Spontaneous bacterial peritonitis in cystic fibrosis

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Abstract

Bacterial peritonitis presents with classic symptoms of fever and abdominal pain. Some patients, however, are completely asymptomatic. Death in the short term is considerable, especially in patients with alcoholic cirrhosis. Cystic fibrosis patients occasionally develop biliary cirrhosis and may have secondary hypersplenism, varices, and ascites. These patients should be at risk for spontaneous bacterial peritonitis. Spontaneous bacterial peritonitis is described in two patients with longstanding hepatic cirrhosis secondary to cystic fibrosis. Both had required splenectomy for complications of portal hypertension. This is a previously unreported, but potentially fatal, complication of cystic fibrosis liver disease. Early diagnostic paracentesis is essential so that appropriate acute management, including antimicrobial treatment can be started. In the long term, these patients deserve immediate paracentesis for any evidence of recurrence. Whether the patient is treated with chronic (continuous) antimicrobial prophylaxis or only receives antimicrobial treatment during periods when bacteraemia is possible (for example, dental work, bronchoscopy), it would seem reasonable in patients with cystic fibrosis to use a wide spectrum antimicrobial agent with activity against *Pseudomonas aeruginosa*, other common Gram negative organisms, and *Staphylococcus aureus*.

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In 1958, Caroli and Platteborse reported on a series of patients with cirrhosis with coliform septicaemia or peritonitis complicating ascities, or both.¹ Two more reports in the 1960s confirmed that this syndrome was more common than generally recognised and was often misdiagnosed.^{2,3} Gram negative organisms, mainly *Escherichia coli* and *Klebsiella* sp, are most commonly encountered; however, Gram positive cocci, including streptococcus, pneumococcus, and staphylococcus, have been reported,⁴⁻⁸ suggesting both bowel and haematological sources for the infection. In a review of published works and summary of their experience with 28 patients with alcoholic cirrhosis, Conn and Fessel introduced the term spontaneous bacterial peritonitis (SBP). They noted a very high in-hospital mortality, suggested that ascites was the sine qua non of the syndrome, and described a wider variety of clinical features than previously appreciated. They also extended the syndrome to include patients without bacteraemia.⁸ SBP is an ascitic infection without a local contiguous source, such as abscess or intestinal perforation.⁹ After an additional report of culture negative, but probable SBP,¹⁰ Runyon

and Hoefs reported 18 episodes of culture negative neutrocytic ascites,¹¹ with many similarities to SBP. Subsequently, SBP and culture negative neutrocytic ascites have been reported in many conditions.¹² Patients with alcoholic cirrhosis and peritonitis have substantial in-hospital mortality,^{3,8} with some improvement after earlier diagnosis and improved antimicrobial treatment.⁷

Patients with cystic fibrosis may have biliary cirrhosis with portal hypertension and ascites.¹³ Although they would be expected to be at risk, to our knowledge SBP has not been reported in cystic fibrosis. We report here two cystic fibrosis patients, ages 21 and 36 years with known liver disease, who developed this complication of ascites.

Case reports

Eight of 1310 cystic fibrosis patients seen at this centre over a 35 year period have had a splenectomy. Two of these patients had no portal systemic shunting procedure, and both subsequently have developed SBP.

CASE 1

Cystic fibrosis presented at birth with meconium ileus. At age 13, acute biliary colic led to a diagnosis of cholelithiasis, and a cholecystectomy was performed. Open liver biopsy showed changes consistent with cystic fibrosis related cirrhosis. The patient stayed in hospital only twice during her teens for intravenous antimicrobial treatment of pulmonary exacerbations. She gradually developed, however, massive splenomegaly, severe splenic pain, and laboratory evidence of hypersplenism. At age 20, a splenectomy was necessary, but a shunt was not performed because of the possibility of rapid hepatic decompensation and need for liver transplant. Postoperatively, liver function was marginal and the patient's functional state and feeling of well being were very poor. Ascites necessitated aggressive diuretic treatment. She was tentatively listed for liver transplant. At age 21, she presented with abdominal pain and fever. The peripheral leucocyte count was $9.1 \times 10^9/l$ ($9100/mm^3$) with 66% neutrophils. A paracentesis showed a leucocyte count of $1.5 \times 10^9/l$ ($1575/mm^3$) with 77% neutrophils. The ascitic fluid glucose was 5.0 mmol/l, the protein 23 g/l, and the LDH (I→P) 144 U/l; the pH was not reported. The ascitic fluid culture showed *E coli*. The patient's sputum culture yielded only *Pseudomonas aeruginosa* on culture; *E coli* had not been present in respiratory tract secretions. The patient responded to intravenous antimicrobials with resolution of abdominal pain and fever, and improved feeling of well being. Repeat ascitic fluid culture yielded no growth.

