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Enchondroma

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Introduction

Enchondromas are cartilaginous tumors of the benign bone tumor family. The common benign bone tumors include enchondroma, osteochondroma, chondroblastoma, and chondromyxoid fibroma all of which hail from a cartilage origin. Enchondromas are medullary cavity tumors classified in an overarching category of chondromas: benign tumors of hyaline cartilage occurring in bones of endochondral origin.

Enchondromas are the most prevalent of the intraosseous cartilage tumors, accounting for approximately 3% of bone tumors and up to 13% of benign bone tumors.[1][2] These tumors are usually solitary, central, metaphyseal lesions of tubular bones, favoring the small bones of the hand and feet followed by the femur and humerus. Enchondromatous tumors typically begin and grow in childhood arising from rests of growth plate cartilage or chondrocytes that proliferate and enlarge, then stop growing but remain present throughout adulthood. Bone sarcomas are rarer than sarcomas of soft tissue. Some benign bone lesions do, however, have malignant potential; enchondromas and osteochondromas can transform into chondrosarcoma.

Etiology

Enchondromas are benign, lobulated neoplasms of hyaline cartilage most commonly occurring in the short tubular bones of the hands and feet. Femur and humerus are the two most common sites for long bone involvement. These tumors can arise in any bone formed from cartilage, and are common, representing approximately 13% of benign bone tumors. Most enchondromas begin in the medullary portion of the diaphysis, arising from ectopic cartilaginous nests in the metaphysical region, and expand outward towards the cortex. Enlarging lesions may cause a pathologic fracture.[1][2]

Epidemiology

Besides solitary lesions, sometimes an individual can display multiple enchondromas, enchondromatosis. One such a syndrome is Ollier disease. With a prevalence estimated to be about 1 in 100,000, Ollier disease characteristically demonstrates multiple enchondromas in a classic unilateral predominance. The enchondromatous tumors of Ollier disease typically locate at the epiphysis and the adjacent regions of the metaphysis and diaphysis. The location of the tumor can prevent normal bone growth: shortening due to the epiphyseal invasion, metaphyseal widening, and long bone bowing.[3] Another condition presenting with multiple enchondromas is Maffucci syndrome. In this syndrome, the enchondromas associate with soft tissue hemangiomas and vascular malformations. Although histologically similar to a solitary enchondroma, cytologically the changes seen in this syndrome appear more bizarre. In both conditions, Ollier disease and Maffucci syndromes, there is an associated increased risk of malignant transformation to chondrosarcoma. In addition, both conditions carry an increased risk for visceral malignancy.

Pathophysiology

Enchondromatosis possesses associations with somatic mutations in isocitrate dehydrogenase-1 (IDH1) and 2 (IDH2) genes. The mutations are rare and often sporadic. Isocitrate dehydrogenase is an enzymatic component of the tricarboxylic acid (TCA) cycle functioning to convert isocitrate to alpha-ketoglutarate.[4][5] Mutations in IDH1 and IDH2 cause malfunction of this enzyme resulting in increased levels of the oncometabolite D-2-hydroxyglutarate (D-2-HG.) D-2-HG competitively inhibits alpha-ketoglutarate dependent enzymes. DNA hypermethylation and histone modification ensue affecting differentiation.[6] Inhibition of the osteogenic differentiation of mesenchymal stem cells occurs via elevations in D-2-HG resulting from IDH1 and IDH2 mutations. All-in-all, blocking osteogenic differentiation during the formation of the skeleton results in cartilaginous tumor formation.[7]

Histopathology

Evidence of a lesion on a radiologic study is not definitive enough to make the diagnosis of an enchondroma. Diagnostic confirmation requires histopathologic examination of the specimen sample. Differentiation between benign and malignant lesions poses an even greater challenge. One must examine all available tissue, and even then the diagnosis may remain in question and remain based on clinical evidence and suspicion. Microscopically enchondromas appear as gray-blue, translucent, hypocellular, non-vascular tumors with abundant hyaline cartilage. The nuclei of these cells are fairly regular with few mitotic figures. Juxtacortical chondromas and enchondromas in regions such as the hands, however, may be hypercellular with atypia and still maintain a benign nature.

Conversely, long bone enchondromas often appear benign microscopically but can recur after removal. As with many tumors, staging classifications are used to classify the tumor further. The staging of bone sarcomas follows the tumor, node, metastasis (TNM) guidelines.

