Case Report

Concurrent Occurrence of Chylothorax, Chylous Ascites, and Protein-Losing Enteropathy in Systemic Lupus Erythematosus

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ABSTRACT. We describe 2 patients with systemic lupus erythematosus (SLE) who presented with chylothorax, chylous ascites, and protein-losing enteropathy. Analysis of pleural or peritoneal fluid revealed a high level of triglyceride and elevated 24 h stool α_1-antitrypsin clearance in keeping with protein-losing enteropathy. One patient failed to respond to high dose corticosteroid therapy but recovered after 3 cycles of monthly cyclophosphamide treatment. The other patient initially responded to high dose corticosteroid therapy, but succumbed to infectious complications. This is the first report of occurrence of chylothorax and chylous ascites associated with SLE. (J Rheumatol 2002;29:1330–3)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS
CHYLOTHORAX
CHYLOPERITONEUM
PROTEIN-LOSING ENTEROPATHIES

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that can affect the skin, joints, kidneys, lungs, nervous system, serous membranes, and other organs of the body. Chylothorax or chylous ascites are characterized by the occurrence of chyle in pleural or peritoneal fluid and are due to damage or blockage of the lymphatics. Protein-losing enteropathy is characterized by a leakage of protein that results in hypoproteinemia and generalized edema. While protein-losing enteropathy is associated with a wide variety of disorders, it is not usually associated with SLE. A concurrent occurrence of chylothorax, chylous ascites, and protein-losing enteropathy has never been reported in patients with SLE. We describe 2 patients whose initial manifestations of SLE were chylous effusion and protein-losing enteropathy.

CASE REPORTS

Case 1. A 47-year-old Korean woman with a 9 month history of progressive abdominal distension, generalized weakness, urinary frequency, and edema was admitted to our hospital for evaluation. She had no history of any previous diseases. On physical examination, diminished sounds of breathing over the bilateral lung fields and a malar rash were apparent. We also noted abdominal distension with shifting dullness and pitting edema on the bilateral lower extremities.

Results of laboratory studies are shown in Tables 1 and 2. Antinuclear

Table 1. Hematologic and biochemical laboratory values of 2 patients at admission.

Variable (normal range)	Case 1	Case 2
Hemoglobin (120–160 g/l)	109	87
WBC (4.0–10.0×10^9/l)	2.8	4.5
Differential count		
Neutrophils	0.79	0.84
Lymphocytes	0.14	0.08
Monocytes	0.05	0.05
Platelets (150–350×10^9/l)	177	418
Protein (60–80 g/l)	43	79
Albumin (3.3–5.2 g/dl)	1.9	2.0
Cholesterol (< 240 mg/dl)	180	136
Triglyceride(< 200 mg/dl)	102	124
LDH (200–430 U/l)	512	890
Creatinine (61–123 μmol/l)	132.6	106.1
Anti-ds-DNA antibody (0–7 IU/ml)	4.7	3.7
C3 (0.88–2.1 g/l)	0.42	0.86
C4 (0.16–0.47 g/l)	0.15	0.15
ESR (0–20 mm/h)	107	76
CRP (0–6 mg/dl)	2.1	6.5
24 h urine protein (25–75 mg/day)	ND	839

WBC white blood cell; LDH: lactate dehydrogenase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ND: not done. Conversion factors (CF) for converting conventional units to SI unit: CF for albumin 10.0, CF for cholesterol 0.02586, and CF for triglyceride 0.01129.

