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Abstract:
Giant cell tumor of bone was originally described in the early 1800s. It is thought to be a benign tumor of bone, although "metastasis" to the lung is not uncommon. It is a tumor that consists of osteoclast like giant cells containing numerous nuclei as well as a mononuclear stromal component consisting of spindled cells and histiocytic cells. Occasionally, giant cell tumor of bone can undergo malignant transformation. This review will examine the clinical and imaging characteristics of giant cell tumor of bone. The pathology and genetics will also be discussed. Treatment, both surgical and nonsurgical will be examined. In addition, unusual presentations of giant cell tumors will also be considered.

Keywords: Giant cell tumor of bone, review, radiology, pathology, therapy, denosumab, surgery

1. Introduction:

Sir Astley Patton Cooper and Benjamin Travers originally described giant cell tumor of bone in 1818 [Cooper and Travers]. The tumor was also referred to by a host of other terms, including osteoclastoma, myeloid sarcoma, osteoblastoclastoma, and myeloplaxic tumors [Karpik, Odesskaia-Mel'nikova, Salmon and Henry, Stewart]. The tumor received the name we are familiar with, giant cell tumor of bone, from Jaffe et al in 1940 [Jaffe et al]. Their description of the tumor separated it from other giant cell rich lesions identified in bone. Furthermore, Jaffe et al noted that it was the stromal cells that are the neoplastic cells of the tumor, impressive when one considers the lack of molecular and immunologic technology at the time [Jaffe et al].

Giant cell tumor is a locally aggressive tumor, most commonly of bone, and most frequently involving the long bones of skeletally mature individuals [Czerniak]. It accounts for approximately 4% of all primary tumors of bone, although some studies quote figures as high as 9.5% [Czerniak, Karpik, Murphey et al]. Patients are most often between the ages of 20 and 50 years old; the tumor is most common in the third decade of life [Czerniak, Thomas and Skubitz]. Recurrence rates are high, with local recurrence ranging from 20-50%; 10 % of recurrences undergo malignant transformation. 1-4% of so-called benign appearing tumors go on to develop pulmonary metastases. These pulmonary metastases are histologically identical to the primary site [Szendröi].

Because giant cell tumor of bone is relatively common in terms of primary osseous tumors (although rare overall), this review is undertaken to increase familiarity with it. Clinical and imaging characteristics of the neoplasm will be examined, and pathologic correlation will be made. The genetics of the lesion will be discussed. Treatment, both surgical and nonsurgical (as some of these tumors are unresectable based on their locations), will be considered. Unusual presentations and prognosis will also be discussed.

2. Clinical Characteristics and Epidemiology:

Giant cell tumor of bone is one of the more common primary neoplasms of bone, and as was discussed in the introduction, is most commonly seen in skeletally mature individuals between 20 and 50 years of age [Czerniak, Werner]. In fact, it is unusual to see these tumors in patients under the age of 20 (to be discussed later) and over the age of 55 [Czerniak, Karpik]. There is a slight female predominance [Chakarun et al, Czerniak, Garcia et al, Karpik]. Interestingly, there appears to be an increased incidence of giant cell tumor of bone in China and India, where it has been reported to account for as many as 20% of all primary tumors of bone [Czerniak, Chakarun et al, Karpik, Murphey et al, Sobti et al, Szendröi, Thomas and Skubitz], significantly more than what has been seen in Western countries. The most common symptoms experienced by patients include swelling, pain, and limitation of joint movement [Garcia et al]. The pain is usually independent of weight bearing [Szendröi]. Synovitis has also been described in some patients [Sobti et al]. Pathologic fracture is seen at diagnosis in approximately 12% of patients [Sobti et al].

The tumor is most commonly seen in the long bones, with the distal femur and proximal tibia being the most common sites [Amanatullah et al, Chakarun et al, Czerniak, Karpik, Mendenhall et al, Szendröi]. The distal radius is the third most common site [Chakarun et al, Karpik, Mendenhall et al]. While less common, giant

cell tumor of bone has been described in most of the other bones of the body as well [Czerniak]. When seen in the craniofacial bones, it is usually associated with Paget disease of bone [Czerniak, Chakarun et al], although it has been reported to occur in long bones involved with Paget disease as well [Hoch et al].

3. Imaging Characteristics:

Standard radiographs are usually the first study performed in patients who present with symptoms suggestive of giant cell tumor of bone, and are the best for demonstrating the lesion. Radiographs reveal a well-defined, eccentric lucency located in the metaphysis of the bone and often involving the epiphysis as well (Fig 1) [Amanatullah et al, Czerniak, Jaffe et al, Thomas and Skubitz]; however, large lesions may appear central in their location [Murphey et al]. The cortex is commonly expanded and may be broken; sclerosis of the margins of the lesion is usually not seen [Czerniak, Murphey et al]. Geographic lysis with a wide zone of transition and more aggressive growth is seen in up to 20% of cases [Murphey et al]. In 5-40% of cases, pathologic fracture may be seen [Czerniak, Murphey et al]. Less commonly, giant cell tumor of bone may involve the metaphysis alone without epiphyseal involvement. Clinically this has been reported in both skeletally mature and immature patients [Czerniak]. Radiographs are also important in the assessment of local recurrence status post resection. If the rim around the cement layer is greater than 5 mm, recurrence is suggested [Amanatullah et al].

Historically, there was a staging system for giant cell tumor of bone based on its radiographic findings. Enneking and Campanacci were two proponents of this system [Campanacci et al, Czerniak, Enneking, Karpik, Murphey et al, Sobti et al]. Giant cell tumor of bone was divided into three stages. Stage 1 lesions are also known as quiescent lesions. This type is characterized by a lytic lesion limited to the medullary cavity with little to no involvement of the cortex [Campanacci et al , Czerniak]. Stage 2 lesions are known as active lesions and are characterized by a thinned cortex and uncertain margins [Campanacci et al, Czerniak]. Finally, the stage 3 or aggressive lesions demonstrate cortical invasion, soft tissue extension, and ill-defined margins [Campanacci et al, Czerniak]. Unfortunately, this system does not correlate to histologic findings and is not an accurate predictor of malignancy [Czerniak, Murphey et al].

Computed tomography (CT) imaging is also known to be advantageous in the examination of lesions of bone as it allows for delineation of the lesion as well as staging of the lesion [Hudson et al, Murphey et al]. The detection of pathologic fracture, cortical thinning, expansion, and periosteal reaction are greatly improved with use of CT imaging (Fig 2) [Hudson et al, Murphey et al]. In aggressive tumors, CT imaging has proven useful in confirming the absence of mineralization in giant cell tumor of bone, important when osteosarcoma is being considered in the differential diagnosis. However, CT imaging will detect callus formation in patients who have experienced pathologic fracture [Murphey et al].

