

CLINICAL VIGNETTE

Acute Pancreatitis Secondary to Systemic Lupus Erythematosus: A Case Report and Literature Review

James Soo Kim MD, Magdalena E Ptaszny MD, Hamid R Hajmomenian MD,
and William Dean Wallace

Introduction:

Systemic lupus erythematosus (SLE) is an autoimmune disorder that can affect a variety of organ systems simultaneously with a myriad of clinical presentations¹. Symptoms can be protean and patients often present with fever, malaise, and fatigue. The musculoskeletal, integumentary and renal systems are most commonly affected by SLE². Although SLE can involve any organ system, there are few reports of pancreatitis as the initial presenting manifestation. We describe a case of lupus pancreatitis and will briefly review SLE-induced pancreatitis as well as drug-induced pancreatitis. Based on evidence in the literature, we feel that SLE is the most likely cause of the patient's presentation.

Case Report:

The patient is a 40-year-old El Salvadorian female who presented with one month of abdominal pain and eye swelling for 4 days. She has hypertension controlled with hydrochlorothiazide and was in her usual state of health until four weeks prior to admission. She developed dull abdominal pain localized primarily to the left side without radiation. She also noted darkening of her urine, intermittent subjective fevers and myalgias that occurred with the fevers. She was diagnosed with a "urinary tract infection" and prescribed a five-day course of ciprofloxacin.

Because of persistent symptoms, the patient presented at the Emergency Department for further evaluation. She was mildly febrile

with a temperature of 100.0 and tachycardia of 100 beats per minute. Laboratories were significant for a blood urea nitrogen of 59 and a

creatinine of 1.7. She was anemic with a hemoglobin of 10.9 and a hematocrit of 32.0, but

had no leukocytosis (white blood cell count was 6.4). In addition, the urinalysis revealed greater than 300 mg/dL of protein, 26-49 red blood cells, and 5-10 white blood cells. She was given a dose of ceftriaxone for presume UTI and sent home with a prescription for cephalexin. The patient noted that her abdominal pain did not improve after discharge from the ED and she presented to a primary care physician to establish care and further evaluate her symptoms. She had a temperature of 100.7°F. Repeat labs revealed blood urea nitrogen of 37 and creatinine of 1.7. Urinalysis 3+ protein and >50 red blood cells. A spot protein to creatinine ratio was 2.6 grams.

The patient also developed progressive bilateral orbital edema, as well as nausea and vomiting. Urine culture was positive for enterococci sensitive to ampicillin and she was again referred to the Emergency Department for additional evaluation.

Pelvic exam in the ED was remarkable for cervical motion tenderness and she was given ceftriaxone and doxycycline for pelvic inflammatory disease and admitted.

She was originally from El Salvador and came to the United States in 2000. She had no recent travel, pets, or sick contacts. She is married with 3 children and worked in a bakery. She denied any tobacco, ethanol, or illicit drug use. There were no allergies nor any significant medical problems in her family.

On physical exam, temperature was 97.9, pulse 76, respirations 20, and blood pressure was

103/70. The patient was awake and in no distress. Eyes were remarkable for bilateral chemosis and orbital edema, with intact extraocular movements. Her ears, nose and throat were unremarkable. The lung and cardiovascular exams were normal and she had no lower extremity edema. Abdomen was non-distended, with active bowel sounds. There was tenderness to superficial and deep palpation in the left lower quadrant. There was no rash or lymphadenopathy and neurologic exam was normal. The mental status exam was entirely normal and revealed a fully alert and oriented person with appropriate responses to questions and her situation. Initial laboratory results are listed in Table 1. A CT scan of the abdomen and pelvis was obtained (Figure 1).

