Clinical Features, Morbidity, and Risk Factors of Intestinal Pseudo-obstruction in Systemic Lupus Erythematosus: A Retrospective Case-control Study

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ABSTRACT. ***Objective.*** To analyze the epidemiology, clinical characteristics, and risk factors for systemic lupus erythematosus-related intestinal pseudo-obstruction (SLE-IPO).

Methods. We retrospectively examined 85 patients with SLE with IPO as the case group and 255 randomly matched patients with SLE without any gastrointestinal manifestations as the control group, out of 4331 inpatients at the Peking Union Medical College Hospital (PUMCH) from 2003 to 2014.

Results. Over the last 11 years at PUMCH, the prevalence of IPO in patients with SLE was 1.96% and the in-hospital fatality rate was 7.1%. Of these patients, 57.6% presented with IPO as the initial affected system of SLE, and the rate of misdiagnosis was about 78%. Pyeloureterectasis was the most common complication (58.9%) in patients with SLE-IPO and the incidence of biliary tract dilation was 7.1%. Patients with SLE with IPO were always diagnosed at an earlier stage of SLE with a higher frequency of hematological disturbance, polyserositis, and hypocomplementemia. Pyeloureterectasis, hypocomplementemia, and elevated C-reactive protein levels in serum were independent risk factors for IPO in SLE disease. Patients with SLE-IPO with long IPO duration and those diagnosed during late stages of SLE or concurrent with pyeloureterectasis and megacholedochus always had an unfavorable outcome.

Conclusion. IPO is a rare complication, but commonly presents as the initial affected system of SLE, which can lead to a difficult diagnosis and delayed treatment. SLE-IPO occurrence concomitantly with pyeloureterectasis and megacholedochus showed a severe clinical situation in our cohort. Thus, patients with SLE-IPO with systemic smooth muscular involvement should be diagnosed early and treated aggressively. (J Rheumatol First Release January 15 2016; doi:10.3899/jrheum.150074)

Key Indexing Terms:
INTESTINAL PSEUDO-OBSTRUCTION SYSTEMIC LUPUS ERYTHEMATOSUS
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Systemic lupus erythematosus (SLE) is a common autoimmune disease characterized by multiple organ involvement, including the gastrointestinal (GI) tract, such as intestinal pseudo-obstruction (IPO), mesenteric vasculitis, protein-losing enteropathy, and others[1,2,3]. IPO is characterized by ineffective intestinal motility[4], intestinal

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obstruction without identifiable organic obstruction lesions, and abdominal distension with sluggish or absent peristalsis[5]. IPO was originally considered to be an uncommon complication of SLE, but growing evidence has shown that it also can be associated with increased morbidity and mortality if treatment is not initiated promptly[6]. Further, IPO can be the initial manifestation of SLE in some patients and is easily misdiagnosed and incorrectly treated in the early stages[7]. Delays in diagnosis and treatment also lead to adverse consequences. Considering the risks of this condition, it is important for clinicians to have a comprehensive understanding of SLE-related IPO (SLE-IPO) and treat the condition at an appropriate time.

The clinical characteristics and prognostic implications of SLE-IPO remain largely unknown. To the best of our knowledge, about 40 cases of IPO secondary to SLE have been reported in the past[8,9,10], but clinical data on this issue have been limited to case reports or small cohorts[11,12,13,14,15,16]. Therefore, additional studies are still needed to improve our understanding of SLE-IPO.

The objective of our study was to determine the epidemiology, characteristics, risk factors, and prognosis of SLE-IPO. We retrospectively evaluated medical records of 85 patients with SLE with IPO and 255 control patients with SLE without IPO in a large monocentric cohort.

