Case Report
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A 14-Year-Old Boy with Fibrodysplasia Ossificans Progressive: Phenotypic Characterization and Genetic Analysis

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Abstract

Objective – The aim of this study was to report an ultra-rare genetic disease in a 14-year-old boy with abnormal ossification, to describe clinical phenotype and to expand the understanding of this genetic abnormality. **Case Report** – The patient was born with hallux valgus. At five years of age diagnosis was made after he injured his shoulder and back and after extraskeletal ossification in muscle and soft tissue at the site of injuries. At 8 year of age after a fall radiological examination showed closed spiral-type fracture of the humeral shaft with dystrophic calcifications within the medial soft tissue. Audiometric testing indicated mild loss noted at 8 kHz in the right ear. At ten year of age the patient developed multiple bony ridges across his back. He had now lost almost completely control of his right arm and was locked at the shoulder and elbow. **Conclusion** – Genetic analysis of patient's DNA showed typical *ACVR1/ALK2* gene mutation most likely de novo change that was not inherited from either parent.

Key Words: Mutation ▪ De-Novo ▪ Heterotopic ossification ▪ Molecular Characterization ▪ Phenotype.

Introduction

Different pathological processes can result in formation of extraskeletal bone in muscle and soft tissue defined as heterotopic ossification (HO). The most common are nongenetic forms of HO and it most commonly occurs after tissue damage and can therefore be considered as aberrant tissue repair (1). The history of trauma as the initiating event is present in up to 75% of cases (2). Predisposing conditions include both local traumas, as bone fracture or dislocation and orthopedic surgery and systemic insults as traumatic brain and spinal cord injury or severe burns (1). Genetic causes of HO are very rare. Fibrodysplasia ossificans progressive (FOP) is an ultra-rare disease presenting in childhood and is caused by *ACVR1* mutation (3). Very rarely, the disease is inherited from one of the parents, is transmitted as autosomal dominant disorder and is associated with abnormal first toe and other malformations (4). However, in most cases the disease is caused by a spontaneous mutation. Progressive and widespread postnatal ossification affects muscles, tendons and ligaments, impair mobility, cause severe pain and leads to premature mortality (5). The formation of HO is usually preceded by flare-up symptoms of unpredictable frequency, duration, and location (6). *ACVR1* gene encodes the bone morphogenic protein (BMP) type I receptor ALK2. Mutant ALK2 protein renders this receptor constitutively active leading to phosphorylation of SMADs and transcription of genes related to cell growth and differentiation to form bone (7). No available therapies have been demonstrated to prevent the formation of HO. The approximate duration of life is four decades and the common cause of death is thoracic insufficiency syndrome or other pulmonary complications (8).

The aim of this study is to describe clinical phenotype and genetic abnormality of heterotopic ossification in order to better understand this ultra-rare genetic disease.

Case Report

Here we report a 14-year-old boy with fibrodysplasia ossificans progressive (FOP), with repeated upper respiratory tract infections and otitis media, and with hearing problem. The patient was born at 33 weeks gestation with hallux valgus and was housed in the new born intensive care unit (NICU) for three weeks. The pediatrician thought the toe malformations were bunions. At one year of age he had first hearing evaluation with results suggesting normal hearing acuity. At four years of age he injured his shoulder and had his back contused. A year later the diagnosis of MOP was made. The patient had characteristic malformed great toes and hallux valgus (see figure 1 A, photo when patient was 12-year-old).

At that period of his life immunizations were up to date (Varicella, MMR, Pneumococcal vaccine, DTP, viral hepatitis and poliomyelitis vaccination and inoculation). For the next three years the patient occasionally complained of aches and pain in muscles after regularly running. At 8 year of age he fell forward and bumped left side of forehead on table and landed on right arm injuring right shoulder. His right upper arm was swollen and significantly tender. Radiological examination showed closed spiral-type fracture of the mid-to-distal humeral shaft (Fig. 2). There were dystrophic calcifications within the medial soft tissue of the mid-humerus.

