

Rheumatoid arthritis: diagnosis and treatment with a particular emphasis on South Sudan

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Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune inflammatory disorder targeting diarthrodial synovial lined joints, usually in a symmetric distribution. The lungs, pericardium of the heart, skin, and eyes may be affected in up to twenty percent of patients. If uncontrolled, RA leads to joint destruction, disability, and a significantly shortened life span.

In developing countries where medical resources are limited, recognition and aggressive management of patients with rheumatoid arthritis may lag behind the treatment of infectious diseases associated with high mortality such as malaria, tuberculosis, HIV, and cholera. However, the burden of progressive pain and disability from the arthritis and its effect on the individual and family unit is considerable. Since specialists in rheumatologic care are rare in developing countries, the focus of this review is to improve the ability of general clinicians to diagnose early rheumatoid arthritis, and to initiate treatment within the limitations of available therapeutic options. A typical case is presented to illustrate key diagnostic features of the disease and management decisions.

A 23 year old female presented to clinic with a three months' history of pain, stiffness, and swelling of the proximal interphalangeal (PIP) joints, wrists, and knees. The symptoms began six months after the birth of her



Figure 1. Early RA affecting the MCP PIP joints (credit C. Radis)



Figure 2. Progressive RA deformities (credit C. Radis)

third child. She was breastfeeding and having difficulty lifting her baby, washing clothes, and cooking. Morning stiffness is present for 2 hours and is accompanied by considerable fatigue. She denied a recent cough, change in bowel habits, weight loss, or fever. A maternal grandmother became crippled at an early age and was bed-bound for the last four years of her life.

On examination, she walks with a slight limp. There is swelling and subtle erythema appreciated in the second, third, fourth, and fifth MCP joints of both hands, and diffuse fusiform swelling in the PIP joints along with tenderness and swelling in both wrists and knees. At the right elbow is a freely movable nodule measuring approximately one centimeter. Her physical exam is otherwise unremarkable.

Epidemiology of rheumatoid arthritis

RA affects women more frequently than men by a ratio of 3:1. Although patients may present in childhood or at an advanced age, the peak incidence is in the child-bearing years. The disease has a world-wide prevalence of 0.8% but there is controversy regarding the incidence of RA in Africa. Some studies suggest that it occurs in only 0.1% of rural Africans, but rigorous epidemiologic studies have not been performed in most regions of Africa. A review of 406 cases at the Mulago Hospital in Uganda in 1980 suggested that RA was not infrequent and it was often severe [1]. A link to urban living may exist, as a study in Soweto, South Africa, showed a prevalence of RA among blacks similar to white Europeans [2].

The triggering event for rheumatoid arthritis is unknown. Many patients with RA have other family members affected by the disease, suggesting a genetic

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predisposition. HLA testing has linked an increased risk for developing RA to the HLA-DR4 region, with the highest risk associated with the HLA-DR01 allele. Since a minority of patients who are HLA-DR4 positive develop the disease, it is postulated that an additional environmental factor(s) may trigger the disease. Known risk factors currently include smoking with a relative risk reported as high as 8.8 [3] in a genetically predisposed individual, and chronic periodontal disease [4].

Extra-articular manifestations of rheumatoid arthritis

Rheumatoid arthritis is a systemic disease in that although synovial lined joints are a major target (see Figures 1 and 2), other organ systems are frequently affected. In general, patients with extra-articular disease have more severe and long-standing RA, but in some patients extra-articular disease may occur early and may be organ threatening. Sjogren's syndrome, with manifestations of dry eyes and dry mouth may affect up to 50% of RA patients over a lifetime. Patients may also present with episcleritis or scleritis (including corneal melt). Diagnosing RA eye involvement and initiating proper treatment may require ophthalmologic consultation.

Rheumatoid nodules affect up to 20% of RA patients. Nodules are most commonly palpable along the ulnar aspect of the elbow and forearm but may also occur at the Achilles tendons or in the hands. They are usually asymptomatic and may recur if surgically excised. Rheumatoid nodules may occasionally involve the lung parenchyma (see Figure 3). Differentiating rheumatoid nodules in the lung from malignancy or infection may require biopsy. The lung pleura and the pericardium may also be targeted by RA. Pleural effusions and pericardial effusions are not uncommon and may require thoracentesis or pericardiocentesis to differentiate from other causes of pleuropericarditis. Interstitial lung disease attributable to RA is usually mild and may be asymptomatic, but aggressive immunotherapy may be necessary in patients with progressive disease. Vasculitis secondary to RA is a feared complication of the disease. Small vessel leukocytoclastic vasculitis involving the skin is often present (see Figure 4). RA vasculitis may trigger mononeuritis multiplex, sensory neuropathy, and the gastrointestinal tract with bowel ischaemia and perforation.

