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Non-communicable diseases (NCDs) are predicted to become leading causes of morbidity and mortality in developing countries including sub-Saharan Africa\(^1\). This region has a particularly high double burden of both communicable and NCDs and the least resources to submit an effective challenge. It is bad enough that WHO estimates suggest that age-specific death rates from non-communicable diseases are not only higher in sub-Saharan Africa (sSA) than in high-income countries and overall match the death rates for infectious diseases but this statistic takes no account of the morbidity imposed by these largely chronic disorders. Fostering political will to address this approaching pandemic is essential and the collection of quality data is the tool needed to open the door of opportunity to allow the resource stream to flow where most needed. Competition for sometimes meagre resources will be fierce. If musculoskeletal conditions (MSC) are not to be left to drown in the wake of a surge to cardiovascular disease diabetic and cancer etc. a start must be made now to build on existing data and gather data where none exists. While there is in general a lack of good quality epidemiological data on chronic NCD burden in sub-Saharan Africa the dearth of robust data on MSC/rheumatological conditions is of particular concern. What meagre data there is however points towards MSC at community level matching the morbidity associated with for example cardio-respiratory conditions. In a recent study from Burkino Faso, 16.2% and 24% respectively of the study population suffered joint pain and backache compared with 17% angina and 11% asthma\(^4\). Evidence from secondary care sources shows rheumatoid arthritis and systemic lupus erythematosus to be increasing in frequency in the indigenous populations of East, Central and Southern Africa. Gout is now more prevalent than ever throughout the subcontinent. HIV has spawned a variety of previously rare spondyloarthropathies (reactive arthritis, psoriatic arthritis, enthesopathy) and changed the epidemiology of pyomyositis and osteomyelitis. Osteoarthritis is a universal problem. Juvenile chronic arthritis is not rare and rheumatic fever is common. Acute and chronic locomotor problems associated with diverse entities such as leprosy, brucellosis, meningococcus, alpha viruses, parasites, fluorosis, rickets and haemoglobinopathies enhance diagnostic diversity and therapeutic and educational requirements\(^5\).

The challenge posed by this burden of rheumatic disorders in sSA is enormous. The near absence of a rheumatology presence in most countries of the sSA region is a major disadvantage and progress has been erratic to say the least. However where a rheumatology presence is established work towards an improved health system can begin. It is crucial to acquire the data required to formulate policies, practices and funding\(^6\). The difficulty is getting started and while there is no standard recipe, crucial to the whole enterprise is the presence of an individual(s) who will, come what may, create the scenario to allow the discipline of musculoskeletal medicine to flourish. A case in point is Kenya.

In February 2000 at the invitation of the Kenya Association of Physicians, a medical nursing team from South Africa and Scotland conducted a series of postgraduate medical and nursing lectures and seminars at the Kenyatta National Hospital and various other hospitals in Nairobi. At that time no formal rheumatology service existed in Kenya and our presence reflected a perceived need and a desire among physicians to see a basic service and teaching capacity established. A major objective of this exercise was to stimulate interest in the speciality and highlight the benefits of a specialist rheumatology workforce in the detection and management of musculoskeletal disorders. The first stage, of necessity, required a trained and experienced individual to take the helm and develop a service to match the then high standard of the other medical services in Kenya. Dr. Omondi Oyoo who organised this inaugural course progressed to establish a fledgling rheumatology service and for the past decade he has been remorseless in his endeavours to develop and expand this service nationally for the benefit of Kenyan citizens.

He brought the AFLAR congress to Nairobi in 2008 and is using his voice as the current President of AFLAR to direct the attention of the rheumatology world to the problems in the developing world and in particular Africa. His ambition is to establish in Nairobi a centre of rheumatological excellence and so over the past decade a steady stream of rheumatologists from the UK, Canada and the USA have been persuaded to give of their time and expertise to help fulfil this dream. A cadre of young Kenyan physicians are now increasingly attracted to the discipline and if current progress continues there is surely cause for optimism. Other activities vigorously pursued include increasing public awareness by education and research and extending professional training through CME, incorporate rheumatology in the medical school curriculum and develop an outreach programme to take to regional and district hospitals. In March 2012 a team led by Professor Anthony Woolf (UK), took a group of eight regional consultant physicians through a comprehensive musculoskeletal training programme specifically designed to enable them to teach basic musculoskeletal skills and awareness issues to health workers in their respective health district. In July 2012 a Copcord (Community Oriented Programme for the Control of Rheumatic Diseases) ILAR study commenced in Nairobi and its environs supervised by Dr. Etu Ekwom. This is the first Copcord study conducted in sub Saharan Africa.
Elsewhere, outwith South Africa, evidence of sustained progress has yet to materialise. However this year saw the launching of the Rheumatic Diseases Association of Zambia at a ceremony in Lusaka preceded by a two day CME course attended by a large assembly of doctors nurses and physiotherapists both local and regional. ILAR funding has enabled the paediatric and adult rheumatology services at the University Hospital Lusaka to commence the acquisition of data essential to designing appropriate future service requirements and direct resource acquisition. The next planned activity is to extend CME activity to the regional centres along the lines of the above “Train The Trainer” programme.

So more than a decade down the road where are we? Well the publication of this first edition of *African Journal of Rheumatology* says it all, a long way forward but a long road to go.

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References


Pulmonary manifestations of rheumatoid arthritis: a review

Biomdo IC, Oyoo GO

Abstract

Background: Pulmonary involvement is a frequent and among the most severe extra-articular manifestations of rheumatoid arthritis. Rheumatoid arthritis can affect the lung parenchyma, airways and pleura. Pulmonary complications are directly responsible for 10-20% of all mortality in RA patients. Objective: To highlight the common and important manifestations of rheumatoid lung disease and discuss the recent studies on each.

Data source: Articles on rheumatoid lung disease, reviews done in the American Thoracic Society and European Respiratory Society, Medscape and Upto date Version 19.3.

Data extraction: This was done over a period of 6 months from November 2011 to April 2012.

Conclusion: A thorough history and examination for pulmonary symptoms and signs should be performed in all RA patients. When abnormalities are found, further investigations are likely to be required to define the process. Lung function tests can be used as the baseline tests to detect those who will need more expensive and/or invasive investigations such as HRCT, bronchoscopy with bronchoalveolar lavage, and transbronchial or surgical lung biopsy, when indicated.

Key words: Rheumatoid arthritis, Lung diseases, Interstitial, Bronchiolitis

Introduction

Rheumatoid arthritis (RA) is the most commonly encountered connective tissue disease. It is a chronic inflammatory and systemic disease which mostly affects the synovial joints with a prevalence ranging from 0.5% to 2%. It is a progressive autoimmune process characterized by symmetrical erosive synovitis. Although the central pathology of RA develops within the synovium of diarthrodial joints, many nonarticular organs become involved, particularly in patients with severe joint disease. The female to male ratio of RA is 2.5:1 most frequently seen in the 25-55 year age group.

The prevalence of widely disseminated lesions in other regions of the body has been highlighted with clinical observation and studies, thus pointing out the systemic nature of the disease. The strongest predictors of premature mortality appear to be the presence of RA-related complications and associated co morbidities, specifically, cardiovascular disease and pulmonary disease.

In recent cohort studies, nearly 40% of patients with RA suffered from some type of extra-articular manifestations. Pulmonary involvement is a frequent and among the most severe extra-articular manifestation of RA. It is a leading cause of excess death in patients with RA and might be the second cause of death in this patient population. RA pulmonary complications are directly responsible for 10 to 20% of all mortality. When compared with control populations, patients with RA and with a respiratory disease have an estimated standardized mortality ratio that ranges from 2.5 to 5.0. The majority of lung disease occurs within the first 5 years after the initial diagnosis, and may be a presenting manifestation in 9 to 20% of patients. The onset of respiratory manifestation may even precede the onset of symptoms of arthritis.

Lung disease directly associated with the underlying RA is more common, even though pulmonary infection and drug toxicity are frequent complications of RA. The lung is involved in rheumatoid disease because of the abundant vasculature and connective tissue which is involved in collagen vascular diseases. RA can affect the lung parenchyma, airways,
and the pleura, with variable amounts of pathological inflammation and fibrosis. The prevalence of a particular complication varies based on: The characteristics of the population studied, the definition of lung disease used and the sensitivity of the clinical investigations employed. However, all studies concur in that a high prevalence of abnormality can be found. Furthermore, while the prevalence of other serious extra-articular manifestations is declining, RA-associated lung disease is increasing and both pulmonary infection and drug-induced lung disease included.

Pleurapulmonary manifestations of rheumatoid arthritis can be considered under seven categories:

1. Pleural disease
2. Parenchymal involvement
   • Interstitial lung disease
   • Rheumatoid nodules
   • Caplans syndrome (rheumatoid pneumoconiosis)
3. Pulmonary airway involvement
   • Cricoarytenoid arthritis
   • Bronchiolitis
   • Bronchiectasis
4. Infections
5. Drug induced disease
6. Thoracic cage abnormality
7. Vascular involvement

(1) Pleural disease:
Pleural involvement is a common, subclinical entity in RA patients. The annual incidence of rheumatoid pleural effusion in the RA population is 0.34% in women and 1.54% in men. The estimated prevalence of pleural effusion in the RA population is 0.34% in RA patients. The annual incidence of rheumatoid pleuritis can be considered under seven categories:

1. Pleural disease
2. Parenchymal involvement
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   • Caplans syndrome (rheumatoid pneumoconiosis)
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   • Bronchiolitis
   • Bronchiectasis
4. Infections
5. Drug induced disease
6. Thoracic cage abnormality
7. Vascular involvement

2. Parenchymal involvement

2.1 Interstitial lung disease: Interstitial lung disease (ILD) is a frequent manifestation of rheumatoid lung disease and a significant cause of morbidity and mortality in the RA patient population, often asymptomatic. Estimates of the prevalence of interstitial lung disease (ILD) in RA range between 19% and 44%. The reported prevalence of ILD in RA patients is highly variable and depends on the methods of detection e.g. high-resolution CT [HRCT] scan, chest radiograph, or pulmonary function testing and the population selected for study i.e. symptomatic or asymptomatic, autopsy series.

Through chest radiography, the diagnosis of rheumatoid lung disease is made in 1% - 5% of RA patients. In most cases it may be normal albeit presence of disease. The estimated prevalence of RA-ILD using HRCT is 20–44% and is a highly sensitive modality to use although expensive investigation in resource limited centres. It has been shown that 40% of patients may have restrictive abnormalities when pulmonary function tests (PFTS) - Spirometry and reduction in CO diffusion capacity (DLCO) when used as diagnostic measures. Asymptomatic ILD often precedes the articular manifestations of RA by months or years. ILD typically becomes symptomatic late in its course when fibrosis is present. Presentation is more common at 50 to 60 years of age, in men, and in association with seropositive and erosive joint disease.

Pathogenesis: Clinical, genetic, and environmental factors have been used to predict the development of lung disease in RA. In contrast to most connective tissue diseases, RA-ILD is three times more common in males than in females, in individuals with late-onset disease, high titre rheumatoid factor and in smokers. High-titre rheumatoid factor (RF) has been associated with the presence of RA-ILD and decreased diffusion capacity for carbon monoxide (DLCO).

One hypothesis for the development of lung fibrosis in RA is that a cellular inflammatory process is required for and initiates a secondary fibro proliferative process, and that the fibro proliferative process may become progressive and independent of its initiating cause.

A similar paradigm has been hypothesized in patients with hypersensitivity pneumonitis. In these patients, reversible granulomatous inflammation is generally seen. However, once the fibro proliferative process begins, the clinical course and gene expression profile become similar to those of idiopathic interstitial fibrosis (IPF), the prototypical fibrosing lung disease, and the disease becomes unresponsive to immunosuppression.
Pathology: A wide variety of histopathology features have been observed in RA, not only various types of interstitial pneumonia, but also airway diseases with frequent overlap between different patterns of interstitial pneumonia in the same patient, making the pathological diagnosis more complicated

These disorders affect not only the interstitium (space between endothelial and epithelial basement membranes) but also the adjacent airspaces, the peripheral airways, and the vessels. Currently available data show that among RA-ILD patients, there is a higher proportion of a patient with usual interstitial pneumonia (UIP) pattern compared to patients with other connective tissue diseases. Lee et al. found UIP to be the most common histopathology pattern in RA-ILD patients (56%). This was followed by non-specific interstitial pneumonia (NSIP)- (33%) and organizing pneumonia (11%). Flaherty et al. demonstrated that patients with collagen vascular disease-associated UIP pattern had fewer fibroblastic foci and better survival compared to patients with the idiopathic type, which may be related to better prognosis of UIP associated with collagen vascular diseases. RA patients with NSIP tend to be women and nonsmokers. Lymphocytic interstitial pneumonia (LIP) usually occurs when RA is complicated by Sjögren’s syndrome.

Diagnosis: The diagnosis of RA-ILD is generally based on the combination of clinical presentation, pulmonary function testing, HRCT, and in some cases, lung biopsy. A careful exposure history (including occupational, environmental and pharmaceutical) should be conducted to evaluate potential alternative causes.

Pulmonary function tests frequently demonstrate reduced lung volumes and Diffusion Capacity of Carbon monoxide (DLCO) even in the absence of symptoms. Reduced DLCO was suggested to be the most sensitive marker for interstitial pneumonia on HRCT. Progressive dyspnea as measured by a standardized questionnaire is a strong predictor of shortened survival. The declining size of the lung as measured by plain chest radiographic study as well as the extent of disease seen on HRCT are powerful predictors of disease. Serial changes in pulmonary physiology with declines in forced vital capacity can be used both in detection, prediction and follow up tool of disease progression. These changes over time are stronger prognostic markers than baseline measures.

Treatment: In general, more aggressive treatment is justified in patients with evidence of inflammation on HRCT, lymphocytes on bronchoalveolar lavage, or a non-UIP pattern on biopsy. Glucocorticoid therapy is the treatment of choice with variable subjective and objective improvement in the treatment of RA-ILD. Other drugs reported to be beneficial include cyclophosphamide, azathioprine, hydroxychloroquine, D-penicillamine, and cyclosporine. Effective treatment of the joint disease should not be used as a surrogate for beneficial or even adequate treatment of the ILD. Just as clinically important diffuse lung disease can precede the development of active joint disease in RA, progressive ILD can occur despite the absence of synovitis. This strongly argues for continued regular pulmonary follow-up of known lung disease in patients with even excellent control of their joint disease as well as early pulmonary referral when respiratory symptoms develop or progress in patients with RA, regardless of the activity of their joint disease.

Despite the absence of effective treatments for advanced respiratory disease it is possible that therapeutic intervention at an early stage may be beneficial. It has been suggested that early diagnosis and treatment with antifibrotic agents may alter the prognosis of pulmonary fibrosis.

2.2 Rheumatoid nodules

Rheumatoid nodule is considered a benign variant of rheumatoid arthritis and is the only pulmonary manifestation specific for the disease. They are more common in men than in women and are usually asymptomatic unless cavitated. They usually present more of a diagnostic than a therapeutic challenge because malignancy has to be ruled out through biopsy. Rheumatoid lung nodules are detected on chest radiograph in about 0.2% of unselected patients with RA and more frequently on HRCT (4%) in chest radiographs they are usually multiple or solitary, well circumscribed masses ranging from a few millimeters to 7cm in diameter. They are located in sub pleural areas or in association with interlobular septa.

Histologically, the pulmonary nodules are similar to nodules at other sites, with central necrosis, palisading epithelioid cells, a mononuclear cell infiltrate, and associated vasculitis. The clinical course of pulmonary nodules is variable. The nodules may precede the clinical manifestation of RA or be concurrent. They may increase in size, resolve spontaneously, or appear at new sites as older nodules resolve. Complications may include pleural effusion, pneumothorax, hemoptyis and infection.

2.3 Rheumatoid pneumoconiosis (Caplan’s syndrome)

Caplan in 1953, defined rheumatoid pneumoconiosis as characterized by rounded, peripheral pulmonary radiological images, 0.5–5.0cm in diameter, with or without small opacities, consistent with pneumoconiosis or massive pulmonary fibrosis, found in patients with RA who were exposed to mineral, coal, or silica dust. The prevalence of this entity among patients with pneumoconiosis is low. Caplan found a prevalence of 0.4% and, more recently, Honma and Vallyathan showed that the incidence was 0.75% in Japan and 1.5% in the USA. Although the syndrome was originally described in coal miners, several cases have since been diagnosed in individuals exposed to free silica or asbestos.

