Clinical Features and Associated Factors of Abdominal Pain in Systemic Lupus Erythematosus

Shiwen Yuan, Fan Lian, Dongying Chen, Hao Li, Qian Qiu, Zhongping Zhan, Yujin Ye, Hanshi Xu, Liuqin Liang, and Xiuyan Yang

ABSTRACT. ***Objective.*** To evaluate the clinical characteristics of systemic lupus erythematosus (SLE)-induced abdominal pain in a cohort in South China and identify the risk factors for SLE-induced abdominal pain.

Methods. This is a retrospective cohort study of SLE patients with complaint of abdominal pain admitted to the first affiliated university hospital of Sun Yat-sen University between 2002 and 2011. Demographic information, clinical features, laboratory findings, SLE Disease Activity Index, and imaging characteristics were documented.

Results. Of the 3823 SLE patients reviewed, 213 patients complained of abdominal pain and 132 cases were considered SLE-induced. The most common causes were lupus mesenteric vasculitis (LMV; 73.5%, 97/132) and lupus pancreatitis (LP; 17.4%, 23/132). Other causes included appendicitis, acute gastroenteritis, and peritonitis. Univariate and multivariate logistic regression analysis indicated the European Consensus Lupus Activity Measurement (ECLAM) score was significantly associated with lupus-induced abdominal pain (OR = 1.858, 95% CI: 1.441–2.394, p < 0.001), LMV (OR = 1.713, 95% CI: 1.308-2.244, p < 0.001), and LP (OR = 2.153, 95% CI: 1.282, 3.617, p = 0.004). The serum D-dimer level (OR = 1.004, 95% CI: 1.002-1.005, p < 0.001) was a strongly associated factor for lupus-induced abdominal pain. Moderate and large amounts of ascetic fluid was significantly associated with lupus-induced abdominal pain and LMV. Elevated liver enzymes was a risk factor for LP (OR = 34.605, 95% CI: 3.591-333.472, p = 0.002).

Conclusion. LMV and LP were the leading causes of SLE-induced abdominal pain. The serum D-dimer was a strongly associated factor for lupus-induced abdominal pain. ECLAM score was a reliable index in assessment of SLE-associated abdominal pain. Elevated liver enzymes, and moderate or large amounts of ascites, were positively associated with lupus-induced abdominal pain. (First Release Nov 1 2013; J Rheumatol 2013;40:2015–22; doi:10.3899/jrheum.130492)

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Abdominal pain is a common manifestation of systemic lupus erythematosus (SLE), reported to occur in 8% to 40% of patients with SLE[1]. Various etiologies of SLE-induced abdominal pain and the concomitant situations can be a challenge for rheumatologists. Side effects of medication and primary gastrointestinal (GI) disorders can lead to diagnostic problems. Prompt and accurate assessment of SLE-induced abdominal pain is essential to devising an appropriate treatment strategy and helping to avoid unnecessary surgical intervention. Lupus vasculitis, affecting vessels of all sizes, plays an important part in the etiology of lupus-induced abdominal pain. Lupus vasculitis can cause lupus mesenteric vasculitis (LMV), vasculitic pancreatitis, and peritonitis, all significantly associated with increased mortality and poor outcome[2,3,4,5]. LMV, usually presenting as acute abdominal pain with severe symptoms and diffuse pathologic changes, is one of the main causes of abdominal pain in patients with SLE. Various GI lesions include mesenteric ischemia, bowel perforation, bowel obstruction and hemorrhage, etc. Prognosis of LMV varies in previous studies[3].

SLE-related acute pancreatitis (LP), a relatively rare but fatal complication of SLE, is characterized by acute abdominal pain, vomiting, and elevation of serum amylase[6,7]. Vasculitis may be the cause. SLE-related pancreatitis may be underdiagnosed[8]. Its mortality rate is higher than that of non–SLE-related pancreatitis[6]. Prompt

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diagnosis can be difficult, especially for the SLE patients with pancreatitis as the initial presentation[9].

Several clinical studies have been dedicated to identifying indicators in the occurrence of SLE-induced abdominal pain[10,11]. However, these studies showed that there are no differences in clinically important factors, such as demographic indices, autoantibody profiles, complements, and other organs involvement. So far, the predictive factors for the occurrence of lupus-induced pain have not been well established[12].

We conducted a retrospective cohort study to systematically examine the cause, differential diagnosis, and putative associated factors contributing to early identification of SLE-induced abdominal pain, particularly LMV and LP, the 2 leading causes of abdominal pain identified in our study, thus improving appropriate treatment administration and outcomes.

MATERIALS AND METHODS

Patients. A retrospective cohort study was conducted. Records were reviewed of 3823 patients with SLE consecutively admitted to the first affiliated hospital of Sun Yat-sen University, Guangzhou, China, between January 2002, and December 2011. Of them, 213 patients (5.6%) had SLE with abdominal pain, and 132 patients (3.5%) were finally diagnosed with SLE-induced abdominal pain. SLE was defined by 1997 revised American College of Rheumatology classification criteria[13].

Lupus mesenteric vasculitis was defined as[13] (1) clinical suggestions of involvement of multifocal bowel or multiple vascular territories, duodenal ischemic changes, and improvement when treated with intravenous steroid or immunosuppressant; or (2) pathological results from endoscope-guided biopsy showing vasculitis changes or at least 3 of the following signs: bowel wall thickening, target sign, dilatation of intestinal segments, engorgement of mesenteric vessels, and increased attenuation of mesenteric fat, which were identified on abdominal computed tomography (CT). Bowel wall thickening was diagnosed if the bowel wall was at least 3 mm thick in an area where the bowel was adequately distended, while the criterion for GI wall thickening was at least 5 mm[14]. The criterion for diagnosis of small-bowel dilation was > 2.5 cm diameter[15]; the criterion for diagnosis of large-bowel dilation was > 8.0 cm diameter[15]. The CT scans were reviewed by 2 independent radiologists blind to outcomes and their disagreements of diagnosis were resolved by consensus.

