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REVIEW ARTICLE / DERLEME

Giant cell tumor of bone: current review of morphological, clinical, radiological, and therapeutic characteristics

Kemiğin dev hücreli tümörü: Morfolojik, klinik, radyolojik ve tedavi özelliklerinin gözden geçirilmesi

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ABSTRACT

Giant cell tumor of bone accounts for about 5% of all primary bone tumors in adults and is still one of the most obscure and intensively examined tumors of bone. This largely results from the lack of uniform clinical, radiographic, histological or morphological aspects that allow prediction of recurrence. Classified by the World Health Organization as "an aggressive, potentially malignant lesion", the giant cell tumor of bone could give lung metastases, could undergo malignant degeneration or could have multicentric localization. It usually develops in long bones but can also occur in unusual locations. The common presenting symptom is increasing pain at the tumor site. Standard treatment ranges from curettage to wide resection, with reports of varying oncological and functional results. The recurrence rate is high during the first 2-3 years after surgery regardless of pre-operative tumor stage. Herein, we discuss the morphological, clinical, radiological, and therapeutic characteristics of this pathologic entity as well as its differential diagnosis. *J Clin Exp Invest 2014; 5 (3): 475-485*

Key words: Giant cell tumor of bone, diagnosis, treatment, review.

ÖZET

Kemiğin dev hücreli tümörü erişkinlerdeki tüm primer kemik tümörlerinin %5'ini oluşturur ve kemik tümörlerinin en güç ve yoğun araştırılanıdır. Bu durum büyük ölçüde tekrarları öngörmeye izin veren tek tip klinik, radyografik, histolojik ve morfolojik özelliklerinin olmayışı nedeniyledir. Dünya Sağlık Örgütü tarafından agresif potansiyeli olan malign bir lezyon olarak sınıflandırılan kemiğin dev hücreli tümörü akciğere metastaz yapar ve malign dejenerasyon veya çok merkezli lokalizasyon gösterir. Tümör genellikle uzun kemiklerde oluşur, ancak alışılmadık lokalizasyonlarda da olabilir. Yaygın semptomu tümör bölgesindeki artan ağrıdır. Standart tedavi küretajdan geniş rezeksiyona kadar değişir ve değişik onkolojik ve fonksiyonel sonuçlar doğurur. Tümör evresine bakılmaksızın, cerrahiyi takip eden ilk 2-3 yılda tekrarlama riski yüksektir. Bu yazıda bu patolojik teşekkülün morfolojik, klinik, radyolojik ve tedavi özellikleri ile ayırıcı tanısı tartışılmıştır.

Anahtar kelimeler: Kemiğin dev hücreli tümörü, tanı, tedavi, derleme

INTRODUCTION

Giant cell tumor of bone (GCTB) is usually a benign bone tumor with a high rate of recurrence and possibility of "benign" pulmonary metastases or transformation in a malignant blastoma [1-4]. Numerous terms including myeloid sarcoma, tumor of myeloplaxus, osteoblastoclastoma, and osteoclastoma have been used to depict this tumor [5,6]. It accounts for about 5% of all primary bone tumors in adults and predominantly occurs in the third and fourth decade of life with a slight predilection for females [2,7,8]. GCTB is described as a locally invasive tumor that arises close to a joint in a mature bone [2,9]. It usually affects the meta-epiphyseal region of long bones, preferably the bones around the knee joint, the distal radius, and the proximal humerus [1-4,10]. The definitive treatment of GCTB varies from intralesional curettage with or without different adjuvants followed by bone grafting and/or bone cement packing to wide resection which could compromise limb function [1-4,10].

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In this report, we review the pathologic features, clinical manifestations, radiological appearance, different forms of GCTB, and the treatment of this lesion.

PATHOLOGICAL FEATURES

Gross findings

GCTB has a variable gross appearance. It usually presents as a large lesion eccentrically located in the epiphysis, extending toward the articular cartilage and toward the metaphysis [7,11]. GCTB is usually meaty, soft, purple-red to brown, and may be uniform or variegated in gross appearance, with small, squishy yellow necrotic foci or extensive areas of cystic change [7,11]. Soft-tissue extensions are not uncommon and appear as a well-defined mass with peripheral calcification [7].