Giant cell tumor of bone is the second most common primary tumor of bone to demonstrate secondary aneurysmal bone cyst. These changes are best characterized on magnetic resonance imaging (MRI) [Czerniak]. Prominent secondary aneurysmal bone cyst components are thought to potentially have a more aggressive radiographic appearance likely attributable to the expansile nature of the cystic component [Murphey et al]. The classic MRI finding of aneurysmal bone cyst

is the multiple fluid-fluid levels throughout the lesion (Fig 3). In the experience of Murphey et al [Murphey et al], the solid areas containing giant cell tumor of bone tend to localize to the periphery of the lesion, while the aneurysmal bone cyst component tends to localize toward the center of the lesion, allowing for effective biopsy to collect diagnostic tissue. Soft tissue extension is also better seen with MRI as MRI is superior to CT for the imaging of soft tissue lesions [Murphey et al].

4. Pathology

4.1 Gross Pathology

The gross features of giant cell tumor of bone are best appreciated in an intact resection specimen. In these specimens, the tumor is red to brown, sometimes with yellow areas. The tumor tends to be soft and friable. Extension to the articular cartilage is common [Czerniak]. As seen in radiographic images, the tumor is eccentrically placed and involves the epiphysis and metaphysis of the bone. In many cases, the cortex is broken and there may be involvement of the surrounding soft tissue [Czerniak]. Necrosis can be seen in cases where the tumor has outgrown its blood supply as well as in cases that are involved by pathologic fracture. Cystic changes may also be seen, particularly in cases involved by a secondary aneurysmal bone cyst. In these specimens, the cystic cavities are filled with blood.

4.2 Histologic Findings

The classic findings of giant cell tumor of bone consist of numerous giant cells, containing 50-100s of nuclei, embedded within a mononuclear cell stroma which consists of mononuclear spindle cells and mononuclear histiocytic cells (Fig 4). Close observation allows one to recognize that the nuclei of the mononuclear stromal cells are morphologically similar to the nuclei of the giant cells (Fig 5). In all three cell types, the nuclei are round to oval with regular nuclear membranes [Czerniak, Werner]. Nucleoli are small but prominent. The giant cells are usually sharply delineated with dense, eosinophilic cytoplasm [Czerniak, Garcia et al]. In some cases, the stromal cells can take on a spindled appearance. This is well within what is accepted in giant cell tumor of bone and should not be confused with true nuclear pleomorphism [Czerniak]. Within the stroma, typical mitoses are usually seen, and in some cases, may be numerous. However, atypical mitoses should not be seen. Furthermore, mitotic figures are not seen within the giant cells [Czerniak]. In cases demonstrating pathologic fracture, bone or cartilage matrix may be seen; this is not indicative of osteoid production by the tumor, but rather callus formation in an attempt to heal the fracture [Czerniak].

As was discussed in earlier sections, a secondary aneurysmal bone cyst component may be identified. A cystic component containing spindle cells, giant cells, and typical mitotic activity, often associated with blood lakes, is demonstrative of the aneurysmal bone cyst component (Fig 6). A secondary aneurysmal bone cyst component is seen in as many as 10% of giant cell tumors of bone [Czerniak].

Other secondary patterns can be seen in giant cell tumor of bone. For instance, the classic histologic picture described above may be altered by the presence of a prominent fibrohistiocytic component (Fig 7). This component consists of a storiform spindle cell component that is likened to the spokes on a bicycle wheel. The nuclei tend to be tapered at the ends and plump in the center. These cells are accompanied by xanthomatous cells. These components are seen in varying amounts in almost all giant cell tumors [Czerniak]. In some cases, these components make up so much of the tumor that the differential diagnoses of benign fibrous histiocytoma (in skeletally mature

individuals) and nonossifying fibroma (in skeletally immature individuals) [Czerniak] are raised. However, if the clinical and imaging features are most consistent with a giant cell tumor of bone, then every effort should be made to sample extensively to find sections diagnostic of giant cell tumor [Czerniak].

In addition to the secondary findings described above, reactive bone deposition and necrosis may also be seen in giant cell tumor. Neither of these things should be taken to assume that one is dealing with malignancy in a giant cell tumor. Furthermore, foci of lymphvascular invasion may be seen. However, these foci do not correlate with malignancy nor do they predict the possibility of pulmonary metastases [Czerniak, Forsyth et al].

4.3 Cytology

Fine needle aspiration cytology is not regarded to be the primary modality in the diagnosis of bone tumors. Bone biopsy is much more commonly used in primary diagnosis [Cardona and Dodd]. However, when fine needle aspiration is employed, the findings are similar to that seen in histologic preparations. There are two cell populations, giant cells containing numerous nuclei and mononuclear stromal cells that are round to spindled in shape [Cardona and Dodd, Czerniak, Jain et al, Saikia et al, Sneige et al, Witt et al]. As seen in histologic examples, the nuclei of the giant cells are morphologically similar to the nuclei of the mononuclear stromal cells, an important finding in giant cell tumor of bone [Sneige et al].

Fine needle aspiration cytology is likely most usual in cases of giant cell tumor of bone that go on to develop pulmonary metastases [Cai et al, Nagesh et al]. In these cases, the patients are already known to have had a giant cell tumor of bone in a primary site; fine needle aspiration cytology is used as a noninvasive method to confirm the diagnosis in a distant site. In two separate reports [Cai et al, Nagesh et al], fine needle aspiration biopsy was used to confirm the diagnosis. Using this approach, and correlating with clinical and imaging findings, cytology may play an important role in the diagnosis of giant cell tumor of bone.

4.4 Differential Diagnosis

Giant cell tumor of bone is most easily confused with reactive lesions such as giant cell reparative granuloma [Czerniak, Murphey et al] and brown tumor of hyperparathyroidism [Czerniak, Sobti et al]. Giant cell reparative granuloma is more common in the craniofacial bones, and particularly in the jaw [Czerniak, Murphey et al]. As mentioned earlier, true giant cell tumor of bone is less likely to arise in the craniofacial bones, aiding in the differential diagnosis [Czerniak]. Histologically, giant cell reparative granuloma tends to have far more uniform giant cells without foci of reactive bone [Czerniak]. There may be foci of hemorrhage, and the stromal component consists of numerous fibroblasts instead of round to spindled stromal cells that morphologically mimic the nuclei of the giant cells [Murphey et al]. In addition, cystic components are uncommon in giant cell reparative granuloma [Murphey et al]. Brown tumor of hyperparathyroidism is essentially a giant cell reparative granuloma of known cause, specifically, hyperparathyroidism [Czerniak].

Histologically, the findings of brown tumor of hyperparathyroidism are similar to giant cell reparative granuloma.

