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Case Report

A case of Fanconi syndrome accompanied by crystal depositions in tubular cells in a patient with multiple myeloma

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Abstract

Fanconi syndrome (FS) is a rare condition that is characterized by defects in the proximal tubular function. A 48-year-old woman was admitted for evaluation of proteinuria. The patient showed normal anion gap acidosis, normoglycemic glycosuria, hypophosphatemia, and hypouricemia. Thus, her condition was compatible with FS. The M peak was found behind the beta globulin region in urine protein electrophoresis. Upon bone marrow examination, we found that 24% of cells were CD138+ plasma cells with kappa restriction. From a kidney biopsy, we found crystalline inclusions within proximal tubular epithelial cells. Thereafter, she was diagnosed with FS accompanied by multiple myeloma. The patient received chemotherapy and autologous stem cell transplantation, and obtained very good partial hematologic response. However, proximal tubular dysfunction was persistent until 1 year after autologous stem cell transplantation. In short, we report a case of FS accompanied by multiple myeloma, demonstrating crystalline inclusion in proximal tubular cells on kidney biopsy.

Introduction

Fanconi syndrome (FS) is a rare disease characterized by defects in proximal tubular function, including impairment of reabsorption of solutes such as glucose, uric acid, phosphate, amino acid, and bicarbonate [1]. Patients with FS may present normoglycemic glycosuria, low molecular weight proteinuria, hypophosphatemia, and normal anion gap metabolic acidosis.

It has been described that Multiple myeloma may induce tubular dysfunction and FS [2]. Multiple myeloma is a neoplastic bone marrow disease characterized by clonal proliferation of plasma cells and overproduction of monoclonal protein [3]. Free light chain overproduction is associated with toxic effects to proximal tubular cells in the kidneys, which may induce FS [4].

In this case, the patient who had presented proteinuria initially was diagnosed with FS and multiple myeloma, after reviewing her results from blood laboratory work, urine analysis, and bone marrow examination. In addition, kidney pathology confirmed the presence of rod-shaped casts in proximal tubules.

Case report

A 48-year-old woman visited the nephrology clinic for proteinuria, which was detected at a local hospital. She had been producing foamy urine and experiencing nocturia for

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2 months, and she was suffering from bilateral flank pain for 6 months. She did not appear to have edema or to gain weight. She had no specific underlying disease or related family history. However, she had been taking a course of Chinese medicine for the past 6 months.

At presentation, her vital signs were stable (blood pressure: 128/80 mmHg, heart rate: 62 beats/minute, respiration rate: 18 breaths/minute, body temperature: 36.4°C), and her general physical examination was unremarkable.

Results from the blood testing, which included complete blood count, coagulation test, total bilirubin, aspartate transaminase, alanine transaminase, cholesterol, glucose, erythrocyte sedimentation rate, C-reactive protein, and thyroid function test were in the normal range. The patient's protein level was 6.6 g/dL and her albumin level was 4.9 g/dL, so her globulin was low (1.6 g/dL). Her creatinine was 1.02 mg/dL, with a mildly decreased estimated glomerular filtration rate of 58 mL/minute/1.73 m^2. Hypouricemia (0.9 mg/dL) and hypophosphatemia (2.3 mg/dL) were observed. Serum sodium/potassium/chloride (139/3.5/109 mmol/L) and calcium (8.8 mg/dL) were in normal ranges. Arterial blood gas analysis showed normal anion gap metabolic acidosis (pH 7.324, pCO_2 31.2 mmHg, pO_2 108.9 mmHg, HCO_3 15.9 mmol/L).

Urine dipstick testing showed the following characteristics: specific gravity (1.036), pH (6.5), blood (+), albumin (++), and glucose (++). A urine electrolyte test showed 51 mmol/L of sodium and 23.5 mmol/L of potassium. Fraction excretion of phosphorus was 44.17%, despite hypophosphatemia. Fraction excretion of uric acid was also increased to 104.16% despite hypouricemia. A spot urine test showed a urine protein/creatinine ratio of 10.61 mg/mgCr and a urine albumin creatinine ratio of 401.69 μg/mgCr. Based on the above information, we concluded that the patient had generalized proximal tubular dysfunction and overflow proteinuria.

An anti-kappa abnormal band was observed in serum and urine immunofixation. The patient had an elevated serum kappa/lambda ratio of 5,113.1. Through urine protein electrophoresis, the M peak was observed behind the beta globulin region (2,911.6 mg/day).

Bone marrow examination showed normocellular marrow with 24% CD138+ plasma cell staining with kappa restriction. The patient was diagnosed with multiple myeloma (kappa type) and FS.

