# Hypophosphatemia

## Approach in India

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# Hypophosphatemia

**Definition**

Serum phosphate $< 2.5$ mg/dl

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Serum phosphate $< 2.5$ mg/dl

**Beware**

Infants have higher values.
$\therefore$ *Normal* $\implies$ *Abnormality*

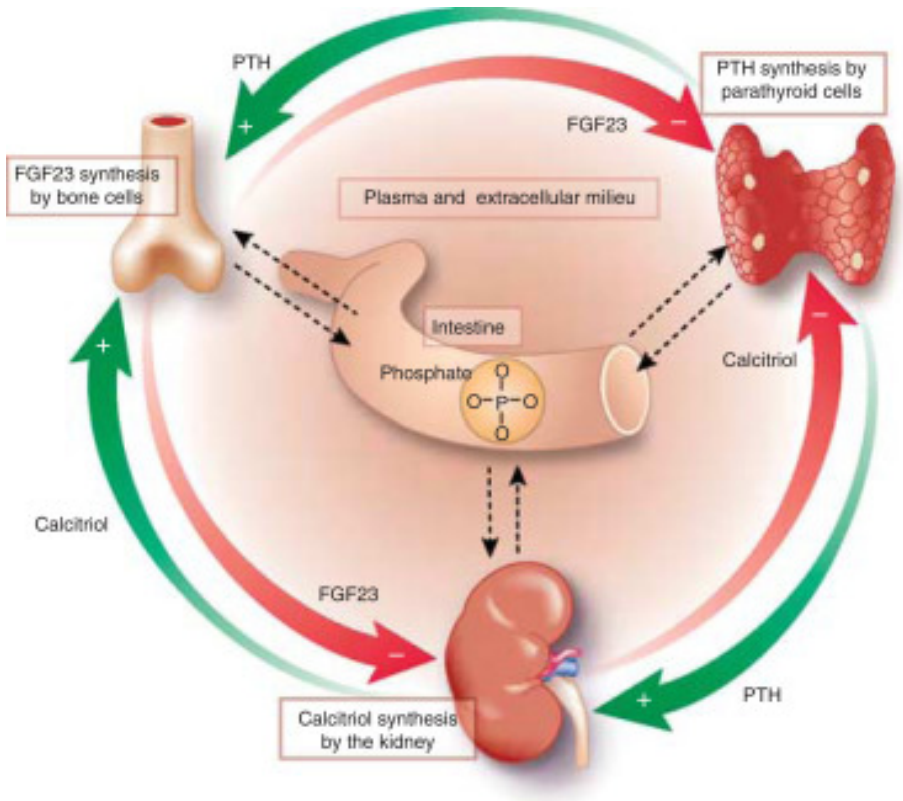
# Hypophosphatemia -Severity

| | |
|---|---|
| Mild | $2 - 2.5 mg/dl$ |
| Moderate | $1 - 2 mg/dl$ |
| Severe | $< 1 mg/dl$ |

# Epidemiology

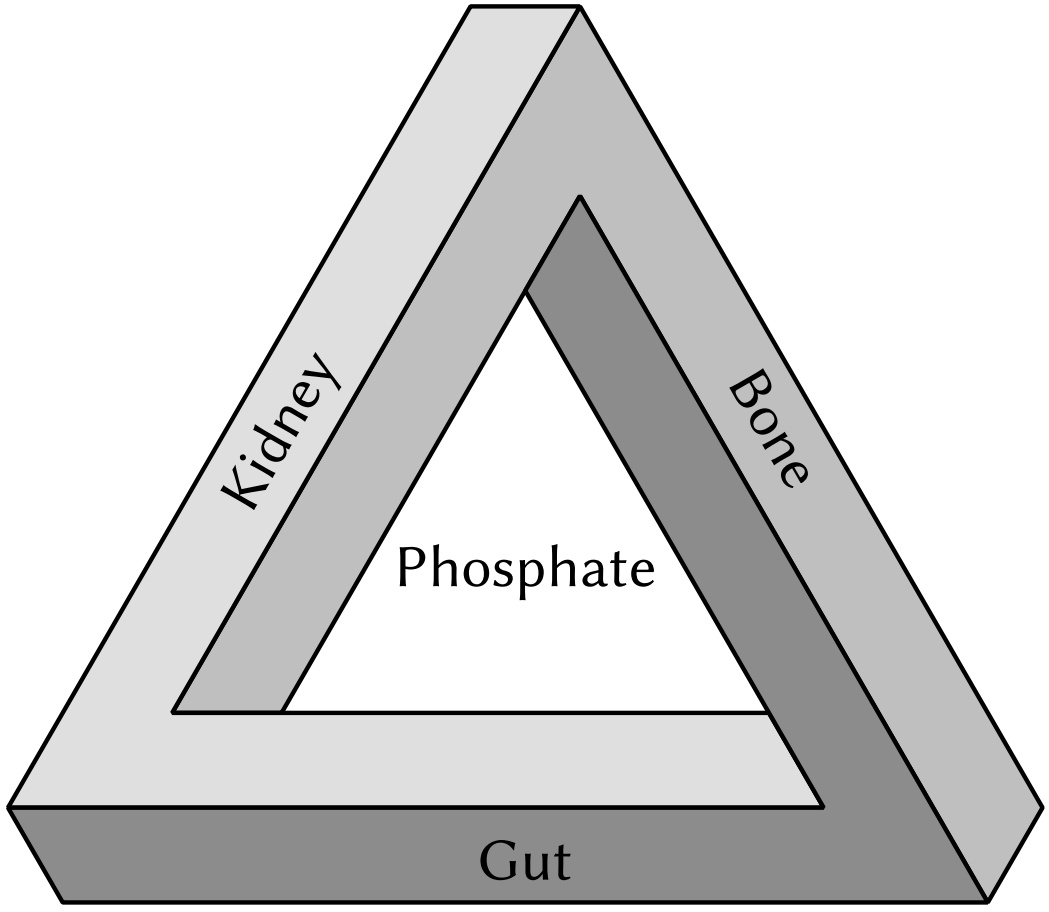
- Upto 5% of hospitalized patients
- 0.5% of them severe
- Chronic hypophosphatemia - limited data

