Bone: Chondrosarcoma

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Published in Atlas Database: January 2000

Online updated version : http://AtlasGeneticsOncology.org/Tumors/chondrosarcoma5063.html

DOI: 10.4267/2042/37602

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Identity

Figure 1: En bloc resection specimen of the proximal fibula of a 43 year old female, containing a lobulated bluish white, translucent tumour (4.5 x 2 x 1.9 cm) located centrally within the medullary cavity, consistent with central chondrosarcoma.

Classification

Note: Approximately 90% of chondrosarcomas are histologically of the conventional type; in addition to conventional chondrosarcoma, some rare variants with distinctive microscopic and clinical features are discerned: clear cell chondrosarcoma (1%), mesenchymal chondrosarcoma (2%), juxtacortical chondrosarcoma (2%) and extra-skeletal myxoid chondrosarcoma (5%). Furthermore, dedifferentiated chondrosarcoma is a relatively rare high grade sarcoma next to a low-grade conventional malignant cartilage-forming tumor, comprising 6-10% of all chondrosarcomas. Conventional chondrosarcoma can be categorized according to their location in bone.

Figure 2: Corresponding macro-slice showing a lobular architecture, and endosteal cortical thinning. Cytonuclear appearance can be more readily appreciated in figure 3.
Figure 3: Micrograph displaying low cellularity with limited cytonuclear atypia, and a high amount of chondroid matrix surrounding tumor cells consistent with a grade I chondrosarcoma. Note the presence of a binucleated cell.

The majority of chondrosarcomas (75%) are located centrally within the medullary cavity (central chondrosarcoma), whereas a minority (15%) develops from the surface of bone (peripheral chondrosarcoma) as a result of malignant transformation within the cartilaginous cap of a solitary or hereditary pre-existent osteochondroma.

**Clinics and pathology**

**Epidemiology**
Primary malignant bone tumours occur 1/100,000, of which 17-24% consists of chondrosarcoma; the majority of patients are between 35 and 60 years old with equal sex distribution.

**Clinics**
Compared to benign cartilaginous tumours, chondrosarcomas more frequently present with pain and tenderness; they usually develop in the trunk, pelvis and long bones.

**Pathology**
There are no apparent cytonuclear differences between central and peripheral conventional chondrosarcomas and both are histologically classified into three grades using the criteria of Evans et al. Grade I chondrosarcomas demonstrate low cellularity, limited cytonuclear atypia, few multinucleated cells, a mainly chondroid matrix and the absence of mitoses; In contrast, grade III chondrosarcomas are highly cellular, with nuclear polymorphism, mitoses and a mostly myxoid matrix; Increasing histological grade is correlated with higher metastatic potential; it is considered difficult to assess the histological grade of cartilaginous tumours and to reliably distinguish between benign tumours and those of low-grade malignancy.

**Treatment**
Because chondrosarcoma is highly resistant to chemotherapy and radiotherapy, surgical treatment is the only option for curative treatment.

**Evolution**
The majority of central chondrosarcomas are considered to arise de novo and malignant transformation of solitary enchondroma is extremely rare (<1%); in patients demonstrating multiple enchondromas, such as Ollier's disease, the incidence of secondary central chondrosarcoma is much higher (30-35%); peripheral chondrosarcomas usually originate from the cartilaginous cap of an osteochondroma; malignant transformation is low in solitary osteochondromas (<1%) but is estimated to occur in 1-5% of cases of hereditary multiple exostoses; furthermore, an occasional recurrent chondrosarcoma may exhibit a higher grade of
malignancy than the original neoplasm, suggesting that tumours may additionally progress from low to high grade.

**Prognosis**

Metastasis in chondrosarcoma highly depends on the histological grade of malignancy; grade I chondrosarcomas demonstrate local recurrence, but seldom metastasize; grade II chondrosarcomas demonstrate metastases in 10-30% of the cases, whereas grade III chondrosarcomas demonstrate metastases in the majority of cases; in contrast to chondrosarcomas located elsewhere in the skeleton, those located in the phalanx behave as a locally aggressive lesion with minimal metastatic potential.

