

# Solid Tumour Section

## Short Communication

## Bone: Enchondroma

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### Abstract

Review on Enchondroma, with data on clinics, and the genes involved.

#### Keywords

Enchondroma; IDH1 mutations; IDH2 mutations

### Identity

#### Other names

Solitary enchondroma

Central chondroma

#### Note

Enchondroma is a common benign hyaline cartilaginous neoplasm that develops within the medullary cavity of bone. As the name suggests, it is located within the bone, either centrally (80% of cases) or eccentric (20% of cases). The most commonly affected bones in order of frequency are the phalanges of the hand, humerus, tibia and femur. Enchondromas are very uncommon in flat bones such as the pelvis, ribs, scapula sternum or vertebrae. Enchondromas are mostly found in the diaphyseal or meta-diaphyseal region of the long bones while they are rarely observed in the epiphysis. Thirty-five percent of enchondromas develop in the hand whereas its malignant counterpart is extremely rare at this location. In general, malignant transformation of enchondroma is extremely rare (overall risk <1% of cases). In rare instances, multiple enchondromas are found to occur in a syndrome (enchondromatosis). At gross specimen the enchondroma tissue looks white-grey and opalescent

while yellow or red foci represent areas of calcification or ossification.

### Clinics and pathology

#### Phenotype / cell stem origin

Since many cartilaginous tumors develop from the medullary region of the bone, mesenchymal stem cells (MSCs) located in the bone marrow are currently considered the cell-of-origin for enchondroma. MSCs are stem cells that have the ability to differentiate into cells of the adipocytic, osteogenic and chondrogenic lineage. The initiating event of enchondroma development was identified after the observation that patients with multiple enchondromas are also at risk of developing other, unrelated, types of cancer like glioma and acute myeloid leukaemia and the finding that mutations in isocitrate dehydrogenase 1 or 2 (IDH1/2) are frequently found in these types of cancer. Therefore, cartilaginous tumors were also investigated for the occurrence of mutations in these genes. Indeed, in 87% of enchondromas in patients with enchondromatosis and in 52% of solitary enchondromas mutations in IDH1 or -2 were found, pointing to this mutation as an early and crucial event in enchondroma development. Further evidence for a causative role of these mutations came from research showing increased chondrogenic and decreased osteogenic differentiation of MSCs upon treatment of MSCs from different donors with the oncometabolite D-2-hydroxyglutarate, the product of IDH mutations. Likewise, introduction of the most common IDH mutation found in enchondroma

into MSCs promoted chondrogenic differentiation, while inhibiting osteogenic differentiation.

### Epidemiology

Enchondroma accounts for 10-25% of all benign tumours. Both sexes are equally affected and it shows a wide age range from 5-80 years, although the majority of patients present within the second to fifth decade of life.

### Clinics

The differential diagnosis between enchondroma and low grade chondrosarcoma is difficult and is therefore based on a combination of clinical, radiological and histological parameters. Usually, enchondromas of the long bones are asymptomatic and detected incidentally after a fracture or bone scans for other reasons. In case of long bones, calcified enchondromas can be found. In contrast, enchondromas of the small bones of the hands and feet lack the calcification and may give palpable swellings, with or without pain. Enchondromas can be easily observed in radiographs since normal bone is replaced by mineralized or unmineralized hyaline cartilage. Radiographically, enchondromas are lytic lesions mostly in the center of the bone, can be mildly expansile with well defined, minimally thickened bony margins, along with intralésional calcification and diaphyseal expansion. There is evidence of cartilaginous matrix (rings and arcs or popcorn-like calcifications).



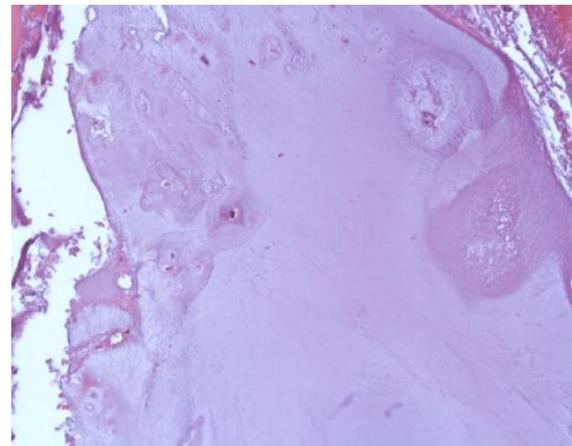
Frontal radiograph of the right hand reveals a lytic lesion in the fourth proximal phalanx (yellow arrow) with subtle areas of calcified matrix within the lesion compatible with an enchondroma. Picture from: <http://www.radiologypics.com>.

