Case report

Journal of Orthopedic Education
Volume 7 Number 1, January – June 2021
DOI: http:// dx.doi.org/10.21088/joe.2454.7956.7121.3

A Rare Case Report of Fibrous Dysplasia of Femur

[1]R B Uppin, [2]S K Saidapur, [3]G S Revanth, [4]Nishant, [5]Umar, [6]Rajkiran

How to cite this article:
R B Uppin, S K Saidapur, G S Revanth, Nishant, Umar, Rajkiran, A Rare Case Report of Fibrous Dysplasia of Femur. J orth. Edu. 2021;7(1):23–28.

Author's Affiliations: [1-6]Department of Orthopedics, KLE Academy of Higher Education & Research, Jawaharlal Nehru Medical College & Dr Prabahkar Kore Hospital & MRC, Nehru Nagar, Belagavi, Karnataka 590010, India.

Corresponding Author: R B Uppin, Department of Orthopedics, KLE Academy of Higher Education & Research, Jawaharlal Nehru Medical College & Dr Prabahkar Kore Hospital & MRC, Nehru Nagar, Belagavi, Karnataka 590010, India.

Email: saswatsamant135@gmail.com

Abstract

Fibrous Dysplasia / McCune Albright syndrome (FD/MAS) represents a wide spectrum of diseases due to somatic gain-of-function mutations of the GNAS gene. The mutation leads to over activity in the target tissues and to a wide phenotype of clinical features that vary in severity and age of onset. The rarity of the disease and its variable presentation to multiple specialities often leads to misdiagnosis and inappropriate variability in investigations and treatments. To address this, our international consortium of clinicians, researchers, and patients' advocates has developed pragmatic clinical guidelines for best clinical practice for the definition, diagnosis, staging, treatment and monitoring for FD/MAS to empower patients and support clinical teams in both general and specialised healthcare settings. With the lack of strong evidence to inform care, the guidelines were developed based on review of published literature, long-standing extensive experience of authors, input from other healthcare professionals involved in the care of FD/MAS patients and feedback from patients and patient groups across the globe. This has led to the formulation of a set of statements to inform healthcare professionals, patients, their families, carers and patient groups of the best practice of care. It is anticipated the implementation of these recommendations will lead to improvement in the care of patients with FD/MAS internationally. One such case of monostatic Fibrous Dysplasia of femur is reported.

Keywords: Monostotic Fibrous Dysplasia; Polyostotic-McCune Albright syndrome; Diagnosis; Management.

Introduction

Fibrous Dysplasia is a congenital, non-inherited, Benign intramedullary lesion in which the normal bone marrow is replaced by abnormal Fibro-osseous tissue. Pathophysiology is it's a sporadic disorder of osseous and fibrous tissue development characterised by post zygomatic mutation of GNAS1 gene coding stimulatory G protein[1] which reveals missense point mutation at the arginine 210 codon which leads to autonomous function in bone skin and various endocrine glands – c-AMP protein kinase. This leads to expression of proto-oncogenes such as c- fos in affected osteoblasts. This has been implicated in the process of osteoblastic differentiation and proliferation that may lead to the formation of Fibrous Dysplasia lesions.

Case Report: 40years old female c/o pain at right upper third of thigh since 1 year pain, pain progressive in nature, dull aching, radiating to knee joint, increases on walking and standing for long time. H/o limp on right side, H/o unable to squat and sit cross leg. On examination tenderness at upper 3rd of Right thigh. Movements of right hip joint painful. Bony thickening and irregularity present. X-ray shows well defined radiolucent, cystic area, expansile with deep scalloping, concentrically sclerotic rings. MRI shows well defined altered signal intensity expansile lesion is seen in the neck of right femur and proximal meta-diaphysis of right femur. It is a narrow zone of transition. No obvious cortical break is seen. It extends over a length of 9 cm, appears benign cystic lesion.

