The patient with end-stage renal failure and ascites

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Case history

A 67-year-old man with chronic renal transplant insufficiency due to recurrent nephrolithiasis and was transferred to maintenance haemodialysis before he received successive cadaveric renal transplantation in November 1984. In February 1990 transurethreal prostatectomy was performed when graft function was still good. In February 1994 onset of nephrotic syndrome with urinary protein excretion of 10 g/day led to renal transplant biopsy, which showed chronic graft failure due to immune-complex-mediated glomerulonephritis. At the time of biopsy the serum creatinine was 3.0 mg/dl and serum samples revealed antibody titres to nuclear antigen of 1:320 and hepatitis C antibodies respectively. Since hepatitis-C-associated lupus nephritis was suspected, immunosuppression with prednisolone, cyclosporin and azathioprine was switched to triple therapy with cyclophosphamide instead of azathioprine. In May 1995 the patient developed an acute increase in serum creatinine which was primarily treated with pulse steroids and antiviral cytomegalovirus drug therapy. During the following months the patient’s serum creatinine progressively increased from 4.7 to 5.6 mg/dl.

In January 1996 the patient was readmitted to the hospital with severe abdominal distension, diffuse abdominal pain and a sensation of fullness and bloating. He has lost appetite and body-weight decreased by 2.5 kg in the course of a month. There was no history of tuberculosis and the patient denied increased alcoholic intake or a change in bowel habits. Physical examination revealed a pale man in reduced general condition weighing 57 kg, height 162 cm, temperature of 38.8 °C, heart rate of 104/min, blood pressure of 160/100 mmHg, respiratory rate of 16/min and a tensely distended abdomen with tightly stretched abdominal skin, bulging flanks and everted umbilicus. Physical examination indicated the presence of peritoneal fluid. Bowel sounds were unremarkable; pedal oedema were not detectable. Cardiac examination revealed a systolic murmur; chest and neurological examinations were normal.

Current medication included prednisolone (5 mg/day), cyclosporin (100 mg/day), cyclophosphamide (50 mg/day), minoxidil (5 mg twice daily), fosinopril (10 mg twice daily), nifedipine (20 mg twice daily), ranitidine (150 mg twice daily), isosorbide dinitrate (40 mg twice daily), acetylsalicylic acid (50 mg daily), benzbramolone (100 mg daily), oral iron (35 mg daily) and L-lactate (28 mmol/day).

Plain X-ray of the abdomen was unremarkable. Abdominal ultrasonography confirmed large amounts of ascitic fluid (Figure 1), a moderately increased liver size with normal echo-texture, small kidneys with nephrocalcinosis, but otherwise no intra-abdominal or retroperitoneal abnormalities. The computerized tomography was in accordance with the ultrasound examination; particularly, there was no evidence for any peritoneal abnormalities. Chest X-ray revealed a small right-sided pleural effusion. Left ventricular hypertrophy was present on the electrocardiogram.

Laboratory data revealed anaemia (haemoglobin 9.8 g/dl, haematocrit 28.5%, reticulocytes 0.6%), white blood cell count 5800/mm³ (neutrophils 79.1%, lymphocytes 7.4%, monocytes 9.7%, eosinophils 2.7%,

Fig. 1. Ultrasonography of ascitic fluid accumulation with bowel loops.
The patient with end-stage renal failure and ascites had 1.1% basophils and mild thrombocytopenia (platelets 122,000/mm³). Abnormal blood chemistry included elevated serum creatinine (5.6 mg/dl), blood urea nitrogen (67 mg/dl), uric acid (10.6 mg/dl), lipase (286 U/l), γ-GT (33 U/l) and cholinesterase (1.4 kU/l); electrolytes, total serum protein, albumin, LDH, amylase, other liver function tests, and clotting were normal. Fibrinogen was increased with 524 mg/dl (normal range 200–400) and C-reactive protein concentration was elevated at 4.2 mg/dl (normal range <1.0).

Serum antibody titres were positive for nuclear antigen (1:20) and negative for double-stranded DNA, neutrophilic cytoplasmatic antigen, glomerular basement membrane antigen and cryoglobulins. Hepatitis A and C antibodies were positive, with negative hepatitis B serology. Serological test for cytomegalovirus, varicella zoster, herpes simplex virus, Epstein–Barr virus, human immunodeficiency virus, parvovirus, rotavirus, and adenovirus did not indicate viral infection. Repeated blood samples for bacterial and fungal cultures were all negative, as was acid-fast stain. Serum tumour marker assays were abnormal for CA 19–9 with 84 kU/l (normal range <37) and for CA 125 with 710 kU/l (normal range <35), whereas carcino-embryonic antigen, α-fetoprotein, human chorionic gonadotropin, neuron-specific enolase, and prostate-specific antigen were within normal ranges. Serum iPTH was 67 pg/ml (normal upper limit 60), serum iron level was reduced to 46 μg/dl as was transferrin saturation with <12%, serum ferritin level and thyroid function test were normal.

