CLINICAL QUIZ (p106) ANSWER

What is the diagnosis?

Fibrodysplasia ossificans progressiva (FOP). Molecular testing of ACVR1 gene in this child confirmed there is heterozygous pathogenic variant ACVR1{NM_001105.4}:c.[617G>A];[=]; ACVR1{NP_001096.1}:p.[(Arg206His)];[=].

FOP is an extremely rare disorder with a frequency of 1 in 2 million people across the globe . The culprit of this disease is ACVR1 gene mutation. ACVR1 gene is located on the long arm of chromosome 2. A point mutation of G>A in the intracellular glycine- and serine-rich domain of ACVR1 gives rise to classical FOP. Mutations found in other amino acid in this domain or protein kinase domain are responsible for atypical FOP. ACVR1 is a receptor for bone morphogenetic protein (BMP). Two main pathological mechanisms of ACVR1 mutation include ligand-independent constitutive activity and ligand-dependent hyperactivity in BMP. A constant activation of ACVR1 leads to overgrowth of bone, fusion of cartilage and heterotopic ossification of soft tissues. FOP is inherited in an autosomal dominant pattern, while the majority of patients have a de novo gene mutation. Thus, patients are commonly identified in the absence of family history with few exceptions having one affected parent. Owing to the fact that most cases of FOP arise from a new mutation of ACVR1 gene, it is important to identify patients even when no significant family history is reported.

What are the usual presenting symptoms?

The age of onset spans from 3 to 69. The average onset age is 5. The first "flare-up", which is defined to be a sudden episode of soft tissue inflammation, can be a result of trauma, intramuscular injections, open operations, dental procedures or simply a spontaneous event. The major feature of FOP is ectopic bone tissue formation over the neck, spine and pectoral girdle regions. Such ossification takes place in a sequence from cranial to caudal, and proximal to distal. Other signs and symptoms include shortened thumbs, fifth finger clinodactyly, malformed cervical vertebrae, short broad femoral necks, deafness, scalp baldness and mild mental retardation. FOP is often misdiagnosed as fibromatosis and fibrosarcoma, or even undiagnosed. This might refrain the patients from prompt management to avoid deterioration of the condition. An early onset of hallux valgus in paediatric patients should always alert clinicians to include FOP as one of the differential diagnoses. Clinical diagnosis of FOP can be substantiated when symmetrical bunion and soft tissue swelling are noted, despite the absence of radiological findings.

What is the management and precautions?

Up to date, there are no curative treatments to FOP patients. The management approach can be mainly categorised into supportive and prophylactic methods. Supportive treatment should be administered in case of flare-ups. The International Clinical Consortium published a management guideline on FOP in 2011. In case of injury, FOP patients first have lymphocyte and monocyte infiltration, followed by fibroproliferative, chondrogenic and eventually ossified lesion formation. NSAIDs and systemic glucocorticoids are useful to tackle with white blood cell infiltration in the inflammation cascade when soft tissues are injured. BMP antagonists can be prescribed before fibroproliferative and chondrogenic lesions are formed. Mineralisation inhibitors can be used to halt further ossification of the injured site. Once an ossified bone is formed, any medications will be in vain. Surgery is discouraged as osteotomy will provoke the body's repair mechanism and more ectopic bones will be formed. Bone marrow transplantation is not curative to this condition.

Since it is difficult to predict the onset, duration, severity and outcome of the flare-ups, the most preferred management to FOP is prophylactic treatment. Patients should be instructed to prevent falls since young age. Intramuscular injections should be avoided in the immunisation program and anesthesia to prevent muscular lesion. Patients with FOP are often misdiagnosed to have other types of soft tissue and musculo-skeletal disorders due to the lack of literature review and rareness of the disease. Unnecessary biopsies may be done, thus triggering flare-ups. Clinicians should be aware and include FOP as one of the differential diagnoses when early onset of bunion is presented to avoid detrimental biopsies.

Further Reading

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3. Chell J , Dhar S. Pediatric hallux valgus. Foot Ankle Clin. 2014;19:235-43.
4. Nix S, Smith M, Vicenzino B. Prevalence of hallux valgus in the general population: a systematic review and meta-analysis. J Foot Ankle Res 2010;3:21.
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