

Fibrodysplasia Ossificans Progressiva and Bone Scintigraphy: Case Report

Sofia Chkikar¹, Assia Seddouki¹, Nadia Ismaili Alaoui¹

¹Department of Nuclear Medicine, Hassan II University Hospital Center, Fez, Morocco

Swiss Journal of Radiology and Nuclear Medicine - www.sjoranm.com - SJORANM GmbH - CH-3072 Ostermundigen bei Bern - Switzerland

1Corresponding author: Sofia CHKIKAR - received: 11.04.2024 - published: 30.04.2024

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 ^{99m}Tc-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.

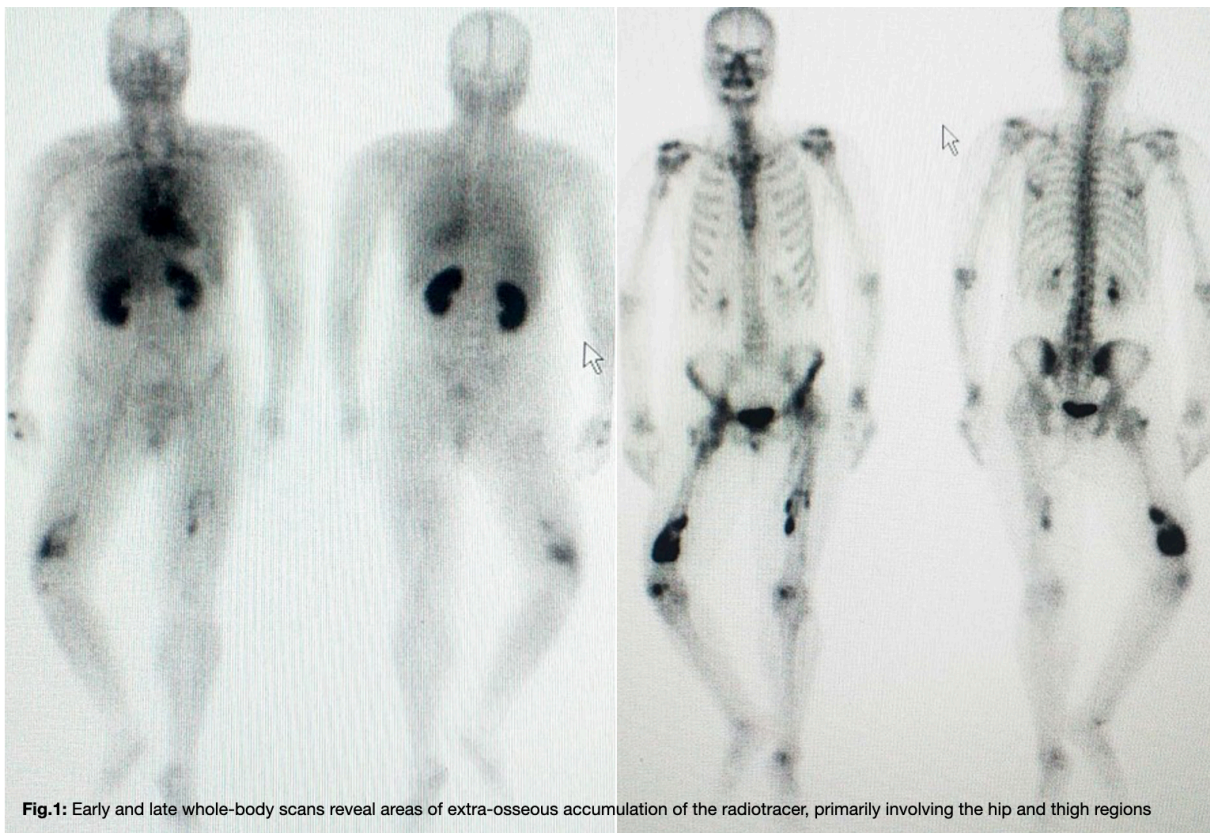


Fig.1: Early and late whole-body scans reveal areas of extra-osseous accumulation of the radiotracer, primarily involving the hip and thigh regions

