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DESCRIPTION OF THE NEPHROLOGY-HYPERTENSION TRAINING PROGRAM AT THE UNIVERSITY OF CALIFORNIA, SAN DIEGO SCHOOL OF MEDICINE

UCSD offers a 2- or 3-yr program in clinical nephrology-hypertension and research training in nephrology-hypertension. This program prepares physicians for careers in both academic and clinical nephrology. There are opportunities for research fellows without clinical training for both MDs and PhDs, and approximately 20 fellows are in the current nephrology-hypertension program. The program offers a balance between clinical training in a very active clinical teaching program and a variety of research opportunities and disciplines. Clinical rotations are supervised by 16 faculty members at UCSD Medical Center, the San Diego Veterans Affairs Medical Center, and the San Diego Naval Regional Medical Center. There are four clinical rotations, which include a rotation on the UCSD Transplant and Pheresis Program. Approximately 120 transplants are performed each year, and several hundred renal transplants are monitored. The Nephrology-Hypertension Consultation Service exposes each fellow to consult experiences in pancreas, liver, lung, and heart transplants as appropriate for these disciplines. There is also an active vigorous medical intensive care unit exposure during all of the rotations. The fellow has the primary responsibility for the care of transplant patients during the acute phase of treatment, and there exists a strong working relationship with the Transplant Surgery Division. More than 100 acute hemodialyses are performed each month at UCSD Medical Center. After clinical training, fellows are exposed to a broad range of laboratory experiences in a unique School of Medicine setting. With the exception of pharmacology, there are no basic science departments at the UCSD School of Medicine, and there is a vigorous interaction among basic scientists and clinical investigators. Within the division, there are laboratories actively engaged in the study of renal physiology and pathophysiology, biochemistry, cellular physiology and molecular medicine, renal and molecular cellular immunology, research and treatment modalities for acute and chronic renal failure, and programs on the clinical mechanisms of systemic hypertension as well as the genetics of hypertension. The School of Medicine provides an extensive training in laboratory methods in research for all research fellows, and there are extensive opportunities for collaboration with Cell and Molecular Medicine and the Department of Pharmacology. There are also extended research opportunities through two Institutional Physician/Scientist Training Grant Programs. Most of the faculty in the Division of Nephrology-Hypertension are actively involved in clinical and basic research activities, which span programs beyond the Division of Nephrology-Hypertension. Each of these laboratories is characterized by a high degree of fellow and faculty interaction. The University of California, San Diego, offers a broad, balanced program directed toward the preparation of individuals for academic careers and the provision of a broad base of scientific techniques that will prepare them for the decades ahead.

Nephrogenic Ascites: A Poorly Understood Syndrome¹

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ABSTRACT

Nephrogenic ascites is a condition characterized by the presence of massive ascites in a patient with ESRD. Neither the exact cause nor the pathogenesis of

ascites formation is clearly understood. Patients frequently present with hypertension, moderate to massive ascites, minimal extremity edema, cachexia, and a history of dialysis-associated hypotension. The ascitic fluid is typically an exudate. Although treatment options are limited, continuous ambulatory peritoneal dialysis, peritoneovenous shunt placement, and renal transplantation appear to be effective in controlling ascites formation. Nephrogenic ascites is associated with a grave prognosis, especially if treatment is not instituted. One patient with nephrogenic ascites is described here.

Key Words: Nephrogenic ascites, hemodialysis, peritoneal dialysis, peritoneovenous shunt, kidney transplant

Nephrogenic ascites is a syndrome of refractory ascites associated with ESRD. It is defined as clinically evident chronic ascites, occurring in pa-

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tients with ESRD without a clear cause (1). Its pathogenesis remains unknown, has limited treatment options, and is associated with a grave prognosis. We describe herein the characteristics and clinical course of a patient with nephrogenic ascites and review the pathophysiology and the available treatment options for this condition.

