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Atypical Stone Man Syndrome: Case Report and Literature Review

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Abstract

Stone man syndrome (SMS) prominently known as Fibrodysplasia Ossificans Progressiva (FOP) is a rare genetic disorder of progressive heterotopic ossification leading to severe restriction of mobility. The misdiagnosis and mismanagement rate of FOP is quite high. Atypical presentations of FOP are even more difficult to diagnose and ultimately end up in lifelong disabilities owing to iatrogenic injury. We present a case of a 10 year old girl who came with complaints of deformity of spine and multiple swellings over the back noted since 1 year with no history of preceding trauma or illness. On examination multiple bony hard swellings of variable sizes on the back with right sided mid-dorsal scoliosis exaggerated on forward bending were noted. Skeletal survey revealed fusion of lower cervical spinous process, hallux valgus deformity in the left foot, bilateral short and broad femoral neck and pseudo-exostosis over the distal femur and proximal tibia. Sequencing of the ACVR1gene revealed p.R206H mutation associated with FOP. Confirmation of the diagnosis by genetic analysis has averted the possibility of misdiagnosis and mismanagement in this atypical presentation of SMS/FOP. Insights into the variable phenotypic expressivity of FOP may pave the way for more effective therapeutic interventions for FOP in the future.

Keywords: *Myositis ossificans progressiva, Fibrodysplasia ossificans progressiva, Heterotopic ossification, ACVR1 gene, Hallux valgus deformity.*

Introduction

Stone Man Syndrome (SMS) is a rare genetic disorder of severely disabling progressive heterotopic ossification with a worldwide prevalence of 1 in 20 lakh population[1]. It is synonymous with Myositis ossificans progressiva, Munchmeyer's disease and Fibrodysplasia Ossificans Progressiva (FOP). Being a very rare entity 90% of FOP cases are misdiagnosed and mismanaged. Atypical presentations of FOP are even more difficult to diagnose. Most often atypical presentations end up with life threatening iatrogenic harm secondary to invasive diagnostic and therapeutic procedures[2]. We present an atypical case of FOP/SMS diagnosed early by the subtle clinico-radiological findings and confirmatory genetic analysis, wherein detrimental iatrogenic injury has been avoided.

Case Presentation

A 10 year old right hand dominant girl presented with the complaints of deformity of spine and multiple swellings over the back noted since 1 year with no history of preceding trauma or illness. She had been examined and extensively evaluated by various doctors in the previous 1 year. As no conclusive final diagnosis was made and the symptoms persisted the child was referred to our hospital for further evaluation and management of deformity of the spine.

The child was the second born offspring of a non-consanguinous couple with no history of similar illness in any of the family members. On examination multiple bony hard swellings of variable sizes were noted on the back extending from neck to the lower lumbar spine predominantly on the left side. Right sided mid-dorsal scoliosis exaggerated on forward bending was noticed (Figure 1). The range of motion of neck and thoraco-lumbar spine was marginally decreased.

Skeletal survey of the child revealed thickened sheet of muscles over the nape of the neck with elongated pedicles of all the cervical vertebrae and fusion of spinous process of 6^{th} and 7^{th} cervical vertebrae. Mild mid-dorsal scoliosis to right with ossific masses attached to 6^{th} and 8^{th} ribs were noted on the left side of the chest wall (Figure 2). Bilateral microdactyly of great toes with hallux valgus deformity in the left foot was noted (Figure 3).Antero-posterior (AP) radiograph of pelvis with both hips revealed short and broad femoral neck bilaterally. AP radiograph of both knees with legs revealed pseudo-exostosis over distal femur and proximal tibia bilaterally (Figure 4).

FOP was considered as a diagnostic possibility. Blood samples of both the parents and the child were collected for sequencing of the *ACVR1*gene wherein the p.R206H mutation associated with FOP was detected in the child confirming the diagnosis.