Urinalysis showed mild proteinuria (1.2 g/24 h), 10–25 red blood cells and polymorphonuclear lymphocytes per high-power field, few bacteria, and no casts. Urinary culture was sterile. Stool was negative for occult blood and cultures were negative for Salmonella, Shigella, Yersinia, Campylobacter, Escherichia coli, Enterobacter and Candida. Diagnostic paracentesis showed yellow clear ascitic fluid, white blood count 2300/mm³ with predominantly lymphocytes and no red blood cells. Total protein content was 3.2 g/dl, albumin 2.0 g/dl, LDH 164 U/l and amylase 36 U/l. The serum-ascites albumin gradient was 2.0 g/dl. Culture test of the fluid was sterile for bacteria, fungi and acid-fast bacilli. CA 125 was highly elevated in the ascitic fluid (1358 kU/l) but cytological examination disclosed no malignant cells. Transoesophageal echocardiography revealed pronounced left-ventricular hypertrophy but overall preserved left-ventricular function and minor aortic-valve sclerosis. Upper gastrointestinal endoscopy showed moderate erosive gastritis, but no ulceration or varices.

The patient was primarily managed with intravenous antibiotic drug therapy which was switched from ciprofloxacin to cefotaxime and netilmicin because he presented with recurrent episodes of fever and progressively increasing inflammatory parameters (leukocytes 18300/mm³, C-reactive protein 19.3 mg/dl). In order to reduce the physically discomfort a therapeutic paracentesis was performed, removing 2400 ml of clear yellow fluid. Ascitic fluid analysis was identical to the previous one, but this time numerous acid-fast bacilli together with giant cells of Langhans type established mycobacterial infection (Figure 2a–c). When antituberculosis therapy with isoniazid, rifampicin and ethambutol was initiated the patient was put on regular

Fig. 2 a–c. a Mixed inflammatory infiltrate with acid-fast bacilli; Ziehl–Neelsen stain (magnification ×1000); b Mixed inflammatory infiltrate with acid-fast bacilli; Ziehl–Neelsen stain (magnification ×600); c Typical giant cell of Langhans type; methylene blue stain (magnification ×700).
haemodialysis. Subsequently immunosuppression was reduced and finally eliminated. Additional diuretic drug therapy with frusemide was administered in a dosage of 80 mg twice daily. After 3 weeks of antituberculosis therapy the patient had improved, with resolution of ascites, and was discharged in good condition for regular haemodialysis therapy.

Comments

Ascites develops in a small proportion of patients with renal failure, usually, but not always, after they have started haemodialysis. The evaluation of a patient with ascites must aim at establishing the cause of the ascites (Table 1).

Dialysis-associated ascites

The association of renal failure and ascites was first described by Clinque and Letteri in 1970 [1] and was later reviewed in several papers [2–4]. The reported incidence varies between 0.7 and 26%, with a wide age range between 11 and 71 years (mean 42 years) and a male but no race predilection (for review see [3,4]). The condition may be less common today as dialysis techniques have improved. Such ascites may occur even before initiation of haemodialysis treatment. The aetiology is still uncertain. The pathogenesis seems to be multifactorial:

1. Chronic fluid overload with hepatic congestion resulting in increased hepatic vein hydrostatic pressure is usual (for review see [3,4]). As volume overload occurs commonly among patients receiving dialysis, while development of intractable ascites is rare, how can we distinguish between these two entities? Aggressive fluid management, including fluid restriction, intensive haemodialysis, and isolated ultrafiltration is usually associated with resolution of extraperitoneal fluid overload (i.e. pedal oedema and pulmonary oedema) without relief of ascites in the specific case of dialysis-associated ascites. Thus overhydration alone cannot account for ascites formation.

2. Changes in the permeability of the peritoneal membrane have been shown in patients receiving continuous ambulatory peritoneal dialysis (CAPD) [5] or after repeated episodes of peritonitis [6]. Peritoneal permeability is generally altered in uraemic patients compared to non-uraemic patients [7]. Such ascites has also been reported in patients who had never received haemodialysis or CAPD [2,8,9]. Apart from uraemic toxins or immune complexes, activation of the renin–angiotensin system, altered peritoneal sodium transport due to exposure to dialysis solution and iron overload of mesangial cells have been discussed in its pathogenesis (for review see [3,4]).

