Multiple Osteochondromatosis

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Abstract

Multiple osteochondromatosis is a familial disease characterized by multiple osteochondromas, defect in metaphyseal remodeling, and asymmetric longitudinal growth retardation. There is a greater incidence in males than females (7:3). It was often first discovered at a younger age than solitary form. There is a predilection for the metaphyseal regions around the knee, hip, and shoulder joints. Radiologically individual lesions are similar to those of solitary form.

The lesions have the same gross and microscopic appearances as seen in solitary osteochondroma. The development of secondary malignancy varies from 5 % to 25 %. The treatment should be considered to correct deformities or functional disturbances.

Definition

- A familial disease characterized by multiple osteochondromas, defect in metaphyseal remodeling, and asymmetric longitudinal growth retardation

Synonyms

- Hereditary multiple exostoses
- Diaphyseal aclasis
- Hereditary deforming chondrodysplasia
- Ehrenfried disease

Clinical Features

Etiology

- Inherited autosomal dominant disorders
- Incomplete penetrance in females

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Epidemiology

Sex

- Greater incidence in males than females (7:3)

Age

- Often first discovered at a younger age than solitary form

Sites of Involvement

- Predilection for the metaphyseal regions around the knee, hip, and shoulder joints.
- The innominate bone and scapula are often affected.

Clinical Symptoms and Signs

- Multiple palpable masses and deformities generally discovered after the age of 2 years.
- Some patients may experience spinal cord compression due to vertebral lesions.

E. Santini-Araujo et al. (eds.), *Tumors and Tumor-Like Lesions of Bone: For Surgical Pathologists, Orthopedic Surgeons and Radiologists*, DOI 10.1007/978-1-4471-6578-1_20, © Springer-Verlag London 2015

Image Diagnosis

- Individual lesions are similar to those of solitary form (Fig. 20.1).
- The deformities are frequently observed.

Pathology

Gross and Histologic Features

- The lesions have the same gross and microscopic appearances as seen in solitary osteochondroma (Figs. 20.2 and 20.3).

Ancillary Techniques

Genetics

- There is evidence that mutations in these two EXT1 and EXT2 genes are responsible for over 70 % of the EXT cases of osteochondromatosis. Among the 49 EXT1 mutations, there are 9 nonsense, 21 frameshift, and 5 splice site mutations; 2 in-frame deletions of 1 and 5 amino acids, respectively; and 12 missense mutations. For EXT2, 8 nonsense, 11 frameshift, 3 splice site, and 3 missense mutations are described. The majority of these mutations are mutations causing loss of function, which is consistent with the presumed tumor suppressor function of the EXT genes.
- Mutations in exostosin-1 (EXT1) or exostosin-2 (EXT2), both tumor suppressor genes of the EXT gene family, are associated with multiple osteochondromatosis. All members of this multigene family encode glycosyltransferases involved in the adhesion and/or polymerization of heparin sulfate (HS) chains at HS proteoglycans (HSPGs). HSPGs have been shown to play a role in the diffusion of Ihh, thereby regulating chondrocyte proliferation and differentiation. EXT1 is located at 8q24.11–q24.13 and comprises 11 exons, whereas the 16 exon EXT2 is located at 11p12–p11. To date, an EXT1 or EXT2 mutation is detected in 70–95 % of affected individuals. EXT1 mutations are detected in +/−65 % of cases versus +/−35 % EXT2 mutations in multiple osteochondromatosis patient cohorts.
- Jamsheer et al. demonstrated EXT1 and EXT2 heterozygous mutations in 54.6 % and 30.3 % probands, respectively, which represents a total of 84.9 % index cases.

Prognosis

- The development of secondary malignancy varies from 5 % to 25 %.
- Most of the secondary malignancies have been chondrosarcomas.
- A few osteosarcomas have also been reported.

Treatment

- The treatment should be considered to correct deformities or functional disturbances, such as reduction of joint motion and/or pain due to pressure phenomenon or bursa formation.

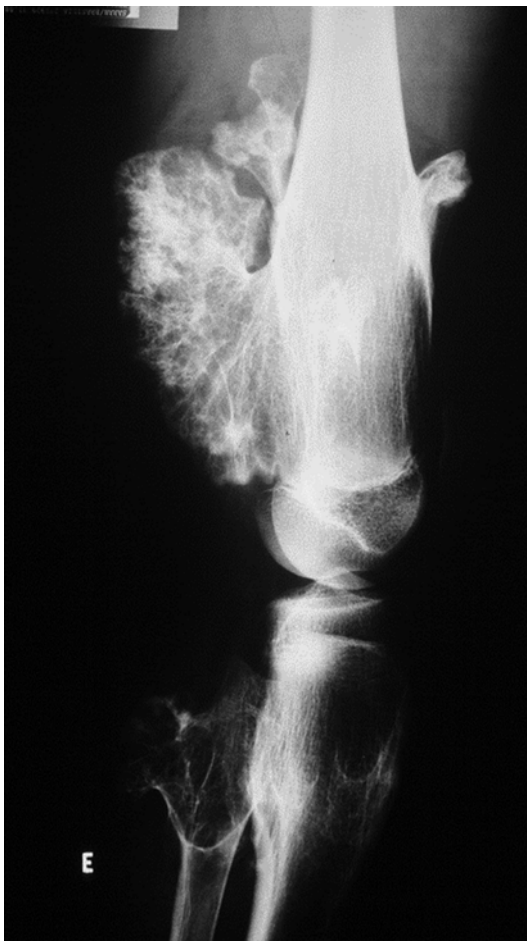

Fig. 20.1 X-ray shows multiple osteochondromas arising from the distal meta- and diaphysis of the distal femur, proximal tibia and fibula

