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Case Research

Chondroblastoma in the long bone diaphysis: a report of two cases with literature review

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Abstract

To investigate the clinical characteristics of chondroblastoma with an emphasis on lesions located in the long bone diaphysis, we reviewed the clinical data of 7 patients with histologically proven chondroblastoma treated in Tianjin Medical University Cancer Hospital and Fudan University Cancer Hospital between January 1995 and May 2009. There were two rare cases of chondroblastoma in the long bone diaphysis. One patient with a lesion in the tibial diaphysis underwent intralesional curettage and bone grafting, and the postoperative bone function was measured as excellent according to the Enneking scoring system. The patient was still alive upon follow-up at 60 months. The other patient with a lesion in the humeral diaphysis underwent resection, and the postoperative bone function was excellent at 48 months, at which there was no evidence of recurrence or metastasis. Thus, except for the distinctive site of the long bone diaphysis, which made diagnosis difficult, the patients' ages, symptoms, X-ray and CT images, treatment, and prognosis were in accordance with typical lesions in the epiphysis and metaphysis. The diagnosis of chondroblastoma in the long bone diaphysis significantly depends on histopathologic characteristics.

Key words Chondroblastoma, long bone diaphysis, primary bone tumor

Chondroblastoma is an uncommon benign bone tumor arising from a secondary ossification center in the epiphyseal plates and apophyses. It usually occurs in adolescents and young adults and involves the tibia, femur, and humerus. The purported neoplastic cell is the chondroblast, a cell that normally populates areas of secondary ossification[1]. Numerous studies have shown that chondroblastoma overwhelmingly arises from the epimetaphyseal region. Only rare cases have been reported in the diaphyseal region, and many of these involve metacarpals or metatarsals, which may lack a true anatomic diaphysis. The remaining cases of diaphyseal chondroblastomas synchronously involve the neighboring epimetaphysis, making determination of the initiation point impossible[2]. Here, we reviewed chondroblastoma, with an emphasis on lesions occurring in the long bone diaphysis, to investigate its characteristics.

Case Presentation

Clinical records of 7 patients with histologically proven chondroblastomas treated at Fudan University Cancer Hospital and Tianjin Medical University Cancer Hospital between January 1995 and May 2009 were reviewed under the Institutional Review Board protocol. Histological criteria for the diagnosis of chondroblastoma were as described in the World Health Organization Classification[1], and all pathologic diagnoses were confirmed by two senior pathologists in both cancer hospitals. The epidemiology, presentation, radiographic findings, treatment, and postoperative bone functions were recorded. Patients were considered to be healed on cessation of symptoms and when marked peripheral sclerosis with central calcification or progressive centripetal ossification with obliteration of the curetted and bone-grafted areas was seen on radiographs. Recurrence was defined as a return of symptoms and an enlarging radiolucency at the operative site. Bone function was measured according to the Enneking

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scoring system of the Musculoskeletal Tumor Society. Patients were followed up at the Tianjin Cancer Registry and Report Center, a member of the International Association of Cancer Registries. Statistical analysis was performed using the Statistical Package for Social Sciences software program version 15 (SPSS, Chicago, Illinois, USA).

Clinical data analysis

In our cohort, 7 patients (2 men and 5 women) aged 15 to 43 years (mean, 27 years) were diagnosed with chondroblastoma. The majority of patients complained of localized pain, often mild and sometimes for a duration of many years. Physical examination showed palpable masses and joint limitation. Soft tissue swelling, joint stiffness and limp were less commonly seen. The tumors located in the epiphysis (2 cases) and the extension from the epiphysis to the metaphysis (3 cases). There were 2 cases in the diaphysis of tibia and humerus, which will be addressed in the next section. Radiologically, most lesions were typically lytic and centrally or eccentrically placed. Computed tomography (CT) scans showed cortical erosion. The lesions on magnetic resonance imaging (MRI) showed low signal intensity on T1-weighted images and variable signal intensity on T2-weighted images. Nuclear medicine studies showed uptake of bone-seeking radiopharmaceuticals. Histopathologically, the tumors were composed of cellular and matrix-rich areas. Cellular areas were composed of so-called "chondroblasts" with an oval to round nucleus and with well-defined eosinophilic cytoplasm. A fine network of pericellular calcification defined the so-called "chicken wire calcification" seen in some cases. The most common treatment was curettage and autograft or allograft bone grafting. Simple curettage and *en bloc* resection were also frequently adopted. Two patients with lesions in the long bone diaphysis were described in detail.

