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Acute Acquired Fanconi Syndrome in Multiple Myeloma After Hematopoietic Stem Cell Transplantation

Janina Paula T. Sy-Go[1], David Dingli[2], Morie A. Gertz[2], Prashant Kapoor[2], Francis K. Buadi[2], Angela Dispenzieri[2], Martha Q. Lacy[2], Mary E. Fidler[3] and Nelson Leung[1,2]

[1]Department of Internal Medicine, Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA; [2]Department of Internal Medicine, Division of Hematology, Mayo Clinic, Rochester, Minnesota, USA; and [3]Department of Laboratory Medicine and Pathology, Division of Anatomic Pathology, Mayo Clinic, Rochester, Minnesota, USA

Correspondence: Janina Paula T. Sy-Go, Department of Internal Medicine, Division of Nephrology and Hypertension, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail: sy-go.janina@mayo.edu

Received 23 October 2020; revised 6 December 2020; accepted 9 December 2020; published online 19 December 2020

Kidney Int Rep (2021) **6,** 857–864; https://doi.org/10.1016/j.ekir.2020.12.007

KEYWORDS: Fanconi syndrome; multiple myeloma; onconephrology; stem cell transplant

INTRODUCTION

Although a rare complication, proximal tubular dysfunction of the kidneys can occur in patients with monoclonal gammopathies, including multiple myeloma (MM).[1–3] Light chain proximal tubulopathy (LCPT) can occur with or without Fanconi syndrome (FS), which is the result of nonselective kidney wasting of electrolytes, uric acid, glucose, and amino acids. Clinical presentation includes hypokalemia, hypophosphatemia, proximal renal tubular acidosis (RTA), hypouricemia, normoglycemic glycosuria, and aminoaciduria.[1–3] Acute kidney injury (AKI) may or may not be present.

Normally, monoclonal immunoglobulin light chains are filtered through the glomerulus, reabsorbed in the proximal tubular epithelial cells, and are subsequently degraded by lysosomes via endocytosis.[4] In LCPT, however, the variable domain of certain light chains has unique physicochemical characteristics that make them resistant to digestion by proteases and intracellular lysosomal enzymes, including pepsin, trypsin, and cathepsin B.[1,5–7,S8] This protease-resistant variable domain can spontaneously form intracellular crystals or inclusions.[S8] As a result, the incomplete catabolism of the light chains leads to a pathologic accumulation in the cells, causing oxidative stress, activation of inflammatory mediators, and apoptosis.[7,8] More than 90% of the light chains associated with this process are kappa (vs. lambda).[1] Cases of lambda light chain LCPT have been reported, but intriguingly, most are without crystal formation.[S7,S8] The proposed theory is that lambda light chains (vs. kappa) lack the capability to spontaneously crystallize.[S7] Despite the absence of crystal formation, the presence of excess light chains by itself is sufficient to inflict injury on the proximal tubular epithelial cells.[S7]

The development of FS is usually detected before or at the time of diagnosis of MM. Late development of FS has been described but is associated with the use of lenalidomide.[S5] Interestingly, we have noted the development of FS after hematopoietic stem cell transplantation (HSCT) in patients with MM that had no previous evidence of electrolyte wasting. To better understand the prevalence and clinical presentation of FS after HSCT among patients who did not present with FS, we undertook this study.

After approval of the protocol by the Mayo Clinic Institutional Review Board (ID 20-000322), we obtained a list of 2744 adult patients with MM who underwent HSCT at Mayo Clinic in Rochester, Minnesota from January 1, 2000 to December 31, 2019. Waiver of informed consent was approved. Forty-five patients without research authorization were excluded. We identified 15 patients after searching for the terms "Fanconi," "Fanconis," and "Fanconi's" in the electronic medical record. We reviewed their medical records and collected relevant data. The diagnosis of FS was made based on features of hypokalemia,

hypophosphatemia, proximal RTA, hypouricemia, normoglycemic glycosuria, and/or aminoaciduria, within 14 days after HSCT. For a comparison group, we also obtained a list of 2221 adult patients with non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) who underwent HSCT during the same period.

PATIENT CHARACTERISTICS

Of the 2744 adult patients with MM who underwent HSCT, 15 patients were identified to have possible FS. Seven patients did not have FS. Three patients were diagnosed with FS before HSCT. Five patients were diagnosed with FS based on aforementioned features that were not present before HSCT. One of the 5 patients was diagnosed with LCPT after a kidney biopsy specimen was obtained but did not present with electrolyte abnormalities before HSCT. Detailed descriptions of the cases appear below.

