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Characteristics and long-term outcomes of patients with lupus-related protein-losing enteropathy: A retrospective study

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Abstract

Objectives: The long-term outcomes of patients with systemic lupus erythematosus (SLE)-related protein-losing enteropathy (PLE) are unclear. This study was aimed to investigate the clinical characteristics and long-term outcomes of patients with SLE-related PLE.
Methods: This retrospective cohort study enrolled 58 patients with SLE-related PLE who were admitted to our center from January 2000 to June 2016. The patients' baseline characteristics and follow-up data were analyzed, and the prognostic outcomes were survival and disease flares. The prognoses were analyzed using Kaplan-Meier curves, log-rank tests, and Cox regression models. Factors with values of $P<0.05$ were considered potential predictors.
Results: Two-thirds of patients had intestinal symptoms, and 77.6% of patients had concomitant organ/system involvement, including serositis (77.6%), lupus nephritis (57.6%), neuropsychiatric lupus (10.3%), and hematological disorders (22.4%). Common abnormalities in the laboratory test results were hypocomplementemia (87.9%), anti-Sjögren syndrome antigen A antibodies (51.7%), and high total cholesterol levels (62.1%). Five flares were recorded in 47 patients. The 1-, 3-, and 5-year survival rates were 93.6%, 91.3%, and 88.4%, respectively. Infection was the cause of death in 60% of patients. High 24-hour urine protein level was an independent risk factor associated with death (P = 0.012). Severe hypoalbuminemia (<12 g/L) was a predictor of disease flares in SLE-related PLE (hazard ratio, 10.345; 95% confidence interval, 1.690–63.321).
Conclusions: Infection causes most of the deaths in patients with SLE-related PLE. High 24-hour urine protein level is an independent risk factor associated with death, and severe hypoalbuminemia is a predictor of disease flares.

Keywords

protein-losing enteropathy • systemic lupus erythematosus • clinical characteristics • prognosis • risk factors

Introduction

Protein-losing enteropathy (PLE) is a rare manifestation of systemic lupus erythematosus (SLE) that is characterized by hypoalbuminemia and symptoms that include edema, susceptibility to infections, and serositis. Our clinical observations indicated that patients with SLE-related PLE had worse outcomes than patients without. However, the current data that describe SLE-related PLE are limited to case reports[1–10] or case series that comprise a limited number of patients,[11–13] and most of these reports described the patients' clinical characteristics and short-term responses to different immunosuppressants.[14–17] To date, the long-term outcomes of patients with SLE-related PLE have not been described. This study aimed to retrospectively analyze the clinical characteristics and long-term outcomes and the risk factors associated with mortality and disease flares in

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the largest cohort of patients with SLE-related PLE studied to date.

Materials and Methods

Patients and data collection

The patients included into this study were admitted to Peking Union Medical College Hospital between January 2000 and June 2016, as described in our previous study,[16] and they were followed until May 2017. The study was approved by the Medical Ethics Committee of PUMCH. Patients diagnosed with SLE who fulfilled ≥4 of the criteria of the American College of Rheumatology 1997 revised criteria for SLE were enrolled into this study. PLE was diagnosed if a patient had (1) definite PLE, which was based on the clinical symptoms, laboratory test results, and evidence of protein leakage from the gastrointestinal (GI) tract that was confirmed by technetium-99m (^{99m}Tc) human serum albumin (HSA) scintigraphy, or (2) probable PLE, which was defined as the presence of PLE-associated clinical symptoms and laboratory test results that included hypoalbuminemia that could not be completely explained by other pathological mechanisms, including urinary protein loss, severe liver disease, or malnutrition; probable PLE was diagnosed based on the independent judgments of ≥2 experienced rheumatologists. The exclusion criteria included patients who were diagnosed with other autoimmune diseases, including inflammatory bowel disease, which can cause PLE, and the presence of other pathological conditions that could account for a patient's hypoalbuminemia, including lupus nephritis (LN) with massive proteinuria, liver dysfunction, and abnormalities in protein synthesis or protein absorption.

The patients' baseline data were collected retrospectively from their medical charts including the demographic data, family histories, clinical characteristics, and laboratory test results. The clinical data were collected in accordance with the Systemic Lupus International Collaborating Clinics 2012 criteria.[18] The laboratory data collected included serum albumin, complement (C) 3, C4, calcium, total cholesterol, and triglyceride levels, and the 24-hour urine protein (24hUPro) levels. Patients' autoantibody profiles, including the levels of antinuclear antibody (ANA), anti-double-stranded DNA (anti-dsDNA) antibody, and anti-extractable nuclear antigen antibodies, including anti-Sjögren syndrome antigen A (SSA) and anti-Sjögren syndrome antigen B (SSB) antibodies, anti-Smith (Sm) antibody, and anti-ribonucleoprotein (RNP) antibody, as well as the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), were obtained from all patients upon their admission to the hospital.

