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Hereditary multiple exostoses: A case report and literature review

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Abstract

Osteochondroma is the most common bone tumor representing 20%–50% of all benign bone tumors and 10%–15% of all bone tumors. Osteochondroma has similar radiological appearance in both solitary and multiple forms; the latter is an autosomal dominant disorder termed hereditary multiple exostoses. Associated complications of osteochondroma include deformity, fracture, neurovascular compromise, bursa formation, and malignant transformation. Measurement of the cartilage cap thickness is an important index suggesting secondary malignancy of osteochondroma. The upper limit of cap thickness after skeletal maturation is 1.5 cm which can be reliably measured on ultrasound or magnetic resonance imaging. Hereditary multiple exostoses are linked to the mutations of different exostoses genes located on chromosome 8, 11, and 19. We reported cases of two siblings presented with multiple osteochondromas managed by surgical excision. We evaluated their clinical and radiological presentation, genetic correlations and compared with the literature.

Keywords

Hereditary multiple exostoses, osteochondroma

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Introduction

Osteochondroma or osteocartilaginous exostosis or exostosis is the most common bone tumor in children.[1–3] Cortical and medullary connection between tumor and parent bone is the typical imaging finding for the diagnosis of osteochondroma.[4,5] Osteochondroma may present as solitary or multiple lesions, the latter is termed hereditary multiple exostoses (HME), which is an autosomal dominant disorder. Complications of osteochondroma were reported including fracture, deformities, bursitis, neurovascular compromise, and malignant transformation.[4–6] Diagnosis of osteochondroma can be made on radiographs. However, cross-sectional imaging is necessary in cases of complications, especially when malignancy transformation is suspected by measuring the cartilage cap thickness.[5] HME syndrome is the hereditary form of osteochondroma, caused by mutations within the EXT1, EXT2, and EXT3 gene.[7–9] This syndrome presents with the development of multiple exostoses in members within a family.[10] We studied a case of a family with HME, in which two siblings were evaluated in details on clinical and radiological aspects. Their genetic correlations including EXT1, EXT2, and EXT3 genes analysis were also evaluated.

Case report

The 13-year-old elder brother admitted to the outpatient clinic because of several palpable and painful masses of the upper and lower limbs (Figure 1). These lesions were detected 10 years ago and gradually grew in number and size. He was diagnosed with HME at 6 years old, for which a surgical excision was done to remove the osteochondromas of bilateral scapula bone. He had been complaining of right shoulder pain for 2–3 months. No signs of neurovascular impingement were found during physical examination.

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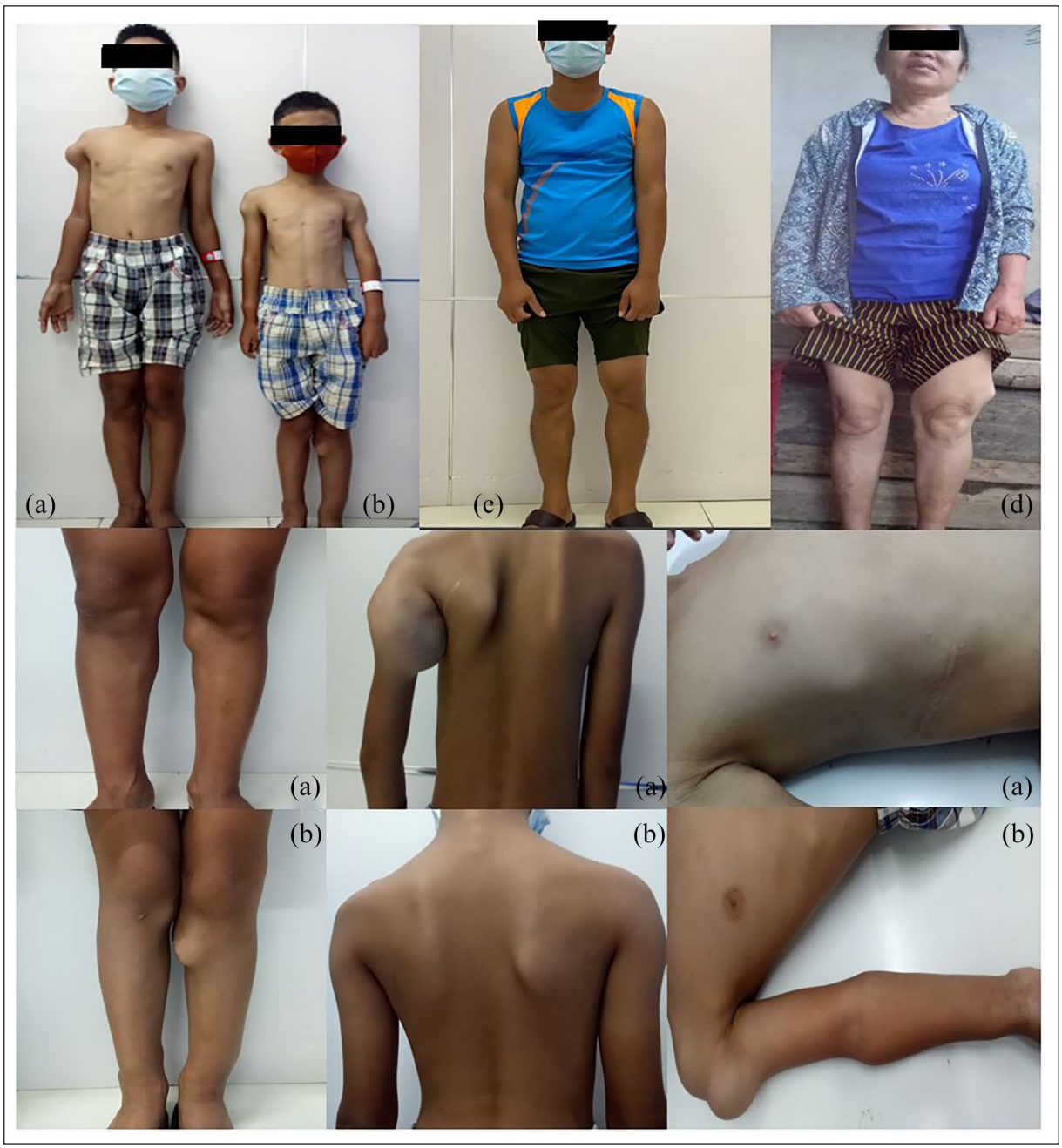

Figure 1. Images of the 13-year-old patient (a), 8-year-old patient (b), their father (c), and grandmother (d) showing multiple palpable masses of their limbs and chest wall.

