

Clear-cell chondrosarcoma of the humerus

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Clear-cell chondrosarcoma is a rare, low-grade variant of chondrosarcoma characterized by slow growth, low metastatic potential, and a predilection for local recurrence long after treatment. We report an unusually aggressive case of clear-cell chondrosarcoma of the humerus with early metastasis to multiple bony sites including femur, thoracic and lumbar spine, sacrum, and iliac bone. Our purpose is to alert physicians to the sarcoma's potential for aggressive behavior, necessitating closer and more frequent followups for early detection and treatment of tumor recurrence and metastasis. We also review the reported imaging and histological features, which may help identify aggressive cases.

Introduction

Clear-cell chondrosarcoma (CCS) was first described by Unni in 1976 as a low-grade variant of chondrosarcoma (1). CCS accounts for less than 2% of the total cases of chondrosarcoma; the target population is predominantly males between the third and fifth decades of life (2). CCS arises most commonly in the proximal epimetaphyseal regions of the femur, followed by the humerus, and patients present typically with a history of longstanding local pain in the affected limb (2). Radiologically, CCS appears on radiographs and CT imaging as a radiolucent lesion in the epiphyseal region of long bones with distinct sclerotic borders, causing bone expansion, increased calcification, and absence of periosteal reaction and soft-tissue mass (3-5). These findings are not specific for CCS and are also shared by other bone tumors, including chondroblastoma and

giant-cell tumor (4). CCS is characterized on MRI by a low-to-moderate signal intensity on T1-weighted, and high signal intensity on T2-weighted, images (4, 6). The gold standard for diagnosis of CCS remains CT-guided biopsy of the tumor.

Histologically, the tumor displays a lobulated pattern of growth. Tumor cells show abundant clear cytoplasm with a centrally located nucleus and a prominent nucleolus. Bony trabeculae may be prominent; in some cases, a component of conventional chondrosarcoma may be present. Although it is a morphologic diagnosis, positive S-100 staining in tumor cells can be a useful adjunct (3).

Definitive treatment for CCS is complete surgical resection of the tumor with wide margins. Simple excision and curettage has been shown in several studies to be associated with increased recurrence and worse prognosis and thus is not an acceptable treatment option (1, 2). CCS is not sensitive to radiation or chemotherapy; nevertheless, radiation therapy is sometimes used to treat lesions that are not amenable to surgical resection (1, 2). The prognosis of CCS is excellent when treated adequately with wide surgical resection, with the 10 years' disease survival approaching 90%. However, CCS has a tendency for very late recurrence and metastasis 20 years after initial diagnosis (1, 2, 7). In this case report, we present an unusual case of CCS with early multiple bony metastasis.

Case report

A 65-year-old Caucasian male was referred to the orthopedic clinic by his primary care physician for evaluation of chronic right proximal humeral pain, increasing in severity

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over the last 2-3 years. The pain was treated intermittently with anti-inflammatory medications before presentation. However, these were not adequate, and his arm pain began to significantly interfere with daily activities.

His past medical history included arthritis, hyperlipidemia, thyroid disease, and acid reflux. His past surgical history was notable for thyroid, spinal, and wrist surgeries, all for benign conditions. The family history was positive for arthritis. He worked in construction, quit smoking 16 years ago, and never consumed alcohol. Neurological and musculoskeletal exams were normal during his initial evaluation except for decreased range of motion with flexion, extension, abduction, and external rotation of the right shoulder.

A series of plain-film radiographs performed by his referring primary care physician to evaluate the right shoulder demonstrated dense calcifications within the epiphysis of the humeral head that had progressed to involve the metaphysis, recontouring it. There was also likely involvement of the right shoulder joint and glenoid (Fig. 1A). The differential diagnosis based on the plain radiographs included primary bone tumors (chondrosarcoma and osteosarcoma), secondary lesions such as metastatic disease, lymphoma, and Paget's disease/Pagetoid sarcoma.

