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Interstitial Lung Disease as the Initial Manifestation of Rheumatoid Arthritis: A Case Report and Review of the Literature

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Abstract Background: Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disorder that primarily affects synovial joints. Approximately 18-41% of patients with RA develop extra-articular manifestations [1]. However, extra-articular manifestations preceding or occurring without articular symptoms in RA have rarely been reported. Such atypical presentations of RA pose a diagnostic challenge to the clinician and may delay treatment. Case presentation: A 57-year-old female with long standing diabetes, hypertension, hyperlipidemia and Raynaud's phenomenon presented shortness of breath, cough and new subcutaneous nodules. Four years before, she had been diagnosed with non specific interstitial pneumonia but had declined treatment. The physical exam did not reveal any signs suggestive of RA however, she was seropositive for rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA). Treatment for RA-associated interstitial lung disease was discussed. Conclusion: Extra-articular involvement of RA can be observed as initial presentation of the disease in a handful of cases. However, RA diagnosis must be achieved to correctly manage these patients which can at that time receive targeted therapeutic interventions. From our literature review, pulmonary involvement was seen in over half of the cases in seropositive RA patients who lacked articular involvement at initial presentation.

Keywords: *Rheumatoid arthritis, Rheumatoid nodules, interstitial lung disease, extra-articular manifestations, seropositive rheumatoid arthritis, non-specific interstitial pneumonia*

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1. Introduction

Rheumatoid Arthritis (RA) is a progressive systemic inflammatory disorder with a prevalence of 1% among Black population characterized by proliferating synovitis and erosive destruction of cartilage and bone [2]. Given that RA is systemic disease, a number of extra-articular manifestations in RA, can be also be present including involvement of the cardiovascular, pulmonary, cutaneous, gastrointestinal, neurological, ophthalmological, renal and vascular systems [1,3]. Extra-articular manifestations in RA occur in about 18-41% of patients and may precede the onset of articular manifestations [1,4]. Early diagnosis and initiation of disease modifying anti-rheumatic drugs (DMARD) therapy is critical to delay or prevent further progression of RA [3]. Atypical manifestations could challenge the diagnosis of RA and subsequently lead to a delay in management.

2. Case Presentation

A 56-year-old woman with type II diabetes, hyperlipidemia and hypertension presented to our Institution with a 4 year-history of productive cough and shortness of breath on exertion. The patient noted the insidious development of dyspnea of exertion and cough four years before, for which she was evaluated at another institution. She had also noticed pain and color changes on the fingers of both hands that were more bothersome during the winter months or upon entering air conditioned rooms. A lung biopsy had been performed, revealing non-specific interstitial pneumonia. Treatment had been discussed however, the patient declined therapy. Cough and shortness of breath gradually worsened. In the interim, the patient noticed the development of subcutaneous (SC) nodules on the elbows and dorsal aspect of the hands bilaterally. The patient interpreted these SC nodules to

be warts and applied OTC salicylic acid without any improvement. One year prior to current presentation, latent tuberculosis was encountered and the patient completed a three month-regimen of weekly isoniazid and rifapentine with good tolerance. The review of systems was negative for sicca symptoms, weight loss, fevers, joint pain, tenderness or swelling, morning stiffness, digital ulcers, skin rashes or red painful eyes. The patient denied any recent travel or sick contacts. FMHX was non-contributory. Patient denied history of smoking, alcohol or drug use. There was no history of asbestos exposure or hypersensitivity pneumonitis. Her home medications consisted of lisinopril, simvastatin and metformin.