Case 1

A 53-year-old woman diagnosed with immunoglobulin G kappa MM in 2005 was treated with dexamethasone before autologous HSCT in 2006. Four days after HSCT she was hospitalized for nausea, vomiting, and poor oral intake. She had hypokalemia (3.2 mmol/l), hypomagnesemia (1.3 mg/dl), hypophosphatemia (1.9 mg/dl), normal anion gap metabolic acidosis (NAGMA; serum bicarbonate 19 mmol/l; serum anion gap 10), urine pH of 5.2, positive urine anion gap (50), and normoglycemic glycosuria (serum glucose 91 mg/dl; urine glucose 26 mg/dl). Serum uric acid was not checked. She also had AKI (serum creatinine 2.2 mg/dl vs. baseline serum creatinine 0.7–0.9 mg/dl). Random urine potassium to creatinine ratio was 5.47 mEq/mmol, suggestive of kidney wasting. She was diagnosed with FS and was treated with intravenous (IV) electrolyte replacement. Her electrolyte abnormalities were rapidly corrected given the degree of her kidney failure. On follow-up 100 days after HSCT, she had stable MM with no FS reoccurrence. Ten years later, she was seen by nephrology for chronic kidney disease with no evidence of FS.

Case 2

A 68-year-old man underwent pre-emptive living unrelated donor kidney transplantation at an outside institution in 2005 for end-stage kidney disease attributed to hypertensive nephrosclerosis and bilateral renal artery stenosis. A native kidney biopsy specimen obtained before transplantation showed glomerulosclerosis thought to be related to his bilateral renal artery stenosis. He also had a bone marrow aspiration and biopsy performed because of his long-standing immunoglobulin A (IgA) kappa monoclonal gammopathy of undetermined significance, which had shown 4% plasma cells. His skeletal survey during that time was negative, but his IgA and free light chain levels were unknown. He underwent kidney transplantation with thymoglobulin induction and maintenance with tacrolimus, mycophenolate mofetil, and prednisone. Four weeks later, he developed acute allograft dysfunction and a biopsy specimen of the transplanted kidney was obtained, which showed borderline rejection and focal tubular epithelial kappa light chain crystalline nephropathy. He was treated with methylprednisolone for the rejection, and a repeat monoclonal gammopathy of undetermined significance work-up was performed. He was also initiated on dexamethasone and referred to our institution for a second opinion.

After evaluation at our institution, the patient was diagnosed with IgA kappa MM in 2006. He also had generalized aminoaciduria, but no other features of FS were present. His native kidney biopsy specimen before transplantation was reviewed at our institution, which, in addition to advanced glomerulosclerosis, showed scattered tubular intracytoplasmic crystals. The patient's end-stage kidney disease was, in fact, secondary to monoclonal gammopathy of renal significance in the form of LCPT. He was continued on dexamethasone and underwent autologous HSCT in the same year. Seven days after HSCT, he developed acute allograft dysfunction (serum creatinine 2.7 mg/dl vs. baseline serum creatinine 1.7 mg/dl). His serum creatinine peaked at 3.4 mg/dl. He also had hypomagnesemia (1.6 mg/dl), NAGMA (serum bicarbonate 17 mmol/l; serum anion gap 7), and urine pH of 4.7. Tacrolimus dosing was adjusted. A biopsy specimen of the transplanted kidney was obtained and showed an acute increase in intratubular crystals consistent with ongoing light chain FS with no evidence of acute cellular rejection (Figure 1). He was empirically treated with plasmapheresis in an attempt to salvage his kidney allograft function, and his kidney function stabilized. On follow-up 100 days after HSCT, he was in complete remission with no FS reoccurrence. He had a rocky course after HSCT, developed multiple complications, and eventually died of disseminated zoster infection about 2 years after HSCT.

Case 3

A 65-year-old woman diagnosed with IgG kappa MM in 2013 who was induced with cyclophosphamide, bortezomib, and dexamethasone underwent autologous HSCT in 2014. Sixteen days after HSCT, she was hospitalized for vomiting, diarrhea, and poor oral intake and was found to have *Clostridium difficile* colitis. She was discovered to have multiple electrolyte

