Hypercoagulability in a patient with chronic chyluria, proteinuria and hypoalbuminaemia

Ladan Golestaneh1, Sabine Karam1, Janis Lawrence2, Sara Yang1 and Mark Greenberg1

1Department of Medicine, Montefiore Medical Center and 2Department of Medicine, Jacobi Medical Center, Bronx, NY, USA

Correspondence and offprint requests to: Ladan Golestaneh; E-mail: lgolesta@montefiore.org

Abstract
We describe the case of a young man with prolonged and severe chyluria from a previous parasitic infection. He presented with an acute myocardial infarction most likely secondary to increased clotting tendency. He had a spontaneously formed blood clot in his left anterior descending coronary artery. In the setting of hypo-albuminemia (which has occurred because of obligate losses of protein from lymphuria), he has increased production of factor VIII levels and increased clotting tendency. In addition, because of obligate and unregulated fluid losses he has chronic dehydration, microvascular ischemia and secondary polycythemia. This polycythemia further increases his risk of hypercoagulability.

Keywords: chyluria; hypercoagulable; hypoalbuminaemia; polycythaemia

Background
Chyluria by definition is the passage of chyle into the urinary tract via an abnormal communication between the intestinal lymphatics and the urinary tract. There are two major classifications of chyluria-parasitic versus non-parasitic. The most common parasitic cause is Wuchereria Bancrofti [1]. The fistula between the lymphatics and the ureteral system most commonly occurs at the renal fornix [2,3]. Diagnosis is based on the appearance of chyluria and radiological tests including cystoscopy, lymphangiography and retrograde pyelography [4]. Prolonged and severe chyluria can result in dehydration, malnutrition and immune dysfunction [5,6]. Hypoalbuminaemia is also commonly secondary to lower urinary tract lymphatic protein wasting. We describe a case in which there is increased clotting tendency as a result of chyluria.

History of present illness
This patient is a 44-year-old Hispanic man who presented to Montefiore Medical Centre with a diagnosis of acute myocardial infarction. He had presented to an outside hospital with chest pain. He was transferred to the catheterization lab of our hospital. On cardiac catheterization, he was found to have distal thrombus in multiple vessels including the distal left anterior descending artery (LAD) and both branches of a large marginal artery. Intravascular ultrasound did not show any evidence of plaque rupture. Some of this thrombus was retrieved using an aspiration catheter. The pathologic description of the retrieved material was: ‘fibrin white cell clot composed predominantly of neutrophils without cellular components’. There was minimal evidence for atherosclerotic coronary artery disease. After his catheterization, he was transferred to the Coronary Care Unit (CCU).

Past medical history
Past medical history was significant for a filarial infection in 1985, while he resided in the Dominican Republic. He was treated with an anti-parasitic for 2 weeks. One year after this infection, the patient started to notice ‘milky urine’ especially after a high protein meal (Figure 1). In the ensuing years, there was gradual and severe weight loss (estimated by the patient as 30 pounds), polyuria, chronic dizziness, weakness, fatigue and chronic thirst. The patient was first seen at Harlem hospital in 2002. He was referred to renal clinic because of the finding of proteinuria and haematuria. He had multiple unremarkable imaging studies including renal ultrasound, computed tomography (CT) scans and magnetic resonance (MR) imaging/MR angiography. He then underwent a kidney biopsy; the results demonstrated normal glomerular and tubular structures. A cystoscopy was done that revealed no bladder lesions, but lateralized the source of the chyluria to the left collecting system.

Physical exam
Vital signs showed sinus tachycardia at a rate of 140 beats per minute and hypotension with a blood pressure measuring 88/47. On physical examination, he was a young man of slightly malnourished appearance with temporal wasting, and mild proximal muscle wasting. He was alert and oriented X3. His lungs were clear to auscultation and his heart
Hypercoagulability in a patient with chronic chyluria, proteinuria and hypoalbuminaemia

Fig. 1. Patient’s urine on left and a negative urine sample on right.

sounds revealed a regular but fast rate without audible murmurs. There was no lower-extremity oedema.

