



Lupus-Associated Pancreatitis: Clinical Aspects

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Abstract

Background: The gastrointestinal tract may be affected in the context of systemic lupus erythematosus (SLE). The objective of this study is to review current evidence regarding lupus associated pancreatitis.

Methods: PUBMED search with the terms "lupus pancreatitis". 140 articles were related to the subject: 20 observational studies, 68 case reports or case series and 6 reviews. 363 patients are described.

Results: Elevated pancreatic enzymes may be as frequent as 30.5%. Lupus-associated pancreatitis is more frequent in women (88%), mean age of 27 years. It's likely to appear as initial manifestation (22%) or within 2 years of disease (60%). Mortality can be as high as 60%. Management starts at exclusion of common conditions, such as cholelithiasis, alcohol, hypertriglyceridemia, drugs, infections or sepsis. Glucocorticoids may be used, with impact on mortality.

Conclusion: Pancreatitis should be suspected in SLE patients with abdominal pain, mainly if the disease is clinically active elsewhere. After ruling out other common causes of pancreatitis, glucocorticoids may be used, since they can improve overall mortality.

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune inflammatory disease, with several different clinical manifestations. Its annual incidence is about 5 cases per 100000 inhabitants [1,2]. The prevalence is around 52 cases per 100000 inhabitants. The gastrointestinal tract may be affected, either by the disease itself or by adverse reactions of medications or by opportunistic infections. Although common, the incidence of gastrointestinal manifestations may be underestimated, as the symptoms may be absent or nonspecific [1,2].

Clinically, there are four main patterns of gastrointestinal commitment in SLE: mesenteric vasculitis, present in 0.2 to 9.7% of patients; protein-losing gastroenteropathy, with estimated prevalence from 1.9 to 3.2%; intestinal pseudo-obstruction, rare and related to dysfunction of the visceral smooth muscles, enteric nerves and/or visceral autonomic nervous system with aperistalsis; and lupus pancreatitis, found in 0.7 to 4% of patients [1,2]. Our objective in this study is to review current evidence about lupus-associated pancreatitis, especially regarding clinical and management aspects.

Methods

In a PUBMED search with the terms "lupus pancreatitis", we retrieved 253 articles, of which 140 were related to the subject. Of these, 90 are summarized in table 1. The literature that fundamentals this article is composed of 20 observational studies (retrospective in its majority), 68 case reports or case series, and 6 reviews mainly about abdominal pain in SLE patients. Together, 363 patients are described.

Epidemiology

Although the 363 patients reported in literature, this number may be underestimated as subclinical pancreatitis - elevated pancreatic enzymes without clinical symptoms - may be as frequent as 30.5% [3,4]. In recent years, there was some increase in reporting this manifestation [5].

SLE induced pancreatitis appears most often in women (88%), in the third decade (mean age 27ys) [4-8].

It seems that pancreatitis is more likely to appear as initial manifestation or within the first two years of disease. It happens as the initial manifestation in up to 22% of patients, and in the first two years in 60% [1,4-6,8-10]. The initial presentation of SLE gives no warning about the potential development of pancreatitis, as patients who had and had not pancreatitis had similar early manifestations [7].

There is association between pancreatitis and lupus activity (including SLEDAI and SLICC indexes) [7,9,11], being common during SLE flares. Multi-organ manifestations are remarkable, as 84% of patients with pancreatitis had other SLE manifestations, being most common: skin (46%), articular (43%), renal (35%), hematological (24%), central nervous system (21%), cardiac (9%) and pulmonary (8%) [5,7-9,11,12]. It appears that inflammation mechanisms involved in SLE activity would be an important cofactor predisposing the pancreas to trigger abnormal inflammatory response [7].

Pathogenesis

Results from studies which evaluated tissue obtained both by surgery and by autopsy show evidence of inflammation or necrosis [5,9,13]. The pathogenic mechanism is still unclear, but vascular damage may be implied. Necrotizing vasculitis, occlusion of arteries and arterioles by thrombi, intimal thickening and proliferation and

Table 1: Summary of previous studies.

