Giant Cell Tumors

11

Dominique G. Poitout

Abstract

Giant cell tumors are benign bone tumors, representing 5% of primary bone tumors with variable biological aggressiveness and controversial treatment. It more commonly occurs between the third and fourth decades of life and affects preferably the epiphysis of long bones, most of them with an eccentric lytic lesion around the knee.

Keywords

Bone neoplasms • Giant cell tumor of bone • Campanacci staging • Neoplasm recurrence • Curetage • Adjuvant therapy • Denosumab

Introduction

The giant cell tumor represents 5% of the primary bone tumors with variable biological aggressiveness and controversial treatment. There is a low prevalence in females between the third and fourth decades of life and affects preferably the epiphysis of long bones, most of them around the knee (Szendroi, 2004). According to Campanacci grades 1 and 2 represent 52% of the total of GCT and grade 3 represents 48%. There was no correlation between this classification and recurrence. There was a better correlation between the aggressiveness of the treatment and the appearance of recurrence [1].

Histopathology

Giant cell tumors were first described in 1818 by Sir Astley Cooper who denominated it as "fungi medular exostosis" [2]. Nowadays it has a very well defined clinical, radiological and histopathological identity. Its local aggressiveness was described by Nelaton and its potential malignancy by Virchow [3, 4].

The WHO has defined this tumor as an aggressive tumor, very well vascularized, formed by ovoids or fusiform cells with an association of multiple giants cells of osteoclastic type, uniformly distributed in the tumoral tissue (Fig. 11.1).

The pathogenesis is still not very well known [5], but its origin may derive from the mono cells of the local stroma or the bone marrow [6].

The typical giant cell of this tumor is not different to those found in other bone lesions where these giant cells appear similar to chondroblastomas, pigmented villonodular synovitis, the brown tumor of hyperparathyroidism, reparative granuloma of giants cells and Paget [3].

The expression of a receptor activator of nuclear factor kappa–B ligand (RANKL) has been found in osteoclast-like macrophages. This is the basis of the use of RANKL inhibition for medical management which interferes with osteoclastic stimulation.

Jaffe et al. tried to establish a histological gradient with a prognostic correlation for this tumor; however, this gradient was not correlated with treatment and long term prognosis, so it was finally discarded [7].

Clinical Features

Age, location and X-ray imaging are the clues for the clinical diagnosis. Local pain and swelling in the affected joint appears slowly over weeks or months. Pathological fractures can occur.

