Feasibility of Bisphosphonate Therapy in an Indian Pediatric Patient of Fibrodysplasia Ossificans Progressiva

Abstract
Fibrodysplasia ossificans progressiva, also known as myositis ossificans progressiva, is a rare autosomal dominant disorder (1 in 2 million). It produces a catastrophic and crippling illness in young people for which there is no effective treatment. This case report presents a case of 7-year-old child misdiagnosed as osteogenesis imperfecta admitted with severe disability and pain. He was diagnosed by clinical and radiological methods, treated with bisphosphonates for pain relief along with calcium and Vitamin D, and followed till 4 years.

Keywords: Bisphosphonates, fibrodysplasia ossificans progressiva, myositis ossificans progressiva, stone man disease

Introduction
Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant hereditary connective tissue disorder characterized by progressive heterotopic ossification of striated muscle and connective tissue associated with pain and disability. It is an extremely rare disease with only <600 cases reported in the literature.[1] This condition manifests in childhood and runs a slowly progressive course. “Stone man disease” and “myositis ossificans progressiva” were the names used initially, but “FOP” more accurately reflects the pathogenesis of the disease.[2] Congenital anomalies of the hands and feet are early signs of this disease. We present a case of FOP with extensive muscle ossifications and feasibility of bisphosphonate treatment in the same.

Case Report
A 7-year-old male child presented to us with a history of recurrent fractures and progressively increasing chest deformity for the past 4 years. The patient came with an acute history of pain in all the four limbs. He was the only child to nonconsanguineous parents, and none of the family members had any similar complaints. He had a normal developmental history. The patient had swelling of both the lower limbs after an injury 3 months back and has been bedridden since then.

On examination, he had pallor and marked pitting edema of the bilateral lower limbs and right upper limb. He also had abdominal wall edema and pectus carinatum. The patient was evaluated earlier and provisionally diagnosed to have osteogenesis imperfecta and treated with nonsteroidal anti-inflammatory drugs and oral calcium. He was referred to us as there was no response to treatment.

Blood investigations done showed Hb: 12 g%, Ca: 6.8 mg%, PO4: 3.8 mg%, alkaline phosphatase (ALP): 473U/L, increased parathyroid hormone level, and low Vitamin D level (9.84 ng/ml). X-rays revealed calcified shadows around the lower end of the femur following which a differential of hematoma/neoplasm/myositis ossificans was kept.

A bone biopsy was done which revealed atrophic skeletal muscles interspersed with loose connective tissue surrounded by a zone of mineralization interwoven to the lamellar bone, suggestive of myositis ossificans, and no neoplastic lesions were seen. Tc-99m bone scan showed fluffy calcific densities surrounding the lower end of the right humerus, both femurs, iliac bones, and scapula.

Replacement with calcium and Vitamin D supplements was started. For...
pain management, he was started on injection pamidronate 23 mg (1 mg/kg b.w./day) for 3 consecutive days, following which the patient had improvement in rest pain and tenderness had also decreased. He was discharged on calcium and Vitamin D with a follow-up planned after 1 month.

The patient was lost to follow-up till the next 2 years following which he presented again with severe pain and restriction of movements [Figure 1]. On investigation, the patient has normal calcium and Vitamin D level and increased ALP level, and X-ray reveals further deterioration [Figure 2]. The patient was again started on injection pamidronate 1 mg/kg/day for 3 consecutive days and pain improved with treatment.

On follow-up, after 3 months, the patient is doing well. His ALP level has decreased, and his bilateral limb swelling has subsided. The patient still has restricted activity but does not complain of any rest pain. He was given total four sessions (every 3 months) of pamidronate therapy each over 3 days over a period of 1 year. He has not deteriorated (no complaint of pain or increase in disability) and received calcium and Vitamin D supplementation (elemental calcium 250 mg daily and Vitamin D3 800 units daily) with every 3-month follow-up for the past 2 years. There was no further deterioration in X-rays. His Vitamin D, calcium, and ALP levels are normal.