The patient was given aggressive fluid resuscitation. Her abdominal pain was controlled with narcotic analgesics. Because of the patient's hematuria and renal insufficiency, a renal biopsy was performed. This revealed diffuse segmental lupus nephritis (ISN/RPS class IV-S) with 50% cellular crescents, corresponding to severe activity (Figure 2). Immunofluorescence revealed "full-house" staining with all immunoglobulins and complement components in a segmental distribution (Figure 3). Electron microscopy studies revealed immune complex deposits in the mesangium and subendothelial space and tubuloreticular structures (Figure 4). There was only minimal tubulointerstitial scarring.

On hospital day (HD) #4, the patient was started on immunosuppressive therapy, initially parenteral methylprednisolone and mycophenolate mofetil, followed by oral prednisone and cyclophosphamide.

Confirmatory laboratory studies included: antinuclear antibody >1:1280, double-stranded DNA antibody 1577, ESR 34, anticardiolipin antibody IgG 28 GPL (normal <15), anticardiolipin antibody IgM 78 MPL (normal <12.5), Russell viper time (DRVVT) was borderline.

During her hospital course, the patient's creatinine initially increased while receiving

pulse steroids and mycophenolate, but began to improve slowly after cyclophosphamide was started. Her swelling and generalized edema also improved. Although the lipase remained elevated throughout her hospitalization, she was able to tolerate oral intake without difficulty early in her hospital course, and was discharged on hospital day #16.

Discussion:

While the development of renal failure and nephrotic syndrome in lupus is well-documented and seen regularly, the presentation of this case was unusual in that abdominal pain and pancreatitis were prominent features in this patient's history. Two possible etiologies of this patient's initial pancreatitis will be discussed, SLE-induced pancreatitis and drug-induced pancreatitis.

SLE-induced pancreatitis has a yearly incidence estimated at 0.4-1.1/1000 lupus patients³. This is relatively uncommon as there are fewer than 100 cases reported⁴. Clinically, abdominal pain is the most frequent GI-related symptom in 88% of these patients although only 23% reported the "classic" description of radiation to the back. Other reported symptoms include: nausea and vomiting (approximately 66%), fever (50%), and diarrhea (9%).

Laboratory manifestations include elevated amylase and lipase (97% of patients), hypoalbuminemia (78%), abnormal transaminases (65%), elevated serum creatinine (44%), and hypocalcemia (23%). Several other reviews and case series noted that subclinical pancreatitis (elevated pancreatic enzymes without clinical symptoms) may be a more frequent occurrence in SLE patients because approximately 30.5% of asymptomatic lupus patients have an elevated amylase level⁵.

The pathogenesis of SLE-induced pancreatitis remains unclear. Proposed mechanisms include vasculitis, microthrombi from antiphospholipid antibodies, anti-pancreatic antibodies, and pancreatic inflammation secondary to immune and complement activation⁵⁻⁶. Furthermore, lupus patients are often on immunosuppressive drugs such as steroids and azathioprine, which

have been reported as etiologic agents in pancreatitis. However, the association between steroids and azathioprine upon review seems to be weak⁷.

Treatment of lupus-associated pancreatitis generally involves corticosteroids. Some report the addition of azathioprine, cyclophosphamide, plasmapheresis, and/or intravenous gamma-globulin in cases where steroids alone do not resolve symptoms. Failure to treat patients with corticosteroids was associated with higher mortality (20% treated versus 61% untreated, $p=0.005$)³. Overall mortality in SLE-induced pancreatitis is slightly higher than patients with non-SLE-induced pancreatitis with reported mortality rates ranging from 18-27%^{3,8}.

Drug-induced pancreatitis is relatively uncommon, but the incidence may be rising. In several European reviews, the incidence has been reported as 0.3-1.4% of all cases of acute pancreatitis⁹⁻¹⁰. The diagnosis of drug-induced pancreatitis depends on clinical suspicion and a precise drug history. The time course from drug use to onset of symptoms varies depending on the drug. Symptoms may develop from a few weeks to many months depending on the mechanism of pancreatic injury (immune mediated versus a buildup of toxic metabolites).

