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Nephrogenic Ascites: Our Experience and Mini-Review

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ABSTRACT

Nephrogenic ascites is an idiopathic cause of ascites developing in ESRD patients, especially in those on maintenance hemodialysis. A clear cause for the development of such ascites is not well understood and the pathogenesis remains elusive. The treatment options for the condition are also limited with a poorer prognosis. We report the experience at our centre, and describe the characteristics of 18 such patients. We also briefly review the presumed pathophysiological mechanisms and the possible therapeutic options for the condition.

KEYWORDS Nephrogenic ascites, Dialysis ascites, ESRD

Introduction

A syndrome of refractory ascites has been to known to occur in patients with End Stage Renal Disease (ESRD) and is termed as 'Nephrogenic ascites' or 'Nephrogenous ascites' or 'Dialysis ascites'. A clear cause for its development is not well understood, [1] and the treatment options are also limited, and is associated with a poorer prognosis.

We describe the characteristics of 18 patients with nephrogenic ascites, evaluated at our centre, and also briefly review the underlying mechanisms and therapeutic options.

Patients and Methods

All patients on maintenance hemodialysis presenting with ascites, between 2010-2016 were evaluated, and 18 patients were diagnosed with nephrogenic ascites. The diagnosis of nephrogenic ascites was made in patients with ESRD on maintenance hemodialysis, when other causes of ascites like infections, liver disorder, cardiac failure, malignancy, etc were excluded. The characteristics were compared with 20 age matched controls on maintenance hemodialysis.

After consent, blood was obtained from all patients and the investigations done included renal function tests, liver function tests, complete blood count, iPTH, prothrombin time and INR. They were also screened for Hepatitis B, HIV, and Hepatitis C infection. Ascitic fluid aspiration was done and sent for analysis, including the cell count, total protein, fluid albumin, Adenosine Deaminase, glucose, cytology and cultures (bacterial, fungal, and mycobacterial). TB Gene Xpert was also done on the ascitic fluid.

Results

Of a total of 18 patients, 9 (50%) were male and 9 (50%) were female. The mean age was 49.4 years (27-65 years). The etiology of ESRD was diabetic kidney disease in 6 (33.3%) patients, presumed chronic glomerulonephritis in 6 (33.3%) patients, and one 1 (5.5%) each due to hypertensive nephrosclerosis, Lupus nephritis, reflux nephropathy, IgA nephropathy, Focal segmental glomerulosclerosis and Autosomal Dominant Polycystic Kidney Disease. The mean duration of chronic kidney disease before the diagnosis of ascites was 40.33 months (11-80 months), were undergoing hemodialysis for a mean period of 30 months (11-50 months) before presentation (Table 1). None of the patients had undergone peritoneal dialysis.

On examination, 14 (77.7%) patients had moderate ascites, while 4 (22.2%) had tense ascites. The mean duration of ascites before diagnosis was 15 weeks (2.5-41 weeks). None of the patients had any clinical features suggestive of peritonitis or chronic liver disease.

The ascitic fluid was clear, straw coloured in all patients. The mean total ascitic fluid protein was 4.0g/dl (2.4-5.0 g/dl), with a mean albumin of 2.1 g/dl (1.4-2.6 g/dl). The SAAG (serum ascites albumin gradient) was 0.89 g/dl (0.4-1.8 g/dl). The mean leukocyte count in the ascitic fluid was 88/mm3 (34-220/mm3), with predominance of mononuclear cells all but four patients, who had neutrophilic predominance. The ascitic fluid was sent for bacterial, fungal and mycobacterial cultures, all of which were negative. Ascitic fluid cytology was found to be normal in all patients and TB Gene Xpert test was negative in all.

Serum bilirubin, prothrombin time, and INR were normal in all patients. Mild transaminitis was found in 2 patients, but there was no other evidence of liver disease, and subsequently returned to baseline. Serum albumin (mean 3.2 g/dl; range 2.7-4.4 g/dl) was found to be similar to the control patients (mean 3.1 g/dl; range 2.1-4.2 g/dl). Serum creatinine (mean 6.79 mg/dl; range 3.3-10.8 mg/dl) was also similar as controls (mean, 6.7 mg/dl; range, 4.1-12.4 mg/dl). Blood urea nitrogen (mean, 52.3 mg/dl; range, 25-81 mg/dl) was also similar to the control patients (mean, 53.4 mg/dl; range, 26-102 mg/dl).

Two (11.8%) patients were found to be HBsAg positive, but did not show any evidence of hepatitis or chronic liver disease. One (6%) patient was positive for Human immunodeficiency Virus (HIV), with CD4 count of 514, and no features of Acquired immunodeficiency syndrome (AIDS).