Observational studies		
Derk [11]	Retrospective; 2947 hospitalizations due to SLE between 1982 and 2002	5 cases of pancreatitis (0.85%)
Pascual-Ramos [7]	Retrospective case-control design - patients with SLE and pancreatitis between 1984 -2001	35 identified patients; In 26 acute pancreatitis was an isolated event, recurrent in 9 patients
Vergara-Fernandez [19]	Prospective; 11 years of follow-up - 73 SLE patients with abdominal pain	21 patients had pancreatitis: 6 caused by gallstones, 5 by drugs, 4 associated to SLE, 4 unknown, 2 alcohol
Campos [20]	Retrospective; 263 patients with juvenile SLE	11 patients with acute pancreatitis, 1 with recurrent episodes. Association of pancreatitis with disease activity and hemophagocytic syndrome
Chang [21]	Retrospective cohort of pancreatitis in patients under 18 years between 1993-2008	7 patients with SLE, 4 died
Makol [16]	Prospective cohort of 1811 SLE patients	76 patients with pancreatitis, in which this was attributable to SLE in 63. Association with hypertriglyceridemia, psychosis, pleurisy, anemia. No association with antiphospholipid syndrome
Xu [22]	Retrospective. Cohort of 177 patients with SLE	3 patients with pancreatitis
Dhir [10]	Retrospective; 550 patients with SLE	10 patients with pancreatitis, the majority in the beginning of disease (less than 1.5ys of SLE)
Proca [23]	Retrospective Cohort of patients submitted to pancreatic resection due to chronic pancreatitis	One of 44 patients had diagnosis of SLE
Wang [12]	Retrospective. 2976 SLE patients. Between 1991-2005	48 episodes of pancreatitis in 40 patients (13 children and 27 adults). Children more frequent than adults; predominantly females; 2 patients as initial manifestation of SLE; adults with bigger survival than children
Tu [24]	Retrospective, SLE patients with abdominal pain	5 pancreatitis cases in 23 children; 14 pancreatitis cases in 88 adults
Dhaou [25]	Retrospective, monocentric	Pancreatitis present in 6 of 110 patients. In 4, it was the initial manifestation of SLE
Goel [6]	Retrospective. Cohort of 551 SLE patients	11 patients with acute pancreatitis, all in the first 12 months of disease
Yang [8]	Retrospective; Follow-up of 4053 SLE patients between 2000-2012	27 patients had acute pancreatitis. Pancreatitis was associated to high SLEDAI, multi-organ involvement, high mortality. 12 patients got recovery with GC
Yuan [2]	Retrospective, cohort of 3823 SLE patients between 2002-11	23 patients with acute pancreatitis (same cohort of Yang 2012, patients not included in counting)
Case reports and case series		
Wolman [26]	1 patient (25ys, female)	Pancreatitis as early manifestation of SLE
Yeh [27]	4 patients	All patients had anticardiolipin antibodies. At autopsy, all had thrombi in the pancreas
Hortas [28]	2 patients, one of them with diagnosed systemic sclerosis	Female, 61ys - 3 episodes of pancreatitis, with overture of clinical SLE just before the third
Lam [29]	1 patient (65ys, female)	Pancreatitis after 1 year of SLE, with death
Marum [30]	1 patient	Pancreatitis as early manifestation of SLE
Cutlan [31]	1 patient (21ys, female)	Pancreatitis and panniculitis as initial manifestations of SLE
Ramanan [32]	1 patient (14ys, female)	Positive anticardiolipin antibodies
Duncan [33]	1 patient	Initial manifestation of SLE
Fan [34]	1 patient (12ys, female)	Pancreatitis as early manifestation of SLE, good response to GC
Fantini [35]	1 patient (23ys, female)	Pancreatitis and hemolytic anemia during SLE flare. Invasive aspergillosis as a complication. Death after 17 days.
Penalva [36]	1 patient (14ys, female)	Calcifying chronic pancreatitis
Singh [37]	1 patient (24ys, female)	SLE and TTP onset after an acute pancreatitis episode. Treatment with GC and plasmapheresis, with full recovery
Swol-Ben [38]	1 patient (59ys, female)	Pancreatic pseudotumor with pancreatic fibrosis; antiphospholipid syndrome. Treatment with cyclosporine, immunoglobulin, GC
Izzedine [39]	1 patient (59ys, female)	One episode of acute pancreatitis preceding relapse of lupus nephritis. She presented pancreatic calcifications and pseudocysts
Wang [3]	1 patient (46ys, female)	Pancreatitis as initial manifestation of SLE; Successful treatment with somatostatin
Nesher [5]	3 patients	High mortality
Agoumi [40]	1 patient	Pancreatitis as initial manifestation of SLE
Ergas [41]	1 patient (male)	Relapsing pancreatitis responding to GC treatment
Kobayashi [42]	1 patient (37ys, female)	Pancreatitis and elevation of IgG4. Treatment with GC
Carducci [43]	2 patients (24 and 34ys, females)	Pancreatitis as initial manifestation of SLE. Treatment with GC and somatostatin
Gutierrez [44]	1 patient (26ys, female)	Calcifying chronic pancreatitis in 2 years of SLE onset
Tominaga [45]	1 patient (12ys, female)	Pancreatitis as initial manifestation of SLE. Treatment with plasmapheresis, methylprednisolone and cyclophosphamide, with full recovery
Noia [46]	3 patients	1 patient; recurrence one month after acute pancreatitis episode, evolution with pancreatitis; 1 patient with recurrent symptoms and pseudo cysts; 1 patient late in evolution of SLE, pancreatitis related to sulphametoxazol
Myung [47]	1 patient (33ys, female)	Pancreatitis, pseudocyst and central nervous system vasculitis; Improved with GC, but had just after infection of pseudocyst, improved with local surgery
Rose [48]	1 patient (14ys, female)	Pancreatitis as initial manifestation of SLE. Treatment with methylprednisolone and oral GC
Vyas [49]	1 patient; Previous diagnosis of SLE and secondary antiphospholipid syndrome	Relapsing ischemic pancreatitis, resistant to CS and anticoagulation. Better results with plasmapheresis, GC, cyclophosphamide and anticoagulation
Cairolì [50]	1 patient (39ys, female)	Acute pancreatitis during a severe lupus flare; pseudocysts; death despite GC use
Campos [51]	2 patients	Female, 27ys: pancreatitis one year after diagnosis of SLE. Good response to GC. Female, 20ys: just after diagnosis of SLE, death by spontaneous rupture of pancreatic pseudocyst
Essadouni [52]	2 patients (16ys, 45ys, females)	One patient with positivity of anticardiolipin antibodies, one patient negative