There are no consistent criteria for associating drugs with acute pancreatitis and the strength of association varies by reviewer. A recent review classified drug-induced pancreatitis into categories based on the strength of association reported in the literature. Class I (required at least one case report with positive re-challenge), class II (at least four cases with >75 percent with consistent latency), class III (at least two cases but no consistency nor re-challenge), and class IV (not fitting into above, single case report with no re-challenge). Class I and II drugs are potential etiologic agents in acute pancreatitis¹¹.

In our case, the only drug that the patient had been taking at the time of onset of symptoms

was hydrochlorothiazide. According to older criteria, this drug is a "probable" cause of pancreatitis¹². In one review, sixteen months passed on average between the start of the drug and pancreatitis symptoms¹³. Our patient had started taking the diuretic approximately 2-4 months prior to presentation, and the patient had been off thiazides for several days prior to admission. In addition, the patient's lipase continued to climb the day after admission, and only resolved as treatment was initiated. Based on newer criteria, thiazide diuretics fall under class III drugs and are not considered a particularly likely cause of drug-induced pancreatitis. None of the other drugs that she received prior to her hospitalization are thought to be likely causes.

Mortality in drug-induced pancreatitis is low¹⁴. In a German study of 1613 cases of acute pancreatitis, twenty-two were thought to be drug-induced pancreatitis (incidence 1.4%), with two deaths (9%). However, these deaths were related to AIDS and tuberculosis and not thought to be directly related to pancreatitis⁹. Long term prognosis follows that of other patients with acute pancreatitis.

Conclusion:

This young woman who presented with abdominal pain and orbital edema was later found to have pancreatitis and renal failure secondary to newly diagnosed lupus. The literature reports several cases of lupus as a primary etiology for pancreatitis although the exact pathophysiology is still uncertain. It is important to appropriately treat these patients with steroids as failure to do so has been demonstrated to increase mortality. While thiazide diuretics have traditionally thought to have significant contributions towards drug-induced pancreatitis, more recent data question the association.

REFERENCES:

1. **D'Cruz DP, Khamashta MA, Hughes GR.** Systemic lupus erythematosus. *Lancet*. 2007 Feb 17;369(9561):587-96. Review. PubMed PMID: 17307106.
2. **Wallace DJ.** The clinical presentation of systemic lupus erythematosus. In: Wallace DJ, Hahn BH, editors. *Dubois' lupus erythematosus*. 5th edition. Baltimore, MD: Lippincott Wilkins & Wilkins: 1997; 627.

3. **Breuer GS, Baer A, Dahan D, Neshor G.** Lupus-associated pancreatitis. *Autoimmun Rev.* 2006 May;5(5):314-8. Epub 2006 Jan 27. Review. PubMed PMID: 16782555.
4. **Essaadouni L, Samar E, Krati K.** Pancreatitis as initial manifestation of systemic lupus erythematosus. *Lupus.* 2010 Jun;19(7):884-7. Epub 2010 Jan 20. PubMed PMID: 20089609.
5. **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 Aug 14;11(30):4766-8. Review. PubMed PMID: 16094728.
6. **Duncan HV, Achara G.** A rare initial manifestation of systemic lupus erythematosus--acute pancreatitis: case report and review of the literature. *J Am Board Fam Pract.* 2003 Jul-Aug;16(4):334-8. Review. PubMed PMID: 12949035.
7. **Pascual-Ramos V, Duarte-Rojo A, Villa AR, Hernández-Cruz B, Alarcón-Segovia D, Alcocer-Varela J, Robles-Díaz G.** Systemic lupus erythematosus as a cause and prognostic factor of acute pancreatitis. *J Rheumatol.* 2004 Apr;31(4):707-12. PubMed PMID: 15088295.
8. **Derk CT, DeHoratius RJ.** Systemic lupus erythematosus and acute pancreatitis: a case series. *Clin Rheumatol.* 2004 Apr;23(2):147-51. Epub 2004 Feb 7. PubMed PMID:15045630.
9. **Lankisch PG, Dröge M, Gottesleben F.** Drug induced acute pancreatitis: incidence and severity. *Gut.* 1995 Oct;37(4):565-7. PubMed PMID: 7489946; PubMed Central PMCID: PMC1382911.
10. **Werth B, Kuhn M, Hartmann K, Reinhart WH.** [Drug-induced pancreatitis: experience of the Swiss Drug Adverse Effects Center (SANZ) 1981-1993]. *Schweiz Med Wochenschr.* 1995 Apr 15;125(15):731-4. *German.* PubMed PMID: 7740286.
11. **Badalov N, Baradaran R, Iswara K, Li J, Steinberg W, Tenner S.** Drug-induced acute pancreatitis: an evidence-based review. *Clin Gastroenterol Hepatol.* 2007 Jun;5(6):648-61; quiz 644. Epub 2007 Mar 28. Review. PubMed PMID: 17395548.
12. **Mallory A, Kern F Jr.** Drug-induced pancreatitis: a critical review. *Gastroenterology.* 1980 Apr;78(4):813-20. Review. PubMed PMID: 6986321.
13. **McArthur KE.** Review article: drug-induced pancreatitis. *Aliment Pharmacol Ther.* 1996 Feb;10(1):23-38. Review. PubMed PMID: 8871441.
14. **Vege SS.** Etiology of Acute Pancreatitis. [Up-to-Date (online database)] Jan 10, 2010. Available at: http://www.uptodate.com/online/content/topic.do?topicKey=pancdis/4409&selectedTitle=1~150&source=search_result#H13. Accessed October 17, 2010.

