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Review

Osteochondromas: Review of the Clinical, Radiological and Pathological Features

PANAGIOTIS KITSOULIS[1], VASSILIKI GALANI[1], KALLIOPI STEFANAKI[2], GEORGIOS PARASKEVAS[3], GEORGIOS KARATZIAS[1], NIKI JOHN AGNANTIS[4] and MARIA BAI[4]

[1]*Department of Anatomy, Histology and Embryology, and*
[4]*Department of Pathology Medical School, University of Ioannina;*
[2]*Department of Pathology, Agia Sophia Children's Hospital, Athens;*
[3]*Department of Anatomy, Medical School, Aristotle University of Thessaloniki, Greece*

Abstract. *Osteochondroma is the most common benign bone tumor and usually occurs in the metaphyseal region of the long bones. This tumor takes the form of a cartilage-capped bony outgrowth on the surface of the bone. The vast majority (85%) of osteochondromas present as solitary, nonhereditary lesions. Approximately 15% of osteochondromas occur as multiple lesions in the context of hereditary multiple osteochondromas (HMOs), a disorder that is inherited in an autosomal dominant manner. Most lesions appear in children and adolescents as painless, slow-growing masses. However, depending on the location of the osteochondroma, significant symptoms may occur as a result of complications such as fracture, bony deformity, mechanical joint problems and vascular or neurologic compromise. Malignant transformation of osteochondromas can occur later in adulthood but rarely metastasize. The treatment of choice for osteochondroma is surgical unless the skeleton is still immature. Pathogenetic analysis showed that HMOs are caused by mutations in either of two genes: exostosis (multiple)-1 (EXT1), which is located on chromosome 8q24.11–q24.13 or exostosis (multiple)-2 (EXT2), which is located on chromosome 11p11–12. Recently, biallelic inactivation of the EXT1 locus was described in nonhereditary osteochondromas. The EXT1 and EXT2 proteins function in the biosynthesis of heparin sulfate proteoglycans (HSPGs) which are multifunctional proteins involved in several growth signaling pathways in the normal epiphyseal growth plate. Reduced EXT1 or EXT2 expression in osteochondromas is associated with disordered cellular distribution of HSPGs, resulting in defective endochondral ossification which is likely to be involved in the formation of osteochondromas. Here the clinical, radiological, pathological and pathogenetic features and the treatment modalities of osteochondroma are reviewed.*

Correspondence to: Panagiotis Kitsoulis, MD, 21 October 28 St, 45332, Ioannina, Greece. Tel: +30 2651079354, e-mail: pkitsoulis@hotmail.com / mbai@cc.uoi.gr

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Osteochondroma is the most common benign bone tumor (1-5). According to the WHO classification, this lesion is defined as a cartilage-capped bony projection arising on the external surface of bone containing a marrow cavity that is continuous with that of the underlying bone (3, 4). Osteochondroma occurs in 3% of the general population and it accounts for more than 30% of all benign bone tumors and 10-15% of all bone tumors (1-26). The vast majority of these tumors present as solitary, nonhereditary lesions. Approximately 15% of osteochondromas occur in the context of hereditary multiple osteochondromas (HMOs), a disorder that is inherited in an autosomal dominant manner. Solitary osteochondromas have a tendency to appear at metaphyses of the long bones, especially the femur, humerus, tibia, spine and hip, although every part of the skeleton can be affected (1-5).

Osteochondroma is usually symptomless and is found incidentally (1-5, 8-15). Malignant transformation of a solitary osteochondroma may occur in 1-2% of patients, while for osteochondromas in the setting of HMO syndrome the occurrence is between 1% and 25% (5-7). The diagnosis of an osteochondroma requires radiological depiction and, in some cases, particularly if there is a suspicion of malignancy, histological examination is also needed (26-61). The treatment of choice for osteochondroma is surgical unless the skeleton is still immature; for a symptomatic solitary lesion, a partial excision is suggested (1, 5, 6, 9, 18).

A large number of studies using cell biology, molecular biology and immunohistochemical methods analyzed the mechanisms involved in the pathogenesis of osteochondroma (62-114). It has been shown that HMO are caused by mutations

in either of two genes: exostosis (multiple)-1 (*EXT1*), which is located on chromosome 8q24.11–q24.13 or exostosis (multiple)-2 (*EXT2*), which is located on chromosome 11p11–12 (75-81). Recently, biallelic inactivation of the *EXT1* locus was described in nonhereditary osteochondromas (104).

The epidimiological, clinical, radiological, histological and pathogenetic features and the treatment modalities of osteochondroma are reviewed here.

Epidemiology

Osteochondromas are usually found in adolescents or children, rarely in infants or newborns (8). There is no predilection for males or females as far as solitary osteochondromas are concerned. HMO syndrome affects males more often than females (9) and is usually found in Caucasians rather than in other races, affecting 0.9-2 individuals per 100,000 of population. About 65% of patients have family members with autosomal dominant transmission of HMO genes (10-12). The HMO syndrome comes to clinical attention during the first decade of life in more than 80% of patients (13, 14). Solitary osteochondromas show a predilection for the metaphyses of the long tubular bones, especially the femur (30%), humerus (26%) and tibia (43%). Lesions are rare in the carpal and tarsal bones, patella, sternum, skull and spine (15).

Clinical Features

Osteochondroma is usually symptomless and, therefore, the only clinical symptom is a painless slow-growing mass on the involved bone (16). However, significant symptoms may occur as a result of complications such as fracture, bony deformity or mechanical joint problems. An osteochondroma can occur near a nerve or blood vessel, the commonest being the popliteal nerve and artery. The affected limb can exhibit numbness, weakness, loss of pulse or changes in colour (17). Although rare, periodic changes in blood flow can also occur. Vascular compression, arterial thrombosis, aneurysm, pseudoaneurysm formation and venous thrombosis are common complications and lead to claudication, pain, acute ischemia, and signs of phlebitis, while nerve compression occurs in about 20% of patients (18, 19). The tumor can be found under a tendon, resulting in pain during relevant movement and thus causing restriction of joint motion. Pain is also present as a result of bursal inflammation or swelling, or even due to a fracture of the basis of the tumor's stalk (4). Generally, the normal function and movement can be limited and asymmetry may be also noted in a slowly and inwardly growing osteochondroma. If there is a tumor at the spinal column, there may be kyphosis, or spondylolisthesis if it is close to the intervertebral space (20). The clinical signs of malignant transformation are pain, swelling and an enlargement of the mass.

