

Fibrous Dysplasia

CMC October 14, 2016
Stephanie M Kaiser
Professor of Medicine
Division of Endocrinology
Dalhousie University

Faculty/Presenter Disclosure

- **Faculty:** Dr. Stephanie M. Kaiser
- **Relationships with commercial interests:**
 - **Grants/Research Support:** Amgen, Eli Lilly
 - **Speakers Bureau/Honoraria:** Amgen, Eli Lilly, Merck
 - **Consulting Fees:** None
 - **Other:** Member of Scientific Advisory Council of Osteoporosis Canada
- **Potential for conflict(s) of interest:**
 - None

Objectives

- To review the definition, epidemiology and pathogenesis of fibrous dysplasia (FD)
- To discuss the clinical features, diagnosis and complications of FD
- To give an overview of current management of FD (both pharmacologic and nonpharmacologic)
- To discuss potential future therapies in FD

Case Presentation

- 34 yo woman referred for evaluation of pain in right leg (hip, knee and ankle) getting progressively worse
- Age 8: noted a “bump” on lateral aspect of right knee, not tender.
- Teenager: noted additional bumps R medial leg below knee and lateral R ankle. Areas started to become painful and worse with activity
- Age 30: fracture of R femur when she “moved the wrong way” and had a partial hip replacement. At that time diagnosed with **fibrous dysplasia**

- Worsening pain since the fracture especially R. ankle and knee.
- Menarche age 13, 2 children ages 2 and 10
- PMH: Panic disorder, TL. No other endocrine disorders.
- Meds: ALN 70 mg weekly ~ past 3 years, clonazepam, oxycodone, Depoprovera, vitamin D 1000 IU daily
- Smokes 1 cig q 2 weeks, rare alcohol, no other drug use
- FH: No fibrous dysplasia. Mother had polio (arm and leg problems). No endocrine problems

- Physical: BP 130/88 HR 90
 - No café au lait spots
 - R leg – palpable lump R lateral knee about 1 cm; 10 cm lesion below R knee on shin, raised about 0.5 to 1 cm, smooth, hard; lateral R ankle 3 cm lesion, visible and hard, slightly raised.
 - None of the lesions tender to palpation
 - Remainder of exam unremarkable

- Lab: 25D 59, calcium N at 2.25, PO4 N 0.9, TSH, CBC, Cr, ALP all normal
- Bone scan October 2013: uptake at R femur and tibia as before, none in ribs.
- MRI: R femur fibrous dysplasia as well as at least 3 T2 hyperintense lobulated lesions vastus intermedius between sartorius and rectus femoris, others are in vastus and rectus femoris more superiorly. Largest one is 4x3.5 cm in axial plane and 5.2 cm in craniocaudal plane. There is mild hyperintensity around it.

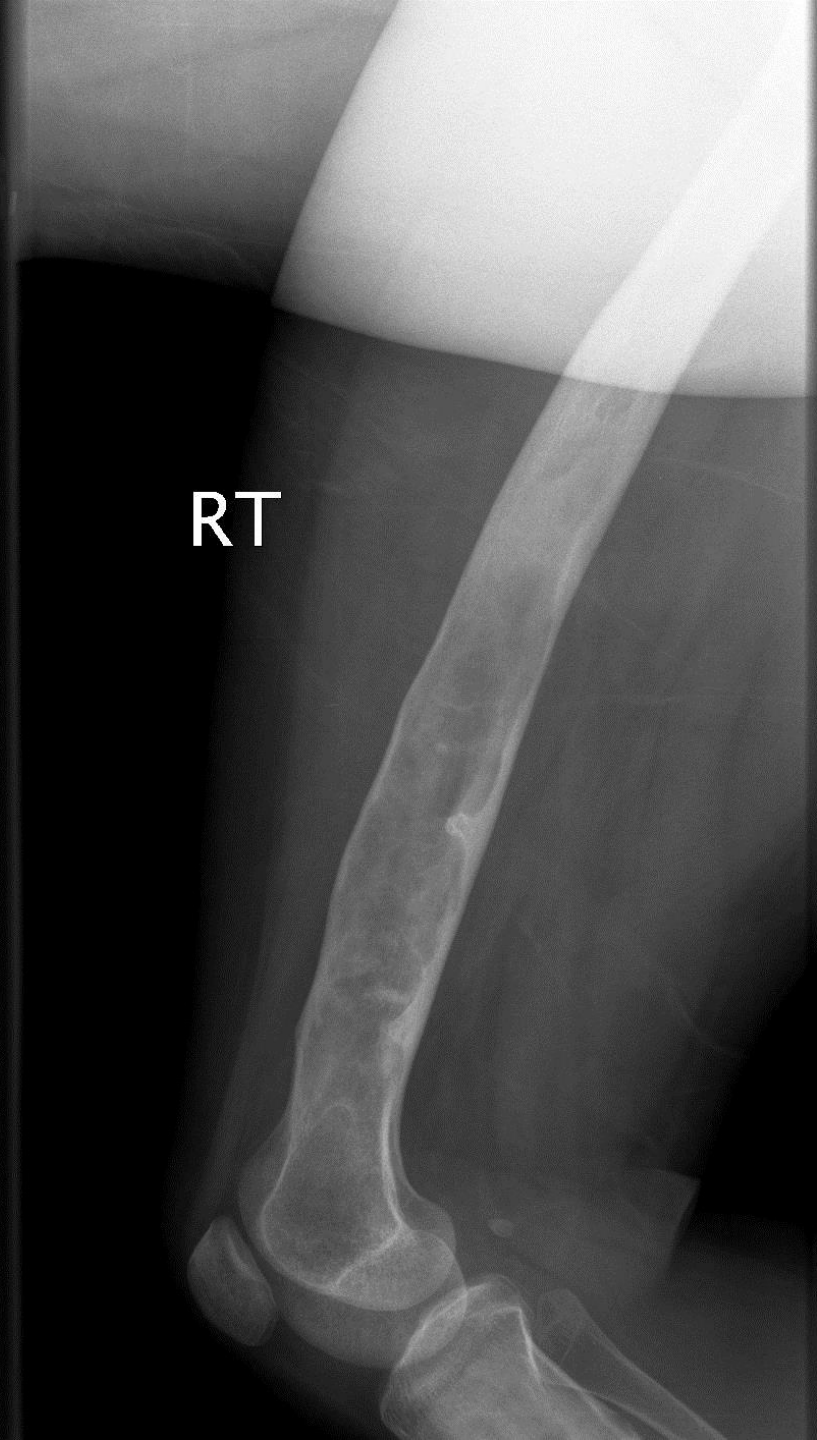
Consistent with multiple intramuscular myxomas seen in Mazabraud's syndrome

