Bone: Chondrosarcoma

Judith VMG Bovée

Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands (JVMGB)

Published in Atlas Database: March 2002

Online updated version: http://AtlasGeneticsOncology.org/Tumors/chondrosarcomaID5063.html

DOI: 10.4267/2042/37884


This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.

© 2002 Atlas of Genetics and Cytogenetics in Oncology and Haematology

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.

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

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 chondrosarcomas can be categorized according to their location in bone. The majority of chondrosarcomas (75%) are located centrally within the medullary cavity (central chondrosarcoma), a small percentage of which arise within a preexisting benign precursor (enchondroma).
While most enchondromas are solitary, patients with Ollier's disease and Maffucci's syndrome demonstrate multiple enchondromas. A minority (15%) of chondrosarcomas 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.
- Grade II chondrosarcomas demonstrate increased cellularity, and increased muco-myxoid degeneration of the matrix. There is moderate cytonuclear atypia and occasional mitoses are found.
- 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.

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.
**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, 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 (especially trisomy 7) were confined to malignant cartilaginous tumours; like in other mesenchymal neoplasms, band 12q13-15 is prominently involved in the aberrations. - Aberrations of chromosome 9, especially the 9p12-22 region are more common in central chondrosarcomas. - The presence of chromosome aberrations was found to strongly correlate with increasing histological grade; complex aberrations were mainly seen in the high-grade chondrosarcomas. - Loss of 13q was found to be an independent factor for metastasis, regardless of tumor grade or size.

**Additional anomalies**

- In a comparative study of central and peripheral chondrosarcomas, 19 of 20 peripheral chondrosarcomas showed LOH at all loci (EXT, EXT1, 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 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 at a wide variation in ploidy status. In contrast, periploidy and a low percentage of LOH in central tumors suggest that a different oncogenic molecular mechanism may be operative; no somatic mutations in the EXT1 and EXT2 genes were found in secondary peripheral chondrosarcoma.

- A mutation (R150C) in the PTH/PTHrP type I receptor was demonstrated in 2 patients with Ollier’s disease (one germline and one somatic), while this mutation was absent in 50 sporadic chondrosarcoma specimens.

- 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, 17p1 alterations 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.

- Dedifferentiated 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.

**References**


content and histopathologic classification. Cancer. 1984 Jan
1;53(1):129-36

Xiang JH, Spanier SS, Benson NA, Braylan RC. Flow
cytometric analysis of DNA in bone and soft-tissue tumors

Castresana JS, Barrios C, Gómez L, Kreicbergs A. Amplification

Barrios C, Castresana JS, Ruiz J, Kreicbergs A. Amplification
of c-myc oncogene and absence of c-Ha-ras point mutation in

Bridge JA, Bhata PS, Anderson JR, Neff JR. Biologic and
clinical significance of cytogenetic and molecular cytogenetic
abnormalities in benign and malignant cartilaginous lesions.
Cancer Genet Cytogenet. 1993 Sep;65(2):79-90

Wadayama B, Toguchida J, Yamaguchi T, Sasaki MS,
Yamamuro T. p53 expression and its relationship to DNA
alterations in bone and soft tissue sarcomas. Br J Cancer.
1993 Dec;68(6):1134-9

Wadayama B, Toguchida J, Yamaguchi T, Sasaki MS,
Yamamuro T. p53 expression and its relationship to DNA
alterations in bone and soft tissue sarcomas. Br J Cancer.
1993 Dec;68(6):1134-9

Coughlan B, Beliz A, Ishaia T, Czerniak B, Dorfman HD. p53
expression and DNA ploidy of cartilage lesions. Hum Pathol.
1995 Jun;26(6):620-4

Hasegawa T, Seki K, Yang P, Hirose T, Hizawa K, Wada T,
Wakabayashi J. Differentiation and proliferative activity in
benign and malignant cartilage tumors of bone. Hum Pathol.

Hecht JT, Hogue D, Strong LC, Hansen MF, Blanton SH,
Wagner M. Hereditary multiple exostosis and chondrosarcoma:
linkage to chromosome II and loss of heterozygosity for EXT-
1995 May;56(5):1125-31

Heiliö H, Karaharju E, Böhling T, Kivioja A, Nordling S.
Chondrosarcoma of bone. A clinical and DNA flow cytometric

Raskind WH, Conrad EU, Matsushita M. Frequent loss of
1995 Jul 15;76(2):223-7

Raskind WH, Conrad EU, Matsushita M. Frequent loss of
heterozygosity for markers linked to hereditary multiple exostoses loci on chromosomes 8 and 11.
Am J Hum Genet. 1995 May;56(5):1132-9