MATERIALS AND METHODS

Patients. We examined the case record of all patients who were admitted to the Peking Union Medical College Hospital (PUMCH) from August 2003 to August 2014. For patients with SLE with IPO, the inclusion criteria were (1) patients who fulfilled the revised American College of Rheumatology classification criteria for SLE[17], and (2) patients who had IPO diagnosed according to clinical symptoms, including abdominal distension, pain, nausea, vomiting, and constipation with absence of bowel sounds; gaseous small bowel distension with air-fluid levels were observed by radiography or thickened gastric wall and dilated small or large bowels by computed tomography (CT) scan[18]. Patients with non-SLE IPO, including infection, intestinal mechanical obstruction, or other connective tissues diseases, were excluded. Pyeloureterectasis and megacholedochus patients were diagnosed by CT scan. Based on these criteria, we identified 85 cases of SLE with IPO out of 4331 patients with SLE (1.96%) as the case group. These were matched 1:3 on the basis of sex and age, then 255 contemporaneous patients without IPO hospitalized in our center were randomly selected as the control group. The disease activity of SLE was evaluated using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[18,19]. Our study was approved by the Review Board of PUMCH, and all patients provided written informed consent.

Clinical and laboratory data. We reviewed and compared the following factors: demographic data, age at SLE onset, age at IPO onset, SLE disease duration (interval time from onset of SLE to hospitalization), IPO disease duration, disease signs and symptoms, and visceral organ disorders, as well as the following laboratory findings[20]: hematological disturbance (thrombocytopenia $< 100 \times 10^9$/l; leukocytopenia $< 4.0 \times 10^9$/l or lymphocytopenia $< 1.0 \times 10^9$/l), erythrocyte sedimentation rate, the serum levels of C-reactive protein (CRP), hypocomplementemia [decrease in CH50, complement factor 3 (C3), or C4 below the lower limit of normal for testing laboratory], antinuclear antibody (ANA), anti-dsDNA antibody, anti-extractable nuclear antigen antibodies (including anti-SSA, anti-SSB, anti-Sm, anti-RNP, anti-Ro52, and anti-rRNP antibodies), anticardiolipin antibody, lupus anticoagulant, SLEDAI, and treatments used. SLEDAI, laboratory investigations, and clinical features were assessed in the first week of hospitalization. SLEDAI could be acquired directly from medical records; if there were missing data of SLEDAI, we calculated the scores according to the medical records and results of routine laboratory tests.

Statistical analysis. Continuous variables were expressed as mean ± standard error (SE), and the Student t test or Wilcoxon signed-rank test were used to analyze the differences between 2 study groups. Categorical data were shown as percentages and compared using a chi-square test or Fisher's exact test, as appropriate. The associations between baseline variables and risk of SLE-IPO were estimated by computing OR and 95% CI using logistic regression analyses. All statistical tests were 2-tailed and a $p < 0.05$ was considered statistically significant. The 19th version of SPSS software (IBM Inc.) was used for the statistical analyses.

RESULTS

General clinical profiles. A total of 85 patients (82 women and 3 men) were diagnosed with SLE-IPO at PUMCH between August 2003 and August 2014. The incidence of SLE-IPO was 1.96% (85/4331). The onset of SLE occurred between ages 10–62 years (mean ± SE 29.7 ± 1.3 yrs) and the SLE disease duration ranged from 0.5 months to 252 months (mean 32.9 ± 5.5 mos; Table 1). The age of onset of IPO was between ages 14 and 62 years (mean 31.5 ± 1.28 yrs) and IPO duration of the patients with SLE-IPO was between 0.3 months and 123.8 months (median 4 mos). Among them, 57.6% of patients (49/85) presented with IPO as the initial affected system of SLE, whereas 36 patients (42.4%) presented with IPO as a complication during the course of SLE. We found that there was a time lag before clinicians realized the underlying SLE process. The median time from onset of IPO to diagnosis was 1.83 months (range 0.1–122.7 mos) and 46 patients (54.1%) were misdiagnosed. Among these 46 patients, 38 demonstrated IPO as the initial presentation of SLE, suggesting that 77.6% (38/49) of patients with SLE with IPO as their first manifestation may have been misdiagnosed by their primary physician. Nevertheless, when IPO occurred secondary to SLE, the misdiagnosis rate significantly decreased (8/36, 22.2%).

Patients with SLE-IPO had significantly shorter SLE disease duration than the control group ($p < 0.05$). The in-hospital mortality of SLE-IPO was 7.1% (6/85), which was similar to the control group. There were no statistically significant differences between the SLE-IPO and control groups in terms of age and sex ($p > 0.05$; Table 1).

