Light chain Fanconi syndrome in a patient with acute myeloid leukemia and monoclonal gammopathy of undetermined significance

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Abstract Proximal tubules are a target for paraproteine-mic diseases. Cast nephropathy, light chain deposition diseases, and amyloidosis are frequently encountered in patients with multiple myeloma. Rarely, a subset of patients develop light chain Fanconi syndrome (LCFS). LCFS has been reported with multiple myeloma, monoclonal gammopathy of renal significance (MGRS), chronic lymphocytic leukemia, Waldenstrom's macroglobulinemia and diffuse large B-cell lymphoma. No cases have been described with other hematologic malignancies. We report the first case of lambda LCFS in a patient with both acute myeloid leukemia (AML) and monoclonal gammopathy of undetermined significance (MGUS).

Keywords Acute myeloid leukemia · Light chain Fanconi syndrome · MGUS · Onconeurology · MGRS

Introduction

Light chain deposition disease (LCDD) is a well described entity that arises when monoclonal light chains damage renal tubular and glomerular cells. Lesions are usually localized to the loop of Henle and the distal tubule [1]. Rarely, a light chain Fanconi syndrome (LCFS) may

develop [2–7]. LCFS is a subset of proximal light chain tubulopathy associated with plasma cell dyscrasias (PCD). Light chain proximal tubulopathy has been reported in non-PCD diseases such as chronic lymphocytic leukemia, Waldenstrom's macroglobulinemia, and diffuse large B-cell lymphoma. We report the first case of lambda light chain Fanconi syndrome in a patient with both acute myeloid leukemia (AML) and monoclonal gammopathy of undetermined significance (MGUS).

Case report

A 61-year-old man with a history of diabetes mellitus type II, chronic kidney disease stage II, and a diagnosis of myelodysplastic syndrome (MDS) made 2 weeks prior was admitted with fever, headache, and found to have transformation to AML. During the first few days following admission the patient's serum creatinine rose from 130.83 $\mu\text{mol/L}$ (1.48 mg/dL) to 175.92 $\mu\text{mol/L}$ (1.99 mg/dL), he was noted to have approximately 27 g of proteinuria, and he was at times profoundly hypokalemic. Table 1 shows the results of his blood and urine tests at the time of admission. At the time that his creatinine was noted to rise his medications included azithromycin, piperacillin/tazobactam, losartan, metoprolol, amlodipine, atorvastatin, allopurinol, and intravenous fluids. His physical examination was significant for fever, mild tenderness over his maxillary sinuses and trace bilateral pedal edema. Initial work-up demonstrated glucosuria (Table 1) on urinalysis with echogenic kidneys without hydronephrosis on ultrasound. Further investigation of the abnormal urinalysis was consistent with proximal tubular wasting (Fanconi syndrome). Fractional excretions of phosphorus, potassium, and uric acid are presented in Table 2. Arterial blood gas to evaluate for renal

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Table 1 Laboratory tests on admission

Blood count	
Hemoglobin	92.00 g/L
White blood cells	3100/ μ L
Platelets	50,000/ μ L
Chemistry	
Sodium	136 mmol/L
Potassium	3.6 mmol/L
Chloride	102 mmol/L
Bicarbonate	25 mmol/L
Blood urea nitrogen	6.43 mmol/L
Creatinine	112.85 μ mol/L
Glucose	7.10 mmol/L
Phosphorus	1.03 mmol/L
Uric acid	226.04 μ mol/L
Hemoglobin A1c	6.6 %
Urinalysis	
Specific gravity	1.022
Dipstick protein	5000 g/L
Nitrite	Negative
Leukocyte esterase	Negative
pH	6.0
Blood	Moderate
Red blood cells	11–25/HPF
White blood cells	3–5/HPF
Glucose	16.65 mmol/L
Protein:creatinine	26.7 (g/g)

tubular acidosis was not clinically indicated and was thus not performed. Immunohistochemistry on bone marrow biopsy showed AML (FAB M2) along with approximately 10 % of cells being plasma cells (CD 138+). In situ staining for kappa and lambda light chains demonstrated polyclonality. Congo red stain was negative. Serum protein immunoelectrophoresis demonstrated IgG lambda paraprotein. The serum free light chain kappa/lambda ratio was 0.4

[65.90 mg/L (6.59 mg/dL): 144.00 mg/L (14.40 mg/dL)]. Quantitative IgG was 16.1 g/L (1,610.00 mg/dL), IgA 5260.00 mg/L (526.00 mg/dL), and IgM 670.00 mg/L (67.00 mg/dL). Urine immunofixation showed IgG lambda paraprotein. This raised suspicion for light chain accumulation as the causative factor of proximal tubular dysfunction. A kidney biopsy was considered, but was not feasible secondary to significant thrombocytopenia.

