Mycobacterium avium complex infection presenting as persistent ascites

Bourne L. Auguste MD, Ashish D. Patel MD, Reed A. Siemieniuk MD

Cite as: *CMAJ* 2018 April 3;190:E394-7. doi: 10.1503/cmaj.170823

A 53-year-old man presented to hospital with a six-month history of weight gain, peripheral edema and abdominal distention. The patient's past medical history included a renal cadaveric transplant in 2016, a 32-year history of HIV infection, type 2 diabetes mellitus, coronary artery disease and dyslipidemia. His immunosuppressive regimen included prednisone 5 mg daily, tacrolimus 0.5 mg every 10 days and mycophenolate mofetil 540 mg twice daily. He was also taking furosemide, metoprolol, acetylsalicylic acid, pantoprazole, rosuvastatin, dapsone, raltegravir, ritonavir, darunavir and etravirine. His regimen did not include nucleoside transcriptase reverse inhibitors, owing to previous adverse reactions with nausea, vomiting and leukopenia. His CD4 nadir before transplant was 260 cells/μL, and 399 cells/μL at the time of transplant. In 2016, he received induction therapy with antithymocyte globulin for his renal transplant. We gave him no additional lymphocyte-depleting therapy beyond the first week after his transplant. He had no previous opportunistic infections.

Initial laboratory investigations revealed stable anemia with a hemoglobin of 92 g/L; other hematologic studies were within normal limits. Serum creatinine was at baseline (112 μmol/L) and all other routine serum biochemistry were within normal limits. Liver enzymes and function tests were normal with the exception of albumin, which was 31 g/L. Serum polymerase chain reaction did not detect HIV or cytomegalovirus infection, but Epstein–Barr virus was detected at 2.63 x 10^3 IU/mL. His CD4 cell count was 141 cells/uL. Non-nephrotic range proteinuria was noted on the 24-hour urine collection for protein with 0.49 g (Box 1).

We diagnosed ascites based on physical examination and abdominal ultrasonography (Figures 1A, 1B). There were no extrahepatic manifestations of liver disease and no lymphadenopathy. A diagnostic paracentesis showed straw-coloured fluid. The serum-ascites albumin gradient was 6 g/L, consistent with exudative ascites. The differential diagnosis for exudative ascites includes malignant disease, lymphatic obstruction and infections. Three different ascitic fluid samples were sent for flow cytometry and cytology. These were negative for malignant disease, and cells were predominantly lymphocytes. There was no evidence of lymphadenopathy on abdominal and pelvic computed tomography (CT). Three samples of 10 mL ascitic fluid were cultured for mycobacteria and were all negative.

KEY POINTS

- Exudative ascites, particularly in immunosuppressed patients, should raise suspicion for infections (especially mycobacterial infections), neoplasms involving the peritoneum and lymphatic obstruction.
- Patients with exudative ascites at risk for mycobacterial infection may require extensive testing and a period of careful observation for the diagnosis to be made.
- Patients with HIV infection and solid-organ transplants can develop opportunistic infections outside of the classic thresholds for CD4 count (i.e., invasive *Mycobacterium avium* complex disease with CD4 > 50 cells/μL and *Pneumocystis jirovecii* pneumonia with CD4 > 200 cells/μL).

Because a cause for his ascites was not identified, we considered a laparoscopic peritoneal and omental biopsy. However, the care team and patient decided together that an ultrasound-guided omental biopsy had a more acceptable risk–benefit ratio. The biopsy showed tiny fragments of fibrous tissue, but no specific abnormality suggestive of infection; no malignant disease was identified. Without a definitive diagnosis, the patient and care team chose to pursue watchful waiting and large-volume paracentesis every 2–3 weeks.