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antibody (ANA) was positive at a titer of 1:320 with a speckled and nucleolar pattern. The anti-Ro (SSA) antibody was positive. The anti-La (SSB) antibody, anti-RNP antibody, anti-Sm antibody, and anti-Scl-70 antibody were negative. Antiphospholipid antibodies including the lupus anticoagulant (LAC), anticardiolipin antibodies (aCL), and $ß_2$-glycoprotein I ($ß_2$-GPI) antibodies were negative. Urinalysis was unremarkable. Using thoracentesis, we obtained a milky fluid with the following biochemical values: white blood cells 150/mm^3, protein 21 g/l, LDH 215 U/l, cholesterol 10 mg/dl, triglyceride 106 mg/dl, adenosine deaminase (ADA) 5.4 U/l, and anti-ds-DNA antibody 2.9 IU/ml. Using paracentesis, we obtained a milky fluid with the following biochemical values: white blood cells 30/mm^3, protein 14 g/l, albumin 1.1 g/dl, cholesterol 16.7 mg/dl, triglyceride 136 mg/dl, LDH 316 U/l, ADA 4.7 U/l. Gram stain and stain for acid-fast bacilli of the pleural and peritoneal fluid did not reveal any microorganisms. Cytologic examinations of the pleural and peritoneal fluid were negative for malignant cells. Lipoprotein electrophoresis of the pleural and peritoneal fluid revealed an increase of the chylomicron fraction. An albumin scan using ^{99m}technetium labeled human serum albumin indicated protein loss from jejunum (Figure 1). A 24 h stool α_1-antitrypsin clearance was 31.4 ml/24 h (normal < 13 ml/24 h) in keeping with protein-losing enteropathy. Biopsies of the stomach, duodenum, colon, and rectum for the etiologies of protein-losing enteropathy showed nonspecific inflammation. A computer tomographic (CT) scan of the abdomen showed a large amount of ascites and bilateral hydronephrosis. Severe trabeculate and thickened bladder wall and patent ureterovesical junction were observed on cystoscopic examination. Biopsy of the bladder wall revealed mucosal erosion with chronic inflammation. We diagnosed the patient as having SLE associated with protein-losing enteropathy, cystitis, and chylous effusion on the basis of a positive ANA, a positive anti-Ro antibody, leukopenia, serositis, a malar rash, and low complement. She was put on a low fat diet with medium-chain triglyceride supplementation and treated with intravenous methylprednisolone of 1 mg/kg/day for 1 month. Despite treatment, there was no improvement of the chylothorax, chylous ascites, or urinary symptoms, including urinary difficulties and frequency. A 500 mg/m^2 bolus of intravenous cyclophosphamide was given every month over the next 3 months. After 3 cycles of monthly intravenous cyclophosphamide, the chylothorax, chylous ascites, and urinary symptoms were completely resolved. The biochemical characteristics of followup paracentesis and thoracentesis are shown in Table 2. A normal level of 24 h stool α_1-antitrypsin clearance (6.5 ml/24 h) was also observed on followup examination. As we tapered prednisolone, we added hydroxychloroquine and azathioprine to control disease flare at 6 and 18 months of followup, respectively. There was no recurrence of chylous ascites, chylothorax, and protein-losing enteropathy. After 27 months, she continues well with 400 mg of hydroxychloroquine and 100 mg of azathioprine per day.

Case 2. A 68-year-old Korean man presented with a 7 month history of general weakness, increased abdominal girth, weight loss, and edema. On initial examination, we noted decreased sounds of breathing on the bilateral lower lung field, abdominal distension with shifting dullness, and pitting edema on the bilateral lower extremities. Laboratory tests are summarized in Tables 1 and 2. ANA was positive at a titer of 1:1280 with a speckled and homogenous pattern. The anti-Ro (SSA) antibody was positive. The anti-La (SSB) antibody, anti-RNP antibody, anti-Sm antibody, and anti-Scl-70 antibody were negative. Antiphospholipid antibodies including LAC, aCL, and $ß_2$-GPI antibodies were negative. An anti-HIV antibody test was negative. Using thoracentesis, we obtained a milky fluid with the following biochemical values: white blood cells 520/mm^3, protein 43 g/l, LDH 612 U/l, cholesterol 85 mg/dl, triglyceride 880 mg/dl, ADA 17.0 U/l, ANA 1:1280 (a speckled and homogenous pattern), and anti-ds-DNA antibody 2.9 IU/ml. Using paracentesis, we obtained a milky fluid with the following biochemical values: white blood cells 190/mm^3, protein 10 g/l, albumin 0.5 g/dl, cholesterol 58 mg/dl, triglyceride 1021 mg/dl, LDH 599 U/l, ADA 9.0 U/l, and ANA 1:1280 (a speckled and homogenous pattern). Gram stain and stain for acid-fast bacilli of the pleural and peritoneal fluid did not reveal any microorganisms. A pleural biopsy and laparoscopic peritoneal biopsy revealed nonspecific chronic inflammation. Cytologic examinations of the pleural and peritoneal fluid were negative for malignant cells. The bone marrow biopsy was unremarkable. A lymphangiography scan showed no evidence of lymphatic leak in the thoracic or peritoneal cavity. There was no protein loss on the albumin scan. The 24 h stool α_1-antitrypsin clearance was 84.9 ml/24 h in keeping with protein-losing enteropathy. A biopsy of the duodenum showed nonspecific inflammation. A needle biopsy of the kidney showed findings compatible with lupus nephritis (class II). We believed this presentation to be most compatible with a lupus induced protein-losing enteropathy and chylous effusion. We instituted a treatment regimen of intravenous methylprednisolone of 1 mg/kg/day for 5 days, followed by 60 mg of prednisolone orally per day for 1 month. At discharge, the 24 h stool α_1-antitrypsin clearance had returned to a normal