Laboratory tests were within normal limit, consisted of complete blood count, urinalysis, and renal function test. A radiographic examination of the axial skeleton demonstrated multiple osteochondromas of bilateral humerus; distal ulna and radius; distal and proximal femurs, tibias, and fibulas (Figure 2). There are deformities of these bones and bilateral distal tibiofibular joints. The osteochondromas of the right humeral metaphysis showed rings and arcs calcification (Figure 2), which were suspected for malignant transformation. Subsequently, contrast-enhanced MRI was performed to determine the composition, the cartilage cap of the lesion and soft-tissue extension. MRI showed a large mass measuring 6 cm of maximal diameter arising from the right humeral metaphysis with lobulated margin, hyperintensity on PD FATSAT and hypointensity on T1w images, heterogeneous enhancement after intravenous injection of gadolinium (Figure 3). This lesion had heterogeneous calcifications and a cartilage cap measuring 2–3 mm in thickness (Figure 2). Considering the clinical symptoms and cosmetic reasons, surgical excision was performed to remove the right humeral

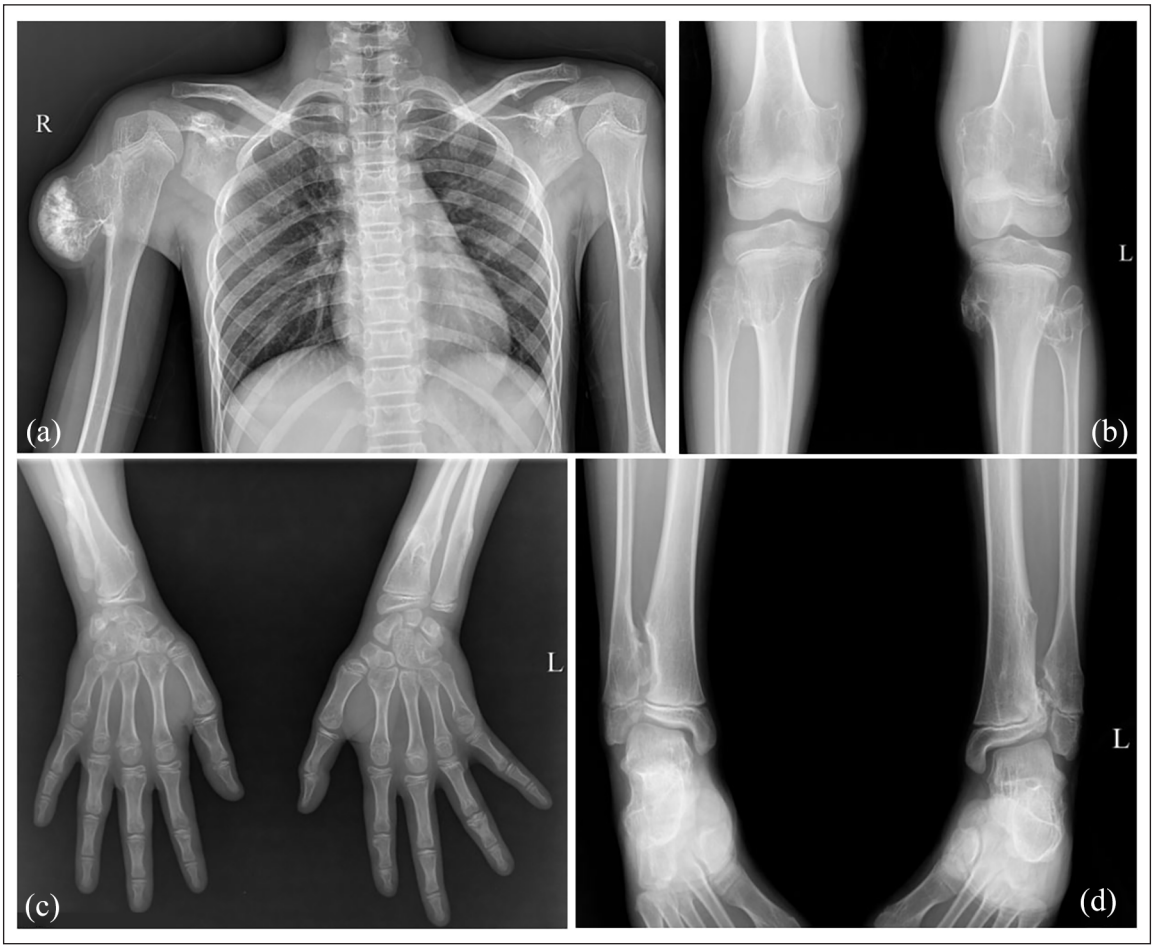

Figure 2. Radiographies of the 13-year-old patient showing multiple sessile or pedunculated bony structure arising from the right proximal humeral metaphysis and left proximal humeral shaft (a), bilateral distal femoral metaphysis (b), bilateral proximal and distal tibial and fibular metaphysis (b and d), bilateral distal radial and ulnar metaphysis (d), consisted with multiple osteochondromas. Both distal tibiofibular joints were deformed. The right proximal humeral metaphyseal osteochondroma showed rings and arcs calcification, typical for osteochondroma.

mass. The operation was uneventful. The tumor was sent for histological evaluation. Histopathology showed the outer perichondrium, the cartilage cap of 2 mm with superficial chondrocytes clustered, and the bony stalk with endochondral ossification at the base. No malignant tissue was found.

The 8-year-old younger brother presented at the outpatient clinic with several painful and palpable masses around the upper and lower limbs and right chest wall (Figure 1), which were noted since he was 2 months old. These lesions have been gradually growing in number and size ever since. He had left shoulder pain began approximately 2–3 months ago without signs of neurovascular impingement of the affected limbs. He was diagnosed with HME at 6 years old with surgical excision done to remove the osteochondromas of left scapula and right ribs. Laboratory tests were within normal range and consisted of complete blood count, urinalysis, and renal function test. The radiographic examinations of the skeleton demonstrated multiple osteochondromas of the right ninth rib, bilateral humerus; distal ulna and radius; distal and proximal femurs, tibias, and fibulas; third proximal phalange (Figure 4). There are deformities of these bones, rib cage, left distal tibiofibular joint, and right inferior radioulnar joint. The osteochondroma of the left humeral metaphysis showed cauliflower-like calcification extending to adjacent soft tissue. The osteochondroma of the right distal ulna is noted with rings and arcs calcification and pathologic fracture of the right distal radius (Figure 4). Malignant transformation of these lesions was suspected. Contrast-enhanced MRI was performed for further investigation which showed a large mass measuring 9 cm of maximal diameter, arising from the left humeral metaphysis and another mass measuring 4 cm arising from the right distal ulna. On MRI, these lesions had lobulated margin, PD hyperintensity and T1 hypointensity, partial diffusion restriction, heterogeneous enhancement after injection of intravenous gadolinium, heterogeneous calcifications, and a cartilage cap measuring 2–3 mm in thickness (Figure 5). Surgical excisions of these osteochondromas were performed. The operation

