Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Solid Tumour Section

Mini Review

Bone: Chondrosarcoma

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Published in Atlas Database: January 2000

Online updated version : http://AtlasGeneticsOncology.org/Tumors/chondrosarcID5063.html
DOI: 10.4267/2042/37602

Identity

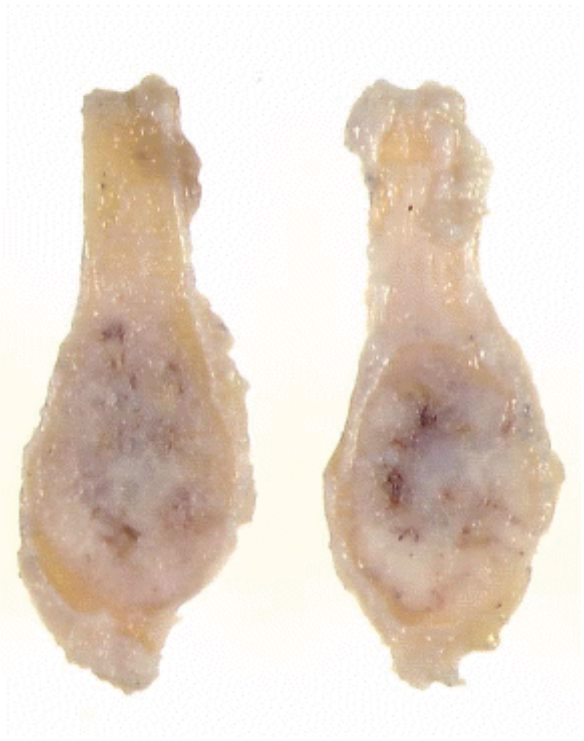

Figure 1: En bloc resection specimen of the proximal fibula of a 43 year old female, containing a lobulated bluish white, translucent tumour (4.5 x 2 x 1.9 cm) located centrally within the medullary cavity, consistent with central chondrosarcoma.

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.

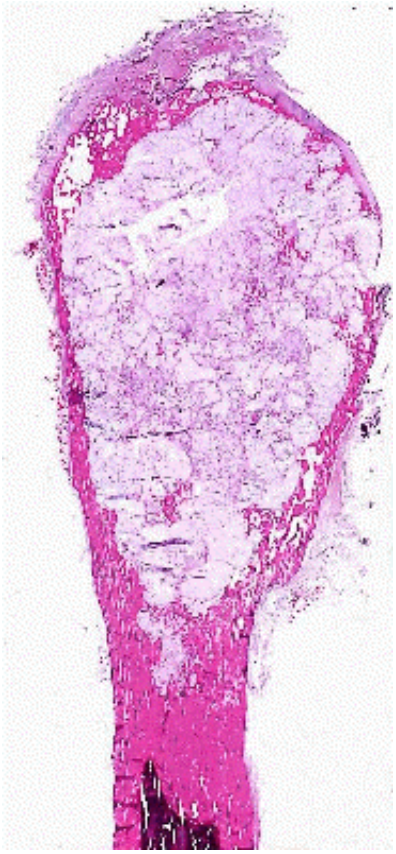

Figure 2: Corresponding macro-slice showing a lobular architecture, and endosteal cortical thinning. Cytonuclear appearance can be more readily appreciated in figure 3.

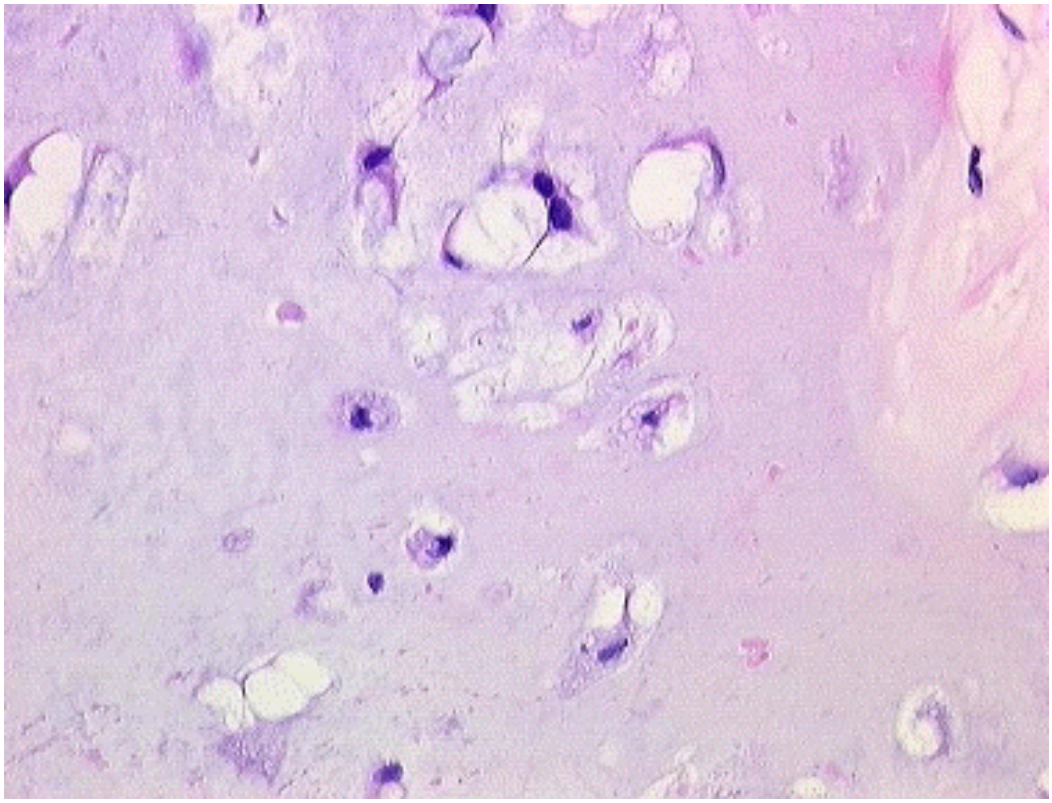

Figure 3: Micrograph displaying low cellularity with limited cytonuclear atypia, and a high amount of chondroid matrix surrounding tumor cells consistent with a grade I chondrosarcoma. Note the presence of a binucleated cell.

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 metasases 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.

Cytogenetic 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 - 2.01), whereas central chondrosarcomas were predominantly peridiploid; 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, peridiploidy 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.

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This article should be referenced as such:

Bovée JVMG. Bone: Chondrosarcoma. Atlas Genet Cytogenet Oncol Haematol. 2000; 4(1):42-45.