A full diagnostic workup was initiated, including a CT and MRI of the right shoulder. This showed an extensive chondroid matrix and extraosseous extension of the tumor compatible with intermediate- to high-grade bone tumor, suspicious for chondrosarcoma (Fig. 1B-F). Results of a CT-guided needle biopsy of the tumor were consistent with a grade 2 chondrosarcoma, and it ultimately proved to be a clear-cell chondrosarcoma of the humerus with invasion into the glenohumeral joint. Further workup with a whole-body bone scan (Fig. 2) identified a worrisome lesion in the right T1 transverse process, and another worrisome lesion in the contralateral left femur (measuring 6 x 8 mm), which was subsequently biopsied under CT guidance and proved to be metastatic clear-cell chondrosarcoma.

The patient underwent extra-articular proximal humerus resection (Figs. 3A-B) and segmental proximal humeral endoprosthesis reconstruction and radiofrequency ablation of the left femoral lesion and transverse process lesions. Histologic examination revealed typical features of clear-cell chondrosarcoma (Figs 3C-D).

Following surgery, the patient did well. He did not receive any systemic adjuvant therapy on the basis of the tumor subtype and grade. He also remained clinically and radiographically without evidence of disease for one year following surgery. Shortly after his one-year followup, he started to experience significant substernal chest pain with shortness of breath, and he was admitted to the hospital. During workup for this pain, a CT scan of the chest demonstrated a lesion in the thoracic spine at T2. Further imaging workup of the spine also showed a lesion in the L1 vertebral body consistent with metastatic disease, and metastatic lesions in the left sacrum and right ilium. Notably, the lesion at the T2 level was the most advanced and involved the central and right lateral vertebral body, pedicle, and posterior elements. There was approximately 50% canal