Other differential diagnostic considerations include benign fibrous histiocytoma, nonossifying fibroma, aneurysmal bone cyst, chondroblastoma, and chondromyxoid

fibroma [Czerniak]. The first three are considered as biopsy specimens may contain areas that look like these. Their histologic findings were described in detail earlier in this manuscript and will not be repeated. Chondroblastoma is a chondroid neoplasm most commonly seen in patients who are skeletally immature which tend to occur in the same sites as giant cell tumor of bone [Garcia et al]. The imaging findings, particularly of standard radiographs, are very similar in chondroblastoma and giant cell tumor of bone; while it is unusual for skeletally immature patients to develop giant cell tumor of bone, it does occur. In addition, chondroblastoma is the most common primary bone tumor to demonstrate secondary aneurysmal bone cyst. However, appropriately sampled biopsy specimens can usually resolve this differential. Chondroblastoma usually contains islands of grey to eosinophilic chondroid material; rarely focal true hyaline cartilage is seen [Garcia et al]. Occasional, randomly distributed osteoclast-like giant cells are identified [Garcia et al]. There is a mononuclear stromal component; these cells are round to polygonal with well-defined cytoplasmic borders. These cells demonstrate clear to eosinophilic cytoplasm and the nuclei, most commonly ovoid, demonstrate nuclear grooves [Garcia et al]. Pericellular calcifications, the so-called chicken wire calcification may also be present [Garcia et al].

Chondromyxoid fibroma is a rare benign bone tumor. It too is often an eccentric lytic lesion, most commonly of the long bones, hence the differential with giant cell tumor of bone. However, chondromyxoid fibroma tends to have a sclerotic border that is not typically seen in giant cell tumor of bone [Garcia et al]. Histologic features of this tumor include lobules of loose, myxoid stroma containing stellate and spindle shaped cells separated by fibrous septa. Occasional osteoclast-like giant cells are seen [Garcia et al]. True hyaline cartilage is not seen.

Malignant differential diagnostic considerations include undifferentiated pleomorphic sarcoma, giant cell rich type [Czerniak, Sobti et al] and giant cell rich osteosarcoma [Czerniak]. The imaging features of both of these tumors are far more aggressive and destructive than that seen in giant cell tumor of bone. In addition, the histology of these tumors is far more malignant in appearance, including hyperchromatic, pleomorphic nuclei within eosinophilic cytoplasm, atypical mitoses, and in the case of giant cell rich osteosarcoma, malignant osteoid [Czerniak].

5. Genetics

Giant cell tumor of bone does not appear to have a recurrent translocation that is pathognomonic for the diagnosis. However, there have been studies attempting to identify some of the genetic features of this lesion. Telomeres are composed of repetitive guanine rich sequences and associated proteins that protect the ends of chromosomes [Bailey and Murnane]. Telomeres are well known to shorten over time and this finding is related to the process of aging, as most cells do not maintain enough telomerase to divide indefinitely. However, malignant cells continue to produce telomerase, allowing for those cells to divide indefinitely [Bailey and Murnane]. Telomeric associations are most commonly described in malignant neoplasms of high histologic grade and are characterized by complex chromosomal aberrations [Forsyth et al]. Therefore, telomeric associations reflect severe genetic instability secondary to damaged, critically shortened telomeres [Forsyth et al]. Forsyth et al identified significant expression of telomere maintenance markers in giant cell tumor of

bone; they concluded that these markers could indicate a highly active mechanism of DNA repair and protection rather than of telomere lengthening [Forsyth et al].

Gorunova et al analyzed 101 giant cell tumors; they were able to analyze karyotypes in 95 tumors and of these 47 demonstrated clonal aberrations. The majority of these chromosomally aberrant tumors had multiple clones identified. Of note, and similar to the findings by Forsyth et al, 70% of the clonally aberrant tumors had identifiable telomeric associations [Gorunova et al]. It seems likely, based on these studies, that telomeric associations are important in the formation of giant cell tumor of bone [Forsyth et al, Gorunova et al] despite the fact that these tumors are benign.

A third group examined the genomic instability of giant cell tumor of bone in 52 cases. They too found telomeric associations in a number of their cases [Moskovszky et al]; however, in their ploidy studies, they noted that random individual cell aneusomy was significantly more frequent in patients who suffered from recurrence of their tumor [Moskovszky et al]. More cases would have to be examined in order to determine if DNA ploidy studies have any role in the ability to predict recurrence in primary tumors.

Isocitrate dehydrogenase (IDH) mutations have been identified in many tumors, including gliomas, chondrosarcoma, acute myelogenous leukemia, osteosarcoma, and intrahepatic cholangiocarcinoma [Kaneko et al]. The IDH genes are a hot area of research in many tumors, and giant cell tumor of bone is not to be excluded. Kaneko et al examined the giant cell tumors of 20 patients, and 13 of 20 patients demonstrated IDH2 mutations; none demonstrated IDH1 mutations [Kaneko et al], and the mutation identified was specifically IDH2-R172S, which is also frequently observed in osteosarcomas and chondrosarcomas. While this is a small study, and does not have prognostic implications at this time, it may eventually be useful to see if IDH mutations are somehow linked to recurrence or metastasis of giant cell tumors.

Rao et al found that allelic losses of 1p, 9q, and 19q regions were frequent in all giant cell tumors of bone, but these losses do not appear to have prognostic or metastatic predictive value [Czerniak, Rao et al]. However, loss of 17p (in proximity to the p53 locus) as well as 9p occurred exclusively in the pulmonary metastases from giant cell tumor. Loss of heterozygosity of 9q and 19q was present in primary as well as recurrent giant cell tumors and in one malignant giant cell tumor [Rao et al]. It stands to reason that these losses of heterozygosity may have some predictive value in the behavior of giant cell tumor of bone, and that benign and malignant giant cell tumors may arise from similar genetic pathways.

6. Treatment

6.1 Surgical Treatment

Most cases of giant cell tumor of bone are amenable to some degree of surgical resection. The tumor is usually localized. Despite en bloc resection having lower recurrence rates (<20% in one report) [Skubitz], intralesional curettage, often with treatment of the tumor cavity is preferred [Biermann]. Recurrence rates with intralesional curettage may be as high as 40-50% [Biermann, Skubitz]; this may be due to the implantable nature of the tumor [Amanatullah et al].

Approximately 10% of tumors will undergo malignant transformation at the time of tumor recurrence [Szendröi]. The tumor cavity can be treated with phenol or cryotherapy agents in an attempt to reduce the incidence of recurrence [Skubitz, van der

Heijden 2014a, van der Heijden 2014b]. The cavity is then packed with polymethyl methylacrylate cement; it is thought that the heat from the cement may have a local antitumor effect [Biermann, Sobti et al, Skubitz]. Steinmann pins have been advocated to reinforce the bone cement used to fill subchondral defects caused by curettage. This approach, however, is controversial; internal fixation may be necessary to augment the construct [Sobti et al].