D. G. Poitout (✉)
Aix Marseille University, Marseille, France
e-mail: Dominique.poitout@live.fr

J. Paulos and D. G. Poitout (eds.), *Bone Tumors*,
https://doi.org/10.1007/978-1-4471-7501-8_11

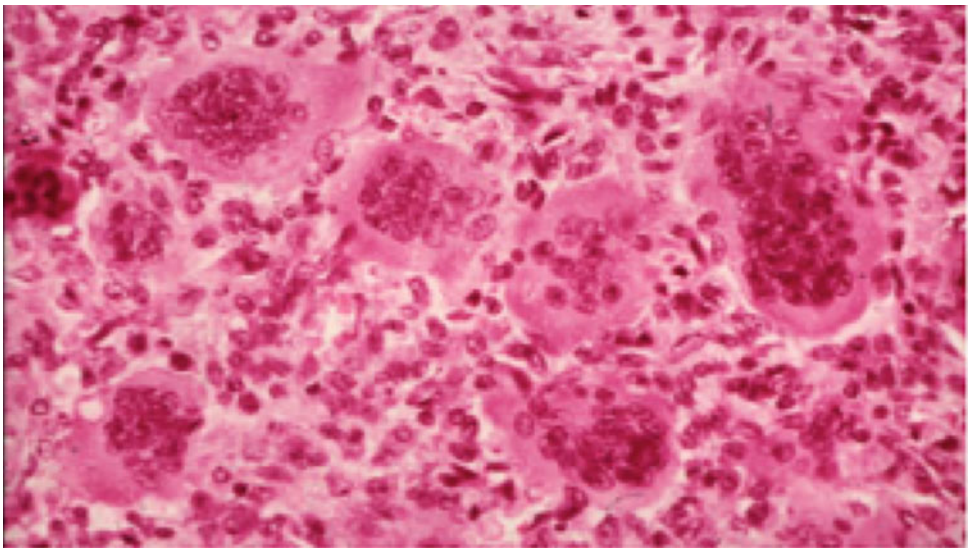

Fig. 11.1 Histologic aspect of giant cell tumors

The GCT is developed in a mature skeleton: 70% appearing in people between 20 and 40 years old [8], with a slightly higher female-to-male ratio (60% females). Its occurrence in children is rare [9]. Less than 2% of cases are found under 10 years of age, and only 10% over 55 years of age.

GCTs are usually located in the epiphysis of the long bones; 55% are developed around the epiphysis of the knee, most commonly found in the distal femur [10], proximal tibia and distal radius. An intermediate frequency is found in the proximal femur, proximal fibula (Fig. 11.2) and distal tibia.

In the axial spine, GCT is most often located in the sacrum. GCT is found infrequently in the vertebral body of the mobile spine and rarely in the posterior elements [11, 12]. It is not found in the clavicle or breastbone and few cases are seen in the scapula, hands or feet [5]. Metachronous and multicentric GCTs of bone are even less common [13].

Imaging

Radiologically the GCT is located in the epiphyseal-metaphyseal zone of the long bones, like a osteolytic and excentric lesion. Sometimes there is a fine trabeculated image like soap bubbles [14]. It is a very destructive local bone tumor (Fig. 11.3).

Campanacci developed a radiological classification in 3 grades [1, 15]:

- **Grade 1**: osteolytic tumor with very well-defined edges in a halo of mature bone with an intact or thinned cortex but not deformed;
- **Grade 2**: well-defined edges without an opaque halo and thin limits and more expansive;
- **Grade 3**: badly defined edges suggesting quick growth and invasion of soft tissues and without bone limits.

Around 50% of the cases are found in grade 1 or 2.

Enneking, using radiological, scintigraphic, angiographic, TC and pathologic parameters classified benign tumors as latent, active and aggressive [16].

MRI in grade 2 or 3 cases is useful to evaluate soft tissue compromise revealing an aggressive behavior. T1-weighted MRI demonstrates a low to intermediate signal, mostly homogenous but in T2 sequences showing heterogeneity, due to hemosiderin producing a lower signal and the high water content a high signal. Gadolinium-enhanced images confirm a solid lesion.

Bone scintigraphy with technetium can be useful in looking for other multifocal lesions, showing multiple increased radiotracer uptake helping with the differential diagnosis with hyperparathyroidism whose histology has multinucleated cells.

Lung metastasis has been described even in benign GCT in about 2% of cases [11, 15]. The malignancy can be primary, secondary (post-radiation) or evolutive [17]. Recurrence cases have a greater chance of GCT metastasis. Metastasis can show a benign GCT tumor like in the initial location.

Treatment

Several treatments have been proposed [18]: curettage [19, 20], curettage and bone grafting [21], cryotherapy post-curettage, phenol or cauterization post-curettage, radiation, embolization, bone cement [22], hydrogen peroxide, argon beam coagulation [23], resection and massive allograft [24] and prosthetic reconstruction.

