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Role of ultrasound in giant cell tumors of tubular bones

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Abstract
Giant cell tumors (GCT) of bone are generally benign; but can be locally aggressive. Campanacci *et al* proposed grading system based on radiographic appearance of tumor. Grade 1 (latent): Well defined margin and intact cortex; Grade 2 (active): Relatively well-defined margin but no radio-opaque rim. Cortex is thinned, moderate expansion of bone; Grade 3: Lesions are aggressive, have indistinct border, and have cortical destruction. Ultrasound with Doppler is useful to evaluate aggressiveness of the tumor by calculating the resistive index (RI) of the lesion. There were 28 cases of extremity GCT. Maximum cases were grade III (n=16), followed by grade II (n=11). Because of cortical thinning or destruction USG was useful in assessing size, site, echo-texture, soft tissue component and vascularity. Most of the tumors are mixed echoic predominantly isochoric solid and cystic component, 5 of 28 cases had ABC component. In our observation 10 out of 11 cases of grade II tumors showed low RI. The 4 cases of grade III tumors having low RI (< 0.64), one of these have thick cortex which may not depict correct RI value. Two of the 14 cases with high RI value had low grades (I or II) and 12 (86% cases) were in grade III. The mean RI of grade III tumors was higher than that of grade II GCT. Thus, USG and Doppler can be used for detecting aggressiveness of GCT.

Keywords: GCT, RI, tumour aggressiveness

Introduction
Giant cell tumors (GCT) of bone are generally benign; but can be locally aggressive. They account for 5% of all primary bone tumors and 20% of all benign bone tumors [1]. Treatment depends on aggressiveness of the tumor. Campanacci *et al* proposed grading system of GCT based on radiographic appearance of tumor [2]. Grade 1 (latent): Well defined margin and intact cortex [Figure-1]; Grade 2 (active): Relatively well-defined margin but no radio-opaque rim. Cortex is thinned, moderate expansion of bone [Figures-2, 3]; Grade 3: Lesions are aggressive, have indistinct border, and cortical destruction [Figures-4, 5].
Ennecking *et al* has also suggested similar classification. Three stages are benign similar to Campanacci's classification. Though grade 3 is benign, it may be having cortical break, rapidly growing (histologically benign), soft tissue component and metastases [Figure-6]. According to Ennecking, grade 4 is malignant with sarcomatous lesion contiguous with benign GCT. Grading classification is important from treatment point of view. Grade 1 and 2 are treated with intra -lesional curettage. Grade 3 requires block resection and reconstruction if necessary [3]. No correlation exists between the grade and chance of recurrence and metastases. The grading of GCT is based on radiographic appearance and was not described in other modalities.
Imaging by conventional X-ray, CT, MRI and ultrasound have their specific diagnostic features. There are some reports of the possibility of using the ultrasound with Doppler to evaluate aggressiveness of the tumor by calculating the resistive index (RI) of the lesion. There is very scare literature about role of ultrasound in bone tumours. There are only a few case-reports of ultrasonic evaluation of GCT. Hence, we are reporting our experience with 28 histopathologically proven cases of GCT who underwent Doppler evaluation and the RI was calculated. Our aim was to find out usefulness of ultrasound in GCT and review the literature about the role of various modalities with special focus on ultrasound.

Material and Methods
This study was conducted in the department of Radiology and Imageology at Nizam's Institute of Medical Sciences, Hyderabad with the approval of ethics committee. It is a prospective study of 17 months from April 2020 to September 2021 that included 28 cases. All these cases of GCT had radiographs, ultrasonography

(USG), MRI. Histopathological confirmation was done in all cases. Three patients had CT scan in addition. Informed consent was obtained in all cases. USG performed in all cases on Esaote Mylab machine, using linear probe of 5-12 MHz or curvilinear 3-5 MHz depending on size and location of lesion. Cross sectional imaging was done with either CT/MRI. CT was done 16 slice Philips or 128 slice SIEMENS. MRI was obtained on 1.5 T/3T MRI GE, SIEMEN machine using protocol T1W, T2W, STIR with or without Gadolinium contrast.
Tumors were analysed in terms of location, size, number, matrix, and characterisation, extent of soft tissue component, enhancement, joint involvement, and adjacent neurovascular bundle involvement. RI was calculated in the lesion with vascularity by analysing pulse wave. A cut-off value of 0.65 was taken for labelling the RI as low or high. Doppler wave form was obtained from vascular area of tissue. All cases had undergone biopsy as gold standard for confirmation of bone lesion.

