



Late-onset fibrodysplasia ossificans progressiva with atypical presentation: A case report

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ABSTRACT

Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disease characterized by progressive heterotopic ossification of connective tissues, episodic flare-ups and bilateral deformities of the great toe (hallux valgus). As faulty tissue repair processes progressively calcify tissue, patients suffer from swelling and limited mobility in that area. We present a case of a 66-year-old woman who had initially presented at age 54 without the hallux valgus deformity or classic-type flare-ups. As there is currently no cure for FOP, management is mainly symptom control. Physicians should still consider FOP if imaging indicates progressive heterotopic ossification in the absence of hallux valgus in an older patient.

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1. Introduction

In heterotopic ossification (HO) ectopic bone tissue develops inside muscle or other soft tissues such as tendons, ligaments, subcutaneous fats, and nerves [1,2]. While the pathophysiology of HO is questionable, it appears to be caused by malfunctioning tissue repair processes [1]. HO is divided into nonhereditary and hereditary forms. The nonhereditary traumatic subtype is a result of soft-tissue injury from trauma or surgery and the most common form of HO [2]. This case report focuses on the hereditary subtype fibrodysplasia ossificans progressiva (FOP), which is also known as myositis ossificans progressiva (MOP), Munchmeyer's disease, or "stone man disease" [3]. Importantly, the hereditary forms of HO differ significantly from the nonhereditary forms in presentation and clinical consequences [1].

FOP is characterized by skeletal malformations of the phalanges, metacarpals and spine with HO at extra-skeletal sites due to calcified edema [4–6]. Patients with FOP can experience extreme limitations in mobility [6]. The first case was reported by Patin in 1692 and Freke later defined the symptoms of FOP in 1739. Stonham, Burton-Fanning, and other clinicians recorded further cases of FOP with different genders, ages, and hereditary forms [7]. It has a prevalence of 1 in 2,000,000, unaffected by ethnicity, sex, or geographic location [5,7].

FOP is autosomal dominant with most cases being sporadic, presenting between birth to 10 years, and slowly progressing to become fatal at age 40 on average due to thoracic insufficiency syndrome [5–7].

The goal of this report is to introduce an atypical case of fibrodysplasia ossificans progressiva (FOP) that presented with nonclassical flare-ups, without the hallux valgus deformity, and later in life.

2. Case Report

A 66-year-old woman presented to the outpatient center for the Department of Orthopaedics with severe hip and knee stiffness. Associated pain was particularly worse after exertion. For multiple days she was bed-bound due to pain, stiffness, and fatigue affecting her lower limbs bilaterally.

At age 54 the patient first reported complaints of ongoing stiffness and discomfort affecting her legs. Due to the extremely late onset and absence of the classic hallux valgus deformity, the diagnosis of FOP eluded clinicians for many years. Electromyography (EMG) done showed diffuse myopathy in the lower limbs. Early diagnoses included polyarthralgia, fibromyalgia, lupus, and Ehlers-Danlos syndrome. The most definitive diagnosis reached during these years was advanced-stage muscle disease or a connective-tissue disease process.

Clinical exam confirmed stiff hips and knees, but the stiffness was primarily in the soft tissues and not the joints. There was a 40° bilateral flexion deformity of the knees, with the right being more severe. While less pronounced than in the lower limbs, there was also stiffness in the upper limbs. Shoulder flexion was restricted to 40°, abduction to 50°, and rotation to 5°. There was limited range of flexion and extension in her spine as well. Small-joint effusion was present.

Abbreviations: FOP, Fibrodysplasia ossificans progressiva; HO, Heterotopic ossification.

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The patient had had a complex medical history, including migraine since age 13, Von Willebrand disease, hepatitis B and C, and Raynaud's phenomena.

Unrelenting stiffness had progressed over the years. Pethidine in oral tablet form had been one of the few analgesics the patient had responded to and could tolerate. At presentation the patient was on low-dose corticosteroids to manage inflammation.

Ultimately, a clinical diagnosis of atypical myositis ossificans progressiva was reached due to progressive stiffness complemented by imaging indicating soft-tissue calcifications seen bilaterally within the appendicular musculature (Fig. 1).

3. Discussion

FOP is a severe and disabling condition as it is irreversible, widespread, and progressive [5]. As the HO arises in the connective tissue in muscles, fascia, ligaments, and joint capsules instead of the actual muscle fibers, the term fibrodysplasia ossificans progressiva (FOP) is favored over myositis ossificans progressiva (MOP) [3].

