

Solid Tumour Section

Mini Review

Bone: Osteochondroma

Liesbeth Hameetman, Judith VMG Bovée

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

Published in Atlas Database: September 2002

Online updated version : <http://AtlasGeneticsOncology.org/Tumors/OsteochondromaID5146.html>

DOI: 10.4267/2042/37937

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Identity

Note

Osteochondroma (osteocartilaginous exostosis) is a cartilage capped bony neoplasm arising on the external surface of bone containing a marrow cavity that is continuous with that of the underlying bone. It arises in bones preformed by endochondral ossification and the most common site of involvement is the metaphyseal region of the long bones of the limbs, like the distal femur, upper humerus, upper tibia and fibula. They also frequently occur in the flat bones, in particular the ilium and scapula. Osteochondromas can occur as a solitary lesion (solitary osteochondroma) or within the context of hereditary multiple exostoses (HME). The literature indicates a slight male sex predominance (male/female ratio 1.5:1) and most osteochondromas are prone to attention in the first three decades of life. Osteochondromas practically never occur in the craniofacial bones. This might be explained by the fact that these bones are not formed by endochondral ossification.

Clinics and pathology

Epidemiology

Osteochondromas are the most common benign bone tumors. They represent 35% of the benign and 8% of all bone tumours, although this is probably an underestimate since the majority are asymptomatic. Approximately 15% of patients with osteochondromas have multiple lesions (HME).

Clinics

The growth of the osteochondroma ceases at skeletal maturation or shortly thereafter. Patients may have a

swelling of years duration causing symptoms related to the location and site of the lesion such as mechanical obstruction, nerve impingement, pseudoaneurysm of an overlying vessel, fracture at the stalk of the lesion, or the formation of a bursa over the osteochondroma. However most lesions are asymptomatic and found accidentally. The most serious complication is malignant transformation towards secondary peripheral chondrosarcoma, which is estimated to occur in <1% of solitary cases and 1-3% of hereditary cases.

Pathology

Pedunculated osteochondromas contain a stalk and are long and slender, while sessile ones are flat. Many exostoses are cauliflower shaped (figure). A fibrous perichondrium covers the cartilage cap and is continuous with the periosteum of the underlying bone. The cartilage cap is less than 2 cm thick and these decreases with age. A thick (greater than 2 cm) and irregular cap may indicate malignant transformation of the tumor. The cap covers the entire elevated surface of a sessile tumor, while it only covers the distal part of a pedunculated one. The cartilage cap merges into the underlying spongiosa. Here the chondrocytes are arranged according to an epiphyseal growth plate. A typical benign chondrocyte has a single small nucleus. During active bone growth, binucleated chondrocytes may be seen in benign tumors. The spongiosa of the stalk is continuous with the underlying cancellous bone. Fractures within the stalk may produce fibroblastic proliferation and even new bone formation. A bursa may develop over the osteochondroma and is usually attached to the perichondrium of the cap. The bursal wall is lined by synovium that may show inflammatory changes.