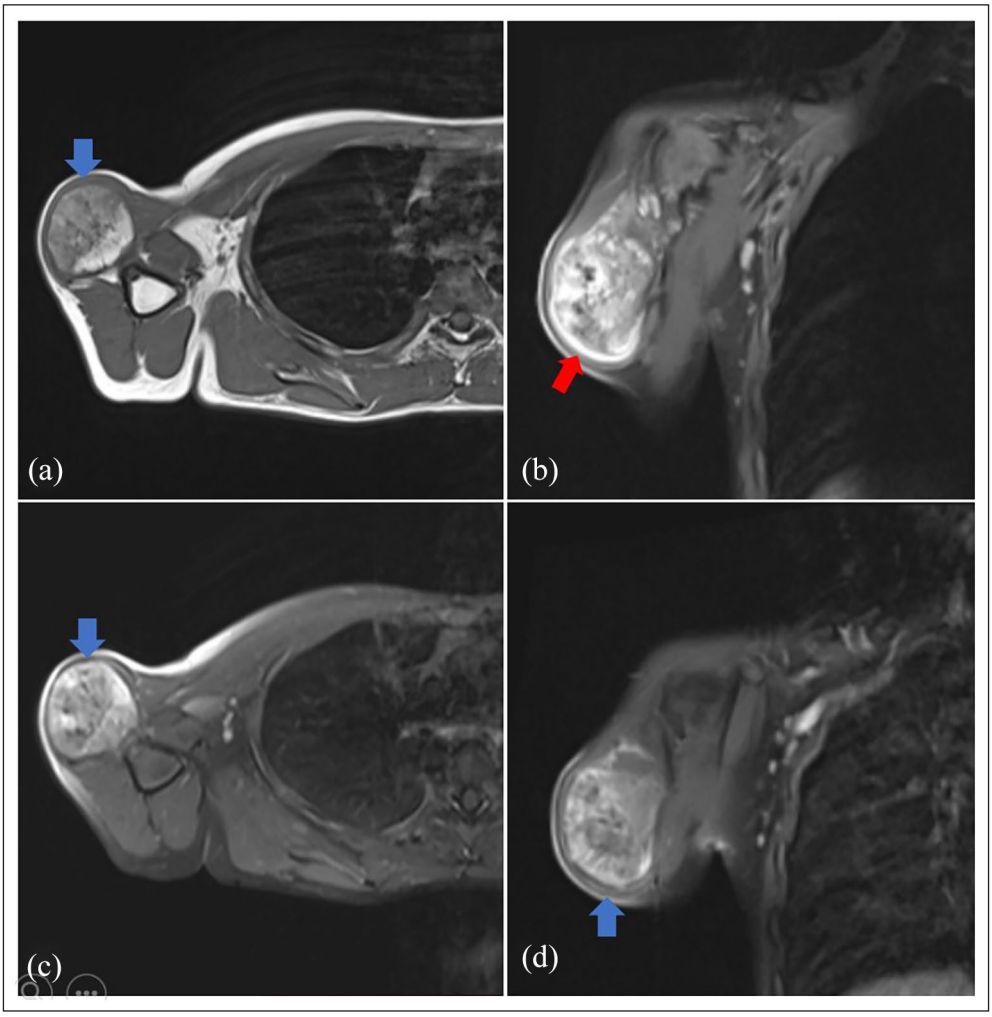

Figure 3. Contrast-enhanced MRI of the right humeral mass (blue arrow) of the 13-year-old male patient showed hypointensity on axial T1w image (a), hyperintensity on coronal PD FATSAT image (b) with a cartilage cap of 2–3 mm thickness (red arrow), well-delineated margin, heterogeneous enhancement after intravenous injection of gadolinium on axial and coronal post-contrast T1 FATSAT images (c and d).

was uneventful. The tumor was sent for histological evaluation. Macroscopic evaluation showed cauliflower-like calcification with a very thin cartilage cap (Figure 6). Histopathology showed the outer perichondrium, the cartilage cap of 2 mm with superficial chondrocytes clustered, and the bony stalk with endochondral ossification at the base (Figure 7). No malignant tissue was observed.

We investigated the medical history and pedigree of our patient's family members. The record showed similar clinical conditions in grandmother, father, paternal aunt and her daughter, and cousins with nearly half of the family members affected (Figure 8). The pedigree also showed incomplete penetration of this condition in both male and female members. We were able to collect pictures of their grandmother and father showing limbs deformities due to multiple osteochondromas (Figure 1). No radiography of the affected family members was done. They had no important complications except for bony deformities. We decided to perform whole-exome sequencing of the 13-year-old elder brother, which was negative for EXT1, EXT2, and EXT3 mutation.

Discussion

Osteochondromas or osteocartilaginous exostoses or simply exostoses are not true neoplastic lesions but rather developmental lesions of bone. The mechanism of osteochondromas formation is still unclear but is thought to be the result of ectopic development of growth plate of cartilage. The epiphyseal cartilage was separated from normal growth plate and herniated into the periosteal bone cuff. The enlargement of this cartilaginous fragment and its eventual enchondral ossification explained the excrescent growth of osteochondroma from bone surface and its cartilage cap.[11–14] The osseous structure must have cortical and medullary continuity with host bone to be diagnosed as osteochondroma on imaging.[11–14]

