Giant Cell Tumour of Bone Revisited - A Study of 50 Cases in a Tertiary Care Centre in South India - Kerala

Vanesa John T.[1], Sumi Thomas[2], Joy Augustine[3]

[1]Department of Pathology, Jubilee Mission Medical College, Thrissur, Kerala, India. [2]Department of Pathology, Sree Narayana Institute of Medical Sciences, Ernakulam, Kerala, India. [3]Department of Pathology, Amala Institute of Medical Sciences, Thrissur, Kerala, India.

ABSTRACT

BACKGROUND

Giant cell tumour (GCT) is a benign, locally aggressive tumour with a relatively high risk of local recurrence. The purpose of this study was to define histopathological features of giant cell tumour of bone with special emphasis on recurrent tumours and denosumab induced changes.

METHODS

This was a descriptive study conducted at the Department of Pathology, Amala Institute of Medical Sciences, Thrissur. The details of the patient were collected from histopathology reports, request forms and case sheets. A total of 50 cases of giant cell tumour of bone were studied after getting approval from the institutional research and ethical committees.

RESULTS

There were 21 males and 29 females (1 : 1.4), whose ages ranged from 11 to 61 (mean 33) years. The tumours involved the tibia (30 %), femur (20 %), radius (20 %), fibula (6 %), talus (6 %), metatarsal (6 %), ulna (2 %), metacarpals (2 %) and phalanx (8 %). Radiographically, the lesions were usually lucent, with well-defined margins. In a few cases, the bone was expanded and focally destroyed with tumour extending into adjacent soft tissue. Microscopically, the neoplasms had oval or plump, spindle-shaped mononuclear cells uniformly interspersed with multinucleated giant cells and variable degrees of mitotic activity. Follow-up information revealed that ten cases (20 %) showed recurrences. Post denosumab changes were noted in six cases. Two cases each of primary and secondary malignant GCT are described in detail.

CONCLUSIONS

Giant cell tumour with recurrences should be dealt with caution. Proper radiological and treatment correlation along with extensive sampling of the lesion to be done.

KEY WORDS

Giant Cell Tumour, Recurrence, Denosumab, Bone

Corresponding Author:
Dr. Sumi Thomas,
Department of Pathology,
Sree Narayana Institute of Medical Sciences, Chalakka P. O., North Kuthiathode, Ernakulam, Kerala, India.
E-mail: sumikthomas90@gmail.com

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BACKGROUND

Giant cell tumour is a benign but locally aggressive neoplasm. It is composed of sheets of neoplastic ovoid mononuclear cells interspersed with uniformly distributed large, osteoclast like giant cells.[1] It occurs most frequently in the epiphysis of long bones of young adults.[2]

Giant cell tumour represents around 4 – 5 % of all primary bone tumours, and approximately 20 % of benign primary bone tumours.[3] The peak incidence is between the ages of 20 and 45. Although 10 – 15 % of cases occur in the second decade, giant cell tumour is seldom seen in skeletally immature individuals and very rarely in children below 10 years.[2,4,5]

Giant cell tumours usually affect the ends of long bones, especially the distal femur, proximal tibia, distal radius and proximal humerus. Around 5 % affect flat bones, especially those of the pelvis.[4,5,6] Patients typically present with pain, swelling and often limitation of joint movement

Numerous classification systems have been proposed over the years.

Jaffe et al.[7] classified GCT as benign, aggressive, and malignant based on the histological appearance of the stromal cells and mitoses.

The typical radiographic features of GCT include a purely osteolytic lesion with a geographic type of bone destruction,[8] a well-defined but non-sclerotic margin, eccentric location, extension to the subchondral bone, closed physes.[9]

Five to ten percent of GCT may undergo malignant transformation.[10,11]

Curettage alone has been the standard treatment for GCT. But it has been associated with a relatively high risk of local recurrence ranging up to 35 – 40 %.[12]

Various local adjuvants such as cryosurgery, bone cement and systemic treatments such as bisphosphonates, interferon alpha (IFN-a) and denosumab have been reported to reduce the risk of recurrence.[13,14]

Objective

The aim of this study was to define histopathological features of giant cell tumour of bone with special emphasis on recurrent tumours and denosumab induced changes.

