CASE IN POINT

Elusive Edema: A Case of Nephrotic Syndrome Mimicking Decompensated Cirrhosis

Jennifer Mansour, MD, MHS[a,b]; Rabih M. Geha, MD[c,d]; Reza Manesh, MD[a,b]; Trilokesh D. Kidambi, MD[e]; Anthony Sisk, DO[a]; Monroy Trujillo, JM, MD[f]

Background: Patients admitted to the hospital from the emergency department are often evaluated with inherent diagnostic biases, particularly when the admitting diagnosis is anchored early. When a patient presents with suspected decompensated cirrhosis, it is important to consider other diagnoses with similar presentations and ensure multiple disease processes are not contributing to the symptoms.

Case Presentation: A 64-year-old male without stable housing was admitted for management of newly diagnosed decompensated cirrhosis based on imaging. Additional analysis of laboratory results, imaging, and clinical presentation suggested that the decompensated cirrhosis diagnosis was not proportionate to the severity of the patient's hypoalbuminemia. Additional workup was conducted, and hepatology, nephrology, and infectious disease specialists were consulted. Extensive laboratory workup and a renal biopsy confirmed a diagnosis of compensated cirrhosis and nephrotic syndrome due to early membranoproliferative glomerulonephritis, both secondary to hepatitis C infection.

Conclusions: This case offers important teaching points on nephrotic syndrome and hepatitis C, and highlights the importance of re-evaluating diagnostic assumptions to prevent delays and errors.

Author affiliations can be found at the end of this article.
Correspondence: Jennifer Mansour (jmansour@mednet.ucla.edu)

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Histology is the gold standard for cirrhosis diagnosis. However, a combination of clinical history, physical examination findings, and supportive laboratory and radiographic features is generally sufficient to make the diagnosis. Routine ultrasound and computed tomography (CT) imaging often identifies a nodular liver contour with sequelae of portal hypertension, including splenomegaly, varices, and ascites, which can suggest cirrhosis when supported by laboratory parameters and clinical features. As a result, the diagnosis is typically made clinically.[1] Many patients with compensated cirrhosis go undetected. The presence of a decompensation event (ascites, spontaneous bacterial peritonitis, variceal hemorrhage, or hepatic encephalopathy) often leads to index diagnosis when patients were previously compensated. When a patient presents with suspected decompensated cirrhosis, it is important to consider other diagnoses with similar presentations and ensure that multiple disease processes are not contributing to the symptoms.

CASE PRESENTATION

A 64-year-old male with a history of intravenous (IV) methamphetamine use and prior incarceration presented with a 3-week history of progressively worsening generalized swelling. Prior to the onset of his symptoms, the patient injured his right lower extremity (RLE) in a bicycle accident, resulting in edema that progressed to bilateral lower extremity (BLE) edema and worsening fatigue, despite resolution of the initial injury. The patient gained weight though he could not quantify the amount. He experienced progressive hunger, thirst, and fatigue as well as increased sleep. Additionally, the patient experienced worsening dyspnea on exertion and orthopnea. He started using 2 pillows instead of 1 pillow at night.

The patient reported no fevers, chills, sputum production, chest pain, or paroxysmal nocturnal dyspnea. He had no known history of sexually transmitted infections, no significant history of alcohol use, and occasional tobacco and marijuana use. He had been incarcerated > 10 years before and last used IV methamphetamine 3 years before. He did not regularly take any medications.

The patient's vital signs included a temperature of 98.2 °F; 78/min heart rate; 15/min respiratory rate; 159/109 mm Hg blood pressure; and 98% oxygen saturation on room air. He had gained 20 lbs in the past 4 months. He had pitting edema in both legs and arms, as well as periorbital swelling, but no jugular venous distention, abnormal heart sounds, or murmurs. Breath sounds were distant but clear to auscultation. His abdomen was distended with normal bowel sounds and no

fluid wave; mild epigastric tenderness was present, but no intra-abdominal masses were palpated. He had spider angiomata on the upper chest but no other stigmata of cirrhosis, such as caput medusae or jaundice. Tattoos were noted.