The hereditary multiple exostosis (HME) syndrome usually presents during the first decade of life or even in newborns. The manifestations include limb undergrowth with normal height, ankle valgus, genu valgum and anomalies of the radio and ulnar deviation. Patients may present with metacarpal, metatarsal and phalangeal shortening, anisomelia, coxa valga, scoliosis and asymmetry of the pectoral and pelvic girdles. Subluxation of the talus or the hip are common symptoms. Tibiofibular synostosis can also take place. Spinal compression syndrome may also be seen (21). Lesions that arise in the head and neck may be assosiated with facial asymmetry and dysfunction of the masseters (22, 23). An inwardly growing osteochondroma can cause injuries of the viscera such as hemothorax, obstruction of the intenstine or the urinary tract and dysphagia (24, 25).

Radiological Features

Apart from a detailed history and a careful physical examination, the diagnosis of an osteochondroma also requires radiological imaging.

X-rays. Plain radiography is the first examination that is required and can be characteristic of the lesion (Figures 1 and 2). An osteochondroma appears as a stalk or a flat protuberance emerging from the surface of the bone. On occasions, it ends up as a hook-like formation. It shows a predilection to metaphyses and the attachment points of tendons on long bones. This is the reason why the metaphysis of the affected bone can be widened. Its margins are usually clear and rarely irregular, although the tumor seems to be continuous with the cortex of the bone. A usual finding is that of calcified flakes or linear interruptions inside the cartilaginous component of the osteochondroma. These calcifications appear as radiopaque areas. On the contrary, if the affected bone shows radiolucent areas under the cortex, which implies degeneration, then the cortex seems like being in the air. An osteochondroma that is found in the thorax can cause pneumothorax, hemothorax or fractures that are easily recognised on a Roentgen image (26).

A common question arising from a radiograph is whether the lesion is benign or malignant. The most important indication that an osteochondroma has turned into an osteosarcoma is that of enlargement of the tumor and the irregularity of its margins (27). Multiplication of the ossifications, pain and a coexisting radiopaque soft tissue mass may suggest a sarcomatous tranformation. Scattered calcifications are generally a sign of malignancy but they are found in benign tumors as well. In addition, the presence of lobulated margins with periostal reaction hint at a osteosarcoma (28). If the tumor is located in the pelvis, it is very difficult to distinguish the malignant changes.

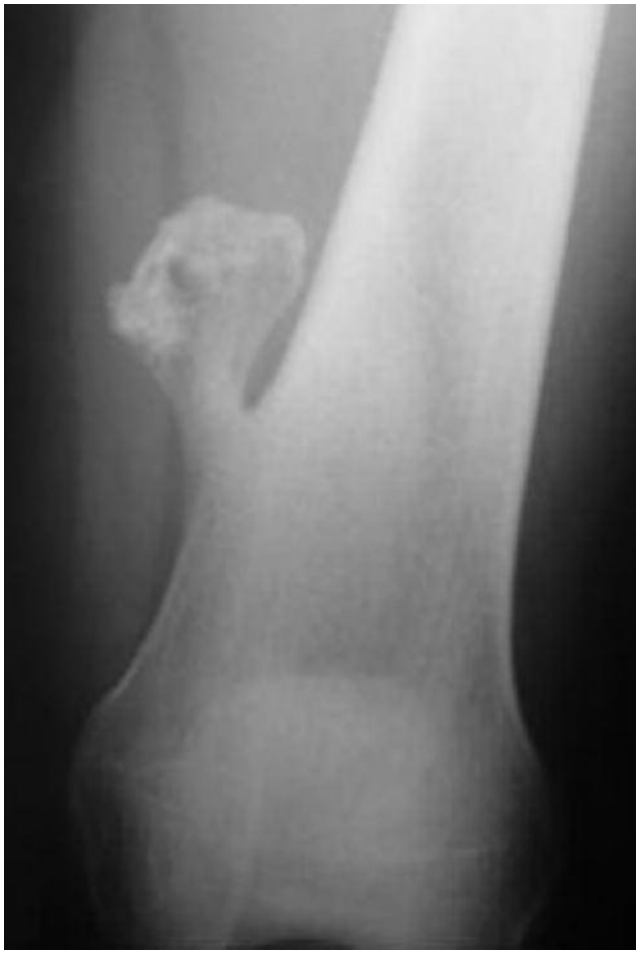

Figure 1. *X-ray: A typical lesion involving the right femur. Note the protuberance on the external surface of the femoral bone. Linear calcifications inside the tumor lesion are also obvious.*