Results

There were 28 cases of extremity GCT with F: M ratio of 15:13. Age of the included patients ranged from 16 to 53 years with maximum in the age group of 20 to 40 years (n=18); 7 were below 20 years and 3 were above 40years of age. All the patients had plain radiograph, MRI and USG. All had histopathological confirmation. The radiographs and MRI were analysed for the site, size, border, expansion, zone of transition, cortical destruction, matrix, periosteal reaction, soft tissue component, pathological fracture and tumor grading. Tumors were graded on basis of Campanacci's grading system. Wherever there was doubt in radiograph, the MRI /CT were evaluated for confirmation. One case had pulmonary metastases [Figure-6].
Most common bone involved was tibia upper end followed by lower end of femur. There were 3 cases involving phalanx and metacarpals [Figures-3, 4] [Table-1]. Maximum cases were grade III (n=16), followed by grade II (n=11) and one case was grade I. Cortical thinning and disruption was observed in all except one. There were 3 cases of pathological fracture [Figures 4, 5, 7] and 4 cases showed periosteal reaction [Figure-7].
USG was done and the echogenicity, vascularity and cortical destruction, soft tissue component were observed. Colour Doppler was carried out with estimation of RI of these lesions. One of these had thick sclerosed cortex and rest had thinned [Figures-5] or destroyed cortex [Figures 6, 7]. 14 cases had soft tissue component [Figures 8], pathological fracture and periosteal reactions were also well appreciated on USG. Most of the tumors are Heteroechoic predominantly isoechoic with solid and cystic components, few are hypoechoic [Figure 1, 2]. Most of these tumors are having solid cystic component. There were 5 cases associated with aneurysmal bone cystic component [Figures 9, 10].
Vascularity was observed in all cases and most of the tumors showed increased vascularity 26 out of 28 [Figures 9, 10]. RI of grade II and grade III tumors were evaluated and analysed (Tables 2 and 3). 10 out of 11 cases were grade II tumor on radiograph and had low RI [Figure 2]. Four cases of grade III had low RI [Figure 7] and rest 12 had high RI. The 2 low grade tumors having high RI were one grade I and one grade II tumor [Figure 1]. Thus 12 of grade III and 2 of low grade, that is 14 cases had high RI. Among the 11 grade II tumors, RI value ranged from 0.18 to 1.3 with a mean value of 0.60 ±0.25, while the 16 grade III tumors showed RI value ranging from 0.4 to 0.83 with a mean value of 0.70 ± 0.126. RI of grade II tumors was significantly lower than that of grade III tumors (p value - 0.04).

Table 1: Showing site of lesion detected

Site	Number	% Confirmation
Femur	6	21.4%
Tibia	12	43%
Fibula	0	0
Humerus	2	7%
Radius	5	18%
Ulna	0	0
Small tubular bone	3	10%

Most common bone involved was tibia upper end followed by lower end of femur. There were 3 cases involving phalanx and metacarpals.

Table 2: Showing Cases with Grade II

No	Age/Sex	Matrix	Grade of Tumor	RI	Mean RI±SD
1	23F	Solid isoechoic	II	0.6	0.605±0.25
2	38M	Cystic with thick wall	II	0.6	
3	40F	Solid isoechoic	II	0.58	
4	16F	Heterogenous solid, cystic	II	0.56	
5	16F	Solid isoechoic, cystic	II	1.3	
6	24F	Hypoechoic	II	0.59	
7	23M	Hypoechoic	II	0.57	
8	32F	Heterogenous solid, cystic	II	0.61	
9	39M	Hypoechoic	II	0.44	
10	30F	Hypoechoic	II	0.62	
11	43M	Hypoechoic	II	0.18	

Table 3: Showing Cases with Grade III

No	Age/sex	Matrix			Mean RI±SD
1	40M	Hypoechoic	III	0.86	0.705±0.126
2	17F	Solid hypoechoic, cystic	III	0.89	
3	53F	Heterogenous isoechoic	III	0.77	
4	27M	Solid isoechoic, cystic (ABC)	III	0.67	
5	25M	Solid isoechoic, cystic (ABC)	III	0.83	
6	23M	Solid isoechoic, cystic (ABC)	III	0.74	
7	35M	Solid isoechoic, cystic	III	0.75	
8	31M	Solid isoechoic, cystic (ABC)	III	0.77	
9	20M	Solid isoechoic, cystic	III	0.75	
10	30F	Hypoechoic	III	0.78	
11	15M	Solid isoechoic	III	0.67	
12	18F	Hypoechoic	III	0.65	
13	24F	Hypoechoic solid, cystic	III	0.6	
14	32F	Hypoechoic	III	0.62	
15	48F	Hypoechoic	III	0.53	
16	40F	Hypoechoic	III	0.4	

Note: RI of grade II GCT is significantly lower than RI of grade III tumors (P=0.0417)