In one study, the authors examined the use of warm Ringer's lactate as an adjuvant therapy during the intralesional resection of giant cell tumor of bone [Waikakul et al]. 21 patients were treated in this manner. After curettage, 50 °C Ringer's lactate was locally applied to the tumor cavity. 2 patients experienced tumor recurrence, and only 1 patient had a complication from the therapy [Waikakul et al]. It could be surmised that the warming of the Ringer's lactate functions similarly to the heat from polymethyl methylacrylate cement in that the heat may have a local antitumor effect decreasing the overall rate of recurrence. Other local treatments used intraoperatively have included aqueous zinc chloride and the addition of zoledronic acid to polymethyl methylacrylate [Thomas and Skubitz].

6.2 Nonsurgical Treatment

There have been several modalities offered as neoadjuvant and adjuvant therapies in the treatment of giant cell tumor of bone. The most prominent of these is the fully human monoclonal antibody denosumab. An understanding of the function of denosumab requires an understanding of the pathophysiology of giant cell tumor of bone.

The receptor activator of nuclear factor kappa B (RANK), osteoprotegerin, and RANK ligand (RANKL) are the major components of the RANK pathway of bone remodeling [Thomas and Skubitz, Wu et al]. Discovered in the mid 1990s, this pathway is a key signaling pathway of bone remodeling; it plays a critical role in the differentiation of osteoprogenitor cells into multinucleate osteoclasts and the activation of those osteoclasts resulting in the resorption of bone [Wu et al].

In giant cell tumor of bone, the stromal cells appear to be the neoplastic cells [Lopez-Pousa et al, Szendröi, Wu et al] as they have been found to express high levels of RANKL [Wu et al]. This is thought to be important in the development of the disease [Werner, Wu et al]. The overexpression of RANKL by the stromal cells results in the production of multinucleate giant cells from monocytes. The result is excessive bone resorption at the site of the tumor [Wu et al]. RANKL was originally isolated from a murine thymoma cell line; it was shown some time after to be important in osteoclast development [Singh et al].

RANKL is therefore an important target, particularly in patients with surgically unresectable disease. The fully human monoclonal antibody denosumab has been studied extensively in the nonsurgical treatment of giant cell tumor of bone [Czerniak, Lopez-Pousa et al, Skubitz, Wu et al]. In most patients, the giant cells are nearly completely eliminated, and there is a reduction in the stromal cell component that is replaced with osteoid lined by RANKL producing cells [Skubitz]; the stromal cells continue to proliferate in vitro, but at a slower rate than they would without exposure to denosumab [Mak et al]. In the clinical trial phase, the majority of patients showed no disease progression 13 months after initiation of therapy; most patients also reported a reduction in pain [Skubitz].

As with all treatments, adverse side effects, including osteonecrosis of the jaw, hypocalcemia, hypophosphatemia, serious infection, anemia, back pain, and pain in the

extremities were reported during clinical trials [Skubitz]; however, the percentages of these were all 5% or less. Denosumab, therefore, is thought to be an effective option in patients for whom surgery would result in unacceptable morbidity as well as those who have surgically unresectable disease. In some cases, therapy might be needed for the remainder of the life of the patient; optimal treatment schedules with denosumab have not yet been determined [Skubitz]. In one reported case, cessation of denosumab therapy resulted in resumed growth of the tumor [Matcuk et al].

Histologically, denosumab treated giant cell tumors can have disturbing findings if the pathologist receiving the specimen is not aware of the patient's treatment history. Wojcik et al examined 16 specimens from 9 patients who had documented treatment of their giant cell tumors with denosumab. The patients were treated anywhere from 2-55 months. These treated cases were compared to 9 malignant tumors that had arisen in known giant cell tumors of bone. The histology varied from case to case and is thought to be related to the length of treatment. As was noted above, all the treated cases showed marked giant cell depletion. Lesions that were early in the treatment course demonstrated high cellularity, and it is this cellularity in combination with nuclear atypia and new bone deposition that caused the lesion to resemble a high-grade osteosarcoma [Wojcik et al]. However, the lack of an infiltrative growth pattern and reduced mitotic activity argue against a diagnosis of malignancy. Patients with longer therapeutic duration showed abundant new bone arranged in long curvilinear arrays or broad cords with less cellularity, reminiscent of low-grade central osteosarcoma [Wojcik et al]. However, negativity for MDM2 (which is positive in many cases of low-grade central osteosarcoma) and lack of an infiltrative pattern again argued against the diagnosis [Wojcik et al]. Similar findings were reported in a single case by a different group [Sanchez-Pareja et al]. These findings demonstrate the importance of getting a full treatment history of a patient who has a known giant cell tumor of bone.

Denosumab has also been used in patients who have lung metastasis from giant cell tumor of bone. In one report, histologic regression of a lung metastasis was seen, possibly indicating that denosumab can be used in the treatment of both primary and metastatic tumors [Dietrich et al].

Bisphosphonates have also been explored as an adjuvant therapy for patients with giant cell tumor of bone. Bisphosphonates target the osteoclast like giant cells resulting in apoptosis [Sobti et al]. In one study, 24 patients were enrolled in a phase 2 multicenter trial to explore the value of treatment with zoledronic acid [Gouin et al]. All patients underwent intralesional curettage. The patients were then treated with 5 courses of zoledronic acid. Most of the patients complained of side effects and local recurrence was not prevented [Gouin et al]. Given the availability of denosumab, bisphosphonates are not considered a first line therapy in the treatment of giant cell tumor of bone.

Radiotherapy has long been regarded as a modality that should not be used in giant cell tumor of bone due to the possibility of inducing malignant transformation. However, a retrospective review of the treatment of 34 giant cell tumor patients was performed at the University of Florida. The treatment dates ranged from 1973-2008 and the patients had a median age of 29 years [Shi et al]. All patients received radiation either for primary gross disease or after resection, the median dose was 45 Gy. Of 34 patients, 3 developed lung metastasis, and

only 1 had transformation of their disease to a high-grade sarcoma [Shi et al]. In another study of 24 patients treated with radiation, only 1 developed a radiation-induced sarcoma [Skubitz]. In yet another study of 77 patients, only 2 developed malignant transformation to sarcoma [Skubitz]. It is possible that, despite the classic teaching, radiation may have some benefit to patients with giant cell tumor of bone [Sobti et al].

7. Unusual Presentations

7.1 Skeletally Immature Patients

Giant cell tumor, as discussed above, is well known to be a tumor of skeletally mature individuals. That said, there have been reports of giant cell tumor of bone occurring in those who are skeletally immature. Giant cell tumor of bone in skeletally immature patients is rare, accounting for approximately 2-6% of all giant cell tumors of bone. Additionally, unlike adult cases where the epiphysis is commonly involved, in cases where the patient is skeletally immature, involvement of the epiphysis is also rare [Akaike et al, Patel and Nayak].