Diagnosis

Despite improvements in laboratory assessment, rheumatoid arthritis continues to be a clinical diagnosis. The 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for the diagnosis of rheumatoid is summarized in Box 1.

Although a clinical diagnosis of rheumatoid arthritis may occasionally be made in patients who have a EULAR score less than 6, the clinical criteria emphasize well known aspects of typical RA patients: small and large joint synovitis of greater than six weeks duration. Differentiating the acute infectious polyarthritis seen in rubella, parvovirus, hepatitis B, and C, and Chikungunya from RA is usually possible by the presence of rash, fever, or the presence of myalgias. In addition, viral polyarthritis usually reaches a peak in several days and gradually resolves while patients with early RA usually add joints over time with increasing stiffness and swelling.

Other forms of chronic inflammatory arthritis must be differentiated from RA. Patients with psoriatic arthritis may present with symmetric small and large joint synovitis but careful skin exam usually demonstrates patches of psoriasis, nail pitting or onycholysis. Patients with systemic lupus erythematosus (SLE) may also present with polyarthritis but often have oral or nasal ulcers, photosensitive rash, pleurisy, or pericarditis. HIV

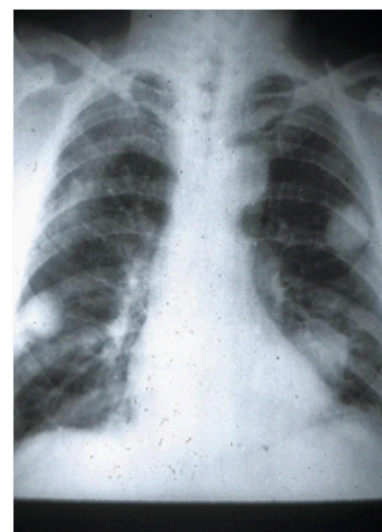


Figure 3. RA rheumatoid nodules

Box 1. Eular Classification criteria for RA

(score-based algorithm: add score of categories A–D; a score of $\geq 6/10$ is needed for classification of a patient as having definite RA)

A. Joint involvement

- 1 large joint: 0
- 2-10 large joints: 1
- 1-3 small joints (with or without involvement of large joints): 2
- 4-10 small joints (with or without involvement of large joints): 3
- >10 joints (at least 1 small joint): 5

B. Serology (at least 1 test result is needed for classification)

- Negative rheumatoid factor (RF) and negative ACPA: 0
- Low-positive RF or low-positive ACPA: 2
- High-positive RF or high-positive ACPA: 3

C. Acute-phase reactants (at least 1 test result is needed for classification)

- Normal C-reactive protein (CRP) and normal ESR: 0
- Abnormal CRP or abnormal ESR: 1

D. Duration of symptoms

- <6 weeks: 0
- ≥ 6 weeks: 1

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may trigger inflammatory arthritis. HIV patients may have significant cervical lymphadenopathy, splenomegaly and a wasting syndrome. If there are risk factors for HIV (multiple sexual partners or IV drug use) in a patient with polyarthritis, testing for HIV is recommended.

Rheumatoid factors are antibodies directed against the Fc portion of native IgG. In early RA, only 50% of patients have a positive rheumatoid factor, while in late disease, about 80% of patients have detectable rheumatoid factors. Rheumatoid factors are often present in other disorders including sub-acute bacterial endocarditis, tuberculosis, sarcoidosis, chronic hepatitis B and C, and HIV disease. Thus, rheumatoid factors have relatively low sensitivity and specificity for the diagnosis of RA. High titre rheumatoid factors however, are much more frequently seen in RA than in other disorders and may predict severe disease.

A newer laboratory test which measure antibodies against cyclic citrullinated peptide (ACPA) has much higher specificity in the diagnosis of RA (about 96% in Caucasians) and similar sensitivity (80%) compared to rheumatoid factor. A recently published study of black South Africans with early RA may point towards differences in ACPA specificity between African and European patients. In this study, ACPA was no more specific for the diagnosis of RA than traditional rheumatoid factors. Nearly a third of systemic lupus patients tested positive for ACPA. Based on this study, the authors suggest testing for ACPA antibodies only if a patient is RF negative [5].

