Multiple Hereditary Exostoses

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Multiple hereditary exostoses (MHE), also known as multiple osteochondromas, *is an autosomal dominant disease that results in the development of osteochondromas throughout the body. The disease typically is diagnosed during childhood and requires lifelong monitoring and treatment of painful osteochondromas. Individuals with MHE must be monitored for complications that can arise and the potential malignant transformation of an osteochondroma into a chondrosarcoma. This article discusses the basic characteristics of MHE, genetic links, the role of medical imaging in diagnosis, and treatment options.*

This article is a Directed Reading. Your access to Directed Reading quizzes for continuing education credit is determined by your membership status and CE preference.

After completing this article, the reader should be able to:

- Define terms such as *exostosis*, *osteochondroma*, and *chondrosarcoma*.
- Describe the basic characteristics of multiple hereditary exostoses (MHE).
- Discuss the genetic components of MHE.
- Explain the roles of various imaging modalities in the diagnosis of osteochondromas and chondrosarcomas.
- Discuss treatment options and prognosis for those affected by MHE.

Multiple hereditary exostoses (MHE) is a rare bone disorder that affects the growth plates or other areas of the body in which cartilage eventually converts to bone.[1,2] Approximately 96% of MHE diagnoses occur in individuals between 2 and 12 years old.[1] Typically involving long bones, this disease results in sometimes painful, abnormal bone growth that can adversely affect the knees, forearms, humerus, pelvis, ribs, or spine.[1,3] MHE produces numerous benign tumors that vary in size and shape, and usually are persistent, even recurring in an area following surgical resection.[1] Genetic mutations are thought to cause MHE.[3]

MHE was reclassified as multiple osteochondromas by the World Health Organization in 2002.[1,2] The explanation for the change was the use of the term *exostosis* by the medical community and the public to describe any type of bone growth, whether the growth was the result of a benign cartilaginous tumor (osteochondroma), a distorted direction in bone growth (eg, Nora lesion or Trevor disease), or a reactive process (subungual exostosis).[4] This clarification of terminology allows for a more specific diagnosis. Other terms often are used to describe MHE (see **Box 1**).[1,5,6]

Although the World Health Organization reclassified MHE as multiple osteochondromas, a review of the literature shows that MHE remains a popular description of the disease process.[3,6-9] MHE is the term used in this article to reflect popular medical literature from the United States and a cited case study.

Normal Bone Anatomy

To understand the significance of abnormal bone growth in patients with MHE, it is necessary to review normal bone anatomy and the bone growth process. Bone is composed of 2 types of osseous tissue: cortical bone and cancellous bone. Cortical bone (also known as *compact bone*) is the outermost layer of bone and contains

elementary units called *osteons* (or Haversian systems). Osteons surround the Haversian canals, which carry blood vessels, lymph vessels, and nerves throughout the cortical bone. The inside surface of cortical bone contains bone-forming cells (osteoblasts) and bone-resorbing cells (osteoclasts). The dense cortical bone is protected by the periosteum, a thin connective tissue membrane that covers and protects the entire bone and also contains osteoblasts, fibroblasts, blood vessels, and nerves (see **Figure 1**).[10,11]

The medullary cavity is within the cortical bone and is composed of cancellous, or spongy, bone.[10,11] Cancellous bone is less dense than cortical bone, consists of trabeculae, is responsible for hematopoiesis (blood formation), and is found in the bony interior and at the epiphyses of long bones.[11] The epiphyseal plate and the adjacent terminal diaphysis represent the most

Box 1

Alternative Names for Multiple Hereditary Exostoses[1,5,6]

The following synonyms for multiple heredity exostoses often are used in practice and in the literature:

Chondral osteogenic dysplasia of direction
Chondral osteoma
Deforming chondrodysplasia
Diaphyseal aclasis (multiple hereditary)
Dyschondroplasia
Exostosing disease
Exostotic dysplasia
EXT
Hereditary deforming chondrodysplasia
Hereditary multiple exostoses
Osteochondromatosis
Osteogenic disease
Multiple cartilaginous exostoses
Multiple congenital osteochondromata
Multiple osteochondromas
Multiple osteomatoses

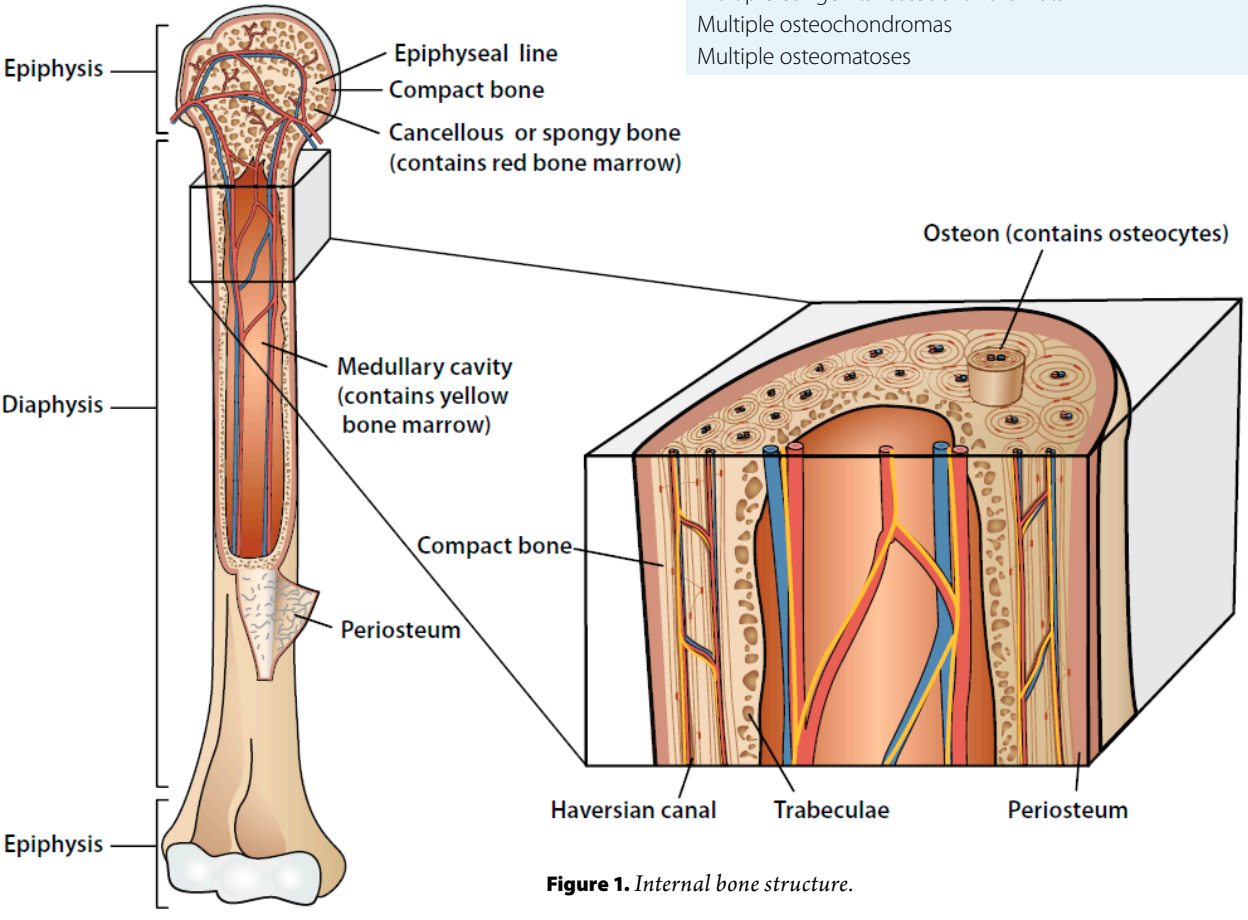

Figure 1. *Internal bone structure.*

metabolically active segment of the long bones until a child reaches puberty, unless trauma or another pathophysiological condition, such as healing of bone fractures, occurs.[10] This area also is known as the *metaphysis* because of its changing nature during growth and development.[10] It is the abnormal osseous transformation of the cartilage cap in the diaphysis, the shaft of the long bones of the axial and appendicular skeleton, that is the primary negative outcome for patients with MHE.[9] Yellow bone marrow is housed within the diaphysis, and the body can convert it to red marrow in cases of heavy blood loss or anemia to increase blood cell production.[11]