METHODS

The details of the patients were collected from case sheets and histopathology requisition forms. Available histologic slides and radiographic images were reviewed. Treatment and follow-up information were obtained from the medical records, clinicians, and referring pathologists.

Statistical Analysis

For statistical analysis, the data were entered into Excel worksheets and coded accordingly. The data was analysed using IBM Statistical Package for Social Sciences (SPSS) version 23.0 statistical software. Qualitative data were presented using the frequency and related percentage.

RESULTS

The study group included 21 males and 29 females (1 : 1.4), whose ages ranged from 11 to 61 (average 33) years). The tumours involved the tibia (30 %), femur (20 %), radius (20 %), fibula (6 %), talus (6 %), metatarsal (6 %), ulna (2 %), metacarpals (2 %) and phalanx (8 %).

On conventional x-rays and computed tomography scans, the lesions were usually lucent, with well-defined margins. In a few cases, the bone was expanded and focally destroyed with tumour extending into adjacent soft tissue. The size of the tumours was known in 14 patients and they ranged from 1 to 7 cm in diameter.

Grossly, they were soft, friable, fleshy, red-brown masses. Cortical breach with soft tissue extension seen in 12 % cases.

Histologically, they showed a moderately vascularised stroma with oval or plump mononuclear cells uniformly interspersed with multinucleated giant cells. The mononuclear cells have poorly defined cytoplasm, spindle-shaped nuclei and show variable degrees of mitotic activity. They were sometimes arranged in storiform pattern. The multinucleated, osteoclast-like giant cells have eosinophilic cytoplasm and vesicular nuclei. Areas of haemorrhage, haemosiderin laden macrophages, and sheets of foamy histiocytes were seen in some cases. A secondary aneurysmal bone cyst was present in 8 % of cases.

In this study, 38 % were excision biopsies. Currettings accounted for another 38 %. Only trucut biopsies were available in rest 24 % cases.

No statistically significant correlation was found between morphologic patterns (fibrosis, reactive bone formation, cystic change, infarct-like necrosis, foamy histiocytes, and secondary aneurysmal bone cyst formation) and anatomic site or patient age in this series. Similarly, mitotic rate and the presence of necrosis also did not correlate with age and site. Ten cases (20 %) showed recurrences. Post denosumab changes noted in six (12 %) cases. Two cases, because of their unusual clinical features are described in detail.

Case 1

A 20-year-old girl presented with pain and swelling around right knee joint for 1 month. X-ray showed a typical well-defined radiolucent lesion in the epiphysis and extending into the metaphysis [Fig. 1]. A trucut biopsy was done from the tumour, which showed an area typical of giant cell tumour [Fig. 2] as well as an area which resembled a sarcoma with atypical spindle cells, osteoid matrix production and increased mitotic activity [Fig. 3]. X-ray picture and histopathology contradicted, which is highly suggestive of primary malignant GCT. It was reported as giant cell tumour with osteosarcoma component. Patient was given 2 doses of denosumab injection and the tumour was resected after 1 month. The final resected specimen

on X-ray showed features of malignancy, break in sclerotic margin, loss of circumscription, and linear extension into the adjacent normal marrow along the internal cortex [Fig. 4a, 4b]. Histopathology slides showed only the high aggressive osteosarcoma component [Fig. 5a, 5b] The giant cell tumour component disappeared by the denosumab injections. Patient underwent chemotherapy.

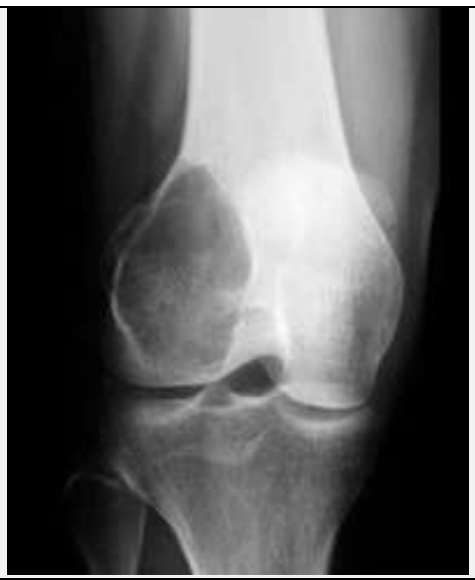

Figure 1. Initial X-Ray – Well Circumscribed Lytic Tumour Involving the Epiphysis and Metaphysis