Microscopic findings

In the current literature, GCTB is described as a predominantly osteoclastogenic stromal cell tumor of mesenchymal origin [12]. It is composed of large multinucleated osteoclast-like giant cells distributed amongst mononuclear spindle-like stromal cells and other monocytes (Figure 1) [12-14].

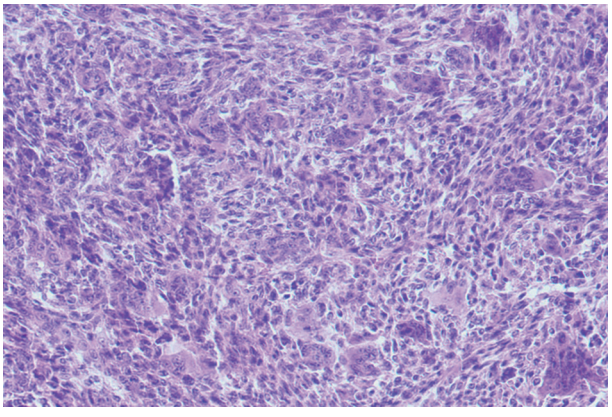

Figure 1. Photomicrograph demonstrating multinucleated giant cells, spindle cells and mononuclear monocyte cells.

The multinucleated giant cells which mimic osteoclasts are principally responsible for the extensive bone resorption that is characteristic of GCTB [14]. Their size is about 60 μm and they contain from 20-30 to 100 or more nuclei located centrally. They react positively with tartrate-resistant acid phosphatase, cathepsin K, carbonic anhydrase II, α-naphthyl esterase enzymes, different matrix metalloproteinases, and with a number of receptors such as receptor activator of nuclear factor kappa-B (RANK), calcitonin receptor, αvβ3 integrin, which are characteristic of osteoclasts [14-17]. On electron microscopy these cells are described as multi-nucleated, osteoclast-like giant cells [18-20]. In the past, particularly in British literature GCTB was called osteoclastoma due to the abundance of these cells.

The spindle-like stromal cells are the main neoplastic component of GCTB and have been shown to express and secrete a variety of chemotactic factors to enlist pathologic components [12,14,21]. They play an important role in the formation of giant multinucleated cells [7,8,14,17]. The spindle-like stromal cells have great potential to proliferate, produce collagen type-I and II, alkaline phosphatase, matrix metalloproteinases and they have receptors for parathyroid hormone. Spindle-like stromal cells secrete macrophage colony stimulating factor (M-CSF), interferon gamma (IFN-gamma), and tumor necrosis factor alpha (TNF-α), which have chemotactic, differentiation-inducing and activating effects on mononuclear monocyte cells and are essential for the differentiation of osteoclasts [8,13,22,23]. Spindle-like stromal cells also have receptor activator of nuclear factor kappa-B ligand (RANKL) which plays an important role in osteoclastogenesis. At the ultrastructural level, spindle-shaped mononuclear cells resemble fibroblasts [18-20].

The monocyte cells are considered to be either reactive macrophages or osteoclast precursors [12,14]. They express monocyte-macrophage markers such as tartrate-sensitive acid phosphatase, α-naphthyl esterase, and react with monoclonal antibodies to CD11a, CD13 , CD18, and CD68, suggesting that these cells have monocyte-macrophage origin [7,8,17,24]. Khurana and McCarthy [17] reported that the giant multinucleated cells are formed by the fusion of these cells, but not from the spindle-like stromal cells. Polygonal mononuclear cells are similar to macrophages, in regard to their ultrastructural characteristics [18-20].

Many authors have attempted to grade these tumors histologically but no grading system has proved to be of prognostic significance in terms of recurrence rates or occurrence of metastases [25-27]. Pulmonary metastases in GCTB histologically do not differ from the bone lesion [17].

The pathologic differential diagnosis of the GCTB includes aneurysmal bone cyst, benign fibrous histiocytoma, foreign body reaction, chondroblastoma, giant-cell-rich osteosarcoma, osteo-

blastoma, and brown tumor of hyperparathyroidism [7,28].

