Delayed diagnosis of plasma cell disorder related Fanconi syndrome in young adults presenting as osteomalacia: report of two cases with normokalemia and normal haematological parameters at the time of presentation

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ABSTRACT

Adult-onset hypophosphatemic osteomalacia is rare and diagnosis is frequently delayed. Fanconi syndrome (FS) due to monoclonal gammopathy is a well-recognized, but rare cause of hypophosphatemia. The relatively young age of patients and normal routine hematological parameters often results in late recognition of this treatable disease entity. Low phosphorus, elevated alkaline phosphatase, mildly impaired renal function and hypokalemia are often the only abnormalities on routine evaluation. We summarize the clinico-pathological features of two cases who initially presented with fractures and proximal myopathy and were subsequently found to have FS secondary to light chain proximal tubulopathy. Atypical features like absence of hypokalemia at presentation and elevated fibroblast growth factor 23 (FGF 23), a marker of oncogenic osteomalacia were noted. Marked clinical improvement and recovery of renal parameters were evident with phosphate supplements and chemotherapy for the plasma cell disorder. FS due to monoclonal gammopathy may present with atypical features and diagnosis may be challenging.

Introduction

Fanconi syndrome (FS) refers to dysfunction of proximal renal tubule characterized by glycosuria, aminoaciduria, uricosuria, phosphaturia and proximal renal tubular acidosis. Clinically, FS is characterized by bone disease and slowly progressive renal failure. Aetiology of FS in adulthood has limited differentials including myeloma, monoclonal gammopathy, amyloidosis and drug/toxin exposure. Monoclonal gammopathy signifies the presence of a monoclonal immunoglobulin or its component. Unlike classical routine hematological parameters are frequently normal. FS in this group of disorders is due to Proximal tubulopathy which is either due to light chain proximal tubulopathy[1] (LCPT) or heavy chain deposits ,the former being more common. LCPT by itself is rare, accounting for just 5% of kidney biopsies in patients with monoclonal gammopathy.[2] Here we describe two patients with FS with atypical features.

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Case Reports

Case #1

A 40-year old female with a background of Type 2 DM, bronchial asthma, recurrent left renal calculi presented with pain over the plantar aspect of right foot. MRI done showed T1 hyperintensity involving proximal and mid 1/3rd of 2nd metatarsal bone with cortical break suggestive of stress fracture. History of body aches, mild proximal weakness and remedial measures in the form of indigenous medications were

forthcoming. On routine evaluation patient was found to have phosphorus of 1.4 mg/dL and hence was referred to Endocrinology services for further workup. Basic investigations revealed low phosphorus,borderline elevated creatinine with normal hemogram. Acidosis was subsequently recorded (Table 1). Serum protein electrophoresis was normal. FGF 23 (Human FGF23 (C-Terminal) ELISA, Quidel Immutopics, Range 0-150 RU/mL, the coefficient of variation <10%) was high, but a subsequent whole body Ga^{68}DOTANOC-PET CT scan failed to detect any tumor. Autoimmune profile (ANA IF) turned out to be negative. Heavy metal contamination of indigenous medications was considered but could not be proven due to non-availability of samples for testing . Light chain estimation done with the suspicion of gammopathy showed elevated kappa level. Further Bone marrow aspiration and biopsy showed plasma cell collections, up to 15% focally.

A final diagnosis of light chain myeloma-ISS 1 stage was made, and patient was started on CyBorD chemotherapy regimen along with phosphorus and alkali supplements. She is currently doing well with minimal alkali and phosphorus supplements.