The observation period spanned from the time of initial visit to the time when admitted to our hospital until May 2017. Most patients attended regular follow-up appointments, and their clinical records were reviewed and the follow-up data were collected. A minority of patients attended the follow-up appointments irregularly, and telephone interviews were conducted to gather some of the data. Lost to follow-up was defined as neither attending follow-up appointments at our clinic nor could be reached by telephone.

Definitions of remission and flares

Clinical remission was defined as SLEDAI-2K ≤4 points that was attained with or without the use of glucocorticoid or immunosuppressant therapy. An SLE flare was defined as an increase in the SLEDAI-2K ≥4 points compared with the previous visit, the appearance of a new SLE manifestation, or the worsening of a preexisting clinical or hematological manifestation that led to the resumption of or an increase in the corticosteroid or immunosuppressant therapies after a patient's first remission. An SLE-related PLE flare was defined as a reoccurrence of PLE-associated clinical presentations that resulted in the resumption of or an increase in corticosteroid or immunosuppressant therapy.

Statistical analyses

The data were expressed as the means and the standard deviations (SDs). Graphpad Prism® software, version 6.0 (GraphPad Software Inc., La Jolla, CA, USA) was used to create the Kaplan-Meier survival curves. Demographic, clinical, and laboratory factors were analyzed as potential predictors of flares or death using IBM®SPSS® software, version 21.0 (IBM Corporation, Armonk, NY, USA). The potential risk factors analyzed included involved organs/systems, the SLEDAI, total cholesterol, serum albumin, 24hUPro, anti-dsDNA antibody, anti-Sm antibody, anti-SSA antibody, anti-SSB antibody, anti-RNP antibody, and hypocomplementemia. Kaplan-Meier curves and log-rank tests were used to perform the univariate analyses that determined potential risk factors, and factors with values of $P<0.10$ in the univariate analyses were included in a stepwise multivariate Cox proportional hazards model. Finally, factors that had values of $P\leq0.05$ were considered statistically significant confounders associated with death or SLE flares. A biomedical statistician undertook a statistical review of the study's data.

Results

Baseline characteristics

Table 1 presents the baseline demographic characteristics of 58 patients who were diagnosed with SLE-related PLE at a median age of 35.3 years (range: 12–71 years). Forty-six patients were female, and the female-to-male ratio was 3.83:1. The mean (SD) time from disease onset to diagnosis was 44.0 (66.1) months. Fifty-three patients presented with

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Table 1: Baseline characteristics of SLE-PLE patients

Characteristics[1]	Results
Gender (female:male), *n*	46:12
Diagnosis age, years, mean ± SD	35.3 ± 13.6
PLE as initial manifestation, *n* (%)	31 (53.5)
SLE duration, months, mean ± SD	44.0 ± 66.1
Clinical characteristics, *n* (%)	
Edema	52 (89.7)
Fluid accumulation in the third space[2]	56 (96.6)
Gastrointestinal symptoms, n (%)	
Distension	40 (69.0)
Diarrhea	27 (46.6)
Abdominal pain	10 (17.2)
Vomiting	11 (19.0)
Other concomitant organ involvement, n (%)	
Skin/mucocutaneous	18 (31.0)
Alopecia	7 (12.1)
Arthritis	9 (15.5)
Serositis	45 (77.6)
Lupus nephritis	34 (58.6)
Neuropsychiatric SLE	6 (10.3)
Hematologic	13 (22.4)
Immune indices, *n* (%)	
α-dsDNA	12 (20.7)
α-Sm	12 (20.7)
α-SSA	30 (51.7)
α-SSB	8 (13.8)
α-RNP	17 (29.3)
α-rRNP	3 (5.2)
Hypocomplementemia	51 (87.9)
Biochemical indices, mean ± SD	
Serum albumin, g/L	16.61 ± 4.90
Total cholesterol, mmol/L	10.80 ± 8.84
24-hour urine protein, g/24 hours	0.62 ± 1.09

[1]Data are presented as mean ± SD or *n* (%), unless otherwise stated.
[2]Fluid accumulation in third space includes ascites, pleural effusion, or pericardial effusion.
SLE, systemic lupus erythematosus; PLE, protein-losing enteropathy; dsDNA, double-stranded DNA; Sm, Smith; SSA/SSB, Sjögren syndrome antigen A/B; RNP, ribonucleoprotein; SD, standard deviation.

symptoms associated with PLE as the initial manifestation of SLE.

