

## CLINICAL CARE CONUNDRUMS

## The \$64,000 Question

The approach to clinical conundrums by an expert clinician is revealed through the presentation of an actual patient's case in an approach typical of a morning report. Similarly to patient care, sequential pieces of information are provided to the clinician, who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring for the patient and the discussant.



This icon represents the patient's case. Each paragraph that follows represents the discussant's thoughts.

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A 40-year-old Sudanese man was admitted due to worsening abdominal pain with recurrent ascites. He had a history of hepatitis B (HBV) infection and diabetes. He previously drank 3 beers per day on the weekends, but he had not consumed alcohol in over a year. He was born in Sudan but lived in Egypt most of his adult life; he immigrated to the United States 6 years previously. He was hospitalized out of state 9 months ago for "a swollen abdomen" and underwent an exploratory laparotomy that reportedly was unremarkable except for ascites.

Portal hypertension due to liver disease is the most common cause of ascites. This patient has a known risk factor for liver disease (history of HBV infection). Although his reported alcohol consumption is low, there is a synergistic effect on liver injury in the setting of chronic hepatitis. Abdominal pain in the setting of ascites needs to be urgently evaluated to exclude spontaneous bacterial peritonitis (SBP). Also, because chronic HBV infection is the major risk factor for hepatocellular carcinoma in the world, malignant ascites is in the differential. Hepatic vascular thrombosis and tuberculous peritonitis (given the patient's country of origin and travel history) also should be considered. The most appropriate initial test would be a diagnostic paracentesis to support or exclude the presence of SBP and direct the evaluation toward liver disease or other less-common causes of ascites.



The patient was seen as an outpatient 5 months prior to admission with transient fever and joint pains. Laboratory studies at that visit were notable for a serum albumin of 3.2 g/dL (normal 3.5–5), 2.4 g of predicted 24-hour protein on urinalysis (normal <30 mg per 24 hours), creatinine of 0.5 mg/dL (normal 0.8–1.3), and a positive hepatitis B surface antibody. The working diagnosis was a nonspecific viral syndrome and his symptoms resolved without treatment. One month later, he developed ascites and mild lower extremity edema. Additional laboratory studies at that time showed a normocytic ane-

mia with hemoglobin 11.7 g/dL (normal 13.5–17.5) and leukopenia with white blood cell count of  $2.4 \times 10^9/L$  (normal 3.5–10.5), neutrophil count of  $1.45 \times 10^9/L$  (normal 1.7–7.0), and lymphocyte count of  $0.58 \times 10^9/L$  (normal 0.90–2.90). Transaminases, serum bilirubin, prothrombin time, alpha fetoprotein, and peripheral blood smear were normal. Human immunodeficiency virus antibody screen and QuantiFERON-TB assay were negative. Hemoglobin A1c was 6.2% (normal 4.0–6.0). Repeat urinalysis demonstrated 883 mg of predicted 24-hour protein. Computed tomography (CT) of the abdomen showed a large amount of intra-abdominal ascites; the liver and spleen were normal, and there were no varices or other evidence of portal hypertension. Echocardiogram was normal except for a small inferior vena cava (IVC) and a mildly increased right ventricular systolic pressure of 32 mm Hg (systolic blood pressure 98 mm Hg). Due to the indeterminate cause for the patient's ascites, referral was made for gastroenterology evaluation with consideration for a paracentesis.

Cirrhotic ascites seems less likely. Postsinusoidal causes of portal hypertension (eg, cardiomyopathy) are also less likely given the absence of suggestive findings on echocardiography. Malignant ascites also appears less probable in the absence of suggestive findings such as mass lesions, lymphadenopathy, or peritoneal carcinomatosis on CT imaging. The suspicion for tuberculous peritonitis is lower with the negative QuantiFERON-TB test. Hypoalbuminemia, normocytic anemia, leukopenia, and proteinuria all suggest a systemic inflammatory condition (eg, systemic lupus erythematosus [SLE]) with inflammatory serositis causing ascites. Nephrotic syndrome can cause hypoalbuminemia, edema, and ascites, but his total urine protein losses of <3.5 grams per 24 hours are not in keeping with this diagnosis. Other uncommon causes of ascites such as chylous ascites have not yet been excluded. The most appropriate next step remains ascitic fluid analysis.