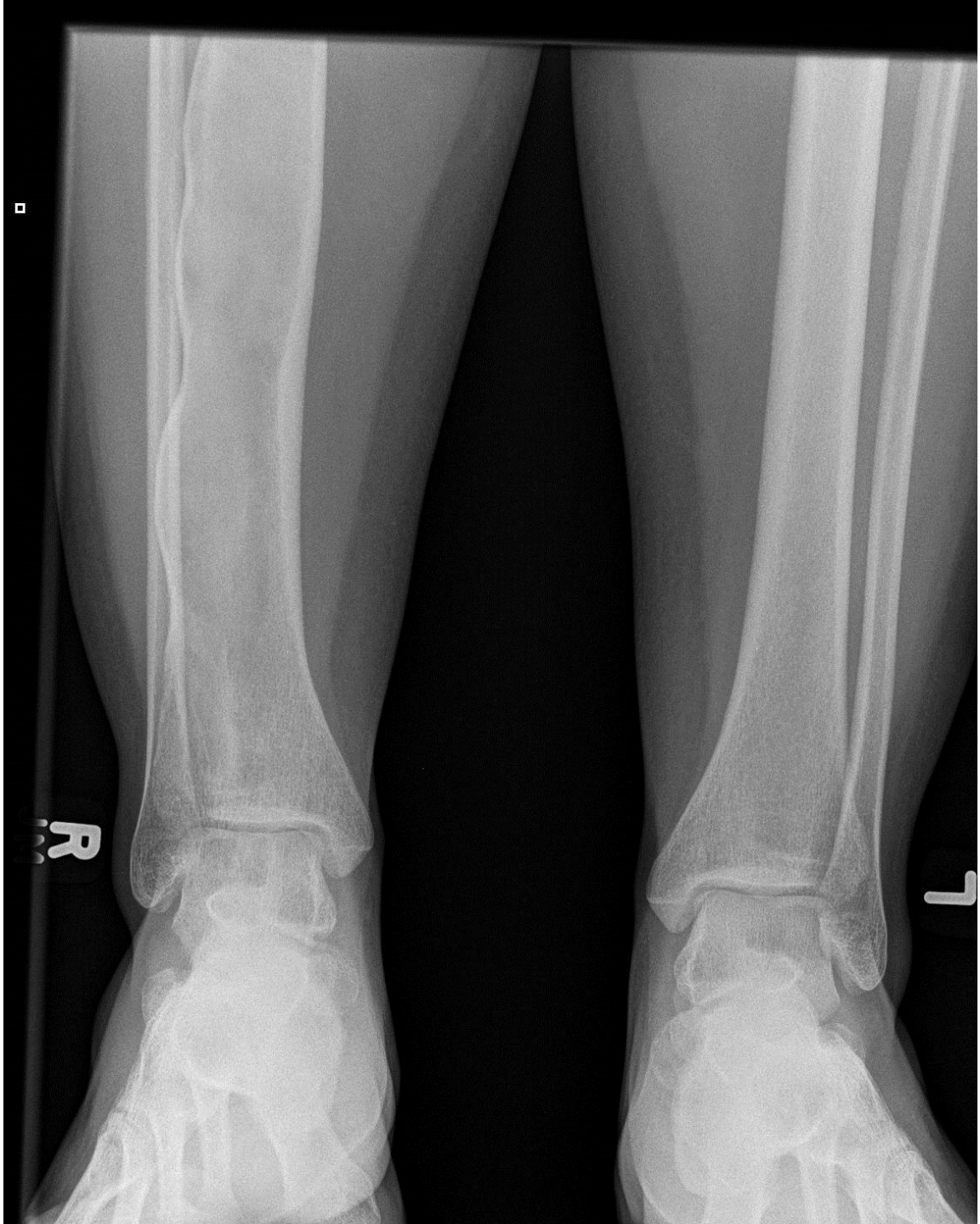
R
JM

□

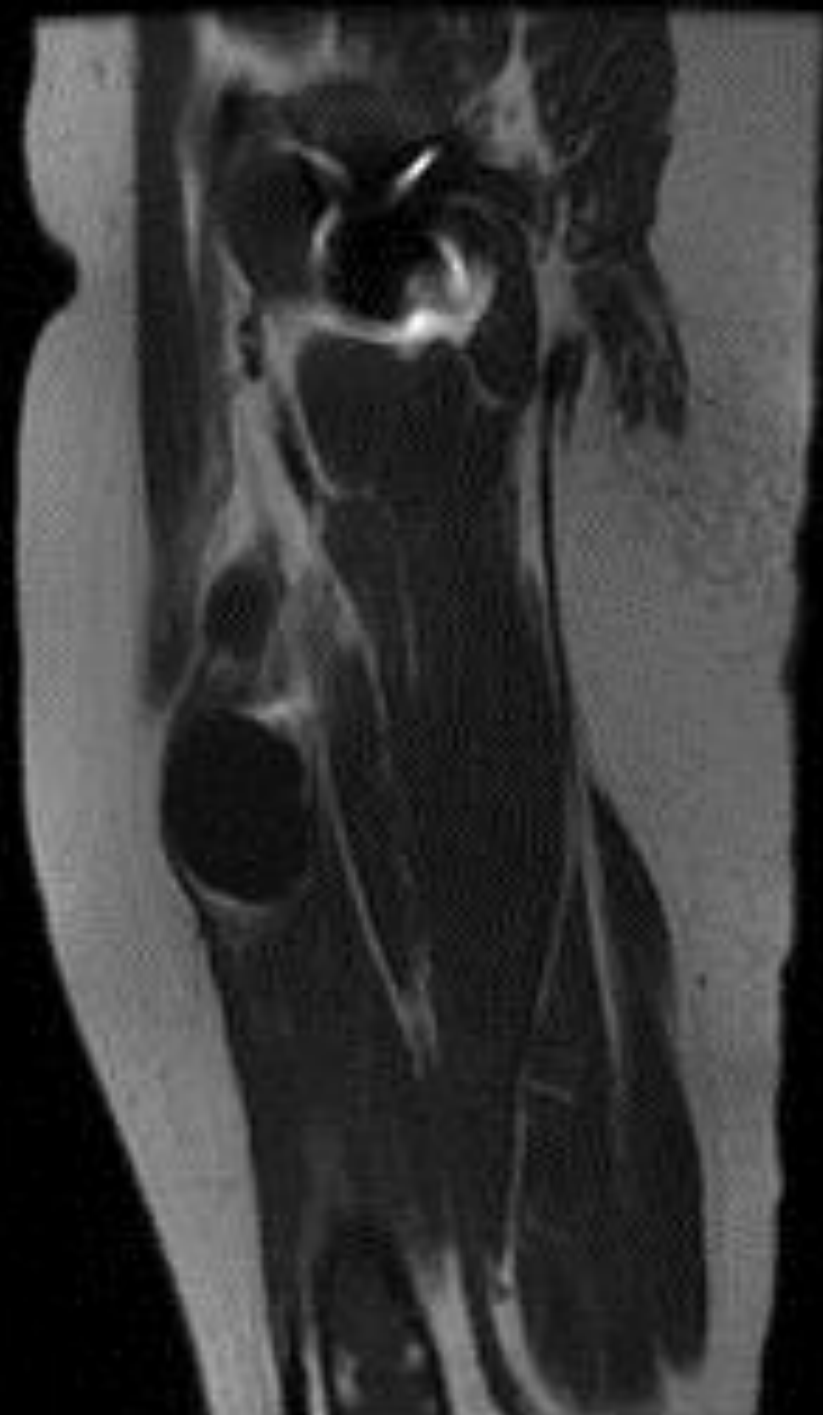


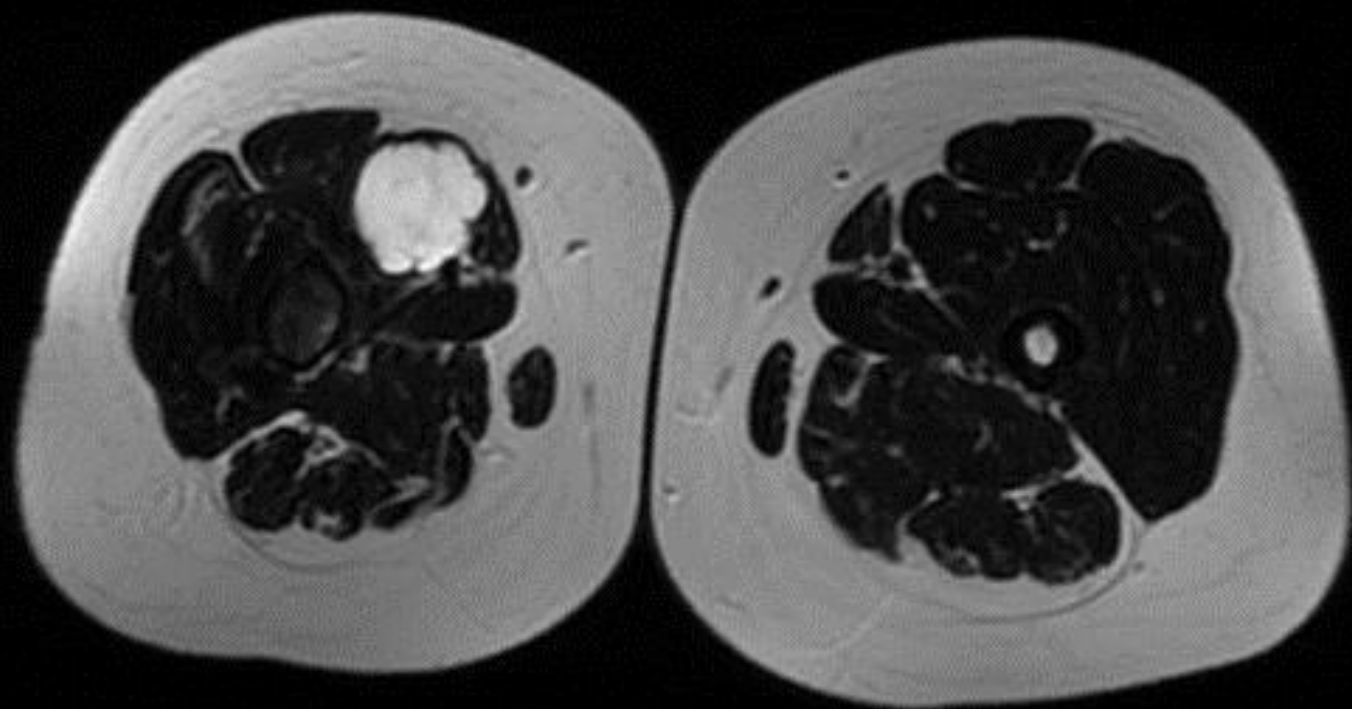
RT











What is Fibrous Dysplasia?

Benign condition where normal bone and bone marrow replaced by fibrous connective tissue and poorly formed trabecular bone tissue.

It is due to a postzygotic gain of function mutation in the guanine nucleotide stimulatory protein (*GNAS1*) gene. The mutation impairs intrinsic GTPase activity of Gs α resulting in persistent stimulation of adenylyl cyclase and cAMP production

Fibrous Dysplasia (FD)

- This leads to fracture, functional impairment, deformity and pain
- FD in combination with one or more **extraskkeletal** manifestations = McCune-Albright syndrome (FD/MAS)

Epidemiology of FD

- Affects both sexes, no race predilection
- Prevalence data not reliable but likely between 1/100,000 to 1/1,000,000
- FD can involve
 - a single skeletal site (**monostotic** FD), or
 - multiple skeletal sites (**polyostotic** FD)
- Most patients present later in life with incidentally found disease; others may present early with disabling disease
- MAS is rare, but FD (especially monostotic form) has been reported to account for up to 7% of all benign bone tumors.

Pathogenesis

- Due to activating missense mutations of the GNAS gene (chromosome 20q13.3), which encodes α -subunit of Gs stimulatory protein (leads to increased activity of adenylyl cyclase and excess cAMP production).
- In bone, this leads to inhibition of differentiation and proliferation of BMSCs, get structurally abnormal bone matrix and fibrosis of marrow space.
- **Remember:** Mutations of GNAS associated with FD and related disorders are NOT inherited! The mutation occurs very early in development (postzygotic).