Simms WW, Ordóñez NG, Johnston D, Ayala AG, Czerniak B.
1995 Jul 15;76(2):223-7

Raskind WH, Conrad EU, Matsushita M. Frequent loss of
heterozygosity for markers on chromosome arm 10q in
chondrosaromas. Genes Chromosomes Cancer. 1996
Jun;16(2):138-43

Yamaguchi T, Toguchida J, Wadayama B, Kanoe H,
Nakayama T, Ishizaki K, Ikenaga M, Kotoura Y, Sasaki MS.
Loss of heterozygosity and tumor suppressor gene mutations in

Brody RJ, Ueda T, Hamelin A, Jhanwar SC, Bridge JA, Healey
JH, Huvos AG, Gerald WL, Ladanyi M. Molecular analysis of
the fusion of EWS to an orphan nuclear receptor gene in
Mar;150(3):1049-58

Larramendy ML, Tarkkanen M, Valle J, Kivioja AH, Ervasti H,
Karaharju E, Salmivalli T, Elomaa I, Knuutilta S. Gains, losses,
and amplifications of DNA sequences evaluated by

Oshiro Y, Chaturvedi V, Hayden D, Nazeer T, Johnson M,
Johnston DA, Ordóñez NG, Ayala AG, Czerniak B. Altered p53
is associated with aggressive behavior of chondrosarcoma: a
long term follow-up study. Cancer. 1998 Dec 1;83(11):2324-34

Bovée JV, Clleton-Jansen AM, Kuipers-Dijkshoorn NJ, van den
Broek LJ, Taminiau AH, Cornelisse CJ, Hogendoorn PC. Loss of
heterozygosity and DNA ploidy point to a diverging genetic
mechanism in the origin of peripheral and central
chondrosarcoma. Genes Chromosomes Cancer. 1999
Nov;26(3):237-46

Bovée JV, Clleton-Jansen AM, Rosenberg C, Taminiau AH,
Cornelisse CJ, Hogendoorn PC. Molecular genetic
characterization of both components of a dedifferentiated
chondrosarcoma, with implications for its histogenesis. J Pathol.
1999 Dec;189(4):454-62

Bovée JV, Clleton-Jansen AM, Wuysts W, Caenhoven G,
Taminiau AH, Bakker E, Van Hul W, Cornelisse CJ,
Hogendoorn PC. EXT mutation analysis and loss of
heterozygosity in sporadic and hereditary osteochondromas
Sep;65(3):689-98

Bovée JV, van der Heul RO, Taminiau AH, Hogendoorn PC.
Chondrosarcoma of the phalanx: a locally aggressive lesion
with minimal metastatic potential: a report of 35 cases and a
review of the literature. Cancer. 1999 Nov 1;86(9):1724-32

Larramendy ML, Mandahl N, Mertens F, Blomqvist C, Kivioja
AH, Karaharju E, Valle J, Böhling T, Tarkkanen M, Rydholm A,
Akerman M, Bauer HC, Aittila JP, Elomaa I, Knuutilta S.
Clinical significance of genetic imbalances revealed by
comparative genomic hybridization in chondrosarcomas. Hum
Pathol. 1999 Oct;30(10):1247-53

Bovée JV, Sciot R, Dai Cin P, Debie-Rychter M, van
Zelder-Bhola SL, Cornelisse CJ, Hogendoorn PC.
Chromosome 9 alterations and trisomy 22 in central
chondrosarcoma: a cytogenetic and DNA flow cytometric
analysis of chondrosarcoma subtypes. Diagn Mol Pathol.
2001 Dec;10(4):228-35

Bovée JVMG, Hogendoorn PCW. Cartilage forming tumors of
bone and soft tissue and their differential diagnosis. Curr Diagn
Pathol. 2001;7(4):223-34

Hopyan S, Gokgoz N, Poon R, Gensure RC, Yu C, Cole WG,
Bell RS, Jüppner H, Andrusil LS, Wunder JS, Alman BA. A
mutant PTH/PTHrP type I receptor in enchondromatosis. Nat
Genet. 2002 Mar;30(3):306-10

Mandahl N, Gustafsson P, Mertens F, Akerman M, Balderot B,
Gisselsson D, Knuutilta S, Bauer HC, Larsson O. Cytogenetic
aberrations and their prognostic impact in chondrosarcoma.
Genes Chromosomes Cancer. 2002 Feb;33(2):188-200

Tallini G, Dorfman H, Brys P, Dai Cin P, DeWever I, Fletcher
CD, Jonson K, Mandahl N, Mertens F, Mitelman F, Rosai J,
Rydholm A, Samson I, Sciot R, Van den Bergh H, Vanni R,
Wills E. Correlation between clinicopathological features and
karyotype in 100 cartilaginous and chordoid tumors. A report
from the Chromosomes and Morphology (CHAMP) Collaborative

This article should be referenced as such:
Bovée JVMG. Bone: Chondrosarcoma. Atlas Genet CytoGenet