

Lupus protein-losing enteropathy patient with protein C and S deficiency-induced thrombosis: a case report with review of the literature

Lertnawapan R¹, Sakonlaya D²

ACTA REUMATOL PORT. 2017;42:265-268

ABSTRACT

A case report of systemic lupus erythematosus with protein-losing enteropathy in an Asian female; presented with edema, pleural effusion, ascites and profound hypoalbuminemia. She also had severe protein C and protein S depletion from gastrointestinal loss, which caused extensive thrombosis. Her disease was refractory to the treatment with high dose steroid, azathioprine, mycophenolate mofetil and cyclophosphamide. Bowel resection was performed without improvement. Fortunately, the patient responded to another course of pulse methyl prednisolone and a second line medication after surgery.

Keywords: Protein-losing enteropathy; Thrombosis; Systemic lupus erythematosus

CASE REPORT

A 48-year-old Asian female, presented with severe edema, dyspnea and ascites. She had diarrhea for 2 months and developed edema without the symptoms of foamy urine, hematuria, arthritis or fever. Having small erythematous patches with active border and central atrophy at her right ear, which was consistent with concha sign. During physical examination, there were puffy eyelids, mild dyspnea, decreased breath sound and vocal resonance in both lungs, marked ascites and edema of both legs. Pleural fluid was positive for antinuclear antibody (ANA) (1:1280) but negative for malignancy,

bacterial infection and tuberculosis. Her laboratory results were: creatinine 0.5 mg/dL, albumin 0.7 g/dL, urine protein 1+, 24hr urine protein 299 mg/day. The results of complete blood count, liver function test (except hypoalbuminemia) and electrolyte were normal. The serological studies found: ANA +ve 1:2560 (speckled pattern), AntidsDNA-ve, AntiSm+ve, C₃<40mg/dL, C₄ 8 mg/dL and direct Coombs' test 1+. She was diagnosed systemic lupus erythematosus (SLE) with criteria: 1.chronic cutaneous lupus 2.serositis 3.ANA+ve 4.AntiSm+ve 5.low complement and 6.direct Coombs' test in the absence of hemolytic anemia. The cause of severe hypoalbuminemia was gastrointestinal (GI) loss due to protein-losing enteropathy (PLE). Alpha-1-antitrypsin clearance confirmed the diagnosis. Abdominal scintigraphy using 99m Tc-labeled human serum albumin showed diffused loss in distal duodenum, jejunum and ileum. Colonoscopy and endoscopy found bowel edema and diffused inflammation without ulcerative lesion. Histopathological finding found PLE and vasculitis (Figure 1)

The patient was prescribed steroids and immunosuppressive agents to control PLE. First she was prescribed prednisolone (1 mg/kg/day) and azathioprine (2 mg/kg/day) orally but there was no response. The regimen was switched to mycophenolate mofetil (2 g/day) and finally to a three-day pulse methylprednisolone (1 g/day) along with intravenous cyclophosphamide (600 mg) monthly. Unfortunately, the hypoalbuminemia was persistently low at 1.2 g/dL. Moreover, the patient had thrombosis in mesenteric, portal, inferior vena cava and right subclavian veins due to the depletion of protein C and protein S from GI loss. The thrombosis was severe and did not respond to warfarin (international normalized ratio (INR) 2.3), then we had to treat intensively with low molecular weight heparin (LMWH). She was prescribed parenteral nutrition due

1. Division of Allergy, Immunology and Rheumatology, Department of Internal Medicine, Faculty of Medicine, Thammasat University
2. Department of Pathology and Forensic Medicine, Faculty of Medicine, Thammasat University