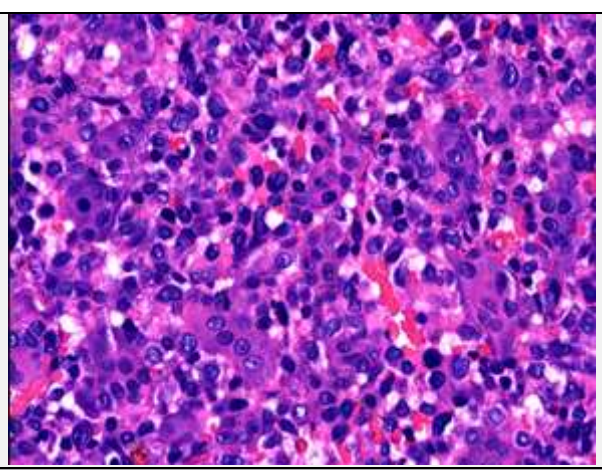

Figure 2. Typical Giant Cell Tumour in the Trucut Biopsy [40x]

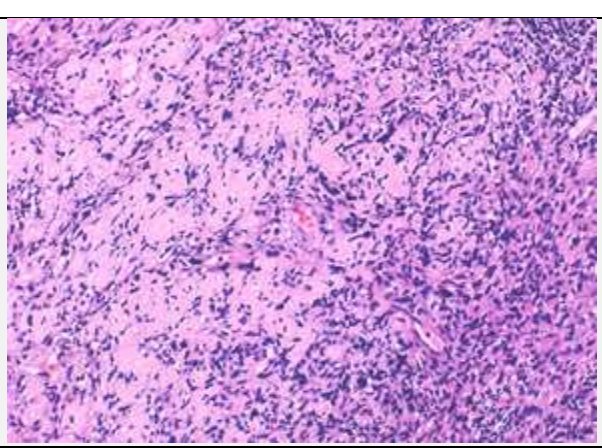

Figure 3. Malignant Cells Producing Osteoid [10x].

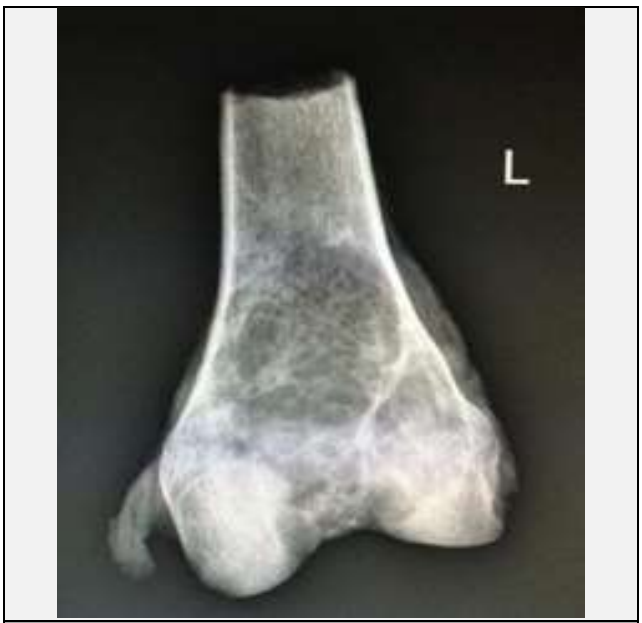

Figure 4a. Post- Op Xray (1Month Later) Showing the Same Tumour with Wide Zone of Transition and Osteoid Production

Figure 4b. Cut Section of Tumour Involving Epiphysis and Metaphysis and Extending into Diaphysis