The mean haemoglobin was 8.50 g/dl (5.4-10.7 g/dl), with 2 requiring blood transfusions, and the all except one being continued on erythropoietin therapy. The mean iPTH levels were 218.2 pg/ml (18.6-431.1 pg/ml), with 6 (35%) patients having a low turnover bone disease. The mean levels of serum calcium (8.86mg/dl), phosphorous (4.61mg/dl) and uric acid (5.16mg/dl) were also within normal limits (Table 2). Two patients has hypothyroidism, with one having serum TSH >150 uIU/ml, while the other had a serum TSH of 27.49 uIU/ml.

16 patients were on twice a week hemodialysis at the time of presentation, and 2 on once a week hemodialysis. In 4 patients, hemodialysis was intensified to thrice weekly with resolution of ascites in 3 patients over a mean period of 32 days (range, 28-36 d). One patient underwent a deceased donor renal transplant followed by resolution of ascites. One was converted to chronic ambulatory peritoneal dialysis, but the ascites persisted. Nine (50%) patients persist to have refractory ascites, and 2 were lost to follow up.

Discussion:

Nephrogenic ascites, also known by several terms, including nephrogenous ascites, idiopathic ascites, dialysis ascites etc,[1] is usually associated with dialysis, but may occur prior to dialysis initiation.[2] There is marked variability in its incidence (0.7 to 20%), and age of onset (11 to 71 yr; mean, 42 yr), with a slight male predominance (male: female = 2: 1).[1] The onset may vary, and may even appear upto 18 months before initiation to as late as 69 months after initiation of hemodialysis.[1]

The exact pathogenesis remains elusive, and increased hydrostatic pressure in the hepatic veins, the retention of salt and fluid, increased permeability of the peritoneal membrane, and impairment in drainage of the regional lymphatics are suggested. Liver disease and increased hepatic outflow pressure may lead to the development of ascites, because sinusoidal endothelium has high permeability to albumin.

Pt. no	Age	Sex	Etiology	DM	HTN	CAD	Others	HCV	HBSAG	HIV	HD dur (yrs)	CKD dur (yrs)	Sessions
1	58	M	CGN	-	+	-	-	-	-	-	2	2	2
2	65	M	DKD	+	+	-	-	-	-	-	1	3.5	1
3	29	F	FSGS	-		-	-	-	-	-	2	2	1
4	60	F	ADPKD	-	+	+	-	-	-	-	1	5.5	2
5	46	M	CGN	-		-	-	-	+	-	3	3	2
6	47	M	DKD	+	+	-	-	-	-	+	4	5	2
7	64	M	DKD	+		-	-	-	-	-	1	6.5	2
8	36	F	IGA	-	+	+	-	-	-	-	4	4	3
9	50	M	CGN	-	+	-	TB Ascites	-	-	-	1	1	2
10	27	M	CIN	-	+	-	hypothyroid	-	-	-	2	2	2
11	65	F	DKD	+	+	-	-	-	-	-	1.5	3	2
12	62	M	HTN	-	+	-	-	-	-	-	3	3	2
13	45	F	SLE	-	+	-	-	-	-	-	5	5	2
14	48	F	CGN	-	+	-	-	-	-	-	3.5	4	2
15	46	F	CGN	-	+	-	-	-	-	-	2	2	2
16	56	F	DKD	+	+	-	-	-	-	-	3	3	2
17	58	M	DKD	+	+	-	Aor Diss.	-	+	-	4	4	2
18	28	F	CGN	+	+	+	-	-	-	-	2	2	2

Table 1: Clinical characteristics and co-morbidities. ADPKD: Autosomal Dominant Polycystic Kidney Disease; Aor Diss: Aortic dissection; CAD: Coronary artery disease; CGN: chronic glomerulonephritis; CIN: chronic interstitial nephritis; DKD: Diabetic Kidney disease; Dur: Duration; FSGS: Focal segmental glomerulosclerosis; IgA: IgA nephropathy; Sessions: number of HD per week; SLE: Systemic Lupus Erythematosus.

Pt. No	BUN	Creat	Alb	T.P.	AST	ALT	ALP	T. Bili	Hb	iPTH	Ca	Pi	UA
1	32	5.5	2.7	5.8	11	10	114	0.22	8.1	234.7	8.2	3.1	6.2
2	25	10.1	3.4	6.8	22	20	110	0.63	6.9	214.7	10.1	3.5	5.6
3	53	9.5	3.7	6.2	16	12	59	0.54	8.8	329.3	7.8	8.9	10.7
4	74	6.3	2.9	6.8	16	21	116	0.83	7.4	148.6	8.5	5.1	4.3