Discussion

Stone Man Syndrome/ Fibrodysplasia Ossificans Progressiva is a dreadful disorder of skeletonisa-tion of connective tissues leading to severe restriction of mobility. Its description dates back to year 1648 when "Gay" expressed it as a case that "turned to wood" [1,3].

The pathogenesis of FOP is directly linked to bone morphogenetic proteins (BMPs) which are a group of highly conserved signalling moieties that regulate cell differentiation and endochondral ossification. BMP signalling is mediated through trans-membrane receptor complexes. Activin receptor 1 A (*ACVR1*)/Activin like kinase 2(*ALK2*) is one of the three BMP type 1 receptors[1,3,4]. It consists of 4 domains: ligand binding domain, transmembrane domain, glycine serine (GS) rich domain, and the protein kinase domain. The GS rich domain plays a critical role in binding and activation of SMAD signalling. It is also a binding site for FKBP12, a protein which inhibits leaky activation of the receptor in the absence of the ligand[3,5]. Majority of FOP cases result from a single nucleotide substitution of arginine with histidine at codon 206 of the *ACVR1* gene (p.R206H). Zhang et al. reported this mutation in 97% of the 72 cases of FOP studied by them [5,6]. In the remaining small number of

cases, other *ACVR1* gene mutations including G356D, R258S, G328R etc. have been reported [5].

Mutation of the *ACVR1* gene leads to a conformational change in the cytoplasmic juxta-membranous GS domain of *ACVR1* leading to gain of function of the receptor by enhanced BMP signalling. This results in aberrant and enhanced endochondral new bone formation in specific locations ultimately ending up in classical deformities and extra-articular ankylosis by progressive heterotopic ossification/ second skeleton formation[1,3,4,7].

FOP can result from a de-novo mutation or may be inherited as an autosomal dominant disorder[2].

Detection of a mutation in the *ACVR1* gene in a suspected case confirms the diagnosis of FOP [7].

Clinical presentation of FOP is variable. Three sets of presentation are described namely classical FOP, FOP plus, FOP variants or atypical FOP. Classical cases of FOP present with bilateral monophalangeal great toe with hallux valgus deformity detectable at birth and early onset rapidly progressive heterotopic ossification in explicit anatomic locations (cranial, axial and dorsal followed by caudal, appendicular and ventral regions of the body). FOP plus cases have classical FOP features with additional features that are not typically associated with FOP. FOP variants or atypical FOP cases show variations of the classical FOP features [2-7]. The case series reported by Zhang et al. had 92% of cases manifesting classic FOP features, with the FOP-plus and FOP variants accounting for 3% and 4% respectively of the total number[7].

Though this child presented with some of the features associated with classical FOP like short and broad femoral necks, proximal tibial exostosis and cervical spine malformations[2-4], features like late onset heterotopic masses limited along the left paraspinal region with gradually progressing scoliotic deformity of spine, insignificant involvement of neck musculature, gradually progressing asymmetrical hallux valgus deformity of left great toe and the absence of monophalangism of great toe favour the diagnosis of atypical FOP.

There are many reported instances of surgical interventions contemplated on such cases misdiagnosing them as hereditary multiple exostosis, Klippel Feil syndrome, adolescent idiopathic scoliosis etc. which ultimately resulted in acute flare up and rapid progression of the disease process[2,3,6,8]. Confirmation of the diagnosis by genetic analysis of the *ACVR1* gene mutation (p.R206H) has averted the possibility of diagnostic and therapeutic misadventures in this case.

Though classical and atypical cases of FOP have the same *ACVR1* gene mutation, there is a siginificant difference in their phenotypic expression and severity, with the disease process being more florid and aggressive in some, delayed and mild in others. The reason for such variable expressivity, though not clearly understood, is believed to be the influence of modifier genes[3]. A better understanding of these modifying influences may pave the way for more effective therapeutic interventions for FOP in future.