There have been several case reports of giant cell tumors in skeletally immature patients [Akaike et al, Alfawareh et al, Patel and Nayak]. These reports demonstrate involvement of unusual locations, including the upper cervical spine [Alfawareh et al] and the diaphysis of the ulna without involvement of the metaphysis or epiphysis [Patel et al]. The treatment of the tumors does not differ from that seen in skeletally mature patients.

7.2 Giant Cell Tumor Presenting in Unusual Locations

Giant cell tumor, as discussed earlier, presents most commonly in the distal femur, proximal tibia, and distal radius. However, giant cell tumor can also present in unusual locations in bone and in other organs. Unusual sites in bone that have been reported include the patella [Song et al], the lateral skull base [Freeman et al] and the internal auditory canal [Jada et al]. In fact, Jada et al performed a meta-analysis where they also identified a number of cases in the bones of the skull including temporal, sphenoid sinus, occipital, frontal, and temporomandibular joint [Jada et al]. There is no mention of an association with Paget's disease in any of these cases despite the association of Paget's disease with giant cell tumor of bone in the craniofacial bones [Czerniak].

There have also been reports of tumors histologically similar to giant cell tumor of bone arising in other organs. Several have been reported in the uterus [Manglik et al, Skubitz and Manivel]; another was thought to be located in the thyroid but appears to have arisen in the thyroid cartilage [Derbel et al]; the thyroid cartilage case was treated with denosumab, and partial laryngectomy was required for complete resection of the tumor. It seems that treatment of these unusual giant cell tumors is no different than those arising in the usual locations in bone.

7.3 Paraneoplastic Syndromes

Paraneoplastic syndromes tend to be more common in malignant tumors than those thought to be benign or of uncertain malignant potential. Prior to 2014 in a report by Fitzhugh et al, paraneoplastic hormone secretion had only been described in malignant tumors of bone, most commonly osteosarcoma [Fitzhugh et al]. The patient in this report came to attention as she developed a positive beta human chorionic gonadotropin prior to surgery for her recurrent giant cell tumor of bone. The presence of beta human chorionic gonadotropin can be problematic as pregnancy and the presence of germ cell tumors must be excluded [Fitzhugh et al, Lawless et al]. A group from the University of Washington also encountered several patients with beta human chorionic

gonadotropin positivity in recurrent and metastatic cases of giant cell tumor of bone [Lawless et al]. It is unlikely that these incidents are isolated and it is important to be aware of this possibility to rule out the presence of pregnancy or germ cell tumors in these patients [Fitzhugh et al, Lawless et al].

8. Prognosis

Giant cell tumor of bone is well known to be a locally aggressive tumor with a propensity for recurrence. It is also well known, despite its benign classification, to metastasize to the lungs [Czerniak]. What is unclear is how to predict prognosis in patients with giant cell tumor of bone. Several genes and markers have been examined in order to attempt to predict recurrence and metastasis in giant cell tumor of bone. p63 overexpression has been observed in giant cell tumors [Lau et al]. In one study, p63 immunohistochemistry was used to confirm the presence of expression by mononuclear stromal cells in giant cell tumor of bone. Real time polymerase chain reaction analysis showed a higher level of p63 activity in giant cell tumors than what was observed in mesenchymal stem cells. In addition, knockdown of the p63 gene resulted in cell cycle arrest and reduced cell proliferation in giant cell tumors [Lau et al]. Another group compared p63 expression in giant cell tumor of bone to that of other giant cell rich tumors including chondroblastoma and aneurysmal bone cyst and found that p63 expression was highest in giant cell tumor of bone [Lee et al]. It seems then that p63 can be used as a diagnostic marker in giant cell tumor of bone [Lee et al] and that it may play a role in giant cell tumor of bone tumorigenensis [Lau et al]. However, there is no prognostic role for p63 at this time. Attempts at gene expression profiling to determine prognostic genes for giant cell tumor of bone have also been performed. In one study, lumican and decorin were found to be tumor specific and that the downregulation of these extracellular matrix components are associated with giant cell tumors that metastasize to lung [Lieveld et al]. In another study, downregulation of connexin43 with gap junction coupling in the stromal cells of giant cell tumor of bone was associated with clinical progression and poorer prognosis in giant cell tumor of bone [Balla et al].

Other groups have attempted to look at clinical risk factors to determine patients at risk for recurrence and/or metastasis in giant cell tumor of bone. One group found, based on their analysis, that patients who are younger, develop local recurrence, and/or present with axial disease have a higher risk of recurrence [Chan et al]. Another study indicated that large tumor size is a risk factor for local recurrence [Teixeira et al].

It seems, despite many attempts, that it remains difficult to predict the prognosis of giant cell tumors of bone. While some clues have been established as to which patients may recur or develop lung metastases, it does not appear that any of these are in regular use in clinical practice.

9. Conclusion

Giant cell tumor of bone is a relatively rare tumor that most commonly affects the long bones but has been reported in many of the bones of the skeletal system. It is most common in skeletally mature patients although reports of involvement in skeletally immature patients exist. There is a slight female predilection. While surgery continues to be the mainstay of treatment in these patients, adjuvant therapies, such as the fully human monoclonal antibody denosumab has emerged as a nonsurgical therapeutic option. It is important for surgeons, radiologists, and pathologists to be aware of giant cell tumor, its presentation,

and the many recent advances in the treatment as well as unusual presentations and possible pitfalls in diagnosis.

