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CASE REPORT

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A novel overlap syndrome: Rheumatoid arthritis, Sjogren's syndrome, antiphospholipid syndrome, and dermatomyositis

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Key Clinical Message: This is an extremely rare case that has not been presented or discussed in the literature to the best of our knowledge. The overlap of connective tissue disease is a challenge for physicians and patients, and it needs special care and regular clinical and laboratory follow-up.

Abstract: This report describes a rare case of overlapping connective tissue diseases in a 42-year-old female with rheumatoid arthritis, Sjogren's syndrome, antiphospholipid syndrome, and dermatomyositis. The patient presented with a hyperpigmented erythematous rash, muscle weakness, and pain, highlighting the challenges of diagnosis and treatment that require regular clinical and laboratory follow-up.

KEYWORDS

antiphospholipid syndrome, dermatomyositis, overlap syndrome, rheumatoid arthritis, Sjogren's syndrome

1 | INTRODUCTION

Many connective tissue diseases have similar signs and symptoms, making it challenging to diagnose a specific rheumatic condition. Rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome, polymyositis, dermatomyositis, overlap connective tissue disease, mixed connective tissue disease, and undifferentiated connective tissue disease can all have comparable clinical symptoms, especially in the first 12 months.[1]

Overlap syndrome is a medical illness that shares characteristics with at least two other conditions. Many medical disciplines have overlap syndromes, such as overlapping connective tissue illnesses in rheumatology and overlapping genetic abnormalities in cardiology.[2]

It refers to a wide range of illnesses that have clinical characteristics and fulfill the categorization criteria for more than one well-defined rheumatic disease. They often develop subacutely, with clinical symptoms involving many organ systems. The pattern of organ involvement reflects the distinctive characteristics of the well-defined rheumatic illnesses that coexist.[3,4]

The usual overlap syndromes that have been reported internationally are for only two or three overlapped connective tissue diseases. But it is rarely reported to have an overlap syndrome with four diseases, which are rheumatoid arthritis, Sjogren's syndrome, antiphospholipid syndrome, and dermatomyositis. In this case report, we present a rare and novel case of overlapping connective tissue diseases, highlighting the challenges of diagnosing and treating such conditions. Its management requires

a tailored approach for each patient. The report aims to raise awareness among clinicians and underscore the importance of early diagnosis and appropriate treatment.

2 | CASE PRESENTATION

A 42-year-old female presented to the rheumatology unit with a hyperpigmented erythematous itchy rash over her shoulders, neckline, hands, elbows, thighs, knees, and feet for 2 months duration, associated with progressive symptoms of muscle weakness and pain, resulting in falls and the need for a walker to mobilize, the inability to wash her hair, and difficulty swallowing food. She also complained of a loss of appetite, arthralgia, Sicca symptoms, cold sensitivity, fatigue, and exertional dyspnea. There was no history of fever, oral ulcers, headache, chest pain, palpitation, travel, or sick contacts. At the age of 18, she was diagnosed with rheumatoid arthritis (RA) after a presentation of multiple joint pain and swelling, and prolonged early morning stiffness. Eight years later, she started to complain of having a dry mouth and eyes. Therefore, the diagnosis of Sjogren's syndrome was made based on clinical presentation and positive antibodies.

However, in 2020, she developed left lower limb pain and swelling that was proven to be deep venous thrombosis along with double-positive anticardiolipin antibodies, which confirmed the diagnosis of antiphospholipid syndrome. The physical examination revealed a normal range of vital signs (temperature of 37°C; pulse rate of 88 beats per minute; respiratory rate of 16 cycles per minute; and blood pressure of 120/70 mmHg).

She looked ill. She had xerostomia, active wrist arthritis (Figure 1), and a diffuse skin rash with Gottron's papules (Images A and B in Figure 2) over her hands, shawl sign over the shoulders and upper back (Images C and D in Figure 2), holster sign over the lateral thighs (Image E in Figure 2), and chilblains over her feet (Image F in Figure 2), which were painful to touch. There was generalized weakness in all limbs, mainly affecting the proximal muscles. However, muscle tone and reflexes were normal. There were bi-basal fine crackles on lung auscultation. The cardiovascular and abdominal examinations were normal.

