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LETTER TO THE EDITOR

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CASE REPORT

Pulmonary hypertension secondary to seronegative rheumatoid arthritis overlapping antisynthetase syndrome: A case report

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Abstract

BACKGROUND

Polyarthritis is the most frequent clinical manifestation in antisynthetase syndrome (ASS) forms of idiopathic inflammatory myositis and may be misdiagnosed as rheumatoid arthritis (RA), particularly in patients with seronegative RA (SNRA). It is unclear whether there is an overlap between ASS and RA, or if ASS sometimes mimics RA. Pulmonary hypertension (PAH) is common in connective tissue diseases (CTDs). However, published reports on CTD-PAH do not include overlapping CTDs, and its incidence and impact on patient prognosis are unclear.

CASE SUMMARY

We report the case of a 63-year-old woman who presented with a 3-mo history of symptom aggravation of recurrent symmetrical joint swelling and pain that had persisted for over 10 years. The patient was diagnosed with RA and interstitial lung disease. The patient repeatedly presented to the hospital's respiratory and rhe-umatology departments with arthralgia, plus shortness of breath after activity. Relevant tests indicated that anti-CCP and RF remained negative, while anti-J0-1 and anti-Ro-52 were strongly positive. It was not until recently that we recognized that this could be an unusual case of SNRA with concurrent ASS. Joint pain was relieved after regular anti-rheumatic treatment. Chest computed tomography scans showed that pulmonary interstitial changes did not progress significantly over several years; however, they showed gradual widening of the pulmonary artery, and cardiac ultrasound indicated elevated pulmonary artery systolic pressure. The prescribed treatment of PAH was not effective in improving shortness of breath.

CONCLUSION

Overlap of RA and ASS may be missed. Further research is necessary to facilitate

early diagnosis, effective evaluation, and prognosis.

Key Words: Rheumatoid arthritis; Arthritis; Antisynthetase syndrome; Pulmonary hypertension; Pulmonary arterial hypertension; Case report

Core Tip: The joint manifestations of antisynthetase syndrome are usually difficult to distinguish from rheumatoid arthritis (RA), particularly seronegative RA (SNRA); consequently, rheumatologists and respiratory pathologists should be aware of this rare and underrecognized special clinical phenotype. Whether this phenotype is more prone to pulmonary hypertension than a single connective tissue disease remains unknown. However, further research into anti-Jo1 antibodies, anti-RO-52, and other extractable nuclear antigen autoantibodies is necessary to facilitate the early diagnosis, evaluation, and prognosis of this overlapping clinical syndrome.

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INTRODUCTION

Rheumatoid arthritis (RA) is a multifactorial, chronic, autoimmune disease characterized by significant heterogeneity in clinical presentations and outcomes among individuals with the same formal diagnosis [1]. The 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA include autoantibodies [rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA)] as biomarkers of the disease[2]. However, a sizeable subgroup of RA patients is negative for both ACPA and rheumatoid factor (seronegative RA, SNRA)[3]. Furthermore, the clinical presentation of SNRA is more heterogeneous than that of seropositive RA[1].

Antisynthetase syndrome (ASS) was first designated in 1990 as the first clinical serological syndrome described in patients with polymyositis and dermatomyositis[4]. This syndrome is characterized by the binding of an autoanthexadese antibody to an aminoacyl-transferred RNA synthase, most commonly the Jo-1 antibody[4]. Clinical manifestations of ASS are diverse, including idiopathic inflammatory myositis (IIM), arthralgia and arthritis, interstitial pneumonia, Raynaud's phenomenon, and skin lesions characterized by "mechanic's hands[5]." The pathogenesis of ASS is unclear, but it is thought to be associated with chronic immune system activation[6]. It is also unclear whether there is an overlap between ASS and RA, or if ASS in some cases mimics RA[4]. In this report, we describe the case of a rare association of SNRA with ASS. Overlap between RA and ASS has only been reported previously in a few case reports[7].

Pulmonary hypertension (PAH) is a life-threatening complication associated with connective tissue diseases (CTD) such as RA[8]. While most patients with CTD have relatively stable interstitial changes in their lungs during follow-up, a disproportionate number of patients with PAH have gradually emerged[9]. Although PAH is relatively common in most forms of CTD, there are currently no reports of PAH secondary to RA overlapping with ASS[10]. In this report, we describe the case of a rare overlap of SNRA with ASS in a patient with PAH.

