Pancreatitis in Systemic Lupus Erythematosus: Frequency and Associated Factors — A Review of the Hopkins Lupus Cohort

ASHIMA MAKOL and MICHELLE PETRI

ABSTRACT. ***Objective.*** Pancreatitis is a rare but potentially life-threatening complication of systemic lupus erythematosus (SLE). Vasculitis of the gastrointestinal tract is the most commonly proposed mechanism. We determined the frequency of SLE-related pancreatitis in the Hopkins Lupus Cohort.

Methods. A large prospective cohort of 1811 patients with SLE was reviewed and clinical and laboratory measures of SLE patients who developed pancreatitis were compared to patients who did not develop pancreatitis.

Results. Four percent of patients with SLE had pancreatitis due to SLE. The best multivariate model of clinical and laboratory associations included hypertriglyceridemia, psychosis, pleurisy, gastritis, and anemia.

Conclusion. Hypertriglyceridemia appears to be a strong associate of pancreatitis in SLE, but antiphospholipid antibodies are not. SLE patients with psychosis and pleurisy are at increased risk for pancreatitis. (J Rheumatol First Release Dec 23 2009; doi:10.3899/jrheum.090829)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS — PANCREATITIS
GASTROINTESTINAL MANIFESTATIONS OF SLE — HYPERTRIGLYCERIDEMIA

Pancreatitis in adult-onset systemic lupus erythematosus (SLE) is a well recognized yet rare complication[1-10]. It was first reported by Reifenstein, *et al* in 1939 as a symptom complex of unknown etiology and fatal outcome[11]. It has also been reported in pediatric lupus, where it follows a more aggressive course and is often noted to be fatal at presentation[12]. The diagnosis of SLE-induced pancreatitis can only be made after excluding all other mechanical and toxic-metabolic etiologies of pancreatitis (including but not limited to cholelithiasis, alcohol, medications, hypertriglyceridemia, hypercalcemia, and infections/sepsis).

The etiopathogenesis of pancreatitis in lupus is not clear[10], with several suggested pathogenic mechanisms. SLE-induced vasculopathy of the gastrointestinal tract is one of the most commonly proposed mechanisms[13], with vasculitis leading to ischemic necrosis of the pancreas[4,12]. Immunosuppressive drugs such as azathioprine and cyclosporine[14,15], as well as corticosteroids[6,9], have also been implicated in several case reports. In a case series of 4 patients, an association with high levels of anticardiolipin antibodies (aCL) was shown, attributing pancreatitis to be a manifestation of antiphospholipid syndrome[16]. Anticardiolipin antibodies have also been found with chronic calcifying pancreatitis in a patient with SLE[17].

We determined the frequency of SLE-related pancreatitis in the Hopkins Lupus Cohort. We then compared the clinical and laboratory measures in patients with SLE who had pancreatitis versus those who did not.

MATERIALS AND METHODS

The Hopkins Lupus Cohort. The Hopkins Lupus Cohort Study has been approved by the Johns Hopkins University School of Medicine Institutional Review Board. All patients gave written informed consent. The Hopkins Lupus Cohort was begun in 1987 and consisted of 1811 patients with SLE at the time of this study. Patients diagnosed with SLE by one faculty member were invited to enroll. After cohort entry, routine visits were scheduled quarterly, or more often if warranted by disease activity or complications. At each visit, clinical assessment of disease activity was ascertained using the physician's global assessment (PGA) and Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA SLEDAI)[18,19]. Laboratory tests included a complete blood count, erythrocyte sedimentation rate, serum cholesterol, serum creatinine, urinalysis (and since 2006, urine protein/creatinine ratio), complement C3 and C4 levels, anti-dsDNA, dilute Russell viper venom time for the lupus anticoagulant, and aCL measures.

Cumulative cohort history and damage index database. A cumulative history was recorded for each patient at cohort entry including demographic variables, clinical and laboratory manifestations of SLE, and treatment (prednisone, hydroxychloroquine, and immunosuppressive drugs) and then

From the Hopkins Lupus Center, Division of Rheumatology, Department of Internal Medicine, Johns Hopkins University, Baltimore, Maryland, USA.