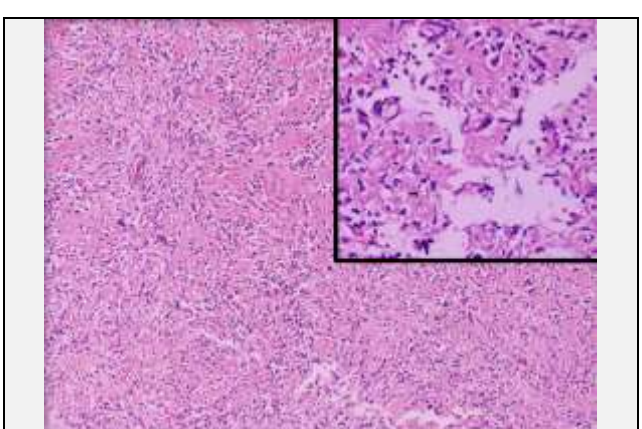

Figure 5a. Post Denosumab Therapy- Resected Tumour Showing a Spindle Cell Neoplasm with Plenty of Osteoid Matrix. Conspicuous Absence of Giant Cell Tumour Component [20x]. Figure 5b. Inset- Malignant Spindle Cell and Osteoid Matrix [400x].

Case 2

A 30-year-old male presented with proximal hip pain and difficulty in walking. Clinically it was suspected to be aneurysmal bone cyst (ABC) /GCT. Trucut biopsy showed only the ABC component. Six years later, he presented with a recurrent lytic lesion at the same site [Fig. 6]. On biopsy, it was reported as giant cell tumour with ABC areas. Third recurrence occurred 3 months later, excision specimen showed similar picture [Fig. 7]. One year later, a large destructive tumour developed at the same site. Patient was given denosumab injection for an optimal debulking. Debulked specimen showed an osteosarcoma with focal areas resembling giant cell tumour. After ten months, tumour recurred. Excision specimen showed an aggressive pleomorphic sarcoma with osteosarcoma component [Fig. 8-10]. The tumour recurred at the same site in a few months. Simultaneously he developed lung metastasis and was lost to follow up. Patient was given denosumab injection each time before surgery to have an optimal debulking.