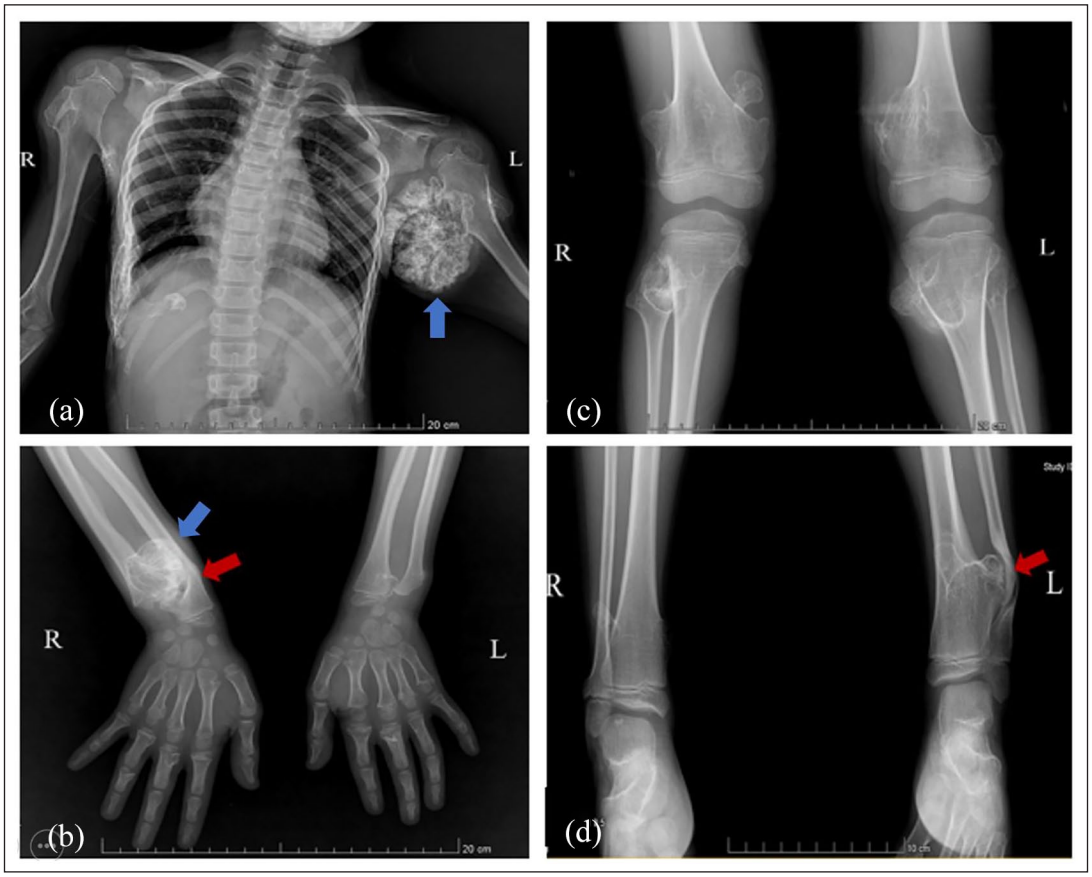

Figure 4. Radiographies of the 8-year-old patient showing multiple sessile or pedunculated bony structure arising from bilateral proximal humeral metaphysis, right ribs and right scapula (a), bilateral distal femoral metaphysis (c), bilateral proximal and distal tibial and fibular metaphysis (c and d), bilateral third proximal phalanges (b), bilateral distal radial and ulnar metaphysis (b), consisted with multiple osteochondromas. The left proximal humeral osteochondroma and right distal ulnar osteochondroma showed rings and arcs calcification. Fracture and deformity of right distal radius and deformity of the left distal fibula due to mass effect (red arrow).

In addition to congenital factors, trauma, surgery, or irradiation are also proved associated factors related to the development of osteochondroma. Damaged epiphyseal plate caused migration of undifferentiated cartilage into the metaphysis and subsequent development of exotoses, which have pathological and radiographical similarities with congenital osteochondromas.[15–17] Osteochondromas are the most common radiation-induced tumor, usually seen in patients having radiation therapy.[17,18]

At macroscopic level, the cartilage cap of an osteochondroma has lobulated and bluish-gray surface, hence the "cauliflower" appearance. The cartilage thickness varies greatly from 1 to 3 cm in young patients to just few millimeters in adults.[11,12] The cartilage cap also has areas of calcifications within its matrix. At microscopic level, the cartilage cap mimics growth plate with columns or clusters of chondrocytes evenly distributed and maturing in an enchondral process.[5]

Solitary osteochondroma is usually asymptomatic and found incidentally during radiological examinations.[11,12,19] These lesions accounted for 20%–50% of benign bone tumors and 10%–15% of all bone tumors.[20,21] Osteochondromas are symptomatic mostly in young patients. 75%–80% of these individuals were diagnosed before the age of 20.[11,19,22] The male-to-female ratio ranges from 1.6 to 3.4.[19]

Osteochondroma usually presents as a painless, deformed, and slowly growing exophytic mass. Other symptoms are related to its complications including osseous deformity, fracture, vascular or neurologic compromise, overlying bursa formation, and malignant transformation.[23] The long bones of lower limbs are mostly affected with 50% of cases.[11,19] Knee is the most common site of osteochondroma with 40% of cases while femur is the most frequently affected bone (30% of cases), followed by humerus (10%–20%), hands and feet (10%), pelvis (5%), scapula (4%), and spine (2%).[12,19,24] The metaphysis is the most commonly affected region of long bones while diaphysis is much rarer location.

Solitary osteochondroma usually has typical findings on radiographs, especially in long bones. The osseous protuberance is typically composed of cortical and medullary bone and in continuous with parent bones. Depending on whether the lesion base exceeded its length or not, osteochondroma is

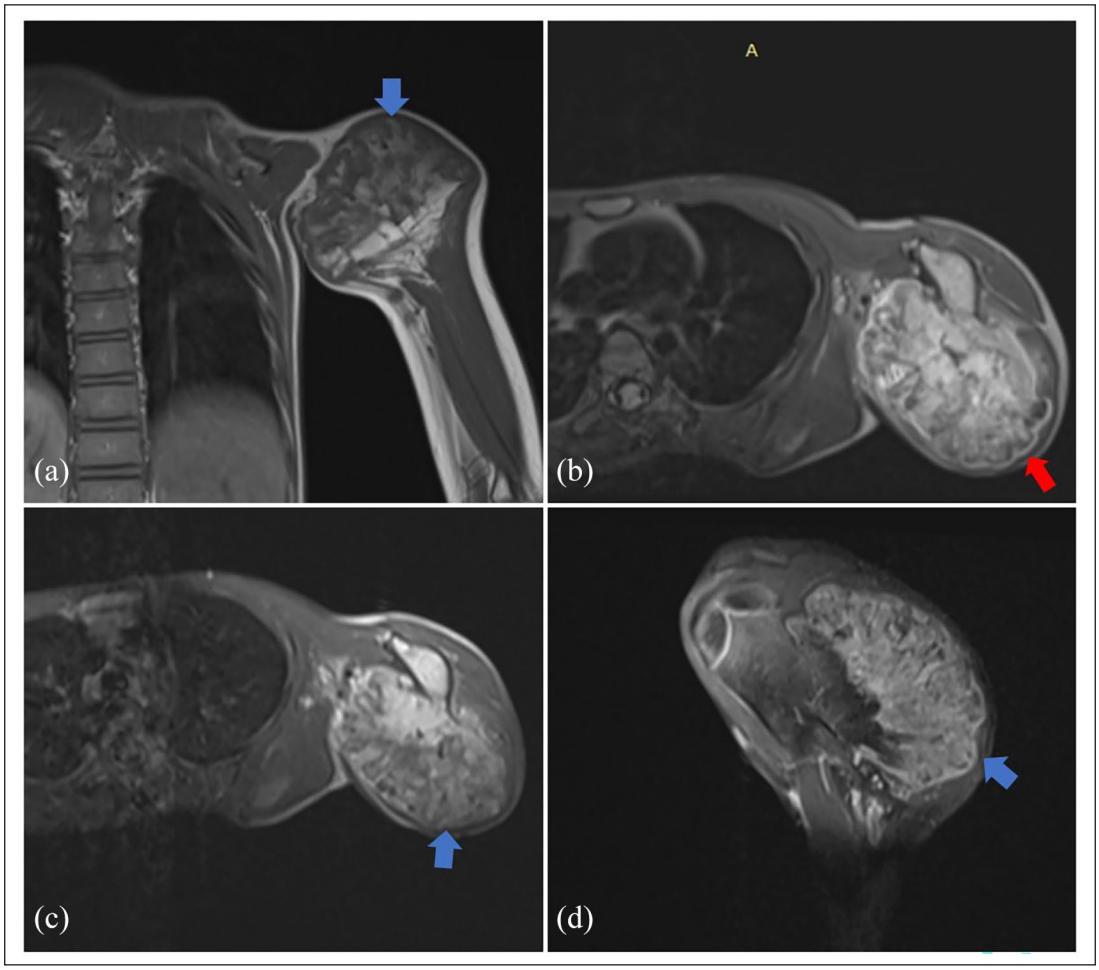

Figure 5. Contrast-enhanced MRI of the left humeral mass (blue arrow) of the 8-year-old male patient showed hypointensity on coronal T1w image (a), hyperintensity on axial PD FATSAT image (b) with a cartilage cap of 2–3 mm thickness (red arrow), clear margin without indistinction, heterogeneous enhancement after intravenous injection of gadolinium on axial and sagittal post-contrast T1 FATSAT images (c and d).