The patient's creatinine worsened to 214.8 μ mol/L (2.43 mg/dL). Eight days after admission, the patient began AML induction therapy with daunorubicin and cytosine arabinoside. Three days later (hospital day 12) the patient's creatinine peaked at 234.26 μ mol/L (2.65 mg/dL) and subsequently trended down to 106.08 μ mol/L (1.20 mg/dL) (Fig. 1). Figure 1 also shows improvement in proteinuria following treatment. Hypouricemia persisted—the patient was taking allopurinol and received rasburicase day 8 of hospitalization. Throughout the illness the patient's serum potassium averaged approximately 3.30 mmol/L (3.30 mEq/L) despite aggressive potassium repletion. Glucosuria persisted despite only mildly elevated serum glucose (Fig. 2). Serum trends of potassium, uric acid, and phosphorus are shown in Table 2. The patient achieved remission of AML, but ultimately relapsed. He passed away approximately 1 year after diagnosis.

Discussion

This patient had profound proximal tubular wasting of phosphorus, potassium, glucose, and uric acid (Table 2). The presence of hyperglycemia might call into question the conclusion of proximal tubular wasting. However, the patient's serum glucose was only mildly elevated and his urine glucose concentration was always higher than his serum. Additionally around the time of chemotherapy he was actually hypoglycemic but continued to have glucosuria (Fig. 2). The degree of proteinuria on presentation is somewhat atypical. As per the patient's history he described many years of diabetes and was told that he had

Table 2 Fractional excretion of potassium, phosphorus, and uric acid on hospital day 7 (before chemotherapy)

	Serum	Urine	Fractional excretion (%)
Potassium	3.60 mmol/L	19.00 mmol/L	32.82
Phosphorus	1.10 mmol/L	7.20 mmol/L	40.79
Uric acid	124.94 μ mol/L	11.00 μ mol/L	32.57
	Admission	At peak creatinine (day 12)	Discharge
Serum concentrations of phosphorus, uric acid, potassium			
Potassium (mmol/L)	3.5	2.8	3.6
Uric acid (μ mol/L)	226.04	136.82	193.30
Phosphorus (mmol/L)	0.81	1.16	1.20

Fig. 1 Trend in serum creatinine and proteinuria over the hospital course. Gray line indicates creatinine before chemotherapy and black line indicates creatinine after chemotherapy

Fig. 2 Trend in serum and urine glucose over the hospital course. Note that urine glucose was checked on hospital day 16 which was 7 days after initiation of treatment

proteinuria about 1 year prior. Therefore, the 26.7 g of proteinuria noted on admission likely represented diabetic nephropathy with superimposed proximal tubular dysfunction. The Fanconi syndrome was most likely related to lambda light chain paraproteinemia, as no other etiology of Fanconi syndrome was readily apparent. LCFS has never been described in a patient with concomitant AML and MGUS.

There have been fewer than 100 cases of LCFS reported in the literature [2–7]. Among these cases, the majority of patients were males with either MM or MGUS who presented with kidney injury and proteinuria. The degree of proximal tubular wasting varies between a partial Fanconi syndrome to a full-blown Fanconi

syndrome including normoglycemic glucosuria, amino aciduria, and phosphaturia [2, 5]. In the case series by Messiaen et al., full-blown Fanconi syndrome was more common than incomplete Fanconi syndrome [5]. Thus, our patient fits the description of a “typical” LCFS patient—a male with full-blown Fanconi syndrome and kidney injury.

Nearly all reported cases of LCFS have been associated with kappa light chains [2, 5]. In these cases, renal biopsy shows crystals and cytoplasmic inclusions within proximal tubular cells on light microscopy. Crystal accumulation is due to the resistance of the Vk1 subgroup on kappa light chains to degradation by cathepsin B. Crystal accumulation in proximal tubule cells results in flattening of epithelial cells and obliteration of the brush border. In contrast, reported cases of lambda LCFS do not have crystallization within the proximal tubule. In 2011, Larsen et al., searched greater than 10,000 renal biopsies to identify any cases where there was light chain restriction isolated to the proximal tubule [4]. Thirteen cases were identified of which 10 exhibited no crystallization. Nine of those patients had lambda light chain restriction. These lambda light chain proximal tubulopathies demonstrated apical blebbing with loss of the brush border on light microscopy and an increased number of lysosomes on electron microscopy. These findings were similar to those reported by Sharma et al., [7]. Although rare, lambda LCFS does occur and our patient likely represents another case.