# How is phosphate regulated[1]?

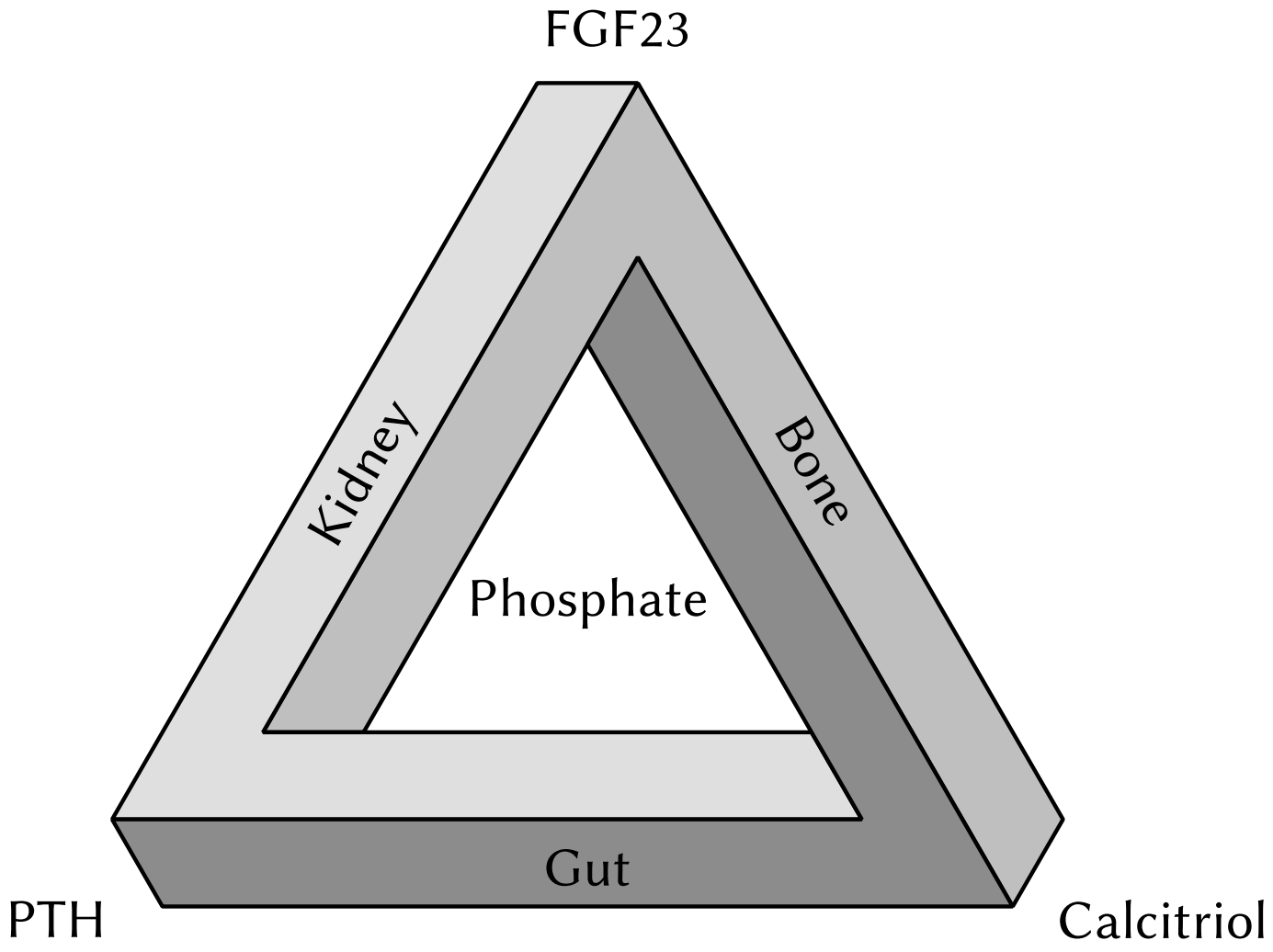



[1]Pablo A. Ureña Torres and David P. De Brauwere (2011). "Three feedback loops precisely regulating serum phosphate concentration". In: *Kidney International* 80.5, pp. 443–445.

# Penrose Triangle of hormones



# Penrose Triangle of hormones



# It takes three to tango

| Hormone | Kidney | Gut | Bone |
|---|---|---|---|
| FGF23 | ☹ | ☹ | ‼ |

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| Hormone | Kidney | Gut | Bone |
|---|---|---|---|
| FGF23 | ☹ | ☹ | ‼ |
| PTH | ☹ | 😀 | 😀 |

# It takes three to tango

| Hormone | Kidney | Gut | Bone |
|---|---|---|---|
| FGF23 | ☹ | ☹ | ‼ |
| PTH | ☹ | 😀 | 😀 |
| Calcitriol | 😀 | 😀 | 😀 |

# History

- 45 year male h/o pain and difficulty walking x 2 years
- Difficulty in getting up from sitting position
- Waddling gait
  - H/o pathological fracture bilateral neck of femur
  - Treated elsewhere with teriparatide

# History

- No h/o chronic drug intake
- No family history of similar illness
- No dental abnormalities or h/o fractures in childhood
- No bony deformities

# Biochemical parameters-Baseline

| Parameter | Baseline | Reference |
|---|---|---|
| Calcium | 9.2 mg/dl | 9-11 |
| Phosphate | 1.3 mg/dl | 2.5-4.5 |
| ALP | 146 IU/L | 40-150 |
| PTH | 50.1 pg/ml | 9 - 52 |
| 25(OH)D | 21.3 ng/ml | 30-100 |
| Creatinine | 1 mg/dl | 0.8 -1.5 |

# What's going on?

- ~~Oral intake~~[2]
- ~~Redistribution~~
- Increased excretion

[2] Jamshid Amanzadeh and Robert F. Reilly (2006). "Hypophosphatemia: an evidence-based approach to its clinical consequences and management". In: *Nature clinical practice. Nephrology* 2.3, pp. 136–148.

