Unusual Presentation of Fibrous Dysplasia in an Elderly Patient

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ABSTRACT

Fibrous Dysplasia is a benign fibro-osseous lesion occurring throughout the skeletal system with a predilection for craniofacial bones, long bones, and ribs. Fibrous dysplasia develops during bone formation and growth with a variable natural evolution. It is considered a genetic nonheritable disease resulting from missense mutations that occur postzygotically in the GNAS1 gene. This mutation leads to a focal congenital failure of proper bone formation and arrest at the woven bone stage. In turn, this leads to a decreased mechanical strength, causing bone pain, pathological fractures, and skeletal deformities. Besides clinical examination, fibrous dysplasia is diagnosed based on the results of radiographic imaging and the microscopic histopathological findings. On CT scan, fibrous dysplasia shows the characteristic "Ground-glass" appearance with well-defined borders. On MRI, fibrous dysplasia has a low signal intensity on T1-weighted MRI and variable signal intensity on T2-weighted MRI. We hereby report a case of an unusual presentation of fibrous dysplasia in a 67-year-old female presenting to the emergency department with generalized malaise and lower limb pain. Fibrous dysplasia may present in the elderly population and can be difficult to differentiate from other malignant and benign lesions affecting the skeletal system.

CASE REPORT

A 67-year-old female, a known case of diabetes mellitus for 10 years, hypertension, dyslipidemia, and ischemic heart disease with no known allergies or recent history of infection. The patient had morbid obesity (BMI=47 kg/m²) and osteoarthritis with a limited mobility. The patient was complaining for one month of abdominal/flank pain, generalized malaise, fullness, and lower limbs pain with a subjective weight loss and decreased oral intake.

The patient, however, did not have any shortness of breath, cough, sore throat/runny nose, or hemoptysis. Radiological imaging including; plain radiographs, CT scan, and MRI, were done at another hospital which showed a large bony lesion in the right superior iliac crest. The patient was advised to have a biopsy of the bony lesion. However, she
refused and signed a discharge against medical advice (DAMA) consent, and then came for follow-up to our hospital. The patient was referred to orthopedic oncology services.

Routine biochemical investigations were performed during the initial presentation to the emergency department, and they included hematology and tumor markers; such as Alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen (CA-125), and cancer antigen (CA 19.9). All biochemical investigations and tumor markers were within normal limits.

**Radiological Data**

The anteroposterior pelvic radiograph showed a large, expansile lesion with calcification and internal seption at the right iliac bone (Figure 1). The abdominal and pelvis CT was performed to assess the large right iliac mass lesion. It showed an expansile mass lesion at the right iliac bone measuring about 11.6 x 12.8 x 8 cm (Figure 2). The pelvis MRI showed a mass with well-defined borders which had no medullary or cortical continuation. No other associated soft tissue masses were noted (Figure 3). Given the age of the patient, location of the lesion, and the radiological appearance, the diagnostic considerations of this lesion included; plasmacytoma, giant cell tumor, and chondromyxoid fibroma.

Upon taking the informed consent of the patient, an ultrasound-guided biopsy of the right pelvic mass was performed. The procedure was performed under aseptic technique. Using coaxial technique, three passes of 16-gauge and seven passes of 18-gauge core biopsy were obtained and sent fresh and in formalin to the pathology department.

**Pathology Results**

Multiple needle core biopsies were microscopically examined. They revealed curvilinear trabeculae of woven bone within bland fibrous tissue (Figure 4).

The differential diagnosis of low-grade medullary osteosarcoma was ruled out based on MDM2 (Murine Double Minute 2) amplification study. This was carried out using a fluorescence in situ hybridization (FISH) analysis for MDM2 gene amplification status on a paraffin-embedded tissue block using differentially-labeled fluorescent probes targeting the MDM2 gene and the chromosome 12 centromere (CEP12). The targeted cells were evaluated from regions of tumor identified on histopathologic review of a matching hematoxylin and eosin-stained section. The MDM2 amplification came as negative (normal) with an MDM2/CEP12 ratio of 1.1. The average MDM2 signal number per cell was 1.8. The presence of MDM2 amplification (MDM2/CEP12 ratio of ≥ 2.0) is useful for distinguishing osteosarcomas from fibrous lesions. MDM2 amplification (MDM2/CEP12 ratio of 2.0 or greater) is observed in a variety of tumor types.