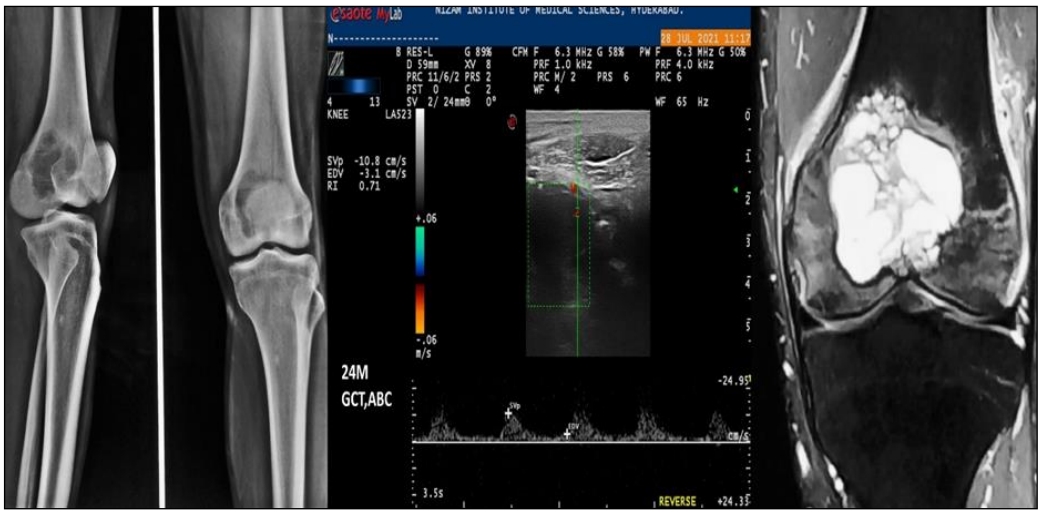

Fig 1: Well defined lytic lesion with sclerotic rim in epimetaphysis of lower end of femur (Grade I). Lesion is having ABC component, clearly depicted as fluid- fluid level in STIR MRI. On colour doppler USG lesion is showing high RI

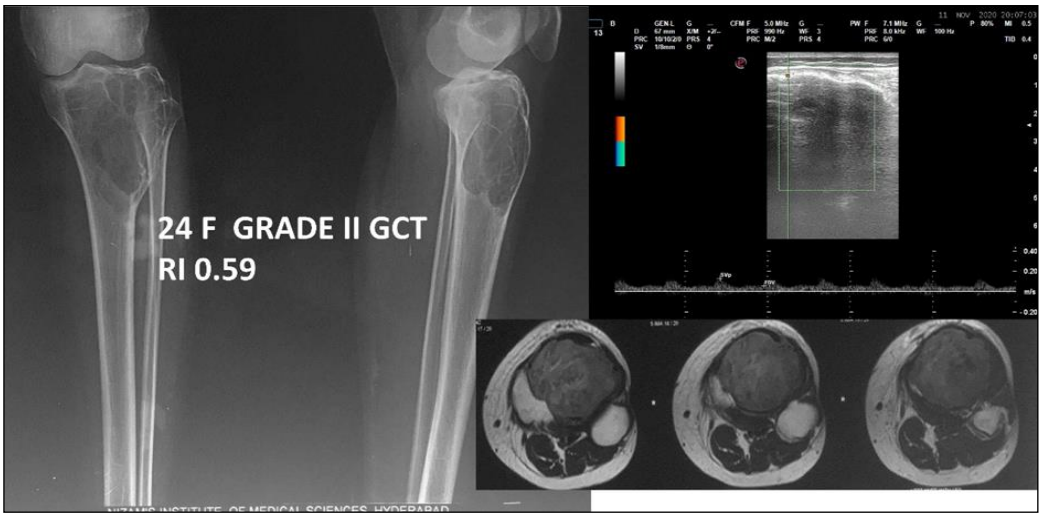

Fig 2: Well defined eccentric lytic lesion in epi-metaphysis of proximal tibia. There is no sclerotic rim and lesion is mildly expansile with multiple trabeculae within. The cortex is intact and is thinned out. The lesion is hypoechoic with intact cortex and on Colour doppler the lesion shows low RI

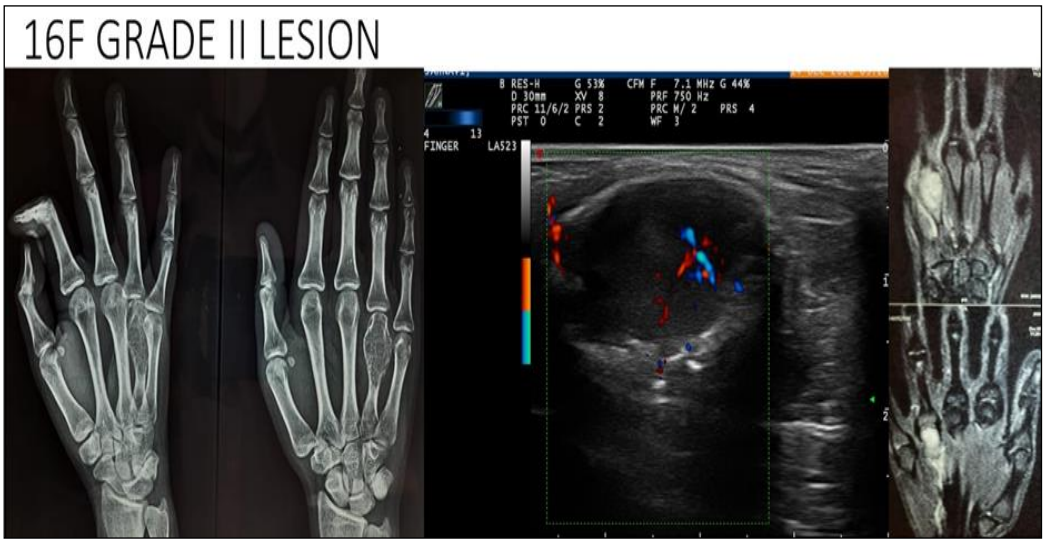

Fig 3: Mildly expansile soap bubble appearing lesion in 4th metacarpal as evidenced on Radiograph (grade II). Internal vascularity and intact cortex are observed in USG and MRI

