

Cardio-pulmonary manifestations of rheumatoid arthritis among rheumatology patients of a tertiary hospital

Oguntona SA, Olatunde OA, Bakare OB

Department of Medicine,
Olabisi Onabanjo University
Teaching Hospital, Sagamu,
Ogun State, Nigeria

Corresponding author:
Dr. A.S. Oguntona,
Department of Medicine,
Olabisi Onabanjo University/
Teaching Hospital, Ogun
State, Nigeria. Email:
oguntonasa@yahoo.com

Abstract

Background: Rheumatoid arthritis is a chronic systemic inflammatory disease, characterized by polyarthritis and extra-articular manifestations. The cardio-pulmonary manifestations of rheumatoid arthritis were studied retrospectively in a cohort of rheumatoid arthritis patients.

Methods: This was a retrospective study of all cases of rheumatoid arthritis seen during the period of January 2011 to December 2013. Case notes of patients that fulfilled the 1987 American College of Rheumatology Criteria for rheumatoid arthritis were retrieved. Data was retrieved from the case notes and analyzed. The case records of patients with pulmonary and cardiac manifestations of rheumatoid arthritis were further studied.

Results: Four hundred and seventy two rheumatology cases were seen; twenty one fulfilled the 1987 American College of Rheumatology Criteria for rheumatoid arthritis. Out of the twenty one cases of rheumatoid arthritis identified, eight cases developed cardio-pulmonary manifestations of rheumatoid arthritis, predominantly serositis. The onset of cardio-pulmonary features was independent of the disease stage. Among patients with cardio-pulmonary manifestations of rheumatoid arthritis, three people died of heart disease while one died of pulmonary complication, representing 50% mortality.

Conclusion: Pulmonary manifestation as represented by pleural effusion was the leading cardio-pulmonary manifestation among the patients studied. Cardiac disease was however the leading cause of mortality. We therefore conclude that cardio-pulmonary manifestation is associated with increased mortality among rheumatoid arthritis patients.

Key words: Cardiopulmonary, Involvement, Hospital, Rheumatoid disease

Introduction

Rheumatoid arthritis is a chronic inflammatory, multisystemic disease

with extra-articular involvement. It has a prevalence of about 1% in most populations¹. The extra-articular manifestations include rheumatoid nodule, cardio-pulmonary disease, neuropathy, ophthalmic manifestations, vasculitis, Felty's syndrome, and amyloidosis². Extra-articular manifestations of rheumatoid arthritis are associated with increased morbidity and mortality. It occurs in 19.8-40.9% of rheumatoid arthritis patients and about 1.5-21.6% of them present as severe forms³. The extra-articular manifestations of rheumatoid arthritis can develop at any time during the course of the disease, even in the early stages³. Factors that have been associated with the development of extra-articular features include, significant positive rheumatoid factor, long-standing severe disease, and smoking³.

Cardio-pulmonary manifestation has been associated with patients with rheumatoid nodule, especially in those patients that develop rheumatoid nodule within two years from the diagnosis of rheumatoid arthritis⁴.

Lung disease is a major contributor to morbidity and mortality. In some cases, respiratory symptoms may precede articular symptoms. Lung involvement could be a direct complication of rheumatoid arthritis or from the immune modulation therapy. The pulmonary manifestations include interstitial lung disease, pleural thickening and effusion, vasculitis and pulmonary hypertension⁵. Prognosis varies depending on the type and severity of involvement⁵. Interstitial lung disease is second only to cardiac disease as a cause of mortality in rheumatoid arthritis⁶.

Based on a review of mortality by Olson *et al*⁷ in the USA from 1988 to 2004, it was found that interstitial lung disease contributed to death in 6.8% of females and 9.8% of males with rheumatoid arthritis. The mean survival for rheumatoid arthritis interstitial lung

disease has been estimated at 2.6 years from time of diagnosis⁸.

Cardiac manifestations of rheumatoid arthritis include pericarditis, cardiomyopathy, myocarditis, coronary vasculitis, arrhythmias and congestive cardiac failure. Majority of rheumatoid arthritis mortality originate from cardiovascular disease⁹. A recent meta-analysis indicated that the risk of cardiovascular disease-associated death could be as much as 50% higher among patients with rheumatoid arthritis compared to controls¹⁰. Several recent studies however suggest a lower frequency of cardio-pulmonary involvement probably due to a better control of disease activity^{11,12}.

Diagnosis of cardio-pulmonary manifestations of rheumatoid arthritis is a challenge, given its variable presentations, the diagnosis is based on clinical recognition and exclusion of other causes of such signs and symptoms¹³⁻¹⁵.

