Acquired Fanconi syndrome secondary to light chain deposition disease associated with monoclonal gammopathy of renal significance
A case report
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Abstract
Rationale: Renal Fanconi syndrome (FS) is a rare complication of monoclonal gammopathy. It is characterized by the impairment of renal proximal tubular function leading to normoglycemic glycosuria, aminoaciduria, hypophosphatemia, hypouricemia and proximal renal tubular acidosis. Renal impairment in monoclonal gammopathy, without fulfilling the criteria of multiple myeloma, is categorized as monoclonal gammopathy of renal significance (MGRS).

Patient concerns: A 54-year-old male presented with progressively aggravated bone pain and limitation of activity was admitted to our department. A proximal renal tubular damage was suggested by hypophosphatemia, compensated metabolic acidosis, renal glycosuria, aminoaciduria, and hypouricemia. M-protein of IgA kappa was detected by immunofixation electrophoresis. Mildly increased plasma cells were found in bone marrow cytomorphologic examination. Renal biopsy revealed diffuse linear monoclonal IgA-kappa light chain deposits along tubular basement membranes (TBMs), while lambda was negative. Electron microscopy showed granular electron-dense deposits along the outer aspect of TBMs.

Diagnoses: The patient was diagnosed as FS induced osteomalacia secondary to monoclonal gammopathy of renal significance (MGRS) (IgA-kappa type) and LCDD.

Interventions: He was treated with bortezomib, supplementation by phosphate, alkali agents, and active vitamin D. He responded well to the treatment symptomatically.

Outcomes: We reported a rare case of adult acquired FS with hypophosphatemic osteomalacia secondary to LCDD associated with MGRS and the patient was successfully treated with bortezomib.

Lessons: Although few cases of LCDD with isolated symptoms of tubulointerstitial nephropathy, rather than glomerular symptoms have been reported. It still needs to be recognized as a differential diagnosis in monoclonal gammopathy.

Abbreviations: FS = Fanconi syndrome, GBMs = glomerular basement membranes, LCDD = light chain deposition disease, MG = monoclonal gammopathy, MGRS = monoclonal gammopathy of renal significance, MIDD = monoclonal immunoglobulin deposition disease, TBMs = tubular basement membranes.

Keywords: Fanconi syndrome, light chain deposition disease, monoclonal gammopathy, monoclonal gammopathy of renal significance

1. Introduction

Fanconi syndrome (FS) is a disease characterized by generalized impairment of proximal renal tubular function, leading to proteinuria, aminoaciduria, hypophosphatemia, hypouricemia, renal glycosuria, and proximal renal tubular acidosis. It often occurs as a congenital disease. However, the acquired form of FS has also been reported. One rare risk factor for acquired FS is monoclonal gammopathy, including monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, Waldenstrom macroglobulinemia, lymphoplasmacytic lymphoma, chronic lymphocytic leukemia, and monoclonal immunoglobulin deposition disease (MIDD).

Here we report a rare case. A 54-year-old man, clinically presenting with aggravated bone pain, was diagnosed acquired FS to MGRS (IgA-kappa type) and LCDD, on the basis of serum and urinary immunoelectrophoresis and renal biopsy. LCDD is a rare plasma cell dyscrasia characterized by deposition of immunoglobulin fragments. About 50% of patients with LCDD have concurrent myeloma, however most present with nephrotic range proteinuria and rapidly deteriorating renal function. Renal biopsy shows nodular glomerulosclerosis, resembling diabetic kidney changes, and linear deposits of monoclonal light chains.
along glomerular basement membranes (GBMs) and tubular basement membranes (TBMs) by immunofluorescence. Contrasting with the pathological typically renal findings reported, patient of our case was diagnosed light chain associated FS which was characterized by pathological isolated symptoms of tubulointerstitial nephropathy, linear light chain deposition predominant along TBMs, while GBMs are negative. It was recognized as a differential diagnosis in monoclonal gammopathy and required specific treatment. Our patient was treated with bortezomib and responded well. This is the first report of the use of bortezomib in the treatment of LCDD associated FS.

