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Acute Onset Seropositive Rheumatoid Arthritis-Associated Interstitial Lung Disease in the Absence of Articular Symptoms: An Atypical Presentation

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Abstract

Rheumatoid arthritis (RA) is a systemic autoimmune disease in which extra-articular manifestations, including interstitial lung disease (ILD), may precede joint involvement. Acute presentations mimicking pulmonary embolism (PE) or infection may delay diagnosis in similar cases.

A 72-year-old previously healthy male presented with progressive dyspnea, cough, chest pain, and palpitations that began during a high-altitude hike in Hawaii. These symptoms persisted upon return home and worsened over almost two weeks. Initially believing he might have contracted pneumonia, the patient self-medicated with amoxicillin-clavulanate and azithromycin, which did not mitigate his symptoms. Ultimately, the severity of these symptoms prompted a call to emergency services. Upon arrival at the ED, he was noted to be hypoxic and tachypneic. CT angiography at the time demonstrated acute left-sided lobar pulmonary emboli and diffuse bilateral ground-glass opacities. Despite full anticoagulation and broad-spectrum antibiotics, his respiratory failure progressed, requiring high-flow oxygen and intermittent bilevel positive airway pressure (BiPAP). Extensive infectious evaluation was negative. Autoimmune workup revealed elevated rheumatoid factor (30.7 IU/mL) and anti-cyclic citrullinated peptide antibodies (>250 U), with no clinical evidence of inflammatory arthritis. Imaging demonstrated diffuse interstitial and air-space disease with mediastinal lymphadenopathy and evolving complications including pneumothorax and subcutaneous emphysema. He was treated with pulse-dose methylprednisolone followed by mycophenolate without significant improvement and was ultimately transferred to a tertiary care center for further management.

This case highlights an atypical, late-onset presentation of seropositive RA manifesting as severe ILD without preceding joint symptoms. The coexistence of acute PE and recent travel complicated early diagnostic reasoning. Clinicians should maintain suspicion for connective tissue disease-associated ILD in older patients with unexplained progressive hypoxemic respiratory failure and a negative infectious workup.

Categories: Rheumatology, Pulmonology, Internal Medicine
Keywords: atypical presentation, immunosuppressant therapy, interstitial lung disease (ild), pulmonary embolism (pe), seropositive rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease primarily characterized by symmetric inflammatory polyarthritis. However, extra-articular manifestations are well described and may involve the lungs, heart, skin, vasculature, and musculoskeletal system [1]. RA-associated interstitial lung disease (RA-ILD) occurs in approximately 10-40% of patients, with a fraction of these having clinical manifestations [2]. Smoking history is a well-known risk factor. Although pulmonary involvement typically follows articular disease within the first five years of diagnosis, lung manifestations may precede joint symptoms in 10-20% of cases [3]. Acute presentations with hypoxic respiratory failure are uncommon and may mimic other etiologies such as infection, bronchiectasis, or pulmonary embolism (PE), leading to diagnostic delay [4]. We report a unique case of severe hypoxemic respiratory failure in a previously healthy 72-year-old male, ultimately attributed to seropositive RA-associated ILD without prior inflammatory arthritis.

Case Presentation

Our patient is a 72-year-old male residing in the Northeast with no significant medical history. He presented with progressive dyspnea of approximately two weeks' duration. Symptoms were triggered during a high-altitude mountain hike while traveling in Hawaii. He reported dyspnea on exertion, mild cough, chest discomfort, and intermittent palpitations. He denied fever, upper respiratory symptoms, prior thromboembolism, smoking history, and any chronic medical conditions. When symptoms did not improve

upon returning home, he self-administered amoxicillin-clavulanate and azithromycin for presumed community-acquired pneumonia without improvement. He was seen by his cardiologist, who conducted an electrocardiogram and echocardiogram but found no acute process per the report; he was advised to go to the ED at that time but opted to wait and see his primary care provider first. During his primary care visit, he was noted to be tachypneic (respiratory rate 20-30/min) and hypoxic (SpO_2 88-91% on room air), and was subsequently sent to the ED.

