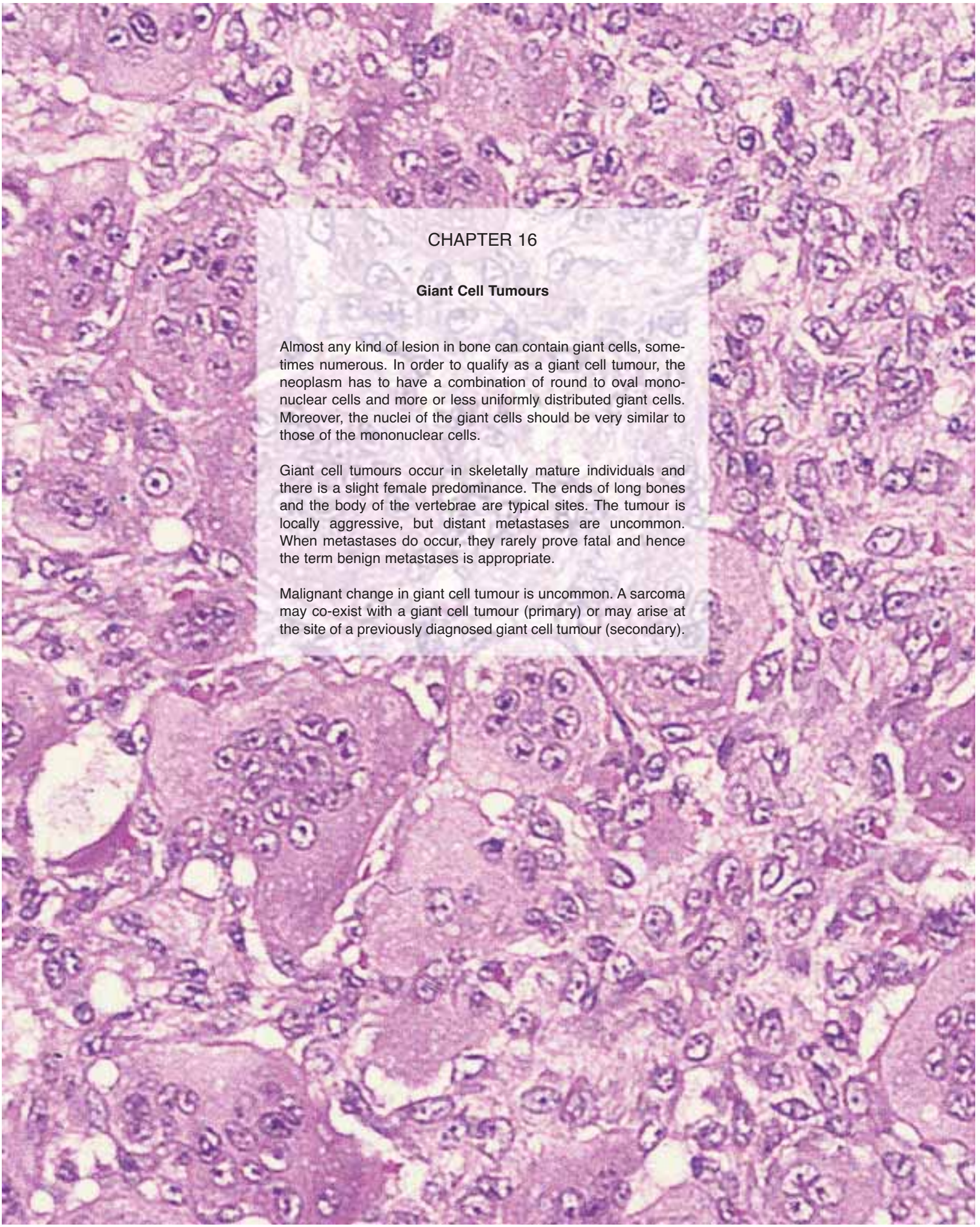

CHAPTER 16

Giant Cell Tumours

Almost any kind of lesion in bone can contain giant cells, sometimes numerous. In order to qualify as a giant cell tumour, the neoplasm has to have a combination of round to oval mononuclear cells and more or less uniformly distributed giant cells. Moreover, the nuclei of the giant cells should be very similar to those of the mononuclear cells.