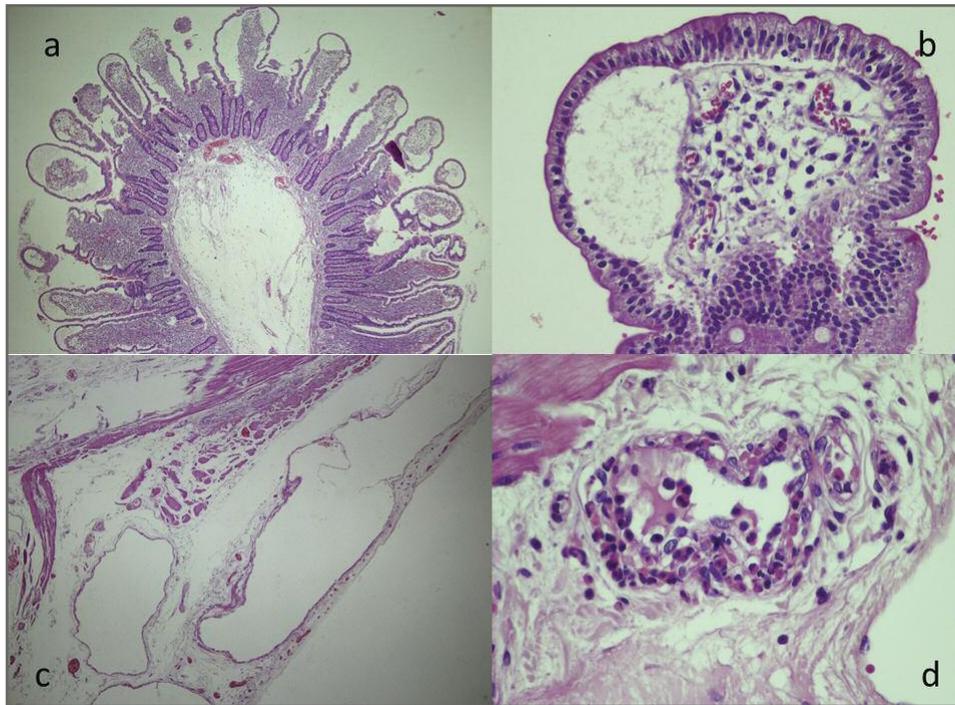


FIGURE 1. Segmental resection of jejunum reveals edema of bowel wall, grossly. Bulbous villi with lymphangiectasia and submucosal edema are observed (Fig. a,b). Subserosal edematous change with focal lymphangiectasia is seen (Fig. c) with foci of small-vessel vasculitis (Fig. d). These changes are consistent with lupus protein-losing enteropathy.

to profound hypoalbuminemia and severe malnutrition. Ultimately, partial bowel resection was performed in which a 3-foot bowel was removed. After surgery, there was no improvement of the albumin level. Technetium tagged albumin scan presented the persistent loss in the remaining of the small bowel. Pulse methylprednisolone was started, followed with intravenous dexamethasone. Cyclosporine (150 mg/day) was prescribed. This time the clinical was improved, albumin was increased to 1.9 mg/dL then the total parenteral nutrition was tapered and offed at albumin level of 2.5 mg/dL. Dexamethasone was tapered to prednisolone, and was finally discontinued. Currently she has cyclosporine, her albumin is 4.4 mg/dL. The level of protein C and protein S are normalized.

DISCUSSION

GI involvement in SLE is usually mild. Fifty percent of cases present with nausea and vomiting (53%), anorexia (49%) and abdominal pain (19%). However in more severe cases with abdominal vasculitis or thrombosis, have higher SLE disease activity index

(SLEDAI)¹. GI manifestations of SLE have wide variety spectrum such as vasculitis, esophageal dysmotility, dysphagia, dyspepsia, peptic ulcer, pernicious anemia, pneumatosis cystoides intestinalis, necrotizing enterocolitis, intestinal pseudoobstruction, malabsorption, protein-losing enteropathy, pancreatitis, peritonitis, ascites, hepatitis and splenomegaly¹. Other concurrent autoimmune diseases such as primary sclerosing cholangitis, autoimmune cholangiopathy, primary biliary cirrhosis or autoimmune hepatitis have been reported¹. Autoimmune hepatitis manifests with hepatitis, hypergammaglobulinemia, and autoantibodies (ANA, anti-smooth muscle antibody (SMA), liver/kidney microsomal antibody (LKM-1, LKM-2, LKM-3)). The most common type, previously known as "lupoid hepatitis", is characterized by chronic active hepatitis and lymphocytic infiltration of the periportal areas². As immunocompromised host, SLE patients may develop opportunistic infections such as cytomegalovirus enteritis or tuberculous colitis. SLE is also prone to infection with *Salmonella*.