Conclusion

FOP is a rare musculoskeletal disorder of genetic aetiology which is misdiagnosed and mismanaged in most of the cases. Biopsy or histopathological analysis that is considered as the gold standard procedure for the diagnosis of tumors and tumor like lesions does not hold good for FOP. Inadvertent iatrogenic injury caused by such invasive procedures end up in rapid progression of the debilitating disease. Clinico-radiological findings may aid in diagnosing classical cases of FOP but mutation analysis of the *ACVR1* gene is the gold standard test for the diagnosis of atypical SMS/FOP. It is essential to improve the awareness about this disorder, lest the trend of misdiagnosis and mismanagement continues. Secondary prevention of injury is the treatment of choice. Gene therapy is the goal for future.

Figure 1. Clinical photograph showing multiple mass lesions over the left para-spinal region of the back with right sided scoliosis on forward bending.

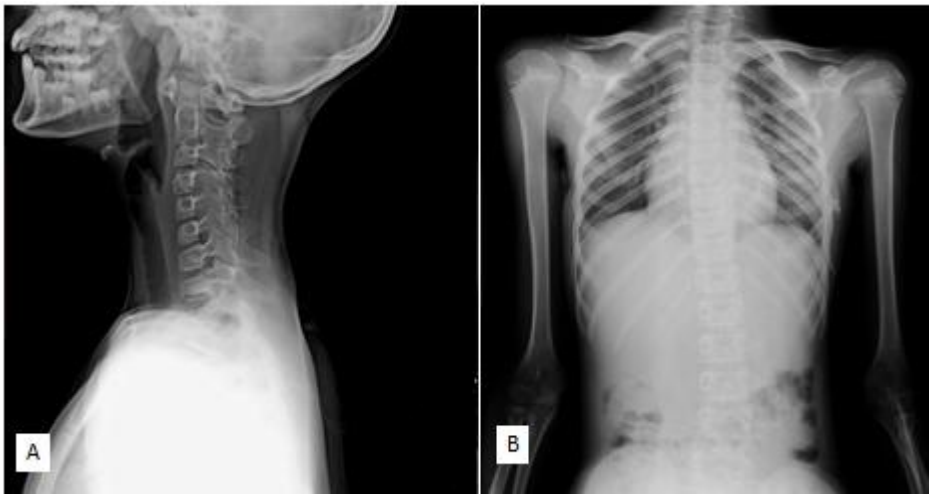

Figure 2.A. Lateral radiograph of cervical spine showing small vertebral bodies with relative enlargement of the pedicles and fusion of the spinous processes of lower cervical vertebral bodies. 2. B. Antero-posterior dorso-lumbar radiograph of spine showing right mid-dorsal scoliosis with ossification over the chest wall adjacent to the mid-dorsal ribs on the left side.

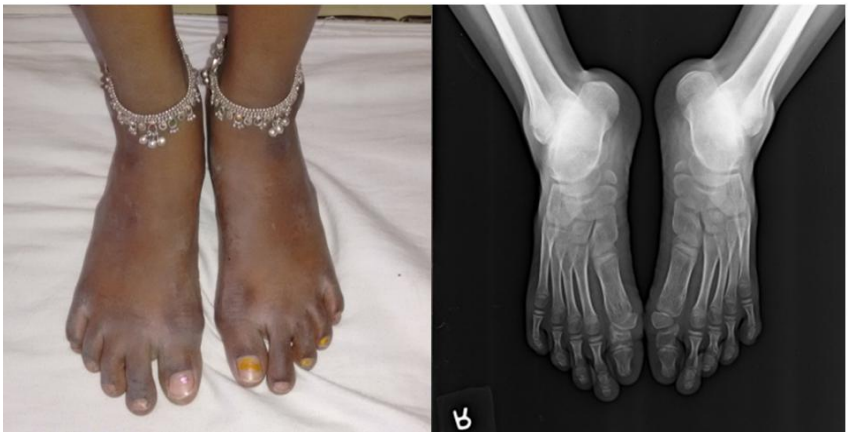

Figure 3. Clinical photograph and dorso-plantar radiographs of both feet showing hallux valgus deformity on left side with short and stubby first metatarsals, hypoplastic proximal phalanges of great toes with associated hypertrophy of the distal epiphyses of first metacarpals bilaterally.