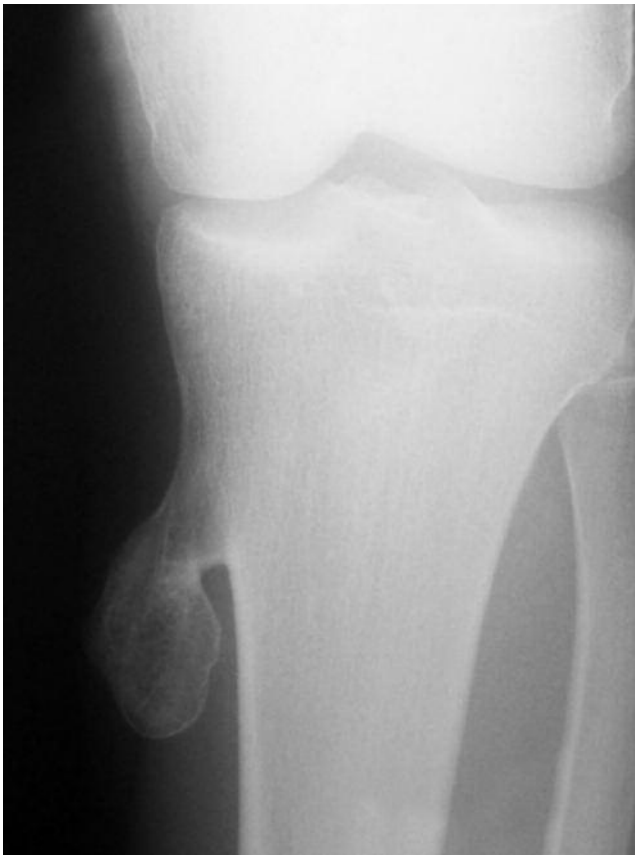

Figure 2. *X-ray: Anteroposterior radiograph of a tibial osteochondroma. Note the protuberance on the external surface of the tibial bone.*

The HME syndrome can present as bilateral lesions that widen a metaphysis. Tarsal and carpal bones are often affected and are shown with a mass emerging from their epiphysis. Joint disturbance and growth anomalies are easily recognized in plain radiography.

Computed tomography. Computed tomography is a very accurate method for depicting osteochondromas of the spinal column, shoulder and pelvis. In particular, if compressive myelopathy has taken place, CT myelography is the examination of choice. CT can depict the bony lesion in detail, as well as showing the presence of calcifications. Its ability in distinguishing an osteochondroma from an osteosarcoma has been a matter of debate (29). The criterion that is used is the thickness of the cartilaginous cap of the tumor, given that an osteosarcoma has a thicker one. CT is currently thought to be unreliable on this subject, as underestimation of the thickness is usual (30). The disadvantage of CT is that it cannot estimate the metabolic activity, a serious indication of malignancy of any tumor.

Ultrasound. Ultrasound is the examination of choice where there is suspicion of aneurysms or pseudoaneurysms and arterial or venous thrombosis. It is an accurate method for examining the cartilaginous cap of the osteochondroma as an hypoechoic area above the cortex of the relevant bone (27, 31). It is also the only way to pinpoint a bursitis. However, ultrasound cannot depict the cap if there is an inward development of the tumor.

Nuclear medicine. Scintigraphic methods are being used in order to examine the metabolic activity of the tumor. A poor metabolic activity is only present in benign lesions. Thallium 201 is used to detect a malignant transformation of HME. It is important to know that it is still impossible to distinguish malignant ossifications, hyperemia and an osteoblastic reaction in chondrosarcoma *via* scintigraphy (32).

Angiography. Angiography is often used for vascular lesions caused by an osteochondroma (33, 34). Aneurysms, thrombosis and occlusions are not rare. These lesions are caused by the ossified cartilaginous cap. Neovascularity, which characterizes malignant lesions, can also be detected in a malignant transformation using angiography.

Magnetic resonance imaging. MRI is the most precise imaging method for symptomatic cases of bone masses as it can depict the exact morphology of a tumor, arterial and venous compromise and nervous lesions. Additionally, MRI can demonstrate a probable recurrence if a malignant tumor is diagnosed. In order to get full depiction of the tumor, MRI is performed in coronal, sagittal, paracoronal and parasagittal planes.

MRI is first of all used in order to verify the continuity of the palpable mass with the cortex of the affected bone and to differentiate an osteochondroma from other surface bone lesions (35). The cartilaginous cap, because it is rich in water, presents a high signal on T2-weighted MRI and a low one on T1-weighted. It is usual to detect above it a low signal zone of the perichondrium. T2-weighted MRI is preferable because it provides better differentiation of signal intensities.

A short time inversion recovery (STIR) depiction can reveal accompanying edema in chondrosarcomas (36). If musculoskeletal complications occur, a T1-weighted series is recommended. If a high signal is obtained, then there is muscular damage because T1 relaxation time is shorter. If a T2-weighted series shows a high signal, then there is certainly edema around the lesion.

MRI can also depict vascular complications caused by the tumor (37). For example, a pseudoaneurysm will present as a nonhomogenous formation and a thrombosis as an onion-shaped formation inside the lumen of a vessel. If denervation of a muscle takes place, an MRI shows a high signal intensity, as fatty tissue will have taken the place of the muscle cells. In addition, a differentiation in the signaling of a nerve may suggest its supression or damage (38-41). An MRI image can easily demonstrate lesions of the spinal column or the cranium, something that is not possible for other methods. A bursitis is the only case where an MRI can give a false-positive indication (42-45).

Distinguishing a malignant from a benign lesion is a challenge for MRI. MRI can nevertheless be used to accurately diagnose even a low-grade osteosarcoma (46, 47). Again, the thickness of the cartilaginous cap is the basic criterion. In this respect, Woertler *et al.* (48) suggested that cartilage cap thickness exceeding 2 cm in adults and 3 cm in children should raise the suspicion of malignant transformation. A chondrosarcoma is also characterized by low T1 signal after intravenous contrast infusion, something that is rarely recorded in a benign cartilaginous tumor. Nowadays, using gadolinium it is also possible to undertake a dynamic examination of neovascularization, which is much more preferable in differentiating an osteosarcoma from an osteochondroma (49-51). All the aforementioned reasons justify the view that MRI is the gold standard technique for detecting a malignant transformation (48-52).