Giant cell tumours occur in skeletally mature individuals and there is a slight female predominance. The ends of long bones and the body of the vertebrae are typical sites. The tumour is locally aggressive, but distant metastases are uncommon. When metastases do occur, they rarely prove fatal and hence the term benign metastases is appropriate.

Malignant change in giant cell tumour is uncommon. A sarcoma may co-exist with a giant cell tumour (primary) or may arise at the site of a previously diagnosed giant cell tumour (secondary).

Giant cell tumour

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Definition
Giant cell tumour is a benign, locally aggressive neoplasm which is composed of sheets of neoplastic ovoid mononuclear cells interspersed with uniformly distributed large, osteoclast-like giant cells.

ICD-O code 9250/1

Synonym
Osteoclastoma.

Epidemiology
Giant cell tumour represents around 4-5% of all primary bone tumours, and approximately 20% of benign primary bone tumours. 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 {299,538,1875,2155}. There is a slight female predominance in some large series. There is no striking racial variation, but there may be some geographic variation.

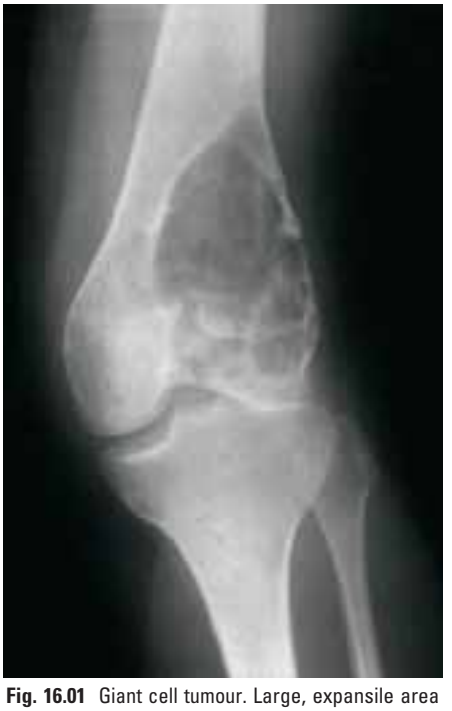

Fig. 16.01 Giant cell tumour. Large, expansile area of lysis with a sclerotic border, cortical thinning, and extension to the subchondral plate.

Sites of involvement
Giant cell tumours typically 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. The sacrum is the commonest site in the axial skeleton, while other vertebral bodies are less often involved. Fewer than 5% of cases affect the tubular bones of the hands and feet {200}. Multicentric giant cell tumors are very rare and tend to involve the small bones of the distal extremities.
Rarely, tumours with the morphology of giant cell tumour arise primarily within soft tissue {702}.

Clinical features / Imaging
Patients with giant cell tumour typically present with pain, swelling and often limitation of joint movement; pathological fracture is seen in 5-10% of patients. Plain X-rays of lesions in long bones usually show an expanding and eccentric area of lysis. The lesion normally involves the epiphysis and adjacent metaphysis; frequently, there is extension up to the subchondral plate, sometimes with joint involvement. Rarely, the tumour is confined to the metaphysis, usually in adolescents where the tumour lies in relation to an open growth plate, but occasionally also in older adults. Diaphyseal lesions are exceptional.
The margins of the lesion vary; this is the basis of a radiological grading/staging system {299}. Type 1, 'quiescent', lesions have a well-defined margin with surrounding sclerosis and show little, if any, cortical involvement. Type 2, 'active' tumours have well-defined margins, but lack sclerosis; the cortex is thinned and expanded. Type 3, 'aggressive' tumours have ill-defined margins often with cortical destruction and soft tissue extension. This grading system does not correlate well with histological appearances. On occasion, a giant cell tumour has a trabeculated 'soap-bubble' appearance. In the tubular bones of the hands and feet, the x-ray appearances are similar to those seen in long bones. Tumours of sacrum and pelvic bones are also lytic, commonly involve adjacent soft tissues and may affect sacro-iliac and hip joints.
There is seldom much reactive periosteal new bone formation. Only occasionally is radiologically evident matrix produced within the tumour, usually in long standing lesions.
CT scanning gives a more accurate assessment of cortical thinning and penetration than plain radiographs. MR imaging is most useful in assessing the extent of intra-osseous spread and defining soft tissue and joint involvement. Giant cell tumour typically shows low to intermediate signal intensity on T1 weighted images and intermediate to high intensity on T2 images. Large amounts of haemosiderin are often present giving areas of low signal in both modalities.

