

Acute Abdominal Pain in Patients with Systemic Lupus Erythematosus

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Abstract

Background Patients with Systemic Lupus Erythematosus (SLE) that present with acute abdominal pain (AAP) represent a challenge for the general surgeon. The purpose of this study was to identify the major causes of AAP among these patients and to define the role of disease activity scores and the APACHE II score in identifying patients with an increased perioperative risk.

Methods We conducted a prospective study of patients admitted to the ER with AAP and SLE in an 11-year period. Demographic, diagnostic, and treatment data were recorded. Systemic lupus erythematosus disease activity index (SLEDAI), systemic lupus international collaboration clinics damage index (SLICC/DI), and APACHE II Score were analyzed. The main outcome variables were morbidity and mortality within 30 days of admission.

Results Seventy-three patients were included. Ninety-three percent were female. Most common causes of AAP were: pancreatitis (29%), intestinal ischemia (16%), gallbladder disease (15%), and appendicitis (14%). Most causes of AAP in patients with LES were not related to the disease. APACHE II score >12 was statistically associated with the diagnosis of intestinal ischemia compared to other causes. No relationship was observed between SLEDAI and outcome. Furthermore, this index did not have impact on diagnosis or decision making. Overall morbidity was 57% and overall mortality 11%. On multivariate analysis, only APACHE II >12 was associated with mortality ($P=0.0001$).

Conclusion This is one of the largest series of AAP and SLE. Most common causes of AAP were pancreatitis and intestinal ischemia. APACHE II score in patients with intestinal ischemia was higher than those with serositis; further studies are needed to examine whether this score may help to differentiate these etiologies when CT findings are inconclusive. APACHE II score was the most important factor associated with mortality. Furthermore, a prompt diagnosis and an appropriate surgical management are essential in order to improve patient outcome.

Keywords Acute abdominal pain · Systemic lupus erythematosus · APACHE II · SLEDAI · Pancreas

Introduction

Despite the fact that acute abdominal pain (AAP) is one of the most common causes of admission to the Emergency Department, it can represent a challenge to surgeons. This is especially true in patients with a concomitant systemic disease like systemic lupus erythematosus (SLE). The incidence of AAP in patients with SLE has been reported to vary from 8% to 40%.^{1,2} A delayed diagnosis in these patients is not uncommon; the use of antirheumatic drugs like steroids and azathioprine, which cause gastrointestinal symptoms, and the gastrointestinal manifestations of the disease itself yield a broad spectrum of differential diagnoses.^{3,4}

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The most frequent etiologies of AAP in patients with SLE remain controversial. A number of studies have found SLE-associated diseases, like lupus enteritis and vasculitis, to be the most common causes.^{5,6} However, other studies have shown that the majority of cases of AAP are caused by conventional illnesses.⁷ Also, there is conflicting data about how factors like lupus activity or delayed surgical intervention influence the final outcome.^{8,9}

The purpose of this study was to identify the major causes of AAP in patients with SLE. Conjointly, we aimed to define the role of acute and chronic disease activity scores and APACHE II score in identifying patients with an increase perioperative risk.

Methods

A prospective study of patients admitted to the Emergency Department of a tertiary care referral center with diagnosis of SLE and AAP in an 11-year period from 1996 to 2007 was performed. Patients who fulfilled more than four of the American Rheumatology Association criteria for the classification of SLE were included.¹⁰ Patients with peritoneal dialysis, abdominal trauma, nonspecific abdominal pain, urinary tract infection, uremia, acute gastroenteritis, obstruction of the ureter, pelvic inflammatory disease, pain from neurologic, toxic, and extraabdominal sources were excluded.