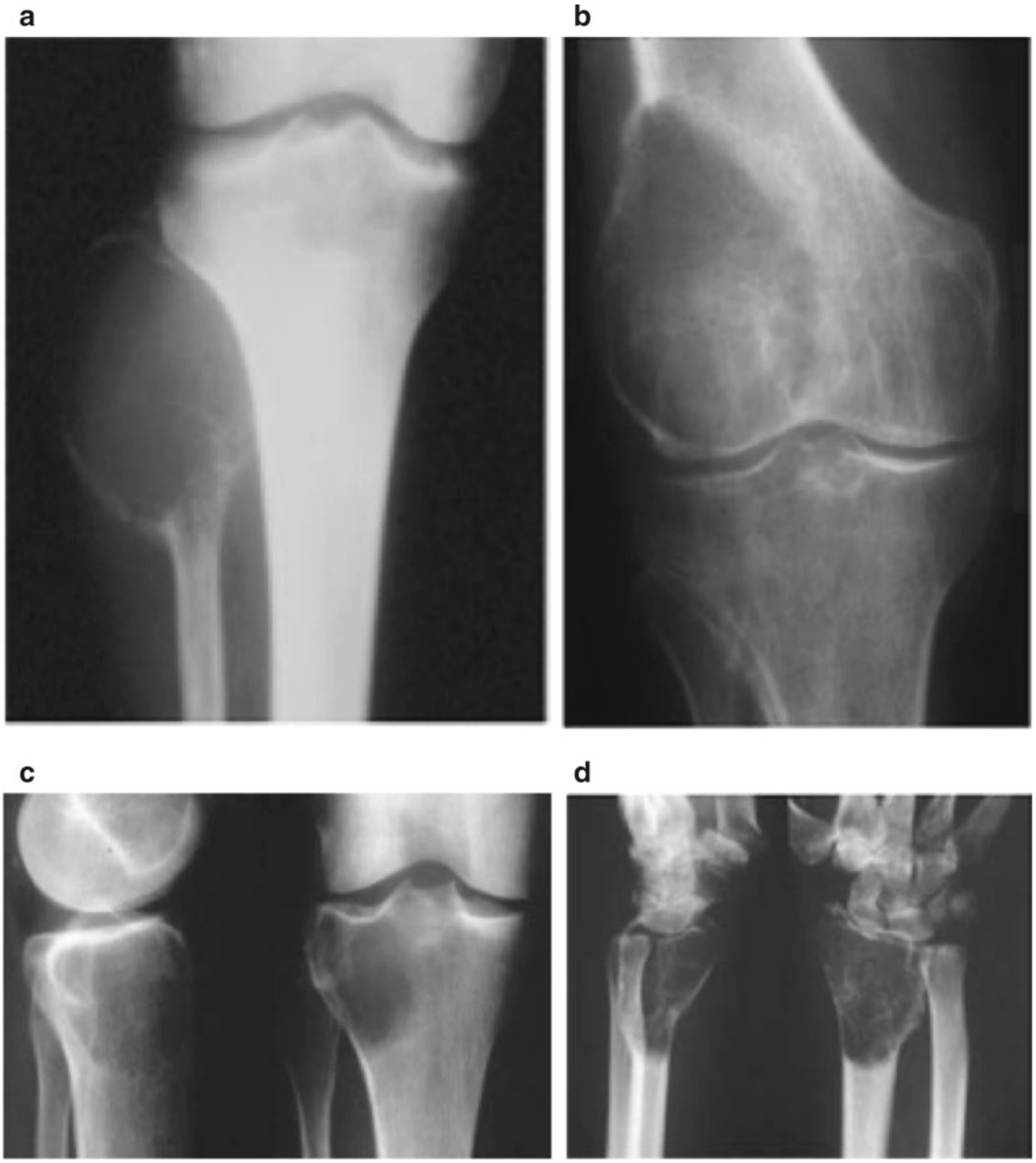

Fig. 11.2 Giant cell tumor located on the epiphysis of long bones: **a** proximal epiphyseal fibula; **b** proximal tibia; **c** and **d** distal epiphyseal femur and distal radius

Most authors recommend curettage or intralesional resection and cryotherapy, phenol or cementing adjuvant therapy (Fig. 11.4)

Curettage must be performed with additional adjuvant therapy, otherwise recurrence is very high (30% or higher).

After a tidy suitable curettage has been performed, a high-speed burr to remove the tumor can be used, but seems insufficient. Cryotherapy with liquid nitrogen poured directly into the tumor cavity reduces the chance of recurrence, but is difficult to manage, with a risk of necrosis of tissuues around the area, so that this technique must be managed by expert hands. Other chemical products have been used, like phenol, but it is a toxic agent, and also ethanol and hydrogen peroxide. Thermal techniques using cementing with PMM (Fig. 11.5) or cauterization from argon beam coagulation have demonstrated better results.

