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Solid Tumour Section

Mini Review

Bone: Osteochondroma

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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 bone 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 osteochondromas) or within the context of Multiple Osteochondromas (MO). The literature indicates slight male sex predominance (male/female ratio 1.5:1). Most osteochondromas are prone to arise in the first 3 decades of life. Osteochondromas hardly 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 underestimation since the majority are asymptomatic. Approximately 15% of patients with osteochondromas have multiple osteochondromas (MO).

Clinics

The growth of the osteochondroma ceases at skeletal maturation or shortly thereafter. Patients may have a swelling of year's 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 0.5-5% of MO cases.

Pathology

Pedunculated osteochondromas contain a stalk and are long and slender, while sessile ones are flat. Many osteochondromas are cauliflower shaped (figure 1). 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 this is decreasing 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.

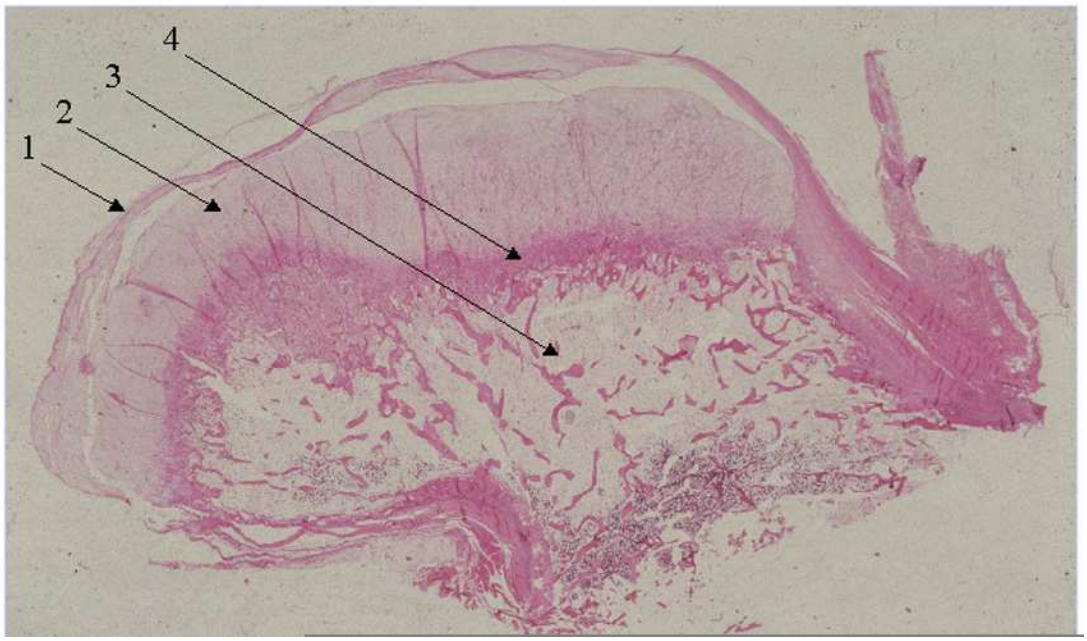

Figure 1: Histological appearance of an osteochondroma. A perichondrium (Bellaiche et al., 1998) covers the cartilage cap (Bernard et al., 2001). The cap merges into the underlying spongiosa (Bornemann et al., 2004), where the chondrocytes are arranged according to an epiphyseal growth plate (Bovée et al., 1999).

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.

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 roentogenographic 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 alleles of EXT1 in cartilaginous cells of the cap is required for the formation of solitary and multiple osteochondromas.

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 multiple osteochondromas. In one sporadic case deletion of 11p11-12 was found. In 7 out of 8 solitary osteochondromas homozygous deletions of EXT1 were identified. Aberrations of chromosome 1p (1p13-p22) were found in five of seven osteochondromas.

Cytogenetics Molecular

Loss of heterozygosity (LOH) was found almost exclusively at the EXT1 locus in both sporadic and multiple osteochondromas using microsatellite analysis. Fluorescence in situ hybridization revealed loss of the 8q24 locus. The EXT genes, involved in MO, 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 multiple 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). Heparan sulphate proteoglycans

(HSPG) are large macromolecules composed of heparan sulphate glycosaminoglycan chains linked to a protein core.

Four HSPG families are syndecan, glypican, perlecan and isoforms of CD44. HSPGs are required for high-affinity binding of fibroblast growth factor to its receptor. Furthermore, studies in Drosophila have shown that EXT (tout-velu, Ttv) is required for the diffusion of the morphogens: Hedgehog (Hh, human homologues Indian Hedgehog (IHh) and Sonic Hedgehog (SHh), decapentaplegic (dpp, human homologues TGB-beta and BMP) and wingless (human homologue Wnt). It was therefore hypothesized that EXT mutations affect IHh/PTHLH, TGF-beta/BMP and Wnt signaling pathways within the normal growth plate. Indeed, altered levels of the EXT1 and EXT2 protein and of their putative downstream effectors (IHh/PTHrP, TGF-beta/BMP and Wnt signalling pathways) were demonstrated in both solitary and multiple osteochondromas. In addition, due to impaired EXT1/EXT2 function the HSPGs appear to be retained in the Golgi apparatus and cytoplasm of the tumour cell, instead of being transported to the cell surface and/or extra cellular matrix where they normally exert their function. Moreover, EXT mutations were described to induce cytoskeletal abnormalities (altered actin distribution) in osteochondroma chondrocytes.

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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