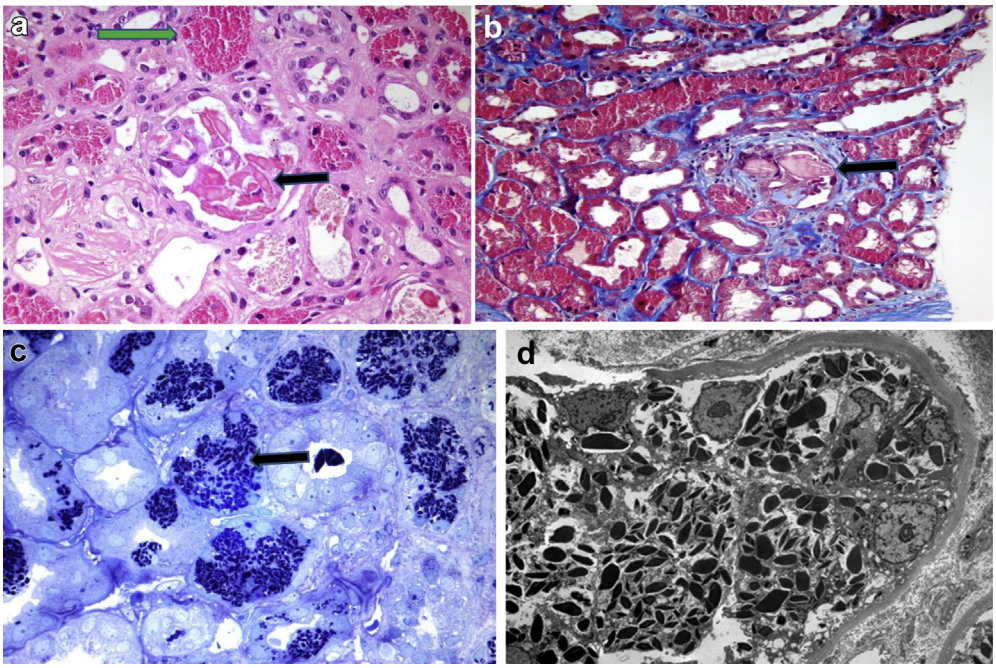

Figure 1. Light microscopy. (a) Hematoxylin–eosin E stain. Tubules with hypereosinophilic intracytoplasmic protein granules (green arrow) and intraluminal (black arrow) crystals. (b) Masson Trichrome stain showing tubular intracytoplasmic protein granules and intraluminal crystals (black arrow). (c) Toluidine blue stain showing tubular intracytoplasmic protein granules with crystal formation (black arrow). Electron microscopy. (d) Tubule with prominent intracytoplasmic light chain crystals.

abnormalities, including hypokalemia (2.6 mmol/l), hypomagnesemia (1.6 mg/dl), hypophosphatemia (1.0 mg/dl), hypouricemia (1.5 mg/dl), and normoglycemic glycosuria (serum glucose 121 mg/dl; urine glucose 151 mg/dl). Kidney function was normal (serum creatinine 0.6 mg/dl; estimated glomerular filtration rate >60 mL/min/1.73 m^2). Random urine potassium to creatinine ratio was 2.5 mEq/mmol while fractional excretions of magnesium and phosphorus were 4% and 61.88%, respectively, suggestive of kidney wasting. Her ongoing diarrhea aggravated her electrolyte losses and impeded oral replacement. She was thus switched to IV replacement and started on amiloride. Her electrolyte levels eventually normalized, and amiloride was discontinued before discharge. On follow-up 100 days after HSCT, she was in complete remission with no FS reoccurrence. Five years later, she had relapsed MM with no evidence of FS.

Case 4

A 51-year-old man diagnosed with IgG kappa MM in 2017 underwent autologous HSCT in the same year. His disease relapsed, and he received several chemotherapeutic regimens before an allogeneic HSCT in 2019 because of refractory disease. Eight days after HSCT, he was hospitalized for poor oral intake in the setting of severe ulcerative mucositis and multiple electrolyte abnormalities despite aggressive replacement. He had hypokalemia (3.3 mmol/l), hypomagnesemia (1.3 mg/dl), hypophosphatemia (1.1 mg/dl), NAGMA (serum bicarbonate 16 mmol/l; serum anion gap 12), urine pH of 5.4, positive urine anion gap (30), hypouricemia (1.3 mg/dl), and normoglycemic glycosuria (serum glucose 83 mg/dl; urine glucose 306 mg/dl). He also had elevated 24-hour urine concentrations of potassium, magnesium, and phosphorus despite low serum levels of these electrolytes, suggestive of kidney wasting. He was diagnosed with FS. He was treated with both IV and oral electrolyte replacement and amiloride. His FS resolved during hospitalization. On follow-up 100 days after HSCT he had minimal residual disease negativity with no FS reoccurrence. Ten months later, he died of respiratory failure caused by influenza A pneumonia.