CASE PRESENTATION

Chief complaints

A 63-year-old woman presented with a 3-mo history of aggravation of recurrent symmetrical joint swelling and pain, which she had experienced episodically over 10 years. She first presented to our hospital in April 2018 for these symptoms.

History of present illness

The patient had a history of painful metacarpophalangeal joints in both hands with no obvious cause, with symmetrical and persistent attacks, starting from the interphalangeal and metacarpophalangeal joints of both hands and gradually involving both wrist joints, elbow joints, shoulder joints, and knee

joints. Her symptoms were accompanied by morning stiffness lasting more than 1 h, which could be relieved by routine daily activities.

History of past illness

The patient was diagnosed with depression more than four years prior and was treated with antidepressant medication (medication type, dose, and duration were unknown). She denied any other disease history, including heart or lung diseases.

Personal and family history

Aside from the depression noted above, the patient's medical history was uneventful. There was no history of a similar illness in the family.

Physical examination

On initial evaluation, the patient's vital signs were as follows: Body temperature, 36.0 °C; pulse, 93 beats/min; respiration, 20 times/min; and blood pressure, 108/72 mmHg. The patient also exhibited anxiety, slightly coarse breath sounds in both lungs, inspiratory dry rales in both lower lung fields, swan neck-like deformity in both hands, localized swelling, elevated skin temperature, abduction deformity of both thumbs, and slightly restricted movement of both knees. No significant abnormalities were observed during cardiac and abdominal examinations. No edema in the lower extremities was observed, and no pathological signs were found.

Laboratory examinations

Initial laboratory examinations were as follows: Erythrocyte sedimentation rate, 74 mm/h; hypersensitivity C-reactive protein, 17.7 mg/L; creatine kinase, 1002.1 U/L; antinuclear antibody cytoplasmic granular positive (1:100); J0-1 +++; and Ro-52 +++. She was negative for anti-CCP and RF. Arterial blood gas analysis under oxygen absorption (nasal cannula 2 L/min) revealed a partial pressure of carbon dioxide (PCO_2) of 29.7 mmHg and a partial oxygen pressure (PaO_2) of 70.6 mmHg. Liver and kidney function, coagulation and D-dimer levels, and white blood cell and neutrophil ratios were normal.

Imaging examinations

Plain radiographs of both hands (Figure 1) suggested degeneration, marked osteoporosis of the wrists, partial interphalangeal joint dislocation, and subluxation consistent with RA. Ultrasound of both knees suggested a luminal effusion and synovitis. Chest computed tomography (CT) revealed emphysema and interstitial degeneration in both lungs and interstitial pneumonia in both lower lung fields (Figure 2A-C). Pulmonary function tests suggested moderate restrictive ventilation dysfunction (forced vital capacity < 80%) and moderate diffuse function (diffusion capacity for carbon monoxide < 80%).

FINAL DIAGNOSIS

Considering the patient's previous medical history and the results of our recent examinations, the patient was diagnosed with RA and interstitial lung disease (ILD).

TREATMENT

The patient refused hormone and anti-rheumatic drug therapy. After providing analgesic and oxygen therapy, the patient's symptoms were relieved, and she was discharged uneventfully.

OUTCOME AND FOLLOW-UP

After 3 mo, the patient was readmitted to the hospital due to a pulmonary infection. Her inflammatory and rheumatic immune indices had not changed significantly compared with the first hospitalization. However, cardiac ultrasound indicated PAH, and she was started on an anti-infective and anti-rheumatic treatment plan of leflunomide 20 mg QD, sulfasalazine enteric-coated tablets 0.5 g TID, and triptolide tablets 10 mg TID. She was instructed to have the treatment plan adjusted at regular follow-up visits with the rheumatology department.