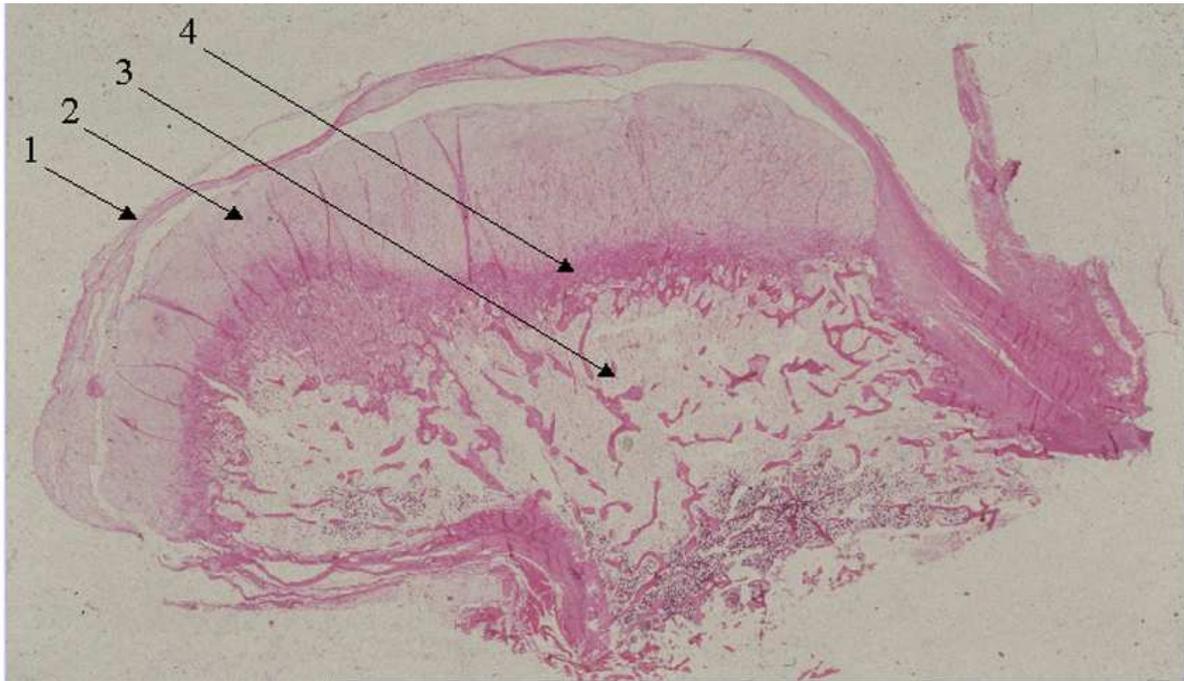


Figure 1: Histological appearance of an osteochondroma. A perichondrium (1) covers the cartilage cap (2). The cap merges into the underlying spongiosa, where the chondrocytes are arranged according to an epiphyseal growth plate (4).

Treatment

The low rate of malignant transformation (<1%) is insufficient reason for resection. Osteochondromas are usually removed for cosmetic reasons, when symptoms of pain, limitation of motion, or impingement on adjacent structures such as nerves and blood vessels occur, or when roentgenographic features or an abnormal increase in tumor size suggest progression towards malignancy. When surgical resection is needed, the entire lesion should be removed, including the complete cartilaginous cap, to avoid recurrence. Multiple recurrence or recurrence in a well-excised lesion should raise suspicion of malignancy.

Evolution

Until recently, there has been a lot of debate about whether an osteochondroma is a developmental disorder or a true neoplasm. It was for long considered to be a perversion in the direction of bone growth. However, recent studies have shown osteochondroma to be a true neoplasm, since presence of loss of heterozygosity (LOH) and aneuploidy in osteochondromas indicate a clonal origin for the cartilaginous tissue of osteochondromas. Inactivation of both copies of an EXT gene in cartilaginous cells in the growth plate is required for the formation of osteochondromas in hereditary cases.

Prognosis

Complete excision of osteochondroma is usually curative. Failure to remove the entire cartilaginous cap or its overlying periosteum is the basis for most

recurrences. Recurrence could also suggest malignancy.

Cytogenetics

Note

Cytogenetic aberrations involving 8q22-24.1, where the EXT1 gene is located, have been found in ten out of 30 sporadic and in 1 out of 13 hereditary osteochondromas. In one sporadic case deletion of 11p11-12 was found.

Cytogenetics Molecular

- Loss of heterozygosity (LOH) was found almost exclusively at the EXT1 locus in both sporadic and hereditary osteochondromas using microsatellite analysis. Fluorescence in situ hybridization revealed loss of the 8q24 locus. The EXT genes, involved in HME, are hypothesized to be tumor suppressor genes. Germline EXT1 mutations, resulting in a truncated EXT1 protein, together with the loss of the remaining wild type allele was demonstrated in both sporadic and hereditary osteochondromas. These findings suggest that inactivation of both copies of the EXT1 gene is required for the development of osteochondromas.

- The EXT proteins are involved in the biosynthesis of heparan sulphate (HS). In chondrocytes these HS proteoglycans are important amongst others in the growth plate signaling and remodeling. EXT mutations would affect the HS synthesis and thereby disturb the intracellular signaling involving Indian Hedgehog (Ihh) and parathyroid hormone-related protein (PTHrP), which regulate proliferation, organization and

differentiation in the growth plate. These downstream effectors of EXT are indeed almost absent in sporadic and hereditary osteochondromas.

- Malignant transformation of osteochondroma is characterized at the DNA level by chromosomal instability, as demonstrated by a high percentage of LOH and aneuploidy in chondrosarcomas compared to LOH restricted to 8q24 and diploidy or mild aneuploidy in osteochondroma. At the protein level, upregulation of PTHrP and BCL2 is found in grade I peripheral chondrosarcomas as compared to osteochondromas.

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This article should be referenced as such:

Hameetman L, Bovée JVMG. Bone: Osteochondroma. *Atlas Genet Cytogenet Oncol Haematol*. 2003; 7(1):42-44.