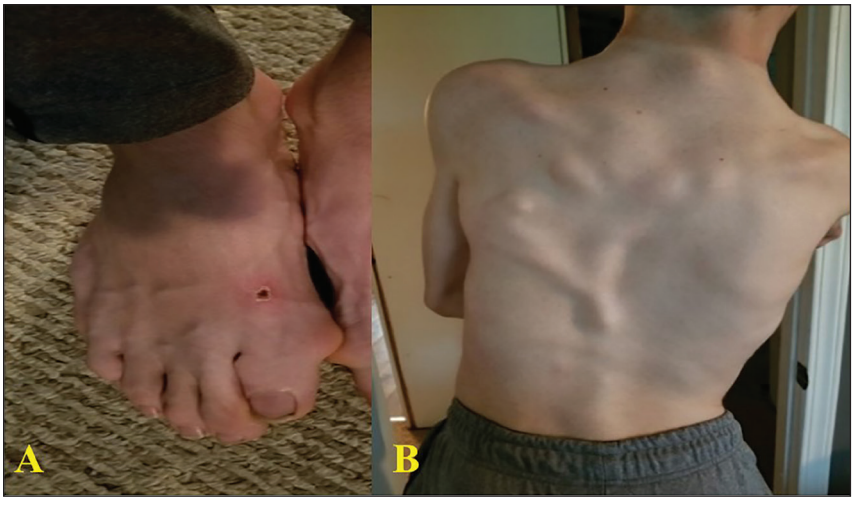

Fig. 1. *Characteristic malformed great toes and hallux valgus (a) swelling and mass at the lumbar muscle region and medial scapular area (b).*

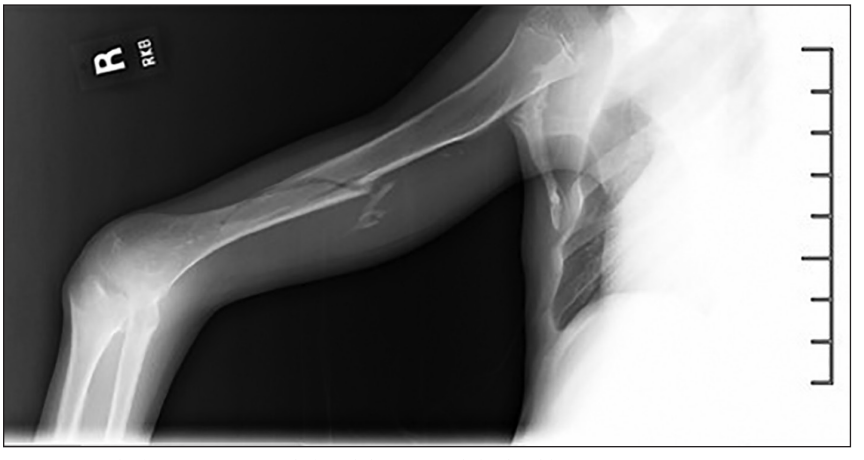

Fig. 2. *Radiologic imaging of closed fracture of shaft of humerus.*

At school he did not pass a hearing screening in his right ear. Audiometric testing indicated normal hearing levels bilaterally through 6 kHz with mild loss noted at 8 kHz in the right ear. A familial history of hearing loss was denied. At ten year of age the patient developed new painful bony lesion on the ventral apex of the left scapula with swelling and mass at the lumbar muscle region and medial scapular area. He had fusion of his shoulder

and right elbow (Fig. 2) and multiple bony ridges across his back (Fig. 1 B). He had now lost almost completely control of his right arm and was locked at the shoulder and elbow. He has also having some difficulty on occasion with his legs.

Actually the patient is well developed and his growth is good. His back is quite fused with bony abnormalities, his right elbow is completely fused, he does not have significant flare ups. He is doing well in school and has restrictions with activities. In the future, he will not receive intramuscular (IM) vaccines, and the flu vaccine will be given subcutaneously. The patient takes prednisone 20 mg one tab by mouth twice a day for five days, additional doses for future traumatic events. Family history is unremarkable. Both parents are healthy and there is no history of a similar disease in the family. Parents were not genetically tested and the *ACVR1* mutation in our patient was confirmed by DNA sequencing analysis, most likely de novo change that was not inherited from either parent. The boy's doctor discussed with the parents the possibility of their son passing his disease onto any future children he may have.