Case #2

A 42-year old female with no known comorbidities presented with bilateral hip pain and inability to walk without support. An initial diagnosis of bilateral avascular necrosis (AVN) of femoral neck was made which led to bilateral hip core decompression with bone marrow aspirate concentrate injection for hip stabilization. Routine hematological parameters and electrolytes were normal. Glycosuria, hypophosphatemia, proteinuria and acidosis were noted which led to consideration of acquired Fanconi syndrome. On radiological review pseudo fractures (Figure 1) were noted in both femoral necks, however with no displacement. AVN of femoral neck has been reported in displaced stress fractures, however we are unsure as to the exact cause of AVN in our patient. Microcirculatory disturbances have been recorded even in monoclonal gammopathy or unknown significance (MGUS).[3] We theorize that stress fractures and microcirculatory disturbances resulting from the plasma cell disorder could have contributed to the AVN. Further workup revealed elevated plasma light chain levels. Bone marrow was suggestive of lymphoplasmacytoid lymphoma (LPL) (Table 1). Renal biopsy showed kappa chain deposition in the proximal tubular epithelium (Figure 2). This was considered as monoclonal gammopathy of renal significance due to LPL. Currently she is on phosphorus/alkali replacement and chemotherapy (R Bendamustine).

Discussion

Classical FS is a well characterized clinical entity. However, when hypokalemia is absent and phosphorus estimation is not done the diagnosis can be delayed. In plasma cell disorders proximal tubule dysfunction is related to cast nephropathy (CN) or light chain injury without casts. CN results from obstructive free light chain plugs in tubules and is usually associated with high tumor burden.[4-6] This is seen in patients with mul-

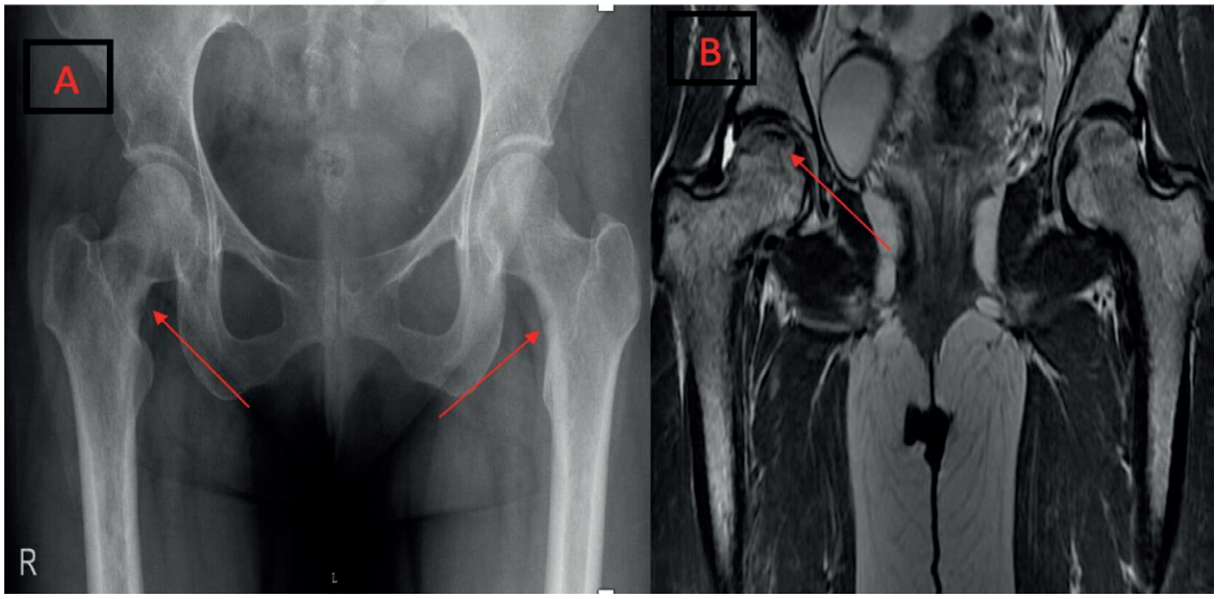

Figure 1. Imaging characteristics of Case #2: A) x-ray pelvis showing pseudo fractures in neck of femur; B) magnetic resonance imaging of the pelvis showing avascular necrosis of femur head.

Table 1. Clinical features of the patients.