Pathology

Gross pathology and histopathology. Osteochondromas may be pendiculated or sessile and their major diameter ranges from 1 to 2 cm (3, 4, 57). The cartilage cap is usually thin; a thick and irregular cap (greater than 2 cm) may be indicative of malignant transformation. Osteochondromas develop only in bones that are formed by endochondral ossification and are believed to result from displacement of the lateral portion of the growth plate, which then proliferates in a direction diagonal to the long axis of the bone and away from the nearby joint. The outer layer of the head of osteochondroma is composed of benign hyaline cartilage and is delineated peripherically by perichondrium that is continuous with the periosteum of the underlying bone. The cartilage has the appearence of disorganized growth plate and undergoes enchondral ossification, with the newly made bone forming the inner portion of the head and stalk. The cortex of the stalk merges with the cortex of the host bone so that the medullary cavity of the osteochondroma and the bone are in continuity. The Figure 3 shows classical histological features of osteochondroma (our case). The differential diagnosis includes post-traumatic lesions, juxtacortical chondromas and osteosarcomas (3, 4, 57).

Rarely (1-2% of cases), osteochondromas give rise to chondrosarcomas. It is estimated that the risk of this complication is substantially higher in patients with HMO (3-20%) (3, 4, 57, 58). It has been noted that the incidence of secondary chondrosarcomas arising at the site of an solitary osteochondroma is difficult to determine and may be lower, as many solitary osteochondromas may go undiagnosed (58).

Interestingly, osteochondroma is the most common precursor lesion for secondary chondrosarcoma (57-60). In a large series reported from the Mayo Clinic, 127 out of 151 (81%) secondary chondrosarcomas arose at the site of an osteochondroma (58). Approximately two-thirds of these were observed in patients with the sporadic form and the remainder in patients with multiple osteochondromas (58). The average age of the secondary chondrosarcoma patient is 35 years, younger than patients with primary tumors (58-60). Most of these tumors affect the pelvic bones. The increased thickness of the cartilage cap (normally 1-2 mm) has been considered as indicator of potential malignant transformation, but in skeletally immature individuals, a

cartilage cap of up to 2 cm might be identified. In addition to a thick cartilage cap, other findings that should raise suspicion of malignant transformation are recent growth of an exostosis in an adult proximal skeletal location, irregular mineralization, the presence of soft tissue bands, a grossly irregular surface, cystic changes, loss of architecture of cartilage, myxoid changes, necrosis, increased cellularity, mitotic activity and atypia of chondrocytes (3, 58). Most secondary chondrosarcomas present histological features of low-grade malignancy (59). These tumors generally carry a good prognosis and surgical treatment without adjuvant chemotherapy or irradiation is the treatment of choice (59). Secondary osteosarcomas arising within an osteochondroma are extremely rare (61).

Expression profile of chondrocytic differentiation-associated proteins. There is growing evidence that, besides conventional histological criteria, analysis of the extracellular matrix gene expression pattern, in particular subtyping of collagen gene expression profiles using immunohistochemical and *in situ* hybridization methods, is helpful for the definition and identification of different phenotypes of normal and pathological chondrocytic cells (63-74). On that basis, it was suggested that the expression profiles of the collagen types might play an important role in classification and diagnosis of chondrogenic neoplasias of the skeleton (63).

Accumulating data suggest that the cellular phenotypes of normal chondrocyte differentiation so far decribed during fetal chondroneogenesis and in fetal growth plate cartilage (chondroprogenitor cells, mature chondrocytes, hypertrophic chondrocytes) display different expression profiles of the collagen types (63, 65, 66). Indeed, normal chondroprogenitor cells are characterized by the expression of their specific gene product, the alternative splice variant of collagen COL2 and COL2A (65, 66). Normal mature chondrocytes express the typical cartilage collagen types COL2B, COL9, and COL11 as well as aggrecan and link protein (63). However, the expression of these collagen types is not specific for cartilage since they are also observed in a few other tissues such as the vitreous body (63). Hypertrophic chondrocytes are characterized by the expression of their unique gene product COL10 (67). Normally, terminally differentiated hypertrophic chondrocytes become to a large extent apoptotic before they get replaced by ingrowing bone forming cells which replace the pre-existing cartilaginous matrix by a bone matrix (63). Interestingly, terminally differentiated hypertrophic chondrocytes that survive and undergo posthypertrophic differentiation to osteoblast-like cells (which start to express COL1) have so far only been identified in the chick (68, 69). "Dedifferentiated" chondrocytes, a phenotype so far only identified *in vitro*, express COL1 and COL3, but not the cartilage-typical collagen types (COL2, COL9, COL11) nor aggrecan proteoglycan (63, 70).

The characteristic feature of osteochondromas, enchondromas and conventional chondrosarcomas is the presence of neoplastic cells displaying a chondrocytic cell shape and the gene expression profile of mature fetal chondrocytes; these neoplastic cells are responsible for the formation of the characteristic hyaline cartilage-like extracellular tumor matrix (71-74). Neoplastic chondrocytes *in vivo* exhibit the full differentiation expression profile of their physiological counterparts. In chondrogenic neoplasias, besides the phenotype of mature chondrocytes, hypertrophic cell differentiation with the expression of COL10 is observed (71, 73). The expression of COL1 without COL3 expression in differentiated neoplastic chondrocytes represents experimental evidence of the potential of mammalian chondrocytes to undergo posthypertrophic differentiation to osteoblast-like cells *in vivo* and implicates the deposition of bone matrix components within pre-existing cartilaginous tumor matrix (71). Whereas enchondromas and conventional chondrosarcomas exhibit a random cellular differentiation pattern, osteochondromas are characterized by a highly structured tissue organization. In osteochondromas, mesenchymal cell layers of fibrous appearance overlay cartilaginous tissue, with chondrocytic cells expressing COL2 and the aggrecan proteoglycan; in the deep zone, chondrocytic cells become hypertrophic, express COL10 and endochondral ossification is observed (73, 74).