# How to check for urinary excretion of $PO_4$ ?

- Fasting urine and serum phosphate
- Fasting urine and serum creatinine
- Calculate TmP/GFR

# How to calculate TmP/GFR ?

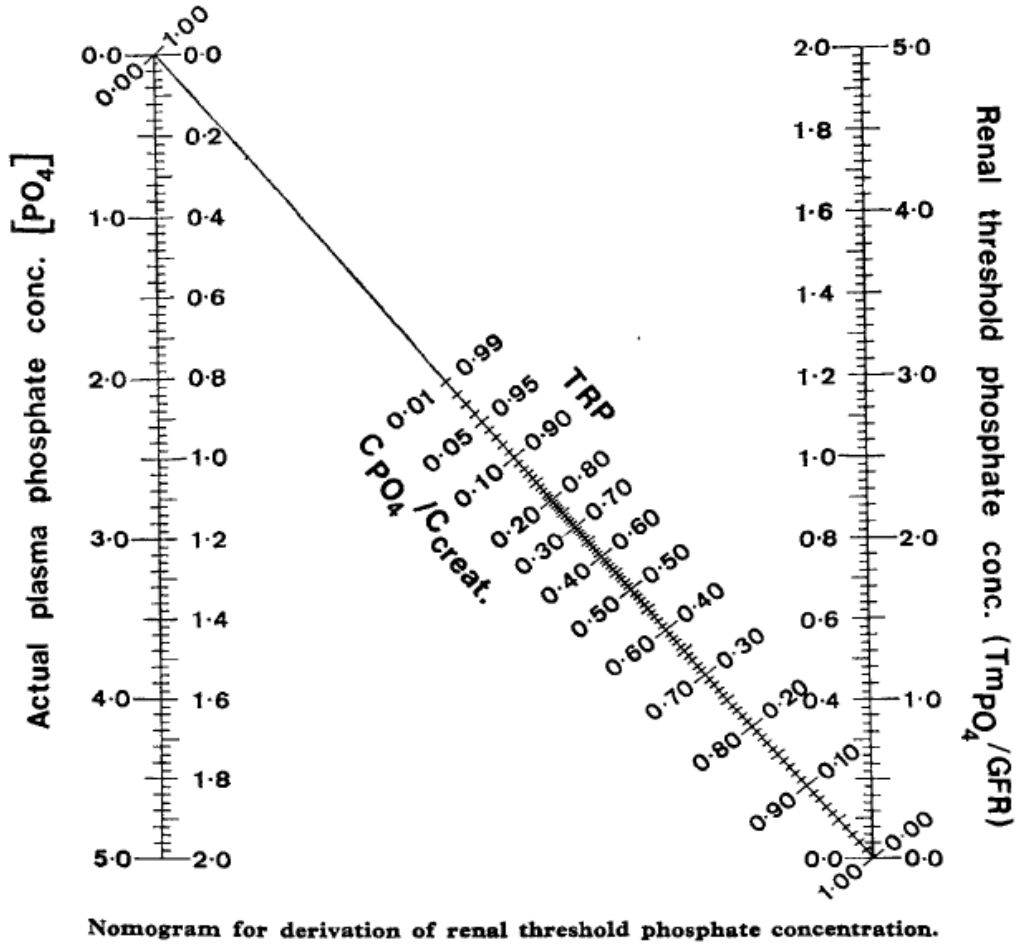


Figure: Walton and Bijvoet nomogram

# How to calculate TmP/GFR?

## Step 1 - Calculate TRP

**TRP**

$$1 - \frac{Urine_P}{Urine_{Cr}} / \frac{Serum_P}{Serum_{Cr}} \tag{1}$$

## Step 2 Calculate TmP/GFR

**TmP/GFR**

$$TmP/GFR = TRP \times Serum_P \tag{2}$$

If TRP $> 0.86$

$$TmP/GFR = [0.3 \times TRP/(1 - (0.8 \times TRP))] \times Serum_P \tag{3}$$

# Calculating TmP/GFR

| S.CA | S.PO4 | ALP | S. CR | URINE PO4 | U.CR | TRP% | TRP | TMP/GFR | INTERPRETATION |
|---|---|---|---|---|---|---|---|---|---|
| 8.9 | 1.3 | 488 | 0.9 | 25.5 | 97 | 81.80 | 0.82 | 1.06 | PHOSPHATURIA |
| 8.7 | 7.1 | 112 | 0.6 | 9.9 | | | | | PHOSPHATURIA |
| 9.2 | 1.3 | 150 | 0.8 | 4.6 | 46.5 | 93.91 | 0.94 | 1.47 | PHOSPHATURIA |
| 8.8 | 3.2 | 746 | 0.5 | 27.3 | 100.2 | 95.74 | 0.96 | 3.93 | NORMAL |
| 8.5 | 2.3 | 2000 | 0.6 | 26.9 | 33.1 | 78.80 | 0.79 | 1.81 | PHOSPHATURIA |
| 7 | 3.6 | 1911 | 4.8 | 6.1 | 33.6 | 75.79 | 0.76 | 2.73 | PHOSPHATURIA |
| 9.6 | 6.3 | 70 | 0.7 | 134 | 93 | 83.99 | 0.84 | 5.29 | RESORPTION |
| 9.5 | 5.1 | 116 | 0.8 | 6.7 | 60.1 | 98.25 | 0.98 | 7.02 | RESORPTION |
| 8 | 5 | 77 | 0.6 | | | | | | |
| | 6 | | 0.7 | 3.1 | 42.2 | 99.14 | 0.99 | 8.63 | RESORPTION |

# Urinalysis

| Parameter | Baseline | Reference |
|---|---|---|
| pH | 6.5 | 4.8 -8 |
| Glucose | 4+ | Nil |
| Aminoacids | Positive | Variable |
| Ca/Cr ratio | 0.12 | $< 0.2$ |
| TMP/GFR | 1.3 | 2.5-4.2 |

# Bone Scan


Figure: Multiple Pseudofractures

# Description

- Hypophosphatemic osteomalacia
- Proximal tubular dysfunction

$\oint$ Under evaluation ...

