvant radiation and novel targeted therapies, such as macrophage colony-stimulating factor 1 receptor (M-CSFR)-targeted tyrosine kinase inhibitors (e.g. imatinib) as non-surgical treatment for aggressive Dt-GCT (PVNS) or for recurrent disease.

Imaging

Conventional radiographs combined with MR imaging will establish the diagnosis of Dt-GCT and accurately determine the extent of the disease. Although the appearance can be characteristic, image-guided percutaneous needle biopsy for histopathological examination may be indicated, particularly if there is doubt about the diagnosis.
Conventional radiographs are often not diagnostic. With advanced disease there may be evidence of soft-tissue swelling, loss of joint space and peri-articular erosion of bone. The peri-articular erosions are more notable in joints with a tight capsule, such as the hips, elbows, hands and feet (Figure 2).
The joint space is preserved until late in the disease. In addition to the absence of peri-articular osteopenia this feature is helpful in differentiating Dt-GCT from an inflammatory synovitis.

On MRI the appearance of Dt-GCT is often characteristic owing to the presence of haemosiderin [9]. The lesions demonstrate predominantly low signal intensity on T1- and T2-weighted spin echo sequences. The presence of haemosiderin deposits causes local changes in susceptibility ('blooming effect'), especially on gradient echo sequences, resulting in disproportionately lower signal intensity areas. Marked enhancement is seen on T1-weighted MR images after the intravenous injection of gadolinium.
The differential diagnosis on MRI includes rheumatoid pannus, amyloid arthropathy, synovial haemangioma, haemophilia, and desmoid-type fibromatosis, which can be resolved on the basis of clinical history and laboratory findings. MR morphology and enhancement characteristics can be confirmed with biopsy and formal histological examination.

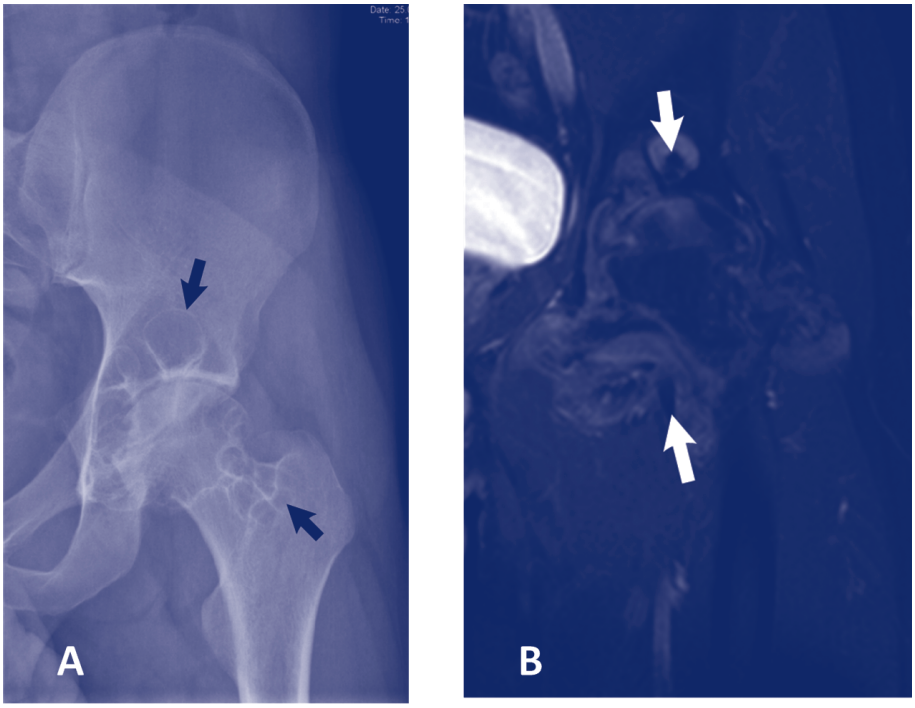

Figure 2 (A) Radiograph of the left hip of a 22-year-old man with a three-year history of progressive pain in his left groin, showing diffuse-type giant cell tumor (Dt-GCT) with erosive destruction of the hip joint. There are lytic lesions with well-defined sclerotic margins on both sides of the joint, (black arrows) consistent with a synovial process. (B) Corresponding coronal T2-weighted MRI with fat suppression demonstrates the erosive destruction of the acetabulum, femoral head and neck as a result of extensive synovial proliferation. The areas of low signal intensity within the synovial mass indicate the presence of haemosiderin deposits characteristic of Dt-GCT (white arrows).