**Laboratory data**

Upon admission to the CCU, laboratory tests revealed a haemoglobin of 168 g/L, and total cholesterol was 4.792 mmol/L (with a low density lipoprotein (LDL) of 3.341 mmol/L). Serum albumin was 26 g/L (see Table 1). Urinalysis revealed 150 red blood cells per high power field and >0.3 g/dL of protein in the urine. Quantification of proteinuria showed 9 g of protein excretion based on a spot protein to creatinine ratio. Serologic workup was negative. Filarisis antibodies and cultures were all negative for active disease.

**Hospital course**

A trans-oesophageal echocardiogram failed to reveal a patent foramen ovale, and lower extremity dopplers were negative for deep vein thrombosis. A diagnosis of dehydration was made and 3 Litres of normal saline was administered with resultant improvement in the patient’s blood pressure and his pulse rate. A lymphangiogram revealed a lympho-ureteral fistula involving the left side of his urinary collecting system (Figure 2).

**Post-hospital care**

The patient was sent for a hypercoagulable workup in the haematology clinic. Apart from high levels of factors V, VIII and antithrombin III, a relatively high erythropoietin

**Table 1. Laboratory data**

<table>
<thead>
<tr>
<th>Sodium (mmol/L)</th>
<th>140 (136–146)</th>
<th>Total protein (g/L)</th>
<th>42 (67–86)</th>
<th>PT (sec)</th>
<th>10.9 (9.5–12.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.2 (3.5–5.0)</td>
<td>SGOT (U/L)</td>
<td>48 (9–48)</td>
<td>PTT (sec)</td>
<td>23.4 (26.1–33.8)</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>106 (98–108)</td>
<td>SGPT (U/L)</td>
<td>29 (5–40)</td>
<td>Factor V (proportion of 1)</td>
<td>1.68 (0.50–1.50)</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>25 (24–30)</td>
<td>Total cholesterol (mmol/L)</td>
<td>4.79 (&lt;5.17)</td>
<td>Factor VIII (Proportion of 1)</td>
<td>2.15 (0.50–1.50)</td>
</tr>
<tr>
<td>Blood urea nitrogen (mmol/L)</td>
<td>3.213 (2.5–7.1)</td>
<td>LDL (mmol/L)</td>
<td>3.34 (&lt;3.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>79.56 (53–106)</td>
<td>Haemoglobin (g/L)</td>
<td>176 (133–162)</td>
<td>Antithrombin 3-IMM (mg/L)</td>
<td>350.0 (208.0–336.0)</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>1.7 (2.2–2.6)</td>
<td>Haematuria (proportion of 1)</td>
<td>0.05 (0.388–0.464)</td>
<td>Protein C (Proportion of 1.0)</td>
<td>1.22 (0.6–1.4)</td>
</tr>
<tr>
<td>Phosphorus (mmol/L)</td>
<td>1.001 (0.81–1.4)</td>
<td>Platelets (x10⁹/L)</td>
<td>271 (165–415)</td>
<td>Protein S (proportion of 1.0)</td>
<td>0.88 (0.48–1.36)</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>26 (40–50)</td>
<td>White blood cell (x10⁹/L)</td>
<td>14.9 (3.54–9.06)</td>
<td>Lupus anticoagulant</td>
<td>neg</td>
</tr>
<tr>
<td>CPK (U/L)</td>
<td>3331 (20–200)</td>
<td>Serum homocysteine (µmoles/L)</td>
<td>8.2 (4.30–15.3)</td>
<td>Cardiolipin IgG (Units)</td>
<td>3.8 (&lt;23.0)</td>
</tr>
<tr>
<td>MB (%)</td>
<td>11.5 (&lt;2.6)</td>
<td>Antiphospholipid screen</td>
<td>Neg</td>
<td>Cardiolipin IgM (Units)</td>
<td>3.2 (&lt;11.0)</td>
</tr>
<tr>
<td>Serum viscosity</td>
<td>1.5 (1.5–1.9)</td>
<td>APC resistance</td>
<td>3.1 (2.0–20.0)</td>
<td>Jak V617F</td>
<td>neg</td>
</tr>
<tr>
<td>PAI-1 functional (IU/mL)</td>
<td>2.3 (2.0–47.1)</td>
<td>Circulating filarial antigen</td>
<td>Neg</td>
<td>Epo level</td>
<td>20.5 (4.1–19.5)</td>
</tr>
</tbody>
</table>

Urinalysis: yellow/turbid/1.017/7.5/>300/glucose neg, ketone neg, bilirubin neg, occult blood large, nitrite neg, leucocyte neg.
(Epo) level, as well as a low partial prothrombin time, the rest of the workup was negative (Table 1).