Differential Diagnosis: Fibrous Dysplasia, Aneurysmal cyst, Simple Bone cyst. Core needle biopsy reported as Fibrous Dysplasia followed by IMIL Nail was done after confirming the diagnosis based on MIRELS score as a prophylactic measure to prevent coxa vara deformity and pathological fractures.

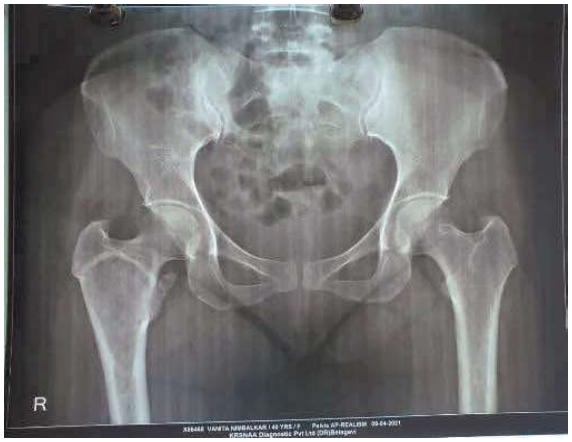

Fig. 1: Pre-Op X-Ray.

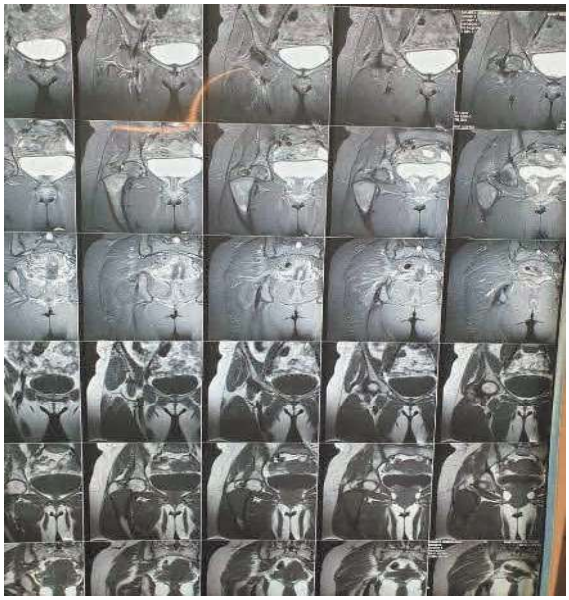

Fig. 2: MRI.

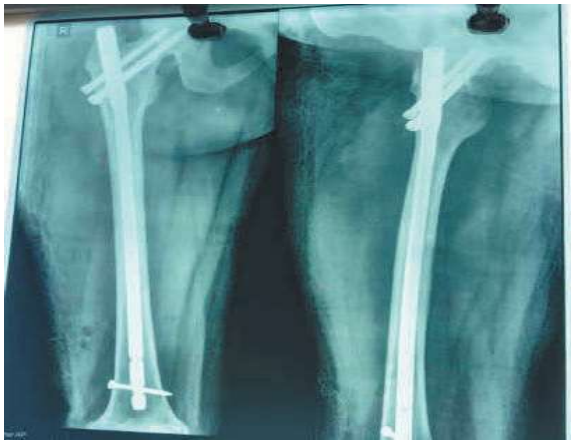

Fig. 2: Post-Operative X-ray.

Table 1: Potential mimics of fibrous dysplasia by skeletal sites.

Site	Differential Diagnosis
General	Cancer (primary or secondary) or hematologic malignancy including solitary plasmocytoma sarcoma
	Enchondromatosis
	Simple bone cyst (unicameral)
	Giant cell tumours
	Aneurysmal bone cyst
	Paget's disease of bone
	Neurofibromatosis type I
	Cutaneous Skeletal Hypophosphatemia syndrome
	Langerhans cell Histiocytosis
	Melorrheostosis
	Osteonecrosis
	Osteitis Fibrosa Cystica (Recklinghausen)
Craniofacial bones	Ossifying fibroma
	Fibro-osseous lesion
	Cherubism
	Aseptic mandibular osteitis (SAPHO syndrome)
	Central giant-cell granuloma
Fronto-sphenoidal	Meningioma
Tibia	Adamantinoma and osteofibrous dysplasia

In same cases molecular diagnosis of affected tissues is indicated when clinical radiological and histological analysis fails to confirm the diagnosis of Fibrous Dysplasia. Specific radiological features dependant on body site.