The following information was recorded: demographic data, medical history, medication used, clinical, laboratory and radiological findings, surgical record, systemic lupus erythematosus disease activity index (SLEDAI),¹¹ systemic lupus international collaboration clinics damage index (SLICC/DI),¹² and APACHE II score.¹³

Radiologic studies and laboratory data were obtained at the Emergency Department at the discretion of the attending physician. If an abdominal CT scan was performed, it was obtained with 8–10-mm thick sections and 8–10-mm intervals with contrast material, as long as patients did not have renal failure (creatinine > 1.5 mg/dl) or a documented allergic reaction. All patients were evaluated by a general surgeon as well as an internist.

We defined lupus activity when SLEDAI score was greater than three points. SLEDAI consists of 24 variables covering nine organ systems; disease activity is measured by weighing the importance of each organ system involved using multiple regression techniques.¹⁴ Eight points are given for each of the following: seizures, psychosis, organic brain syndrome, visual disturbances, cranial nerve disorder, lupus headache, CVA, and vasculitis; four points for arthritis, myositis, urinary casts, hematuria, and proteinuria; two points for pyuria, new rash, alopecia, mucosal ulcers, pleurisy, pericarditis, low complement, increased DNA

binding, and fever; and one point for thrombocytopenia and leucopenia.¹¹ The SLICC/DI is valid and reliable for assessing accumulated damage—during the past 6 months—in patients with SLE 20. The index has 41 items covering 12 systems. It includes specific comorbidities associated with SLE and features that are often due to toxicity attributable to treatment.¹² We analyzed this index as positive or negative.

The diagnosis of pancreatitis was based on the presence of typical clinical symptoms, more than threefold increase in serum amylase or lipase and/or anatomical confirmation by CT scan, ultrasonography, or laparotomy. Diagnosis of LES-associated pancreatitis was made in patients with biochemical evidence of pancreatitis and active LES, without radiological evidence of mechanical obstruction and no other explainable cause (including toxic-metabolic etiologies).¹⁵

When surgery was indicated, the type of operation was based on clinical judgment and personal preference of the attending surgeon. The main outcomes were morbidity and mortality within 30 days of admission. Operative mortality was defined as death occurring within 30 days of the surgical procedure or at any time during the same hospital admission. Means and standard deviations were used as data summaries for continuous measures and counts, and percentages were used for discrete variables. Fisher's exact test was used to evaluate each risk factor with operative mortality and associations were performed with Spearman correlation test. A logistic regression model using stepwise selection was used, including each of the univariately significant factors as potential covariates. The analyses were performed using SPSS (16.0) statistical software. All statistical test were two-sided, and $P < 0.05$ were considered as statistically significant.

Results

Seventy-three patients met the study criteria. Sixty-seven (93%) were female; mean age was 32 (range 14–68) years. Mean time from the diagnosis of SLE to the episode of AAP was 8 years (range 1 month to 40 years). Mean duration time of abdominal pain before admission was 3.3 days (range <24 h to 13 days). The principal causes of AAP were: pancreatitis (29%), intestinal ischemia (16%), cholecystitis (15%), and appendicitis (14%). Other etiologies are shown in Table 1.

In 21 patients (29%), a diagnosis of pancreatitis was made. The mean serum amylase and lipase levels were 1,076 and 1,314 U/L, respectively. Mean APACHE II score was 16. Thirteen patients (62%) had severe pancreatitis (APACHE II score > 8). Pancreatitis was associated to gallstones in 28.5% and to drugs in 23.8% of the cases. Of the patients with drug-associated pancreatitis, five were