Bone grafting makes the identification of recurrences difficult. The remodeling associated with bone graft integration can lead to difficulties in image interpretation when looking for local recurrences (Fig. 11.6).

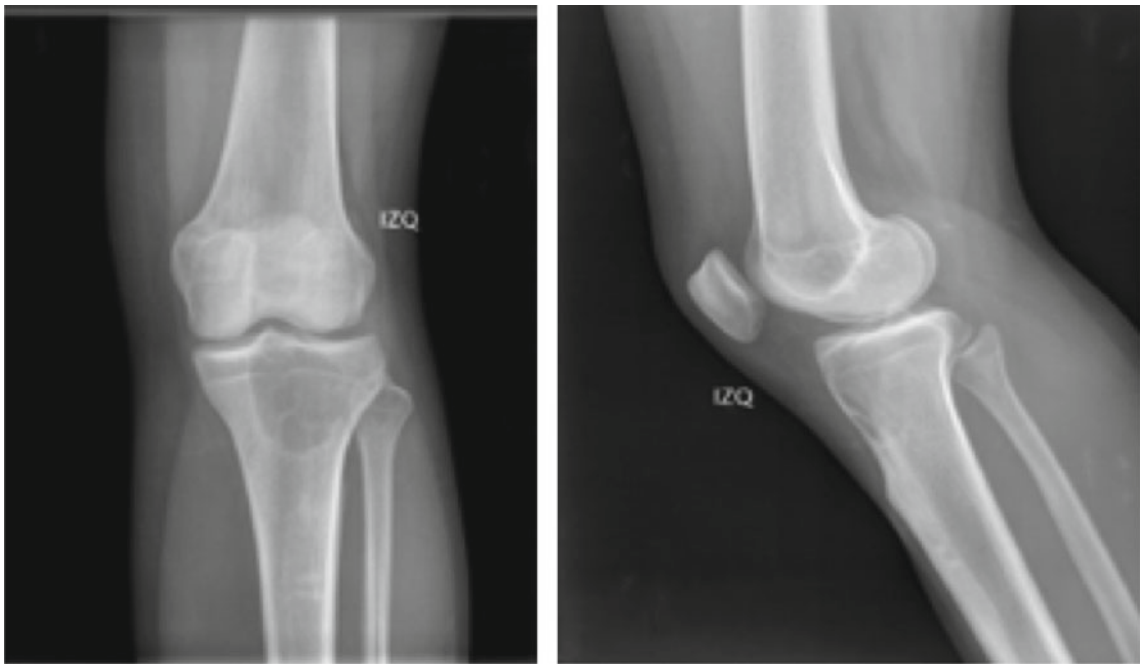

Fig. 11.3 X-ray of giant cell tumor epiphyseal proximal tibia grade 1

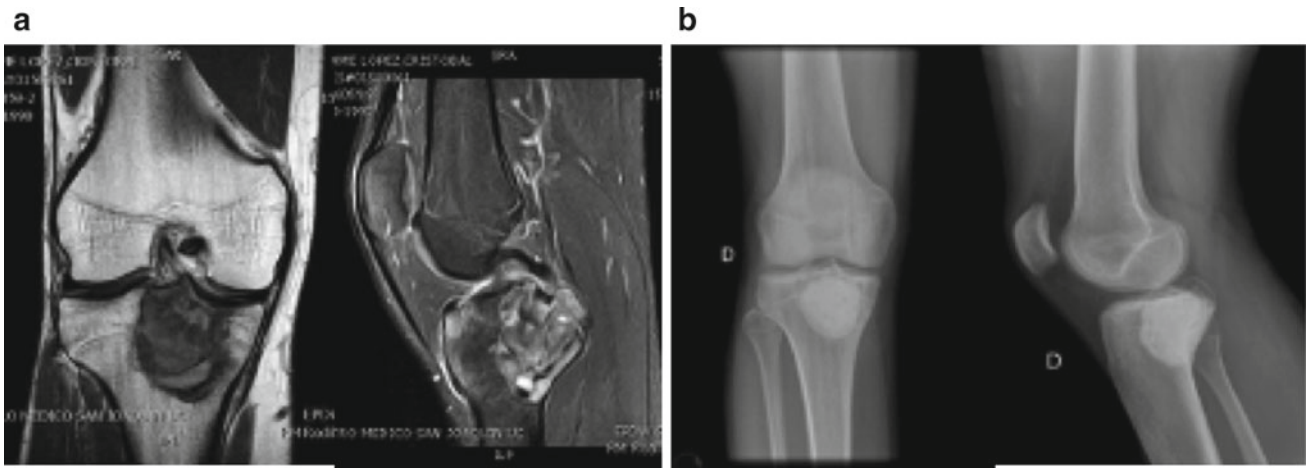

Fig. 11.4 Treatment of GCT, curettage and filled with polymethylmethacrylate (PMM): **a** and **b** preoperative MRI, post-operative X-ray of curettage and cement adjuvant PMM therapy

Bone tumoral resection can be indicated in aggressive Campanacci grade 3 GCT and replacement with allograft. The wrist is a good example of this procedure with an arthrodesis (Fig. 11.7).

Amputation has been necessary in some cases in advanced recurrences.

Radiotherapy is not recommended except when there are no available surgical locations, there is danger of secondary malignization or secondary radioirritation of surrounding tissues. Embolization to reduce the volume of the tumor and with difficult anatomical locations can be useful [25, 26].

Medical management has been used in GCT with biphosfonates (pamidronate, zoledronate) but in recently years with denosumab, a human monoclonal antibody and a RANKL inhibitor [25, 27]. Very good results have been reported decreasing the tumoral mass and the potential agressivity [28–30]. Denosumab is used monthly; the optimal duration of therapy is not yet determined but reports indicate that after stopping the medication the tumor becomes activate again. So surgical treatment continues to be the treatment of choice.

