

Imaging of giant cell tumors of bone

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Learning objectives

This educational exhibit aims to:

- Illustrate typical and less frequent imaging features of giant cell tumor of bone.
- Highlight the role of magnetic resonance imaging in giant cell tumor of bone characterization, staging and monitoring.
- Describe magnetic resonance findings of giant cell tumor of bone and denote tumor modifications after medical therapy with Denosumab.

Background

Giant cell tumor (GCT) of bone is typically a benign neoplasm occurring primarily in long bones of skeletally mature individuals. It is characterized by richly vascularized tissue, containing proliferating mononuclear stromal cells and multinucleated giant cells uniformly distributed. It was first described by Sir Astley Cooper in 1818 [1] and has previously been referred by numerous terms, namely osteoclastoma due to the similar appearance of multinucleated giant cells and osteoclasts. Despite the benign histological appearance, some GCT may be locally aggressive and recur after surgical excision.

Epidemiology and clinical characteristics

GCT is the sixth most common primary osseous neoplasm, accounting for 5% of all primary bone tumors and approximately 20% of benign skeletal tumors. [2,3]

It shows a slight female preponderance, with 80% of GCT occurring in patients between 20 and 50 years of age, with peak prevalence in the third decade of life. It is rare in patients above 50 years of age (13%) and extremely rare below 14 years of age (3%). [2,3]

Most GCT are located in long bones (75%-90%), being the knee the most common specific location (50%-65%) and the distal femur the single most common site (23%-30%). Other preferred sites include the proximal tibia (20%-25%), distal radius (10%-12%), sacrum (4%-9%) and proximal humerus (4%-8%). When GCT occurs in the sacrum it usually displays an eccentric position relative to midline (which is a helpful finding in differentiating GCT in this location from chordoma). Less frequent sites of involvement include the proximal femur (4%), ilium (3%), vertebral bodies (3%- 6%), distal tibia (2%-5%), proximal fibula (3%- 4%), hand and wrist (1%-5%) and foot (1-2%). GTC may also occur in sesamoid bones and in apophyses, the latter being epiphyseal equivalents. [1,2]

GCT are typically located in the meta-epiphyseal region, often extending to the articular subchondral bone or even abutting the cartilage. These lesions are thought to arise in the metaphysis and extend into the epiphyseal region after physeal closure. As such, in the rare instances when GCT occurs in skeletally immature patients, it will be centered in the metaphysis.

Multifocal GCT are rare (less than 1% of cases) and most commonly arise in patients with Paget disease. [1,4] In cases of patients with multifocal lesions or GCT-like lesions with unusual clinicoradiographic features, one should consider brown tumor of hyperparathyroidism, which is also rich in giant cells. When in doubt, patients should be tested for serum calcium, phosphorus, and parathyroid hormone levels.

About 5-10% of GCT are said to be malignant. The term *malignant GCT* is used to describe tumors capable of malignant behavior and of producing distant metastasis to the lung. This entity comprises benign metastasizing GCT, malignant transformation of a former benign GCT (including primary malignant transformation from spontaneous tumor dedifferentiation and secondary malignant transformation following radiation therapy, repeated curettage or resection), and osteoclastic (giant-cell) sarcoma. Benign metastasizing GCT, reported in 1-6% of cases, is thought to arise from hematogenous seeding of the tumor to the lungs (usually after treatment), with implants demonstrating histologically benign appearance identical to that of the primary tumor. Both malignant transformation of GCT and osteoclastic (giant-cell) sarcoma consist of sarcomatous growth, the former occurring at the site of a previously documented GCT, and the latter arising *de novo* in a patient with no history of GCT or in association with severe polyostotic Paget disease. [1,2,5]

Patients with GCT commonly experience pain (usually reduced by rest), local swelling and limited range of motion. Acute onset of pain is usually related to pathologic fracture, which may be the presenting symptom in 10-12% of patients. [1,4]

Diagnosis and staging

Though radiographic findings usually suggest the diagnosis, there is considerable overlap in imaging features of benign and malignant GCT, as well as with other entities that may mimic this tumor. As such, accurate diagnosis of GCT demands not only careful clinicoradiographic correlation, but also histological confirmation with core-needle or open biopsy.

Histologic diagnosis of GCT requires numerous multinucleated giant cells, uniformly dispersed among a large population of mononuclear cells. Other characteristic features include a highly vascular stroma, containing numerous thin-walled capillaries, often with

small areas of hemorrhage. Blood-filled cavities may also be seen amongst solid GCT areas, denoting the presence of secondary aneurysmal bone cyst (ABC).

For precise assessment of tumor extension, a full staging strategy should also be conducted. This strategy could include:

- Computed tomography (CT) and/or magnetic resonance (MR) for local staging
- Total body bone scan to rule out additional asymptomatic bone lesions
- Chest radiograph/chest CT to exclude lung involvement

Findings and procedure details

Radiographic features

GCT almost exclusively occurs in patients with closed physes and typically presents as an eccentric meta-epiphyseal lytic lesion abutting the articular surface, with a narrow non-sclerotic zone of transition (Fig.1a). Rarely it may present sclerotic margins (Fig.1b) or a wide zone of transition (10%-20% of cases). [1]

Though it is usually eccentrically located, large lesions and lesions located in small caliber bones can appear central in location.

GCT may show expansile bone remodeling (47%-60%) and have a multiloculated appearance due to pseudotrabeculation (33%-57%), derived from uneven bone destruction in three dimensions. Pronounced trabeculation may create a "soap-bubble" appearance (Fig 1c). [1,6]

GCT may demonstrate aggressive features, with cortical bone thinning, cortical penetration and soft tissue extension (Fig. 1d), features reported to be more common in small-caliber bones such as the fibula or ulna. Although invasion of the ligaments is possible, articular cartilage is usually preserved and intra-articular extension of the tumor is extremely rare.

Characteristic radiographic findings of GCT:

- 1) Patients with closed physes
- 2) Extension to the subchondral bone
- 3) Well defined lytic lesion with non-sclerotic margin
- 4) Eccentric location

Uncommon radiographic findings

GCT is less likely to demonstrate the above-described classic appearance when it is located in flat bones (ilium, sacrum, spine, ribs, calvaria and calcaneus) or apophyses (namely the greater trochanter of the femur).

Other uncommon features may include periosteal reaction, reported in 10%-30% of cases (Fig.2), fluid-fluid levels due to secondary ABC, described in 14% of cases, and pathologic fracture, occurring in 11-37% of patients (Fig. 3). [1]

Imaging GCT with CT and MR

Although radiographic features usually suggest the diagnosis, CT and MR imaging are required for accurate tumor staging.

CT allows better detection of cortical thinning, periosteal reaction, pathologic fractures, and expansile remodeling of the bone compared with radiography (Fig. 4). It also confirms the absence of calcified matrix in GCT, identifies callus formation after pathologic fracture and demonstrates a calcified peripheral rim after medical therapy with Denosumab.

Solid portions of the tumor show attenuation similar to that of the muscle. Identifying fluid attenuation areas alerts to the presence of secondary ABC.

Although less accurate in detection of calcified matrix, MR imaging is paramount to define soft tissue extension of the tumor due to its superb contrast resolution (Fig. 5).

GCT usually appears as a well-defined lesion, with intermediate or decreased signal intensity on T1-weighted images (T1WI) and increased signal intensity on T2-weighted images (T2WI) (Fig.6). GCT may show a low signal intensity margin due to osseous sclerosis or pseudocapsule. Although hyperintensity is the most frequent finding on T2 WI, GCT may also show low signal intensity due to the presence of hemosiderin or high collagen content (Fig.7) [7]. After intravenous administration of gadolinium the tumor shows avid enhancement (Fig. 5e, 8d).

MR is also superior to radiography and CT in demonstrating the presence of areas of ABC, which translate into cystic areas with fluid-fluid levels, markedly hyperintense on T2WI and hypo or hyperintense on T1WI (Fig. 8). This appearance may mimic a primary ABC, however, unlike the primary counterpart, secondary ABC will show solid components enhancing diffusely after contrast administration (Fig.8). By identifying solid portions in the tumor, MR imaging is not only essential to differentiate these two entities, but is also vital to direct the biopsy to the solid parts.