Clinical characteristics and laboratory test results

Peripheral edema was present in 52 patients (89.7%), and it was the most common symptom. Almost 2/3 of the patients had GI symptoms, including distension (*n* = 40, 68.9%), diarrhea (*n* = 27, 46.6%), vomiting (*n* = 11, 19.0%), and abdominal pain (*n* = 10, 17.2%). Fifty-one patients (88.0%) had ascites, 44 (75.8%) had pleural effusion, and 32 (55.2%) had pericardial effusion.

Only 16 patients (27.6%) presented with GI symptoms didn't have other organ/system involvement, and 42 patients had other organ/system involvement, including serositis (*n* = 45, 77.6%), LN (*n* = 34, 57.6%), neuropsychiatric SLE (*n* = 6, 10.3%), and hematologic disorders (*n* = 13, 22.4%). Of the 34 patients with LN, 13 (22.4%) had baseline 24hUPro secretions >0.5 g, including 2 with nephrotic syndrome. The mean (SD) SLEDAI-2K score was 7.9 (4.9) points (range: 2–27 points). Regarding the SLEDAI scores, 15 patients (25.86%) had inactive or mildly active (0–4 points) disease, 26 patients (44.8%) had mild (5–9 points) disease, 12 patients (20.7%) had moderate (10–14 points) disease, and 5 patients (8.6%) had severe (≥ 15 points) disease.

The laboratory test results showed that 98.3% of the patients were ANA-positive, 87.9% had hypocomplementemia, 51.7% were anti-SSA antibody-positive, and 62.1% had high total cholesterol levels. These were the most common abnormalities in the laboratory test results. The mean (SD) serum albumin level was 16.61 (4.90) g/L.

Diagnosis and sites of protein leakage

Twenty-six patients (44.8%) underwent ^{99m}Tc HSA scintigraphy, and all had PLE. Most of these patients had proteinuria and intractable hypoalbuminemia, and ^{99m}Tc HSA scintigraphy helped to differentially diagnose the causes of hypoalbuminemia in these patients. The most common site of protein leakage was small intestine in 21 of 26 patients (80.8%), followed by large intestine in 15.4% and the stomach in 3.8% of the patients.

Treatment

Initially, glucocorticoids were administered to all 58 patients, of whom 18 (31.0%) received methylprednisolone pulse therapy. Immunosuppressants were administered to 91.3% of the patients. Cyclophosphamide (CTX) was administered to 48 patients (82.8%), and it was the most commonly used immunosuppressant. Other immunosuppressants administered included mycophenolate mofetil, cyclosporine A, and *Tripterygium wilfordii*.

Mortality and survival analysis

Eleven patients were lost to follow-up and excluded; so, 47 patients were finally enrolled in the survival analysis. All 47 patients were followed for >12 months, with an average follow-up duration of 58.6 months.

Five (10.6%) deaths occurred during follow-up. The causes of death were septic shock (*n* = 2), SLE flare (*n* = 2), and

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leukemia (*n* = 1). The 1-, 3-, and 5-year survival rates were 93.6%, 91.3%, and 88.4%, respectively (Figure 1A).

Table 2 compares the characteristics of the patients who died and survived. The groups were similar regarding the average serum albumin and total cholesterol levels. Patients who died had a significantly higher mean (SD) 24hUPro level (2.19 [2.70] g) than the patients who survived (0.51 [0.76] g) (*P* = 0.002).