Macroscopy
The appearance of an intact specimen mirrors the radiological appearances in

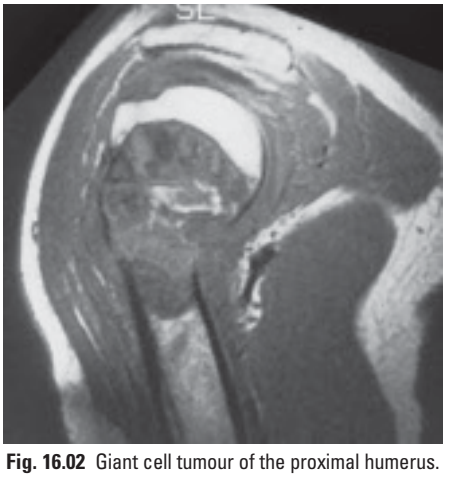

Fig. 16.02 Giant cell tumour of the proximal humerus. MRI shows a well demarcated lesion with focal destruction of cortex and extension into the epiphysis.

its eccentric location and fairly well defined area of bone destruction. This is often bounded by a thin and often incomplete shell of reactive bone. Although the tumour frequently erodes the subchondral bone to reach the deep surface of the articular cartilage, it seldom penetrates it. The tissue is usually soft and reddish brown, but there may be yellowish areas corresponding to xanthomatous change, and firmer whiter areas where there is fibrosis. Blood-filled cystic spaces are sometimes seen and, when extensive, this may cause confusion with an aneurysmal bone cyst.

Histopathology

The characteristic histopathological appearance is of round to oval polygonal or elongated mononuclear cells evenly mixed with numerous osteoclast-like giant cells which may be very large and contain 50 to 100 nuclei. The nuclei of the stromal cells are very similar to those of the osteoclasts, having an open chromatin pattern and one or two small nucleoli. The cytoplasm is ill-defined, and there is little intercellular collagen. Mitotic figures are invariably present; they vary from 2 to 20 per ten high power fields. Atypical mitoses are not, however, seen and their presence should point to a diagnosis of a giant cell rich sarcoma. Occasional binucleate and trinucleate cells are seen.

It is now generally accepted that the characteristic large osteoclastic giant cells are not neoplastic. The mononuclear cells, which represent the neoplastic component, are thought to arise from primitive mesenchymal stromal cells. They express RANKL, which stimulates formation and maturation of osteoclasts from osteoclast precursors {1814,2342}; these cells of monocyte lineage represent a second, minor, component of the mononuclear cells.

There are variations from these standard appearances. In some cases, the mononuclear cells are more spindle shaped, and they may be arranged in a storiform growth pattern. Commonly, small numbers of foam cells are present, and in rare cases this is the predominant pattern thus simulating a fibrous histiocytoma. There may be areas of fibrosis, while secondary aneurysmal bone cyst change occurs in 10% or so. Small foci of bone formation within the tumour are found, especially after pathological fracture or biopsy. When the tumour extends into soft tissue or is present in lung, the histological features are identical to the primary lesion, and there is often a peripheral shell of reactive bone. A striking feature, in one third of cases, is the presence of intravascular plugs, particularly at the periphery of the tumour; this does not appear to be of prognostic significance. Areas of necrosis are common, especially in large lesions. These may be accompanied by focal nuclear atypia which may suggest malignancy.