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A. Makol, MD, Department of Internal Medicine, Michigan State University, East Lansing, Michigan; M. Petri, MD, MPH, Division of Rheumatology, Johns Hopkins University School of Medicine.

Address correspondence to Dr. M. Petri, Division of Rheumatology, Johns Hopkins University School of Medicine, 1830 East Monument Street, Suite 7500, Baltimore, MD 21205, USA. E-mail: mpetri@jhmi.edu

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updated at least every 3 months at followup visits. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index[20] was also similarly recorded at the first visit and updated at least every 3 months.

Data extraction. The Hopkins Lupus Cohort database was reviewed to identify all patients who developed episodes of acute pancreatitis since the diagnosis of SLE. A patient was classified as having acute pancreatitis in the presence of clinical features of abdominal pain or tenderness with at least a 3-fold elevation of pancreatic enzymes (amylase or lipase) and confirmation of the diagnosis by an imaging study [computed tomography (CT) scan/magnetic resonance imaging scan or ultrasound of the abdomen]. Patients with isolated elevation of enzymes without evidence of pancreatitis on imaging studies were excluded from the analysis.

The number of episodes of pancreatitis, the laboratory evaluation, therapeutic management, and outcome were determined through outpatient or inpatient records of the hospital stay. For patients whose records were incomplete, the patient was contacted by telephone to obtain relevant information. Patients whose records were not available and who were not able to recall events from their hospital admission for episodes of pancreatitis were excluded from the study.

Using the cohort database, clinical and laboratory measures of SLE patients who developed pancreatitis were compared to SLE patients who did not develop pancreatitis.

Statistical analysis. Statistical analysis was done using the JMP software system (SAS, Cary, NC, USA). The chi-square test or Fisher's exact test was used for dichotomous variables and the Student t test for continuous variables. For demographic, physical, and laboratory variables that were different between patients with and without pancreatitis, multiple logistic regression analysis was used to identify the variables that independently predicted pancreatitis. A 2-tailed p value < 0.05 was considered statistically significant in all comparisons.

RESULTS

Out of a total of 1811 patients with SLE, 76 (4.2%) developed one or more episodes of pancreatitis. One patient was excluded because of the presence of isolated hyperamylasemia without evidence of pancreatitis on CT of the abdomen. An additional 4 patients were excluded because of nonavailability of records (Figure 1).

The 71 remaining SLE patients developed 152 episodes of pancreatitis, with a mean of 2.1 episodes/person and an average frequency of 0.10 episodes/person/year. The etiology of pancreatitis was found to be idiopathic, and hence related to SLE, in 63 patients (3.5% of the cohort), while it was attributed to other causes in 7 patients (2 alcohol abuse, 1 post-traumatic, 1 sepsis, 1 cholelithiasis, 1 related to Depakote toxicity, and 1 due to abnormal anatomy consistent with annular pancreas and abnormal pancreaticobiliary junction). The complete evaluation to exclude other etiologies was not available in one patient.

Of all 63 patients with pancreatitis due to SLE, only 1 (1.6%) patient had hypercalcemia (the level was only mild-

