Integrating Morphology and Genetics in the Diagnosis of Cartilage Tumors

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KEYWORDS

• Cartilaginous tumors • Enchondroma • Osteochondroma • Chondrosarcoma • IDH mutations • HEY1-NCOA2 fusion

Key points

- Cartilaginous tumors of bone form a histologic spectrum ranging from benign (enchondroma, osteochondroma) to intermediate (atypical cartilaginous tumor/chondrosarcoma grade 1) to malignant (grade 2 and grade 3 chondrosarcoma, dedifferentiated chondrosarcoma).
- The diagnosis of a cartilage tumor can be made only in a multidisciplinary team.
- Criteria to distinguish between benign and malignant are different depending on age, the presence of multiple lesions, and the location of the tumor.
- Molecular alterations that can be used for diagnosis include *IDH1* (R132C; R132H) or *IDH2* (R172S) mutations in enchondromas, atypical cartilaginous tumor/grade 1 central chondrosarcoma, grade 2/3 central chondrosarcoma, and dedifferentiated chondrosarcoma; and HEY-NCOA2 fusion genes in mesenchymal chondrosarcoma.

ABSTRACT

Cartilage-forming tumors of bone are a heterogeneous group of tumors with different molecular mechanisms involved. Enchondromas are benign hyaline cartilage–forming tumors of medullary bone caused by mutations in *IDH1* or *IDH2*. Osteochondromas are benign cartilage-capped bony projections at the surface of bone. *IDH* mutations are also found in dedifferentiated and periosteal chondrosarcoma. A recurrent *HEY1-NCOA2* fusion characterizes mesenchymal chondrosarcoma. Molecular changes are increasingly used to improve diagnostic accuracy in chondrosarcomas. Detection of *IDH* mutations or *HEY1-NCOA2* fusions has already proved their immense value, especially on small biopsy specimens or in case of unusual presentation.

OVERVIEW

Cartilaginous tumors are the most common primary bone neoplasms, characterized by the production of a cartilaginous matrix. They are classified based on their clinical and histologic features and location within bone. A multidisciplinary approach is imperative for appropriate diagnosis and management. Conventional radiography is the cornerstone of the diagnosis of cartilage tumors. The presence of matrix mineralization in the form of "popcorn" calcifications in the tumor is characteristic. Cartilaginous tumors are

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clinically divided according to their behavior into benign, intermediate, and malignant. The most common benign lesions are enchondromas and osteochondromas, which together constitute more than 60% of benign bone tumors. They can be the precursor lesions of central and peripheral chondrosarcoma, respectively, accounting for 10% to 20% of malignant bone tumors.

Histologically, enchondromas and osteochondromas are formed by chondrocytes embedded in a cartilaginous extracellular matrix (ECM). The ECM is a rich network of cartilage-specific collagens (predominantly type II collagen) and proteoglycans (including heparan sulfate proteoglycans). Its function goes beyond providing physical support for chondrocytes and cartilage integrity and elasticity: it is a dynamic structure that is constantly remodeled to control tissue development and homeostasis.[1]

Cartilaginous tumors are complex diseases and different molecular mechanisms are involved in the different subtypes. Point mutation(s) in a single gene underlies the formation of enchondromas and osteochondromas. They may occur early during development, resulting in a somatic mosaicism causing nonhereditary enchondromatosis or can be present in the germline causing hereditary multiple osteochondromas syndrome. Additional secondary mutations drive multistep malignant progression forward. On the other hand, in mesenchymal chondrosarcoma a recurrent translocation is found.[2]

Here, we summarize the morphology as well as the molecular and genetic mechanisms involved in enchondromas, osteochondromas, and different subtypes of chondrosarcomas.

ENDOCHONDRAL BONE FORMATION

Most of the skeleton develops by endochondral ossification, a process in which the skeletal elements are preformed in a cartilage model. Cartilage tumors arise mainly in those parts of the skeleton formed by endochondral ossification. The face and skull are therefore rarely affected. Endochondral ossification is a stepwise physiologic process in which chondrocytes undergo a coordinated process of cell proliferation, differentiation, and programmed cell death within the normal growth plate. Cartilaginous matrix surrounding apoptotic chondrocytes mineralizes and blood vessels bring in osteoblasts replacing hyaline cartilage by bone.[3]

Endochondral ossification is coordinated by various growth factors, signaling molecules and cytokines.[4,5] Some of these molecules function in a gradient fashion, generating short- and long ranges of signaling activity.[6,7] Proteoglycans (eg, heparan sulfate proteoglycans) are involved in signaling gradients formation.[8–10] Prehypertrophic chondrocytes secrete the growth factor Indian Hedgehog (IHH). IHH diffuses away from its site of synthesis, and signals to the proliferating chondrocytes to increase their proliferation rate.[3,4] IHH also acts as a long-range signaling molecule stimulating perichondrial cells to secrete parathyroid hormonelike hormone (PTHLH; also known as parathyroid hormone–related protein). PTHLH inhibits both chondrocyte differentiation and the expression of IHH, keeping chondrocytes in a proliferating state. When the PTHLH levels decrease below a certain threshold, chondrocytes stop proliferating and begin hypertrophic differentiation and ossification.[3,5] Deregulation of signaling pathways that coordinate endochondral ossification (eg, IHH signaling pathway) are associated with the formation of enchondromas, osteochondromas, and chondrosarcomas (**Table 1**).[2,11]

The ECM in cartilage is mainly composed of type II collagen. Mutations in several different types of collagen I, II, IX, X, and XI genes are related to cartilage abnormalities in humans.[12] Mutations in the *COL2A1* gene have been found in many forms of chondrodysplasias, cartilage tumors, and in cartilage degeneration. *COL2A1* gene mutations alter the formation of the triple helical assembly of collagen in cartilage. Several studies in humans have shown that the severity of the clinical phenotype corresponds to the number of altered collagen fragments left unfolded and to their altered mobility.[13]

BENIGN CARTILAGE TUMORS

Chondromas are relatively frequent, and most are located centrally within the medulla of bone (enchondroma), whereas a minority are classified as periosteal (juxtacortical) chondromas. The incidence of these benign tumors cannot reliably be assessed, as they often go unnoticed and are detected by coincidence, with a radiological examination that was requested for other reasons. Occasionally there is a pathologic fracture.

ENCHONDROMA

Enchondromas are benign hyaline cartilage–forming tumors of medullary bone. They are located in the metaphyses and diaphysis of short and long tubular bones of limbs, especially hands and feet.[14] Enchondromas usually appear as single lesions (solitary enchondromas) (**Fig. 1**). Multiple lesions are seen in the setting of nonhereditary