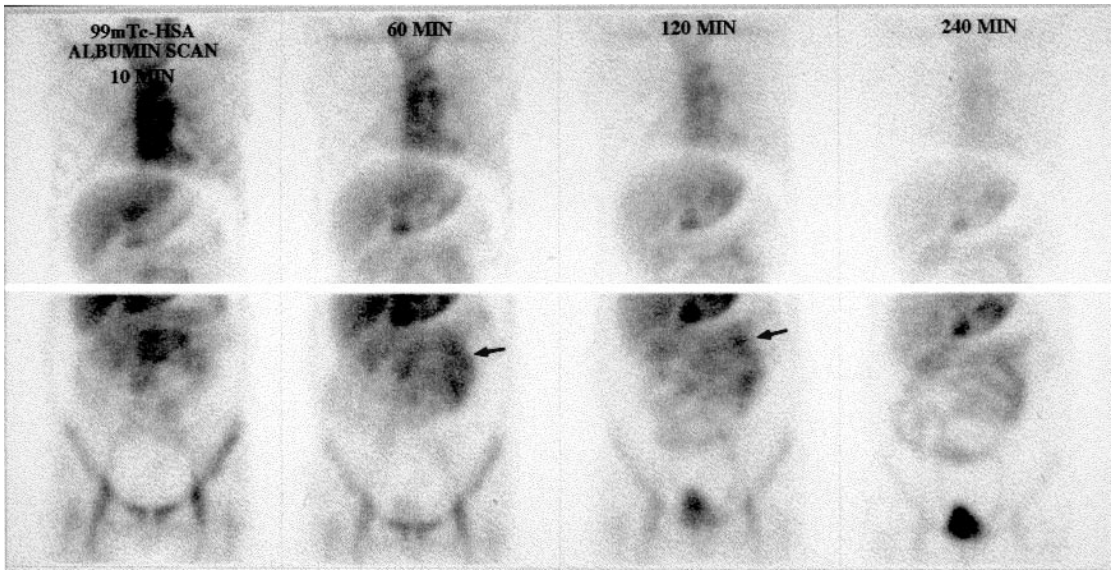

Figure 1. ^{99m}Tc-human serum albumin scintigraphy shows protein loss from small bowel (jejunum). Serum albumin was shown to leak into jejunum (arrow).

Table 2. Pleural fluid and ascites characteristics of 2 patients.

Date	Sample	Protein (60–80 g/l)*		LDH (U/l) (200–430 U/l)		TG (mg/dl) (< 200 mg/dl)		Chol (mg/dl) (< 240 mg/dl)		Alb (g/dl) (3.3–5.2 g/dl)		AT (ml/24h) (< 13 ml/24 h)
		SP	SP/S	SP	SP/S	SP	SP/S	SP	SP/S	SP	SAAG	
Case 1												
July 98	PF	21	0.49	215	0.42	106	1.03	10	0.05			
	A	14	0.33	316	0.62	136	1.33	16.7	0.09	1.1		
											0.8	31.4
	S	43	1	512	1	102	1	180	1	1.9		
Sep 98	PF	18	0.37	156	0.30	81.6	0.31	22.5	0.08			
After 1st cycle of CYC	A	18	0.37	207	0.39	106	0.4	10	0.03	1.1		
											1.1	
	S	49	1	523	1	265	1	278	1	2.2		
Oct 98	A	22	0.46	316	0.71	42.8	0.18	23.1	0.09	1.1		
After 2nd cycle of CYC											0.8	6.5
	S	48	1	443	1	232	1	247	1	1.9		
Case 2												
Feb 01	PF	43	0.54	612	0.69	880	7.09	85	0.63			
	A	10	0.13	599	0.67	1021	8.23	58	0.43	0.5		84.9
											1.5	
	S	79	1	890	1	172	1	136	1	2.0		
June 01	A	14	0.3	329		218.2		31.1	0.5	0.6		6.3
											1.5	
	S	46	1	ND		ND		62	1	2.1		

LDH: lactate dehyrogenase; TG: triglyceride; Chol: Cholesterol; Alb: albumin; AT: 24 h stool α_1-antitrypsin clearance; SP: sample; S: serum; SP/S: sample fluid to serum ratio; SAAG: serum to ascites albumin gradient; PF: pleural fluid; A: ascites; CYC: cyclophosphamide; ND: not done. * Numbers in parentheses indicate normal ranges. Conversion factors (CF) for converting conventional units to SI unit: CF for albumin 10.0, CF for cholesterol 0.02586, and CF for triglyceride 0.01129.

level (6.3 ml/24 h). Minimal pleural effusion remained on the left side and ascites had decreased significantly. There was a 50% decrease of the abdominal girth increment. Two months later, however, he began to have fever, headache, and altered mental status. Two sets of blood and cerebrospinal fluid cultures yielded *Streptococcus bovis*. We diagnosed bacterial meningitis and the patient received ampicillin. A transthoracic echocardiogram did not reveal any vegetation. Colonoscopy showed no significant abnormalities. Over the next few days, he deteriorated and he died from acute respiratory failure, even though broad spectrum antibiotics had been started. Paracentesis, bronchoalveolar lavage (BAL), and blood and stool cultures were performed just before he died. *Klebsiella pneumoniae* was cultured in the blood and BAL fluid. The ascites and stool contained *Strongyloides stercoralis* larvae.