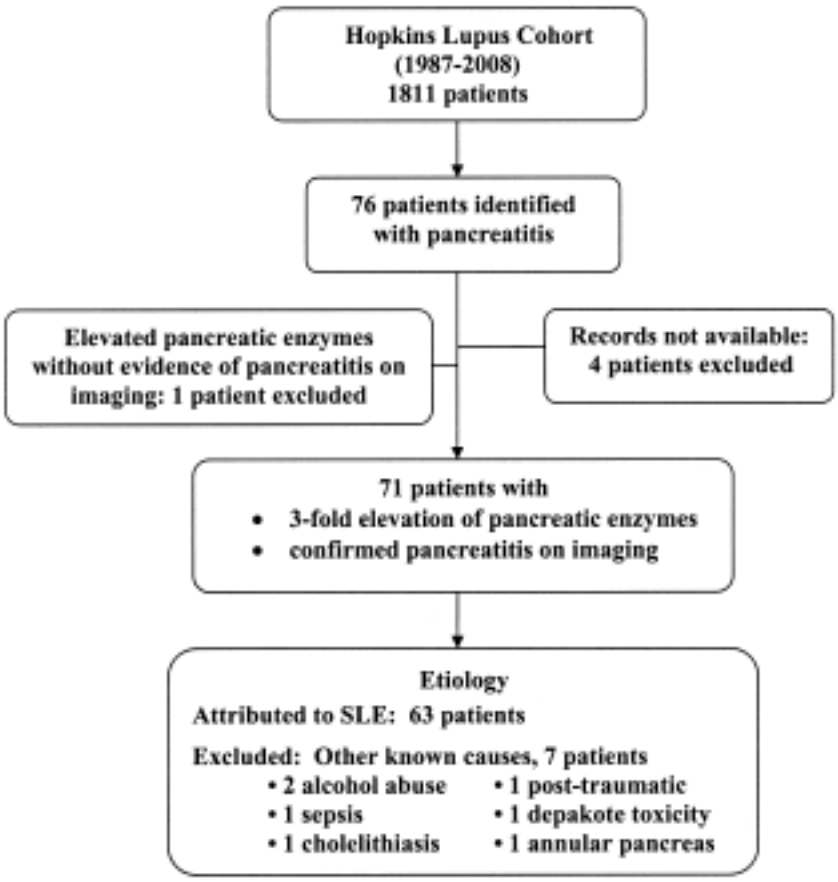

Figure 1. Selection of participants.

ly elevated and was not presumed to be the cause for pancreatitis). Elevated triglyceride levels were noted in 12 (19%) patients. None had triglyceride levels > 200 mg/dl, nor were they on therapy for hypertriglyceridemia. Eight patients had a history of alcohol abuse, but only 2 were consuming any alcohol at the time of their pancreatitis. Eight patients had a history of cholecystectomy, 6 for cholelithiasis and 2 for abdominal pain of unknown etiology. Twenty-nine (46%) patients were positive for antiphospholipid antibodies, of which 21 (72%) had aCL, 12 (41%) had lupus anticoagulant, and 3 (10%) had anti-ß$_2$-glycoprotein I antibody. Eleven patients (17%) were taking an immunosuppressive drug during their episode of pancreatitis, including 5 on azathioprine, 2 cyclophosphamide, and 1 each taking methotrexate, mycophenolate mofetil, chlorambucil and cyclosporine.

Forty-six (73%) patients showed complete resolution of pancreatitis whereas the others developed complications, recurrences, or chronicity. Nine patients developed various complications of pancreatitis including 6 with pancreatic pseudocysts, 4 with secondary diabetes mellitus, and 2 with exocrine pancreatic insufficiency. Twenty-seven (43%) patients developed recurrent pancreatitis (more than one episode) and 9 (14%) developed chronic pancreatitis. The pancreatitis was severe enough to lead to mortality in 2 patients (3%).

Table 1 shows the demographic comparison of the 63 SLE patients with pancreatitis due to SLE versus 1740 SLE patients without pancreatitis. Pancreatitis attributed to SLE was associated with lower income, less private insurance, more disability, and smoking.

Table 2 summarizes the clinical manifestations and conditions associated with pancreatitis attributed to SLE. These included fever, vasculitis, pleurisy, psychosis, organic brain syndrome, cognitive impairment, anemia, Sjögren's syndrome, anti-La, hypertension, and diabetes mellitus. Table 3 summarizes the comparison of laboratory measures. Hypertriglyceridemia was strongly associated with pancreatitis, but antiphospholipid antibodies were not.

Table 4 shows that SLE patients with pancreatitis attributed to SLE have accrued more permanent organ damage, including pancreatic insufficiency.

Table 5 shows the multivariate model of the most significant variables. This model included hypertriglyceridemia, psychosis, pleurisy, gastritis, and anemia.