PLE is a leakage of serum proteins from GI tract with profound edema and hypoalbuminemia. PLE can be associated with variety of disorders, including cardiac

disease, intestinal lymphangiectasia, Waldenstrom macroglobulinemia, intestinal lymphoma, systemic amyloidosis, Crohns' disease, sarcoidosis, tuberculosis, parasitic infection, amyloidosis, pemphigus vulgaris, allergic gastroenteritis and autoimmune diseases (such as SLE, scleroderma, Sjogren, rheumatoid arthritis, mixed connective tissue disease (MCTD), and undifferentiated connective tissue disease (UCTD))³⁻⁵.

Most of the previous PLE in SLE reports were from Asia, indicating that this manifestation may be more common in oriental patients^{6,7}. PLE was predominant in Asians (64.7%) while 29.5% were white or Hispanic patients³. A systematic review found that the average time to development of PLE after diagnosis of SLE was 34±14.2 years; the female to male ratio was 5.8:1⁴. Most patients were presented with peripheral edema (80%), ascites (48%), diarrhea (46%), abdominal pain (27%), nausea (22%) and vomiting (19%)⁴. Almost all patients (96%) had positive ANA with predominated speckled patterns (55%) and hypocomplementemia (79%). Hypoalbuminemia was frequently found (96%), in which lupus nephritis, malnutrition, liver disease, and malabsorption should be excluded. Gornisiewicz *et al.* reported that PLE often happened in patients with severe SLE. Tang *et al.* concordantly found that PLE was more likely to happen in lupus with multiple-system involvement^{7,8}. PLE was diagnosed by 24-hour stool alpha-1 antitrypsin clearance (AATC) and 99mTc-human serum albumin scintigraphy (99m Tc HAS)⁹. Fecal alpha-1-antitrypsin clearance also can be used as a monitoring test of the responsiveness. However, alpha-1-antitrypsin clearance cannot distinguish the gastric loss from intestinal loss. The 99m Tc HAS has very high both sensitivity (95.8%) and specificity (100%)⁴. It is a non-invasive, fast, safe and convenient test for demonstrating albumin loss in GI tract. 99mTc is traced, by which the site of leakage can be shown^{4,9}. 99m Tc HAS can also be used as the surveillance for PLE activity. The drawback of 99m Tc HAS is the GI bleeding may result in false-positive because the radiotracer can leak into the GI tract. *In vivo* breakdown of the radiotracer which results in free pertechnetate concentrating in the gut may mimic radiotracer exudation⁹.

Majority of the PLE patients had diffused non-erosive erythematous GI mucosa with chronic inflammatory cells in lamina propria. Li *et al.* reported protein leakage at small bowel (31.3%), terminal ileum/caecum (33.3%) and ascending colon (22.9%) of patients⁹. The intestinal histology either presented mu-

cosal edema, infiltration of the inflammatory cells, lymphangiectasia, mucosa atrophy or vasculitis⁴. Nevertheless a significant percentage of PLE patients had normal histopathological features, indicating that the pathological involvement is patchy or a segmental disease⁴.

The proposed pathological mechanisms are: a) complement-mediated vascular injury (activated complement and immunoglobulin deposit in the capillary wall of vessels in GI tract. The immune complex which activates the inflammatory reaction and causes increased capillary permeability as a consequence); b) non-necrotizing mesenteric or intestinal vasculitis and mucosal ulceration; c) intestinal lymphangiectasia (inflammation of mesentery can cause the dilation and rupture of lacteals within the villi, resulting in lymphatic leakage); and d) increased microvascular/endothelial permeability.⁹

Thromboembolism, primarily from data in nephrotic syndrome, of which pathogenesis results from the loss of coagulation regulatory proteins. Besides albumin, the loss including anti-thrombin III, protein C, protein S and plasminogen, and this leads to increased coagulability. Counterbalancing the renal loss and hypoalbuminemia is the increased hepatic synthesis of fibrinogen^{10,11}. The hemostatic balance shifts to prothrombotic stage^{10,11}. Thrombosis may occur in either arteries or veins¹⁰. Children (2.8%) are less likely than adults (26.7%) to develop thrombosis¹⁰. Even though the risk of thromboembolism is high in nephrotic syndrome, there is inadequate data regarding the routine prophylaxis therapy^{10,11}. There were few reports on the thromboembolism in SLE with PLE⁹. This lower incidence might be due to the lower risk of thromboembolism in Asian populations, in which PLE is frequent. However, thromboembolic complications should be considered in severe and persistent loss, especially if antiphospholipid antibodies are presented. Severe PLE causes profound loss of natural anticoagulant (such as protein C and protein S), which causes extensive thrombosis. Of which patients, anticoagulation therapy should be considered.