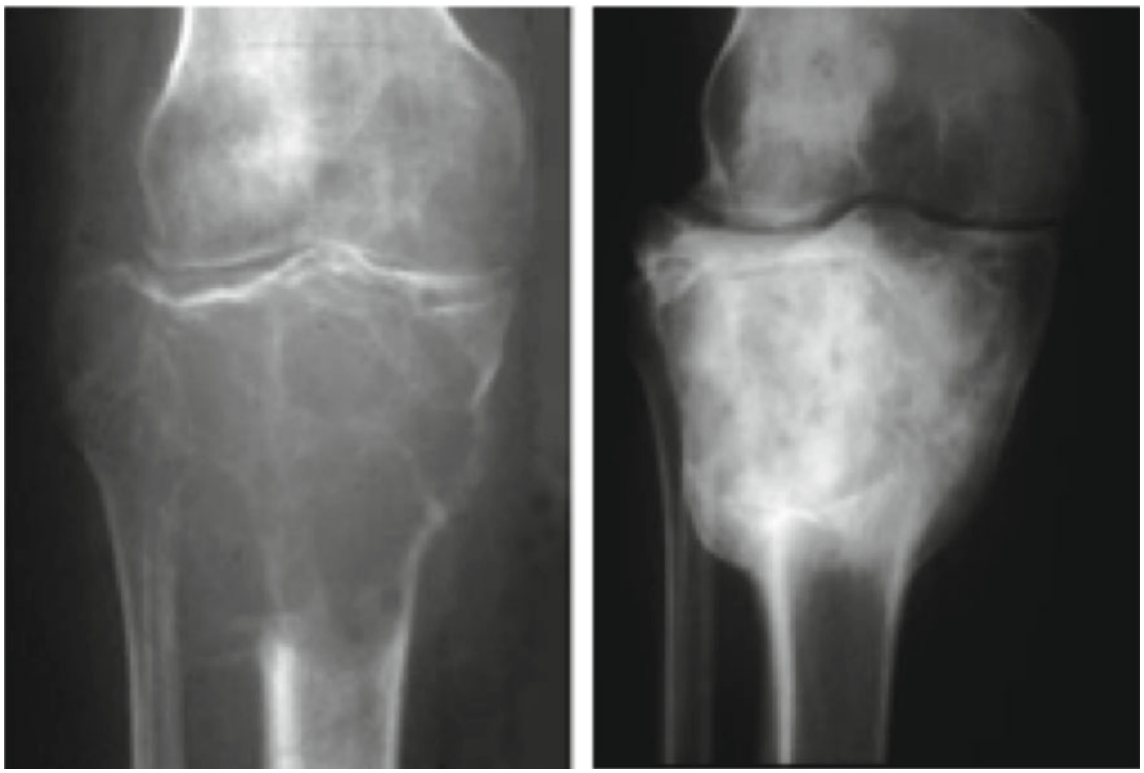

Fig. 11.5 GCT treated with curettage and filled with PMM; 9 years follow-up

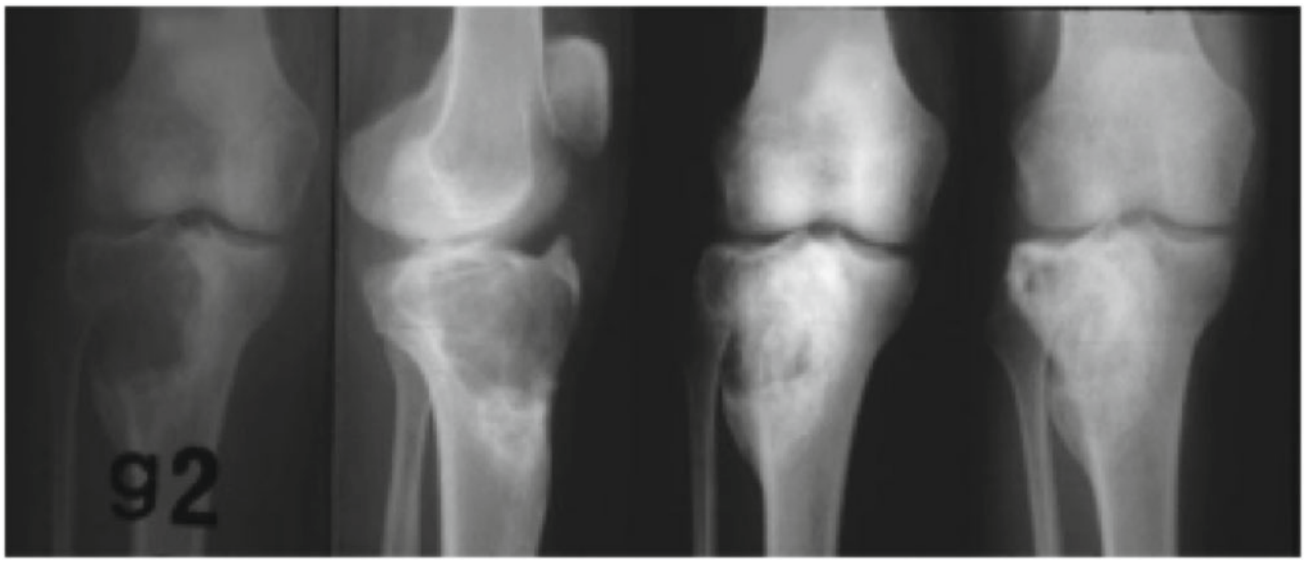