Clinical manifestations

The main clinical symptoms are non-specific and include pain of variable severity, local swelling, tenderness of the affected area, and limited range of motion of the adjacent joint [1,7,8,17,28]. The duration of symptoms varies from two to six months. Rarely, a pathologic fracture may be the first symptom [1,7,8,17,28]. Neurologic symptoms may be associated with spinal lesions [7].

RADIOLOGICAL APPEARANCE

The most important feature that often strongly suggests the diagnosis of GCTB is the location of the lesion [29,30]. Commonly, this tumor affects the distal femur (27%), followed by the proximal tibia (21%) [1-4,10]. Other locations reported in the literature are the distal radius (8%), the sacrum (6%), and the proximal humerus (5%) [31-33]. Rarely, GCTB could involve the proximal femur, the vertebra, the distal tibia, the proximal fibula, the hand, and the foot [34-36]. Extremely rarely, this tumor could affect the greater trochanter [30].

On radiographs, GCTB typically presents as a lucent lesion without matrix calcifications growing often, but not exclusively, eccentrically in the epimetaphyseal region of the bone, generally in a skeletally mature patient [1,2,7,8,10]. In indolent and static tumors, the margins of the lesion are well-defined, without sclerosis changes. In aggressive cases, margins are poorly demarcated and the cortex may be thinned, distended, or destroyed with soft tissue extension, but a periosteal reaction is generally lacking [7,8,10]. Marginal sclerosis may be present in old or inactive lesions, and peripheral ossification around a soft tissue recurrence or a lung metastasis [28]. Complete or incomplete pathologic fracture after bony destruction could also be detected [37].

Campanacci et al. [38] classified GCTB in three grades: grade 1 - a static form with minimal involvement of the cortex, grade 2 in which the cortex is thinned and expanded, and grade 3 in which the lesion penetrates the cortex and has a soft tissue component.

The radiographic differential diagnosis of GCTB includes juvenile solitary or aneurysmal bone cysts, chondroblastoma, chondromyxoid fibroma, giant-cell reparative granuloma, nonossifying fibroma, eosinophylic granuloma, high-grade central osteosarcoma [7,8].

As with any suspicious bone lesion, full staging with MRI and CT should be undertaken [7,39]. CT is useful in the evaluation of the cortical bone and could clearly present thinning of the cortex, pathologic fracture, periosteal reaction, and absence of matrix mineralization [8,37]. In cases of cortical destruction and soft-tissue tumor extension, MRI is superior to CT in delineation of GCTB [7,8]. The tumor appears with a nonhomogenous signal on MRI: low in T1-weighted images and high in T2-weighted images [28]. Moreover, MRI could also present fluid-fluid levels typical for the aneurysmal bone cyst, thus helping in distinguishing the aneurysmal bone cyst from the GCTB [7]. Bone scintigraphy could also be used for the evaluation of giant cell tumor of bone [40, 41]. However this imaging modality is not specific and it is only helpful in evaluating patients with multicentric or metastatic GCTB [42].

Malignant GCTB

Malignant GCTB is rare and is divided into primary and secondary [7,43]. Primary malignant GCTB is the rarest (about 1-3 % of all cases of GCTB) and has cells characteristic of a sarcomatous process located in areas of typical benign GCTB [7,32,43]. Secondary malignant GCTB is present in 5-10 % of cases and is described as a metachronous highly differentiated sarcoma that is superimposed on a primary histologically benign GCTB after surgery or radiotherapy [7,9,32,43]. The clinical features of primary and secondary malignant GCTBs are similar to those of a benign lesion; the primary is virtually indistinguishable by radiography while the secondary has a much more malignant radiographic appearance but sometimes it too is indistinguishable from a benign lesion [43]. It is believed that secondary malignant GCTB has two types with different etiology - post-surgical and radiation-induced although they cannot be distinguished from each other either radiographically or histologically [43]. Primary malignant GCTB must be distinguished from an osteosarcoma rich in giant cells. Differentiating these two tumors is sometimes difficult, with limited application in clinical practice. More importantly, they are both difficult to be differentiated from a benign GCTB. The diagnosis of primary malignant GCTB is difficult, because it contains benign areas and therefore biopsies may not detect malignancy of the tumor in the beginning [43-45]. Sakkers et al. [45] propose a theory regarding the malignant transformation of a GCTB treated with curettage and autograft and they assume that reparative proliferative changes that occur in the bone graft could serve as a nidus for the formation of a malignant

tumor. In the literature there are cases in which sarcomatous degeneration happened even 25 years after primary surgery of GCTB [46].