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The patient had one recurrence of abdominal pain. Ascitic fluid cultures were negative, but the patient was taking antimicrobials. Subsequently, she continued on antimicrobial prophylaxis (norfloxacin) and has not had a recurrence of abdominal pain for 23 months.

CASE 2

A 36 year old pharmacist with cystic fibrosis, had a long history of gastrointestinal and pulmonary symptoms. At age 26 years, he had a splenectomy for hypersplenism. The liver was fibrotic and multinodular, consistent with biliary cirrhosis. A shunting procedure could not be performed because the splenic vein was too thin walled and fragile. At 36 years, during a pulmonary exacerbation, the total serum protein was 55 g/l and albumin 28 g/l; bilirubin total 46.2 $\mu\text{mol/l}$ and direct 29.1 $\mu\text{g/l}$, alkaline phosphatase 237 U/l, serum aspartate aminotransferase (AST), 1170 $\text{nmol/sec}^{-1}/\text{l}$, serum alanine aminotransferase (ALT) 1173 $\text{nmol/sec}^{-1}/\text{l}$, and γ -glutamyl-transferase 167 U/l. He had no ascites. He returned to full time work. Seven months after, he developed abdominal swelling, mild peripheral oedema, and some dyspnoea, all unresponsive to salt restriction. Abdominal swelling increased, and an ultrasound at another centre confirmed massive ascites, which they attributed to an albumin of 24 g/l. He was in hospital elsewhere but discharged two days later despite low grade fever, moderate diffuse abdominal pain, and an increasing white blood count ($8.8 \times 10^9/\text{l}$ to $12.7 \times 10^9/\text{l}$). He presented at our centre the next day. Paracentesis yielded 700 ml of cloudy fluid with a leucocyte count of $6.27 \times 10^9/\text{l}$ (80% neutrophils), glucose 8.1 mmol/l , protein 4.0 g/l. Cultures for fungi, mycobacteria, viruses, and repeated bacterial cultures were all negative; however, he had received oral ciprofloxacin for several days. Total serum protein at admission was 50 g/l, and the albumin 19 g/l. Alkaline phosphatase 275 U/l, AST 2122 $\text{nmol/sec}^{-1}/\text{l}$, ALT 1207 $\text{nmol/sec}^{-1}/\text{l}$, and γ -glutamyltransferase 211 U/l. Total and direct bilirubin were 13.68 $\mu\text{mol/l}$ and 3.4 $\mu\text{mol/l}$. Additional paracenteses yielded large amounts (up to 1700 ml) of cloudy fluid, which remained culture negative. He responded to antimicrobial treatment with disappearance of fever, decrease in white blood count, rise in albumin 22 g/l, and no reaccumulation of ascites. He was discharged on prophylactic antimicrobial (norfloxacin). He has not had a recurrence of abdominal pain, and at follow up 10 months later, there was minimal ascites.

Discussion

Up to 10% of patients with alcoholic cirrhosis and overt portal hypertension with ascites develop SBP.⁸ SBP also complicates other diseases, including nephrotic syndrome, disseminated lupus erythematosus, haemochromatosis, primary biliary cirrhosis, chronic active hepatitis, and acute hepatitis.¹² Focal biliary cirrhosis has been reported in 5–9% of cystic fibrosis patients^{13,14} with a few progressing to diffuse multilobular involvement.^{15,16} Only a

small percentage progress to symptomatic portal hypertension, including ascites or clinically significant oesophageal varices, or both. A substantial number (36%) have low concentrations of serum albumin ($<25 \text{ g/l}$).¹⁶

Because bacterial peritonitis may present with minimal or no symptoms^{7,8,10} and may be afebrile,⁹ a high index of suspicion is necessary to ensure the early treatment needed to prevent death. Bacterial peritonitis should be excluded by a diagnostic peritoneal tap in any patient with ascites and abdominal pain or fever, or both.¹⁰ The bedside inoculation of blood culture bottles¹⁷ decreases the incidence of negative cultures from 40 to 10%.⁹ The pH of the ascitic fluid may aid in discriminating between infected (pH 7.25 (0.06), range 7.25–7.31) and uninfected (7.47 (0.07), range 7.39–7.58) ascitic fluid.¹⁸