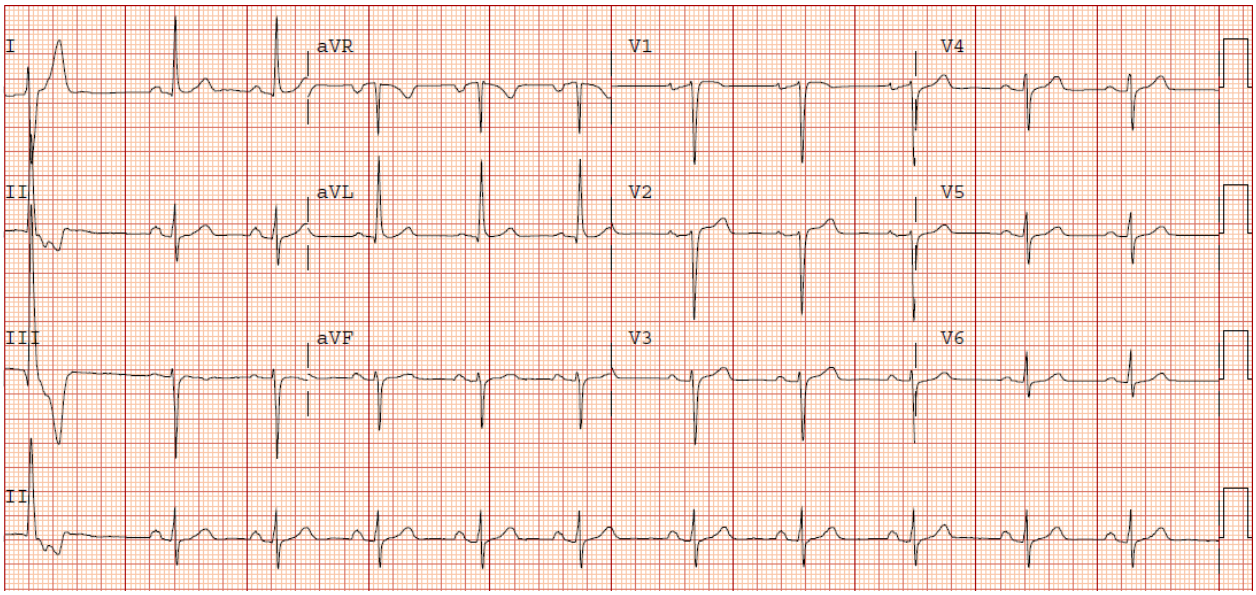

Figure 1. Sinus arrythmia, ventricular premature complex, probable left atrial abnormality and left ventricular hypertrophy

Table 1. Laboratory Data

Serum	Patient	Reference Range
WBC (K/uL)	4.43	4.5-10.9
RBC (M/uL)	4.08	4.2-5.4
Hemoglobin (g/dL)	12.7	12.0-16.0
Hematocrit (%)	41.4	37.0-47.0
Platelets (K/uL)	296	130-400
Sodium (mmol/L)	147	136-146
Potassium (mmol/L)	5.5	3.5-5.0
Chloride (mmol/L)	103	98-106
BUN (mg/dL)	9	6-20
Creatinine (mg/dL)	0.81	0.4-1.2
Calcium (mg/dL)	10	8.4-10.3
Total Protein (g/dL)	7.9	6.0-8.5
Albumin (g/dL)	4.4	2.8-5.7
AST (U/L)	20	10-35
ALT (U/L)	11	0-31
Alk Phos (U/L)	61	25-125
Total Bilirubin	0.3	0.0-1.2
Glucose (mg/dL)	112	70-99
ESR (mm/h)	56	0-20
CRP (mg/dL)	6.51	1.0-4.0
Immunological work-up		
Anti-citrullinated peptide antibodies(U)	20	0-20
Rheumatoid factor (IU)	61	0-14
Antinuclear antibodies	Negative	<1:40
dsDNA (IU/ml)	Negative	<100
Anti-Jo	Negative	Negative
Anti- Mi	Negative	Negative
Anti-topoisomerase	Negative	Negative
Anti-SSA/Ro	Negative	Negative
Anti-SSb-La	Negative	Negative
Pulmonary Function Tests		
Forced vital capacity (FVC)	1.17 L	(65% of predicted)
Forced expiratory volume in 1 sec (FEV1)	1.05 L	(70% of predicted)
FEV1/FVC	89.70	(≥80% of predicted)
Total lung capacity (TLC)	2.18 L	(70% of predicted)