Patient	Case #1	Case #2
Gender	F	F
Age at diagnosis (years)	41	42
Presenting complaint	Right foot pain	Bilateral hip pain
WBC count (10^9/L)	11	6.9
Hemoglobin (g/L)	138	119
ESR	7	16
Total protein (64-83 g/L)	66.7	75
Albumin (35-52 g/L)	43.5	46
Globulin (25-40 g/L)	23.2	28.7
S. calcium (2.1-2.5 mmol/L)	2.27	2.35
S. phosphorus (0.84-1.45 mmol/L)	0.45	0.68
S. creatinine (0-79.56 umol/L)	111.38	121.11
eGFR	53.2	47.8
Proteinuria	+	+
Renal glycosuria	+	+
Uric acid (154.65-356.88 umol/L)	89.22	89.22
ABG-pH/HCO_{3-}	7.266/17.7	7.27/15.1
Potassium (3.5-5 mmol/L)	3.6	3.5
PTH (12-65 ng/L)	59.9	8.94
25(OH)vit D3 (75-175 nmol/L)	NA	143.27
ALP (30-120U/L)	175	213
FGF23 (<150 RU/mL)	191	NA
Skeleton changes	T1 hyperintensity involving proximal and mid third of 2nd metatarsal bone with cortical break-Stress fracture	B/l Avascular necrosis of femoral head
Kappa freelite (3.3-19.4 mg/L)	636	44.69
Lambda freelite (5.7-26.3 mg/L)	6.26	9.3
Serum paraprotein	Kappa	Kappa
% of M protein in SPE	Negative	Negative
% of plasma cells in BM aspiration	14	1
Bone marrow biopsy	Normo to hypercellular marrow with large plasma cell collection	Normo to focally hypercellular marrow showing trilineage maturation and focal nodular and diffuse interstitial infiltrate of mature lymphoid cells with admixed plasma cells. In view of IHC showing diffuse positivity for CD20 with CD38, possibility of lymphoplasmacytic lymphoma may be considered
Treatment	CyBorD phosphorus and bicarbonate supplements	R-Bendamustine phosphorus and bicarbonate supplements
Initial replacements a) Phsophorus b) Alkali c) Potassium	 1500 mg/day 144 mEq/day Nil	 1250 mg/day 100 mEq/day 100 mEq/day
Replacements during follow-up a) Phosphorus b) Alkali c) Potassium	 500 mg/day Nil Nil	 1250 mg/day 136 meq/day 136 meq/day
Duration of follow up (months)	36	6

NA, not available; WBC, white blood count; ESR, erythrocyte sedimentation rate; eGFR, estimated glomerular filtration rate; ABG, arterial blood gas; PTH, parathyroid hormone; 25(OH)Vit D3, 25 hydroxy vitamin D3; ALP, alkaline phosphatase; FGF23, fibroblast growth factor 23.

tiple myeloma, lymphoplasmacytoid lymphoma and high grade CLL. More subtle direct obstructive light chain induced injury resulting from misfolding and resistance to proteolytic cleavage leading to toxic amyloid multimers, tubule and crystals.

The term monoclonal gammopathy of renal significance (MGRS)[6] has been suggested to highlight the target organ damage in patients who do not fit in the 2014 revised criteria for multiple myeloma or other plasma cell disorders but has enough light chain disease burden to cause tubular damage and renal dysfunction. Patient 2 comes under MGRS category as she does not satisfy hematological criteria for chemotherapy.

In one large series from Mayo Clinic,[5] 32 patients with acquired Fanconi syndrome secondary to plasma cell dyscrasia were included. 31% had multiple myeloma (MM), 6% had lymphoplasmacytoid lymphoma, 19% smouldering MM, and 44% monoclonal gammopathy of undetermined significance (MGUS). Most common presenting symptom was bone pain followed by fatigue. As far as biochemical parameters are concerned 44% had hypokalemia, 50% had hypophosphatemia, and 66% had hypouricemia. In a recent series[7] of 46 patients, 21 cases of MGRS were noted.