10. Figures

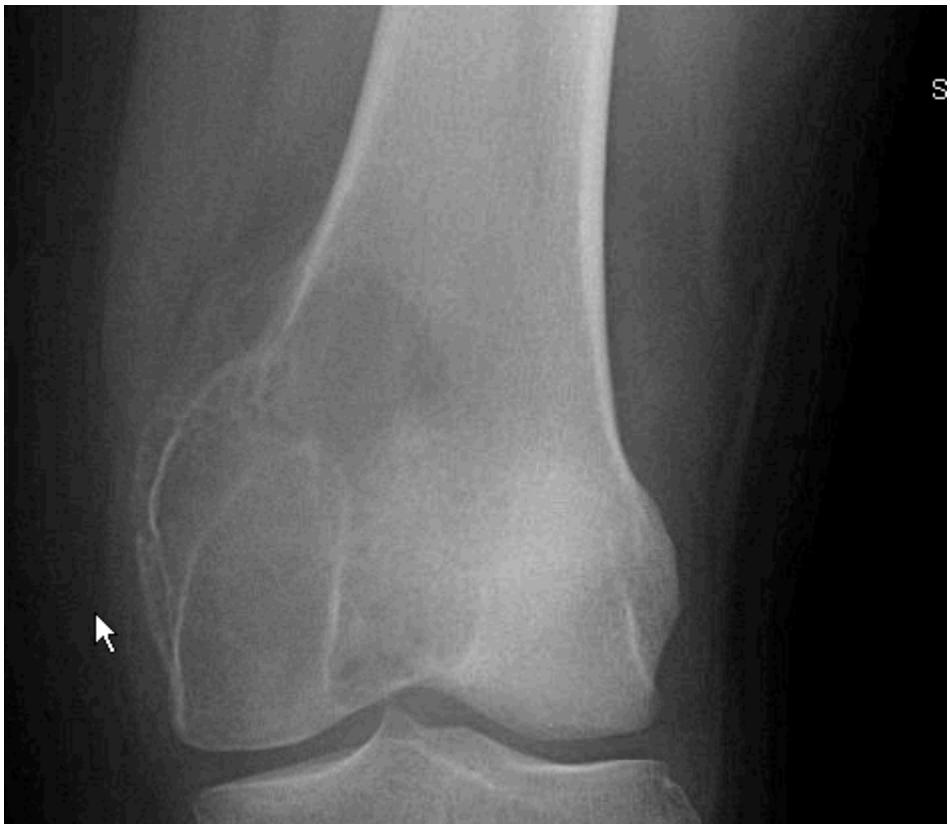

Fig 1: Standard radiograph of a giant cell tumor of bone. The image demonstrates an eccentric lytic lesion of the distal femur involving the epiphysis and metaphysis. There is no sclerotic border about the edges of the lesion.

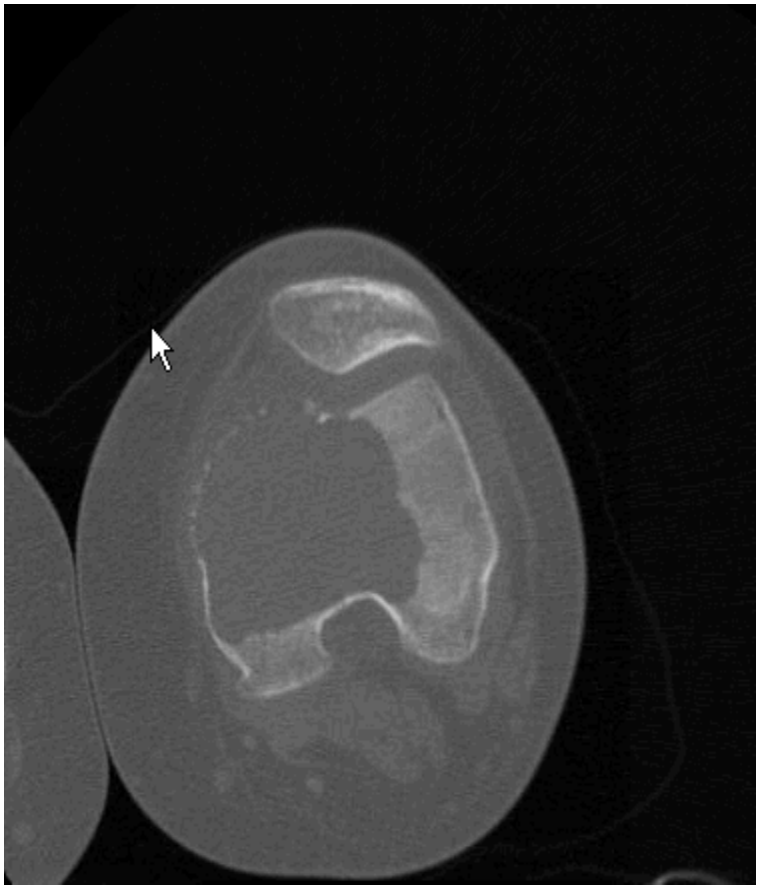

Fig 2: Computed tomography scan of giant cell tumor of bone of the distal femur. There is no bony sclerosis, but the cortex has been broken by the tumor.

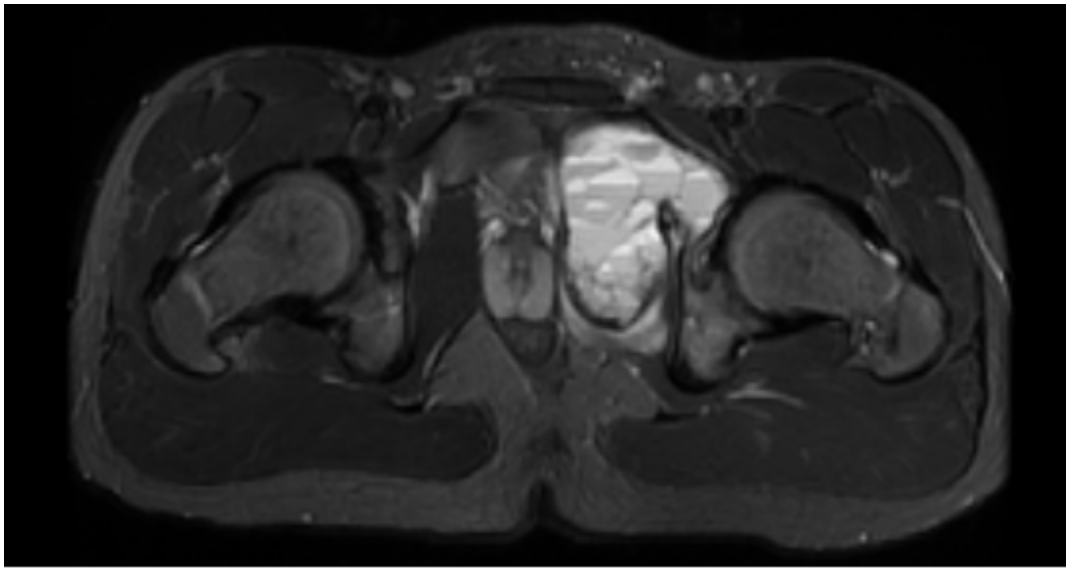

Fig 3. Numerous fluid-fluid levels appreciated on magnetic resonance imaging of a tumor with an extensive aneurysmal bone cyst component.