The patient returned to hospital one week later with shortness of breath, a new nonproductive cough and fever of 38.1°C. Computed tomography of his thorax showed small pleural effusions and a new consolidation in the anterior basal right lower lobe, with patchy, ground-glass opacity (Figure 2). A mycobacterial culture obtained via bronchial alveolar lavage was positive for *Mycobacterium avium* complex. We began antimycobacterial therapy, including moxifloxacin, azithromycin and ethambutol, with plans to continue therapy for one year. Despite not having received additional diuretic therapy or therapeutic paracentesis, the patient had a marked decrease in his abdominal girth. A CT scan of his abdomen confirmed substantial radiographic improvement in his ascites after he began treatment for *M. avium* complex (Figures 1C, 1D). At six months of follow-up, the patient was doing well, without recurrence of the ascites or symptoms.

Discussion

Exudative ascites is described as a serum-ascites albumin gradient of less than 11 g/L. The serum albumin-ascites gradient is a simplified measurement of imbalances in hydrostatic pressures, which can either be high (> 11 g/L) or low gradient (< 11 g/L).[1] Although nonhepatic causes account for only about 15% of all patients with ascites, the differential diagnosis is quite broad and includes neoplasms of the peritoneum, lymphatic obstruction, nephrotic syndrome and pancreatitis (Figure 3).[1] This differential should also include mycobacterial infections, particularly in immunosuppressed patients.

Box 1: Laboratory investigations on the patient's initial presentation

Laboratory investigation	Results	Normal range
Complete blood count		
Leukocyte count (× 10^9/L)	6.9	4.0–11.0
Hemoglobin (g/L)	92	140–180
Platelet count (× 10^9/L)	185	150–400
Serum biochemistry		
Creatinine (μmol/L)	112	64–110
Sodium (mmol/L)	139	135–145
Potassium (mmol/L)	3.9	3.2–5.0
Liver enzymes and function tests		
Aspartate transaminase, U/L	17	5–34
Alanine transaminase, U/L	24	7–40
Alkaline phosphatase, U/L	107	40–150
Bilirubin (μmol/L)	14	20
Albumin (g/L)	31	38–50
Viral serology		
CD4 cell count (cells/L)	141	380–1736
HIV viral load	Undetectable	–
CMV PCR	Undetectable	–
EBV PCR	2.62 × 10^3 IU/mL	–
Ascitic fluid biochemistry		
Leukocyte count (× 10^9/L)	100	< 250
Lymphocytes, %	93	
Macrophages, %	7	
Neutrophils, %	0	
Protein (g/L)	34	–
Albumin (g/L)	22	–
LDH (U/L)	237	–
Urine biochemistry		
24-hour urine protein (g)	0.49	0.14

Note: CMV = cytomegalovirus, EBV = Epstein–Barr virus, LDH = lactate dehydrogenase, PCR = polymerase chain reaction.

