Fibrodysplasia Ossificans Progressiva – A Rare Genetic Disorder and the Role of Technetium-99m Methylene Diphosphonate Bone Scan

Nitin Gupta, Ankur Pruthi[1], Suneel Kumar, Ritu Verma, Ethel Shangne Belho

Department of Nuclear Medicine and PET/CT, Mahajan Imaging Centre, Sir Ganga Ram Hospital, [1]Department of Nuclear Medicine, Manipal Hospital, New Delhi, India

Abstract

Fibrodysplasia ossificans progressiva is a rare genetic disease believed to occur in approximately 1 in 2 million people worldwide and is characterized by progressive extraosseous ossification over the course of a lifetime in an inevitable and unpredictable episodic manner, with most patients being confined to a wheelchair by the third decade of life and requiring life-long care. The extraosseous calcification involves ligaments, tendons, muscles, and connective tissue leading to severe restriction of movements. Another hallmark of this condition is abnormal great toes. The diagnosis is often made on clinical and radiological examination, but Technetium-99m methylene diphosphonate (Tc-99m MDP) bone scan is usually indicated to determine the extent of the disease. We hereby present a case series comprising of four patients suffering from this debilitating illness who underwent Tc99m MDP bone scan for initial diagnosis and localizing sites of heterotopic ossification.

Keywords: *Extraosseous calcification, fibrodysplasia ossificans progressiva, heterotopic bone formation, myositis ossificans progressiva, progressive ossifying myositis, single-photon emission computed tomography-computed tomography, technetium-99m methylene diphosphonate bone scan*

Introduction

Fibrodysplasia ossificans progressiva (FOP), a rare autosomal dominant genetic disease, characterized by heterotopic bone formation involving ligaments, tendons, muscles, fascia, and connective tissue leading to severe restriction of movements and hallux valgus. In the first decade of life, painful soft-tissue swellings are precipitated by falls, fatigue, intramuscular injections, or soft-tissue injury. The inevitable progression of disability is seen, and most patients are confined to a wheelchair by the age of 30 years.

There are high chances of misdiagnosis in FOP, leading to inappropriate investigations. However, characteristic bone scan findings of extraosseous ossification, combined with hallux valgus can help to reach the diagnosis.

Technetium-99m methylene diphosphonate (Tc-99m MDP) concentration in normal tissues is proportional to their calcium content. Extraosseous bone-producing disorders have an affinity for Tc-99m MDP like that of normal bone. MDP acts as a ligand adsorbing onto tissue calcium, localizing the Tc-99m in the mineral phase. MDP bone scan helps in scanning the whole body. It is easily available and has better sensitivity as compared to other conventional modalities such as X-ray. In patients with this rare disease, bone scan helps in screening the entire skeleton, assessing the extent of disease, localize the site of extraosseous calcification, not apparent clinically.

The recent advancements in nuclear imaging such as newer single-photon emission computed tomography-computed tomography (SPECT-CT) scanners, which provide a hybrid of cross-sectional functional and anatomical imaging, are rapidly replacing the conventional planar gamma cameras in nuclear medicine centers across the world. SPECT-CT imaging can play a vital role in the evaluation of this rare disease as it can provide better anatomical information for both osseous and extraosseous sites of disease involvement.

Cases Reports

Here, we present clinical, radiological, and Tc-99m MDP bone scan findings of four patients suffering from FOP. In one patient,

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Address for correspondence:
Dr. Nitin Gupta, Department of Nuclear Medicine and PET/CT, Mahajan Imaging Centre, Sir Ganga Ram Hospital, New Delhi, India.
E-mail: drnitingpt@gmail.com

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contrast-enhanced CT (CECT) was already done before bone scan. In one patient, we did noncontrast CT (NCCT) scan apart from the bone scan.

Case 1

A 14-year-old female child presented with swelling over the left side of neck, gradually progressive and associated with restriction of neck movements. CECT scan of the neck was suggestive of large ossification and calcification in the left paraspinal muscles, and similar calcifications were seen in the left pectoralis minor muscle and upper intercostal muscles. On further clinical examination, hallux valgus was seen, thus, raising suspicion of FOP. Subsequently, the patient was referred for Tc-99m MDP bone scan to determine the extent of extraosseous ossification. Bone scan findings were suggestive of increased extraosseous MDP uptake around the left periscapular region and around the right distal tibia, suggestive of extraosseous ossification [Figure 1].