A paracentesis yielded 7.8 L of clear-yellow fluid and improvement in his abdominal discomfort. Analysis showed 224 total nucleated cells/ $\mu L$  with 2% neutrophils, 57% lymphocytes, and 37% monocytes. Ascites total protein was 3.8 g/dL and glucose was 55 mg/dL. Gram stain and culture were negative, and cytology was negative for malignancy but showed lymphocytes, plasma cells, monocytes, and reactive mesothelial cells interpreted as consistent with chronic inflammation. The serum-ascites albumin gradient (SAAG) was not obtained.

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Additional Supporting Information may be found in the online version of this article.

Received: June 14, 2014; Revised: November 21, 2014; Accepted: November 30, 2014

2014 Society of Hospital Medicine DOI 10.1002/jhm.2304

Published online in Wiley Online Library (Wileyonlinelibrary.com).

With a low leukocyte count and a paucity of neutrophils, this is not SBP. The ascites fluid did not have a chylous appearance. The SAAG, which can distinguish between portal hypertensive and nonportal hypertensive causes for ascites using a cutoff of 1.1 g/dL, was not done. The total protein was high, arguing against cirrhosis. High protein ascites with a high SAAG would suggest a posthepatic source of portal hypertension (eg, Budd-Chiari syndrome, constrictive pericarditis). High protein ascites with a low SAAG would suggest an inflammatory or malignant source of ascites. The relative lymphocytosis in the ascites fluid suggests an inflammatory process, but is a nonspecific finding. The negative cytology does not completely exclude a malignancy, but given the absence of findings on the CT, malignant ascites is less likely.

Three months before admission, the patient underwent a repeat large-volume paracentesis and a liver biopsy. The biopsy showed ectopic portal vein branches consistent with hepatoportal sclerosis, but no actual sclerosis was identified. The pathologist concluded that the findings suggested noncirrhotic portal hypertension due to a vascular in-flow abnormality. Abdominal ultrasound with Doppler was unremarkable other than slightly increased echogenicity of the liver. Magnetic resonance (MR) angiogram showed narrowing of the intra-abdominal IVC at the level of the diaphragm. Because of concern that hepatic congestion from high pressures in the narrowed IVC was leading to poor vascular inflow as suggested by the biopsy findings, an inferior vena cavagram was performed. This study was normal, although no transhepatic pressure measurements were obtained. Three stool specimens and 2 urine specimens were negative for parasites. The patient required repeat large-volume paracenteses monthly. SBP was again ruled out, but no other diagnostic labs were obtained. He had anorexia with poor oral intake each time his abdomen became distended.

The patient was started on furosemide 1 month prior to admission to the hospital but had only a slight improvement in the ascites. His other medications included insulin, tamsulosin, and hydrocodone-acetaminophen. Five days prior to admission, he underwent a diagnostic laparoscopy, which showed only ascites and small adhesions to the anterior abdominal wall. There was no visual evidence of malignancy, and the surgeon commented that “the liver was normal.” No additional biopsies were obtained.

The liver biopsy findings could be seen in non-cirrhotic portal hypertension, although this diagnosis would be unlikely without splenomegaly, varices, or other signs of portal hypertension. However, 2 possible etiologies for non-cirrhotic portal hypertension in this patient would be hepatic congestion from the narrowed IVC (although the normal IVC study argues against this) and hepatic schistosomiasis. Schistosomiasis is an important cause of non-cirrhotic portal hypertension in endemic areas like this patient’s country of origin, but the negative stool and urine studies, combined with the lack of granulomas or fibrosis seen on biopsy, make this condition unlikely.

Systemic amyloidosis (primary or secondary) could also be a cause of ascites and could present with multiorgan involvement (diarrhea and nephrotic syndrome). Amyloid deposits would have probably been seen in the liver biopsy, if present, but may not have been apparent unless specific stains (Congo red) were performed.

Evaluation for systemic, inflammatory autoimmune processes is indicated. Serum autoantibodies (anti-nuclear antibody [ANA] and extractable nuclear antigens), and a serum and 24-hour urine protein electrophoresis would be appropriate diagnostic tests. Peritoneal biopsies would have been helpful to assess for serosal diseases.