LP was defined as (1) the presence of typical clinical symptoms (including abdominal pain, nausea, and vomiting) and confirmed by more than a 3-fold elevation of serum amylase or lipase or evidence of image findings (CT scan or ultrasonography) or endoscopic retrograde cholangiopancreatography[16]; and (2) common causes of pancreatitis other than SLE, such as mechanical obstruction of pancreatic duct (most frequently a result of choledocholithiasis) and toxic-metabolic (secondary to alcohol intake, effect of certain drugs including steroid, hypercalcemia, or hypertriglyceridemia) having been ruled out.

The diagnosis of intestinal pseudoobstruction was made when (1) symptoms appeared such as subacute abdominal pain, nausea, vomiting, diarrhea, or constipation; (2) there were diffusely tender and absent bowel sounds on physical examination; (3) abdominal radiographs showed dilated loops of small bowel and air-fluid levels or circumferential thickening of the bowel on CT scan without mechanical obstruction; (4) antroduodenal-manometry motility studies showed intestinal hypomotility; and (5) other possible causes of intestinal obstruction were excluded[17,18,19,20,21].

The diagnosis of lupus urinary tract involvement (after ruling out other causes such as lithangiuria, infection, neuropathy, drug side effects, and malignancy) was considered if the following signs were identified on abdominal CT/ultrasound (US): bladder wall thickening, stenosis/dilatation of ureters, and hydroureteronephrosis[17,18].

The SLE Disease Activity Index (SLEDAI)[22] and the European Consensus Lupus Activity Measurement (ECLAM) score[23] were used to evaluate SLE activity.

Ascites were divided into 4 grades according to the amount detected by abdominal US: none, low, medium, and large. Low amounts of ascites was defined as an amount that can be recognized only by US around liver and between intestinal loops, but not by physical examination (< 0.5 l). Medium amounts of ascites indicated an amount not causing distension in the abdomen but with palpable liver and spleen easily visualized on US (0.5–2.0 l). Large amounts of ascites indicated distension in the abdomen and visualization on US (> 2 l)[23,24].

We documented demographic information, clinical symptoms, biochemical parameters, colonoscopy and gastroscopy, lactulose hydrogen breath test, antroduodenalmanometry motility study, abdominal and pelvic US, CT scanning and biopsy, and medications.

Statistical analysis. Logistic regression was used for associated factors contributing to SLE-induced abdominal pain, lupus mesenteric vasculitis, and LP. The Mann-Whitney U test and t test was used to compare continuous variables among 2 groups, and the chi-squared test was used to compare categorical variables. Mean ± SD is presented for continuous and ordinal data, while categorical data are presented as the absolute count and percentage.

Statistical analyses were performed using SPSS 16.0. A p value < 0.05 was considered statistically significant.

RESULTS

Causes of abdominal pain in patients with SLE. The causes of abdominal pain in patients with SLE are listed in Table 1. Among the 213 patients admitted during the study period for abdominal pain, 132 patients (62%) were diagnosed with SLE-induced pain, indicating SLE origin as a major cause of abdominal pain in these patients. GI tract and pancreas were the 2 most involved organs. About one-third of the patients (81/213, 38%) were diagnosed with infection, malignancy,

Table 1. Diagnosis of patients with systemic lupus erythematosus (SLE) who have abdominal pain.

Final Diagnosis	No. (%)
SLE-induced	132 (62.0)
Pancreatitis	23 (10.8)
Mesenteric vasculitis	97 (45.5)
Intestinal pseudoobstruction	7 (3.3)
Peritonitis	3 (1.4)
Renal vein thrombosis	2 (0.9)
Primary gastrointestinal disorder	47 (22.0)
Acute gastroenteritis	23 (10.8)
Acute appendicitis	9 (4.2)
Peptic ulcer	7 (3.3)
Gastroesophageal reflux disease	8 (3.8)
Primary hepatobiliary disease	18 (8.5)
Acute cholecystitis	10 (4.7)
Acute biliary pancreatitis	3 (1.4)
Acute cholangitis	5 (2.3)
Primary genitourinary diseases	14 (6.6)
Urinary tract infection	8 (3.8)
Pelvic inflammatory disease	4 (1.9)
Ovarian cyst torsion	2 (0.9)
Malignancy	2 (0.9)

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drug side effects, primary GI diseases, or pelvic disease not related to SLE.

Demographic and clinical characteristics of patients with SLE-induced abdominal pain. The majority of patients were female (108/132, 81.8%) and mean age at the onset of abdominal pain was 30.95 ± 14.94 years. The median time between the diagnosis of SLE and abdominal pain was 1 month, range 0 to 240 months.

The most frequent abdominal symptoms apart from abdominal pain were similar in LMV, LP, or pseudo-obstruction, such as abdominal distention (68/97, 70.1% for LMV; 11/23, 47.8% for LP; 7/7, 100% for pseudo-obstruction), diarrhea (57/97, 58.8% for LMV; 4/23, 17.4% for LP), nausea and vomiting (70/97, 72.2% for LMV; 17/23, 73.9% for LP; 5/7, 85.7% for pseudoobstruction), abdominal tenderness (65/97, 67% for LMV; 18/23, 78.3% for LP), or rebound tenderness and abdominal muscle guarding (19/97, 19.6% for LMV; 9/23, 39.1% for LP). Causes for abdominal symptoms other than SLE-induced abdominal involvements such as infectious serositis or lupus peritonitis were ruled out.