Treatment

Surgical treatment with curettage is the typical treatment for GCT, with recurrence rates of 15%-45%. With the use of a high-speed burr and allograft or bone cement (polymethylmethacrylate) placement (Fig.9), recurrence rates after intralesional surgery dropped to 12%-14%. Aggressive GCT usually require wide excision and reconstruction with endoprosthesis (Fig.10), with reported recurrence rate of 6%. [2,8,9]

Patients submitted to curettage and cement placement should be monitored carefully with serial radiographs, always comparing the follow-up images with the baseline postoperative images. Local recurrences usually occur between 12 and 18 months after surgery (being rare after 3 years) and should be suspected when new lucencies appear at the cement-bone interfaces (Fig. 11). [4] CT, and particularly MR, may be diagnostic in equivocal cases, presenting signal alterations similar to that of the primary tumor.

Postoperative complications of endoprosthesis may include fracture or dislocation of the implant, instability, infection and aseptic loosening (Fig.12).

Radiotherapy was previously used to treat GCT in difficult locations, such as the spine and sacrum, however long-term risk of malignant transformation of GCT and post-radiation sarcoma has limited its routine use.

Presently, patients with aggressive or recurrent tumors, with tumors in difficult locations and with multiple lesions, as well as patients who are poor surgical candidates, may be treated with a monoclonal antibody - Denosumab. Denosumab inhibits the receptor activator of nuclear factor κ B ligand (RANKL), which is an essential mediator of osteoclast formation, function, and survival, present in osteoclast-like giant cells and their precursors, as well as some of the mononuclear stromal cells. By inhibiting osteoclast-mediated bone destruction, Denosumab induces tumor necrosis, sclerosis and reconstitution of the cortical bone (Fig. 13). [9,10]

Review of 20 cases of GCT

We retrospectively analyzed 20 cases of patients with histologically confirmed GCT that were assessed, staged with MR, and treated at Hospitais da Universidade de Coimbra (Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal) from 2003 to 2013.

Our series demonstrated a slight female preponderance (55%), in agreement with results from other authors [11]. 65% of GCT occurred between 20 and 50 years of age, with 45% occurring in the third and fourth decades (Fig. 14).

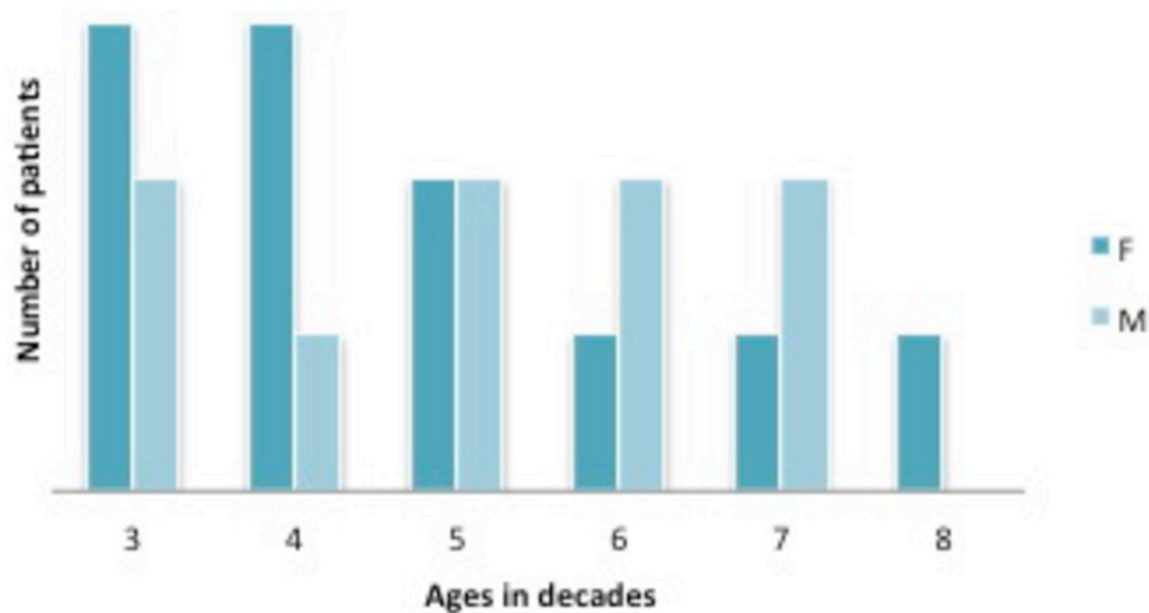


Fig. 14: Age (per decades of life) and gender of patients included in our series.

References: Radiology, Centro Hospitalar e Universitário de Coimbra, Hospitais da Universidade de Coimbra - Coimbra, Portugal

Tumors primarily originated near the knee (55%) (Fig. 15), with 35% located on the proximal tibia (Fig. 16), 15% on the distal femur and 5% on the proximal fibula. Other locations included the distal tibia (15%), ilium and sacrum (15%) and radius (5%). One case occurred in the second metacarpal bone of the hand (Fig. 17). One case occurred within an apophysis, in the greater trochanter of the femur (Fig.2). We report no cases of multifocal GCT.

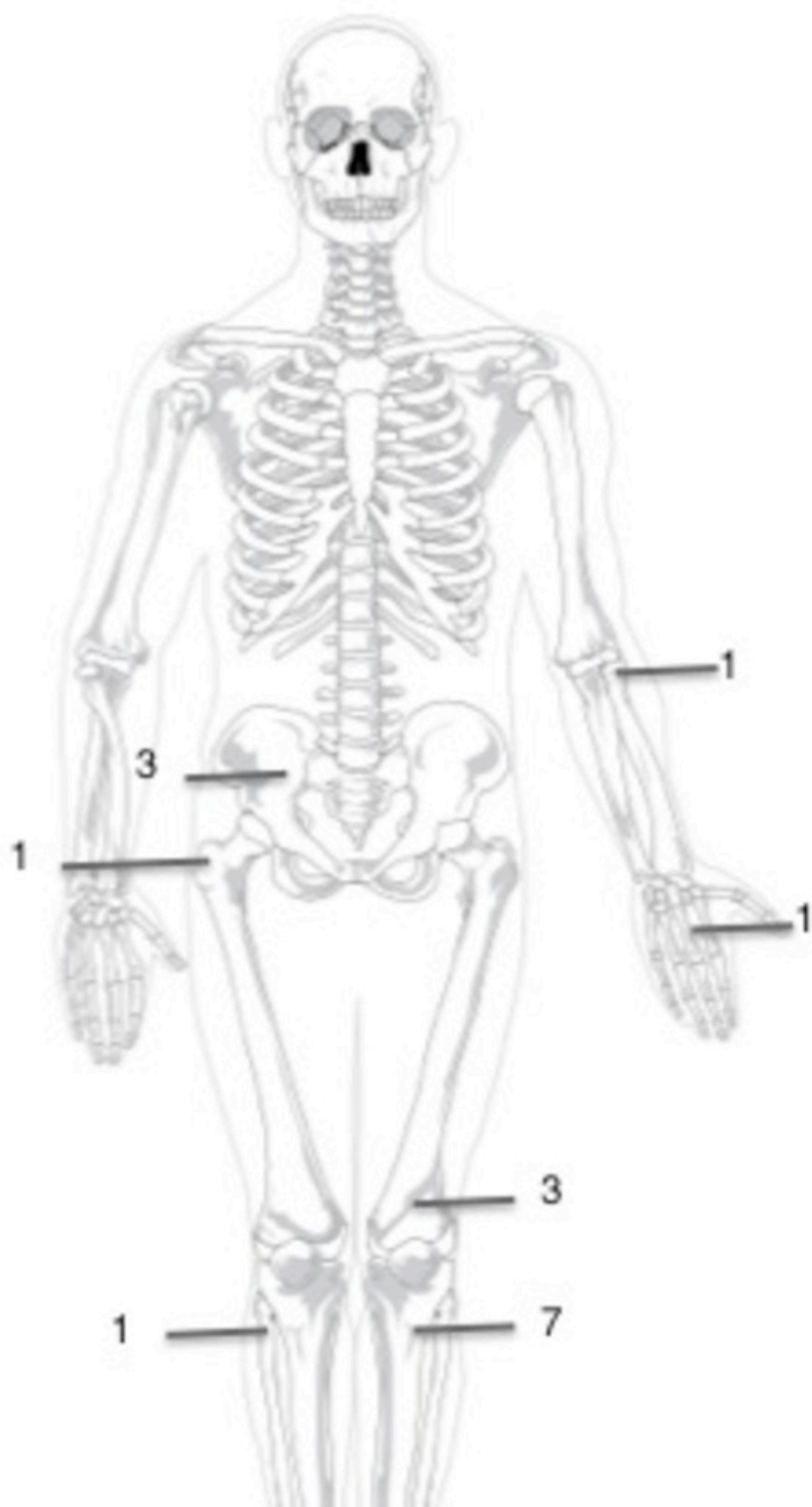


Fig. 15: Different locations of GCT in our series.