IPO features of the patients with SLE-IPO. Among the 85 patients with SLE-IPO studied, 79 (92.9%) had abdominal pain and distention, 74 (87.1%) had nausea and vomiting, 44 (51.8%) had diarrhea, 16 (18.8%) had urinary frequency, and 31 (36.5%) were sluggish or lacked peristalsis. Each patient with SLE-IPO had radiological abnormalities, and 51 patients (60.0%) lost at least 2 kg during IPO progression.

Further, 50 patients with SLE-IPO (58.9%) experienced concurrent pyeloureterectasis, and 6 of them had complications of biliary tract dilation (7.1%). This rare triad of GI, genitourinary, and hepatobiliary hollow viscera dilatation has

Table 1. Clinical characteristics of patients with SLE-IPO and controls. Values are mean ± standard error or n (%) unless otherwise specified.

Variable	Cases, n = 85	Control, n = 255	p
Demographics			
Female	82 (96.5)	246 (96.5)	1
Age, yrs	32.4 ± 1.3	32.3 ± 0.8	0.975
Clinical manifestations			
SLE onset age, yrs	29.7 ± 1.3	32.4 ± 2.7	0.594
Disease duration, mos	**32.9 ± 5.5**	**52.2 ± 4.7**	**0.011**
Mucosal ulcers	20 (23.5)	41 (16.1)	0.338
Alopecia	**42 (49.4)**	**57 (22.3)**	**0.01**
Arthritis	34 (40.0)	96 (37.6)	0.789
Polyserositis	**68 (80.0)**	**102 (40.0)**	**< 0.001**
Nephrotic syndrome	**14 (16.5)**	**117 (45.8)**	**0.01**
Nervous system disturbance	15 (17.6)	57 (22.4)	0.426
Pyeloureterectasis	**50 (58.8)**	**5 (2.0)**	**< 0.001**
Laboratory tests			
Hematological disturbance	**50 (58.8)**	**109 (43.0)**	**0.013**
Thrombocytopenia	26 (30.6)	56 (21.9)	0.129
Leukocytopenia	**38 (47.7)**	**55 (21.6)**	**< 0.001**
Elevated ESR	53 (62.4)	173 (67.8)	0.97
Elevated CRP	**40 (47.1)**	**75 (29.3)**	**0.001**
Hypoalbuminemia	**63 (74.1)**	**146 (57.2)**	**0.007**
Hypocomplementemia	**77 (90.6)**	**169 (66.3)**	**< 0.001**
ANA positivity	**79 (92.9)**	**196 (76.9)**	**0.001**
Anti-dsDNA antibody positivity	30 (35.3)	121 (47.5)	0.055
Anti-SSA antibody positivity	**50 (58.8)**	**116 (45.5)**	**0.046**
Anti-SSB antibody positivity	**16 (18.8)**	**11 (4.3)**	**< 0.001**
ANCA positivity	2 (2.4)	5 (1.9)	0.724
SLEDAI	**12.1 ± 0.8**	**10.0 ± 0.4**	**0.017**
High-dose steroids pulse	44 (51.8)	100 (39.2)	0.094
Mortality	6 (7.1)	14 (5.5)	0.598

Statistically significant values ($p < 0.05$) are in bold face. SLE: systemic lupus erythematosus; IPO: intestinal pseudo-obstruction; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ANA: antinuclear antibody; SLEDAI: SLE Disease Activity Index; ANCA: antineutrophil cytoplasmic antibodies.

been described previously[8,21]. In our study, 6 cases out of 85 patients with SLE-IPO had this triad.

SLE features of the case group. The incidence of alopecia, polyserositis, hematological disturbance (leukocytopenia), and pyeloureterectasis in patients with SLE-IPO was significantly higher than the control group ($p < 0.01$). Patients with SLE-IPO showed a lower incidence of nephrotic syndrome ($p < 0.05$) and a higher disease activity based on the SLEDAI score compared with patients with SLE without IPO (12.1 ± 0.8 vs 10.0 ± 0.4, respectively, $p < 0.05$). Comparisons of laboratory findings showed that hypoalbuminemia, hypocomplementemia, positive ANA, and elevated CRP levels were more common in patients with SLE-IPO than in the control group. In addition, the incidence of positive anti-SSA antibodies and anti-SSB antibodies was significantly higher in patients with SLE-IPO ($p < 0.05$; Table 1).