There is some variability in the recommendation for antimicrobial treatment. Munoz and Maddrey suggest that intravenous antimicrobial treatment, regardless of Gram stain or culture results, should be started when more than $0.25 \times 10^9/\text{l}$ neutrophils are present in ascitic fluid.¹⁹ Conn and Atterbury propose that antimicrobial treatment should be started whenever the clinical picture of SBP is present, even in the absence of polymorphonuclear leucocytes in the ascitic fluid; whenever the number of polymorphonuclear leucocytes in the ascitic fluid is greater than $0.5 \times 10^9/\text{l}$, and the clinical picture is compatible with SBP – that is, unexplained fever, abdominal pain; and whenever the number of neutrophils is greater than $1 \times 10^9/\text{l}$, even in the absence of any evidence of SBP.¹² Because of the increased risk of nephrotoxicity in alcoholic patients with SBP,²⁰ some caution in the use of aminoglycosides may also be indicated in cystic fibrosis patients with SBP.

SBP in alcoholic cirrhosis is an ominous event with high in-hospital mortality.^{3,8} One report shows that only a few patients survive three years.⁷ A large series of patients with predominantly non-alcoholic cirrhosis, found SBP to be comparatively common (24%).¹⁰ The bacteriological results were similar to those of alcoholic cirrhosis, but the in-hospital mortality was lower: 48% of all the SBP cases, and 22% if the culture was positive but the neutrophil count was less than $0.25 \times 10^9/\text{l}$.

Both of our cystic fibrosis patients had biliary cirrhosis and hypersplenism requiring splenectomy. A shunt procedure was possible in the other six of eight patients who required splenectomy. Splenectomy without shunt may put cystic fibrosis patients at greater risk of SBP in the presence of ascites. Early diagnostic paracentesis and prompt antimicrobial treatment led to clearing of symptoms and signs in both patients. Based on clinical experience with patients with alcoholic cirrhosis and peritonitis, both of our patients were given prophylactic antimicrobial treatment and have survived 23 months and 10 months respectively without recurrence. The antimicrobial agent we chose (norfloxacin) is effective against *Staphylococcus aureus*, as well as common Gram negative organisms, including *P. aeruginosa*.

While peritonitis may recur in alcoholic

cirrhosis,⁸ there is no reported experience in cystic fibrosis. In the prospective, predominantly non-alcoholic cirrhosis series,¹⁰ morphological diagnosis was available in only 13% and there was no follow up information. Depending on the culture and white blood cell findings, these authors found a 50–75% inhospital survival, which they felt could be attributed to early treatment or less advanced peritonitis, or both.¹⁰ Depressed phagocytic activity, reduced serum complement concentrations, low opsonin activity in ascitic fluid, impaired leucocyte function^{21 22} and low concentrations of serum albumin (less than 30 g/l in all 23 patients with a reported albumin concentration)⁸ are reported in alcoholic cirrhosis. There is no comparable information available in cystic fibrosis except that albumin concentrations of 32 g/l or greater were noted in 9 of 14 cystic fibrosis patients with symptomatic hepatic disease.¹⁶ These results may reflect the differing pathophysiology in the two conditions and may have some influence on prognosis or indications, or both for liver transplant.

Conn and Fessel⁸ showed that ascitic cirrhotic patients seem to have as great a risk of infection after dental procedures as do patients with rheumatic valvular disease. They suggested that prophylactic antimicrobial treatment for dental procedures, colonic preparation for sigmoidoscopy or barium enema, and paracentesis might be indicated in these cirrhotic patients. Lacking definitive data and appreciating the high risk of recurrence, we have elected to use continuous prophylaxis instead. Furthermore, as our patients with SBP were the only cystic fibrosis patients (out of 1310 patients seen over 35 years) who had a splenectomy without a shunting procedure, it may be reasonable to use prophylactic antimicrobials on all such patients who develop ascites.

In summary, we report two cystic fibrosis patients with cirrhosis who had a splenectomy who developed SBP complicating ascites. Prompt treatment and subsequent antimicrobial prophylaxis was successful and both have survived 23 and 10 months respectively without recurrence. Bacterial peritonitis is a potentially fatal complication of ascites in cirrhotic cystic fibrosis patients. Early diagnosis and intravenous antimicrobial intervention may be as

important to short term survival and longterm outcome in cirrhotic cystic fibrosis patients as they are in alcoholic cirrhosis.

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