References: Radiology, Centro Hospitalar e Universitário de Coimbra, Hospitais da Universidade de Coimbra - Coimbra, Portugal

Most GCT located on tubular bones had an eccentric position (76%), with exception to GCT of small caliber bones and extremely large lesions, which had a central location (23%).

Of the three pelvic GCT of our series, one was confined to the ilium, another to the sacrum (Fig.22), and one extended through the sacroiliac joint affecting both the ilium and sacrum (Fig.13).

To assess the MR signal of GCT we classified tumor intensity as follows (Fig.18):

- T1-WI:

Hypointense
Isointense
Hyperintense

- T2-WI:

Hypointense
Hyperintense
Mixed signal intensity

- With cystic areas
- Without cystic areas

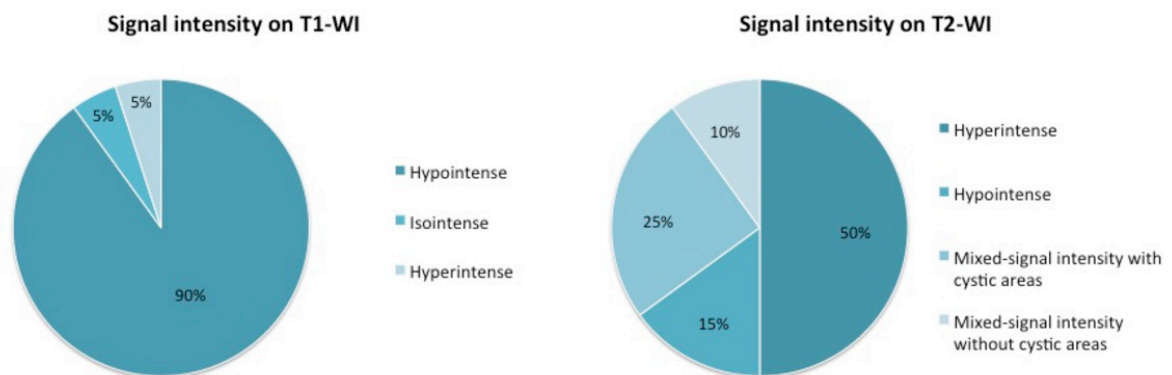


Fig. 18: Signal intensity characteristics of GCT in our series on T1-WI and T2-WI.

References: Radiology, Centro Hospitalar e Universitário de Coimbra, Hospitais da Universidade de Coimbra - Coimbra, Portugal

Most GCT were hypointense on T1WI (90%), one being isointense, and one being slightly hyperintense comparing to skeletal muscle. Three tumors (15%) showed focal areas of hyperintensity due to hemorrhage (Fig. 19).

Signal intensity on T2WI was more variable, with 50% of cases showing hyperintensity (usually heterogeneous) and 15% showing hypointensity. Tumor hypointensity on T2WI is reported to be secondary to hemosiderin deposition or dense collagen matrix. These two components can be distinguished by gradient-recalled-echo sequences, with the former showing signal loss with increasing TE (time to echo) due to the magnetic susceptibility effect of hemosiderin (Fig.20). [7] 35% of the tumors in our series had hemosiderin at histological examination (of which 42% showed characteristic MR features).

35% of GCT showed mixed-signal intensity on T2WI, with 25% showing internal cystic areas.

Two GCT (10%) contained fluid-fluid levels due to secondary ABC, confirmed with histological analysis.

Solid parts of GCT showed avid enhancement after contrast administration.

Most of the tumors exhibited aggressive imaging features (Fig.21), with cortical bone destruction (85%) and soft-tissue extension (60%).

Periosteal reaction, described as unusual in the literature, was present in only one case of GCT located on the greater trochanter (Fig.2).

Three of the tumors were treated with Denosumab (due to their location - iliac bone and sacrum), with dramatic response. Tumors became hypointense on T2WI and developed a sclerotic border with reconstitution of the cortical bone, the latter better depicted with CT (Fig. 22).

Images for this section:

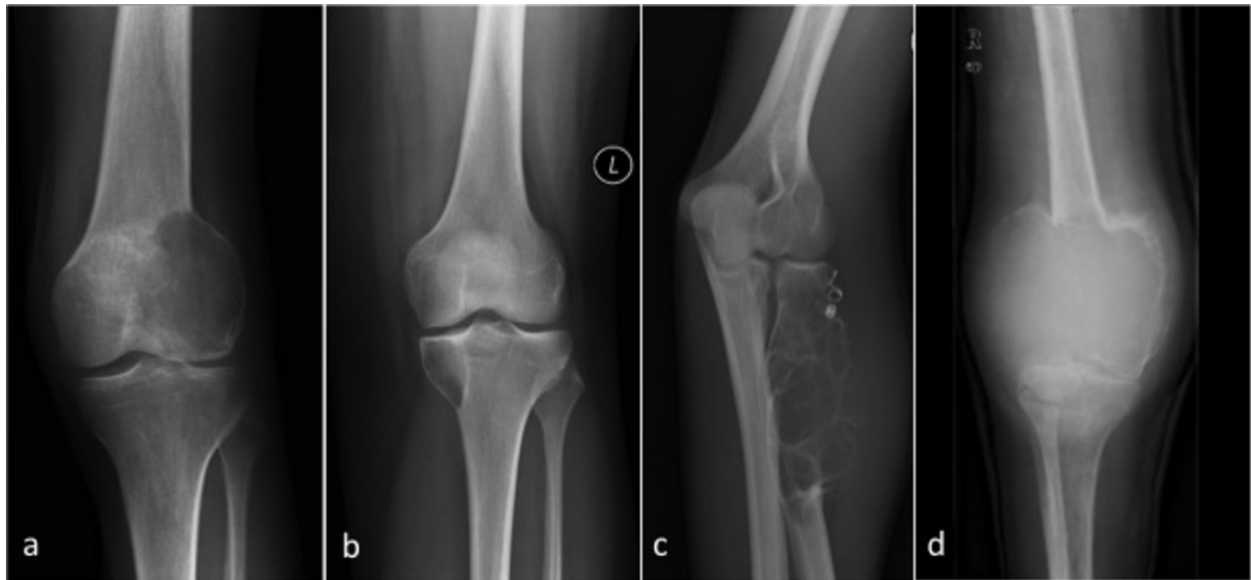


Fig. 1: Different radiographic appearances of GCT. Anteroposterior radiographs of the knee show GCT of the distal femur (a) and of the proximal tibia (b) presenting as eccentric lytic lesions with sharp margins (non-sclerotic in a), sclerotic in b)), abutting the articular surface. Anteroposterior radiograph of the elbow (c) shows GCT of the proximal radius with multiloculated ("soap-bubble") appearance. Anteroposterior radiograph of the knee (d) shows large GCT located centrally on the distal femur with aggressive appearance due to extensive bone destruction and cortical disruption.