Geraldino [53]	1 patient (29ys, female)	Pancreatitis as early manifestation of SLE (2 months), accompanied of parotiditis. Resolution with GC in high dosage
Ko [54]	1 patient	In the post-partum period, manifestations of SLE started, followed by acute pancreatitis
Al-Musawi [17]	1 patient with recurrent attacks of acute pancreatitis	Patient was treated with rituximab (antiCD20 monoclonal antibody), maintaining remission for 2 years
Hoorn [55]	1 patient (25ys, female)	Pancreatitis with pseudocyst. Treatment with GC, azathioprine, immunoglobulin, with recovery
Malavya [56]	1 patient (55ys, female), history of 6 ys of SLE	Treatment with cyclophosphamide and methylprednisolone
Linwattana [14]	3 patients (11ys, 7ys and 18ys, female)	Successful treatment with GC
Domingues-Pinilla [57]	1 patient (12ys, female)	Pancreatitis as early manifestation of SLE. Treatment with methylprednisolone and hydroxychloroquine
Nguyen [58]	1 patient (38ys, female)	Antiphospholipid syndrome, initial manifestation. Thrombotic microangiopathy in the pancreas and kidneys
Studies without full text available or text in languages other than English, French, Portuguese, Spanish or Italian		
György [57]	1 patient (52ys, female)	histology: nucleophagocytosis, leukophagocytosis, erythrophagocytosis in the pancreas
Hamed [58]	3 patients with SLE	2 died of hemorrhagic pancreatitis and 1 had pseudocysts
Reynolds [59]	Retrospective	20 patients out of 63 SLE patients had pancreatitis, 4 attributable to SLE, with recovering with GC
Ossi [60]	1 patient	SLE with pancreatitis during flare, recovery with plasmapheresis and GC
Simons-Ling [61]	1 patient (12ys, female)	pancreatitis, panniculitis and calcynosis
Zanen [62]	1 patient (33ys, female)	Pancreatitis during severe flare. Recovery with plasmapheresis and GC
Brujin [63]	1 patient (16ys, female)	pancreatitis without histologic findings of autoimmune activation in pancreas
Giordano [64]		Pancreatitis as initial manifestation of SLE, treatment with methylprednisolone
Rupprecht [65]	1 patient (17ys, female)	Chronic pancreatitis since her 11 years, then onset of SLE. Use of azathioprine, GC, plasmapheresis and cyclophosphamide
Eaker [66]		Pancreatitis as initial manifestation of SLE
Pereira [67]		Pancreatitis during flare of SLE, recovery with GC
Levy [68]		Cohort of pancreatic patients with unfavorable outcomes of SLE – 1 patient with pancreatitis
Serrano-López [69]	autopsy of a patient with SLE	Pancreatitis with vascular damage and intimal proliferation
García-Consuegra [70]	1 patient (15ys, female)	Acute pancreatitis with pseudocyst formation
Wang [71]	1 patient (39ys, female)	Elevated anticardiolipin. Postmortem examen with generalized thrombi formation. In the pancreas, chronic inflammation with thrombi in pancreatic arteries, without vasculitic changes
Borum [72]		2 patients with chronic pancreatitis
Braun [73]	1 patient (15ys, female)	Mixed disease of the connective tissue - widespread vasculopathy with intima proliferation and minimal fibrosis
Huang [74]	1 patient (13ys, female)	Pancreatitis as early manifestation of SLE. Treatment with GC
Huong [75]		5 patients, 3 died
Kolk [76]	1 patient (16ys, female)	Autoimmune vasculitis
Leong [77]		1 patient - good response to GC high doses
Saab [78]	Retrospective cohort	8 patients with lupus pancreatitis in 10 years, with good response to GC
Tahara [79]	1 patient (22ys, female)	Pancreatitis as early manifestation of SLE. Good response to GC
Hani [80]		2 patients, both died
Saito [82]	1 patient	Concomitant onset of SLE and pancreatitis. Treatment with GC
Abdallah [82]	1 patient, SLE for 7 years	Pancreatitis and hemofagocytic syndrome.
Ozenc [83]		1 patient; pseudocyst
Perrin [84]	1 patient (13ys, female)	Pancreatitis as initial manifestation of SLE. Treatment with mycophenolate mophetil and GC
Suzuki [85]		1 patient with overlap of systemic sclerosis and SLE. Treatment with GC and plasmapheresis
Duval [86]		1patient, 27ys, female. Pancreatitis as early manifestation of SLE
Wang [87]	Retrospective, 28 autoimmune disease related pancreatitis	20 SLE, 6 Sjögren's syndrome
Soyibo [88]		1 patient (50ys, female)
Ghamarchehreh [18]	1 patient (24ys, female),	2 episodes in the onset of SLE. Use of GC and rituximabe, evolution to death
Koga [89]	1 patient (55ys, female)	pseudo cysts with rupture
Medeiros [90]	retrospective	136 patients, 3 with clinical pancreatitis, 7 with subclinical pancreatitis
Elgatni [91]		Pancreatitis and hemophagocytosis as initial manifestation of SLE