Since the histomorphology was highly suggestive of fibrous dysplasia, further confirmatory PCR-based DNA sequencing for GNAS mutation limited to exon 8 (including mutation hot spot codon 201) and exon 9 (including mutation hot spot codon 227) of the GNAS gene was performed.

A mutation was detected in codon 201 (CGT to TGT) in exon 8 of the GNAS gene, that changes the encoding amino acid from Arg to Cys (R201C). The Standardized nomenclature for this mutation is “NM_000516: c.601C>T p.Arg201Cys”. As such, the final diagnosis of fibrous dysplasia was rendered. It is noteworthy to mention that absence of the GNAS mutation does not essentially rule out fibrous dysplasia as this may occur in tumor mosaicism. In spite of the low sensitivity of the PCR-based DNA sequencing for GNAS, presence of the GNAS mutation can be utilized as a complementary diagnostic tool to detect such mutations that are specific to fibrous dysplasia.

**Outcome and Follow-Up:**

Further interval radiological studies up to 36 months - which included a plain radiograph (Figure 5), pelvis CT (Figure 6), and pelvis MRI (Figure 7) - showed no significant change. The overall morphology and size appeared unchanged upon comparison to the previous radiological studies. Subsequent management included reassurance and observation with annual clinical assessments.

**DISCUSSION**

**Etiology & Demographics:**

Fibrous Dysplasia is a benign fibro-osseous lesion occurring throughout the skeletal system with a predilection for craniofacial bones, long bones, and ribs which develops during bone formation and growth with a variable natural evolution. Fibrous dysplasia can be monostotic [involving one bone] or polyostotic [involving several bones]. The vast majority of cases of fibrous dysplasia are asymptomatic, monostotic lesions that are identified incidentally and managed conservatively by patient education and observation [1].

Increased incidence of fibrous dysplasia has been noted in patients with McCune-Albright syndrome, a genetic disorder constituting: skin pigmentation, polyostotic fibrous dysplasia, and multiple endocrine dysregulations. At the cellular level, patients diagnosed with McCune-Albright syndrome have an increased activation of adenylate cyclase, leading to a marked cell proliferation and inappropriate cell differentiation. Consequently, a disorganized fibrotic bone matrix is excessively produced, resulting in polyostotic fibrous dysplasia [1].

Fibrous dysplasia presents at any age during childhood and adulthood, with the majority of cases being detected by the age of 30 years. Worldwide, it affects all racial groups with no gender predilection [1,2]. Fibrous dysplasia is a genetic nonheritable disease resulting from missense mutations that occur postzygotically in the GNAS1 gene which codes the alpha subunit of the G stimulatory protein, Gs [3]. This mutation leads to a focal congenital failure of proper bone formation and arrest at the woven bone stage. In turn, this leads to a decreased mechanical strength, causing bone pain, pathological fractures, and skeletal deformities [4].
Clinical & Imaging findings:
Traditionally, fibrous dysplasia has been considered a disease of childhood, since most symptoms develop within the first two decades of life. After puberty, the dysplastic expansion noted in fibrous dysplasia tends to become quiescent in 60-80% of the patients. Enlargement of the lesion, however, is still unpredictable and has been reported throughout the seventh decade [5].

The most common presenting symptom noted clinically is an asymmetry of the face caused by a painless enlargement of the craniofacial bones. In long bones, fibrous dysplasia might present as limb pain, malformation of the extremities, or pathological fractures. Furthermore, upon exerting a direct pressure on a neural/cranial nerve foramen or distorting a bony cavity, proptosis, strabismus, tinnitus, facial paralysis might occur [6].

Besides clinical examination, fibrous dysplasia is diagnosed based on the results of radiographic imaging and the microscopic histopathological findings. Radiologically, the appearance varies with the stage of the lesion and the amount of bony matrix involved. In the early stages, the lesion is well-defined and more radiolucent. Whereas, in the later stages, the lesion becomes more radiopaque [6]. An 8-year-retrospective study which investigated the radiological findings of 14 cases of fibrous dysplasia concluded that the most common radiological sign is “ground-glass” appearance followed by “orange-peel” appearance [7].