Case 1

A 15-year-old boy was admitted to hospital because of persistent pain in the left leg for 2 weeks. Physical examination revealed a tender swelling and pressing pain in the media region of the left leg. There was no evidence of soft tissue mass or concurrent illness. The patient had no history of trauma or irradiation in this region. A plain radiograph showed a well-defined lytic defect, measuring 5-6 cm in diameter in the diaphysis of the left tibia (Figure 1A). CT scans demonstrated an area of extensive lytic bony destruction with little discernible residual cortex and no significant periosteal reaction. The margins were well delineated, and there was no matrix formation within the lesion (Figure 1B). T1-weighted MRI showed an irregular, slightly low signal intensity mass with central nodularity (Figure 1C), which exhibited heterogeneity and slightly high signal intensity on T2-weighted images (Figure 1D). The bone emission computed tomography (ECT) showed clearly defined radiopharmaceutical uptake in the media part of the left leg (Figure 1E). A benign osseous lesion, such as non-ossifying fibroma, fibrous dysplasia, and eosinophilic granuloma, was suspected because of the less aggressive radiological features. Examination of frozen sections was performed during the operation and the pathologic diagnosis was chondroblastoma. Curettage and bone grafting were performed with subsequent cessation of pain. The final pathologic diagnosis was consistent with the frozen section diagnosis (Figure 1F). Postoperatively, the function of the leg was excellent and no recurrence was found at the 60-month follow-up.

Case 2

A 21-year-old woman was admitted because of a fixed palpable mass in the right humerus over 1 month. On physical examination, an approximately 2 cm, firm, fixed mass was noted in the media of the brachium. The overlying skin was normal and there was no sensory or motor deficit. There was no evidence of soft tissue mass or concurrent illness. A plain radiograph showed an osseous protuberance in the diaphysis of the right humerus (Figure 2A). CT scans demonstrated an ossifying bony protuberance arising from the cortex. There was no evidence of extension to the adjacent soft tissue (Figure 2B). A benign lesion was suspected. *En bloc* resection from the bottom of the protuberance, including some normal cortex, was performed. The final pathologic diagnosis was chondroblastoma, with tumor cells positive for S-100 (Figure 2C-E). After the operation, the function of the arm was excellent, and there was no recurrence at the 48-month follow-up.

These two atypical cases indicate that, except for the distinctive site of long bone diaphysis, which made diagnosis difficult, the patients' ages, symptoms, X-ray and CT images, treatments, and prognosis were in accordance with typical lesions in the epiphysis and metaphysis.

Discussion

Chondroblastoma is a benign, cartilage-producing neoplasm usually arising in the epiphyses of skeletally immature patients. The synonyms of this rare tumor include calcifying giant cell tumor and epiphyseal chondromatous giant cell tumor. However, tumor epidemiology, etiology, location, symptoms, imaging, pathology, genetics, treatment, and prognosis are still