GC = glucocorticoids

immune complex deposition with complement activation in the wall of pancreatic arteries have been postulated [1,7]. Direct inflammation of the parenchyma may result from autoantibody production or abnormal cellular immune response [4,8].

Clinical Features

Abdominal pain is the most characteristic manifestation, present in 80% of patients. Only 23% had pain radiated to the back [9]. 66% have nausea and vomiting. Fever is present in up to 47% of patients. Diarrhea is less common (9%) and a few patients have panniculitis [1,5,12]. As the clinical manifestations are nonspecific and similar to non-SLE acute

pancreatitis or other gastrointestinal diseases or adverse reaction of medications, there should be a high rate of suspicion [14].

Associated laboratory findings may include elevated serum amylase and lipase, but also hypoalbuminemia, abnormal liver function, elevated creatinine and hypocalcemia [1,5]. Low complement, especially C3, is a common finding [7]. A remarkable fact is that up to 59% of patients with lupus-associated pancreatitis may show leucopenia, and only 15% of them show leukocytosis [5], in contrast with non-lupus populations, in which leukocytosis is more common, even being included in severity indexes, such as Ranson's [15].

Regarding serologic markers and autoantibodies, there is no well-defined pattern. Some authors have found association to the anti-SSB/La and secondary Sjögren's syndrome [16]. ANA is present in 98% and anti-dsDNA in 73% [5] of SLE patients with pancreatitis. It is also controversial the association between antiphospholipid syndrome and pancreatitis. Series of cases found similar anticardiolipin antibody prevalence in SLE patients with pancreatitis and with other causes of abdominal pain [6,16]. In another one, 20% of secondary antiphospholipid syndrome was found [7].