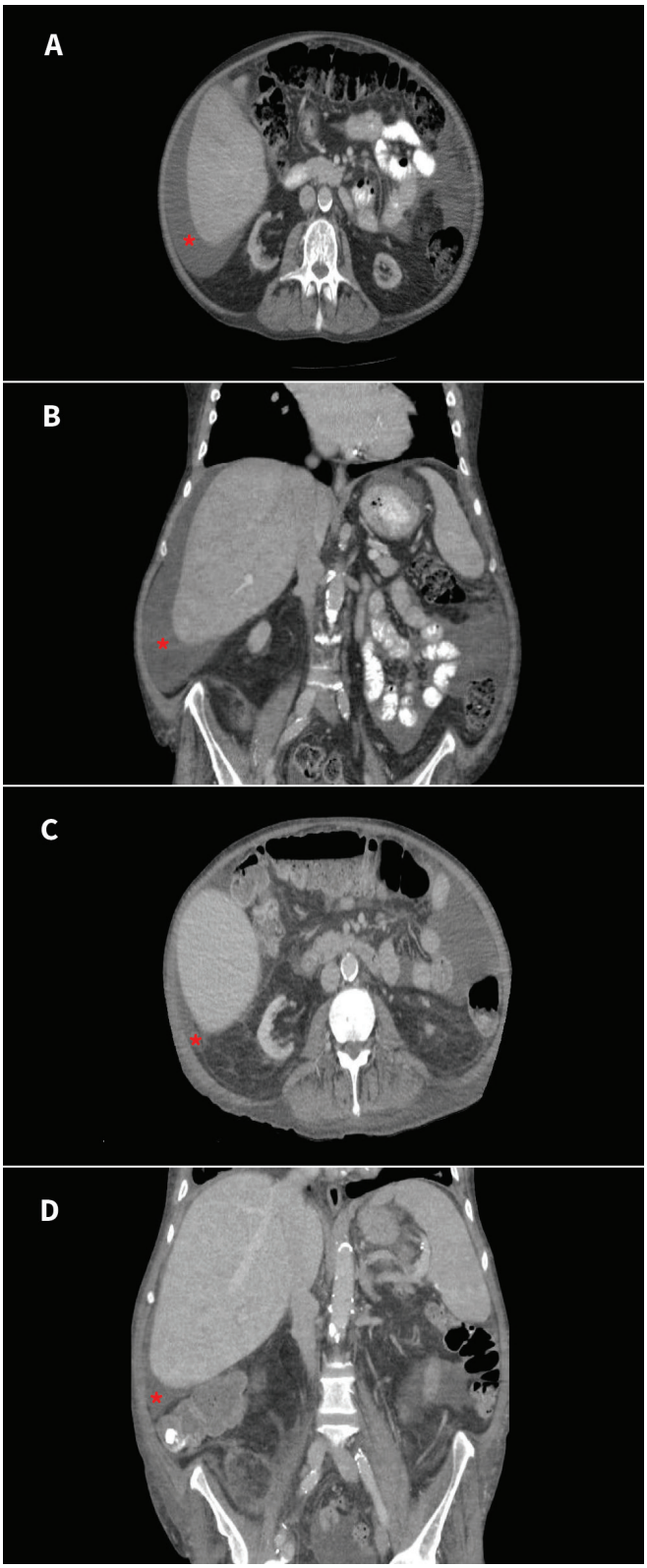

Figure 1: Computed tomography images of the abdomen of a 53-year-old man, showing ascites (denoted by *) before and after the treatment of pulmonary *Mycobacterium avium* complex infection. (A) and (B): Axial and coronal images show substantial ascites before the diagnosis and treatment of the pulmonary mycobacterial infection. (C) and (D): Four weeks after treatment with ethambutol, moxifloxacin and azithromycin, a substantial reduction in the ascites occurred.

Fluid analysis should always be performed on patients with new or recurrent ascites. Testing for ascitic fluid should include cell count and differential along with albumin, protein and bacterial cultures to rule out spontaneous bacterial peritonitis. Additional testing may be helpful, including lactate dehydrogenase, amylase or mycobacterial cultures when there is suspicion of pancreatitis, malignancy or tuberculosis.[1,2]

Patients who are at increased risk of tuberculous involvement of the peritoneum should be tested for the infection.[3] Ascitic fluid culture for mycobacteria has a sensitivity approaching only 50%.[3] Collectively, polymerase chain reaction testing for mycobacteria and laparoscopic biopsy is the most accurate method for diagnosing tuberculous involvement of the peritoneum.[1] It is reasonable to begin with less invasive investigations, but if they are inconclusive, subsequent consideration must be given to peritoneoscopy with biopsy as it has a sensitivity approaching 100% for diagnosing tuberculous peritonitis.[3]

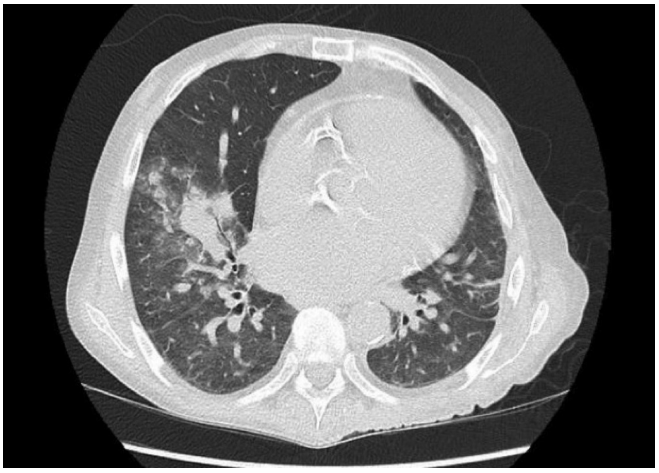

Figure 2: Computed tomography images of the thorax of a 53-year-old man with exudative ascites, showing right middle and lower lobe consolidation with air bronchograms. Bronchoalveolar lavage culture was later positive for *Mycobacterium avium* complex.