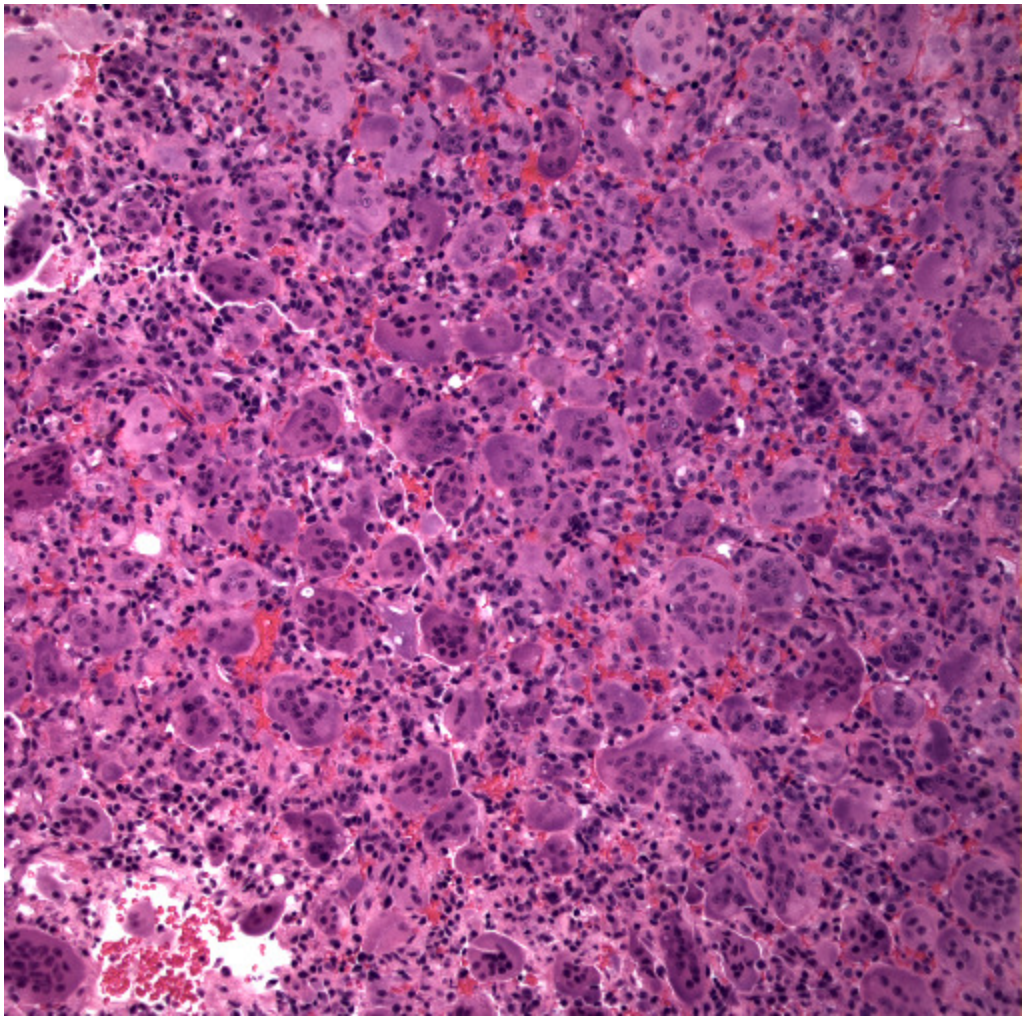

Fig 4. Giant cell tumor of bone demonstrating numerous osteoclast-like giant cells with intertwined stromal cells (hematoxylin and eosin stain, 20X original magnification).

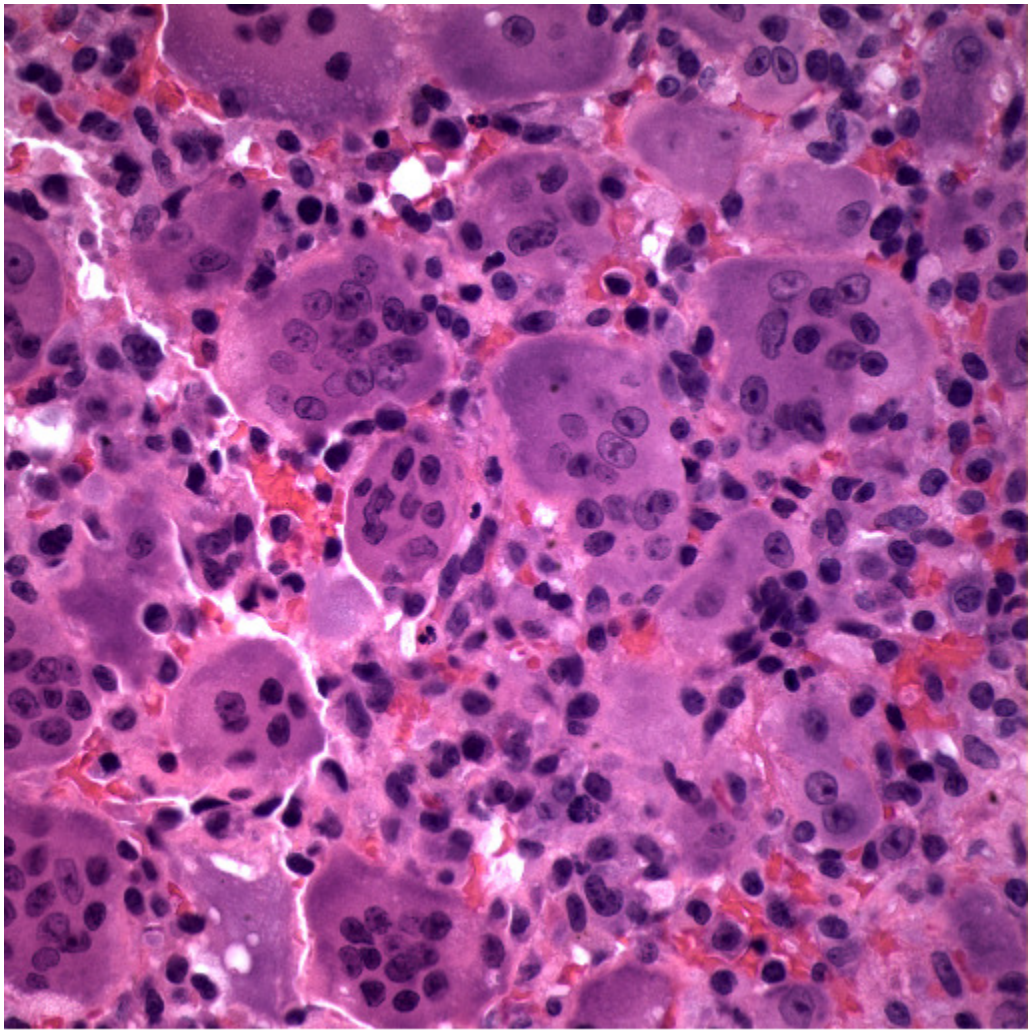

Fig 5. Giant cell tumor of bone again demonstrating evenly distributed giant cells with interspersed mononuclear cells without distinct cell borders (hematoxylin and eosin stain, 60X original magnification).