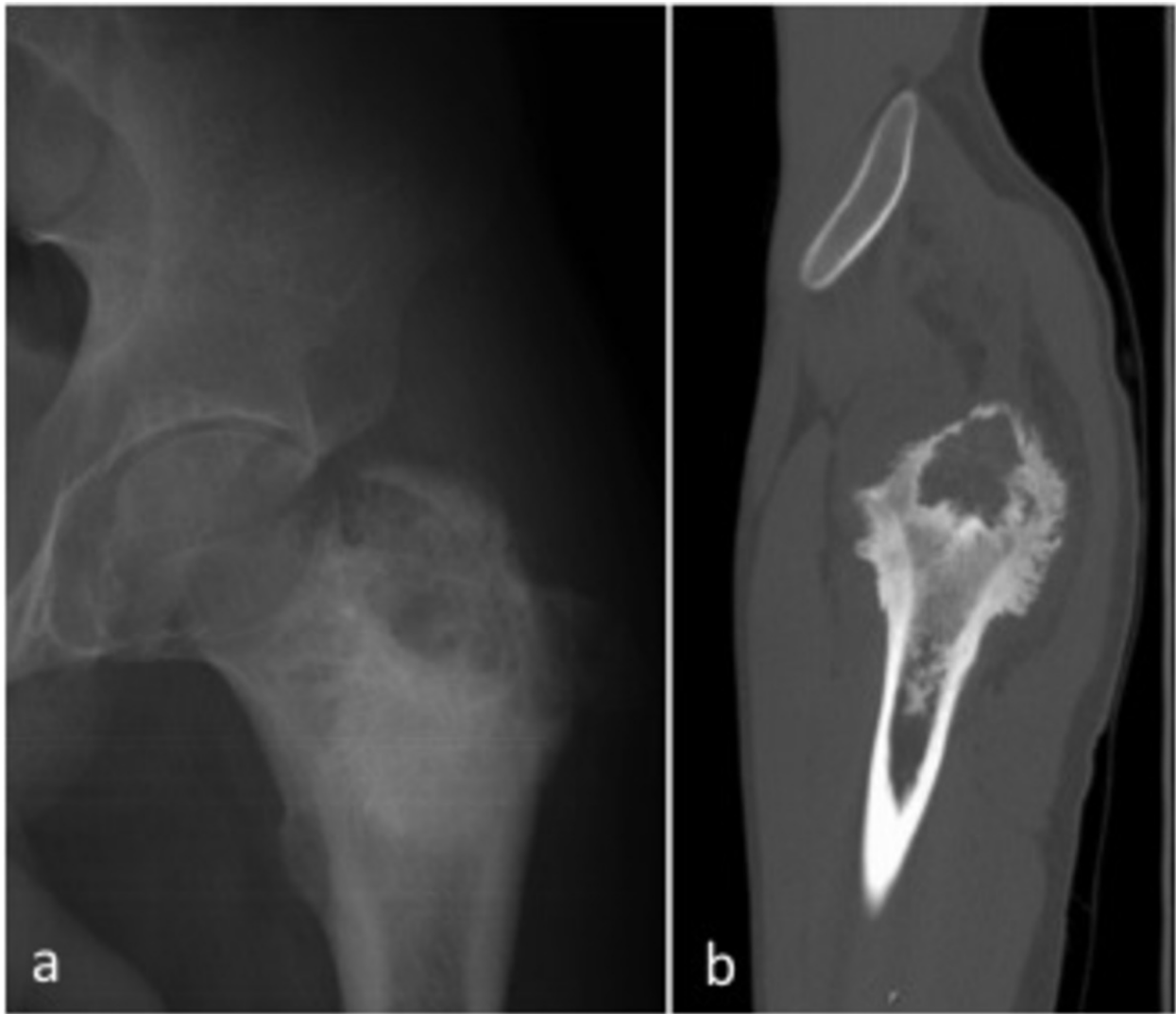


Fig. 2: GCT within an apophysis. Anteroposterior radiograph of the hip and coronal reformatted computed tomography (CT) image show a lytic lesion located on the greater trochanter of the femur exhibiting extensive periosteal reaction.



Fig. 3: Pathologic fracture associated with GCT. Anteroposterior radiograph of the knee shows a pathologic fracture (blue arrows) through a lytic lesion in the distal femur.



Fig. 4: Value of CT over radiography in GCT evaluation. Anteroposterior and lateral radiographs of the ankle of two different patients (a,b,c,d / e,f,g,h) show eccentric lytic lesions of the distal tibia with pseudotrabecular appearance abutting the articular cartilage (a,b / e,f). Axial and sagittal reformatted CT images allow better delineation of the bone cortex, which is thinned but intact in the first patient (c,d) and disrupted with associated soft tissue extension in the second (g,h).

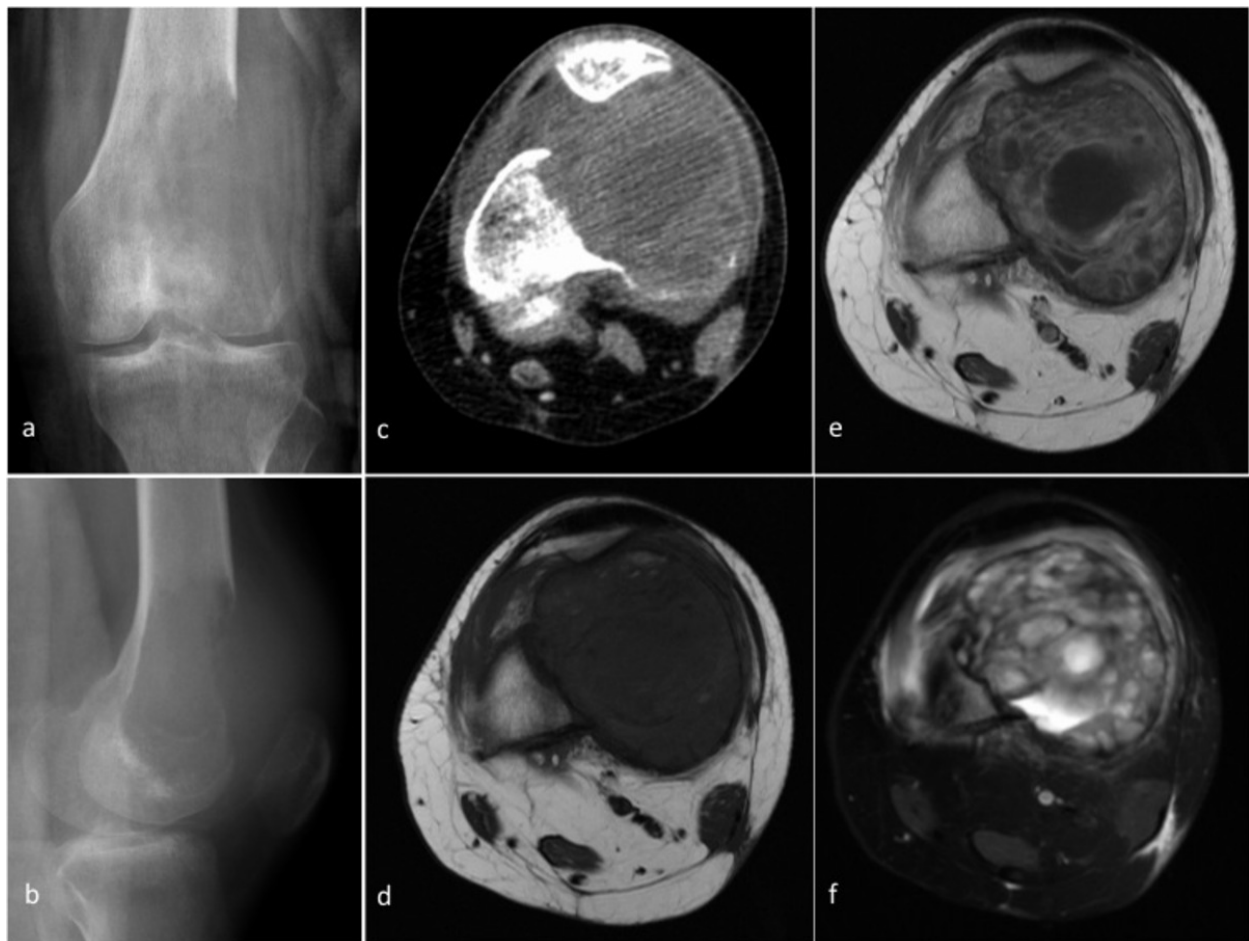


Fig. 5: Evaluation of soft tissue extension with radiography, CT and MR. Anteroposterior and lateral radiographs of the knee (a,b) show an eccentric lytic lesion of the distal femur, with a wide zone of transition, cortical disruption and soft tissue extension. Axial CT (c) and MR (d,e,f) images accurately show tumor extension into the periarticular soft tissue, with MR showing superior contrast resolution, tumor delimitation and characterization. (d) T1 WI, (e) T1 WI after contrast administration, (f) T2 WI with Fat Saturation.