Bone Tumors

Primary bone tumors are rare, accounting for fewer than 1% of all clinically diagnosed tumors.[10] Of these, approximately 50% result from neoplasms of the blood-forming cells of the bone marrow, such as multiple myeloma and leukemia. The other 50% of primary bone tumors are the result of bone-forming cells (osteoid osteoma and osteosarcoma), cartilage cells (chondroma and chondrosarcoma), osteoclasts, and primitive mesenchymal bone marrow cells (Ewing sarcoma).[10]

Primary Bone Tumors

Multiple Myeloma

Multiple myeloma is a malignant disease of plasma cells. Plasma accounts for approximately 55% to 60% of total blood volume and 5% of cells found in healthy bone marrow. Descendants of B lymphocytes, plasma cells proliferate and produce antibodies in the form of various immunoglobins. Multiple myeloma is the result of a malignant transformation of a single plasma cell, which is known as *plasmacytoma*.[10] In plasmacytoma, the malignantly transformed bone marrow cell produces numerous clones with the same mutation that spread to other sites and become multiple myeloma.[10,11] As the number of immunoglobulins specific to the plasmacytoma increases, a spike in the abnormal plasma cell mutation can be detected through serum protein testing.[10]

Multiple myeloma eventually destroys bone marrow and the surrounding bone, creating multiple lytic bone lesions that appear on radiographs.[10,11] Complications include[10,11]:

- Calcium deposits in various organs throughout the body (especially the kidneys).
- Renal failure.
- Anemia.
- Leukopenia.
- Osteoporosis.
- Bone fractures.

Chemotherapy and radiation therapy are the standard methods of treatment, but the prognosis for this disease is grim. Most individuals survive 3 to 4 years, but few survive beyond 10 years.[10,11]

Leukemia

Discovered in 1845 almost simultaneously by Rudolf Virchow in Berlin and John Hughes Bennett in Edinburgh, leukemia is a malignant disease involving white blood cells in the bone marrow and peripheral blood.[10] White blood cells are produced by flat bones, such as the sternum and pelvis, and by lymph nodes in adults because the blood-producing red bone marrow of long bones is replaced by fat as people mature. However, during infancy and adolescence, white blood cells can be produced by the thymus, lymph nodes, long bones, or flat bones. In cases where hematopoietic bone marrow is destroyed, hematopoiesis might resume in the spleen, liver, and lymph nodes.[10]

The term *leukemia* means "white blood," referring to the milky white appearance of blood when the number of white cells reaches approximately 1 million cells/μL. However, with modern medicine, most patients are diagnosed and treated for the disease well before white cell levels progress to this point. Symptoms of leukemia include anemia, recurrent infections, and uncontrollable bleeding. According to Damjanov, overwhelming infection is the leading cause of death in all forms of leukemia.[10]

Osteoid Osteoma

Osteoid osteomas are benign bone tumors representing approximately 10% of benign skeletal neoplasms[12] that usually affect the long bones of young adults.[13] Small and spherical in shape, these tumors typically have a diameter of 1.5 cm or less.[12] Although an osteoma can appear anywhere in the skeletal system, the lesion usually is seen in the long bones of the lower extremities. Approximately one-quarter of these lesions occur in the proximal femur.[12]

Pain and swelling of the affected area, as well as possible restriction of motion, are the most common clinical symptoms. Diagnosis generally is supported by radiography, computed tomography (CT), or magnetic resonance (MR) imaging.[12] Bone scintigraphy also can be used and demonstrates an unusually intense uptake in the center of a lesion.[14] Osteoid osteomas generally are corrected by open resection or CT-guided resection of the tumor.[13]

Osteosarcoma

Osteosarcoma is the most common primary malignant tumor (excluding marrow malignancies of myeloma, lymphoma, or leukemia) and represents approximately 20% of bone cancers.[11,15] The condition most commonly affects adolescents or young adults whose bones are still growing, or older adults with a history of Paget disease.[10,11,14,15] Typically found in the long bones of the extremities, osteosarcomas are most prevalent in the metaphyses near the knee.[10,14,15] Similar to osteochondromas, osteosarcomas primarily are diagnosed using radiography, whereas secondary examinations with MR imaging, CT, radionuclide bone scans, and positron emission tomography (PET) generally are used to determine the extent of soft tissue involvement or metastasis.[15]

Treatment of osteosarcomas includes surgical resection, chemotherapy, and radiation therapy.[10,11] Chemotherapy is an essential component of treatment because only 10% of patients survive 5 years without it.[10] However, with chemotherapy, 5-year survival rates have reached 60%, and some patients have been cured completely.[10]

Chondrosarcoma

Although most chondrosarcomas are primary bone tumors, they also can occur as a malignant transformation of MHE or other osteochondroma pathologies.[5,10,11] The malignant transformation of an osteochondroma is estimated to occur in approximately 1% to 5% of patients with solitary osteochondromas[1] but can be as high as 25% in patients with MHE.[3,16] However, these estimates fluctuate within the literature, and it is suggested that higher reported percentages result from subject selection in studies.[16]

Chondrosarcomas typically originate in the axial skeleton (pelvis, ribs, and vertebrae) and the adjacent portion of long bones (proximal femur and humerus).[10,11] Patients might describe a dull pain of long duration, an increase in the size and pain of an existing osteochondroma, or the growth of an osteochondroma after puberty. Adults might have a cartilage cap thickness of 2 cm or more.[1,3,11] Most benign and malignant tumors can be indistinguishable on radiographs.[11] Patients are encouraged to obtain a baseline bone scan following skeletal maturation, with periodic routine screenings to evaluate changes or new developments.[1]

Osteochondromas

Osteochondromas represent the most common bone tumor (20%-50% of all benign tumors) and can be solitary or multiple. An osteochondroma is a cartilage-capped bony projection arising on the external surface of a long bone or other marrow-containing cavity (see **Figure 2**).[1] Previously considered a developmental abnormality, osteochondromas now are recognized as neoplasms because recent genetic studies have demonstrated chromosomal and genetic mutations.[17] Multiple osteochondromas are primary bone tumors associated with MHE and are known as *multiple hereditary osteochondromas*.[5,9] The osteochondromas associated with MHE tend to be asymptomatic and can be pedunculated or sessile (attached by a broad base) lesions.[1,6]

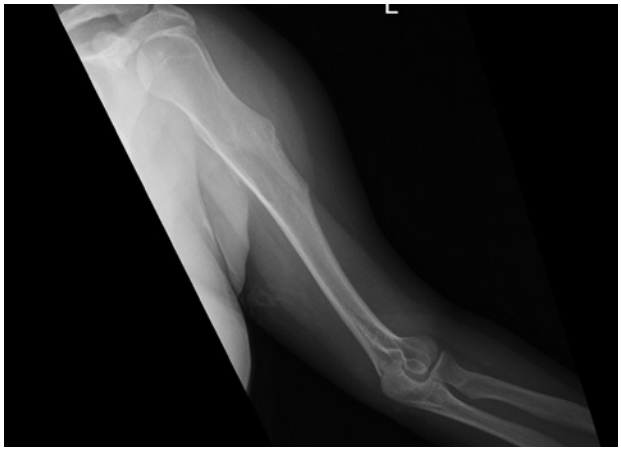

Figure 2. *Radiograph demonstrating an osteochondroma on the diaphysis of the left humerus. Image courtesy of Meaghan Nix.*

Although rare, osteochondromas can develop in adults following injury or trauma.[14]

Ewing Sarcoma

Ewing sarcoma represents the second most common tumor of bones in children.[10] In this disease, bone tumor cells invade the cortical bone and spread into the surrounding soft tissue. In 85% of cases, the tumors present with a translocation between chromosomes 11 and 22, resulting in a fusion protein that affects their pathogenesis.[10] Diagnosis can be made with surgical biopsy, radiographs, MR imaging, or a bone scan.[11]

Affecting more boys and men than girls and women, these tumors mostly appear in young, white individuals aged 10 to 20 years but can affect anyone aged 5 months to 60 years.[10,11] This highly malignant tumor usually is located in the diaphysis of long bones, can metastasize via the blood, and is invariably lethal.[10] Chemotherapy, radiation therapy, and surgery are the preferred treatment options, with a 5-year survival rate possible for patients who have easily accessible tumors.[10,11] Large, inaccessible tumors, including tumors in the pelvis, are associated with a poorer prognosis.[10,11]