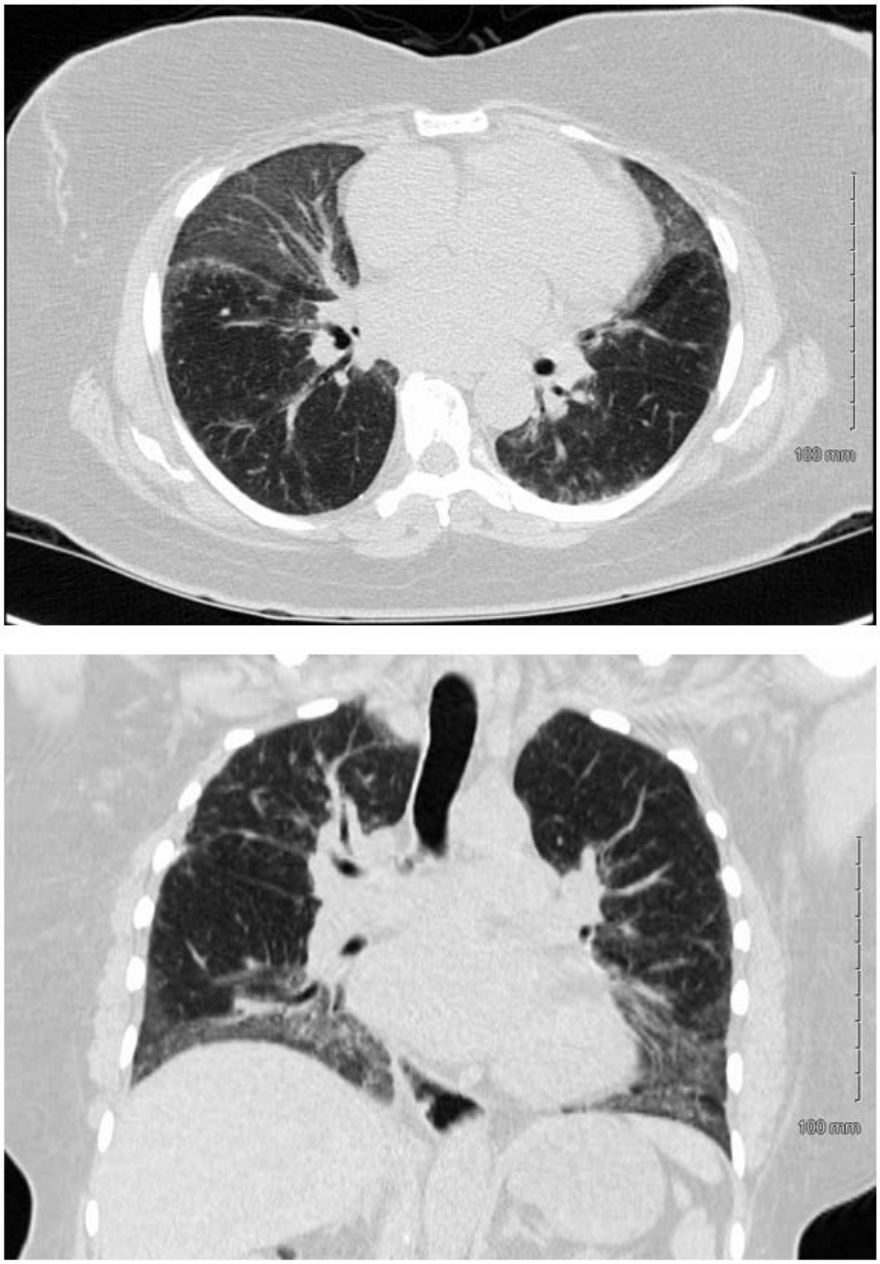

Figure 2. CT chest demonstrates bibasilar predominant diffuse ground glass opacities, minimal associated volume loss and bronchiectasis without honeycombing with stable bi-apical scarring and pleural thickening. Major diagnostic consideration is nonspecific interstitial pneumonia

On examination, her temperature was 37.6°C, pulse of 81 beats per minute, blood pressure 112/75 mmHg, respiratory rate 17 breaths per minute, and her oxygen saturation at rest was 92% on ambient air. The physical exam was remarkable for decreased air entry with bilateral fine inspiratory crackles at the bases. Skin exam revealed multiple, 1-2 cm., firm, painless, subcutaneous nodules located on the extensor surface of both elbows and over the right 3rd proximal interphalangeal joint (PIP), the left 2nd PIP joint, and the left 4th PIP joint. Musculoskeletal exam revealed no joint abnormalities, as such there was no evidence of joint swelling, tenderness, effusion, deformities or decreased range of motion.

Laboratory tests were significant for anti-citrullinated peptide antibodies (ACPA) 29 U (reference range 0-20), rheumatoid factor (RF) 61 IU/ml (reference range 0-14), and erythrocyte sedimentation rate (ESR) 56 mm/hr. Normal or negative tests included antinuclear antibodies (ANA), anti-double stranded DNA (anti-dsDNA), anti-Jo antibodies, anti-Mi antibodies, anti-topoisomerase antibodies (anti Scl-70), anti-SSA/Ro antibodies, and anti-SSB/La antibodies (Table 1). Her pulmonary function test (PFT) showed a forced vital capacity (FVC) of 1.17L (65% than expected), forced expiratory volume (FEV1) of 1.05L (70% than expected), FEV1/FVC ratio of 89.7% [Normal value: Equal to or greater than 80%], and total lung capacity (TLC) of 2.18L (70% than expected), which suggested restrictive lung disease. EKG showed sinus arrythmia, ventricular premature complex, probable left atrial abnormality and left ventricular hypertrophy (Figure 1). Her transthoracic echocardiograph revealed an ejection fraction of 60% with mild functional mitral and tricuspid regurgitation, and a pulmonary artery systolic pressure (PASP) of 29 mmHg.