Case 2

A 7-year-old male child, presented with painful swelling over left scapula and left upper chest, associated with restricted movements of bilateral upper limbs for 2 months. On clinical examination, painful and tender swellings were observed over neck and left shoulder and pathognomic feature of FOP, i.e., hallux valgus was also noticed. The patient was referred for three-phase Tc-99m MDP bone scan, which provides information regarding perfusion, blood pool, and osteoblastic activity. The bone scan was suggestive of extraosseous increased soft-tissue tracer uptake in the neck posteriorly, around the left shoulder joint and left scapula and within the erector spinae muscles at the level of L3-L4 vertebrae [Figure 2a]. NCCT images show soft-tissue calcifications and areas of neo-osteogenesis within the aforementioned areas [Figure 2b].

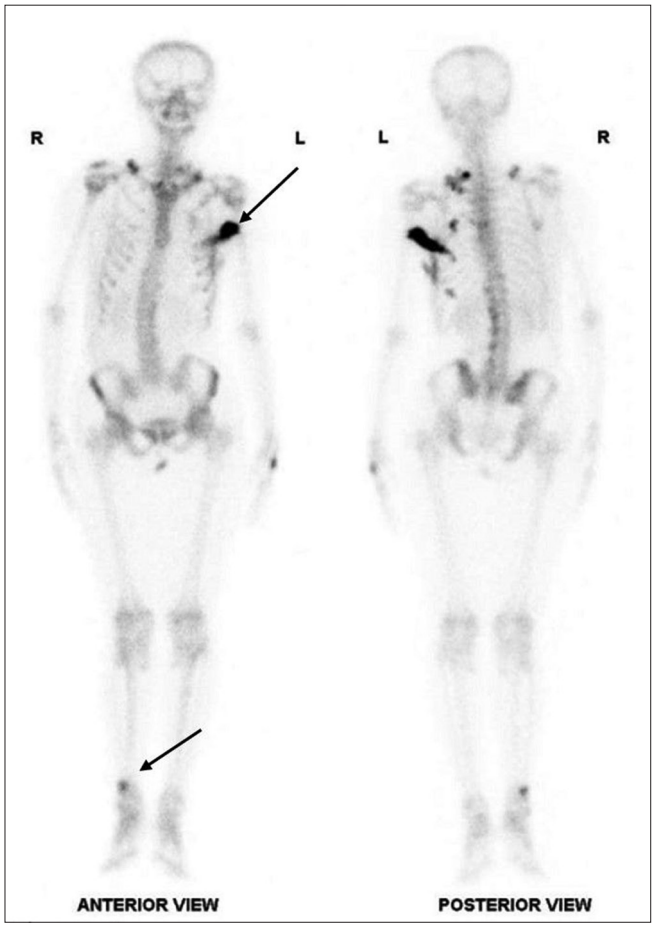

Figure 1: Whole-body methylene diphosphonate bone scan images of case 1, with abnormal intensely increased extraosseous tracer uptake around the left periscapular region and around the right distal tibia

Case 3

An 11-year-old female child presented with progressive stiffness in major joints. Physical examination confirmed hallux valgus, the common finding in patients of FOP. Bone scan findings were suggestive of increased MDP uptake in the bilateral major joints of the body [Figure 3], correlating with clinical findings of stiffness.

Case 4

A 4-year-old male child, with a history of stiffness around bilateral shoulder joints and hallux valgus, with suspicion of FOP, was referred to us for Tc-99m MDP bone scan to determine the extent of heterotopic ossification. Bone scan findings revealed focal area of extraosseous MDP uptake inferior to inferior angle of the left scapula [Figure 4a] suggestive of heterotopic ossification. The patient was again referred for follow-up bone scan after 6 years with no history of new swelling. Follow-up Tc-99m MDP bone scan was suggestive of extraosseous MDP uptake inferior to inferior angle of bilateral scapulae [Figure 4b] suggestive of disease progression.

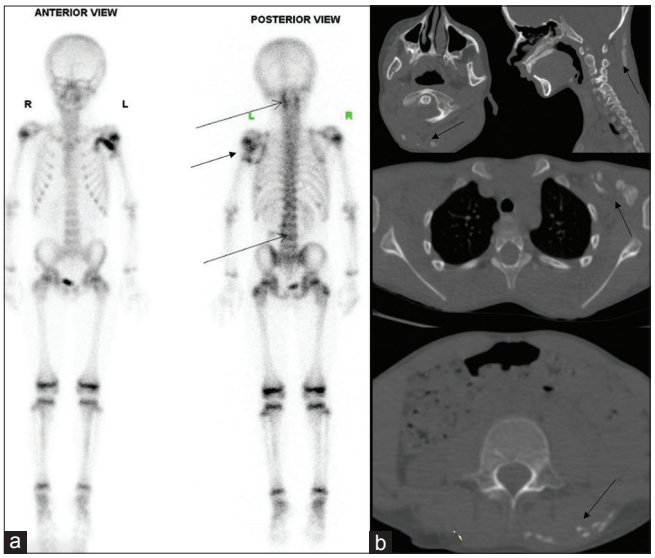

Figure 2: (a) Whole-body methylene diphosphonate bone scan images of case 2, with extraosseous increased soft-tissue tracer uptake in the neck posteriorly, around left shoulder joint and left scapula and within the erector spinae muscles at the level of L3-L4 vertebrae. Low dose Noncontrast computed tomography images (b) show soft-tissue calcifications and areas of neo-osteogenesis, corresponding to sites of increased methylene diphosphonate uptake in bone scan