divided into sessile or pedunculated form. Due to the forces of attached tendons and ligaments, pedunculated lesions usually develop away from the closest joint. The cartilage cap usually presents as arcs and rings or flocculent calcification on radiograph due to its chondroid nature. Radiograph cannot well delineate the thickness of cartilage cap except in cases with important mineralization.[5]

Computed tomography (CT) with three-dimensional and thin-session reconstruction is optimal for assessing the pathognomonic cortical and medullary continuity of the osteochondroma and its parent bone.[25] The role of CT is higher than MRI in regions with complex anatomy, such as pelvis or spine, as CT can easily depict the connection of broad-base lesions.

Measurement of cartilage cap thickness can be performed on CT. The non-mineralized cap of osteochondroma often has lower attenuation than muscle on CT due to its high-water content (75%–80%). The mineralized cartilage cap always has high attenuation on CT equal to calcific material, and its measurement on CT is often more accurate than on MRI. According to the study of Kenny et al. and Hudson et al.,[25,26] the benign osteochondroma often has cartilage cap thickness ranging from 6 to 8 mm with a maximum of 2.5 cm. The measurement is highly dependent on skeletal maturity. Therefore, the cap thickness augmentation should not be interpreted as malignant sign in skeletally immature patients.[5]

For cartilage cap thinner than 2 cm, ultrasound (US) has high accuracy with measurement error below 2 mm.[20] The accuracy of US is similar to MRI and higher than CT in this study. The advantage of US is high tissue resolution which enables differentiation between fat and muscle layer with the hypoechoic non-mineralized cartilage cap. US has difficulty in evaluation of mineralized cartilage cap due to posterior acoustic shadowing. US accuracy also depends on operator experience and lesion's depth.[20,21,26]

MRI is the optimal imaging modality for assessing osteochondroma. The cartilage cap is well delineated on MRI for measurement. The mineralized cap has low signal intensity

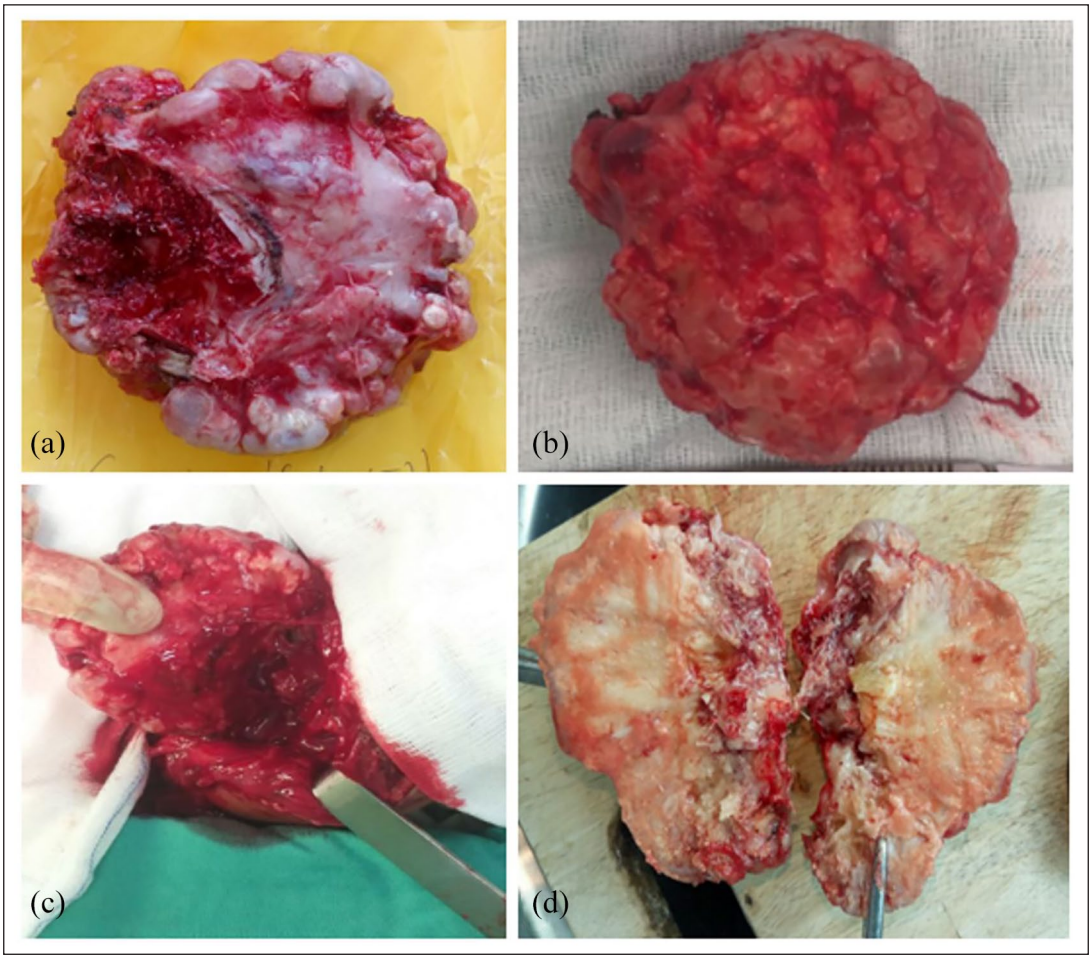

Figure 6. Resected left humeral mass of the 8-year-old male patient in full observation (a, b, c) and cut in half (d). Macroscopic evaluation showed cauliflower-like calcification with a very thin cartilage cap.