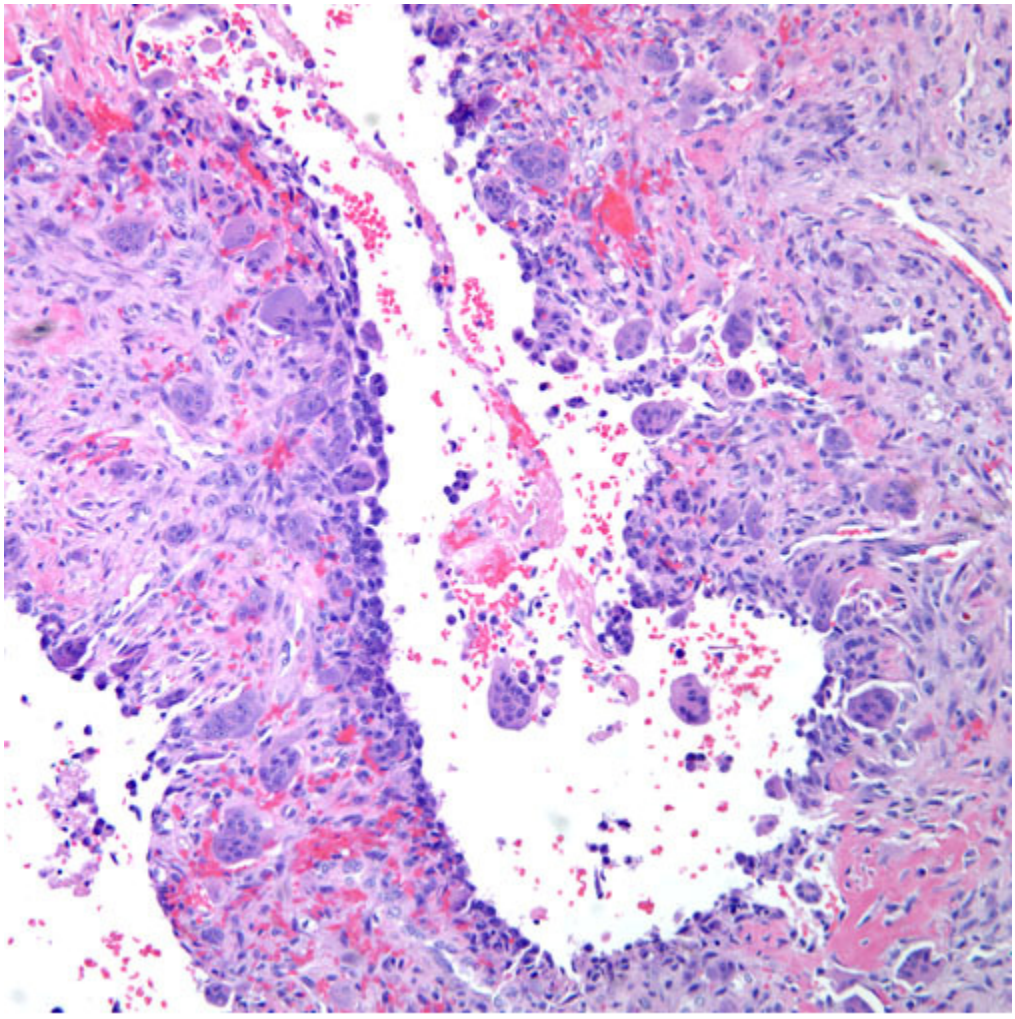

Fig. 6- Aneurysmal bone cyst component. The stroma of the cyst contains occasional multinucleate giant cells, benign osteoid, and fibroblast cells (hematoxylin and eosin stain; 10x original magnification).

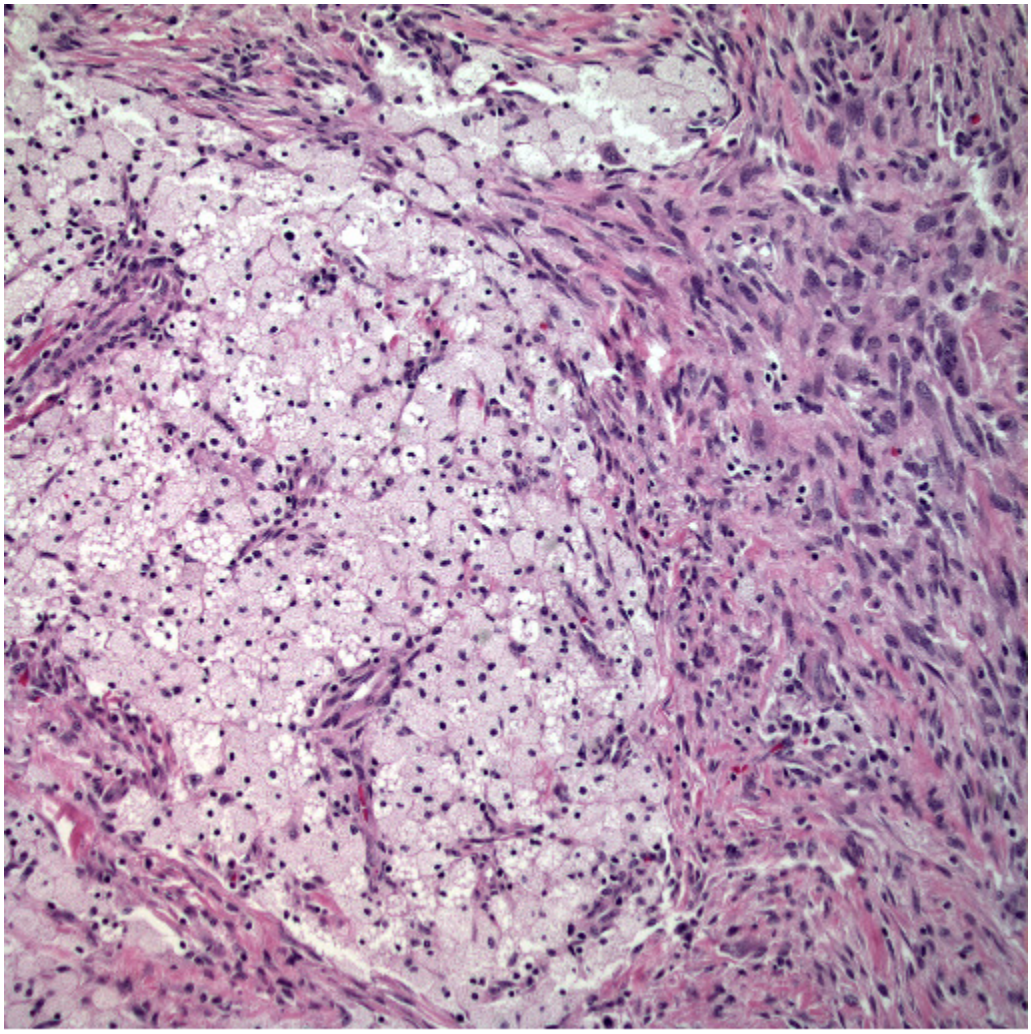

Fig 7: Hematoxylin and eosin stained image of the fibrohistiocytic component within a giant cell tumor of bone. There is a storiform spindle cell component (right side of the image) and numerous xanthomatous cells (left side of the image) (original magnification 20X).

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