Histopathologically, punctate calcifications of the chondroid matrix define the appearance of enchondromas. On examination, the typical enchondroma is smaller than 3 centimeters. The enchondroma is composed of well-circumscribed nodules of benign hyaline cartilage. The nuclei of the chondrocytes are small and uniformly round with condensed chromatin. Rarely, binucleate forms are present. Foci of endochondral ossification may be present in heavily calcified enchondromas. Syndromes characterized by multiple enchondromas, Ollier’s disease and Maffucci syndrome, exhibit more cellularity and atypia than classic, single enchondromas. The increased cellularity and atypia makes distinguishing enchondroma from chondrosarcoma more difficult. Distinctions between benign cartilaginous lesions and atypical cartilaginous tumor/chondrosarcoma grade 1 (ACT/CS1) is difficult. The cartilaginous lesions are typically hypocellular while ACT/CS1 has a hypercellular appearance.

History and Physical

The symptoms of enchondroma are often nonspecific and found as a result of a pathologic fracture/trauma or localized versus radiating pain. However, many are ultimately found incidentally on radiographic imaging.[8] Enchondromas may present at any age although the classic presentation is in the second decade of life: 15 to 35 years of age. Enchondromatosis syndromes present earlier in life; typically before age 10.[9]

Enchondromas are the most common benign tumor to present in the hand. The classic location of the lesions is in the proximal metaphysis of the proximal phalanx with a predilection for the ulnar side of the bone.[10]

Evaluation

Radiographically, enchondromas have varied appearance based on location and extent of calcification, and they may resemble medullary bone infarcts. Enchondromas typically appear as well-defined solitary defects in the metaphysical region of bones. Their appearance depends heavily on the location and extent of calcification of the tumor. Centrally

located lesions usually appear as well-circumscribed areas of rarefaction, most frequently diaphyseal, with an expanded cortex around it. Juxtacortical lesions are eccentric and beneath the periosteum in well-defined cortical defects. Small, flocculent foci of calcification are visible within the tumor. Radiographically visible calcifications appear as fine, punctate stipplings, and if pronounced, may suggest a bone infarct. The calcifications can range in size from punctate to rings. Larger lesions can cause endosteal scalloping along with expansion and thinning of the cortex.

A centrally located lesion appears well-circumscribed with diaphysial rarefaction and an expanded cortical region. Juxtacortical lesions are eccentric and subperiosteal with distinct cortical defects. Larger lesions present with endosteal scalloping with an expansile and thinning cortex. Heavily calcified lesions may resemble bone infarct or *bone islands* while an unclassified lesion may appear lytic.

Computed tomography (CT) is useful for detecting matrix mineralization and cortex integrity while MRI adds insight into the aggressive and destructive features of the tumor. Indicators of potential malignancy include large size, a large unmineralized component, significant thinning of the adjacent cortex, and bone scan activity greater than that of the anterior superior iliac spine (ASIS). Progressive destruction of the chondrite matrix by an expanding, non-mineralized component, an enlarging lesion associated with pain, or an expansile soft tissue mass strongly associate with malignant transformation of an enchondroma.

Magnetic resonance imaging (MRI) is an additional modality used for evaluation of bone lesions. Enchondroma and chondrosarcoma often have a similar appearance on first pass analysis. Both exhibit low signal intensities on T1 with reciprocal high-intensity changes on the T2-weighted images with a lobular growth pattern. Both enhance with gadolinium contrast in peripheral and spatial areas. Neither dynamic contrast-enhanced MRI nor advanced techniques such as diffusion-weighted imaging and hydrogen proton spectroscopy has proved effective in differentiation enchondroma from chondrosarcoma. To differentiate the two, peritumoral edema must be assessed. Although this finding has not undergone prospective examination, case series have revealed consistency. In the case series analysis, no peritumoral edema was noted with enchondromatous lesions while chondrosarcoma lesions showed the edema. Both CT and MRI can easily distinguish bone infarct from enchondroma.[2]

Only two known biomarkers exist that can distinguish enchondroma from chondrosarcoma: periostin and alpha-methylacyl-CoA racemase (AMACR). Periostin, a stromal-related protein, is reported absent in enchondroma but is present in low-grade chondrosarcoma. AMCR, a mitochondrial and peroxisomal enzyme, is expressed in most enchondromas. Conversely, AMCR is present in a minority of chondrosarcomas.[11] Further investigation is needed to further validate and confirm these biomarkers as reliably entities.

Treatment / Management

Management of enchondroma lesions typically requires simple curettage with bone grafting. The bone graft used may be allogeneic bone, autogenous, or synthetic bone substitutes. The impact of the type of graft on healing, recurrence, complications, and malignant transformation is unknown. Currently, no standardized algorithm for surgical treatment of this kind of tumor exists. The necessity of curettage with grafting remains unproven. The timing of surgical intervention has also not been shown to have significant benefit. Early and delayed surgical intervention was shown to have similar functional outcomes.[10]

Needle biopsy is not required and is actually discouraged by pathologists.[2] When treating bone lesions non-surgically, bone structure and integrity can undergo compromise following the treatment. Pathologic fracture risk increases with the size of the lesion. Lesions in weight-bearing bones with a diameter greater than 25 millimeters or that involve over 50% of the diameter of the boney cortex have the highest risk of fracture.

