A CASE SERIES OF PLEURO-PULMONARY MANIFESTATIONS IN RHEUMATOID ARTHRITIS PATIENTS AT A TERTIARY CARE HOSPITAL IN KANCHIPURAM

General Medicine

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ABSTRACT

Rheumatoid Arthritis is a systemic inflammatory disorder that most commonly affects the joints, causing progressive, symmetric, erosive destruction of cartilage and bone and is usually associated with autoantibody production. Although joint disease is the main presentation, there are a number of extra-articular manifestations including subcutaneous nodule formation, vasculitis, inflammatory eye disease and lung disease. Of these manifestations, lung disease is a major contributor to morbidity and mortality. There are a variety of pulmonary manifestations of rheumatoid arthritis, including pulmonary parenchymal disease (interstitial lung disease) and inflammation of the pleura (pleural thickening and effusions), airways (bronchiectasis) and pulmonary vasculature (pulmonary hypertension). The present article reports five clinical cases in order to elucidate the diversity of the pathophysiological mechanisms that underlie rheumatoid arthritis associated pulmonary diseases. The five manifestations are: interstitial lung disease, pulmonary hypertension, pleural effusion, bronchiectasis and pulmonary tuberculosis (due to prolonged use of pneumotoxic anti-rheumatoid drugs). This case series illustrates the diagnostic challenges that may occur in pleuro-pulmonary disease associated with RA and also the importance of early diagnosis.

KEYWORDS

Rheumatoid Arthritis, Interstitial Lung Disease, Pleural Effusion, Pulmonary Tuberculosis, Bronchiectasis, Pulmonary Hypertension

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease whose distinctive feature is the development of symmetrical polyarthritis. It has a prevalence of 1% in the general population, predominating in females and peaking between the ages of 30 and 50 years^[1]. Ellman and Ball first described lung disease in association with RA[2], and since that time, various pulmonary manifestations, including pleural effusions, lung nodules, obstructive lung disease, and vasculitis have been identified. In addition to problems caused by the auto-immune disease itself, immunosuppressant agents and other medications used to treat RA can be directly pneumotoxic and predispose the patient to opportunistic infection like Pulmonary Tuberculosis. The majority of respiratory manifestations occur within the first 5 years of disease. Respiratory symptoms may precede onset of articular symptoms in 10–20% of cases. However, they may be masked by poor functional status from joint disease or chronic inflammation^[3].

CASE SUMMARIES

Case 1

A 67 year old female presented in June 2018 with cough with minimal whitish mucopurulent expectoration and progressive shortness of breath (mMRC-3) for 6 months. She also complained of pain in the small joints of her hands and lower back pain. On examination she had pallor, was dyspneic, afebrile. No cyanosis, jaundice and clubbing. No palpable lymph nodes and room air saturation was 89%. On auscultation she had fine inspiratory velcro crackles in infrascapular and infra-axillary areas. Chest X Ray (PA view) revealed reticular opacities. There was elevated ESR, low Hb, normal TLC and Platelets. Her C-RP was raised and RA factor was positive along with an elevated level of Anti-CCP antibodies (14U/ml). An HRCT of Chest confirmed features like interlobular septal thickening, subpleural, basal predominant, reticular abnormalities with honeycombing, and traction bronchiectasis with a relative absence of ground-glass opacities. Interstitial Lung Disease of Usual Interstitial Pneumonia pattern was confirmed.

Fig.1 HRCT Chest shows interlobular septal thickening, subpleural, basal predominant, reticular abnormalities with honeycombing, and traction bronchiectasis.