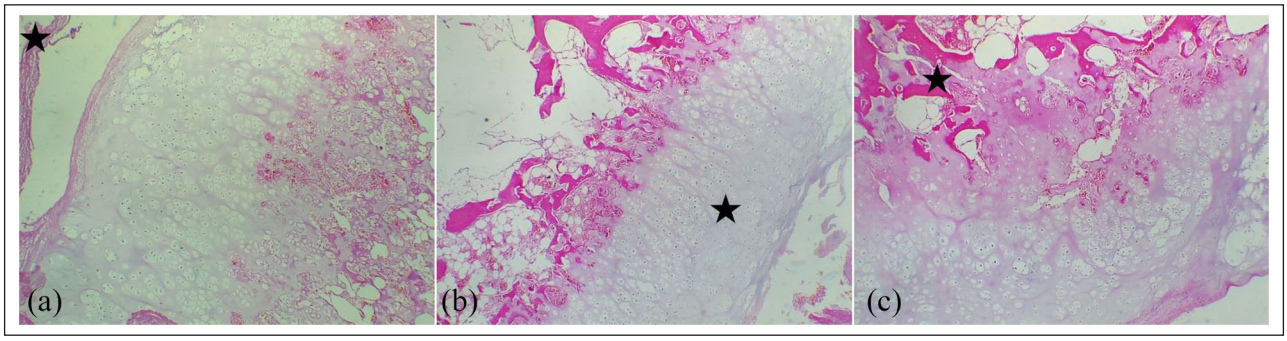

Figure 7. Microscopic evaluation of the resected humeral mass of the 8-year-old male patient. Histopathology showed the outer perichondrium (Star, a, H.&E ×200), the cartilage cap of 2 mm with superficial chondrocytes clustered (Star, b, H&E ×40), and the bony stalk with endochondral ossification at the base (Star, c, H&E ×400).

on all MR pulse sequences while the non-mineralized cap has low signal intensity on T1-weighted images and very high signal intensity on T2-weighted images.[20,27] These findings allow accurate measurement of the cartilage cap thickness, differentiation from surrounding soft tissue and mass effect of the lesion on overlying muscle and neurovascular structures. Heterogeneity of signal intensity is noted in young patients due to active growth of the cartilage cap. The cartilage cap demonstrated septal and peripheral enhancement on contrast-enhanced MRI.[28,29]

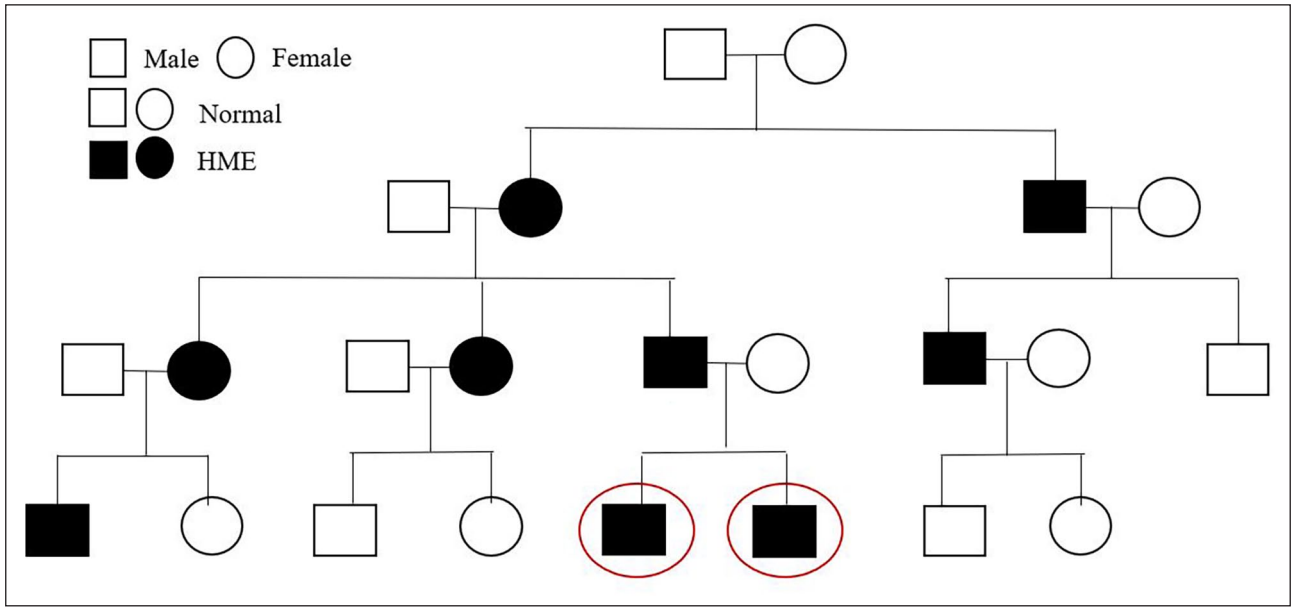

Figure 8. Three-generation pedigree of our patients (red circles) with members diagnosed with HME marked by black square or circle.

The appearance of multiple osteochondroma in an individual is called HME, also known as familial osteochondromatosis.[11,12] In 1814, Boyer reported the first case of an affected family.[30] The estimated prevalence of HME is 1:50,000 to 1:100,000 in Western populations.[3,31] This condition shows an autosomal dominant inheritance pattern, with incomplete penetrance in females.[32,33] There is also significant heterogeneity within families in number of osteochondroma, severity of deformity, and rate of malignant transformation.

In HME patients, genetic analysis detected abnormalities in three different loci on chromosomes 8, 11, and 19.[34,35] These were termed EXT1 on chromosome 8q23-q24; EXT2 on 11p11-p12; and EXT3 on the short arm of chromosome 19.[36] Sequence analysis suggested that these genes act as tumor suppressor.[34,35] Inactivation of EXT genes cause osteochondroma formation and also malignant transformation.[33,34] Genetic analysis of HME families performed in a study showed only 42% EXT1 mutation and 33% EXT2 mutation.[36] Another French study linked genetic abnormalities to HME families, in which 28% had EXT1 mutation, 17% had EXT2 mutation, and 10% had EXT3 mutation. Another study that analyzed 73 Chinese pedigrees with HME patients found 93% mutations of EXT1 and/or EXT2 genes.[37] A study of 33 Polish patients diagnosed with HME found EXT genes mutations in 84.9% of cases.[38] The rate of mutations varied between cohorts. In our patients, genetic analysis was done to find EXT1, EXT2, and EXT3 mutations but all were negative. However, the genetic result could not rule out EXT genes deletion, which is also common in patients with HME. Therefore, the absence of EXT genes mutations did not change the final diagnosis.

Comparing to solitary osteochondroma, HME is diagnosed earlier, probably due to family history, multiplicity of lesions and associated severe deformity.[34] Mostly all patients were diagnosed before age of 12[12,34], and children older than 12 without lesion detected will not manifest the condition.[34] Except calvaria, every bone could be involved, including scapula and ribs (40% of cases), humerus (50%–98%), elbow (35%–40%), wrist (30%–60%), hands (20%–30%), pelvis (5%–15%), hips (30%–90%), knees (70%–98%), ankles (25%–54%), and feet (10%–25%).[12,19,22,39] Different genotypes have different forms of manifestation, either symmetric or asymmetric distribution of exostoses.[34]

Comparing to the solitary form, radiological findings of osteochondroma are indifferent in the multiple hereditary form. The increased number of lesions and severity of deformity in forearms and distal legs might be indicator of overall disease severity.[34] Sessile lesions are more common than pedunculated ones and associated with more severe deformity and shortening of the affected limbs.[34] A study of Taniguchi et al.[40] suggested that children with osteochondroma involved at the distal forearm with shortening of radius and ulna would have more severe clinical symptoms, higher rate of malignant transformation and younger age at diagnosis.