Benign metastasizing GCTB

Benign metastatic GCTB represents 1% to 3% of all GCTB and 6% of the recurrences [47-49]. Its biological behavior is unpredictable [50,51]. The most frequent benign GCTB metastases are in the lung but although extremely rare, metastases have been described in lymph nodes and even in the scalp [50]. In those cases, the metastases were histologically identical to those of the bone lesion [47]. "Benign" lung metastases (single or multiple) were divided into three groups: (1) fixed or ones that show spontaneous regression, (2) with slow growth, and (3) with rapid growth [51]. Disappearance of metastases after biopsy has also been reported in the literature [52]. Some authors believe that such metastases are due to secondary emboli in a peripheral vascular lesion and that they should be accepted as implantable in the lung but not as true metastases [53,54]. Others, however, have found no relationship between the incidence of tumor emboli in these vessels and pulmonary metastases [55,56]. Rock et al. [57], Maloney et al. [56], Prosser et al. [48] have suggested that metastases occur more frequently in cases of aggressive lesions with soft tissue components and after of one or more recurrences. Tubbs et al. [58] noted that lesions of the distal radius more frequently produce lung metastases.

Any authors indicate elevated MMPs, higher expression of p53 protein and over expressed C-myc oncogene in metastatic GCTB [59,60]. Lung metastases often occur two or three years after the treatment of the primary lesions [47,61]. Sometimes they are present at the time of detection of the bone lesion. Therefore, it is necessary to obtain chest radiographs before primary surgery and during the follow-up. Lung metastases could show peripheral ossification on radiographs but in general they have nonspecific imaging characteristics [7]. The presence of lung metastases in GCTB does not necessarily mean a poor prognosis [53,56].

Multicentric GCTB

The multicentric form of GCTB represents about 1 % of all cases (Figure 2a-d) [62-64]. There are different theories about the mechanism of GCTB that affects multiple locations: contiguous spread, iatrogenic dissemination, benign metastasis, malignant transformation, and de novo formation [65]. Lesions may occur simultaneously or with an interval of more than a decade [63]. Hoch et al. [63] present the most frequent localizations: around the knee, followed by the proximal humerus and the distal radius. Dhillon and Prasad [65] reported that multicentric GCTB often affects bones of the hand and the foot, and it is more often located in the meta-diaphysis of the long bone than solitary lesions and that it has a higher incidence in females and in subjects with incomplete bone growth. Multicentric GCTB does not differ from the solitary tumor regarding its radiological, histological, and therapeutic aspects. Radiological and histological characteristics, as well as in the treatment of multicentric GCTB, are not different from that of the solitary lesions [2,66].