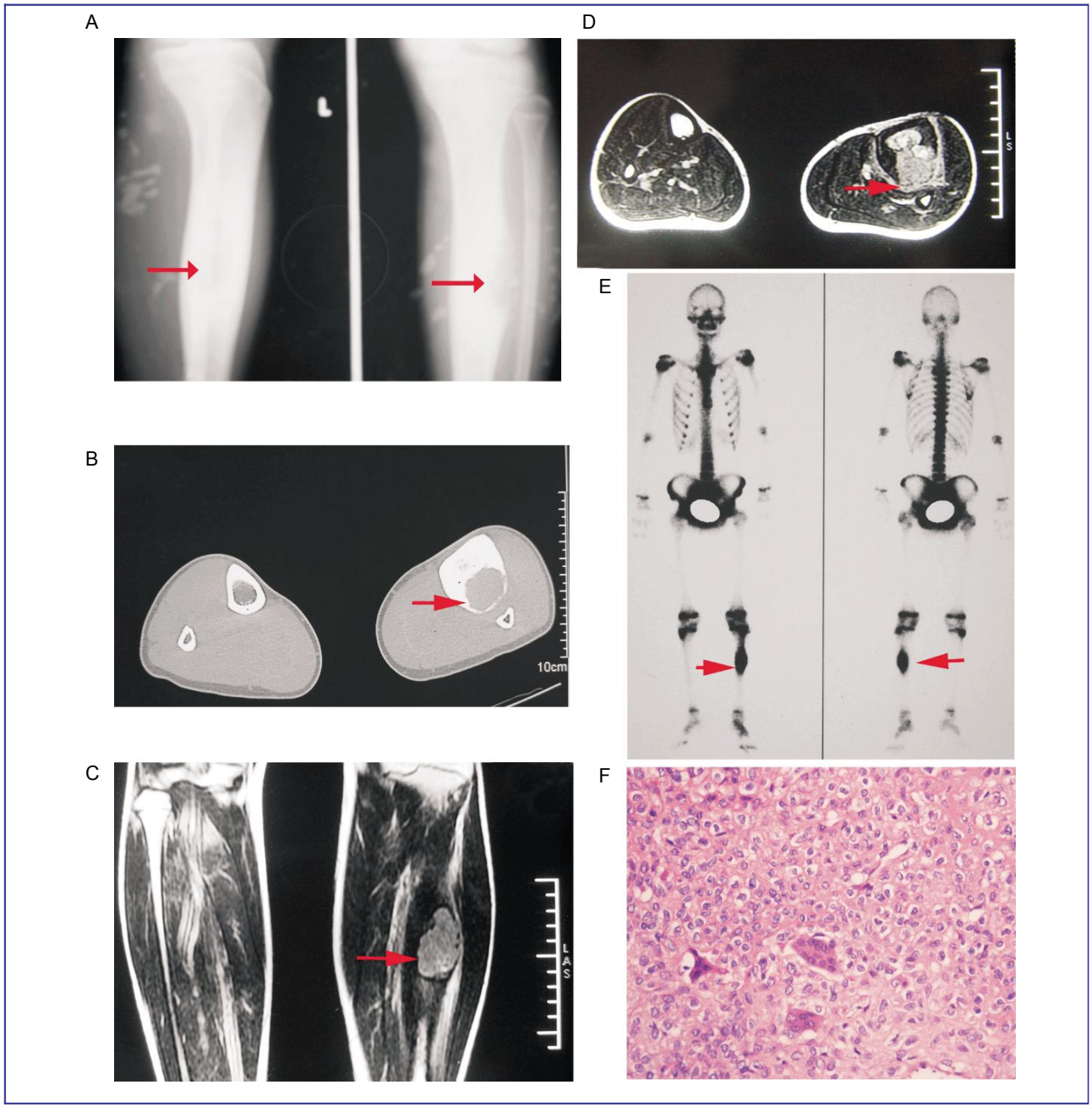

Figure 1. **Chondroblastoma located in the left tibial diaphysis.** A, X-ray radiograph shows a lytic lesion in the diaphysis of the left tibia. B, computed tomography (CT) scan shows a lytic cortical destruction without periosteal reaction. C, T1-weighted magnetic resonance image (MRI) shows a low signal nodular mass within the diaphysis. D, T2-weighted MRI shows a medium-to-high signal nodule in the tibia. E, emission computed tomography (ECT) shows clearly defined uptake of radiopharmaceuticals in the media part of the left leg. F, pathologic examination with HE staining shows so-called "chondroblast" cells with an oval to round nucleus and with well-defined eosinophilic cytoplasm (HE ×100).

controversial. Retrospective analyses are required to address these issues.