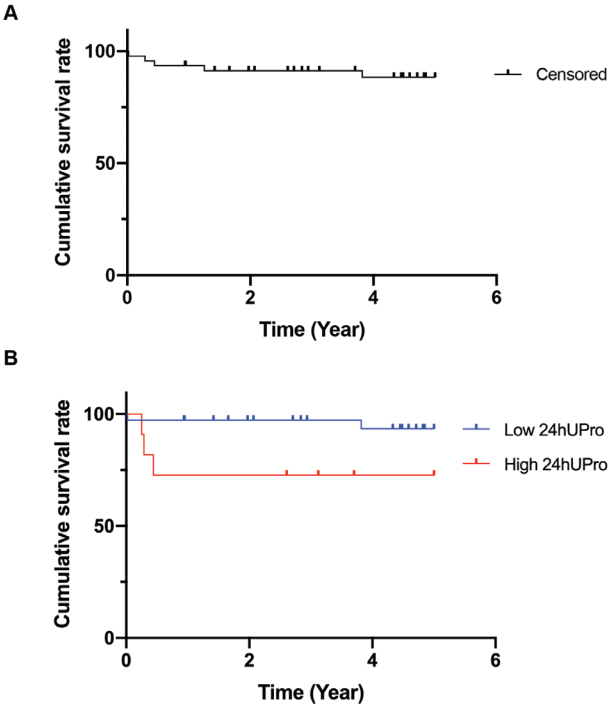

Figure 1: (A) Kaplan-Meier survival curve for 47 patients with systemic lupus erythematosus (SLE)-related protein-losing enteropathy (PLE). The 1-, 3-, and 5-year survival rates were 93.6%, 91.3%, and 88.4%, respectively. (B) Kaplan-Meier survival curve for patients with SLE-related PLE stratified according to the presence of high levels of urine protein, defined as a 24-hour urine protein (24hUPro) levels ≥0.5 g. The patients with 24hUPro ≥0.5 g had a higher mortality rate (χ^2 = 4.518, P = 0.033).

Table 2: Comparison of clinical characteristics between survival group and death group

Characteristics[1]	Survival (*n* = 42)	Death (*n* = 5)	*P*-value
Female, no. of patients (%)	33 (78.6)	5 (100)	NA
Age, years	34.9 ± 13.4	40.0 ± 20.2	0.452
Biochemical indices			
Serum albumin, g/L	16.75 ± 5.11	16.26 ± 6.04	0.840
Total cholesterol, mmol/L	10.61 ± 9.32	13.92 ± 0.43	0.623
24-hour urine protein, g	0.51 ± 0.76	2.19 ± 2.70	0.002
SLEDAI-2K	7.5 ± 4.9	10.6 ± 4.3	0.178

[1]Data are presented as mean ± SD or *n* (%), unless otherwise stated.
NA, not applicable; SD, standard deviation; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

The Kaplan-Meier analysis, log-rank test, and univariate Cox regression model identified neuropsychiatric involvement, LN, and the 24hUPro level as possible risk factors associated with mortality. The Cox multivariate regression model determined that the 24hUPro level was the only independent risk factor associated with death (β coefficient = 0.440 [0.174], *P* = 0.012). Figure 1B presents Kaplan-Meier curves that stratified survival according to the presence of high 24hUPro levels that were defined as >0.5 g/24 hours.

Flares and associated risk factors

Five flares were recorded in 47 patients after the first clinical remissions, and all occurred during the processes of immunosuppressant dosage tapering or treatment withdrawal. The 5-year flare rate was 10.64%. Flares manifested as PLE (*n* = 3), LN (*n* = 1), or hematological disorder (*n* = 1). Applying a limit of 1 SD, we stratified the patients into 3 groups according to their serum albumin levels as follows: mild hypoalbuminemia (Alb ≥22 g/L) (10.3%), moderate hypoalbuminemia (12 g/L≤ Alb <22 g/L) (77.6%), and severe hypoalbuminemia (Alb <12 g/L) (12.1%). The Kaplan-Meier analysis, log-rank test, and a Cox regression model confirmed that severe hypoalbuminemia, i.e., a serum albumin concentration <12 g/L, was a risk factor associated with flares (hazard ratio, 10.345; 95% confidence interval, 1.690–63.321) (Figure 2).

Discussion

To the best of our knowledge, this is the first study to explore the long-term prognoses of SLE-related PLE from a relatively large cohort of patients. The patients in our cohort mainly presented with symptoms associated with hypoalbuminemia, including edema and polyserositis, especially ascites. As many patients with SLE-related PLE were complicated by serositis (77.6%), we supposed that the polyserositis fluid could be exudative or transudative or sort of in between. This notion was supported by the findings from a previous study by Law *et al*.,[17] who showed that contrary to the general belief that most PLE patients had transudative polyserositis fluid caused by hypoalbuminemia, fluid accumulation can be either transudative or exudative.

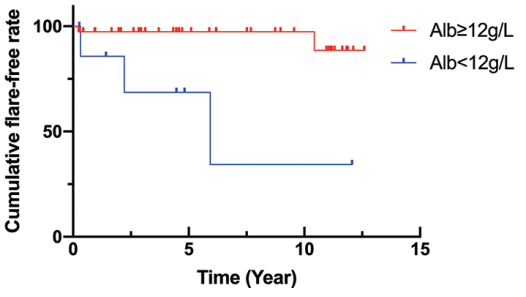

Figure 2: Kaplan-Meier curve showing the flare-free rate for patients with systemic lupus erythematosus-related protein-losing enteropathy. Patients with an albumin level ≥0.5 g had higher flare rates (χ^2 = 9.675, P = 0.002).