Table 1 Causes of Acute Abdominal Pain

	Parameter (n)	Percentage (%)
Pancreatitis	21	29
Gallstones	6	
Medications	5	
Associated to lupus activity	4	
Unknown	4	
Alcohol	2	
Intestinal ischemia	12	16
Arterial thrombosis	7	
Vasculitis	3	
Mesenteric venous thrombosis	2	
Gallbladder diseases	11	15
Acute cholecystitis	8	
Pyocholecystitis	3	
Acute appendicitis	10	14
Non-complicated	6	
Complicated	4	
Gynecological causes	6	8
Ruptured ovarian cyst	5	
Endometriosis	1	
Miscellaneous	5	7
Negative laparotomies	2	
Perforated colonic cancer	1	
Perforated pseudomembranous colitis	1	
Fungal peritonitis due to <i>Actinomyces</i>	1	
Serositis	4	5
Intestinal obstruction	4	5
Adhesions	1	
Internal hernia	1	
Intussusception	1	
Incarcerated inguinal hernia	1	
TOTAL	73	

on prednisolone, of these two, were on low-dose prednisolone (<0.2 mg/kg/day), one on moderate-dose (0.2–0.5 mg/kg/day), and two on high-dose (>0.5 mg/kg/day). Three patients were taking azathioprine; one was on methotrexate and another patient was taking phenytoin. Four patients had lupus-associated pancreatitis. Mean SLEDAI score in this subgroup was 17 (range 14–20). Patients with this etiology improved with medical treatment and steroid pulse therapy. Of the entire pancreatitis group, 18 patients improved with nonsurgical management. Four patients with severe pancreatitis required CT-guided drainage; three of them presented infected necrosis and underwent pancreatic necrosectomies. Three patients with pancreatitis died, all due to sepsis, while two had drug-associated pancreatitis and one pancreatitis secondary to gallstones.

Intestinal ischemia was diagnosed in 12 patients. All of them had an APACHE II score >9, with a mean of 14 (range 10–29) and a mean SLEDAI index of 4 (range 0–

15). Initially, because of SLE-associated mesenteric vasculitis, these patients received steroid pulse therapy. The intestinal ischemia mortality rate was 42%; four deaths occurred due to sepsis and one due to pulmonary hemorrhage. Excluding patients with pancreatitis who received nonsurgical management, only APACHE II score >12 was statistically associated with the diagnosis of intestinal ischemia (5/12) compared to other causes of acute abdominal pain (3/43; 41.6% vs. 6.9%, respectively; $P=0.0001$). Neither symptoms lasting more than three days (25% vs. 13%, $P=0.23$), antiphospholipid antibodies (25% vs. 15%, $P=0.388$), SLEDAI >4 (11.3% vs. 24%, $P=0.154$), SLICC/DI >1 (23% vs. 9%, $P=0.104$), nor LDH >200 UI/l (17% vs. 16%, $P=0.943$), correlated with intestinal ischemia. However, lactate >2.2 mmol/L (36% vs. 13%) and leukocytosis (29% vs. 12%) showed a borderline significance with P values of 0.05 and 0.07, respectively. Regarding radiologic evaluation, ten out of 12 CT scans showed positive findings for intestinal ischemia

including bowel wall thickening (one patient), typhlitis (one patient), pneumatosis (two patients), bowel dilatation (three patients), and free-air (three patients).

Other observed causes of AAP are described on Table 1. Six patients underwent a negative a laparotomy or laparoscopy. In four of these patients, the operative findings were diagnostic of serositis; nonbacterial peritonitis without bowel perforation. These four patients presented with severe abdominal pain, absent peristalsis, systemic inflammatory response, and negative CT scans that did not provide enough evidence to rule out ischemia or serositis. In order to exclude medical causes of AAP, laparotomy was delayed in these patients after a 6-h observation period with a short course of steroids. Mean age in this subset was 28 years (ranges, 18 to 42), mean SLEDAI index was 5 (ranges, 3–11), and mean APACHE II score was 6.5 (ranges, 6 to 8). Laparoscopy was only used in one patient, a 19-year-old woman, without postoperative complications. Taking into account only patients who underwent surgical procedures, the rate of negative laparotomies was 11%.

