Mercury Intoxication as a Rare Cause of Membranous Nephropathy in a Child

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In adults, membranous nephropathy is the second most common cause of nephrotic syndrome. In contrast, minimal change disease and focal segmental glomerulosclerosis constitute the most common forms of nephrotic syndrome in children, while membranous nephropathy accounts for <5% of cases. In adults, causes of membranous nephropathy include autoantibodies directed against phospholipase A_2 receptor and thrombospondin type 1 containing 7A, various infections, environmental toxicities, autoimmune disorders, malignancies, and other secondary forms. The most common causes of secondary membranous nephropathy in children are infections, autoimmune diseases, and neoplasia. We discuss an unusual presentation of new-onset membranous nephropathy due to mercury toxicity in a 14-year-old male with reflux nephropathy. This case underscores the importance of a high index of suspicion for uncommon causes of nephrotic syndrome in pediatric patients with membranous nephropathy.

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Teaching Cases focus on interpretation of pathology findings, laboratory tests, or imaging studies to educate readers on the diagnosis or treatment of a clinical problem.

Introduction

Causes of nephrotic syndrome include autoantibodies to specific glomerular antigens, podocytopathies, infections, paraneoplastic syndromes, metabolic disorders, and certain genetic mutations.[1-4] The most common forms of nephrotic syndrome in childhood are due to minimal change disease (72%) or focal segmental glomerulosclerosis (24%).[5] In contrast to adults, for whom membranous nephropathy (MN) is the second most common form of nephrotic syndrome, MN accounts for <5% of pediatric patients with primary glomerular disease.[6,7] MN is characterized by subepithelial glomerular immune complexes, resulting in a thickened glomerular basement membrane and membrane "spikes" when stained with Jones methenamine silver. MN can be caused by autoantibodies to specific glomerular antigens such as M-type phospholipase A_2 receptor (PLA_2R; identified in >70%) and thrombospondin type 1 domain containing 7A (THSD7A; identified in 5%) on podocyte membranes[8,9] or by other secondary causes (Box 1).[7,10,11] Rarely, MN in infants can be due to alloantibodies against neutral endopeptidase (NEP) in mothers lacking NEP, who then develop an immune reaction to fetal NEP.[12] We describe a pediatric patient with underlying reflux nephropathy and stage 3 chronic kidney disease who developed MN and nephrotic syndrome due to mercury exposure.

Case Report

In 2012, during an evaluation for suspected appendicitis, a 14-year-old male adolescent with stage 3 chronic kidney disease due to reflux nephropathy was found to have an atrophic right kidney. A renal nuclear scan revealed 8% function on the right kidney and 92% on the left. A voiding cystourethrogram confirmed grade III vesicoureteral reflux bilaterally and he underwent a surgical procedure to reduce reflux on the left side. Three years later, an iothalamate sodium I 125 study measured glomerular filtration rate of 49 mL/min/1.73 m^2, and serum creatinine level was 1.5 mg/dL. He subsequently developed hypertension, secondary hyperparathyroidism, mild proteinuria (protein excretion, 500 mg/d), and mild anemia. In 2016 at a routine office visit, he reported new-onset facial swelling for 2 days. He denied fever, sore throat, rash, abdominal distension, shortness of breath, dysuria, or gross hematuria. He had gained 7.5 kg over the previous 5 months. The family history was previously negative for kidney disease but interestingly, his stepfather now also reported new-onset ankle swelling, and nephrotic syndrome was recently diagnosed. The patient was living with his parents and 2 sisters.

The patient's temperature was 36.3°C, heart rate was 78 beats/min, and blood pressure was 128/86 mm Hg. There was no overt facial or pedal edema. Laboratory test results showed urinalysis with protein (4+), microscopic hematuria, and protein-creatinine ratio of 15.6 (Fig 1A). Serum albumin level was 1.8 g/dL (Fig 1A), and serum creatinine level was 1.6 mg/dL (from a baseline of 1.3-1.6 mg/dL). Serum cholesterol level was elevated at 292 mg/dL. The 24-hour urine

Box 1. Causes for Membranous Nephropathy

Antibodies[a]
- PLA_2R
- THSD7A
- Neutral endopeptidase
- Cationic BSA (in infants)

Infections
- Cytomegalovirus
- Epstein-Barr virus
- Hepatitis B and C viruses
- HIV
- Malaria
- Schistosomiasis
- Syphilis
- Tuberculosis

