Chyluria presenting as milky urine and nephrotic-range proteinuria

J-T Cheng[1], S Mohan[1], SH Nasr[2] and VD D'Agati[2]

[1]Department of Medicine, Harlem Hospital Center, New York, New York, USA and [2]Department of Pathology, College of Physicians and Surgeons, Columbia University, New York, New York, USA

CASE PRESENTATION

A 41-year-old woman was admitted to Harlem Hospital Center for the evaluation of nephrotic-range proteinuria, microhematuria, hypoalbuminemia, and edema. The patient was born in the Dominican Republic and came to the United States 10 years ago. She gave a history of episodic cloudy urine for the past 28 years. Five years before admission during her last pregnancy, she was noted to have proteinuria (2 g/24 h). Two years before admission, she was treated for filariasis at another hospital, and after 1 year, she was admitted to the same hospital for edema and was found to have chronic active hepatitis C infection with incipient cirrhosis by liver biopsy. For the past 3 months, the patient noted progressive swelling of both lower extremities associated with episodic passage of cloudy urine and flank pain. There was no history of diabetes mellitus, hypertension, renal stones, or gross hematuria. She was on no medications and denied alcohol, illicit drug, and tobacco use.

Physical examination revealed a thin and malnourished woman weighing 55.5 kg with a temperature of 37°C, pulse 92/min, and blood pressure 104/60 mmHg. There was no skin rash. The heart and lung examinations were normal. The abdomen was soft with the liver palpable 3 cm below the right costal margin. The spleen was not palpable and there was no shifting dullness. There was 3+ pitting bilateral pedal edema.

Laboratory data on the current admission included hematocrit 46% (reference interval, 42–52%), white blood count 6.6×10^9/l (reference interval, 4.0–10.5×10^9/l) with normal differential, platelet count 381×10^9/l (reference interval, 150–500×10^9/l), blood urea nitrogen 7 mg/dl (2.5 mmol/l) (reference interval, 7–18 mg/dl, 2.5–6.4 mmol/l), serum creatinine 0.7 mg/dl (63 μmol/l), total protein 4.1 g/dl (41 g/l) (reference interval 6.0–7.8 g/dl, 60–78 g/l), albumin 1.9 g/dl (19 g/l) (reference interval 3.5–5.0 g/dl,35–50 g/l), bilirubin 0.5 mg/dl (8.6 μmol/l) (reference interval 0.2–1.0 mg/dl, 3.4–17.1 μmol/l), aspartate aminotransferase 100 U/l (reference interval 10–40 U/l), alanine aminotransferase 38 U/l (reference interval, 10–35 U/l), alkaline phosphatase 408 U/l (reference interval, 20–80 U/l), serum cholesterol 208 mg/dl (5.38 mmol/l) (recommended <200 mg/dl, <5.18 mmol/l), and triglyceride 108 mg/dl (1.22 mmol/l) (recommended 35–135 mg/dl, 0.40–1.52 mmol/l). Serologic work-up showed positive hepatitis C antibody and positive hepatitis B core antibody. Serologic tests for hepatitis B surface antigen, hepatitis B surface antibody, syphilis, human immunodeficiency virus, antinuclear antibody, and cryoglobulin were negative. The serum complement levels including C3, C4, and CH50 were within the normal ranges.

Five days before admission, a routine urinalysis was reported as showing clear yellow urine with 2+ protein, 4+ blood, and negative leukocyte esterase. A follow-up urinalysis on the day of admission, however, showed milky urine with clots, 4+ protein, and 3+ blood. Microscopic examination of the urine sediment showed many red blood cells and a few epithelial cells per high-power field. There were no oval fat bodies, fatty casts, cellular casts, or crystals. Examination of stained urine sediment by modified Wright stain (Hansel's stain) revealed many isomorphic red blood cells and lymphocytes (Figure 1). Addition of Sudan III to an aliquot of this milky urine, followed by mixing and shaking with an equal volume of chloroform and centrifugation, produced clearing of the cloudy urine with the appearance of stained fatty globules in the organic layer (Figure 2).

A 24-h urine collection yielded 6.5 g of protein and a creatinine clearance of 91 ml/min. A urine protein electrophoresis showed non-selective proteinuria. A chest X-ray and an electrocardiogram were normal. An abdominal ultrasound showed a 14 cm liver with increased echotexture; the kidneys were normal in size and echotexture.