Prophylactic intervention aiming to prevent impending fracture via internal fixation methods is unknown and

controversial. Retrospective studies have formed a basis to guide the indications, but limits of these guidelines are the use of plain radiographs, subjective patient information, and inadequate understanding of the biomechanical factors involved in the neoplastic process. The Mirels criteria were developed to quantify the risks of fracture pertaining to bone neoplasms. These criteria take into account the location, pain, lesion type, and lesion size. A score greater than 8 dictates significant risk of fracture and a need for a prophylactic internal fixation. A bone tumor with a score less than seven can undergo observation according to these criteria. In applying these criteria, the defined fracture risk uses the load-bearing requirement of the bone divided by its load-bearing capacity. The parameters for load-bearing requirement and capacity were also stipulated and analyzed. The patient's age, weight, activity level, and ability to protect the site dictate the load-bearing requirement. The load-bearing capacity depends on the amount of bone loss, modulus of the remaining bone, and location of the defect with respect to the type of load applied. Graphic representation of the Mirels criteria is depicted below.

Differential Diagnosis

When considering a lesion to be an enchondroma, the clinician must also consider bone infarction on the differential as both may have a similar radiographic appearance. Tuberculous dactylitis and low-grade chondrosarcoma are also considerations in patients with enchondroma who have pain without the presence of fracture at their index presentation.[12]

Staging

The staging of bone sarcomas follows the tumor, node, metastasis (TNM) guidelines.

Prognosis

Solitary enchondromatous lesions are typically self-limited. Recurrence is rare following curettage and bone grafting, however, higher risks of recurrence are associated in enchondroma lessons involving long bones.[1]

Complications

As these tumors arise in the medullary portion of the bone, their expansile properties may ultimately result in pathologic fracture as the cartilaginous tumor encroaches on the cortical bone. If surgery is delayed until fraction union has occurred, the patient may be exposed to extended periods of immobilization. Hospital costs are also higher for patients treated with primary surgery for their pathologic fracture. Patients treated with primary surgery of the pathologic fracture had a shorter time to return to work than did the delayed surgical candidates whose procedure was held until fracture union.[10]

Malignant transformation to chondrosarcoma usually occurs following skeletal maturity. Transformation of a singular enchondromatous lesion is rare, less than 1%.[13] Malignant transformation risk increased with Ollier disease and Maffucci syndrome.[14][15] They also associate these two syndromes with non-sarcomatous, extraosseous neoplasms, including brain tumors.[16]

Deterrence and Patient Education

The discovery of benign bone tumors is often incidental. Symptomatic presentation of these tumors is dependent on size and location. Localized pain, swelling, deformity, and pathologic fracture are some common symptoms of benign bone tumors. The diagnostic approach to these tumors revolves around radiographic imaging. More extensive, invasive diagnostic testing is not recommended.[2] The management of these conditions is conservative. Serial examination and radiographs are common practice. Curettage with bone grafting is the recommended treatment of choice for symptomatic or aggressive nonmalignant tumors. As the mutations in the isocitrate dehydrogenase-1

(IDH1) and 2 (IDH2) genes are somatic, there is no genetic inheritance pattern for benign enchondromas, Ollier disease, or Maffucci Syndrome.[4][5]

Pearls and Other Issues

The mean length of a cartilaginous lesion may hint to its classification. The length of the typical enchondroma is classically less than 5 centimeters while the mean length of a chondrosarcoma is greater than 5 centimeters. This measurement should not serve as the only diagnostic feature, however. Larger lesions should not be considered suspicious solely based on length if no other concerning features are present. These lesions may be labeled as enchondromas without the necessitation of further workup. Of note, chondrosarcoma lesions may present with a smaller mean diameter in the fibula.[2]

Enhancing Healthcare Team Outcomes

As the discovery of many enchondroma lesions occurs incidentally, care providers and radiologists alike must be diligent in their evaluation of ordered radiographic studies. Open communication between the radiology, medical, and surgical teams are required to manage this condition. A holistic, team-based approach should be employed to provide the best outcomes for patients. Enchondromas, although benign, nonaggressive cancers, still require expert care and unwavering vigilance. As there is no current guideline-recommended treatment for this condition future investigation needs to focus toward definitive management strategies.