Ascites occurred in more than half the patients (73/132, 55.3%) with lupus-induced abdominal pain, being the most common concomitant GI manifestation. Other manifestations included oral ulcers (51/132, 38.6%) and elevated liver enzymes (39/132, 29.5%). Of all the lupus-induced abdominal pain, 7 patients (7/132, 5.3%) did not have other concomitant organ-system involvement.

Thromboembolism was noted in 4 cases of (4/132, 3.0%), all of which were LMV, including 2 splenic artery thrombosis, 1 pulmonary embolism, and 1 retinal vein occlusion, in which 2 cases presented positive antiphospholipid antibodies (aPL). Two patients were diagnosed with antiphospholipid syndrome. No thrombosis was found in other patients with SLE-induced abdominal pain. For the patients (51/132, 38.6%) with positive aPL, 49 had no specific evidence for thrombosis, and 2 cases of LMV presented thrombosis (1 retinal vein occlusion and 1 splenic artery thrombosis). None of the patients with positive aPL had gastrointestinal vascular thrombosis on CT scan. There was no difference in aPL between SLE-induced abdominal pain and non–SLE-induced abdominal pain.

Seven cases were diagnosed with intestinal pseudo-obstruction. All of them presented subacute abdominal pain, 5 cases presented nausea and vomiting, 1 presented diarrhea, and 1 presented constipation. Diffuse tender and absent bowel sounds were observed when performing the physical examination. Dilated bowel loops, multiple fluid levels, and circumferential thickening of the bowel were found on abdominal radiographs. Antroduodenalmanometry motility studies showed intestinal hypomotility.

Urinary tract involvement occurred in about one-fifth of the cases (28/132, 21.2%), which were 22 out of 97 lupus mesenteric vasculitis, 5 out of 7 intestinal pseudo-obstruction, and 1 out of 23 LP, respectively, but only one-third (9/28, 32.1%) of the patients exhibited frequency, urodynia, suprapubic pain, or dysuria. Few abnormal urinalysis results were found in those patients.

The patients with SLE-induced abdominal pain exhibited significantly increased ratio of D-dimer, polyserositis/ascites, lupus urinary tract involvement, elevated liver enzymes, oral ulcer, and ECLAM (Table 2).

Demographic and clinical characteristics of patients with LMV. The diagnosis of LMV in our cases was based on clinical features of involvement of multifocal bowel or multiple vascular territories, CT scan, and improvement in the treatment of intravenous steroid and/or immunosuppressant. CT features included bowel wall thickening, target sign, dilatation of intestinal segments, engorgement of mesenteric vessels, and increased attenuation of mesenteric fat.

Ninety-seven patients out of 213 (45.5%) were diagnosed with LMV, indicating that LMV was the main cause of abdominal pain in patients with SLE. In 47 cases out of 97 (48.5%), abdominal pain occurred as the initial symptom of SLE. Other SLE-related GI manifestations included nausea and vomiting (70/97, 72.2%), abdominal distension (68/97, 70.1%), and diarrhea (57/97, 58.8%). In some cases, this was accompanied by abdominal tenderness (65/97, 67.0%) and rebound tenderness or abdominal muscle guarding (19/97, 19.6%). Abdominal CT scan showed that 22 cases (22.7%) had both enteritis and cystitis, of which only 9 cases (9.3%) presented with urinary symptoms. In lupus enteritis, the small intestines were the sites most commonly affected. Rectal involvement was rare. Typical CT images included bowel dilation, focal or diffuse bowel wall thickening, abnormal bowel wall enhancement (a double halo or target sign), and engorgement of mesenteric vessels (comb sign). The incidence of intestinal perforation was 2.1% (2/97). Thromboembolism was noted in 4 cases (4.1%), including splenic artery thrombosis, pulmonary embolism, and retinal vein occlusion.

The patients with LMV exhibited a significantly increased ratio of D-dimer, polyserositis/ascites, lupus urinary tract involvement, oral ulcer, and ECLAM (Table 3).

Demographic and clinical characteristics of patients with LP. Twenty-three out of 213 patients (10.8%) were diagnosed with LP and 3 cases (13.0%) had abdominal pain as the first symptom. The majority of the patients (18, 78.3%) were female. The mean age of onset of LP was 26.48 ± 11.42 years. The time interval between SLE and LP diagnosis ranged from 0 to 33 months, and three-fifths of the patients (14, 60.9%) developed acute pancreatitis soon after SLE diagnosis (< 1 yr). Other symptoms such as diarrhea, fever, and vomiting were similar to LMV. Three patients (13.0%) had elevated pancreatic enzymes before abdominal symptoms. Five patients (21.7%) had what was considered severe pancreatitis based on the CT severity index[25]. All

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Table 2. Demographic and clinical characteristics of the patients with SLE-induced abdominal pain.