Hematological parameters showed that hemoglobin was 9.7 g/dL (normal range: 12–16 g/dL for women and 13–18 g/dL for men), leukocytes 6.1×10^9/L (normal range: 4–10×10^9/L), platelets 309×10^9/L (normal range: 150–450×10^9/L), erythrocyte sedimentation rate (ESR) of 10 mm/h (normal range <15 mm/h), and a carbohydrate reactive protein (CRP) of 48 mg/L (normal range <5 mg/L).

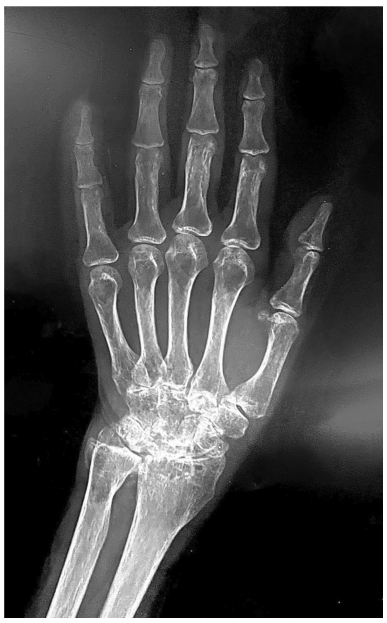

FIGURE 1 Radiographic findings of rheumatoid arthritis in the hand: Almost total loss of radiocarpal, carpometacarpal, and intercarpal joint spaces associated with diffuse demineralization.

The metabolic panel showed an elevated level of alanine aminotransferase (ALT) of 85 IU/L (normal range: 0–33 IU/L), aspartate aminotransferase (AST) of 94 IU/L (normal range: 0–33 IU/L), alkaline phosphatase (ALP) of 145 IU/L (normal range: 44–147 IU/L), serum lactate dehydrogenase (LDH) of 587 IU/L (normal range: 140–280 IU/L), and serum creatine phosphokinase (CPK) of 810 IU/L (normal range: 10–120 IU/L).

The results of the thyroid function test, the kidney function test, the serum electrolytes test, the hepatitis B and C serology test, the HIV test, the tumor marker test, and the urinalysis test were all unremarkable.

The antibody screen showed strongly positive rheumatoid factor (RF) of 160 IU (normal range <20 IU), anti-cyclic citrullinated peptide antibodies (ACPA) of 226 IU (normal range <30 IU), anti-Ro60 and anti-Ro52 antibodies of 5.1 IU and 3.3 IU, respectively (normal range <1.1 IU), anti-La antibodies of 4.5 IU (normal range <1.1 IU), anticardiolipin (ACL) antibodies of 47 IU (normal range >22 IU), and antinuclear antibodies (ANA) of 6 IU (normal range <1.1 IU). Whereas, anti-dsDNA antibodies, anti-Smith antibodies, and other antibodies tested were negative.

According to the past medical history of the patient, she had symmetric polyarthritis of small, medium, and large joints; significant morning stiffness; high acute phase reactants; positive RF and ACPA antibodies; and typical radiographic features. Therefore, the diagnosis of RA is definite based on the 2012 ACR/EULAR classification criteria for RA.