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

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 mobi-

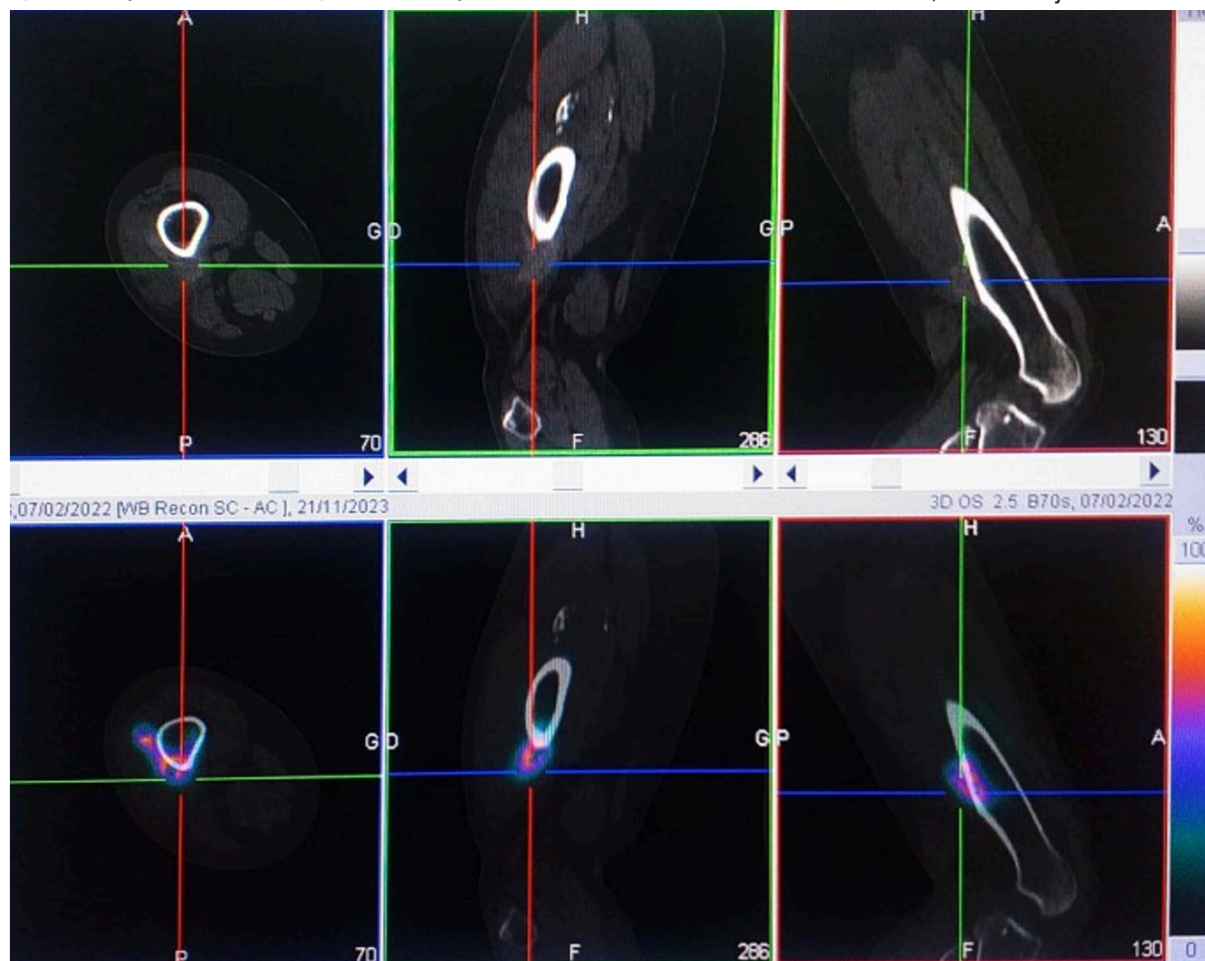


Fig.2: SPECT CT reveals intense hyperuptakes corresponding to early hyperdense lesions on the identification scan sections, indicative of active heterotopic ossifications.

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].