	SLE-induced Abdominal Pain, n = 132	Non–SLE-induced Abdominal Pain, n = 81	p
Female, n (%)	108 (81.8)	73 (90.1)	0.10
Age at SLE diagnosis, yrs, mean ± SD	30.95 ± 14.94	32.64 ± 14.47	0.42
Duration of SLE, mos, median (IQR)	1.0 (0.0, 24.1)	1.5 (0.2, 12.0)	0.31
WBC ($\times 10^9$/l), median (IQR)	5.0 (2.7, 6.9)	5.3 (3.8, 7.2)	0.38
Hb (g/l), mean ± SD	89.62 ± 22.80	94.21 ± 23.35	0.16
PLT ($\times 10^9$/l), mean ± SD	159.16 ± 120.42	175.22 ± 110.54	0.33
CRP (mg/l), mean ± SD	16.31 ± 22.95	14.34 ± 26.20	0.56
ESR (mm/h), mean ± SD	41.13 ± 27.61	35.10 ± 23.91	0.11
C3 Complement (g/l), mean ± SD	0.39 ± 0.22	0.44 ± 0.22	0.08
ALB (g/l), mean ± SD	27.75 ± 7.09	29.26 ± 6.12	0.11
SCr (μmol/l), mean ± SD	128.32 ± 171.06	116.85 ± 125.19	0.60
IgG (g/l), mean ± SD	15.20 ± 6.60	13.81 ± 5.74	0.12
D-dimer (100 μg/l), median (IQR)	7.6 (5.4, 12.9)	2.7 (1.5, 4.6)	< 0.01*
ACL (IgM/IgG), n (%)	51 (38.6)	24 (29.6)	0.18
Anti-ß2-GP1 (IgG), n (%)	19 (14.4)	9 (11.1)	0.49
ANA, n (%)	128 (97.0)	80 (98.8)	0.40
Anti-dsDNA, n (%)	98 (74.2)	64 (79.0)	0.43
Anti-Sm, n (%)	37 (28.0)	29 (35.8)	0.23
Anti-Ro, n (%)	87 (65.9)	50 (61.7)	0.54
Anti-La, n (%)	28 (21.2)	18 (22.2)	0.86
Anti-U1RNP, n (%)	43 (32.6)	30 (37.0)	0.51
Polyserositis, n (%)	30 (22.7)	4 (4.9)	< 0.01*
Arthralgia, n (%)	44 (33.3)	35 (43.2)	0.15
Lupus nephritis, n (%)	96 (72.7)	52 (64.2)	0.19
Lupus urinary tract involvement, n (%)	28 (21.2)	0 (0)	< 0.01*
Pulmonary involvement, n (%)	21 (15.9)	13 (16.0)	0.99
Cardiac involvement, n (%)	50 (37.9)	24 (29.6)	0.22
CNS involvement, n (%)	22 (16.7)	11 (13.6)	0.55
Oral ulcer, n (%)	51 (38.6)	16 (19.8)	< 0.01*
Ascites, n (%)	73 (55.3)	19 (23.5)	< 0.01*
Elevated liver enzymes, n (%)	39 (29.5)	8 (9.9)	< 0.01*
Disease activity (SLEDAI), mean ± SD	15.75 ± 7.14	13.40 ± 5.10	0.01*
Disease activity (ECLAM), mean ± SD	6.59 ± 1.84	4.44 ± 1.49	< 0.01*

* Statistically significant. WBC: white blood (cell) count; Hb: hemoglobin; PLT: platelet; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ALB: albumin; SCr: serum creatinine; IgG: immunoglobulin G; ACL: anticardiolipin antibodies; CNS: central nervous system; IQR: interquartile range; SLE: systemic lupus erythematosus; ANA: antinuclear antibody; SLEDAI: SLE Disease Activity Index; ECLAM: European Consensus Lupus Activity Measurement.

patients with LP had active SLE, with the average SLEDAI score of 18.26 ± 7.33 at the onset of acute pancreatitis.

The patients with LP exhibited significantly increased levels of C3 complement, D-dimer, ascites, elevated liver enzyme, and ECLAM score (Table 4).

Associated factors of lupus-induced abdominal pain. All the demographic and clinical variables were included in the univariate logistical regression model. Univariate logistical regression showed that C3 complement, serum D-dimer, ECLAM score, oral ulcers, polyserositis, ascites, and elevated liver enzymes were significantly associated with occurrence of SLE-induced abdominal pain.

All of the variables above that associated with outcome at $p < 0.1$ were included in the multivariate logistic regression model. Serum D-dimer, ECLAM score, and ascites (moderate or large amount) were considered strongly associated factors for the occurrence of lupus-induced abdominal pain. Other factors were not statistically significant. Demographic data and autoantibodies, including anticardiolipin antibody, were not significantly related.

Associated factors of LMV. All the demographic and clinical variables were included in the univariate logistical regression model. Univariate logistical regression shown that serum D-dimer, ECLAM score, oral ulcers, polyserositis, and ascites were significantly associated with the occurrence of LMV.

All of the variables above that associated with outcome at $p < 0.1$ were included in the multivariate logistic regression model. Serum D-dimer, ascites (moderate or large amount), and ECLAM score were considered strongly associated factors for LMV.

Associated factors of LP. All the demographic and clinical variables were included in the univariate logistical regression model. Univariate logistical regression shows

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Table 3. Demographic and clinical characteristics of the patients with lupus mesenteric vasculitis (LMV).