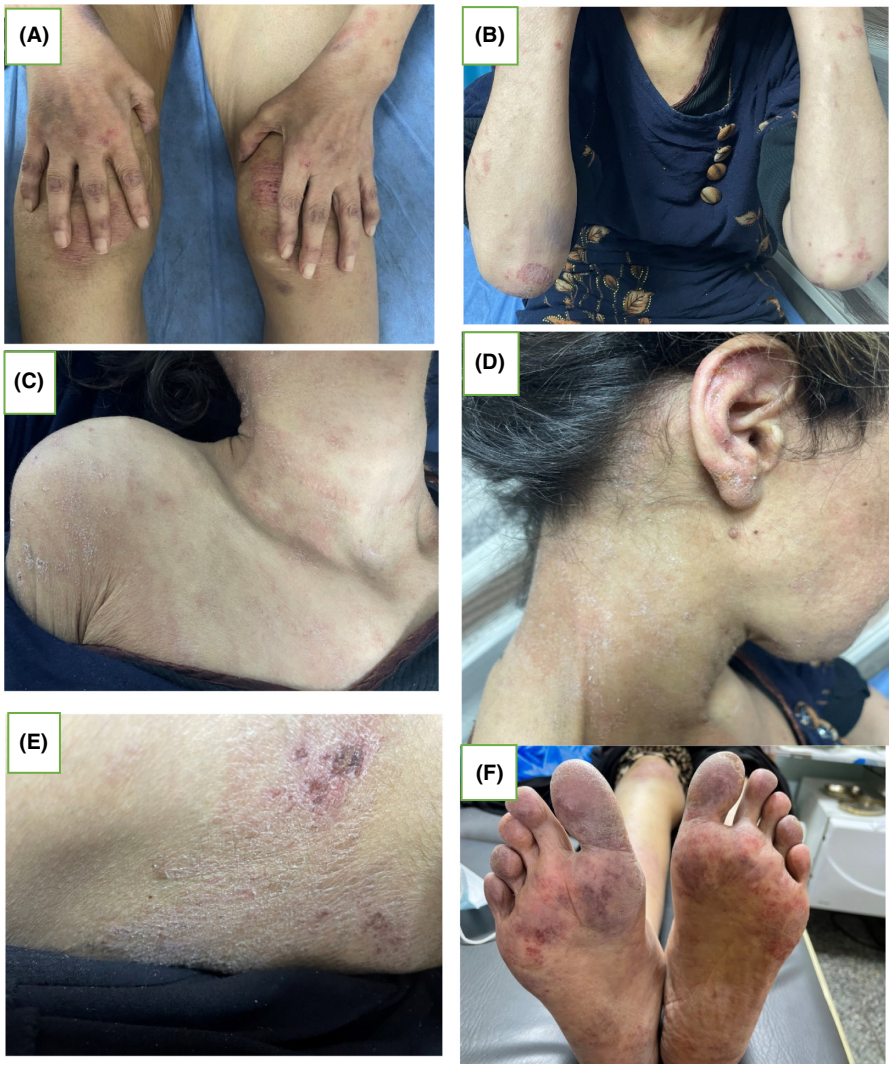

FIGURE 2 The clinical cutaneous manifestations for the patients, Gottron's papules over the knuckles, elbows, and knees (A, and B), shawl sign over the shoulders and upper back (C, and D), holster sign over the lateral thighs (E), and Chilblains sign (F).

The patient had a dry mouth, dry eyes, and sand sensation. A Schirmer strip showed less than 3 mm of wetting per 5 min, an unstimulated whole salivary flow of less than 0.1 mL per minute, as well as positive anti-Ro60, anti-Ro52, and anti-La antibodies. Actually, the patient had fulfilled the 2017 ACR-EULAR classification criteria for primary Sjogren's syndrome; therefore, the minor labial salivary gland biopsy was not done.

Additionally, she underwent an old thrombotic attack as a result of a deep venous thrombosis of the left lower limb and a positive ACL antibody on two occasions, 12 weeks apart. Lupus anticoagulant Anti-B2-glycoprotein I antibodies were negative. Other coexisting factors for thrombosis have been excluded. And based on the revised Sapporo classification criteria for antiphospholipid syndrome, the diagnosis of APS was made.

Whereas, the clinical presentation is unlikely for systemic lupus erythematosus in the absence of oral ulcers, malar rash, renal involvement, hematological involvement, and neurological involvement. Additionally, the specific antibodies, like anti-dsDNA and anti-Smith antibodies, were returned negative. Therefore, the diagnosis of SLE was carefully excluded.

A further electromyogram (EMG) revealed increased spontaneous activity with fibrillation potential typical for dermatomyositis.

According to the pathognomonic cutaneous manifestations (Gottron's papules, the shawl sign, and the holster sign), elevated muscle enzymes (CPK, ALT, AST, and LDH), abnormal EMG findings, and the exclusion of all other causes of myopathies, the diagnosis of dermatomyositis was made according to the Bohan and Peter criteria for polymyositis and dermatomyositis. Actually, the patient was very ill and depressed at the time of presentation; therefore, she refused to do a muscle biopsy.

Based on these findings, a recent diagnosis of dermatomyositis was made. Tests for disease complications and hidden cancers came back normal, unremarkable, or negative. Mammography, abdominal computed tomography,

echocardiography, and ultrasounds of the neck, axilla, breast, and abdomen were also done.

A computed tomography (CT) of the chest showed interstitial lung disease, ground glass opacification with the lower lobes of both lungs being the most affected, and a small amount of pleural thickening on both sides (Figure 3).

Previously, she was on methotrexate 20 mg/week, hydroxychloroquine 200 mg/day, warfarin 8 mg/day, artificial tears, and artificial salvia.