Secondary Bone Tumors

Secondary tumors metastasize from a primary site and outnumber primary bone tumors in incidence by a ratio of 10:1.[10] When a primary tumor from any type of cancer metastasizes, the malignant cells travel through the blood or lymph fluid to sites histologically similar to the primary tumor, thereby indicating the source of the spread.[11] The most common primary sites of such malignant lesions are the breast, prostate, lungs, kidneys, and thyroid.[10]

In MHE, the primary bone tumor includes multiple osteochondromas that can be found throughout the axial and appendicular skeleton, with the exception of the calvarium.[5] Chondrosarcomas are secondary bone tumors that sometimes arise from MHE and involve the malignant transformation of an existing osteochondroma.[5,10,11]

History of Multiple Hereditary Exostoses

MHE was differentiated from the solitary form of osteochondroma in 1786 by John Hunter in his *Lectures on the Principles of Surgery*.[6] The earliest description of an afflicted family was reported in 1814 and was followed with reports of a second family in 1825.[5,6,18] Most of the clinical characteristics of MHE had been described by the late 1800s, with Virchow coining the phrase "multiple exostoses" in 1876.[6]

MHE was introduced into American literature in 1915 by Albert Ehrenfried.[6] Understanding of MHE continued to grow in the 1900s, as the condition was distinguished from Ollier disease and Trevor disease.[6] Individuals with Ollier disease also have multiple benign cartilaginous lesions, but these lesions are enchondromas, located within the tubular bones.[6] Trevor disease is rare, and osteochondromas arise from an epiphysis.[6] Unlike MHE, Trevor disease typically affects only the lower extremity on one side of the body and usually is restricted to either the medial or lateral side of the affected extremity.[1]

Epidemiology

Although some have argued that both sexes are affected equally by MHE,[6] others report that prevalence is higher in male patients than in female patients, with an estimated ratio of 1.5:1.[1,9,16] Typically found in whites, osteochondromas develop and increase in size in the first decade of life but usually stop growing when the growth plates close.[3,6,9] Although exostoses usually are not present at birth, more than 80% of MHE cases are diagnosed in people younger than 10 years.[3] Osteochondroma growth past puberty indicates the transformation of benign osteochondromas to malignant chondrosarcomas, which is estimated to occur in 1% to 5% of adult patients.[1,9]

The estimated prevalence of MHE is 1:50 000 to 1:100 000 in Western populations and could be as high as 1:1000 in the Chamorro people of Guam.[5,6] A study of the isolated Ojibway Indian community in Manitoba, Canada, showed an incident rate as high as 1:77.[6]

MHE is an inherited genetic disorder, and those with MHE can be asymptomatic or develop clinical symptoms leading to diagnosis.[3] Because MHE is an autosomal dominant disorder, patients with the disease have a 50% risk of transmitting MHE to their offspring.[1,19] The literature reports that 62% to 90% of patients with

MHE have a positive family history.[9,19] Of those who carry the gene, MHE is 95% to 100% penetrant, meaning that those who have the gene exhibit clinical manifestations.[19,20] Patients also must understand the risk of malignant transformation, which varies from family to family.[16] It is possible that the percentage of people with a positive family history is higher than reported; however, false negatives due to failure to recognize the disorder in family members or decreased penetrance might lead to lower prevalence.[19]

The number of osteochondromas present varies from family to family, as well as between family members.[5] The mean number of osteochondroma locations is 15 to 18, with most of the tumors occurring in the long bones of the extremities, predominantly near the knee, whereas the facial bones are not affected.[6,9] Approximately 10% of MHE patients are thought to have a *de novo* mutation, meaning that neither parent possessed nor transmitted the altered gene.[19]

Classification System

In a 1995 study, Taniguchi classified MHE pediatric patients into 3 groups[5,9]:

- Group I – no involvement of the distal forearm and whose condition is associated with mutation of the gene encoding exostosin-1 (*EXT1*).
- Group II – involvement of the distal forearm, but no shortening of the radius or ulna and association with mutation of the gene encoding exostosin-2 (*EXT2*).
- Group III – involvement of the distal forearm that results in shortening of the radius or ulna and with MHE associated with mutation of the gene encoding exostosin-3 (*EXT3*).

Children in group I are more likely to have mild symptoms and to receive a diagnosis at a later age, and children in group III have more aggressive symptoms, receive diagnoses at earlier ages, and are more likely to present with malignant lesions.[5]

Symptoms

Osteochondromas are classified as benign bone tumors that consist of a pedicle of normal bone rimmed with proliferating cartilage cells.[11] These tumors usually appear as small growths and are discovered incidentally on radiographs taken for other reasons, or the pain they produce can be an indication for radiographs.[10] Symptoms generally include osseous pain and deformity at the growth site.

Osteochondromas might appear unilaterally, but most often bilaterally, and they can involve any bone in the body except the calvarium.[3] Because they are benign, these tumors are removed only if they cause pain, if they transform into a malignant neoplasm (chondrosarcoma), or if their continued growth leads to complications in the joint or spine (see **Figure 3**).[10,11]

Pain

Most patients with MHE experience pain, and approximately half demonstrate generalized pain.[1] Pain can be associated with MHE-related complications or associated surgery.[1] Approximately 70% of patients with MHE undergo surgery by 18 years of age, and 67% require surgical correction as adults.[20] Complications arising from MHE, with the resulting pain, have been shown to negatively affect social functioning, vitality, and general health perception in these patients.[20]

Orthopedic Disorders

Many patients with MHE exhibit a variety of orthopedic disorders (see **Figure 4**).[9] The most common disorders involve[1,9]:

- Shortening of the ulna with secondary bowing of the radius (39%-60%).
- Deformed ankle (2%-54%).
- Unequal limb length (10%-50%).
- Short stature (37%-44%).
- Varus or valgus angulation of the knee (8%-33%).

Coxa valga (a hip deformity in which the femoral neck angle is increased above 135°) and coxa magna (enlargement of the femoral head) might predispose patients to early degenerative osteoarthritis.[16]

Complications

Complications associated with osteochondromas are more frequent with MHE and can include[1,3,5,16]:

- Fracture.
- Vascular compromise.

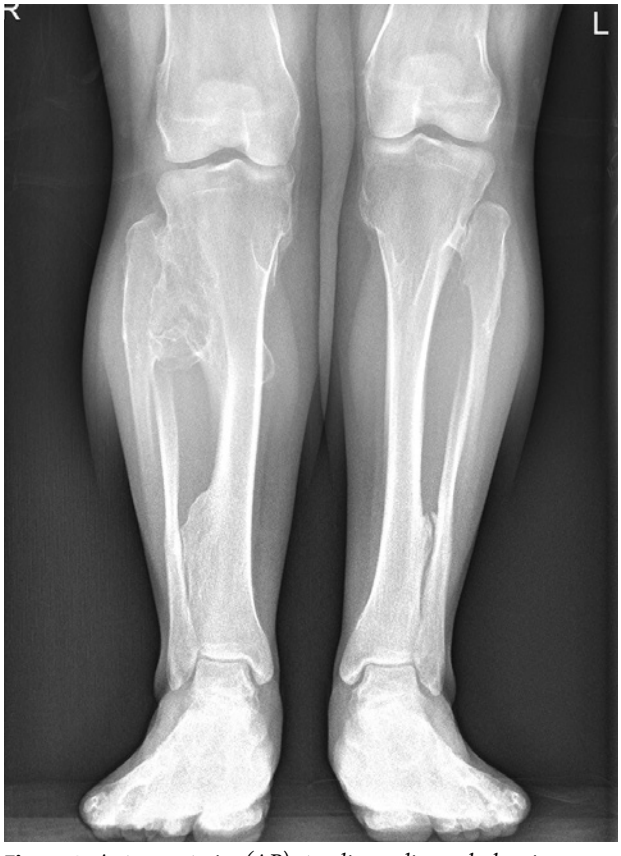

Figure 3. *Anteroposterior (AP) standing radiograph showing a large osteochondroma on the proximal end of the right tibia and fibula. Osteochondromas on the distal ends of both tibias and the left proximal fibula also are present. Image courtesy of Meaghan Nix.*

- Overlying bursa formation.
- Osteoarthritis.
- Abnormal scar formation.
- Impingement on adjacent tendons, nerves, vessels, or the spinal cord that causes pain and limits movement.

