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The Silent Tubule, the Fragile Bone: Adult Fanconi Syndrome Presenting with Pathological Fracture

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Abstract

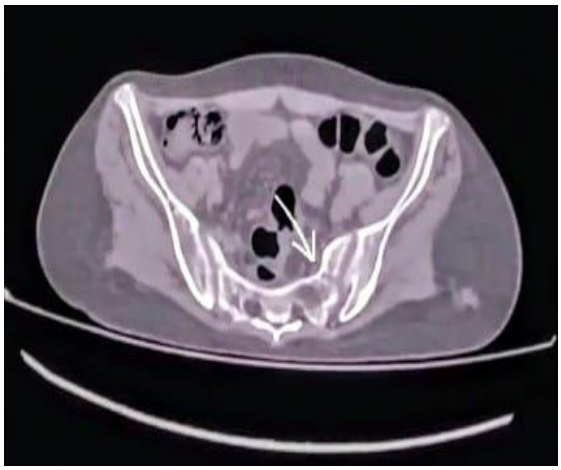
Background: Fanconi syndrome is characterized by generalized proximal tubular dysfunction leading to urinary wasting of phosphate, glucose, bicarbonate, amino acids, and other solutes. Adult-onset disease is uncommon and typically secondary to drugs, toxins, or systemic disorders. Genetic forms presenting in early adulthood are rare and may remain unrecognized until skeletal complications occur.[1] **Case Report:** A 20-year-old previously healthy woman presented with chronic low back and bilateral hip pain and was found to have bilateral iliac stress fractures. Biochemical evaluation revealed persistent hypophosphatemia, Vitamin D deficiency, normoglycemic glucosuria, aminoaciduria, phosphaturia, tubular proteinuria, and proximal renal tubular acidosis, consistent with Fanconi syndrome. Secondary causes were excluded. Genetic testing identified a pathogenic SLC34A1 mutation, confirming inherited proximal tubular dysfunction. She was treated with alkali therapy (sodium bicarbonate and potassium citrate) and phosphate supplementation, resulting in biochemical improvement and no further fractures on follow-up. **Conclusion:** This case underscores the importance of considering proximal tubular disorders in young adults with unexplained hypophosphatemia and stress fractures. Early recognition and targeted metabolic correction are crucial to prevent progressive skeletal morbidity and preserve renal function.

Keywords: Stress fracture, renal Fanconi syndrome, renal tubular acidosis, glucosuria.

CASE PRESENTATION

A 20-year-old female, born out of a non-consanguinous marriage, with no significant family history, presented with complaints of 3-year long progressive low back pain, bilateral hip and shoulder pain, that gradually worsened, resulting in difficulty in walking and performing activities of daily living. This was not associated with proximal muscle weakness, early morning stiffness, or increased urinary frequency. There was no history of trauma, long-term drug use like steroids or antiepileptics, or chronic systemic illness.

On examination, she was conscious and oriented, with preserved higher mental functions. Neurological examination revealed proximal muscle weakness (power 3/5 in lower limbs) with intact reflexes and sensation. Diffuse bony tenderness was noted, particularly over the pelvic girdle and lumbar spine. Antalgic gait was noted.
Radiological Imaging done by CT Hip showed diffuse osteoporotic changes in the Dorso-lumbar vertebrae, pelvic bones, and femur (Figure 2). Pathological Undisplaced fracture noted in Right Ala of Sacrum (Figure 1)



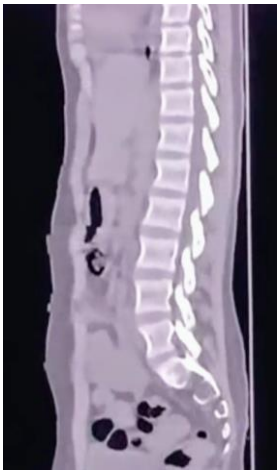


Figure 1 – Arrow mark depicting Right Sacral Ala Fracture Line.
Figure 2 – Diffuse Osteoporotic Changes across Dorsolumbar Vertebra and Pelvic bones.