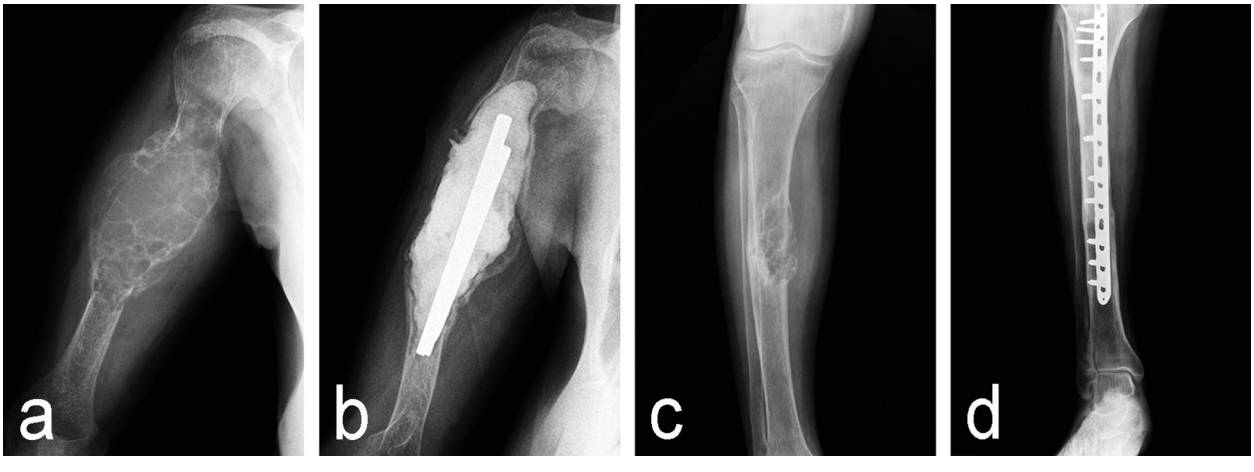

Figure 2. A case of a multicentric GCTB: **a**) preoperative antero-posterior radiograph of a diaphyseal GCTB of humerus; **b**) AP radiograph after extended intralesional curettage and cementation reinforced with Küntscher nails; **c)** preoperative AP radiograph of a diaphyseal GCTB of tibia; **d**) AP radiograph after segmental resection and structural allogenic bone grafting.

TREATMENT

GCTB is one of the most discussed bone tumors today. This result from the fact that there are no single clinical, radiographic, histological aspects that provides a reliable predictive value in terms of recurrence. Wang et al. [67] believes that the definition of the ideal method of treatment of GCTB is too subjective and varies depending on the experience and expertise of the surgeon. The recommendations regarding the treatment of GCTB were based on retrospective analysis of the non-randomized series of one or many centers. Most surgeons believe that the best treatment should provide good local control and preserve limb function, curettage being their method of choice.

CURETTAGE

The main classifications determining surgical treatment are those of Enneking [68] and Campanacci et al. [38]. Although their prognostic significance is still under discussion, they are used consistently for preoperative planning [69-71]. Many authors do not regard these staging systems as predictive of the prognosis [8,10,25,26,47,69]. However, other authors describe an increased incidence of recurrence in third grade lesions [48,72-74].

In the literature various adjuvants have been used in the treatment of GCTB after curettage but no prospective randomized trials compare their effects. The adjuvants have been used after curettage because of their physical (cryotherapy, hyperthermia, high-pressure pulsatile lavage, high-speed dental burr, argon beam coagulation) or chemical (phenol, hydrogen peroxide, alcohol, methotrexate) effects [2,7,8,25,26,75,76]. Fracture, skin necrosis, nerve injury, and osteoarthritis have been reported as potential complications from cryotherapy and phenol application [77].

The most widely used adjuvant in the treatment of GCTB is polymethylmetacriylate (PMMA) bone cement (Figure 2b) [2,49,70,78,79]. Packing the defect with bone cement after curettage is advantageous in that it is cheap, allows immediate weight-bearing, and provides optimal radiological conditions to easily identify local recurrences by radiography, CT, and MRI [2,8,49,70,76,78,79]. The other option of filling the cavity after curettage is bone grafting. There are no prospective randomized trials to demonstrate the effect of different methods of filling the cavity [69]. The advantages of bone grafting are restoration of normal biomechanics to the joint surface, decreasing the risk of osteoarthritis, and restoration of bone stock (Figure 3a-d). The disadvantages of this method are the need of prolonged protection of the limb because of the risk of pathological fracture and the difficulty in distinguishing recurrent GCTB from graft resorption.

