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A case report on overlap syndrome: diagnostic and management challenges

Jibin Simon[1], Saranya C.[2], Indhumati E.[3], Ananthakumar P.K.[1], Manoj Sivasamy[1], Sharan Bose[1]

[1]Department of General Medicine, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India
[2]Department of Rheumatology, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India
[3]Department of Nephrology, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India

ABSTRACT

Overlap syndromes are inflammatory rheumatic conditions in which patients show clinical manifestations suggestive of multiple distinct immune diseases. This case report discusses a complex instance involving Sjögren's disease, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) in a woman in her 30s. Lupus nephritis, a severe kidney inflammation associated with SLE, and diffuse alveolar hemorrhage (DAH), a life-threatening lung complication characterized by bleeding into the alveolar spaces, further complicated her clinical course. Initially presenting with acute lower limb pain, swelling, and rash, suggesting systemic involvement beyond RA, laboratory findings of hypocomplementemia and renal involvement raised suspicion of SLE. The subsequent development of polyserositis, mesenteric vasculitis, and DAH underscored the complexity of her condition. This case highlights the importance of a holistic approach that integrates clinical expertise, advanced diagnostics, and tailored therapeutic interventions to optimize patient outcomes. Early recognition and prompt management of complications are crucial in mitigating morbidity and improving prognosis, emphasizing the need for vigilant monitoring and interdisciplinary collaboration in the management of connective tissue diseases.

Keywords: connective tissue diseases, overlap syndrome, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, renal involvement, diffuse alveolar hemorrhage

INTRODUCTION

The term "connective tissue disease" describes a collection of conditions that impact the tissues rich in protein that support the body's organs as well as other components like bone, cartilage, and fat. Overlap syndrome is a term used to describe a disease entity among connective tissue diseases that fulfil the diagnostic criteria for at least two widely recognized autoimmune diseases [1]. Most frequently, overlap syndrome is encountered in association with systemic lupus erythematosus (SLE)/systemic scleroderma (SSc), which includes autoimmune illnesses such as polymyositis, dermatomyositis, rheumatoid arthritis, and Sjögren's syndrome [2]. Overlap syndrome is a challenging diagnosis since patients have many similar clinical and immunologic features. One condition can begin years before another and not exhibit novel symptoms until considerably later [3]. This case involves a lady in her 30s who has overlapping autoimmune illnesses of Sjögren's disease and rheumatoid arthritis, resulting in a complicated constellation of symptoms and multi-organ involvement. This case demonstrates complexities and the complexity of managing such intricate autoimmune symptoms by exploring further into her clinical presentation, diagnostic journey, and therapeutic approaches.

CASE REPORT

A 32-year-old female presented with bilateral lower limb pain and swelling with lower limb rashes for three days. The pain was dull aching, progressively involving both legs from thigh to foot. She denied joint pains, fever, recognizable aggravating or reliev-

Corresponding author:
Jibin Simon
E-mail: jibinsimon97@gmail.com

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ing factors. She reported bilateral lower limb swelling, which was acute in onset and progressively worsening, with no diurnal variation, breathlessness, chest pain, facial puffiness, or decreased urine output noted. The patient described rashes over both lower limbs for the past three days, initially appearing as red spots and later progressing to involve both limbs. Notably, she denied bluish discoloration of her fingers and toes on cold exposure..

The patient's past medical history revealed a diagnosis of rheumatoid arthritis three years prior with high titre RF and anti-CCP positivity, for which she was initiated on tab Prednisolone 10 mg OD, tab Methotrexate 15 mg once a week, tab folic acid, and tab Tofacitinib 5 mg BD. Three months back, she was admitted with a 10-day history of low-grade fever, cough, and expectoration, diagnosed and treated for lower respiratory tract infection based on sputum culture sensitivity reports. Further probing revealed symptoms of dry eyes, dry mouth, and dysphagia for one month, along with multiple white patches and mucosal ulcerations in the oral cavity. On examination, bilateral parotid gland swelling with few palpable purpuric lesions on both lower limbs was noted. ANA profile was positive for 1:100 dilution with a mixed homogenous and speckled pattern. ANA immunoblot showed SS-A, SS-B, and Ro-52 antibodies strong positivity; Ku, AMA-M2 and Nucleosome positive, with low C3 and C4 levels noted. Urine PCR was 0.3. Her CBC showed bicytopenia, and upper GI endoscopy confirmed esophagal candidiasis, for which she was started on tab Fluconazole 200 mg OD. She was diagnosed with rheumatoid arthritis - SLE with high disease activity / Sjögren / secondary vasculitis and acute pulmonary infection, and it was started a medication on tab Prednisolone 30 mg OD, tab HCQ 200 mg HS. Methotrexate was stopped in view of bicytopenia. Lip biopsy was deferred as the patient was not consenting to the procedure. Immunosuppression was withheld in view of the current respiratory infection and it was planned to start on the follow-up visit.