Laboratory test results showed a platelet count of 178 x 10^3 /µL (reference range, 140-440 × 10^3/µL). Creatinine was 0.80 mg/dL (reference range, < 1.28 mg/dL), with an estimated glomerular filtration rate (eGFR) of 99 mL/min/1.73 m^2 using the Chronic Kidney Disease-Epidemiology equation (reference range, > 60 mL/min/1.73 m^2), and Cystatin C was 1.14 mg/L (reference range, < 1.15 mg/L). His electrolytes and complete blood count were within normal limits, including sodium, 134 mmol/L; potassium, 4.4 mmol/L; chloride, 108 mmol/L; and carbon dioxide, 22.5 mmol/L.

Additional test results included alkaline phosphatase, 126 U/L (reference range, < 94 U/L); alanine transaminase, 41 U/L (reference range, < 45 U/L); aspartate aminotransferase, 70 U/L (reference range, < 35 U/L); total bilirubin, 0.6 mg/dL (reference range, < 1 mg/dL); albumin, 1.8 g/dL (reference range, 3.2-4.8 g/dL); and total protein, 6.3 g/dL (reference range, 5.9-8.3 g/dL). The patient's international normalized ratio was 0.96 (reference range, 0.8-1.1), and brain natriuretic peptide was normal at 56 pg/mL. No prior laboratory results were available for comparison.

Urine toxicology was positive for amphetamines. Urinalysis demonstrated large occult blood, with a red blood cell count of 26/HPF (reference range, 0/HPF) and proteinuria (100 mg/dL; reference range, negative), without bacteria, nitrites, or leukocyte esterase. Urine white blood cell count was 10/HPF (reference range, 0/HPF), and fine granular casts and hyaline casts were present.

A noncontrast CT of the abdomen and pelvis in the emergency department showed an irregular liver contour with diffuse nodularity, multiple portosystemic collaterals, moderate abdominal and pelvic ascites, small bilateral pleural effusions with associated atelectasis, and anasarca consistent with cirrhosis (Figure 1). The patient was admitted to the internal medicine service for workup and management of newly diagnosed cirrhosis.

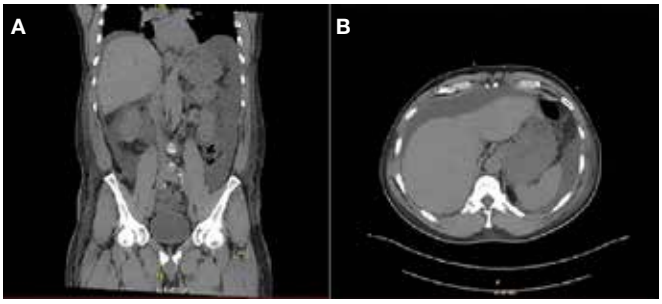

FIGURE 1. Computed tomography of the abdomen and pelvis demonstrating undulation of the liver contour with moderate abdominal and pelvic ascites and anasarca. A, coronal plane; B, axial plane.

Paracentesis revealed straw-colored fluid with an ascitic fluid neutrophil count of 17/µL, a protein level of < 3 g/dL and albumin level of < 1.5 g/dL. Gram stain of the ascitic fluid showed a moderate white blood cell count with no organisms. Fluid culture showed no microbial growth.

Initial workup for cirrhosis demonstrated a positive total hepatitis A antibody. The patient had a nonreactive hepatitis B surface antigen and surface antibody, but a reactive hepatitis B core antibody; a hepatitis B DNA level was not ordered. He had a reactive hepatitis C antibody with a viral load of 4,490,000 II/mL (genotype 1a). The patient's iron level was 120 µg/dL, with a calculated total iron-binding capacity (TIBC) of 126.2 µg/dL. His transferrin saturation (TSAT) (serum iron divided by TIBC) was 95%. The patient had nonreactive antinuclear antibody and antimitochondrial antibody tests and a positive antismooth muscle antibody test with a titer of 1:40. His α-fetoprotein (AFP) level was 505 ng/mL (reference range, < 8 ng/mL).