There was no prior study of extra-articular manifestations of rheumatoid arthritis in the country. This study therefore aimed to retrospectively examine the clinical presentations of cardio-pulmonary involvement among the patients with rheumatoid arthritis in our tertiary hospital rheumatology clinic.

Materials and Methods

Cases were the patients seen at the Olabisi Onabanjo University Teaching Hospital, Ogun State, South West of Nigeria. The medical outpatient records and the in-patients records were studied to determine patients that were diagnosed and treated for rheumatoid arthritis. The case notes of such patients were retrieved from the medical records and studied. Patients with cardio-pulmonary involvement were further studied.

The study was carried out over a three year period from January 2011 to December 2013. Excluded from the study were patients with inconclusive diagnosis, juvenile idiopathic arthritis and unclassified arthritis. Those patients that fulfilled the 1987 American College of Rheumatology Criteria for rheumatoid arthritis were therefore included in the study. The duration of rheumatoid arthritis before the onset of cardiopulmonary manifestation was noted for each patient. Other extra-articular manifestations of rheumatoid arthritis were noted. Simple statistical analysis was used to calculate the percentages.

The affected patients were offered the standard treatment for rheumatoid arthritis at the point of contact in the teaching hospital. They were all placed on the triple therapy consisting of methotrexate, hydroxychloroquine and sulphasalazine, and where necessary, non-steroidal anti-inflammatory agents. Those with cardio-pulmonary complications were offered further therapies as indicated.

The socio-demographic characteristics of the patients were documented (age, sex, marital status and the occupation). The identity of the patients was concealed. Ethical clearance was obtained for this retrospective study from the ethical committee of the hospital.

Case definition

Rheumatoid Arthritis (RA): RA was defined according to the classification criteria of the American College of Rheumatology 1987. A person is said to have RA if he/she has four out of the seven criteria, and the symptoms have been persistent for at least six weeks¹⁶. The classification criteria are:

- (i) Early morning joint stiffness duration longer than one hour
- (ii) Polyarthritis – arthritis affecting three or more joints simultaneously
- (iii) Arthritis affecting joints of the hands (proximal inter-phalangeal joint, metacarpo-phalangeal joint, wrist)
- (iv) Symmetrical arthritis
- (v) Subcutaneous nodules
- (vi) Positive rheumatoid factor
- (vii) Radiological changes of peri-articular osteopenia or erosion.

Criteria for inclusion in the cardio-pulmonary manifestations

Fulfillment of the 1987 American College of Rheumatology Criteria for rheumatoid arthritis and any of the following;

- (i) *Pericarditis*: Clinical suspicion and detection of effusion by echocardiogram.
- (ii) *Arrhythmia*: Clinically detected and confirmation by electrocardiogram.
- (iii) *Congestive cardiac failure*: Clinically detected and supported by chest radiograph and echocardiograph.
- (iv) *Pleural effusion*: Clinical suspicion and detection by chest-X-ray
- (v) *Pulmonary nodule*: Detection by plain chest-X-ray
- (vi) *Pulmonary fibrosis*: Clinical suspicion and detection by plain chest radiograph.

Laboratory and radiological investigations

All the patients had rheumatoid factor, erythrocyte sedimentation rate and full blood count done. Plain radiograph of the hands and feet were done where necessary. Electrocardiography and echocardiography were carried out as necessitated by the clinical condition. Chest –X- ray was done in all patients with symptoms referable to the lung and the heart. Pulmonary function was ordered when necessary.

Results

Twenty eight cases were identified but seven were excluded as the diagnosis was polyarticular inflammatory

disease without a conclusive diagnosis of rheumatoid arthritis. Twenty one patients fulfilled the 1987 American College of Rheumatology Criteria for rheumatoid arthritis over the study period.

Eight (38%) patients fulfilled the inclusion criteria for cardio-pulmonary manifestations of rheumatoid arthritis, there were three males (37.5%) and five females (62.5%). Table 1 shows the socio-demographic characteristics of the patients with cardio-pulmonary manifestations of rheumatoid arthritis. Serositis and arrhythmia were the leading manifestations.