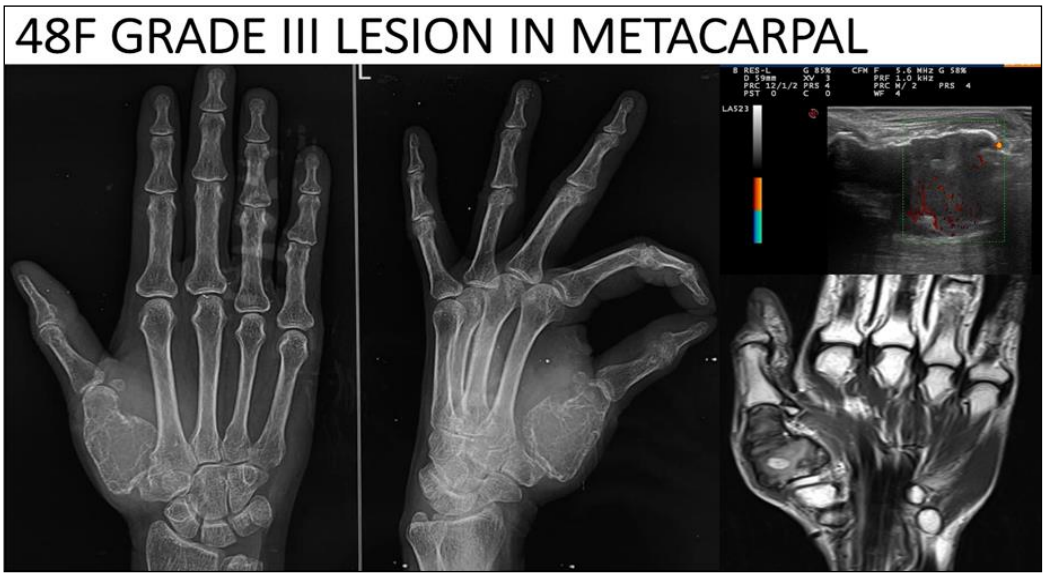

Fig 4: Grade III lesion in 1st metacarpal. Gross expansion of bone and soap bubble appearance and cortical discontinuity are well depicted on radiograph

Fig 5: Radiograph and Coronal reconstruction of CT scan reveals expansile lytic lesion with pathological fracture. The cortex and matrix are well seen on CT. On USG there is cystic component in solid hypoechoic lesion and is highly vascular

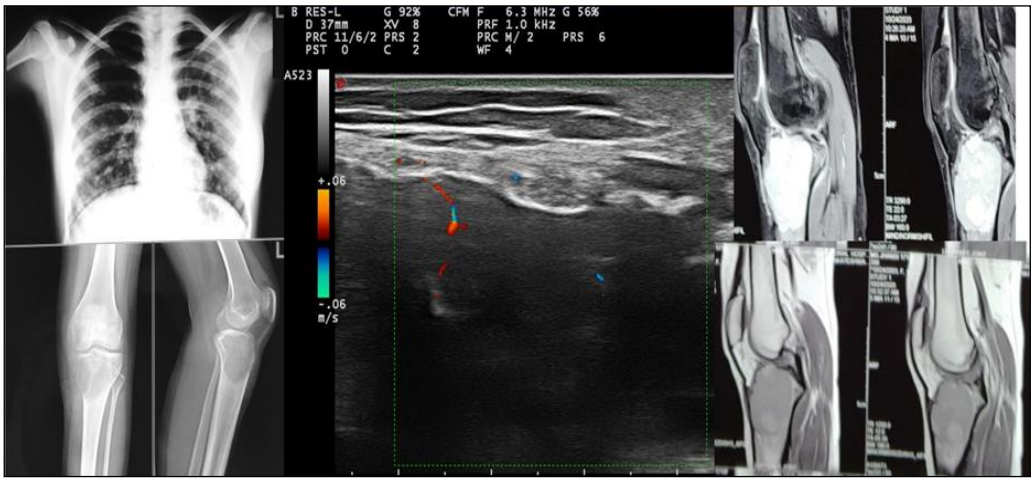

Fig 6: 17/ F Grade III lesion in tibia with pulmonary metastases as shown in chest Radiograph. Lesion is isointense on T1W and hyper on T2W images and no extension to joint