Molecular pathology and pathogenesis. The neoplastic nature of osteochondroma has only recently come to light with the discovery of the loss of heterozygosity (LOH) at the *EXT1* locus as well as other clonal abnormalities in a subset of these tumors (75-79). Multiple osteochondromas is caused by mutations in either of two genes: exostosis (multiple)-1 *EXT1*, Online Mendelian Inheritance in Man (OMIM) No. 133700, which is located on chromosome 8q24.11–q24.13, or exostosis (multiple)-2 (*EXT2*; OMIM No. 133701), which is located on chromosome 11p11–12 (75-77). Both genes are ubiquitously expressed (75-77). Most of the germline mutations that have been identified in *EXT1* and *EXT2* result in premature truncation of the EXT proteins and loss of protein function (78). Most hereditary osteochondromas demonstrate heterozygous mutations in *EXT1* or *EXT2* (79-81). Some hereditary osteochondromas, in addition to carrying an *EXT1* mutation, exhibit loss of the remaining wild-type allele of *EXT1* (82); this is consistent with Knudson's two-hit model of tumorigenesis (83) and indicates that *EXT1* acts as a classical tumor suppressor gene in multiple osteochondromas. On the other hand, somatic mutations in

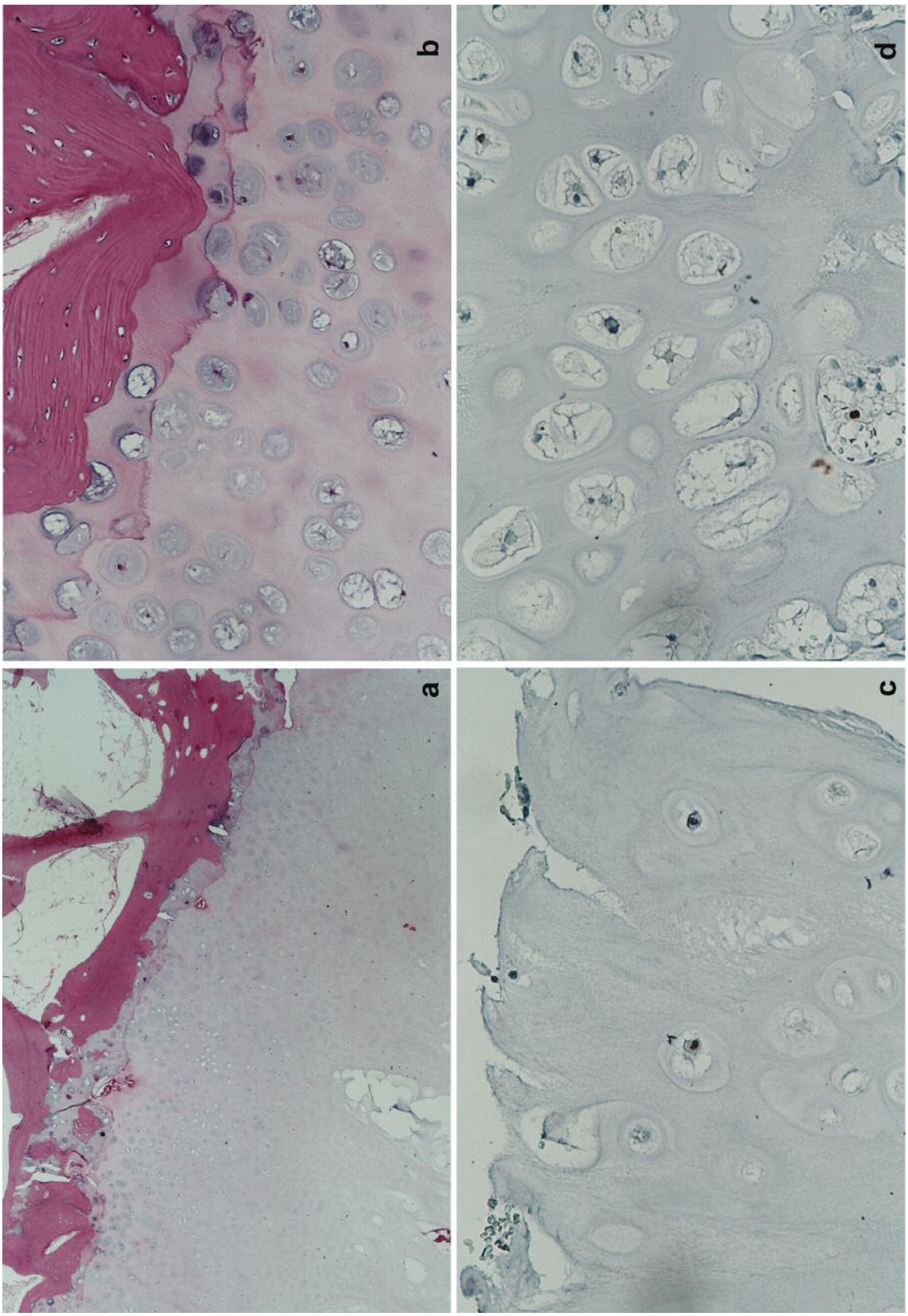

Figure 3. *a: Histological appearance of osteochondroma (hematoxylin-eosin staining, magnification ×250); b: Histological appearance of osteochondroma (hematoxylin-eosin staining, magnification ×400); c and d: Immunohistochemical staining of osteochondroma with Ki-67 antibody (magnification ×400).*

the *EXT* genes are extremely rare in nonhereditary osteochondromas and have been described in only three cases (84-86), one of which (86) was a nonhereditary secondary peripheral chondrosarcoma arising from a preexisting osteochondroma (87). LOH and clonal rearrangement at 8q24 (*EXT1* locus) were as frequent in nonhereditary osteochondromas as were *EXT1* gene mutations in patients with hereditary osteochondromas (82, 88, 89). By contrast, LOH at the *EXT2* locus has been reported in only one nonhereditary osteochondroma (89).

The mRNA expression of *EXT1* and *EXT2* was examined in hereditary and nonhereditary osteochondromas. Patients with hereditary multiple osteochondromas who had a germline mutation in either of the *EXT* genes had reduced mRNA expression of the corresponding *EXT* gene in their tumors compared with the expression found in normal epiphyseal growth plates (90). By contrast, in nonhereditary tumors with undetectable *EXT1* or *EXT2* gene mutations, only *EXT1* mRNA expression was reduced (90).