Case 2

A 50 year old female presented to our OPD in June 2019 with complaints of cough with copious amounts of mucoid expectoration, occasionally blood tinged and shortness of breath (mMRC-2) for the past 4 months. Sputum production had postural variation. She also complained of fever for 2 weeks. No complaints of weight loss or loss of appetite. Her complaints also included morning stiffness and photophobia. She had no past H/O ATT or contact exposure or dust allergy. 15 years back, she was diagnosed with Rheumatoid Arthritis by a physician and was started on Tab.Sulfasalazine (1000mg) ever since. On examination she was pale, febrile and poorly nourished. Room air saturation was 96%. On auscultation, there were coarse crackles that were heard bilaterally. Her recent blood investigations revealed an elevated ESR, CRP (12mg/L) and RA factor +ve (32 IU/ml). HRCT of Chest showed cystic bronchiectasis in B/L Lower lung fields. Her Sputum C/S showed Klebsiella sp. and was started on Inj.Ceftriaxone, Tab.Azithromycin (500mg) along with other bronchodilators. The patient was discharged after 7 days of admission and is on regular follow up.

Fig.2 HRCT Chest shows bronchiectasis Left>Right

Case 3

A 60 year old male who complained of pain in the knees and wrist joints for the past 3 months was referred from the Orthopedics Department to us in September 2018 with complaints of dry cough and right sided chest pain for the past 1 month. There was no loss of weight or appetite. He was a chronic smoker. He had no H/O past ATT or contact exposure or dust allergies and seasonal variation of respiratory symptoms. On examination, there was no pallor, cyanosis or jaundice. On auscultation there were absent breath sounds in the Right Inter and Infrascapular regions along with decreased vocal resonance. His blood

tests which were advised from the afore mentioned department revealed that he was a patient of rheumatoid arthritis with elevated Anti-CCP, C-RP and ESR along with positivity for RA factor. On examination he had clubbing (grade-I). A Chest X Ray and HRCT Chest showed right sided pleural moderate effusion. The pleural fluid was tapped and sent for analysis which showed an exudative neutrophilic effusion with low glucose content, elevated LDH. Malignant cytology was negative. AFB stain, Gram Stain and Culture Sensitivity of pleural fluid was not significant. He was referred back to the Orthopedic Dept. to start DMARD's.

Fig.3 HRCT Chest shows Right sided pleural effusion

Case 4

A 75 year old female had presented to our Chest OPD in October 2018 with complaints of severe progressive shortness of breath (mMRC-4) for the past 3 months along with cough with scanty amount of expectoration. She also complained of chest pain and palpitation. She had no previous H/O ATT or contact exposure/dust allergy/seasonal variation of symptoms. She was a known case of Rheumatoid Arthritis for the past 20 years. She was frail and her room air saturation was 75%. On examination, she had pallor, clubbing (grade-2), was dyspneic and tachypneic. Her hands were deformed. On auscultation, she had basal fine crepts. Her ABG revealed hypoxemia but no hypercarbia. A 2D Echo showed severe pulmonary hypertension with a PASP of 45mm Hg. HRCT of chest showed subpleural linear strands with inter lobular septal thickening with areas of traction bronchiectasis with fibrotic strands distributed throughout the lungs. Pulmonary artery was dilated, diffuse GGO's and B/L pleural thickening. She was started on Tab. Sildenafil (20mg) thrice daily and was advised Long term oxygen therapy for 2-4L/min for 15 hours a day at home post-discharge.

Fig.4 HRCT Chest shows subpleural linear strands with inter lobular septal thickening with areas of traction bronchiectasis with fibrotic strands distributed throughout the lungs. Pulmonary artery was dilated, diffuse GGO's and B/L pleural thickening

Case 5

A 65 year old female presented in March 2019 with cough with whitish mucoid expectoration along with drowsiness and shortness of breath (mMRC-4), loss of weight and appetite for 1 month. She also had high grade fever for the past 10 days. She also complained of pain the lower back and wrist joints. She was a known patient of Diabetes Mellitus and Rheumatoid Arthritis and was on Methotrexate and Prednisolone along with oral hypoglycemics for the past 10 years. She had no H/O past ATT or contact exposure. On examination, she had Pallor, febrile (Temp-101 F), dyspneic and tachycardic, room air saturation of 85%. On auscultation she had velcro crackles that were heard in the basal regions. Blood reports showed Hb-7.9gm%, TC-12,000/cu.mm, ESR 110mm (1hr). Chest X Ray showed reticular opacities in LZ and a cavity in the left UZ which was confirmed by HRCT Chest which showed pulmonary fibrosis with subpleural involvement and a large cavity. Sputum for AFB detected 1+ and CBNAAT confirmed no resistance. She was started on Anti-Tubercular drugs.