3.1. Mechanism

The molecular mechanisms of pathogenesis are not completely understood, but multiple studies show a link between the upregulation of the bone morphogenetic protein (BMP) signaling pathway and FOP [8]. BMP ligands in the TGF- β family bind type II receptors, such as BMP receptor type II (BMPR-II), activin receptor type IIA (ActR-IIA) or activin receptor type IIB (ActR-IIB), which then recruit a type I receptor, activin type IA/activin-like kinase 2 (ACVR1/ALK2), in the cell membrane [5]. The type II receptors are constitutively active Ser/Thr kinases that phosphorylate a GS (glycine-serine) domain on the type I ACVR1/ALK2 receptor. An activated ACVR1/ALK2 receptor phosphorylates downstream cytoplasmic substrates in the Smad signaling family, which can subsequently modify gene expression in the nucleus [4,5]. The mutated ACVR1/ALK2 type II receptor linked to FOP has a GS domain that is hypersensitive to phosphorylation by type II receptors. If the GS domain is mutated, the inhibitory protein, FKBP12, is unable to bind to prevent constitutive activation of the type 1 receptor in absence of a ligand [6]. This causes constitutive BMP signaling and implies a gain-of-function mutation [4].

3.2. Clinical Presentation

The common clinical features that define FOP are progressive HO in soft tissues and congenital malformations of the great toes (hallux valgus) [5]. While deformity of the great toe appears at birth in 80% of

patients with FOP, our patient didoes not have this [3,4]. The HO in FOP normally presents between birth and 26 years of age, with presentation in the first decade being the most common. There are a few case reports of patients presenting with FOP in their late forties, but age 54 is the oldest presentation reported in the literature to date [9]. Although the rate of HO can vary in FOP patients, our patient's ossification had progressed along a normal time course [5]. The stiffness had intensified over a decade, to the point where the patient had to walk with a shuffling gait. The HO had presented primarily in the hips and shoulders. This is consistent with the anatomic pattern in classic FOP patients, where the axial and proximal regions of the appendicular skeleton are affected before the distal regions [5]. Patients with FOP usually suffer from recurrent episodes, termed flare-ups, which are defined by soft-tissue swellings that are inflammatory and painful [5]. These flare-ups are an endochondral process transforming connective tissues into ribbons or sheets of heterotopic bone that can cross joints, causing limited mobility [3]. Our patient did appear to undergo the usual flare-ups, but had flu-like symptoms and widespread feelings of stiffness throughout the body. She had been diagnosed with hemiplegic migraines since age 13. Recurrent headaches are not associated with FOP, but many patients with FOP do report having them, and females with FOP are four times more likely to report recurrent headaches than males with FOP [10].

3.3. Radiographic Features

Often the typical presentation of soft-tissue lesions and the bilateral hallux valgus deformity allow for the clinical diagnosis of FOP, rendering radiographs unnecessary [6]. However, as the great toe deformity was absent in our patient, diagnosis by imaging became more pertinent. Recent radiographs of the hips and shoulders showed bilateral densely calcified soft-tissue masses that had progressed over the years, indicative of FOP [2].

3.4. Diagnosis

Clinicians often misdiagnose FOP as aggressive juvenile fibromatosis, lymphedema, bursitis, or soft-tissue sarcoma, as it is challenging to relate flare-ups on the head, neck, and back with the bilateral congenital deformity of the great toes [6,7]. This can lead to incorrect treatments (e.g. biopsies), which can worsen the symptoms of the disease [3]. The most definitive way to diagnose FOP is through genetic analysis of the ACVR1/ALK2 gene mutation. Over 90% of individuals with the classic form of FOP have the same mutation (c.617G>A; R206H) in the GS domain, while patients with an atypical presentation have a different mutation, but still in the GS domain of the ACVR1/ALK2 gene [4].

3.5. Treatment

There is currently no cure for FOP. Management is aimed at symptom control and the prevention of flare-ups, which can be provoked by surgery, trauma, viral infections, intramuscular injections, muscle strain, and fatigue [6]. Administration of glucocorticoids at the onset of a flare-up can manage inflammation and tissue edema in the appendicular skeleton. Ongoing flare-ups and chronic pain can be treated with nonsteroidal anti-inflammatory drugs (NSAIDs), mast cell stabilizers, leukotriene inhibitors, and cyclo-oxygenase-2-inhibitors. Ascorbic acid can control the rate of progression of ossification, probably by altering the synthesis of procollagen type III during the inflammatory periods [3].

With the discovery that the ACVR1/ALK2 mutation promotes upregulation of the BMP signaling pathway in the absence of ligand, leading to HO, developing drugs to inhibit these processes is under current investigation [7]. Proposed strategies include ALK2 protein inhibitors, osteoblastic progenitor cell activity inhibitors, compounds that inhibit the Ser/Thr kinase activity of ALK2, and RNAi techniques that inhibit mutant



Fig. 1. X-ray showing bilateral heterotopic ossification of the thigh muscles.

forms of ALK2 [4,6]. All-trans retinoic acid (RA) agonists are also a consideration, as they have been shown to inhibit chondrogenesis in mouse models by reducing the level of Smad proteins and subsequently HO [4].

Contributors

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Patient Consent

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Provenance and Peer Review

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Declaration of Competing Interest

All authors declare that they have no conflict of interest regarding the publication of this case report.

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