The EXT1 and EXT2 proteins form a heterooligomeric complex in the Golgi apparatus, where they function in heparan sulfate proteoglycan (HSPG) biosynthesis (91). HSPGs are large, multifunctional macroproteins that are involved in several growth signaling pathways in the normal epiphyseal growth plate (92, 93). Reduced *EXT1* or *EXT2* mRNA expression in osteochondromas and chondrosarcomas was associated with intracellular accumulation of HSPGs in the Golgi apparatus (90). By contrast, in normal growth plates, where expression of HSPGs is extracellular, the *EXT* genes are normally expressed (90). Lack of HSPGs at the cell surface affects growth signaling pathways in the normal growth plate (94) and, possibly, those in osteochondromas (95, 96). Loss of *EXT* expression in osteochondromas results in the disordered distribution of HSPGs, *i.e*. HSPGs are not detected at the cell surface but in the cytoplasm, where they are concentrated in the Golgi apparatus (96).

Since HSPGs are involved in several signaling pathways in the growth plate (92), it is possible that the lack of HSPGs at the cell surface in osteochondromas might have functional effects on HSPG-dependent signaling pathways, *e.g*. Indian hedgehog (IHH) signaling. These signaling pathways are involved in normal endochondral ossification and in osteochondroma pathogenesis (97). Indeed, normal bone development depends on the tight regulation of the cartilage progenitor cells which go through subsequent stages of proliferation, prehypertrophy, hypertrophy and apoptosis. Two signaling molecules, the mammalian Hh homolog IHH and parathyroid hormone-related peptide (PTHrP), negatively regulate chondrocyte progression from proliferation to hypertrophy in a coordinated way. According to the current signaling model (98), the prehypertrophic chondrocytes localized within the growth plate (borderline chondrocytes) produce IHH, which binds to its receptor, Patched (Ptc), on the osteogenic cells of the periarticular perichondral region. This signal stimulates chondrocyte proliferation by up-regulating the second signaling molecule, PTHrP. PTHrP binds to the PTH/PTHrP receptor on a subpopulation of proliferating and prehypertrophic chondrocytes, postponing differentiation and eventual cell death by inducing production of the antiapoptotic protein Bcl-2 (99). This feedback loop favors continued longitudinal cartilage growth until a shift in the expression of IHH or PTHrP disrupts the equilibrium, resulting in chondrocyte apoptosis and subsequent ossification. Interesting information about the role played by the EXT proteins in normal bone development has come from the invertebrate *Drosophila melanogaster*, in which the *Drosophila EXT1* homolog *Ttv* is responsible for the synthesis of HSPGs that are needed for Hh diffusion during development (100); it is probable that mammalian EXT proteins synthesize HSPGs that are required for the diffusion and/or efficient signaling by IHH in the growth plate of developing normal bone. Consistent with the current signaling model (98), *in situ* hybridization studies in wild-type mice have shown that EXT1 and EXT2 are expressed in the proliferative and prehypertrophic chondrocytes, but not in the hypertrophic zone, and that their expression pattern overlaps with that of IHH (101). Furthermore, it has been recently shown that IHH is incapable of associating with the cell surface of target cells in murine *EXT1*$^{-/-}$ embryos, indicating that HSPG expression is essential for IHH binding (102).

While in the normal growth plate, IHH requires interaction with HSPGs to diffuse through the extracellular matrix to its receptor (94), two studies (95, 96) demonstrated the presence of IHH signaling in osteochondromas despite the absence of HSPGs at the cell surface. Benoist-Lasselin *et al*. (96) also showed IHH expression in all cells of the cartilage cap, whereas IHH expression in the normal growth plate was restricted to the transition zone (103). It has been hypothesized that osteochondroma cells may circumvent the impaired diffusion capacities that result from reduced amounts of HSPGs at the cell surface by producing IHH in every cell of the cartilage cap, resulting in cell-autonomous (*i.e*. autocrine) IHH signaling (104). On the other hand, there is evidence that another HSPG-I-dependent growth signaling pathway that is affected in osteochondroma is the fibroblast growth factor (FGF) pathway (105). Indeed, Bovée *et al*. (105) investigated the immunohistochemical expression of FGF2, FGF-receptor 1 (FGFR1) and FGFR3 in osteochondromas (n=24) and peripheral (n=29) and central (n=20) chondrosarcomas. The FGF signaling molecules FGF2, FGFR1 and FGFR3 were mostly absent in osteochondromas. By contrast, in chondrosarcomas, re-expression of FGF2 and FGFR1 was found and expression levels increased with increasing histological grade.

Some investigators focused on the molecular pathogenesis of nonhereditary osteochondromas (82, 85, 90, 104, 106, 107). *EXT1* mRNA expression was reduced in nonhereditary osteochondromas (90), suggesting that the loss of *EXT1* mRNA expression is important for the development of these tumors. However, somatic mutations or promoter methylation at the *EXT1* gene were not detected in such tumors (82, 85, 90, 106, 107). This may imply that other mechanisms may be used to inactivate *EXT1* and decrease its mRNA expression.