Fig. 11.6 GCT grade 2 treated with curettage and bone graft impaction

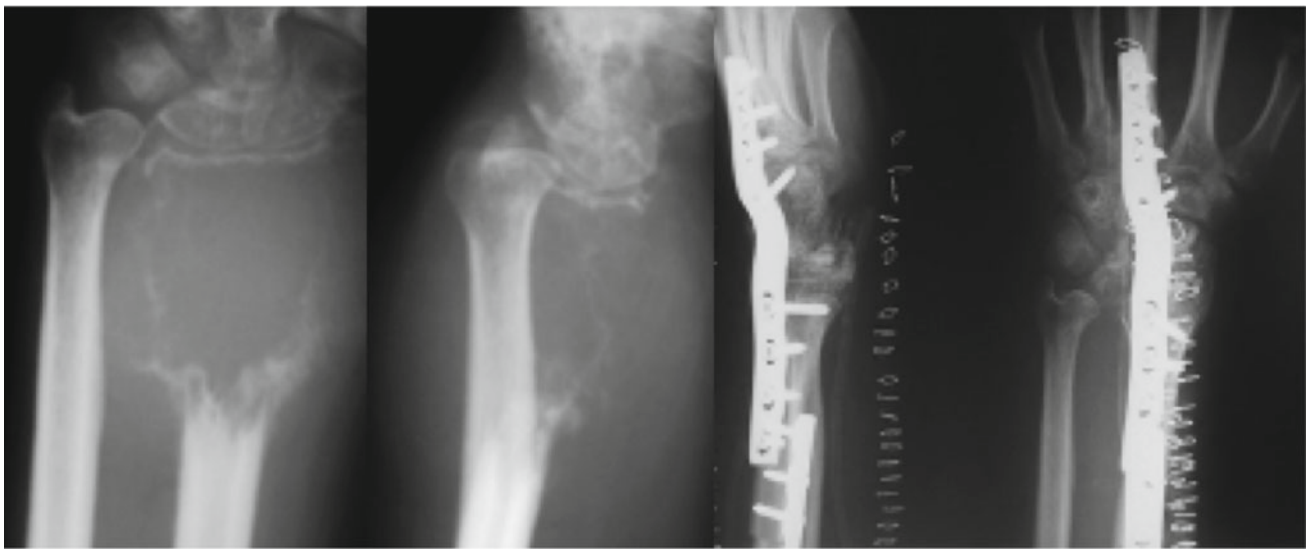

Fig. 11.7 Distal radius GCT, grade 3, bone resection, allograft and wrist arthrodesis

