A Patient with a Leg Rash, Pedal Edema, Renal Failure, and Thrombocytopenia

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CASE

A 57-year-old man was referred for assessment and management of malaise and leg edema, which had increased 2 weeks after the onset of a productive cough, for which clarithromycin had been prescribed. His course was complicated by the development of a pruritic skin eruption. The patient’s medical history included type II diabetes mellitus of 5 years’ duration and stage III chronic kidney disease. He also had a chronic infection with hepatitis C virus (HCV)6 (genotype 1A) and had been lost to follow-up for the previous 19 years. Medications included antihypertensive drugs (calcium channel blocker, β-blocker, angiotensin-converting enzyme inhibitor, and furosemide), a lipid-lowering drug (ezetimibe), analgesics (hydromorphone HCl and acetaminophen), and ipratropium bromide aerosol. A physical examination revealed the following: blood pressure, 140/65 mmHg; pulse, 55 beats/min; temperature, 36.9 °C; oxygen saturation, 94% on room air; body mass index, 46 kg/m². Abdominal distention was noted and felt to be compatible with the presence of ascites. The spleen was palpable. There was bilateral lower-extremity pitting edema and a hyperpigmented pretibial rash that was not palpable.

Initial laboratory investigations included typical findings for electrolytes, aspartate aminotransferase, alanine aminotransferase, total bilirubin, and the international normalized ratio. The patient’s laboratory test results are summarized in Table 1. His fasting plasma glucose concentration was impaired, and his alkaline phosphatase was slightly raised. The patient was anemic and thrombocytopenic with hypoalbuminemia and an increased serum creatinine concentration. A urinalysis dipstick screen and a microscopy evaluation revealed hematuria, proteinuria, and the presence of red blood cell casts in the urine. A 24-h evaluation of urine protein excretion confirmed an abundance of protein in the urine. The glomerular filtration rate, as estimated with the Cockcroft–Gault equation, was very low. An ultrasound analysis revealed bilateral echogenic kidneys of typical size. In the setting of a chronic, untreated HCV infection and evidence of nephrotic syndrome, a cryocrit was requested to investigate the possibility of membranoproliferative glomerulonephritis secondary to cryoglobulinemia. A renal biopsy demonstrated diffuse, proliferative glomerulonephritis and immune-complex deposits.

DISCUSSION

PATIENT FOLLOW-UP

We requested further workup, including complement measurements [complement 3 (C3) and C4], serum protein electrophoresis, a cryoglobulin screen, and viral serology analysis (HIV, hepatitis B virus, HCV). Table 1 summarizes the laboratory results. Complement concentrations were slightly low, and electrophoresis of serum proteins showed a diffuse γ region without an M band. A cryocrit of 5% was reported for 2 blood samples drawn on different days after storage of serum at 4 °C for 10 days. The patient was documented to be immune to hepatitis B virus with the presence of hepatitis B core and surface antibodies. His hepatitis C viral load was moderate.

PATIENT DIAGNOSIS

The patient has glomerulonephritis with cryoglobulins present. A liver biopsy confirmed the diagnosis of chronic hepatitis and cirrhosis with an activity score of 1–2 and a Laennec fibrosis stage of 4B. Consequently, the patient began a combination therapy of pegylated interferon α and ribavirin and demonstrated some improvement in his proteinuria, plasma viral load, and cryocrit. He has an ongoing requirement for large doses of diuretic therapy to control his peripheral edema; he was not deemed suitable for kidney and/or liver transplantation.

ADULT NEPHROTIC SYNDROME

Gross changes in glomerular permeability due to injury to the glomerular filtration barrier characterize ne-
phrotic syndrome. Features of nephrotic syndrome that are also present in this patient include proteinuria (adult, urine excretion >3 g/day), hypoalbuminemia, edema, and hyperlipidemia (1). Etiologic considerations of glomerular disease include those of primary renal diseases, systemic diseases with renal involvement, and renal injury secondary to drugs (Fig. 1). Diabetes mellitus is the most common cause of nephrotic syndrome (1). In type II diabetes mellitus, renal disease includes a spectrum: asymptomatic microalbuminuria, nephrotic syndrome, and end-stage renal disease requiring renal transplantation (1). Nephrotic syndrome may also be associated with infections. The predominant renal disease presenting in HCV-infected patients, including the patient we describe, is membranoproliferative glomerulonephritis, which is often associated with type II cryoglobulinemia (2).