Epidemiology

Chondroblastoma accounts for less than 1% of all bone tumors. Most patients are between 10 and 25 years of age at diagnosis with a male predominance[3,4]. In our study, the mean age of the patients was 27 years, which is consistent with global epidemiologic data. However, our observations show a male:female ratio of 2:5, which, although the numbers are small, is different

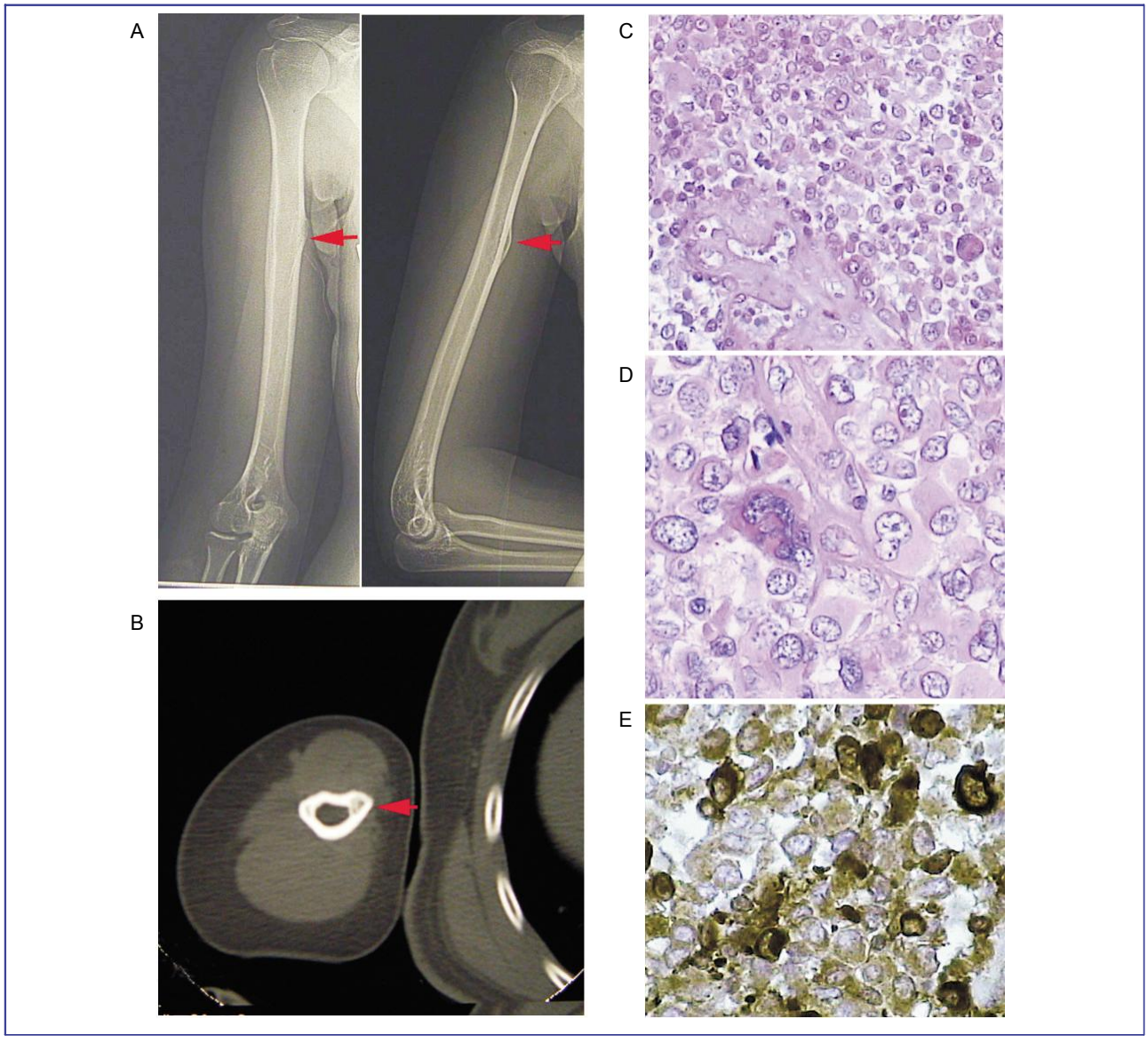

Figure 2. **Chondroblastoma located in the right humeral diaphysis.** A, X-ray radiograph shows an osseous protuberance in the diaphysis of the right humerus. B, CT scan shows an ossifying bony protuberance (arrow) arising from the cortex without periosteal reaction and soft tissue mass. C, pathologic examination shows lular calcification, so-called "chicken wire calcification" (HE ×200). D, plenty of well-differentiated chondroblasts are seen in the lesion (HE ×400). E, immunohistochemistry examination shows that most tumor cells express S-100 protein (Envision$^+$ ×400).

with other reported data.

Etiology

No risk factors and pathogenesis are known for chondroblastoma. Case reports describing chondroblastoma located in the metatarsal base and other non-epiphyseal locations imply that the cell of origin may not exclusively be derived from the physeal plate [5-7]. There is only one analysis referring to tumor differentiation. The extracellular matrix composition and gene expression pattern analysis of chondroblastoma shows that type II collagen, which is the main component of all cartilage matrix, is not expressed by chondroblastoma cells and is not deposited into the extracellular tumor matrix. Instead, osteoid and fibrous matrix is formed, with its typical biochemical composition. There is multifocal expression of aggrecan proteoglycan in most chondroblastomas, which explains

the bluish, pseudochondroid appearance of some matrix-rich areas [8]. This study suggests that chondroblastoma should be classified as a specific bone-forming rather than cartilage-forming neoplasm. However, there are no other data to support this view, and for this reason, further cases need to be investigated.

Location