In 2014, Herrera reviewed 57 cases of proximal tubulopathies associated with monoclonal light chains [2]. He found that the pathology of these cases could be divided into four categories: (1) proximal tubulopathy without cytoplasmic inclusions, (2) proximal tubulopathy with interstitial inflammation, (3) proximal tubulopathy with cytoplasmic inclusions, and (4) proximal tubulopathy with lysosomal indigestion and constipation. There were 50 patients without cytoplasmic inclusions or interstitial inflammation and the predominant clinical picture was one of the progressive renal failure. Seven patients had either cytoplasmic inclusions or lysosomal indigestion and the clinical picture was of aminoaciduria, glucosuria, phosphaturia, and type II renal tubular acidosis—Fanconi syndrome. In these seven cases of Fanconi syndrome, the inciting light chain was kappa in all but one. Herrera’s findings were congruent with the earlier case series by Messiaen et al., 2000 who found that LCFS was mostly associated with low-mass kappa light chain-excreting myelomas [5].

It is noteworthy that our patient had AML. There have been case reports of LCFS in patients with chronic lymphocytic leukemia, Waldenström’s macroglobulinemia, and diffuse large B-cell lymphoma, but never in a patient

with AML [5]. Plasmacytosis is an uncommon occurrence in AML and so it is more likely that this patient had both AML and, coincidentally, MGUS with LCFS [8, 10, 11]. The frequency of MGUS in patients over 50 is about 3 % and this increases with age [9]. Therefore, it is reasonable to conclude that this patient had two separate processes.

The salient point in our case is that the patient's LCFS and AKI improved following chemotherapy for AML (Fig. 1). This improvement may have occurred because the chemotherapy eliminated any clonal plasma cells producing toxic light chains. LCFS is an under recognized condition and is often present years before the diagnosis of a plasma cell dyscrasia. In this case the patient only came to our attention after MGUS had transformed to AML so we can never know if Fanconi syndrome was present before the diagnosis. It is crucial to identify cases of LCFS early because treatment can effectively reverse kidney injury, as in our case. Nephrologists and hematologists alike must always consider MGUS when evaluating proximal tubular dysfunction and AKI. Our case highlights the fact that MGUS is a common condition and therefore clinicians should consider this entity even in the setting of other disease processes.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest and have no disclosures. No patient identifying information is presented in this case report.

References

1. Jimenez-Zepeda VH. Light chain deposition disease: novel biological insights and treatment advances. *Int J Lab Hematol*. 2012;34:347–55.
2. Herrera GA. Proximal tubulopathies associated with monoclonal light chains. *Arch Pathol Lab Med*. 2014;138:1365–79.
3. Kapur U, Barton K, Fresco R, et al. Expanding the pathologic spectrum of immunoglobulin light chain proximal tubulopathy. *Arch Path Lab Med*. 2007;131:1368–72.
4. Larsen CP, Bell JM, Harris AA, et al. The morphologic spectrum and clinical significance of light chain proximal tubulopathy with and without crystal formation. *Mod Pathol*. 2011;24:1462–9.
5. Messiaen T, Deret S, Mougenot B, et al. Adult fanconi syndrome secondary to light chain gammopathy. *Medicine*. 2000;79:135–54.
6. Said S, Adel A, Cerda J, et al. Light chain tubulopathy without fanconi syndrome. *Nephrol Dial Transpl*. 2006;21:3589–90.
7. Sharma SG, Bonsib SM, Portilla D, et al. Light chain proximal tubulopathy: expanding the pathologic spectrum with and without deposition of crystalline inclusions. *ISRN Pathol*. 2012;2012:541075.
8. Rosenthal NS, Farhi DC. Reactive plasmacytosis and lymphocytosis in acute myeloid leukemia. *Hematol Pathol*. 1994;8:43–51.
9. Kyle RA, Therneau TM, Rajkumar SV, et al. Prevalence of monoclonal gammopathy of undetermined significance. *N Engl J Med*. 2006;34:1362–9.
10. Wulf GG, Jahns-Streubel G, Hemmerlein B, et al. Plasmacytosis in acute myeloid leukemia: two cases of plasmacytosis and increased IL-6 production in the AML blast cells. *Ann Hematol*. 1998;76:273–7.
11. Aruna R, Bhavna A, Pooja E, et al. Florid plasmacytosis in a case of acute myeloid leukemia: a diagnostic dilemma. *Indian J Med Paediatr Oncol*. 2010;31(1):36–8.