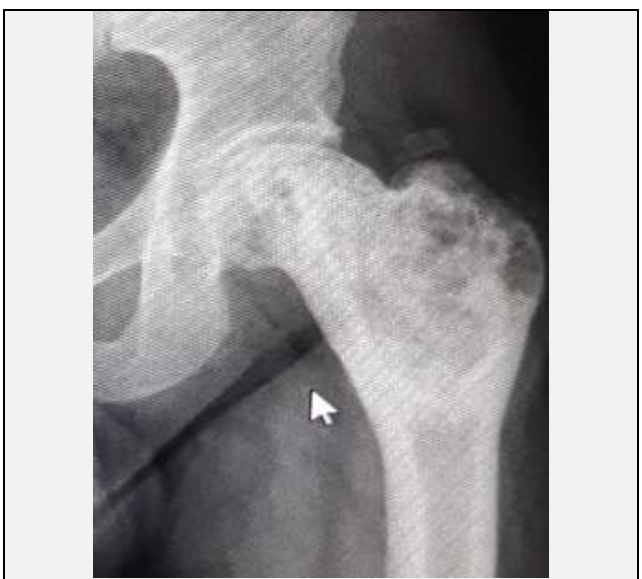

Figure 6. Recurrent Tumour. Biopsy Showed Typical Giant Cell Tumour

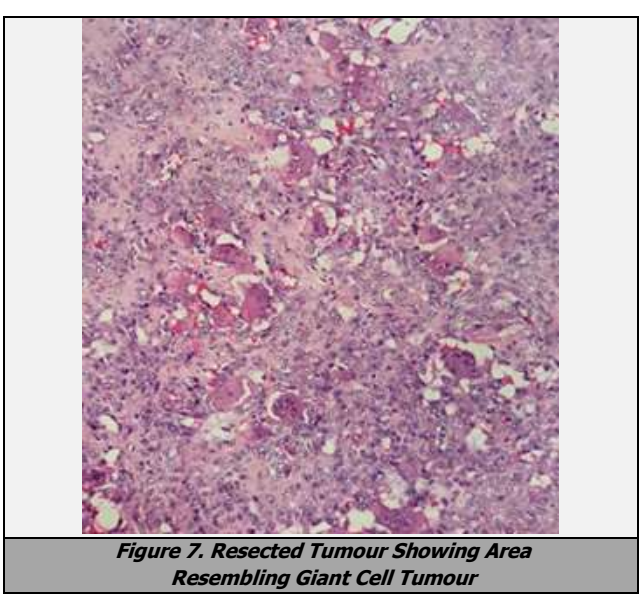

Figure 7. Resected Tumour Showing Area Resembling Giant Cell Tumour

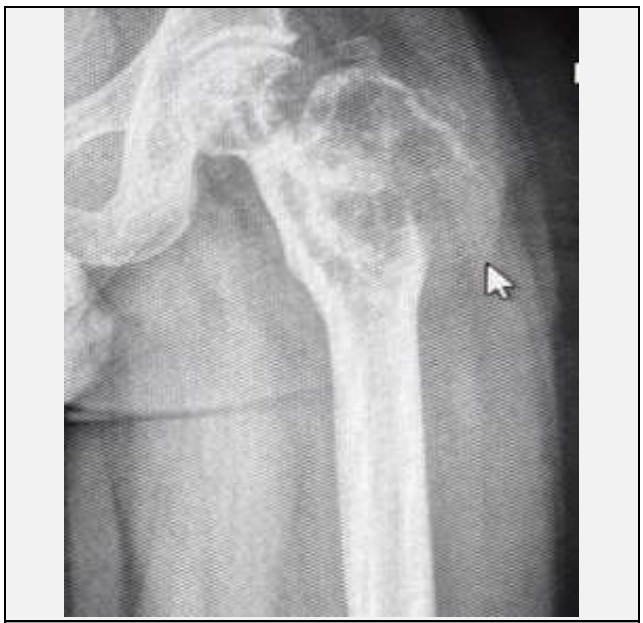

Figure 8. Recurrence with Soft Tissue Extension, Destruction of Femur Head

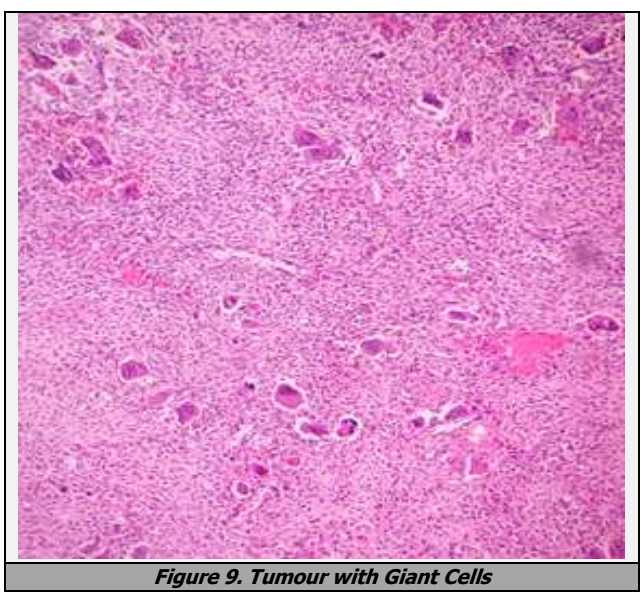

Figure 9. Tumour with Giant Cells

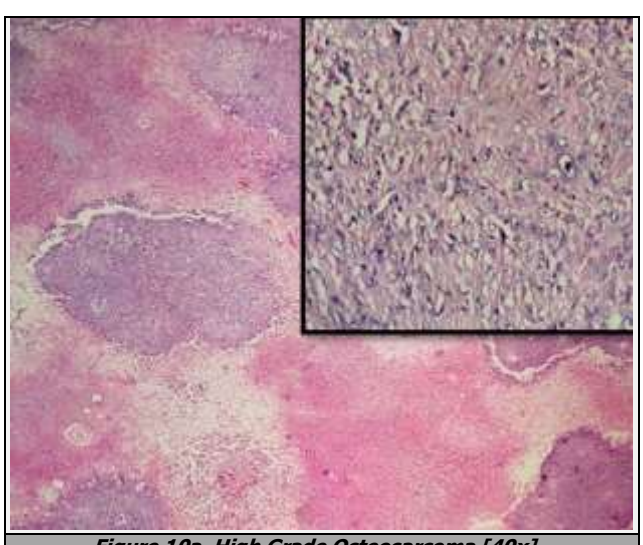

Figure 10a. High Grade Osteosarcoma [40x]. Figure 10b. Inset [400x]

DISCUSSION

GCT is a primary bone tumour, classically involving the epiphysis with a peak incidence in early to middle adulthood (20 - 40 years of age). Its incidence tapers off in the sixth decade and beyond.[15,16,17]