Table 1: Socio-demographic characteristics of the patients with cardio-pulmonary rheumatoid arthritis

Demography	No.	(%)
Age (years)		
18-24	1	12.5
25-34	2	25
35-44	3	37.5
45-54	2	25
55 and above	-	-
Sex		
Male	3	37.5
Female	5	62.5
Occupation		
Student	1	12.5
Artisan	2	25
Civil servant	4	50
Professional	1	12.5

Table 2 shows the cardio-pulmonary manifestations detected in the patients. Three people developed the manifestations after eight years of diagnosis of rheumatoid arthritis, two people developed symptoms about four years of diagnosis, while three others were not very sure of the time but ranges between three to six years. Table 3 shows the extra-articular manifestations of rheumatoid arthritis among patients seen in the rheumatology clinic.

Table 2: Cardio-pulmonary manifestations of rheumatoid arthritis encountered in our patients

Cases	Female	Male	Total
Pericardial effusion	2	1	3
Atrial fibrillation	3	1	4
Ventricular ectopic	0	1	1
Congestive cardiac failure	3	2	5
Pleural effusion	6	2	8
Pulmonary nodule	0	1	1
Pulmonary fibrosis	2	1	3

Table 3: Extra-articular manifestations of rheumatoid arthritis among patients seen in the rheumatology clinic.

Affected tissue/organ	Extra-articular manifestation
General symptoms	Weight loss Fever Early morning stiffness Fatigue Generalized muscle weakness Depression
Skin	Rheumatoid nodule Cutaneous vasculitis Raynaud's phenomenon
Eyes	Keratoconjunctivitis sicca Scleritis Episcleritis
Pulmonary system	Pulmonary nodule Pleural effusion Pulmonary fibrosis
Cardiovascular system	Pericardial effusion Atrial fibrillation Ventricular ectopics Congestive cardiac failure
Nervous system	Mononeuritis multiplex Sensory neuropathy Cervical myelopathy
Renal system	Analgesic nephropathy
Haematology system	Anaemia Felty's syndrome

Laboratory and radiology results: Erythrocyte sedimentation rate was elevated in all the patients, rheumatoid factor was significantly positive in all the patients, and all of them also had sub-cutaneous nodules. Chest-X-ray revealed pleural effusion in two males and six females, while five patients had cardiomegaly and features suggestive of heart failure. Plain radiograph also showed pulmonary nodule in one patient, while one male and two females had pulmonary fibrosis. Pulmonary function test showed restrictive pattern in patients with pulmonary fibrosis. Cardiovascular work-up with electrocardiography showed atrial fibrillation in four patients, while one had ventricular ectopics. Echocardiography showed a male and two females with pericardial effusion.

Mortality and morbidity: Four patients out of the eight patients with cardio-pulmonary manifestations are still being followed up in the clinic. Mortality was higher in men than women. A male (33.3%) died of pulmonary fibrosis, while two males and a female (60%) died of heart failure. Three males and a female died with a male to female mortality of 37% versus 12.5%.

Discussion

Rheumatoid arthritis is characterized by extra-articular manifestations. Many different tissues and organs can be involved in addition to the characteristic peripheral polyarthritis¹⁷. The extra-articular manifestation has a significant impact on mortality and morbidity. Availability of more efficacious drugs has led to a better control of disease activity and therefore a lower frequency of extra-articular manifestations of rheumatoid arthritis¹⁸.

Eight of our patients developed cardio-pulmonary manifestations of rheumatoid arthritis out of a total of twenty-one patients diagnosed of rheumatoid arthritis over a three year period. Pulmonary manifestation was the leading of the systems as manifested by radiological finding of pleural effusion. Women were three times more affected than men. This is however not surprising because women were predominantly affected in our cohort, and this follows the trend as reported by earlier studies¹⁹.

Pleural effusion was the leading pulmonary manifestation. The pleural effusion in our patients was not detected clinically but was detected on chest radiograph when being investigated for breathlessness and cough. Mantoux and plain chest X-ray were able to rule out infective causes of pleural effusion like tuberculosis. Chest X-ray was also able to rule out lung malignancy. Pleural effusion however has been reported in the literature to be more common than pericardial effusion in patients with rheumatoid arthritis²⁰.

Three patients had complication of pulmonary fibrosis. Our patients with pulmonary fibrosis presented with progressive breathlessness and cough. Lake and Proudman²¹ however documented that the presentation of pulmonary fibrosis in rheumatoid arthritis is similar to that of idiopathic pulmonary fibrosis, but response to immunosuppressive is usually better. Pulmonary fibrosis in our patients was detected clinically and further confirmed by pulmonary function test. The investigation of choice is however High Resolution Computerized Tomography (HRCT)^{22,23} but this was not available at our centre. A study of pulmonary function in rheumatoid arthritis patients in Nairobi by Biomdo *et al*²⁴ among 166 rheumatoid arthritis patients found a prevalence abnormality of 38.5%. Obstructive ventilatory (20.4%) abnormality was the leading abnormality, followed by restrictive pattern (16.8%) and least was the mixed pattern (1.2%). Age and rheumatoid arthritis disease activity were the independent factors associated with pulmonary function abnormalities²⁴. The single male with pulmonary fibrosis died while the females are still being followed up in the clinic.