Initial evaluation

On arrival, the patient was afebrile, heart rate 80-90 bpm, and normotensive. There was persistent hypoxia requiring supplemental oxygen, with mild respiratory distress without wheezes or peripheral edema. ECG showed normal sinus rhythm without ischemic changes. Point-of-care ultrasound demonstrated preserved ejection fraction, no right ventricular dilation, and no pericardial effusion. The patient's WBC, Na^+, troponin, and blood glucose levels from initial evaluation to day 13 are summarized in Table *1*.

Lab	Day 1	Day 2	Day 5	Day 10	Day 13	Normal Range
WBC	12.9 × 10^9/L	12.7 × 10^9/L	16.9 × 10^9/L	22.3 × 10^9/L	23.1 × 10^9/L	4.23-9.07 × 10^9/L
Na^+	129 mmol/L	132 mmol/L	133 mmol/L	136 mmol/L	133 mmol/L	135-145 mmol/L
Troponin	25.7 ng/L	19.3 ng/L	x	x	x	2-20 ng/L
Blood glucose	146 mg/dL	139 mg/dL	126 mg/dL	128 mg/dL	157 mg/dL	74-106 mg/dL

TABLE 1: Laboratory results from days 1-13

Laboratory values, including white blood cell count (WBC), serum sodium (Na^+), troponin, and blood glucose, on hospital days 1, 2, 5, 10, and 13. Reference ranges are provided for comparison. “x” indicates that the value was not available.

Imaging

CT pulmonary angiography, as shown in Figure *1*, revealed acute pulmonary emboli in the left upper and lower lobar branches (Figure *1D*), diffuse bilateral ground-glass opacities (Figures *1B*-*1C*), mild mediastinal and hilar lymphadenopathy, and an enlarged pulmonary artery (Figure *1A*) without evidence of right ventricular strain. Lower extremity duplex ultrasound showed no evidence of deep vein thrombosis.

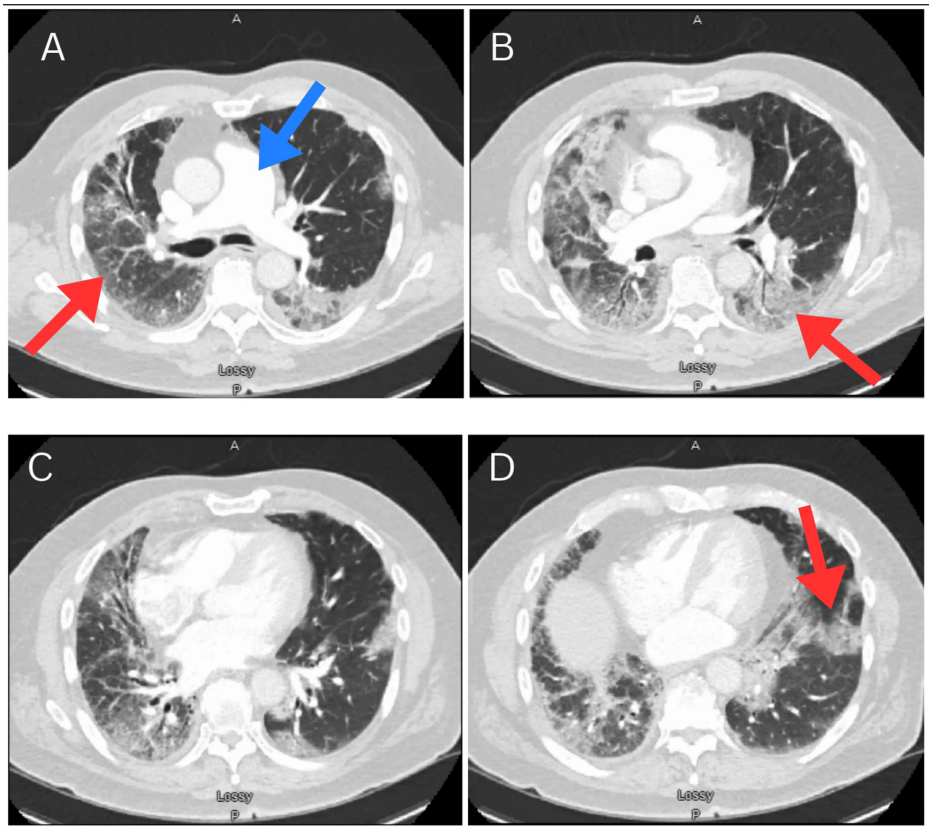


FIGURE 1: Selected slices from CT chest on day 1 (admission)

Axial computed tomography (CT) images of the chest were obtained on hospital day 1 (admission), demonstrating bilateral pulmonary opacities and areas of ground-glass attenuation (red arrows), along with an enlarged pulmonary artery (image A, blue arrow). A filling defect is shown in images B & C. A mass-like opacity is shown in image D.