The patient subsequently developed acute right-sided abdominal pain requiring urgent evaluation and admission to the hospital. He was initially assessed by a general surgeon, who found no evidence of postoperative complications. His temperature was 36.7°C, blood pressure 105/64, heart rate 82, respiratory rate 16, and oxygen saturation 97% on room air. He appeared chronically ill, but he was in no distress and he had a normal mental status. Cardiac exam was normal except for mild jugular venous distension. He had mild bibasilar lung crackles. His abdomen was distended with superficial abdominal tenderness and a fluid wave, but he had normal bowel sounds and no peritoneal signs. He had mild scrotal edema but no peripheral edema. Joint exam did not suggest synovitis and there were no rashes or oral ulcers. Lactate was 0.9 mmol/L (normal 0.6–2.3), albumin was 2.6 g/dL, and prealbumin was 9 mg/dL (normal 19–38). Erythrocyte sedimentation rate and C-reactive protein were 46 mm/hour (normal <22) and 33.1 mg/L (normal ≤8), respectively. He had a normocytic anemia and leukopenia. Liver tests and routine chemistries were normal. Serum protein electrophoresis indicated no monoclonal protein. Complete 24-hour urine collection showed 1.2 g of protein (normal <102 mg). Paracentesis of 3.4 L demonstrated 227 total nucleated cells/μL with 2% neutrophils. Following the fluid removal, he had improvement in his pain, which he felt was related to the ascites rather than the recent surgery. Ascites total protein was 3.9 g/dL and ascites albumin was 1.7 g/dL. Ascites culture was negative for infection. Serum *Schistosoma* immunoglobulin G (IgG) antibody was positive at 3.53 (normal <1.00).

Further history revealed prior episodes of polyarticular joint pain and swelling in his hands and knees 5 years before admission. At that time, he reported a diffuse, pruritic, papular body rash. In addition, he noticed that his fingertips and toes turned white with cold exposure.

Importantly, surgical and infectious complications have been excluded. High protein ascites with a low SAAG of 0.9 suggests an inflammatory source of ascites. The follow-up clinical data (arthritis, normocytic anemia, leukopenia, rash, Raynaud’s phenomenon) suggest a systemic inflammatory syndrome such as SLE, with accompanying serositis. Serologic testing for autoantibodies would be recommended. Peritoneal biopsies, if obtained, may have demonstrated chronic, inflammatory infiltrate (nonspecific) or leukocytoclastic vasculitis (strongly supportive).

ANA enzyme immunoassay was >12 U (normal ≤1.0 U). Extractable nuclear antigens revealed positive autoantibodies for anti-SSA, anti-SSB, and anti-ribosomal P. Moreover, double-stranded DNA IgG antibody was 120 IU/mL (normal <30 IU/mL) and C3, C4, and total complement levels were low.

The clinical data support a diagnosis of SLE with serositis. Treatment of the underlying connective tissue disease will typically result in resolution of the ascites; diuretic therapy is generally ineffective.

 In consultation with rheumatology and gastroenterology specialists, the diagnosis of SLE was made based on criteria of serositis, persistent leukopenia, arthritis, renal disease (proteinuria), positive ANA, elevated ds-DNA antibodies, and hypocomplementemia. MR imaging of the abdominal vasculature demonstrated no evidence of vasculitis. The patient was given intravenous methylprednisolone 1 g daily for 3 days followed by high-dose oral corticosteroids with a gradual taper. He was also started on mycophenolate mofetil as a steroid-sparing medication (which was later changed to leflunomide due to persistent leukopenia) and hydroxychloroquine. His isolated positive *Schistosoma* IgG antibody in the absence of other findings was consistent with past exposure or infection. The infectious disease specialist felt there was no evidence of active schistosomiasis, but recommended treatment with a single dose of praziquantel due to the potential benefit with low risk of side effects. The patient had ongoing improvement following dismissal. He had 1 additional paracentesis of 4.1 L, 10 days after his hospitalization, and his ascites and proteinuria resolved. At the 5-year follow-up visit, there had been no recurrence of abdominal ascites or abdominal pain. He remains on low-dose prednisone at 5 mg daily, leflunomide, and hydroxychloroquine.