Histological and genetic characterisation: Biopsy with histological evaluation of suspected bone disease is usually only necessary in unusual or questionable cases, and/or if malignancy is suspected. The risks and benefits of a biopsy should be clearly explained to patients, including that a biopsy does not typically lead to regrowth of FD. The benefit of genetic testing in patients with a clear clinical diagnosis is uncertain. A genetic diagnosis is recommended where the diagnosis is in question. This especially applies to isolated/monostotic lesions in the skull, after exclusion of other associated skeletal and/or extra-skeletal features- e.g. other bones / skin features/ endocrinopathies. Diagnostic biopsies should be processed as fresh or fresh frozen material to enable genetic testing for GNAS mutation. False negatives may occur if the biopsy contains normal tissue and the biopsy may need to be repeated. Mutation

analysis can also be performed in paraffin-embedded samples although false negatives are then more likely.[5] Next generation sequencing (NGS) has a lower false negative outcome than Sanger sequencing. False positives have not been described using NGS and this sequencing technique can be used to differentiate FD/MAS from osteosarcomas.[6] Use of blood for mutation analysis cannot exclude the diagnosis of monostotic FD, but a positive result is informative.

Table 2: Specific radiological features dependent on body site.[4]

Bone	Features
Pelvis and ribs	• Fibrous dysplasia is the most common cause of a benign expansile lesion of a rib. • Expansile lytic lesion • Fusiform enlargement of the rib • Minor calcifications within the lesion may be seen
Extremities	• Bowing deformity, in particular of the large weight-bearing bones (e.g. shepherds crook deformity of the proximal femur) • Looser zones • Co-existent precocious puberty may lead to premature fusion of growth plates resulting in short stature
Skull and cran -iofacial	• Bone expansion showing ground-glass appearance • Calvarial deformity resulting in exophthalmos

Fibrous Dysplasia occurs at the age of 20-40yrs origin at metaphysio-diaphysis. Incidence is 5% of all Benign bone tumors. There are two types Monostotic & Polyostotic type. Polyostotic types are associated with extra-skeletal manifestations (skin hyperpigmentation and hyperfunct -ioning endocrinopathies)[7,8] is called McCune Albright syndrome. Conservative treatment in literature Bisphosphonate IV pamidronate 60mg/day for 3 days every 6 months with calcium 500-1500mg/day and vit-D 800-1200 IU/day. Surgical treatment is fixed angle internal device. The clinical management is challenging and multiple barriers exist to provide consistent, high quality care.

Management of Fibrous Dysplasia

General Measures:

Provision of information about the disease Provision of sufficient information about the disease to the patient and families is of outmost importance for this rare disease, which may be associated with debilitating manifestations, and for which there is no cure and no approved treatment. The aim is to empower patients and support them to develop to the best of their abilities. Patients and their families should be informed of the non-inherited genetic nature of disease and that while malignant transformation can very rarely occur, FD/ MAS lesions are almost invariably benign. They should also be informed that there are no known exposures that cause FD/MAS. Patients and their families should be given written information material about FD/ MAS and informed of the local regional / national / international patient groups including those based on social media for additional support. Patients should also be given details of "Expert" patients and specialist clinical centres / networks (e.g. European Reference Networks). Given the gaps in our knowledge of FD/MAS, research is high priority and patients should be given information about local research studies or trials.