Histologically, the findings are similar to those with simple rheumatoid nodules, except that the nodules in Caplan’s syndrome are surrounded by pigmented cells. There is no effective treatment for Caplan’s syndrome, but the prognosis is good.

3.0 Pulmonary airway involvement

Rheumatoid arthritis is known to cause both upper and lower airway disease. Cricothyroiditis and bronchiectasis are the major manifestations of large airways involvement. Major manifestations of small airway disease encompass bronchiolitis; follicular bronchiolitis, constrictive bronchiolitis/obliterative bronchiolitis, fibrosing alveolitis and panbronchiolitis.

3.1 Cricoarytenoid arthritis

The cricoarytenoid joints are small diarthrodial joints that rotate with the vocal cords as they abduct and adduct to vary the pitch and tone of the voice. Though not disabling, the cricoarytenoid joint may become inflamed and immobilized with the vocal cords adducted to midline, causing inspiratory stridor and upper airway obstruction. Upper airway involvement is more common in women and in patients with long-standing RA. Jurik and Pedersen\(^4^9\) found arthritis of the cricoarytenoid joint in 55% of 150 patients with RA. The incidence was higher in females (65%) than in males (20%). When HRCT and fiber optic laryngoscopy were used, cricoarytenoid abnormalities were seen in up to 75% of the patients although symptoms were reported in only about half this number \(^4^9\).

3.2 Bronchiolitis

Bronchiolitis is a generic term that encompasses a group of diseases with diverse etiologies. In general, it indicates the presence of inflammation in the small airways, which by definition measure less than 2mm in diameter. These include bronchiolar diseases such as follicular bronchiolitis and constrictive bronchiolitis (also called bronchiolitis obliterans). These diseases are usually seen in patients with positive rheumatoid factor and active joint disease. The symptoms are characterized by dyspnea and nonproductive cough.

Although chest radiograph is generally normal, computed tomography may show areas of air trapping, small nodular opacities in centrilobular distribution (follicular bronchiolitis and bronchiolitis obliterans), patchy areas of low attenuation (bronchiolitis obliterans), and peribronchial thickening (follicular bronchiolitis and bronchiolitis obliterans). Pulmonary function tests reveals airflow obstruction with normal DLco.

Follicular bronchiolitis: In RA, follicular bronchiolitis represents lymphoid hyperplasia in response to an extrinsic immune stimulus or altered systemic immune response, situated in the walls of the bronchioles and, to some extent, in larger bronchi. Although in the past lymphocytic bronchiolitis was thought to be rare and there are only few series and case reports in the literature, Tansey et al\(^5^0\) and Rangel-Moreno et al\(^5^1\) showed that in biopsies from patients with RA, most patients had follicular bronchiolitis as the main pattern of pulmonary disease, or as a finding occurring with another form of RA-associated pulmonary disease.

Constrictive bronchiolitis or obliterative bronchiolitis: Constrictive bronchiolitis (CB) or obliterative bronchiolitis (OB) is a rare, usually fatal, condition characterized by progressive concentric narrowing of membranous bronchioles \(^5^2\). Although Geddes et al\(^5^3\) first reported CB with RA in 1977 only a few years later, it became clear that the disease was related to RA. Patients typically present with the rapid onset of dyspnea and dry cough. The rapidity of onset and severity of symptoms are out of keeping with most other forms of lung disease and should lead to suspicion of the diagnosis. The prognosis and response to therapy are poor. Although no therapy has proven consistently effective, a trial of high dose glucocorticoids (e.g., prednisolone 1–1.5mg/kg per day) is warranted.

The reported prevalence of obstructive dysfunction in small airways in RA patients, estimated on the basis of decreases in FEF 25-75 values, varies among studies, ranging from 8% to 65%. This variation may be explained by the different criteria used in different studies to assess small-airway disease as well as by variation in the patient populations examined. Shunsuke et al\(^5^4\) in Japan obtained evidence suggesting that obstructive dysfunction of small airways is common among 155 RA patients, even among those without a diagnosis of interstitial pneumonia or bronchiolitis pattern on HRCT. Prevalence of obstructive small-airway disease in RA patients without the IP or bronchiolitis HRCT pattern was 30.3%. In Africa, a study done by Amir et al\(^5^5\) on Egyptian patients with rheumatoid arthritis (non smokers) revealed that out of the 36 patients studied 23 (64%) demonstrated abnormalities in PFTs and 47% in HRCT. Mixed restrictive and obstructive pattern was the commonest and reported in nearly 31%. ILD was the commonest pulmonary affection detected by HRCT at 39%.

Pathogenesis: The reason for the high incidence of small-airway obstruction in RA patients remains unclear. One of the most attractive explanations is that the obstructive changes are due to frequent and recurrent infections in the small airways\(^5^3\). Colonization of the small airways by pathogenic microorganisms has been reported in patients with clinically stable bronchiectasis\(^5^5,5^6\) the evidence indicates that RA patients may have an increased susceptibility to airway infections or a reduced ability to eradicate these infections.

Chronic colonization, secondary persistent inflammation, and progressive lung injury may contribute to the frequent development of airway obstruction during the disease course. As an alternative explanation, several stud-
ies have proposed that bronchi/bronchioles are one of the main targets of autoimmunity in RA patients. Bronchiolar inflammation may secondarily induce mucosal edema, which eventually leads to development of small-airway obstruction. Such pulmonary lesions may create a favorable environment for persistent infections. It is uncertain whether microbial colonization may precede bronchiolar obstructive changes or not. Regardless of which came first, a vicious spiral of infections and obstructive changes in the small airways can develop in the lungs of RA patients.

**Diagnosis:** The diagnosis of RA-associated pulmonary disease should be supported by clinical features (signs, symptoms and laboratory tests), abnormal pulmonary function tests, and either a compatible computed tomography or a lung biopsy.

Pulmonary function testing (PFT) has proved valuable in detection of RA-associated lung disease. High resolution computed tomography (HRCT) has been widely used and is highly sensitive for detecting the presence of interstitial lung disease (ILD), with variable incidence of reported abnormalities may reach up to 80% of the patients in some studies.

The precise characterization of obstructive changes in small airways that is enabled by both PFT and HRCT appears to be helpful in evaluating not only their long-term significance as pulmonary complications of RA but also their implication in RA pathogenesis.

**3.3 Brochiectasis**

An association between bronchiectasis and RA has been noted and bronchiectasis may result from recurrent infections, retraction in interstitial lung diseases-traction bronchiectasis, or the progression of lymphocytic/constrictive bronchiolitis.

Walker and Wright have shown that patients with RA are more prone to respiratory tract infections than patients with osteoarthritis, and bronchiectasis is also more common. The prevalence of bronchiectasis in HRCT among RA patients is 16.6–58%.  

**4.0 Infections**

Patients with RA have been shown to have an increased risk of infections compared with the general population, even after adjustment for age, sex, smoking status, leukopenia, corticosteroid use, and diabetes mellitus. Several treatment modalities for RA may induce infections, including corticosteroids, disease-modifying agents (DMARDs), TNF antagonist, and new biotherapies. Opportunistic infections may also appear.

Pneumonia is a major cause of mortality in patients with RA and is probably the most common respiratory cause of death. The relative risk for pneumonia and lower respiratory tract infections is 1.68 and 1.88 respectively. Wolfe et al. reported an incidence density of pneumonia of 17 per 1000 patient-years. They found a dose-related relationship between prednisone use and pneumonia risk in RA patients, and no increase in risk for anti-TNF therapy or methotrexate use.

Treatment of RA and other autoimmune disorders with anti-TNF agents is associated with an increased risk of reactivation of latent Mycobacterium tuberculosis. The rate of TB in patients with RA treated with anti-TNF therapy is three to four times higher in patients receiving infliximab and adalimumab than in those receiving etanercept.

Geddes et al. attributed the high prevalence of obstructive airway disease in RA patients may be due to frequent respiratory tract infections.

**5.0 Drug-induced lung disease**

Several of the medications used to treat RA can be associated with lung injury. The incidence of pulmonary toxicity in patients treated with methotrexate for RA is 1–5%. There appears to be no relationship between the occurrence of pulmonary toxicity and cumulative dosage. Toxicity is rare with doses less than 20 mg per week, although more recent studies have reported that methotrexate pneumonitis occurs with a dose of 5 mg per week.

**Methotrexate:** MTX lung injury is most often a subacute process, in which symptoms are present for several weeks before diagnosis. Approximately 50% of cases are diagnosed within 32 weeks of initiation of MTX treatment. Predominant clinical features of MTX lung injury include shortness of breath, cough, and fever. Hypoxemia and a restrictive pattern on pulmonary function testing are observed. Chest X-rays and CT demonstrate diffuse infiltrates. In 70% of cases, HRCT demonstrates diffuse homogeneous ground-glass opacity (GGO) with sharp demarcation by interlobular septa-type A GGO.

Methotrexate should be temporarily stopped in any patient with RA on MTX therapy who complains on nonproductive cough and dyspnea, without evidence of upper respiratory infection. In patients with new evidence for interstitial lung disease, it should be stopped permanently. Earlier recognition and drug withdrawal may avoid the serious and sometimes fatal outcomes that have been observed. Patients generally respond to withdrawal of methotrexate and the prognosis is usually good. Uncontrolled studies suggest that glucocorticoids can hasten recovery and may be important for severely ill patients.

**Leflunomide:** Interstitial pneumonia as an adverse reaction of leflunomide is rare. The incidence of such cases is reported to be 0.02% in Western countries. In Japan in 2003, 16 cases (0.48%) of ILD, including five fatal cases (0.15%), were associated with leflunomide therapy among 3360 registered patients. Leflunomide has been reported to induce interstitial lung disease and cases of new or accelerated pulmonary nodule formation, which stabilized after cessation of the drug.
6.0 Thoracic cage abnormality

Abnormalities of thoracic cage mobility can be present in RA and is associated with pleurisy, myopathy, and thoracic rigidity. Restrictive patterns with reduced lung volumes with a low or normal DLCO and a high DLCO/VA have been reported 9.

7.0 Vascular involvement

Vascular inflammation is considered the primary event in the formation of rheumatoid nodules. During nodule formation, small-vessel vasculitis leads to fibrinoid necrosis that forms the core of the lesion, surrounded by fibroblastic proliferation. However, primary vasculitic involvement of the lung is uncommon and must be distinguished from interstitial lung disease that is not vasculitic in nature.

Conclusion

A thorough history and examination for pulmonary symptoms and signs should be performed in all RA patients. When abnormalities are found, further investigations are likely to be required to define the process. Lung function tests can be used as the baseline tests to detect those who will need more expensive and/or invasive investigations such as HRCT, bronchoscopy with bronchoalveolar lavage, and transbronchial or surgical lung biopsy, when indicated.

References


6.0 Vascular involvement

7.0 Interstitial lung disease

8.0 Thoracic cage abnormality

9.0 Abnormalities of thoracic cage mobility

10.0 Pleiomedial effusion and pleural abnormalities


Viscosupplementation in the treatment of osteoarthritis of the knee: Outcome and literature review

Adelowo OO1, Ima-Edomwonyi EU2, Oduenyi I3

Abstract

Background: Viscosupplementation is a recognised mode of management of osteoarthritis (OA) of the knee, especially in patients who have failed treatment with NSAIDs.

Objectives: To review the literature on viscosupplementation as well as assess its efficacy in Nigerians with OA of the knee.

Methods: Patients presenting to a private practice rheumatology clinic with symptomatic and radiographically proven OA of the knee were included, having failed two or more NSAIDs. Intra articular cross linked hyaluronan (synvisc) was given in three consecutive weekly doses. Assessment were by both patients' verbal numeric pain rating scale and physician's global pain assessment at six and twelve weeks.

Results: There was improvement in both assessments. There were few minor and transient adverse effects.

Conclusion: Viscosupplementation is both efficacious and safe in Nigerians with OA knee, as shown elsewhere.

Introduction

Osteoarthritis (OA) is the commonest type of arthritis, especially among the elderly. It is responsible for considerable clinical and economic burden in the affected. OA is also associated with reduction in quality of life due to pain, as well as decreased mobility and eventual disability. The pathogenetic mechanism of OA is due to the associated progressive loss of the articular cartilage and chondrocytes within the synovial joints. These processes manifest as joint pains and eventual loss of function. An additional pathogenic factor is the associated reduction in the concentration and molecular weight of the lubricating hyaluronic acid (hyaluronate, hyaluronan) in the synovial fluid. Such reduction leads to loss of its lubricating and shock absorbing properties. The reduction in the molecular weight of hyaluronic acid (HA) in arthritic joints has been attributed to its dilution from joint inflammatory effusions as well as presence of abnormal synoviocytes and molecular fragmentations.

Hyaluronan, as the compound sodium hyaluronate, is a highly viscous polysaccharide normally found in extracellular matrix and is a major constituent of synovial fluid and cartilage. It belongs to the family of glycosaminoglycan and is composed of 1000’s of repeating disaccharides units (N-acetyl glucosamine and glucuronic acid) to form a long polysaccharide chain of varying length with a high molecular weight of 5-7 x 10^6 da. When this molecule is fully hydrated, it occupies a large spheroidal shape. After synthesis in the joint by the chondrocytes and synoviocytes, HA is released into the synovial ligament and cartilage.

Synovial fluid elastoviscosity is essential for normal joint function. HA has both viscous and elastic properties, depending on the joint loading and conditions. For instance in the presence of slow and low loading, HA exhibits high viscosity with reduced elasticity. On the contrary, with increased high and fast loading, it becomes more elastic, hence acting as a shock absorber. Apart from this viscoelasticity property, other pharmacologic properties have been identified. These include inhibition of inflammatory mediators, inhibition of phagocytic cell function, stimulation of cartilage matrix synthesis, and decreased degradation of cartilage.

On the basis of the foregoing, extrinsic HA is being increasingly used in the management of pain and stiffness for patients presenting with moderate to severe OA of the knee. This is particularly so in patients not responding or unsuitable for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). It has been recommended for the control of knee pain by both the...
American College of Rheumatology (ACR) as well as the European League Against Rheumatism (EULAR). The recommendations are especially in patients with osteoarthritis of the knee and hip who have failed to respond adequately to other therapies11-14.

Although intra-articular HA has been mostly used in OA of the knee, clinical efficacy have also been reported in OA of the hip and shoulder joints. Randomised controlled trials and open trials have shown significant decrease in pain at rest, on movement as well as functional index15-20. Osteoarthritis of the knee and other joints have been reported among Nigerians21. However there has been no documented report on the use of HA in the management of OA of the knee. The objectives of this study are to assess the efficacy of HA in Nigerian patients presenting with OA of the knee and who have failed two or more NSAIDs; as well as to review the literature.

Materials and Methods

Subjects presenting with moderate to severe knee pain to a private practice rheumatology clinic, located in Lagos, Arthrimed Specialist Clinic, were recruited into the study. These patients were seen between the period January 2009 and July 2011. The patients fulfilled the American College of Rheumatology (ACR) criteria for diagnosis of osteoarthritis of the knee. Such patients were included if they had failed to respond to at least two previous NSAIDs or narcotic analgesics such as codeine based compound and tramadol. Radiographs of both knees were requested and those fulfilling radiographic criteria for OA of the knees were included. Subjects fulfilling criteria for other diagnostic types of arthritis were excluded, even if they showed radiographic features of OA.

Standard procedure of arthrocentesis was carried out. Standard cleansing of the site of arthrocentesis was done with savlon and methylated spirit. The skin was infiltrated with lignocaine (2%) at the lateral aspect of the knee, and occasionally the medial aspect. Intra-articular hyaluronan (Synvisc Hylan GF - 20 Genzyme Corporation) was administered in weekly consecutive doses (Days 1, 8, 15). Effusions were aspirated at each visit (when present) before injecting hyaluronan. Patients were seen every two weeks for at least three months and beyond. Assessments were by a) patient’s numerical pain rating on a 10 point scale with zero being ‘no pain’ and 10 being ‘pain as bad as it can be’. b) Physician’s assessment of pain as ‘mild’ - no pain at rest but on severe physical exertion; ‘moderate’ - pain on moderate physical exertion as walking up the staircase; ‘severe’ - pain at rest and disturbing patient’s sleep. Patients were allowed rescue medications such as NSAIDs or Co-Codamol.