Osteofibrous dysplasia appears histologically different from fibrous dysplasia. The location of the lesion in osteofibrous dysplasia almost always involves the tibia or the fibula with most cases being diagnosed in the first decade of life. Radiologically, osteofibrous dysplasia tends to demonstrate lytic lesions of the proximal tibia. The lesion in osteofibrous dysplasia tends to be intracortical as opposed to medullary in fibrous dysplasia. Given the age of the patient in the present case and the location of the lesion, osteofibrous dysplasia was ruled out.

Treatment & Prognosis:
Although fibrous dysplasia is considered benign with a good prognosis, malignant transformation rarely occurs in less than 1% of all cases. Most fibrous dysplasia malignancies are osteosarcomas arising from craniofacial and monostotic lesions. Radiographically, the most common feature for malignant transformation is the extension of the lesion throughout the bony cortex within the surrounding soft tissue. Therefore, clinicians should keep high index of suspicion for malignancy in any lesion that is rapidly growing, painful, and associated with a rise in serum alkaline phosphatase (ALP) [8-10].

Management of fibrous dysplasia can be divided into: observation/conservative management, medical therapy, and surgical therapy (radical excision with remodeling). Surgical treatment options aim to control pain, reduce bony deformities, and prevent pathological fractures from occurring. Surgical procedures are usually postponed until puberty, hoping that the bony lesion might undergo remission [6]. Medical treatment, on the other hand, may include the use of bisphosphonates to reduce pain, decrease fracture rates, and improve function in patients diagnosed with symptomatic, polyostotic fibrous dysplasia [1].

Differential Diagnoses:
Given the age of the patient, location of the lesion, and the radiological appearance of the lesion, the differential diagnoses of fibrous dysplasia include: plasmacytoma, giant cell tumor, and chondromyxoid fibroma:

Plasmacytoma:
Solitary plasmacytoma tends to affect people older than 40 years of age. Patients might present with pain at the affected bone or back pain, if there is involvement of the vertebrae. Plasmacytoma can present as an expansile lytic lesion with aggressive features, such as cortical breakthrough with extra osseous soft tissue.

On plain radiography, plasmacytomas may demonstrate “punched-out” lytic lesions with well-defined borders. On CT scans, plasmacytoma may show subtle lytic lesions that are expansile with cortical breakthrough that might not be visible on plain radiographs. CT features of solitary pelvic plasmacytoma can be divided into: multilocular type, unilocular type and complete osteolytic destruction.

On MRI, plasmacytoma usually demonstrates low T1 signal intensity and high T2 signal intensity. It may show homogenous enhancement and is usually multilocular in appearance. Plasmacytoma usually shows a linear low signal intensity in the soft tissue mass or dark signal of the bone cortex around the mass.

Giant Cell Tumor:
Clinically, giant cell tumors may present with pathological fractures at the site of bony involvement. Decreased range of motion and swelling might be noted at the affected limb. On plain radiographs, the lesion is usually osteolytic, radiolucent, expansile, and eccentrically-located. Giant cell tumors may demonstrate the “soap-bubble” appearance.

On CT scans, giant cell tumor is usually subarticular and eccentric in location. Giant cell tumors tend to be expansile with non-sclerotic margins. The tumor usually demonstrates soft tissue attenuation that may contain foci of hemorrhage or necrosis represented by low attenuation. On MRI, giant cell tumors tend to have heterogenous signal intensities in both T1 and T2. On T2-weighted MRI, low to intermediate heterogeneous signal intensities are usually noted in solid areas of the tumor.

Chondromyxoid Fibroma:
Chondromyxoid fibromas may present with a limited range of motion and chronic, progressive pain in the affected limb. Rarely, pathological fractures may occur. On plain radiographs, chondromyxoid fibromas may demonstrate well-defined, radiolucent and lobulated eccentric bony lesions. On CT, chondromyxoid fibroma may contain calcifications in the lesion that are not readily apparent on plain radiography. CT
scans are best for detecting sclerotic margins and lesion’s
cortical integrity.

On MRI, peripheral nodular enhancement might be seen
in the majority of cases upon gadolinium administration.
Chondromyxoid fibroma demonstrates low signal intensity on
T1-weighted MRI and high signal intensity on T2-weighted
MRI.