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Regarding organ involvement, LN was the most common concomitant disorder, followed by hematological disorders and neuropsychiatric SLE. Diarrhea was the most common GI symptom, but >⅓ of the patients in our cohort did not have any GI symptoms, which is largely consistent with the findings from previous studies[16,19–21]; hence, GI involvement in patients with SLE-related PLE could be overlooked by clinicians.

Most patients in our cohort showed moderate-to-severe reduction in serum albumin levels and hypercholesterolemia, making it hard to be differentiated from NS, especially when both conditions coexisted. Our previous study proposed that a combination of serum albumin <22 g/L and 24hUPro <0.8 g had the greatest diagnostic accuracy for SLE-related PLE, with a sensitivity of 0.818 and a specificity of 0.989.[16] In this extended cohort, 81.0% patients met the criteria, indicating a high sensitivity for this screening test in SLE patients. These criteria might help clinicians screening patients with SLE for the presence of PLE. However, to confirm a diagnosis, ^{99m}Tc HSA scintigraphy should be performed. Half of the patients in this study underwent ^{99m}Tc HSA scintigraphy, and all of the patients had PLE. In addition to its high level of diagnostic specificity, ^{99m}Tc HSA scintigraphy can locate sites of protein leakage.[22] In our cohort, protein leakage was most commonly found in small intestine, followed by large intestine and stomach.

Interestingly, unlike patients with nephrotic syndrome, who tend to develop venous or arterial thrombosis, patients in our study were free from thromboembolic events. Further studies are needed to understand the low prevalence of thromboembolic events in patients with SLE-related PLE.

The overall mortality rate among the patients with SLE-related PLE was 10.64%. The 1-, 3-, and 5-year survival rates of the SLE-related PLE patients were 93.6%, 91.3%, and 88.4%, respectively, and they were lower than patients with typical SLE (98.4%, 95.5%, and 93.8%, respectively) in our center (unpublished data). Infections caused 3 of the 5 deaths in our cohort. Li *et al*.[20] undertook a systematic review of 184 patients with SLE and showed that the overall mortality rate was 2.17%, and the deaths were caused by infections, including bacterial meningitis (1/4), pneumonia (2/4), and a superimposed infection (1/4). The follow-up time of this study is long, so this may lead to the differences between the results of the 2 studies. Vulnerability to infections might be caused by a loss of immunoglobulins as a consequence of PLE and/or corticosteroid and immunosuppressant usage. Avoiding infection is crucial for patients with SLE-related PLE.

Analysis of the risk factors revealed that the 24hUPro level was associated with increased mortality. Urine protein loss can exacerbate hypoalbuminemia caused by PLE, leading to further internal environment disturbance. Therefore, we suggest that nutrition support should be timely administered on SLE-related PLE patients who are complicated with increased 24hUPro, so as to decrease the odds of infection and mortality.

The 10-year flare rate was 10.64% in our cohort. Most flares (4/5) in our cohort occurred during the processes of glucocorticoid dosage tapering or withdrawal. Although the results from previous studies have shown that most patients respond well to a combination of high-dose prednisone and azathioprine/CTX initially, more gradual tapering could be considered to prevent flares in patients with SLE-related PLE. Furthermore, severe hypoalbuminemia (≤12 g/L) was a predictor of SLE flares. Hence, more intensive treatment and nutrition support might be appropriate to achieve better disease control in these high-risk patients.

The key limitation of our study is the relatively small number of patients, which is a consequence of the rarity of the PLE disease subtype. Moreover, this was a retrospective study, and some of the data were missing and difficult to obtain. Future prospective studies are necessary that involve large number of patients to further explore the prognosis of and risk factors for PLE patients.

Conclusions

Patients with SLE-related PLE seem to have worse outcomes compared with patients with typical SLE symptoms, and they may be more easily overlooked as a consequence of the absence of typical GI symptoms. Infection was the leading cause of death among patients with SLE-related PLE in this study, and the 24hUPro level was associated with increased mortality. Most disease flares occurred during the processes of glucocorticoid tapering or withdrawal, and they were associated with severe hypoalbuminemia. Therefore, clinicians must prevent infections, provide more comprehensive monitoring of patients with severe proteinuria, and exercise more care while tapering glucocorticoid dosages.

Declarations

None.

Conflict of Interest

The authors declare no conflicts of interest.

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Ethical Statement

There are no ethical related issues to this article.

Informed Consent

Informed consents have been obtained.

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