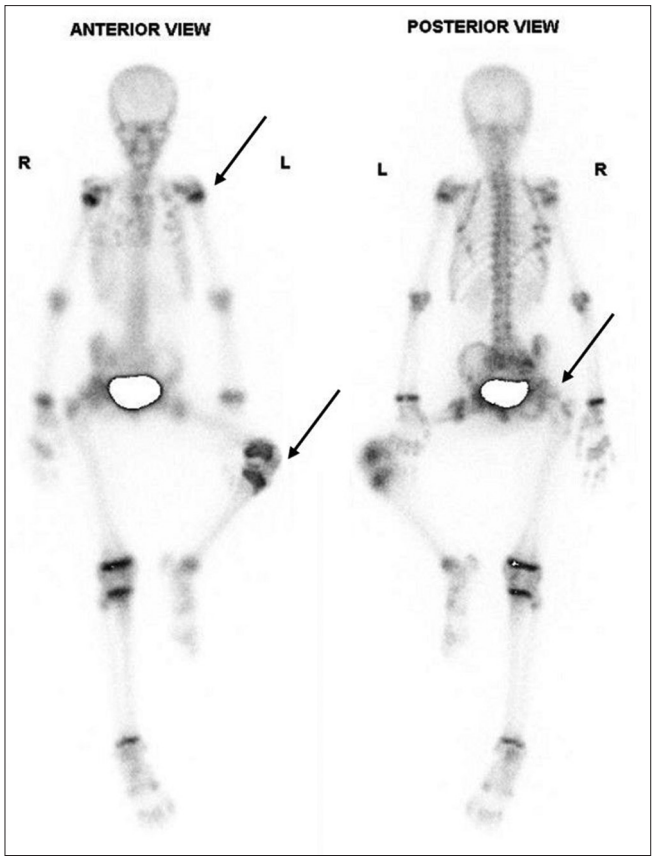

Figure 3: Whole-body methylene diphosphonate bone scan images of case 3, with abnormal increased methylene diphosphonate uptake in the bilateral major joints of the body

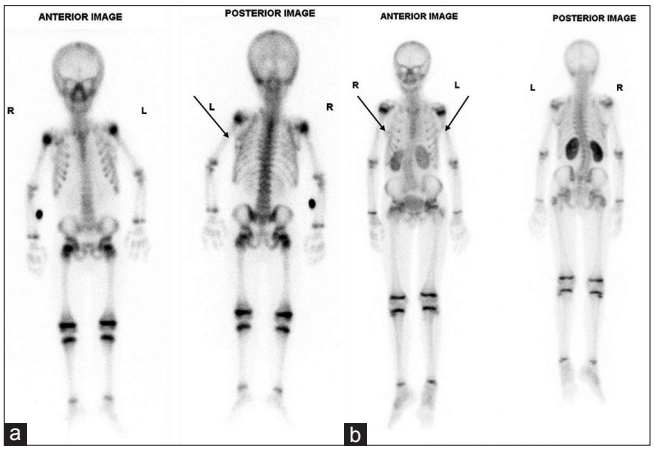

Figure 4: (a) Whole-body methylene diphosphonate bone scan of case 4, with focal area of extraosseous methylene diphosphonate uptake inferior to inferior angle of the left scapula, suggestive of heterotopic ossification. Follow-up methylene diphosphonate bone scan (b), after 6 years, with extraosseous methylene diphosphonate uptake inferior to inferior angle of bilateral scapulae

Discussion

FOP is a rare and debilitating disease. It was first described, by Guy Pating in 1962, about a woman turning into wood.[1] The prevalence of FOP is approximately 1 in 2 million.[2] The disease is caused by mutations in the ACVR1 gene. The ACVR1 gene provides instructions for producing a member of a protein family called bone morphogenetic protein type I receptors. Overexpression of this potent bone inducing morphogen in lymphocytes is associated with the disabling ectopic osteogenesis of FOP.[3] This condition is inherited in an autosomal dominant pattern. Most cases of FOP result from new mutations in the gene. In a small number of cases, an affected person has inherited the mutation from one affected parent.