HCV AND CRYOGLOBULINEMIA

Cryoglobulins are a heterogeneous group of immunoglobulins that precipitate from the serum or plasma at temperatures <37 °C (3). Cryoglobulinemia is classified as type I (simple, monoclonal), type II (mixed, monoclonal-polyclonal immune complex), or type III (mixed, polyclonal-polyclonal immune complex) (3). Type I cryoglobulinemia usually accompanies lymphoproliferative disorders and represents a small fraction of patients with cryoglobulins (10%–15%), whereas most patients with mixed cryoglobulinemia have infectious or autoimmune disorders (4). More than 80% of cases of mixed cryoglobulinemia are associated with HCV infection (2).

Cryoglobulinemia develops from overstimulation of the immune system or impaired clearance of large immune complexes. In HCV-associated type II cryoglobulinemia, immune complexes of viral DNA, RNA, antigens, anti-HCV antibodies, or lipoproteins directly modulate B-cell function, causing activation and expansion of single dominant clones of rheumatoid factor–producing cells (often IgM) (5). The precipitated immune complexes obstruct small blood vessels and induce complement activation, leading to ischemia and systemic vasculitis, particularly in the skin, nerves, kidney, liver, and joints (6).

Cryoglobulinemia has a variable clinical presentation with nonspecific signs and symptoms and can be easily overlooked if a high index of suspicion is not maintained in the correct clinical context. Palpable purpura is the main feature observable on physical examination of cryoglobulinemia and lasts 1–2 weeks. Lesions appear on the lower limbs, as observed in this patient, and less frequently on the buttocks, trunk, or...

Table 1. Initial and follow-up patient laboratory results with corresponding reference intervals.a

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Reference interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial investigation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>6.1 (110 mg/dL)</td>
<td>4–6 (72–108 mg/dL)</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/L</td>
<td>146</td>
<td>≤110</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>117 (11.7 g/dL)</td>
<td>140–180 (14–18 g/dL)</td>
</tr>
<tr>
<td>Platelet count, ×10³/L</td>
<td>108</td>
<td>150–400</td>
</tr>
<tr>
<td>Plasma albumin, g/L</td>
<td>29 (2.9 g/dL)</td>
<td>38–50 (3.8–5.0 g/dL)</td>
</tr>
<tr>
<td>Plasma creatinine, μmol/L</td>
<td>334 (3.8 mg/dL)</td>
<td>Male, ≤109 (1.2 mg/dL); female ≤99 (1.1 mg/dL)</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Red blood cells (+2), protein (+5) Negative</td>
<td></td>
</tr>
<tr>
<td>Urine protein, g/day</td>
<td>8</td>
<td>&lt;0.15</td>
</tr>
<tr>
<td>Glomerular filtration rate, mL/min</td>
<td>&lt;15</td>
<td>≥90</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3, g/L</td>
<td>0.90 (90 mg/dL)</td>
<td>0.9–1.8 (90–180 mg/dL)</td>
</tr>
<tr>
<td>C4, g/L</td>
<td>0.08 (8 mg/dL)</td>
<td>0.1–0.4 (10–40 mg/dL)</td>
</tr>
<tr>
<td>Cryocrit, %</td>
<td>5</td>
<td>Negative &lt;5</td>
</tr>
<tr>
<td>Hepatitis B core antibody</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Hepatitis B surface antibody</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Hepatitis B surface antigen</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Hepatitis C virus RNA, ×10⁴ IU/L</td>
<td>62</td>
<td>Cutoff &lt;15</td>
</tr>
<tr>
<td>HIV antibody</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

aData in conventional units are in parentheses.
Symptoms of type I cryoglobulinemia often appear locally at sites of cold exposure. Mixed cryoglobulinemia is more systemic and is commonly associated with the clinical triad of palpable purpura, arthralgia, and asthenia (3). About 50%–70% of symptomatic patients have liver involvement (hepatosplenomegaly), 25% have renal involvement (membranoproliferative glomerulonephritis), and 36% have nervous system involvement (peripheral sensory-motor neuropathy) (4, 5). Respiratory symptoms, although rare, present as pulmonary interstitial infiltrates, dyspnea, or cough (6).

