A Rare Case of Acquired Fanconi's Syndrome With Monoclonal Gammopathy in an Infant

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Background: Monoclonal gammopathies associated with acquired Fanconi's syndrome (AFS) have been reported in the adult population. AFS is characterized by renal dysfunction resulting in proteinuria, aminoaciduria, hypophosphatemia, glucosuria, and hyperchloremic metabolic acidosis. In this case report, we document the clinical and laboratory findings of a preterm infant with features of both AFS and monoclonal gammopathy in the urine. **Methods:** Clinical suspicion of AFS prompted the following laboratory studies to be performed: urine protein electrophoresis (UPEP), urine immunofixation, and urine amino acid anal-

ysis with high performance liquid chromatography (HPLC). **Results:** Urine amino acid analysis revealed aminoaciduria. On UPEP, nonselective glomerular proteinuria was seen with a faint band in the gamma region. Urine immunofixation confirmed the presence of a monoclonal IgG lambda component with free monoclonal lambda light chains. **Conclusion:** To the best of our knowledge, this is the first case of pediatric AFS reported with a monoclonal gammopathy and monoclonal free light chains. *J. Clin. Lab. Anal.* 30:510–512, 2016. © 2015 Wiley Periodicals, Inc.

Key words: congenital; MGUS; paraprotein; metabolic; acidosis

INTRODUCTION

Monoclonal gammopathies are characterized by a group of disorders in which clonal plasma cells or B-lymphocytes produce excess amounts of immunoglobulins or components of immunoglobulins. This overproduction of immunoglobulins can be detected in serum and/or urine specimens by protein electrophoresis. When a monoclonal immunoglobulin is recognized, it is seen as a band of restricted migration on serum or urine electrophoresis (M-protein). When the band represents a monoclonal free light chain, it is referred to as a Bence Jones' protein (1).

The differential diagnosis of an M-protein includes monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, solitary plasmacytoma of bone or extramedullary plasmacytoma, macroglobulinemia, lymphoma, chronic lymphocytic leukemia, and primary systemic amyloidosis (2). Of these, MGUS accounts for the majority of monoclonal gammopathies and is characterized by the presence of a monoclonal component without clinical findings or symptoms of the previously mentioned entities and a serum M-protein concentration less than 3.0 g/dL. MGUS is found in approximately 1% of otherwise healthy persons over the age of 50 years and

with a frequency of 3% in those over the age of 70 (3). In children, monoclonal gammopathies are rare, having been reported with a frequency of only 3.9% (4). Unlike adults, the majority of homogeneous immunoglobulin component (H-Ig) described in children is transient (4).

Acquired Fanconi's syndrome (AFS) is a rare complication that has been described with monoclonal gammopathies (5, 6). It is characterized by renal dysfunction caused by crystal formation in the proximal tubules from failure of degradation of free light chains endocytosed in lysosomes (6). This accumulation of light chain fragments and formation of crystals in the proximal tubule leads to proteinuria, aminoaciduria, hypophosphatemia, glycosuria, hypercalciuria, phosphaturia, and hyperchloremic metabolic acidosis. Additionally, AFS is commonly seen with osteomalacia resulting from hypophosphatemia and chronic metabolic acidosis. Although this condition has

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TABLE 1. Analysis of Urine Amino Acids Showing Aminoaciduria

Amino acid	$\mu\text{Mol/g}$ (range)
Alanine	4450 (124–1958)
Asparagine	1751 (1–774)
Beta-alanine	402 (0–353)
Citrulline	276 (0–137)
Cystine	485 (4–237)
Glutamine	10834 (42–2709)
Glycine	8262 (142–7576)
Histidine	2529 (15–552)
Phenylalanine	647 (13–278)
Serine	2756 (22–2057)
Threonine	2288 (34–985)
Valine	1132 (4–262)

frequently been reported in adults (5, 6), there is limited information of its presentation in the pediatric population. Herein, we present a case of a 6-month-old preterm male found to have features consistent with both AFS and a monoclonal gammopathy in the urine.

REPORT OF THE CASE

An infant born preterm at 25 weeks was transferred to our institution for higher level of care at 5 months of age for worsening respiratory status. Prior to transfer, his hospital course had been complicated by necrotizing enterocolitis (NEC) managed conservatively without surgical intervention and reintubation for repeat episodes of apnea. Throughout his admission at our institution, his disease course was complicated by chronic lung disease, pulmonary hypertension, metabolic acidosis, and repeat episodes of NEC complicated by perforations requiring segmental small bowel resection and eventually reanastomosis. Additionally, during his admission he was noted to have cyclical creatinine levels ranging from 0.3 to 0.7 that were attributed to multiple episodes of acute kidney injury.

At 6 months of age, his primary team had become concerned given a high creatinine peak of 1. At this point in his hospital course, he was also noted to have new-onset hypernatremia. Additional lab tests were done to clarify the etiology of hypernatremia that was later found to be attributed to free water loss secondary to gastrointestinal losses and tachypnea. However, at the time of this work-up, he was also found to have a constellation of findings including glucosuria, proteinuria, hypophosphatemia, and metabolic acidosis with normal anion gap, raising the possibility of congenital versus AFS. Urine amino acid analysis was performed with high-performance liquid chromatography (HPLC) using the ninhydrin reaction and showed aminoaciduria (Table 1).

Fig. 1. Urine immunofixation performed following UPEP demonstrates IgG-lambda paraprotein (arrows) with free monoclonal lambda light chains (diamond arrow).

