Clear-cell chondrosarcomas: Fine-needle aspiration cytology, radiological findings, and patient demographics of a rare entity

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Funding information
Barncancerfonden; Cancerfonden; Cancerforeningen i Stockholm; Karolinska Institutet; Stockholm County Council; Cancer Society in Stockholm; Swedish Childhood Cancer Foundation; Swedish Cancer Society

Abstract
Background: Clear-cell chondrosarcomas (CCCSs) constitute a very rare subtype of chondrosarcoma. CCCS may radiologically mimic chondroblastoma, and given the difference in surgical approach, it is important to distinguish these two entities preoperatively.

Design: Using the institutional digital records, we identified histologically verified CCCS between 1996 and 2013, where preoperative fine-needle aspiration (FNA) cytology was available. Clinical characteristics were categorized and described, and FNAs were reviewed by a panel of senior cytopathologists. In addition, corresponding radiological imaging was reviewed by senior radiologists, and a literature review on CCCS and chondroblastoma was conducted.

Results: A total of seven CCCS FNAs were identified from six patients. The cytomorphology showed low to intermediate cellular smears of clusters and single round or oval tumor cells. Tumor cells had rounded (sometimes binucleated) nuclei with limited pleomorphism and rich vacuolated cytoplasm. Chondroid background matrix was always found. While CCCS patients had a significantly higher age at diagnosis compared to chondroblastoma, no age cut-off would distinctly separate the two.

Conclusions: CCCS has distinguished cytomorphological features on FNA smears. CCCS should be considered as a possible differential diagnosis in adults (>25 years) with a radiological suspicion of chondroblastoma. Since radiology and patient age cannot conclusively distinguish CCCS from chondroblastoma, FNA may prove an important tool for correct preoperative diagnosis of CCCS.

KEYWORDS
cytomorphology, epidemiology, radiology, sarcoma

1 | INTRODUCTION

Clear-cell chondrosarcomas (CCCSs) are malignant tumors of bone origin and a rare subtype of chondrosarcoma with an estimated occurrence of only 1% to 2% of all diagnosed CS.1 The neoplasm may affect patients of all age groups but is more common in adults in the third and fourth decade of life.1-4

CCCS most commonly arise in the long bones, with the epiphysis of the proximal femur and the proximal humerus as most frequent locations, but it may also arise in other locations of the skeleton.5

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A majority of CCCSs are considered low-grade lesions, and patients may experience symptoms for as long as years prior to diagnosis. However, local recurrence as well as late metastasis to the lung and other bones are not uncommon.4,6 A single institution study including 16 patients found a 10-year disease-free survival of 68% and overall survival of 89%.6

The typical histology can be described as a chondroid tumor with lobulated growth pattern and epithelioid tumor cells with clear to pink cytoplasm which may have a foamy appearance. CCCS commonly have peripheral and intermingling bone trabeculae and adjacent areas with conventional chondrosarcoma. Occasionally osteoclastic giant cells can be identified.4,7,8 Due to its rarity, cytological descriptions of CCCS are few and limited to small groups and single cases, and the cytomalorphological features have not been reviewed in series. Differential cytomalorphological diagnoses include both benign and malignant chondroid tumors, such as giant cell tumor, osteoblastoma, and osteosarcoma, as well as metastatic clear-cell renal carcinoma.

Radiologically CCCS are described as lytic (epiphyseal) lesions, with sclerotic margins and matrix mineralization present in up to one-third of cases, while cortical destruction and extraosseous extension are rare. The most common radiological differential diagnosis is chondroblastoma, which may have a similar radiological presentation.5,9-11

While chondroblastomas can be removed with local resection, CCCS, like low-grade chondrosarcomas, should preferably be resected en bloc. It is therefore important to distinguish between these lesions preoperatively and correct fine-needle aspiration (FNA) cytology or histomorphology is crucial.

In this study, we systematically examined the cytologic features of CCCS by reviewing FNA smears from cases diagnosed at our department. To present an up-to-date profile of the clinical presentation, a literature review on CCCS was conducted. After reviewing the cases we believe that FNA cytology can, with sufficient experience and in conjunction with radiology and clinical data, offer an accurate primary diagnosis which is prerequisite for planning an optimal surgical approach.