The patient was admitted, methotrexate was stopped, and methylprednisolone was initiated. Intravenous pulse therapy of methylprednisolone 1000 mg/day for three consecutive days provided some relief from itching and arthralgia. On day 4 of admission, intravenous pulse therapy of cyclophosphamide 600 mg (750 mg/m^2) was initiated. In addition to oral prednisolone 40 mg/day (0.75 mg/kg), calcium carbonate 1000 mg/day (in divided doses), vitamin D 800 IU/day, and alendronate 70 mg/week.

One month later, her condition slightly improved, and the dosage of intravenous monthly pulse therapy of cyclophosphamide was increased to 800 mg (1000 mg/m^2).

Two months later, the skin rash disappeared, the arthralgia subsided, her appetite improved, her muscle weakness improved, and her laboratory muscle enzymes returned to normal levels. Therefore, tapering of the oral prednisolone was started and intravenous monthly pulse therapy of cyclophosphamide 800 mg was continued.

Six months later, she had good control of dermatomyositis. Her muscle strength was good, as she could walk and dress independently. The dyspnea had subsided, but there was RA flare, and she had arthritis in the small joints of her hands, wrists, elbows, and knees. Therefore, cyclophosphamide was discontinued, and oral methotrexate was reconsidered.

At a follow-up visit 8 months later, both her dermatomyositis and rheumatoid arthritis were under control.

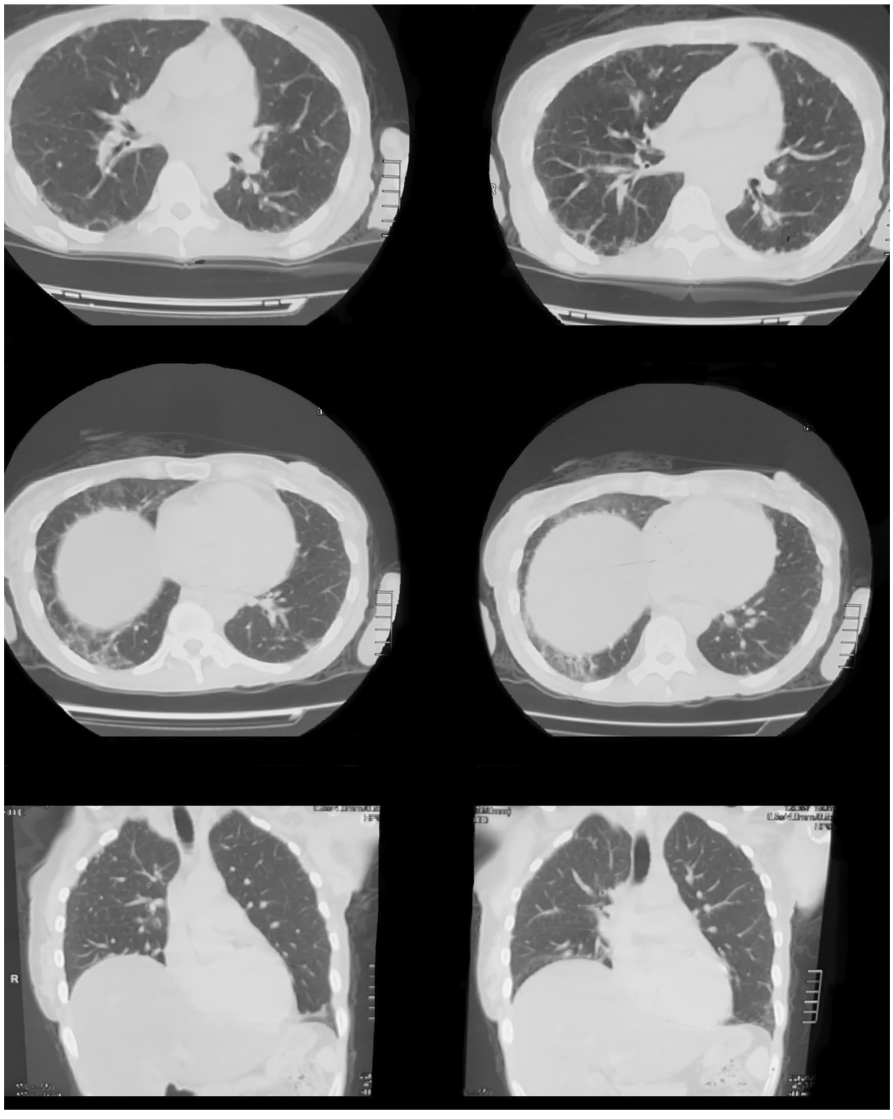

FIGURE 3 A computed tomography (CT) of the chest showed that both lungs had interstitial changes, ground glass opacification with the lower lobes being the most affected, and a small amount of pleural thickening on both sides.