He was started on low-molecular-weight heparin (LMWH) for therapeutic anticoagulation at a dose of 1 mg/kg administered subcutaneously (SC) every 12 hours and empiric antibiotics for community-acquired pneumonia. Despite therapy, he developed progressive hypoxemic respiratory failure with persistent tachypnea and increasing oxygen requirements, prompting transfer to the intensive care unit for close monitoring and advanced respiratory support.

Clinical deterioration

Over the subsequent week, serial chest radiographs demonstrated persistent and progressive bilateral infiltrates, right greater than left. Later imaging suggested a possible mass-like opacity and worsening bilateral interstitial disease, as shown in Figure *2*. He developed a small right pneumothorax and extensive subcutaneous emphysema involving the neck, chest, axillae, and mediastinum. Imaging revealed progressive multilobar air-space disease with diffuse ground-glass infiltrates.

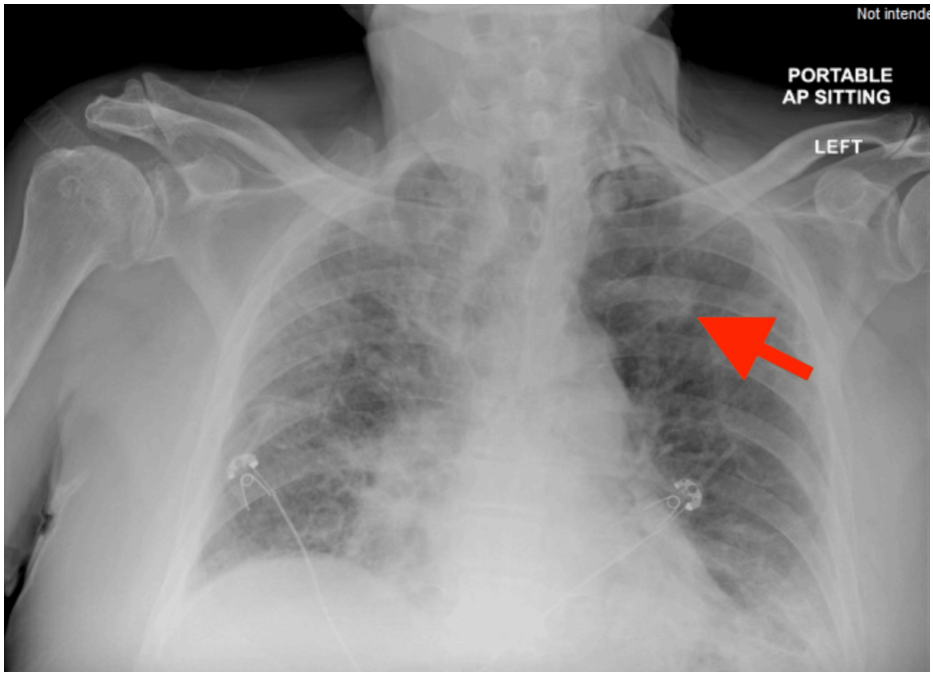


FIGURE 2: Chest radiograph from day 9

Day 9 portable anteroposterior (AP) chest radiograph showing a possible left upper lung mass-like opacity (red arrow) and worsening bilateral interstitial opacities.

While the patient's white blood cell count fluctuated during that time, with a high of 23.1× 10^9/L, infectious evaluation was extensive and negative, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), respiratory syncytial virus (RSV), influenza virus, human immunodeficiency virus (HIV), hepatitis C virus (HCV), *Aspergillus*, *Legionella* antigen, QuantiFERON test, and β-(1,3)-D-glucan. He required escalating respiratory support, including high-flow nasal cannula up to 60 L/min at 95-100% FiO_2 and intermittent bilevel positive airway pressure (BiPAP), and would continue to desaturate with minimal exertion.