Serious complications include neurologic sequelae and malignant transformation. More rarely, complications of osteochondromas can include urinary and intestinal obstruction due to inwardly growing osteochondromas, dysphagia secondary to ventral cervical exostoses, spontaneous hemothorax secondary to rib exostoses, and interference with vaginal delivery, resulting in cesarean delivery.[3,17]

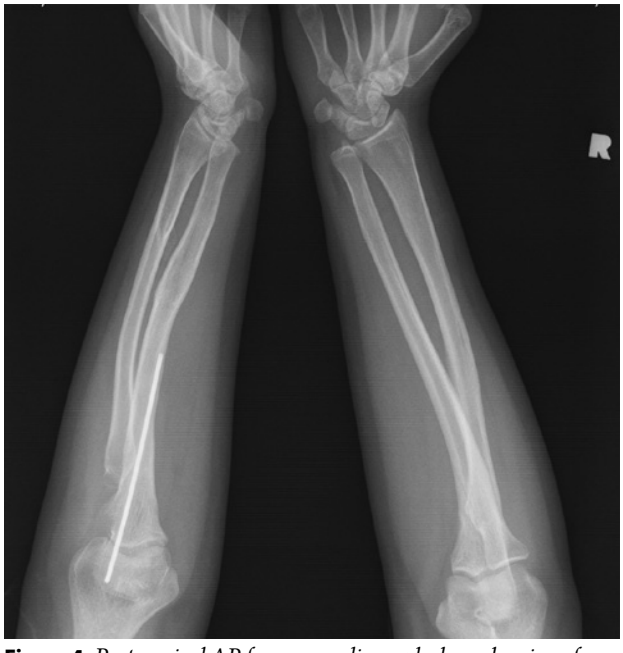

Figure 4. *Postsurgical AP forearm radiograph shows bowing of the left ulna and radius, as well as a shortened radius. The patient had undergone excision of an osteochondroma. Image courtesy of Meaghan Nix.*

Fracture

Although fracture from an osteochondroma is unusual, it is not impossible. Reported cases typically result from localized trauma and are most likely to occur near the knee.[5] Osteochondromas increase the risk of fracture of the bony stalk during physical exercise, and it is estimated that a fracture occurs in approximately 5% of osteochondroma cases.[1] Nonunion of the fracture does not appear to be a concern.[5] In fact, regression or resorption of solitary osteochondroma occurring both spontaneously and following a fracture has been reported.[5]

Vascular Compromise

Vascular compromise occurs as a result of vessel compression or displacement caused by osteochondroma growth. Although typically asymptomatic, compression or displacement could result in stenosis with subsequent occlusion or pseudoaneurysm formation.[3,5] According to Murphey et al, osteochondromas situated adjacent to an artery can chronically abrade

and ultimately lacerate the arterial surface with normal movement or repetitive trauma.[5] Clinical symptoms include pain, swelling, and sometimes a palpable pulsatile mass.[5]

A common location for a pseudoaneurysm is the posterior portion of the knee and involves the popliteal artery.[5,21] A pseudoaneurysm in this location is formed as a result of arterial compression and abrasion from a distal femoral or proximal tibial osteochondroma.[5,21] The frequency of popliteal artery involvement most likely is related to the frequency of osteochondroma occurrence in the knee, coupled with the inability of the popliteal artery to displace, thereby becoming tethered over the osteochondroma.[5]

Neurologic Sequelae

Neurologic complications are the result of direct impingement of osteochondromas on adjacent nerves.[3] Although spinal cord and cranial nerve impingements have been reported, it is more common to see peripheral nerve entrapment neuropathy, which frequently involves the radial and peroneal nerves.[3] When visualized on diagnostic imaging examinations, spinal lesions usually are solitary, with 50% of lesions appearing in the cervical spine, followed by fewer lesions in the thoracic spine and lumbar spine.[5] Myelopathic symptoms, such as dysphagia, hoarseness, and vascular compromise, are found in 77% of patients with MHE.[5]

Overlying Bursa Formation

Bursa formation from osteochondromas most frequently is seen in the scapula, hip, and shoulder and is the result of repetitive mechanical friction between exostoses and soft tissue.[3,5] The bursa is a fluid-filled structure that might be inflamed, and infection, hemorrhage, or synovial osteochondromatosis could develop.[5,21] Inflammation or bursitis might result at the osteochondroma site,[3] simulating malignant transformation.[5] Medical imaging plays an important role in helping to differentiate bursitis associated with osteochondromas from malignant transformation.[5]

Malignant Transformation

The most worrisome aspect of an osteochondroma is its potential to transform into a malignant chondrosarcoma. Once formed, chondrosarcomas can be classified as grade I through III, with grade I having a better prognosis than grade II or III tumors. Grade I tumors have a 5-year survival rate of 90%. They usually do not metastasize but can frequently recur and could evolve into a more aggressive and higher grade tumor. Grade II tumors are associated with areas of necrosis and a 60% 5-year survival rate. Grade III tumors lack mineralization and might vary in shape or size. The 5-year survival rate for grade III chondrosarcomas is 40%.[10] Treatment typically involves surgical resection and radiation therapy because the tumor cells are insensitive to chemotherapy.[10]

Survival rates depend on the size of the tumor, its location (ie, whether it can be resected), and histologic grade.[10] The presence or absence of pain is an indicator of aggressiveness, with absence of pain indicating a less aggressive, lower grade tumor.[11] If the entire low-grade chondrosarcoma is removed, the patient has a better prognosis than patients with higher grade tumors, which are associated with an increased risk of metastasis.[11]

Impingement

The formation of osteochondromas on vertebrae can lead to compression of the spinal cord or the nerve roots. Clinical symptoms of vertebral exostoses include gait disturbance, weakness or numbness, amplified reflex responses and spasticity, and incontinence.[20] Anterior formation of exostoses on the cervical spine can lead to dysphagia, and anterior formation of exostoses on the thoracic vertebrae can interfere with lung function and cause spontaneous hemothorax, pneumothorax, and pericardial effusion.[20]

Rare Complications

Although rare, complications from osteochondromas can be fatal. For example, the literature included the case of a neonate born with a single osteochondroma in the thorax that had caused compression and shifting of the mediastinum during development. This resulted in malformation of the thorax and lungs, as well as circulatory failure upon delivery.[17] Although prenatal sonograms demonstrated a hydrothorax as early as 29 weeks of gestation, physicians were unable to predict the severity of the condition before the neonate's premature birth at 34 weeks of gestational age.[17]

Prenatal testing is possible by analysis of fetal cells obtained via amniocentesis if the mutated gene is identified in the mother.[19] This typically is performed between 15 and 18 weeks of gestation. Another option is chorionic villus sampling, which usually occurs between 10 and 12 weeks of gestation.[19]

Another rare and unusual case involved a 14-year-old boy with symptoms of dizziness and a severe headache.[22] No trauma was associated with his symptoms, which resolved after approximately 12 hours. The patient returned one week later with sudden-onset dizziness and a weakened gait. An MR scan and MR angiogram were ordered, and a right vertebral artery occlusion resulting from an osteochondroma on the right lateral mass of C1 was discovered. Considering that the right vertebral artery was already occluded and the patient appeared to have compensatory flow from the posterior inferior cerebral artery and left vertebral artery, physicians decided not to operate. They prescribed anticoagulants to minimize the risk of future emboli.[22]

Rare complications arising from osteochondromas can be found throughout the body, including the extremities. A 21-year-old male patient presented with bruising and swelling of his left thigh.[23] Radiographs revealed multiple osteochondromas near the knee joint, with one tumor projecting posteriorly. Ultrasonography and CT angiography detected a ruptured popliteal pseudoaneurysm with a large surrounding hematoma. The patient underwent surgical removal of the osteochondroma, a vascular graft to bypass the damaged artery, and a blood transfusion.[23]