A renal biopsy was performed for accurate diagnosis of FS and to exclude renal amyloidosis or monoclonal immunoglobulin (Ig) deposition disease. The biopsy revealed 26 glomeruli, three of which showed global sclerosis. The other glomeruli were unremarkable with no evidence of proteinous deposits. Mesangial matrix was not increased. Capillary loops were thin and delicate. Tubules revealed focal acute damage without interstitial fibrosis (Fig. 1A). Immunofluorescence staining for IgA, IgG, IgM, C3, kappa, and lambda was negative.

Under electron microscopy, the glomerular basement membrane was slightly irregular in contour with mild effacement of epithelial foot processes. Numerous rod- or rhomboid-shaped crystalline inclusions were present in the cytoplasm of proximal tubular epithelial cells (Fig. 1B). Most of the crystalline inclusions were electron dense and floating in the cytoplasm (Fig. 1C). However, they were not found in the glomerular cells

Table 1. Renal and hematologic laboratory results at baseline and during treatment*

	Admission (October 2012)	Prior to transplantation (February 2013)	After 1 year from transplantation (March 2014)†
Serum phosphate (mg/dL)	2.3	1.5	3.0
Serum uric acid (mg/dL)	0.9	0.8	1.3
Serum HCO_3 (mmol/L)	15.9	15.3	22.5 (tCO2)
Serum potassium (mmol/L)	3.1	3.3	4.0
Glycosuria	++ (S.G. 1.036)	++++ (S.G. 1.020)	++ (S.G. 1.015)
Albumin/creatinine ratio (μg/mgCr)	401.69	–	439.89
Protein/creatinine ratio (mg/mgCr)	10.61	–	1.69
Serum immunofixation	Anti-kappa	Anti-kappa	Absent
Serum κ/λ ratio	5,113.1	591.55	7.20
Urine M protein (mg/day)	2,911.6	649.1	98.2

* Treatment (thalidomide/cyclophosphamide/dexamethasone): from October 2012 to January 2013; autologous peripheral blood stem cell transplantation: March 2013.
† One year after transplantation, she was taking 2,040 mg of phosphate, 0.75 μg of calcitriol, 3,600 mg of potassium chloride, 100 mg of spironolactone, and 3,000 mg of sodium bicarbonate daily.
S.G., specific gravity.

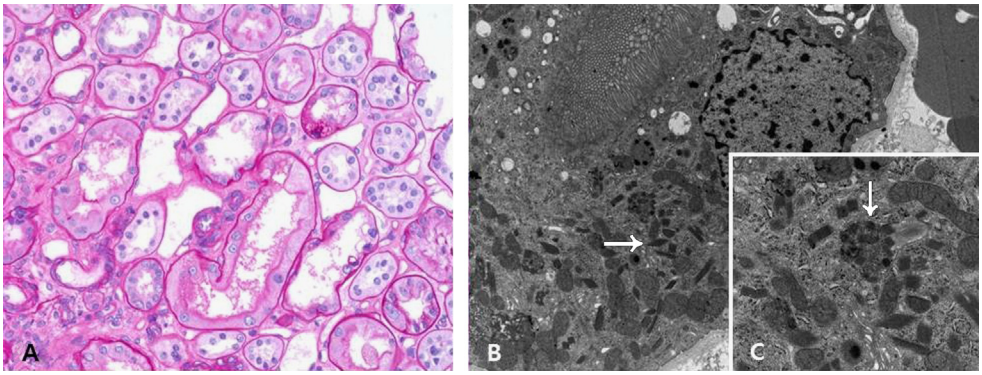

Figure 1. Histopathologic features. (A) Minimal mononuclear cell infiltration with focal atrophy is seen in tubule after staining with hematoxylin and eosin (light microscope, ×400). (B) Cytoplasm of proximal tubular epithelial cell contains multiple intracellular rectangular shape crystalline inclusions (arrow) (electron microscope, ×17,000). (C) Numerous rod-shaped and rhomboid-shaped crystalline inclusions are lying free within cytoplasm (arrow) (electron microscope, ×55,000).

including podocytes. There were no amyloid fibrils, granular deposits, or immune type electron densities.

Finally, she was diagnosed as having multiple myeloma (kappa type) with FS. Kidney pathology confirmed the presence of rod-shaped crystalline inclusions in proximal tubular cells.

The patient received four cycles of dexamethasone, cyclophosphamide, and thalidomide. Autologous stem cell transplantation with melphalan conditioning was performed 5 months after diagnosis. The patient showed very good partial hematologic response 3 months after stem cell transplantation. Her free serum kappa/lambda ratio decreased to 5.5. Her 24-hour-urine M-protein decreased to 80 mg/day. Plasma cells were observed in $< 5\%$ of aspirated bone marrow, although CD138+ cells were counted in up to 5% of bone marrow with kappa restriction. Currently, the patient has survived for 1 year after autologous stem cell transplantation and she has received thalidomide maintenance; however, her proximal tubular dysfunction has not improved (Table 1).