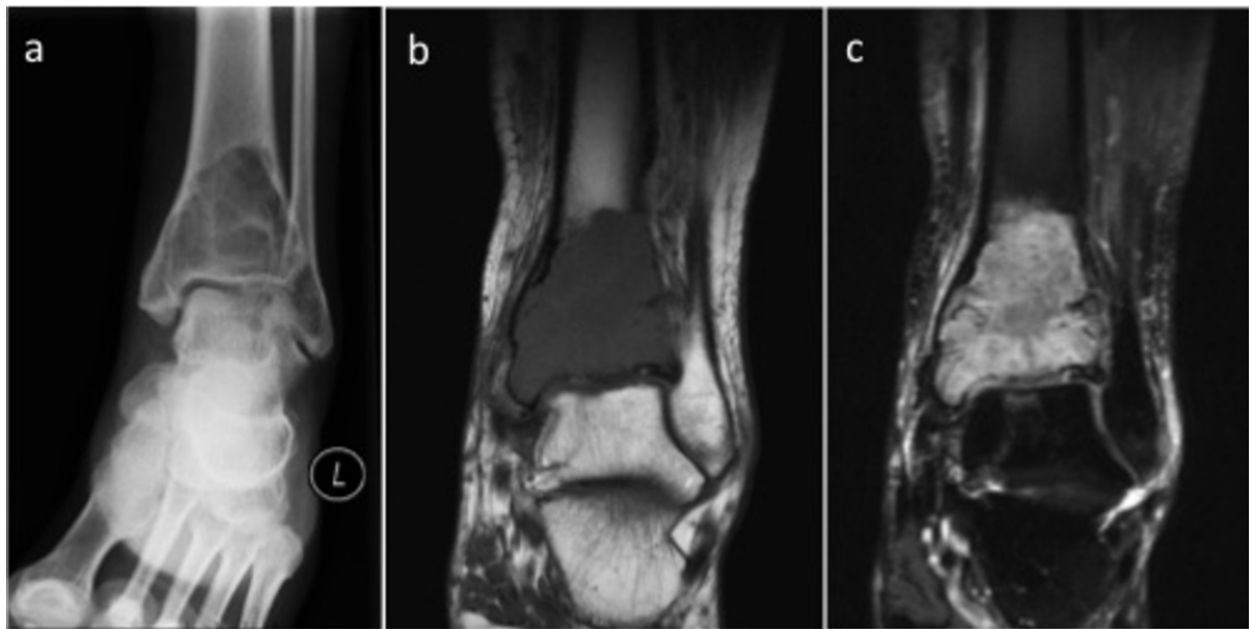


Fig. 6: Typical appearance of GCT at MR imaging. Anteroposterior radiograph of the ankle shows an osteolytic lesion with pseudotrabecular appearance located on the distal tibia abutting the articular surface with a narrow zone of transition (a) - same patient as Fig.4 a-d. At coronal MR images, this lesion shows intermediate signal intensity on T1WI (b) and increased signal intensity on T2 WI with Fat Saturation (FS T2 WI) (c).

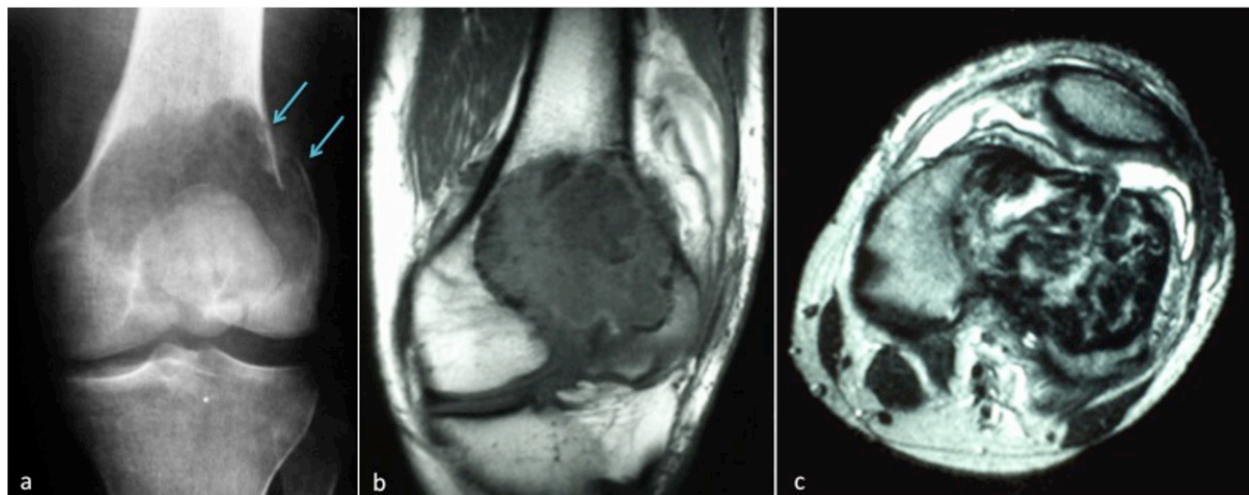


Fig. 7: GCT with low signal intensity on T2 WI. Anteroposterior radiograph of the knee (a) shows an osteolytic lesion of the distal femur abutting the articular surface with a narrow zone of transition associated with pathologic fracture (blue arrows) - same patient as Fig. 3. The tumor shows low signal intensity on T1 WI (b) and on T2 WI without FS (c).

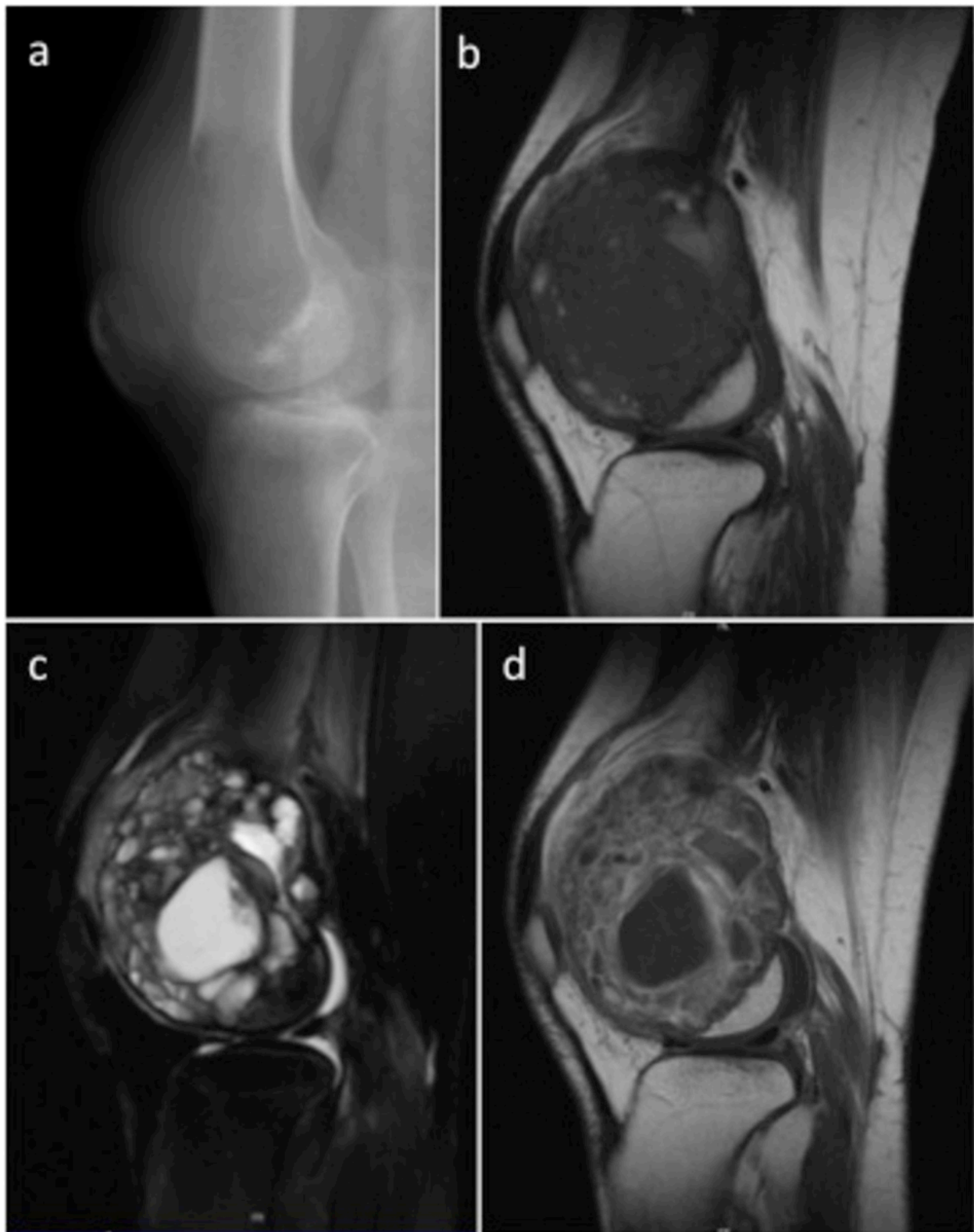


Fig. 8: Secondary aneurysmal bone cyst (ABC). Lateral radiograph of the knee shows a lytic lesion of the distal femur with aggressive appearance (a) - same patient as Fig.5. At sagittal MR images the lesion shows predominantly low signal intensity on T1 WI (with small hyperintense areas of hemorrhage) (b), mixed signal intensity on FS T2 WI

with large cystic areas of secondary ABC (c), and enhancement of the septa and solid components after contrast administration on T1 WI (d).