# Differential Diagnosis[3]

| Increased renal excretion | | Impaired intestinal absorption or intake | Transcellular shifts | Others |
|---|---|---|---|---|
| **FGF23-mediated** | **Non-FGF23-mediated** | | | |
| XLH (*PHEX*) | Hyperparathyroidism | Impaired dietary intake | Refeeding syndrome | Mannitol |
| ADHR (*FGF23*) | HHRH | Phosphate binders | Glucose infusion | Bisphosphonates |
| ARHR (*DMP1, ENPP1*) | Diuretics: acetazolamide, thiazides, loop diuretics | Sevelamer | Insulin infusion | |
| TIO | | Antacids containing calcium, magnesium, aluminum | Salicylate poisoning | |
| FD | Fanconi syndrome | | Hyperventilation | |
| Linear sebaceous nevus syndrome | Genetic causes: Dent's disease, cystinosis, NaPi2a mutations, others | Alcoholism | Respiratory alkalosis | |
| Postrenal transplantation hypophosphatemia | Drug induced: toluene, streptozocin, ifosfamide, cisplatin, tetracyclines, aminoglycosides, antiretrovirals (tenofovir, adefovir), and imatinib | Premature infants | Catecholamines | |
| Iron polymaltose infusions | | Malabsorption | | |
| | | Vitamin D deficiency | | |
| | | Vitamin D metabolism defects | | |
| | | 1$\alpha$-hydroxylase deficiency | | |
| | | Vitamin D receptor mutation | | |

[3] Erik A. Imel and Michael J. Econs (2012). "Approach to the hypophosphatemic patient". In: *The Journal of clinical endocrinology and metabolism* 97.3, pp. 696–706.

# FGF23

**C-Terminal FGF23**

256.7 RU/ml (Normal: 0-150 RU/ml)

**Remember**

FGF 23 should not be sent in serum as it gets degraded.[a]
$\therefore$ *FGF 23 assay* $\implies$ *EDTA sample*

[a] Justine Bacchetta and Isidro B. Salusky (2012). "Evaluation of hypophosphatemia: lessons from patients with genetic disorders". In: *American journal of kidney diseases : the official journal of the National Kidney Foundation* 59.1, pp. 152–159.

# Interpretation

- Hypophosphatemia
- Phosphaturia
- Normal PTH
- Suppressed Calcitriol
- High FGF 23

- Adult onset
- No family history

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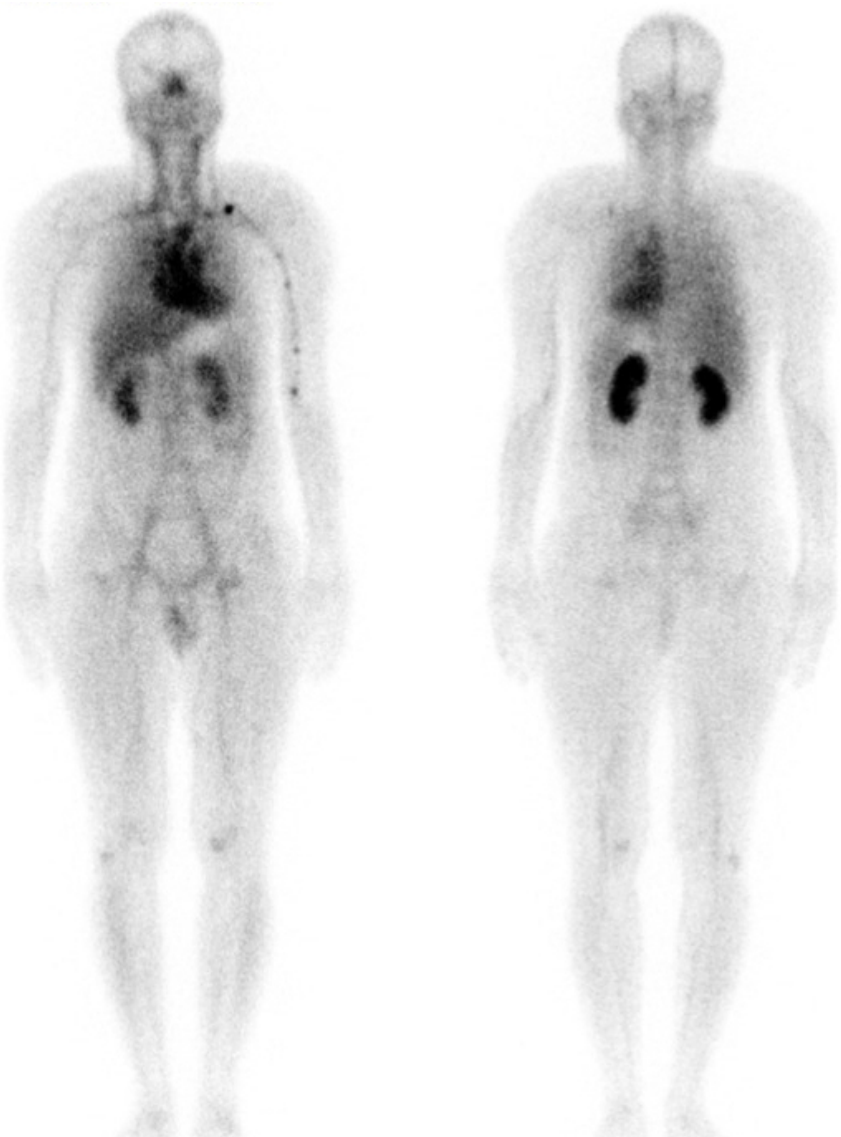
$\Longrightarrow$ TIO Vs ADHR