Hypouricemia (1.3 mg/dL) and glycosuria were still observed in her last laboratory tests. Phosphate level was normal (3.0 mg/dL) under intake of 2,040 mg of phosphate and 0.75 μg of calcitriol daily. To maintain a potassium level of 4 mmol/L and prevent metabolic acidosis, the patient was taking 3,600 mg of potassium chloride, 100 mg of spironolactone, and 3,000 mg of sodium bicarbonate daily. Urine albumin to creatinine ratio showed a similar level with baseline (440 μg/mgCr) and urinary protein to creatinine ratio was much decreased to 1.69 mg/mgCr, which reflected reduced overflow proteinuria and persistent tubular proteinuria.

Discussion

This patient presented with proteinuria and upon evaluation was found to have normal anion gap metabolic acidosis, normoglycemic glycosuria, hypophosphatemia, and hypouricemia. Therefore, we suspected that she had FS. The M peak behind the beta globulin region was detected by urine protein electrophoresis. Bone marrow examination showed normocellular marrow with 24% CD138+ plasma cells in kappa restriction. Crystalline inclusions were observed in proximal tubular cells on kidney biopsy. Therefore, she was diagnosed with multiple myeloma and light chain proximal tubulopathy.

In multiple myeloma, renal insufficiency is a common complication [5]. Up to 50% of patients with multiple myeloma initially present with kidney injury. Acute renal failure in myeloma is often caused by excessive production and filtration of free light chains.

Overproduced light chains can exert direct toxic effects onto kidney cells and generate myeloma casts by binding to Tamm-Horsfall proteins [4]. Cast nephropathy is the most common pattern of renal parenchymal disease associated with multiple myeloma [5]. Amyloidosis and monoclonal immunoglobulin deposition disease are the other types of deposition diseases that occur less frequently. Hypercalcemia, drug toxicity, and volume depletion also contribute to acute kidney injury in multiple myeloma cases [4].

FS is a relatively uncommon renal manifestation of multiple myeloma [5]. Excessively filtrated monoclonal light chains, usually composed of kappa light chains restricted to the V_{κ} I subgroup, generate crystals within the cytoplasm of proximal tubular epithelial cells [2]. These monoclonal kappa light chains have variable domains that are resistant to degradation by proteases in lysosomes [6]. Mutations of variable domains of kappa light chain, which is changing serine 30 to alanine, isoleucine, or leucine residue, increase the hydrophobicity of the CDR-L1 loop [7]. Fragments of the variable domain that accumulate in the cytoplasm are responsible for intracellular crystal formation and tubular dysfunction [8]. The crystalline inclusions generated from light chains can induce cytotoxicity in the proximal tubular epithelial cells [2]. They are associated with proximal tubular dysfunction including hypophosphatemia, hypouricemia, aminoaciduria, glycosuria, and metabolic acidosis [4]. Also, disruption of phagocytes that contain crystals may induce tissue injury, subsequently leading to tubular atrophy and interstitial fibrosis [4].

It is unclear whether achieving a hematologic response by treating multiple myeloma can resolve renal proximal tubular dysfunction. Gailani et al [9] reported a hematologic response in a myeloma case by irradiation, followed by melphalan, prednisone, and vincristine. After myeloma treatment, the patient's hypophosphatemia, hypouricemia, and glycosuria were normalized. Uchida et al [10] found that after treatment for multiple myeloma, urinary Bence-Jones protein disappeared and glycosuria, aminoaciduria, phosphaturia, and metabolic acidosis all improved [10]. It was reported by von Scheele [11] that glycosuria improved in a patient with FS with myeloma after 6 weeks of melphalan therapy; however, despite achieving a partial hematologic response after myeloma therapy, renal tubular acidosis, glycosuria, and hypophosphatemia persisted in the patient.

Conservative management of FS is a correction for hypophosphatemia [12]. It is important to prescribe both phosphate and vitamin D to correct hypophosphatemia and to prevent metabolic bone disease, because impairment of vitamin D activation mechanisms also contributes to hypophosphatemia in FS [13]. For normalization of metabolic acidosis, 10–15 mEq/kg/day of sodium bicarbonate is required [12]. Because alkali therapy may induce bicarbonaturia and urinary potassium loss, patients should take a potassium supplement [14].

In conclusion, we report a case of FS without renal failure, where the patient was ultimately diagnosed with multiple myeloma, demonstrating crystalline inclusion in proximal tubular cells on kidney biopsy. Adult patients with FS should be evaluated for the presence of Bence-Jones proteinuria and plasma cell dyscrasia should be excluded as an underlying factor.

Conflicts of interest

The authors declare no conflict of interest.

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