Over the next 2 years, the patient repeatedly presented to the hospital's respiratory and rheumatology departments with arthralgia, shortness of breath after activity, and dyspnea. Relevant tests (Table 1) indicated that anti-CCP and RF remained negative while anti-nuclear antibody titers gradually increased, and anti-J0-1 and anti-Ro-52 were strongly positive. After two years of treatment and testing, we recognized that this could be an unusual case of SNRA with concurrent ASS. Joint pain was relieved

Table 1 Primary laboratory test results

Lab	Apr-18	Apr-19	Sep-20	Apr-21	Reference values
ESR	74.0	88.0	56.3	82.1	0-20 mm/h
CRP	17.7	55.8	28.7	36.8	< 10 mg/L
Rheumatoid factor	< 20	20.3	< 20	< 20	< 20 U/mL
Anti-cyclic citrullinated peptide antibody	0.9	0.9	< 0.5	< 0.5	< 5.0 U/mL
Antinuclear antibody titer	1/100	1/100	1/100	1/1000	Negative
C3	0.82	0.9	1.01	1.08	0.79-1.52 g/L
C4	0.13	0.18	0.20	0.19	0.16-0.38 g/L
R0-52 antibody	Positive	Positive	Strong positive	Strong positive	Negative
JO-1 antibody	Positive	Positive	Strong positive	Strong positive	Negative
p-ANCA	Negative	Negative	Negative	Negative	Negative
c-ANCA	Negative	Negative	Negative	Negative	Negative
Creatine kinase	700.8	159.5	-	358.0	26-140 U/L
$PaCO_2$	70.6	68.4	-	62.8	83-108 mmHg
PaO_2	29.4	29.4	-	29.0	35-45 mmHg
Pulmonary artery systolic pressure	47	55	-	72	15-30 mmHg

ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ANCA: Anti-neutrophil cytoplasmic antibodies; PaO_2: Partial oxygen pressure; $PaCO_2$: Partial carbon dioxide pressure.

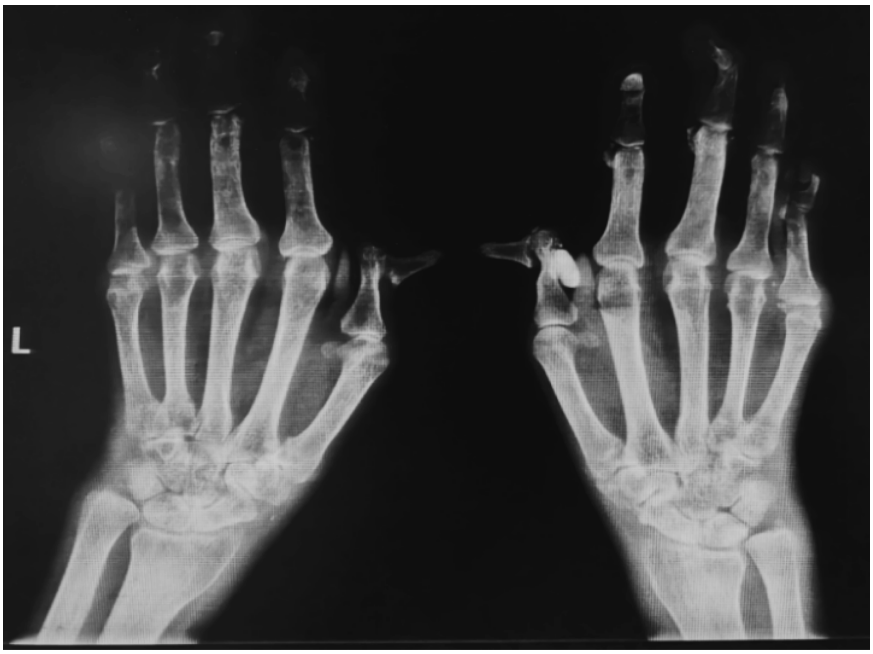

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Figure 1 Plain radiograph of both hands and wrists. Most of the interphalangeal joints, metacarpal joints, and wrist joints in both hands are narrowed and exhibit bone hyperplasia. Decreased bone density, multiple joint deformities, multiple areas of testicular and insect erosion bone absorption, and soft tissue spindle swelling are also visible.

after regular anti-rheumatic treatment (prednisone acetate tablets 30 mg QD and leflunomide 20 mg QN) and anti-pulmonary fibrosis treatment (pirfenidone 100 mg TID and acetylcysteine vescent tablets 0.6 g BID). Chest CT scans (Figure 2A-C) showed that the pulmonary interstitial changes did not progress significantly over several years; however, they did show gradual widening of the pulmonary artery (Figure 2D-F), and cardiac ultrasound indicated elevated pulmonary artery systolic pressure. The prescribed treatment for PAH (ambrisentan tablets 5 mg BID) was not effective in improving the