# History & Examination Revisited

Subcutaneous nodule of size 1.5 cm in the medial aspect of left thigh

# Wholebody blood pool imaging



# Imaging

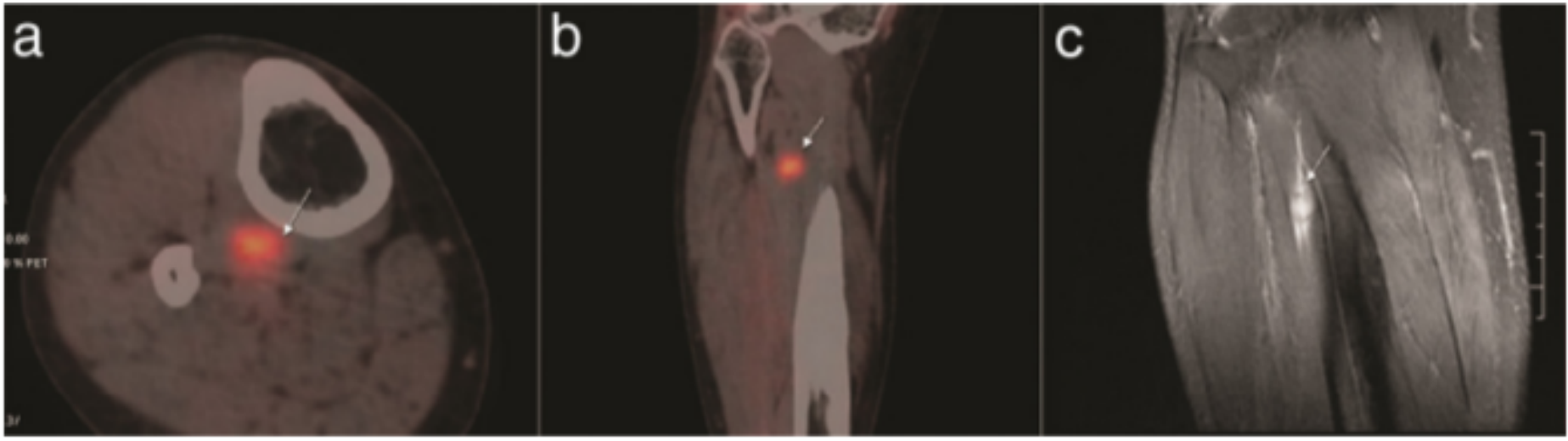



Figure: **a**- Fused PET-CT axial images showing FDG-avid soft tissue lesion posterolateral right proximal tibia.
**b** -Fused PET-CT sagittal image of right leg showing same lesion seen on coronal section.
**c** - T2 magnetic resonance coronal view shows hyperintense signal intensity right leg-SUV max : 4.86 gms/ml