Treatment for SLE-IPO. All patients with SLE-IPO were treated with systemic corticosteroids combined with immunosuppressants (e.g., cyclophosphamide, cyclosporine, tacrolimus, and hydroxychloroquine). Forty-four patients (51.8%) received methylprednisolone intravenous pulse therapy in the SLE-IPO group, which was not statistically different from the number in the control group (100/255, 39.2%, $p = 0.094$; Table 1).

Prognosis for SLE-IPO. Most of the patients (65/85; 76.5%) recovered after steroid and immunosuppressant treatment in combination with parenteral nutrition and symptomatic treatment. Nevertheless, a total of 14 patients (16.5%) developed the following complications: 6 had irreversible pyeloureterectasis, 3 total parenteral nutrition dependence, 2 experienced infection, 1 had severe pancreatitis, 1 had diffuse alveolar hemorrhage, and 1 experienced renal failure. Six patients with SLE-IPO (7.1%) died of infection because of delayed medical treatment: 5 of them had pyeloureterectasis as a result of delayed diagnosis and surgery, 1 had neuropsychiatric SLE, and 1 died of suboptimal corticosteroids therapy.

Those who died and the patients with complications (20/85) were more likely to be older at the onset of SLE and have GI symptoms as the initial presentation ($p = 0.005$). Patients with SLE-IPO who recovered also had a shorter IPO disease duration (8.02 ± 2.53 vs 22.10 ± 5.65 months,

p = 0.013), lower incidence of misdiagnosis (49.2% vs 70.0%, p = 0.047), and received a quicker diagnosis (7.08 ± 2.57 vs 16.82 ± 4.65 months, p = 0.056) and higher incidence of hypocomplementemia compared with those who died and those with complicated SLE-IPO (Table 2). The incidences of these conditions in the patients with SLE-IPO who recovered were significantly lower than in the patients who did not recover: nephrotic syndrome, pyeloureterectasis, and megacholedochus (Table 2).

Risk and prognosis factors for SLE-IPO. As shown in Table 3, pyeloureterectasis (OR 90.322, p < 0.001), hypocomplementemia (OR 5.519, p = 0.011), hypoalbuminemia (OR 5.215, p = 0.015), and elevated CRP (OR 3.056, p = 0.045) were independent risk factors for IPO in patients with SLE. In addition, nephrotic syndrome (OR 30.54, p = 0.007), pyeloureterectasis (OR 24.50, p = 0.045), and megacholedochus (OR 16.99, p = 0.042) were independent poor prognostic factors for patients with SLE-IPO (Table 4).

DISCUSSION

Patients with SLE might present or develop IPO concomitant to their primary disease[14]. Although the number of emerging case reports continues to increase, there is still a paucity of quality data regarding the detailed clinical features and risk factors of SLE-IPO. To improve our understanding of this rare disorder, we retrospectively reviewed the largest size of SLE-IPO samples that has ever been assessed. In our study, the incidence of IPO in patients with SLE was 1.96% and the in-hospital mortality was 7.1%. In addition, 57.6% of patients with SLE-IPO presented with the condition as the initial symptom of SLE, and the rate of misdiagnosis was about 78%. When IPO presents as the initial affected system of SLE, it is difficult for clinicians to identify the underlying disease[11]. In fact, most of the patients with SLE-IPO had good therapeutic response to corticosteroid and immunosuppressants[22]. However, misdiagnosis and delayed treatment always leads to an unfavorable outcome. Moreover, some

Table 2. Clinical data comparison for different prognostics of patients with SLE-IPO. Values are mean ± standard error or n (%) unless otherwise specified.