Results

A total of fifty patients with radiographic OA of the knees were included in the study having fulfilled the ACR criteria for OA of the knees. The demographic characteristics are as shown in Table 1. Most of the subjects were female and the mean age was 62.8 years. Both knees were involved in 41 patients (82%) while the left knee and right knee involvement were in 5 (10%) and 4 (8%) respectively. The duration of symptoms varied between 8 to 300 months with a mean of 72.9 months. Pain intensity in all patients before viscosupplementation was 8-10 by Patients Numerical Pain score and ‘Moderate’ to ‘Severe’ by the physician’s global pain rating. The patient’s numerical pain rating at six weeks and twelve weeks are as in Tables 2 and 3. Eleven patients were not assessed at 12 weeks as they had defaulted. More than 80% had little or no pain at both times.

Physician’s global assessment of pain at onset of trial and subsequently are as shown in Tables 4, 5 & 6.

Table 1: Demographic characteristics of 50 OA patients treated with viscosupplementation

<table>
<thead>
<tr>
<th>Demography</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>41 (82)</td>
</tr>
<tr>
<td>Male</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Female:Male</td>
<td>4:6:1</td>
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<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>37 - 86</td>
</tr>
<tr>
<td>Mean</td>
<td>62.8</td>
</tr>
<tr>
<td>Median</td>
<td>66</td>
</tr>
<tr>
<td>Duration of symptoms (months)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>8 - 300</td>
</tr>
<tr>
<td>Mean</td>
<td>72.9</td>
</tr>
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</table>

Table 2: Patients numerical pain score at six weeks after viscosupplementation

<table>
<thead>
<tr>
<th>Pain score</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>42 (84)</td>
</tr>
<tr>
<td>4-7</td>
<td>6 (12)</td>
</tr>
<tr>
<td>8-10</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

Table 3: Patients numerical pain score in 36 patients at 12 weeks after viscosupplementation

<table>
<thead>
<tr>
<th>Pain score</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>32 (82.1)</td>
</tr>
<tr>
<td>4-7</td>
<td>4 (10.3)</td>
</tr>
<tr>
<td>8-10</td>
<td>3 (7.6)</td>
</tr>
</tbody>
</table>
Table 4: Physician’s assessment before viscosupplementation

<table>
<thead>
<tr>
<th>Physician’s pain assessment</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Mild</td>
<td>0</td>
</tr>
<tr>
<td>Moderate</td>
<td>4 8</td>
</tr>
<tr>
<td>Severe</td>
<td>46 92</td>
</tr>
</tbody>
</table>

Table 5: Physician’s Global pain assessment at 6 weeks

<table>
<thead>
<tr>
<th>Physician pain assessment</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>38 76</td>
</tr>
<tr>
<td>Mild</td>
<td>8 16</td>
</tr>
<tr>
<td>Moderate</td>
<td>3 6</td>
</tr>
<tr>
<td>Severe</td>
<td>1 2</td>
</tr>
</tbody>
</table>

Table 6: Physician’s pain assessment at 12 weeks

<table>
<thead>
<tr>
<th>Pain assessment</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>29 66.6</td>
</tr>
<tr>
<td>Mild</td>
<td>9 23.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>3 7.7</td>
</tr>
<tr>
<td>Severe</td>
<td>3 7.7</td>
</tr>
</tbody>
</table>

Table 7: Adverse effects

<table>
<thead>
<tr>
<th>Effects</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post injection enthesopathy</td>
<td>7 14</td>
</tr>
<tr>
<td>Joint effusion</td>
<td>6 12</td>
</tr>
<tr>
<td>Localised reaction - pruritus</td>
<td>5 10</td>
</tr>
<tr>
<td>Fever</td>
<td>3 6</td>
</tr>
<tr>
<td>Headache</td>
<td>1 2</td>
</tr>
</tbody>
</table>

Discussion

Our study of fifty patients with radiographic OA of the knees has confirmed the usual female preponderance and the occurrence in the middle aged to elderly (Table 1). The patients numerical pain rating was in the range of 8-10 at the onset of the study but at 6 weeks, 84% had virtually no pain (0-3) with another 12% having moderate pain of 4-7, though 4% still had severe pain. The number with virtually no pain (82.1%) remain high at 12 weeks though three of the patients still rated their pain as severe (Tables 2, 3). The number assessed at 12 weeks (39 patients) was however lower consequent to default. There was also improvement in Physician’s global assessment of pain between the baseline of severe pain and at both 6 and 12 weeks with 92% and 84.6% respectively having ‘none’ to ‘mild’ pain (Tables 4-6). It was difficult to follow these patients up beyond this period as the number defaulting thereafter was high. One can only assume that these patients did not come for further follow up because they were better. Adverse effects were seen in 12 cases, all of them mild. Joint effusions were the commonest, seen in six patients (Table 6) while localized transient pruritus, usually with the first injection was seen in five cases. Fever and headache were also seen. The three subjects who reported fever, one associated with the headache, could most likely have had malaria fever considering that this is endemic in Nigeria. Eleven cases presented with medial knee tendon enthesopathy usually after completion of the course of injections. Such patients, however, improved with intralesional steroid injection or local application of diclofenac. This adverse event (medial knee tendon enthesopathy) has rarely been reported in other studies. It is possible that it was present with the knee arthralgia before viscosupplementation and only came to the fore with the improvement of the knee joint pain.

Previous studies have demonstrated the efficacy and safety of intra-articular hyaluronate in the treatment of OA of the knee. There are numerous hyaluronate preparations with different molecular weights available in medical practice. Such preparations are available either as three dose or five dose packs. These preparations include Synvisc (hylan G-F 20 Genzyme); Hyalgan (sodium hyaluronate, Sanofi - Aventis); Supartz (sodium hyaluronate, Smith and Nephew); Euflexxa (sodium hyaluronate Ferring Pharmaceuticals); Orthovisc (high molecular weight hyaluronan Depuyi Mitek).

The mode of action of hyaluronate does not seem to depend on the resident time of the compound in the synovial cavity of the knee. Exogenous hyaluronate actually begins to leave the joint within two hours of injection, though Synvisc remains up to 3 days following injection. On the other hand, Supartz, Euflexxa and Orthovisc remain in the joint less than 24 hours after injection. It has been suggested that the major effect of these agents depends on their ability, among others, to stimulate production of good synovial fluid by synovial cells and not on their resident time in the joints.

There have been conflicting reports on the role the molecular weight of hyaluronate plays in its properties of elastoviscosity in the joints. Balazcs and Denlinger have suggested that increase in the molecular weight of exogenous hyaluronan increases its elastoviscosity. Other studies have however indicated otherwise.

Studies comparing the clinical efficacies of various preparations have reached different conclusions. For instance, Wobig and colleagues have shown the efficacy of cross-linked hyaluronate (MW 800Kda). Another retrospective study comparing Synvisc (a cross-linked hyaluronate preparation) with hyaluronan (MW 615 Kda) reported statistical improvement in both preparations but also concluded that the former was superior to the latter in many parameters.

Major constraints in the use of these agents are their cost and availability. A dose of three injections costs about US$700. There are, however, some generics available in the Nigerian market. While they are about five times cheaper than the branded names like Synvisc, there is a dearth of studies on their efficacy and safety and most of
them depend on the data from the branded compounds. Our study has shown, that as reported in other studies, hyaluronan, Synvisc GF-20 is an efficacious and safe agent in the treatment of knee OA especially in patients not responding to NSAIDs.

References


Cardiovascular risk factors in patients with rheumatoid arthritis at Kenyatta National Hospital

Kirui F, Oyoo GO, Ogola EN, Amayo EO

Abstract

Background: Rheumatoid arthritis is associated with excessive cardiovascular morbidity and mortality. This is predominantly due to accelerated coronary artery and cerebrovascular atherosclerosis. Traditional cardiovascular risk factors as well as extra-articular disease have been associated with occurrence of myocardial infarction.

Objective: To identify cardiovascular risk factors in patients with rheumatoid arthritis at Kenyatta National Hospital and compare with healthy controls.

Design: This was a comparative cross sectional survey.

Setting: Kenyatta National Hospital medical outpatient clinic. The study population were patients with rheumatoid arthritis and the controls were individuals without RA age and sex matched staff of KNH. All those who consented were enrolled and a clinical evaluation was done as per the study protocol.

Results: One hundred patients with RA were screened out of which 80 were enrolled. The prevalence of hypertension among RA patients was 41.3%, diabetes 6.3%, dyslipidemia 71.3%, smoking 5%, obesity 22.5%, abnormal WHR 33.8%, family history of sudden death 5%, no family history of stroke or heart attack was reported. In the control group one hundred and five were screened and twenty five were excluded. The prevalence of hypertension was 22.5%, diabetes 5%, dyslipidemia 73.8%, smoking 2.5%, obesity 32.5%, abnormal WHR 33.8% family history of sudden death 5%, no family history of stroke or heart attack was reported. Eighty percent of patients with RA were on at least one DMARD, 57.5% were on steroids and 37.5% were on NSAIDS.

Conclusion: There was a high prevalence of hypertension among RA patients (41.3%) than in the controls (22.5%) and this was statistically significant (OR 2.42 (95 CI 1.22-4.81) P = 0.017). Hypertension was also significantly associated with the use of DMARDS OR 2.189 (95% CI 1.111-4.312) P= 0.022 and steroids OR 2.06(95% CI 1.008-4.207) P= 0.022. No significant difference between patients with RA and controls in other risk factors including diabetes, dyslipidemia, smoking, obesity, abnormal waist hip ratio and family history of cardiovascular events was found.

Recommendations: Clinicians should keenly look out for hypertension in patients with RA for early identification and if necessary aggressive management of hypertension. Screening of cardiovascular risk factors in patients with RA should be done routinely and a larger study with normal controls from the general population should be undertaken in order to measure this cardiovascular risk factors and cardiovascular disease in this population.

Key words: Cardiovascular, Rheumatoid arthritis, KNH.

Introduction

Rheumatoid arthritis is a chronic systemic autoimmune inflammatory disorder. It is characterized by deforming symmetrical polyarthritis of varying extent and severity, associated with synovitis of joint and tendon sheaths. It is also associated with articular cartilage loss, erosion of juxta-articular bone and, in most patients, the presence of IgM rheumatoid factor in blood. In some patients systemic and extra-articular features may be observed during the course of the disease and, rarely prior to onset of joint disease. These include anemia, splenomegaly, weight loss, vasculitis, serositis, mononeuritis multiplex, interstitial inflammation in the lungs and exocrine salivary and lacrimal...
glands as well as nodules in subcutaneous, pulmonary and scleral tissue.

Rheumatoid arthritis (RA) is associated with excessive cardiovascular morbidity and mortality. This is predominantly due to accelerated coronary artery and cerebrovascular atherosclerosis. Traditional cardiovascular risk factors as well as extra articular disease have been associated with occurrence of myocardial infarction (MI).

A study done by Han and colleagues, showed that individuals with rheumatoid arthritis are 30% to 60% more likely to suffer a cardiovascular event compared to the general population, especially myocardial infarction. The incidence and prevalence of stroke generally has been reported to be similar in rheumatoid arthritis as in the general population or in patients with osteoarthritis. One study found a higher prevalence of stroke in patients with rheumatoid arthritis than in controls.

The main objective of this study was to identify cardiovascular risk factors in patients with rheumatoid arthritis at Kenyatta National Hospital, Nairobi, Kenya. It also sought to determine the prevalence of hypertension, diabetes, dyslipidemia and smoking. We also wanted to determine anthropometric measures in patients with RA, mainly Basal Metabolic Index (BMI), Waist Hip Ratio (WHR), family history of cardiovascular events such as sudden death, MI or stroke. We also sought to compare the cardiovascular risk factors in patients with rheumatoid arthritis with the controls.

The other objectives in this study were to document cardiovascular events (stroke, MI, HF) in patients with RA and to document the use of DMARDS (disease modifying anti rheumatic drugs), steroids, NSAIDS, biologic DMARDS, anti-hypertensives, anti-diabetics, statins, and aspirin in patients with RA.

### Materials and Methods

This was a descriptive comparative cross sectional survey done at the Medical Out Patient Clinics (MOPC) at Kenyatta National Hospital. Patients included in the study were above 18 years, confirmed to have rheumatoid arthritis as per ACR criteria and gave an informed consent. The controls were healthy individuals above 18 matched for age and sex. They were also confirmed not to have rheumatoid arthritis as per the ACR criteria. Patients below 18 years and those who declined to give consent were excluded.

Sample size was calculated based on the current data available with a prevalence of 30% for hypertension at 95% confidence interval and a 5% margin of error. The minimum sample size needed was 80 with rheumatoid arthritis and 80 controls (Figure 1).

A total of 205 patients with rheumatoid arthritis and healthy controls were screened for recruitment into the study. Patients with or suspected to have RA were 100 and of these four individuals did not consent, 88 fulfilled ACR criteria and were recruited, 8 were lost to follow up and 80 were enrolled. One hundred and five healthy individuals without RA were screened for enrollment, 15 refused consent, 90 were recruited and 10 were lost to follow up. A total of 160 cases and controls were enrolled, 22 (13.75%) were males and 138 (86.25%) were female (Table 1).

### Results

The mean age for patients with RA was 44.7 years, the median age 48 years and [range 18-75 years]. For the healthy individuals without RA, the mean age was 44.6 years, the median was 43 years and [range 22-75 years] (Table 1). There were two peaks of disease in the patients with RA with the peaks at age ranges 20-29 and 50-59 years (Figure 2).

### Figure 1: Flow chart showing patient flow in the study

---


16
Table 1: Demographic characteristics of patients with rheumatoid arthritis and healthy controls

<table>
<thead>
<tr>
<th>Variables/ categories</th>
<th>Case No. (%)</th>
<th>Control No. (%)</th>
<th>Total No. (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 13.8</td>
<td>11 13.8</td>
<td>22 13.8</td>
<td>1.000</td>
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<tr>
<td>Female</td>
<td>69 86.2</td>
<td>69 86.2</td>
<td>138 86.2</td>
<td></td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>56 70</td>
<td>47 58.8</td>
<td>103 64.4</td>
<td>0.264</td>
</tr>
<tr>
<td>Single</td>
<td>19 23.8</td>
<td>24 30</td>
<td>43 26.9</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>3 3.8</td>
<td>8 10</td>
<td>11 6.9</td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>2 2.5</td>
<td>1 1.3</td>
<td>3 1.9</td>
<td></td>
</tr>
<tr>
<td><strong>Level of education</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
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<td>4 5</td>
<td>2 2.5</td>
<td>6 3.8</td>
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<td>Primary</td>
<td>28 35</td>
<td>10 12.5</td>
<td>38 23.8</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>15 18.7</td>
<td>9 11.3</td>
<td>24 15</td>
<td></td>
</tr>
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<td>College</td>
<td>20 25</td>
<td>47 58.7</td>
<td>67 41.9</td>
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<tr>
<td>Tertiary</td>
<td>13 16.3</td>
<td>12 15</td>
<td>25 15.6</td>
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<tr>
<td><strong>Employment</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td>Unemployed</td>
<td>24 30</td>
<td>20 25</td>
<td>44 27.5</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>29 36.3</td>
<td>48 60</td>
<td>77 48.1</td>
<td></td>
</tr>
<tr>
<td>Self employed</td>
<td>19 23.7</td>
<td>8 10</td>
<td>27 16.9</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>8 10</td>
<td>4 5</td>
<td>12 7.5</td>
<td></td>
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<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.894</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>44.7±15.3(18-75)</td>
<td>45.0±13(22-75)</td>
<td>44.8±14.2 (18 – 75)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>48</td>
<td>43</td>
<td>45</td>
<td></td>
</tr>
</tbody>
</table>

There was significant association between level of education and rheumatoid arthritis (P= 0.001). Majority with education less than college level had higher disease burden compared to those who had college education and above. There was a significant association between type of employment and disease status. Majority of those who had rheumatoid arthritis were self employed, and unemployed (P = 0.012) (Table 1).

Figure 2: Age distribution of patients with rheumatoid arthritis

Thirty three patients (41.3%) with RA had hypertension compared to 18 (22.5%) healthy controls. This difference was statistically significant, (OR 2.42 (95 CI 1.22-4.81) P = 0.017) Five (6.3%) patients with rheumatoid arthritis had diabetes while controls were 4(5%) controls. This was not statistically significant (OR 1.28 (95 CI 0.33-4.90) P =1.0).