2 MATERIALS AND METHODS

2.1 Patient samples

The archives of the Department of Clinical Pathology and Cytology at Karolinska University Hospital were searched for cases of CCCS from 1992 to 2018. Six patients with a diagnosis of CCCS and available cytological material were included. Clinical data were retrieved from the digital patient records and were available for all patients. All patient cases except for one had formalin-fixed paraffin-embedded material from either a biopsy or surgical specimen which confirmed the diagnosis. All resection specimens except for one had been submitted for external second opinion.

All FNA material was obtained by radiologic or palpation guided biopsies by cytopathologists using a 0.6 mm needle. The smears were air-dried and then stained with May–Grünwald–Giemsa. Reviews of cytological smears were performed by a panel of senior cytopathologists at our department.

2.2 Radiology and literature review

Corresponding radiology for patients above was only available in three cases and reviewed by senior radiologists. After an initial review of the diagnostic radiological imaging, we concluded that all CCCS cases were difficult to distinguish from chondroblastomas. To facilitate future differential diagnostic considerations between the two, a literature review was made for CCCS and chondroblastoma. A search was performed in PubMed using the keywords chondroblastoma or CCCS. All articles containing information on patient gender, age, and tumor size were included. Mean values for age and tumor size were calculated, as well as gender ratio. The age of individual patients, when available, was extracted to generate age histograms for both diagnoses. Primary tumor location for CCCS was extracted when available.

2.3 Ethical permission

All patients had received informed consent. The study was approved by the local ethical board (Regionala etikprövningsnämnden Stockholm, registration number 2013 1979-31).

3 RESULTS

3.1 Clinical data and patient demographics

A total of seven FNAs from six patients were reviewed. In five cases, FNAs were taken from primary tumors. The sixth patient had two samples, one from a local recurrence and one from a metastasis.

In this series, the gender distribution was even (1:1 male to female ratio) with a median age at diagnosis of 35 years (mean 34 years, min-max 16–46 years). Anatomically, all tumors were located in the extremities, most commonly in the humerus (n = 3). The median tumor size measured 5 cm (mean 5 cm, min-max 2–11 cm). Most patients had previously experienced various grade of pain with symptom duration ranging from months to years. A full summary of the clinical information is available in Table 1.

3.2 Initial FNA diagnosis

All patients had FNA performed prior to tissue biopsy and/or surgery. Four cases were recognized as sarcomatous tumors of bone or chondroid origin but not specifically CCCS; the remaining case was initially diagnosed as chondroid tumor, NOS. In the patient with tumor occurrence and metastasis a conclusive diagnosis of CCCS was given.
3.3 | Histological correlation to FNA diagnosis

All six patients had corresponding histological material available, either from tumor biopsy or surgical resection (Table 1). On histological material, three primary tumors were initially diagnosed as CCCS. The two remaining primary cases were first diagnosed as either chondroblastoma/chondroblastoma-like tumor or osteosarcoma, which were then changed to CCCS following external consultation. In three patients, a conventional chondrosarcoma component was graded histologically (I-III according to WHO-criteria): two cases were considered grade II and one case as grade III. No cases exhibited sarcomatous dedifferentiation.

3.4 | Cytomorphological features of CCCS

Upon review of the series, the cytomorphology of CCCS was found to be homogenous. All seven FNAs presented as blood-rich smears with cell clusters, single tumor cells, and a chondroid matrix in the background. In five cases, occasional benign giant cells could be identified.
The cellularity varied between low (n = 4), intermediate (n = 2), and high (n = 1). All FNA smears contained cells with rich cytoplasm and varying amounts of vacuoles. The nuclei were round (n = 5) or oval (n = 2) and eccentrically located (n = 7) with prominent nucleoli (n = 2). In four cases, binucleated cells were present. Cellular atypia was generally low, but one case had some nuclei with high-grade

**FIGURE 1** Photomicrographs showing, A, FNA smears of clear-cell chondrosarcoma showing a distinct clear-cell morphology with rich cytoplasm, rounded eccentric nuclei and occasional double nuclei. A pink chondroid matrix is visualized in the background; and, B, FNA smears of chondroblastoma, with polygonal cells, “chicken wire calcification” and chondroid matrix. All photomicrographs were captured at ×400 magnification and are presented in the same magnification.
CCCS constitute a rare subtype of chondrosarcoma and may pose a substantial diagnostic challenge. To make a correct preoperative diagnosis it is of importance to consider the clinical, radiological and cytological presentation of this entity. In this article, we describe distinct cytological and radiological features, and patient demographics of CCCS.