To answer this question, Hameetman *et al.* (104), in a very recent elegant study, subjected eight nonhereditary osteochondromas to high-resolution array-based comparative genomic hybridization (array-CGH) analysis of tumor DNA and demonstrated that all cases had a large deletion of 8q; five tumors had an additional small deletion of the other allele of 8q that contained the *EXT1* gene. By multiple ligation-dependent probe amplification (MLPA) analysis (high resolution technique allowing identification of homozygous deletions that are as small as single exons) for *EXT1*, Hameetman *et al.* (104) confirmed the array-CGH results and identified two additional deletions that were smaller than the limit of resolution of array-CGH (104). The demonstration by Hameetman *et al.* (104) that biallelic inactivation of *EXT1* also occurs in nonhereditary osteochondromas indicates that *EXT1* acts as a classical tumor suppressor gene in these tumors (104). They further supported this indication by using *EXT1* locus-specific fluorescent *in situ* hybridization (FISH) analysis of the three tissue components of osteochondroma (cartilage cap, perichondrium, bony stalk) and showing that these homozygous *EXT1* deletions were present only in the cartilage cap of osteochondroma (104). Other previous studies (82, 88, 89, 98) had provided evidence that the cartilage cap of osteochondroma is of clonal origin and, thus, is neoplastic but it had not been elucidated whether cells that form the bony stalk and the overlying perichondrium are also of clonal origin. The recent finding that the cartilage cap is the only neoplastic component of osteochondroma (104) provides useful information about the cell of origin of osteochondromas (108-110).

Recently, it was suggested that specific cells in the perichondrium may give rise to chondrocytes that are necessary for the development and continued growth of osteochondromas (110). However, this hypothesis is inconsistent with the FISH results of Hameetman *et al.* (104), which suggest that the cell of origin most likely resides in the growth plate. Furthermore, Hameetman *et al.* (104) summarized the pathogenetic significance of genomic alterations in osteochondromas as follows: According to Knudson's two-hit model for tumor suppressor genes (83), both alleles of *EXT1* must be inactivated for hereditary and nonhereditary osteochondromas. For hereditary osteochondromas, after inactivation of the first allele, inactivation of the second allele can be achieved either by physical loss of the remaining wild-type allele or by homologous recombination of the mutated allele. In nonhereditary osteochondromas, both wild-type alleles are lost, usually by loss of 8q and a small *EXT1* deletion, resulting in homologous *EXT1* deletion.

Expression profile of cell cycle-and apoptosis-associated proteins. It is well established that cell cycle and apoptosis deregulation is involved in the pathogenesis of neoplasia. Thus, some authors attempted to elucidate the expression patterns of cell cycle-and apoptosis-associated proteins and their potent significance in osteochondroma as well as in the progression of osteochondroma towards chondrosarcoma (96, 105, 111-114). Since defective endochondral ossification is likely to be involved in the formation of osteochondromas, Benoist-Lasselin *et al.* (95) investigated the potential changes in chondrocyte proliferation and/or differentiation in osteochondroma samples from HMO patients by immunohistology using the antiproliferating cell nuclear antigen (PCNA) antibody. Numerous cells forming osteochondromas, although resembling prehypertrophic chondrocytes, stained positively with PCNA antibody. In addition, ectopic expression of collagen type I and abnormal presence of osteocalcin (OC), osteopontin (OP) and bone sialoprotein (BSP) were observed in the cartilaginous osteochondromas. On the basis of these data, the authors (95) concluded that most chondrocytes involved in the growth of osteochondromas can proliferate and that some of them exhibit bone-forming cell characteristics. Furthermore, Huch *et al.* (112) compared the immunohistochemical expression of the cell proliferation antigen Ki-67 in patients aged 7-26 years (n=9) with solitary osteochondroma and patients aged 11-42 years (n=6) with multiple osteochondromas with their expression in human fetal and postnatal growth plates. They showed that the proliferative activity of osteochondromas from children younger than 14 years of age was comparable to that of postnatal growth plates, whereas in cartilage from individuals older than 14 years of age, significant proliferative activity was undetectable. In Figure 3, immunohistochemical staining of osteochondroma with Ki-67 antibody is shown (our case).

Since osteochondroma is the most common precursor lesion for secondary chondrosarcoma, some investigators performed a comparative analysis of various cell cycle proteins and the antiapoptotic protein Bcl-2 (which is induced by IHH/PTHrP signalling) in osteochondroma and chondrosarcoma (105, 111, 114). Si (111) reported that in osteochondroma of the jaws, CDK4 and E2F-1 showed an equal positivity in 1 out of 8 cases, whereas p27 was positive in 7 out of 8 cases. In chondrosarcoma of the jaws, CDK4, p27 and E2F-1 were positive in 60% (12 of 20 cases), 25% (5 of 20 cases) and 65% (13 of 20 cases), respectively. The positive rate of CDK4, p27 and E2F-1 was

significantly different between chondrosarcoma and osteochondroma of the jaws ($p<0.05$). Since CDK4 and E2F-1 are over expressed and p27 is underexpressed, Si concluded that cell cycle regulatory proteins are altered in chondrosarcoma of the jaws.

Bovee *et al*. (105) investigated the immunohistochemical expression of Bcl-2 as a diagnostic marker for malignancy in osteochondromas (n=24) and peripheral (n=29) and central (n=20) chondrosarcomas. Bcl-2 was mostly absent in osteochondromas. In chondrosarcomas, expression of Bcl-2 was found and expression levels were found to increase with increasing histological grade. Up-regulation of Bcl-2 characterized malignant transformation of osteochondroma because Bcl-2 expression was significantly higher in borderline and grade I peripheral chondrosarcomas compared with osteochondromas. In contrast, up-regulation of Bcl-2 seems to be a late event in central cartilaginous tumorigenesis because expression is mainly restricted to high-grade central tumors. In a subsequent study from the same group, Hameetman *et al*. (114) investigated Bcl-2 expression as diagnostic marker in a large series including 71 osteochondromas and 34 chondrosarcomas. They concluded that in cases where the distinction between osteochondroma and chondrosarcoma is difficult, Bcl-2 is a valuable diagnostic marker for malignancy, regardless of tumour size, patient gender or age.