DISCUSSION

This case series demonstrates the different pleuro-pulmonary disease

associated with RA and escalating management approaches, as well as the morbidity and mortality associated with this process. It is difficult to be certain about the proportion of patients with RA in whom pulmonary manifestations develop as many patients may be asymptomatic or never undergo relevant investigations. A key observation on recent data suggest the incidence of RA associated lung disease is on the rise^[4] and represents a major cause of morbidity and mortality in these patients^[5,6].

The presence of a pleural effusion in a patient with RA should prompt diagnostic investigation, with ultrasound guided thoracentesis being the first-line test. Pleural fluid in RA is usually exudative, non-odorous, and often turbid with a low pH 7.3 and glucose level (50 mg/dL or 2.8 mmol/L), whereas more longstanding effusions may become chyliform^[7,8].

Meta-analysis of observational studies noted a dose-dependent, increased risk of serious infections in patients with rheumatoid arthritis being treated with glucocorticoids^[9]. TNF- α is involved in the host defence against invasions of viruses and bacteria. Particularly, mycobacterial disease has been highly associated with anti-TNF therapy^[10, 11]. A retrospective study found a high incidence of active tuberculosis soon after starting therapy with infliximab (median time 12 weeks) leading to the recommendation that patients started on anti-TNF therapy should be screened for latent tuberculosis infection^[12].

Obliterative bronchiolitis is more common in females and those with positive rheumatoid factor. It may also occur in the setting of certain medications including penicillamine and sulfasalazine. In contrast to other rheumatoid lung manifestations, obliterative bronchiolitis presents acutely with rapidly progressive dyspnoea, cough and bronchorrhea in the absence of other systemic symptoms^[13]. HRCT findings are nonspecific, but may show centrilobular emphysema, bronchiectasis, bronchial wall thickening or mosaic attenuation. However, the overall prognosis is poor^[14]. Macrolide antibiotics in particular may also be effective^[13,16]. Bronchiectasis has been demonstrated on HRCT in ~30% of cases of rheumatoid arthritis, although it may be clinically silent^[17,18]. Bronchiectasis may precede or follow the development of rheumatoid arthritis^[19].

Both rheumatoid factor and anti-CCP have been linked to the development of ILD, particularly when present in high titres^[20]. In patients with known rheumatoid arthritis, and in the absence of clinical suspicion for infection and/or other respiratory complications, HRCT may be used to make a diagnosis of interstitial pneumonia. A variety of patterns are seen on HRCT scans in rheumatoid arthritis, with the most common being usual interstitial pneumonia (UIP), which occurs in 40–62% of cases^[21, 22]. Pulmonary hypertension occurs usually within the context of interstitial lung disease, but cases of isolated pulmonary hypertension due to vasculopathy have also been reported^[23]. Chronic inflammation reduces patient's functional capacity and conceals early symptoms of cardiovascular disease and pulmonary hypertension.

Fig.5 HRCT Chest shows showed pulmonary fibrosis with subpleural involvement and a large cavity in the Left upper lobe.

CONCLUSION

Pulmonary involvement is common among patients with long standing rheumatoid arthritis and has a variety of manifestations, with ILD, pleural disease and pulmonary drug toxicity being the most common. Mechanisms of lung injury have been attributed to genetics, environmental exposure and medications. Pulmonary disease may precede the development of other rheumatoid arthritis manifestations, such as articular involvement, but patients with pulmonary disease may also be asymptomatic. Overall, morbidity and mortality from rheumatoid arthritis associated-lung disease are high. To date, there are no prospective randomised clinical trials for RA-ILD and, thus, treatment for RA-ILD is essentially immune-modulating agents that

are used for rheumatoid arthritis in general. Patients should be counseled on the increased risk of further complications and failure for any therapeutic intervention, whereas clinicians should consider what long-term options are available in case initial management is unsuccessful.

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