Differential diagnosis of the renal abnormalities included nephrotic syndrome owing to hepatitis C-associated membranous or membranoproliferative glomerulonephritis, minimal change disease, and chyluria. A renal biopsy was performed.

Correspondence: *VD D'Agati, Department of Pathology, Columbia University, College of Physicians and Surgeons, 630 West 168th Street, VC14-224, New York, New York 10032, USA. E-mail: vdd1@columbia.edu*

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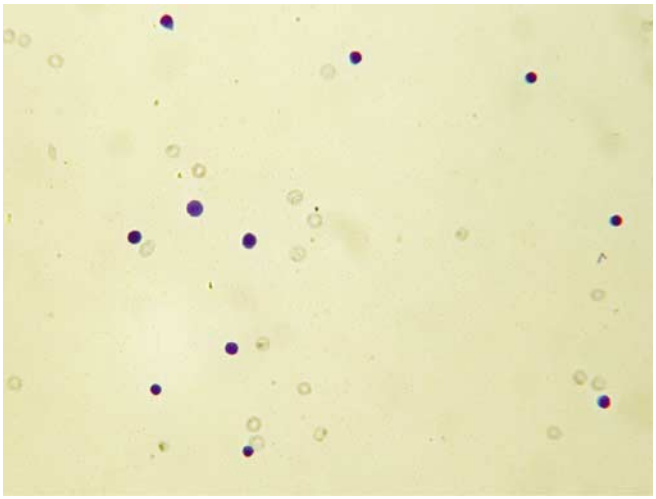

Figure 1 | Thin smear of urine sediment stained with modified Wright stain (Hansel's stain) showing lymphocytes and isomorphic erythrocytes (original magnification $\times$ 400).

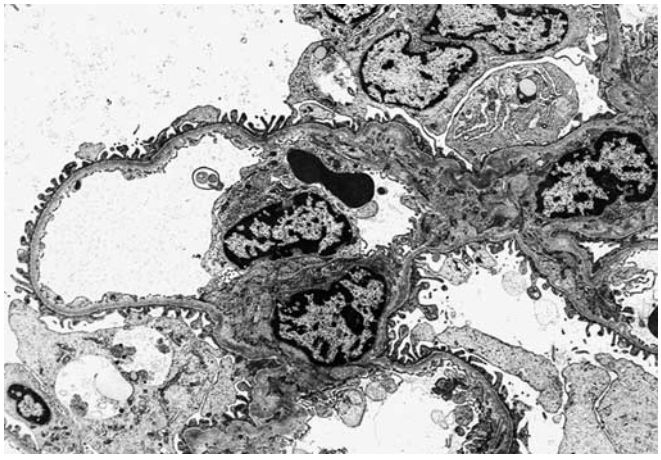

Figure 3 | A representative electron micrograph shows normal glomerular basement membrane thickness with intact foot processes and absence of electron dense deposits (original magnification $\times$ 2000).