Fig. 16.03 Giant cell tumour. Large haemorrhagic tumour of the proximal humerus with extensive cortical destruction and soft tissue extension.

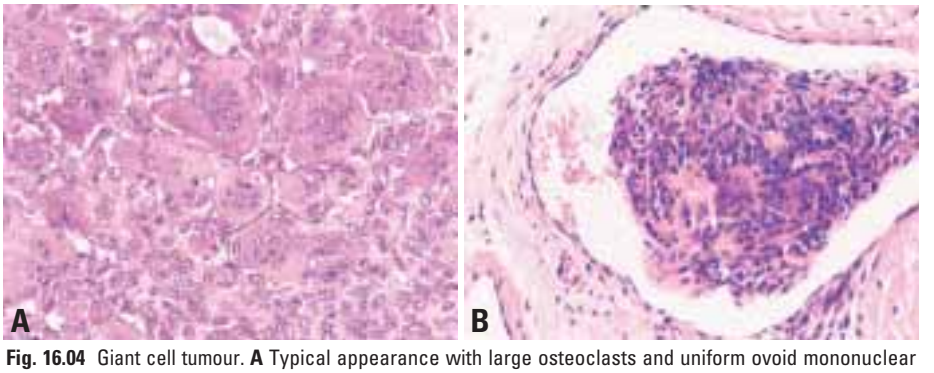

Fig. 16.04 Giant cell tumour. **A** Typical appearance with large osteoclasts and uniform ovoid mononuclear cells. **B** The vascular lumen contains a mixture of spindle and giant cells.

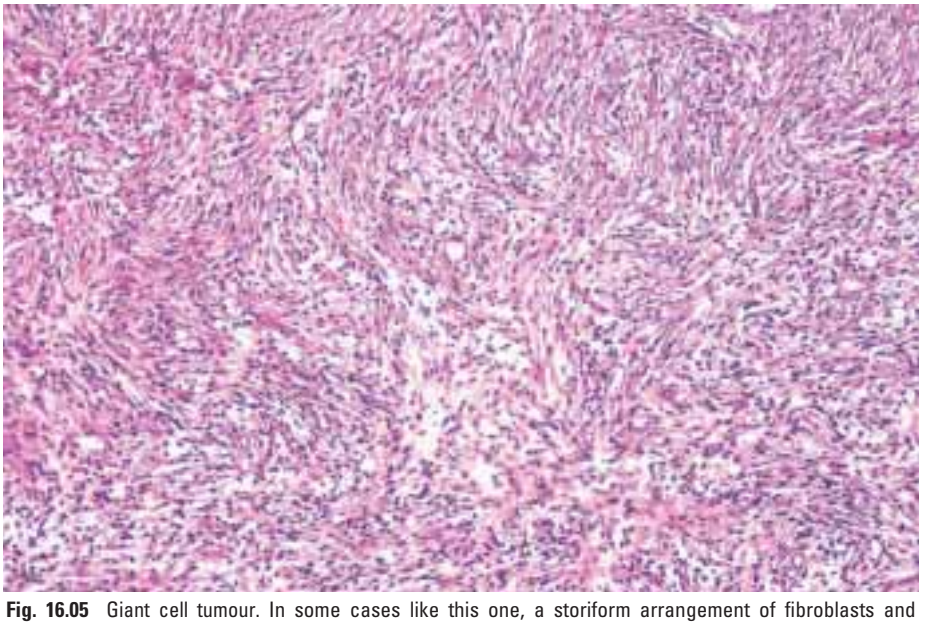

Fig. 16.05 Giant cell tumour. In some cases like this one, a storiform arrangement of fibroblasts and macrophages resembles a benign fibrous histiocytoma.