Case 5

A 64-year-old man diagnosed with IgG kappa MM in 2018 received several chemotherapeutic regimens before autologous HSCT in 2019. Eight days after HSCT, he was hospitalized for rigors, exertional dyspnea, and fatigue in the setting of culture-negative neutropenic fever, *Clostridium difficile* colitis, and multiple electrolyte abnormalities despite symptomatic improvement. He had hypokalemia (3.2 mmol/l), hypomagnesemia (1.5 mg/dl), hypophosphatemia (2 mg/dl), NAGMA (serum bicarbonate 12 mmol/l; serum anion gap 12), urine pH of 4.8, and positive urine anion gap (38). Serum uric acid was low normal at 4.6 mg/dl. He also had AKI (serum creatinine 2.1 mg/dl vs. baseline serum creatinine 1.7 mg/dl). Random urine potassium to creatinine ratio was 4.19

Table 1. Demographic data and characteristics of patients with MM who developed acute acquired FS or had an exacerbation of FS after HSCT

	Case 1	Case 2	Case 3	Case 4	Case 5
Age, yrs	53	68	65	51	64
Sex	Female	Male	Female	Male	Male
Race/ethnicity	White	White	White	White	White
Medical comorbidities	Hypertension, dyslipidemia, and kidney stones	ESKD caused by hypertensive nephrosclerosis and bilateral renal artery stenosis s/p pre-emptive living unrelated donor kidney transplant, and hypertension	CKD, hypertension, dyslipidemia, and hypothyroidism	Hypothyroidism	CKD
MM					
Light chain restriction	20–30% IgG kappa	10–20% IgA kappa	60–70% IgG kappa	10–15% IgG kappa	90% IgG kappa
Treatment	Dexamethasone	Dexamethasone	CyBorD	VRD daratumumab, pomalidomide, dexamethasone, and carfilzomib anti-BCMA BiTE, immunotherapy, and VDT-PACE	Plasmapheresis and methylprednisolone, CyBorD, daratumumab, bortezomib, and dexamethasone, and daratumumab, lenalidomide, and dexamethasone
Kidney biopsy	N/A	Light chain FS	N/A	N/A	Acute myeloma case nephropathy, kappa type
Conditioning regimen before HSCT	Melphalan	Melphalan	Melphalan	First, melphalan; second,melphalan and TBI	Melphalan
At MM diagnosis, laboratory parameter (reference range)					
M spike, g/dl	2.6	Unknown	5	Unknown	3.6
Immunoglobulin					
IgG (767–1590 mg/dL)	3490		7010	882	5750
IgA (61–356 mg/dL)		1420			
Serum FLCs					
Kappa (0.33–1.94 mg/dL)	33.7	9.38	<0.09	98.3	1050
Lambda (0.57–2.63 mg/dL)	0.299	1.35	<0.07	0.5	1
Kappa/lambda FLC ratio	113	6.95	Incalculable	178	>1000
24-hour urine total protein (<102 mg/24 hours)	62	1418	Unknown	1351	402
Before HSCT, laboratory parameter (reference range)					
M spike, g/dl	2	Unknown	1.2	Unknown	1.1
Immunoglobulin					
IgG (767–1590 mg/dl)	2600		1660	80	1410
IgA (61–356 mg/dl)		292			
Serum FLCs					
	4.8	1.71	0.678	<0.0061	57.7

(Continued on following page)

Table 1. (Continued) Demographic data and characteristics of patients with MM who developed acute acquired FS or had an exacerbation of FS after HSCT

	Case 1	Case 2	Case 3	Case 4	Case 5
Kappa (0.33–1.94 mg/dl)					
Lambda (0.57–2.63 mg/dl)	0.154	1.41	0.163	<0.0051	1.09
Kappa/lambda FLC ratio	31.2	1.21	4.16	Incalculable	52.9
24-hour urine total protein (<102 mg/24 hours)	206	781	65	<186	477

BCMA, B-cell maturation antigen; BiTE, bispecific T cell engager; CKD, chronic kidney disease; CyBorD, cyclophosphamide, bortezomib, and dexamethasone; ESKD, end-stage kidney disease; FLC, free light chain; FS, Fanconi syndrome; HSCT, hematopoietic stem cell transplantation; IgA, immunoglobulin A; IgG, immunoglobulin G; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; N/A, not applicable; TBI, total body irradiation; VDT-PACE, Velcade (bortezomib), dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide; VRd, Velcade (bortezomib), Revlimid (lenalidomide), and dexamethasone.

mEq/mmol, suggestive of kidney wasting. He was diagnosed with FS. He was treated with both IV and oral electrolyte replacement and sodium bicarbonate. After discharge, his electrolyte wasting persisted even after kidney function recovery, so he remained on the replacements. On follow-up 100 days after HSCT, he was in partial remission with no FS reoccurrence, but his medications were continued. He was started on maintenance lenalidomide and dexamethasone in 2020 with good response. His electrolyte abnormalities, however, reoccurred about 2 months after starting lenalidomide. Four months later, he was seen by nephrology for persistent electrolyte wasting. He was asked to continue his oral electrolyte supplements and was started on amiloride for concurrent hypertension and peripheral edema.

