Systemic Review

Antinuclear Antibody Negative Systemic Lupus Erythematosus Presenting as Cryoglobulinemic Vasculitis: A Diagnostic Challenge

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Abstract

Systemic Lupus Erythematosus (SLE) is an autoimmune disorder marked by persistent immune system activation, leading to the production of autoantibodies and immune complex–driven damage to tissues and organs. The condition predominantly affects females, with a female-to-male ratio of about 9:1, largely due to hormonal influences. The most frequent initial presentations include constitutional symptoms such as fever, followed by cutaneous and joint involvement. We report the case of a 47-year-old female who presented with chronic diarrhoea leading to acute kidney injury, which was managed conservatively. She later developed progressive digital gangrene, prompting further systemic evaluation, following which a diagnosis of SLE was established.

Keywords: Systemic lupus erythematosus, cryoglobunemia, vasculitis, Antinuclear antibody.

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Introduction

Systemic Lupus Erythematosus is a multisystem autoimmune condition characterized by sustained immune system activation, resulting in the formation of autoantibodies and protein products that cause immune complex–mediated damage to tissues and organs.

Hippocrates was the first to describe the skin ulcers associated with SLE. The first formal clinical description was provided by Laurent-Théodore Biett in 1833 under the term Erythema centrifugum.

The global prevalence of SLE is approximately 5 per 100,000 person-years. In India, the prevalence has been reported as 3.2 per 100,000 individuals. Survival data indicate that nearly 85% of patients live at least 10 years after diagnosis, while about 75% survive for 20 years. Mortality rates are higher among younger patients, with SLE-related deaths occurring in 78.9% of individuals under 20 years of age compared to 18.7% among those aged 70–79 years.[1]

This case is reported due to its atypical features, including postmenopausal age of presentation, unusual initial manifestations, and initial ANA negativity.

Case Description

A 47-year-old female, a known hypertensive, hypothyroid, and diabetic, presented with chief complaints of vomiting for 10 days and loose stools for 10 days. The stools were not blood-stained and were suggestive of large bowel diarrhoea. She also reported loss of weight and appetite for the past 6 months. There was a history of a similar episode 6 months prior.

On examination, the patient was conscious and oriented. Vital signs were stable. General examination revealed a left axillary lymph node measuring 2 × 1 cm, which was firm and mobile. The abdomen was uniformly distended, and shifting dullness was present.

Basic laboratory investigations were as follows:

Investigation	Value	Reference range
Hemoglobin	12.2g/dl	12-15g/dl
Totalcount	9500/microlitre	3540-9060/microlitre
Platelet count	312000/microlitre	165000-415000/micro litre
Urea	52mg/dl	15-40mg/dl
Creatinine	2.2mg/dl	0.5-1.3mg/dl
Total bilirubin Directbilirubin	0.4mg/dl 0.1mg/dl	0.3-1.3mg/dl 0.1-0.4mg/dl
ESR	40 mm/hr	0-20mm/hr
CRP	2 mg/litre	0.0-10.0mg/litre

Her CT abdomen showed massive ascites and abdominal

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lymphadenopathy. CT chest revealed features of minimal left pleural effusion and bilateral axillary lymphadenopathy.

The patient developed acute kidney injury and was initiated on peritoneal dialysis. Subsequently, the acute kidney injury resolved, following which she developed gangrenous changes in her left index finger.

Up to this point, the patient had presented with recurrent diarrhoea, renal failure, and digital gangrene. Further evaluation was undertaken to assess and correlate these findings.

Stool Routiene	Normal
Ascitic fluid analysis	Low SAAG High Protein
Ascitic fluid AFB	Negative
Ascitic fluid cell count	50 cells/30% Mesothelial cells.
Ascitic fluid culture	No growth
Blood culture	No growth

In order to rule out gastrointestinal causes, an oesophagogastroduodenoscopy (OGD scopy) was performed, which showed features of corporal gastritis. Colonoscopy findings were normal.

To evaluate the digital gangrene, a bilateral upper limb arterial and venous Doppler study was performed, which demonstrated normal flow.

The p-ANCA, c-ANCA, and antiphospholipid antibody (APLA) workup were negative. Complement levels revealed normal C3 levels but low C4 levels. In view of C4 hypocomplementemia, antinuclear antibody (ANA), anti-Ro, and anti-La antibodies were tested and found to be negative. However, serum cryoglobulins were positive.

Urine protein–creatinine ratio (PCR) values over three consecutive days were 2.1, 2.2, and 2.3, respectively. The 24-hour urinary protein excretion was 1.5 g/day.

In view of proteinuria and cryoglobulinemia, a renal biopsy was performed, which showed a membranous pattern of glomerular injury.

To determine the underlying cause of both cryoglobulinemia and membranous nephropathy, further investigations were undertaken.

Viralmarkers for HCV and HBsAg	Negative
PLA2R and Exostosin staining	Negative
Skeletal Survey	Normal
Serum protein electrophoresis	Polyclonal hypergammaglobulinemia
Axillary lymphnode biopsy	Reactive lymphoid hyperplasia.
Bone marrow aspiration and biopsy	Normal study
PETCT	No abnormal uptake

Despite excluding all possible causes, a definitive diagnosis could not be established. The patient was discharged after initiation of the Modified Ponticelli regimen.