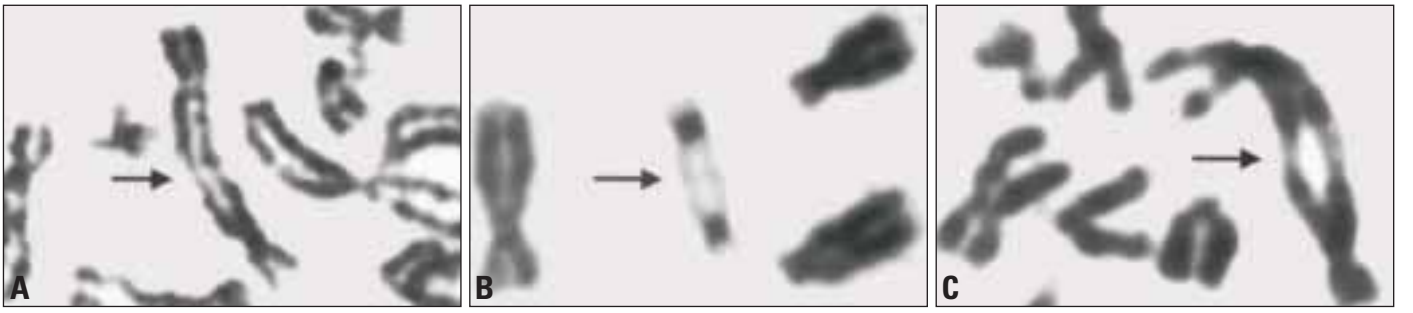

Fig. 16.06 Giant cell tumour. G-banded partial metaphase spreads **(A,B,C)**. Telomeric associations are indicated by arrows.

Immunophenotype

The giant cells have the typical immunophenotype of normal osteoclasts, expressing markers of histiocytic lineage.

Genetics

Telomeric association is the most frequent chromosomal aberration. A reduction in telomere length (average loss of 500 base pairs) has been demonstrated in giant cell tumour cells when compared to leukocytes from the same patients {1898}. The telomeres most commonly affected are 11p, 13p, 14p, 15p, 19q, 20q and 21p {262,1644, 1909,2090,2343}. Giant cell tumours with a fibrohistiocytic reaction do not differ karyotypically from the others {1909}. This observation supports the hypothesis that these lesions are true giant cell tumours rather than a different entity like a fibroxanthoma. It is of interest that four cases of giant cell tumour also showed rearrangements in 16q22 or 17p13 {262,1488,1909}. These findings might indicate the possible presence of an associated aneurysmal bone cyst. It has been suggested that there is an association between the the presence or absence of chromosomal aberrations and clinical behaviour of giant cell tumours {262}.

Prognostic factors

Giant cell tumour is capable of locally aggressive behaviour and occasionally of distant metastasis. Histology does not predict the extent of local aggression. Following treatment by curettage, supplemented with bone grafting, cementation, cryotherapy, or instillation of phenol, local recurrence occurs in approximately 25% of patients. Recurrence is usually seen within 2 years. Block excision for lesions in small bones results in fewer local recurrences. Pulmonary metastases are seen in 2% of patients with giant cell tumours, on average 3-4 years after primary diagnosis {1947}. These may be solitary or multiple. Some of these metastases are very slow growing (benign pulmonary implants) and some regress spontaneously. A small proportion are progressive and may lead to the death of the patient.

Local recurrence, surgical manipulation and location in distal radius may increase the risk of metastasis {1350}. Histological grading does not appear to be of value in predicting which giant cell tumour will metastasise, providing that giant cell rich sarcomas have been excluded. True malignant transformation is rare {1346}, and often follows radiotherapy.

Malignancy in giant cell tumour

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M. Bansal

Definition
Malignancy in GCT is a high grade sarcoma arising in a giant cell tumour (primary) or at the site of previously documented giant cell tumour (secondary).

ICD-O code 9250/3

Synonyms
Malignant giant cell tumour, dedifferentiated giant cell tumour.

Epidemiology
Malignancy arising in a giant cell tumour can occur after treatment usually including radiation or de novo. Most sarcomas arise following radiation therapy. Primary malignant giant cell tumour is the least common type. Overall, malignant transformation can be expected in less than 1% of giant cell tumours. There is a slight female predominance and patients are generally about a decade older than patients with giant cell tumour.