In this study, the age ranged from 11 - 61 years. As per recent World Health Organization (WHO) classification of bone tumours, the essential criteria is bone tumour with compatible imaging; an osteolytic circumscribed tumour involving the epiphysis, generally in a skeletally mature individual; numerous large osteoclasts together with a mononuclear cell neoplastic component without atypia. Clonal aberrations occur in a background of epigenetic histone modifications (especially G34W mutation of H3F3A gene) Detection of H3.3 p.Gly34 - mutated cells is the desired criteria.[18] The principal tumour cells are mononuclear cells and express RANKL, which stimulates the formation of osteoclasts via the RANK-RANKL mechanism.[19] The giant cells resemble osteoclasts morphologically, ultrastructurally and immunohistochemically.[20] The neoplastic mononuclear stromal cells express receptor activator of NF kappa beta ligands and various chemokines and cytokines.

The anatomic distribution of GCT in a study by Broehm et al.[21] is most cases involving the long bones (71 %), including radius (21 %), followed by the femur and tibia (18 % each), and then humerus (12 %). In this study the tumours involved the tibia (30 %), femur (20 %), radius (20 %), fibula (6 %), talus (6 %), metatarsal (6 %), ulna (2 %), metacarpals (2 %) and phalanx (8 %).

Many benign lesions with giant cells have been confused with giant cell tumour in the past. Fibrous cortical defect, non-ossifying fibroma, chondromyxoid fibroma, chondroblastoma, brown tumour of hyperparathyroidism, giant cell reparative granuloma and aneurysmal bone cyst are to name a few. The main microscopic difference between true giant cell tumour and the mimics reside in the spatial relationship between the giant and stromal cells. Giant cells tend to be distributed regularly and uniformly in giant cell tumour. In other lesions, foci containing numerous, clumped giant cells alternate with large areas lacking it. An alternate diagnosis should be sought if the patient is a child; lesion is located in the metaphysis or diaphysis of a long bone, multiple lesions, and unusual sites as vertebrae, jaw or bones of hands and feet. In differentiating GCT from brown tumour of hyperparathyroidism, laboratory measurement of calcium, phosphorus, and parathyroid hormone levels is critical.[22,23] Furthermore, brown tumour may be multifocal on imaging, a feature rarely seen in GCT. Giant cell reparative granuloma almost exclusively arises in the craniofacial bones, a site uncommonly affected by GCT.[24,25]

Aneurysmal bone cyst-like areas are frequently detected in GCT. Especially solid areas in aneurysmal bone cyst may be misdiagnosed as GCT. In ABC, giant cells are smaller and giant cells are unevenly distributed. In solid type of ABC, stroma is more fibrotic than that of GCT.[26] Secondary ABC formation occurs in up to 14 % of cases of GCT of bone.[27]

Extensive surrounding soft-tissue and marrow oedema at magnetic resonance (MR) imaging may help differentiate chondroblastoma from GCT. Chondroblastoma may also demonstrate a sclerotic margin and central calcification with a "rings-and-arcs" pattern that represents chondroid matrix.[9]

The mechanism by which malignant transformation occurs is unknown. TP53 and HRAS mutations have been identified in malignant giant cell tumour not associated with prior irradiation.[18]

True malignant GCT, which are defined as high-grade sarcomas arising in GCT (primary) or at the site of a previously documented GCT (secondary) Areas constituted by undifferentiated pleomorphic cells and atypical mitosis suggest malignancy in GCT.[18]

Primary malignancy in a giant cell tumour is uncommon and is typically represented by a nodule of highly pleomorphic, neoplastic mononuclear cells in an otherwise conventional giant cell tumour. Bertoni and colleagues reported 5 cases of primary malignancy among 924 patients with GCTB (0.5 %); four had osteosarcomas, and 1 had malignant fibrous histiocytoma.[28] At the Mayo Clinic, of 671 patients with GCTB, only 5 (0.7 %) had primary malignancies.[29] The Cancer Hospital, Kolkata, reported the lowest primary malignancy incidence with no cases among the 445 patients with GCTB, despite a follow-up of up to 21 years.[30] Malignant transformation in a giant cell tumour is more common than the primary subtype and occurs after treatment of a conventional giant cell tumour with radiotherapy. The malignant component of a giant cell tumour does not have specific histological features and may be either an undifferentiated sarcoma or an osteosarcoma. The cumulative incidence of secondary malignancy was 2.4 %. In the Mayo Clinic series of 671 patients, 34 of the 39 malignant cases were secondary (5.1 %)[29]In the series from the Rizzoli Institute, 12 (71 %) of the 17 malignancies among the 924 patients were secondary; equal numbers were treated with radiation and surgery.[28] There were 5 cases each of secondary malignancy at the Cancer Hospital, Kolkata (445 patients with GCTB) all cases were treated with radiation.[30] Secondary malignancy cases with short latent periods may be a result of radiation-induced enhancement of the propensity for GCTB to malignant transformation. In secondary malignancy occurring after curettage and bone grafting, it has been postulated that reparative proliferation occurring at the border of dead bone could serve as the source of malignant transformation.[31,32]