Fifty seven patients with RA (71.3%) had dyslipidemia, while 59(73.8%) of the healthy controls had dyslipidemia, however this was not statistically significant. (OR 0.88 (95 CI 0.44-1.77) P =0.723). Four (5%) patients with rheumatoid arthritis smoked and 2 (2.5%) healthy controls smoked cigarette. There was no statistical significance (OR 0.49 (95 CI 0.09-2.74) P =0.687)

Eighteen (22.5%) patients with rheumatoid arthritis were obese while 26 (32.5%) of the controls were obese. This was however not statistically significant. O.R 0.603 (95 CI 0.299-1.218) P =0.157. Twenty seven (33.7%) of patients with RA had a high waist hip ratio, a similar number was observed in the controls and this was not statistically significant. OR 1 (95 CI 0.519-1.926) P=1.0.
There was no family history of myocardial infarction among the patients with rheumatoid arthritis and the healthy controls, one person from the controls reported a family history of stroke. Four patients with RA reported a family history of sudden death while 8 people in the healthy control group did report it; however, when compared, this was not statistically significant. OR 0.47 95%CI (0.137-1.641) P = 0.369. Only one patient with RA reported past history of heart failure; none of the patients or healthy controls reported a previous history of myocardial infarction or stroke. Drug therapy as used by all the patients is summarized in Table 2.

Table 2: Drug therapy in patients with RA and controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases No.</th>
<th>Cases (%)</th>
<th>Controls No.</th>
<th>Controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>46</td>
<td>57.5</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Statins</td>
<td>1</td>
<td>1.3</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>Nitrates</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1</td>
<td>1.3</td>
<td>3</td>
<td>3.8</td>
</tr>
<tr>
<td>DMARDs</td>
<td>64</td>
<td>80</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Biological DMARDs</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>NSAIDS</td>
<td>30</td>
<td>37.5</td>
<td>6</td>
<td>7.5</td>
</tr>
<tr>
<td>Proportion of hypertensive patients on medication</td>
<td>8</td>
<td>24.2</td>
<td>1</td>
<td>5.5</td>
</tr>
<tr>
<td>Proportion of diabetics on treatment</td>
<td>3</td>
<td>60</td>
<td>2</td>
<td>50</td>
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</table>

Data Analysis

Table 3: Bivariate analysis on correlates of cardiovascular risk factors in patients with rheumatoid arthritis and healthy controls

<table>
<thead>
<tr>
<th>Factors</th>
<th>Category</th>
<th>Disease outcome</th>
<th>P. value</th>
<th>OR</th>
<th>CI OR</th>
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<tr>
<td></td>
<td></td>
<td>Case No. (%)</td>
<td>Control No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>33 41.3</td>
<td>18 22.5</td>
<td>0.017</td>
<td>2.42</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>5 6.3</td>
<td>4 5</td>
<td>0.681</td>
<td>0.49</td>
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<tr>
<td>Smoking</td>
<td></td>
<td>4 5</td>
<td>2 2.5</td>
<td>0.52</td>
<td>0.27</td>
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<tr>
<td>Abnormal WHR</td>
<td></td>
<td>27 33.8</td>
<td>27 33.8</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sudden death</td>
<td></td>
<td>4 5</td>
<td>8 10</td>
<td>0.369</td>
<td>0.474</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td></td>
<td>57 71.3</td>
<td>59 73.8</td>
<td>0.723</td>
<td>0.882</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td>18 22.5</td>
<td>26 32.5</td>
<td>0.157</td>
<td>0.603</td>
</tr>
</tbody>
</table>

By controlling for disease outcome 19 (44.2%) patients with RA and obesity were hypertensive, however there was no statistically significance between hypertension and obesity. Likewise in the control group there was no association between hypertension and obesity. OR 1.96 (95 C I 0.67 -5.76) P = 0.259. The controls who were obese were almost two times more at risk to have hypertension than those not obese. One patient with RA and diabetes (20%) was hypertensive, while two controls who were diabetic had hypertension. The odds of being hypertensive among diabetics compared to non diabetic was three times more, however this was not statistically significant OR 3.75(95% C.I 0.490-28.727) P= 0.217. Twelve (40%) individuals with RA who used NSAIDS regularly were hypertensive while one control had hypertension; however this was not statistically significant (Table 4).
Among the patients with rheumatoid arthritis 64 (80%) were on DMARDs, 49 (61.3%) were on one DMARD, 14 (17.5%) were on two DMARDs and only one patient with rheumatoid arthritis was on treatment with three DMARDs.

(Figure 3).

**Figure 3:** Use of DMARDs among individuals with rheumatoid arthritis

![Diagram showing the use of DMARDs among individuals with rheumatoid arthritis.]

**Table 4:** Bivariate analysis – Controlling for disease status

<table>
<thead>
<tr>
<th>Disease outcome category</th>
<th>Case No. (%)</th>
<th>Control No. (%)</th>
<th>95% CI</th>
<th>P value</th>
<th>Control No. (%)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension/Obesity</td>
<td>8 (24.2)</td>
<td>8 (44.4)</td>
<td>1.2 (0.41-3.42)</td>
<td>0.791</td>
<td>1.96 (0.67 - 5.76)</td>
<td>0.259</td>
<td></td>
</tr>
<tr>
<td>Hypertension/Diabetes</td>
<td>1 (20)</td>
<td>2 (50)</td>
<td>0.34(0.04-3.15)</td>
<td>0.399</td>
<td>3.75 (0.49-28.7)</td>
<td>0.217</td>
<td></td>
</tr>
<tr>
<td>Hypertension/NSAIDS</td>
<td>12 (40)</td>
<td>1 (16.7)</td>
<td>0.92 (0.37-2.3)</td>
<td>1</td>
<td>0.67(0.73-6.14)</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5:** Hypertension in relation to drug therapy in patients with RA and controls

<table>
<thead>
<tr>
<th>Variables/categorical</th>
<th>Hypertension No. (%)</th>
<th>No Hypertension No. (%)</th>
<th>O. R</th>
<th>95% O.R Lower</th>
<th>Upper</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of DMARDs</td>
<td>27 (42.2)</td>
<td>37 (57.8)</td>
<td>2.189</td>
<td>1.111</td>
<td>4.312</td>
<td>0.022</td>
</tr>
<tr>
<td>No use of DMARDs</td>
<td>24 (25.0)</td>
<td>72 (75.0)</td>
<td>2.06</td>
<td>1.008</td>
<td>4.207</td>
<td>0.045</td>
</tr>
<tr>
<td>Use of steroids</td>
<td>20 (43.5)</td>
<td>26 (56.5)</td>
<td>2.06</td>
<td>1.008</td>
<td>4.207</td>
<td>0.045</td>
</tr>
<tr>
<td>No use of steroids</td>
<td>31 (27.2)</td>
<td>83 (72.8)</td>
<td>1.279</td>
<td>0.586</td>
<td>2.79</td>
<td>0.536</td>
</tr>
<tr>
<td>Use of NSAID</td>
<td>13 (36.1)</td>
<td>23 (63.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No use of NSAID</td>
<td>38 (30.6)</td>
<td>86 (69.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

None of the patients seen at the clinic were using biological agents for the treatment of rheumatoid arthritis (Table 2).

Twenty seven patients who used DMARDs were hypertensive as compared to 24 who did not. Those who used DMARDs were significantly more likely to have hypertension. OR 2.189(95% CI 1.111-4.312) P= 0.022. Likewise those patients with RA who used steroids were more likely to be hypertensive than the controls and this was statistically significant OR 2.06(95% CI 1.008-4.207) P= 0.022 (Table 5).

Forty six (57.5%) individuals with RA were on treatment with steroids. Only one patient with rheumatoid arthritis was on treatment with statins while two controls were using statins. Only one patient with RA who was using antiplatelet agent while three controls were on antiplatelet agents. None of the cases or controls was on treatment with nitrates.

Eight (24.2%) individuals who had RA and hypertension were on treatment for hypertension while three (60%) individuals were on treatment for diabetes. Thirty (37.5%) individuals with RA were taking NSAIDS regularly as compared to six individuals in the control group. Among the individuals with RA taking NSAIDS regularly 12(40%) were hypertensive. More than half the patients with rheumatoid arthritis 46(57.5%) were using glucocorticoids (Table 2).

Eleven patients with RA had no risk factor measured in this study, 20 patients had 1 risk factor, 27 two risk factors, 18 three risk factors and 4 with four risk factors.
In the control arm 7 did not have any risk factor, 31 had 1 risk factor, 27 two risk factors, 10 three risk factors, 4 had four risk factors and 1 with five risk factors. When the cases and controls were compared there was no statistical significance in terms of number of risk factors.

Figure 4: Distribution of risk factors by cases and controls

Discussion

From our results we found women were the most affected by the disease accounting for 69 (86.2%) of the individuals with RA, as opposed to eleven (13.8%) males. A local study done by Owino et al. found 86.7% females with a male to female ratio of 1:6.5. This observation was in agreement to what we observed in our study.

The mean age of patients with RA in this study was 44.7 ± 15.3 years and this was almost similar to that observed by owino et al but older than that observed by Bagg et al. In the study done by panoulas and colleagues the mean age for patients with RA was 61 ± 12.02 years. This was an older population than what we saw in our study and could explain our higher prevalence of rheumatoid arthritis among women, since the disease has been shown to be more common in younger women compared to younger males; but the difference diminishes as the age increases.

In this study the prevalence of hypertension among the patients with rheumatoid arthritis was 41.3%, and this was higher than the 22.5% observed in the healthy controls and was statistically significant.

Owino et al. found the prevalence of hypertension among patients with rheumatoid arthritis to be around 14%. This was much lower than what we observed in our study. The mean age of his patients was 41.3 years indicating a younger population than in ours. This may partly explain the lower prevalence although other factors might have contributed to the difference observed. Owino and his colleagues relied on patient’s records and there was no physical measurement by the clinician or study assistant of blood pressure and this may partly explain the low prevalence he got from his study.

A study done by panoulias et al in the UK found a higher prevalence of 70% with a mean age of 62 years. This population was older than our study population and it has been shown that hypertension is more common in older age group of individuals. The prevalence of hypertension might have been also high in Panoulas study population and this with the high mean age might explain the difference with our study.

Use of medium dose steroids for long term (more than six months) in patients with RA has been associated with a high prevalence hypertension. In this study 46 (57.5%) patients with RA were on steroids out of which 20 (43.5%) had hypertension. Those who used steroids were twice at risk of being hypertensive than those who did not use and this was statistically significant. We did not document the daily steroid use in our study and therefore would not have a daily steroid dose to correlate with other studies findings. The use of steroids in patients with RA could explain the higher prevalence of hypertension in this patient group compared to the controls. The study done by Owino and colleagues had 66.7% of patients with RA on steroids; which was much higher than in our study but this cannot explain the difference in the prevalence of hypertension, probably other factors could explain this observation.

Antonio et al. found 33% of patients with RA had hypertension. This was a multicentre study and involved different geographical and demographic groups globally but mostly in Europe and North America. This prevalence of hypertension was lower than what we observed in our study. Their mean age was 57 years. These findings were not in agreement with what has been observed in other studies, our study included.

Only 24.2% of the individuals with rheumatoid arthritis and hypertension were on treatment for hypertension in our study, and this shows a significant proportion of individuals are not diagnosed with hypertension and therefore could not benefit from early treatment. Panoulas and colleagues observed that 39.4% of the individuals with RA were undiagnosed for hypertension and therefore could not get treatment in his study. This is despite the fact that patients with RA in that country (UK) were regular attendees of the rheumatology clinics where vital signs were recorded regularly.

In our study the prevalence of diabetes was 6.5% among patients with rheumatoid arthritis and 5% in the controls. In a study done by Owino 3.5% of individuals were diabetic and hypertensive. Other studies like the one done by Antonio and his colleagues observed a prevalence of diabetes of 8%. This was a multicentre study and had varied demographic characteristics although 90% of the patients were Caucasians and they had a higher mean age than in our study. Another study done by Del Rincon et al., found a prevalence of 8.3% of diabetes among patients with RA and 6.3% in his controls, however, this was not statistically significant. This finding was observed in patients and controls below 55 years of age. He did observe a higher prevalence in those who were above 55 years. The patients in his study were older than in our study and this could explain the higher prevalence
he observed in his study or probably the prevalence of diabetes was higher in his study population. Steroids have been shown to predispose patients to diabetes and we may associate to the higher prevalence of diabetes in patients with RA in our study since over half (57.5%) of them were on steroids.

Fifty seven (71.3%) of our patients with RA had dyslipidemia and almost a similar number was observed in the control group. We have no local data on dyslipidemia among patients with RA. This was higher than what was observed by Antonio and his colleagues (14%). The low prevalence observed by Antonio and colleagues could have been due to the difference in the cut off levels for lipid profiles or their definition of dyslipidemia.

Crowson et al² observed a higher prevalence of dyslipidemia in his study (59.4%). This was a study done in the US looking at risk of developing heart failure attributable to traditional cardiovascular risk factors in patients with RA. A small proportion of our patients with Rheumatoid arthritis smoked, likewise this trend was observed in the healthy controls. This low prevalence might have been influenced by the cultural trends in our society since majority of the study population were women. Older women in the Kenyan society tend to be conservative and therefore few of them smoke, although of late the trend of smoking has been seen to be rising among young women in Kenya.

Our findings were in sharp contrast to what was seen in the quest RA study where the prevalence of ever smoking was at 43%. These could be explained by the population studied in Quest RA study which was more of a western society where a significant proportion of women smoke cigarettes. Panoulas et al observed a prevalence of 18.5% of smoking in his study and this was still higher than what we saw in our study.

Obesity particularly central obesity is associated with an increased risk of cardiovascular risk. In our study the prevalence of obesity among patients with rheumatoid arthritis was 22.5% compared to 32.5% in the controls. Antonio and his colleagues in the quest RA study found a lower prevalence of 18%. Patients with RA tend to present with weight loss when the disease is active and while on treatment and this might explain the difference we got from our study when we compared our cases and the controls. Other studies in the general population have observed that overweight and obese are important mediators of hypertension in the context of ex-smokers with insulin resistance (Yokoyama 2004), and associate with current or future hypertension and relevant end organ damage in non RA population.

The number of individuals with RA using DMARDS was 64(80%) in our study. Owino et al observed that 46.7% of patients with RA were on treatment with at least one DMARD these was lower than what we observed in our study. We think that there could have been some improvement in knowledge of the healthcare workers in the use of DMARDS in patients with RA and therefore more people are being put on DMARDS now than before, or may be DMARDS are now more affordable.

A study done by Panoulas et al⁷ found out that 87.5% of patients with RA were using DMARDS. This was higher than what we found in our study although the trend was almost similar with over two thirds of our patients with RA using DMARDS.

In our study in patients with RA; 61.3% were on one DMARD, 17.5% on two DMARDS and one 1.3% on three DMARDS as compared to the ones in a study done by Panoulas et al where 56.8% of patients with RA were on only one DMARD. This was lower than what we observed in our study, the reason being that more patients were on more than one DMARD (30.8%) in that study. These might reflect on our local practice because in other parts of the world rheumatologist are increasingly prescribing combination therapy because single DMARD therapy often fails to control clinical symptoms or prevent disease progression.

The use of NSAIDS especially Cox 2 inhibitors have been associated with hypertension, unlike in our study where there was no significant association of hypertension and use of NSAIDS. None of the patients in our study were using biological agents such as Rituximab, which has been shown to be quite effective in treating RA. This is most likely due to its prohibitive cost and also most of the patients coming to Kenyatta Hospital have a lower socio economic status.

The family history of documented cardiovascular events was lower than that observed by Crowson et al in the US. There could have been recall bias among our patients on current disease or their social desirability might have influenced their response. Recording and maintaining updated records of this information in our local setup might have posed a significant challenge and this might explain the low prevalence we got from our study.

Most of the controls in our study were individuals working at the hospital. They included the nursing staff, clinical officers and supportive staff, a large proportion of them had dyslipidemia (73.8%) and this was more than in the cases. Although this was not statistically significant it still shows that this population was at risk.