Treatment

Treatment of osteochondroma depends on whether it is symptomatic or not, on the presence of complications and on cosmetic reasons. The treatment of choice is surgery. The tumor has to be completely excised in order to avoid recurrences. The complete evaluation of the patient requires physical examination, CT, MRI and a biopsy of the lesion. The presence of a solitary asymptomatic osteochondroma is not an indication for surgical excision, as the risks of surgery are more serious than those posed by the tumor. When an exostosis becomes so large as to cause symptoms of persistent pain or pain during activity, then the lesion must be excised. Other indications are nerve lesions such as compression. Spinal cord compression has been recorded to occur at a rate of 4% (115). Growth retardation, deformity of the limbs, loss of joint motion, compression of tendons or lesions of the soft tissue are also reasons for surgical treatment (116-118). Surgical excision is obligatory if changes of the thickness of the cartilaginous cap or an enlargement of the tumor are noticed. Surgical treatment remains the treatment of choice if there are complications from the osteochondroma. The most common complications include fractures, symptoms of peripheral nerves such as paresthesia, paraplegia, peroneal neuropathy and upper limb neuropathy (119, 120). Vascular compression, arterial and venous thrombosis, aneurysm and pseudoaneurysm are common findings, occurring in 91% of cases and can lead to ischemia or phlebitis. Rarer, but also possible, are bursitis, obstruction of the urinary or the intestinal tract and hemothorax. Recurrence is thought not to happen in osteochondroma but there is a chance of transformation into an osteosarcoma, thus the tumor has to be excised totally without leakage of myxomatous tissue or part of the cartilaginous cap. Chemotherapy and radiotherapy have not been proven to be effective, but in dedifferentiated tumors are the only choice as their prognosis is worse. Metastases are unusual, occurring in approximately 3-7% of patients, and most commonly affect the lungs. The treatment results of a large series of osteochondromas are summarized below.

Shapiro *et al*. (9) described the surgical therapy of thirty-two patients with HME, including removal of the exostoses, epiphyseal arrest, excision of the radial head and corrective osteotomy. They found that an average of 2.7 surgeries had taken place for each of thirty-two patients, since the age of twenty.

Wirganowicz *et al*. (121) described the surgical risk for elective excision of benign exostoses on 285 osteochondromasa. They noted that in 12.5% of the surgeries, there were complications, with neurological being the most common. In addition, 33% of postoperative neurapraxia was associated with surgeries near the proximal fibula.

Canella *et al*. (5) studied 408 cases of exostosis at the Tumor Centre of the Rizzoli Institute and concluded that the chance of transformation into malignancy for multiple exostoses was 13%, however they concluded that the incidence for solitary lesions cannot be determined.

Saglik *et al*. (1) described the manifestations and management of 382 cases of osteochondromas (313 with solitary and 69 with multiple). They concluded that it is essential to resect the mass as well as reconstruct the deformities.

Bottner *et al*. (122) described the surgical treatment of symptomatic osteochondroma in 86 patients. They found that 93.4% of the pre-operative symptoms resolved after surgery and that 4.7% of the patients developed postoperative complications; 7% of the whole patients had minor complications. According to their findings, 5.8% of the patients who undertook surgery had a local recurrence.

Vasseur and Fabre (123) studied 97 cases of osteochondromas with vascular complications. A solitary osteochondroma was found in 66.6% of them. They suggested that a prophylactic resection of osteochondromas must be performed if the tumor is located at the vicinity of a vessel.

Garrison *et al*. (6) described the surgical treatment of 75 osteosarcomas that had arisen from osteochondromas. They suggest the division of surgical treatment into excision, resection and amputation. They reported a 52% recurrence for

the entire group, of whom 70% had multiple osteocartilaginous exostoses and 31% solitary osteochondromas. They also reported that the recurrence rate was 78% for excisional and 15% for resectional therapy and that benign osteochondromas have a recurrence rate of 2% .

Pierz *et al*. (124) studied 43 patients with HME, twenty of whom had a family history of HME. Twenty-seven out of their 43 patients required between one to five surgeries to control their lesions.

Shin *et al*. (125) evaluated the outcomes of the Sauve-Kapandji technique for HMO in 29 patients. They concluded that in young patients, a simple excision of the tumor may improve the range of movement of the forearm but it cannot control the progress of the disease.

Most authors conclude that the treatment of choice for osteochondroma is surgical (1, 5, 6, 9, 115-125). The tumor should be excised when symptoms or complications have presented. A prophylactic resection is suggested only if the lesion lies next to a vessel. An osteochondroma must be completely excised, without leakage of myxomatous tissue or part of the cartilaginous cap, especially when a sarcomatous change is suspected. In addition to resection, reconstructive techniques have to be undertaken. Chemotherapy and radiotherapy are suggested in dedifferentiated tumors.

Prognostic factors. Excision of osteochondroma is usually curative (3). Recurrence may be seen when the removal is incomplete. Multiple recurrences or recurrence in a well-excised lesion should raise the suspicion of malignancy.

Conclusion

Osteochondroma is the most common benign bone tumor and the most common precursor for secondary chondrosarcoma. Eighty-five percent of osteochondromas present as solitary lesions and 15% as multiple due to HMO syndrome. The HMO syndrome is caused by mutations of the *EXT1* and *EXT2* genes. The tumor usually presents at the external surface of long tubular bones and is rarely symptomatic. Several complications can occur including nerve suppression, aneurysms, thrombosis, bone deformities and fractures. The diagnosis is done using X-rays, CT, MRI, ultrasound, angiography, scintigraphy and histological examination. The tumor appears as a protuberance on the bone surface while calcified flakes can be present as well. The change in metabolic activity of the tumor, its enlargement, the irregularity of its margins and a cap thickness more than 2 cm in adults and 3 cm in children are signs of malignant transformation. The already mentioned complications, esthetic reasons and the suspicion of malignant transformation (1-2%) are indications for surgical treatment. A complete surgical resection of the tumor is the treatment of choice. No myxomatous tissue nor pieces of the cartilaginous cap should be left. Several reconstructive surgeries might then be needed, while in 5.8% of the cases a recurrence can occur. The Sauve-Kapandji technique is preferable for HMO and a prophylactic resection should be undertaken only if the tumor exists in the proximity of vessels. Chemotherapy and radiotherapy are used only in dedifferentiated tumors.

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