# Imaging

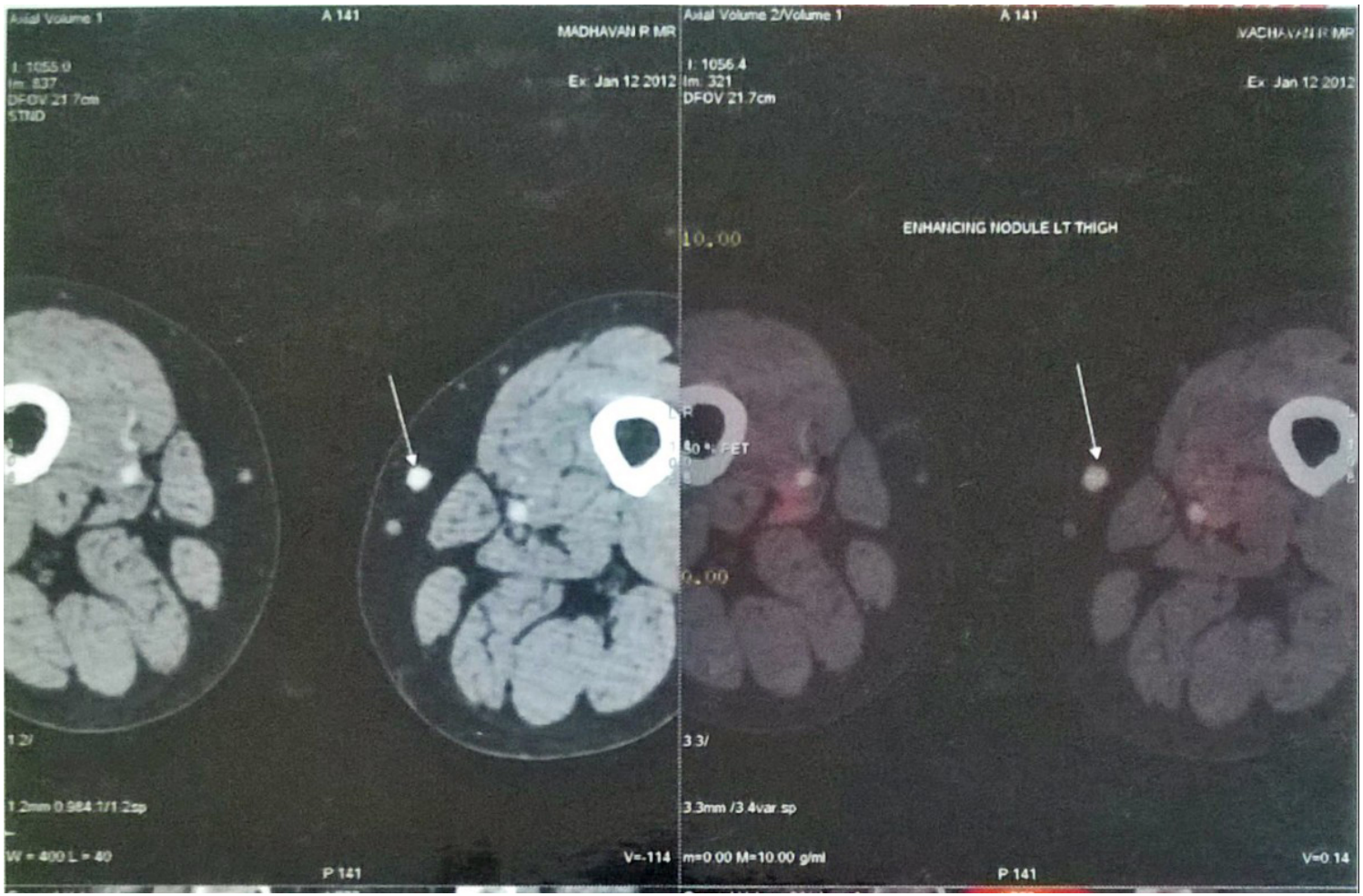



Figure: CT Left thigh

# Imaging

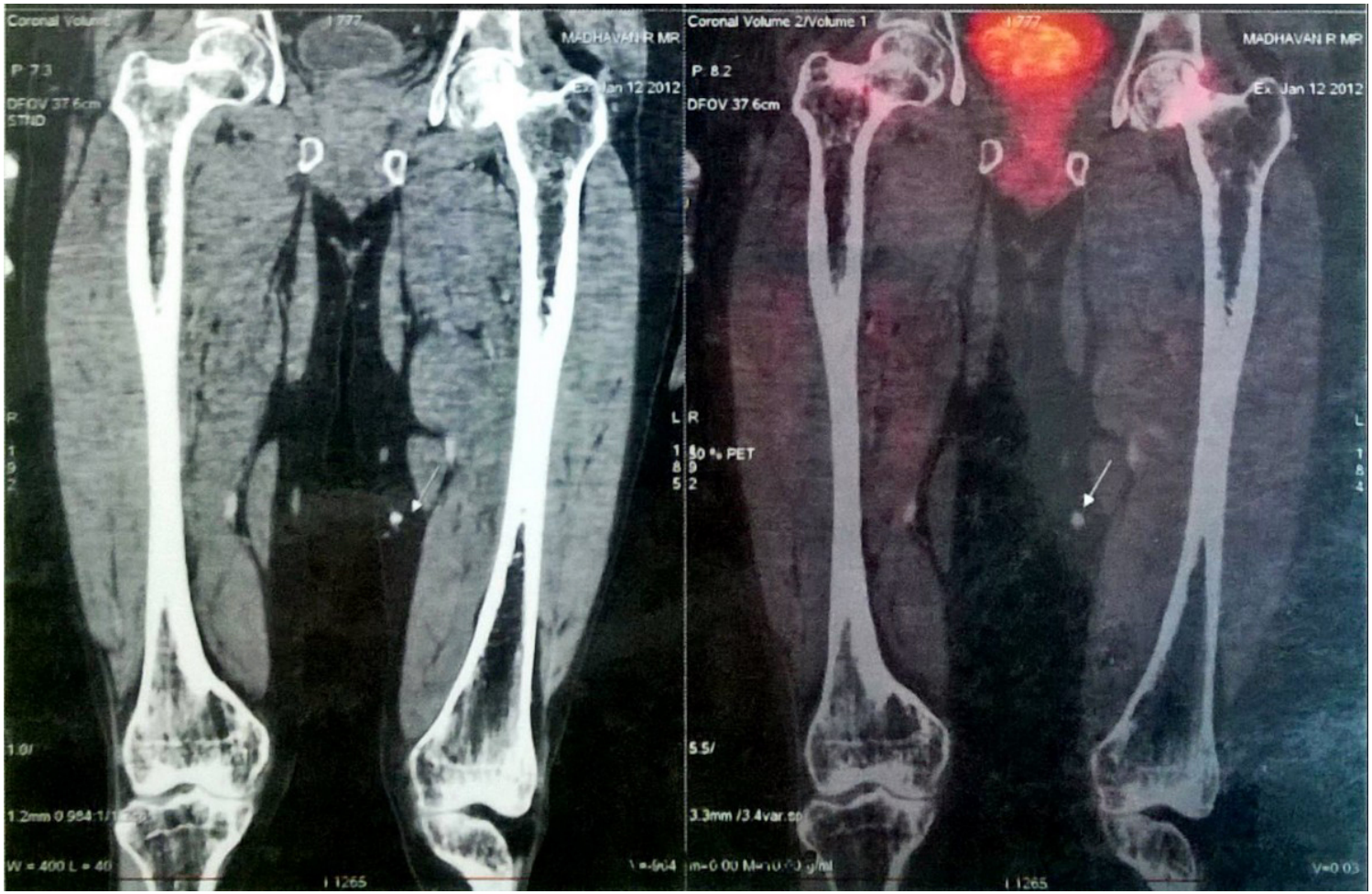



Figure: PET CT(fused) Left thigh

# Imaging options[4]

- FDG-PET CT
- $^{99}Tc$—HYNIC-TOC SPECT CT
- $^{68}$ Ga DOTATATE

[4] Swati Jadhav et al. (2014). "Radiofrequency ablation, an effective modality of treatment in tumor-induced osteomalacia: a case series of three patients". In: *The Journal of clinical endocrinology and metabolism* 99.9, pp. 3049–3054.