CT chest showed bibasilar predominant diffuse ground glass opacities with volume loss and bronchiectasis, without evidence of honeycombing; bi-apical reticular opacities associated with architectural distortion and pleural

thickening consistent with scarring. No mediastinal lymphadenopathy (Figure 2). During the hospital stay, lisinopril was discontinued and amlodipine was started for blood pressure control.

Clinical presentation, laboratory results and imaging findings were consistent with a diagnosis of connective tissue disease associated interstitial lung disease (ILD), non-specific interstitial pneumonia (NSIP) subtype. Treatment options were discussed with the patient and eventually mycophenolate mofetil (MMF) was initiated after discharge during a follow-up clinic visit. She was given a 2 week-office follow-up to monitor the response of the treatment, tolerance and side effects.

3. Discussion and Literature Review

Among the extra-articular manifestations of RA, the most frequently encountered are: cardiovascular disease, cutaneous manifestations including rheumatoid nodules, interstitial lung disease, vasculitis, ocular involvement, gastrointestinal, neurological, and nephropathy. [3]

Interstitial lung disease (ILD), among the extra-articular manifestations of RA warrants special attention, since up to 10% of RA patients can develop clinically significant ILD [5,6,7,8]. First described in 1948, RA-related ILD was described as fine to widespread heavy reticulation in chest radiographs (CXR) of patients of RA [9]. RA-ILD confers the patients a higher mortality rate in comparison to RA without ILD likely due to the comorbid conditions including ischemic heart disease, congestive heart failure, and diabetes that affect this patient population. Lack of definitive prognostic indicators or gold standard treatment therapies for RA-ILD, is a likely explanation for the higher mortality rates observed among these patients [10,11]. The most common subtype of ILD in RA is the usual interstitial pneumonia followed by the NSIP pattern, organizing pneumonia, desquamative interstitial pneumonia lymphocytic interstitial pneumonia and diffuse alveolar damage have been documented [12,13]. A recent study of our RA patient population revealed that UIP was the common pattern affecting mainly women with a mean age of 62.6 years of age, with smoking history found in only 31% of the cases. NSIP pattern was found in 25% of the RA-associated ILD cases, a second autoimmune disease was reported in 75% of the NSIP patients [14]. The typical UIP CT pattern features honeycombing, reticular pattern with peripheral traction bronchiectasis or bronchiolectasis in a predominantly basal (occasionally diffuse) and sub-pleural distribution that is often heterogeneous [15]. Chest CT imaging demonstrating a homogenous and bilateral pattern of ground glass opacities associated with fine reticulations, pulmonary volume loss, traction bronchiectasis and sparing of the sub-pleural space were classified as non-specific interstitial pneumonia (NSIP) [16]. Cases of RA-related ILD presenting in patients without articular symptoms may pose a diagnostic challenge, delay treatment, and lead to unfavorable outcomes. Our case is an unusual initial presentation of RA that prompted us to review of the literature in search of RA cases that initially presented with extra-articular manifestations.

We performed a systematic review of English literature on PubMed from 1990 to 2019 using the keywords “rheumatoid arthritis,” “rheumatoid arthritis with lung disease”, “rheumatoid arthritis with rheumatoid nodules”, and “rheumatoid arthritis with extra-articular manifestations”. Two hundred four articles were identified and reviewed. Twelve articles describing cases in which RA patients had initially presented without articular symptoms were selected for further review. See Table 2.

Tomioka et al. reported on a 53-year-old woman who initially was diagnosed with nonspecific interstitial pneumonia (NSIP). Six months later, the patient developed mild arthralgia in the wrist and knee joints and was found to be seropositive for rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA). Disease modifying anti-rheumatic drugs (DMARDs) were initiated with subsequent improvement. [17] Watanabe et al. presented a 70-year-old woman with respiratory symptoms who had NSIP pattern on lung biopsy. A few months later, after knee arthritis developed, she was diagnosed with RA; the lung opacities gradually improved once steroids were introduced. [18] Laria et al. published about a 54-year-old male who was initially diagnosed with NSIP and was found to be seropositive for RF and ACPA. The patient was first treated for infectious etiology, however he did not show improvement; weeks later, the patient developed right knee arthritis and his pulmonary disease was recognized as RA-related ILD, NSIP subtype, and improved clinically once immunosuppressive therapy was initiated. [29] In all three cases, the RA diagnosis and treatment were delayed due to the initial RA presentation without joint involvement.