In total, fifty-five (75%) patients underwent a surgical procedure. The types of surgical procedures are shown in Table 2. Overall morbidity was 57%. The most common complications were intra-abdominal abscesses (23%) and pneumonia (11%); other morbidities are shown in Table 3. There were eight perioperative deaths, five patients had intestinal ischemia and three had pancreatitis. All of these patients had APACHE II score greater than 9 (mean 19; range 10–26). The overall mortality rate was 11%. Causes of death were sepsis (87.5%) and pulmonary hemorrhage (12.5%).

On the univariate analysis, factors associated with mortality were intestinal ischemia, pancreatitis, APACHE II score >12, SLICC/DI >1, leukocytosis, lactate >2.2 mmol/L,

Table 2 Surgical Procedures

Type of procedures	Parameter (n)
Cholecystectomies	11
Small bowel resections with primary anastomosis	8
Appendectomies	7
Ovarian cyst resections	6
Right hemicolectomies	6
Laparotomies	5
Pancreatic necrosectomies	3
Left hemicolectomies	3
Total colectomies	2
Diagnostic laparoscopy	1
Adhesiolysis	1
Sigmoid colonic resection	1
Hernioplasty with small bowel resection	1
TOTAL	55

Table 3 Postoperative Complications

Type of complications in 73 patients ^a	Parameter (n)
Abdominal abscess	14
Pneumonia	7
Septic shock	5
Wound infection	4
Lobar atelectasia	4
Urinary tract infection	3
Wound dehiscence	3
Wound seroma	3
Disseminated intravascular coagulation	3
Respiratory distress syndrome	3
Seizures	2
Anastomotic leak	2
Others	6
TOTAL	59

^a There were patients with more than one complication

hypoxemia, and antiphospholipid syndrome. On multivariate analysis only APACHE II score >12 maintained statistical significance ($P=0.0001$). Seven out of 25 patients with APACHE II >12 deceased (28%), compared to one out of 48 patients with APACHE II ≤12 (2%; Table 4).

Discussion

Diagnosing and offering optimum treatment to patients with SLE who present with AAP can be a challenging task. The attending physician or surgeon is faced with a wide range of differential diagnoses including infrequent conditions such as vasculitis, segmental intestinal ischemia, spontaneous rupture of liver and spleen, and total colonic necrosis.^{16–20} If the leading causes of AAP among patients with SLE are lupus-associated pathologies or common illness remains controversial. A number of studies have reported intestinal vasculitis as the leading cause of AAP. Medina et al.⁵ found this etiology in 43% of patients. Conversely, Al-Hakeem et al.⁷ reported a series of 13 patients in whom common causes of AAP were diagnosed. Our results show that most causes of AAP in patients with LES are not related to the disease. Nevertheless, when compared with the general population the expected frequency for each etiology differs with increase rates of pancreatitis and intestinal ischemia.

In accordance to other reports,²¹ we found that pancreatitis was the leading cause of AAP; seen in 29% of the patients. Even though some studies show that lupus activity is the primary etiologic factor of SLE pancreatitis,^{22–24} we found that biliary and drug-related pancreatitis were the

Table 4 Univariate Analysis of Factors Associated with Mortality

		Mortality (%)	P value
Length of abdominal pain	≥5 days	33	0.03
	<5 days	9	
Intestinal ischemia		38	0.003
	Other causes	8	
SLEDAI	≥4	18	0.61
	<4	12	
SLIC	(+)	20	0.07
	(-)	3	
WBC	≥12,000/mm ³	29	0.006
	<12,000/mm ³	6	
Creatinine	≥1.2 mg/dL	26	0.02
	<1.2 mg/dL	6	
Oxygen	≤55 mmHg	39	0.01
	>55 mmHg	12	
Lactate	≥2.2 mmol/l ^a	50	0.001
	<2.2 mmol/l	37	
aPL	(+)	37	0.01
	(-)	9	
APACHE II	>12 ^b	28	0.007
	≤12	2	

^a Only in 15 patients

^b On multivariate analysis only APACHE II score >12 retained statistical significance ($P=0.0001$)

main etiologies. Additionally, mortality rate was 14% lower than other series of lupus-associated pancreatitis.²⁵ This study supports findings reported by other groups in our institution that the most frequent cause of acute pancreatitis in SLE patients is mechanical obstruction due to biliary disease.²⁶ The incidence of drug induced pancreatitis in the general population is 0.1–2%.²⁷ This is much lower of what we observed in our study. However, one the reasons that could explain this is that most of the individuals included in our study are taking at least one of the drugs associated with this condition.