TEACHING POINT
Fibrous dysplasia may present in the elderly population and
can be difficult to differentiate from other malignant and
benign lesions affecting the skeletal system. The bony lesion
tends to appear well-circumscribed with no periosteal reaction.
Serial follow-up assessments may be required to detect
possible malignant transformation of fibrous dysplasia.

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Figure 1: A 67-year-old female with fibrous dysplasia in the
pelvis.
Findings: Anteroposterior pelvic radiograph showing a well-
circumscribed lesion with peripheral and internal calcification,
projecting over the right iliac bone. No periosteal reaction or
cortical breakthrough are noted. The adjacent structures appear
intact.
Technique: kVp 80, mA 320, mAs 38, pelvis AP.
Figure 2: A 67-year-old female with fibrous dysplasia in the pelvis.
Findings: (a) Axial CT scan at initial presentation. (b) Coronal CT scan at initial presentation. (c) Sagittal CT scan at initial presentation. (a), (b), & (c) CT scan of the pelvis with and without IV contrast, showing a large, expansile bony lesion originating from the right iliac bone. The bony lesion is measuring 11.6 x 12.8 x 8 cm. There are well-circumscribed calcified margins with areas of internal calcification. No cortical or medullary continuation are noted. The lesion is showing heterogenous densities with areas of septation. There are no associated soft tissue mass lesions noted. The acetabulum appears spared.
Technique: (a) Axial CT, without contrast, kVp 110, 217 mA, 1.2 mm slice thickness. (b) Coronal CT, 3 mm slice thickness, kVp 120, mA 349, Xenetix 100 ml IV. (c) Sagittal CT, 3 mm slice thickness, kVp 120, ma 349, Xenetix 100 ml IV. Contrast venous phase 90 seconds after contrast.

Figure 3: A 67-year-old female with fibrous dysplasia in the pelvis.
Findings: (a) Axial T1-weighted MRI of the pelvis, showing an expansile non-aggressive bony lesion in the right iliac bone with intermediate T1 signal intensity. (b) Axial T2-weighted MRI with fat saturation, showing a heterogenous, predominant high T2 signal intensity. (c) & (d) Axial and coronal T1-weighted MRI with fat saturation after IV gadolinium administration, showing diffuse enhancement.
Technique: (a) Axial T1, TR 566, TE 20, slice spacing 5.579, machine 3 Tesla Philips Ingenia, 1.5 Tesla. (b) T2-weighted SPAIR, TR 4664, TE 80, slice thickness 4.45, 1.5 Tesla (c) Axial T1 post gad: Dotarem 0.2 ml/kg, TR 653.7, TE 20, slice thickness 4.559. (d) T1 post gad: Dotarem 0.2 ml/kg, TR 697.7, TE 20, slice thickness 4, 1.5 Tesla.

Figure 4: A 67-year-old female with fibrous dysplasia in the pelvis.
Findings: (a) & (b) A bland fibro-osseous lesion is seen. The osseous component appears as spicules and trabeculae of woven bone with no osteoblastic rimming. The fibrous component lacks significant cytologic atypia or mitotic activity.
Technique: (a) Paraffin-embedded/Formalin-fixed Hematoxylin & Eosin-stained section at intermediate power (8x). (b) Paraffin-embedded/Formalin-fixed Hematoxylin & Eosin-stained section at high power (30x).
Musculoskeletal Radiology: Unusual Presentation of Fibrous Dysplasia in an Elderly Patient

Alkhairaby et al.

Figure 5 (left): A 67-year-old female with fibrous dysplasia in the pelvis. Findings: The anteroposterior pelvic radiograph re-demonstrated the large, expansile lesion with internal septation at the right iliac bone with no significant interval changes. No periosteal reaction or cortical breakthrough are noted. The adjacent structures appear intact. Technique: kVp 80, mA 320, mAs 32, pelvis AP.