Dual-energy X-ray absorptiometry (DXA) demonstrated Severe osteoporosis with markedly reduced bone mineral density. Ultrasound of the abdomen showed normal-sized kidneys with normal echoes.

Table 1: Depicts the Blood investigations done through the course of her hospital stay

	Parameter	**Result**	**Units**	**Reference Range**	**Interpretation**
Serum Biochemistry	Calcium	8.7–10.3	mg/dL	8.6–10.4	Normal
	Phosphorus	**0.8–1.5**	**mg/dL**	**2.5–4.5**	**Low**
	Sodium	137	mEq/L	136–146	Normal
	Potassium	3.5	mEq/L	3.5–5.0	Low-normal
	Chloride	109	mEq/L	98–110	Normal
	Creatinine	0.8	mg/dL	0.5-1.3 mg/dL	Normal
	eGFR	108	mL/min/1.73m^2		Normal
	Albumin	4.3–4.8	g/dL	3.5–5.0	Normal
	Total Protein	6.6	g/dL	6.5–8.0	Normal
	ALP	201–213	IU/L	35–130	Mildly elevated
	AST	20	IU/L	12–38	Normal
	ALT	13	IU/L	7–41	Normal
Acid–Base Status	Arterial pH	7.28	–	7.35–7.45	Low
	HCO_3^-	20.2	mmol/L	22–26	Low
	Anion Gap	Normal	–	8–12	Normal
	Urine pH	**6.0–6.5**	**–**	**5.5–7.0**	**Inappropriately high**
Urine Findings	**Glucose**	**2+**	**–**	**Negative**	**Renal glucosuria**
	Protein	2+	–	Negative	Tubular proteinuria
	Leukocytes	-	–	Negative	–
	Blood	1+	–	Negative	–
	Specific Gravity	1.020	–	1.015–1.025	Normal
	Microprotein	183	mg/dL	–	Elevated
	UPCR	**3.38**	**–**	**<0.20**	**Elevated**
	Urine Sodium	124	mEq/L	–	–
	Urine Potassium	23.9	mEq/L	–	–
	Urine Creatinine	54.1	mg/dL	-	Elevated
Phosphate Handling	Urine Phosphate	13.7	–	–	**Renal phosphate wasting**
	Tubular Reabsorption of Phosphate	**0.584**	**–**	**>0.85**	**Reduced**

	Ca/Cr Ratio	0.5	–	<0.2	Elevated
Endocrine Evaluation	PTH	23	pg/mL	16–65	Normal
	Vitamin D (25-OH)	**5.48**	**ng/mL**	**30–80**	**Severely low**
	TSH	1.86	µIU/mL	0.3–4.2	Normal
	Free T4	1.16	ng/dL	0.93–1.7	Normal
	Free T3	5.6	pmol/L	3.1–6.8	Normal
	Intact FGF23	**8.55**	pg/mL	23–95	**Low**

Given her young age and progressive musculoskeletal symptoms, secondary causes of osteoporosis were evaluated. MRI Lumbar Spine showed no evidence of compressive or intrinsic cord pathology. Hematological parameters, renal function, calcium levels, and imaging findings were not suggestive of plasma cell dyscrasia. Inflammatory markers were normal, and there were no clinical features of rheumatologic disease. There was no history of drug exposure or toxin intake. Although vitamin D deficiency was present, the associated hypophosphatemia, metabolic acidosis, normoglycemic glycosuria, proteinuria, and aminoaciduria suggested a proximal tubular defect, a Fanconi – like syndrome rather than isolated nutritional deficiency.

Genetic analysis was done, which confirmed the presence of a mutation in the **SLC34A1** gene locus on Chromosome 5q. This confirmed our diagnosis of **Fanconi Renotubular Syndrome 2.** Her parents and her sister subsequently tested negative for Fanconi's syndrome with a urinary amino acid screen.

The patient was managed with oral sodium bicarbonate and oral potassium citrate. Vitamin D and oral Phosphorus supplementation was given. Her stress fracture was managed conservatively, and the patient was followed up at regular intervals. After 3 months and 6 months of follow-up, her pain has significantly subsided, and she has resumed her regular daily activities with ease. Serum Calcium, Phosphorus, and Bicarbonate were maintained within normal limits.