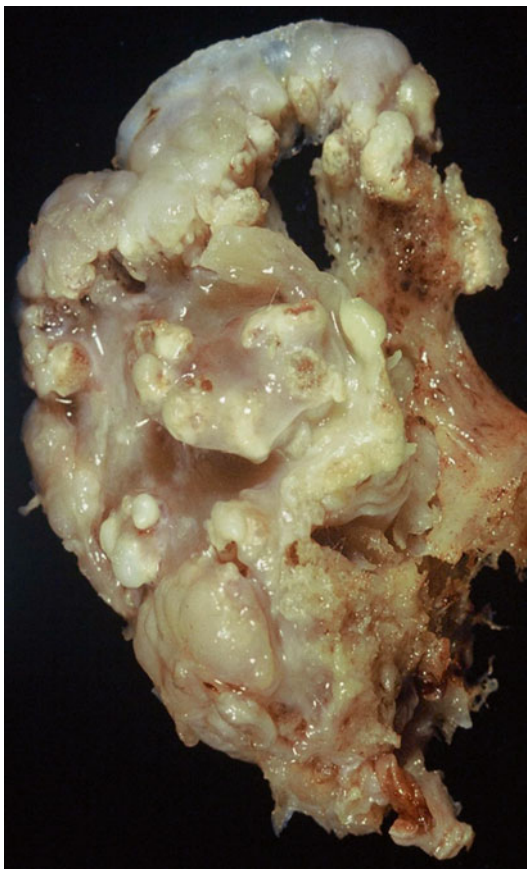

Fig. 20.2 Outer surface of one of the multiple osteochondromas shows multi-knobby appearance with *gray-white* calcified areas

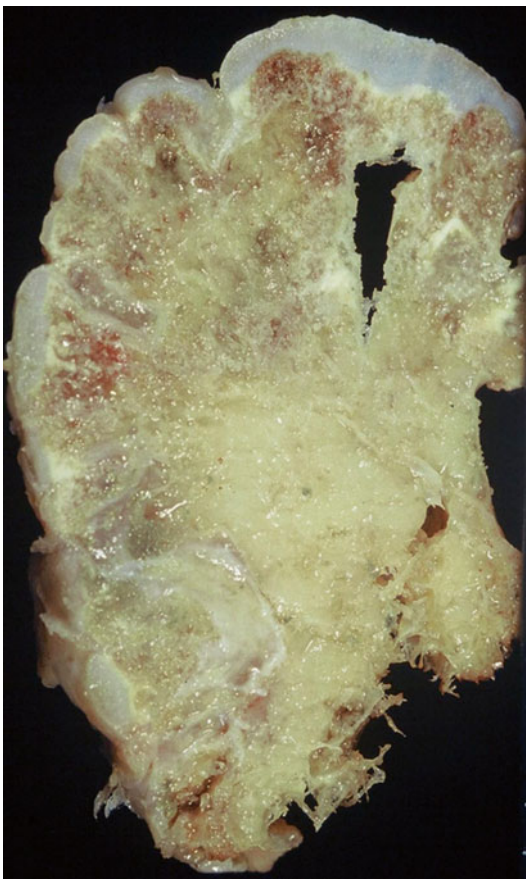

Fig. 20.3 Cut surface shows hyaline cartilage cap with myxoid degeneration

Recommended Reading

Jaffe HL. Tumors and tumorous conditions of the bones and joints. Philadelphia: Lea & Febiger; 1958. p. 150–62.

Jamsheer A, Socha M, Sowińska-Seidler A, Telega K, Trzeciak T, Latos-Bieleńska A. Mutational screening of EXT1 and EXT2 genes in Polish patients with hereditary multiple exostoses. J Appl Genet. 2014;55:183–8.

Jennes I, Pedrini E, Zuntini M, Mordenti M, Balkassmi S, Asteggiano CG, et al. Multiple osteochondromas: mutation update and description of the multiple osteochondromas mutation database (MOdb). Hum Mutat. 2009;30:1620–7.

Johnston II CE, Sklar F. Multiple hereditary exostoses with spinal cord compression. Orthopedics. 1988;11:1213–6.

Matsuno T, Ichioka Y, Yagi T, Ishii S. Spindle-cell sarcoma in patients who have osteochondromatosis. A report of two cases. J Bone Joint Surg Am. 1988;70:137–41.

Tian C, Yan R, Wen S, et al. A splice mutation and mRNA decay of EXT2 provoke hereditary multiple exostoses. PLoS One. 2014;9:e94848.

Wuyts W, Van Hul W. Molecular basis of multiple exostoses: mutations in the EXT1 and EXT2 genes. Hum Mutat. 2000;15:220–7.