Only 5 patients (0.18% of the cohort) developed acute acquired FS or had an exacerbation of FS after HSCT. The median age was 64 years (range 53–68 years; Table 1). All patients were white, and 2 were female. Three patients had hypertension. Two patients had chronic kidney disease, dyslipidemia, and hypothyroidism. One patient had a history of kidney stone, and another had bilateral renal artery stenosis. All patients had kappa light chain–restricted MM with 4 IgG and 1 IgA heavy chain isotypes. Because of AKI on initial presentation, 1 patient underwent a kidney biopsy procedure that showed acute myeloma cast nephropathy, for which he was treated with plasmapheresis and methylprednisolone. A biopsy specimen was obtained from the transplanted kidney in another patient because of allograft dysfunction and ongoing light chain FS. In terms of chemotherapy, 2 patients received lenalidomide. Patients were diagnosed with FS with a mean of 10.2 days (range 8–16 days) after HSCT. All of them underwent melphalan conditioning and had at least partial remission as a hematologic response to chemotherapy before HSCT (Table 1).

All five patients had hypomagnesemia. Four patients had hypokalemia and hypophosphatemia. Four patients had NAGMA with 3 having positive urine anion gaps. Four patients had serum uric acid checked, and 3 had low to low-normal levels while 1 had a normal level. Lastly, 3 of 5 patients tested had normoglycemic glycosuria. One patient had glycosuria but with no concurrent serum glucose available for interpretation. Random urine potassium to creatinine ratios were calculated in 3 patients and were elevated. One of these 3 patients also had fractional excretions of magnesium and phosphorus performed, which were elevated. One patient also had elevated 24-hour urine concentrations of potassium, magnesium, and phosphorus. All of these urinary indices indicated kidney wasting. Three patients had AKI.

Table 2. Laboratory data before HSCT and after HSCT at diagnosis of FS

Laboratory parameter (reference range)	Case 1	Case 2	Case 3	Case 4	Case 5
Before HSCT					
Kappa light chain (0.33–1.94 mg/dl)	4.8	1.71	0.678	<0.0061	57.7
Na^+ (135–145 mmol/l)	142	137	141	142	145
K^+ (3.6–5.2 mmol/l)	3.8	5.2	4.6	4.5	3.7
Cl^- (98–107 mmol/l)	100	103	101	102	104
$HCO3^-$ (22–29 mmol/l)	33	23	28	24	22
Anion gap (7–15)	9	11	12	16	19
Mg^{2+} (1.7–2.3 mg/dl)	1.5	1.5	1.9	1.6	1.7
PO_4^{3-} (2.5–4.5 mg/dl)	4.4	4.8	2.5	3	3.3
Uric acid (3.7–8.0 mg/dl)	7.6	9.9	4.7	N/A	4.2
Creatinine (0.74–1.35 mg/dl)	1.1	1.7	0.9	0.77	1.7
Creatinine-based eGFR (≥60 ml/min/BSA)	54	41	67	105	42
Glucose (70–140 mg/dl)	99	124	116	86	140
Urine glucose (0–15 mg/dl)	4	19	17	17	22
Predicted 24-hour urine total protein (mg)	112	696	166	361	2706
After HSCT at diagnosis of FS					
Kappa light chain (0.33–1.94 mg/dl)	14	0.374	2.23	0.0483	28.5
Na^+ (135–145 mmol/l)	140	140	143	135	141
K^+ (3.6–5.2 mmol/l)	3.2	4.6	2.6	3.3	3.2
Cl^- (98–107 mmol/l)	111	116	103	107	116
$HCO3^-$ (22–29 mmol/l)	19	17	26	16	13
Anion gap (7-15)	10	7	14	12	12
Mg^{2+} (1.7–2.3 mg/dl)	1.3	1.6	1.6	1.3	1.5
PO_4^{3-} (2.5–4.5 mg/dl)	1.9	3.3	1	1.1	1
Uric acid (3.7–8.0 mg/dl)	N/A	7.8	1.5	1.3	4.6
Creatinine (0.74–1.35 mg/dl)	2.2	3.4	0.6	1.01	2.07
Creatinine-based eGFR (≥60 ml/min/BSA)	25	18	67	86	33
Glucose (70–140 mg/dl)	91	N/A	121	83	126
Urine glucose (0–15 mg/dl)	26	26	151	306	12
Predicted 24-hour urine total protein, mg	1848	846	857	2350	1540
Random urine electrolytes					
Na^+, mmol/l	117	N/A	140	N/A	37
K^+, mmol/l	30		14		33
Cl^-, mmol/l	135		90		32
Mg^{2+}, mg/dl			49		
PO_4^{3-}, mg/dl			66		
Creatinine, mg/dl	62		64		89
Urine anion gap	50	N/A	N/A	30	38
Random urine K^+/creatinine ratio,[a] mEq/mmol	5.47	N/A	2.5	N/A	4.19
$FeMg^{2+}$, %	N/A	N/A	4[b]	N/A	N/A
$FePO_4^{3-}$, %	N/A	N/A	61.88[c]	N/A	N/A
24-hour urine electrolytes					
Na^+ (41–227 mmol/day)	N/A	N/A	N/A	338	N/A
K^+ (17–77 mmol/day)				109[d]	
Cl^- (40–224 mmol/day)				417	
Mg^{2+} (51–269 mg/day)				225[e]	
PO_4^{3-} (<1100 mg/day)				413[f]	
Creatinine (601–1689 mg/day)				1202	