**Discussion**

FOP is a rare genetic disorder in which ossification occurs in muscles or associated connective tissues or both. FOP is extremely rare with a worldwide prevalence of approximately one in two million. Diagnosis of FOP depends on the clinical and radiological recognition of the characteristic congenital malformations of the great toes and the progressive ossification of soft tissues.

The common sites of heterotopic ossification are head, neck, spine, and shoulder. The bone develops independently of the normal skeleton and forms discrete skeletal elements that can fuse with normal skeletal bone. The patient presented with severe musculoskeletal deformities but no congenital malformation.

The disorder usually manifests between birth and 10 years and it is most common around 3 years of age. Spine and shoulder stiffness develops by 10 years, and restricted hip movements develop by 20 years. These patients are usually confined to bed by the age of 30 years. The most common cause of death is cardiovascular failure such as pneumonia and right-sided heart failure. The treatment of FOP is multifactorial and is based on injury prevention and clinical therapy. The prevention of soft-tissue injury and muscle damage, as well as the prevention of falls, is extremely important. Intramuscular injections, including vaccines, must be avoided. Moreover, in routine dental care, overstretching of the jaw and intramuscular local anesthetic injections should also be avoided.

Bisphosphonates are structurally similar to naturally occurring inorganic pyrophosphatase, which play an important role in calcium–phosphate metabolism. The mechanism of action is understood to involve suppression of bone turnover, slowing down the mineralization process by binding to hydroxyapatite and transformation of amorphous calcium phosphate into hydroxyapatite crystals.

Bone turnover was increased, as reflected by measurement of serum total ALP. Treatment with pamidronate was associated with marked reduction in ALP. The ALP fell to within the expected range for age similar to other cases. Other conservative treatments such as nonsteroidal anti-inflammatory medications, cyclo-oxygenase-2 inhibitors, leukotriene inhibitors, and mast cell stabilizers.
have been used with no apparent positive results. Surgical excision of heterotopic bone is doomed to failure because of new ectopic bone forms rapidly at the operative site. Bone formation at the operative site usually occurs within 4 months after operation.\(^4\)

This case illustrates that intravenous bisphosphonate may be an effective treatment option for the management of pain in FOP. Further research including case series and randomized control trials may help to confirm this and should also aim to establish the optimum dose regimen and safety in children.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient’s parent has given her consent for her child’s images and other clinical information to be reported in the journal. The patient’s parent understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Baysal T, Elmali N, Kuthu R, Baysal O. The stone man: Myositis (fibrodysplasia) ossificans progressiva. Eur Radiol 1998;8:479-81.
2. Pignolo RJ, Shore EM, Kaplan FS. Fibrodysplasia ossificans progressiva: Clinical and genetic aspects. Orphanet J Rare Dis 2011;6:80.
3. Shore EM, Feldman GJ, Xu M, Kaplan FS. The genetics of fibrodysplasia ossificans progressiva. Clin Rev Bone Miner Metab 2005;3:201-4.
4. Seok Y, Cho S, Lee E. Surgical treatment combined with NSAIDs in fibrodysplasia ossificans progressiva. Ann Thorac Cardiovasc Surg 2012;18:61-3.
5. Kaplan FS, Zasloff MA, Kitterman JA, Shore EM, Hong CC, Rocke DM, et al. Early mortality and cardiorespiratory failure in patients with fibrodysplasia ossificans progressiva. J Bone Joint Surg Am 2010;92:686-91.
6. Cullen N, Perera J. Heterotopic ossification: Pharmacologic options. J Head Trauma Rehabil 2009;24:69-71.
7. Hanson DA, Weis MA, Bollen AM, Maslan SL, Singer FR, Eyre DR, et al. A specific immunoassay for monitoring human bone resorption: Quantitation of type I collagen cross-linked N-telopeptides in urine. J Bone Miner Res 1992;7:1251-8.