More than 75% of chondroblastoma lesions involve the long bones, and the most common anatomic sites are the epiphyseal and epimetaphyseal regions of the distal and proximal femur, proximal tibia, and proximal humerus [4,9]. Equivalent sites within flat bones, such as the acetabulum and ilium, are also common. Other unusual but classic sites of involvement include the talus, calcaneus, and patella [10]. Within the craniofacial region, the temporal bone is most frequently affected [11]. This lesion almost invariably involves a single bone, but there are reports of patients who developed two chondroblastomas in two distinct anatomic sites (the tibia and calcaneus) over 7 years, with no clinical or histological features of malignant disease [12]. Generally, half of chondroblastomas were confined to the affected epiphysis or apophysis itself, but most of the remainder had traversed the growth plate to involve also the adjacent metaphysis. The bones around the knee and the proximal ends of the humerus and femur were preferential sites. A minority affected flat bones and short tubular bones of the hand and foot, with a peculiar affinity for the calcaneus and talus[1].

In our investigation, the sites of involvement were consistent with the reported data. However, 2 of our patients presented with lesions in the distinctive site of the long bone diaphysis. There are only 3 cases in the long bone diaphysis in the worldwide literature. Ippolito *et al*. [13] described 4 cases of cystic chondroblastoma, 3 located in the epiphysis and 1 in the diaphysis. Azorin *et al*. [14] reported a single case in the diaphysis of a long bone, where the patient was a 13-year-old girl who presented with pain over her right thigh. Radiographs showed a lytic lesion in the diaphysis of her right femur. A core biopsy and a subsequent surgical resection were performed and the pathologic diagnosis was chondroblastoma. Clapper *et al*. [2] reported the third case of chondroblastoma confined to the femoral diaphysis. Here, we document 2 cases. The findings from these 2 cases and the reported cases suggest that the age, physical examination, imaging characteristics, histopathology, treatment, and prognosis for chrondroblastoma are similar to typical lesions arising from the epiphysis and metaphysis of the long bone, while the atypical sites of long bone diaphysis may be a cause of diagnostic uncertainty.