An abnormal abdominal case study involved a 45-year-old man with a history of MHE and a large, hard mass in the left side of his abdomen.[24] Ultrasonography revealed a retroperitoneal mass with mixed echogenicity. Radiography and abdominal CT images also were acquired and showed a large heterogeneously enhancing soft tissue mass lesion. The mass was displacing the iliopsoas muscle anteriorly, the bowel medially, and the left external iliac artery to the right. A biopsy identified the mass as a chondrosarcoma. The malignant tumor was surgically removed.[24]

Clinical Diagnosis

Genetic testing of the *EXT* genes and medical imaging are common methods of diagnosing MHE, which is a genetically heterogeneous disease, meaning that the genetic disorder could be caused by one of a multiple number of mutations.[1] This is explained by the mutation of *EXT1*, *EXT2*, or *EXT3* genes. Osteochondromas typically are displayed on radiographs or MR scans, and both modalities are endorsed by the American College of Radiology (ACR) as appropriate for use in diagnosing osteochondromas.[25] A diagnosis of MHE can be made when at least 2 osteochondromas are seen on radiographs of long bones and are accompanied by a positive family history, a mutation in one of the *EXT* genes, or both.[1,9]

Genetic Mapping

Families of those affected by MHE demonstrate abnormalities in the genetic mapping of specific chromosomes in the body. *EXT1* has been mapped to chromosome 8q23-24; *EXT2* has been mapped to chromosome 11p11-p12; and *EXT3* is linked to chromosome 19p.[9] Of these abnormalities, *EXT1* mutations have been found in 44% to 66% of families with MHE, and approximately 21% to 30% of families harbor mutations of *EXT2*.[9,26] The most severe form of MHE, with associated malignant transformation, appears to be linked to the *EXT1* mutations.[26]

Multiple articles discuss *EXT1* and *EXT2*, but only a few discuss *EXT3*.[3,5,9,19,26] One article suggested that a link between MHE and *EXT3* has not been corroborated and could lead to a false-positive diagnosis.[19] However, a study by Francannet et al showed that although *EXT1* and *EXT2* are the 2 major disease loci, *EXT3* still is viable as a minor locus.[26] The authors even introduced 3 new terms: exostosin-like glycosyltransferase 1 (*EXTL1*), *EXTL2*, and *EXTL3*, but admit that even though these 3 new loci have been mapped to chromosomes, the loci have not yet been linked to an MHE family.[26]

A sequence analysis of genes *EXT1* and *EXT2* detects mutations in 70% to 85% of affected individuals.[19] Performing a deletion/duplication analysis increases the detection rate to 85% to 95%.[19] Some evidence suggests that *EXT1* and *EXT2* might have tumor suppressor activity due to a loss of heterozygosity (eg, dominant and recessive genes) observed between *EXT*-related and non-*EXT*–related chondrosarcomas.[19,26]

Heparan Sulfate

EXT1 and *EXT2* are involved in the synthesis of heparan sulfate polysaccharides.[27] Heparan sulfate is an essential component in the body and is present in the growth plates. Heparan sulfate has numerous functions including regulating the distribution and availability of the growth and signaling proteins and their respective interactions.[20] This means that heparan sulfate plays an integral role in bone development including overdevelopment that might lead to the formation of osteochondromas.[20] It also is thought that a loss of heparan sulfate might lead to less obvious problems including delayed wound healing, learning disabilities, and dental problems.[20]

Heparan sulfate levels in both sampled plasma and cellular fractions might help diagnose MHE. Anower-E-Khuda et al compared the blood of patients with MHE to that of healthy individuals. The authors found that blood in those with MHE demonstrated lower levels of heparan sulfate and that the ratio of heparan sulfate to chondroitin sulfate was nearly one-half that of healthy individuals.[27] These results suggest that heparan sulfate and its ratio to chondroitin sulfate could be used as a diagnostic biomarker for MHE.[27]

Research on *EXT1*, *EXT2*, and heparan sulfate is relatively new. Although a link appears to exist between levels of heparan sulfate and MHE, it is unclear what, if any, changes can be made to cure this hereditary disease.[20,27,28]

Medical Imaging

The osteochondromas associated with MHE can involve any bone in the body except the calvarium. The most common sites include the knee, wrist, hand, humerus, ankle, pelvis, and ribs.[3] Patients should have a baseline imaging examination with periodic follow-up examinations to look for new osteochondromas and to measure the growth of existing osteochondromas and associated cartilage caps.[3,11]

Because of the bony involvement of MHE, the disease can be diagnosed using various medical imaging modalities. The ACR has developed appropriateness criteria that physicians can use to determine the most appropriate imaging modality, depending on the indications and suspected diagnosis. Modalities are ranked from 1 to 9, with 1 being the least appropriate and 9 the most appropriate modality for a given diagnosis.[25]

The ACR Appropriateness Criteria lists osteochondroma with soft-tissue masses because of its soft-tissue component and its clinical presentation as a deep soft-tissue mass. According to the ACR, an imaging analysis of a general soft-tissue mass with nonspecific clinical assessment begins with radiography (receiving a ranking of 9), and all other modalities receive a 1 for appropriateness as the initial examination. In the event of a nondiagnostic radiologic evaluation, MR imaging receives a 9 for appropriateness, followed by ultrasonography with a ranking of 5 and CT with a ranking of 4. However, the appropriateness chart for a soft-tissue mass with prominent calcification on radiologic evaluation shows MR imaging still ranked at 9, followed by CT at 5.[25]

Visit www.asrt.org/as.rt?sKnUh2 to see the ACR Appropriateness Criteria.

Radiography

Radiography continues to be the primary diagnostic imaging method for MHE because of its ability to readily demonstrate exostoses and bony deformities. Osteochondroma lesions are composed of cortical and medullary bone protruding from and continuous with the underlying bone.[5] Images of long bones usually better display cortical and medullary continuity between a lesion and the parent bone, but flat bones might require use of a different modality to achieve an accurate diagnosis.[5]

Radiographs of patients with MHE commonly demonstrate foreshortening of the ulna in relation to the radius or areas of abnormal growth in the lower limbs around the knee joint.[3] Another visual characteristic of an osteochondroma is its tendency to point away from the nearby articulation.[14] Deformity of the femur might produce a more vertical orientation of the femoral neck, limb length discrepancies, and short stature (see **Figure 5**).[3]

Magnetic Resonance Imaging

Although radiography can rapidly identify exostoses and bony deformities, it is not ideal for measuring the cartilage cap. MR imaging is described as the

secondary examination of choice when diagnosing MHE and is ideal for measuring the cartilage cap associated with osteochondromas.[3,21] MR is the primary modality of choice for suspicion of malignancy and is chosen for its high tissue contrast capability, which facilitates evaluation of the lesion's relation to the surrounding tissues.[21] MR scanning of the spine also has been recommended as a screening technique to identify any osteochondromas that could lead to spinal cord impingement.[19]

Osteochondromas appear on MR scans as bony protuberances demonstrating cortical and medullary continuity with the parent bone (see **Figure 6**).[14] Although the signal intensity varies depending on the amount of osseous and cartilaginous tumor tissue, the mixed signal intensity generally is intermediate to high on T2-weighted images and low to intermediate on T1-weighted images (see **Figure 7**).[14] Localized bursa can become inflamed and painful, mimicking malignant transformation.[14]

Similar to osteochondromas, chondrosarcomas typically are lobulated, with intermediate signal intensity on T1-weighted MR images and high signal intensity on T2-weighted MR images.[21] However, the mineralized portions of the cartilage cap have low signal intensities on all pulse sequences.[21] Use of dynamic contrast-enhanced MR and subtraction techniques should be considered to differentiate between benign and malignant lesions.[21]

Ultrasonography

As with MR imaging, ultrasonography is useful in measuring the thickness of the cartilage cap of an osteochondroma.[3] The cartilage cap thickness helps to indicate malignant transformation; a cap that is greater than 2 cm is considered highly suggestive of transformation to a chondrosarcoma in a skeletally mature adult. However, the cartilage cap varies greatly on skeletal maturity and could be as high as 3 cm in the pediatric population.[3]