3 | DISCUSSION

Overlap syndrome is a term used to describe the simultaneous or sequential occurrence of signs, symptoms, and immunological features of two or more connective tissue diseases in the same patient. Mixed connective tissue disease (MCTD), on the other hand, is a specific autoimmune disorder that is made up of a mix of lupus, scleroderma, and polymyositis symptoms and signs.[5] MCTD has clear diagnostic criteria and is a distinct clinical entity. In contrast, overlap syndrome is a less-defined condition that includes a range of autoimmune disorders with overlapping symptoms and features. As such, overlap syndrome is a broader term than MCTD and can encompass a variety of connective tissue diseases.[5,6] However, the pathogenesis and genetic basis of overlap syndrome remain unclear, making its diagnosis challenging. Rheumatoid arthritis, lupus, scleroderma, and myositis are the most prevalent disorders associated with overlap syndromes.[3,4]

While the origin of connective tissue disorders is unclear, individual case categorization will continue to rely on detecting patterns in clinical and laboratory findings. As many as 25% of patients with connective tissue disease have an overlap syndrome with features of systemic lupus erythematosus, systemic sclerosis, polymyositis, or dermatomyositis, with rheumatoid arthritis and Sjögren's syndrome developing concurrently or sequentially during the disease's course.[7,8] It is used to describe multiple connective tissue diseases that are present in the same patient at the same time. In this case, we are reporting a very rare overlap syndrome with four diseases: rheumatoid arthritis, Sjogren syndrome, antiphospholipid syndrome, and dermatomyositis.

A 42-year-old female presented to the rheumatology unit with a hyperpigmented erythematous itchy rash and progressive symptoms of muscle weakness and pain, resulting in falls and the need for a walker to mobilize, difficulty swallowing food, loss of appetite, arthralgia, Sicca symptoms, fatigue, and exertional dyspnea. The patient had a history of rheumatoid arthritis, Sjogren's syndrome, and antiphospholipid syndrome. She was diagnosed with dermatomyositis and interstitial lung disease. Intravenous pulse therapy with methylprednisolone and cyclophosphamide was initiated. Her condition slightly improved, and 6 months later, she had good control of dermatomyositis.

It is critical to identify overlapping clinical traits in each patient since treatment may need to be targeted precisely at certain of these aspects. Autoantibody profiles and potential genetic connections may be most beneficial in predicting treatment response and long-term prognosis in overlap patients.[9,10]

Autoantibodies are employed in clinical settings to establish the diagnosis, assess the prognosis, track disease progression, and evaluate therapy regimens. Some are illness indicators that play an important role in establishing diagnostic criteria. In certain circumstances, the autoantibody profile, together with other clinical markers, assists in diagnosis.[11,12]

4 | CONCLUSION

This case describes a rare overlap syndrome characterized by clinical manifestations related to four distinct diseases: rheumatoid arthritis, Sjogren syndrome, antiphospholipid syndrome, and dermatomyositis. To the best of our knowledge, this complex presentation has not been previously reported or discussed in the literature. Overlapping connective tissue diseases pose significant challenges for both patients and physicians, requiring careful monitoring and follow-up using autoantibodies and other markers specific to each syndrome to assess treatment efficacy, determine appropriate treatment modalities, and establish optimal treatment duration.

AUTHOR CONTRIBUTIONS

Maab Jasim Mohammed: Conceptualization; project administration; resources; supervision; writing – original draft; writing – review and editing. **Hashim Talib Hashim:** Formal analysis; project administration; supervision; writing – original draft; writing – review and editing. **Ahmed Dheyaa Al-Obaidi:** Conceptualization; data curation; software; writing – original draft; writing – review and editing. **Assim Al shammari:** Data curation; investigation; methodology; validation.

FUNDING INFORMATION

No source of funding was received.

CONFLICT OF INTEREST STATEMENT

We declare that we have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data will be available on reasonable request from the corresponding author.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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