Making a diagnosis of exudative ascites can be challenging and sometimes requires a period of watchful waiting with intermittent large-volume paracentesis for symptomatic relief. Definitive management necessitates diagnosing and treating the underlying cause of exudative ascites. Importantly, patients with a high suspicion for mycobacterial infections may need extensive testing and close monitoring for the diagnosis to be made.

M. avium complex are environmentally ubiquitous organisms found in soil, fresh water, and dairy and poultry products. Although the modes of transmission are not well understood, it is believed that the respiratory and gastrointestinal systems are the main portals of entry.[7] Disseminated *M. avium* complex infection involving the spleen, lymph nodes, gastrointestinal tract and bone marrow is seen classically in people living with HIV who have a CD4 count of less than 50 cells/μL.[7] The incidence of invasive *M. avium* complex disease has decreased substantially in recent years, possibly as a result of earlier HIV diagnoses, *M. avium* complex prophylaxis and new potent protease inhibitors integrase strand inhibitors.[8]

Combination therapy for disseminated *M. avium* complex infection typically includes a macrolide plus ethambutol and rifabutin. In the common situation where there is resistance or

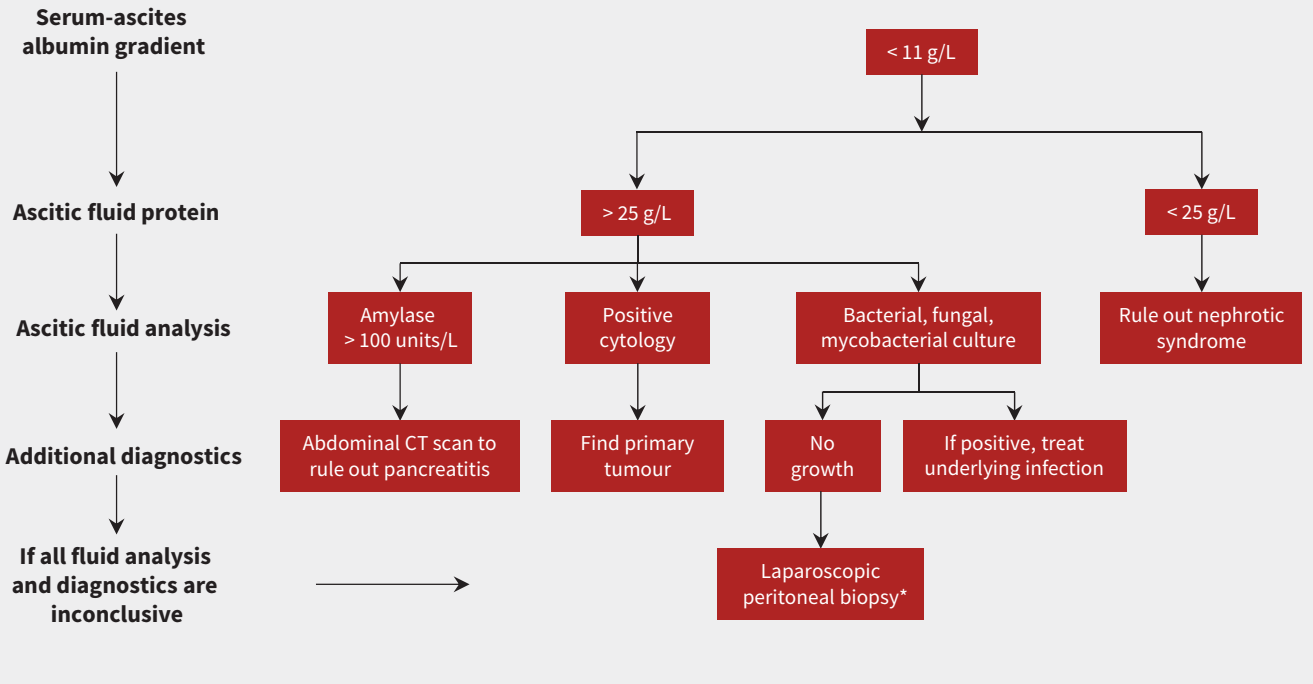

Figure 3: Suggested diagnostic approach to a patient with exudative ascites. Low ascitic fluid protein should direct practitioners to rule out nephrotic syndrome as a cause for exudative ascites. *Consideration of lymphangioscintigraphy can be done at this point to rule out lymphatic obstruction before invasive procedure. Note: CT = computed tomography.[1,4,5,6]

intolerance to rifabutin, a fluoroquinolone or amikacin can be used instead.[9] In our patient, we avoided rifabutin and clarithromycin because of concerns about a drug–drug interaction with tacrolimus. Rifabutin leads to an upregulation in activity of intestinal P-glycoprotein drug efflux pumps and cytochrome P450 3A4 (CYP450 3A4), reducing the absorption and augmenting the clearance of tacrolimus.[10] Likewise, clarithromycin is a much more potent inhibitor of CYP450 3A4 than azithromycin. Wherever possible, management of *M. avium* complex should be overseen by infectious diseases specialists and pharmacists to reduce risk of harmful drug–drug interactions.

HIV infection and disseminated mycobacterial infection

Recipients of solid-organ transplants who are living with HIV are at increased risk of developing opportunistic infections, because of the immunosuppression resulting from both causes.[11] This is especially true in patients receiving lymphocyte-depleting agents such as thymoglobulin: cellular immunity is affected by both HIV and lymphocyte depletion.[10] A few case reports have documented ascites associated with *M. avium* complex infection; typically, chylous ascites.[12]