	LMV, n = 97	Non–SLE-induced Abdominal Pain, n = 81	p
Female, n (%)	79 (81.4)	73 (90.1)	0.10
Age at SLE diagnosis, yrs, mean ± SD	31.70 ± 15.43	32.64 ± 14.47	0.68
Duration of SLE, mos, median (IQR)	0.5 (0.0, 24.2)	1.5 (0.2, 12.0)	0.21
WBC ($\times 10^9$/l), median (IQR)	5.2 (2.7, 7.2)	5.3 (3.8, 7.2)	0.52
Hb (g/l), mean = SD	91.97 ± 23.43	94.21 ± 23.35	0.53
PLT ($\times 10^9$/l), mean ± SD	167.40 ± 122.74	175.22 ± 110.54	0.66
CRP (mg/l), mean ± SD	14.68 ± 21.86	14.34 ± 26.20	0.93
ESR (mm/h), mean ± SD	40.42 ± 29.93	35.10 ± 23.91	0.20
C3 Complement (g/l), mean ± SD	0.42 ± 0.23	0.44 ± 0.22	0.42
ALB (g/l), mean ± SD	27.71 ± 7.41	29.26 ± 6.12	0.13
SCr (μmol/l), mean ± SD	125.59 ± 172.30	116.85 ± 125.19	0.70
IgG (g/l), mean ± SD	14.78 ± 6.93	13.81 ± 5.74	0.32
D-dimer (100 μg/l), median (IQR)	7.9 (5.4, 13.2)	2.7 (1.5, 4.6)	< 0.01*
ACL (IgM/IgG), n (%)	36 (37.1)	24 (29.6)	0.29
Anti-ß2-GP1 (IgG), n (%)	15 (15.5)	9 (11.1)	0.40
ANA, n (%)	93 (95.9)	80 (98.8)	0.25
Anti-dsDNA, n (%)	72 (74.2)	64 (79.0)	0.45
Anti-Sm, n (%)	29 (29.9)	29 (35.8)	0.11
Anti-Ro, n (%)	63 (64.9)	50 (61.7)	0.66
Anti-La, n (%)	20 (20.6)	18 (22.2)	0.80
Anti-U1RNP, n (%)	28 (28.9)	30 (37.0)	0.25
Polyserositis, n (%)	22 (22.7)	4 (4.9)	< 0.01*
Arthralgia, n (%)	30 (30.9)	35 (43.2)	0.09
Lupus nephritis, n (%)	67 (69.1)	52 (64.2)	0.49
Lupus urinary tract involvement, n (%)	22 (22.7)	0 (0)	< 0.01*
Pulmonary involvement, n (%)	15 (15.5)	13 (16.0)	0.92
Cardiac involvement, n (%)	32 (33.0)	24 (29.6)	0.63
CNS involvement, n (%)	10 (10.3)	11 (13.6)	0.50
Oral ulcer, n (%)	42 (43.2)	16 (19.8)	< 0.01*
Ascites, n (%)	54 (55.7)	19 (23.5)	< 0.01*
Elevated liver enzymes, n (%)	22 (22.7)	8 (9.9)	0.02*
Disease activity (SLEDAI), mean ± SD	15.10 ± 6.84	13.40 ± 5.10	0.07
Disease activity (ECLAM), mean ± SD	6.28 ± 1.75	4.44 ± 1.49	< 0.01*

* Statistically significant. WBC: white blood (cell) count; Hb: hemoglobin; PLT: platelet; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ALB: albumin; SCr: serum creatinine; IgG: immunoglobulin G; ACL: anticardiolipin antibodies; CNS: central nervous system; IQR: interquartile range; SLE: systemic lupus erythematosus; ANA: antinuclear antibody; SLEDAI: SLE Disease Activity Index; ECLAM: European Consensus Lupus Activity Measurement.

that hemoglobin, C3 complement, serum albumin, D-dimer, ECLAM score, central nervous system involvement, cardiac involvement, ascites, and elevated liver enzymes were significantly associated with the occurrence of LP.

All of the variables above that associated with outcome at $p < 0.1$ were included in the multivariate logistic regression model. Serum D-dimer, ECLAM score, and elevated liver enzymes were considered strongly associated factors for LP.

DISCUSSION

The early and appropriate diagnosis of abdominal pain in SLE is a challenging problem. Some of the lesions can lead to life-threatening consequences. However, SLE-induced abdominal pain may be underdiagnosed[26]. The prognosis of SLE-induced abdominal disorders could be improved if prompt corticosteroid/immunosuppressive therapy were implemented. Identification of the highly associated factors predictive for SLE-induced abdominal pain is crucial to better outcome.

GI involvement induced by SLE could be LMV, protein-losing enteropathy, intestinal pseudoobstruction, acute pancreatitis, or inflammatory bowel diseases.

LMV, also described as mesenteric arteritis, lupus enteritis, lupus arteritis, lupus vasculitis, GI vasculitis, intraabdominal vasculitis, and acute GI syndrome, are the most common causes of SLE-induced abdominal pain in previous reports[21,27,28], which was consistent with our data.

The results showed that LMV was particularly common in our patients, ranging from minor to severe events. More than half of the LMV cases experienced ascites besides abdominal pain, and multiple system involvements were very common, which indicated that even minor GI complaints should be addressed, because insidious manifes-

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Table 4. Demographic and clinical characteristics of the patients with lupus pancreatitis (LP).

	LP, n = 23	Non–SLE-induced Abdominal Pain, n = 81	p
Female, n (%)	18 (78.3)	73 (90.1)	0.13
Age at SLE diagnosis, yrs, mean ± SD	26.48 ± 11.42	32.64 ± 14.47	0.06
Duration of SLE, mos, median (IQR)	2.0 (0, 33.0)	1.5 (0.2, 12.0)	0.79
WBC ($\times 10^9$/l), median (IQR)	5.8 (2.6, 7.8)	5.3 (3.8, 7.2)	0.84
Hb (g/l), mean = SD	81.13 ± 20.63	94.21 ± 23.35	0.02*
PLT ($\times 10^9$/l), mean ± SD	125.39 ± 110.17	175.22 ± 110.54	0.06
CRP (mg/l), mean ± SD	22.86 ± 30.53	14.34 ± 26.20	0.19
ESR (mm/h), mean ± SD	41.43 ± 25.11	35.10 ± 23.91	0.27
C3 complement (g/l), mean ± SD	0.32 ± 0.09	0.44 ± 0.22	< 0.01*
ALB (g/l), mean ± SD	26.22 ± 5.92	29.26 ± 6.12	0.04*
SCr (μmol/l), mean ± SD	177.78 ± 220.28	116.85 ± 125.19	0.09
IgG (g/l), mean ± SD	15.68 ± 4.43	13.81 ± 5.74	0.15
D-dimer (100 μg/l), median (IQR)	8.5 (6.4, 14.9)	2.7 (1.5, 4.6)	< 0.01*
ACL (IgM/IgG), n (%)	10 (43.5)	24 (29.6)	0.21
Anti-ß2-GP1 (IgG), n (%)	3 (13.0)	9 (11.1)	0.80
ANA, n (%)	23 (100)	80 (98.8)	0.59
Anti-dsDNA, n (%)	16 (70.0)	64 (79.0)	0.34
Anti-Sm, n (%)	9 (39.1)	29 (35.8)	0.77
Anti-Ro, n (%)	17 (73.9)	50 (61.7)	0.28
Anti-La, n (%)	6 (26.1)	18 (22.2)	0.70
Anti-U1RNP, n (%)	9 (39.1)	30 (37.0)	0.86
Polyserositis, n (%)	4 (17.4)	4 (4.9)	0.05
Arthralgia, n (%)	9 (39.1)	35 (43.2)	0.73
Lupus nephritis, n (%)	19 (82.6)	52 (64.2)	0.09
Lupus urinary tract involvement, n (%)	1 (4.3)	0 (0)	0.06
Pulmonary involvement, n (%)	15 (15.5)	13 (16.0)	0.92
Cardiac involvement, n (%)	12 (33.0)	24 (29.6)	0.05
CNS involvement, n (%)	8 (34.8)	11 (13.6)	0.02*
Oral ulcer, n (%)	7 (30.4)	16 (19.8)	0.28
Ascites, n (%)	12 (52.2)	19 (23.5)	< 0.01*
Elevated liver enzymes, n (%)	12 (52.2)	8 (9.9)	< 0.01*
Disease activity (SLEDAI), mean ± SD	18.26 ± 7.33	13.40 ± 5.10	< 0.01*
Disease activity (ECLAM), mean ± SD	7.30 ± 1.72	4.44 ± 1.49	< 0.01*