lity, 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

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

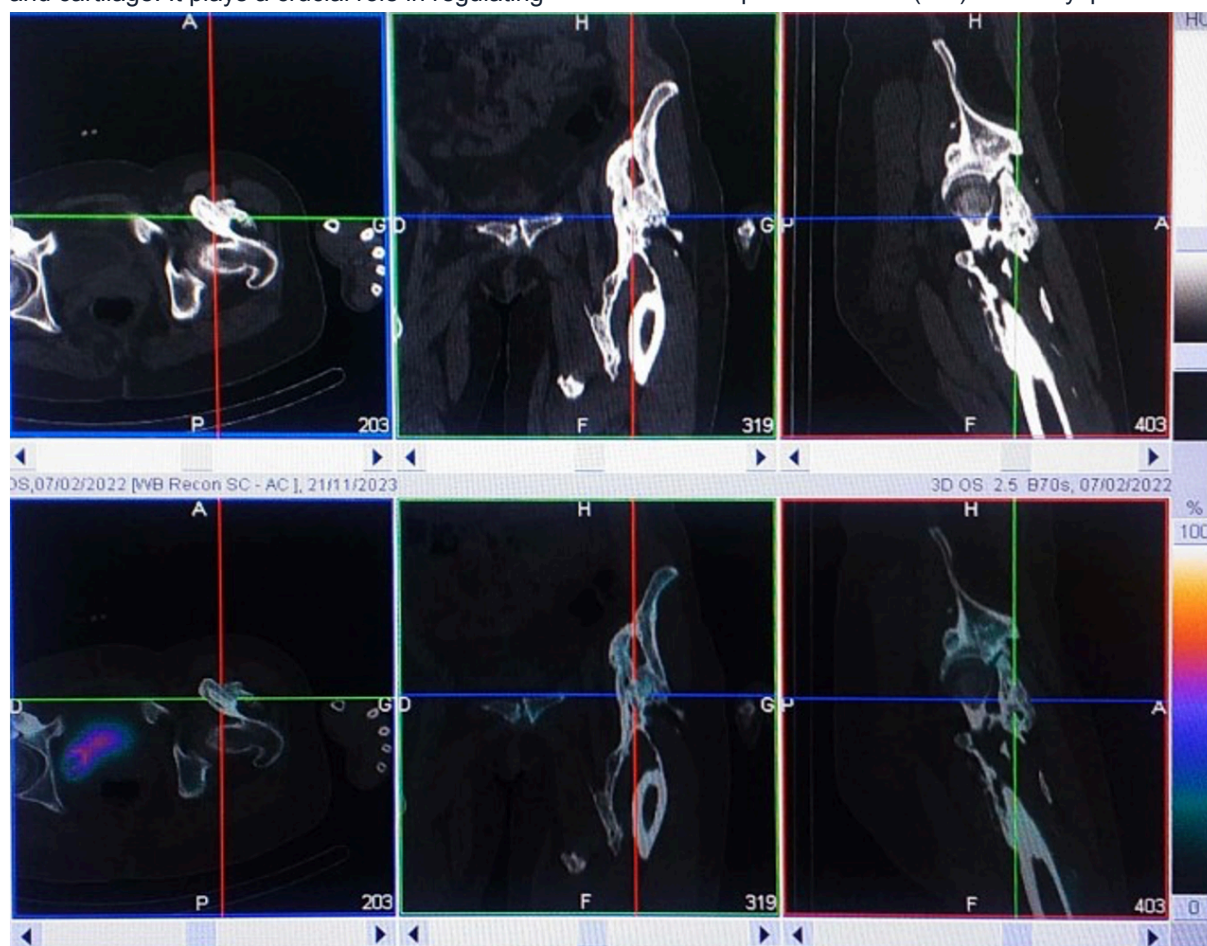


Fig.3: SPECT CT reveals several mature heterotopic ossifications adjacent to the muscular compartments of the hips and thighs, with no uptake of the radiotracer.

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,

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

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 im-

Fibrodysplasia Ossificans Progressiva (FOP)
• Exceptionally rare autosomal dominant disorder • Mutations in the Activin-A-receptor of bone morphogenetic protein • Malformations of the big toes • Gradual formation of extra-skeletal bone in specific anatomical patterns. • Heterotopic ossifications - spontaneously - as consequence of trauma • Median life expectancy: 40 years • Treatment options: only palliative
Tab. 1: Common patterns of FOP [1,2,3].

portant 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 tra-

jectory. 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.

Correspondence to
Sofia Chkikar
Centre Hospitalier Universitaire Hassan II
Fès, Morocco

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.