FS, Fanconi syndrome; HSCT, hematopoietic stem cell transplantation; N/A, not applicable.
[a]A random urine K^+/creatinine ratio of >2.5 mEq/mmol suggests inappropriate response by the kidneys to hypokalemia and kidney K^+ wasting.
[b]A $FeMg^{2+}$ of >3% suggests inappropriate response by the kidneys to hypomagnesemia and kidney Mg^{2+} wasting.
[c]A $FePO_4^{3-}$ of >5% suggests inappropriate response by the kidneys to hypophosphatemia and kidney PO_4^{3-} wasting.
[d]A 24-hour urine K^+ of >25–30 mmol/day suggests inappropriate response by the kidneys to hypokalemia and kidney K^+ wasting.
[e]A 24-hour urine Mg^{2+} of >10–30 mg/day suggests inappropriate response by the kidneys to hypomagnesemia and kidney Mg^{2+} wasting.
[f]A 24 hour urine PO_4^{3-} of >100 mg/day suggests inappropriate response by the kidneys to hypophosphatemia and kidney PO_4^{3-} wasting.

All patients, except 1, had worsened proteinuria (based on the predicted 24-hour urine total protein on urinalysis). Of note, aminoaciduria was confirmed in 1 patient before HSCT, but it was not checked in any of the patients after HSCT (Table 2).

In comparison, using the same search protocol, none of the 2221 adult patients with NHL and HL who underwent HSCT in the same period developed electrolyte wasting consistent with FS after HSCT.

Table 3. Teaching points

FS is characterized by proximal tubular dysfunction of the kidneys resulting in nonselective urinary wasting of electrolytes, uric acid, glucose, and amino acids, all of which are normally reabsorbed in the proximal tubule.
The clinical presentation of FS includes hypokalemia, hypophosphatemia, proximal renal tubular acidosis, hypouricemia, normoglycemic glycosuria, and aminoaciduria. It is classified as complete if all of the aforementioned features are present or partial if not.
FS can be inherited or acquired. One rare cause of acquired FS is MM as the monoclonal immunoglobulin light chains are toxic to the proximal tubular epithelial cells.
The development of severe electrolyte depletion, metabolic acidosis, hypouricemia, and/or normoglycemic glycosuria after HSCT in patients with MM should raise the clinical suspicion of FS—even in the presence of concurrent gastrointestinal symptoms, which are not uncommon after the procedure. The pathogenesis is unclear because these patients have already been partially treated and have lower free light chain levels than at diagnosis.
The mMajority of the patients who developed FS after HSCT had IgG kappa MM. These kappa light chains that cause proximal tubulopathy have been found to be highly resistant to proteolysis and capable of spontaneously forming intracellular crystals (vs. lambda).
Lenalidomide is a chemotherapeutic agent used in patients with MM that has been implicated to cause FS.
Acute acquired FS in patients with MM after HSCT appears to be a self-limited and transient phenomenon that requires timely and adequate electrolyte repletion and close monitoring.