Fig. 9: GCT treatment with curettage and bone cement. Lateral radiograph of the knee showing GCT of the proximal tibia, before (a) and after curettage and bone cement placement (b).

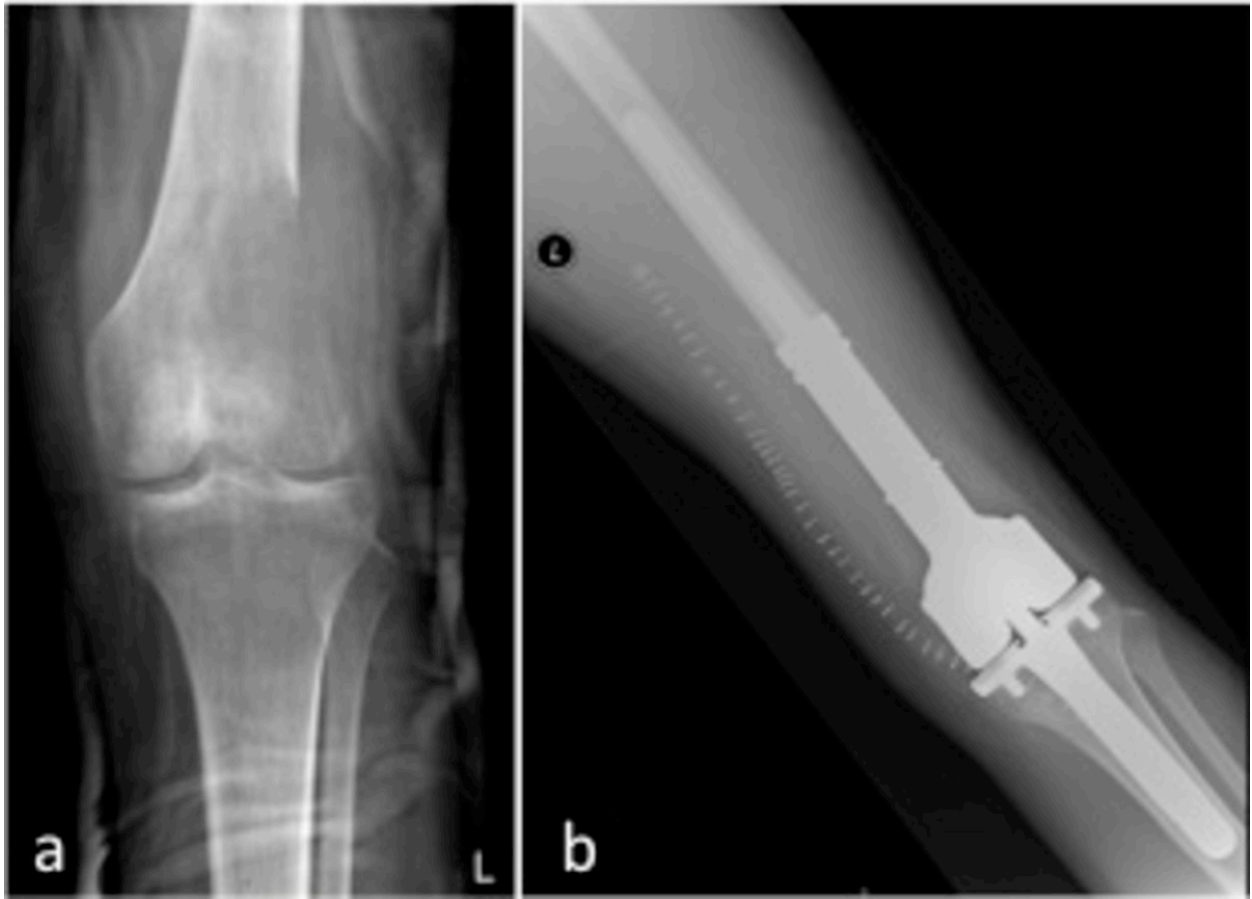


Fig. 10: GCT treatment with wide excision and reconstruction with endoprosthesis. Anteroposterior radiograph of the knee shows GCT of the distal femur with aggressive radiographic features (same patient as Fig. 5 and 8) before (a) and after excision and reconstruction with endoprosthesis (b).

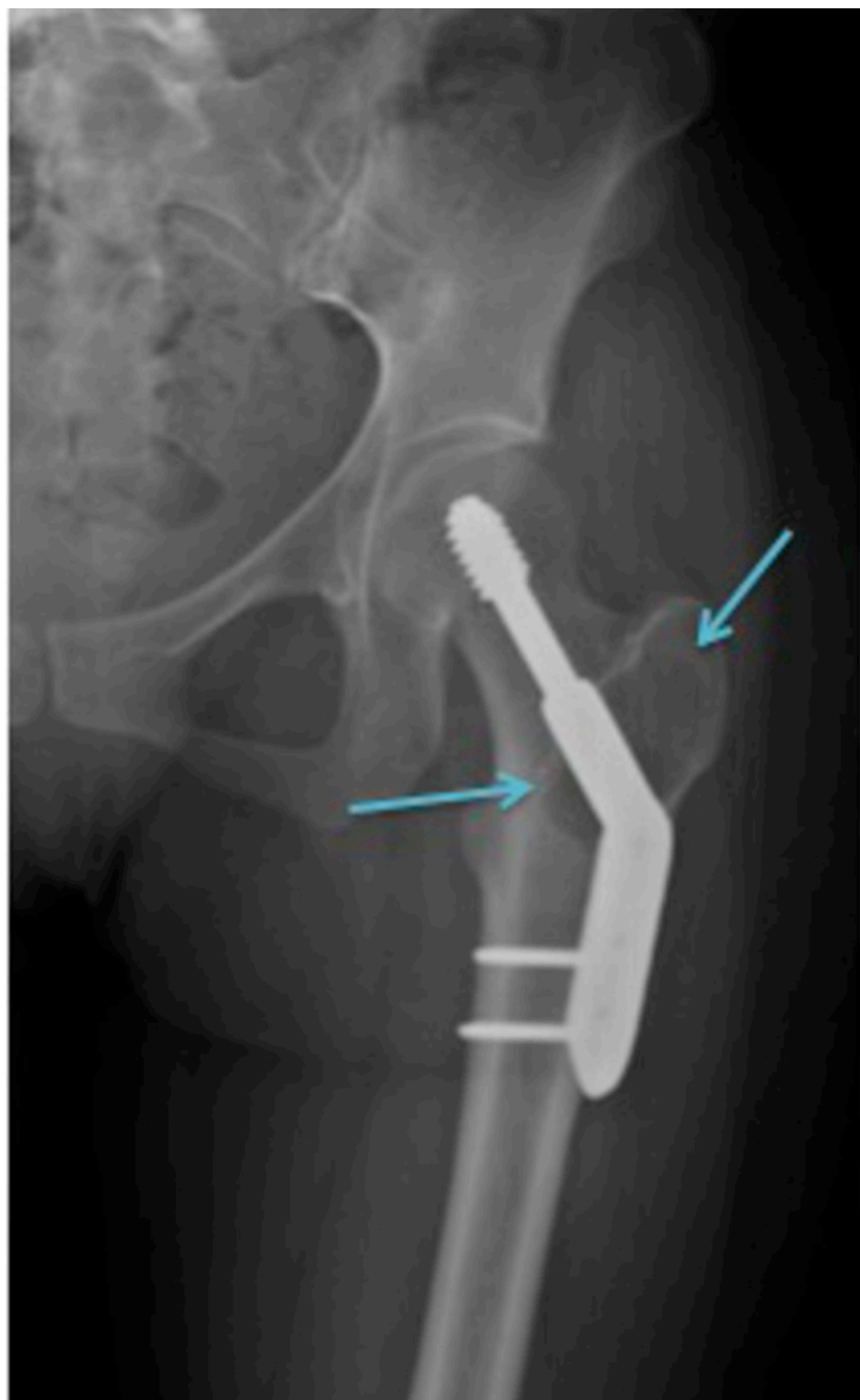


Fig. 11: GCT recurrence after treatment. Anteroposterior radiograph of the hip reveals increased lucency at the greater trochanter, 10 months after curettage and implant placement, confirmed histologically as recurrence of GCT.