Four of our patients presented with atrial fibrillation, while one presented with ventricular ectopic. Arrhythmia is an important cause of mortality in rheumatoid arthritis and may be secondary to ischaemia, conduction abnormality due to rheumatoid nodule, amyloidosis or

congestive cardiac failure²⁵. It has been shown that QT-dispersion and corrected QT- dispersion intervals were significantly longer in rheumatoid arthritis compared with healthy controls, and it was suggested that QT- dispersion may be a useful marker of cardiovascular morbidity and mortality in rheumatoid arthritis²⁶.

Congestive cardiac failure was the leading cardiac complication of rheumatoid arthritis in this study. Five individuals had congestive cardiac failure comprising two males and three females. Two males and a female died of congestive cardiac failure with a male to female mortality ratio of 2 to 1. This study has shown an excess of cardiovascular mortality among males over females. An earlier study however documented that the excess mortality associated with extra-articular manifestations is greater in men than in women²⁷.

The pericardial effusion found in our patients was generally asymptomatic because of its small volume. It was detected by echocardiography while investigating them for heart failure. Ibrahim-Sayo *et al*²⁷ in a study of patients with rheumatoid arthritis at the Kenyatta National Hospital found cardiac abnormalities echocardiographic prevalence of 62.5%. Pericardial effusion was the leading cardiac lesion (39.4%). Tricuspid valve was affected commonly with 15.4% of patients presented with tricuspid regurgitation. Pulmonary hypertension was found in 5.5% of patients²⁸.

Three of our patients died of cardiovascular disease while one died of pulmonary disease. This study has shown an excess of cardiovascular mortality over the pulmonary disease. Several studies have shown that cardiovascular disease account for the major part of excess mortality in rheumatoid arthritis²⁹. People with other extra-articular manifestations of rheumatoid arthritis tend to have higher cardiovascular co-morbidity such as congestive cardiac failure and arrhythmias than people without extra-articular manifestations of rheumatoid arthritis. A study in people with severe rheumatoid vasculitis demonstrated a more frequent cardiovascular co-morbidity than rheumatoid arthritis patients without vasculitis²⁹. The excess of cardiovascular death in our patients also confirmed the findings from earlier studies.

Five of our patients developed congestive cardiac failure and three eventually died from the disease. Earlier studies have shown that patients with rheumatoid arthritis are at significantly higher risk for congestive cardiac failure³⁰. The risk in them cannot however be explained by any increase incidence of traditional cardiovascular risk factors^{31,32}. It has been shown that rheumatoid arthritis is associated with increased left ventricular mass which is independently related to disease duration, while the systolic function is typically preserved³². Congestive cardiac failure presentation may be subtle but mortality from the complication is significantly more than non-rheumatoid arthritis patients³¹.

One of our patients died at the age of 33 years, while the other ones died at age 34, 37 and 40 years. Early mortality was observed in our patients with cardio-pulmonary involvement as compared with other rheumatoid arthritis without cardio-pulmonary disease. Earlier studies have claimed that there is a relative concentration of risk for cardiovascular events in younger rheumatoid arthritis patients, therefore higher mortality in younger individuals with rheumatoid arthritis^{4,34}.

Extra-articular complication in rheumatoid arthritis is associated with delayed diagnosis, delayed institution of appropriate anti-rheumatic drugs, and inappropriate dosage of the medications³⁵. All the patients were already on prednisolone as at the point of visit to our hospital, three patients were on methotrexate, prescribed by the referring doctor. None of the patients was on the triple disease modifying anti-rheumatic drugs that we normally prescribe for rheumatoid arthritis patients.

The limitations of this study include small number of rheumatoid arthritis patients probably due to low awareness. Being a retrospective study, there is a likelihood of missing information. Inability to perform pleural fluid analysis is also a limitation to this study.

Conclusion

Cardiac and pulmonary involvements in rheumatoid arthritis are associated with increased mortality. The clinician must therefore be familiar with the clinical presentations of extra-articular involvement of rheumatoid arthritis and its management.

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Conflict of interest: The authors declare that there was no conflict of interest.

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