Bone pain with stress fractures were the presenting symptom in our patients which is similar to other reports available in literature.[5,8] In patient 1, FGF23 (ELISA, Quidel Immutopics) was not suppressed, raising concerns of an FGF 23 dependent etiology as Fanconi syndrome is usually associated with low FGF23. Whole body Ga-DOTANOC-PET scan did not reveal any tumor. Protein electrophoresis was normal. FGF 23 concentrations are classically elevated in mesenchymal tumors.[9] In previous reports of plasma cell dyscrasias with elevated FGF 23 phosphorus was found to be normal. The absence of hypophosphatemia was attributed to the systemically bio inactive FGF 23 produced by abnormal plasma cells.[4] Thus, it is likely that FGF 23 may not have contributed to hypophosphatemia in patient #1. In the second patient, we proceeded directly to monoclonal gammopathy workup which showed elevated light chains. BM biopsy showed lymphoplasmacytic lymphoma.

Both patients had mildly deranged renal function at the time of diagnosis which showed partial recovery after initiation of chemotherapy. Progression to end stage renal failure has been reported in 8-15% of patients.[5,7] Familiarity with the atypical presentation is the key to early diagnosis and subsequent early initiation of chemotherapy and supportive treatment options.

Conclusions

FS and consequent bone related symptoms are a rare complication of monoclonal gammopathy which is often missed due to lack of familiarity with the clinical presentation. A simple urine routine examination can provide leading clues. Apparently normal routine hematological parameters should not be a deterrent for workup directed at plasma cell disorders.

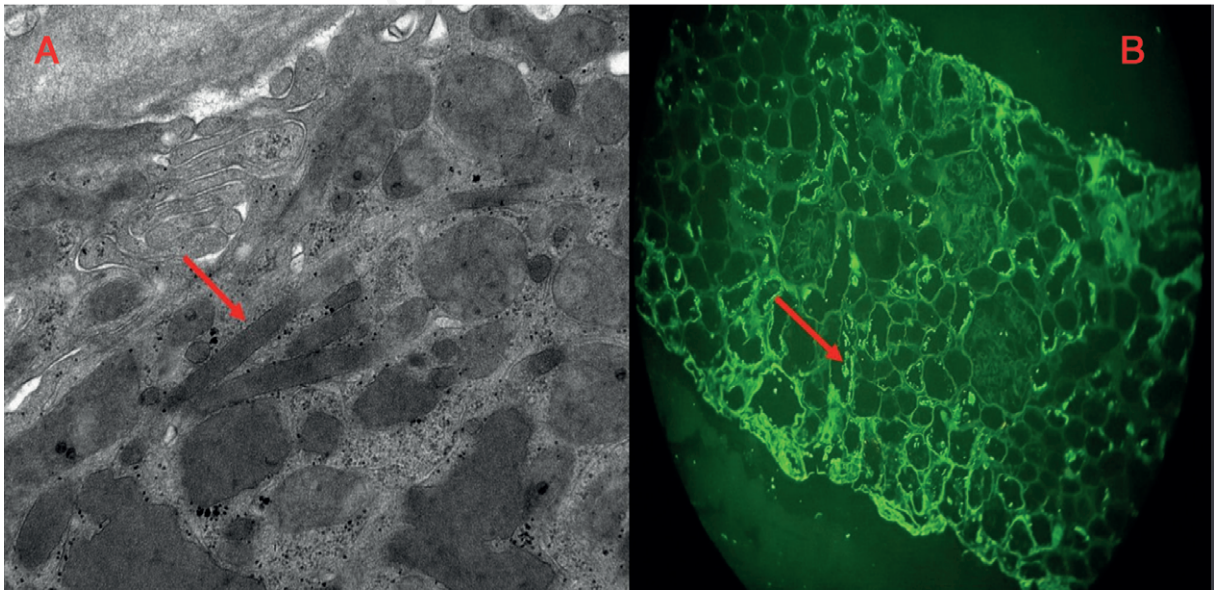

Figure 2. Renal biopsy findings of Case #2: A) electron microscope image of renal biopsy - arrow showing crystalline material in proximal epithelial cell cytoplasm; B) paraffin - IF image: fluorescence noted in tubular epithelium with kappa light chain restriction.

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