Disclaimer/Publisher’s Note:
The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of Swiss J. Radiol. Nucl. Med. and/or the editor(s). Swiss J. Radiol. Nucl. Med. and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

References

- 1 Kaplan FS, LeMerrer M, Glaser DL, Pignolo RJ, Goldsby RE, Kitterman JA, et al. Fibrodysplasia ossificans progressiva. Best Pract Res Clin Rheumatol 2008;22:191-205.
- 2 Shore EM, Feldman GJ, Xu M, Kaplan FS. The genetics of fibrodysplasia ossificans progressiva. Clin Rev Bone Miner Metab 2005;3:201-4.
- 3 Kaplan FS, Xu M, Seemann P, Connor JM, Glaser DL, Carroll L, et al. Classic and atypical fibro- dysplasia ossificans progressiva (FOP) pheno- types are caused by mutations in the bone mor- phogenetic protein (BMP) type I receptor ACVR1. Hum Mutat 2009;30:379-90.
- 4 Kitterman JA, Kantanie S, RockeDM, Kaplan FS. Iatrogenic harm caused by diagnostic errors in fibrodysplasia ossificans progressiva. Pediatrics 2005;116:654-61.

- 5** Kaplan FS, Glaser DL. Thoracic insufficiency syndrome in patients with fibrodysplasia ossificans progressiva. *Clin Rev Bone Miner Metab* 2005;3:213-6.
- 6** Kaplan FS, Zasloff MA, Kitterman JA, Shore EM, Hong CC, Rocke DM. Early mortality and cardiorespiratory failure in patients with fibrodysplasia ossificans progressiva. *J Bone Joint Surg Am* 2010;92:686-91.
- 7** Kaplan FS, Al Mukaddam M, Pignolo RJ. A cumulative analogue joint involvement scale for fibrodysplasia ossificans progressiva (FOP). *Bone* 101: 123-128, 2018a.
- 8** Cohen RB, Hahn GV, Tabas J, Peeper J, Levitz CL, Sando A, Zasloff M, Kaplan FS. The natural history of heterotopic ossification in patients who have fibrodysplasia ossificans progressiva. *J Bone Joint Surg Am* 75: 215-219, 1993.
- 9** Pignolo RJ, Bedford-Gay C, Liljestrom M, Durbin-Johnson BP, Shore EM, Rocke DM, Kaplan FS. The natural history of flare-ups in fibrodysplasia ossificans progressiva: a comprehensive global assessment. *J Bone Miner Res* 31:650-656, 2016.
- 10** Zaghloul KA, Heuer GG, Guttenberg MD, Shore EM, Kaplan FS, Storm PB. Lumbar puncture and surgical intervention in a child with undiagnosed fibrodysplasia ossificans progressiva. *J Neurosurg Pediatrics* 1: 91-94, 2008.
- 11** Pignolo RJ, Durbin-Johnson BP, Rocke DM, Kaplan FS. Joint-specific risk of impaired function in fibrodysplasia ossificans progressiva (FOP). *Bone* 109:124-133, 2018.
- 12** Rocke DM, Zasloff M, Peeper J, Cohen RB, Kaplan FS. Age and joint-specific risk of initial heterotopic ossification in patients who have fibrodysplasia ossificans progressiva. *Clin Orthop* 301: 243-248, 1994.
- 13** Schaffer AA, Kaplan FS, Tracy MR, O'Brien ML, Dormans JP, Shore EM, Harland RM, Kusumi K. Developmental anomalies of the cervical spine in patients with fibrodysplasia ossificans progressiva are distinctly different from those in patients with Klippel-Feil syndrome. *Spine* 30: 1379-1385, 2005.
- 14** Kitterman JA, Kantanie S, Rocke DM, Kaplan FS. Iatrogenic harm caused by diagnostic errors in fibrodysplasia ossificans progressiva. *Pediatrics* 2005;116:e65461.
- 15** Chuang TL, Ho KW, Wang YF. A Bizarre bone scan of fibrodysplasia ossificans progressiva. *Clin Nucl Med* 2018;43:4335.
- 16** Tulchinsky M. Diagnostic features of fibrodysplasia (myositis) ossificans progressiva on bone scan. *Clin Nucl Med* 2007;32:6169.
- 17** Pawar SU, Sahoo S, Manglunia A, Tilve GH. Fibrodysplasia ossificans progressiva: A familial presentation. *Indian J Nucl Med* 2015;30:2901.
- 18** Reinig JW, Hill SC, Fang M, Marini J, Zasloff MA. Fibrodysplasia ossificans progressiva: CT appearance. *Radiology* 1986;159:1537.
- 19** Pignolo RJ, Shore EM, Kaplan FS (2013) Fibrodysplasia Ossificans Progressiva: Diagnosis, management, and therapeutic horizons. *Pediatr Endocrinol Rev* 10: 437-448 Link.