### Pathology

Macroscopically, most enchondromas are <5 cm in size. The tissue is grey-white and opalescent.

Gritty, yellow and red foci represent areas of calcification and ossification, respectively. Microscopically, enchondromas are hypocellular, avascular tumours with abundant hyaline cartilage matrix. The nuclei are small and round with condensed chromatin. Occasionally, binucleated cells without cytologic atypia are found.

There is no mitotic activity. Myxoid matrix and endosteal erosion can be present in phalangeal tumors. There is often encasement (deposition of bone at the edges of the lobuli), while entrapment of preexisting host bone is absent and should be regarded a sign of progression to atypical cartilaginous tumour. More worrisome histological criteria such as increased cellularity, myxoid change, cytological atypia and nuclear hyperchromasia are only tolerated in case of 1) location in the small bones of the hands and feet, 2) in the context of enchondromatosis, 3) in young patients in which the growth plates are still open.



Cartilaginous tumour with very low cellularity and abundance of chondroid matrix. Atypical cells and mitoses are absent.

### Treatment

A wait-and-see policy is justified for asymptomatic lesions considered benign at radiography. Tumor growth can be determined clinically and by means of periodic radiographic examination. Biopsy can be done when asymptomatic lesions become large and symptomatic. Large or symptomatic tumours or borderline cases in which the distinction with low grade chondrosarcoma can not be made histologically nor radiographically can be treated surgically with margin improvement by means of phenol or cryosurgery. Recurrence of enchondroma is highly uncommon after curettage.

### Evolution

Malignant transformation of solitary enchondroma is extremely rare (<1%). In the context of enchondromatosis (Ollier disease, Maffucci syndrome) the risk of malignant transformation is increased up to 40%, depending on their location.

While enchondromas are most common at the phalangeal bones, chondrosarcoma of the phalanges is extremely rare. Local recurrence is uncommon, although occasionally an enchondroma will recur many years later, but rarely as an atypical cartilaginous tumor or low-grade chondrosarcoma.

### Prognosis

Enchondroma is a benign lesion. Recurrence is highly uncommon after curettage. Progression towards malignancy is rare (5 cm) could indicate malignant transformation. Only those tumors that cause symptoms such as increase in size, pain or swelling should be further investigated and treated.

### Genetics

Enchondroma is associated with heterozygous gain-of-function mutations in the genes for IDH1 or IDH2 (isocitrate dehydrogenase 1 (2q34) or 2 (15q26.1)). In 86% of enchondromas in enchondromatosis patients and in 52% of solitary enchondromas mutations in these genes have been found, as described above. IDH1 mutations are more frequent than IDH2 mutations in enchondroma, with R132C representing the most common mutation in cartilaginous tumors, followed by R132H.

The normal function of IDH is in the TCA cycle, where it catalyzes the conversion of isocitrate into alpha-ketoglutarate. In the case of an IDH mutation, however, the enzyme converts alpha-ketoglutarate into D-2-hydroxyglutarate (D-2-HG), which is considered an oncometabolite. D-2-HG and alpha-ketoglutarate are structurally similar, causing D-2-HG to compete with alpha-ketoglutarate for binding to alpha-ketoglutarate-dependent enzymes. Most of these enzymes are involved in epigenetic regulation and examples include Jumonji-C domain-containing histone demethylases and the TET family of 5-methylcytosine hydroxylases. Inhibition of these enzymes due to binding of D-2-HG results in DNA hypermethylation and histone modifications. Indeed, increased levels of D-2-HG and DNA hypermethylation have been found in enchondromas with IDH1/2 mutations. Another group of alpha-ketoglutarate-dependent enzymes are the prolylhydroxylases, enzymes that promote degradation of HIF1A (hypoxia-inducible factor 1 $\alpha$ ). Indeed, IDH mutations, via an increase in D-2-HG, have been shown to lead to a stabilization of HIF1A, which in turn results in the stimulation of angiogenesis, an important feature of cancer.

Interestingly, it was shown that while IDH1/2 mutations may be crucial for initial enchondroma development, they are not essential anymore after progression towards chondrosarcoma has occurred. It is likely that other mutations occur, facilitating chondrosarcoma growth.

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