Variable	With Complications or Dead, n = 20	Recovery Group, n = 65	p
Demographics			
Female sex	20 (100)	62 (95.4)	0.775
Age, yrs	33.85 ± 2.63	31.98 ± 1.51	0.546
SLE flare age, yrs	30.65 ± 2.87	29.42 ± 1.39	0.678
SLE duration, mos	34.92 ± 8.06	32.37 ± 5.99	0.828
IPO onset age, yrs	31.85 ± 2.78	31.39 ± 1.45	0.879
IPO duration, mos	22.10 ± 5.65	8.02 ± 2.53	0.013
IPO as initial presentation	**17 (85.0)**	**32 (49.2)**	**0.005**
With misdiagnosis	**14 (70.0)**	**32 (49.2)**	**0.047**
Time of final diagnosis, mos	16.82 ± 4.65	7.08 ± 2.57	0.056
Clinical manifestations			
Mucosal ulcers	1 (5.0)	18 (27.7)	0.031
Arthritis	6 (30.0)	28 (43.1)	0.434
Alopecia	13 (65.0)	29 (44.6)	0.131
Polyserositis	17 (85.0)	51 (78.5)	0.523
Nephropathy	14 (70.0)	47 (72.3)	1.000
Nephrotic syndrome	**8 (42.1)**	**6 (9.2)**	**0.001**
Nervous system disturbance	3 (15.0)	12 (18.5)	0.723
Hematological disturbance	8 (40.0)	42 (64.6)	0.066
With pyeloureterectasis	**17 (85.0)**	**33 (50.8)**	**0.009**
With megacholedochus	**4 (20.0)**	**2 (3.1)**	**0.010**
With pancreatitis	2 (16.7)	5/56 (8.9)	0.598
Laboratory tests			
Elevated ESR	16 (84.2)	37 (63.8)	0.153
Elevated CRP	9 (45.0)	31 (47.7)	1.000
Hypoalbuminemia	16 (80.0)	47 (73.4)	0.769
Hypocomplementemia	**15 (75.0)**	**62 (95.4)**	**0.006**
Anti-dsDNA antibody positivity	6 (30.0)	24 (36.9)	0.790
Anti-SSA antibody positivity	12 (60.0)	38 (58.5)	1.000
Anti-SSB antibody positivity	4 (20.0)	12 (18.5)	0.878
High-dose steroids pulse	12 (60.0)	32 (49.2)	0.451
SLEDAI	11.70 ± 1.64	12.16 ± 0.84	0.796

Statistically significant values (p < 0.05) are in bold face. SLE: systemic lupus erythematosus; IPO: intestinal pseudo-obstruction; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SLEDAI: SLE Disease Activity Index.

Table 3. Risk factors for patients with SLE-IPO.

Variables	OR	95% CI	p
Pyeloureterectasis	90.322	21.283–383.32	< 0.001
Hypocomplementemia	5.519	1.482–20.552	0.011
Hypoalbuminemia	5.215	1.375–19.773	0.015
Elevated CRP	3.056	1.026–9.106	0.045

SLE: systemic lupus erythematosus; IPO: intestinal pseudo-obstruction; CRP: C-reactive protein.

Table 4. Prognosis factors for patients with SLE-IPO.

Variables	OR	95% CI	p
Nephrotic syndrome	30.54	2.02–188.36	0.007
Pyeloureterectasis	24.50	1.07–558.94	0.045
Megacholedochus	16.99	1.11–259.77	0.042
IPO as initial presentation	8.94	0.86–93.26	0.067

SLE: systemic lupus erythematosus; IPO: intestinal pseudo-obstruction

SLE-IPO complications could be life threatening if not treated promptly. Therefore, it is clinically important for gastroenterologists, surgeons, and emergency physicians to recognize these IPO manifestations and avoid misdiagnosis and treatment delay.

The underlying mechanisms involved in SLE-IPO development are far from being fully elucidated. Previous studies indicate that it is a result of vasculitis of the visceral smooth muscles, which leads to muscular damage and hypomobility[11,13,14,23]. Our results suggest that 58.9% of the patients with SLE-IPO had concurrent pyeloureterectasis or megacholedochus, and the underlying mechanism of SLE-IPO might be because of vasculitis of the visceral smooth muscles, thus leading to muscular damage and hypomotility. This hypothesis is consistent with a previous report[14]. Pardos-Gea, *et al* first demonstrated an association between IPO and pyeloureterectasis and biliary tract dilatation[14,24], and Chen, *et al* named this rare triad as visceral muscle dysmotility syndrome (VMDS)[15]. Similar to our findings, biliary tract dilatation occurred more often with pyeloureterectasis in patients with SLE-IPO. The VMDS is a rare clinical syndrome and a determinant complication[8]. In our study, the incidence of VMDS in patients with SLE-IPO was 7.1%, and in patients with SLE was 0.139%. To our knowledge, ours is the first report of the morbidity of this rare trilogy in a large cohort of patients with SLE. Moreover, we found that pyeloureterectasis was an independent risk factor for IPO in patients with SLE. Therefore, patients who have IPO concurrent with pyeloureterectasis or biliary tract dilatation, even in the absence of typical SLE manifestations, should also be carefully assessed for underlying SLE[7].