Genetics

Dt-GCT and GCT-TS are giant cell tumors that both express an osteoclast-like antigenic phenotype; the cells show calcitonin receptors and are capable of lacunar resorption of bone [10-13]. It is thought that osteoclast-like giant cells are formed from mononuclear macrophage precursors by a receptor activator of nuclear factor-kappa B ligand (RANKL)-dependent mechanism similar to that seen in giant cell tumors of bone and soft tissues [10, 14-16].

The tumors are driven by overexpression of macrophage colony-stimulating factor 1 (M-CSF1). In 30% to 60%, M-CSF over-expression results from a t(1;2) translocation, which fuses the M-CSF gene on chromosome 1p13 to the collagen 6A3 (COL6A3) gene on chromosome 2q35 [3, 17]. M-CSF1 is only expressed by

a minority of tumor cells, which in turn attract non-neoplastic inflammatory cells that express M-CSF1R through a paracrine or so-called landscape effect [3]. M-CSF is produced by synovial fibroblasts with increased expression of M-CSF by proliferating cells, leading to the accumulation of macrophages and the formation of a tumor-like mass [3]. In benign disease mitotic activity is less but in the aggressive form, mitotic rates are increased to > 20 mitoses per ten high-power fields.

This molecular characterization of Dt-GCT has resulted in the development of new systemic targeted therapies for the aggressive form and for recurrent disease [18]. A malignant form of the disease was first reported by Bertoni *et al.* [19] but is thought to be a debatable entity that needs to be proven by linear studies [20].

Pathology

Macroscopically, Dt-GCT is red-brown or yellow and contains numerous capillary fronds and nodular areas that in the diffuse form often involve the whole synovium. However, focal interrupted areas in normal synovium may be a feature of disease in the knee [1].

Histological examination reveals villous hypertrophy of the synovial membrane with subintimal macrophage infiltration. There are numerous lipid-laden foamy macrophages and scattered multinucleated giant cells. The tumor has a fibrous stroma and may contain bands of collagen with brisk mitotic activity in the subintimal stromal cells. Haemosiderin may be present within the synovial lining cells and the subintimal macrophages (siderophages), and it may be extracellular within the subintima. Its presence is significant because it produces the characteristic signal appearances noted on MRI, which are useful for diagnosis of this disease.

Surgery

Giant cell tumor of tendon sheath (GCT-TS)

In the hand and foot this presents as a solitary swelling next to a small joint, whereas in the knee and ankle it may be an intra-articular solitary lesion or a peri-articular lesion fixed to a tendon sheath or bursa.

As with any solitary solid tumor that is fixed to the deep tissues it is important that imaging supports the diagnosis of GCT-TS; if there is any doubt about the diagnosis a formal tissue biopsy must be undertaken. Rarely peri-articular malignant conditions may mimic GCT-TS, including synovial, epithelioid and clear cell sarcoma in the hand; these conditions can present in similar fashion as can other common benign solid soft-tissue lesions (such as haemophilia, synovial hemangioma, rheumatoid pannus, amyloid arthropathy and desmoid-type fibromatosis) [4]. Careful clinical examination, MR morphology and enhancement characteristics can usually differentiate between these conditions. Planned surgical excision, aiming for a clear margin, is advised when a solid diagnosis is established.

In the hand and the foot GCT-TS is a solitary non-invasive firm tumor, generally 0.5 cm to 3.5 cm in size [4]. As it is a slow-growing lesion it displaces adjacent structures and rarely involves nerves and blood vessels. In our opinion an extensile approach centered over the lump in the long axis of the digit is recommended, so that adjacent neurovascular structures can be identified first and separated from the pseudo-capsule. Skin flaps need to be developed carefully, fully identifying the tumor, which has the characteristic appearance of a well-circumscribed lobular mass. The cut surface has a variegated pink-grey appearance with flecks of yellow and brown tissue. In principle, a solitary tumor can be excised marginally with associated affected soft tissue. After careful excision of solitary tumors of the digits and of the larger joints, a recurrence rate of <15% is expected [21]. Histological confirmation is mandatory, and the patient must be advised that if further soft-tissue masses develop they should seek review that should include MR imaging.

Arthroscopic resection has been advocated for solitary tumors of the large joints, notably the knee [22, 23], which in expert hands can be technically successful for focal intra-articular disease and small accessible solitary solid tumors. However, if the lesion is misdiagnosed pre-operatively and afterwards appears to be malignant (i.e. not Dt-GCT), intra-articular spread of a malignant tumor and incomplete excision of the disease may result.

