Case 013: Fever in a cirrhotic patient.

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A 61 year-old female patient with history of chronic hepatitis C infection presented to hospital with fever and chills for the past 2 days. She claimed her appetite and bowel habit were normal and she had gained some weight lately. She was diagnosed to have essential hypertension 5 years ago for which she was prescribed a thiazide diuretic by her family doctor.

She had a low grade fever of 37.6 ºC on admission. Her blood pressure was 124/62 mmHg, pulse rate 78 beats/min and regular, respiratory rate 20/min. Physical examination revealed obvious jaundice, palmar erythema, mild pitting ankle edema and a small left pleural effusion. Her abdomen was distended; shifting dullness was present; there was no tenderness or guarding; neither the liver nor the spleen was palpable. The rest of a comprehensive examination revealed no other positive signs.

1. What is the differential diagnosis?

   This patient had fever of unknown origin and the list of differential diagnoses should include:
   
   o Occult infections
   o Occult malignancies
   o Connective diseases
   o Granulomatous diseases
   o Drug related pyrexia.

Bedside ultrasound was performed in this patient and confirmed the presence of a large ascites together with shrunken cirrhotic liver and moderate splenomegaly. A paracentesis was performed and microscopy revealed a polymorphonuclear cell count of 570/mm³. Gram stain of ascites fluid sediment was negative for bacteria.
2. What do these results indicate?

A polymorphonuclear cell count $> 250/mm^3$ in ascites fluid is suggestive of spontaneous bacterial peritonitis, even when Gram stain of ascites fluid sediment is negative for bacteria.

3. What is spontaneous bacterial peritonitis?

Spontaneous bacterial peritonitis is a serious primary infection of ascites fluid seen in patients with cirrhosis and ascites. The mortality rate is as high as 25%. The infection is commonly caused by a single species of bacteria and occurs in the absence of a surgical cause of bacterial contamination of the peritoneal cavity (e.g. perforated viscus). The 3 most common organisms responsible are Escherichia coli, Klebsiella pneumoniae, and Streptococcus pneumoniae, although infections by Enterococcus, Staphylococcus aureus, and anaerobic, fungal, mycobacterial, and viral pathogens have also been reported. The infecting organism gains entry to the peritoneal cavity by hematogenous spread and infection is facilitated by the poor opsonic capacity of ascites fluid and the impaired systemic immune response of the cirrhotic host.

4. How does spontaneous bacterial peritonitis present itself?

The condition affects 10 – 30 % of cirrhotic patients with ascites. Mode of presentation may be subtle and a heightened degree of awareness of this possibility is advised. An unexplained deterioration in the clinical condition of a cirrhotic patient with ascites may be the only clue.

- Symptoms and signs which may or may not be present include fever, chills, nausea and vomiting, diarrhea, abdominal pain or tenderness, disturbance of mental status, and renal impairment.
- Paracentesis is diagnostic: Typically ascites fluid has a polymorphonuclear cell count $> 250/mm^3$. 

Smear of ascites fluid sediment or culture of ascites fluid does not always reveal the offending organism. Some clinicians suggest that inoculating sampled ascites fluid directly into blood culture bottles at the bedside, instead of sending free fluid sample to the laboratory, would reduce the instances of falsely negative culture results.

5. How does secondary peritonitis differ from primary spontaneous bacterial peritonitis?

A surgical cause of secondary peritonitis, often a perforated viscus, is usually obvious from the history and physical signs. Peritoneal fluid samples of secondary peritonitis also differ from samples of spontaneous bacterial peritonitis in the following results:

- Much higher polymorphonuclear cell count, usually in the thousands.
- Total protein > 10 g/L.
- LDH level greater than the upper limit of normal for plasma.
- Glucose concentration < 3.9 mmol/L.
- Culture results reveal the presence of multiple organisms.

The presence of these features should prompt a diligent search for a treatable surgical cause of secondary peritonitis.

6. What is the treatment for spontaneous bacterial peritonitis?

- Cefuroxime is usually effective and is often the antibiotic of choice in Hong Kong although many guidelines overseas recommend the use of cefotaxime or other third generation cephalosporins.
- Patient receiving the right choice of antibiotic should show improvement within 48 hours. Sampling ascites fluid to show a fall in polymorphonuclear cell count is not necessary. If the patient failed to respond, ascites fluid may have to be
re-examined for the possibility of a missed pathogen and a surgical cause of secondary peritonitis should be considered.

7. What else is important in the treatment of spontaneous bacterial peritonitis?

Renal impairment is a major complication in cirrhotic patients with spontaneous bacterial peritonitis. In addition to early treatment with an appropriate antibiotic, administration of albumin 1.5 g/kg at the time of diagnosis and 1 g/kg on day 3 has been reported to reduce morbidity from renal failure.

8. Is there a place for antibiotic prophylaxis in cirrhotic patients with ascites?

The issue of antibiotic prophylaxis against spontaneous bacterial peritonitis is controversial. The following subgroups of patients are at high risk of developing spontaneous bacterial peritonitis:

- Those whose ascites fluid protein concentration is < 10 g/L.
- Those hospitalized with an upper gastrointestinal hemorrhage.
- Those who have survived a previous episode of spontaneous bacterial peritonitis.

“Cleansing” the microflora of the gastrointestinal tract of these patients with norfloxacin, ciprofloxacin, or trimethoprim-sulfamethoxazole has been shown to reduce markedly the incidence of spontaneous bacterial peritonitis. However, long term survival of these patients is dependent on their residual hepatic function. It has not been shown that prophylactic antibiotic improves their survival.

Further Readings