The healthy individuals who were used as controls were also more obese (32.5%) than the patients with RA indicating that they were at more risk, although this was also not statistically significant. They also documented more family history of sudden death than in the cases with RA. From our findings it seems the control group which was presumed healthy had actually more risk factors than thought and these might have influenced our results especially looking at the lipid profile where we expected to have more dyslipidemia in patients with RA than in the controls as seen in a study done by Situnayake and kitas.

Most of the patients and controls had clustering of risk factors and when the two groups were compared there was no significance in the number of risk factors. It seems the increased risk of cardiovascular events in RA is independent of traditional cardiovascular risk factors. This suggests other additional mechanisms are
Conclusions

This study has shown that:

(i) There is a high prevalence of hypertension in patients with RA as compared to the controls.

(ii) Hypertension was also associated with the use of DMARDS and steroids.

(iii) A large proportion of patients with RA and healthy controls had dyslipidemia.

(iv) There was no significant difference between patients and controls in terms of other risk factors i.e. diabetes mellitus, dyslipidemia, smoking, BMI, WHR, and family history of cardiovascular events.

(v) There was clustering of risk factors among patients and the healthy controls although this was not significant. From this it seems the increased risk of cardiovascular events in RA is independent of traditional cardiovascular risk factors. This suggests other additional mechanisms are responsible for cardiovascular disease in RA.

References

Characteristics of systemic sclerosis patients in Nairobi, Kenya: a retrospective study

Ilovi CS, Oyoo GO

Abstract

Objectives: Systemic sclerosis is a rare rheumatologic disorder that has not been well characterized in African populations. No previous studies have been carried out in Kenya, or in the East African region.

Design: A retrospective descriptive study.

Methods: Records of patients at the Kenyatta National Hospital and Nairobi Arthritis Clinic with a diagnosis of systemic sclerosis based on the American College of Rheumatology criteria were recruited into the study. The study covered a ten year period between 2001 and 2011.

Results: A total of 50 patients were identified, with a predilection of the disease to the female gender (M:F 1:4). The mean age of presentation was 41.7 years with a range of 4 years to 70 years. Majority of the patients (82%) presented with diffuse cutaneous systemic sclerosis. Overlap syndromes were documented in eight of the patients. Skin manifestation was the commonest presentation (100%), followed by Raynaud’s phenomenon (64%), pulmonary disease (56%) and esophageal disease (54%). Antinuclear antibodies were present in 67% of the patients tested. Of the patients tested for anti-SCL-70 autoantibodies, only 28% were positive. Most of the patients (80%) were on immunosuppresants whereas 54% were on proton pump inhibitors/prokinetics.

Conclusion: Patients in Nairobi with systemic sclerosis have similar characteristics as cases described elsewhere in Africa.

Key words: Systemic sclerosis, Scleroderma, Kenyatta National Hospital, Nairobi Arthritis clinic

Introduction

Systemic sclerosis is an autoimmune disease of unknown etiology which is characterized by vasculopathy, thickening of the skin, internal organ involvement especially gastrointestinal system, lungs, kidney and heart as well as development of autoantibodies1-3.

The etiology of the disease is not well understood, but possible triggers have been described. These include viruses such as cytomegalovirus and retroviruses, environmental triggers such as silica and industrial fumes, gadolinium contrast agent and some cytotoxic medications used in cancer treatment4.

There are four main subtypes of the disease depending on the extent of fibrosis and internal organ involvement. In limited cutaneous systemic sclerosis, scleroderma is limited to the skin distal to the elbow and has minimal internal organ manifestation. The diffuse cutaneous form is widespread; skin thickening can involve the whole body including the face. It is associated with more internal organ disease. Localized scleroderma, also called morphea, is limited to the skin with no internal organ disease. Systemic sclerosis sine scleroderma has purely internal organ fibrosis with no features of scleroderma.

Very few studies have been carried out on the African continent on systemic sclerosis, and none in Kenya or the East African region. The estimated prevalence of the disease ranges from 50 to 300 cases per 1 million persons5. Females are more predisposed to developing the disease as compared to males, with a male: female ratio of between 1:3 and 1:14. Studies carried out in North America have shown increased cases of systemic sclerosis in African Americans compared to Caucasians6,7.

The hallmark of systemic sclerosis is thickening of the skin (scleroderma). Internal organ fibrosis occurs mainly in the lungs, gastrointestinal system, kidneys, muscle, joints and the heart. Vasculopathy
presents as pulmonary arterial hypertension, Raynaud’s phenomenon, digital ulcers, acro-osteolysis and renal disease. Other clinical presentations include calcinosis cutis and arthritis. It is these clinical presentations that result in the high morbidity and mortality of the disease.

A study carried out in 30 countries (24 European, 6 non-European), involving 3656 patients was undertaken between 2004 and 2006. The male to female ratio was 1:6. Diffuse cutaneous systemic sclerosis was present in 36.9% while limited cutaneous disease was present in 63.1%. Patients with localized scleroderma were excluded from this study. Antinuclear antibodies against SCL-70, which is highly specific for the disease, were positive in 36.4% of the patients.8

A South African study carried out in Johannesburg in a black population, involving 63 patients found the mean age of onset at 36.1 years, with a male: female ratio of 1:4.6. Of the 63 patients, 13 had been exposed to silica from gold mines, a possible trigger factor of the disease in susceptible individuals. Raynaud’s phenomenon was the most common symptom, occurring in 90% of the patients, with 98% of the patients having antinuclear autoantibodies.9 Another study, also carried out in South Africa, found antinuclear autoantibodies in 96% of the 160 patients.10 Studies done elsewhere have also implicated silica in the pathogenesis of systemic sclerosis.11-15

A study undertaken in Nigeria and involving 14 patients showed a predilection of the female gender, with a male: female ratio of 1:6. Diffuse cutaneous was the commonest variant in 57.1% of the study patients. Raynaud’s phenomenon was present in only 14.3% of the patients. Antinuclear antibodies were positive in 64.3% of the patients.16 A study that reviewed the cause of death in systemic sclerosis from 1972 to 2002 in an American centre found that from 1972 to 1976 the commonest cause of death was scleroderma renal crisis. The trend declined and at the end of the study period (1997-2001), pulmonary disease, either pulmonary fibrosis or pulmonary arterial hypertension, was the commonest cause of death. This was attributed to better management of scleroderma renal crisis by use of dialysis services and drugs such as angiotensin converting enzyme inhibitors.17 A study evaluating the radiological hand involvement in systemic sclerosis in 120 patients found that arthritis, distal phalange resorption, flexion contractures and extra articular calcification were the commonest radiological findings 18

A study which evaluated cardiac involvement by using cardiac MRI in 52 systemic sclerosis patients found an abnormality in 75% of them. These included pericardial effusion, altered ejection fractions of the right or left ventricle and ventricular kinetic abnormalities.19 Systemic sclerosis is a poorly understood and rarely studied disease in the African population. Few studies have been carried out in Africa, with majority done in South Africa9-14,15 and the rest in Nigeria.16,20,21 Kenyatta National Hospital is a tertiary referral and teaching hospital situated in Nairobi, Kenya; and is one of two in the country. It is the only public hospital with a rheumatology clinic, which has been in operation for one year, having been started in February 2010. Prior to the inauguration of this clinic, patients were seen in the general medical outpatient clinics. The rheumatology clinic is run under the auspices of qualified rheumatologists who review patients attending the clinic together with the registrars/residents from internal medicine attached to the unit. Nairobi arthritis clinic, a private rheumatology clinic based in Nairobi caters for a large number of patients with rheumatologic disorders including systemic sclerosis. These two rheumatology centers serve as the catchment area for the whole country due to the paucity of rheumatologists in Kenya.

Patients and methods

Patient’s records covering a 10 year period between January 2001 and August 2011 were reviewed and those fulfilling the American College of Rheumatology criteria for systemic sclerosis were recruited into the study. Clinical presentation, age, gender, organ involvement, laboratory and radiological investigations, treatment modalities were documented.

Results

A total of 55 patients were identified. Five patients were excluded from the final analysis as they had localised scleroderma/morphea. The mean age at diagnosis was 41.7 years with a range of 4 to 70 years. Only one patient was aged less than 18 years. Female patients were 44 while 11 were male (M:F 1:4) (Table 1).

Table 1: Demographics

<table>
<thead>
<tr>
<th>Feature</th>
<th>No.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>44</td>
<td>80%</td>
</tr>
<tr>
<td>Male</td>
<td>11</td>
<td>20%</td>
</tr>
<tr>
<td>Mean age</td>
<td>41.7 years</td>
<td></td>
</tr>
<tr>
<td>Age range</td>
<td>4 years- 70 years</td>
<td></td>
</tr>
</tbody>
</table>

Majority of the patients (41) presented with diffuse cutaneous systemic sclerosis. Nine patients had limited cutaneous disease and no patient with systemic sclerosis sine scleroderma was identified. Fourteen of the patients had an overlap of scleroderma with another connective tissue disease (Tables 2, 3).

Table 2: Clinical variants

| Diffuse cutaneous          | 41 (82%) |
| SSc sine scleroderma       | 0        |
| Limited cutaneous          | 9 (18%)  |
The commonest clinical presentation was skin manifestation which was present in all the patients. Raynaud’s phenomenon was present in 32 of the patients. In the rest of the patients, the information in the patient records did not indicate that symptoms of Raynaud’s were not present or it was that they were not asked for. Therefore the actual incidence of Raynaud’s phenomenon may have been higher. Esophageal involvement; either from symptoms or confirmed by barium studies was present in 27 of the patients. Pulmonary involvement was present in 20 of the patients, with the 18 having pulmonary fibrosis both radiologically and on pulmonary function test and 10 having pulmonary arterial hypertension on echocardiogram (Table 4).

One patient with diffuse cutaneous systemic sclerosis and rheumatoid arthritis presented with rapidly progressive glomerulonephritis which was managed successfully with intravenous cyclophosphamide. The other patient with scleroderma renal disease presented with proteinuria and was managed with ACE inhibitors. Three deaths were documented, with all three patients having died from severe pulmonary disease and the attendant cor pulmonale.

### Table 4: Clinical features

<table>
<thead>
<tr>
<th>Feature</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin involvement</td>
<td>50 100</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>32 64</td>
</tr>
<tr>
<td>Pulmonary involvement</td>
<td>28 56</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>18 36</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension</td>
<td>10 20</td>
</tr>
<tr>
<td>Esophageal involvement</td>
<td>27 54</td>
</tr>
<tr>
<td>Myopathy</td>
<td>16 32</td>
</tr>
<tr>
<td>Cardiac</td>
<td>11 22</td>
</tr>
<tr>
<td>Calcinosi</td>
<td>5 10</td>
</tr>
<tr>
<td>Acro-osteolysis</td>
<td>3 6</td>
</tr>
<tr>
<td>Scleroderma renal crisis</td>
<td>2 4</td>
</tr>
<tr>
<td>Arthritis/arthalgia</td>
<td>8 16</td>
</tr>
<tr>
<td>Alopecia</td>
<td>4 8</td>
</tr>
<tr>
<td>Sicca symptoms</td>
<td>2 4</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>1 2</td>
</tr>
<tr>
<td>Telengectasia</td>
<td>1 2</td>
</tr>
</tbody>
</table>

Various autoantibodies were carried out in the patients. Antinuclear antibody (ANA) test was carried out in 40 of the patients and was positive in 27 of the patients. Antibody to SCI-70 was carried out in 23 patients and was positive in six patients only (Table 5).

### Table 3: Overlap syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE/ Diffuse cutaneous</td>
<td>5</td>
</tr>
<tr>
<td>SLE/ Localised cutaneous</td>
<td>2</td>
</tr>
<tr>
<td>Rheumatoid arthritis/ Diffuse cutaneous</td>
<td>2</td>
</tr>
<tr>
<td>Sjogrens / Diffuse cutaneous</td>
<td>2</td>
</tr>
<tr>
<td>Dermatomyositis/ Diffuse cutaneous</td>
<td>3</td>
</tr>
</tbody>
</table>

### Table 5: Autoantibody profile

<table>
<thead>
<tr>
<th>Antibody</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear</td>
<td>27/40 67.5</td>
</tr>
<tr>
<td>Anti- SCL-70</td>
<td>6/23 28.6</td>
</tr>
<tr>
<td>Anti- ds-DNA</td>
<td>4/16 25</td>
</tr>
<tr>
<td>Anti- CCP</td>
<td>0/8</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>7/27 25.9</td>
</tr>
<tr>
<td>Anti- SM</td>
<td>2/28 7.1</td>
</tr>
<tr>
<td>Anti- SSA</td>
<td>3/29 10.3</td>
</tr>
<tr>
<td>Anti- SSB</td>
<td>2/29 6.9</td>
</tr>
<tr>
<td>Anti- J01</td>
<td>2/27 7.4</td>
</tr>
<tr>
<td>Anti- RNP</td>
<td>4/28 14.3</td>
</tr>
</tbody>
</table>

### Table 6: Treatment modalities

<table>
<thead>
<tr>
<th>Modality</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid/ antiplatelet agent</td>
<td>18 36</td>
</tr>
<tr>
<td>PPI/H2 blocker</td>
<td>27 54</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>31 62</td>
</tr>
<tr>
<td>Prokinetic agent</td>
<td>6 12</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>2 4</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>40 80</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>20/40 50</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>9/40 22.5</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>5/40 12.5</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>5/40 12.5</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>4/40 10</td>
</tr>
<tr>
<td>Prednisone</td>
<td>20/40 50</td>
</tr>
</tbody>
</table>

Treatment modalities in the patients varied according to the presenting symptoms and extent of organ involvement. Twenty seven of the patients were on a proton pump inhibitor (PPI)/H2 receptor blocker, 31 were on a calcium channel blocker, 18 were of acetylsalicylic acid and 40 were on immunosuppressant therapy, either in combination or as a single agent (Table 6).

### Discussion

Systemic sclerosis/ scleroderma is a rare condition with an estimated prevalence of 50 to 300 cases per 1 million persons and an incidence ranging from 2.3 to 22.8 cases per 1 million persons per year with an increased incidence reported amongst blacks. The mean age of at diagnosis was 41.7 years; compared to 40.3 years in the Nigerian series and 36.1 years in the South African study. The male to female ratio was 1:4 which is comparable to South African data (M:F 1:4.6) and Nigerian study M:F 1:6. The youngest patient in our study was a four year old male who presented with localized scleroderma with negative autoantibody profile, while the oldest were three patients aged 70 years.

Diffuse cutaneous was the commonest clinical variant, occurring in 74%, with no cases being described with systemic sclerosis sine scleroderma. A Nigeria study had 57% of their patients presenting as diffuse cutaneous while a South African study had 65% of the patients presenting as diffuse cutaneous. Patients with systemic sclerosis sine
scleroderma may have presented to other specialties such as gastroenterologists or chest physicians depending on the predominant organ involved. This may account for the absence of this variant at our rheumatology clinic. Similarly, patients with localized forms of scleroderma may have presented to the dermatology clinic and thus lead to underreporting in our series.

Skin involvement was the commonest manifestation (100%), followed by with Raynaud’s phenomenon at 58% and esophageal disease was present in 49% of the patients. The relatively lower incidence of Raynaud’s compared to other largely western studies may be due to hotter climate and darker skin pigmentation leading to underreporting in our population. Nigerian study documented Raynaud’s in only two patients (14%). The South African study, which was carried out in blacks, reported occurrence of raynaud’s in 90% of their patients. The lower incidence of Raynauds may also be attributed to the retrospective nature of the study.

Antinuclear antibody was done in 21 patients and was positive in 67%. Anti-SCL-70 autoantibody, which is specific for scleroderma was, present in only 4 out of the 14 patients tested (28%). All the patients with antibodies to SCL-70 had the diffuse cutaneous variant. Anti-SCL-70 antibodies are more common in the diffuse cutaneous variant and are associated with severer forms of the disease. Two of these patients had severe lung restrictive patterns on pulmonary function tests, two had esophageal dysmotility whereas one had peripheral gangrene. One of the mortalities reported in our case series had anti-SCL-70 antibodies.