FS, Fanconi syndrome; HSCT, hematopoietic stem cell transplantation; IgG, immunoglobulin G; MM, multiple myeloma.

DISCUSSION

In our study, we report 5 patients with MM who developed acute acquired FS after HSCT that was new and transient. Acquired FS is reported with monoclonal gammopathies, including MM and monoclonal gammopathy of renal significance, but it is typically an early manifestation.[1,2,9,S6,S9] Our study is the first report of acute acquired FS occurring after HSCT in patients with MM. All of our patients had kappa light chain isotype, 4 with IgG heavy chain isotype and 1 with IgA heavy chain isotype, which is consistent with the published literature.[1] One of the patients was previously diagnosed with LCPT by crystalline deposits after a kidney biopsy specimen was obtained, but the patient had experienced no electrolyte abnormalities. The acquired FS did not become clinically significant until after HSCT. To determine if FS was caused by HSCT, we used the same search protocol in patients with NHL and HL who underwent HSCT during the same period and found no cases of new FS. The only cases found were present before HSCT due to chemotherapy injury with ifosfamide and carboplatin.

FS is a clinically important phenomenon relevant to both nephrology and hematology. While the pathogenic mechanism of FS because of MM and monoclonal gammopathy of renal significance is well-studied, the reason why it occurs after HSCT remains poorly understood. DeCourt *et al.*[6] found the chemical properties peculiar to the variable domain of these light chains are important in the development of MM-associated FS in an animal model.[2] The light chains themselves serve as a nidus for crystal formation and interfere with various transporters lining the apical membranes of the proximal tubular epithelial cells, such as megalin and cubilin, causing LCPT.[S2] While this phenomenon explains the pathogenesis of FS in patients with monoclonal gammopathies, including MM, it does not explain the pathogenesis of FS in patients who underwent HSCT because these patients have already been partially treated and have lower free light chain levels than at diagnosis. It is interesting that patients with NHL and HL do not seem to develop FS after HSCT. While the conditioning regimens are not identical, both groups received high-dose melphalan, which is the only medication used as conditioning for HSCT in patients with MM.

Diagnosing FS after HSCT can be a challenge. The severe prolonged thrombocytopenia after HSCT makes obtaining a kidney biopsy specimen difficult. In addition, Magnano *et al.*[2] concluded that the absence of histopathologic changes does not rule out the diagnosis as these findings are uncommon. The findings of severe electrolyte depletion, metabolic acidosis, and low to low-normal uric acid, especially in the setting of AKI, should raise the suspicion of FS. It is also not mandatory for all biochemical features of hypokalemia, hypophosphatemia, proximal RTA, hypouricemia, and normoglycemic glycosuria to be present to diagnose a patient with FS. FS is classified as complete if all the aforementioned features are present and partial if 1 or 2 features is or are lacking.[S1] In our case series, all patients had partial FS—but all of the relevant laboratory values were not tested in all patients. In this study, all patients except 1 demonstrated nonspecific worsening proteinuria, which is also a feature of FS. This proteinuria is most likely overflow proteinuria from decreased reabsorption by the proximal tubules.[S3,S4] Finally, it is not uncommon for patients to develop gastrointestinal adverse effects after HSCT that could exacerbate ongoing electrolyte losses. Determining the source of the electrolyte losses is vital for the diagnosis. Urinary indices, such as fractional excretions of electrolytes, could be calculated to confirm kidney wasting and aid in the diagnosis.

It is important to note that lenalidomide has been implicated to cause FS in patients with MM. Glezerman *et al.*[S5] reported a case of FS that developed after the introduction of lenalidomide and reversed with its discontinuation and that was not correlated with the kappa free light chain level. In our study, 2 of 5 patients received lenalidomide as part of their chemotherapeutic regimen; however, lenalidomide was discontinued for ≥2 weeks before HSCT as part of the protocol. None of the patients had electrolyte abnormalities before HSCT, suggesting that the development of FS was unrelated to lenalidomide. One patient did

have FS reoccurrence after reintroduction of lenalidomide, and its association cannot be ruled out.