Clinical features

Chondroblastomas in epiphyseal and epimetaphyseal regions typically present as pain near a joint without a history of trauma. Localized tenderness or pain is remarkable in most patients. Soft tissue swelling, mass, or joint effusion is present in about 20% of cases. Muscular atrophy or decreased joint mobility is less common[4,15]. Fractures are uncommon and proportionally more likely to occur in tumors of increasing size. Without surgical excision, the tumor may extend into the adjacent soft tissues or synovium and, although rare, may metastasize to distant organs. Metastasis, when it occurs, most frequently involves the lungs and tends to occur at the time of primary tumor recurrence. Widespread metastases and death have been reported[6,10,16].

In the 7 cases of chondroblastomas reported here, 5 were typical lesions and 2 localized in atypical sites. One patient presented with persistent pain, and the other had no pain but a firm mass in the arm.

Imaging characteristics

Chondroblastomas usually show round or oval, geographic, lucent lesions with sharply marginated borders on radiograph[3,9]. CT scans can depict matrix mineralization, soft tissue extension, and cortical erosion. The signal intensity characteristics of chondroblastoma on MRI reflect the prominent cellular stroma of the tumor, which has low signal intensity on T1-weighted images and high or variable signal intensity on T2-weighted images[6,17].

As to our two cases with lesions in the long bone diaphysis, the lesion in the tibial diaphysis showed typical imaging magnifications except the lesional sites. The roentgenogram and CT showed a sharply marginated, lobulated, lucent defect in the diaphysis. The tumor involved the medullary bone in an eccentric fashion, and the cortex was thinned. Periosteal reaction and soft tissue extension were not found. The lesion in the humerus showed protuberance in the cortex, and these features required histopathologic examination for precise diagnostic evaluation.

Pathologic characteristics

Grossly, chondroblastoma is lobulated and round and is made up of friable, soft, grayish pink tissue that may be gritty. Curetted fragments are tan with areas of white [18]. Histologically, the most characteristic finding of chondroblastomas is linear deposition of calcification surrounding individual chondroblasts, creating a chicken wire pattern[4,19]. Immunohistochemical staining shows reactivity of the neoplastic cells for S-100 protein and vimentin, although the expression of other antigens has

been reported, with cytokeratin being among the most commonly observed[20].

In one investigation of 7 patients with proven metastatic chondroblastomas, de Silva *et al.*[21] concluded that the histomorphologic features, local recurrence, and metastatic lesions of aggressive chondroblastomas differed in no way from conventional chondroblastomas. Because of the lack of cellular criteria for malignant lesions, it is impossible to predict the potential biological behavior of chondroblastoma, especially with respect to their ability to metastasize. Sometimes, the presence of tumor emboli in the primary lesion is highly suggestive of a subsequent development of metastatic disease[19,21,22].

Genetics

Sjögren *et al.*[23] found recurrent breakpoints at 2q35, 3q21-23, and 18q21 and detected rearrangements of chromosome band 8q21 exclusively in aggressive chondroblastomas. Ostrowski *et al.*[24] reported a patient with malignant transformation of a recurrent pelvic chondroblastoma with a *p53* mutation. There have also been other reports of abnormalities in chromosomes 5, 8, 11, and 17 in patients with chondroblastoma. These recurrent structural chromosomal abnormalities suggest that there may be preferential involvement of these chromosomes in chondroblastoma[25,26].