Two patients presented with diffuse cutaneous systemic sclerosis after having been diagnosed to have breast cancer and subsequently underwent mastectomy followed by radiation and chemotherapy consisting of cyclophosphamide, methotrexate and 5-flourouracil. One patient developed the disease three years after the diagnosis of breast cancer. In this patient the autoantibodies done were all negative. The other patient developed diffuse cutaneous disease 10 years after the diagnosis of cancer. In this patient rheumatoid factor as well as SCL-70 antibodies were positive. Cytotoxic medications have been implicated in the pathogenesis of this disease. Treatment modalities varied depending on the clinical presentation. Forty-nine percent of the patients were on either prokinetic or PPI/HF blocker. Immunosuppressants were administered to 72% of the patients, mainly due to internal organ involvement especially pulmonary involvement.

The three deaths reported were as a results of pulmonary involvement (both fibrosis and pulmonary arterial hypertension) and cor pulmonale. The two cases of scleroderma renal crisis were documented in our series were managed successfully with immunosuppressants and angiotensin converting enzyme inhibitors. This is in keeping with data that shows the commonest cause of death currently is as a result of pulmonary involvement.

Limitations of the study included loss of follow up of majority of the patients. More than half of the patients had not presented to the clinic in over one year. Some of these patients may have succumbed to their disease in peripheral health facilities. This is a recurrent problem in most of the outpatient clinics due to a variety of reasons such as lack of financial resources and residing far from the hospital. There was a limitation of the investigations carried out due to financial constraints. Being a retrospective study, some data may have been missing from the patients’ records. It is hoped that this study will provide vital information for a rare disease, which has not been studied much in the African population and that it will serve as a reference for future studies.

References

The disease can be treated with immunosuppressants, which have been shown to be effective in many cases. In our study, 72% of the patients were managed successfully with immunosuppressants.

The lower incidence of Raynaud’s may also be attributed to hotter climate and darker skin pigmentation leading to underreporting in our series. Being a tertiary care center, most of the investigations were carried out due to financial constraints. Being a tertiary care center, most of the investigations were carried out due to financial constraints. Being a tertiary care center, most of the investigations were carried out due to financial constraints.

Similarly, patients with localized forms of scleroderma may have presented to other specialties such as gastroenterologists or chest physicians depending on where and how the disease presented. The patients who were managed successfully with immunosuppressants were managed particularly if their illness involved internal organs and they had to be referred to other specialists. The patients who were managed successfully with immunosuppressants were managed particularly if their illness involved internal organs and they had to be referred to other specialists.

The three deaths reported were as a result of internal organ involvement. One patient developed the disease three years after being diagnosed with breast cancer and subsequently underwent mastectomy. However, his disease progressed rapidly and he died within a year of the mastectomy.

Immunosuppressants were administered to 72% of the patients, mainly due to internal organ involvement. In this patient, rheumatoid factor was positive in 67%. Anti-SCL-70 autoantibody is specific for scleroderma and was present in only 4 out of the 100 patients. The other patients had antivariants and are associated with severer forms of the disease. Two of these patients had severe lung restrictive pattern on pulmonary function tests, two had esophageal disease. Two of these patients had severe lung restrictive pattern on pulmonary function tests, two had esophageal disease.

The lower incidence of Raynaud’s may also be attributed to hotter climate and darker skin pigmentation leading to underreporting in our series. Being a tertiary care center, most of the investigations were carried out due to financial constraints. Being a tertiary care center, most of the investigations were carried out due to financial constraints. Being a tertiary care center, most of the investigations were carried out due to financial constraints.

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The reference list contains a variety of sources, including studies on the prevalence, incidence, survival, and disease manifestations of systemic sclerosis. The references cited include studies from various regions, such as Africa, Asia, and Europe, highlighting the diversity of research on systemic sclerosis across different populations.
Platelet counts in patients with rheumatoid arthritis at the Kenyatta National Hospital- Nairobi, Kenya

Mbuthia BM¹, Oyoo GO¹, Kitonyi GW²

Abstract

Background: Rheumatoid arthritis (RA) is a disease associated with significant morbidity and mortality. Thrombocytosis is one of the haematological manifestations of rheumatoid arthritis that occurs in active disease. Platelet counts may vary depending on disease activity and the variation has been shown to correlate with clinical and laboratory indices of disease activity in RA. Occasionally patients with RA may have drug induced thrombocytopenia.

Objectives: To determine the relationship between platelet counts and clinical disease activity in patients with RA at Kenyatta National Hospital (KNH).

Design: A cross-sectional descriptive study.

Setting: Rheumatoid arthritis patients attending the KNH Rheumatology Outpatient Clinic (ROPC).

Methods: Patients presenting to the clinic were screened and those meeting the inclusion criteria recruited into the study. Consecutive sampling technique was done. A targeted history was obtained, following which a physical exam was done on the recruited patients. The patients’ platelet counts were measured using Abbot Cell Dyn 1300. The patients’ erythrocyte sedimentation rate (ESR) was measured with the Wintrobe’s method. The patients’ clinical disease activity using the DAS 28 score was recorded.

Results: One hundred and four patients were recruited over the 6 months period between November 2010 and April 2011. Females were 90 (86.5%) and 14 (13.5%) were males giving a male to female ratio of 1:6.4. The mean age of the patients was 48 years. Regarding medication use, 75% of the patients were on disease modifying anti-rheumatic drugs (DMARDs), 72.1% on non-steroidal analgesics (NSAIDs) and 46.2% on steroids. The mean platelet count was 313.2 ±SD94 x 10⁹/L with a range of 152 -611 x 10⁹/L. Only 15 (14.4%) had thrombocytosis (>400x 10⁹/L). No case of thrombocytopenia was recorded. Ninety two had active disease (88.5%) while 10 (11.5%) were in remission. Among those with active disease, 10 (9.6%) had mild disease, 51 (49%) moderate disease and 31 (29.6%) high disease activity. The DAS28 score was not significantly different between those who had thrombocytosis and those who had normal platelet counts (p=0.413). However, HB, MCV and MCH were significantly lower in those with thrombocytosis at P values of 0.02, 0.002, 0.03 respectively. No correlation was found between platelet counts and clinical disease activity (DAS28).

Conclusion: While thrombocytosis was found in 14.4% of patients with RA, this study demonstrated that no relationship exists between platelet counts and disease activity in patients with rheumatoid arthritis seen at KNH.

Introduction

Rheumatoid arthritis is a chronic systemic inflammatory disorder characterised by deforming symmetrical polyarthritis often leading to joint destruction, deformity and loss of function. Extra-articular features and systemic symptoms can commonly occur and may antedate the onset of joint symptoms¹. Chronic pain, disability and excess mortality are common sequelae. High standardised mortality rates have been observed in the RA population compared with the general population²,³. Thrombocytosis is among one of the haematological manifestations of rheumatoid arthritis (RA). Various studies have demonstrated thrombocytosis in RA with prevalence ranges from 16% to 51% in different studies⁴-⁷. Several possible mechanisms are thought to cause the increased platelet count. These include, decreased platelet survival, increased erythropoietin levels, inflammatory cytokines, increased...
thrombopoietin levels and analgesic-induced occult gastrointestinal bleeding. Thrombocytosis has been shown to have consistent correlation with disease activity in different studies. Thrombocytosis is associated with more active disease and extra-articular manifestations are more common. Elevated platelet counts are also associated with more joint damage. Platelet counts have also been shown to positively correlate with acute phase reactants such as ESR, CRP in RA.

This study was undertaken to describe the platelet counts in patients with RA and determine any relationship to clinical disease activity.

**Materials and Methods**

This was a cross-sectional descriptive study carried out at the Kenyatta National Referral and Teaching Hospital from November 2010 to April 2011. The study population were patients with RA on follow up at the KNH ROPC. The inclusion criteria were patients aged 18 years and above with rheumatoid arthritis attending the ROPC and those who gave informed consent. Patients excluded included those with acute febrile illnesses, bleeding disorders, haematological conditions, patients known to have malignancies and RA with mixed connective tissue disease. The main outcome variables were clinical disease activity and platelet count. Clinical disease activity as per DAS28 scores was classified as follows: Remission ≤ 2.6, Mild 2.6-3.2, Moderate >3.2-5.1 and High ≥ 5.1. Platelet count was graded as follows: Thrombocytopenia <150 x 10^9/L, Normal platelet 150-400 x 10^9/L, Mild thrombocytosis 400-600 x 10^9/L, Moderate thrombocytosis 650-800 x 10^9/L, Marked thrombocytosis >800 x 10^9/L.

In the ROPC, all patients on follow up for RA were screened for recruitment into the study. The files of eligible patients who met the inclusion criteria were selected and consecutively sampled for study. Of the eligible patients, informed consent was obtained from them to participate in the study. Once consent was given, history was taken, physical examination performed and blood collected from them for laboratory investigation as outlined below. The principal investigator obtained socio-demographic data which included age, gender, marital status, place of residence, and occupation from both the patients and/or the patients’ records. Disease history obtained included duration of illness, when first diagnosed, whether on any treatment, response to treatment and any current concurrent illness. Physical examination was carried out to check for features of active RA. All joints were examined for swelling and tenderness. The number of joints swollen and/ tender was recorded on the DAS28 score sheet. The patient was asked to assess his/her general well being using the Visual Analog Scale (VAS) and this too recorded in the DAS28 score sheet.

Three millilitres of venous blood was drawn aseptically from the forearm and collected in an EDTA bottle for a full blood count and ESR estimation in consenting patients. The blood was analyzed using Abbot Cell Dyn 1300 in the Department of Pathology, Haematology unit University of Nairobi. The ESR was also carried out by the Wintrobe’s method. The ESR level was then recorded in the DAS score sheet. The total DAS score was then calculated using the DAS28 calculator.

All data was collected on the study proforma and entered into a computer data base MS Access. Statistical analysis was done using Statistical Package for Social Scientists (SPSS) version 17.0 software. Continuous variables such as age, DAS 28 scores platelet counts and ESR are summarized into means, median, and ranges. Comparison of means was done using Student’s t test for normally distributed data and Mann Whitney U test for non-normal data. Platelet count was correlated to DAS28 score using the spearman Rho coefficients. Bivariate analysis was done using the Man Whitney test, Pearson’s chi-square or Fisher exact test. Multivariate analysis was done by linear regression was used to determine the relationship between platelet count and DAS28 adjusting for various factors. Comparisons were considered statistically significant at a P value ≤ 0.05. Ninety five percent confidence limits were used as a measure of certainty. Results are presented in form of charts, graphs and tables. The study was carried out upon approval by the local ethics board.

**Results**

In a period of 6 months, among the patients attending ROPC, 104 patients with RA were identified. These were screened and recruited into the study. Most of the patients were aged between 40 to 59 years at 53.9% with a mean age of 48 years ± 14 and a median age of 49 years (18-79 years) and a male to female ratio of 1: 6.4. Most of the patients had been diagnosed with RA over the last 1 to 5 years at 43.3% while in 25 (24%) the diagnosis had been made over the last one year. Majority of the patients were on DMARDs at 78 (75%) while on 48 (46.2%) were on steroids. The most commonly used DMARD was methotrexate in 72(69.2%) of the patients while only one patient was on leflunomide.

The platelet counts in the study population varied between 152 to 611 x10^9/L with a mean of 313.2 ±SD 94.0 and a median of 294.5 x10^9/L. Eighty nine (85.6%) had normal platelet counts while 15 (14.4%) had thrombocytosis. No case of moderate (more than 650 x10^9/L) or severe thrombocytosis (>800 x10^9/L) was recorded. Among those with thrombocytosis, 12(80%) were female and 3(20%) were male. Platelet counts of the study population are shown in Table 1.
Table 1: Platelet counts in study population

<table>
<thead>
<tr>
<th>Platelet counts</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>294 x10⁹/L</td>
</tr>
<tr>
<td>Mean</td>
<td>313.2±94 x10⁹/L</td>
</tr>
<tr>
<td>Range</td>
<td>152-611 x10⁹/L</td>
</tr>
<tr>
<td>Normal platelet counts (150- 400 x 10⁹/L)</td>
<td>89 (85.6%)</td>
</tr>
<tr>
<td>Thrombocytosis (mild)</td>
<td>15 (14.4%)</td>
</tr>
<tr>
<td>Above 400 x 10⁹/L</td>
<td></td>
</tr>
</tbody>
</table>

Comparison of various parameters between those with thrombocytosis and those with normal platelet counts was done. Comparison between those with normal versus elevated platelet counts showed that the median DAS28 score was slightly lower in those with normal platelet scores at 4.2 versus 4.6 in those with thrombocytosis but insignificant (p 0.413). Differences in the median age and erythrocyte sedimentation rate (ESR) levels were also insignificant and P values of 0.715 and 0.185 respectively. Significant differences in the median of the haemoglobin levels, RBC indices and WBC counts were found between the two groups. Lower HB, MCV and MCH were associated with elevated platelet counts while higher WBC was associated with thrombocytosis (Table 2).

The significant values were then subjected to a multivariate analysis by linear regression as shown in Table 5. While haemoglobin lost significance MCV remained significant demonstrating that the MCV is independently associated with platelet levels as is WBCs.

Table 2: Comparison of various parameters in those with normal vs high platelet counts

<table>
<thead>
<tr>
<th>Laboratory parameters</th>
<th>Platelet count (&gt;400x10⁹/L)</th>
<th>Platelets count (150- 400x10⁹/L)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Median (Range)</td>
<td>No.</td>
</tr>
<tr>
<td>DAS28 Score</td>
<td>15</td>
<td>4.6 (2.2-7.1)</td>
<td>89</td>
</tr>
<tr>
<td>Age (years)</td>
<td>15</td>
<td>46.0 (25.0 - 76.0)</td>
<td>89</td>
</tr>
<tr>
<td>ESR(mm/hr)</td>
<td>15</td>
<td>40.0 (6.0-60.0)</td>
<td>89</td>
</tr>
<tr>
<td>HB(g/dl)</td>
<td>15</td>
<td>11.5 (4.4-13.9)</td>
<td>89</td>
</tr>
<tr>
<td>MCV(fl)</td>
<td>15</td>
<td>72.0 (56.0-87.0)</td>
<td>89</td>
</tr>
<tr>
<td>MCH(pg)</td>
<td>15</td>
<td>22.8 (15.6-28.9)</td>
<td>89</td>
</tr>
<tr>
<td>WBC x10⁹/L</td>
<td>15</td>
<td>7.6 (4.8-13.6)</td>
<td>89</td>
</tr>
</tbody>
</table>

Regarding the clinical disease activity, the mean DAS28 score was 4.5 ± 1.5 with a median of 4.3 and a range of 1.7-8.4. Majority of the patients had moderate disease activity at 52 (49 %) while only 12 (11.5 %) % had their disease in remission. Thirty (29.8%) had high disease activity and 10 (9.6%) mild disease as shown in Figure 1.

Figure 1: Distribution of clinical disease activity.

In terms of platelet counts for the various levels of disease activity, the median platelet count for those in remission was 285x 10⁹/L, mild disease 310x10⁹/L, 285x10⁹/L for moderate disease and 311x10⁹/L for those with high disease activity. This is best illustrated in Figure 3.
The mean platelet count in the study population was 289.64 ± 5.27 x10^9/L in healthy Kenyan adults. A more recent study by Rajab et al. on haematological parameters in healthy Kenyan blood donors found a mean platelet count of 241.2 ± 86.6 x10^9/L and median of 235.1 x10^9/L. Bain et al. found even lower platelet counts of a mean of 183 x10^9/L in black females and 207 x10^9/L in black males in a study comparing ethnic and gender differences in healthy adults though in a different set up. It can therefore be inferred from these previous studies that patients with RA have higher platelet counts. Our results are comparable to a Turkish study by Yacizi et al. who found mean platelets of 307±99 x10^9/L in patients with active RA compared to a mean of 258 ±58 x10^9/L in healthy controls.

It is worth noting that despite the significant use of DMARDs, no case of thrombocytopenia was recorded. The prevalence of thrombocytopenia in various studies ranges from 0.8 to 3.1% in patients using DMARDs. In a study in India found only 2 out of 245 patients (0.8%) had thrombocytopenia. This is close to our study that recorded no case of thrombocytopenia. The consistent concurrent use of folate use in our patients may account for this finding as folate has been shown to reduce the adverse effects of methotrexate.