References

1. Campanacci M, Baldini N, Boriani S, Sudanese A (1987) Giant-cell tumor of bone. J Bone Joint Surg Am 69(1):106–114.
2. Cooper A, Travers B (1818) Surgical Essays Part 1. Cox and Son.
3. Coley B (1960) Giant cell tumor (osteoclastoma). In: Neoplasms of bone and related conditions, 2nd ed. p. 196–235.
4. Coley B, Higinbotham N. Giant cell tumor of bone. J Bone Joint Surg Am. 1938;20(4):870–84.
5. Prince H. Giant cell tumor of the os calcis. J Orthop Surg. 1916;2–14(11):641–53.
6. Schajowicz F. Giant cell tumors of bone (osteoclastoma): a pathological and histochemical study. J Bone Joint Surg Am. 1961;43(1):1–29.
7. Jaffe HL (1953) Giant-cell tumour (osteoclastoma) of bone: its pathologic delimitation and the inherent clinical implications. Ann R Coll Surg Engl 13(6):343–355. https://pubmed.ncbi.nlm.nih.gov/13114840.
8. Lichtenstein L (1951) Giant-cell tumor of bone; current status of problems in diagnosis and treatment. J Bone Joint Surg Am 33(1):143–150.
9. Picci P, Manfrini M, Zucchi V, Gherlinzoni F, Rock M, Bertoni F, Neff JR (1983) Giant-cell tumor of bone in skeletally immature patients. J Bone Joint Surg Am 65(4):486–490.
10. Szendroi M (2004) Giant-cell tumour of bone. J Bone Joint Surg Br. 86(1):5–12.
11. Donthineni R, Boriani L, Ofluoglu O, Bandiera S (2009) Metastatic behaviour of giant cell tumour of the spine:497–501. https://doi.org/10.1007/s00264-008-0560-9.
12. Scott D, Pedlow F, Hecht A, Hornicek F. Primary benign and malignantant extradural spine tumors. In: Frymoyer J, Wiesel S, editors. The adult and pediatric spine, 3rd edn. Lippincott Williams and Wilkins; 2003.
13. Hoch B, Inwards C, Sundaram M, Rosenberg AE (2006) Multicentric giant cell tumor of bone: clinicopathologic analysis of thirty cases. J Bone Joint Surg Am 88(9):1998–2008. https://doi.org/10.2106/JBJS.E.01111.
14. Raskin KA, Schwab JH, Mankin HJ, Springfield DS, Hornicek FJ. Giant cell tumor of bone abstract. J Am Acad Orthop Surg. 2013;21:118–26.
15. Campanacci M (1999) Giant cell tumor of bone. In: Bone and soft tissue tumors, 2nd ed. Springer Verlag, p. 99–132.
16. Enneking W (1983) Musculoskeletal tumor surgery, 1st ed. Churchill Livingstone.
17. Domovitov SV, Healey JH (2010) Primary malignant giant-cell tumor of bone has high survival rate:694–701. https://doi.org/10.1245/s10434-009-0803-z.