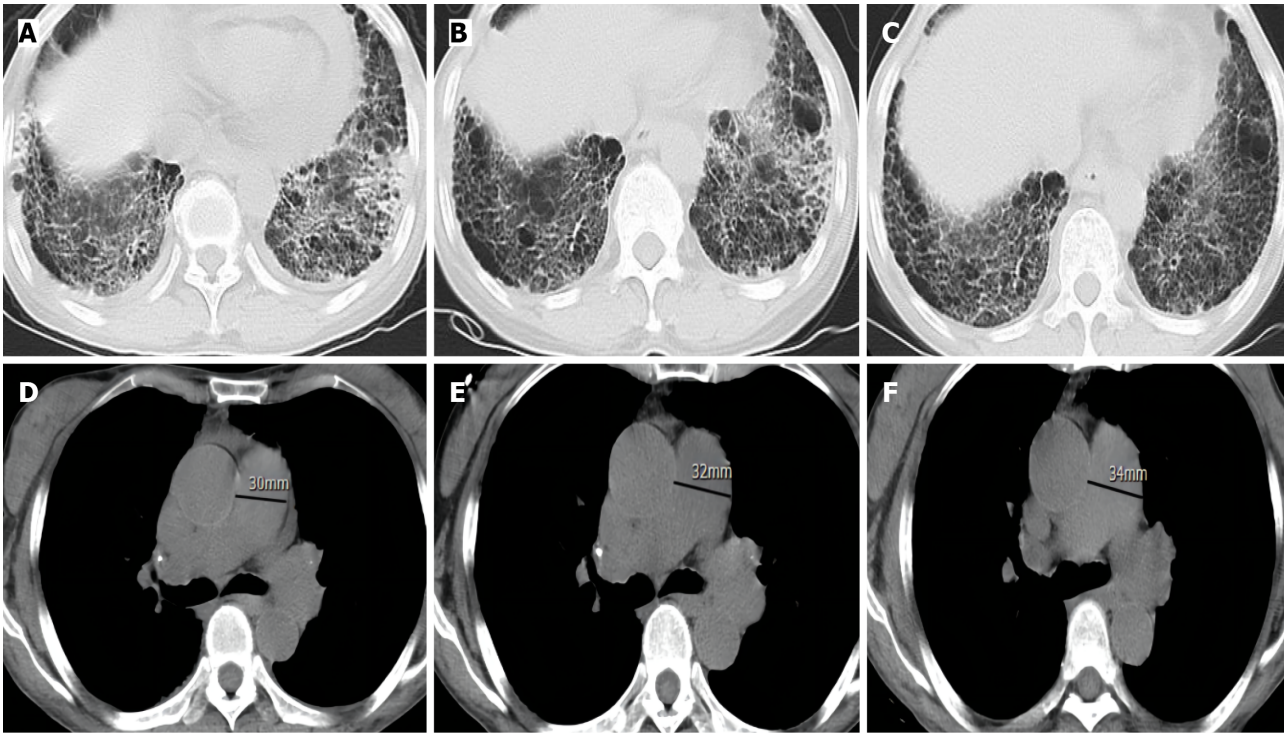

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Figure 2 Computed tomography scans over 3 years. A-C: Chest computed tomography (CT) shows the thickening of both lungs, a subpleural and lower lung mesh texture, and multiple patchy, blurred shadows in the lower lobe of both lungs; the left to right contrast showed no significant progression over 3 years; D-F: Chest CT mediastinal window, with contrast from left to right, showing gradual widening of the pulmonary artery over 3 year.

patient's shortness of breath.

DISCUSSION

RA is a heterogeneous systemic inflammatory disease characterized by painful polyarthritis, which has a significant impact on a patient's quality of life, morbidity, and mortality[11]. Serological typing divides this condition into seropositive and seronegative RA based on the presence or absence of RF and anti-CCP antibodies, and both RA subtypes may have similar clinical manifestations despite different etiologies[12].

This report describes the case of a patient with SNRA who was previously treated for depression. Her diagnosis of ASS was delayed for 2 years because the joint manifestations of this condition were indistinguishable from RA, despite the presence of positive antibodies related to ASS. A review of cardiac ultrasound and chest CT images also revealed that the patient had progressively developed disproportionate PAH, based on stable interstitial lung changes. The following sections discuss these puzzling clinical presentations.