DISCUSSION

Chylothorax or chylous ascites are the occurrence of chyle in the pleural or peritoneal cavity and are due to damage or blockage of the lymphatic channel. Chyle may have its origin in the thorax or abdomen, or both. Diagnosis is made by an analysis of the fluid. A triglyceride concentration > 110 mg/dl supports the diagnosis; a level < 50 mg/dl excludes a chylous effusion with reasonable likelihood; and an intermediate level between 50 and 110 mg/dl should be followed by lipoprotein analysis of the fluid[1].

The etiologies of chylothorax or chylous ascites can be categorized as nontraumatic or traumatic. The most common cause of nontraumatic chylous effusion is malignancy[2,3]. Malignant lymphoma has been considered the most frequent cause, followed by metastatic carcinoma. Besides malignancy, nontraumatic chylous effusion includes idiopathic, congenital, and other relatively infrequent multiple causes. The miscellaneous causes of chylous effusion include lymphangioleiomyomatosis (LAM), intestinal lymphangiectasis, protein-losing enteropathy, regional ileitis, pleuritis, cirrhosis[4], sarcoidosis[5], tuberculosis, amyloidosis, thrombosis of the superior vena cava or other central veins, heart failure[6], filariasis, nephrotic syndrome[7], and Behçet's disease[8]. When chylothorax or chylous ascites of unknown etiology occur, the first suspicion should be an underlying malignancy, especially lymphoma.

We conducted a vigorous search for underlying malignancies in our patients. Repeated cytologic examination of pleural and peritoneal fluids, a bone marrow examination, biopsies of pleura and peritoneum, CT scans of the abdomen, and biopsies of the duodenum or colon were all unremarkable. The incidence of the combined occurrence of chylous ascites and chylothorax was from 9 to 55% of chylous effusions[4,9]. The mechanism of combined occurrence of chylous ascites, chylothorax, and protein-losing enteropathy is still unknown. It could be that exudation of chyle from lymphatics in the wall of the bowel and in the mesentery is caused by obstruction of the lymphatics at the base of the mesentery or the cisterna chyli due to inflammation. Obstruction of this normal outflow may produce lymphedema in the gut with a subsequent loss of chyle to the peritoneal cavity or lumen[10,11]. Subsequently, chylous

ascites can cross the diaphragm, causing chylothorax. Chylous ascites that is either absorbed by diaphragmatic lymphatics or passed through by congenital diaphragmatic defects may also cause chylous pleural effusion[4,12,13]. Tanabe, *et al* reported manidipine hydrochloride induced chyloperitoneum in a patient with SLE[14]. However, our patients had not taken any dihydropyridine-type calcium channel blockers. Compared with low gradient serum to ascites albumin gradient (SAAG) (< 1.1 mg/dl), implying peritoneal disease as seen in the first case, we noted high gradient SAAG (> 1.1 mg/dl), indicating ascites on the basis of portal hypertension in the second case. Previous reports indicated that chylous effusions secondary to liver cirrhosis[4], cardiac failure[6], and nephrotic syndrome[7] were transudate according to Light's criteria. As a result of dilution in coexisting portal hypertension ascites, the chylous ascites due to portal hypertension has a lower triglyceride concentration than other causes of chylous ascites. However, ascites and pleural fluid in the second case were exudates. Moreover, a higher concentration of triglyceride was found than previously reported in chylous ascites due to portal hypertension (Table 2). It was unclear why a discrepancy of SAAG occurred in the same underlying disease.

Because chylothorax and chylous ascites are manifestations of many types of disease rather than diseases themselves, the prognosis depends on the treatment of the underlying disease. Nevertheless, supportive measures are often needed to relieve the symptoms of chylothorax or chylous ascites together with the treatment of the primary disease. Low fat diets with medium-chain triglyceride supplementation have been widely used to diminish the lymphatic flow. We put our patients on a low fat diet with medium-chain triglyceride supplementation to decrease lymphatic flow. We also instituted intravenous methylprednisolone of 1 mg/kg/day and subsequently switched to 60 mg of oral prednisolone per day. One patient (Case 1) failed to respond to corticosteroid therapy, but was successfully treated with monthly intravenous cyclophosphamide therapy for 3 months. The other patient (Case 2) initially responded to corticosteroid therapy, but died of infectious complications.

We describe the first concurrent occurrence of chylothorax, chylous ascites, and protein-losing enteropathy in SLE. Because of their low incidence, the concurrent occurrence of these rare disorders is not a coincidence. Therefore, we suggest that SLE should be included as a cause of chylothorax and chylous ascites.

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