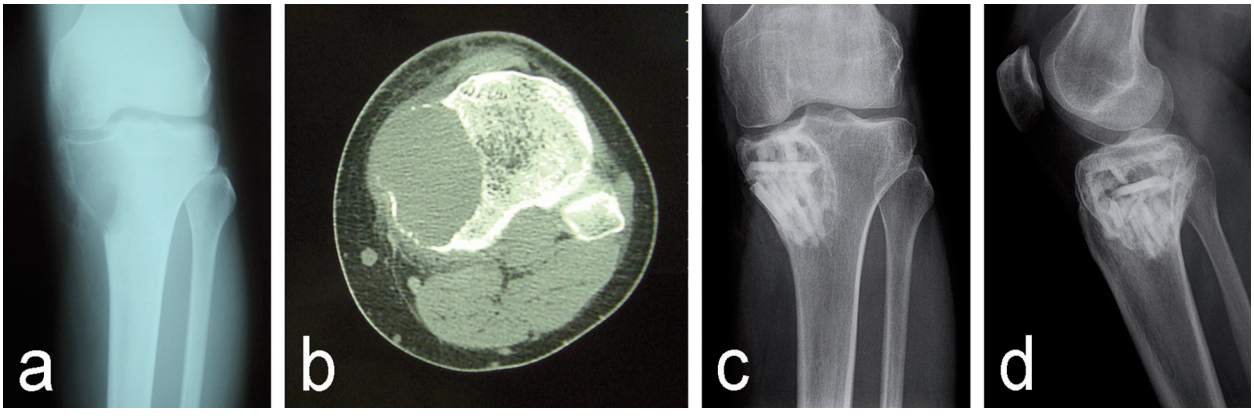

Figure 3. Preoperative AP radiograph (**a**) and CT (**b**) of a meta-epiphyseal GCTB of proximal tibia; **c, d**) AP and lateral radiographs after extended intralesional curettage and allografting with freeze-dried cancellous bone and cortical struts.

Although many authors believe that the use of an adjuvant lowers the risk of recurrence, other authors suggest that aggressive curettage through a large window that allows inspection of the entire lesion is the single most important factor in treatment outcome [48,75,80,81]. Algawahmed et al. [81] based on a meta-analysis of six retrospective studies have found no evidence in favor of the use of an adjuvant after curettage and high-speed burring in terms of local control of the disease.

According to some authors, a soft tissue component is not a contraindication for curettage

[2,70,78,79]. The advantage is avoiding a complex skeletal reconstruction at an early age, and the disadvantage is a higher risk of recurrence. Considering the benign nature of the lesion, the young age of the patients, and the possible complications, it is believed that resection as primary treatment should be avoided [82,83]. Resection is used in patients with significant soft tissue components and lesions with more aggressive localization.

EN-BLOC RESECTION

In cases of excessive cortical destruction, soft-tissue tumor extension (stage 3) with a large bone defect and destroyed joint surface, en-bloc resection is indicated. However, the main problem in the choice of surgical treatment of third stage lesions is that there is no precise definition of "large" and "excessive" destruction of the cortex and soft tissue component [2,67,69-71].

After resection, reconstruction with bone grafting or a metal prosthesis is necessary (Figure 2 c,d; Figure 4a-d). Autografts (nonvascularised or vascularised fibula) have been used in aggressive lesions at the distal radius and distal tibia with consequent arthrodesis or arthroplasty of these joints [7,8,84-87]. Resected portions of the distal femur or proximal tibia have been replaced by osteoarticular allografts or tumor prostheses [88,89]. In cases when GCTB is localized in the proximal fibula, distal ulna, and the wing of the ilium reconstruction after en-bloc resection is not necessary [8]. Location in the vertebral column, the sacrum or the periacetabular region of the pelvis impedes the surgical procedure [8,90]. Preoperative transcatheter arterial embolization could reduce blood loss during surgery [8].

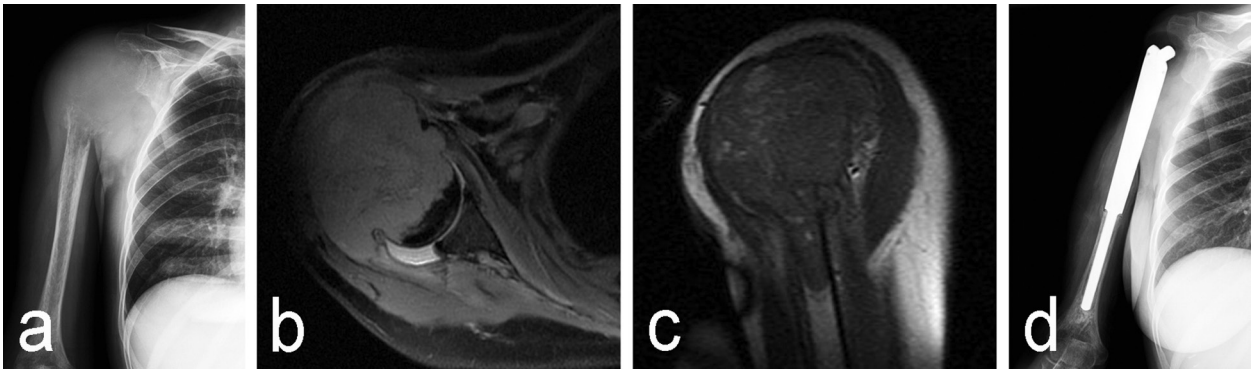

Figure 4. Preoperative AP radiograph (**a**) and MRI slices (**b, c**) of a GCTB of proximal humerus; **d**) AP view after wide resection and replacement of the proximal humerus with a custom-made prosthesis.