Medications and environmental causes
- Captopril
- Clopidogrel
- Gold & D-penicillamine
- Lithium
- Mercury
- NSAIDs & COX2 inhibitors
- Tiopronin

Autoimmune disorders
- Ankylosing spondylitis
- Autoimmune thyroiditis
- Dermatomyositis
- Mixed connective tissue disease
- Sjögren syndrome
- Systemic lupus erythematosus
- IgG4-related disease
- Leukemias (eg, CLL)
- Lymphomas
- Neuroblastoma

Other
- Diabetes mellitus
- Sarcoidosis
- Sickle cell disease
- Hematopoietic stem cell transplant
- Transplant glomerulopathy

Note: Based on causes reviewed in[7,26].
Abbreviations: BSA, bovine serum albumin; CLL, chronic lymphocytic leukemia; COX2, cyclooxygenase 2; HIV, human immunodeficiency virus; IgG, immunoglobulin G; NSAIDs, nonsteroidal anti-inflammatory drugs; PLA_2R, M-type phospholipase A_2 receptor; THSD7A, thrombospondin type 1 domain containing 7A.
[a]List comprises the antigens eliciting the antibody response.

protein excretion was 9.7 g. Complete blood cell count, antinuclear antibody, and C3 and C4 complement levels were normal. Viral studies were negative for hepatitis B and C virus and human immunodeficiency virus (HIV). Kidney ultrasound showed right renal atrophy and interval growth of the left kidney.

A kidney biopsy was performed. Light microscopy showed mild enlargement of glomeruli without basement membrane thickening or spikes (Fig 2A). Immunofluorescence microscopy demonstrated strong (4+), diffuse, global, granular glomerular capillary loop and mesangial staining for immunoglobulin G (IgG; Fig. 2B) and C3. Electron microscopy showed severe (60%-70%) podocyte foot-process effacement and numerous irregularly distributed subepithelial electron-dense deposits (Fig 2C and D). These findings were consistent with membranous glomerulopathy. Immunofluorescent staining for PLA_2R and THSD7A was unsuccessful due to lack of sufficient glomeruli in the tissue block. Serum was tested for PLA_2R and THSD7A autoantibodies; both gave negative results (anti-PLA_2R IgG titer, <1:10; THSD7A immunofluorescence negative, no THSD7A autoantibodies detected).

Because both stepfather and son developed new-onset nephrotic syndrome, we sought a possible environmental cause for nephrotic syndrome. When prompted regarding possible mercury exposure, the patient's mother reported that the family had moved into a used trailer home 3 months previously. Inside, there were small bottles containing mercury, and some of the bottle contents had been spilled on counter tops, under the floor tiles, and on the carpet. They attempted to clean the trailer by vacuuming the visible mercury. Because the patient and his sisters were fascinated by the shiny characteristics of mercury, the parents, not appreciating the risk, had allowed the children to play with the liquid metal.

The patient's blood mercury level, 41 μg/L, was more than 4 times greater than the reference range (≤10 μg/L; Fig 1B). His 24-hour urine mercury level, which provides a more accurate quantitative measure of total-body mercury content, was also elevated at 42.9 (reference range, ≤20) μg/d (Fig 1B). The Environmental Protection Agency contacted the family and evacuated them from the trailer home, which eventually was removed and destroyed. Zeeman mercury spectrometry resulted in readings > 50,000 (reference range, <3,000) ng/m^3 in the family car, 20,000 to 37,000 ng/m^3 in the home, and >50,000 ng/m^3 in various items of clothing.

Given the evidence of nephropathy, chelation therapy with succimer (dimercaptosuccinic acid [DMSA]) was initiated. He received a short course of high-dose corticosteroid therapy (prednisolone at 60 mg/d), but with only marginal improvement (Fig 1A). The patient developed gross edema during his evaluation for the cause of proteinuria and was treated with diuretics. His 24-hour urine mercury level initially increased to 85.3 μg/d due to mobilization with chelation therapy but thereafter began to decline (Fig 1B). Despite chelation therapy, the patient continued to have significant proteinuria and hypoalbuminemia (albumin level, 2 g/dL). His kidney function worsened to chronic kidney disease stage 4. Fortunately, the patient's siblings did not require chelation therapy because their urine mercury levels were only mildly elevated.

Discussion

Mercury exists in 3 forms: (1) elemental mercury, (2) inorganic salts, and (3) organic compounds. Elemental