The crux of the diagnosis of enchondroma comes by differentiating enchondroma from atypical cartilaginous tumor/chondrosarcoma grade 1 (ACT/CS1). Pathologists recommend against biopsy which for many other oncologic processes is the diagnostic modality of choice. Coordination between radiologists, oncologists, pathologists, surgeons, and the primary medical team is needed to arrive at the diagnosis of an enchondroma. To date, no singular serologic or radiologic test may differentiate ACT/CS1 from enchondroma. This differentiation has limited clinical and therapeutic value, however. The treatment for enchondroma and ACT/CS1 is identical: curettage with adjuvant phenol application or cryosurgery.

Realistically, most enchondromas require nothing more than supportive care and close monitoring. As this may pose a shock to the patient and the family, presentation with a multidisciplinary approach and a unified front and plan of action is the best policy.

If the patient sustains a pathologic fracture requiring surgical intervention, prompt intervention is recommended despite increased hospital costs. The benefit of early, primary intervention is a faster return to work.[10] Following surgical treatment of enchondromas, the majority of patients exhibit complete bone healing and range of motion despite the type of bone grafting material used.[17] (Therapeutic Level IV)

Questions

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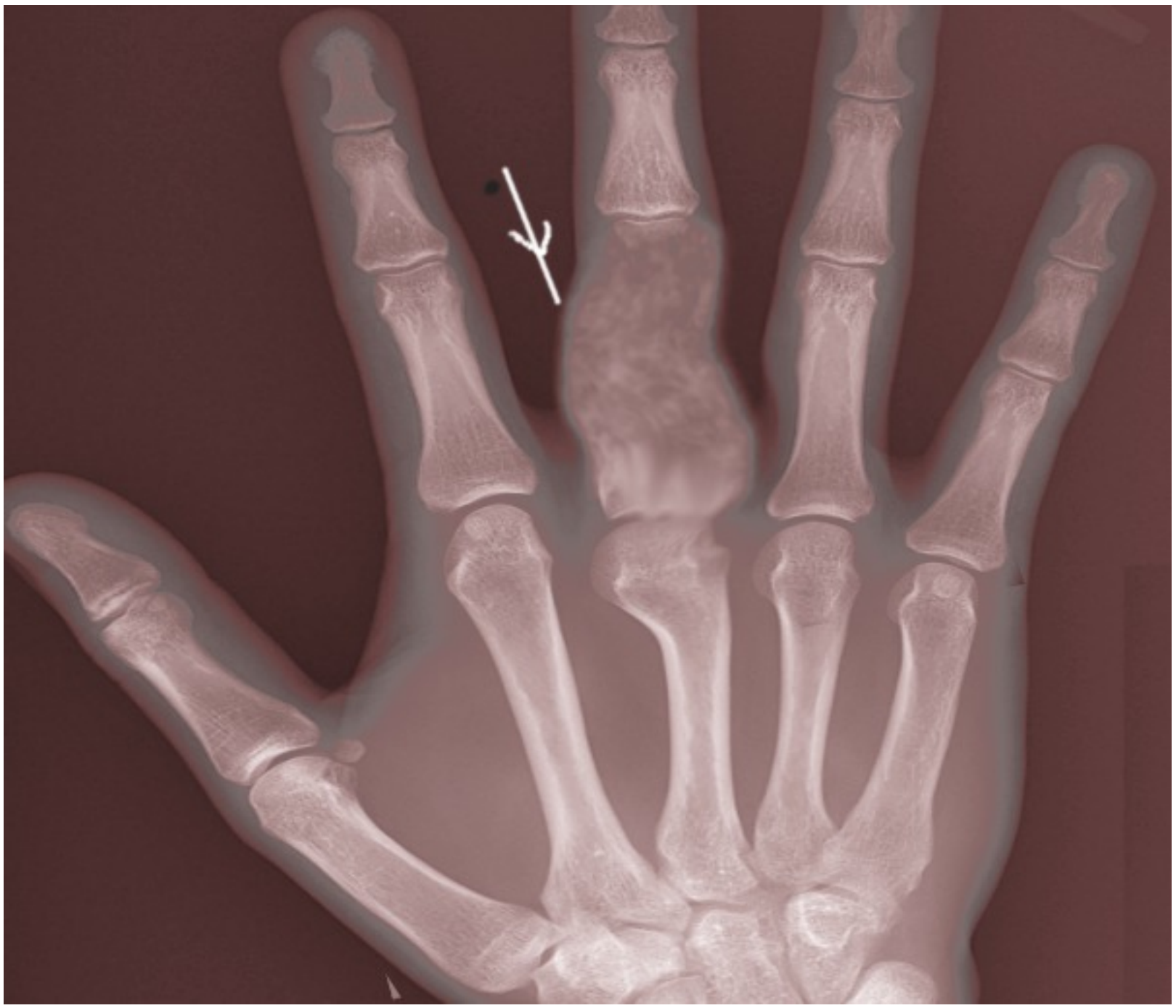
Figures



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