Lifestyle Advice:

Advice should be given to optimize lifestyle factors which are associated with optimal bone health. Patients should be advised to achieve appropriate dietary calcium intake per age and achieve sufficient 25-OH vitamin D levels as per national guidelines, especially if pharmacological treatment with anti-resorptives is contemplated. Smoking cessation, alcohol moderation to < 3 units/ day and maintaining healthy weight should be advised. Appropriate, safe and sufficient physical exercise to optimize fitness should be recommended with referral for physical therapy as required. Regular dental examinations should be recommended according to national guidance including control before starting medication. Patients should be advised about optimizing oral health to reduce the risk of oral infection. Educational materials, occupational advice and information on sexual health should be available and, where appropriate, how to access additional support. Consideration should be made for specific referral to a psychologist for those with moderate to severe disease, especially in the presence of significant physical disability and/or craniofacial impact. Referral to a social worker may also be required.

Management of Scoliosis:

Patients with scoliosis should be regularly monitored for progression. Early consultation with spinal team and therapists is recommended and surgical fixation should be considered if Cobb angle is greater than 30 degrees, depending on the rate of progression and location of the curve.[9-11]

Management of Bone Pain:

The strategy is to induce symptom remission.[12,13] Key assessment tools for bone pain in FD are outlined above. The presence of night pain is red flag and the patient should be evaluated for complications including imminent fracture, bleeding into a cyst and malignant transformation. The presence of focal and/or acute onset pain may also indicate an acute or impending fracture (especially in a deformed long bone) or an aneurysmal bone cyst. Mechanical/ weight bearing bone pain can also signal a stress or impending fracture. The presence of a stress fracture should trigger consideration for correction of alignment, and/or consideration for the necessity of a surgical procedure, possibly involving the use of an intramedullary titanium nail or of a custom-made titanium angled blade plate, to stabilize the bone to prevent bone pain.

Management of Endocrinopathies Ovarian Pathology[14-19]

In general, ovarian surgery for cysts should be avoided, as disease is usually bilateral. Ovariectomy should only be performed when there is a risk of torsion and after expert consensus. Patients should be informed that the risk of torsion is small. Treatment for precocious puberty

is indicated if bone age is advanced and there is frequent bleeding. Psychological distress and the patient's age need to be taken into account as the height outcome is only improved in those <6yrs at onset i.e the very young group. First line therapy is Letrazole with tamoxifen or fulvastrant as second line or adjuvants. Patients should be monitored for central puberty and the need to add to add an gonadotropin releasing hormone analogue (GnRHa). eg. Leuprolide.

Adult women should be monitored for dysfunctional uterine bleeding. For contraception and HRT it may be prudent to avoid additional estrogenic compounds to avoid a possible increase in the risk for breast cancer, since patients with MAS may be at an increased risk of estrogen positive breast cancer [20], and patients with precocious puberty have both longer exposure as well as continued intermittent autonomous production of high levels of estrogen up until the menopause.

Testicular Pathology[21]

In general, surgery should be avoided. Structural lesions are rarely of clinical significance. Treatment for precocious puberty is indicated in case of an associated elevated serum testosterone and/or bone age advancement. Combination of testosterone receptor blocker and aromatase inhibitor are needed as well as monitoring for central precious puberty, in which case GnRHa may need to be added. Testicular lesions should be examined annually and males informed to perform self-examinations. Annual ultrasonography is indicated for palpable lesions or for lesions causing an overall increase in the size of the testes (relative to other testis or stage of puberty).). In adulthood no routine ultrasounds are advised, unless lesions are changing. Consider biopsy for lesions that are changing in size.

Thyroid Pathology[22-24]

In the short-term, carbimazole or methimazole are recommended for hyperthyroidism, whereas thyroidectomy or radio-ablation are recommended for long standing hyperthyroidism of more than 5 years.. Patients can be treated with I-131 but considering the evaluation of thyroid nodules one should perform full evaluation of the nodule before treating with I-131. Annual long-term monitoring is advised due to the possibility of regrowth. For, children aged less than 10 years with an abnormal US and normal thyroid function tests (TFTs), physical examination, growth velocity, and TFT's should be monitored every 6 to 12 month. In case lesions are found, follow up of patients with FD/MAS related thyroid disease should be performed according to current (inter) national guidelines.[25-27]

Growth Hormone Excess[28,29–33]