DIFFERENTIAL DIAGNOSIS FOR ADULT GLOMERULAR DISEASE
Because the patient had proteinuria, edema, microscopic hematuria, isolated systolic hypertension, and impaired renal function (low glomerular filtration rate), further investigations for glomerulonephritis were warranted, including chemistry, serology, and renal ultrasound evaluations and histopathologic examination of the kidneys (7). The vasculitic leg purpura and hematuria suggested that the patient’s nephrotic syndrome was more likely due to a complication of his systemic HCV infection than to his diabetes mellitus. An initial approach to the diagnosis of the renal disease in this patient, pending kidney biopsy, could include measurement of complement levels [total hemolytic complement (CH50), C3, C4] to divide the causes of glomerulonephritis into those with low serum complement levels and those with typical serum complement levels (1). About 80% of cryoglobulinemia cases show low levels of serum complement (1). A low C4 concentration with a typical to moderately low C3 concentration is typically seen in type II cryoglobulinemic patients and was observed in this patient (2). Other useful laboratory tests include serum protein/immunofixation electrophoresis and assay of free light chain to differentiate malignancy, tests for autoantibodies to rule out rheumatologic disease, and cryoglobulin characterization with blood cultures to exclude a diagnosis of infective endocarditis (1). Noninvasive radiologic investigations, including renal ultrasound, provide information on renal size. Small kidneys (<9 cm) suggest extensive scarring and low reversibility (7). An echogenic cortex is a nonspecific density change usually seen in medical causes of renal disease (7). A renal biopsy with an examination of the deposition pattern of immune complexes helps clarify the pathology.
In cryoglobulinemia, a histologic examination of kidney biopsies usually reveals glomerular infiltration by activated macrophages and intraluminal microthrombi (cryoprecipitates) in vessels; immunofluorescence or electron microscopy analysis may reveal subendothelial deposits of IgM, IgG, and complement (2). Renal biopsy also establishes/validates the diagnosis of renal pathology and helps guide treatment (1).

COLLECTION, ANALYSIS, AND REPORTING OF CRYOglobulINS AND PITFALLS
Improper sample collection and handling, especially inadequate temperature control, lead to missed diagnosis of most cryoglobulinemia cases (3). This patient is hyperlipidemic. It is essential that fasting serum samples be collected at 37 °C to avoid false positives due to cryoprecipitation of lipoproteins or false negatives due to premature cryoprecipitation of immunoglobulins, rheumatoid factor, and complement (3). All cryoprecipitates should be characterized for the presence of monoclonal components. In mixed cryoglobulinemia, cryoglobulin concentrations are often low, making collection of sufficient blood crucial (4). Daily observations with reporting of precipitate appearance and redissolution allows early detection of false positives (4). Sodium azide and precipitate washes reduce contamination by bacteria and serum proteins, respectively (3). Many laboratories screen for cryoglobulins by measuring the cryocrit percentage: (precipitate volume)/(total volume of serum sample) × 100%. Cryocrit does not differentiate type II and III cryoglobulins. It is recommended that laboratories measure total protein concentration on a washed cryoprecipitate and determine the cryoglobulin subtype with serum protein electrophoresis and immunofixation (4). A diffuse γ region visible after protein electrophoresis of this patient’s serum suggested the presence of polyclonal γ-globulins. Fig. 1 summarizes the collection, analysis, and reporting of cryoglobulins.

DIAGNOSIS AND MANAGEMENT OF CHRONIC HEPATITIS
Chronic hepatitis is characterized by ongoing inflammation and liver destruction (8). It is usually defined by increased alanine aminotransferase and/or aspartate aminotransferase activities over 6 months. Some individuals, including this patient, have intermittently or persistently typical alanine aminotransferase activity despite biopsy evidence of inflammation and fibrosis (1). Viral markers (hepatitis B surface antigen, hepatitis B virus DNA, HCV RNA) are more reliable than enzymes for diagnosing and monitoring antiviral therapy (8). For HCV, determination of the genotype before treatment is important. HCV genotype 1 is linked to insulin resistance, responds more poorly to combination therapy with pegylated interferon α and ribavirin, and may contribute to the poor prognosis of this patient (9, 10).

[Table]

**POINTS TO REMEMBER**

- Cryoglobulinemia should be included in the differential diagnosis of adult nephrotic syndrome, particularly in HCV-infected patients presenting with features of membranoproliferative glomerulonephritis.
- Cryoglobulinemia has a heterogeneous clinical presentation, and the diagnosis can be easily overlooked.
- Proper sample collection, handling, analysis, and reporting procedures for cryoglobulins are essential and should be updated regularly. Small amounts of cryoglobulins can cause or be associated with severe symptoms or disease.
- The HCV genotype predicts insulin resistance and responsiveness to anti-HCV therapy.