CASE REPORT

The patient, a 55-yr-old white man with ESRD secondary to Type 1 diabetes mellitus, was admitted with a 4-month history of increasing abdominal girth, cramping abdominal pain, watery stools, nausea, anorexia, and weight loss. He had been on hemodialysis for the past 18 months, and dialysis treatment was frequently complicated by hypotensive episodes requiring hypertonic saline or mannitol administration for blood pressure support. His dry weight was estimated at 59 to 60.3 kg.

His past medical history was notable for hypertension, below-the-right-knee amputation, peptic ulcer disease, coronary artery disease, hepatitis B, and colonic angiodysplasia. He denied alcohol or iv drug use.

Physical examination revealed a cachectic man in moderate distress with a blood pressure of 190/108 mm Hg, a pulse of 92 beats/min, and a temperature of 97.8°F; a II/VI systolic murmur at the left sternal border; a markedly distended abdomen with normoactive bowel sounds and massive ascites; liver size of about 10 cm; and 1+ left lower extremity edema. The remainder of the physical examination was unremarkable.

Laboratory examinations showed a hemoglobin of 11.0 g/L, a white blood cell count of 5,800/mm³, a normal platelet count, a blood urea nitrogen level of 16.8 mmol/L (47 mg/dL), a serum creatinine level of 570 μmol/L (6.5 mg/dL), a total protein level of 58 g/L (5.8 mg/dL), an albumin level of 29 g/L (2.9 mg/dL), a calcium level of 2.8 mmol/L (11.1 mg/dL), a phosphate level of 0.97 mmol/L (3.0 mg/dL), an aspartate aminotransferase level of 45 U/L, an alanine aminotransferase level of 44 U/L, and a lactic dehydrogenase (LDH) level of 228 U/L. A serum iron level was 7.0 μmol/L (39 μg/dL), iron-binding capacity was 41.0 μmol/L (229 μg/dL), and a ferritin level was 209 μg/L (209 ng/ml). The parathyroid hormone level was 708 ng/L (708 pg/mL). Coagulation studies, thyroid function tests, and serum sodium, potassium, chloride, and bicarbonate concentrations were all normal. A chest x-ray showed bibasilar atelectasis, and an abdominal film was unremarkable except for ascites. An electrocardiogram was unremarkable.

A diagnostic/therapeutic paracentesis was performed with the removal of 3 L of clear yellow fluid. Fluid analysis revealed a white blood cell count of 81/mm³ with 96% lymphocytes, a red blood cell count of 70/mm³, an LDH level of 105 U/L, a total protein level of 38 g/L (3.8 g/dL), an albumin level of 20 g/L

(2.0 g/dL) with a serum to ascites albumin gradient of 9 g/L (0.9 g/dL), and an amylase level of 24 U/L. Cultures for bacteria, fungus, and acid-fast bacilli and cytology were also all negative. An abdominal computed tomography showed ascites, good portal vein flow, no masses, and normal liver size with a homogeneous consistency. Skin tests demonstrated him to be anergic. Similar creatinine concentrations in both ascitic fluid and blood and a normal retrograde pyelogram ruled out urinary extravasation.

After a single episode of hematemesis, an upper gastrointestinal endoscopy was performed. Mild esophagitis was noted, but there were no varices or ulcerations.

A diagnostic laparoscopy showed a grossly cirrhotic liver. A liver biopsy revealed cirrhosis and chronic hepatitis. Peritoneal biopsies showed mesothelial cell hyperplasia, chronic inflammation, fibrin deposition, and fibrosis. Serum ceruloplasmin and α-1-antitrypsin levels were normal, and antinuclear and anti-smooth muscle antibodies were not detected. A hepatitis C serology was negative.

He continued to require frequent, large-volume paracentesis every 48 to 72 h for symptomatic relief. All subsequent ascitic fluid studies were essentially unchanged, with a serum to ascites albumin gradient of 5.0 to 8.0 g/L (0.5 to 0.8 g/dL). His hemodialysis sessions were notable, as before, for hypotension requiring hypertonic saline and mannitol for support and limited ultrafiltration.