Follow-up MRI of the abdomen and pelvis showed cirrhotic morphology with large-volume ascites and portosystemic collaterals, consistent with portal hypertension. Additionally, it showed multiple scattered peripheral sub centimeter hyperenhancing foci, most likely representing benign lesions.

The patient's spot urine protein–creatinine ratio was 3.76. To better quantify proteinuria, a 24-hour urine collection was performed and revealed 12.8 g/d of urine protein (reference range, 0-0.17 g/d). His serum triglyceride level was 175 mg/dL (reference range, 40-60 mg/dL); total cholesterol was 177 mg/dL (reference range, ≤ 200 mg/dL); low-

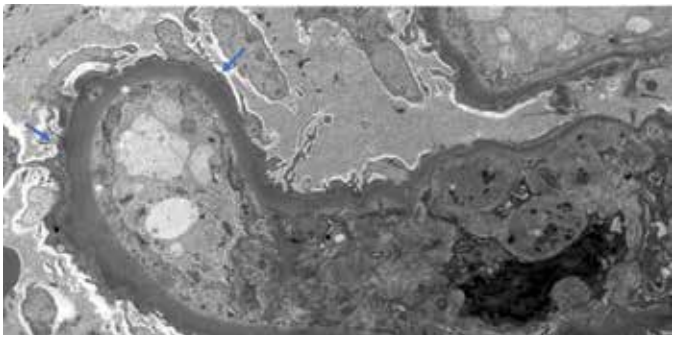

FIGURE 2. Electron microscopy of the capillary loop of the glomerulus displaying overlying foot process effacement as indicated by arrows; endothelial cell swelling, and a few small subendothelial deposits are indicated by asterisk.

density lipoprotein cholesterol was 98 mg/dL (reference range, ≤ 130 mg/dL); and high-density lipoprotein cholesterol was 43.8 mg/dL (reference range, ≥ 40 mg/dL); C3 complement level was 71 mg/dL (reference range, 82-185 mg/dL); and C4 complement level was 22 mg/dL (reference range, 15-53 mg/dL). His rheumatoid factor was < 14 IU/mL. Tests for rapid plasma reagin and HIV antigen-antibody were nonreactive, and the phospholipase A2 receptor antibody test was negative. The patient tested positive for QuantiFERON-TB Gold and qualitative cryoglobulin, which indicated a cryocrit of 1%.

A renal biopsy was performed, revealing diffuse podocyte foot process effacement and glomerulonephritis with low-grade C3 and immunoglobulin (Ig) G deposits, consistent with early membranoproliferative glomerulonephritis (MPGN) (Figures 2 and 3).

The patient was initially diuresed with IV furosemide without significant urine output. He was then diuresed with IV 25% albumin (total, 25 g), followed by IV furosemide 40 mg twice daily, which led to significant urine output and resolution of his anasarca. Given the patient's hypoalbuminemic state, IV albumin was necessary to deliver furosemide to the proximal tubule. He was started on lisinopril for renal protection and discharged with spironolactone and furosemide for fluid management in the context of cirrhosis.

The patient was evaluated by the Liver Nodule Clinic, which includes specialists from hepatology, medical oncology, radiation oncology, interventional radiology, and diagnostic radiology. The team considered the patient's medical history and characteristics of the nodules on imaging. Notable aspects of the patient's history included hepatitis C virus (HCV) infection and an elevated AFP level, although imaging showed no lesion concerning for malignancy. Given these findings, the patient was scheduled for a liver biopsy to establish a tissue diagnosis of cirrhosis. Hepatology, nephrology, and infectious disease specialists coordinated to plan the management and treatment of latent tuberculosis (TB), chronic HCV, MPGN, compensated cirrhosis, and suspicious liver lesions.