* Statistically significant. WBC: white blood (cell) count; Hb: hemoglobin; PLT: platelet; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ALB: albumin; SCr: serum creatinine; IgG: immunoglobulin G; ACL: anticardiolipin antibodies; CNS: central nervous system; IQR: interquartile range; SLE: systemic lupus erythematosus; ANA: antinuclear antibody; SLEDAI: SLE Disease Activity Index; ECLAM: European Consensus Lupus Activity Measurement.

tations could be neglected or taken as adverse drug interaction.

Examination of bowel specimens, autoantibody presence, and other laboratory findings are of limited value when diagnosing LMV. Pathological information is usually not available or nonspecific. CT can aid the diagnosis[3]. The diagnosis of LMV in our cases was based on clinical features of multifocal bowel or multiple vascular territories, identified through CT scan, as well as suggested by improvement in the treatment of intravenous steroid and/or immunosuppressant[29,30]. Jejunum and ileum were the most commonly affected sites observed on CT scan, which is in agreement with the previous study by Lee, *et al*[10].

The second leading cause of abdominal pain in our study is LP. LP is a relatively rare but life-threatening complication of SLE. Twenty-three out of 3823 patients (0.6%) with LP were found within the research interval, which was comparable with previous studies from the United States and Europe[7,8,10,31,32]. For the asymptomatic patients or patients with hyperamylasemia before manifestations, laboratory evidence and radiological findings are essentially helpful. Anti-La antibody was reported to be associated with LP; however, our data did not suggest a similar tendency[9].

There were no specific indices for early differential diagnosis of SLE-induced abdominal pain and little information, except a few cross-sectional studies have been provided to identify the associated factors to date. In our study, we conducted univariate and multivariate logistic regression models, to try to recognize the patients at high risk and help with decision making on advanced therapies.

We found that high levels of serum D-dimer were frequently observed in the subset of SLE-induced abdominal pain, as well as confirmed cases of LMV and LP. D-dimer was significant in the univariate and multivariate

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analysis, indicating that it was a strongly correlated factor with SLE-induced abdominal involvement. To our knowledge, this finding has not been reported in the literature. The pathology of high levels of D-dimer in SLE-induced abdominal pain is not clear. It is possible that the small vessel injuries in SLE contributed to the overexpression of tissue factors, such as FVIIa complex, FXa, and thrombin. This in turn generated the extrinsic pathway of coagulation, thrombin, and fibrin, and D-dimer was the product[33,34,35,36,37]. D-dimer is not a specific marker for LMV and/or LP, because it is also elevated in active SLE involving other organ systems and thrombosis. However, it is a serum marker that is easy to monitor or operate. D-dimer could be used as a preliminary screen test. Other examinations including CT scan or endoscopy for GI disorders should be considered for SLE patients with abdominal pain when D-dimer is increased. Other correlated variables were ascites (medium or large amount), ECLAM, or elevated liver enzymes for LP.

GI complications may have higher ratio of occurrence when the factors above were positive. However, what is important was that some LMV or LP patients had relatively low SLEDAI or ECLAM scores, and some abdominal episodes broke out in the tranquil stage. Low activity score could not absolutely rule out severe GI complications, though ECLAM was a strongly correlated factor statistically.

Several studies have been performed to assess the importance of aPL in patients with SLE[38]. They may contribute to various types of vasculitis[39,40,41]. However, Lee, *et al* reported that aPL did not correlate with the occurrence of lupus enteritis, which is in accord with our data[10].

For the patients with SLE-induced abdominal pain, about one-third had positive aPL, in which only 2 cases exhibited thrombosis. And none of them had abdominal vascular thrombosis on CT scan. There was no difference in aPL levels between SLE-induced abdominal pain and non–SLE-induced abdominal pain. In our study, aPL did not contribute to the occurrence of SLE-induced abdominal pain.