Among the patients with primary tumors, a cytological diagnosis of malignant bone tumor was made in four out of five patients, three of which showed chondroid features (Table 1). However, none received a conclusive diagnosis of CCCS. On surgical biopsies of these primary tumors, one was initially diagnosed as chondroblastoma and another as osteosarcoma, but both were changed to CCCS following external consultation. The sixth patient had a long course of disease with an initial diagnosis of chondroblastoma but had several recurrences, and after several years, the diagnosis was also changed to CCCS following external consultation. From these results, it is clear that CCCS offers considerable diagnostic difficulties on FNA as well as surgical biopsy material.

Due to the rarity of CCCS, it is difficult to establish a learning curve with solely clinical everyday work. With the systematic review of the FNAs, we recognize that these tumors present relatively homogenous cytological features, and a precise preoperative diagnosis should be possible in conjunction with radiology. Cytological features of CCCS include tumor cell clusters admixed with round or oval single cells with low-grade atypia. The most distinct features are the clear-cell morphology with rich and sometimes vacuolated cytoplasm and rounded eccentric nuclei. A chondroid background matrix was seen in all cases indicating a cartilage-forming tumor. This is in line with previously described cytology of CCCS.7,8

### TABLE 2

| Common cytological features of clear-cell chondrosarcomas |
|----------------------------------------------------------|
| Low to intermediate cellularity                           |
| Round to oval tumor cells                                 |
| Rich cytoplasm, occasionally with vacuoles                |
| Round, eccentric nuclei, occasionally binucleated         |
| Low-grade cellular atypia                                 |
| Chondroid matrix                                          |
| Occasional giant cell in background                        |

atypia. The typical cytological features of CCCS are shown in Figure 1A and summarized in Table 2. A typical chondroblastoma is shown in Figure 1B for comparison.

### 3.5 | Radiology

Only three out of six patients had available radiological imaging available for review. One patient (Table 1, case 2) presented with an osteolytic destruction in the epimetaphysis of the proximal femur with a partial sclerotic border on X-ray. The second patient (Table 1, case 3) had an osteolytic destruction in the epimetaphysis of the proximal tibia on X-ray and computed tomography (CT) with an extraskeletal soft-tissue component on magnetic resonance imaging (MRI) (Figure 2). The third patient (Table 1, case 4) presented with an osteolytic destruction in the epimetaphysis of the proximal humerus, with soft-tissue calcifications on X-ray and an extraskeletal soft-tissue component on MRI.

![Figure 2](image-url) Clear-cell chondrosarcoma (case 3) in tibia with a pathological fracture, osteolytic destruction with no sclerotic margins, and a small extraskeletal posterior soft-tissue component. Modalities are, A, X-ray, B, coronal CT, and, C, sagittal T2-weighted magnetic resonance image.
The cytomorphology of chondroblastomas has previously been described, including abundant cellular smears of polygonal cells with vacuolated cytoplasm and grooved nuclei mixed with cartilage, “chicken wire calcification” and chondroid background matrix. Benign giant cells are always present and frequently ample. In the preoperative evaluation, it is of importance to conclusively differentiate between CCCS and chondroblastoma, which we believe is possible on FNA material.

Radiology is fundamental in the evaluation of bone tumors, and radiologically CCCS may simulate a chondroblastoma due to its benign appearance, occasionally with a sclerotic border. Peritumoral edema is often seen in chondroblastomas but may also appear in CCCS. In our limited material, a soft-tissue component clearly favored a CCCS, as was seen in two out of three cases available for review. A larger size is often described as an important feature when differentiating CCCS from chondroblastomas, but was not evident in our review. In concordance with previous studies, we found that CCCSs are most often located in the epiphysis or epimetaphysis of long bones. Radiological differential diagnoses include chondroblastoma, giant cell tumors, and osteomyelitis. Both giant cell tumors of bone and osteomyelitis can often be excluded due to the clinical presentation and differences in radiological appearance. An epiphyseal or epimyseal lesion suggesting chondroblastoma on radiology, especially in older adults, should include CCCS as a differential diagnosis.