# What do we want to know?

## Conditional Probability

$$P(OtherScan+|FDG-) = \frac{P(OtherScan+ve) \cap P(FDG+)}{P(FDG+)} \quad (4)$$

# What would you do?

1. Remove the FDG avid lesion
2. Remove the non FDG avid lesion
3. Remove both
4. Do some other scan

# Course

- Patient underwent surgical excision of FDG avid lesion in the posterolateral region of right leg
- Post operative biochemical evaluation done

# Biochemical parameters-Post surgery

| Parameter | Post Surgery |
|---|---|
| Calcium | 7.7 mg/dl |
| Phosphate | 1.2 mg/dl |
| ALP | 105 IU/L |
| TMP/GFR | 1.5 |
| **C-Terminal FGF23** | 102 RU/ml |

# Histopathology

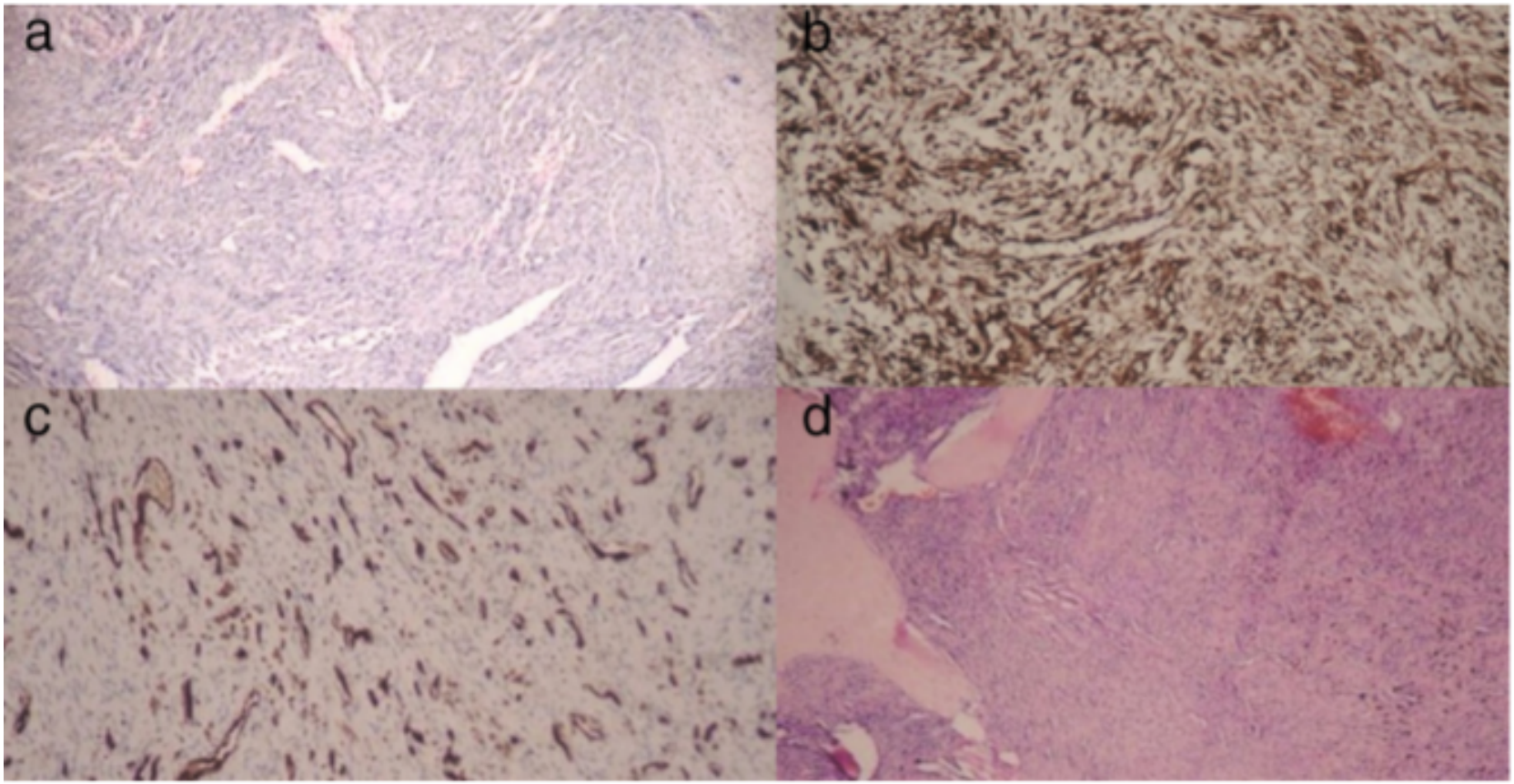



Figure: A, Proliferation of spindle cells in small fascicles and the striking hemangiopericytomatous pattern. B, Positivity of the tumor cells for vimentin. C, CD 34 highlighting the blood vessels and thus the hemangiopericytomatous pattern. D, Tumor composed of spindle cells and metaplastic osteoid formation along with focal areas showing hemosiderin-laden macrophages

# Course...

- Failed first surgery in spite of complete tumor excision
- Waited for 8 weeks to rule out delayed remission
- Underwent removal of FDG negative lesion in left medial thigh