Submitted on July 30, 2011

Figure Legend:

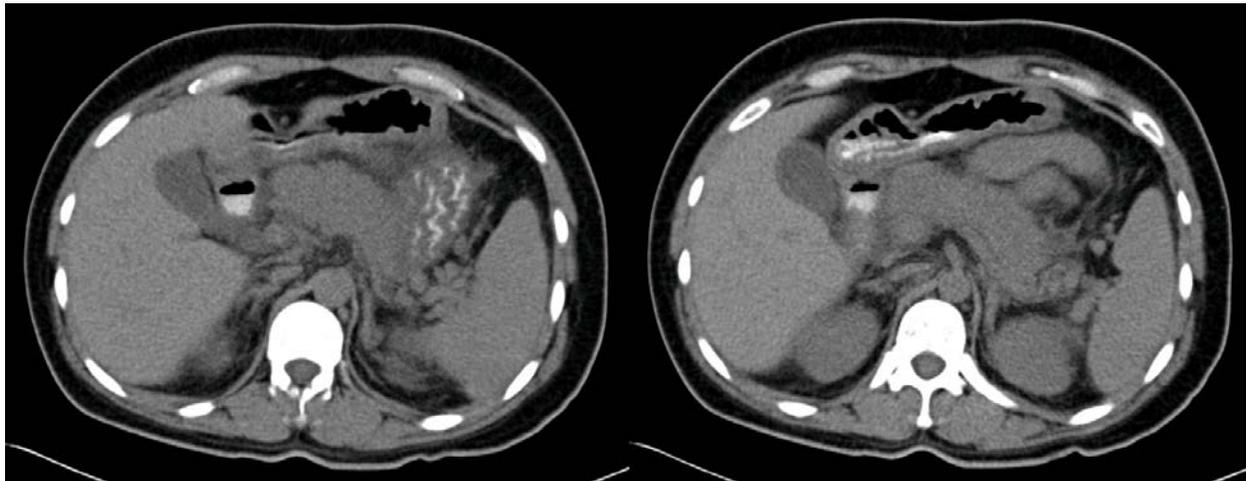


Figure 1: CT abdomen/pelvis with oral contrast - There is a small amount of intra-abdominal and pelvic ascites. There is marked stranding surrounding the pancreas and a diffusely edematous appearance, which are concerning for acute pancreatitis. There are no radiopaque gallstones. The biliary tree and pancreatic duct do not appear dilated. A 7 mm radiopaque calculus is seen in the right renal pelvis a 5 mm renal calculus is seen in the right lower pole calyx. A punctate renal calculus is seen in the left lower pole renal calyx measuring approximately 3 mm. There is no evidence of hydronephrosis or ureteral calculi.