Fig. 12: Aseptic loosening of the endoprosthesis. Anteroposterior and lateral radiographs of the knee show endoprosthesis with normal appearance after surgery (a,b). Two years after endoprosthesis placement, anteroposterior and lateral radiographs reveal bone resorption and periprosthetic osteolysis at the femoral component. Pathologic analysis revealed histiocytic response to the components of the prosthesis.

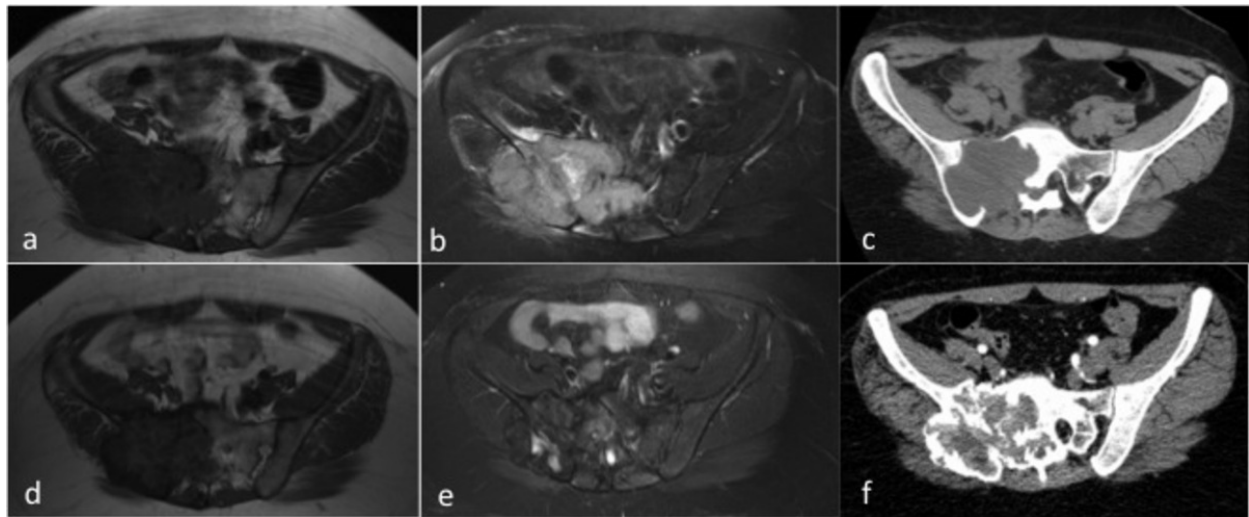


Fig. 13: GCT response to Denosumab. Axial MR images reveal GCT of the right ilium and sacrum with low signal intensity on T1 WI (a) and high signal intensity on FS T2 WI (b). Axial CT image shows that the tumor presents soft tissue attenuation, without internal or peripheral calcification (c). After treatment with Denosumab (d - f) the tumor maintained low signal intensity on T1 WI (d), became predominantly hypointense on FS T2 WI (e) and developed a peripheral sclerotic rim, accurately demonstrated on axial CT image (f).



Fig. 16: Frequent location for GCT. Anteroposterior radiograph of the knee shows GCT of the proximal tibia with low signal intensity on T1 WI (b) and high signal intensity on FS T2 WI (c).

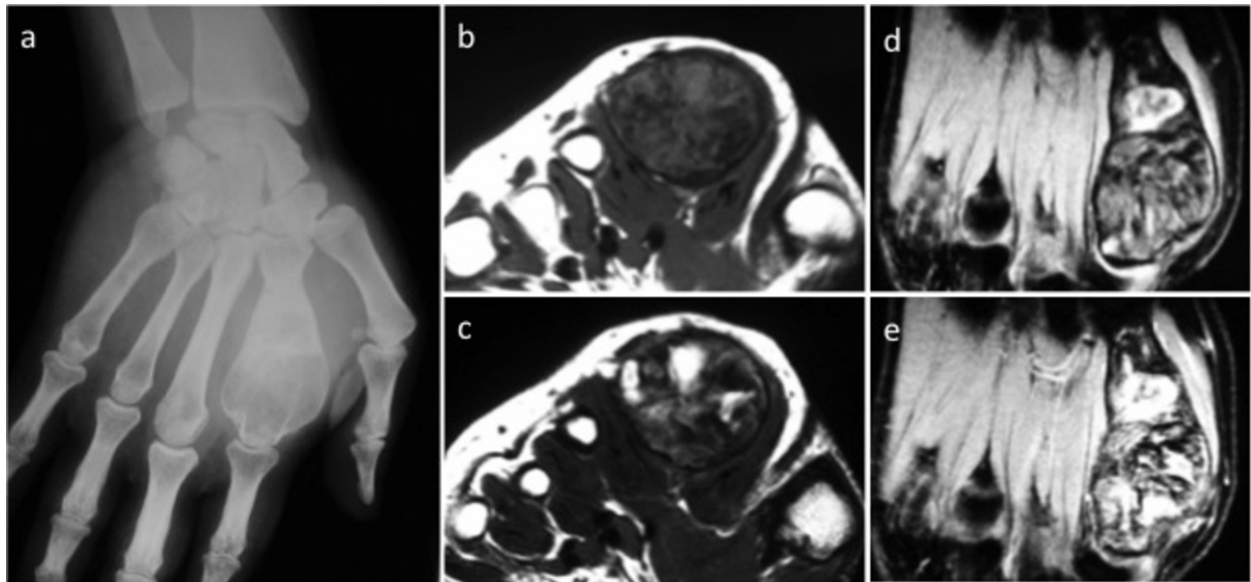


Fig. 17: Infrequent location for GCT. Anteroposterior radiograph of the hand shows an expansile lytic lesion of the second metacarpal bone extending to the articular surface (a). At MR the tumor shows low signal intensity on T1 WI (b) and predominantly low signal intensity (with cystic areas) on T2 WI without FS (c). Coronal FS T1 WI before (d) and after (e) contrast administration accurately demonstrate tumor heterogeneity.

