CASE REPORT

JIACM 2023; 24 (3-4): 228-33

Acute Pancreatitis in Systemic Lupus Erythematosus: Rare Presentation of a not so Common Disease

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Abstract

Introduction: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder characterised by formation of autoantibodies, complement activation and altered cellular immunity, culminating in end organ damage. Acute pancreatitis in SLE is rare (0.4 - 1.1%) but carries high mortality (78.5%) if severe[1].

Case report: 16-year-old girl presented with Raynaud's phenomenon, skin lesions and polyarthralgia for 6 months, anasarca for 2 months and epigastric pain for one day. Investigations showed thrombocytopenia, raised serum lipase, low SAAG ascites, urine protein - 2.81 g/24 hours ANA+, anti-dsDNA+, pANCA+, anticardiolipin antibody and lupus anticoagulant+. CECT showed features of acute pancreatitis, hypoperfusion complex and shock bowel.

Skin biopsy showed Discoid Lupus Erythematosus (DLE), kidney biopsy revealed class II lupus nephritis. The patient was managed with pulse methylprednisolone and IVIg. She developed acute pulmonary thromboembolism after 2 weeks and was started on anticoagulants. In view of SLE/Lupus Nephritis/ Acute pancreatitis/Pulmonary thromboembolism/APS/? vasculitis, rituximab was started, to which she responded and is doing well.

Conclusion: Acute pancreatitis in SLE is a marker of disease activity. Autoimmune cause should be ruled-out in a young girl with pancreatitis. Patients with high SLEDAI score not showing adequate response with conventional treatment may be given a trial of B cell depletor therapy – like rituximab, especially in those with pANCA positivity and vasculitis.

Keywords: SLE, pancreatitis, rituximab.

Introduction

Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune illness that classically affects women of childbearing age; is characterised by autoantibodies formation and deposition into tissues and complement activation culminating in end organ damage[1]. Although gastrointestinal manifestations are common and are seen in about 50% patients[2], pancreatic involvement is quite rare with an annual incidence of only 0.4 - 1.1%[3,4]. Acute pancreatitis is commonly seen in patients with high SLEDAI score and is associated with involvement of many organs and systems (liver, kidney, haematological), serositis, frequent fever, high CRP and anti-La antibodies[3]. Acute pancreatitis in SLE is responsible for morbidity as well as substantial mortality especially if severe (78.5% in severe vs 27.5% in all SLE related acute pancreatitis[3,5]. Various non-immune causes like mechanical obstruction, infection, toxic-metabolic and trauma need to be ruled out before attributing SLE as a cause of acute pancreatitis[3]. Pathogenesis of acute pancreatitis in SLE is multifactorial – characterised by autoantibody production, immune complex deposition, abnormal cellular immunity, complement activation, drug toxicity, vascular damage due to vascultis, intimal thickening and occlusion of arterioles and arteries by thrombosis[2,3].

This case report highlights pancreatitis as a presentation of SLE in a young girl who also had involvement of skin, joints, kidney, and Raynaud's phenomenon and showed remarkable improvement with steroids and rituximab. It emphasizes the fact that in a young patient without any obvious cause of pancreatitis, autoimmune cause should always be worked up for.

Case report

This 16-year-old girl, a resident of Delhi, had polyarthralgia since 6 months, involving PIP, MCP joints, but sparing DIP joints. There was associated history of pandigital Raynaud's phenomenon, on exposure to cold water, of similar duration. She developed anasarca with passage of frothy urine for 2 months. There was history of erythematous, non-pruritic, palpable rash on her left leg 1 month before

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presentation which had resolved completely over 1 week. She was having 6 - 7 episodes of watery loose stools since 1 day, associated with epigastric pain which relieved on stooping forward. This was also associated with non-bilious, non-projectile, non-blood tinged vomiting and abdominal distension. For this, she presented to the medicine emergency. She had 1 episode of fever on the day of presentation, documented to be 99.8° F. It was noticed by the patient that her urine output had decreased to approximately 200 - 300 mL in the last 24 hours. She had received her 1st dose of Covaxin 2 months before presentation. There was no history of haematuria, burning micturition, pain abdomen, jaundice, chest pain, cough or shortness of breath.