In our study, the average SLE duration of SLE-IPO was significantly shorter than the duration of SLE without IPO. This may be because most of the SLE-related IPO manifested as the initial presentation. Second, GI symptoms (e.g., abdominal pain, distention, nausea, and vomiting) have a direct effect on patients' lives and drive patients to consult their doctor for treatment during early stages of the occurrence[7]. In addition, the shorter duration of SLE-IPO indicated that IPO may occur at early or active stages of SLE.

To date, no specific autoantibody has been detected in SLE-IPO[6]. However, a few case reports have noted the high prevalence of anti-SSB antibodies in patients with SLE-IPO[8,13,14]. Consistent with previous reports, we found that the frequency of positive anti-SSA and anti-SSB antibodies in patients with SLE-IPO was significantly higher than in control patients.

In our study, patients with SLE-IPO had increased incidences of alopecia, polyserositis, hematological disturbance (leukocytopenia; the cases caused by immunosuppressive agents were excluded), and elevated CRP levels, as well as higher SLEDAI scores. Moreover, we found that elevated CRP levels and hypocomplementemia were independent risk factors for IPO in patients with SLE. These results confirmed that the incidence of IPO is related to the activity of SLE disease.

The prognosis of SLE-IPO often depends on the severity of vital organ involvement[15]. Most of these patients showed a good response to therapy if SLE-IPO was diagnosed very early in the disease course and patients received optimal treatment. However, some patients (16.5%) had irreversible organ dysfunction despite aggressive treatment, and 7.1% of the patients with SLE-IPO died from infection or sepsis or had a delayed diagnosis and suboptimal corticosteroid therapy. We found that patients with SLE-IPO who were misdiagnosed, had a long IPO duration, were diagnosed during late stages of SLE, or who experienced concurrent systemic visceral muscle dysmotility always had an unfavorable prognosis. Therefore, early diagnosis and treatment are critically important for a favorable outcome.

We therefore propose that a thorough assessment for systemic diseases such as SLE be carried out in young female patients who have a recurrent acute abdomen without an obvious predisposing reason, and that they should be assessed for systemic disease involvement. If laboratory results indicate leukocytopenia or concurrent pyeloureterectasis, which is inconsistent with intestinal obstruction of acute abdomen, SLE should be considered as the underlying disease. Therefore, a comprehensive assessment of these patients at the time of acute abdomen provides important diagnostic information that may affect treatment and outcome.

Our study also found that the incidence of nephrotic syndrome is low in SLE-IPO, but it was a poor prognostic factor of patients with SLE-IPO. IPO will lead to hypoalbuminemia, and nephrotic syndrome might worsen this situation by increasing the susceptibility of infection, intes-

tinal absorption disturbance, therapeutic use disability, thrombosis, and even death. Therefore, supportive therapy is essential for these patients.

Although SLE-IPO in-hospital data from a large cohort were presented in our study, there were still several limitations. First, ours was a retrospective study from a single center, and we acknowledge that unmeasured factors might have influenced the outcomes. Further, the effect of SLE-IPO on longterm mortality cannot be determined from our analysis, and therefore further studies are still needed to confirm the results of the present study and determine the effect of SLE-IPO on late outcomes.

Despite the limitations, our study supports the contention that IPO usually occurs as the initial presentation of SLE, thus leading to difficult diagnosis. SLE-IPO always occurs concomitantly with pyeloureterectasis. Moreover, patients with SLE with visceral smooth involvement always have a poor prognosis. These findings suggest that early recognition of SLE-IPO is very important, because prompt treatment could significantly improve prognosis.

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