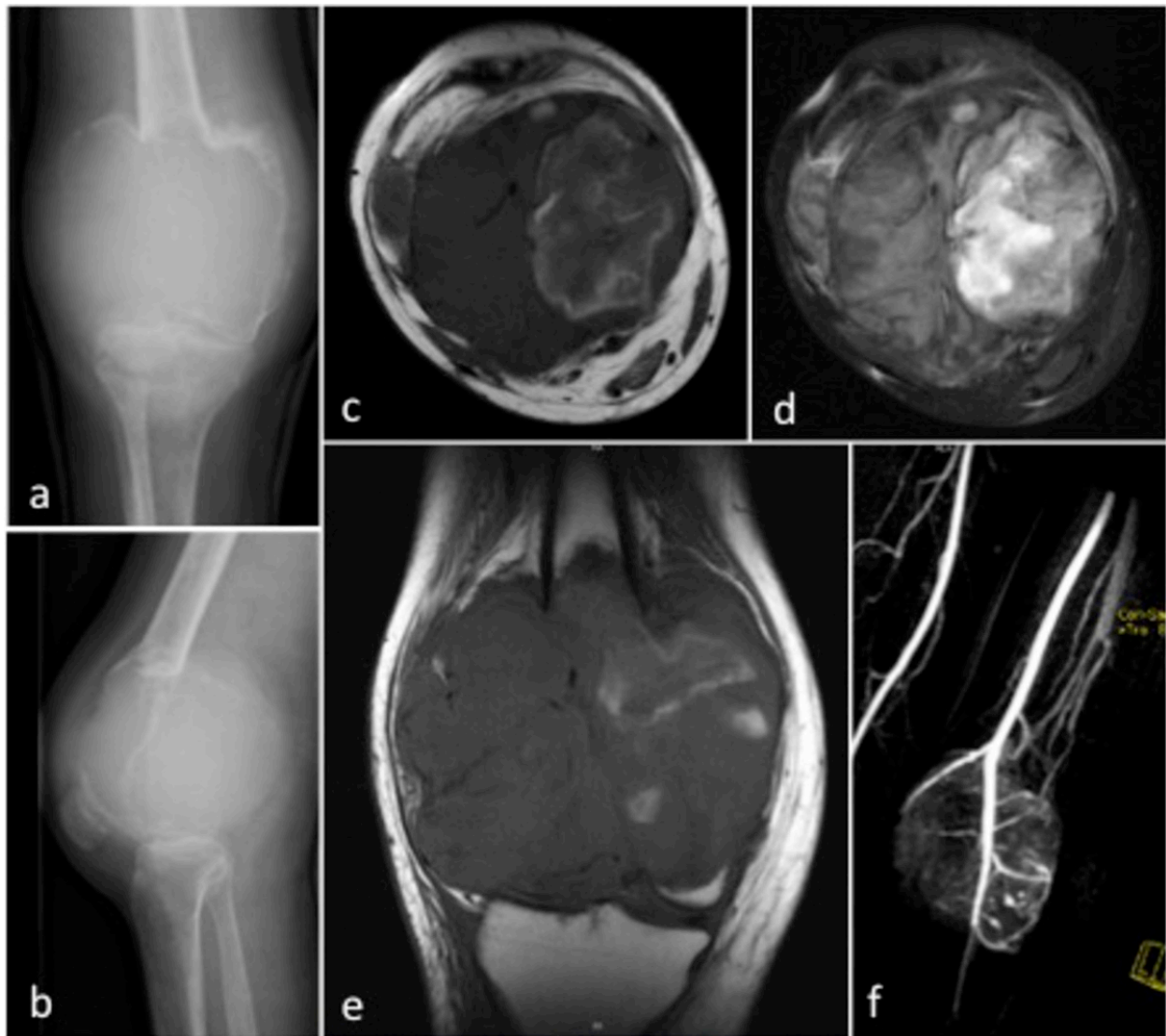


Fig. 19: Presence of hemorrhage in GCT. Anteroposterior and lateral radiographs of the knee (a,b) show GCT of the distal femur with cortical disruption and soft tissue extension (same patient as Fig. 1d). This lesion presents hyperintense areas of hemorrhage intermingled with solid component of low signal intensity on axial and coronal T1 WI (c,e). FS T2 WI reveals mixed signal intensity, with markedly hyperintense areas due to tumor necrosis (d). MR angiography reveals tumor vascularity (f).



Fig. 20: Presence of hemosiderin in GCT. Anteroposterior radiograph of the knee shows GCT of the proximal tibia (a). Tumor presented low signal intensity on T1 WI (b). Though this tumor presented high signal intensity on FS T2 WI (c), signal intensity on T2 FS without Fat Saturation was low (d), with progressive signal loss with increasing TE (time to echo) on gradient-recalled-echo sequences (e -TR 45 TE 4; f - TR 45 TE 17) due to the magnetic susceptibility effect of hemosiderin.

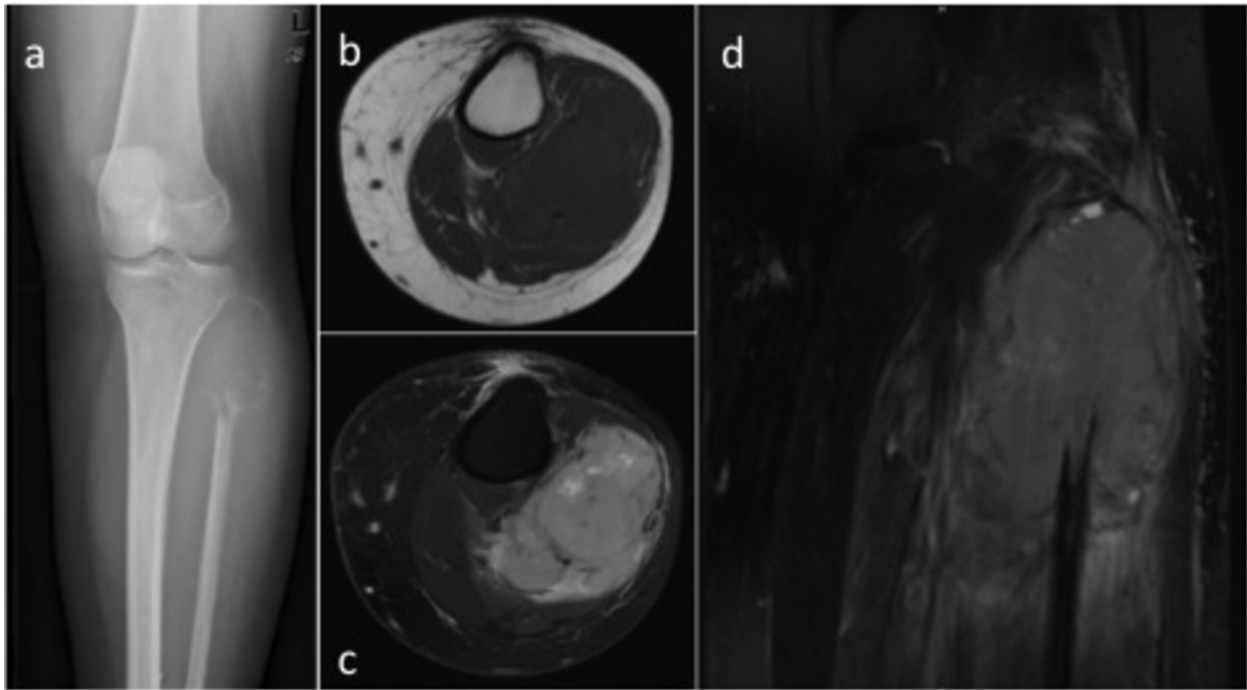


Fig. 21: GCT with aggressive appearance. Anteroposterior radiograph of the knee shows GCT of the proximal fibula with aggressive appearance (a). Tumor presented hypointensity on T1 WI (b) and hyperintensity on axial (c) and coronal FS T2 WI (d).

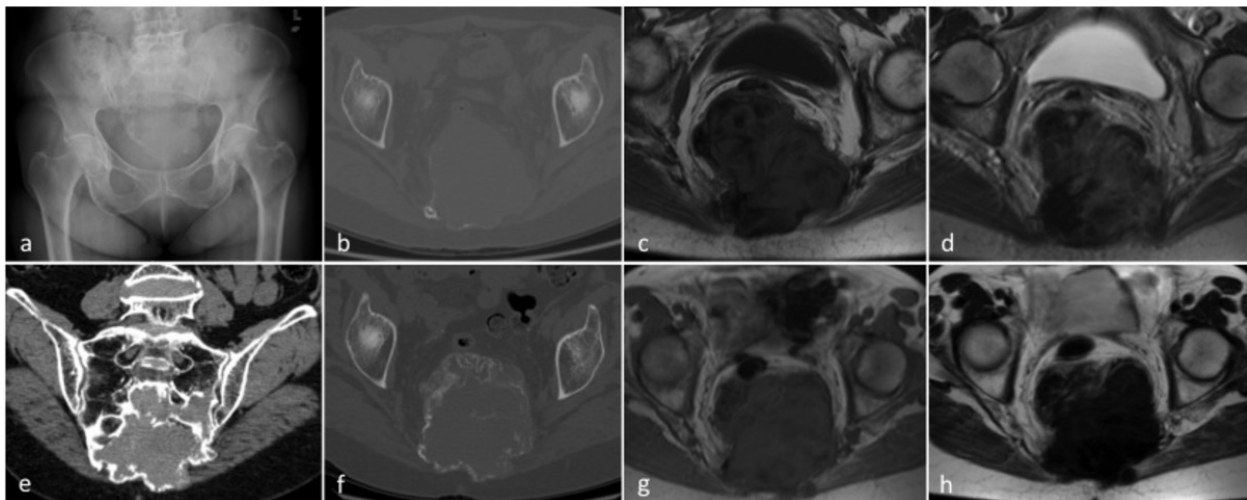


Fig. 22: Tumor response to Denosumab. Anteroposterior radiograph of the pelvis shows an eccentric lytic lesion located on the sacrum (a). Axial CT with bone window confirms the absence of calcified matrix (b). At MR imaging, tumor presents heterogeneous hypointensity on T1 WI (c) and on T2 WI (d). After treatment with Denosumab (e-h) the tumor developed a sclerotic rim with reconstitution of the cortical bone, features demonstrated on coronal reformatted CT (e) and axial CT with bone window (f). At MR imaging, tumor became less heterogeneous on T1 WI (g) and showed lower signal intensity on T2 WI (h).

Conclusion

- GCT is typically a benign lesion, frequently exhibiting aggressive imaging features.
- Though radiographic findings usually suggest the diagnosis of GCT, histological confirmation is mandatory and CT and/or MR are required for accurate tumor assessment.
- MR imaging allows precise characterization, staging and monitoring of GCT, which are essential to patient management.
- Typical MR features of GCT include hypointensity on T1WI, heterogeneous hyperintensity on T2WI and avid enhancement after intravenous contrast administration. Some tumors may also show low signal intensity on T2WI due to the presence of hemosiderin or high collagen content.
- GCT treatment remains mostly surgical; nonetheless Denosumab has shown excellent results and may be an option for recurrent and surgically unsalvageable GCT.

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