Discussion

Complications associated with chyluria are rare. Haematuria occurs in up to 20% of cases [7]. It is believed to be due to rupture of minute blood vessels adjacent to the site of fistula formation. In severe cases, weight loss, recurrent clot colic, clot retention, severe anaemia, hypoproteinaemia and anasarca are described [8]. Chylous clot formation may subsequently lead to urinary tract obstruction [9]. Loss of lipid-rich protein in urine is also responsible for depletion of body fat stores with loss of triglycerides, phospholipids including fat-soluble vitamins [10].

This case of a 44-year-old man with chronic chyluria complicated by an acute myocardial infarction illustrates several points which we will summarize:

• Firstly, the patient had large, continuous losses through his left collecting system, putting him at risk for chronic dehydration, malnutrition and microvascular ischaemia. Microvascular ischaemia at the level of the kidney led to secondary polycythaemia as evidenced by high Epo levels in his blood in the presence of high haemoglobin.

• Secondly, he had proteinuria and haematuria that originally raised suspicion for glomerular disease. He was ultimately found to have wasting of protein and blood from his lower urinary tract; his kidney biopsy was completely normal. His spot urine showed lipiduria and enzymuria (Table 1). (A spot protein to creatinine ratio as a means to estimate 24-h proteinuria was inaccurate in this patient because the amount of creatinine in his urine was not reflective of his glomerular filtration rate; it was being excreted through his lymphatic fistula and could not serve to quantify his proteinuria.) The patient’s significant proteinuria made him hypo-albuminaemic, but he did not have hyperlipidaemia or oedema.

• Thirdly, in this patient the pathology of his clot was described as ‘neutrophil containing thrombus’. This finding is associated with in situ formation of thrombus in the blood, and without any organization, suggesting that it had formed recently. His polycythaemia and his hypoalbuminaemia put him at risk for increased clotting tendency. While the relationship between polycythaemia and hypercoagulability is well described, the relationship between hypoalbuminaemia and the hypercoagulable state merits further consideration.

Venous and arterial thromboses in association with severe proteinuria are well described in the literature. Coronary arterial thrombosis is a well-recognized entity in the setting of nephrotic syndrome and is attributed to lipid, plasma protein and clotting factor derangements present with this condition [11,12]. In nephrotic syndrome, there is wasting of anti-clotting factors in the urine, clotting factor production is increased and the liver produces cholesterol in response to hypoalbuminaemia. Hypoalbuminaemia is inversely related to hyperlipidaemia and clotting tendency in these patients [13,14]. Increased levels of factor VIII and factor V have been observed in the nephrotic syndrome and have been referenced as one reason for increased clotting tendency [15]. In the general population, the relative risk of recurrent venous thrombosis was shown to be 1.08 (95% confidence interval, 1.04–1.12; P < 0.001) for each increase of 10 IU/dL in the plasma level of factor VIII [16]. Our patient’s factor VIII level was 0.65 times higher than the upper limit of normal, and twice as high as the average normal level.

Because of large obligate losses of lymphatic fluid, the patient lost albumin, globulins and other specialized proteins. Lymphatic fluid from the thoracic duct has ~66% of the protein content as plasma and 75% of the serum albumin content [17]. In our patient, the hypoalbuminaemia was not associated with hyperlipidaemia but with increased factor levels and clotting tendency. This illustrates that while the liver’s synthetic capacity is increased, lipiduria may be protecting the patient from hyperlipidaemia. Appel et al. examined the relationship between hypoalbuminaemia and hyperlipidaemia as well as plasma oncotic pressure and plasma viscosity in patients with nephrotic syndrome [13]. They found that hypoalbuminaemia and decreased oncotic pressure correlate with increased synthetic activity in the liver independent of plasma viscosity. Our patient’s plasma viscosity was normal, which supports the relationship between high factor levels and low albumin levels independent of plasma viscosity. In this case, hypoalbuminaemia led to increased clotting factors and a low partial prothrombin time, both of which contributed to his in situ clot formation. Clotting tendency in association with severe and prolonged chyluria has not been previously described.

Conflict of interest statement. None declared.