3. Impaired lymphatic peritoneal resorption was proposed as a pathogenic mechanism and confirmed by lymphatic flow rate studies [10]. The fact that the rate of removal is much slower in uraemic patients compared to non-uraemic subjects and increases after successful renal transplantation, suggests an effect of uraemia on lymphatic drainage.

4. Contributing causes may include hypoproteinaemia, secondary hyperparathyroidism, congestive heart failure, constrictive pericarditis, pancreatitis, or liver cirrhosis with portal hypertension [3].

The onset of ascites in a patient with chronic renal failure requires thorough evaluation as the diagnosis of dialysis-associated ascites is established only by exclusion. Typical physical signs are increased abdominal girth due to ascitic fluid combined with minimal pedal oedema, anorexia, and cachexia. Haemodialysis-associated hypotension is common. Paracentesis should include measurements of complete blood cell count and differential, total protein and albumin level with serum-ascites gradient, LDH, amylase, urea and creatinine, along with Gram stain, cultures for bacteria, fungi and acid-fast bacilli, and cytology. Diagnostic criteria for dialysis-associated ascites are usually a straw coloured appearance and a high protein content (protein concentration >2.5 g/dl, serum–ascites albumin gradient <0.9 g/dl). Some diagnostic possibilities can be rapidly eliminated with the results of a thoroughly performed examination of the ascitic fluid (i.e. spontaneous bacterial peritonitis, pancreatic ascites, and chylous ascites).

Depending on the clinical setting and physical examination, consideration should be given to further investigations such as echocardiography, abdominal computed tomography, magnetic resonance imaging, or invasive vascular studies to exclude pericardial effusion as well as vena cava inferior obstruction due to lymphoma, hepatic cysts, or Budd–Chiari syndrome. Furthermore, thyroid function tests, iron studies, and

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serum iPTH level are useful to exclude ascites due to myxoedema, haemosiderosis, or secondary hyperparathyroidism. Mauk et al. [8] believed that additional peritoneoscopy is useful to evaluate patients with suspected dialysis-associated ascites. Thus, normal findings from a laparoscopic examination eliminate various possibilities, whereas abnormal findings lead to a specific diagnosis, e.g. tuberculosis or cirrhosis in this series. Histological examination of the peritoneum often reveals chronic inflammation and mesothelial-cell proliferation with variable degrees of fibrosis [2,5,8,10]. However, microscopic examination may also be normal.

Dialysis-associated ascites carries a grave prognosis. Reported survival ranges between 7.0 and 10.7 months [2–4,8]. Forty-four per cent of the patients die within 15 months and one-third develop severe cachexia [8].

What are the therapeutic options? Salt and fluid restriction is recommended. Vigorous haemodialysis with ultrafiltration, isolated ultrafiltration, and intravenous albumin infusions can obviously control ascites formation, but hypovolaemia with severe hypotension may become the limiting factor [2,10]. Peritoneovenous shunt placement and renal transplantation have been reported to control ascites formation. It has been claimed that the placement of either a Denver or LeVeen peritoneovenous shunt improves ascites formation, haemodynamic stability during haemodialysis, nutritional status, and life quality respectively [9]. Yet the decision should not be taken lightly because of the high risk for shunt complications (over one-half with shunt occlusion, catheter dislocation, and infection).

Peritoneal dialysis has been shown to resolve such ascites [2,3,10] by reducing intraperitoneal fluid protein concentration which draws fluid into the peritoneal cavity by oncotic forces [5]. Therefore peritoneal dialysis should be recommended in a patient with end-stage renal disease and therapy resistant ascites. The most effective treatment so far is kidney transplantation. Almost all reported cases had complete resolution of the ascites within 2–6 weeks. For unknown reasons recurrence of the ascites often occurs at the time of graft failure or any time thereafter. There are even two reports in the literature that ascites recurred despite good graft function (for review see [3,4]).

Successful treatment of ascites in a haemodialysis patient with ACE-inhibitors was reported by Roy-Chaudhury and Edward [11]. As possible mechanisms by which ACE-inhibitors may effect ascites formation the authors suggested improvement of occult myocardial dysfunction or, more speculatively, a possible anti-proliferative effect on the mesothelial lining of the peritoneum, thus reducing fluid secretion.