## COMMENTARY

This patient had recurrent ascites with 29.6 L removed over the 4 months prior to admission and an additional 3.4 L during his hospitalization. His outpatient providers initially considered a portal hypertensive etiology of his ascites due to his history of HBV and prior alcohol use. They also appropriately investigated for a possible infectious process. They next directed their evaluation toward the liver biopsy findings, which raised concern for a vascular inflow abnormality. However, the evaluation could have been performed more rapidly and far more cost-efficiently had a diagnostic paracentesis with calculation of the SAAG been performed early in the evaluation.

The SAAG, which was first described in 1983 by Paré and colleagues, is “a parameter reflecting the oncotic pressure gradient between the vascular bed and the interstitial splanchnic or ascitic fluid”.<sup>1</sup> In the classic study by Runyon and colleagues, a SAAG difference of  $\geq 1.1$  g/dL correctly differentiated causes of ascites due to portal hypertension from those that were not due to portal hypertension 96.7% of the time.<sup>2</sup> Conditions such as nephrotic syndrome, peritoneal carcinomatosis, and serositis (lupus peritonitis) can cause ascites in patients without portal hypertension.

Serositis in the form of pleuritis and/or pericarditis is a common feature of SLE, and ascites has been described in 8% to 11% of SLE patients.<sup>3</sup> However, massive ascites due to lupus peritonitis as a presenting symptom is rare.<sup>4</sup> More common causes of ascites in the setting of SLE include nephrotic syndrome, heart failure, protein-losing enteropathy, constrictive pericarditis, Budd-Chiari syndrome, indolent infections such as tuberculosis, and chylous ascites.<sup>5–7</sup> Of note, lupus peritonitis may be chronic or acute. Chronic ascites develops insidiously with few manifestations of active lupus and may be painless, whereas ascites from acute lupus peritonitis typically develops rapidly and presents with acute abdominal pain and other signs of increased lupus activity.<sup>3,5,6,8,9</sup>

Ascites from lupus peritonitis may be due to marked serosal exudative accumulation with reduced absorptive capacity in

the peritoneum.<sup>3,4,10</sup> Other possible causes include peritoneal inflammation from deposition of immune complexes or vasculitis of peritoneal vessels and visceral serous membranes.<sup>4,9,11</sup> Although subserosal and submucosal vasculitis have been found in acute ascites, chronic ascites may be related to scarring from vasculitis and serosal inflammation leading to poor venous and lymph drainage.<sup>9</sup> Ascitic fluid characteristics from lupus peritonitis include a SAAG  $< 1.1$ , presence of white blood cells anywhere in a broad range from 10 to 1630/ $\mu$ L, and a range of fluid protein from 3.4 to 4.7 mg/dL.<sup>3</sup> Although not tested in this patient, findings of low complement levels, positive ANA, and elevated anti-DNA antibody in the ascitic fluid would be supportive of lupus peritonitis, but not specific.<sup>5,9,12</sup> Lupus erythematosus cells are occasionally found in the ascitic fluid, but do not rule out other causes of ascites.<sup>9</sup> On retrospective analysis, lupus erythematosus cells were not seen in this patient's pathology specimens.

Treatment of lupus peritonitis and ascites is with high-dose glucocorticoid therapy, but many patients may need a second immunosuppressant, possibly because of impaired peritoneal circulation from chronic inflammation leading to decreased drug delivery.<sup>13,14</sup> Chronic ascites may be recalcitrant to systemic glucocorticoids,<sup>3</sup> so a possible alternative therapy is intraperitoneal injection of triamcinolone, which successfully treated massive ascites in a patient who did not respond to oral glucocorticoid treatment.<sup>13</sup> Although ascites may be refractory in some patients, those with chronic lupus peritonitis can generally achieve remission, yet the overall prognosis depends on the presence and severity of multiorgan involvement from SLE. As with any SLE patient, there are also risks of infection from immunosuppression and increased cardiovascular risks.