Three months later, she presented again with progression of gangrene in the left index finger.

On repeat testing, the antinuclear antibody (ANA), which had previously been negative, was found to be positive with a 4+ speckled immunofluorescence pattern, along with concomitant anti-dsDNA positivity.

The patient was subsequently diagnosed with Systemic Lupus Erythematosus (SLE) and was started on Rituximab, following which she showed clinical improvement. She is currently on maintenance therapy with Mycophenolate mofetil. The gangrenous digit was surgically amputated.

Discussion

Systemic Lupus Erythematosus is a multisystem autoimmune disorder with diverse clinical phenotypes and a strong female predominance, particularly among women of reproductive age. The clinical spectrum ranges from mild disease limited to mucocutaneous manifestations to severe, life-threatening illness with multiorgan involvement.

Constitutional symptoms are seen in more than 90% of patients and may be the earliest manifestation.[2] These include fatigue, malaise, fever, anorexia, and unintentional weight loss.

Mucocutaneous and Musculoskeletal Manifestations

Mucocutaneous manifestations occur in more than 80% of patients and may present as acute, subacute, or chronic cutaneous lupus erythematosus, including discoid lupus erythematosus.

Musculoskeletal involvement is common and typically presents as non-erosive, symmetric inflammatory polyarthritis affecting small joints of the hands, wrists, and knees, although any joint may be involved.

Hematologic and Neurological Manifestations

More than 50% of patients experience anemia, most commonly anemia of chronic disease. Leukopenia (due to neutropenia or lymphopenia) and thrombocytopenia may also occur.

SLE may involve both the central and peripheral nervous systems. The most common central nervous system manifestation is intractable headache, reported in over 50% of patients. Seizures may be focal or generalized. Other neurological manifestations include aseptic meningitis, demyelinating syndromes, cranial neuropathies, peripheral neuropathies, and autonomic neuropathy. The pathogenesis involves immune-mediated injury to cerebral vasculature.[3]

Cardiovascular Manifestations

The most frequent cardiac manifestation is pericarditis with exudative pericardial effusion. Cardiac tamponade is rare. Myocarditis is uncommon and has been associated with anti-Ro (SSA) antibodies. Libman–Sacks endocarditis, most commonly involving the mitral valve, is another recognized complication.

Renal Manifestations

Lupus nephritis is a well-known and common complication of SLE. Renal involvement ranges from mild subnephrotic proteinuria to diffuse proliferative glomerulonephritis leading to chronic kidney damage. Other renal manifestations include thrombotic microangiopathy, interstitial nephritis, lupus vasculopathy, vasculitis, and arteriolosclerosis.[4]

Gastrointestinal Manifestations

Gastrointestinal symptoms are relatively common in SLE but are often related to medication adverse effects or secondary infections rather than primary disease activity.

Oral ulcers are among the most common disease-specific manifestations. The prevalence of lupus enteritis ranges from 0.2% to 5.8%.[5] Common gastrointestinal symptoms include abdominal pain, vomiting, and diarrhoea. Manifestations may include abdominal serositis, pancreatitis, mesenteric vasculitis,

and peritonitis.

Typical CT abdominal findings in lupus enteritis include the "target sign" (bowel wall thickening with abnormal enhancement) and the "comb sign" (engorgement of mesenteric vessels), although these findings are non-specific.[6]

Cryoglobulinemia in SLE

Cryoglobulinemia is characterized by the presence of abnormal circulating immunoglobulins that precipitate at low temperatures. A recent study reported that 66% of patients with SLE had detectable cryoglobulinemia; however, only 15% developed cryoglobulinemic vasculitis.[7]

In the present case, cryoglobulinemic vasculitis manifested as progressive digital gangrene, which is a relatively rare presentation in SLE.

ANA-Negative SLE

The diagnosis of SLE is currently based on the 2019 EULAR/ACR classification criteria, which require an ANA titre of at least 1:80 as an entry criterion.

A recent study reported the prevalence of ANA-negative SLE to be 2.11%.[8] One possible explanation for initial ANA negativity in our patient is the renal excretion of autoantibodies in the setting of active lupus nephritis, potentially leading to undetectable serum antibody levels. In such situations, serial ANA testing is recommended, and alternative body fluids such as urine or pleural fluid may be considered for antibody detection.[9]

Among patients who initially test ANA-negative and subsequently undergo seroconversion, the mean time to positivity ranges from months to years.[10] In our case, seroconversion occurred within three months.

Conclusion

SLE typically manifests in females of reproductive age. This case posed multiple diagnostic challenges, as the initial manifestation occurred in a postmenopausal woman with atypical features including recurrent diarrhoea, acute kidney injury, cryoglobulinemic vasculitis, and initial ANA negativity.

Late-onset SLE is associated with increased mortality risk, with cardiovascular disease being a leading cause of death. Cryoglobulinemic vasculitis is an uncommon manifestation compared to other classical features of SLE.

The initial negative ANA result prompted extensive evaluation for alternative causes of cryoglobulinemia, including hepatitis C virus infection and malignancy. Following careful follow-up and repeat serological testing, a diagnosis of SLE was established. The patient is currently on Mycophenolate mofetil maintenance therapy and has shown clinical improvement.

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Conflicts of interest

There are no conflicts of interest.

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