We would recommend open excision for extra-articular solitary tumors of large joints and for inaccessible intra-articular disease, such as for the posterior knee or fixed synovial disease, an extensile approach should be used, with arthrotomy, which can be extended if revision surgery is required [22, 23].

Formal excision, either marginally or with a cuff of tissue, is required and histological examination mandatory.

Diffuse-type giant cell tumor (Dt-GCT)

The current management of this is controversial, owing in part to the rarity and heterogeneity of the disease and the limited evidence available, particularly in the knee. What is recognized is the high recurrence rate, at 25% for intra-articular and 50% for extra-articular disease, which is dependent on the site, volume of disease, intra- or extra-articular extent and previous surgery [1, 8].
In the knee arthroscopic synovectomy has been advocated, with better functional results and lower rates of post-operative stiffness. Local recurrence can occur if excision is incomplete [24].
Arthroscopic synovectomy requires technical expertise, and complete excision is rarely achieved even by experienced arthroscopic surgeons. In order to treat diffuse disease, many portals may be required to access the posterior and collateral joint recesses, with the risk of seeding the disease into the soft tissues around the portals.
The posterior joint, collateral ligaments and cruciate attachments are often difficult to visualize and treat arthroscopically. The recommended treatment for large-volume diffuse disease therefore remains open arthrotomy [25-27]. Combined or staged surgery may be considered if there is limited anterior disease that is accessible to arthroscopic synovectomy. However, with posterior disease an open posterior approach is required. We prefer an extensile approach, with a lazy-S incision, and elevation of the origin of the medial or lateral heads of gastrocnemius to allow protection of the neurovascular structures. Formal arthrotomy to visualize the posterior cruciate ligament and articular surfaces must be undertaken to obtain access to the synovium.
A midline anterior approach is advised for anterior disease, as this allows good visualization of the synovial cavity, fat pad, cruciate and collateral ligaments. Residual tumor adjacent to the joint line and unilateral gutters can be safely resected.
Although an open approach with complete synovectomy for diffuse disease remains the standard treatment, high recurrence rates can still be expected. A multidisciplinary approach, including careful assessment with MRI of the knee and complete synovectomy, either as a single or a staged procedure, results in

a lower recurrence rate and fewer complications [28]. However, arthrotomy of the knee is associated with a prolonged hospital stay and rehabilitation, with the incidence of joint stiffness as high as 24% [29].

Dt-GCT is also not uncommonly found in the elbow and ankle joints. A similar approach as for the knee is advised, with careful imaging and a tissue diagnosis with planned open surgery [30]. An extensile approach with identification and protection of the neurovascular structures should be undertaken, and attention should be paid to complete clearance of the synovium under direct vision.

With extensive joint destruction or the development of secondary arthritis, arthroplasty is indicated. In the hip, ankle or knee a conventional procedure is advocated, although with Dt-GCT the failure rate is reported as higher than with conventional arthritis [31, 32]. A failure rate of 22% has been reported following total knee replacement and complete synovectomy for Dt-GCT [32]. A marginally improved rate is reported in the hip [33]. These patients are generally younger than those who undergo conventional joint replacement and often have multiple procedures, with an increased risk of complications.

Radiosynovectomy

Intra-articular injection of yttrium-90 (^{90}Y)-labeled colloid can be used as a local adjuvant after synovectomy, but only for localization of intra-articular disease. At present, doses of 15 mCi to 25 mCi (555 MBq to 925 MBq) are administered six to eight weeks post-operatively, depending on the volume of the joint and body size [34-37]. Although caution is needed when using radioactive agents in the treatment of benign lesions, instillation of intra-articular radioactive colloids seems safe and effective after subtotal synovectomy. Recurrence rates of 0% to 25% are reported, but there is little evidence regarding outcomes, as the number of cases in most series is small [34, 35, 38]. Ottaviani *et al.* [39] presented the largest, albeit mixed, group of patients with Dt-GCT (n=122) treated by radiosynovectomy with a relatively high recurrence rate of 30% in the knee (15 of 50) and 9% in other locations (two of 23). However, it is unclear from their report whether the lesions were localized or diffuse, and for which lesions an open or arthroscopic approach was used. Both parameters significantly influence the recurrence rate.