She did not have a significant personal or family history. During examination, she appeared conscious, oriented, and cooperative with vital signs indicating BP: 140/100 mmHg, PR: 90/min regular, RR: 18 cycles per minute, and a room air oxygen saturation of 98%. Physical examination revealed pallor, bilateral pitting pedal edema, bilateral palpable purpuric lesions extending up to the thighs, and bilateral parotid gland swelling. Cardiorespiratory and abdominal examinations were unremarkable, with no focal neurological deficits noted.

On initial lab investigations, her Hb was 6.3 g/dl with an MCV of 82.9 fl. Her serum albumin levels were 1.6 g/dl, ESR 58 mm/hr and CRP 21.3 mg/L. Her liver function test, renal function test and serum electrolytes were within normal limits. The urine routine showed 3+ protein and granular cast. HIV, HBsAg and HCV serology were negative. Direct coombs tested positive, and LDH was 333. Peripheral smear showed normocytic normochromic anemia with lymphopenia. ANCA profile was negative. Her C3 was less than 8 mg/dl and her C4 was less than 40 mg/dl. Urine PCR increased from 0.3 to 4.84 from her previous visit and 24-hour urine protein showed proteinuria of 3550 mg/ day. Cardiology 2D echo showed normal LV function, mild pulmonary artery hypertension and trace pericardial effusion. She was started on tab Prednisolone 60 mg OD along with other medication.

Serum cryoglobulins were sent to rule out cryoglobulinemic vasculitis which was found to be negative. With a high suspicion of underlying lupus nephritis, a renal biopsy was planned.

On the third day of her admission, she developed a sudden onset of breathlessness and abdominal pain which was diffuse and tender on palpation. She had reduced air entry in bilateral infrascapular and infraxillary areas. Ultrasound showed bilateral pleural effusion, minimal pericardial effusion and mild ascites. Given polyserositis and extending purpuric rash, she was given pulse Methylprednisolone 1 g once daily I.V OD. Subsequently, she developed hemoptysis and hematochezia with diffuse abdominal tenderness and guarding and was transferred to the ICU. CECT abdomen showed diffuse, circumferential wall thickening involving the cecum (predominantly), throughout the ascending and transverse colon, till the splenic flexure. CT chest showed bilateral pleural effusion with interlobar septal thickening. With features suggesting mesenteric vasculitis and high suspicion of a diffuse alveolar haemorrhage, she underwent two sessions of plasmapheresis following pulse steroid therapy. A renal biopsy was done which showed features suggestive of class II lupus nephritis, with a glomerular full house staining pattern (Figure 1). She was started on Inj cyclophosphamide 800 mg. The patient was changed from I.V. to oral steroids and was discharged with, oral steroids, Hydroxychloroquine and ARBs. She was on regular follow-up and is receiving Inj cyclophosphamide 800 mg IV once monthly. After 6 months of follow-up, her symptoms and lab parameters showed improvement and her urine PCR was 0.4. She is at present in remission, and was started on Mycophenolate mofetil.

DISCUSSION

The phrase "overlap syndrome" refers to the development of two or more connective tissue diseases' signs, symptoms, and immunological characteristics in a single patient either simultaneously or sequentially. Conversely, mixed connective tissue disease