Fig 7: 24/F Grade III GCT on CT coronal reconstruction images the lesion appears grossly expansile few thick trabeculae and periosteal reaction with pathological fracture. Hypoechoic matrix and cortical disruption, periosteal reaction is well visualised on USG. RI is 0.6

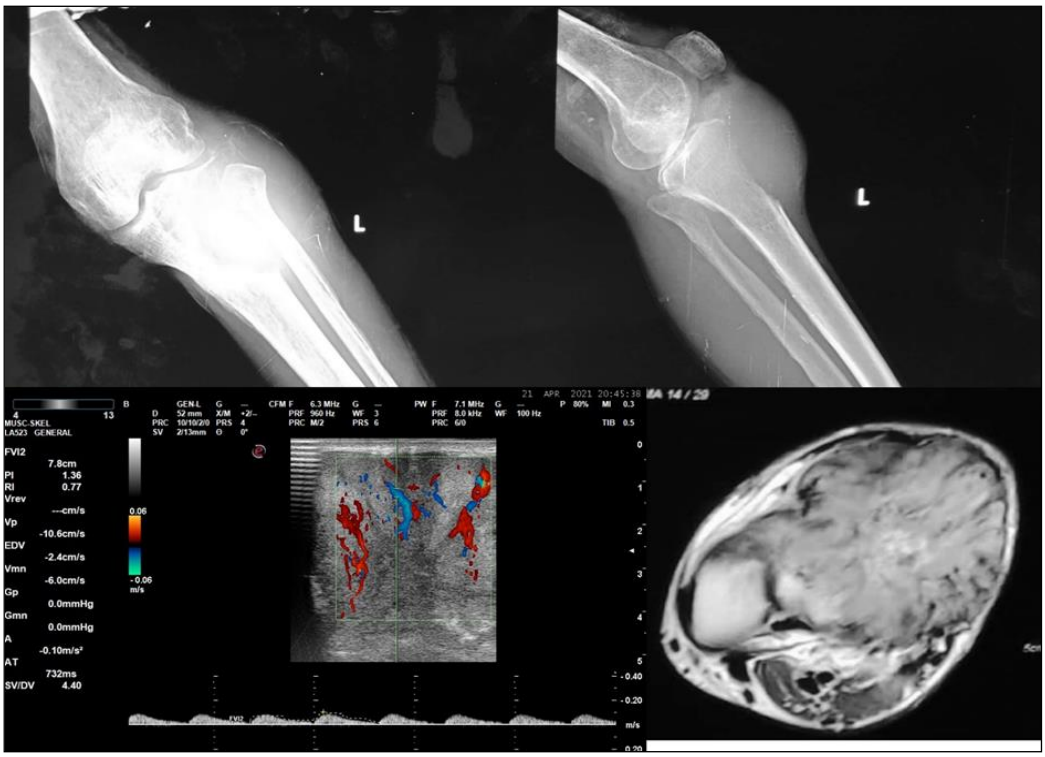

Fig 8: 31/M Grade III tumor having large soft tissue component, Lesion is highly vascular with high RI on USG

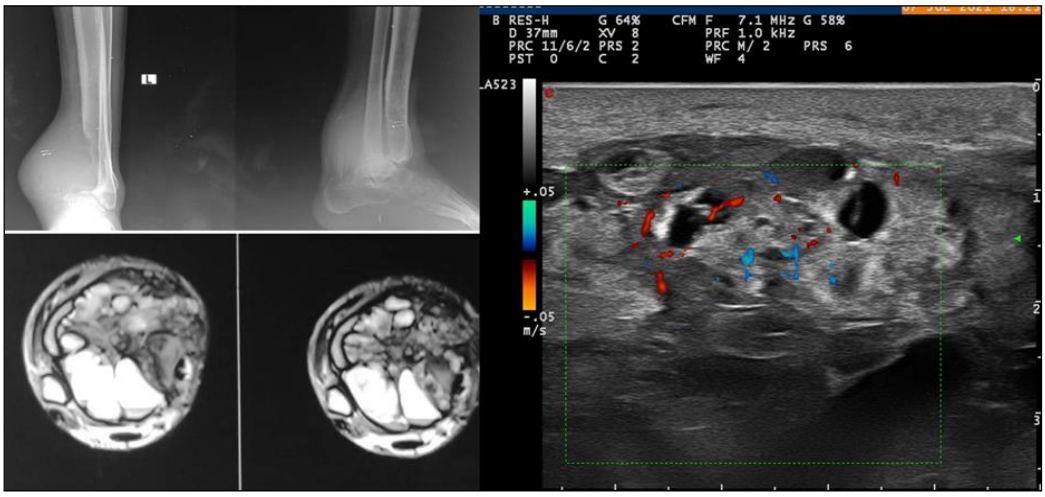

Fig 9: 31M Grossly expansile eccentric lytic lesion on radiograph. The wall is imperceptible laterally with no internal trabeculation (Grade III). Lesion is heteroechoic with increased vascularity on USG, MRI shows fluid-fluid level s/o secondary ABC