**Pancreatitis**

Acute ascites may occur during acute pancreatitis, a complication which is not uncommon in patients with renal failure and for unexplained reasons specially in those treated with peritoneal dialysis. The low pH of dialysis solutions and the presence of infectious peritonitis may be predisposing factors [12]. Secondary hyperparathyroidism, atherosclerosis, hyperlipidaemia, and hypercalcaemia have been considered to play an additional role [12–14]. However, pancreatitis can also be induced by virus infections. Studies have shown that in uraemia the prevalence of structural and functional pancreatic disorders other than pancreatitis is high, e.g. fibrosis, fatty infiltration, haemosiderosis, and disturbed pancreatic exocrine function [13]. It is of note that clinical signs and symptoms of pancreatitis may be similar to those of peritonitis and that both entities frequently coexist in patients on peritoneal dialysis [14,15]. Increased serum amylase and lipase levels are a common finding in patients with ESRD even in the absence of pancreatitis, making these biochemical markers of pancreatitis useful only when they are markedly elevated [12,14–16].

Abdominal computerized tomography is considered as the method of choice to confirm diagnosis of pancreatitis, showing pancreatic oedema, inflammatory mass, or extrapancreatic fluid collections. Ascitic fluid is usually turbid, haemorrhagic, or even chyloous. Analysis will often reveal a protein concentration >2.5 g/dl, increased amylase and variable white and red blood cell counts. Treatment include discontinuation of oral alimentation and initiation of parenteral nutrition. Peritoneal dialysis should temporarily be converted to haemodialysis. Our patient, however, did not show any evidence of pancreatitis.

**Malignancy-related ascites**

Malignancy-related ascites has to be considered at any time a patient develops intra-abdominal fluid accumulation. Overall, analysis of ascitic fluid samples will show malignant ascites in about 10% of patients, whereas peritoneal carcinomatosis will be detected in approximately 5% [17,18]. Malignancies that originate in or metastasize to the abdomen can cause ascites by various mechanisms: (1) Peritoneal carcinomatosis, (2) portal hypertension due to hepatocellular carcinoma or to massive liver metastases originating from extrahepatic tumours, (3) combination of peritoneal carcinomatosis and liver metastases, (4) malignant lymph node obstruction (5) Budd–Chiari syndrome from tumour occluding the hepatic veins [17].

Patients suspected of having malignancy-related ascites should have their ascites tested for total protein, albumin concentration, cell count, and cytology. Ascitic fluid cytology is positive only when malignant tumour cells line the peritoneal cavity and slough off into the peritoneal fluid. This happens only in the setting of peritoneal carcinomatosis, and thus sensitivity of ascitic cytology is almost 100% in this condition [17]. However, cytology does not detect all patients with malignancy-related ascites because not all patients with malignancy-related ascites have peritoneal carcinomatosis. Malignancy in the liver, hepatic veins, or lymph nodes does not lead to a positive cytology. About two-thirds of patients with cancer and ascites will have peritoneal carcinomatosis; therefore ascitic
cytology will be positive in about 66% of these patients, provided that cytology is processed optimally [17]. The utility of 'humoral tests of malignancy' in ascitic fluid (i.e. cholesterol and fibrinectin) is disputed. Screening tests, i.e. tumour markers, are not specific and may be more confusing than helpful [18,19]. Particularly, CA 125 is elevated in almost all ascitic fluid samples, regardless of the cause of ascites (for review see [18]). This might be due to chronic mesothelial-cell activation. Serum α-fetoprotein (AFP) may be helpful if hepatocellular carcinoma is suspected, but the test is neither specific nor sensitive (53% with a cut-off of 200 ng/ml) (for review see [18]). Gross appearance of malignant ascites may be straw-coloured, haemorrhagic (10%), mucinous, or chylous. White blood cell count of the fluid may be elevated (>1000/mm³), causing confusion with spontaneous bacterial peritonitis [20]. Because of the predominance of lymphocytes in the differential, tuberculous peritonitis has to be considered in differential diagnosis, particularly in patients who have high protein, low albumin-gradient ascites and a negative ascitic fluid cytology [17]. In this condition a larger-volume paracentesis for cytological analysis and culture for tuberculosis should be performed.

The ascitic fluid analysis of malignancy-related ascites is further complicated by the presence of cirrhosis and portal hypertension in some patients; Runyon et al. [17] reported an incidence of 11%. Total protein content of malignant ascites is usually >2.5 g/dl. However, the protein concentration of ascitic fluid is almost completely determined by serum protein concentration (direct relationship) and portal pressure (inverse relationship). The serum-ascites albumin gradient has been reported to correlate with portal pressure such that patients with normal portal pressure have a gradient <1.1 g/dl and patients with portal hypertension have a gradient >1.1 g/dl [21]. Ascitic fluid that is of a 'mixed' nature, i.e. portal-hypertension-related ascites with superimposed peritoneal carcinomatosis or tuberculosis, has been reported to retain a serum-ascites albumin gradient >1.1 g/dl, similar to portal hypertension-related ascites that is not associated with a superimposed condition [17]. Finally serum alkaline phosphatase was found to discriminate perfectly between subgroups of malignant ascites patients and separated patients with massive liver metastases from those without [17]. In the uraemic patient, however, secondary hyperparathyroidism is common, thus making the test non-specific.