Lupus urinary tract involvement is uncommon, reported to occur in 0.5% to 1% of patients with SLE. The majority of the patients presented with a combination of GI manifestations, which suggested a strong connection with these lesions. Lupus GI tract involvement and lupus cystitis can occur simultaneously or independently[17,42,43]. Our study showed that about one-fifth of the cases of SLE-induced abdominal pain (28/132, 21.2%) were associated with urinary tract involvement (diagnosis based on ruling out other causes and CT scan), but only one-third (9/28, 32.1%) of the patients exhibited urinary symptoms. Alarcón-Segovia, *et al* also reported that subclinical lupus cystitis was commonly seen[44]. The reason for the association of GI involvement and urinary tract lesions is possibly that GI wall and bladder shared a common autoantigen[45]. Our data indicated that clinicians should take more precautions to avoid latent bladder involvement in patients with SLE and abdominal pain, and further examination may help with early diagnosis and effective treatment.

Differential diagnosis between SLE-induced abdominal pain and non–lupus-induced related abdominal pain is essential, but sometimes difficult. LMV and LP were the leading causes of SLE-induced abdominal pain in our research. Our study demonstrated that serum D-dimer was a strongly associated factor for the occurrence of lupus-induced abdominal pain. ECLAM score and ascites (medium and large amounts) was highly correlated with SLE-induced abdominal pain, and elevated liver enzymes gave a strong indicator for LP. Autoantibodies, including aPL, might not be diagnostically useful for SLE-induced abdominal pain.

REFERENCES

1. Kwok SK, Seo SH, Ju JH, Park KS, Yoon CH, Kim WU, et al. Lupus enteritis: clinical characteristics, risk factor for relapse and association with anti-endothelial cell antibody. Lupus 2007; 16:803-9.
2. Grimbacher B, Huber M, Von Kempis J, Kalden P, Uhl M, Köhler G, et al. Successful treatment of gastrointestinal vasculitis due to systemic lupus erythematosus with intravenous pulse cyclophosphamide: a clinical case report and review of the literature. Br J Rheumatol 1998;37:1023-8.
3. Ju JH, Min JK, Jung CK, Oh SN, Kwok SK, Kang KY, et al. Lupus mesenteric vasculitis can cause acute abdominal pain in patients with SLE. Nat Rev Rheumatol 2009;5:273-81.
4. Luman W, Chua KB, Cheong WK, Ng HS. Gastrointestinal manifestation of systemic lupus erythematosus. Singapore Med J 2001;42:380-4.
5. Malaviya AN, Sharma A, Agarwal D, Kapoor S, Garg S, Singh S, et al. Acute abdomen in SLE. Int J Rheum Dis 2011;14:98-104.
6. Breuer GS, Baer A, Dahan D, Nesher G. Lupus-associated pancreatitis. Autoimmun Rev 2006;5:314-8.
7. Nesher G, Breuer GS, Temprano K, Moore TL, Dahan D, Baer A, et al. Lupus-associated pancreatitis. Semin Arthritis Rheum 2006;35:260-7.
8. Wang F, Wang NS, Zhao BH, Tang LQ. Acute pancreatitis as an initial symptom of systemic lupus erythematosus: a case report and review of the literature. World J Gastroenterol 2005;11:4766-8.
9. Makol A, Petri M. Pancreatitis in systemic lupus erythematosus: frequency and associated factors-a review of the Hopkins Lupus Cohort. J Rheumatol 2010;37:341-5.
10. Lee CK, Ahn MS, Lee EY, Shin JH, Cho YS, Ha HK, et al. Acute abdominal pain in systemic lupus erythematosus: focus on lupus enteritis (gastrointestinal vasculitis). Ann Rheum Dis 2002; 61:547-50.
11. Lian TY, Edwards CJ, Chan SP, Chng HH. Reversible acute gastrointestinal syndrome associated with active systemic lupus erythematosus in patients admitted to hospital. Lupus 2003; 12:612-6.
12. Eilertsen GØ, Becker-Merok A, Nossent JC. The influence of the 1997 updated classification criteria for systemic lupus erythematosus: epidemiology, disease presentation, and patient management. J Rheumatol 2009;36:552-9.
13. Tu YL, Yeh KW, Chen LC, Yao TC, Ou LS, Lee WI, et al. Differences in disease features between childhood-onset and adult-onset systemic lupus erythematosus patients presenting with acute abdominal pain. Semin Arthritis Rheum 2011;40:447-54.