The cartilage cap generally is hypoechoic, with a sonographic appearance similar to the hyaline cartilage that covers an infant's femoral head.[29] Ultrasonography is helpful in distinguishing anechoic bursal formation from the hypoechoic tissue of the underlying cartilage cap, helping to diagnose bursitis from malignant transformation.[5] Posterior acoustic shadowing from calcified chondral or fibrinous bodies might be seen.[5] US also can be used to evaluate a pseudoaneurysm of the popliteal artery or other vascular compromise caused by the presence of an osteochondroma.[29]

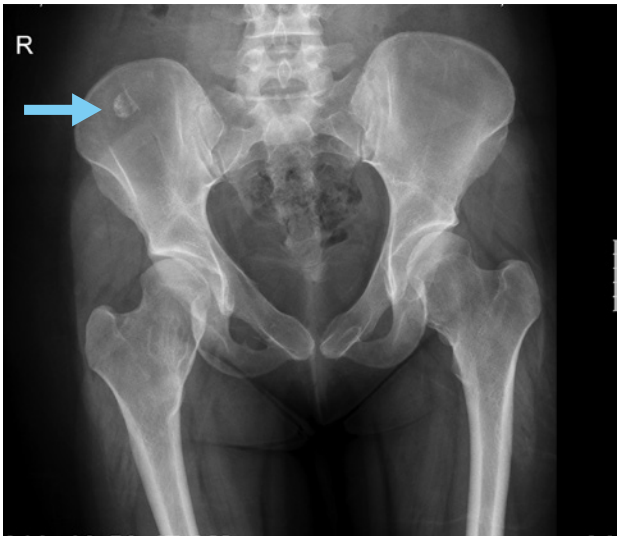

Figure 5. *AP radiograph of the pelvis shows thickening of bilateral femoral necks and a calcification on the right ala (arrow). Image courtesy of Meaghan Nix.*

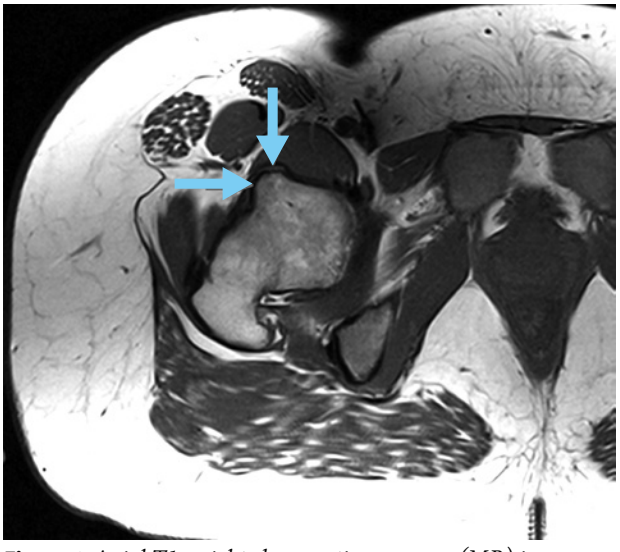

Figure 6. *Axial T1-weighted magnetic resonance (MR) image of the left hip demonstrates an anterior osteochondroma on the femoral head (arrows). Image courtesy of Meaghan Nix.*

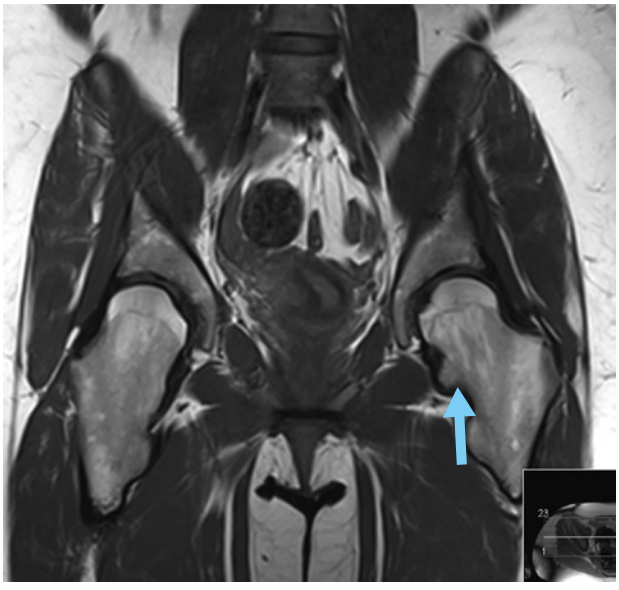

Figure 7. *Coronal T1-weighted MR image of the pelvis demonstrates bilateral thickening of the femoral neck and a prominent osteochondroma medial to the left femoral neck (arrow). Image courtesy of Meaghan Nix.*

Computed Tomography

Murphey et al describe CT as the modality of choice for demonstrating osteochondromal abnormalities in the rib head, skull base, and spine.[5] Thin-section CT displays the narrow stalk attachment of the osteochondroma to its corresponding long bone or joint, which might be difficult or impossible to see on radiographs (see **Figure 8**).[5] Also, several case studies have used CT as a complementary modality for the diagnosis of osteochondromas and chondrosarcomas.[5,22,24] However, for presurgical assessment of surrounding structures, MR imaging is considered superior to CT.[5]

Nuclear Medicine

Bone scintigraphy is considered unable to display differentiating characteristics between a benign osteochondroma and malignant transformation because of increased uptake in both benign and malignant lesions.[3,16,21] However, bone scintigraphy can aid diagnosis by identifying metabolically active osteochondromas.[5]

PET with fludeoxyglucose F 18 has been reported to be useful in the differentiation of benign osteochondroma and malignant transformation.[3] For PET

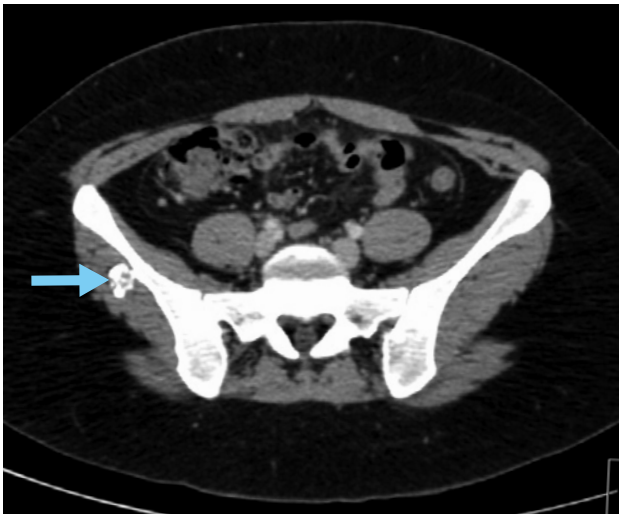

Figure 8. *Axial computed tomography scan of the pelvis demonstrates an osteochondroma and its bony stalk attachment on the posterior aspect of the right ilium (arrow). Image courtesy of Meaghan Nix.*

imaging, the reported maximum standard uptake cutoff of 2.0 can be used to differentiate benign from malignant cartilaginous tumors.[30] PET-CT was used in one study as the sole modality to differentiate between periosteal chondrosarcoma and periosteal chondroma in a 40-year-old woman.[30]

Differential Diagnoses

Trevor Disease

Trevor disease, also known as *dysplasia epiphysealis hemimelica*, is a developmental disorder with cartilaginous overgrowth of one or more epiphyses.[1] Unlike MHE, Trevor disease typically affects only the lower extremity on one side of the body and usually is restricted to either the medial or lateral side of the affected extremity. It is similar to MHE in that usually it is diagnosed before an individual reaches age 15, is found more often in boys than in girls, and the growth of its lesions ends with skeletal maturation.[1] It is believed that malignant transformation does not occur, nor does there appear to be genetic transmission.[1]

Metachondromatosis

Metachondromatosis is a rare, autosomal dominant disorder caused by mutation of the *PTPN11*

gene.[19] This disorder is characterized by both multiple osteochondromas and intraosseous enchondromas.[1,19] Patients with metachondromatosis present with osteochondromas predominantly in the hands and feet, and patients with MHE typically present with osteochondromas in the long or other tubular bones.[1,19] Of great clinical significance is the differentiation that osteochondromas in these patients might spontaneously decrease in size or resolve completely and typically point toward the nearby joint.[1] In addition, metachondromatosis does not cause shortening or bowing of the long bone, joint deformity, or subluxation.[1,19]