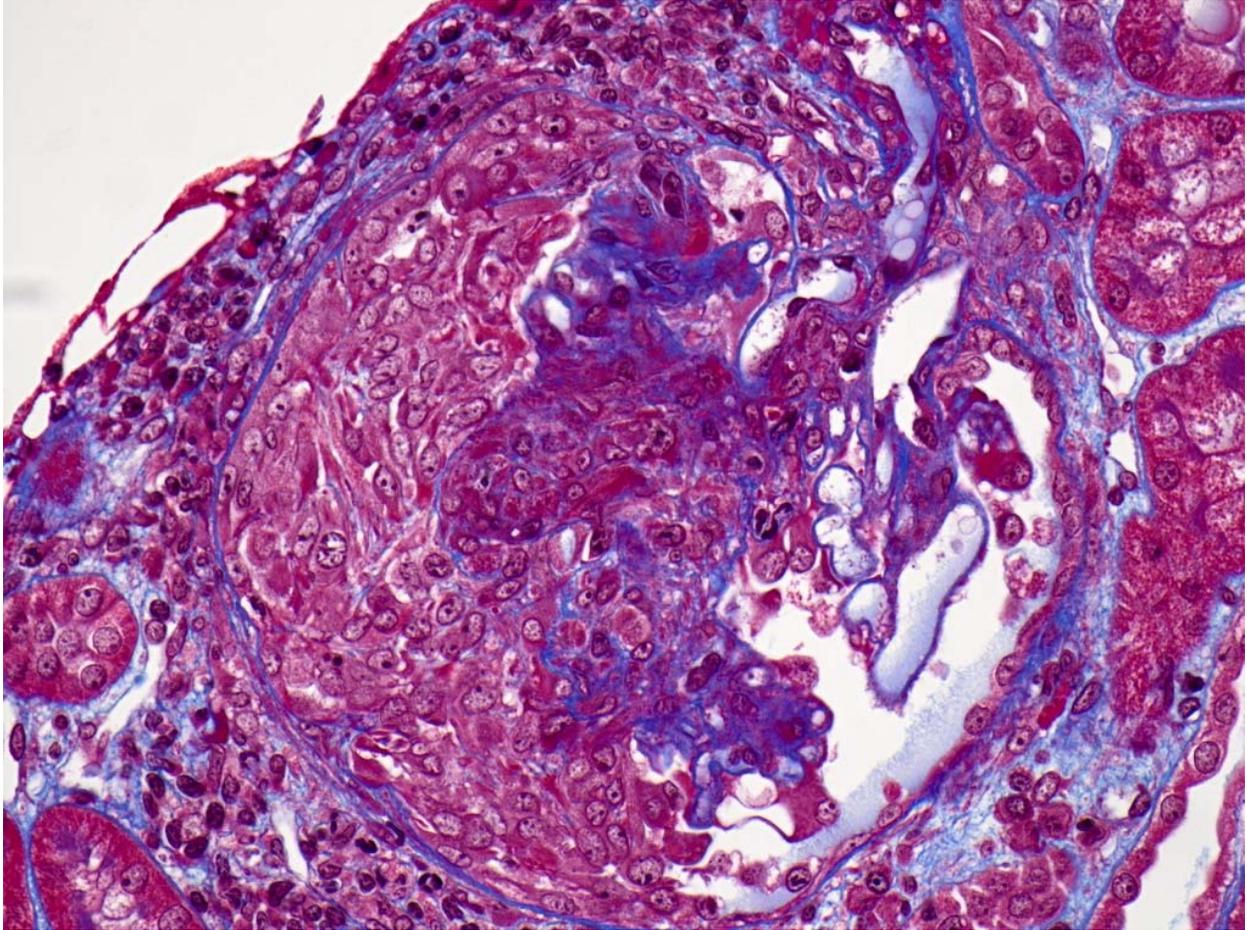


Figure 2: Masson Trichrome stain, crescentic glomerulus with immune complex deposits; original magnification 600x