Treatment options depend on the underlying malignant disease on one side and on the patient's condition on the other. In general the possibilities of curative therapy and prevention are limited. Therefore optimal conservative management is indicated instead of useless chemotherapies or radiation therapies. Priority should be given to relief of symptoms using large-volume paracentesis and appropriate analgesics supported by additional parenteral nutrition and psychological assistance. No evidence for any malignoma was found in our patient.

**Cirrhotic ascites**

Since patients with chronic renal failure are at a high risk of acquiring viral hepatitis as a complication of haemodialysis, renal transplantation, and blood transfusions, one must take into account the high prevalence of chronic liver disease in the uraemic patient with ascites. Predisposing factors include the defective immune system favouring chronic antigenic carrier state for type B hepatitis, hepatitis C, and other viral infections, and iron accumulation and drug toxicity.

In advanced cirrhosis ascites is a common finding. In the pathogenesis of cirrhotic ascites formation, traditionally, the initiating factor was thought to be either primary retention ('overflow') or decrement in effective arterial volume ('underfilling') [22,23]. A third theory emphasizes mismatch between the increased volume capacitance of the circulation and the blood volume, which is not decreased absolutely but is low in relation to such capacitance [24]. Portal hypertension is the initial trigger, but multiple factors further contribute to ascites formation. (1) Portal hypertension raises hydrostatic pressure within the splanchic capillary bed. In hepatic cirrhosis, as well as in Budd–Chiari syndrome, veno-occlusive disease or thrombosis of the inferior vena cava and intrahepatic obstruction of the hepatic venous outflow alters the hydrostatic forces regulating fluid exchange in the liver sinusoids. (2) Hepatic lymph formation increases from normal value of 1 litre/day to as much as 10 litres/day. This rate exceeds the capacity of lymphatic return, with consequent development of ascites. (3) Decreased plasma oncotic pressure due to hypoalbuminaemia favours the extravasation of fluid from plasma to the peritoneal cavity. (4) If renal function is still preserved, increased sodium reabsorption due to secondary hyperaldosteronism and renal vasoconstriction may contribute. Several lines of evidence indicate that the reduction of effective arterial blood volume that accompanies peripheral arterial vasodilatation initiates sodium and water retention through baroreceptor-mediated activation of the renin–angiotensin–aldosterone, sympathoadrenal, and arginine–vasopressin system.

The clinical presentation of a patient with advanced liver cirrhosis and ascites is characteristic for the most part. Medical history, laboratory assays, ultrasonography, ascitic fluid examination, computed tomography, and on occasion measurement of a wedge hepatic venous pressure, or finally liver biopsy confirm the diagnosis of cirrhosis. Even in the presence of an obvious cause (i.e. chronic hepatitis) a thorough evaluation of the patient with ascites is necessary to avoid missing a process such as occult hepatoma, carcinoma peritonei, peritonitis, dialysis-associated ascites, or even tuberculosis. Laboratory, bacteriological and cytological examinations of the ascitic fluid are again helpful measures for diagnosis and differential diagnosis. Sterile cirrhotic ascites is usually straw-coloured or bile-stained. For the most part red blood cell count reveals <10 000 cells/mm³ and white blood cell count <250 cells/mm³. Ascitic fluid protein concentration is
The patient with end-stage renal failure and ascites

highly variable because serum protein and portal pressure vary considerably in this setting, bacteriology and cytology are negative. A recent study of Gupta et al. [25] showed that both serum–ascites protein gradient <0.5 g/dl and ascitic fluid cholesterol <55 mg/dl had 94% diagnostic accuracy for differentiating cirrhotic from malignant and tuberculous ascites.