DISCUSSION

Fanconi Renotubular Syndrome 2 is a rare inherited proximal tubular disorder characterized by impaired reabsorption of phosphate and other solutes in the proximal tubule, leading to phosphaturia, glycosuria with normoglycemia, aminoaciduria, and varying degrees of metabolic acidosis. Mutations in the SLC34A1 gene, located on chromosome 5q, encode the sodium–phosphate cotransporter (NaPi-IIa), a key transporter responsible for renal phosphate reabsorption.[2] Dysfunction of this transporter results in chronic phosphate wasting, defective bone mineralization, and subsequent osteomalacia or severe osteoporosis, particularly in young individuals.[3]

Our patient presented with progressive musculoskeletal pain, pathological sacral fracture, and severe osteoporosis at the age of 20 years, an age at which primary osteoporosis is uncommon. The chronicity of symptoms, absence of trauma, and lack of systemic inflammatory features prompted consideration of a broad differential diagnosis. Neurological causes such as compressive myelopathy were ruled out by a normal MRI spine. Plasma cell dyscrasia was unlikely given normal hemogram, renal function, calcium levels, and absence of lytic lesions. Inflammatory myopathy and rheumatological disorders were excluded based on clinical and laboratory parameters.

Although vitamin D deficiency was present, it could not account for the constellation of severe hypophosphatemia, euglycemic glycosuria, aminoaciduria, proteinuria, and metabolic acidosis. The presence of these findings with preserved renal function strongly suggested a generalized proximal tubular defect, consistent with a Fanconi-like syndrome.[4] Unlike acquired forms of Fanconi syndrome—which are commonly secondary to drugs (e.g., tenofovir, ifosfamide), heavy metal toxicity, or systemic diseases—our patient had no relevant exposure history, making an inherited etiology more likely.
Genetic confirmation of an SLC34A1 mutation established the diagnosis of Fanconi Renotubular Syndrome 2. This condition may demonstrate variable phenotypic expression, ranging from nephrolithiasis and hypercalciuria to hypophosphatemic rickets or osteomalacia.[5] Interestingly, despite being born to a non-consanguineous marriage and having no significant family history, the patient manifested clinically significant disease in early adulthood. Negative screening of her parents and sibling suggests either a de novo mutation or a recessive inheritance with carrier status not detected on urinary screening alone.[6]

The pathophysiology of skeletal involvement in this disorder is primarily driven by chronic phosphate depletion. Phosphate is essential for hydroxyapatite formation and bone mineralization; persistent losses result in defective mineralization, bone pain, fractures, and proximal muscle weakness[7]. The pathological sacral fracture observed in our patient likely represents an insufficiency fracture secondary to prolonged osteomalacia.

Management of proximal tubular disorders is largely supportive and aimed at correcting metabolic derangements. Alkali therapy with sodium bicarbonate and potassium citrate corrects metabolic acidosis, thereby improving bone buffering and reducing further mineral loss. Phosphate supplementation and vitamin D replacement address hypophosphatemia and improve mineralization.[8][9] Our patient demonstrated significant symptomatic improvement within six months of therapy, along with normalization of serum calcium, phosphate, and bicarbonate levels, underscoring the importance of early recognition and targeted metabolic correction.

CONCLUSION

This case highlights several important clinical lessons. First, severe osteoporosis or pathological fractures in young adults should prompt evaluation for secondary causes, particularly renal tubular disorders. Second, the presence of hypophosphatemia with euglycemic glycosuria and normal renal function is a key diagnostic clue toward proximal tubular dysfunction. Finally, genetic confirmation not only establishes the diagnosis but also aids in counseling and prognostication.[10] In conclusion, this case emphasizes the need for high clinical suspicion for inherited proximal tubular disorders in young patients presenting with unexplained osteoporosis and fractures. Early diagnosis and metabolic correction can significantly improve functional outcomes and prevent long-term skeletal morbidity.

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