| Diagnosis                     | Males | Females | Male to female ratio | Age (mean, years) | Tumor size (mean, cm) |
|-------------------------------|-------|---------|----------------------|-------------------|----------------------|
| Clear-cell chondrosarcoma     |       |         |                      |                   |                      |
| All                           | 198   | 78      | 2.5:1                | 41.4              | 6.6                  |
| Current study                 | 3     | 3       | 1:1                  | 33.5              | 5.3                  |
| Chondroblastoma               |       |         |                      |                   |                      |
| All                           | 2504  | 1195    | 2.1:1                | 20.7              | 3.5                  |
| Extra-craniofacial            | 2413  | 1130    | 2.3:1                | 19.8              | 3.5                  |
| Craniofacial                  | 91    | 65      | 1.4:1                | 39.6              | 4.9                  |

The gender distribution of clear-cell chondrosarcoma, which is usually male-biased. B, Age histogram of clear-cell chondrosarcoma, illustrating a peak at the fourth decade of life. C, Anatomical distribution of clear-cell chondrosarcoma [Color figure can be viewed at wileyonlinelibrary.com]
A literature review was also conducted and a full summary is shown in Table 3. Using PubMed search, 237 articles were found to contain the “phrase clear cell chondrosarcoma.” Of these, 76 articles contained clinical data from a total of 276 patients and were included. Gender distribution was male-biased and CCCS was more common in adults, with average age at diagnosis in the fourth decade of life. Primary tumor location was available from 235 patients and the majority of CCCS were located in either the femur (53%, n = 124) or the humerus (14%, n = 33). These findings are visualized in Figure 3.

A total of 1400 articles were found containing the phrase chondroblastoma. Of these, 385 articles contained information on patient age, gender, and tumor size, and were included. In total, data from 3699 chondroblastoma patients were gathered. Gender distribution was biased toward males (similar to CCCS), and average age at diagnosis was 21 years. The patients were subsequently divided into two categories: craniofacial and extra-craniofacial chondroblastomas. In both sub-categories, gender distribution remained male-biased. Craniofacial chondroblastomas were more common in adults, while extra-craniofacial chondroblastomas were more common in young adults.

When available, the age of individual patients was extracted (n = 1016 for chondroblastoma and n = 209 for CCCS) and were used for plotting age histograms for the diagnoses (Figure 3). Statistically, the age at diagnosis was significantly higher for CCCS than chondroblastoma (Mann-Whitney U, P < .0001), but there was no clear age at which one clearly could dismiss one or the other diagnosis (Figure 4).

In summary, CCCS has distinguished cytomorphological features, although its anatomical distribution and radiological presentation is very similar to the more common chondroblastoma. While patients with CCCS are significantly older than patients with chondroblastoma, no clear age cut-off can differentiate between the diagnoses. Nonetheless, a patient aged ≥25 years with a radiological presentation of chondroblastoma should raise suspicion for CCCS. Since radiology, clinical presentation, and patient demographics insufficiently distinguish CCCS from chondroblastoma, FNA may prove an important tool for correct preoperative diagnosis.

ACKNOWLEDGMENTS
This study was funded by the Swedish Cancer Society, the Swedish Childhood Cancer Foundation, the Cancer Society in Stockholm, the Stockholm County Council, and Karolinska Institutet. The authors would like to thank the senior cytopathologists Johan Wejde, Kristina Åström, Sandra Wessman, and Lambert Skoog at the Karolinska University Hospital for valuable discussion and reviewing of cases.

CONFLICT OF INTEREST
The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS
Felix Haglund designed the study; Felix Haglund, Yifan Zhang, Edneia Tani, Zlatan Alagic, and Mikael Skorpil reviewed cases; Yifan Zhang, Zlatan Alagic, Mikael Skorpil, and Panagiotis Tsagkos collected the data; Yifan Zhang, Felix Haglund, and Zlatan Alagic analyzed the data, Yifan Zhang, Felix Haglund, Mikael Skorpil, and Edneia Tani wrote the manuscript.

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