The patient chose to handle management and treatment as an outpatient. He was discharged with furosemide and spironolactone for anasarca management, and amlodipine and lisinopril for his hypertension and MPGN. Follow-up appointments were scheduled with infectious disease for management of latent TB and HCV, nephrology for MPGN, gastroenterology for cirrhosis, and interventional radiology for liver biopsy. Unfortunately, the patient was unhoused with limited access to transportation, which prevented timely follow-up. Given these social factors, immunosuppression was not started. Additionally, he did not start on HCV therapy because the viral load was still pending at time of discharge.

DISCUSSION

The diagnosis of decompensated cirrhosis was prematurely established, resulting in a diagnostic delay, a form of diagnostic error. However, on hospital day 2, the initial hypothesis of decompensated cirrhosis as the sole driver of the patient's presentation was reconsidered due to the disconnect between the severity of hypoalbuminemia and diffuse edema (anasarca), and the absence of laboratory evidence of hepatic decompensation (normal international normalized ratio, bilirubin, and low but normal platelet count). Although image findings supported cirrhosis, laboratory markers did not indicate hepatic decompensation. The severity of hypoalbuminemia and anasarca, along with an indeterminate Serum-Ascites Albumin Gradient, prompted the patient's care team to consider other causes, specifically, nephrotic syndrome.

The patien's spot protein-to-creatinine ratio was 3.76 (reference range < 0.2 mg/

mg creatinine), but a 24-hour urine protein collection was 12.8 g/day (reference range < 150 mg/day). While most spot urine protein-to-creatinine ratios (UPCR) correlate with a 24-hour urine collection, discrepancies can occur, as in this case. It is important to recognize that the spot UPCR assumes that patients are excreting 1000 mg of creatinine daily in their urine, which is not always the case. In addition, changes in urine osmolality can lead to different values. The gold standard for proteinuria is a 24-hour urine collection for protein and creatinine.

The patient's nephrotic-range proteinuria and severe hypoalbuminemia are not solely explained by cirrhosis. In addition, the patient's lower extremity edema pointed to nephrotic syndrome. The differential diagnosis for nephrotic syndrome includes both primary and secondary forms of membranous nephropathy, minimal change disease, focal segmental glomerulosclerosis, and MPGN, a histopathological diagnosis that requires distinguishing between immune complex-mediated and complement-mediated forms. Other causes of nephrotic syndrome that do not fit in any of these buckets include amyloidosis, IgA nephropathy, and diabetes mellitus (DM). Despite DM being a common cause of nephrotic range proteinuria, it rarely leads to full nephrotic syndrome.

When considering the diagnosis, we reframed the patient's clinical syndrome as compensated cirrhosis plus nephrotic syndrome. This approach prioritized identifying a cause that could explain both cirrhosis (from any cause) leading to IgA nephropathy or injection drug use serving as a risk factor for cirrhosis and nephrotic syndrome through HCV or AA amyloidosis, respectively. This problem representation guided us to the correct diagnosis. There are multiple renal diseases associated with HCV infection, including MPGN, membranous nephropathy, focal segmental glomerulosclerosis, and IgA nephropathy.[2] MPGN and mixed cryoglobulinemia are the most common. In the past, MPGN was classified as type I, II, and III.

The patient's urine toxicology revealed recent amphetamine use, which can also lead to acute kidney injury through rhabdomyolysis or acute interstitial nephritis (AIN).[3] In the cases of rhabdomyolysis, urinalysis would show positive heme without any red blood cell on microscopic analysis, which was not present in this case. AIN commonly manifests as acute kidney injury, pyuria, and proteinuria but without a decrease in complement levels.[4] While the patient's urine sediment included white blood cell (10/high-power field), the presence of microscopic hematuria, decreased complement levels, and proteinuria in the context of HCV positivity makes MPGN more likely than AIN.