On presentation, her BP was 76/50 mmHg, PR was 110/min, all peripheral pulses were palpable and her SpO_2 was 97% on room air. There was facial and periorbital puffiness to the extent that the patient was unable to open her eyes. She was found to have signs of dehydration. On systemic examination, air entry was decreased and dull note on percussion was present in bilateral lower zones in chest. On abdominal examination, abdomen was distended with shifting dullness, epigastric tenderness, and absent bowel sounds. Rest of the clinical examination was found to be normal. The initial investigations are shown in Table I and Table II.

Table I: Investigations.

Date	17 days before presentation	6 days before presentation	On day of admission
Hb (g/dL)	10.1	9.9	11.6
TLC (cells/µL)	6530	5700	7000
DLC (Polymorphs%/ lymphocytes%/monocytes%/ eosinophils%)	71/27/1/1	61/31	59/37
PLC (cells/µL)	97k	97k	41,000
Chol (mg/dL)	115	110	97
TG (mg/dL)	247	242	274
LDL (mg/dL)	28.6	42	30
HDL (mg/dL)	37	33	28
Urea (mg/dL)	45	33	78
Creatinine (mg/dL)	1.0	0.9	1.2
TP/SA (g/dL)	7.0/3.2	7.2/3.4	6.2/2.9
Urine alb	2+	4+	
Urine RBC	Nil	3 - 5/hpf	
RBS (mg/dL)			110
CXR	WNL		
2D echo	WNL		
HIV	Non-reactive		
HBsAg	Non-reactive		
Anti-HCV	Non-reactive		
Amylase (U/L)			128
Lipase (U/L)			1507
LDH (U/L)			313
UA (mg/dL)			13.6

Table II: Investigations.

Date	On day of admission
ICT/DCT	Negative
P/S	Microcytic normochromic anaemia with thrombocytopenia, no toxic granules
Dengue serology	Negative
PSMP	Negative
Procalcitonin (ng/mL)	0.397
Blood culture	No growth
Urine examination	Inactive sediment with moderate proteinuria
Protein creatinine spot ratio	0.40
Ascitic fluid SAAG	0.85 (low SAAG)
Ascitic fluid protein (g/dL)	4.79 (high protein)
Ascitic fluid TLC (calls/mm^3)	10
Ascitic fluid DLC	All mononuclear
Renal artery Doppler	Normal
CECT chest and abdomen (Fig. 1)	Bilateral pleural effusion (R > L) with moderate ascites, reduced calibre of IVC and aorta with bulky pancreas and peripancreatic and perinephric fat stranding s/o CT hypoperfusion complex with shock bowel.

Patient was initially managed conservatively for pancreatitis by Ryle's tube decompression and Central Venous Pressure guided fluids. Further investigations are shown in Table III and Table IV. Since the autoimmune profile was suggestive of SLE with activity, and in view of autoimmune pancreatitis and lupus nephritis, she was started on methylprednisolone pulse therapy (1 g/day intravenous) for 5 days, followed by tablet prednisone 1 mg/kg/day.

On day 4, she developed 6 - 8 non-blanching, erythematous, palpable, non-pruritic, circular skin lesions on her leg and back, 0.5 - 0.8 cm in diameter. These lesions were biopsied, the findings of which are given in Table IV. Patient improved symptomatically and bowel sounds returned, hence she was allowed oral fluids. Her BP and PR stabilised, urine output improved and on investigations,

acute kidney injury settled. On day 8, triglyceride (TG) levels increased dramatically (780 mg/dL) despite statin therapy and platelet counts kept on dropping requiring multiple transfusions. In view of high TG levels, patient was started on D5 with insulin infusion 0.1 units/kg/hr on day 8 to maintain blood sugar levels between 150 - 200 with 12 hourly triglyceride monitoring. Triglycerides dropped to 337 mg/dL in 24 hours and insulin and D5 infusion were stopped. Patient was also given IVIg on day 8 for persistently low platelet counts for 2 days, suspecting ITP, but there was no improvement.