2. Case report

A 54-year-old man presented with progressively increasing fatigue and multiple skeletal pain for more than 2 years. At admission, his blood pressure was 120/80 mm Hg. Physical examination was unremarkable except multiple bone pain on palpation. Laboratory investigations revealed a hemoglobin of 137 g/L, white blood count (WBC) 5.6 × 10^9/L, platelet count 150 × 10^9/L, erythrocyte sedimentation rate (ESR) 2 mm/hour, serum albumin 39.6 g/L, total protein 60.2 g/L, globulins 20.6 g/L [albumin/globulin (AG) ratio: 1.9], serum creatinine 111 μmol/L, estimated glomerular filtration rate (eGFR) 64 mL/min, blood urea nitrogen 21 mmol/L, serum potassium 3.04 mmol/L, serum bicarbonate 19.0 mmol/L, total serum calcium 2.1 mmol/L, serum phosphate 0.57 mmol/L, serum uric acid 118 mmol/L, hormone (iPTH) level was 33 pg/mL, blood sugar 4.2 mmol/L, and serum bicarbonate 19.0 mmol/L. Arterial blood gas analysis revealed metabolic acidoses with normal anion gap. Urine analysis revealed 2+ protein, 2 to 3 RBCs per high power field, urine glucose 4+, 24-h urine protein excretion was 1.8 g, urine microalbumin/creatinine ratio was 356.76 mg/g cr with generalized low-molecular-weight proteinuria (alpha1-microglobulin 335 mg/g cr and N-acetylglucosaminidase 27.81 IU/g cr), impairment of proximal renal tubular reabsorption of uric acid and phosphate were present with FEUA = 43.92% (reference range: 2%–10%), FEPI = 47.12% (reference range: 5%–15%).

Urine Bence Jones protein was negative. Serum electrophoresis showed an intense monoclonal M band in the gamma region, with markedly elevated serum IgA 6.07 g/L (normal 0.7–4.0 g/L), while IgG 4.37 g/L (normal 7.0–16.0 g/L) and IgM 0.3 g/L (normal 0.4–2.3 g/L), normal C3 and C4. Immunofixation of serum and urine showed IgA-kappa monoclonality with an elevation of serum light chain kappa/lambda ratio 5.7 (normal 1.35–2.65) (Table 1). Serum free light chain (FLC) was not measured due to the lack of free light chain testing at our institute.

99mTc-hydroxymethane diphosphonate (HMDP) bone scintigraphy revealed multiple foci of tracer accumulation in the left maxillary bone, bilateral ribs, right sacroiliac joint, bilateral hip, knee, and ankle (Fig. 1), while conventional bone radiograph and magnetic resonance imaging (MRI) did not show osteolytic lesions. Dual-energy x-ray absorptiometry of the bilateral hip, sacral spine revealed that patient had a low bone mineral density (T score –3.4 SD). Bone marrow biopsy revealed 1% plasma cells. Immunofluorescent study and electron microscopy of the bone marrow specimen was not done.

Based on these findings, a diagnosis of acquired Fanconi syndrome was established. In this case, plasma cell dyscrasia did not play a role.
not meet the diagnostic criteria for multiple myeloma.\cite{5} Radiograph and MRI of the bone could not demonstrate the osteolytic lesions suggesting myeloma (skeletal survey did not reveal any lytic bony lesions). Therefore, low hypophosphatemic osteomalacia secondary to FS was thought to be responsible for bone lesions, and a diagnosis of monoclonal gammopathy of undetermined significance (MGUS) was made.

A renal biopsy was performed to obtain a definitive diagnosis. Among the eighteen glomeruli sampled for histopathology, 6 glomeruli were global sclerosis, and other glomeruli showed no abnormalities. There were neither mesangial expansions nor nodular mesangial glomerulosclerosis observed. Glomerular basement membranes (GBMs) showed no thickening. Capillary loops were patent. There was focal tubular atrophy with diffuse thickening of tubular basement membranes (TBMs). Interstitial showed minor fibrosis and chronic inflammatory infiltrate. Rare myeloma casts were observed within distal tubule lumens. Vessels showed no specific changes. Immunofluorescence with IgG, IgA, IgM, C3, and C1q was negative. Immunofluorescence staining for kappa and lambda light chain showed diffuse linear monoclonal kappa light chains deposits along tubular basement membranes (TBMs), while lambda was negative (Fig. 2A). Linear light chain deposits along the glomerular basement membranes (GBMs) and around arteriolar myocytes were not identified. There was no evidence of amyloid deposits for Congo red stain was negative. Electron microscopy showed characteristic dark, finely granular electron-dense deposits along the outer aspect of TBMs (Fig. 2B). These findings strongly supported a diagnosis of LCDD of \(\kappa\) type with predominant tubulointerstitial lesions.

For clinical trials are rare, and treatment guidelines are based on individual experiences.\cite{5} Following the diagnosis of LCDD associated with MGRS (IgA-\(\kappa\) type), the patient was treated with intravenous bortezomib and oral dexamethasone (BD therapy: bortezomib 1.3 mg/m\(^2\) on days 1, 4, 8, 11, and dexamethasone 40 mg on days 1 to 4 every 21 days as 1 cycle and totally up to 6 cycles as standard protocol). In addition, he had treatment of correction of acidosis, phosphate supplementation, and active vitamin D. He responded well and symptoms including bone pain ameliorated after one cycle chemotherapy. However, he refused to further chemotherapy as economic reason and was lost to follow-up.