Radiation therapy

External beam radiotherapy can be used as primary treatment for unresectable disease or as local adjuvant treatment in incompletely resected or extensive Dt-GCT, improving local tumor control [40-44]. An average dose of 30 Gy to 50 Gy (in 15 to 20 fractions) has the advantage of staying under the threshold for fibrosis formation and avoiding long-term radiotherapy-related toxicity. Recurrence is reported to be between 7% and 67% for different tumor sites [41, 43, 45-47]. No significant complications of radiotherapy were seen in this group of patients [7, 34, 44, 45, 48, 49].

Neo-adjuvant systemic targeted therapy

The molecular characterization of Dt-GCT facilitates the use of systemic targeted therapies as a novel method of treatment for patients in whom surgery would produce significant functional impairment, or for those with unresectable Dt-GCT.

Although M-CSF over-expression is present in a minority of neoplastic cells, the majority of mononuclear and multinucleated stromal cells in Dt-GCT express high levels of M-CSFR, which is thought to be responsible for the formation of a tumor mass [3, 17, 50]. This signaling pathway seems a promising target for systemic therapy with tyrosine kinase inhibitors such as imatinib or related compounds. Imatinib is an approved drug for the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GIST); it acts on cells of the monocyte/macrophage lineage with M-CSFR [50]. Recently, it has been shown to induce some tumor regression in patients with advanced Dt-GCT [18, 28, 51].

In 2008, the first case report of the activity of imatinib in recurrent M-CSFR-dependent Dt-GCT was published [51]. The patient was treated with imatinib 400 mg/day. After a complete response at five months, the Dt-GCT recurred when the drug was stopped. At re-introduction a secondary complete remission was reported.

Additionally, it showed promising activity in two preliminary case series [18, 28]. In one, five of six patients reported pain relief, three had regression of disease, and two patients found the disease stabilized with this treatment [28]. The second series revealed one complete remission, four partial remissions,

and in 20 of 27 patients the disease was stabilized [18]. The most common side effects were mild fluid retention, fatigue, nausea and skin toxicity.

Although blockade of M-CSFR by imatinib in Dt-GCT would seem to be the most likely mechanism of action, the potential contribution of blockade of other tyrosine kinases by imatinib cannot be ruled out. Currently the role of imatinib and other tyrosine kinase inhibitors (e.g. nilotinib and sunitinib) is under investigation as a neo-adjuvant systemic treatment in advanced Dt-GCT (www.clinicaltrials.gov, NCT01261429 and NCT01207492). There may also be a therapeutic role for blockade of M-CSFR through other cytokines, notably interleukin (IL)-34, which interacts with this receptor [52]. In addition, as the formation of giant cells in Dt-GCT is known to be by a RANKL-dependent mechanism [16], there may be a role for RANKL antibody treatment to inhibit the formation of giant cells in this lesion, as in giant cell tumor of bone [14].

Summary

GCT of the tendons and synovium is now classified into two forms: localized (GCT-TS, nodular tenosynovitis) and diffuse (Dt-GCT, pigmented villonodular synovitis). The former principally affects the small joints and presents as a solitary slow-growing tumor with a characteristic MRI appearance, and is treated by planned surgical excision.

Dt-GCT is a more aggressive intra-articular form affecting both small and large joints, most commonly the knee. Both local and diffuse diseases were previously thought to be of reactive inflammatory origin; however, both forms are now regarded as tumors of peri-articular tissue, as they share a common chromosomal aberration.

There is a significant risk of multiple recurrences in diffuse disease. A multidisciplinary approach with dedicated MR imaging, histological assessment and planned surgery, with either adjuvant radiotherapy or systemic targeted therapy, is required to improve outcome in recurrent and refractory Dt-GCT (Figure 3).