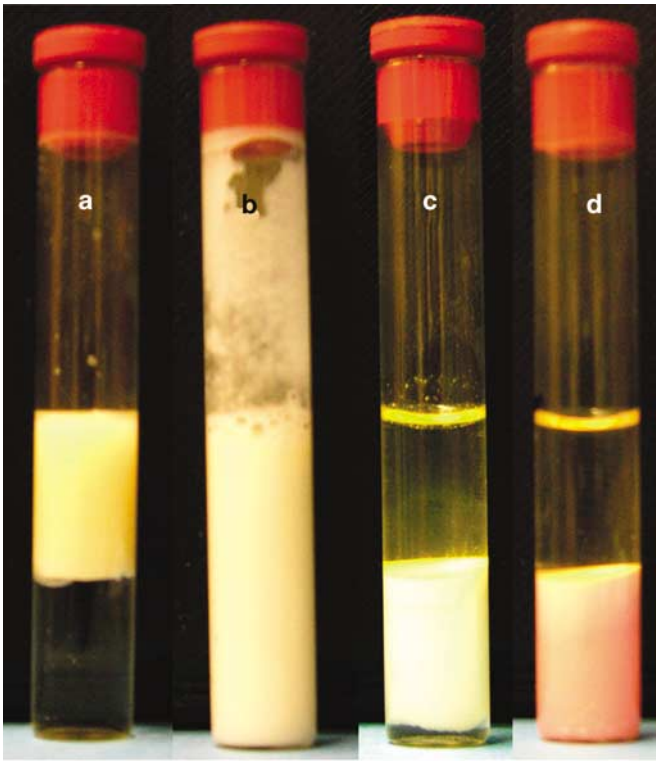

Figure 2 | Chloroform extraction of fat globules from chyluria. (**a**) To an aliquot of milky urine, an equal volume of chloroform is added. (**b**) Result of mixing and agitation of the mixture. (**c**) After centrifugation of the agitated mixture, there is clearing of milky urine with extraction of fat globules in the chloroform layer (bottom). (**d**) Chloroform extraction after the addition of Sudan III to the milky urine. Note the appearance of red-stained fat globules in the bottom chloroform layer and clearing of the milky urine.

RENAL BIOPSY FINDINGS

Light microscopic examination disclosed one core of renal cortex containing 32 glomeruli, none of which were segmentally or globally sclerotic. Glomeruli appeared normal in size and cellularity. There was mild focal segmental increase in mesangial matrix. The glomerular basement membranes appeared normal in thickness and contour, without evidence of podocyte swelling. No double contours, spikes, or immune deposits were detected with the silver or trichrome stains. There were several minute foci of interstitial fibrosis and lymphocytic inflammation surrounding tubules containing Tamm–Horsfall casts. No intracytoplasmic protein or lipid resorption droplets were identified within the proximal tubular epithelial cells. There was no evidence of lymphatic or interstitial capillary dilatation. Vessels were unremarkable. No filarial organisms were identified.

Immunofluorescence staining was negative for all immune reactants (IgG, IgA, IgM, C3, C1q, albumin, fibrinogen, kappa, and lambda light chains) in the glomeruli and tubules. Of note, no protein resorption droplets were detected in the tubular epithelium. By electron microscopy, the mesangial areas and glomerular basement membranes appeared unremarkable. No immune-type electron dense deposits were identified. The podocyte foot processes appeared intact (Figure 3). The tubulointerstitial compartment was unremarkable; no intraepithelial protein resorption droplets were identified.

In short, the renal biopsy showed no evidence of immune complex-mediated glomerulonephritis related to hepatitis C infection. The absence of foot process effacement ruled out minimal change disease. By exclusion, the normal renal biopsy findings supported proteinuria on a non-glomerular basis, as might occur secondary to chyluria.

CLINICAL FOLLOW-UP

The patient was referred to urologic service for further evaluation and management of chyluria. Before work-up for chyluria and filariasis could be initiated, she returned to the Dominican Republic and was lost to follow-up.

DISCUSSION

Chyluria is the excretion of chyle from the urinary tract.[1–3] Chyle is defined as the lymphatic fluid in the intestinal lacteals that contains absorbed fat in the form of chylomicrons. The presence of chylomicrons in a stable emulsion gives this intestinal lymph a milky appearance.[2] Chyluria indicates the presence of an abnormal communication between intestinal lymphatics and the urinary tract. This communication is caused by the obstruction of lymphatic drainage proximal to intestinal lacteals, resulting in variceal dilatation of distal lymphatics and eventual rupture of lymphatic vessels into the urinary tract, creating a lymphaticourinary fistula.[1–5] The location of lymphaticourinary fistula is most commonly at the calyceal fornix in the renal pelvis, but can also occur at the level of the ureter or urinary bladder.[2,4,5]

The etiology of chyluria can be classified as either parasitic or non-parasitic.[2,5] Lymphatic filariasis is the most common cause of parasitic chyluria in persons living in endemic areas, namely tropical and subtropical regions between latitude 40° North and 30° South, including India, China, Southern Japan, Southeast Asia, the South Pacific islands, tropical sub-Saharan Africa, the Caribbean islands, including Cuba, Haiti and the Dominican Republic, and the northeast coast of South America.[3,6] *Wuchereria bancrofti* infection accounts for most of the lymphatic filariasis worldwide.[3,6] Chyluria is a late and uncommon manifestation of chronic lymphatic filariasis.[2,3] In one epidemiologic study, chyluria was present in 0.7% of the population in an endemic area,[7] and in another clinical study, chyluria was diagnosed in 2% of urologic patients with filarial infection.[8]