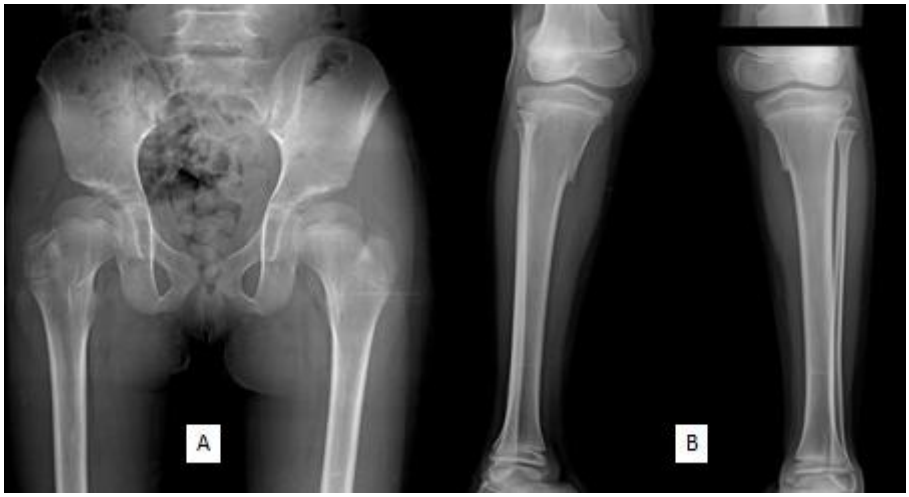

Figure 4 A. Antero-posterior radiograph of pelvis showing short and broad femoral necks on both the sides; 4B. Antero-posterior radiograph of both legs showing pseudo-exostosis over the proximal medial tibia and distal femur bilaterally.

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References

1. Kishan A B, Raghavendra K, Vikram M P, Harman S G. Stone Man Syndrome : A Case Report and Review of Literature. J Pub Health Med Res, 2014;2(2):47-51.
2. Kaplan FS, Xu M, Glaser DL, Collins F et al. Early diagnosis of fibrodysplasia ossificans progressiva. Pediatrics. 2008; 121(5):e1295-300. doi: 10.1542/ peds .2007-1980.
3. Kaplan FS, Xu M, Seemann P, Connor JM. Classic and atypical fibrodysplasia ossificans progressiva (FOP) phenotypes are caused by mutations in the bone morphogenetic protein (BMP) type I receptor ACVR1. Hum Mutat. 2009;30 (3):379-90. doi: 10.1002/humu.20868.
4. Shore EM, Kaplan FS. Insights from a Rare Genetic Disorder of Extra-Skeletal Bone Formation, Fibrodysplasia

Ossificans Progressiva (FOP). Bone 2008;43(3):427-
33. doi: 10.1016/j.bone.2008.05.013.

5. Huning I, Gillessen-Kaesbach G. Fibrodysplasia ossificans progressiva: clinical course, genetic mutations and genotype-phenotype correlation. Mol Syndromol.2014; 5:201-11.
6. Zhang W, Zhang K, Song L, Pang J, Ma H, Shore EM, Kaplan FS, Wang P. The phenotype and genotype of fibrodysplasia ossificans progressive in China: a report of 72 cases. Bone.2013;57: 386-91.
7. Shore EM[1], Xu M, Feldman GJ, Fenstermacher DA et al. A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. Nat Genet. 2006;38(5):525-7.
8. Kamal AF, Novriansyah R, Rahyussalim, Prabowo Y et al. Fibrodysplasia Ossificans Progressiva: Difficulty in Diagnosis and Management A case report and literature review. Journal of Orthopaedic Case Reports 2015;5(1): 26-30.