Treatment of ascites in patients with cirrhosis [26] is based on the combination of sodium and water restriction and administration of diuretics, which are also commonly used in advanced renal insufficiency. Treatment with spironolactone, the mainstay of diuretic therapy for ascites, is contraindicated in ESRD. The proportion of cirrhotic patients who become resistant or even refractory to diuretics is 10–20% [27]. It is conceivable that the proportion of non-responders is higher when ESRD is present. Management of refractory ascites includes peritoneovenous shunting, paracentesis, and dialytic ascitic ultrafiltration. Repeated large-volume paracentesis (4–6 litres/day) or even complete mobilization of ascites in only one tap associated with i.v. albumin infusions (6–8 g/l of ascitic fluid removed) are effective and safe in eliminating refractory ascites. This provides an alternative to peritoneovenous shunting, which has a high rate of serious complications [28]. Extracorporeal dialysis of ascites, so-called dialytic ascitic ultrafiltration, is a simple procedure that can be used as an alternative measure in the treatment of massive ascites in cirrhotic patients as well as in patients with combined hepatic and renal failure [29]. If renal replacement therapy has to be started, patients with ascites may benefit from peritoneal dialysis, with the advantage of more effective mobilization of ascites accumulation and haemodynamic stability compared to haemodialysis. We have had no evidence for liver cirrhosis in our patient.

**Spontaneous bacterial peritonitis**

The uraemic patient is more susceptible to infections [30]. Thus ascites due to peritonitis is not an uncommon finding in end-stage renal disease. Spontaneous bacterial peritonitis (SBP) is recognized as a common complication of cirrhotic patients with ascites. Since the threshold for performing diagnostic paracentesis has increased, the overall prevalence of SBP has been documented in 10–27% of patients with ascites, particularly alcoholic cirrhosis (for review see [31]). However, SBP has also been reported in haemodialysis patients without ascites. Pre-existing intra-abdominal fluid may be a prerequisite for the development of SBP [32].

The pathogenesis is elusive. SBP is thought to result from spontaneous bacteraemia with seeding of a 'susceptible ascites' in the absence of any obvious intra-abdominal source for this infection. Susceptible ascites is defined as low-protein-concentration ascites (<1.0 g/dl) with deficient ascitic fluid opsonic activity (i.e. endogenous antimicrobial activity) and which is usually associated with portal hypertension and childhood nephrotic syndrome [33,34]. Conversely, high-protein-concentration ascitic fluid seen in malignant and cardiac ascites is typically resistant to the development of SBP. It appears that the decreased ability to kill bacteria in low-protein ascites predisposes the ascitic fluid to infection. Uraemia and chronic liver disease are associated with defects in host defence [30,35,36], therefore frequent and prolonged bacteraemia would be expected. Clinically the severity of SBP may range from asymptomatic to fulminant and should be considered whenever unexplained fever, onset of abdominal symptoms, and/or unexplained leukocytosis are present.

A major problem in the diagnosis of SBP are the frequently observed negative culture tests of ascites with high neutrophil counts (>500 cells/mm³). Negative cultures may reflect lack in sensitivity of certain culture methods or may reflect resolution of SBP by host defences, but with persistence of elevated ascitic fluid neutrophil count. Optimal culture methods are necessary. The insensitivity of conventional culture techniques with only 35–65% of successful bacterial isolation from neutrophilic ascites has been markedly improved to around 90% positive cultures by directly inoculating 10 ml of ascitic fluid in routine blood culture bottles at the bedside at the time of paracentesis [37].

A variant of SBP is monomicrobial non-neutrocytic bacterascites, in which the ascitic fluid yields growth of bacteria (pure growth of a single type of organism), but the ascitic fluid neutrophil count is less than 250 cells/mm³ [31,38]. More than one-third of these episodes will progress to SBP, presenting with signs and symptoms of infection [38]. Prior to antibiotic therapy additional blood and urine cultures should be obtained in all patients suspected of having SBP. In approximately 33% of patients blood cultures are positive. Neutrophil count, culture, and their response to treatment help to distinguish SBP from secondary peritonitis, which necessitates further work up and imaging procedures.

Typical is the colonization by one single organism, predominantly of enteric origin (90%) and particularly of aerobic Gram-negative bacilli. The most commonly identified micro-organisms are *Escherichia coli* (43%), various *Streptococci* (26%) and *Klebsiella pneumoniae* (8%) (for review see [31]). Polymicrobial infection is unusual (10%) in SBP, in contrast to peritonitis after perforation.

All patients with SBP, culture-negative neutrocytic ascites, or symptomatic bacterascites should be treated aggressively with parenteral antibiotic drug therapy. Cefotaxime, a third-generation cephalosporin, has been shown to be more efficacious than the previously recommended combination of ampicillin and aminoglycosides [39]. Since cefotaxime has a broad spectrum of action (Gram-positive and Gram-negative aerobes as well as many anaerobes) it is effective in approximately 85% of SBP with fewer side-effects, lower incidence of superinfection, and low nephrotoxicity. Alternatively amoxicillin-clavulanic acid is effective as first-line therapy, achieving a cure rate of 85% [40].
When antibiotics are started the ascitic fluid becomes rapidly sterile and neutrophil counts decrease below 250 cells/mm³. In that case therapy over a period of 5 days is safe and nowadays recommended [41]. If ascitic fluid neutrophil counts increase or cultures remain positive despite chemotherapy, either resistance or secondary peritonitis should be suspected. The antibiotic has to be changed and if perforation is suspected evaluation must be performed promptly, since prognosis is very poor without surgical intervention.