Langer-Giedion Syndrome

Langer-Giedion syndrome also produces multiple osteochondromas and is a contiguous deletion syndrome (the deletion of several genes within close proximity) involving *EXT1*.[19] Affected individuals display characteristic craniofacial and digital anomalies.[19] According to Hamouda et al, patients with Langer-Giedion syndrome display a proportionate short stature, hypotonia (poor muscle tone), cutis laxa (a disorder of connective tissue that results in loss of elasticity), macrocephaly, and intellectual and developmental disability.[9]

Potocki-Shaffer Syndrome

Potocki-Shaffer syndrome (also known as *proximal 11p deletion syndrome*) is a contiguous gene deletion syndrome involving *EXT2* and *ALX4*.[19] Affected individuals present with parietal foramina and ossification defects of the skull, and might also possess craniofacial abnormalities, syndactyly (webbing or fusion of 2 or more digits), and intellectual disability.[19]

Fibrodysplasia Ossificans Progressiva

Fibrodysplasia ossificans progressiva is another rare, autosomal dominant disease characterized by heterotopic ossification in the soft tissues following a simple injury.[28] Similar to MHE, patients with this condition receive a diagnosis within the first decade of life as soft connective tissue begins its painful transformation into bone.[28]

Affecting 1 in 2 million individuals, the disease is associated with periodic but cumulative damage that leads to increasing disability.[28] Many patients experience iatrogenic trauma, as physicians unknowingly exacerbate the damage through diagnostic testing and biopsies.[28] There is no cure for fibrodysplasia ossificans progressiva, so once diagnosed, management includes limiting associated pain and unwarranted trauma.[28]

Adult-Stage Hereditary Hypophosphatemia

Hypophosphatemia is an inherited metabolic bone disorder that results in low levels of calcium and phosphorus, and many individuals with this disorder experience osteomalacia (softening of the bones), also known as *rickets*.[28] Estimated to affect 1 in 100 000 individuals, this disorder has a wide range of clinical manifestations from stillbirth without mineralized bone to early loss of teeth without bone symptoms.[31] This disorder is due to gene mutation of tissue-nonspecific alkaline phosphatase (*TNSALP*), and might be detected in 95% of severe cases using DNA sequencing.[28,31]

The 6 clinical forms of the disorder are dependent on the diagnostic stage of the disease. The stages include perinatal (lethal), perinatal benign, infantile, childhood, adult, and odontohypophosphatasia (the least severe form characterized by premature tooth loss and severe dental caries).[31] Adult-stage hereditary hypophosphatemia is characterized by stress fractures, thigh pain, chondrocalcinosis, marked osteoarthropathy, and recurrent and long-lasting orthopedic difficulties.[28,31] Similar to MHE, there is no cure for the disorder, but nonsteroidal anti-inflammatory drugs and teriparatide (parathyroid hormone) have been shown to alleviate symptoms.[31]

Treatment

Developmental and genetic bone diseases such as MHE remain incurable.[10,28] Patients with MHE and their affected family members should be informed of the significant risk of chondrosarcoma during genetic counseling and orthopedic assessment.[16] Patients also should be advised about the importance of their role in care and treatment, with accurate and timely documentation of the accelerated growth or pain at sites of exostosis, as well as attending annual clinical follow-ups and radiologic screenings.[16]

Typically, osteochondromas are removed only if they cause pain.[9] Once removed, the osteochondroma

generally is checked for malignant transformation toward chondrosarcoma.[9]

Surgery

The treatment of choice appears to be excision of the painful osteochondroma.[1,17] Resection of the lesion should be complete and include tumor-free margins to avoid recurrences.[1,17] In a study by Donati et al, a 3% local recurrence rate was found after adequate resection vs a 23% recurrence following inadequate excision of the tumor.[1]

Because of potential injury to epiphyseal plates, some physicians recommend delaying surgery until the osteochondroma has grown away from the physis.[19] However, others argue that early resection of osteochondromas in the forearm might decrease associated shortening and bowing of the forearm.[19] Research also suggests the use of epiphysiodesis (growth plate arrest) of the longer leg or osteotomies to correct angular misalignment of the lower limbs.[19]

Bone Growth Stimulation

It is common for MHE patients to experience deformities of the forearm or lower leg. Deformities might occur because of shortening of the ulna with secondary bowing of the radius, inequality of limb length, varus or valgus angulation of the knee, or deformity of the ankle.[1,9] Surgical correction might be advised for moderate to severe cases of deformity. In some cases, ulnar lengthening procedures can improve pronation, supination, and forearm alignment, and the lower limb can be lengthened or adjusted to correct damaging angulations.[19,32]

One bone lengthening or bone stimulation method uses an Ilizarov apparatus.[32] An Ilizarov apparatus is a 3-ringed external fixator that helps to elongate bones and correct for valgus deformity. The device is applied in an operating suite, and the procedure includes resection of the affected bone to facilitate bone growth and correction of an angled joint or long bone deformity. The procedure is invasive, and the time from application to removal of the Ilizarov apparatus can be up to 4.6 months.[32]

Radiation Therapy

Radiation therapy is not recommended for benign osteochondromas but can be coupled with surgery and chemotherapy to treat secondary chondrosarcomas and osteosarcomas.[19,21] Radiation therapy doses between 40 Gy and 70 Gy delivered over several fractions have produced some response in patients with inoperable but malignant disease.[11] However, it is generally agreed that chondrosarcomas respond poorly to both radiation therapy and chemotherapy.[24]

Prognosis

MHE lesions are benign; they can cause patients discomfort but do not affect life expectancy.[1] However, most MHE patients undergo numerous surgeries within their lifetime to remove new or recurring osteochondromas.

Approximately 1% to 5% of patients will experience malignant transformation.[1] Typically, osteochondromas transform into chondrosarcomas when patients are aged 20 years or older.[24] The prognosis for patients who have chondrosarcoma is favorable if the cancer is detected early,[16] but it also depends on the histologic grade, the surgical stage, the subtype of chondrosarcoma, adequate margins of resection, and the tumor's location.[24] Of those with malignant transformations, the 5-year survival rate is better for grade I than for grade III chondrosarcomas.[10] The 10-year survival rates are approximately 83% for grade I chondrosarcomas and 29% for grade III chondrosarcomas.[1]

Although there is no cure for MHE, there is reason to be optimistic. Genetic testing and gene research, coupled with the advancement of knowledge about heparan sulfate and its relationship to tumor suppression, could lead to help for individuals with this disease (see **Box 2**).

Conclusion

MHE is an autosomal dominant disease that results in the formation of osteochondromas throughout the body. MHE is thought to be caused by mutations of the *EXT* genes. Generally diagnosed within the first decade of life, this disease can negatively affect a child's social and physical growth.

Although MHE is not considered a terminal disease, case studies demonstrate how the growth of an osteochondroma can cause urinary or intestinal obstruction, dysphagia, hemothorax, pneumothorax, spinal cord stenosis, and other potentially life-threatening

Box 2

Case Study

A 23-year-old woman received a diagnosis of multiple hereditary exostoses (MHE) at a young age. Her diagnosis was the product of an awkward gait that resulted from the foreshortening of her right leg when she was a toddler. Because of her family history, a diagnosis was made quickly. It is unknown why her father and aunt developed MHE because neither grandparent nor ancestors were known to have the disease. This patient and her cousin are both only children and both have MHE. However, this patient received her diagnosis earlier than her cousin and appears to have more significant symptoms, which coincides with reports that the earlier the diagnosis, the more severe the disease and its progression.[5]

The disease affects each family member differently. This woman develops multiple osteochondromas in the joints throughout her body, while the disease affects her father's shoulders and knees and her cousin's ribs. Because of MHE's effects on her joints, she has not grown since the seventh grade, and although she is an average height of 5 ft 4 in (1.63 m), she is the shortest member of her immediate family. Repeated surgeries for osteochondroma removal is common with MHE, and this patient has endured 4 surgeries within the past 10 years.

The patient also has experienced some psychosocial effects of MHE, admitting to depression and suicidal thoughts during adolescence. Although she was physically active in her youth, her gait and actions were different from other children. As a result, she garnered the attention of bullies who would make her feel "like a freak" as she was desperately trying to fit in with the group. Constant visits to doctors and subsequent surgeries to correct bone deformities made socialization difficult. At 10 years of age, an external fixator was applied to lengthen her ulna. Although this procedure and the device corrected her foreshortened limb, it did not help her become socially accepted, as the other children continued to ridicule her for her differences. The patient has denied any continued suffering as an adult, but agrees that being bullied as a child has made her more empathetic to others. She works full time in the medical profession and is thrilled with her ability to help children on a daily basis.