18. Johnson EWJ, Dahlin DC (1959) Treatment of giant-cell tumor of bone. J Bone Joint Surg Am 41(5):895–904.
19. Meyerding H. Treatment of benign giant cell tumors. J Bone Joint Surg Am. 1936;18(4):823–41.
20. Miller G, Bettelli G, Fabbri N, Capanna R. Curettage of giant cell tumor of bone. La Chirurgia Degli Organi Di Movimento. 1990;75(1 Suppl.):203.
21. McDonald DJ, Sim FH, McLeod RA, Dahlin DC (1986) Giant-cell tumor of bone. J Bone Joint Surg Am 68(2):235–242.
22. O'Donnell RJ, Springfield DS, Motwani HK, Ready JE, Gebhardt MC, Mankin HJ (1994) Recurrence of giant-cell tumors of the long bones after curettage and packing with cement. J Bone Joint Surg Am 76(12):1827–1833. https://doi.org/10.2106/00004623-199412000-00009.
23. Lewis VO, Wei A, Mendoza T, Primus F, Peabody T, Simon MA. Argon beam coagulation as an adjuvant for local control of giant cell tumor. Clin Orthop Relat Res. 2007;454:192–7. https://doi.org/10.1097/01.blo.0000238784.98606.d4.
24. Mankin HJ, Hornicek FJ. Treatment of giant cell tumors with allograft transplants: a 30-year study. Clin Orthop Relat Res. 2005;439:144–50. https://doi.org/10.1097/01.blo.0000174684.85250.b5.
25. Chawla S, Henshaw R, Seeger L, et al. Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: Interim analysis of an open-label, parallel-group, phase 2 study. Lancet Oncol. 2013;14(9):901–8.
26. Onishi H, Kaya M, Wada T, Nagoya S, Sasak IM, Yamashita T. Giant cell tumor of the sacrum treated with selective arterial embolization. Int J Clin Oncol. 2010; 15(4): 416–419.

27. Thomas D, Henshaw R, Skubitz K, et al. Denosumab in patients with giant-cell tumour of bone: an open label, phase 2 study. Lancet Oncol. 2010;11(3):275–80.
28. Karras NA, Polgreen LE, Ogilvie C, Manivel JC, Skubitz KM, Lipsitz E. Denosumab treatment of metastatic giant-cell tumor of bone in a 10-year-old girl. J Clin Oncol. 2013;31(12):e200–2.
29. Branstetter DG, Nelson SD, Manivel JC, et al. Denosumab induces tumor reduction and bone formation in patients with giant-cell tumor of bone. Clin Cancer Res. 2012;18(16):4415–24.
30. Sung HW, Kuo DP, Shu WP, Chai YB, Liu CC, Li SM. Giant-cell tumor of bone: analysis of two hundred and eight cases in Chinese patients. J Bone Joint Surg Am. 1982; 64(5):755–761.
31. Stewart M, Richardson T. Giant cell tumor of bone. J Bone Joint Surg Am. 1952;34(2):372–86.