Early diagnosis and treatment will help to decrease the very high mortality of SBP, which ranges between 30 and 78% (for review see [31]). One must be aware of the high recurrence rate of SBP (69% at 1 year), with a frequently fatal outcome (31%). Thus every effort should be made to prevent recurrent infection in patients who survived the first episode. Since low-protein ascites is associated with a high rate of recurrence, increased diuresis has been shown to elevate ascitic fluid protein concentration twofold and opsonic activity 10-fold. This may help to prevent recurrence [38]. This approach is obviously only feasible in patients with adequate diuresis.

**Tuberculous peritonitis**

Garcia-Leoni *et al.* [42] analysed incidence and clinical characteristics of mycobacteriosis in renal patients. Twenty-two new cases of tuberculosis were detected among 525 patients studied. The estimated overall annual incidence of tuberculosis in these patients was approximately eight times higher than the national annual incidence in Spain. Tuberculous peritonitis, the most common form of abdominal tuberculosis, is relatively infrequent, but cases continue to occur in certain patient populations (0.5–1% of all cases of tuberculosis) [43]. Tuberculous peritonitis has also been reported in peritoneal dialysis patients, masquerading as bacterial peritonitis unresponsive to routine antibiotics and diagnosed by culture [44]. Overall ascitic fluid specimens will reveal tuberculosis in <2% [21]. Its diagnosis is complicated because of insidious clinical symptoms. Since antituberculous chemotherapy is highly effective early diagnosis is mandatory.

Tuberculous peritonitis most commonly derives from reactivation of latent tuberculous foci in the peritoneum resulting from haematogenous spread. The original primary focus in the lung can heal and may no longer be radiographically apparent. The next most common cause is haematogenous spread from active pulmonary or miliary tuberculosis. As the disease progresses, the visceral and parietal peritoneum become increasingly studded with tubercles. Tuberculous peritonitis manifests itself in two ways. About 97% of the patients have the exudative or moist type with ascites, 3% of the patients represent the rare fibroadhesive form, with a plastic or dry type of tuberculous peritonitis resulting in the typical 'doughy' abdomen [45,46]. The commonest clinical feature is therefore abdominal swelling in about 82% of cases; fever is present in about 74%, weight loss in 62%, abdominal pain in 58%, and diarrhoea in 16% [45,46].

Tuberculous of the peritoneum can mimic a variety of other abdominal disorders and unless a high index of suspicion is maintained, the diagnosis can easily be missed or delayed. Mantoux testing is positive in about 70% of patients with tuberculous peritonitis [45] and chest X-ray was found to be abnormal in 40–50%, but active pulmonary tuberculosis was detected in 14% only [45,46]. Routine biochemical investigations are usually unhelpful in the diagnosis of tuberculous peritonitis. Laboratory data may reveal elevated white blood count (<15%), mild normochromic normocytic anaemia (60%), thrombocytosis and other findings of chronic inflammation. High serum levels of CA 125 should lead to consideration of tuberculous peritonitis in the differential diagnosis of a patient with ascites and increased tumour markers. The concentration decreases significantly after 1–2 months of tuberculous therapy [47]. However, CA 125 is raised in many other non-malignant conditions, suggesting that increased CA 125 is a non-specific marker of inflammation or trauma (for review see [47]). Analysis of the ascitic fluid, including cultures and cytology, help to establish the cause of the ascites. The diagnosis of tuberculous peritonitis is difficult because of the paucity of *Mycobacterium tuberculosis* in the peritoneal fluid. Fast-acid stain smear of ascites is positive in less than 3% and the frequency of positive bacteriological studies for *M. tuberculosis* varies between 20 and 83%, depending on the amount of ascites being cultured (20 ml versus 1 litre) and the use of ascitic fluid sedimentation respectively (for review see [43]). Besides, culture for *M. tuberculosis* requires up to 4–8 weeks. The fluid is usually straw coloured, and sometimes blood-stained. The ascites shows a high protein content (total protein >3.0 g/dl) with a serum-ascites albumin gradient <1.0 g/dl; red blood cells are commonly found in the ascitic fluid; white blood count is usually 150–4000/mm³ and consists predominantly of lymphocytes [46,48,49]. For unknown reasons tuberculous peritonitis in CAPD patients is sometimes associated with a neutrophilic rather than lymphocytic response [44].