Thrombocytosis was found in only 15 (14.4%) of the study population. Studies elsewhere have recorded higher prevalences of thrombocytosis. Hutchingsons et al. and Selroos found prevalences of 51% and 33% respectively. Notably these studies were done in the 70s and 80s when use of DMARDs was not widespread. A higher prevalence of thrombocytosis in Caucasians could also be attributable to the fact that Caucasians have been shown to have higher levels of platelets compared to Africans in several studies. Therefore a relatively lower baseline platelet count to start with will result to fewer cases of thrombocytosis when using the same cutoff as the Western studies despite a similar increase in platelet counts. A case control study in future may bring out these differences. A more recent Saudi Arabia study found a prevalence of 16%. This is comparable to the findings of this study. No similar study has been done in Africa to which the findings can be compared.

Most of the patients had active disease at 88.5% (DAS28 scores >2.6). The majority of these had moderate disease activity (49%) while 29.7% had high disease activity and only 9.6% had mild disease activity. This is probably because a significant number of the patients (24%) were diagnosed during the study period and had previously not been on treatment and therefore had high disease activity. Another possible explanation is that more aggressive treatment maybe needed for these patients such as anti-TNF antagonist or use of biological agents of which none of the patients was on. The study did not assess compliance to treatment which could also affect the levels of disease activity seen in the study population.

While comparing different parameters in those with thrombocytosis versus normal PCs, no significant difference was found in the median DAS28 scores between the groups i.e 4.6 versus 4.2 (p=0.413). This precludes any meaningful relationship between platelet counts and disease activity in this study. The Hb, MCV
and MCH were however noted to be significantly lower in the group with thrombocytosis at p of 0.20,0.002 and 0.001 respectively. This is similar to what other studies have reported. Hutchingsons et al\(^7\) found higher platelet counts in those with lower Hb mean of 12.47(50.10) in platelets <450 x10\(^9\)/L and 11.27±0.77 in >450 x10\(^9\)/L. The lower Hb was noted to be mainly microcytic hypochromic. This was confirmed by the multivariate analysis that confirmed MCV to be an independent contributor to platelet counts. The microcytic anaemia is usually due to either iron deficiency anaemia(IDA) or less commonly anaemia of chronic disease (ACD). IDA is usually associated with a reactive thrombocytosis. ACD may also be associated with a reactive thrombocytosis secondary to chronic inflammation\(^1\). This can explain the association between thrombocytosis and low MCV. Further studies are needed to define the exact cause(s) of the low MCV/MCH in our study population.

Correlation between disease activity and platelet count revealed no significant correlation at \(p<0.394\). These findings are in contrast to earlier studies by Hutchingsons et al\(^2\) and Farr et al\(^9\) who both found a positive correlation. However they used different measures of disease activity with Hutchingsons et al\(^2\) including a presence of extraarticular manifestations, morning stiffness and grip strength which are not assessed in the DAS 28 score. Farr et al\(^9\) used the total articular index i.e summation of pain on movement, stiffness, swelling, heat and tenderness of each joint. Notably, the other studies had recorded higher levels of thrombocytosis to start with.

Our findings are more comparable to Yacizi’s et al\(^5\) who used the DAS score in assessment of disease activity. The study demonstrated a fall in mean platelet counts after a period of treatment but the platelet counts did not correlate with disease activity however.

In conclusion, patients with RA have relatively increased platelet counts compared to the general population in our black patients. While thrombocytosis was found in 14.4% of the patients with RA, no relationship was found between platelet counts and disease activity in patients with RA in this study.

References

Abstract

Background: Osteoarthritis is an age related degenerative disease seen predominantly in the elderly. Non-steroidal anti-inflammatory drug (NSAID) is a major therapeutic component in the management of osteoarthritis. Selective NSAID was developed to reduce the incidence of gastric irritation and erosion caused by the regular NSAIDS.

Methods: All elderly patients with clinical and radiographic features of osteoarthritis were included in the study. Some patients were placed on regular NSAIDS while others were placed on selective NSAIDS, being randomly selected. The trial was carried out in a private clinic over three years. Proton pump inhibitor was added as soon as patients complain of abdominal discomfort.

Results: Osteoarthritis was made up of 30.9% of the total rheumatology cases seen over the three years period. Both patients on non-selective and selective NSAIDS presented with gastric discomfort. Symptoms were more noticeable in patients on non-selective NSAIDS. Females were more affected. Only two patients (2.1%) presented with symptomless gastro-intestinal bleeding. Proton pump inhibitor was helpful in majority of patients.

Conclusion: Gastric discomfort is very common in elderly patients on NSAIDS. Selective NSAIDS is not an exception though better than non-selective NSAIDS. Contributory factors may be co-intake of low dose aspirin and few others on corticosteroid and anticoagulant.

Key words: NSAIDS, Gastric discomfort, Osteoarthritis, Elderly.

Introduction

Peptic ulcer disease is a heterogeneous group of disorder involving the gastrointestinal tract and results from an imbalance between the aggressive forces of acid and pepsin and the defensive mechanism of the gastric mucosa\(^1\)\(^-\)\(^3\). There has been a decline in the prevalence of uncomplicated peptic ulcer disease since the discovery of *Helicobacter pylori*\(^4\), however, among the elderly people has been found a rise in admission for ulcer haemorrhage and perforation. The rise has been attributed to the increased use of NSAIDS and low dose aspirin\(^5\). Symptoms usually do not correlate with the severity of mucosa damage. Elderly patients however need to understand the prudent use of NSAIDS to prevent serious complications\(^5\)\(^-\)\(^6\). NSAIDS are commonly prescribed for a variety of musculoskeletal conditions such as rheumatoid arthritis, systemic lupus erythematosus and osteoarthritis\(^7\).

NSAIDS cause damage to the gastric mucosa through inhibition of gastric prostaglandin synthesis. The inhibition leads to the reduction in the level of protection of the gastric mucosa by the prostaglandin (PGE\(_2\), PGI\(_2\)) and also leads to alteration in mucus and bicarbonate production as well as blood flow into the gastric mucosa, all of which are prostaglandin dependent functions\(^8\). When NSAID is taken orally, it dissociates in the gastric lumen and concentrates in the gastric mucosa. Once within the gastric mucosa cell, acidic NSAID inhibit prostaglandin production and prostaglandin dependent cell protection function\(^9\). NSAID gain access to the gastric mucosa via three routes. Direct contact of the ingested drug with the gastric mucosa, indirect route via secretion in the bile and backward reflux into the stomach, and systemic route via circulation in the blood\(^10\).
bleeding, and patients on concomitant anticoagulant or steroid. All rheumatology cases seen over 3 years were noted and all cases of primary osteoarthritis of the knee were extracted and the percentage of knee osteoarthritis in the total rheumatology cases determined. Patients were randomly selected, some were placed on regular NSAIDS (diclofenac, ibuprofen), and others on selective NSAID (e.g. Celebrex). Patients that developed symptoms of gastric irritation were given proton pump inhibitor (omeprazole).

Results

Osteoarthritis represented 30.9% of the total cases seen over 3 years. Gastrointestinal disturbances were noted in both groups (regular and selective NSAIDS). The disturbances were more noticeable in patients on regular NSAIDS. Total of 84 patients presented with gastrointestinal disturbances (80.8%), 24 males (28.6%) and 60 females (71.4%). Proton pump inhibitor was helpful in majority of symptomatic patients. Two patients (1.9%) however presented with symptomless gastrointestinal bleeding while eight patients (7.7%) were lost to follow-up.

Discussion

There are so many people on NSAIDS both prescribed and over-the-counter consumption. There is an increased prevalence of NSAIDS induced gastrointestinal injury because of widespread use of the drug. The readily availability of NSAIDS as over-the-counter medications adds to the incidence of gastrointestinal injury because people tend to consume more than the recommended doses. Some of the studied patients combined two or more NSAIDS.

The pathogenesis of NSAID-induced gastrointestinal mucosa injury is complex. The direct-injury hypothesis suggests that both NSAID-mediated direct acidity damage and the suppression of prostaglandin synthesis are necessary to induce gastric damage. The first insult to the gastro-duodenal mucosa is as a result of the acidic property of the NSAIDS, and the later mucosa damage is as a result of active hepatic metabolites of NSAIDS and the NSAID-related decrease in the gastric mucosa prostaglandins. When the hepatic metabolites in the bile are secreted into the duodenum, they cause mucosa damage to the stomach by duodenogastric reflux and to the small intestine by antegrade passage through the gastrointestinal tract.

Prostaglandins maintain an intact gastric mucosa barrier by increasing secretion of mucus and bicarbonate maintaining mucosal blood flow, and decreasing acid-secretion. Suppression of prostaglandin synthesis can occur systemically with both oral and parenteral NSAID therapy. The antiplatelet activity of some NSAIDS in low doses may cause bleeding from pre-existing ulcers. There are two isoforms of the enzymes cyclooxygenase (cox) and NSAIDS inhibit both isoforms. The isoform cox1 produces protective prostaglandins in the stomach and the isofom cox2 is inducible at sites of inflammation. Researchers have developed a new type of NSAIDS that specifically inhibits cox2 while sparing cox1. Selective inhibitors should theoretically provide analgesics and anti-inflammatory effects of older NSAIDS with a reduced risk of gastrointestinal injury. It was however found out that the selective cox2 are not completely devoid of gastric mucosa injury.

When NSAIDS irritate the gastric mucosa, they weaken the resistance to acid, causing gastritis, ulcers, bleeding, or perforation. The damage ranges from superficial injury to single or multiple ulcers, some of which may bleed. The clinical manifestations seen in our patients include dyspepsia, nausea and vomiting. Only very few presented with diarrhea. Two patients however presented with symptomless gastro-intestinal bleeding. The clinical features however do not correlate with the severity of the mucosa damage. The NSAIDS differ with regard to their risk of inducing upper gastrointestinal bleeding and or perforation.

Elderly patients are especially at risk for NSAID-induced gastro-duodenal mucosa injury because of their multiple medical conditions and polypharmacy. Risk factors include concomitant corticosteroid or anticoagulant therapy. Patients with a history of peptic ulcer disease and gastritis are also at risk.

The prevalence of endoscopically confirmed gastro-intestinal ulcers in NSAIDS users is quoted to be between 15 and 30%. Between 12 to 30% of NSAID induced ulcers are gastric ulcer, whereas 2 to 19% are duodenal ulcers. NSAID-induced ulcers are symptomatic only in 1% of patients after 3 to 6 months and in 2 to 4% of patients after one year. This study has shown that 8 out of 10 elderly patients on prolonged NSAIDS eventually develop some degree of gastro-intestinal discomfort, and that the symptoms are more noticeable in elderly women. It is therefore advisable that drugs causing gastrointestinal toxicity as a consequence of a systemic effect should be co-prescribed with suitable prophylactic agents such as proton pump inhibitors and misoprostol in elderly patients. The importance of gastro-protection is vital in preventing patient morbidity and mortality especially in patients with a number of risk factors which include patients over the age of sixty years, smokers, patients with a history of peptic ulcer disease, or concomitant use of anti-coagulants, bisphosphonates, or corticosteroids.
The hypothesis suggests that both NSAID-mediated direct mucosa injury and the decrease in gastric prostaglandins are necessary to induce gastric damage. When the hepatic metabolites of NSAIDS and the NSAID-related decrease in the gastric acidic property interact, the gastrointestinal tract may be more vulnerable. The symptoms of gastric irritation are given proton pump inhibitors (PPIs) such as omeprazole.

Table 1: Spectrum of rheumatology cases seen over 3 years (July 2009- June 2012)

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Condition</th>
<th>Number</th>
<th>Male (%)</th>
<th>Female (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Osteoarthritis</td>
<td>104</td>
<td>32</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>Rheumatoid arthritis</td>
<td>12</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>Cervical spondylolisthesis</td>
<td>36</td>
<td>23</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>Lumbar spondylolisthesis</td>
<td>25</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>Low back pain</td>
<td>48</td>
<td>37</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>Gout</td>
<td>28</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>SLE</td>
<td>6</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>Shoulder pain syndrome</td>
<td>12</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>Hypermobility syndrome</td>
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<td>0</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>Fibromyagia</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
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<td>Polymyalgia rheumatica</td>
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<td>0</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>Bursitis</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>Trigger finger</td>
<td>16</td>
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<td>17</td>
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<td>0</td>
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<td>0</td>
<td>2</td>
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<td>Psoriatic arthropathy</td>
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<td>1</td>
<td>0</td>
</tr>
<tr>
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<td>Plantar fasciitis</td>
<td>7</td>
<td>2</td>
<td>5</td>
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<td>Carpal tunnel syndrome</td>
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<td>1</td>
<td>2</td>
</tr>
<tr>
<td>23</td>
<td>Archilis tendinitis</td>
<td>8</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>336</td>
<td>160</td>
<td>176</td>
</tr>
</tbody>
</table>
References


Infl iximab induced remission in a case of severe Crohns enteropathic arthropathy with pyoderma gangrenosum

Ghetia TA1, Ghetia HA2, Kenawy SA3

Abstract

Background: The indications for anti-TNFα therapy for inflammatory bowel diseases (IBD) have increased to include demonstrable mucosal healing, improvement in quality of life, and treatment of extraintestinal manifestations including arthritis, sacroiliitis and pyoderma gangrenosum (PG).

Case report: A male smoker, 27 years old, with enteropathic arthropathy on top of Crohn's disease (CD) had a disease duration of 2.25 years. He had severe Crohn's disease activity index (CDAI = 473) and a poor health status as assessed by the IBD questionnaire (IBDQ) of 39. He had oligoarthritis and bilateral sacroiliitis. There was limited chest expansion and lumbar spine mobility. The patient had PG on the dorsum of the right foot and mild bilateral uveitis. He was receiving sulphasalazine 2000 mg/day and low dose corticosteroids 10 mg/day and was then given cyclosporine for a month and the steroid dose elevated (60 mg/day) but with partial improvement. Cyclosporine was stopped and the patient remarkably improved after receiving, in addition to the corticosteroids, IV induction regimen of infliximab 5mg/kg at 0,2 and 6 weeks. A remission occurred (CDAI 98.5) with fading of arthritis, notable decrease in the size and severity of the PG lesion and a significant disappearance of the back stiffness with an increase in the chest expansion and lumbar spine mobility. The IBDQ significantly improved to be 159.

Conclusion: Anti-TNFα such as infliximab could be considered as a promising option for treatment of severe CD patients and for those with PG.

Keywords: Crohns disease, Infliximab, Pyoderma gangrenosum

Introduction

Inflammatory bowel diseases (IBD) are intestinal inflammatory conditions of unknown etiology, characterized by remissions and exacerbations, with Crohn's disease (CD) as one of the main phenotypes. The pathogenesis of CD is not totally understood, but bowel damage is induced by uncontrolled immune activation and inappropriate response to luminal antigens resulting in an imbalance between pro and anti-inflammatory cytokines which maintains chronic tissue damage. Arthritis is the most common extraintestinal manifestation of IBD having an impact on morbidity and quality of life, yet the mechanisms surrounding its development remain unclear.

Major advances have been achieved over the last decade both in the clinical and scientific understanding of the spondyloarthritides (SpA). The proven high efficacy of TNF blocker treatment has meant a breakthrough for SpA patients, who until recently had only quite limited treatment options.

Case report

A male smoker, 27 years old, with enteropathic arthropathy on top of Crohns disease (CD) fulfilled the European spondyloarthropathies study group (ESSG) spondyloarthropathy classification criteria. The disease duration was 2.25 years. The Crohns Disease Activity Index (CDAI) was assessed as well as the Inflammatory Bowel Disease Questionnaire (IBDQ). Thorough rheumatologic examination was performed for any joint or axial involvement. Plain X-ray of the affected and sacroiliac joints was performed. The New York scoring method for the sacroiliac joints (SIJ) was followed. The study was approved by the local ethics committee and a written consent was obtained according to the Declaration of Helsinki.
The patient had severe CD (CDAI = 473) and IBDQ of 39. He had oligoarthritis involving the left knee and ankle. There was severe tenderness of the ankle and moderate in the knee with moderate effusion in both. There was associated bilateral clinical sacroiliitis with moderate tenderness. The plain X-ray of the SIJ showed grade II-III while the X-ray of the knee and ankle were free. The patient had enthesitis of the tendoachillis of the left side and chostochondritis. There was back stiffness for 40 minutes and limited lumbar spine mobility as measured by the Schöber test (which increased from 15 cm to 16.7 cm). The chest expansion was limited (2 cm).