Portal venous pressures were measured directly via the right common femoral vein with a 5 French Cobra catheter (Medi-tech, Watertown, MA) wedged in the right hepatic vein. Hepatic vein wedge pressure was 21 mm Hg, and free hepatic vein pressure was 15 mm Hg with a corrected sinusoidal pressure (portal venous pressure) of 6 mm Hg.

A Denver peritoneovenous shunt (Storz Instrument Co., St. Louis, MO) was placed, to improve ascites drainage, without complications. Ascites decreased with subsequent relief of his abdominal discomfort and dyspnea. He tolerated hemodialysis better without the need for hypertonic saline or mannitol. He remained stable and was discharged on hospital day 45 to a nursing facility. Despite good control of his ascites and better hemodynamic stability on hemodialysis, he continued to fail to thrive, with his dry weight decreasing to 47.9 kg over the following 3 months.

Four months later, the shunt became obstructed, resulting in rapid reaccumulation of his ascites. He again experienced hemodialysis-associated hypotension, and his dry weight was increased to 57.8 kg. An analysis of the ascitic fluid yielded results similar to those of previous studies. Repeat cultures were negative.

Urokinase administration failed to correct a malfunction in the outflow of the pumping chamber noted on an angiogram. Replacement of the shunt was delayed because of an infected diabetic ulcer on the

left foot that ultimately required a below-the-knee amputation.

His condition continued to deteriorate, and the patient subsequently died, 6 months after the initial diagnosis was made. An autopsy was not performed.

DISCUSSION

Incidence, Diagnosis, and Patient's Characteristics

Nephrogenic ascites has been known by several names such as nephrogenous ascites, hemodialysis-associated ascites, dialysis ascites, idiopathic ascites, or ascites associated with ESRD (1). Nephrogenic ascites is preferred, because the onset of ascites may occur before the initiation of dialysis (2).

Nephrogenic ascites is characterized by a marked center-to-center variability in incidence (0.7 to 20%), a wide age range of onset (11 to 71 yr; mean, 42 yr), and a male sex (male:female = 2:1), but no race predilection (white:black = 1:1) (1). Chronic ambulatory peritoneal dialysis preceded hemodialysis in 69% of the patients (1). Ascites accumulation can occur as early as 18 months before or as late as 69 months after the initiation of hemodialysis (1). Approximately 70% of reported cases in the past occurred in association with the glomerulonephritides and hypertensive renal disease (1,3). The high percentage of those conditions may be lower today because there are significantly more patients with diabetic nephropathy on hemodialysis today. Diagnostic criteria and recommended evaluation for patients with suspected nephrogenic ascites are outlined in Table 1.

Pathogenesis

The pathogenesis of ascites formation remains elusive. Several pathogenetic factors including elevated hepatic vein hydrostatic pressure, fluid retention, increased peritoneal membrane permeability, and impaired lymphatic drainage have been considered (Table 2).

An increase in hepatic outflow pressure secondary to liver disease could result in the accumulation of protein-rich fluid because an intact sinusoidal endothelium is highly permeable to albumin. The question arises whether ascites formation in the case under study was the result of chronic liver disease and portal hypertension. The relationship between portal pressure elevation and ascites formation and/or gastrointestinal bleeding from varices has been previously studied in 124 patients with chronic liver disease (4). Patients with evidence of either ascites or bleeding from varices had mean portal pressures of 16.6 ± 3.4 and 16.2 ± 3.0 mm Hg, respectively (4). On the other hand, patients without evidence of these complications had a mean pressure of 11.7 ± 3.0 mm Hg (4). Only 2 of 124 patients who had evidence of either ascites or gastrointestinal bleeding had portal pressures of less than 10 mm Hg (8 and 9 mm Hg, respectively) (4). Clearly, these complications of chronic liver disease are associated with portal pressures above 8 to 9 mm Hg (4). In comparison, the patient under study had marginally elevated portal pressure (6 mm Hg). Furthermore, the absence of varices on endoscopy and a serum-ascites albumin gradient repeatedly of less than 11 g/L (1.1 g/dL) (5) do not support the presence of a clinically significant degree of portal hypertension. All of the above findings