Differential diagnosis

Chondroblastoma sometimes must be differentiated with giant cell tumor, clear cell chondrosarcoma, chondromyxoid fibroma, eosinophilic granuloma, and chondroblastoma-like chondroma. Giant cell tumor of the bone may mimic chondroblastoma, as the epiphyseal location can be quite similar. However, the former are almost exclusively seen in patients who are skeletally mature, whereas chondroblastoma tends to arise in skeletally immature patients. The presence of a sclerotic rim helps to differentiate chondroblastoma from giant cell tumor of the bone, which generally lacks a sclerotic border[27]. Clear cell chondrosarcoma shows some characteristics similar to those of chondroblastoma, but the varied T2 signal intensity and the histopathologic characteristics help in the differentiation from chondroblastoma[28]. Chondromyxoid fibroma may mimic chondroblastoma radiographically, but it is devoid of calcification and has a characteristic myxoid, pseudolobular pattern of organization as well as more pleomorphic stellate cells[20]. Eosinophilic granuloma may appear in rare instances as a radiolucent epiphyseal lesion similar to chondroblastoma. However, a more heterogeneous collection of cells, including histiocytes, granulocytes, and eosinophils, might help to differentiate it[29]. Even the histological appearance of some chondroblastoma-like chondromas closely resembles that of chondroblastoma of the bone, but the extraosseous location, dense cellularity, and poorly formed cartilage of these tumors can clarify the diagnosis[30].

Intervention

No evidence suggests that chondroblastoma resolves spontaneously, so surgical treatment is indicated. The most common surgical procedure for this lesion is curettage, with or without autograft or allograft bone grafting. Other options, used less frequently, include substituting polymethylmethacrylate or fat implantation for bone grafting, treating the curetted lesion with chemical cauterization (phenol), liquid nitrogen cryotherapy, and marginal resection. These rare aggressive lesions may be treated with *en bloc* resection and reconstruction when intralesional curettage would leave a large bony defect[17,31-34]. Radiotherapy has been used to treat chondroblastoma but has essentially no current role. Chemotherapy has not been reported in the treatment.

Complications

Local recurrence is the most frequent complication. There is no significant difference in the recurrence rates, regardless of the age or sex of the patient, size of the lesion, amount of calcification or vascular invasion seen on histological examination, duration of follow-up, or method of treatment. Recurrence may be treated with repeat curettage, with or without bone grafting or cementation, and with marginal excision of any soft tissue component[15,32].

A small subset of chondroblastomas behaves in a much more aggressive or malignant fashion. Although some of these tumors retain their benign microscopic features, these lesions can become very large or metastasize to the lungs and soft tissues. Metastases can occur even without surgical manipulation or local recurrence of the primary tumor[35].

Another rare subset of chondroblastomas may become malignant. Malignant transformation usually occurs many years (usually >10 years) following treatment of the initial benign lesion. Pulmonary metastases may develop along with the malignant bony lesion[24,35]. In rare cases in which radiotherapy is used, development of a post-radiation sarcoma as late as 18 years after diagnosis has been reported[36].

Prognostic factors

The prognosis of chondroblastomas is good, with about 80% to 90% successfully treated by simple curettage with bone grafting. The recurrence rate is

between 14% and 18%, mainly occurring within 2 years after surgical operation and primarily happening in cases of temporal bone location[4,9,15]. Huvos *et al.*[18] documented a higher recurrence rate among chondroblastomas with a concomitant aneurysmal bone cyst component; however, others have not observed this association[4,15]. The rare development of pulmonary metastases is clinically non-progressive and can often be satisfactorily treated by surgical resection and/or simple observation[37]. Unfortunately, there are no reliable histological parameters capable of predicting more aggressive behavior. The existence of a true "malignant" variant of chondroblastomas is controversial, and many investigators propose that such tumors represent post-radiation sarcomas or simply misdiagnosis[4].

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