Ultrasound examination and computerized tomography usually reveal non-specific findings. Laparoscopy and peritoneal biopsies will allow a presumptive diagnosis of tuberculous peritonitis in 85–95% of cases [45,46,49,50] and should be particularly considered in patients with unexplained ascites. Characteristic changes are thickened peritoneum with or without whitish to yellowish miliary tubercles studied over the peritoneum, and adhesions. With target biopsies caseating granulomas will be detected in about 85–90% of cases. Bowel perforation or intraperitoneal bleeding are usually rare complications.

A major recent advance in the diagnosis of tuberculous peritonitis is the measurement of adenosine deaminase activity (ADA) [51–54]. Increased ADA levels are the result of stimulation of T-lymphocytes in response to cell-mediated immunity to mycobacterial
antigens [54]. This chemical test performed on ascitic fluid appears to be a simple and accurate method for rapid diagnosis of tuberculous peritonitis. At a cut off value of > 30 U/l the test provides a high sensitivity (93%) and specificity (96%). A false negative ADA result was reported in patients with AIDS-related tuberculous peritonitis [51,52] and in those patients with low ascites protein concentration [52]. A false positive test can occur in patients with ascites due to malignancies [53]. Determination of ADA activity could potentially supersede invasive procedures and could, together with a good response to antituberculosis therapy, become an accepted approach to management. In a recently published study [51] high concentrations of γ-interferon (γ-IFN) in ascitic fluid were as valuable as the ADA activity in the diagnosis of tuberculous peritonitis. γ-IFN, secreted by antigen-triggered CD4+ lymphocytes, is a key lymphokine that activates macrophages, increasing their bactericidal activity against M. tuberculosis [55]. However, Ribera et al. [53] did not observe a significant correlation between ADA and γ-IFN levels in patients with tuberculous peritonitis; thus the value of γ-IFN needs further evaluation.

The preferred treatment of tuberculous peritonitis are the drug regimens used for treating pulmonary tuberculosis [43,56]. Three-drug antituberculous chemotherapy with isoniazid (INH), rifampicin, and ethambutol or pyrazinamide (first-line antituberculous drugs) should be started as soon as tuberculous peritonitis is suspected and until drug sensitivity tests become available. A commonly used regimen is to give the drugs daily for 9 months, either orally or in parenteral form if vomiting precludes oral therapy. In renal insufficiency dosage modification is not usually necessary for INH and rifampicin. The recommended dose of INH 300 mg/day should be only reduced to 150–200 mg/day in marked renal failure of slow acetylators or by one-half in hepatic failure. Metabolism of INH occurs initially by liver N-acetyltransferase, and diminished acetylation capacity is inherited as an autosomal recessive trait (prevalence rate between 5 and 83%). Rifampicin is recommended at a dosage of 600 mg/day. Only liver failure requires moderate dose reduction, but it is of note that the drug is removed by peritoneal dialysis. Ethambutol or pyrazinamide are indicated as companion drugs for susceptible infections due to M. tuberculosis. Dose reduction of ethambutol 15–25 mg/kg/day or pyrazinamide 20–35 mg/kg/day becomes necessary in significant renal failure because both drugs and their metabolites are predominately excreted by the kidneys. Also, pyrazinamide is dialysable, so that supplemental dosage may be advisable after dialysis sessions. Side-effects such as hepatotoxicity, optic and peripheral neuritis, hypersensitivity reactions, and drug interactions need careful monitoring of the patients, particularly regular ophthalmological examinations. Adjuvant corticosteroids have been claimed to prevent intestinal obstruction, but this is not widely recommended. Good nutrition plays also an important role.

If treatment is started early a high proportion of patients with tuberculous peritonitis will respond to medical therapy alone, showing resolution of ascites, weight gain, and improvement of well-being and life quality [57]. If appropriate treatment is delayed, the outcome still is occasionally tragic for this eminently curable disease [57]. Surgery is reserved for complications such as obstruction, perforation, abscess, or fistula [56,58]. We treated our patient with INH 200 mg/day, rifampicin 600 mg/day, and ethambutol 750 mg after each haemodialysis session three times a week.

In conclusion, we discuss a patient with end-stage renal disease suffering from tuberculous peritonitis. We emphasize the difficulties in diagnosis. Successful tuberculous therapy resulted in prompt disappearance of the ascites and clinical improvement of the patient.

References