Discussion

The two most important typical symptoms of MOP are abnormal ossification of the joints and soft tissues such as skeletal muscles, tendons, and ligaments and congenital hallux valgus (9). Ossification can be spontaneous or caused by soft-tissue trauma, including iatrogenic trauma from intramuscular vaccinations, falls, and surgical procedures. Painful, recurrent soft-tissue swelling may precede localized heterotopic ossification. Myocardium and smooth muscle are not involved. The largest number of patients (92%) with classic disease presentation has the *ACVR1/ALK2* gene mutation (R260H, c.617G> A), while in a smaller number of cases (8%) with atypical symptoms mutations are at other sites of *ACVR1 / ALK2* or other bases of R260H (10). *ACVR1* encodes ACVR1, a transmembrane serine/threonine kinase. Gain of the function is the mechanism of disease causation. This mutation causes partial deletion of the ACVR1/ALK2 inhibitory protein FKBP12, so ACVR1/ALK2 remains weakly activated in the absence of stimulation by BMP signals, causing HO.

FOP is an ultra-rare disease. French (11) and British (12) population studies showed prevalence of one in one million without any ethnic, racial, gender or geographic predisposition. As there are no formal diagnostic criteria for this disease, FOP should be suspected in individuals with congenital hallux valgus deformity that is most often bilateral and with early-onset heterotopic ossification (13). Our patient was born with hallux valgus but pediatrician thought the toe malformations were bunions. Because the specific pathogenesis of FOP is not always clear, the early phenotype of the disease can be easily confused with other diseases, including tumors, fibromas, and bursitis (14). Hallux valgus may be identifiable on prenatal imaging but can be absent in a minority of individuals with atypical FOP (15). After shoulder injury and back contusion in the fourth year of life and after inflammatory soft-tissue swellings caused by that trauma the diagnosis of MOP was made a year later. By the age of seven the patient was healthy, only occasionally complaining of muscle pain after running. The first serious problem arose in the eighth year of life, when a fall on the right shoulder caused a fracture of the upper arm on the same side. Then, dystrophic calcification was radiologically shown within the medial soft tissue of the mid-humerus. Usually fractures in these individuals heal with minimal heterotopic bone formation but reduction and internal fixation should be avoided because they can lead to rapid onset of heterotopic ossification. In order to prevent soft-tissue injuries, contact sports, overstretching of soft tissues, muscle fatigue and falls should be avoided (16). Also intramuscular vaccinations and all diphtheria-tetanus-pertussis (DTP) type vaccinations should be avoided (16) and when the benefit is assessed to outweigh the harm, subcutaneous vaccination may be given.

Our patient was regularly vaccinated (Varicella, MMR, Pneumococcal vaccine, DTP, viral hepatitis and poliomyelitis vaccination and inoculation)

before he started to show symptoms and before the diagnosis was made. It is especially important for these patients to prevent respiratory infections (pneumococcus, influenza) and therefore family members of these patients should be vaccinated (influenza, pertussis). The predominant cause of mortality is thoracic insufficiency syndrome because HO in the thoracic region, intercostal muscles, paravertebral muscles, and aponeuroses, along with progressive spinal deformity and kyphoscoliosis may seriously affect respiratory function. At the start of school the patient did not pass a hearing screening in his right ear (a familial history of hearing loss was denied). In 50% of individuals with FOP conductive slowly progressive hearing loss is present and is caused by middle ear ossification (17) but in some individuals a sensorineural component may be present.

An individual diagnosed with FOP has rarely an affected parent, the disorder is the result of a *de novo ACVR1* pathogenic variant. This is confirmed by not finding the same *ACVR1* pathogenic variant in the tested leukocyte parental DNA. Another possible explanation is germline mosaicism in a parent (18). FOP very rarely can be inherited in an autosomal dominant manner. Although somatic gain-of-function variants in *ACVR1* have been identified in 20%-25% of diffuse intrinsic pontine gliomas there is no reported increased incidence of this tumor in individuals with FOP (19). It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

There is no effective treatment for FOP, but some drugs can be used to relieve initial symptoms. Our patient takes prednisone 20 mg 1 tab by mouth twice a day for 5 days when flare-ups begin, additional doses for future traumatic events. The frequent use of corticosteroids to treat swelling is not recommended due to the difficulty in assessing the onset of flare-ups (14). COX-2 inhibitors could be used to treat later flare-ups corticosteroids are discontinued, and small dose of a muscle relaxant may help to relieve muscle spasms (20).

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Conflict of Interest: The authors declare that they have no conflict of interest.

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