5	55	7.19	3.1	7.1	18	22	104	0.43	8.5	231.2	8.7	4.6	5.2
6	52	10.8	3.8	7.1	13	23	107	0.46	12	431.1	8.1	5.4	6.4
7	71	5.4	2.8	8.3	12	10	124	0.45	7.7	238.6	8.4	4.1	2.9
8	22	3.3	4.1	7.7	35	42	114	1.41	12	34.2	10.7	5.2	2.9
9	73	5	3.3	8.4	26	19	126	0.64	10.7	18.6	9.2	3.3	5
10	52	7	3.4	6.3	13	15	96	0.97	7.3	44.6	10.1	1.2	4.5
11	36	7.7	3.4	6.9	28	19	119	1.22	6.8	247.1	9.2	4.3	4.1
12	54	8	3.4	6.5	20	25	112	0.93	9.5	268.4	8.8	3.4	3.2
13	64	4.2	3	7.1	21	18	108	0.53	8.4	224.5	8.7	4.6	5.9
14	51	6.39	3.5	6.4	18	22	96	0.43	8.5	378.9	8.2	5.2	4.8
15	81	5.3	4.4	6.9	21	17	124	0.71	5.4	419.3	9.1	5.6	6.3
16	60	6.6	3.1	7	16	15	134	0.43	10.6	88	9.5	4.1	4.8
17	35	5.5	2.9	6	31	50	109	0.44	5.9	224.3	8.2	4.4	6.1
18	53	8.5	2.9	5.4	14	19	106	0.23	8.6	387.3	8.1	7.1	4.1

Table 2: Laboratory characteristics of the patients. Alb: Albumin (g/dl); Ca: Calcium (mg/dl); Creat: serum creatinine (mg/dl); Hb: Hemoglobin (g/dl); iPTH: intact parathyroid hormone (pg/ml); Pi: serum phosphorous (mg/dl); T.Bili: Total bilirubin (mg/dl); T.P: Total protein (g/dl); U.A: serum uric acid (mg/dl). BUN (mg/dl). AST, ALT, ALP (U/l).

The effect of fluid retention has not been clearly defined, as many patients undergoing hemodialysis have fluid overload in the absence of significant ascites. The altered permeability of the peritoneal membrane by uremic toxins,[1,3] activation of renin-angiotensin system and immune complexes[4] or deposition of iron[5] are also proposed. On microscopy, the peritoneum may be normal [6,7] or can show chronic inflammation with variable fibrosis and mesothelial proliferation.[1,2,7-9] The circulating immune complexes may also alter the peritoneal membrane permeability.[8] Hemosiderosis has been reported among 4 patients having nephrogenic ascites. The decrease in ascites following treatment with deferoxamine and erythropoietin, suggests a possibility of alteration in iron deposition.[5]

Also, the rate of fluid removal is slower, suggesting lymphatic peritoneal drainage may be impaired. Uremia may be a causative factor. [3,10,11] Other factors which have been proposed include: hypoproteinemia, pancreatitis, constrictive pericarditis, congestive heart failure, serositis due to secondary hyperparathyroidism, portal hypertension.[1,2]

Various therapeutic modalities have been proposed. Fluid and salt restriction, intensifying the hemodialysis, increasing ultrafiltration, albumin infusion, hyper-alimentation, multiple paracentesis etc may be initially done to gain control of progression of ascites. The intensification of dialysis and ultrafiltration may be limited by hypotension.[1] In some, reinfusion of ascitic fluid,[12] extracorporeal ascites dialysis[13] has been tried. The use of peritoneovenous shunt can be used as a palliative measure, and also reduces hypotension tendency during hemodialysis.[14-17] There is also improvement in the nutritional status, with increase in the muscle mass and better exercise tolerability. Half of the cases with shunt placement may develop complications, like occlusion, migration, infection etc. CAPD is also effective in the management of nephrogenic ascites.[1,7,8,18,19]. The total amount of protein excreted in the effluent can decrease from 26.5 - 50 g/day to as much as 7.8 - 9.44 g/day within 6 months of CAPD, and reduce the oncotic pull of ascitic fluid.[10] Intraperitoneal steroid administration,[1,2,19] bilateral nephrectomy[1,3,17,18] are not of proven benefit. Among all, renal transplantation is the best option, with complete resolution within 2 to 6 weeks post transplant.[1,3,6,7,10,16,18] Also, ascites may recur after graft loss or dysfunction, upto 3 years.

Summary

To conclude, nephrogenic ascites is a condition to be looked for while evaluating ascites in ESRD patients, as it is associated with a poorer prognosis. The exact etiology is unknown, but probably has a multifactorial pathology. Randomized controlled trials comparing the different treatment strategies have not been widely done, but based on the current evidence, renal transplant, Continuous ambulatory peritoneal dialysis, and peritoneo-venous shunt placement, may be the best options for improving the quality of life and decreasing ascites formation.

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