Diagnosis

- The diagnosis of FD/MAS is based on finding ≥ 2 typical clinical features of MAS. If the only finding is monostotic FD, must identify a somatic activating mutation of GNAS to diagnose.
- However, detection of a mutation depends on the degree of mosaicism in the tissue and sensitivity of the technique
- Missense mutations occur at one of 2 amino acid residues: Arg201 (>95%), or Gln227 (<5%)

FD

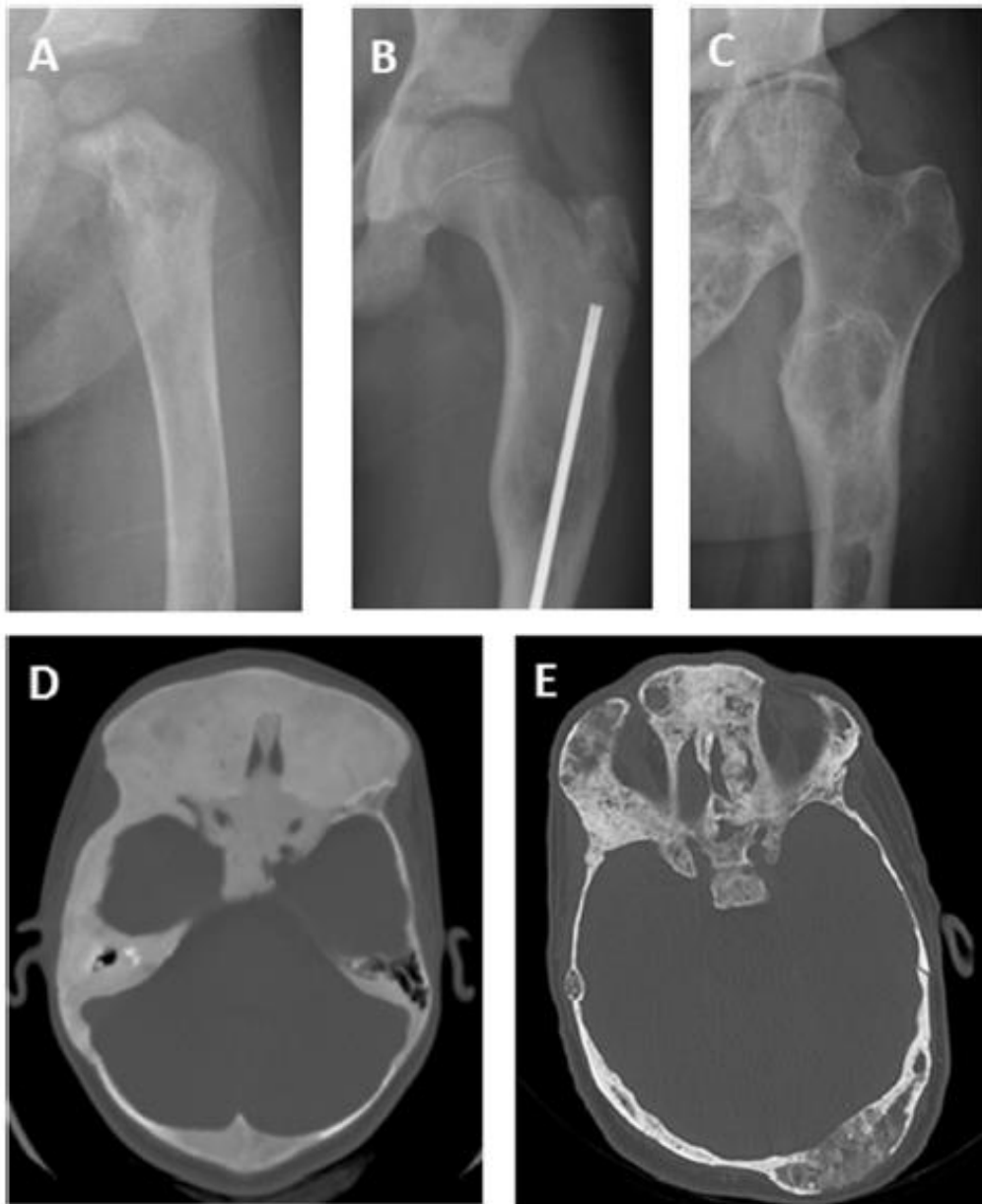
MAS was originally defined by the triad of

1. polyostotic fibrous dysplasia of bone (FD)
 2. café-au-lait skin pigmentation
 3. precocious puberty (but can get other hyperfunctioning endocrinopathies like hyperthyroidism, GH excess, Cushing's syndrome [in infants])
- Extraskeletal manifestations also seen – most common is FGF-23 mediated renal phosphate wasting (seen with polyostotic disease)
 - Rarely see FD in association with myxomas of skeletal muscle (Mazabraud's syndrome)