Complications of solitary osteochondroma and HME are similar, including cosmetic and osseous deformity, fracture, vascular compromise, neurologic sequelae, bursa formation, and malignant transformation. HME complications present earlier and more severely due to their multiplicity.

Malignant transformation is the most important complication of osteochondroma and was first described in 1886.[41] The prevalence of this complication is estimated to be 1% in

solitary lesions and higher in HME, from 3 to 20% of these patients.[11,12,42] The malignant lesions can be chondrosarcoma developed in the cartilage cap or osteosarcoma at the base of the osteochondroma.[43,44] Increase in size of lesion and appearance of focal pain after skeletal maturity are signs of suspected malignancy.[45] Osteochondromas of pelvis, hips, and shoulders are more likely to develop malignant transformation. The average age of detection is 50–55 for solitary exostoses and 25–30 in HME patients. Malignant transformation is rare before the age of 20. The cartilage cap is suggested to be the origin site of malignant transformation. Features of malignancy include the following: (a) growth of a previously unchanged osteochondroma in a skeletally mature patient, (b) irregular or indistinct lesion surface, (c) focal regions of radiolucency in the interior of the lesion, (d) erosion or destruction of the adjacent bone, and (e) a significant soft tissue mass particularly containing scattered or irregular calcification.[42,46–48] The hyaline cartilage cap thickness is reliable indicator of malignancy. With the cartilage cap thickness cutoff of 2 cm, MRI can have the sensitivity and specificity of 100% and 98%, respectively, for the detection of malignant transformation.[49] With this criterion, no malignant lesions were missed and few benign lesions were resected.

In our patient, MRI of suspected lesions demonstrated regular, well-delineated margin with cartilage cap of only 2–3 mm. Minimal enhancement was observed, and no bony destruction was found. These signs did not suggest malignant transformation but surgical resection was indicated due to large size of lesion, local deformity, and fracture of involved bones. The final histological examination revealed no malignant signs on the specimen. Patients were continued on surveillance and regular clinical and radiological follow-up.

Treatment of solitary osteochondromas is not complex with follow-up for asymptomatic and small lesions, surgical resection for symptomatic and larger lesions. Adequate excision must include overlying perichondrium to reduce the risk of recurrence. Management of HME is more complex including lesion excision, deformity correction, and long clinical and radiological follow-up for surveillance of lesion progression.[5] The average number of surgical procedures for patients with HME is 2.7 per patient according to a study by Shapiro et al.[39] Osteochondromas with malignant transformation usually require large surgical resection. Preoperational MRI exploration is essential for staging and evaluating lesion extension and mass effect on surrounding tissue.[41] These secondary chondrosarcomas are mostly low grade with favorable prognosis. 70%–90% of cases have long-term survival.[50] Wide resection often results in only 0%–15% of recurrence while inadequate excision results in 57%–78% recurrence.[41,50] Distal metastases, most commonly lung, occur in approximately 3%–7% of cases.[41,50] A systematic review suggested that annual MRI screening for malignant transformation is effective for patients with HME in their 20s and 30s.[51]

Conclusion

Osteochondroma is the most common bone tumor with similar radiological appearance in solitary and multiple form. The pathognomonic finding is abnormal bony structure with cortical and medullary continuity with parent bone, best assessed on CT or MR imaging. Many complications can occur with malignant transformation representing the most feared one. The multiple form of osteochondroma, HME, has higher chance of developing secondary malignancy. MRI is essential in evaluating malignant signs and measuring cartilage cap thickness for early detection of malignant transformation, with the upper limit of 1.5 cm. EXT1, EXT2, and EXT3 mutations are all negative in many cases similar to ours. Thorough evaluation with long-term follow-up in patients with HME allows proper management and improvement of prognosis in these patients.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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Informed consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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References

1. Black B, Dooley J, Pyper A, et al. Multiple hereditary exostoses. An epidemiologic study of an isolated community in Manitoba. *Clin Orthop Relat Res* 1993(287): 212–217.
2. David R and Lucas M. Dahlin's bone tumors: general aspects and data on 11,087 cases. *Am J Clin Pathol* 1996; 106(5): 693.
3. Schmale GA and Raskind WH. The natural history of hereditary multiple exostoses. *J Bone Joint Surg Am* 1994; 76(7): 986–992.
4. Garcia RA, Inwards CY and Unni KK. Benign bone tumors: recent developments. *Semin Diagn Pathol* 2011; 28(1): 73–85.
5. Murphey MD, Choi JJ, Kransdorf MJ, et al. Imaging of osteochondroma: variants and complications with radiologic-pathologic correlation. *Radiographics* 2000; 20(5): 1407–1434.