Treatment after pathological fracture

It is believed that larger lesions with more aggressive course may cause pathological fracture [67]. In the literature, 20-30% of GCTBs had a pathologic fracture at presentation [49,91].

Deheshi et al. [91] indicate that there is no difference in terms of recurrence after curettage in patients with or without a pathological fracture. Dreinhöfer et al. [92] also believe that pathological fracture is not a contraindication for curettage and PMMA. In contrast Dreinhöfer et al. [92] and Lewis et al. [93] considered pathological fractures to indicate potentially more aggressive lesions where more aggressive treatment was needed as those cases showed a higher rate of recurrence and worse functional results. Turcotte et al. [27] in a Canadian multicenter study involving 186 patients present that displaced fracture is a prognostic factor for local recurrence. In the literature, however, there is little data regarding the incidence of local recurrence in patients with and without pathological fracture [48,49,69].

Treatment of recurrences

In the literature there is no consensus on treatment of recurrences. An early diagnosis of recurrence allows repeated curettage and avoids resection and subsequent reconstruction [32, 49,94,95]. Some authors [48,96] recommend wide resection followed by reconstruction with individual prostheses. Others recommend repeated curettage and PMMA [2,82]. Balke et al. [97] studied the outcome of treatment of recurrences of GCTB and reported on implantation of 14 endoprostheses in 67 patients (21 %), which is too high a percentage for a benign lesion.

Treatment of multicentric lesions, malignant GCTB, pulmonary metastases

With respect to treatment of multicentric lesions, it should be noted that the indications for the type of surgery are the same as in the case of a solitary lesion [2,66].

The treatment of malignant GCTB includes a resection according to oncological criteria and combined with chemotherapy [8]. However, the prognosis of this tumor is not good: five years survival in 50% of cases [8,98].

Complete excision of the pulmonary metastases in most cases leads to good results, but 16% to 25% of reported cases have been described as deathly [25,26,51,53,56,99]. Radiation therapy and chemotherapy have only a limited application [52,57].

RECURRENCE

The recurrences rate of GCTB most often ranges about 12-65 % after curettage and osteoplasty [2,10,27,48,75] 12-27 % after curettage of an additional adjuvant, such as high-speed burring, hydrogen peroxide, phenol, PMMA [2,49,78] and 0-12% after en-bloc resection [2,69]. Errani et al. [69] believe that the exact frequency of recurrences after curettage is very difficult to be established. Some authors present series without recurrences, [80,100] while in others it varies from 6-8% [101] to 30-75% [96]. The reoccurrence rate is 25-35 % in older series and 10-20 % in recent series [69]. Despite the lowest rate of recurrence observed in patients after resection, it is not recommended for primary treatment because it leads to significant impairment of limb function [2,10,49,69,78].

PROGNOSTIC FACTORS

Kivioja et al. [49] determined the age of the patient and the surgical margins as prognostic factors of recurrence. Younger patients have a slightly higher risk of recurrence; it decreases every year by about 2 percent. Klenke et al. [70] analyzed the results in 118 patients with GCTB and found that age at diagnosis predicted the probability of recurrence regardless of the stage of the lesion and the aggressiveness of the approach chosen. The higher risk of recurrence in young patients is probably related to more intensive bone turnover [73]. This hypothesis is supported by studies showing that the inhibition of bone turnover with bisphosphonates reduces the risk of recurrence [102]. However, many authors believe that the recurrence rate does not correlate with age [2,10,27,69,71,73,74].