SLE related PLE responds well to steroid and immunosuppressive therapy³. A systematic review from Al-Mogairen reported that 30% of patients responded to steroid, while 66% resolved with immunosuppressive therapy⁴. From the literature, the frequent used immunosuppressive are azathioprine, cyclosporine, mycophenolate mofetil or combination^{3-9,12}. Supplementary treatment modality including serum albumin

infusion, nutritional support and diuretics should be given along with the mainstay therapy. Octreotide can reduce intestinal microvasculature blood flow, decrease local lymph formation, and ameliorate lymphatic dilatation¹³. Additionally, it has immunomodulatory effect after specific binding with somatostatin receptor subtype 2A (SSTR2A)⁷. From the literature, 20-30% of patients had relapsed but responded again to the increment of steroids⁷.

This patient was refractory to all modalities of treatment with glucocorticoids and immunosuppressive agents. The leakage did not resolve even after bowel resection. However, her ultimate responsiveness after steroid and cyclosporine might be explained by the reduction of pathologic bowel segment by surgical resection. This reduction in pathologic bulk facilitated the resolution, simultaneously with the response of the remaining bowel to the treatment. Along with the decrement of bowel leakage of protein indicated by the rising of albumin level, the level of protein C and protein S were resumed.

CORRESPONDENCE TO

Ratchaya Lertnawapan
Dept. Internal Medicine 7th Fl. Kunokorn Bldg.
Thammasat University, Klong Nueng
Klong Laung, Pthumthani, Thailand 12120
E-mail: ratchayas@yahoo.com

REFERENCES

- Ebert EC, Hagspiel KD. Gastrointestinal and hepatic manifestations of systemic lupus erythematosus. *J Clin Gastroenterol* 2011;45:436-441.
- Hall S, Czaja AJ, Kaufman DK, Markowitz H, Ginsburg WW. How lupoid is lupoid hepatitis? *J Rheumatol* 1986; 13:95-98.
- Law ST, Ma KM, Li KK. Clinical characteristics of concurrent and sequentially presented lupus-related protein-losing enteropathy: What are their differences? *Rheumatol Int* 2013;33:85-92.
- Al-Mogairen SM. Lupus protein-losing enteropathy (LUPLE): A systematic review. *Rheumatol Int* 2011;31:995-1001.
- Awazawa R, Yamamoto Y, Mine Y, Nakamura I, Kishimoto K, Kinjyo F, et al. Systemic lupus erythematosus complicated with protein-losing enteropathy: A case report and review of the published works. *J Dermatology* 2012;39:454-461.
- Chen Z, Li MT, Xu D, Yang H, Li J, Zhao JL, et al. Protein-losing enteropathy in systemic lupus erythematosus: 12 years experience from a Chinese academic center. *PLoS ONE* 2014;9:e114684.
- Zheng WJ, Tian XP, Li L, Jing HL, Li F, Zeng XF, et al. Protein-losing enteropathy in systemic lupus erythematosus: Analysis of the clinical features of fifteen patients. *J Clin Rheumatol* 2007;13:313-316.
- Gornisiewicz M, Rodriguez M, Smith JK, Saag K, Alarcon GS. Protein-losing enteropathy in a young African-American woman with abdominal pain, diarrhea and hydronephrosis. *Lupus* 2001;10:835-840.
- Law ST, Ma KM, Li KK. The clinical characteristics of lupus related protein-losing enteropathy in Hong Kong Chinese population: 10 years of experience from a regional hospital. *Lupus* 2012;21:840-847.
- Kerlin BA, Ayoob R, Smoyer WE. Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. *Clin J Am Soc Nephrol* 2012;7:513-520.
- Al-Azzawi HF, Obi OC, Safi J, Song M. Nephrotic syndrome-induced thromboembolism in adults. *Int J Crit Illn Inj Sci* 2016;6:85-88.
- Park JM, Ahn SY, Shin JI, Yun MJ, Lee JS. A systemic lupus erythematosus patient with protein losing enteropathy. *Yonsei Med J* 2004;45:923-926.
- Ossandon A, Bombardieri M, Coari G, Graziani G, Valesini G. Protein-losing enteropathy in systemic lupus erythematosus: role of diet and octreotide. *Lupus* 2002;11:465-466.