TABLE 1. Diagnostic criteria and recommended evaluation for nephrogenic ascites

Criteria	Recommended Evaluation
History/Physical Signs	History and physical examination
Increasing abdominal girth	General chemistries including BUN, creatinine, total protein, and albumin
Anorexia and early satiety	
Dialysis-associated hypotension	
Cachexia	
Massive ascites combined with minimal edema	
Ascitic Fluid Characteristics	Paracentesis for complete blood cell count with differential, total albumin, amylase, culture, cytology, urea, protein, and creatinine
Straw color	
White blood cell count of 25 to 1,600/mm ³	
Serum-ascites gradient <9 g/L (0.9 g/dL)	
Negative culture and cytologies	
No Evidence of:	
Portal hypertension	Thyroid function tests, iron studies, parathyroid hormone level, peritoneoscopy with liver/peritoneal biopsy, abdominal computed tomography/magnetic resonance imaging, portal venous pressure measurement
Cardiac/pericardial disease	
Peritoneal infection or malignancy	
Pancreatic pseudocyst	
Inferior vena cava obstruction	
Budd-Chiari syndrome	
Urinary extravasation	
Hypothyroidism	

TABLE 2. Possible pathogenetic processes of nephrogenic ascites

Elevated Hepatic Venous Hydrostatic Pressure
Volume Overload
Increased Peritoneal Membrane Permeability
Secondary to
Uremic toxins
Prior exposure to dialysis solutions
Renin-angiotensin activation
Circulating immune complexes
Hemosiderosis
Impaired Lymphatic Drainage

as well as the exudative nature of the patient's ascites, in contrast to the transudative nature of cirrhotic ascites (6), and normal liver function tests argue against cirrhosis as the basis of this patient's ascites formation.

Fluid retention has been observed in two-thirds of reported cases in one review (1). However, the role of fluid retention and ascites formation is not clearly defined because dialysis patients frequently display signs of fluid overload without notable ascites. Thus, fluid retention *per se* seen in patients with nephrogenic ascites is unlikely to account solely for ascites formation.

Changes in peritoneal membrane permeability due to uremic toxins (1,7), exposure to dialysis solution (1), renin-angiotensin activation, circulating immune complexes (CIC) (8), or iron deposition (9) have also been implicated in ascites formation. Histologically, the peritoneum is grossly normal; microscopic examination can be normal (3,10,11) but more often shows chronic inflammation and mesothelial cell proliferation with variable degrees of fibrosis (1-3,11-13). Whether uremic serositis or exposure of the membrane to particulate matter or buffers contained in the dialysate contributes to these pathologic changes is unclear. Alteration in peritoneal sodium transport due to the dialysate may also contribute to ascites forma-

tion (7). A role for CIC in altering peritoneal permeability has been suggested by the decrease in ascites in some patients after continuous ambulatory peritoneal dialysis (CAPD), a dialytic modality known to efficiently remove CIC (12). Hemosiderosis was reported in four patients with nephrogenic ascites. Ascites decreased in response to iv deferoxamine and recombinant human erythropoietin therapy, suggesting a role for iron deposition-induced alteration in peritoneal permeability (9).

The rate of ascites removal in patients with nephrogenic ascites is much slower than in patients with ascites and normal kidney function, suggesting impaired lymphatic peritoneal drainage in this condition. Interestingly, ascites removal is enhanced after renal transplantation, suggesting a causative effect of uremia in impaired lymphatic drainage (6,7,14). Other possible contributing causes of ascites in patients with ESRD include hypoproteinemia, secondary hyperparathyroidism-induced serositis, congestive heart failure, constrictive pericarditis, pancreatitis, and liver cirrhosis with portal hypertension (1,2).

Clinical Course and Therapy

Nephrogenic ascites is associated with a grave prognosis. The average survival ranges from 7 to 10.7 months, with 44% dying within 15 months of diagnosis. Over one-third of patients develop cachexia (1,3), and most patients die with persistent ascites.