**Cytogenetics**

**Cytogenetics Morphological**

Extra-skeletal myxoid chondrosarcoma, comprising 5% of all chondrosarcomas, is characterized by a reciprocal translocation t(9;22)(q22;q12), fusing the EWS to the CHN gene. Cyto genetic analysis on a heterogeneous group of chondrosarcomas revealed that structural aberrations of chromosomes 1, 6, 9, 12 and 15 and numerical aberrations of chromosomes 5, 7, 8 and 18 were most frequent; abnormalities of chromosome 1 and 7 were confined to malignant cartilaginous tumours; like in other mesenchymal neoplasms, band 12q13-15 is prominently involved in the aberrations; the presence of chromosome aberrations was found to strongly correlate with increasing histological grade; complex aberrations were mainly seen in the high-grade chondrosarcomas.

**Cytogenetics Molecular**

In a comparative study of central and peripheral chondrosarcomas, 19 of 20 peripheral chondrosarcomas showed LOH at all loci (EXT, EXTL, 13q14, 17p13, 9p21 and chromosome 10) tested while only 3 of 12 central chondrosarcomas exhibited LOH, restricted to 9p21, 10, 13q14 and 17p13. DNA-flow-cytometry demonstrated a wide variation in the ploidy status in peripheral chondrosarcomas (DNA-indices 0.56 to 2.01), whereas central chondrosarcomas were predominantly periploid; these results indicate that peripheral chondrosarcomas, arising secondarily to an exostosis, may obtain genetic alterations during malignant transformation, with subsequent genetic instability as demonstrated by a high percentage of LOH and a wide variation in ploidy status; in contrast, periploid and a low percentage of LOH in central tumors suggest that a different oncogenic molecular mechanism may be operative; no mutations in the EXT1 and EXT2 genes were found in secondary peripheral chondrosarcoma. Investigating both the cartilaginous as well as the high-grade malignant component of dedifferentiated chondrosarcoma, an identical somatic 6 bp deletion in exon 7 of p53 and loss of the same copy of chromosome 13 provided compelling evidence for a common origin instead of the 'collision tumor' theory; in addition, many different genetic alterations were found, indicating that the separation of the two clones is a relatively early event in the histogenesis of dedifferentiated chondrosarcoma. Unfortunately, most other genetic analyses on chondrosarcoma were performed on a heterogeneous group including all different subtypes of chondrosarcoma; ploidy-analysis of chondrosarcomas has been described and aneuploidy is more frequently found in high-grade chondrosarcomas; two series of chondrosarcomas (n=23 and n=50) studied by CGH revealed extensive genetic aberrations; the majority of these changes were gains of whole chromosomes or whole chromosome arms, most frequent at 20q (32-38%), 20p (24-31%), and 14q23-qter (24-28%); a correlation between gain at 8q24.1 and shorter overall survival was reported; amplification of the c-myc proto-oncogene, located at 8q24, was found in four of 12 chondrosarcomas, and was not associated with any clinicopathological features; the only recurrent high-level amplification, seen in two tumours (7%), affected the minimal common region 12cen-q15; although both cytogenetic analysis and CGH point at 12cen-q15, CDK4, MDM2 and SAS were not frequently amplified in chondrosarcoma. Partial allelotypings of a heterogeneous group of chondrosarcoma revealed that in addition to LOH at the EXT-loci on chromosomes 8 (4/17) and 11 (7/17), LOH was found at 10q11 (12/18), the Rb - (9/25) and p53-locus (7/28). Overexpression of the p53 protein and TP53 mutations have been observed mainly in high-grade chondrosarcomas, suggesting that the p53 gene could play a role in the progression of chondrosarcoma.

**References**


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