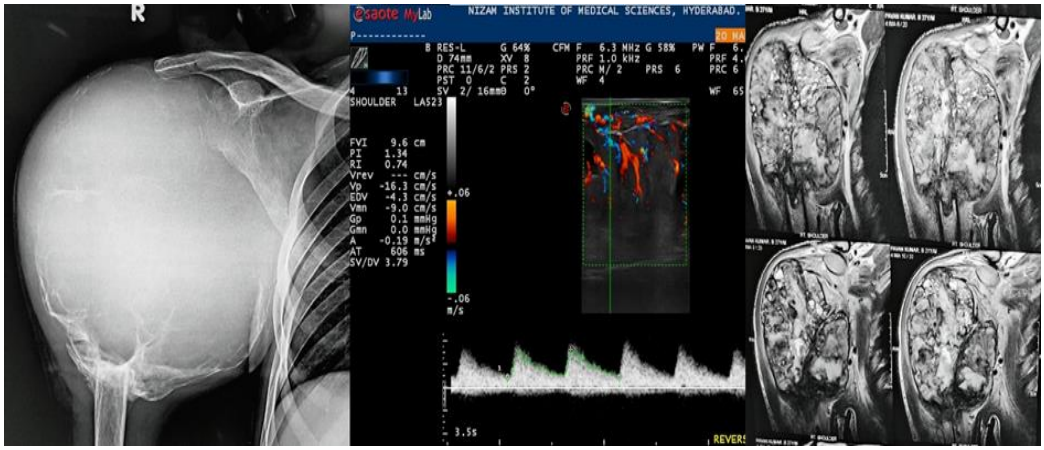

Fig 10: 23/M Grossly expansile lytic lesion with imperceptible wall and no internal trabeculae. Increased vascularity seen on USG and Fluid- Fluid levels are well appreciated on T2W MRI

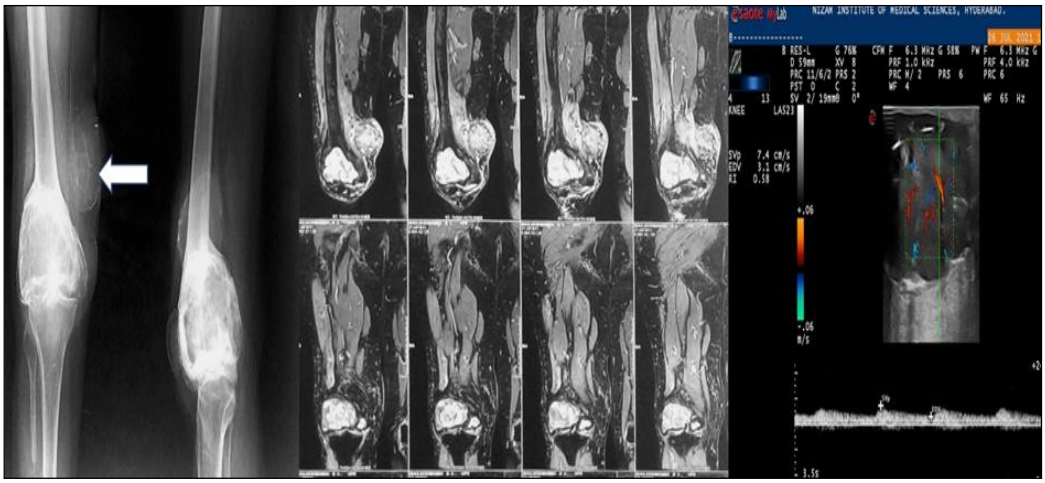

Fig 11: 40/F Recurrence of operated GCT of lower end of femur with adjacent soft tissue deposit. Note: the deposit is having soap bubble appearance as indicated by arrow in the Radiograph