6. Khare GN. An analysis of indications for surgical excision and complications in 116 consecutive cases of osteochondroma. *Musculoskelet Surg* 2011; 95(2): 121–125.
7. Cook A, Raskind W, Blanton SH, et al. Genetic heterogeneity in families with hereditary multiple exostoses. *Am J Hum Genet* 1993; 53(1): 71–79.
8. Le Merrer M, Legeai-Mallet L, Jeannin PM, et al. A gene for hereditary multiple exostoses maps to chromosome 19p. *Hum Mol Genet* 1994; 3(5): 717–722.
9. Wuyts W, Ramlakhan S, Van Hul W, et al. Refinement of the multiple exostoses locus (EXT2) to a 3-cM interval on chromosome 11. *Am J Hum Genet* 1995; 57(2): 382–387.
10. Wim W, Wim Kristel Jan H, Egbert B, et al. Mutations in the EXT1 and EXT2 genes in hereditary multiple exostoses. *Am J Hum Genet* 1998; 62(2): 346–354.
11. Mirra JM. *Bone tumors: clinical, radiologic, pathologic correlations: Benign cartilaginous exostoses: osteochondroma and osteochondromatosis*. Philadelphia, PA: Lea & Febiger, 1989, pp. 1626–1659.
12. Feldman F and Resnick D. *Diagnosis of bone and joint disorders*. Philadelphia, PA: WB Saunders Co, 1995.
13. Milgram JW. The origins of osteochondromas and enchondromas. A histopathologic study. *Clin Orthop Relat Res* 1983(174): 264–284.
14. Keith A. Studies on the anatomical changes which accompany certain growth-disorders of the human body: I. The nature of the structural alterations in the disorder known as multiple exostoses1. *J Journal of Anatomy* 1920; 54(Pt. 2–3): 101.
15. Langenskiold A and Edgren W. Imitation of chondrodysplasia by localized Roenten ray injury–an experimental study of bone growth. *J Acta Chirurgica Scandinavica* 1950; 99(4): 353.
16. Murphy FD and Blount W. Cartilaginous exostoses following irradiation. *J Bone Joint Surg Am* 1962; 44(4): 662–668.
17. Jaffe N, Ried HL, Cohen M, et al. Radiation induced osteochondroma in long-term survivors of childhood cancer. *Int J Radiat Oncol Biol Phys* 1983; 9(5): 665–670.
18. Frantz CH. Extreme retardation of epiphyseal growth from roentgen irradiation: a case study. *Radiology* 1950; 55(5): 720–724.
19. Giudici M, Moser R Jr and Kransdorf M. Cartilaginous bone tumors. *J Radiologic Clin North Am* 1993; 31(2): 237–259.
20. Malghem J, Vande Berg B, Noël H, et al. Benign osteochondromas and exostotic chondrosarcomas: evaluation of cartilage cap thickness by ultrasound. *Skeletal Radiol* 1992; 21(1): 33–37.
21. Van Holsbeeck M and Introcaso J. Sonography of tendons. *J Musculoskeletal Ultrasound* 1991: 77–131.
22. Scarborough MT and Moreau G. Benign cartilage tumors. *Orthoped Clin North Am* 1996; 27(3): 583–589.
23. Karasick D, Schweitzer ME and Eschelman DJ. Symptomatic osteochondromas: imaging features. *AJR Am J Roentgenol* 1997; 168(6): 1507–1512.
24. Dahlin D and Unni K. Chondrosarcoma (primary, secondary, dedifferentiated, and clear-cell). *Bone Tumors* 1986; 11: 190–192.
25. Kenney PJ, Gilula LA and Murphy WA. The use of computed tomography to distinguish osteochondroma and chondrosarcoma. *Radiology* 1981; 139(1): 129–137.
26. Hudson TM, Springfield DS, Spanier SS, et al. Benign exostoses and exostotic chondrosarcomas: evaluation of cartilage thickness by CT. *Radiology* 1984; 152(3): 595–599.
27. Lee JK, Yao L and Wirth CR. MR imaging of solitary osteochondromas: report of eight cases. *AJR Am J Roentgenol* 1987; 149(3): 557–560.
28. Aoki J, Sone S, Fujioka F, et al. MR of enchondroma and chondrosarcoma: rings and arcs of Gd-DTPA enhancement. *J Comput Assist Tomogr* 1991; 15(6): 1011–1016.
29. Geirnaerdt MJ, Hogendoorn PC, Bloem JL, et al. Cartilaginous tumors: fast contrast-enhanced MR imaging. *Radiology* 2000; 214(2): 539–546.
30. Boyer A. *Traite des maladies chirurgicales*. Paris: Migneret, 1814.
31. McCormick C, Duncan G and Tufaro F. New perspectives on the molecular basis of hereditary bone tumours. *Mol Med Today* 1999; 5(11): 481–486.
32. Peterson HA. Multiple hereditary osteochondromata. *J Clinical Orthopaedics Related Research* 1989(239): 222–230.
33. Legeai-Mallet L, Munnich A, Maroteaux P, et al. Incomplete penetrance and expressivity skewing in hereditary multiple exostoses. *Clin Genet* 1997; 52(1): 12–16.
34. Carroll KL, Yandow SM, Ward K, et al. Clinical correlation to genetic variations of hereditary multiple exostosis. *J Pediatr Orthop* 1999; 19(6): 785–791.
35. Wu YQ, Heutink P, de Vries BB, et al. Assignment of a second locus for multiple exostoses to the pericentromeric region of chromosome 11. *Hum Mol Genet* 1994; 3(1): 167–171.
36. Wuyts W, Van Hul W, De Boulle K, et al. Mutations in the EXT1 and EXT2 genes in hereditary multiple exostoses. *J the American Journal of Human Genetics* 1998; 62(2): 346–354.
37. Li Y, Wang J, Tang J, et al. Heterogeneous spectrum of EXT gene mutations in Chinese patients with hereditary multiple osteochondromas. *Medicine* 2018; 97(42): e12855.
38. Jamsheer A, Socha M, SowiÅ„ska-Seidler A, et al. Mutational screening of EXT1 and EXT2 genes in Polish patients with hereditary multiple exostoses. *J Appl Genet* 2014; 55(2): 183–188.
39. Shapiro F, Simon S and Glimcher MJ. Hereditary multiple exostoses. Anthropometric, Roentgenographic, and clinical aspects. *J Bone Joint Surg Am* 1979; 61(6A): 815–824.
40. Taniguchi K. A practical classification system for multiple cartilaginous exostosis in children. *J Pediatr Orthop* 1995; 15(5): 585–591.
41. Wuisman PI, Jutte PC and Ozaki T. Secondary chondrosarcoma in osteochondromas medullary extension in 15 of 45 cases. *Acta Orthop Scand* 1997; 68(4): 396–400.
42. Willms R, Hartwig CH, Böhm P, et al. Malignant transformation of a multiple cartilaginous exostosis–a case report. *Int Orthop* 1997; 21(2): 133–136.
43. Tsuchiya H, Morikawa S and Tomita K. Osteosarcoma arising from a multiple exostoses lesion: case report. *Jpn J Clin Oncol* 1990; 20(3): 296–298.
44. Nojima T, Yamashiro K, Fujita M, et al. A case of osteosarcoma arising in a solitary osteochondroma. *J Acta Orthopaedica Scandinavica* 1991; 62(3): 290–292.
45. Krieg JC, Buckwalter JA, Peterson KK, et al. Extensive growth of an osteochondroma in a skeletally mature patient. *J Bone Joint Surg Am* 1995; 77(2): 269–273.

46. Fischgrund JS, Cantor JB and Samberg LC. Malignant degeneration of a vertebral osteochondroma with epidural tumor extension: a report of the case and review of the literature. *J Spinal Disord* 1994; 7(1): 86–90.
47. Bell RS. Musculoskeletal images. Malignant transformation in familial osteochondromatosis? *Can J Surg* 1999; 42(1): 8.
48. Ostlere SJ, Gold RH, Mirra JM, et al. Case report 658: chondrosarcoma of the proximal phalanx of right fourth finger secondary to multiple hereditary exostoses (MHE). *Skeletal Radiol* 1991; 20(2): 145–148.
49. Bernard SA, Murphey MD, Flemming DJ, et al. Improved differentiation of benign osteochondromas from secondary chondrosarcomas with standardized measurement of cartilage cap at CT and MR imaging. *Radiology* 2010; 255(3): 857–865.
50. Garrison RC, Unni KK, McLeod RA, et al. Chondrosarcoma arising in osteochondroma. *J Cancer* 1982; 49(9): 1890–1897.
51. Fei L, Ngoh C and Porter DE. Chondrosarcoma transformation in hereditary multiple exostoses: a systematic review and clinical and cost-effectiveness of a proposed screening model. *J Bone Oncol* 2018; 13: 114–122.