Table III: Further investigations.

24 hr urinary protein	0.81 g/day
ANA	homogeneous (+), speckled (1 to 2+), 1:80 dilution
AntidsDNA	1+
Nucleosomes	3+
Histones	1+
RPP/PO	4+
Anti-dsDNA by ELISA	> 400 IU/mL
P-anca	28 U/mL (positive)
C-anca	3 U/mL (negative)

Table IV: Skin biopsy and kidney biopsy.

Skin biopsy	Focal epidermal atrophy and spongiosis. Dermis showed mild chronic inflammatory infiltrate perivascular and periadnexal location with dermal fibrosis with paucity of skin adnexa. Direct Immunofluorescence for IgA and IgM were negative. (suggestive of Discoid Lupus Erythematosus).
Kidney biopsy (Fig. 2 and Fig. 3)	Enlarged glomeruli with mild increase in mesangial matrix and cellularity with no evidence of proliferative activity in the form of endocapillary proliferation or crescent formation. There was no basement membrane thickening or spike formation on silver methenamine stain. IF showed coarse granular deposits of IgG, C3, IgM, IgA, C1q, kappa, lambda in predominantly the mesangium and focally along the peripheral capillary walls. The extra glomerular immune deposits of IgG, C3, IgA, IgM , C1q, Kappa, Lambda are also seen along the blood vessels and peritubular capillaries. Findings s/o mesangial lupus nephritis class II.

On day 10 of illness, patient developed sudden onset shortness of breath without cough and expectoration. It was not associated with fever. On respiratory examination, bilateral normal vesicular breath sounds were present. ECG showed sinus tachycardia. D- dimer was raised (19,000 ng/mL). CXR showed bilateral lower lobe heterogeneous opacities. CECT chest with CTPA showed multiple thin linear concentric filling defects seen in bilateral lower lobe segmental arteries and their branches circumferentially surrounded by contrast. Pericardial effusion and bilateral pleural effusion with diffuse ground glass opacities and

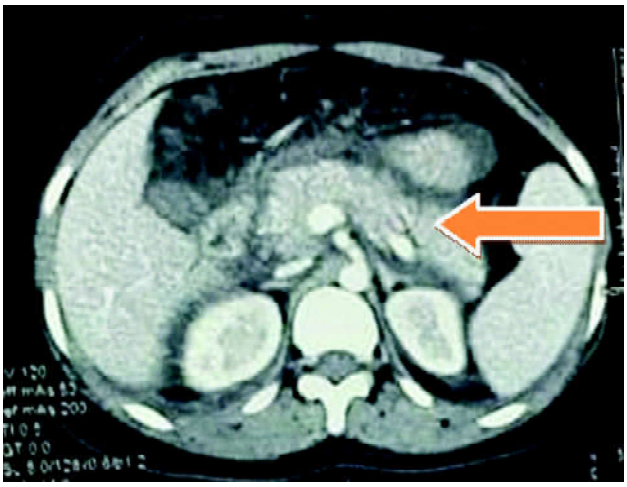

Fig. 1: The image shows CECT abdomen of the patient demonstrating bulky pancreas, predominantly the tail with peripancreatic fluid and fat stranding suggestive of acute pancreatitis.

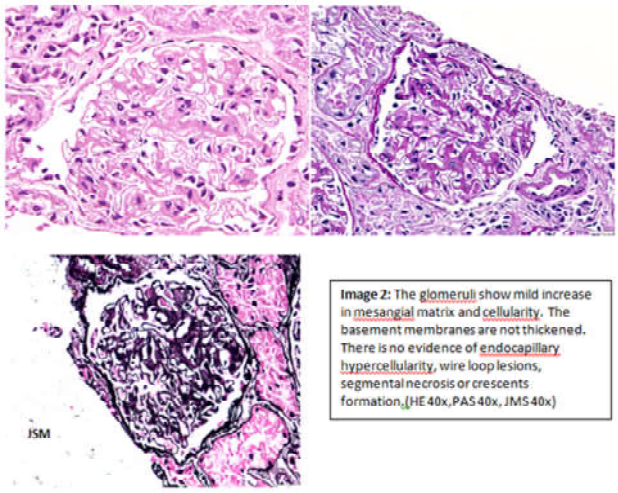

***Fig. 2:** The glomeruli show mild increase in mesangial matrix and cellularity. The basement membranes are not thickened. There is no evidence of endocapillary hypercellularity, wire loop lesions, segmental necrosis or crescents formation. (HE 40X, PAS40X, JMS 40X).*