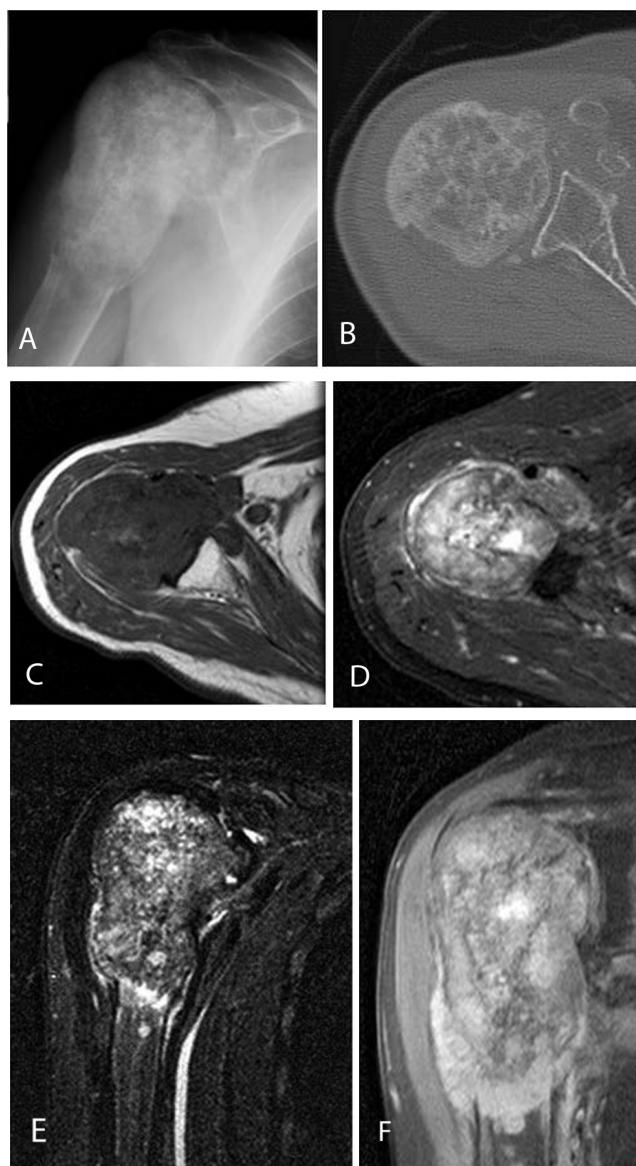


Figure 1. 67-year-old male with clear-cell chondrosarcoma of the humerus. **A.** Plain radiograph of proximal right humerus demonstrates diffuse sclerosis. Also evident are articular margins, irregularities reconstituted by tumor matrix, ill-defined glenoid, and increase in matrix density in the subcoracoid bursal space. **B.** Axial CT of proximal humerus at tip of coracoids demonstrates intra-articular bodies and tumor matrix in the medullary canal with disorganized cortical margination and reactive sclerosis. **C** and **D.** Comparable axial T1 and T2 with fat saturation at inferior glenoid. Note complete fat marrow replacement and extension of tumor into anteromedial joint recess and expansion of lesser tuberosity. **E.** Coronal inversion recovery demonstrates diffuse marrow involvement, and tumor involving the articular segment and extending into the metadiaphyseal junction with permeation of the cortices and medial subcoracoid extension into the joint. **F.** Postgadolinium imaging shows heterogeneous enhancing tumor, replacement of marrow cavity cortices, and periosteal surface with extension along undersurface of the supraspinatus tendon of the rotator cuff and diaphyseal satellite lesions.

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Figure 2. 67-year-old male with clear-cell chondrosarcoma of the humerus. Technetium MDP total body bone scan with notable uptake in primary tumor location in right shoulder, secondary site uptake in mid left femur, and right transverse process of T1 consistent with metastatic disease.

compromise at this level, but the patient remained neurovascularly intact. He was discharged on a course of dexamethasone treatment with early followup with his orthopedic oncologist. Due to impending neurologic compromise, a low likelihood of response to systemic or radiation treatment, and the absence of any visceral disease, intralesional decompression and resection of the metastatic lesion at T2, followed by C4 to T5 posterior spinal instrumentation and fusion, was undertaken. Histologic examination of that tumor showed an identical appearance to the patient's primary tumor without high-grade transformation. Three years after his initial surgery, the patient has had slowly progressive bony disease without other intervention and remains asymptomatic; his only disability is poor shoulder range of motion and function due to his shoulder replacement.