The patient had an associated skin lesion diagnosed as pyoderma gangrenosum (PG) on the dorsum of the right foot (8.5 x 6 cm). The histopathology revealed infiltrate of inflammatory cells with predominance of lymphocytes and polymorphonuclear leukocytes and few histiocytes. The patient had mild bilateral uveitis.

**Figure 1:** A male patient with enteropathic arthritis with underlying Crohn's disease. (a) dorsum of the foot showing Pyoderma gangrenosum. (b) Plain X-ray showing bilateral sacroiliitis.

The laboratory investigations of the patient were unremarkable; rheumatoid factor was negative, hemoglobin level (9.8 g/dl), white blood cell (WBC) count (4.85 x10^9/mm³), platelets (152.97 x10^9/mm³), and erythrocyte sedimentation rate (ESR) (46.12 mm /1st hr). The HLA-B27 was negative. The patient received azathioprine 100 mg/day for 5 variable periods after the disease onset with different doses and periods of oral steroids and sulphasalazine. On presentation, the patient was receiving sulphasalazine 2000 mg/day and low dose corticosteroids 10 mg/day.

The patient was given cyclosporine for a month and the steroid dose elevated (60 mg/day) but with partial improvement. The cyclosporine was stopped and the patient remarkably improved after receiving, in addition to the corticosteroids (60mg/day), IV induction regimen of infliximab 5mg/kg at 0,2 and 6 weeks. A remission occurred (CDAI 98.5) with fading of arthritis, notable decrease in the size and severity of the PG lesion and a significant disappearance of the back stiffness with an increase in the lumbar spine mobility (from 15 cm to 18.6 cm). The chest expansion increased to be 3.5 cm. The uveitis resolved in one eye and remained mild in the other. The IBDQ significantly improved to be 159. The patient was then maintained on infliximab 5mg/kg every 8 weeks and 20 mg prednisolone. Figure 1 shows the skin lesion and sacroiliitis in this patient at his initial presentation.

**Discussion**

In the present case with an IBD (Crohn disease), arthritis and sacroiliitis was present. It has been reported in other studies that seronegative spondyloarthropathy (SpA) symptoms are present in up to 50% of IBD patients with articular involvement being the most common extraintestinal manifestation occurring in 16% to 33% of the cases.

The present case also had an associated rare skin lesion, pyoderma gangrenosum (PG) which improved more after the administration of infliximab. The advent of biological therapies for IBD began in 1998 with the approval of infliximab for the treatment of refractory (to conventional agents) Crohn’s disease. Since then, the indications for anti-TNFα therapy for IBD have increased to include demonstrable mucosal healing, improvement in quality of life, reduction in surgeries and hospitalizations, and the treatment of extraintestinal manifestations including arthritis, sacroiliitis and PG. Pyoderma gangrenosum is an uncommon and challenging inflammatory, neutrophilic ulcerative dermatosis, highly associated with co morbidities, but poorly characterized from a therapeutic perspective.

In this case, HLA typing was negative. This is supported by the findings that the association with HLA-B27 is less strong in IBD-associated SpA than in ankylosing spondylitis (AS). The adaptive immune response in IBD is thought to be strictly differentiated through Th1 in CD. Recent findings, suggested that novel effector pathways could drive tissue damage, the most important pathway now emerging is the IL-23/IL-17 axis. A common inflammatory pathogenic pathway has been suggested in gut and joint inflammation in IBD. Treatment of SpA associated with IBD has gained important progress with the introduction of anti-TNF-α therapy.

This patient remarkably improved regarding the peripheral and axial arthritis with a notable decrease in the PG size after a combination of high dose corticosteroids and infliximab therapy. In another study, PG was 34% associated with IBD and 19% with seronegative arthritis. Similarly, it was most commonly located on the lower leg; contrarily, was found to be more frequent in females and unfortunately had a high mortality rate (16%) in. Pyoderma gangrenosum is associated with a variety of systemic diseases including IBD as CD and arthritis. The pathogenesis of PG remains unknown. Some patients with PG have abnormalities in cell and humoral immunity, with an increase in interleukin expression, particularly...
TNF-a 11. It has been reported that treatment of IBD is not always sufficient for control of arthritis and treatment with biologic agents is promising 4.

Over recent years, the management of IBD has dramatically changed. In particular, advances in understanding the pathogenesis and the natural course of the disease have substantially changed the therapeutic algorithms with the introduction of new biological drugs. Among these the anti-TNF-a monoclonal antibodies infliximab is currently approved for the management of CD, in particular for patients with moderately and severely active luminal disease who are nonresponders to conventional therapy 5. These newly developed treatment modalities are proving to be valuable additions to the current therapeutic armamentarium and add to our knowledge so that IBD patients could be treated with the right drug at the right time.

In conclusion, anti-TNFα such as infliximab could be considered as a promising option for treatment of severe CD patients and for those with PG. To confirm our results we propose that more cases of CD and/or PG are studied and for longer periods of follow up.

Conflicts of interest: none.

References

Association of sarcoidosis and myasthenia gravis: Case report

Kaouther BA2, Khaoula BA1, Sami T1, Zakraoui L2, Khedher A1

Abstract
Whereas the coexistence of different autoimmune or rheumatologic diseases with myasthenia gravis (MG) is well documented, its combination with sarcoidosis is extremely rare. Presented here is an interesting case with coexisting MG and sarcoidosis.

Case report
A 42-year-old female patient suffered from a facial palsy. Clinical examination was normal, as well as brain MRI. A chest CT scan confirmed multiple mediastinal adenopathy with interstitial syndrome. Spirometry showed a restrictive lung disease. The bronchoalveolar lavage showed a lymphocytic alveolitis at 48%. The patient's calcium level was normal. Further tests showed increased serum angiotensin converting enzyme (ACE) levels. The tuberculin test was negative. Mediastinoscopy was performed and a lymph node biopsy showed multiple typical noncaseating granulomas. The diagnosis of systemic sarcoidosis with pulmonary and neurological involvement was established. The patient was treated with 1mg/kg/day corticosteroids leading to clinical improvement of her facial palsy. Then, steroid treatment was declined. Two years later, she suffered from recurrence of facial palsy with episodes of dysphonia, ptosis and swallowing difficulties. Neurological examination revealed weakness in all her extremities, both proximal and distal. Amplification of symptom intensity after exercise was also reported and documented on examination. The tensilon test, as well as the repetitive nerve stimulation test, was positive. Acetylcholine receptor (AChR) binding antibodies were elevated consistent with MG. Based on all the above-mentioned findings, the patient was diagnosed with having coexistent MG and sarcoidosis. A new CT of the thorax revealed no signs of thymic hyperplasia or thymoma. Oral administration of pyridostigmine was started. Since no full symptom remission was achieved, prednisone was added leading to further clinical improvement. During her hospital stay, she developed respiratory distress and hypoxemia for which the patient was intubated. Intravenous immunoglobulins were performed, providing rapid but transitory improvement. Plasmapheresis was slightly more efficient.

Discussion
The coexistence of sarcoidosis and MG is very rare. Based on a literature review, only 12 cases were reported. In some cases, MG came first, while in others, sarcoidosis was already diagnosed when myasthenic features began. The originality of our case is the occurrence of sarcoidosis and the MG at the same time. Neurosarcoidosis is a complication in around 5% of patients with sarcoidosis. Its most frequent manifestation is cranial neuropathy. The facial nerve is most commonly affected, often bilaterally (around 25% in all reports). In our patient's case, systemic disease was also present, affecting the chest. This clinical data had clearly supported the diagnosis of neurosarcoidosis. At this moment, other cranial nerve examinations were normal. According to the literature, the AChR binding antibodies were elevated in all cases except one, where antibodies to muscle-specific tyrosine kinase were found. Whether a common immunogenetic basis between MG and sarcoidosis exists or not, remains unclear. Indeed, on the one hand MG is antibody-mediated. On the other hand, sarcoidosis is characterized by the accumulation of activated T-cells in the affected tissues with subsequent granuloma formation. However, the finding of granulomas in cases of MG has recently been reported.

Conclusion
It is noteworthy to report this case because of the multiple interesting features observed as well as the rarity of occurrence.

Conflict of interest: none
References


An atypical case of systemic lupus erythematosus presenting as fleeting hemorrhagic pleural effusion with normal complement level

Ochieng PO, Abrudescu A

Abstract

Background: Systemic lupus erythematosus (SLE) is a multisystem disease that can be a diagnostic conundrum.

Case report: We describe a patient who presented with recurrent fleeting exudative and hemorrhagic pleural effusion. It took multiple visits over 3 months and renal biopsy to confirm the diagnosis of SLE.

Management: The patient was treated with immunosuppression.

Results: She had a favorable clinical response and continues to be followed up as an outpatient.

Conclusion: Systemic lupus erythematosus can be difficult diagnosis to make as it may present with atypical features.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune multisystem disease with a myriad of presentation. The varying manifestations and progression make SLE a potential diagnostic challenge. We present an atypical case of SLE that was a diagnostic enigma.

Case report

Forty five year old black female first presented in March 2011 with acute onset right side pleuritic chest pain and fever. She reported a dry cough and no other symptom. At admission, she was in mild respiratory distress with respiratory rate of 20/min with the rest of the vitals normal. Chest exam was consistent with right pleural effusion and the rest of systemic examination was normal. Haemogram revealed normocytic anemia and leucocytosis. Urea, creatinine and electrolytes were within normal limits. Hepatic panel was unremarkable except for low protein and albumin. Chest X-ray (CXR) revealed right pleural effusion (Figure 1). On thoracocentesis the pleural fluid was hemorrhagic and exudative with parameters as shown in Table 1. Pleural cytology and microbiology tests were negative.

Antinuclear antigen (ANA) was positive with speckled pattern and titre of 1:160. Other connective tissue markers (Anti-DNA antibodies, anti-smith antibody, anti-Ro, anti-La and Rheumatoid factor) were negative. Hepatitis B and C and HIV screening were negative. Complement 3 and 4 levels were within normal limits with levels of 129 mg/dl and 29 mg/dl respectively. She was treated as with antibiotics for community acquired pneumonia with para pneumonic effusion and she improved and was discharged home.

In May 2011, she returned to the Emergency room with three days history of left side pleuritic chest pain and dyspnea. The pain was similar to her pain on previous admission but she had no fever or cough on this admission. Examination was consistent with left pleural effusion which was confirmed on CXR (Figure 2). Chest CT scan revealed pulmonary emboli in the left main pulmonary artery with no lung infarct and left pleural effusion (Figure 3). Pleural fluid was exudative and hemorrhagic with parameters on table 1. Pleural cytology revealed reactive mesothelial cells and no malignant cells and microbiology studies were negative. Repeat connective tissue work-up was again negative except for ANA titers that increased to 1:640. Complement 3 and 4 levels were normal at 79 mg/dl and 29 mg/dl respectively. Antiphospholipid and anti-beta 2 glycoprotein were negative. Urinalysis revealed proteinuria and 24 hour urine protein was 4.1g. Right kidney biopsy was consistent with membranous nephritis classified as lupus nephritis WHO class V (microscopy- glomerular capillary loops thickening with subepithelial spikes and no endocapillary proliferation or crescents. Electron microscopy- podocyte effacement with intramembranous, transmembranous and subepithelial immune deposits and
proliferation of basement membrane around the deposits. Immunopathology - glomerular capillary wall and mesangial nodular IgM/IgG and C3 deposits with tubular basement membrane, interstitium and blood vessel sparing.

On follow-up, to discuss the renal biopsy results in June 2011, the pleural effusion had resolved spontaneously and proteinuria had improved (to 0.8g proteinuria in 24 hours) but she had developed atypical desquamating rash with malar distribution (Figure 4). At this point she was treated with steroids. On follow-up she had improvement of proteinuria and resolution of her rash. She continued with follow-up at the outpatient clinic.

### Table 1: Pleural fluid analysis results

<table>
<thead>
<tr>
<th>Date</th>
<th>PH</th>
<th>prot (ser)</th>
<th>alb (ser)</th>
<th>ldh (ser)</th>
<th>gluc (ser)</th>
<th>RBC/ml</th>
<th>WBC/ml</th>
<th>neut %</th>
<th>lymph %</th>
<th>mon %</th>
<th>mes %</th>
<th>mQ</th>
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<tbody>
<tr>
<td>22/3/11</td>
<td>7.43</td>
<td>3.8 (ser 6)</td>
<td>1.8 (ser 2.2)</td>
<td>150</td>
<td>90 (mg/dl 179)</td>
<td>1020/69%</td>
<td>2600/31%</td>
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<td>21%</td>
<td>3%</td>
<td>1%</td>
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<td>7.2</td>
<td>4.1 (ser 5.7)</td>
<td>1.7 (ser 1.9)</td>
<td>584</td>
<td>116 (mg/dl 206)</td>
<td>2210/86%</td>
<td>2640/9%</td>
<td>86%</td>
<td>9%</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key to abbreviations: Prot = Total protein, alb = Albumin, ldh = Lactate dehydrogenase, glu = Glucose, RBC = Red blood cells, WBC = White blood cells, neut = Neutrophils, lymph = Lymphocytes, mon = Monocytes, mes = Mesothelial cells and mQ = Macrophages

### Figures 1 to 4: I (upper left) CXR in March, 2 (upper right) CXR in May, 3 (lower left) Chest CT scan in May and 4 (lower right) facial rash in June

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**References**

4. Tjalma WAA. Ascites, pleural effusion and CA 125 elevation in an SLE patient, either a Tjalma syndrome or, due to the migrated Filshie clips, a pseudo-Meigs syndrome. J Reprod Med 2001; 46:159-166.
Discussion

Although our patient did not meet the criteria for SLE during the first two admissions, she eventually had at least four of the diagnostic criteria including serositis, renal manifestation, positive ANA and malar rash. This took about 3 months from the initial presentation and underscores the fact that the American College of Rheumatology criteria was developed as a research criterion and not a clinical criterion.

Pleuropulmonary manifestations of SLE are vast entailing pleural, parenchymal, bronchial, pulmonary vasculature and diaphragmatic pathologies. Pleural effusions have been recorded in up to 50% of patients with SLE with this number increasing to over 90% at autopsy.

The fleeting nature of her pleural effusion that was initially on the right then left is not uncommon in SLE but hemorrhagic nature of the pleural effusion makes this case atypical. Only a few cases of hemorrhagic pleural effusion of SLE have been reported in literature with prevalence not documented. Other differential diagnoses considered for the pleural effusion included Pseudo-meigs’ syndrome and pseudo-pseudo meigs’ or Tjalma’s syndrome but these were considered less likely with no ascites noted on imaging. Occult malignancy including lymphoma were also explored as a differential diagnosis with negative work-up.

Pathophysiology of SLE is postulated to entail uncontrolled autoreactivity of B and T lymphocytes leading to the production of autoantibodies against self-directed antigens and tissue destruction. The loss of self tolerance is an evolving area of medical knowledge and probably involves genetic factors, deficiency of regulatory T cells and B cells, hormonal factors and environmental factors. Complement system is central in this pathogenesis process. Studies have revealed that reduced levels of hemolytic complement, C1q, C4, C3 in pleural fluid from lupus patient when compared to pleural effusions due to other conditions even after adjustment for the total protein content of the pleural fluid. This makes this case atypical considering the normal complement levels during active serositis on both admissions. This normal complement is hard to explain and underscores the fact that knowledge on the complexity pathophysiology of SLE is in evolution. Another interesting phenomenon was paradoxical decline, albeit mild, in level of complement after the pleural effusion resolved and the proteinuria improved.

Conclusion

Differential diagnosis of SLE should be retained even in atypical cases particularly if no alternative diagnosis is made. It may also present with features not consistent with the conventional clinical and laboratory features.

References

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Guidance to authors

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Studies on patients and volunteers require informed consent and this must be clearly stated in the paper. Authors of this kind of papers must as well state the study has been cleared by the relevant ethics committee.

Submitted papers should follow the guidelines below:

1. Original research papers should follow the IMRAD format and the abstract should be structured and not more than 30 references. The paper should not exceed 3000 words.
2. Reviews should have an abstract, introduction and the rest of the review should have the necessary sub-headings with no more than 50 references. The review should have no more than 4500 words.
3. Case reports should have a background, introduction followed by the discussion with not more than 20 references. The word count should not exceed 2000 words. Perspectives or scientific letters should be in prose form and should not exceed 1500 words.
4. References should be numbered in order of appearance (Vancouver style) and only those cited should appear in the reference list.