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**References**

Commentary

Robert M.A. Richardson

In their case presentation, Schnabl et al. ask readers to consider approaches to an adult with the diagnosis of nephrotic syndrome, the primary and secondary renal pathologies that may be seen in adult glomerular disease, and tests that might be ordered to help differentiate the cause of this patient’s renal disease.

Most adult patients with nephrotic syndrome require a kidney biopsy for a pathologic diagnosis to be made (the one common exception being presumed diabetic nephropathy). Clues to diagnosis from the results of laboratory testing may help limit the differential but are not a substitute for biopsy, except in situations in which a biopsy is too risky (e.g., a bleeding tendency).

The commonest causes of primary nephrotic syndrome are membranous nephropathy, focal segmental glomerulosclerosis, and minimal-change disease. No laboratory tests are very helpful in distinguishing these diseases.

About 30% of cases of nephrotic syndrome have a secondary cause in adults. Autoimmune disease (lupus), infections (hepatitis B and C, malaria), malignancy (lymphoma), drugs (gold, pamidronate, and so forth), monoclonal gammopathy (primary amyloidosis), and chronic inflammatory conditions (secondary amyloidosis) are some of them.

The urinalysis findings of blood and red blood cell casts strongly suggest that the pathologic process is either proliferative or necrotizing. Therefore, non-proliferative lesions (such as diabetic nephropathy, amyloidosis, and secondary minimal-change disease, membranous nephropathy, or focal segmental glomerulosclerosis) are unlikely.

The presence of hypocomplementemia makes necrotizing processes such as antineutrophil cytoplasmic antibody–associated diseases (such as Wegener granulomatosis and microscopic polyangiitis) unlikely. Proliferative lupus nephritis (class III and IV), hepatitis C–associated cryoglobulinemia, and postinfectious glomerulonephritis would be the most likely diagnoses. All are associated with hypocomplementemia. Postinfectious glomerulonephritis does not usually present as nephrotic syndrome but should be included in the differential. The key laboratory tests for this patient are therefore for serum complements, hepatitis C viral load, antinuclear antibodies, anti-DNA antibodies, and serum cryoglobulins. Hepatitis B and HIV should also be evaluated, given the history of HCV infection.

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Commentary

Charles E. Alpers

Schnable et al. describe a patient with a nearly 20-year history of hepatitis C virus (HCV) infection who developed acute manifestations of glomerulonephritis associated with concurrent cryoglobulinemia. A renal biopsy demonstrated “proliferative glomerulonephritis” that we are meant to infer was membranoproliferative glomerulonephritis of the type typically associated with cryoglobulinemia and HCV infection.

HCV has been associated with multiple extrahepatic manifestations, including cryoglobulinemia, glomerulonephritis, skin disorders (porphyria cutanea tarda, lichen planus), arthritis, a sicca-like syndrome, and lymphoproliferative disorders. The strongest asso-
ciations are with cryoglobulinemia and membrano-proliferative glomerulonephritis. Renal manifestations are usually associated with long-standing (i.e., >10 years) HCV infection, as in the reported case. Most often, there are concurrent clinical and laboratory features of chronic hepatitis and/or cirrhosis. Renal manifestations may occur in the absence of other signs of cryoglobulinemia or liver disease, however, and the diagnosis of HCV infection may be made during evaluation of a renal disorder. Pathologic findings in a renal biopsy (including glomerular intracapillary globular accumulations of eosinophilic material containing precipitated cryoglobulins, and glomerular immune complex deposits with a finely fibrillar or tactoid pattern of organization visualized by electron microscopy) can sometimes be the first clue to a diagnosis of cryoglobulinemia and corresponding HCV infection. Circulating cryoglobulins, either at the time of presentation or at some point in the patient’s history, are generally detected in only approximately 50%–70% of patients with HCV-associated glomerulonephritis.

This case report is timely in view of several recent studies that point to the potential magnitude of the problem of HCV infection and kidney disease. A recent analysis of the current National Health and Nutrition Examination Survey that involved >15 000 patients indicates stable prevalences in the US of HCV seropositivity (1.6%, estimated 4.1 × 10^6 infected persons) and HCV viremia (1.3%, 3.2 × 10^6 actively infected persons) (1). Because the incidence of acute HCV infection has declined to its lowest rate ever (2), the sustained high prevalence is due to a reservoir of infections acquired decades previously. Because kidney disease and cryoglobulinemia are late manifestations of HCV infection, as was the case for the described patient, an increase in HCV-associated renal disease and cryoglobulinemia can be anticipated in the near term. A heightened awareness of this growing problem should lead to more timely diagnoses and improve management strategies for infected patients.

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