wedge-shaped area of consolidation in bilateral lower lobe were also seen suggestive of acute pulmonary thromboembolism with pulmonary infarction. (Fig. 4 and Fig. 5) 2D echo showed mild TR/ moderate PAH (RVSP - 50+ RAP)/normal LVSF. Patient was started on LMWH (Enoxaparin) subcutaneous BD injection with T. warfarin with INR monitoring. T. aspirin 75 mg OD was started. Investigations during hospital stay are shown in Table V.

Antiphospholipid antibody profile showed normal beta 2 glycoprotein (4.97 SGU) and borderline raised cardiolipin antibody (18.90 GPL) and lupus anticoagulant (54.70 seconds, control - 38.20 seconds. CECT abdomen with angiography done on day 14 revealed bulky body of

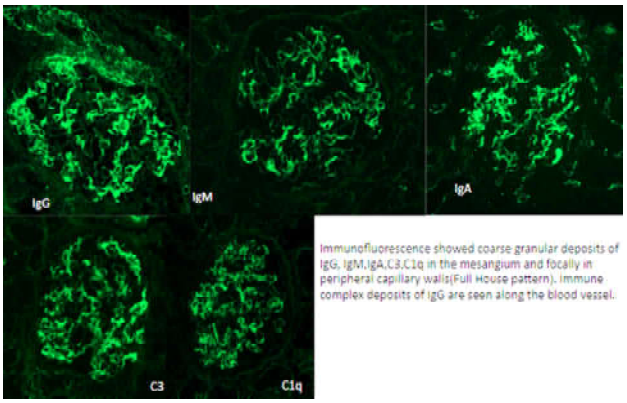

Fig. 3: *Kidney biopsy immunofluorescence. Immunofluorescence showed coarse granular deposits of IgG, IgM, IgA, C3, C1q in the mesangium and focally in peripheral capillary walls (full house pattern). Immune complex deposits of IgG are seen along the blood vessel.*

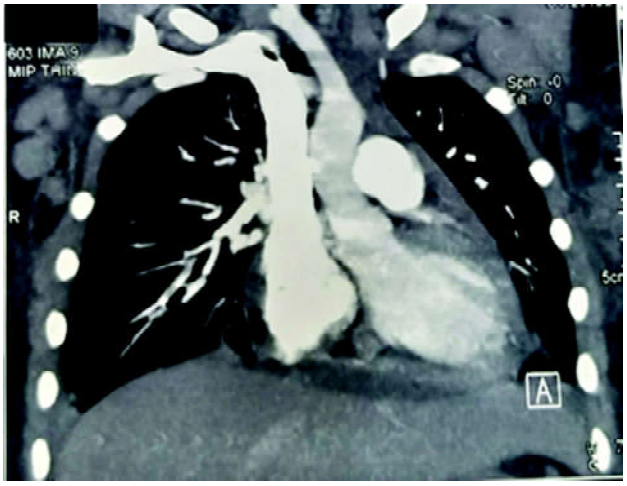

Fig. 4: *The image shows multiple thin linear concentric filling defects in bilateral lower lobe segmental arteries and their branches s/o thrombi circumferentially surrounded by contrast.*

pancreas with minimal ascites and normal angiography.

A diagnosis of antiphospholipid syndrome with APS with secondary ITP with class II lupus nephritis with acute pancreatitis (? SLE induced ?? secondary to pANCA vaculitis) with DLE with anal fissure with pulmonary thromboembolism was made.