Table 2. Cases Reported with Extra-articular Manifestations as Initial RA presentation

Author	Patient’s age	Gender	Initial RA manifestation	RF positive	ACPA positive
Tomioka [17]	53	F	NSIP	+	+
Watanabe [18]	70	F	NSIP	+	n/a
Laria [19]	54	M	NSIP	+	+
Cavascalla [20]	65	M	OP	+	+
Komiya [21]	86	F	OP	+	+
Hoshino [22]	71	M	OP	+	+
Norman [23]	39	F	Eosinophilic pneumonia	+	n/a
Chen [24]	52	F	Optic neuritis	+	n/a
Campanati [25]	52	F	Diffuse normo-lipemic plane xanthoma	+	+
Haddiya [26]	30	F	Membranous nephropathy	n/a	+
Mirzaei [27]	23	F	Acute tubular injury	+	+
Sacks [28]	38	M	Polyarteritis nodosa	+	+

Organizing pneumonia (OP) preceding RA articular involvement has also been reported. Cavallasca et al. reported cryptogenic organizing pneumonia (COP) on lung biopsy in a 65-year-old Caucasian man. The patient improved on steroids but six months after, while the steroids were being tapered he developed fever, arthralgias, myalgias and morning stiffness. He was diagnosed with seropositive RA (RF+ and ACPA+), and was started on DMARDs. [20] Komiya et al. described a 86-year-old Japanese woman initially diagnosed with OP. Although initially known to be double seropositive, RA diagnosis was only reached after small joint involvement and morning stiffness developed eight months later. [21] Hoshino et al. in 2011 also described a case in which organizing pneumonia preceded articular symptoms in a 71-year-old male with RA. [30]

Eosinophilic pneumonia was described by Norman et al. in a 39-year-old woman found to have. The patient subsequently developed polyarthritis, was found to be seropositive for ANA and RF, and improved clinically on corticosteroids. [23]

Optic neuritis was described by Chen et al. on a 52-year-old woman who had repeated episodes of optic neuritis, eleven years after initial presentation she demonstrated joint involvement and morning stiffness and RA was made. [24] Campanati et al. published about a 52 year-old woman diagnosed with diffuse normolipemic plane xanthoma (DNPX). Four months later, the patient was hospitalized due to morning stiffness and polyarthralgia and was found to be seropositive for RF and ACPA [25]. Haddiya et al. presented a case of idiopathic membranous nephropathy (MN) in a 30 year old woman; two years later, at the time the MN relapsed, she also manifesed morning stiffness and polyarthritis. Once RA diagnosis was reached and DMARDs initiated, she maintained remission of both her articular symptoms and the MN. [26] A renal involvement case was also reported by Mirzaei et al. on a 23-year-old woman diagnosed with acute tubular injury by kidney biopsy. She was found to be double seropositive for RF and ACPA which suggested RA. Rituximab administration led to the complete remission of the disease. However, six weeks later, along with steroid dose reduction, the symptoms of arthralgia was observed, which was managed with methotrexate [27]. Finally, Sacks et al. published a case in which a 38-year-old male was diagnosed with polyarteritis nodosa. Six years later, the withdrawal of immunosuppressive therapy resulted in the patient developing symmetrical inflammatory polyarthritis. [31]

In conclusion, from our in-depth review, we have observed that a broad range of extra-articular manifestations can precede articular symptoms in RA. An atypical presentation of RA results in a delay in the treatment of extra-articular manifestations resulting in increased mortality and morbidity. Hyldgaard et al. described a one-year all cause mortality risk in RA-ILD patients to be 13.9% versus 3.8% in non-ILD RA patients. [32] As our patient exemplifies, many patients with atypical manifestations of RA do not satisfy the 2010 American College of Rheumatology criteria [33]. Physicians should explore the possibility of RA in patients not responding to initial treatment measures. ACPA antibodies and RF have been found to be elevated in preclinical and early RA subjects and should be used to screen and diagnose patients suspected to have RA. [34] Increased awareness of atypical symptoms for RA is critically important among health care providers and should be emphasized in future practices.

In conclusion, extra-articular involvement can be observed as initial presentation of RA in a handful of cases, affecting the pulmonary, renal, neurological and vascular systems. Despite the diagnostic challenge and masked presentations, RA pathogenesis must be elucidated to correctly manage the disease course in this patient population; for many of the patients, RA diagnosis was reached during follow-up by the advent of new articular manifestations. From our literature review, pulmonary involvement was seen in over half of the cases in seropositive RA patients who lacked articular involvement at initial presentation.

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