Our patient's exudative ascites was almost certainly a presentation of invasive *M. avium* complex disease, because it rapidly resolved after we began antimycobacterial therapy. Both the patient's HIV and immunosuppressive regimens probably led to his opportunistic infection. We initially postulated that infection may have translocated from the abdomen to the lungs across the diaphragm. However, in the absence of any evidence of diaphragmatic defects, we believe that this was simply disseminated *M. avium* complex infection.

Our patient had a CD4 count cell of 141 cells/μL at the time of diagnosis, challenging the current school of thought in clinical practice that *M. avium* complex infections are usually seen with CD4 count less than 50 cells/μL. *Pneumocystis jirovecii* pneumonia can also be seen with CD4 cells counts of more than 200 cells/μL.[11] However, high HIV RNA levels (> 100 000 copies/mL), previous opportunistic infections and impaired immune response to mycobacterial antigens from dysfunctional T cells can also increase infection risk.[11,12]

The incidence of nontuberculous mycobacterial infection is high in recipients of solid-organ transplants (kidney 0.16%–0.38%, lung 0.24%–2.80% and heart 0.46%–2.30% per year) because of impaired cell-mediated immunity (AIDSinfo website for more information on disseminated *M. avium* complex disease, at https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/326/mac). Patients who are colonized with nontuberculous mycobacterial infection may be at a higher risk of infection.[13]

After our experience, we suggest that patients with exudative ascites be counselled about the risks and benefits of invasive diagnostic tests and the consequences of possible diagnostic delay. Additionally, with the increasing number of solid-organ transplants and patients with possible HIV coinfection, overall immunosuppressive burden (historic and present) should be recognized as a major risk for opportunistic infections.

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Competing interests: None declared.

This article has been peer reviewed.

The authors have obtained patient consent.

Affiliations: Divisions of Nephrology (Auguste) and Cardiology (Patel); Postgraduate Medical Education (Auguste, Patel), University of Toronto, Toronto, Ont.; Department of Health Research Methods, Evidence and Impact (Siemieniuk), McMaster University, Hamilton, Ont.

Contributors: All authors contributed to the conception and design of the work, drafted the manuscript, revised it critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Correspondence to: Bourne Auguste, bourne.auguste@mail.utoronto.ca