In view of persistent thrombocytopenia despite Ivlg and suspecting vasculitis leading to pulmonary embolism, she was started on rituximab and mycophenolate mofetil after ruling-out infections (Mantoux, HBsAg, Anti HCV and HIV were negative) and premedication with anthelmintics, on day 14. Swelling started resolving on day 16, and completely resolved on day 20. The patient developed severe neutropenia during follow-up, hence MMF had to be stopped and patient was kept on maintenance with low dose steroids (tapered over 6 months to 5 mg/day) and rituximab 6 monthly

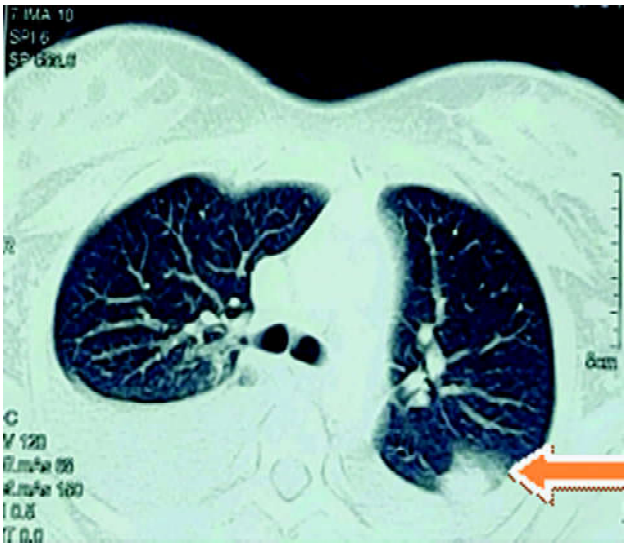

Fig. 5: *This image shows diffuse ground glass opacities in bilateral lung parenchyma with wedge-shaped areas of consolidaton in superior segment of left lower lobe and basal segments of bilateral lower lobes.*

dosing. She has since then been following up in OPD and is currently doing well with no disease activity (as monitored clinically, by anti-dsDNA levels and 24-hour urinary proteins).

Table V: Investigations during hospital stay.

Date	Day 5 of admission	Day 8 of admission	Day 10 of admission	Day 15 of admission	Day 20 of admission
Hb (g/dL)	9.3	10.3	9.2	9.8	9.2
TLC (cells/µL)	5,340	6,410	7,800	5,900	5,420
DLC (Polymorphs%/ lymphocytes%)	64/34	78/17	70/21	72/22	80/16
PLC (cells/µL)	51,000	10,000	18,000	22,000	82,000
TG (mg/dL)	323	780	337	288	156
Urea (mg/dL)	96	77	54	43	23
Creatinine (mg/dL)	1.3	0.9	0.8	0.9	0.6
TP/SA (g/dL)	6.1/2.5	6.7/2.8	7.0/3.1	7.0/3.0	7.2/3.1
Urine alb	2+	3+	2+	1+	Trace
Urine RBC	8/hpf	6 - 8/hpf	8 - 10/hpf	4 - 5/hpf	Nil
Amylase (U/L)	109	96	82	78	74
Lipase (U/L)	331	230	182	124	108
D-dimer (ng/dL)	892	2,084	19,000	10,337	2,731

Discussion

Acute Pancreatitis in SLE not only masquerades as gastroenteritis[3], but can also have a subclinical presentation in high proportion of cases[6]. So there are chances of misdiagnosis (as high as 88.6%), delay in diagnosis and improper treatment which may contribute to unfavorable

prognosis, even life threatening events[3,6]. In this case, the patient presented with pain abdomen, loose motion, and hypotension. Keeping a high index of suspicion, acute pancreatitis was suspected and investigated. It is also true that acute pancreatitis is more commonly seen with high SLEDAI score, more organ system involvement, high frequency of fever, liver involvement, haematological disorder, serositis, elevated CRP, positive anti-La[3]. Also, paediatric-onset acute pancreatitis is generally more severe than adult-onset[3]. Richer *et al*, found that pancreatitis in paediatric-onset lupus developed severe acute pancreatitis in 57% patients and mortality rate of 45%[7]. The index case was a case of SLE with high SLEDAI (SLE disease activity index) score of 26, multi-organ involvement in the form of lupus nephritis and pulmonary thromboembolism, haematological involvement, serositis.