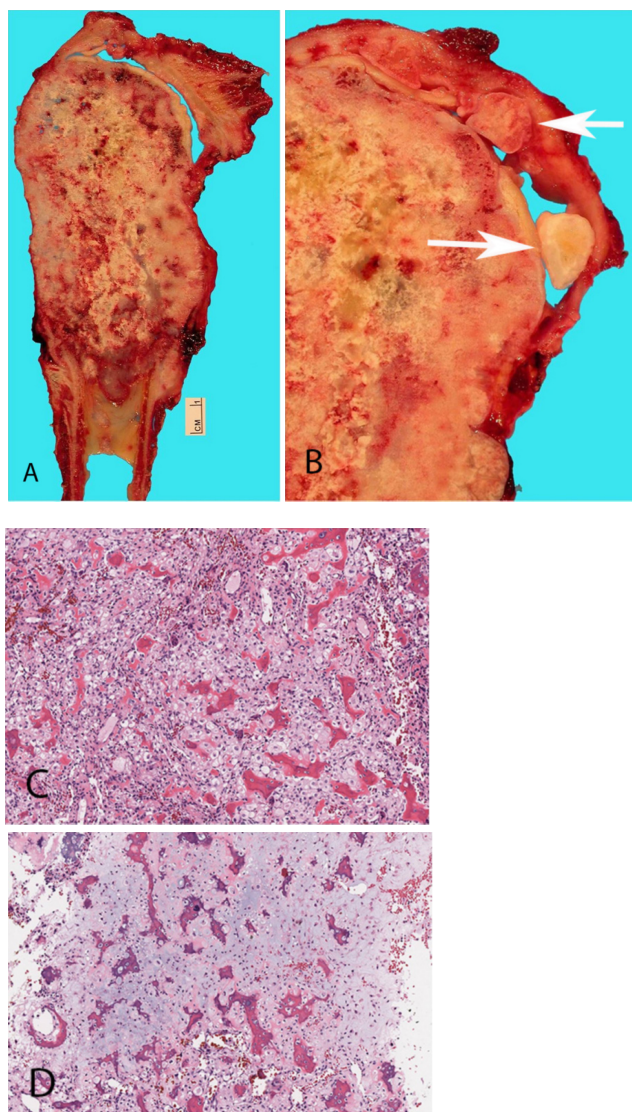


Figure 3. 67-year-old male with clear-cell chondrosarcoma of the humerus. **A.** Resection specimen shows epimetaphyseal-based lesion with cortical invasion. **B.** Resection specimen shows intra-articular tumor loose bodies (arrows). **C.** Sheets of clear cells with scattered multinucleated giant cells and bony trabeculae (H&E x200). **D.** Transition to hyaline cartilage-rich foci (H&E x200).

Discussion

CCS is a very rare low-grade malignant bone tumor that accounts for less than 2% of all cases of chondrosarcoma. The main diagnostic challenge in CCS is that it typically presents with nonspecific symptoms such as longstanding limb pain. The radiographic findings are also nonspecific and may invoke several benign bone lesions, accounting for missed or late diagnosis. In this case, the patient complained of chronic pain in his right shoulder for several years. Although his primary care physician followed him

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with serial radiographs, the radiographic findings were very subtle and nonspecific, leading to a late diagnosis of his tumor.

As reported in the literature, the majority of CCS cases are characterized by a protracted clinical course with a low rate of recurrence and metastasis, which may occur many years after initial diagnosis. However, it is important to recognize that (rarely) CCS may recur and/or metastasize early, despite complete surgical resection. Currently, no diagnostic features or markers predict which tumors are associated with early recurrence and worse prognosis. Interestingly, CCS tumors presenting in the proximal humerus have been associated with more aggressive radiological features, and a more aggressive clinical course compared to lesions in other long bones (4, 7). Notably, a report by Corradi et al. (8) compared the morphologic features of low-grade to aggressive cases of CCS. The authors concluded that aggressive CCS are characterized histopathologically by the presence of tumor cells with decreased cell differentiation, evidenced by round cell membranes lacking microvilli (which are typical of the low-grade tumors) and by more widespread staining for matrix metalloproteinase 2 (MMP-2), known to be important for tumor invasion and metastasis (9). Other groups have tried to identify novel diagnostic features that may help in the diagnosis and followup of CCS. A report by Ogose et al. in 2001 showed that CCS secreted serum alkaline phosphatase (SAP), suggesting that SAP may be used as a tumor marker for CCS (10). Donati et al. recently tested this hypothesis by comparing the levels of SAP pre- and post-surgical resection of CCS (7). In 11 out of the 17 patients, SAP levels were elevated. The majority of cases with elevated SAP levels before surgery had decreased or returned to normal following resection. Importantly, 4 cases with later CCS recurrence were also evaluated for SAP blood levels, and in 3 out of the 4 cases, SAP levels were increased, suggesting that SAP may be an important diagnostic adjunct to be used in addition to radiological imaging for diagnosis, treatment, and followup of patients with CCS (7).

In conclusion, while the vast majority of cases of CCS pose only a local problem with low metastatic potential, rare cases of CCS behave in an aggressive fashion and require close monitoring. Tumor characteristics found to correlate with aggressive behavior include tumor location (proximal humerus), poor tumor differentiation on histopathology with widespread positive MMP-2 staining, and increased SAP levels following resection of tumor. The presence of any of these features may be used clinically to identify the subset of CCS with the potential for aggressive behavior.

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