Al-Hakeem and Medina et al. found overall morbidity rates of 44% and 31%, respectively.^{5,7} The latter author concludes that systematic measurement of lupus activity and early laparotomy may improve prognosis in these patients. In our series, a systematic measurement of lupus activity was performed with morbidity and mortality rates of 57% and 11%, respectively. However, SLEDAI did not have impact on diagnosis or decision making when medical causes of acute abdominal pain have been excluded.

Lee et al.⁶ found that SLEDAI calculated at the time of AAP was lower than at the time of lupus diagnosis, emphasizing that AAP may occur in patients whose disease activity had been under control. In our study, neither SLEDAI nor aPL correlated with intestinal ischemia; this is similar to the results reported by Lee et al. when analyzing lupus enteritis.⁶ Other studies have demonstrated that SLICC/DI has a high predictive value for survival in SLE patients.²⁸ In our series, SLICC/DI had statistical

significance in the univariate analysis. Hence, our data does not support the hypothesis that acute lupus activity influences the mortality; it rather implies that chronic damage may be associated with it.

The hypothesis for the development of the APACHE score was that severity of the acutely ill patient can be measured by the abnormality degree of multiple physiological variables.¹³ The APACHE II score is available in most of hospitals worldwide and has been validated as predictor of morbidity and mortality in surgical patients.^{29–32} We recognize that this score is complex to calculate and not often used for clinical care. However, since it has shown to be a strong predictive factor and can be easily calculated with the aid of most handheld devices we encourage clinicians to take it into account when managing these patients. Additionally, since fever is the only superimposed value between APACHE II score and SLEDAI index, these scores can be considered independently in patients with SLE.^{11,13}

In some patients, it is difficult to determine whether abdominal pain is due to enteritis or serositis because some CT signs are subjectively interpreted.³³ CT findings such as bowel-wall thickening, increased or decreased bowel wall enhancement, bowel dilatation, and ascites are superimposed in patients with intestinal ischemia and vasculitis involving the gastrointestinal tract.^{33,34} Due to the fact that APACHE II score in patients with intestinal ischemia was higher than those with serositis, we propose to evaluate whether this score may help to differentiate these etiologies when CT findings are inconclusive.

Lee et al. emphasized on his report that laparotomy could be delayed unless there is definite evidence that GI perforation has occurred. However, it is important to highlight that most of the patients included in their series had medical causes of AAP; such as lupus enteritis, urinary tract infections, acute gastroenteritis, pancreatitis, and serositis.⁶ Our findings support evidence that the evaluation of patients with AAP and SLE must be individualized because some of them will benefit from an early surgical intervention.

In summary, this is one of the largest reported series of acute abdominal pain and systemic lupus erythematosus. Most causes of AAP in patients with LES are not related to the disease. Pancreatitis was the main cause of AAP and intestinal ischemia was the main cause of death. Intestinal ischemia can present without lupus activity or antiphospholipid syndrome. APACHE II score in patients with intestinal ischemia was higher than those with serositis; we feel that further studies are needed to examine whether this score may help to differentiate these etiologies when CT findings are inconclusive. Furthermore, since SLE disease activity index does not impact on patient's outcome, this has no bearing on the diagnosis and the management when medical causes have been excluded. APACHE II score was the most important factor associated with mortality in this group of patients. A prompt diagnosis and an appropriate surgical management are essential in order to improve patient outcome.

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