DISCUSSION

In this large series of patients with SLE we found that SLE-attributable pancreatitis was rare: 3.5% (63/1810). Chronic pancreatitis occurred in 14% and death in 3% of these patients. The mortality rate was lower in comparison to other studies[21], but this may be as a result of close monitoring and followup of these SLE patients enrolled in a prospective cohort study, increasing the likelihood of earlier diagnosis and treatment. Appropriate therapeutic strategy, particularly treatment with corticosteroids, which was done in a relatively large proportion of our patients with pancreatitis, may have also added a survival benefit.

Patients with SLE-attributable pancreatitis had a significantly higher Damage Index score (3.54 vs 1.98; $p \leq 0.001$), which represents an overall higher disease burden and disease severity in this subset of SLE patients.

This series sheds some light on potential mechanisms. First, there was no association with any antiphospholipid antibody. However, events associated with hypercoagulability (deep venous thrombosis and stroke) were significantly more common with SLE-attributable pancreatitis. In univariate analyses, cutaneous vasculitis had occurred significantly more often in SLE-attributable pancreatitis (27% vs 14%; $p = 0.015$). Vasculitis has been a proposed mechanism for SLE pancreatitis[4,12,13]. However, cutaneous vasculitis did not remain independently associated with SLE-attributable pancreatitis in our multiple regression model.

Table 1. Demographic characteristics of SLE patients with and without SLE-attributed pancreatitis.

	Pancreatitis Present, N = 63	Pancreatitis Absent, N = 1740	p	OR (95% CI)
Sex				
Male	2	130	NS	
Female	61	1610		
Ethnicity				
African American	33	638	NS	
Caucasian	25	988		
Asian	3	52		
Other	2	62		
Socioeconomic status, %				
Household income > US $50 thousand	24	44	0.0054	0.41 (0.21–0.78)
High school graduate	91	90	1.0000	
Private insurance, %	71	80	0.127	0.62 (0.34–1.13)
Disability, %	44	21	0.0001	3.00 (1.75–5.13)
History of smoking, %	31	17	0.013	2.17 (1.23–3.83)

NS: Not statistically significant.

Table 2. Comparison of clinical manifestations in SLE-attributable pancreatitis.

Factor	Pancreatitis Present, %	Pancreatitis Absent, %	p	OR (95% CI)
Fever	57	39	0.0069	2.06 (1.22, 3.46)
Photosensitivity	70	55	0.0241	1.94 (1.11, 3.40)
Cutaneous vasculitis	27	14	0.0150	2.15 (1.19, 3.87)
Pleuritis	72	44	< 0.0001	3.17 (1.79, 5.59)
Hematuria	29	41	0.0606	1.66 (0.98, 2.82)
Renal insufficiency	27	17	0.0542	1.80 (1.00, 3.24)
Seizure	18	9	0.0414	2.16 (1.10, 4.23)
Psychosis	12	3	0.0048	3.85 (1.68, 8.83)
Organic brain syndrome	12	5	0.0313	2.55 (1.13, 5.78)
Cognitive impairment	14	6	0.0206	2.61 (1.21, 5.66)
Sjögren's syndrome	27	14	0.0082	2.28 (1.26, 4.11)
Hepatomegaly	10	4	0.0327	2.75 (1.15, 6.63)
Splenomegaly	10	5	0.0618	2.32 (0.97, 5.55)
Obesity	54	39	0.0274	1.84 (1.08, 3.12)
Moon fascies	72	40	< 0.0001	3.76 (2.13, 6.64)
Hypertension	62	45	0.0116	2.00 (1.18, 3.39)
Diabetes mellitus	18	9	0.0207	2.30 (1.17, 5.52)
Cataracts	22	13	0.0515	1.89 (1.01, 3.55)
Gastritis	45	21	< 0.0001	3.11 (1.85, 5.24)
Peptic ulcer disease	25	9	0.0004	3.29 (1.80, 6.04)
Deep venous thrombosis	23	12	0.0151	2.23 (1.20, 41.2)
Stroke	18	8	0.0063	2.73 (1.38, 5.37)
Myocardial infarction	10	4	0.0415	2.59 (1.08, 6.21)
Thrombosis (venous)	33	17	0.0027	2.45 (1.41, 4.25)
Thrombosis (arterial)	30	14	0.0021	2.64 (1.49, 4.65)

Table 3. Comparison of laboratory measures in SLE patients with and without SLE-attributable pancreatitis.