Errors in sampling larger tumours owing to biopsies missing coexistent sarcoma have been well documented.[28,31] Primary malignancy may be detected only retrospectively when specimens are reevaluated.[31,33] Therefore, multiple biopsy specimens should be analyzed before excluding primary malignancy[31] to avoid misdiagnoses of secondary malignancy later on.

The treatment of giant cell tumour is usually surgical for tumours in most sites and consists of curettage with or without bone grafting.[34] The use of radiation therapy is reserved for cases in which surgical removal is impossible.

This is in view of the high number of reported cases of malignant transformation following radiotherapy.

Clinically, GCT presents as a benign but often aggressive lesion with a tendency toward local recurrence. Depending on the type of treatment and the local presentation of the tumour, recurrence rates range from 0 % to 65 %.[35]

In this study follow-up information revealed that ten cases (20 %) showed recurrences. Although surgery is the standard primary treatment for GCT, denosumab, a monoclonal antibody drug that inhibits RANKL, has shown considerable activity regarding disease control.[12,13,14]

Neoplastic mononuclear stromal cells expressing NF kappa beta ligands are associated with monocyte recruitment and reactive multinucleated giant cells (osteoclastogenesis).[36] Denosumab, a human monoclonal antibody that specifically inhibits RANKL reducing tumour-associated bone lysis, has shown considerable activity regarding disease control in selected cases of GCT.[12,13,14] Radiologically, lack of progression, calcification and better delineation of the target lesion was demonstrated. At the microscopic level, the changes include reduction in the number of giant cells as well as replacement by fibrous and osseous tissue. Giant cell tumours treated with denosumab for several months show substantial new bone formation, associated with bland neoplastic mutant spindle cells and a striking depletion of osteoclast-like giant cells. However, variable amounts of conventional giant cell tumour may persist.[36]

These features may mimic de novo osteosarcoma or secondary malignant giant cell tumour.

In a study by Alberghini et al. RANKL inhibitors (denosumab) was only used in 6 patients and 2 of these patients showed recurrence in spite of therapy.[32]

Branstetter et al. who found that denosumab-treated GCT of bone show, under the microscope, a reduction of giant cells and mononuclear stromal cells with replacement by fibrous tissue and woven bone.[37] This study also revealed the same.

The natural history of giant cell tumour is that of a low grade malignancy. A small number metastasize following surgical manipulation. No relationship has been found between metastasis and invasion of blood vessels. Metastases are more likely in younger age and following local recurrences.

One patient with secondary malignant GCT developed lung metastasis within 7 years. Pulmonary metastases are thought to represent pulmonary implants that result from embolization of intravascular growths of giant cell tumour.[18] The rate of pulmonary metastases in a study by Klenke et al. was 4 %, similar to previous reports ranging from 0 % to 4 %.[38] So all patients are staged with imaging of the chest.

CONCLUSIONS

Conventional giant cell tumour is quite common in routine practise. But those giant cell tumours which show a history of recurrence more than two times or recurrences occurring in a short interval of time should be dealt with caution.

Extensive sampling of high-grade areas, deeper and thinner sections need to be examined before reporting. Concurrently it is particularly important to check the x-rays for invasion anywhere along the circumference of the tumour.

Treatment effects of denosumab is also to be examined and correlated. So, it is recommended to have comprehensive histologic sampling to establish an accurate diagnosis; careful follow-up, particularly for patients treated with radiation; and timely treatment of local recurrence.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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