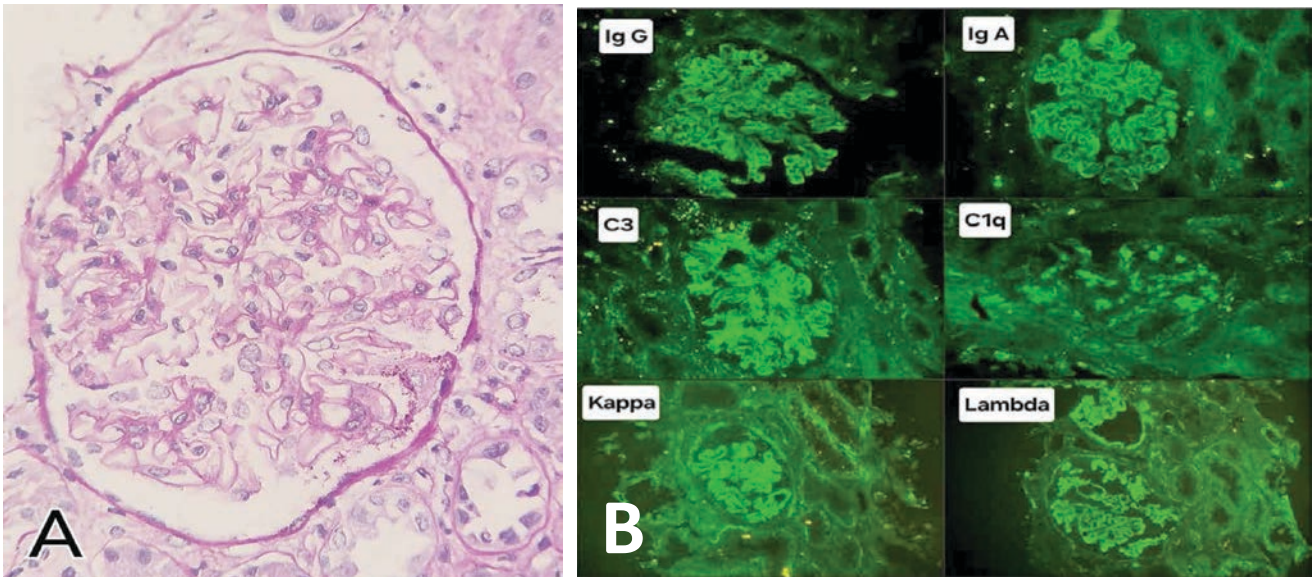

FIGURE 1. A - mesangial hypercellularity; B- Full house immunofluorescence (positive IgG, IgA, C3, C1q, kappa and lambda light chains)

(MCTD) is a unique autoimmune condition characterized by a combination of polymyositis, scleroderma, and lupus symptoms and signs [4]. MCTD is a separate clinical entity with well-defined diagnostic criteria. On the other hand, overlap syndrome is a broad term encompassing several autoimmune diseases that share similar characteristics and symptoms. Therefore, overlap syndrome can refer to a range of connective tissue illnesses and is a broader term than MCTD [5]. Overlap syndrome's genetic foundation and pathophysiology are still unknown, which complicates diagnosis. The most common conditions linked to overlap syndromes are lupus, rheumatoid arthritis, scleroderma, and myositis [6]. Although the cause of connective tissue illnesses remains unknown, patterns found in clinical and laboratory data will continue to be the basis for classifying individual cases. Up to 25% of people with connective tissue disease have an overlap syndrome, which combines characteristics of polymyositis, dermatomyositis, systemic sclerosis, and systemic lupus erythematosus. Sjögren's syndrome and rheumatoid arthritis may manifest concurrently or sequentially during the disease [7]. Here, we are presenting a rare case of overlap syndrome that started as rheumatoid arthritis, then progressed to Sjögren's syndrome characteristics, and then ultimately developed systemic lupus erythematosus manifestations and complications.

In our case, the initial manifestation of bilateral lower limb pain, edema, and rash, without identifiable aggravating factors, suggested potential systemic involvement beyond rheumatoid arthritis. Laboratory tests revealed severe normocytic normochromic anemia with coomb's positivity, hypoalbuminemia, elevated inflammatory markers (ESR, CRP), and renal involvement evidenced by nephrotic-range proteinuria. The presence of glomerulonephritis with nephrotic-range proteinuria, undetectably low complement levels, polyserositis and diffuse purpuric rash increased the clinical suspicion of an underlying systemic lupus erythematosus (SLE) and secondary vasculitis. Utilizing the 2019 EULAR/ACR Classification Criteria (Figure 2) the patient was classified as having SLE [8]. The onset of hemoptysis, hematochezia, and diffuse abdominal tenderness further complicated the clinical course, necessitating urgent imaging studies and transfer to the intensive care unit. Imaging findings indicative of mesenteric vasculitis and diffuse alveolar hemorrhage highlighted the multisystem involvement and severity of the patient's condition.

Patients with class I or class II LN typically have microscopic hematuria and normal kidney function, or at most low-grade proteinuria well below the nephrotic range. No additional immunosuppressive medication beyond that prescribed for nonrenal lupus is required for these patients [9]. Lupus podocytopathy is diagnosed in patients with class I or II histology who also have nephrotic syndrome (NS) or nephrotic range proteinuria. By using electron microscopy to show diffuse podocyte effacement, this diagnosis may be verified. Individuals with podocytopathy frequently respond well to glucocorticoid treatment, and their clinical and histologic symptoms are comparable to those of individuals with focal segmental glomerulosclerosis (FSGS) or minimal change disease (MCD) [10]. After diagnosis, confirmed by a kidney biopsy, LN treatment consists of an initial induction phase and a longer maintenance phase [11].