Clinical Presentations of FD

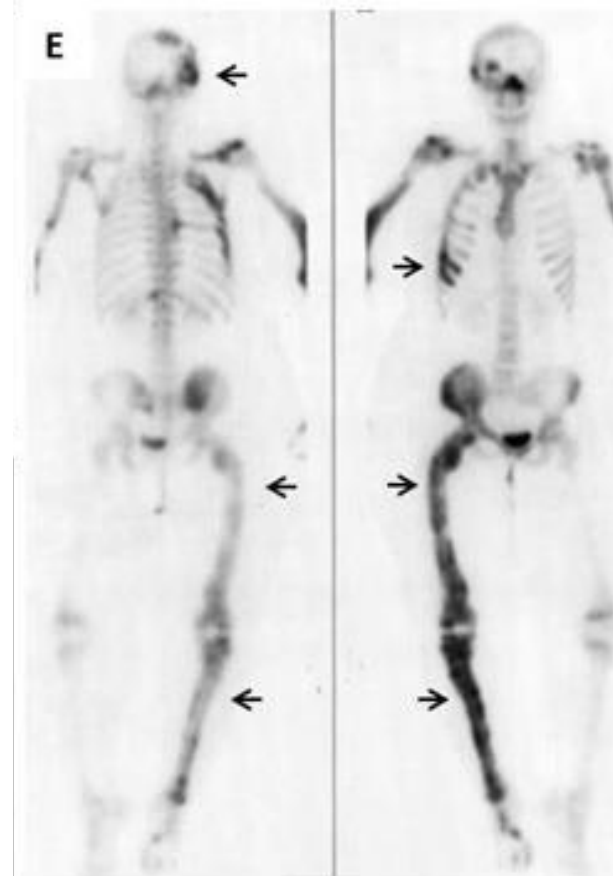
- Appendicular skeleton:
 - limb pain
 - pathologic fractures
- Craniofacial bones :
 - a painless “lump”, frontal bossing or facial asymmetry
- Radiographs: (appearance depends on location)
 - Appendicular skeleton: expansile lesions with endosteal scalloping, thinning of cortex and “ground glass” appearance
 - Craniofacial: expansile lesions, appear sclerotic on xray, “ground glass” appearance on CT
 - With ↑age – appendicular lesions look more sclerotic on xray, and craniofacial lesions look cystic

Fig. 3 Age-related radiographic features of fibrous dysplasia (FD). **a** Radiograph from a 2 year old demonstrates a typical heterogeneous-appearing FD lesion in the proximal femur. **b** Radiograph from an 11 year old shows a characteristic “ground glass” lesion, which appears homogeneous and radiolucent. **c** Radiograph from a 57 year old demonstrates the tendency of FD to become more heterogeneous and sclerotic over time. **d** Head computed tomography from an 11 year old shows diffuse FD involvement with homogenous “ground glass” appearance. **e** Head computed tomography from a 54 year old demonstrates the tendency for FD to become more heterogeneous, with focal areas of lucency throughout



Bone scan:
See patchy tracer uptake at affected sites, related to mosaic pattern of expression.
Do bone scan at diagnosis to determine extent of FD. Most skeletal lesions are seen on bone scan by age 5

Note presence of cox vara (“shepherd’s crook”) deformity of R femur



Clinical Presentation of FD

- 90% of total body skeletal disease burden is usually established by age 15
- The “Rule of 90”:
 - Craniofacial lesions, 90% by age 5
 - Appendicular lesions, 90% by 13.7 yo
 - Axial skeletal involvement, 90% by 15.5 yo
- The appearance of new lesions later in life (after 15 yo) is a very uncommon presentation. In fact, FD lesions usually become less active in adults, probably due to apoptosis of mutation-bearing cells.