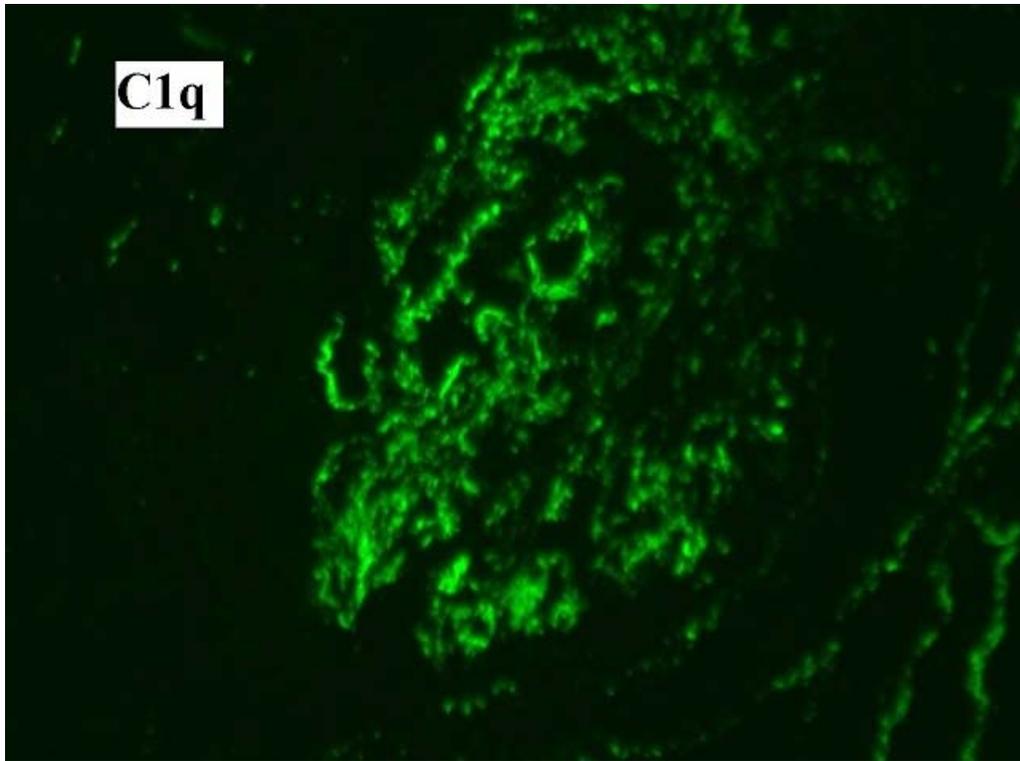


Figure 3: Immunofluorescence, glomerular C1q deposits; original magnification 400x

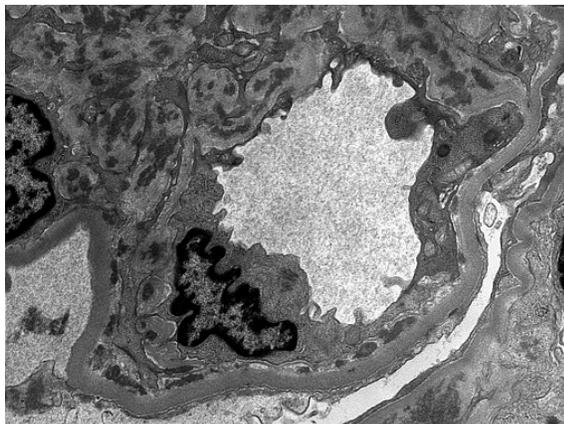


Figure 4: Electron micrograph, Mesangial and subendothelial deposits; original magnification 8000x