SNRA and ASS

It has been reported that 18%-55% of patients with IIM have arthritis. As with RA, the most typical manifestation of joint disease in patients with IIM is symmetric non-erosive polyarthritis, primarily affecting the small joints of the hand[13]. Arthritis is particularly common in the ASS-associated form of IIM (20%-70%), with the highest prevalence associated with anti-Jo-1 positivity[13]. Radiological erosions are occasionally found in ASS, particularly in patients with overlapping RA[13]. RF and ACPA are relatively common in ASS patients with arthritis, as seen in 27.0%-31.5% and 11.0%-13.5% of patients with active arthritis, respectively[14]. The absence of arthritis is associated with a much lower prevalence of these antibodies, with only 8.0% and 1.5% of cases being positive for RF and ACPA, respectively[14,15]. Notably, our patient had arthritis but was negative for RF and ACPA, thereby complicating the distinction between RA and ASS. A study by Kumar *et al*[16] reported six patients with ASS and RA; while RA was diagnosed after the development of symmetrical facet polyarthritis, ASS was only detected many years after the development of IIM and ILD. We also considered RA first in our patient, and only 2 years later were we able to diagnose ASS owing to the increased severity of ILD and PAH. It is unclear whether there is true overlap between ASS and RA, or whether ASS in some cases only mimics RA[4]. Polyarthritis is the most frequent clinical manifestation among patients with IIM

and may be misdiagnosed as RA[13]. ASS should be specifically considered as a differential diagnosis in patients with SNRA and ILD or Raynaud's phenomenon.

SNRA-ASS-associated ILD progressed steadily, but with disproportionately increased PAH

PAH is a life-threatening complication associated with CTD, particularly in systemic sclerosis and systemic lupus erythematosus. RA is the most common CTD, but the prevalence of PAH in patients with RA is lower than that in patients with CTDs such as scleroderma, mixed collagen tissue disease, and dermatomyositis/polymyositis[17]. Fayed *et al*[18] provided an overview of CTD-associated PAH types and reported that post-capillary PAH is most common in patients with RA, while lung disease-associated PAH is commonly seen in patients with IIM and sarcoidosis. The case of RA-associated PAH presented by Szturmowicz *et al*[17] illustrates the complexity of PAH in a single individual, with ILD-PAH dominating the early stage and CTD-PAH developing later.

Among patients with ASS, ILD is the main clinical feature and prognostic factor with an incidence of up to 80%, while PAH secondary to ILD is also frequently reported[9]. Approximately 7.9% of patients with ASS develop PAH[19]. It has been shown that PAH is usually severe and is believed to be related to Raynaud's phenomenon, which is commonly associated with ASS[19]. A case report and literature review by García-Fernández *et al*[9] explored the relationship between ASS and PAH, and revealed that while their patients had stable and mild ILD, PAH at follow-up was disproportionate and unrelated to ILD severity. This study suggested that direct vascular involvement may lead to PAH in patients with ASS; both anti-Jo-1 positive and anti-PL-12 positive cases were found to have intimal proliferation on histological analysis of pulmonary arterial muscles, further supporting this pathophysiological theory [9].

PAH is common in most forms of CTD, but there are no reports of PAH secondary to RA overlapping ASS[10]. Current reports on CTD-PAH do not include overlapping CTDs, and its incidence and impact on patient prognosis are unclear[10]. There are currently no specific recommendations or guidelines for screening or treating patients with CTD, particularly those with PAH and ASS; however, routine echocardiography, electrocardiograms, pulmonary function tests, and timely initiation of specific treatments may improve prognosis[10].

There is no standardized protocol for the treatment of RA-ASS. While our patient's case primarily manifested as joint and pulmonary conditions, for such an unusual clinical phenotype of SNRA overlapping with ASS, more clinical studies are required to specify and confirm an appropriate treatment protocol. One strength of our case study is that it is the first report of this particular phenotype, but a limitation is that although cardiac ultrasound can screen for PAH, our patient did not undergo the "gold standard" test.

CONCLUSION

The joint manifestation of ASS is usually difficult to distinguish from RA, particularly in patients with SNRA; as a result, rheumatologists and respiratory pathologists should be aware of this rare and underrecognized clinical phenotype. Whether patients with this phenotype are more prone to PAH compared with those with a single CTD remains unknown. However, further research into anti-Jo1 antibodies, anti-RO-52 antibodies, and other extractable nuclear-antigen autoantibodies is necessary to facilitate the early diagnosis, effective evaluation, and prognosis of this overlapping clinical syndrome.

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FOOTNOTES

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