Histology of FD lesions

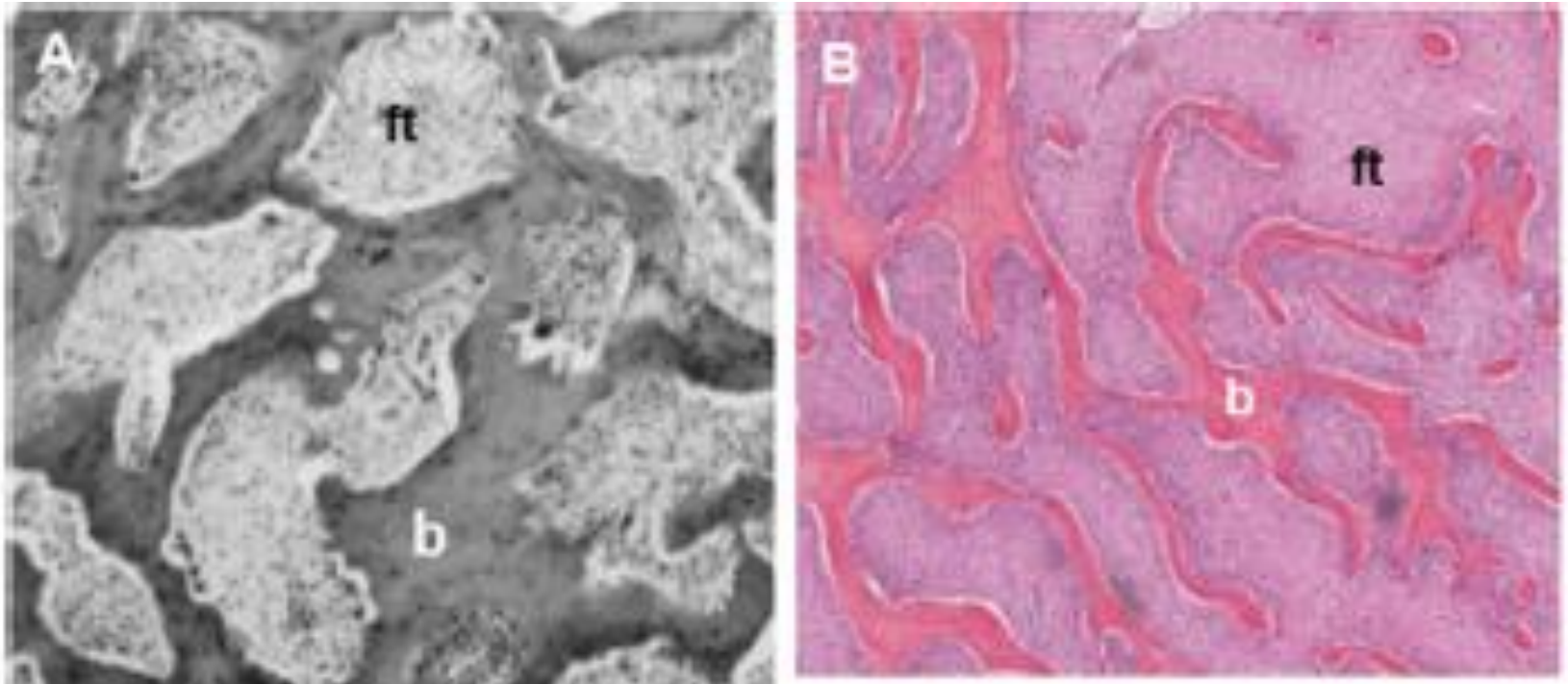


Fig.2: Histologic features of FD of the calvarium with complexes of bony trabeculae (b) embedded in areas of fibrous tissue (ft).

The trabeculae are mainly nonmineralized woven bone and are in a bland cellular and collagenous matrix (Chinese letters)

Clinical Presentation of MAS

- Generally, the signs and symptoms of either precocious puberty (PP) or FD account for the initial presentation
- PP is common in girls (seen in 85% with FD/MAS)
 - Recurrent ovarian cysts with intermittent estrogen production results in early onset vaginal bleeding or spotting
 - Early development of breast tissue
 - Growth acceleration
- PP less common in boys (10-15%)
 - Autonomous testosterone production with bilateral (or unilateral) testicular enlargement, penile enlargement, body odour, pubic and axillary hair, acne and precocious sexual behaviour

MAS

- In PP seen with MAS:
 - Prolonged autonomous production of sex steroid results in activation of the hypothalamic-pituitary-gonadal axis and can then develop central PP
- Testicular abnormalities seen in ~85% of males with MAS
 - US shows hyper- and hypo- echoic lesions corresponding to areas of Sertoli and/or Leydig cell hyperplasia
 - usually not detectable on physical examination
 - ultrasound of the testes is recommended in all males with FD and MAS
 - Low risk of malignant transformation

Other Features of MAS

- Endocrinopathies: G protein dependent hormones
 - MSH
 - LH/FSH
 - TSH
 - GHRH
 - ACTH
 - FGF23 mediated phosphate wasting
- Liver (hepatitis in infants); GERD in children; pancreatitis and intraductal papillary mucinous neoplasms; intramuscular myxomas (Mazabraud syndrome)
- Malignancies

Café-au-Lait Spots in MAS

- Usually present at or shortly after birth and in retrospect are usually the first manifestation of MAS
- No correlation between size of skin lesions and extent of disease, nor between location of skin lesions and location of FD
- Large melanotic macules (MSH)
- Asymmetrical, and usually do not cross the midline
- Look at the nape of the neck and base of the spine
- Edges are jagged (Coast of Maine)
- DDx: Neurofibromatosis – smooth margins (Coast of California), skeletal involvement less common (kyphoscoliosis, cortical thinning of long bones, bowing and dysplasia of tibia)

MAS: Doesn't cross midline
Irregular borders
Coast of Maine



NF: Crosses midline
Smooth borders
Coast of California



Complications of Polyostotic FD

1. Bone pain common, may be severe. Ribs, long bones, craniofacial bones especially
2. Pathological fractures, especially the weight-bearing bones
3. Bony deformities, especially weight-bearing bones – due to expansion
4. Nerve compression especially in the skull. Sclerosis at the base of the skull in the region of the cavernous sinus causes optic and auditory nerve compression with **hearing or visual loss.**



Malignancies in FD/MAS

- Rare overall
- Malignant transformation of FD lesions also uncommon, but <1% in FD/MAS.
- High dose external beam radiation is a risk factor for sarcomatous transformation.
- Other cancers reported include thyroid and breast
- Precocious puberty and GH excess may also result in an increased cancer risk.