	Pancreatitis Present, %	Pancreatitis Absent, %	p	OR (95% CI)
Anemia	78	59	0.004	2.42 (1.30–4.53)
Abnormal liver function tests	53	37	0.0140	1.95 (1.16–3.26)
Hypertriglyceridemia	50	18	< 0.0001	4.56 (2.45–8.49)
Hypercholesterolemia	69	52	0.0108	2.07 (1.18, 3.65)
Anti-Ro	38	29	0.1759	1.49 (0.86, 2.60)
Anti-La	24	12	0.0175	2.35 (1.24–4.46)
Antiphospholipid antibodies				
Anticardiolipin	40	48	0.2809	0.72 (0.42, 1.23)
Lupus anticoagulant	25	26	NS	
Anti-ß$_2$-glycoprotein I	19	34	0.1000	0.44 (0.16, 1.16)
Anti-Sm	16	16	NS	
Anti-dsDNA	53	57	NS	
Low C3	55	53	NS	
Low C4	48	48	NS	

NS: Not statistically significant.

Our series found that secondary Sjögren's syndrome (p = 0.0082) and anti-La (p = 0.0175) were associated with pancreatitis. Pancreatitis is a known complication of primary Sjögren's syndrome[22]. These variables, however, did not retain their significance in the multiple regression model.

The variable with the strongest association was triglyceridemia, which was very significant in both univariate (p < 0.0001) and multiple regression models (p < 0.0001). The triglyceridemia was modest in comparison to the hypertriglyceridemia known to cause pancreatitis[23].

Some other SLE manifestations were independent associates of SLE-attributable pancreatitis, namely psychosis (p = 0.0032) and pleurisy (p = 0.0004). Two nonspecific conditions, gastritis and anemia, also remained in the multiple regression model. Physicians treating patients with SLE with a history of these conditions who develop abdominal pain should have a high index of suspicion of pancreatitis.

Our series showed that SLE-attributed pancreatitis, although rare, identified a subset of SLE patients with much higher degree of organ damage and mortality. Antiphos-

Table 4. Prevalence of organ damage in SLE patients with and without SLE-attributable pancreatitis.

Organ Damage	Pancreatitis Present	Pancreatitis Absent	p
Ocular	0.31 ± 0.54	0.18 ± 0.44	0.0276
Neuropsychiatric	0.53 ± 0.75	0.32 ± 0.67	0.0168
Renal	0.52 ± 1.15	0.20 ± 0.68	0.0004
Pulmonary	0.19 ± 55	0.14 ± 0.42	NS
Cardiovascular	0.21 ± 0.55	0.16 ± 0.51	NS
Peripheral vascular	0.09 ± 0.28	0.07 ± 0.31	NS
Gastrointestinal	0.71 ± 0.99	0.17 ± 0.44	< 0.0001
Musculoskeletal	0.56 ± 0.85	0.39 ± 0.78	NS
Dermatologic	0.12 ± 0.38	0.08 ± 0.31	NS
Total	3.54 ± 2.82	1.98 ± 2.34	< 0.0001

Table 5. Multivariate regression model of variables associated with SLE-attributable pancreatitis.

Variable	p
Hypertriglyceridemia	< 0.0001
Psychosis	0.0023
Pleurisy	0.0001
Gastritis	0.0147
Anemia	0.0031

pholipid antibodies were not found to be associated, but a history of thrombosis, cutaneous vasculitis, secondary Sjögren's syndrome, and triglyceridemia were all suggested as potential mechanisms. Only triglyceridemia remained significant in the multiple regression model for a strong association with pancreatitis attributable to SLE.

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