Although she is able to work and live on her own, she continues to have physical complications from the disease. For example, she must undergo diagnostic testing to determine the level of degeneration in her right hip, which might be the result of the varied length of her legs. She will likely undergo a right hip replacement procedure. In addition, an exostosis on her iliac crest has grown despite her being well past skeletal maturity. Osteochondroma growth is an indication of malignancy risk, and she continues to be monitored frequently.

As a young adult in a healthy relationship, she has considered the possibility of passing MHE to her potential future children as well as complications she might incur during pregnancy. Although she has not undergone genetic testing, she understands there is a 50% chance of passing MHE on to her children. She has been counseled that a ceserean delivery is most likely, as an osteochondroma has formed on her left pubic symphysis, limiting movement of the pelvis and making vaginal delivery almost impossible.

Despite her extended illness and future concerns, this young woman appears upbeat and optimistic. Instead of allowing her disease to limit her, she demonstrates an amazing strength of character and willpower, constantly pushing herself to achieve more and to prove naysayers wrong. She obtained a college degree, has a job she loves, and has even managed to skydive in her spare time.

complications. Even without these difficulties, patients with MHE usually endure acute and chronic pain, physical deformity, and sometimes limiting disabilities. In a small percentage of cases, an osteochondroma transforms into a chondrosarcoma; the diagnostic grade of the malignancy primarily determines the patient's 5-year survival rate.

Diagnosing MHE involves a combination of genetic testing and medical imaging studies. General radiography and MR imaging are the modalities of choice for support of an MHE diagnosis, but recent studies in PET and PET-CT show promise in the differentiation of benign osteochondromas vs malignant chondrosarcomas. Advances in genetic research and testing also are encouraging, as more information on affected chromosomes and the effect of heparan sulfate levels on the body could lead to a cure for this disease.

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Multiple Hereditary Exostoses

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Read the preceding Directed Reading and choose the answer that is ***most correct*** based on the article.

1. Which of the following terms is ***not*** a synonym for multiple hereditary exostoses (MHE)?
   a. hereditary deforming chondrodysplasia
   b. diaphyseal aclasis
   c. metachondromatosis
   d. multiple cartilaginous exostoses

2. Dense cortical bone is protected by which of the following?
   a. periosteum
   b. cancellous bone
   c. osteons
   d. osteoblasts

3. The _____ is the ***most*** metabolically active segment of long bones during growth and development.
   a. Haversian canal
   b. metaphysis
   c. periosteum
   d. cartilage cap

4. Primary bone tumors account for ***fewer*** than _____% of all clinically diagnosed tumors.
   a. 1
   b. 10
   c. 50
   d. 90

5. Which of the following is a malignant disease of plasma cells?
   a. multiple myeloma
   b. leukemia
   c. chondrosarcoma
   d. Ewing sarcoma

continued on next page

6. Complications of multiple myeloma include which of the following?
    1. calcium deposits in various organs
    2. osteoporosis
    3. bone fractures

    a. 1 and 2
    b. 1 and 3
    c. 2 and 3
    d. 1, 2, and 3

7. The term *leukemia* means:
    a. plasma cell mutation.
    b. infection.
    c. white blood.
    d. loss of red blood cell generation.

8. Which of the following is the ***most*** common primary malignant tumor besides the marrow malignancies of myeloma, lymphoma, or leukemia representing approximately 20% of bone cancers?
    a. osteosarcoma
    b. chondrosarcoma
    c. adamantinoma
    d. Brown tumor

9. Which of the following might appear as a primary bone tumor or as the malignant transformation of another pathology?
    a. multiple myeloma
    b. osteoid osteoma
    c. osteosarcoma
    d. chondrosarcoma

10. Chondrosarcoma might be suspected if the thickness of a cartilage cap of an adult with osteochondroma is:
    a. less than 1 cm.
    b. 1 cm or less.
    c. 2 cm or more.
    d. greater than 3 cm.

11. Which of the following statements regarding bone tumors in MHE is ***true***?
    a. Primary multiple osteochondromas can be found throughout the appendicular skeleton and most of the axial skeleton.
    b. Primary bone tumors are found mostly in the calvarium.
    c. Secondary bone tumors are found in the axial skeleton including the calvarium.
    d. Secondary bone tumors involve the transformation of chondrosarcoma into an osteochondroma.

12. Trevor disease differs from MHE in which of the following ways?
    1. Osteochondromas arise from an epiphysis.
    2. It affects only the lower extremity on one side of the body.
    3. It is usually restricted to either the medial or lateral side of the affected extremity.

    a. 1 and 2
    b. 1 and 3
    c. 2 and 3
    d. 1, 2, and 3

13. According to the article, some report the prevalence of MHE with an estimated male-to-female patient ratio of:
    a. 0.5:1.
    b. 1:2.
    c. 1.5:1.
    d. 2:1.

14. Patients with MHE have a _____% risk of transmitting the disease to their offspring.
    a. 1
    b. 10
    c. 50
    d. 90

continued on next page

15. Most patients with MHE have a positive family history for the disease.
    a. true
    b. false

16. Which of the following statements is ***false*** regarding osteochondromas?
    a. The tumors most often appear unilaterally.
    b. They are classified as benign bone tumors.
    c. The tumors usually appear as small growths on radiographs.
    d. They are associated with osseous pain.

17. Which of the following is ***not*** a complication of MHE?
    a. fracture
    b. vascular compromise
    c. facial anomalies
    d. malignant transformation

18. A common location for a pseudoaneurysm resulting from an osteochondroma involves which artery?
    a. popliteal
    b. medial collateral
    c. posterior tibial
    d. femoral

19. Inflammation can result from _____, simulating malignant transformation.
    a. fracture
    b. neurologic sequelae
    c. bursa formation
    d. impingement

20. The 5-year survival rate for patients with grade III chondrosarcomas is _____%.
    a. 40
    b. 50
    c. 60
    d. 80

21. Anterior formation of exostoses on the cervical spine can cause:
    a. hemothorax.
    b. pneumothroax.
    c. pericardial effusion.
    d. dysphagia.

22. Which of the following signs can lead to a diagnosis of MHE?
    1. at least 2 osteochondromas on long bones
    2. positive family history
    3. a mutation in one of the exostosin (*EXT*) genes

    a. 1 and 2
    b. 1 and 3
    c. 2 and 3
    d. 1, 2, and 3

23. *EXT1* and *EXT2* genes are involved in the synthesis of:
    a. fibroblasts.
    b. red bone marrow.
    c. heparan sulfate polysaccharides.
    d. plasma.

24. According to Anower-E-Khuda et al, patients with MHE had a ratio of heparin sulfate to chondroitin sulfate that was nearly _____ that of healthy individuals.
    a. one-quarter
    b. one-third
    c. one-half
    d. three-quarters

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25. Osteochondromas associated with MHE can involve which of the following bones?
    1. wrist
    2. ribs
    3. calvarium

    a. 1 and 2
    b. 1 and 3
    c. 2 and 3
    d. 1, 2, and 3

26. Which of the following is the primary method of diagnostic imaging of MHE?
    a. computed tomography (CT)
    b. radiography
    c. magnetic resonance (MR) imaging
    d. positron emission tomography (PET)

27. Radiographs of flat bones are sufficient to achieve an accurate diagnosis of MHE.
    a. true
    b. false

28. Which modality has been recommended as a screening technique to identify possible osteochondromas on the spine?
    a. CT
    b. MR
    c. PET
    d. ultrasonography

29. Metachondromatosis differs from MHE in which of the following ways?
    1. The osteochondromas typically appear in the hands and feet, not the long bones.
    2. In these patients, osteochondromas might spontaneously decrease or resolve completely.
    3. Metachondromatosis does not cause shortening or bowing of the long bones.

    a. 1 and 2
    b. 1 and 3
    c. 2 and 3
    d. 1, 2, and 3

30. Chondrosarcomas respond well to radiation therapy and chemotherapy.
    a. true
    b. false