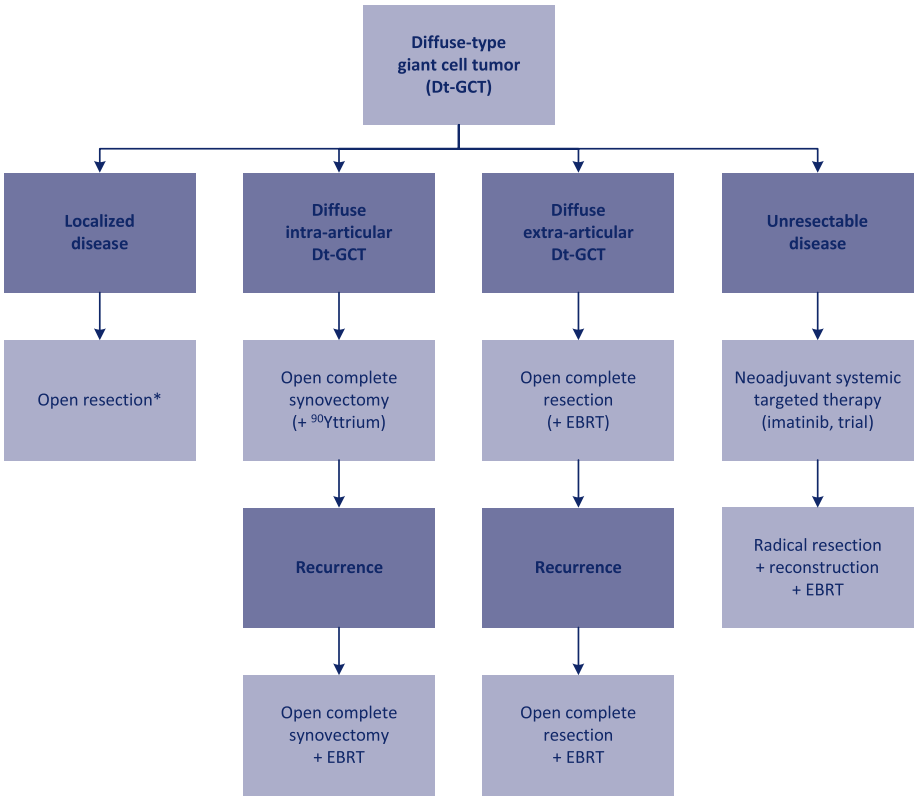

Figure 3 Multidisciplinary integrated treatment protocol for local (GCT-TS) and diffuse (Dt-GCT) forms of disease (* although good results have been published on arthroscopic treatment, an open approach prevents contamination and potentially reduces the risk of recurrence); EBRT, external beam radiation therapy.

Although good results have been published for arthroscopic treatment of diffuse intra-articular disease [23-25], particularly of the knee, an open approach allows a more complete resection and potentially reduces the risk of recurrence. It is recommended that with both local and diffuse forms of the disease, resection and formal histological examination of the lesion should be undertaken.

Open synovectomy is recommended for diffuse intra-articular involvement of the joint. After arthroscopic synovectomy for Dt-GCT of the knee, there is a high risk of incomplete excision and hence a risk of recurrence. Arthroscopy is advised to obtain a tissue diagnosis or for treatment of easily accessible solitary or focal disease.

In selected cases without extra-articular spread, instillation of intra-articular radioactive colloid can be a safe and potentially effective local adjuvant treatment, although there is still little evidence to support its universal application.

Diffuse local recurrences in the knee can be treated with open two-stage synovectomy and resection of all affected tissues, possibly followed by moderate-dose external beam radiation. Moderate-dose radiotherapy will improve midterm local control (75% to 98%) and minimize long-term radiotherapy complications. Radiotherapy is recommended prior to advanced joint destruction, particularly in recurrent disease; it can safely be used for the knee, shoulder and hip, but is not advocated for the hands and feet.

If the Dt-GCT has an extra-articular component, one- or two-stage open synovectomy with resection of all affected soft tissues is advised. Radioactive colloid instillation is not indicated, and external beam radiotherapy should be considered in the presence of extensive soft-tissue disease.

For unresectable disease, MRI with radical planned resection, joint reconstruction with joint replacement and consideration of radiotherapy is advised. Inclusion in a trial of neo-adjuvant systemic targeted therapy (targeting MCSFR, for example imatinib or related tyrosine kinase inhibitors) can be considered, notably when radiotherapy is contraindicated. Data on systemic treatment in large study populations will follow in the near future, and with the new systemic targeted treatments for Dt-GCT treatment optimization will require review and validation. This includes mono versus combination therapy, obtaining the optimal balance between the benefits of alleviating functional impairment against the potential toxicity of the treatment and its duration, the timing of operation and the mechanism of resistance to treatment.

Although arthroscopic synovectomy through multiple portals has been advocated as an alternative to arthrotomy [20, 39-41], there is a significant risk of inadequate excision and subsequent recurrence, particularly in the posterior compartment of the knee. For local disease, partial arthroscopic synovectomy may be sufficient at the risk of recurrence. Open surgery for both local and diffuse intra-articular disease is advised for recurrent disease. Marginal excision with focal disease will suffice, not dissimilar to the treatment of GCT-TS [42]. With recurrent and extra-articular soft-tissue disease adjuvant therapy, including intra-articular radioactive colloid or moderate-dose external beam radiotherapy should be considered.

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