The optimal immunosuppressive agents for induction therapy are Mycophenolate Mofetil (MMF) and Cyclophosphamide; low-dose Cyclophosphamide (Euro-Lupus regimen) is better than high-dose Cyclo-

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

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If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

FIGURE 2. 2019 EULAR/ACR Classification Criteria for SLE [8]

phosphamide due to its similar efficacy and decreased risk of gonadotoxicity [11]. In severe forms of LN associated with a higher risk of progression into end-stage renal disease (reduced glomerular filtration rate, histological presence of fibrous crescents or fibrinoid necrosis, or tubular atrophy/interstitial fibrosis), published data support the use of MMF and high-dose CYC [11]. As maintenance therapy, MMF or Azathioprine may be used; the former is linked to fewer relapses; Rituximab may be taken into consideration in cases of refractory or relapsing disease [11]. Calcineurin inhibitors (CNI) are currently classified as second-line agents for induction or maintenance therapy, primarily in membranous LN, podocytopathy, or in proliferative disease with refractory nephrotic syndrome, despite standard-of-care within 3-6 months [12]. In the latter situation, they can be taken alone or in combination with MMF, as small observational studies have suggested that the CNI/MMF combination is helpful in disease that is resistant to standard therapy [11]. In our case prompt initiation of pulse methylprednisolone and plasmapheresis, followed by cyclophosphamide therapy, contributed to symptom improvement and stabilization. Renal biopsy results revealed class II lupus nephritis, which confirmed the clinical suspicion of underlying SLE. The patient's treatment was then customized, including a shift to oral steroids, hydroxychloroquine, and angiotensin receptor blockers (ARBs) for long-term illness management.

Diffuse alveolar hemorrhage (DAH) is an unusual but devastating complication of systemic lupus. It occurs in three separate but overlapping phenotypes: acute capillaritis, bland pulmonary hemorrhage and diffuse alveolar injury, each of which is associated with a different set of underlying diseases [13]. A higher risk of death is linked to certain factors, including the onset of acute catastrophic hemoptysis, the need for mechanical ventilation, infections, and thrombocytopenia. A decrease in hemoglobin level and diffuse infiltrates that can be seen on a chest X-ray (CXR) or high-resolution chest computed tomography are typical symptoms of the illness [14]. Active renal disease has been linked to an increased risk of DAH, particularly when it presents as lupus nephritis. Up to 80% of instances have been reported to have such a connection [15]. Dyspnea, a decrease in hemoglobin, an increased carbon monoxide single-breath diffusing capacity, and lung interstitial or alveolar infiltrates should raise the alarm for risk of DAH. Patients with active SLE in particular should consider this [16]. Sudden symptoms of breathlessness and hemoptysis in our patient led to the suspicion of diffuse alveolar hemorrhage (DAH). Imaging findings, including bilateral pleural effusion and interlobar septal thickening, raised further suspicion, especially in the context of the patient's background of systemic lupus erythematosus (SLE) with renal involvement and systemic vasculitis. Randomized clinical trials to improve the care of individuals with SLE-associated DAH are scarce, and treatment is still done on an individual basis [14]. The more commonly used therapies are methylprednisolone, cyclophosphamide, and plasmapheresis [17]. Methylprednisolone with cyclophosphamide combination are linked to a higher survival rate [18]. The treatment for diffuse alveolar hemorrhage (DAH) in our case involved a multi-faceted approach. Initially, the patient was given pulse methylprednisolone at a dose of 1 gram daily intravenously for three days to control the severe inflammation. Subsequently, she underwent two sessions of plasmapheresis to remove circulating immune complexes and reduce systemic inflammation. Additionally, the patient was started on intravenous cyclophosphamide at a dose of 800 mg every month to provide long-term immunosuppression and prevent further progression of the disease.

CONCLUSION

In conclusion, this case highlights the complexity of diagnosing and managing overlap syndrome, where multiple connective tissue diseases manifest in a single patient. The patient's transition from rheumatoid arthritis to Sjögren's syndrome, and ultimately to systemic lupus erythematosus with severe complications such as diffuse alveolar hemorrhage and lupus nephritis, underscores the need for a vigilant, multidisciplinary approach. The use of a tailored treatment strategy, including pulse methylprednisolone, plasmapheresis, and cyclophosphamide, proved crucial in stabilizing the patient's condition. This case emphasizes the importance of early recognition and aggressive management of severe manifestations in overlap syndromes.

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