The usual presenting complaint in this rare disorder is soft-tissue swelling after minor trauma. The common sites are upper paraspinal muscles or the pelvic girdle.[4] On general physical examination, abnormal great toe, i.e., hallux valgus is almost invariably present in all patients.[5] Progression leads to restriction of daily life activities, and most of the patients are wheelchair bound by the third decade of life.[6] The diaphragm, tongue, extraocular muscles, cardiac muscle, and smooth muscles are however spared from heterotopic ossification. The diagnosis is based on the general physical examination (clinical), radiological (CT scan), and Tc-99m MDP bone scan findings. The differential diagnosis includes progressive osseous heteroplasia, soft-tissue sarcoma, desmoid tumors, aggressive juvenile fibromatosis, and nonhereditary (acquired) heterotopic ossification.

Tc99m MDP bone scan demonstrates sites of heterotopic ossification at early stage, and it can also help to determine the extent of the disease. Being a whole-body examination, it has an advantage over other conventional imaging modalities, for example, CT scan with much lesser radiation exposure. Follow-up scans can help in finding new sites of extraosseous ossification.[7] Various cases have been reported in literature describing the role of Tc-99m MDP bone scan in FOP[8-10] Here, we have discussed four cases where Tc-99m MDP bone scan helped in assessing the extent of extraosseous ossification. On follow-up one patient had no new lesion clinically over a period of 6 years, thus was referred for bone scan to assess any new sites of heterotrophic ossification. Early diagnosis prevents catastrophic harmful diagnostic and treatment procedures. The bone scan also helps in excluding other differential diagnoses such as fibrous dysplasia, infections, and tumors.

Latest advances in nuclear imaging such as SPECT-CT hybrid imaging combines both functional information from SPECT and anatomical information from NCCT scan. SPECT CT scan helps in better localization of the radiotracer uptake at osseous and extraosseous sites. In addition, Tc-99m MDP SPECT-CT scan provides an accurate anatomic location of a preosseous lesion, which is seen as swelling and edema of the muscular fascial planes and swelling of muscular bundles.[11] Typical anomalies of the cervical spine in FOP such as large posterior elements, tall narrow vertebral bodies, and fusion of the facet joints between cervical vertebrae are better

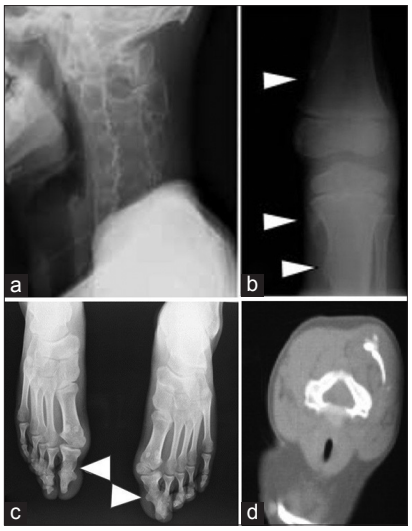

Figure 5: Typical radiological findings of fibrodysplasia ossificans progressiva. Lateral cervical spine radiograph (a) showing expansion of posterior elements with ossification and bony fusion. Antero-posterior radiograph of the knee (b), showing small sessile distal femoral and proximal medial tibial osteochondromas. Radiography of the feet (c) showing bilateral hallux valgus, congenital malformation as a hallmark of FOP. CT scan (d) showing soft tissue ossification in paravertebral soft tissue masses

visualized with SPECT-CT imaging.[12] Malformation of the great toes, thumbs, cervical spine, and proximal femurs, along with the presence of proximal medial tibial osteochondromas, can almost confirm the diagnosis of FOP [Figure 5].[13] Whereas, Tc-99m MDP planar bone scan can provide a differential diagnosis in such cases, a Tc-99m MDP SPECT-CT scan can conclusively diagnose FOP. The definitive diagnosis of FOP can be made by the simple clinical evaluation that associates rapidly appearing soft-tissue lesions with malformations of the great toes and correlating with radiological and scintigraphy findings.

The limitations of Tc-99m MDP SPECT CT scan include longer acquisition times, lesser availability and higher radiation exposure compared to a planar MDP bone scan. However, whenever available, TC-99m MDP SPECT-CT scan has the potential to be an investigation of choice for confirming the diagnosis of FOP and evaluating the extent/progression of the disease.

Conclusion

Tc-99m MDP bone scan plays an important role in diagnosis, extent evaluation and prognosis assessment of this rare disabling condition, i.e., FOP. Latest advancements in the form of hybrid imaging, for example, Tc-99m MDP SPECT-CT scan has the potential to become investigation of choice for this rare disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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