Autoimmune evaluation

The rheumatologic workup revealed a rheumatoid factor of 30.7 IU/mL and an anti-cyclic citrullinated peptide (anti-CCP) antibody level of >250 U. Antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA; myeloperoxidase (MPO)/proteinase 3 (PR3)), anti-Jo-1, anti-Scl-70, and anticardiolipin antibodies were negative. Serum protein electrophoresis was negative for a monoclonal spike.

Notably, the patient had no history or signs of clinical inflammatory arthritis, joint swelling, or other systemic connective tissue disease (CTD) manifestations. The working diagnosis became CTD-associated ILD (CTD-ILD), most consistent with seropositive RA-associated ILD.

Treatment and outcome

He received pulse-dose methylprednisolone (500 mg IV daily for five days), transitioned to mycophenolate mofetil (up-titrated to 1 g PO twice daily), and continued therapeutic anticoagulation. Despite aggressive immunosuppressive therapy, he demonstrated minimal respiratory improvement and remained severely hypoxemic. Given continued clinical deterioration, he was transferred to a tertiary care center for advanced pulmonary management and multidisciplinary evaluation.

Discussion

This case illustrates several important diagnostic and pathophysiologic considerations.

RA-ILD without articular disease

High-titer anti-cyclic citrullinated peptide 2 (anti-CCP2) antibodies, as seen in this patient (>250 U), are known to be strongly associated with RA and have been shown to correlate with increased risk of ILD: A 2015 study by Giles et al. demonstrated that median levels of CCP2 and all specific anti-citrullinated peptide antibodies (ACPAs) were 46-273% higher among RA patients with ILD versus those without ILD (p-values <0.05). Additionally, the higher the level of ACPAs, the worse the restriction in pulmonary function and

impaired diffusion were observed. The association remained significant after adjusting for various characteristics including age, gender, current and former smoking status, and Disease Activity Score for 28 joints [5]. However, less is known about the pathogenesis in patients who develop RA-ILD independently of joint involvement. Fischer et al. discussed the subject in their 2013 retrospective cohort study, involving 74 anti-CCP seropositive patients with respiratory symptoms and lacking joint disease. They identified four radiographic phenotypes of airway disease among this cohort, 14% of which presented with isolated ILD and 26% presenting with mixed airway disease and ILD on thoracic high-resolution computed tomography (HRCT). Of those patients who had high anti-CCP titres, 9% went on to develop articular symptoms with a median follow-up period of 449 days. Of these, only one patient had a smoking history [6]. A 2014 retrospective chart review by Gizinski et al. identified four patients with ILD, RF, and anti-CCP positivity and no articular findings of RA; their demographics were strikingly similar to our patient, all being male with a mean age of 70 years at the time of diagnosis and rapidly progressive symptoms. Three of the subjects passed away within two years of disease onset without ever developing joint involvement, whereas the one subject who survived ultimately developed full criteria for RA, including joint involvement years later. All four subjects had a smoking history [7]. Another case report from 2025 by Gongireddy et al. described a 66-year-old female never-smoker who presented with progressive dyspnea, worsening cough, unintentional weight loss, and voice hoarseness; her workup revealed evidence of ILD on chest CT as well as high rheumatoid factor (RF) of 66 IU/mL and CCP antibodies IgG/IgA of 123 units despite the absence of joint or systemic symptoms. However, unlike our patient, her symptoms manifested gradually over the course of a year rather than rapidly over weeks to months [8]. Thus, our case illustrates an exceedingly rare instance of seropositive anti-CCP ILD in an elderly male patient without joint disease and with rapid symptom progression and no smoking history. Collectively, these findings highlight that the absence of arthritis in patients presenting with severe respiratory symptomology should not delay consideration of autoimmune-associated ILD once emergent and common infectious causes of dyspnea have been ruled out.