Abdominal image should be performed, as suggestive findings reinforce the hypothesis and biliary origin must be ruled out. Both computerized tomography (CT) and ultrasonography may be performed for this purpose, with sensitivity of 76% and 55%, respectively [9]. Characteristic CT findings are diffuse or segmental enlargement of the pancreas, blurring of peripancreatic fat, low/high density area in contrast and peripancreas effusion. For ultrasonography, positivity is defined as pancreatic enlargement, decreased echo density and fluid collections [8].

Management

The treatment should begin as soon as lupus pancreatitis is considered the most probable cause of the pancreatitis. Common conditions which predispose to pancreatitis, such as mechanic obstruction associated to cholelithiasis, alcohol, hypertriglyceridemia, drugs (eg. Azathioprine, glucocorticoids, furosemide, isoniazid, metronidazole, sulindac), infections (eg. Cytomegalovirus) or sepsis must be excluded.

Delayed diagnosis and improper treatment may contribute to unfavorable prognosis, then; glucocorticoids should be used as soon as they are excluded as the cause of pancreatitis.

Mortality among patients who received glucocorticoids following the diagnosis of pancreatitis was 20%, compared to 61% of those who did not receive this therapy [5,11]. Other immunosuppressive agents can also be used, such as azathioprine or cyclophosphamide. Severe cases may be treated with plasmapheresis or intravenous gamma-globulin. There is recent experience with the use of rituximab, with reports of both success and failure [17,18,53].

Although glucocorticoids and azathioprine may be implicated as potential causes of pancreatitis, available data suggest that in most cases they did not trigger acute pancreatitis or increase mortality, and should be promptly offered to the patient with suspected lupus-related pancreatitis [5,7,9,12]. Re-exposure to these drugs after resolution of pancreatitis did not worsen prognosis [7].

Prognosis

The rate of complications if lupus pancreatitis remains untreated is as large as 57%, with mortality of up to 45%, higher than those observed in non-SLE populations [6,9]. Complications include respiratory failure (22%), recurrent pancreatitis (22%), ascites (19%), pleural effusion (18%), acute renal failure (14%) and circulatory shock (12%) [5].

Mortality increases as lupus activity is higher, especially if heart, central nervous system and kidneys are involved at the same time [1,6,8,16]. Other risk factor for mortality are renal dysfunction with high creatinine, hypoalbuminemia, presence of anti-dsDNA antibodies, thrombocytopenia, low complement, hypocalcemia, hyperglycemia and elevated liver enzymes [1,5,6,9,12]. Hematuria and granular casts can also be considered factors of worse prognosis [8].

Treatment with azathioprine and glucocorticoids reduces mortality [5,6,9]. There used to be concern about these two medications, as they can induce pancreatitis, but evidence did not support this worry [5,6,9]. Patients who were taking glucocorticoids before the onset of pancreatitis also had a better prognostic in comparison to those who were not [5,6,9]. Prior immunosuppressive therapy did not affect the outcome of pancreatitis [9].

Recurrent acute pancreatic crises may happen in 22% of patients,

while 12% develop pseudocysts and 5 to 14% have a chronic course (chronic pancreatitis or recurrent episodes of acute pancreatitis) [1,5].

Children-onset SLE usually exhibits more major organ involvement and worse prognosis. There are two studies comparing those two populations - adult and pediatric. One of them found that, in the pediatric subset, acute pancreatitis occurs more frequently (5.22 vs. 0.99%), tends to be more severe, with higher prevalence of complications (76.4 vs. 33.3%) and is associated with higher mortality (53.8 vs. 25.9%) [12]. The other one found in pediatric lupus a higher rate of severe pancreatitis (60 vs. 11.76%), higher serum amylase level, lower percentage of positive anti-Ro and anti-La antibodies, without difference in mortality [8].

Limitations

Most of the evidence presented derives from review of individual or series of cases and it is difficult to define clear conclusions from individual patterns and with the possibility of milder cases may be neither recognized nor published.

Conclusions

High vigilance is the most important suggestion to improve knowledge and survival from this still unknown condition. Pancreatitis should be suspected in lupus patients with abdominal pain, especially if the disease is clinically active elsewhere. As pancreatitis may be the first clinical manifestation of SLE, investigation of lupus is suggested in patients with idiopathic pancreatitis, especially in younger females. After ruling out other common causes of pancreatitis, glucocorticoids may be used in SLE patients, as they can improve overall mortality.

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