Clinical features / Imaging
The recurrence of pain and swelling many years following treatment of a giant cell tumour should suggest the possibility of malignant transformation. The symptomatology of primary malignant giant cell tumour is non specific. In secondary malignant giant cell tumour plain roentgenograms show a destructive process with poor margination situated at the site of a previously diagnosed giant cell tumour, usually at the end of a long bone. Mineralization may be present. In primary malignancy in giant cell tumour, the tumour presents as a lytic process extending to the end of a long bone. Rarely the roentgenograms show typical features of giant cell tumour and a sclerotic destructive tumour juxtaposed to it.

Sites of involvement
Bones involved with giant cell tumour are also affected by malignancy in giant cell tumour. The distal femur and the proximal tibia are the most common sites. There have been no cases reported in the small bones of the hands and feet or the skull.

Macroscopy
The gross appearance of a secondary malignant giant cell tumour is that of any high grade sarcoma: a large fleshy white tumour with soft tissue extension. Primary malignant giant cell tumours occur at the ends of bones and have dark red or tan colour.

Histopathology
In secondary giant cell tumour the neoplasm is a high grade spindle cell sarcoma which may or may not produce osteoid. No residual giant cell tumour is usually present. In primary malignant giant cell tumour areas of conventional giant cell tumour with proliferations of round to oval mononuclear cells and multinucleated giant cells are present. There is an abrupt transition to a spindle cell tumour with marked cytological atypia. Multinucleated giant cell may or may not be present.

Prognostic factors
The prognosis in secondary malignant giant cell tumours is similar to that of a high grade spindle cell sarcoma. The prognosis in primary malignant giant cell tumours has been reported to be better {1536}. In this series of eight patients only one died of disease.

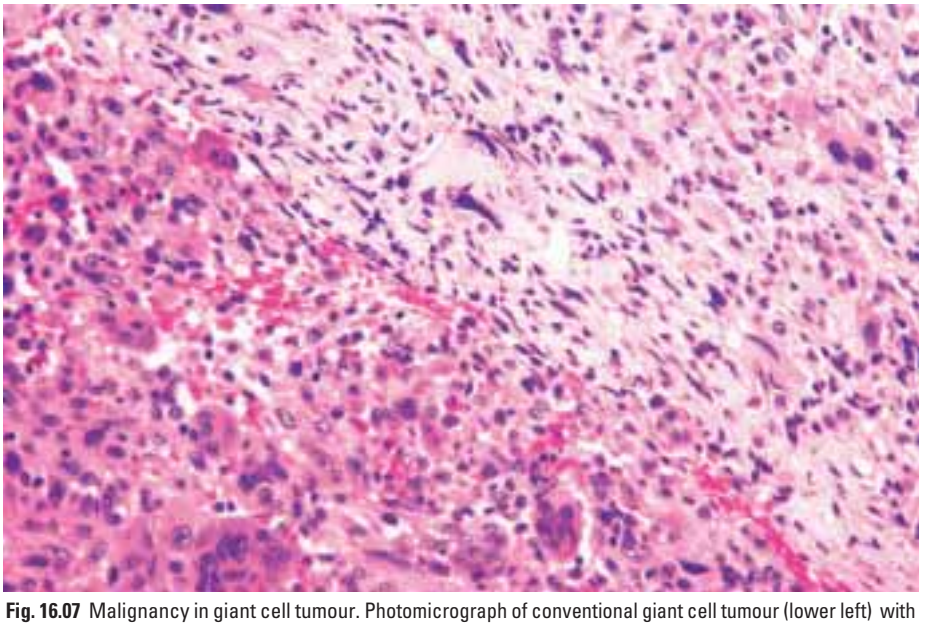

Fig. 16.07 Malignancy in giant cell tumour. Photomicrograph of conventional giant cell tumour (lower left) with mononuclear cells uniformly interspersed with multinucleated giant cells and an adjacent area of malignant anaplastic tumour cells (upper right).