Confounding acute PE

The presence of confirmed lobar pulmonary emboli provided an early, plausible explanation for hypoxia. However, the degree of respiratory failure and progressive radiographic abnormalities exceeded what would be expected from the clot burden, particularly so when considering the lack of right ventricular strain [9]. A recent systematic review and meta-analysis highlights ILD's three-fold risk of increased venous thromboembolism, particularly PE [10]. While this risk of inflammation-associated hypercoagulability likely explains this patient's PE, the severity and progressive nature of his dyspnea despite appropriate anticoagulation signalled an alternative etiology.

Acute exacerbation (AE) pattern

Radiographically, the diffuse ground-glass opacities and rapid deterioration observed in this patient's imaging resembled the usual interstitial pneumonia pattern most commonly seen in RA-ILD and idiopathic pulmonary fibrosis (IPF) [11]. Acute inflammatory presentations can occur, and these carry comparably high mortality in both RA-ILD and IPF, with one multicenter cohort reporting post-AE cumulative survival rates at three, six, and 12 months of 51.7%, 46.6%, and 41.0%, respectively, in the overall AE-RA-ILD group, versus 63.2%, 53.7%, and 42.1%, respectively, in the overall AE-IPF group [12]. Our patient's clinical course is consistent with these findings.

Poor response to first-line immunosuppression

While discourse on the optimal treatment of ILD associated with systemic autoimmune rheumatic diseases (SARD-ILD) remains open, glucocorticoids, mycophenolate, rituximab, cyclophosphamide, and azathioprine are considered first-line therapies by the 2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) guidelines. In recent years, JAK inhibitors have also entered the scene with increasing evidence of efficacy. Failure to improve with pulse steroids and mycophenolate underscores the aggressive nature of some RA-ILD phenotypes and the need for early tertiary referral. Conversely, caution is warranted with disease-modifying antirheumatic drugs (DMARDs) like methotrexate and tumor necrosis factor (TNF) inhibitors given mixed evidence of pulmonary injury or disease exacerbation [13]. Existing literature seldom addresses treatment modality specifically for RA-ILD in the setting of absent joint involvement, warranting further investigation into the management of this apparently severe and rapidly progressive disease manifestation.

Travel and altitude as trigger

Though the timing of this patient's symptom onset may be incidental, the sudden change in environment, which temporally correlated with the development of his dyspnea, makes a potential environmental trigger difficult to ignore. Higher altitude environments, as our patient encountered while hiking in Hawaii, are a plausible but little-investigated trigger for ILD exacerbation. One recent two-center, retrospective, observational study investigating patients with IPF and CTD-ILD in Qinghai and Tibet revealed a higher prevalence of CTD-ILD amongst their designated high-altitude group. Despite the limitations of this study, its hypothesis that a chronic hypoxic environment may accelerate the progression of lung fibrosis and vascular remodelling by inducing oxidative stress, inflammation, and fibrotic processes, further compromising lung function and gas exchange in ILD patients living at high altitudes, is worth further

investigation [14]. Patient history revealed several prior trips to Hawaii from the Northeast without symptoms; however, symptom onset during high-altitude exertion may have unmasked previously subclinical ILD or triggered an inflammatory exacerbation of an occult disease process. Moreover, the question of exposure to crystalline silica dust - another known risk factor for RA-ILD - from volcanic ash particles in the environment is one worth posing. Though the content of crystalline silica specifically in Hawaiian volcanoes is below detectable limits (<~0.03 mg/m^3), these geologic entities expel various other volatile and hazardous compounds such as hydrochloric acid and hydrofluoric acid, which could have theoretically exacerbated an underlying disease process [15].

Conclusions

This case demonstrates a rare and severe presentation of seropositive RA manifesting initially as acute hypoxemic respiratory failure due to ILD, without preceding articular symptoms. Much remains unclear about this particular subgroup of ILD patients, including disease course, whether all surviving patients ultimately develop joint involvement, or if they would eventually represent a distinct pathophysiology. Continued research is also needed for optimal medical management strategies when lung transplantation is not readily available. For our patient, concomitant PE and recent travel obscured the diagnosis. Thus, in older patients with progressive hypoxia, diffuse ground-glass infiltrates, and negative infectious workup, CTD-ILD should be strongly considered, even in the absence of joint disease. Early rheumatologic evaluation and multidisciplinary management are critical, as RA-ILD can progress rapidly and may require advanced immunosuppression or referral to specialized centers.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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