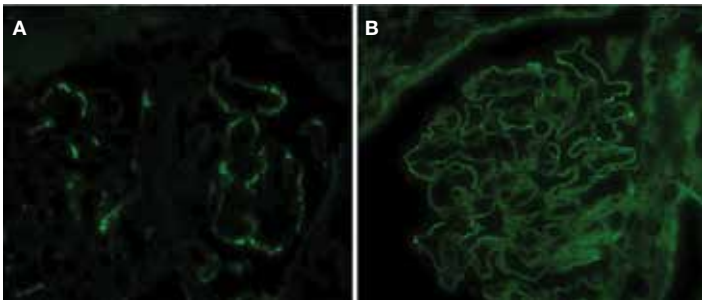

FIGURE 3. Immunofluorescent segmental staining of capillary loops of the glomerulus demonstrating low-grade C3 (A) and immunoglobulin G deposits (B).

Recently, there has been greater emphasis on using immunofluorescence for kidney biopsies. MPGN is now classified into 2 main categories: MPGN with mesangial immunoglobulins and C3 deposits in the capillary walls, and MPGN with C3 deposits but without Ig.[5] MPGN with Ig-complement deposits is seen in autoimmune diseases and infections and is associated with dysproteinemias.

The renal biopsy in this patient was consistent with MPGN with immunofluorescence, a common finding in patients with infection. By synthesizing these data, we concluded that the patient represented a case of chronic HCV infection that led to MPGN with cryoglobulinemia. The normal C4 and negative RF do not suggest cryoglobulinemic crisis. Compensated cirrhosis was seen on imaging, pending liver biopsy.

Treatment

The management of MPGN secondary to HCV infection relies on the treatment of the underlying infection and clearance of viral load. Direct-acting antivirals have been used successfully in the treatment of HCV-associated MPGN. When cryoglobulinemia is present, immunosuppressive therapy is recommended. These regimens commonly include rituximab and steroids.[5] Rituximab is also used for nephrotic syndrome associated

with MPGN, as recommended in the 2018 Kidney Disease: Improving Global Outcomes guidelines.[6]

When initiating rituximab therapy in a patient who tests positive for hepatitis B (HBcAb positive or HBsAb positive), it is recommended to follow the established guidelines, which include treating them with entecavir for prophylaxis to prevent reactivation or a flare of hepatitis B.[7] The patient in this case needed close follow-up in the nephrology and hepatology clinic. Immunosuppressive therapy was not pursued while the patient was admitted to the hospital due to instability with housing, transportation, and difficulty in ensuring close follow-up.

CONCLUSIONS

Clinicians should maintain a broad differential even in the face of confirmatory imaging and other objective findings. In the case of anasarca, nephrotic syndrome should be considered. Key causes of nephrotic syndromes include MPGN, membranous nephropathy, minimal change disease, and focal segmental glomerulosclerosis. MPGN is a histopathological diagnosis, and it is essential to identify if it is secondary to immune complexes or only complement mediated because Ig-complement deposits are seen in autoimmune disease and infection. The management of MPGN due to HCV infection relies on antiviral therapy. In the presence of cryoglobulinemia, immunosuppressive therapy is recommended.

Author affiliations

[a]University of California Los Angeles
[b]Greater Los Angeles Veterans Affairs Medical Center, California
[c]University of California San Francisco
[d]San Francisco Veterans Affairs Medical Center, California
[e]City of Hope National Medical Center, Duarte, California
[f]Johns Hopkins University School of Medicine, Baltimore, Maryland

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

Ethics and consent

The patient provided oral informed consent to be included in a case report and is aware that his anonymity cannot be guaranteed even though all steps have been taken to protect his privacy.

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