The prognostic significance of cortical destruction and the presence of a soft tissue component is still debatable [2,69,70,78]. Prosser et al. [48] believes that the risk of recurrence correlates with the degree of cortical destruction; it is only 7% in patients with endosteal tumors and 29% in patients with evidence of an extraosseous component. O'Donnell et al. [74] reported that the presence of pathologic fracture is associated with an increased incidence of recurrence. Balke et al. [2] believe that extraosseous component is prognostic of recurrence, giving a fourfold increase in the risk of relapse. In contrast, Errani et al. [69] found no statistically significant difference in recurrence rate and the presence of cortical destruction and a soft tissue component. Wang et al. [67] believe that the cortical destruction and size of the lesion can be objective factors to determine the type of surgical treatment. Klenke et al. [70] indicate that gender, localization, stage of the lesion, the presence of a soft tissue component and a pathological fracture are unrelated to the risk of recurrence. O'Donnell et al. [74] and Errani et al. [69] believe that lesions of the distal radius have a greater tendency to recur.

FOLLOW-UP

After surgery, patients with GCTB require long-term follow-up. Most commonly this tumor recurs within the first 12 to 36 months, rarely after five to six years [8,7,103]. About 70% of recurrences occur during the first 2 years after the operation [2,27,69,76,82]. In the literature there is evidence of recurrence observed after 20 and even 42 years after surgery [104]. Errani et al. [69] and Niu et al. [71] suggest that patients with GCTB should be monitored until the tenth year after surgery. It is assumed that relapses are due to activation of the remaining "dormant" tumor cells [105]. Patients with GCTB should be evaluated for local recurrence and pulmonary metastases at 4-month intervals for the first 2 years and at 6-month intervals thereafter up to 5 years [7,8,103]. The first symptom of recurrence is pain. Follow-up of patients with GCTB is done with periodic radiographs that are compared with the previous ones; this helps to differentiate recurrence from postoperative changes. Bone graft usually undergoes bone remodeling. The combination of osteolysis and cortical expansion is particularly important for differentiation between bone resorption and re-

currence [106]. The presence of a soft tissue recurrence may present on conventional radiographs as peripheral calcifications. In cases of recurrence, CT is used to evaluate bone changes and MRI - the eventual soft tissue component. When PMMA is used to pack the cavity, it is important to determine whether the defect has been initially filled completely during surgery, which could otherwise be wrongly interpreted as osteolysis and respectively a relapse [106]. PMMA is not resorbable and its high radiographic density is in sharp contrast with the lower density of the adjacent bone. It should be noted that after curettage and packing with PMMA, an osteolytic zone of about 2 mm around the cement has been observed, caused by the thermal damage of the surrounding bone. This radiolucent zone is surrounded by a thin outer sclerotic rind for about six months [107]. The presence of larger or longer-lasting osteolysis or the absence of a sclerotic rind between the cement and the surrounding cancellous bone suggests a recurrence [103,106]. In cases of doubt it is appropriate to obtain a MRI where PMMA has low signal intensity in all sequences and is readily distinguishable from the existing relapse [97,106].

Chest radiographs and CT evaluate the pulmonary metastases [25,26]. Although the prognosis of the metastases, with or without surgical removal, is usually good [25,26] there are reports of lethal outcome due to metastasizing GCTB [99].

RADIOTHERAPY

Although surgery remains the method of first choice in the treatment of GCTB, in some cases with locations in the spine, sacrum or pelvis which hinder surgery the use of adjuvant radiotherapy is appropriate [8,90]. Radiotherapy is also warranted in inoperable cases [4]. Several cases of malignant GCTB after radiotherapy have been described. The use of modern technologies in the field and applying megavoltage radiotherapy techniques reduces the risk of malignant transformation and longer and better local control [108].

Molecular adjuvant therapy in the treatment of GCTB

In recent years a number of studies have demonstrated that the receptor activator of nuclear factor kappa-B ligand (RANKL) plays a key role in the pathogenesis of GCTB. Promising results have been achieved by the neoadjuvant use of Denosumab which inhibits RANKL [109-111]. This therapy induces calcification of the affected soft tissues which allows the extension of the indication for curettage and additional adjuvants [79]. According to Branstetter et al. [112] the neoadjuvant use of Denosumab significantly reduced or eliminated RANK-positive tumor giant cells. Denosumab also reduced the presence of proliferative, dense stromal cells, replacing them with non-proliferative, well differentiated new bone.

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