Malignancies in FD/MAS

- Elevated risk of breast cancer
 - ASBMR 2016 (FR0324): Majoor et al, Leiden University Medical Centre.
 - Found 10/134 patients with FD had diagnosis of breast cancer (7.4%); younger age at diagnosis (median age 46 vs. 61 without MAS); found an increased risk with FD lesions of the thorax versus those without. Suggested that screening for breast cancer be considered in FD patients, especially those with thoracic lesions.
- ? Increased thyroid cancer due to increased surveillance in this population (as in the rest of the population)

Treatment for FD

- There are no medications that can alter the disease course in FD
- Treatment of FD lesions is mainly palliative, with an emphasis on optimizing function and minimizing morbidity related to fractures and deformities

Nonpharmacologic Treatment for FD

- Orthopedic surgery to repair fractures, prevent and correct deformities
- Diagnose and treat scoliosis (related to spinal FD) as it may be rapidly progressive
- Aneurysmal bone cysts can form in existing areas of FD and present with acute onset of severe pain, rapidly expanding localized deformity and need urgent surgical evaluation
- Physical therapy to optimize function and reduce loss of mobility
- Careful monitoring of hearing and vision

What about Pharmacologic Treatment?

- IV bisphosphonates such as zoledronic acid and pamidronate may help with FD-related bone pain. Dosing should be based on symptoms, not on a fixed interval or bone turnover markers (oral ALN shown ineffective to treat bone pain [Boyce et al, 2014])
 - BP therapy does NOT change the natural history of the disease!
 - Observational studies (Pamidronate) suggested reduced bone pain, decreased BTMs, improved radiographic appearance (Liens et al, Lancet 1994; Chapurlat et al, JBMR 1997)
 - Open label prospective study showed pain relief, but no benefit radiographically or histologically (Plotkin et al, JCEM 2003)

What about Pharmacologic Treatment?

- Analgesia and anti-inflammatories for bone pain
- Denosumab: A few reports in the literature of using denosumab to treat severe polyostotic FD (given every 3 mo) – immunohistochemistry on bone biopsy of FD lesions has shown markedly increased RANKL expression. Case reports have shown a reduction in pain, BTMs and lesion growth rate.
- Tocilizumab: IL-6 receptor antagonist - *in vitro* data indicates a role for IL-6 excess in the pathophysiology of FD (trial underway)

Future Directions

- Critical need to develop medical therapies for FD
- Skeletal stem cells? – since skeletal progenitors are the disease-causing cells in FD. Preclinical studies suggest that in vivo stem cell/BMSCs transplantation may work, but have knowledge gaps re precise nature, function, and optimal handling and delivery.
- Alter activity of mutant $G\alpha$ – 90% of mutations in FD/MAS occur at R201 position. Develop therapies that target the mutated protein and modify its GTPase activity

Our case:

Mazabraud's syndrome:

- Rare benign disorder of FD (usually polyostotic) associated with single or multiple intramuscular myxomas (benign mesenchymal tumours)
- The myxomas typically are seen near affected bones and are usually multiple
- Mean age at Dx 44, women more than men (2x)
- First described by Henschen in 1926, and a pattern of association between FD and soft tissue myxomas first presented by Mazabraud et al in 1957
- In 2013, ~80 cases reported
- MRI shows that the myxomas are well defined and strictly muscular, low intensity on T1 images and high intensity on T2

Mazabraud's syndrome

- Most common sites for myxomas are thighs, shoulders, buttocks and forearms
- Find GNAS mutation in the myxomas as well
- Myxomas are benign, but can cause pressure symptoms which is an indication for removal (wide excision)
- Conflicting reports about recurrence after removal of the myxomas - some say no recurrence, others report high recurrence rate either locally or in adjacent muscles with time to recurrence of several years (up to >10 years): need longterm follow-up!
- ? Increase in risk of sarcomatous transformation of the FD lesions in presence of myxomas (6 cases reported), so should be followed up more closely with clinical and radiologic follow-up of FD lesions, especially of weight-bearing bones.

Objectives

- To review the definition, epidemiology and pathogenesis of fibrous dysplasia (FD)
- To discuss the clinical features, diagnosis and complications of FD
- To give an overview of current management of FD (both pharmacologic and nonpharmacologic)
- To discuss potential future therapies in FD

Questions?



References

1. Curr Osteoporos Rep. 2016 Oct; 14(5):178-86. Fibrous Dysplasia/MAS: Clinical and Translational Perspectives
2. Curr Osteoporos Rep. 2015 Jun; 13(3):146-58. GNAS Spectrum of Disorders
3. GeneReviews [Internet] Feb. 26, 2015. FD/MAS
4. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 8th Edition. Chapter 94: Fibrous Dysplasia.
5. Acta Radiologica Short Reports 2013: 2(8). Mazabraud's syndrome: case report and literature review. [\[?\]](#)
6. The American Journal of Orthopedics 2012 July; 41(7): 332-5. Mazabraud Syndrome