After ruling-out other causes of acute pancreatitis – like trauma, obstruction, infection (sterile urine and blood culture, normal procalcitonin), hypertrigiceridaemia (only mildly raised at beginning), toxic exposure to alcohol, steroid, azathioprine, and considering high SLE disease activity index, underlying autoimmune condition was attributed as the cause of acute pancreatitis[3]. Although the patient had hypertriglyceridaemia, it could not be established as the cause of hypertriglyceridaemia as on presentation, the triglyceride levels were only mildly raised (< 500 mg/dL) when pancreatitis symptoms had started and it never reached >1,000 mg/dL, which is a strong risk factor for pancreatitis. According to a study by Scherer *et al*, the risk of pancreatitis was 5% in patients with triglyceride levels >1,000 mg/dL and 10 - 20% in levels >2,000 mg/dl[8].

Steroid treatment for autoimmune pancreatitis was considered controversial because of fear of steroid-induced pancreatitis, however, this concern is regarded as minimal and immunosuppressive effect of steroid can significantly improve prognosis and is recommended for autoimmune pancreatitis[9].

The index patient had incomplete improvement of disease including pancreatitis (CECT abdomen showed bulky pancreas) despite pulse steroids, so immunosuppressants were given for adequate response. Azathioprine itself can cause pancreatitis so it was not chosen. Cyclophosphamide has issues of infertility, teratogenesis and carcinogenesis. B cell depleter (Rituximab and Belimumab) were good choices in view of accompanying vasculitis (suspected because of associated pulmonary thromboembolism and pulmonary infarct and Raynaud's phenomenon) and positive pANCA. Rituximab (chimeric monoclonal antibody against CD - 20 cells) has been beneficial in RA and cANCA associated vasculitides[10]. Belimumab is approved for use in SLE with moderate disease activity but Rituximab use in SLE is restricted to off label as found to be beneficial only in particular subset of patient who are severe aggressive phenotype and greatly based on B cell driven pathogenesis[1] as shown in EXPLORER[11] and LUNAR trial[12]. Rituximab was preferred because of its in-hospital availability and better adverse event profile. The patient showed remarkable improvement when rituximab was given in combination with basal steroids.

This case helps conclude that autoimmune diseases – like SLE can affect almost every organ of the body and that wark-up for autoimmune diseases should be a routine in case of acute pancreatitis especially in a young girl where other non-autoimmune causes have been ruled-out.

A similar case was reported in Peru by Rodriguez in which a 21-year-old lady, a known case of SLE and lupus nephritis on steroids and pulse cyclophosphamide presented with acute pancreatitis. In this case also, SLE was attributed as the cause of pancreatitis after ruling-out other causes, and as the patient had received the last pulse dose of cyclophosphamide 6 months ago and she high anti-dsDNA values and low C3 and C4 suggesting disease activity of SLE. This patient also did not respond to conservative management – like our patient, but responded well to pulse methylprednisolone[13].

Jia *et al* reported a case in which a 23-year-old lady presented with acute pancreatitis which worsened despite conservative management and the patient was eventually diagnosed with SLE with class III lupus nephritis with mesenteric vasculitis with high anti-ds DNA levels and low C3 and C4 levels. This patient was treated with methylprednisolone, cyclophosphamide, levofloxacin, metronidazole, bactrim, and mesna; and the patient improved[14].

Conclusion

Acute pancreatitis in SLE is a marker of disease activity. Autoimmune causes should be ruled-out in a young girl with pancreatitis. Patients with high SLEDAI score not showing adequate response with conventional treatment may be given a trial of B cell depletor therapy – like rituximab – especially in those with pANCA positivity and vasculitis.

Patient Consent: Informed consent for the publication of this case report was obtained from the patient's father.

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