Somatostatin analogues are first line therapies with second line options including pegvisomant, alone or in combination with octreotide or lanreotide at the discretion of the treating physician. Pituitary surgery is recommended for patients resistant to medical therapy. Total hypophysectomy is required as the whole gland is usually involved and removing just the adenoma is not enough to control the excess production of growth hormone. Surgery is almost universally complicated by coexistent craniofacial FD, and so always challenging. Maximal medical therapy is standard of care, and pituitary radiation should be a final recourse due to the risk of malignant transformation of skull base FD [34, 35]. The treatment goals are to achieve an IGF-1 Z-score between − 2 and + 1. Treatment should be monitored by annual growth velocity, head circumference, and IGF-1 in all growing children. Assessment of additional pituitary hormone deficiencies is recommended after hypophysectomy and/or radiation therapy.

Management of Craniofacial FD (CFFD)[36,37-41]

FD of the craniofacial skeleton is variable in its behaviour and the multidisciplinary team caring for patients with CFFD needs its combined expertise to cater for all treatment options. Any planned surgical treatment should be carefully coordinated with other specialists involved in patient's care. Working within a multidisciplinary team, thus ensures among other aspects of management, optimal phosphate status, adequate vitamin D and preoperative correction of endocrine abnormalities, such as GH excess and T3 thyrotoxicosis, that may exacerbate skeletal disease. The balance of risks and benefits of extensive resection and/or reconstruction needs to be carefully outlined in great detail in patients with CFFD. Active watch and wait policies are often the preferred management strategy, as long-term outcomes in terms of regrowth and pain are very variable and generally poorly predictable. If CFFD is identified at baseline or at subsequent monitoring evaluations, the patient should be referred for a formal assessment to a craniofacial service with experience in the care of patients with CFFD.

The goals of treatment are:

- Prevention of functional loss–especially hearing and vision.
- Arrest or reduction of physical disfigurement.
- Prevention of secondary deformity.
- Minimisation of long-term morbidity from CFFD and its treatment.

The structure of the individualised package of care of CFFD is based on the extent of craniofacial involvement and on the following concepts. If possible, care is to be provided locally, but any decisions regarding surgical intervention should be taken by a multidisciplinary specialised team including physicians and surgeons with experience in managing CFFD. Scheduling of periodic evaluations should be organised by the central coordinating CF team with CFFD patients being reviewed at least annually or more frequently depending on the extent of their disease and risk of complications. Baseline and periodic CT scans of the head should be performed in children, usually every 2 years or less frequently based on the localisation and severity of the lesion(s). Regular imaging is not indicated in adults, and timing of the scans should be based on symptoms, at most every 5 years in those without symptoms. Although the primary aim of treatment should always be to preserve function, treatment of primary deformity and prevention of secondary deformity are also important. Advanced imaging techniques and 3-dimensional analysis of scans together with virtual surgical planning and computer-aided manufacturing and design of

patient-specific implants should be regarded as the standard of care in surgery of FD of the craniofacial skeleton. Simple curettage is not recommended as it is ineffective and may increase the risk of complications.

Conclusion

These best practice guidelines have been developed by an international collaboration between multiple clinical specialities, patients and patient advocacy groups, using the best evidence available. The FD/MAS guidelines are intended to improve the clinical care of patients across the world by addressing diagnosis, staging, treatment and monitoring aspects of their care given the potential serious risks to patient outcomes with late diagnosis.[42] The FD/ MAS consortium commits to developing an audit tool of key performance and experience measures to an international audit of practice and to reviewing these recommendations at least every 5 years to reflect new evidence in FD/MAS natural history and management. The percentage of malignant change of polyostotic fibrous dysplasia is 0.4-4% as such monostotic is very rare. Prophylactic Nailing is advised to prevent pathologic fracture and coxa vera deformity (shepherd crook deformity) based on the MIRELS score. The rarity of the disease and its carriable presentation to multiple specialities often leads to misdiagnosis and in inappropriate variability in investigations and treatments.

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