Figure 6: A 67-year-old female with fibrous dysplasia in the pelvis. Findings: (a) axial CT scan. (b) coronal CT scan. A pelvis CT scan with and without IV contrast, re-demonstrating a large, expansile bony lesion originating from the right iliac bone. The bony lesion is measuring 11.6 x 12.8 x 8 cm. There are well-circumscribed calcified margins with some internal calcification. No cortical or medullary continuation are noted. The lesion is showing heterogeneous densities with areas of septation. No associated soft tissue mass lesions are noted. The acetabulum appears spared. Technique: (a) Axial CT, with IV contrast, kVp 120, mA 413, 1.2 mm slice thickness, Xenetix 100 ml IV, GE Medical System, Light Speed VCT. (b) Coronal CT, 3 mm slice thickness, kVp 120, mA 413, Xenetix 100 ml IV, 1.2 mm slice thickness. Contrast venous phase 90 seconds after contrast.
Etiology | Missense mutations that occur postzygotically in the GNAS1 gene which codes the alpha subunit of the G stimulatory protein, Gs.
---|---
Incidence | The true incidence is unknown. However, it is estimated to be 5-7% of all benign bone tumors.
Gender predilection | F=M.
Age predilection | Second decade.
Risk factors | Unknown.
Treatment | Observation/conservative management, medical therapy, and surgical therapy.
Prognosis | Good, malignant transformation occurs rarely (<1%).
Findings on imaging | XR: Well-circumscribed lesion with no periosteal reaction. CT: Ground-glass appearance and well-defined borders. MRI: Low signal intensity on T1-weighted and variable signal intensity on T2-weighted sequences.

Table 1: Summary table of Fibrous Dysplasia.
Unlike presentation of fibrous dysplasia in an elderly patient

<table>
<thead>
<tr>
<th>Differential Diagnoses</th>
<th>Clinical History</th>
<th>Plain Radiograph Findings</th>
<th>CT Findings</th>
<th>MRI Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrous dysplasia</td>
<td>• Asymptomatic.</td>
<td>• Well-circumscribed lesions.</td>
<td>• “Ground-glass” appearance.</td>
<td>• Low signal intensity on T1-weighted MRI.</td>
</tr>
<tr>
<td></td>
<td>• Facial asymmetry/paralysis.</td>
<td>• No periosteal reactions.</td>
<td>• Well-defined borders.</td>
<td>• Variable signal intensity on T2-weighted MRI.</td>
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<td>• Limb pain.</td>
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<td></td>
<td>• Pathological fractures.</td>
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<td>• Proptosis.</td>
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<td>• Strabismus.</td>
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<tr>
<td>Plasmacytoma</td>
<td>• Pain at the affected bone.</td>
<td>• “Punched out” lytic lesions.</td>
<td>• Subtle lytic lesions.</td>
<td>• Low T1 signal intensity.</td>
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<tr>
<td></td>
<td></td>
<td>• Well-defined borders.</td>
<td>• Expand.</td>
<td>• High T2 signal intensity.</td>
</tr>
<tr>
<td>Giant cell tumor</td>
<td>• Pathological fractures at the site of bony involvement.</td>
<td>• Radiolucent osteolytic lesions.</td>
<td>• Subarticular and eccentric in location.</td>
<td>• Homogenous enhancement.</td>
</tr>
<tr>
<td></td>
<td>• Decreased range of motion.</td>
<td>• Expand.</td>
<td>• Expand with non-sclerotic margins.</td>
<td>• Multilocular.</td>
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<td></td>
<td>• Swelling might be noted at the affected limb.</td>
<td>• Eccentrically-located.</td>
<td>• Soft tissue attenuation that may contain foci hemorrhage or necrosis represented by low attenuation.</td>
<td></td>
</tr>
<tr>
<td>Chondromyxoid fibroma</td>
<td>• Limited range of motion.</td>
<td>• Soap-bubble appearance.</td>
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<td></td>
<td>• Chronic, progressive pain in the affected limb.</td>
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<td>• Rarely, pathological fractures may occur.</td>
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Table 2: Differential diagnoses table for Fibrous Dysplasia.

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**ABBREVIATIONS**

AP = Anteroposterior
CEP12 = Centromeric Probe to Chromosome 12
CT = Computed Tomography
H & E = Hematoxylin and Eosin
MDM2 = Murine Double minute 2 homolog
MRI = Magnetic Resonance Imaging
PCR = Polymerase Chain Reaction

**KEYWORDS**

Fibrous Dysplasia; Fibro-osseous; FD; GNAS; Fibrocartilagenous dysplasia; monostotic; polyostotic; MRI

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