# Biochemical parameters-Post surgery

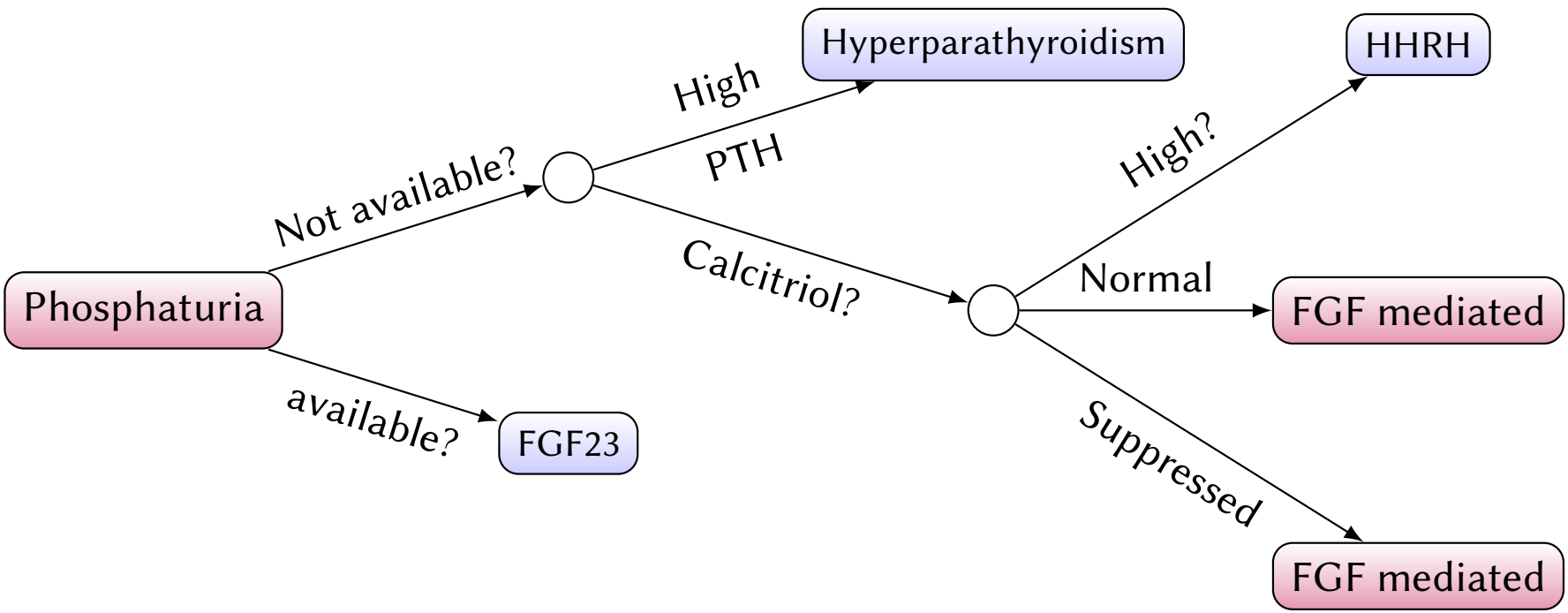
| Parameter | Post Surgery-1 | Post Surgery-2 |
|---|---|---|
| Calcium | 7.7 mg/dl | 9.3 mg/dl |
| Phosphate | 1.2 mg/dl | 4.3 mg/dl |
| ALP | 105 IU/L | 162 IU/L |
| TMP/GFR | 1.5 | 2.4 |
| **C-Terminal FGF23** | **102 RU/ml** | **22 RU/ml** |

# Final Diagnosis

Tumor(s) Induced Osteomalacia[5]

[5] Jayaprakash Sahoo et al. (2014). "Tumor(s) induced osteomalacia–a curious case of double trouble". In: *The Journal of clinical endocrinology and metabolism* 99.2, pp. 395–398.

# I can't do FGF 23 !



# Tumor not found 😢

- Wait for it to show up
- Supplement Phosphate (40 mg/kg/day) in divided doses
- Give Calcitriol at 1- 3 $\mu g/day$

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**Watch out**

- Secondary hyperparathyroidism
- Nephrocalcinosis

# Tumor inoperable 😢

- Radiofrequency ablation[6]
  - Close to joint
  - Inside bone
  - Multifocal
- Octreotide
- Total parathyroidectomy[7]
- Anti FGF 23 antibodies
- PPRT

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[6] Swati Jadhav et al. (2014). "Radiofrequency ablation, an effective modality of treatment in tumor-induced osteomalacia: a case series of three patients". In: *The Journal of clinical endocrinology and metabolism* 99.9, pp. 3049–3054.

[7] Sanjay K. Bhadada et al. (2013). "Deliberate total parathyroidectomy: a potentially novel therapy for tumor-induced hypophosphatemic osteomalacia". In: *The Journal of clinical endocrinology and metabolism* 98.11, pp. 4273–4278.

# Case 2

- Similar biochemical picture
- Deformities started in childhood
- Strong family history
- Dental abscess

# Clinical Details

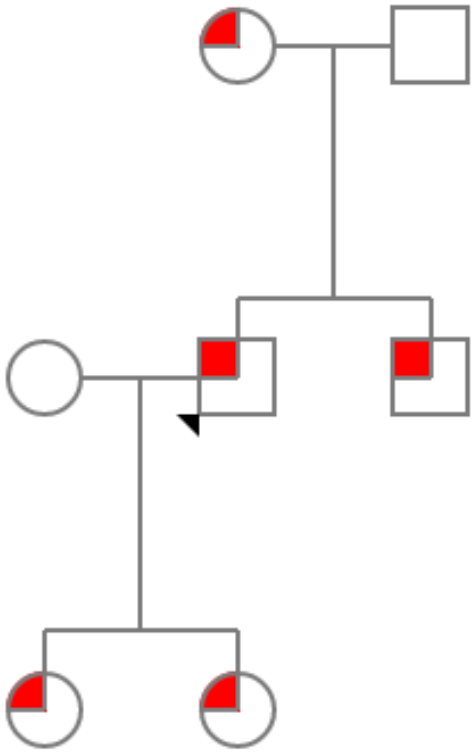

Figure: Family Tree

# Clinical Details[8]

Figure: Anterior interosseous membrane calcification

[8] Ritesh Kumar et al. (2015). "A unique cause of interosseous membrane calcification". In: *BMJ case reports* 2015.

# Approach

Table: *Calcipenic vs Phosphopenic rickets*

| Feature | Calcipenic rickets | Phosphopenic rickets |
|---|---|---|
| Muscle weakness | Present | Absent(except in TIO) |
| Bony pain | Common | Uncommon |
| Extremities involved | All limbs equally | Lower limb predominant |
| Tetany | May be present | Absent |
| Enamel hypoplasia | May be present | Absent |
| Dental abcess | Absent | May be present |
| Family history | Less common | More common |
| Interosseous membrane calcification | Absent | May be present |
| Enthesopathy | Absent | May be present |

# Diagnosis

X linked Hypophosphatemic Rickets

## Take home

- History,Clinical Examination and basic labs are the most important tools
- First principles approach and judicious use of 'fancy' investigations
- Multidisciplinary care is important

# Thank You😄

Slides and source available @`www.github.com/karthikjipmer`