Fibrodysplasia Ossificans Progressiva and Bone Scintigraphy: Case Report

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Abstract

Fibrodysplasia ossificans progressiva (FOP) is an extremely uncommon autosomal dominant condition marked by abnormalities in the big toes and the gradual development of extra-skeletal bone in specific anatomical formations. In FOP, heterotopic ossification (HO) arises episodically, triggered by spontaneous flare-ups or trauma, and can lead to progressive disability over time. Utilizing bone scintigraphy with 99mTc-MDP in conjunction with SPECT-CT plays a crucial role in the early identification, diagnosis, staging, and ongoing monitoring of the disease, as it helps to pinpoint the sites of HO formation.

Keywords: fibrodysplasia ossificans progressiva, episodic formation of heterotopic ossification, bone scintigraphy combined with SPECT-CT.
Introduction
Fibrodysplasia ossificans progressiva (FOP) is an exceptionally rare autosomal dominant disorder resulting from activating mutations in the activin A receptor of bone morphogenetic protein (BMP) type I. This condition is marked by malformations of the big toes and the gradual formation of extra-skeletal bone in specific anatomical patterns. [1,2,3].

In FOP, heterotopic ossification (HO) occurs episodically and can arise spontaneously or following trauma, resulting in cumulative disability [1]. Due to the rarity of FOP, most patients experience misdiagnosis [4].

The median life expectancy for individuals with FOP is approximately 40 years, with respiratory failure due to severe chest wall restriction being the most common cause of death.

Treatment options are palliative and aim to alleviate symptoms [Tab.1]. Currently, there are no effective treatments available to prevent or cure the disease [1].

Objective
In this study, we present the case of a patient in whom rheumatologists suspected fibrodysplasia ossificans progressiva (FOP), and the results of bone scintigraphy aided in confirming the diagnosis.

Case report
A 41-year-old woman presented with inflammatory spinal and joint pain, accompanied by intermittent knee stiffness, restricted joint mobility, and bilateral hallux valgus exacerbations. Clinical examination uncovered tender swellings around the pelvis and thighs. Standard X-rays detected ectopic ossifications near the joints, prompting suspicion of fibrodysplasia ossificans progressiva. Subsequent bone scintigraphy showed early tracer accumulation in the thighs, progressing to intense fixation in later stages, corresponding to emerging hyperdense lesions and active heterotopic ossifications. Further evaluation via SPECT-CT scans revealed mature heterotopic ossifications adjacent to the muscle compartments of the hips and thighs, unresponsive to tracer binding.
Discussion:
All patients with fibrodysplasia ossificans progressiva (FOP) reported to date have carried heterozygous gain-of-function mutations in the ACVR1 gene, located on chromosome 2 (2q23-24), as it is the case in our patient. ACVR1 encodes a bone morphogenetic protein (BMP) receptor type 1, also known as activin A receptor type 1, which is expressed in many tissues of the body, including skeletal muscle and cartilage. It plays a crucial role in regulating the growth and development of bone and muscle, including the progressive replacement of cartilage with bone / ossification [1,8].

Individuals with fibrodysplasia ossificans progressiva (FOP) typically appear normal at birth, except for characteristic malformations of the big toes, which are present in all classically affected individuals [5], as observed in our patient with bilateral hallux valgus. During the first decade of life, most children with FOP experience episodic, painful, inflammatory soft tissue swellings [9,10]. These swellings are often mistaken for tumors, resulting in misdiagnosis and delayed diagnosis [5,11]. While some flare-ups may regress spontaneously, most lead to the development of sheets and plaques of heterotopic bone in fascia, ligaments, tendons, and skeletal muscles. Minor trauma, such as intramuscular injections, muscle fatigue, trauma, and viral diseases, can trigger new painful flare-ups of FOP, leading to progressive heterotopic ossification (HO). Attempts to surgically remove heterotopic bone often result in new explosive and painful episodes of bone growth [5].

Heterotopic ossification (HO) in fibrodysplasia ossificans progressiva (FOP) progresses in characteristic anatomical and temporal patterns, typically appearing first in the dorsal, axial, cranial, and proximal regions of the body, and later in the ventral, appendicular, caudal, and distal regions. However, in contrast to typical patterns, our patient exhibited predominant involvement in the appendicular skeleton. Several skeletal muscles, including the diaphragm, tongue, and oculomotor muscles, were spared, as were the cardiac and smooth muscles [5,9,12].

HO in FOP occurs episodically, but disability accumulates over time. Most FOP patients present with a significant motor deficit by the

![Fig.3: SPECT CT reveals several mature heterotopic ossifications adjacent to the muscular compartments of the hips and thighs, with no uptake of the radiotracer.](image)
third decade of life, and severe wasting may result from ankylosis of the jaw [7,9,12]. The estimated median life expectancy is 40 years, with death often resulting from complications of respiratory failure syndrome or pneumonia [6]. While progressive HO is characteristic, additional anomalies may develop, including malformations of the big toes, enlarged vertebral bodies, and fusion of the facet joints between C2 and C7 [13]. Bone scintigraphy using 99mTc-MDP is very important in the early detection of heterotopic ossification (HO) sites, contributing significantly to diagnosis, lesion extent determination, and disease monitoring [13]. Numerous cases reported in the literature underscore the crucial role of bone scintigraphy in fibrodysplasia ossificans progressiva (FOP) [14-18]. In this study, we present a case where bone scintigraphy facilitated the assessment of disease extent, early lesion detection, and maturity evaluation of other lesions. The integration of SPECT-CT, combining anatomical and functional information, enhances topographical and lesion accuracy [18]. Beyond its primary role in FOP management, it is important to underscore other advantages of CT, such as whole-body assessment with minimal radiation exposure, distinguishing it from alternative imaging modalities.

Therapeutic management primarily focuses on supportive care, with glucocorticoids, NSAIDs, COX-2 inhibitors, leukotriene inhibitors, and mast cell stabilizers being beneficial in managing long-term discomfort and intermittent flare-ups. Chronic immunosuppression may offer some benefits. However, surgical interventions, including surgical release of joint contractures, are typically unsuccessful [19].

Conclusion:

Fibrodysplasia ossificans progressiva is a genetic condition characterized by sporadic heterotopic ossification. Timely diagnosis and intervention are pivotal in shaping the disease trajectory. Bone scintigraphy coupled with SPECT-CT is instrumental in managing the condition, aiding in prompt diagnosis, early lesion detection, and precise mapping of ossification patterns.

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Conflict of interest:

The authors declare that there were no conflicts of interest within the meaning of the recommendations of the International Committee of Medical Journal Editors when the article was written.

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