This patient's evaluation and treatment could have been expedited if he had undergone a paracentesis with determination of the SAAG early in his workup. It is not known why the SAAG was not obtained despite multiple outpatient visits and paracenteses, his history of HBV, and prior alcohol use. This may have been simply an unfortunate oversight. Alternatively, it may have been that his outpatient providers focused on tantalizing clues such as his country of origin, which led to concern for schistosomiasis, and the biopsy findings suggestive of a vascular inflow abnormality that led to further extensive testing. In so doing, the clinicians committed several diagnostic errors, including multiple alternatives bias, anchoring, and confirmation bias.<sup>15</sup> As a result, the patient accrued excess charges of \$64,000 from multiple tests, laparoscopic surgery, and 2 hospitalizations. This case highlights how cognitive errors introduce costly variability into patient care, especially when a simple and accurate test is at the beginning of the decision tree.

## CLINICAL TEACHING POINTS

1. Diagnostic paracentesis, with calculation of the serum-ascites albumin gradient, should be the first test in the workup for ascites and can distinguish portal hypertensive causes from non-portal hypertensive causes.
2. Ascites related to SLE can be acute or chronic and caused by bowel infarction, perforation, pancreatitis,

mesenteric vasculitis, nephrotic syndrome, heart failure, protein-losing enteropathy, constrictive pericarditis, lupus peritonitis, Budd-Chiari syndrome, or serositis (lupus peritonitis).

3. Ascites caused by lupus peritonitis is rare. Once treated, management should be directed toward keeping the SLE in remission.

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Disclosure: Nothing to report.

## References

1. Paré P, Talbot J, Hoefs JC. Serum-ascites albumin concentration gradient: a physiologic approach to the differential diagnosis of ascites. *Gastroenterology*. 1983;85(2):240–244.
2. Runyon BA, Montano AA, Akriviadis EA, et al. The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. *Ann Intern Med*. 1992;117:215–220.
3. Forouhar-Graff H, Dennis-Yawingu KA, Parke AL. Insidious onset of massive painless ascites as initial manifestation of systemic lupus erythematosus. *Lupus*. 2011;20:754–757.
4. Weinstein JP, Noyer CM. Rapid onset of massive ascites as the initial presentation of systemic lupus erythematosus. *Am J Gastroenterol*. 2000;95:302–303.
5. Ebert EC, Hagspiel KD. Gastrointestinal and hepatic manifestations of systemic lupus erythematosus. *J Clin Gastroenterol*. 2011;45:436–441.
6. Prasad S, Abujam B, Lawrence A, Aggarwal A. Massive ascites as a presenting feature of lupus. *Int J Rheum Dis*. 2012;15:e15–e16.
7. Lee CK, Han JM, Lee KN, et al. Concurrent occurrence of chylothorax, chylous ascites, and protein-losing enteropathy in systemic lupus erythematosus. *J Rheumatol*. 2002;29:1330–1333.
8. Richer O, Ulinski T, Lemelle I, et al. Abdominal manifestations in childhood-onset systemic lupus erythematosus. *Ann Rheum Dis*. 2007;66:174–178.
9. Schousboe JT, Koch AE, Chang RW. Chronic lupus peritonitis with ascites: review of the literature with a case report. *Semin Arthritis Rheum*. 1988;18:121–126.
10. Salomon P, Mayer L. *Nonhepatic Gastrointestinal Manifestations of Systemic Lupus Erythematosus*. London, United Kingdom: Churchill Livingstone; 1987:747–760.
11. Pott Júnior H, Neto AA, Teixeira MAB, Provenza JR. Ascites due to lupus peritonitis: a rare form of onset of systemic lupus erythematosus. *Rev Bras Reumatol*. 2012;52(1):113–119.
12. Trock D, Volnea A, Wolk J, Majoros A. New-onset lupus presenting as serositis in an 80-year-old woman: does a high-titer ANA in pleural, pericardial, or peritoneal fluid help confirm the diagnosis? *J Clin Rheum*. 2005;11(5):292–293.
13. Zhou QG, Yang XB, Hou FF, Zhang X. Successful treatment of massive ascites with intraperitoneal administration of a steroid in a case of systemic lupus erythematosus. *Lupus*. 2009;18:740–742.
14. Ito H, Nanamiya W, Kuroda N, et al. Chronic lupus peritonitis with massive ascites at elderly onset: case report and review of the literature. *Intern Med*. 2002;41:1056–1061.
15. Croskerry P. The Importance of cognitive errors in diagnosis and strategies to minimize them. *Acad Med*. 2003;78:775–780.