Another unique feature of acute acquired FS after HSCT is that it appears to be self-limited and transient. Despite the severity of electrolyte abnormalities, the electrolyte concentrations in all patients eventually normalized either before discharge or on short-term follow-up. One patient did undergo plasmapheresis for biopsy-proven LCPT. Two patients with long-term follow-up had no FS reoccurrence. Close surveillance shortly after FS diagnosis with repeat laboratory tests every 1 or 2 weeks is recommended. Electrolyte replacement, whether oral or IV, is the cornerstone of management. Potassium-sparing diuretics are another therapeutic option. In addition to its potassium-sparing effect, amiloride also decreases urinary magnesium excretion, and a normal serum magnesium concentration is necessary for proper potassium handling by the kidneys.[S10,S11] Patients on both trimethoprim-sulfamethoxazole as part of post-HSCT infectious prophylaxis and potassium-sparing diuretics should be closely monitored as both can cause hyperkalemia. Finally, patients can also have hypocalcemia, and oral calcium replacement could affect gastrointestinal phosphorus absorption. The supplements will need to be separated either by timing or by route of administration (Table 3).

CONCLUSION

In conclusion, FS is a rare complication that can occur in patients with MM even after HSCT, particularly in patients whose monoclonal gammopathy has kappa light chain restriction. The development of severe electrolyte depletion, metabolic acidosis, hypouricemia, and/or normoglycemic glycosuria after HSCT should raise the clinical suspicion of FS—even in the presence of concurrent gastrointestinal symptoms, which are not uncommon after the procedure. It appears to be a self-limited and transient phenomenon requiring timely and adequate electrolyte repletion and close monitoring. Rarely, plasmapheresis may be necessary for crystal-induced AKI. Lenalidomide is a chemotherapeutic agent commonly used to treat MM that has been reported to induce FS.

DISCLOSURE

MAG has received personal fees from Ionis/Akcea, personal fees from Alnylam, personal fees from Prothena, personal fees from Janssen, grants and personal fees from Spectrum, personal fees from Annexon, personal fees from Appellis, personal fees from Amgen, personal fees from Medscape, personal fees from Physicians Education Resource, personal fees for Data Safety Monitoring board from Abbvie and Celgene, personal fees from Research to Practice workforce training from Sanofi, speaker fees from Teva, speaker fees from Johnson and Johnson, speaker fees from Medscape, speaker fees from DAVA oncology, has been on the advisory board for Pharmacyclics and the advisory board for Proclara, and has developed educational materials for i3Health, all of which are outside the submitted work. PK has received grants from Amgen, Sanofi, Takeda, AbbVie, and GSK and honoraria from Karyopharm, Pharmacyclics, Cellectar, Sanofi, and GSK, all of which are outside the submitted work. AD has received other compensation from Alnylam, Intellia, and Janssen, grants from Takeda, grants from Pfizer, grants from Prothena, grants from Celgene, grants from Alnylam, and grants from Janssen, all of which are outside the submitted work. NL reports other compensation from AbbVie and Takeda, personal fees from Aduro, and grants from Omeros during the conduct of the study. All the other authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplemental References.

REFERENCES

1. Ma CX, Lacy MQ, Rompala JF, et al. Acquired Fanconi syndrome is an indolent disorder in the absence of overt multiple myeloma. *Blood*. 2004;104:40–42.
2. Magnano L, Fernández de Larrea C, Cibeira MT, et al. Acquired Fanconi syndrome secondary to monoclonal gammopathies: a case series from a single center. *Clin Lymphoma Myeloma Leuk*. 2013;13:614–618.
3. Castillo B, Chang BN, Wahed A, Tholpady A. A rare case of acquired Fanconi's syndrome with monoclonal gammopathy in an infant. *J Clin Lab Anal*. 2016;30:510–512.
4. Sanders PW, Herrera GA, Lott RL, Galla JH. Morphologic alterations of the proximal tubules in light chain-related renal disease. *Kidney Int*. 1988;33:881–889.
5. Leboulleux M, Lelongt B, Mougenot B, et al. Protease resistance and binding of Ig light chains in myeloma-associated tubulopathies. *Kidney Int*. 1995;48:72–79.
6. Decourt C, Rocca A, Bridoux F, et al. Mutational analysis in murine models for myeloma-associated Fanconi's syndrome or cast myeloma nephropathy. *Blood*. 1999;94:3559–3566.
7. Stokes MB, Valeri AM, Herlitz L, et al. Light chain proximal tubulopathy: clinical and pathologic characteristics in the modern treatment era. *J Am Soc Nephrol*. 2016;27:1555–1565.
8. Sanders PW. Mechanisms of light chain injury along the tubular nephron. *J Am Soc Nephrol*. 2012;23:1777–1781.
9. Messiaen T, Deret S, Mougenot B, et al. Adult Fanconi syndrome secondary to light chain gammopathy. Clinicopathologic heterogeneity and unusual features in 11 patients. *Medicine (Baltimore)*. 2000;79:135–154.