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14. Byun JY, Ha HK, Yu SY, Min JK, Park SH, Kim HY, et al. CT features of systemic lupus erythematosus in patients with acute abdominal pain: emphasis on ischemic bowel disease. Radiology 1999;211:203-9.
15. Taourel PG, Deneuville M, Pradel JA, Régent D, Bruel JM. Acute mesenteric ischemia: diagnosis with contrast-enhanced CT. Radiology 1996;199:632-6.
16. Yang Y, Ye Y, Liang L, Wu T, Zhan Z, Yang X, et al. Systemic-lupus-erythematosus-related acute pancreatitis: a cohort from South China. Clin Dev Immunol 2012;2012:568564.
17. Kornu R, Oliver QZ, Reimold AM. Recognizing concomitant lupus enteritis and lupus cystitis. J Clin Rheumatol 2008;14:226-9.
18. Rasalkar DD, Paunipagar BK. Mesenteric vasculitis with genitourinary tract involvement in systemic lupus erythematosus. Postgrad Med J 2011;87:503-4.
19. Joly F, Amiot A, Coffin B, Lavergne-Slove A, Messing B, Bouhnik Y. Chronique pseudo-obstruction intestinale [in French]. Chronic intestinal pseudo-obstruction. Gastroenterol Clin Biol 2006; 30:975-85.
20. Chng HH, Tan BE, Teh CL, Lian TY. Major gastrointestinal manifestations in lupus patients in Asia: lupus enteritis, intestinal pseudo-obstruction, and protein-losing gastroenteropathy. Lupus 2010;19:1404-13.
21. Tian XP, Zhang X. Gastrointestinal involvement in systemic lupus erythematosus: insight into pathogenesis, diagnosis and treatment. World J Gastroenterol 2010;16:2971-7.
22. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The committee on prognosis studies in SLE. Arthritis Rheum 1992;35:630–40.
23. Algan Ocal P, Akşahin A, Cetin T, Yildirim IS. Cancer antigen 125 levels in patients with ascites. Turk J Gastroenterol 2003;14:257-61.
24. Dubbins PA. The peritoneum. In: Cosgrove D, Meire HB, Dewbury K, Wildeet P, eds. Clinical ultrasound, abdominal and general ultrasound: a comprehensive text, 1st ed. London: Churchill Livingstone; 1993:737-50.
25. Balthazar EJ. Acutepancreatitis: assessment of severity with clinical and CT evaluation. Radiology 2002;223:603-13.
26. Takeno M, Ishigatsubo Y. Intestinal manifestations in systemic lupus erythematosus. Ann Intern Med 2006;45:41-2.
27. Drenkard C, Villa AR, Reyes E, Abello M, Alarcón-Segovia D. Vasculitis in systemic lupus erythematosus. Lupus 1997;6:235-42.
28. Medina F, Ayala A, Jara LJ, Becerra M, Miranda JM, Fraga A. Acute abdomen in systemic lupus erythematosus: the importance of early laparotomy. Am J Med 1997;103:100-5.
29. Ha HK, Lee SH, Rha SE, Kim JH, Byun JY, Lim HK, et al. Radiologic features of vasculitis involving the gastrointestinal tract. Radiographics 2000;20:779-94.
30. Mok CC. Investigations and management of gastrointestinal and hepatic manifestations of systemic lupus erythematosus. Best Pract Res Clin Rheumatol 2005;19:741-66.
31. Pascual-Ramos V, Duarte-Rojo A, Villa AR, Hernández-Cruz B, Alarcón-Segovia D, Alcocer-Varela J, et al. Systemic lupus erythematosus as a cause and prognostic factor of acute pancreatitis. J Rheumatol 2004;31:707-12.
32. Lariño Noia J, Macías García F, Seijo Ríos S, Iglesias García J, Domínguez Muñoz JE. Pancreatitis and systemic lupus erythematosus. Rev Esp Enferm Dig 2009;101:571-9.
33. Mitroulis I, Kambas K, Anyfanti P, Doumas M, Ritis K. The multivalent activity of the tissue factor-thrombin pathway in thrombotic and non-thrombotic disorders as a target for therapeutic intervention. Expert Opin Ther Targets 2011;15:75-89.
34. Criado PR, Criado RFJ, Maruta CW, Martins JEC, Rivitti EA. Urticaria. Ann Bras Dermatol 2005;80:613-30.
35. Muhlfelder TW, Niemetz J, Kreutzer D, Beebe D, Ward PA, Rosenfeld SI. C5 chemotactic fragment induces leukocyte production of tissue factor activity: a link between complement and coagulation. J Clin Invest 1979;63:147-50.
36. Ikeda K, Nagasawa K, Horiuchi T, Tsuru T, Nishizaka H, Niho Y. C5a induces tissue factor activity on endothelial cells. Thromb Haemost 1997;77:394-8.
37. Ritis K, Doumas M, Mastellos D, Micheli A, Giaglis S, Magotti P, et al. A novel C5a receptor-tissue factor cross-talk in neutrophils links innate immunity to coagulation pathways. J Immunol 2006;177:4794-802.
38. Basiri Z, Gholyaf M, Faridnia M, Nadi E, Bairanvand M. The prevalence of anticardiolipin antibody in patients with systemic lupus erythematosus and its association with clinical manifestations. Acta Med Iran 2013;51:35-40.
39. Kawakami T, Watabe H, Mizoguchi M, Soma Y. Elevated serum IgA anticardiolipin antibody levels in adult Henoch-Schönlein purpura. Br J Dermatol 2006;155:983–7.
40. Rees JD, Lanca S, Marques PV, Gómez-Puerta JA, Moco R, Oliveri C, et al. Prevalence of the antiphospholipid syndrome in primary systemic vasculitis. Ann Rheum Dis 2006;65:109–11.
41. Yokoi K, Hosoi E, Akaike M, Shigekiyo T, Saito S. Takayasu's arteritis associated with antiphospholipid antibodies. Report of two cases. Angiology 1996;47:315–9.
42. Akitake R, Nakase H, Ueno S, Miyamoto S, Iehara N, Chiba T. Involvement of lupus enteritis in a patient with lupus cystitis and nephritis. Digestion 2009;80:160-4.
43. Shimizu A, Tamura A, Tago O, Abe M, Nagai Y, Ishikawa O. Lupus cystitis: a case report and review of literature. Lupus 2009;18:655-8.
44. Alarcón-Segovia D, Abud-Mendoza C, Reyes-Gutiérrez E, Iglesias-Gamarra A, Díaz-Jouanen E. Involvement of the urinary bladder in systemic lupus erythematosus: A pathologic study. J Rheumatol 1984;11:208-10.
45. Nakauchi Y, Suehiro T, Tahara K, Kumon Y, Yasuoka N, Ohashi Y, et al. Systemic lupus erythematosus relapse with lupus cystitis. Clin Exp Rheumatol 1995;13:645-8.

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Corrections

Clinical Features and Associated Factors of Abdominal Pain in Systemic Lupus Erythematosus

Yuan S, Lian F, Chen D, Li H, Qiu Q, Zhan Z, Ye Y, Xu H, Liang L, Yang X. Clinical features and associated factors of abdominal pain in systemic lupus erythematosus. J Rheumatol 2013;40:2015–22. Drs. F. Lian and X. Yang contributed equally to this study and should be considered as co-first authors. Address correspondence also to Dr. Yang; E-mail: yang_xiu_yan@hotmail.com. We regret the omission.

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