3. Discussion

Acquired Fanconi syndrome (FS) is a rare complication of monoclonal gammopathy. FS typically complicates MGUS or a low-grade MM, which is almost always of the \(\kappa\) type.\cite{1,6} Few cases have been described in WM.\cite{3} Renal impairment in monoclonal gammopathy without fulfilling the criteria of multiple myeloma is categorized in the recent literature as monoclonal gammopathy of renal significance (MGRS).\cite{7} Typical FS is characterized by the impairment of renal proximal tubular function leading to normoglycemic glycosuria, aminoaciduria, hypophosphatemia, hypouricemia, and proximal renal
tubular acidosis.[11] FS can also cause metabolic changes, osteomalacia, and renal dysfunction from chronic kidney disease (CKD) to end-stage renal failure (ESRD).

Kidney biopsy is indicated in most cases to determine the exact lesion associated with MGRS. In our case, renal biopsy was diagnostic of light-chain deposition disease (LCDD) predominant tubular basement membranes deposition. Previously, the clinical dogma has held that patients with LCDD present with proteinuria, usually nephrotic range. Only 16% of patients with LCDD were previously reported to have <1 g/day proteinuria.[4] However, Sicard et al[8] recently reported 14 patients with biopsy-proven renal LCDD and proteinuria \(<0.5 g/day\) at diagnosis. In addition, renal involvement in LCDD is pathologically typically characterized by nodular glomerulosclerosis, linear light-chain deposition in glomerular basement membranes, Bowman’s capsule, and around arteriolar myocytes is observed in most cases.[9] However, rare cases of LCDD with isolated symptoms of tubulointerstitial nephropathy have been reported.[8] In our case, 24-hour urine protein excretion was 1.8 g. Monoclonal kappa light chains deposit only along tubular basement membranes (TBMs), while GBMs are negative. It is possible that light-chain deposits localized to TBMs without GBMs deposits could result in only mild tubular proteinuria from altered tubular resorption but without glomerular proteinuria.[10] However, the precise characteristics underlying the heterogeneous localization and response to monoclonal light chains remain mostly unknown.

In this case, patient was diagnosed as acquired FS induced osteomalacia secondary to MGRS (IgA-k type) and LCDD. To date, there is no standard treatment for patients with MGRS. Current treatment of MGRS is based on therapies targeting the causal B-cell clone with treatment choices based on extrapolation of treatments used for the equivalent overt malignancy.[11] Chemotherapy with alkylating agents and steroids has shown modest results.[9] Bortezomib, a reversible proteasome inhibitor, has shown significant activity in myeloma patients and is safely administered to patients with renal failure, even those under dialysis.[19]

As for LCDD associated FS, very few series have been published and the efficacy of the antimyeloma agents has not been evaluated. In most cases, FS appears to slowly progress toward ESRD and rarely symptomatic myeloma.[11,6] Accordingly, therapeutic decisions should take into account treatment side effects, particularly the potential risk of secondary myelodysplastic syndrome from alkylating agents.[6] Symptomatic measures to prevent osteomalacia are mandatory. All patients with an associated overt lymphoid disorder should receive appropriate chemotherapy.[11] Otherwise, treatment choices should be adapted to the degree of renal failure: in patients with stages 1 to 3 CKD, should be considered to try to slow progression to ESRD. Cyclophosphamide, bortezomib, or thalidomide based regimens are the best options.[11]

Based on the above data we administered BD therapy. The patients received the combination of bortezomib 1.3 mg/m² on days 1, 4, 8, 11, and dexamethasone 40 mg on days 1 to 4 according to the protocol.[5] The patient was also given bicarbonate, phosphate, and vitamin D supplementation to prevent osteomalacia. He responded well and symptoms including bone pain ameliorated after 1 cycle chemotherapy. Unfortunately, the patient’s follow-ups were lost after he declined further chemotherapy due to financial reasons. Tests for urine protein and glucose were not done. The levels of serum creatinine and phosphate were unknown. Monoclonal proteins in the serum and urine were not analyzed using immunofixation electrophoresis. Thus, therapeutic evaluation of our treatment is inconclusive. In the future, well-designed prospective studies are required to assess long-term outcome.

4. Conclusions
In conclusion, we present a rare case of adult acquired FS secondary to LCDD associated with MGRS. Our case highlights that diagnostic work-up searching for monoclonal gamopathy should systematically be performed in patients with non-glomerular proteinuria kidney disease and renal biopsy should be considered, as this atypical form of tubulointerstitial LCDD is probably underdiagnosed, and it may require specific treatment.
Author contributions

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