Diagnosis of lymphatic filariasis is usually made by the detection of microfilariae on thick Giemsa-stained blood smears, which requires late night examination (around midnight) because of the nocturnal periodicity of the circulating parasites. During the day, microfilariae reside in the capillary beds of deep visceral organs, such as the lungs, and enter the blood stream during the night, coinciding with the time of peak biting frequency of the mosquito vector. Parasite concentration techniques such as the membrane filtration of venous blood increase the sensitivity of detecting the microfilariae. In recent years, circulating filarial antigen detection tests have been introduced, including the commercially available enzyme-linked immunosorbent assay antigen test using monoclonal antibodies and the immunochromatography filarial antigen test using polyclonal and monoclonal antibodies. The filarial antigen tests are more sensitive than thick smear or membrane filtration for the detection of *W. bancrofti* and can be performed on samples collected during the day. Detection of filarial DNA by polymerase chain reaction is also available in some centers.

The non-parasitic causes of chyluria are rare and include granulomatous disease (such as tuberculosis, fungal infection, and leprosy), congenital anomalies of lymphatic system (such as lymphangioma), malignancy, trauma, venous stasis, pregnancy, aortic aneurysm, and lymphatic obstruction after surgery or cardiac catheterization.[2,5,9,10] A past history of residing in the tropical or subtropical endemic area for lymphatic filariasis will suggest a possible parasitic etiology of chyluria, whereas a history of invading malignancy or tuberculosis will suggest obstruction of lymphatic drainage by malignant cells or mycobacterial infection. The presence of unilateral lymphedema may occur in patients with congenital anomalies of the lymphatic system.

Patients with chyluria typically describe the passage of milky white urine. However, some patients may be entirely asymptomatic, whereas others may complain of renal colic with passage of clots. Gross inspection of a freshly voided urine specimen typically shows milky and cloudy urine, which remains turbid after centrifugation. On standing, the urine may separate into three layers: a top layer of chylomicrons, a middle layer containing protein, and a bottom layer of fibrin clots and cellular elements.[2] It should be noted that the average laboratory technician may not be able to detect a chylous urine without appropriate training or prior experience.[1] A dipstick test for urine chemistry usually shows heavy protein and moderate blood, but leukocyte esterase (an enzyme present in granulocytes, but not lymphocytes) is usually negative, unless there is a complicating urinary tract infection. Because the lymphatic fluid contains albumin, as well as higher molecular weight globulins and fibrinogen, with a total protein concentration in the range of 3–6 g/dl,[11] a 24 h urine collection in patients with chyluria often reveals nephrotic-range proteinuria that appears 'non-selective' on urine protein electrophoresis.

Despite the presence of nephrotic-range proteinuria, microscopic examination of the urinary sediment does not reveal the lipid-laden oval fat bodies or fatty casts typically seen in patients with nephrotic syndrome.[1,12] This is because the proteinuria is not originating from glomeruli or renal tubules, but is 'post-nephron' in origin. Instead, one may see large numbers of lymphocytes (not neutrophils) in the urine sediment, consistent with the leakage of lymphatic fluid into the urine.[1,2,5,11] In chyluric patients with hematuria, which is caused by the rupture of blood vessels into the urinary tract during the formation of lymphaticourinary fistula, the red cells in the urine sediment are typically isomorphic, and no red blood cell casts or white blood cell casts are observed. The presence of dysmorphic red cells in the urinary sediment associated with significant proteinuria, oval fat bodies, granular casts, or cellular casts in a patient with chyluria should raise the suspicion of a coexistent glomerular disease.[13] Table 1 compares the clinical features of nephrotic proteinuria and chylous proteinuria.