During his admission, he had multiple imaging studies including chest and abdominal X-rays showing stable osseous structures; however, he was found to have an elevated serum alkaline phosphatase level (732 units/l). The serum parathyroid hormone (PTH) was normal at 39.1 pg/ml and serum 1,25-dihydroxyvitamin D level was at 15 pg/ml (no reference range has been established for this age group). Hypophosphatemia was present (3.4 mg/dl) with normal calcium levels. There was no evidence of immunodeficiency as his WBC was 6.2 with 57% lymphocytes.

A random urine protein electrophoresis (UPEP) was performed and showed all protein fractions with a dominant albumin fraction consistent with nonselective glomerular proteinuria. In addition, a faint band was seen in the gamma region. Urine immunofixation was performed to further characterize the paraprotein and showed a monoclonal IgG lambda and free monoclonal lambda light chains (Fig. 1). Serum protein electrophoresis was not performed.

Given that the patient had repeated episodes of acute kidney injury with new findings of proteinuria, aminoaciduria, glucosuria, and a hyperchloremic metabolic acidosis, a diagnosis of Fanconi's syndrome was entertained. To rule out the genetic conditions associated with the clinical presentation and lab values consistent with Fanconi's syndrome, molecular genetic testing was performed for Fanconi-Bickel's syndrome and Lowe's syndrome. Fanconi-Bickel's syndrome is a rare autosomal recessive type of glycogen storage disease characterized by mutations in GLUT 2 and presents with aminoaciduria, phosphaturia, glucosuria, small stature, malabsorption, hepatomegaly, fasting hypoglycemia, and glucose intolerance (7). Lowe's syndrome (oculocerebrorenal syndrome) is a rare X-linked recessive disorder presenting with congenital bilateral cataracts, central nervous system dysfunction characterized by hypotonia and areflexia, and facial dysmorphisms (8). Although both of these entities have features consistent with Fanconi's syndrome, no

genetic mutations in SLC2A2 gene and OCRL gene were identified in this patient. Further, there were no grossly congenital abnormalities seen in the patient to support a diagnosis of congenital Fanconi's syndrome.

Based on the clinical findings and laboratory values, it was determined that the Fanconi's syndrome was acquired secondary to his kidney injury and attributable to the monoclonal gammopathy and Bence Jones' protein. In this case, a renal biopsy would have aided in the exact etiology of the Fanconi's syndrome and the correlation with the associated monoclonal gammopathy. Unfortunately, the infant passed away, and an autopsy was declined by the family.

COMMENT

It has been well established that AFS occurs in adults and that this disorder can result from monoclonal gammopathies, amyloidosis, tubulointerstitial nephritis, heavy metal poisoning, and toxic drug reaction (5). In cases associated with monoclonal gammopathies, there is a failure of reabsorption at the proximal tubules in the kidney leading to glucosuria, aminoaciduria, and hypophosphatemia (6).

Monoclonal gammopathies in children are rarely seen and follow-up studies have shown that most of these monoclonal gammopathies are transient (4). Clinical conditions associated with monoclonal gammopathies seen in the pediatric population include primary and secondary immunodeficiencies, hematological malignancies, severe aplastic anemia, autoimmune disorders, infectious diseases, atopic asthma, and other associated conditions including Hyper-IgD syndrome, Gaucher's disease, von Willebrand's disease, congenital nephritic syndrome, and hydronephrosis (4).

The patient described in this case report was initially found to have progressive worsening of renal dysfunction and elevated creatinine. Additional laboratory studies showed glucosuria, hypophosphatemia, aminoaciduria, and a non-anion gap metabolic acidosis. UPEP showed the presence of a monoclonal IgG lambda and free monoclonal lambda light chains.

In patients with this type of electrolyte abnormalities and monoclonal gammopathy, one must rule out hyperparathyroidism. In one study, monoclonal gammopathies had been detected in 10% of patients with primary hyperparathyroidism (9). In our pediatric patient, there was normal serum PTH level as well as vitamin D level in the acceptable adult range. Based on these findings, a diagnosis of primary or secondary hyperparathyroidism was excluded.

Given the presence of a monoclonal gammopathy with no evidence of congenital Fanconi's syndrome by molec-

ular genetic testing, a presumptive diagnosis of AFS was considered. Typically, patients with AFS present with osteomalacia caused by hypophosphatemia and chronic metabolic acidosis (5). In our patient there was no radiographic evidence to support the presence of osteomalacia. However, in the absence of radiographic findings, the presence of osteomalacia may be suggested by an elevated serum alkaline phosphatase level (6). Our patient did indeed have a persistently elevated alkaline phosphatase level.

Definitive diagnosis of AFS can only be confirmed by renal biopsy. The renal histopathological findings seen in patients with monoclonal gammopathy associated AFS include cytoplasmic crystals in the proximal tubular cells or tubulointerstitial damage without glomerular lesions (5). Additionally, immunofluorescence studies, electron microscopy, and immunoelectron studies reveal that these crystals are composed of monoclonal light chains (5).

Another interesting finding in this case is the presence of lambda-type Bence Jones' proteinuria. In cases of AFS, the presence of Bence Jones' proteinuria is almost exclusively of the kappa type (6). However, there have been rare reported cases demonstrating the presence of lambda-type free light chains (10).

In conclusion, we describe a case of pediatric AFS in the presence of a monoclonal gammopathy and monoclonal free light chains. To our knowledge, there have been no previous reported cases of AFS in an infant. Additionally, this case serves as an extremely rare variant of monoclonal gammopathy associated AFS in that the lambda-type gammopathy is present.

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