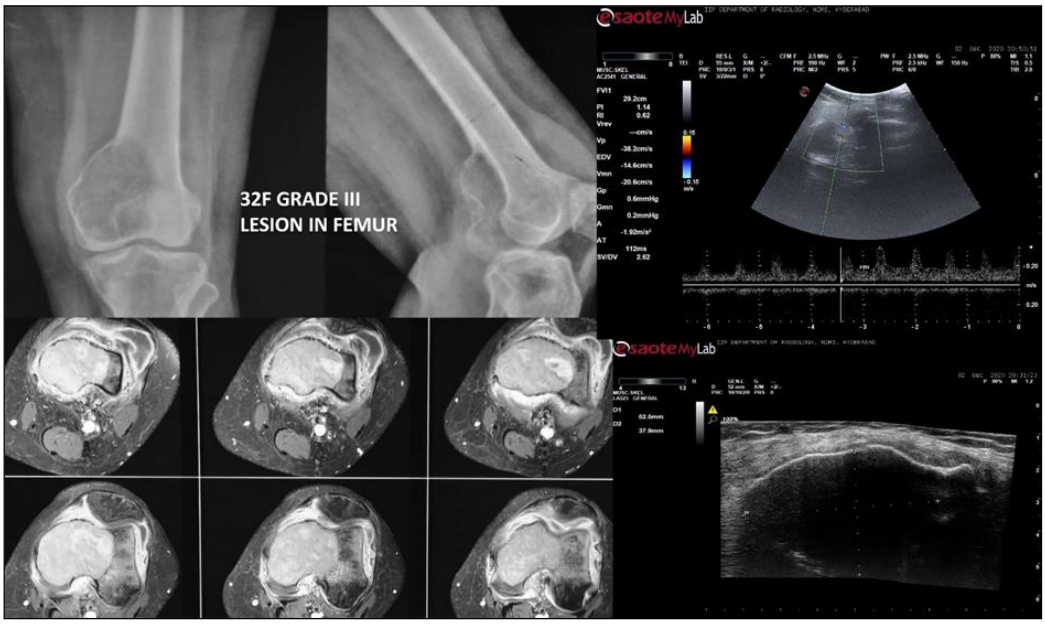

Fig 12: 32/F Contrast enhanced MRI in axial plane shows heterogenous enhancement. Lesion is heteroechoic with low RI on colour doppler USG

Discussion

Giant cell tumors (GCT) of bone are generally benign; but have malignant potential. Peak prevalence is in 3rd decade with 80% occurring in 20 to 50 years of age. They are not seen in children and adults beyond 65 years of age. They occur in females more males. Most of the tumors develop in long bones, 75% occurring around knee (1). We had similar observation. There were 28 cases of extremity GCT with F: M ratio of 15:13. Most common bones involved were tibia upper end followed by lower end of femur. There were 3 cases involving phalanx and metacarpals [Figures 3,4]. Our cases were between 16 to 53 years with maximum (n=18) in age group of 20-40years. 7 cases were below 20 years and 3 were beyond 40 years of age.

On conventional radiograph the lesions appear well defined eccentric geographic lytic with subarticular extension. Lesions are epi-metaphyseal in location with 80-90% extending within 1 centimetres of the articular margin. The border is non-sclerotic. GCT may show expansile remodelling in 47-60% and have multiloculated appearance due to pseudo- trabeculations in 33 to 57% due to uneven destruction in all the three dimensions. Prominent trabeculae may create '*soap bubble*' appearance (4) [Figures 3,4].

Campanacci *et al* proposed grading system of GCT based on radiographic appearance of tumor (2). There was a single case of grade I and rest were grade II or III in our series. Maximum cases were grade III (n=16), followed by grade II (n=11) and one case was grade I. Hence because of cortical thinning or destruction USG was useful in assessing size, site echo-texture, soft tissue component and vascularity. Most of the tumors are mixed echoic predominantly isochoric solid and cystic component, 5 of 28 cases are having ABC component [Figures 9,10]. According to Murphey *et al* fluid-fluid level was seen in 14% cases of GCT due to secondary ABC component and may be due to pathological fractures in 11-37% [4]. Cortical thinning and disruption were observed in all except one. There were 3 cases of pathological fracture [Figures 4,5,7] and 4 cases showed periosteal reaction [Figure 7] Soft tissue component was appreciated in 14 cases [Figures 8].

Ultrasound is useful in differentiating malignant bone tumors from benign. Cortical break, calcification and ossification, echo texture of lesion, periosteal reaction all are very significant parameters to differentiate benign from malignant tumor. Prabhakaran Palani *et al* found that Doppler along with gray scale imaging is helpful in 88% for diagnosis and differentiating benign from malignant tumor [5].

Role of USG in primary bone tumors are not well studied. Available literature is very scarce. There was a study by Saifuddin SJ *et al* in 1998 [6]. They studied 73 patients of suspected primary or recurrent bone tumors of appendicular skeleton and pelvis. USG was used to analyse the extra-osseous component of malignant and aggressive benign lesion and those tumors arising from the surface of bone. Periosteal reaction, cortical destruction, pathological fracture, matrix mineralisation, fluid- fluid level and neurovascular bundle were assessed. There were 3 cases of GCT and all the tumors were showing heterogenous echo texture with areas of necrosis. Fluid- fluid level was also well identified.

Colour Doppler was useful for detecting vascularity of the lesions. Majority of Osteosarcoma and GCT were hypervascular with regions of either pulsed type or contiguous type of flow. Chondrosarcoma and round cell tumors in their series were hypovascular. Most of our cases are hyper vascular similar to the observation by Saifuddin [Figures 9, 10]. Necrotic and cystic components were also well visualised in our series**.** 5 of our series have ABC component [Figures 9, 10].

A 31 old female described by EL Mehendi Kabir showed poorly delineated opacity in left first rib and on USG, it appeared heterogenous hypoechoic mass, oval shaped, poorly vascularised. CT revealed 4x 4 x3 cm osteolytic lesion with cortex thinning. CT guided biopsy confirmed it to be GCT [7].