The presence of chyle in the urine can be confirmed by shaking an aliquot of turbid urine with equal volume of chloroform or ether, which extracts the triglyceride-rich fatty emulsion into the organic layer, leaving the remaining urine clear (Figure 2). The diagnosis of chyluria can also be confirmed by demonstrating a timed increase in the excretion of urinary triglyceride approximately 4 h after a fatty meal.[14] The presence of lymphocytes in the urinary sediment is also consistent with the presence of chyle in the urine.[1,2,5]

Table 1 | Comparison of nephrotic proteinuria and chylous proteinuria

	Nephrotic proteinuria	Chylous proteinuria
Onset and time course	Gradual and persistent Increased with high-protein diet	Episodic with remissions Increased with fatty meal Decreased with fat-free diet
Flank pain and renal colic	Unusual	Frequent
Hypertension	May be present	Unusual
Pitting edema	Present	Only present in malnourished patients
Hypoalbuminemia	Present	Only present in malnourished patients
Hyperlipemia	Common	Unusual
Cloudy and milky urine	Rare	Typical
Clots in urine	Rare	Common
Gross hematuria	Rare	May be present
Microhematuria	May be present	Common
Morphology of urinary erythrocytes	Dysmorphic	Isomorphic
Urinary lymphocytes	Absent	Present
Urinary casts	May contain red cell casts, fatty casts, or cellular casts	No casts or cylindroids seen
Urine protein electrophoresis	Mainly albumin	Albumin, globulin, and lipoprotein
Lipids in urine	Fatty droplets, oval fat bodies, fatty casts in urine sediment	No oval fat bodies or fatty casts in urine sediment Chylomicrons and triglycerides are in the supernatant Increase in urine triglyceride after a fatty meal
Renal function	Normal or decreased	Normal

The differential diagnoses of turbid urine should also include pyuria owing to urinary tract infection and crystalluria resulting from precipitation of phosphate in an alkaline urine. The former can be diagnosed by the presence of many neutrophils, rather than lymphocytes, in the urinary sediment and the latter can be diagnosed by acidification of the urine with acetic acid, which dissolves the precipitated phosphate.[15]

Further evaluation of chyluria includes localization of the side, the site, and the level of lymphaticourinary fistula, and the assessment of the underlying etiology. This is best achieved by performing cystoscopy after a fatty meal, allowing the identification of the ureteral orifice that is passing milky urine or a site of chylous efflux into the bladder or urethra.[2,8] This is followed by lymphangiography for the detection of the level and site of lymphaticourinary fistula formation. Although lymphangiography is the procedure of choice for localization of lymphaticourinary shunt, it requires cannulation of small lymphatic vessels in the foot and injection of lipid contrast medium (Ethiodol) into the lymphatic system, followed by serial pelvic and abdominal radiography for visualization of lymphatics and lymph nodes in the pelvic, retroperitoneal, and para-aortic regions.[4,16] In patients with chyluria, lymphangiography typically shows marked dilatation and tortuosity of the lymphatics around the hilar regions of the kidneys, followed by opacification of the calyceal systems.[4,16] In a minority of patients, the lymphaticourinary communication may be seen at the level of ureter or urinary bladder. It should be noted that the procedure of lymphangiography is technically challenging, requiring a skilled operator, and is not without complications. A non-invasive and equally accurate lymphoscintigraphy has been increasingly utilized for the evaluation of chyluria; it allows the clear and precise analysis of the lymphatic system function in patients with filarial infection.[3]

Because spontaneous remission of chyluria may occur in 50% of patients,[17] patients may not require treatment if the chyluria enters a long interval of remission without nutritional complications. However, in patients with persistent chyluria and malnutrition from excessive urinary losses of lipids and protein, a specifically designed low-fat, high-protein diet supplemented with medium-chain triglycerides has been demonstrated to decrease the proteinuria, lipiduria, and hematuria.[18] In some patients, diagnostic contrast lymphangiography may prove to be therapeutic by causing serendipitous closure of the lymphaticourinary fistula owing to its sclerosing effect on the lymphatic vessels.[4] For patients with recurrent or persistent chyluria unresponsive to medical management, instillation of sclerosing solutions (such as silver nitrate) into the renal pelvis has 80% success rate in achieving closure of the lymphaticopelvic communication.[19] For those patients who fail the renal pelvic instillation sclerotherapy, surgical or retroperitoneoscopic renal pedicle lymphatic disconnection is the treatment of choice.[20]

In summary, chyluria is a rare condition that can be mistaken for nephrotic syndrome because of its presentation with heavy proteinuria, hypoalbuminemia, and edema in malnourished individuals. The renal biopsy findings of intact foot processes and absence of glomerular histologic abnormalities are helpful to exclude intrinsic renal disease and should prompt an appropriate work-up for chyluria. Chyluria should be considered in the differential diagnosis of the patient who presents with cloudy or milky urine.

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