A variety of therapeutic modalities, both medical and surgical, have been used (Table 3). Fluid and salt restriction, intense hemodialysis with ultrafiltration, isolated ultrafiltration, albumin infusion, hyperalimentation, and repeated paracentesis should be initially undertaken to gain control of the ascites. Hemodialysis, however, may be limited, as seen in our patient, by the tendency of these patients to develop hypotension (1). Reinfusion of the ultrafiltered ascites fluid (15) and extracorporeal ascites dialysis (16) have been attempted in some patients with subsequent

TABLE 3. Therapeutic options for nephrogenic ascites

Modality	Advantage	Disadvantage
Fluid and Salt Restriction With Intensified Hemodialysis With Ultrafiltration and/or Albumin Infusion	Decreases ascites	Limited by hypovolemia and hypotension
Hyperalimentation	Improves nutrition	Not proven to reduce ascites
Repeated Paracentesis	Reduces symptoms	Excessive protein loss
Reinfusion of Ultrafiltered Ascites/Extracorporeal Ascites Dialysis	Conserves protein, reduces ascites, avoids dialysis-associated hypotension	Fever, peritoneal catheter malfunction
CAPD	Improved nutrition, reduces ascites	Self-limited early protein loss
Peritoneovenous Shunt	Reduces ascites, improves nutrition, prevents dialysis-associated hypotension	Shunt malfunction/infection
Kidney Transplant	Resolution of ascites	Recurrence after graft failure

improvement in hemodynamic stability, a reduction in ascites, and improvement in the quality of life as well.

The placement of either a Denver or LeVeen peritoneovenous shunt (Becton and Dickinson, Sunnyvale, CA), as in our patient, has been associated with a reduction, although palliative, in ascites formation and improvement in hemodynamic stability during hemodialysis (4,17-19). Objective improvements are also noted in the nutritional status with weight gain and subjective improvement in appetite and physical activities. Complications of shunt placement, seen in over one-half of the cases, include malfunction from occlusion or migration of the venous end out of the superior vena cava and infection. These complications require either minor revisions or removal of the shunt. Shunts remained functional for up to 18 months in one series (Denver) (17) and for more than 3 yr in another (LeVeen) (9). Thus, shunt placement should be seriously considered early in the treatment of such patients.

CAPD is also effective in the treatment of ascites (1,11,12,20,21). The combination of routine daily exchanges and control of fluid and salt intake allows control of the ascites. The patients subjectively feel better, with improved caloric and protein intake and subsequent weight gain. Within 6 months of continued treatment, the amount of total protein excretion in the dialysis effluent decreases from 26.5 to 50 to 7.8 to 9.44 g/day, with a subsequent rise in the serum protein and albumin levels and the resolution of ascites. CAPD may be beneficial in controlling ascites formation by reducing ip fluid protein concentration, which normally would osmotically draw fluid into the peritoneal cavity (13). Other treatments attempted with only partial success that are no longer recommended include the ip administration of steroids (1,2,21) and bilateral nephrectomy (1,3,19,20).

Of all of the therapeutic modalities, kidney transplantation appears to be the most effective in controlling ascites formation. Nearly all reported cases (22 out of 24 cases) had complete resolution of the ascites within 2 to 6 wk after transplantation, with a single case requiring 12 months for the complete resolution of ascites (1,6,7,10,11,18,20). Two patients, on the other hand, had a recurrence of ascites despite adequate renal graft function 2 yr (with creatinine of 1.6 mg/dL) (13) and 4 months (with a creatinine clearance of 52 mL/min) (8) after transplantation. Interestingly, ascites often recurs after the loss of graft function for whatever reason (1,19,20). The ascites can recur at the time of graft failure (20) or anytime thereafter for up to 3 yr (19,20).

In conclusion, nephrogenic ascites is a rare condition with a grave prognosis and an unknown but probably multifactorial cause. Although no prospective studies have been performed comparing various treatment modalities, on the basis of current data, CAPD, peritoneovenous shunt placement, and renal transplantation offer the best hope for an improvement in the quality of life and recovery.

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