Another case report by Lukka Dudand *et al* [8] described a case of GCT of ulna in a 28-year-old male patient. On Radiograph, CT, MRI the lesion was osteolytic in epimetaphysis of lower end of ulna. There was heterogenous enhancement of the lesion and soft tissue component on contrast. USG was done and showed a relatively hypoechoic, solid mass with central cystic necrotic portion. On colour Doppler, there was chaotically organised low resistance arterial flow in solid region of mass. It was low to intermediate stiffness on elastography. Biopsy was confirmed it to be GCT [8].

According to above studies and the case reports, it is clear that vascularity of GCT and the RI value may be variable. There is varied experience with RI in GCT according to the literature. In our observation 10 out of 11 cases of grade II tumors have low RI [Figure2]. The 4 cases of grade III tumors having low RI [Figure 7], one of these have thick cortex which may not depict correct RI value. Total 14 cases with high RI value. Two of low grades (I and II) and 12 (86% cases) of grade III had high RI value [Figures 1]. The mean RI of grade III tumors was higher than the mean RI of grade II GCT, an observation that has potential diagnostic value if confirmed in larger series.

Case report by Lukka Dudand [8] the GCT of ulna was showing low resistance flow in colour Doppler. In the study by Palaniswami Prabhakaran [5], there were 21 cases of GCT and 13 cases of Osteosarcoma around knee. USG and colour Doppler was done in all. Vascularity was absent in 3 of their 21 GCT cases and was observed in rest. RI was below 0.6 in 84% cases and was more than 0.6 in 19% cases with GCT. In their study, there were 13 cases of Osteosarcomas around knee-joint and most of them had RI more than 0.6. Hence, it can be concluded that benign tumor has lower RI as compared to aggressive one as observed in our series.

Naoto Oebisu studied soft tissue tumors and their Power Doppler ultrasound (PDUS) analysis of benign tumours showed RI and PI of 0.95(0-1.7) and 4.67 (0.03-49.5) compared to malignant tumours group showing 1.14 (0.14-10.8) and 3.46 (0.16-18.7) respectively. In other words, the RI and PI of benign tumors are less than malignant counterparts (9). According to a study by Gerd Bradman *et al* [10], the distribution of RI within the tumour tissue is expressed by the ratio of RI min to RI max [RI-min/Ri-max] for all vessels is measured. It is different significantly between malignant tumours (0.5±0.9) and the benign masses (0.79 ±0.12) [10].

Aggressive features of GCT in MRI, CT and radiographs are wide zone of transition, cortical thinning, expansile remodelling, cortical destruction, loss of trabeculations, and associated soft tissue mass. Spontaneous malignant transformation like Osteosarcoma, Fibrosarcoma, and Malignant Fibrous Histiocytoma may occur. Recurrence rate is 15-25% and lung metastases are seen in 1-6%. We had a case with pulmonary metastases and there were 2 cases of soft tissue deposits in post-operative periods [Figures 6, 11].

Multifocal GCT may be seen in metaphysis/diaphysis**.** Presence of more than one GCT in same patient is rare and accounts for less than 1% which may be synchronous either present at diagnosis or within 6months of diagnosis, metachronous if second one develops after 6 months [11, 12].

MRI is done to know the extent of tumor. On MRI the tumor appears intermediate or low signal on T1W and increased signal on T2W and STIR. On contrast injection there is enhancement. Two of our series had contrast study and there was heterogenous enhancement [Figure 12]. ABC component is better appreciated on MRI. Intramedullary component is better seen on T1W. MRI also demonstrates the intra articular extension of tumor. We had no cases of multifocal GCT in our series.

CT demonstrates cortical thinning, periosteal reaction, pathological fractures, and expansion remodelling [Figures 5]. Absence of osseous matrix and calcifications are confirmed on CT [Figure 5]. Solid portion of lesion appears isodense to muscle and fluid density represent ABC component. On bone scan there is peripheral uptake with central area remaining photopenic. The uptake does not correlate with histologic grade of tumor. It also detects multicentricity of lesion.

Traditionally open biopsy is the technique of choice for diagnosis. However, imaging guided USG or CT guided biopsy is the gold standard, because of low risk of tumor spread or contamination, minimal invasiveness and reduced risk of biopsy. All our cases had histopathological confirmation in surgical specimen.

Chondroblastoma is a close differential for GCT. It can occur in skeletal immature skeleton and epicentre is in epiphysis whereas it is in metaphysis n GCT. Sclerotic margin and matrix calcification are unique to CB. Peri-lesional edema is seen in both the conditions.

Curettage alone has been the standard treatment with high frequency of recurrence 35-40% [13]. To reduce local recurrence various treatment options like cryosurgery, bone cement and systemic chemotherapy are tried with variable prognosis. Currently there is no reliable predictor of local recurrence or metastases [14].

Conclusions

FGCTs are locally aggressive benign neoplasms with a large histopathological spectrum. For treatment point of view, it is essential to differentiate benign from aggressive one.

USG and colour Doppler are useful imaging modalities, which not only depict the morphology and can detect the pathological fracture, periosteal reaction soft tissue component and can to some extent differentiate benign from aggressive nature of lesion in Giant Cell Tumors.

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