References

Cryptococcal granulomatous interstitial nephritis and dissemination in a patient with untreated lupus nephritis

Vinoi George David¹, Anila Korula², Lisa Choudhrie², Joy Sarojini Michael³, Shibu Jacob¹, Chakko Korula Jacob¹ and George T. John¹

¹Department of Nephrology, ²Department of Pathology and ³Department of Microbiology, Christian Medical College, Tamil Nadu, Vellore 632004, India

Correspondence and offprint requests to: George T. John; E-mail: george@cmcvellore.ac.in

Abstract
Infection is a significant cause of mortality and morbidity in systemic lupus erythematosus (SLE). There are many reports of cryptococcal infection in patients with SLE, on immunosuppression. However, untreated lupus with cryptococcal infection and dissemination is rare. CD4 lymphopenia is not reported in such patients. We describe a patient with untreated SLE to be having cryptococcal granulomatous interstitial nephritis and dissemination with CD4 lymphopenia.

Keywords: cryptococcus; dissemination; interstitial nephritis

Introduction
Patients with systemic lupus erythematosus (SLE) have an increased risk for infections with common pathogens as well as with opportunistic organisms. Disseminated cryptococcal infection can not only mimic but also coexist with active untreated lupus and present with cryptococcal granulomatous interstitial nephritis (GIN).

Case report
A 38-year-old man presented with fever, anasarca and acute renal failure for 2 months. He was not known to be a hypertensive or diabetic. There was no history of previous treatment or past history of nephritic or nephrotic illnesses, headache, arthritis, rash or myalgia. He was normotensive. There was fever (102°F), pedal oedema and pallor, but meningismus was absent and neurological examination was unremarkable.

Laboratory examination revealed anemia (Hb: 84 g/L), white cell count of 5600/mm³, neutrophilia (neutrophil 96 and lymphocytes 4), renal failure (serum creatinine: 212.16 µmol and serum urea: 76.75 mmol), urine (RBC: 25–30, WBC: 2–4) and proteinuria with severe hypoalbuminaemia (UP/UC: 1.71, serum albumin: 13 g/L). He had hyponatraemia (Sr Na: 117 mmol/L), hypothyroidism (TSH: 185 µIU/ml) and transaminase elevation (AST: 259 IU, ALT: 84 IU). Immunological markers were positive for SLE: [elevated dsDNA: 94 Au/ml (normal: <30)], ANA: positive-nucleolar pattern and hypocomplementaemia, C3: 0.25 g/L (normal: 0.94–1.8 g/L) and C4: 0.06 g/L (normal: 0.1–0.4 g/L). The C-reactive protein was elevated: 88.6 mg/L (normal: <6 mg/L). Direct Coombs test was positive.

The cerebrospinal fluid (CSF) analysis suggested chronic meningitis (glucose: 25 mg%, white cell count of 4500/mm³, neutrophilia (neutrophil 96 and lymphocytes 4), renal failure (serum creatinine: 212.16 µmol and serum urea: 76.75 mmol), urine (RBC: 25–30, WBC: 2–4) and proteinuria with severe hypoalbuminaemia (UP/UC: 1.71, serum albumin: 13 g/L). He had hyponatraemia (Sr Na: 117 mmol/L), hypothyroidism (TSH: 185 µIU/ml) and transaminase elevation (AST: 259 IU, ALT: 84 IU). Immunological markers were positive for SLE: [elevated dsDNA: 94 Au/ml (normal: <30)], ANA: positive-nucleolar pattern and hypocomplementaemia, C3: 0.25 g/L (normal: 0.94–1.8 g/L) and C4: 0.06 g/L (normal: 0.1–0.4 g/L). The C-reactive protein was elevated: 88.6 mg/L (normal: <6 mg/L). Direct Coombs test was positive.

The cerebrospinal fluid (CSF) analysis suggested chronic meningitis (glucose: 25 mg%, protein 125 mg% with presence of 20 cells in the CSF with 80% of lymphocytes) and the latex agglutination test (Remel Inc., Lenexa, KS, USA) was positive for the cryptococcal antigen.

Cultures of the CSF, blood, bone marrow aspirate and urine after an expressed prostatic massage grew mucoid cream colonies of Cryptococcus neoformans on Sabouraud dextrose agar and brown colonies on birdseed agar. These colonies were identified as C. neoformans var. grubii.