Treatment of rheumatoid arthritis

Timely and aggressive treatment of early rheumatoid arthritis with disease modifying medications (DMARDs) may prevent or slow the progression of joint damage. Although anti-inflammatories (NSAIDs) such as ibuprofen, naproxyn sodium, diclofenac, and others, may help with pain and stiffness, they do not prevent joint damage. NSAIDs are frequently prescribed for joint pain and stiffness in rheumatoid arthritis, but clinicians need to be vigilant with clinical and laboratory monitoring to ensure these medications do not trigger renal or hepatic damage. Patients with congestive heart failure, diabetes mellitus, uncontrolled hypertension, or advanced age may be at particular risk for renal insufficiency. Heavy alcohol use and cigarette smoking increase the risk of



Figure 4. RA small vessel vasculitis

peptic ulcer disease or NSAID induced gastritis. Regular monitoring of serum creatinine and complete blood counts are recommended in patients at risk for NSAID side-effects.

Judicious use of corticosteroid injections and/or oral prednisone or methylprednisolone may reduce pain and improve function. Oral corticosteroids are often dramatically effective short-term but cumulatively have a host of side-effects including weight gain, fluid retention, glaucoma, diabetes mellitus, adrenal insufficiency, reduced bone density, and recurrent infections. Because these medications are relatively inexpensive and widely available, clinicians may find that benefits versus risks favour their use. At doses of 5 mg prednisone or 4 mg methylprednisolone

daily, risks may be minimized. Above these daily doses, long-term side-effects are inevitable and sometimes catastrophic. There is conflicting evidence as to whether low-dose oral corticosteroids prevent joint damage [6].

Most, if not all, RA patients should be prescribed a disease modifying medication. DMARDs do not cure RA, but when used singly or in combination, they may slow down or prevent joint destruction and offer patients the greatest hope of living a more comfortable and productive life. Current DMARDs include hydroxychloroquine, sulfasalazine, leflunomide, methotrexate, and an expanding family of medications termed biologic response modifiers. Biologic response modifiers block the function of key drivers of the immune system in rheumatoid arthritis. Infliximab, etanercept, and adalimumab are antibodies to tumor necrosis factor (TNF), while tocilizumab is an antibody directed against the receptor for the cytokine interleukin-6. An antibody against the CD20 antigen present on B cells is the target of Rituximab. This B cell depleting drug leads to decreased B cell help in the complex immune response which perpetuates rheumatoid arthritis.

The drawbacks to the routine use of biologic response modifiers in developing countries are considerable. The average cost for these medications is more than \$20,000 U.S. dollars yearly. The re-emergence of latent TB or the new development of TB and fungal diseases may be seen in patients prescribed TNF blockers, particularly in countries where the incidence of TB is high. Nevertheless, biologic response modifiers play a critical role in controlling RA in patients with severe disease unresponsive to traditional

DMARDs and in future years, these medications should be available to clinicians in South Sudan.

At a recent lecture at the Juba Teaching Hospital, this writer was made aware that DMARDs are not generally available in South Sudan. RA patients and their doctors must obtain these medications from outside countries. Thus, even with increasing recognition of the crippling effects of RA, this limits therapeutic options for patients. The traditional DMARDs such as Hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide are the cornerstone of effective treatment in most RA patients. Hydroxychloroquine and sulfasalazine are inexpensive, generally well tolerated, and do not require extensive laboratory monitoring. Because of the risk of retinal toxicity with hydroxychloroquine, a baseline eye check is recommended by the American College of Ophthalmology with a second eye evaluation at five years and then yearly thereafter for patients who remain on the drug [7]. The effective dose of hydroxychloroquine is 400 mg/day and the drug may take 2-4 months to reach full effectiveness. Patients taking Hydroxychloroquine should not exceed a total daily dose of greater than 6.5 mg/kg/day. Sulfasalazine is another DMARD which is relatively inexpensive, well tolerated, and effective in many patients with RA. The usual dose is 2-3 grams daily in divided doses. A baseline Complete Blood Count (CBC) is recommended, with a repeat CBC at 3-6 month intervals due to the risk of leucopenia or thrombocytopenia.

Methotrexate is considered a cornerstone of therapy in most RA patients. It should be prescribed in early disease with monitoring of liver enzymes and complete blood counts. Patients with pre-existing liver disease or renal insufficiency should not be prescribed methotrexate. Baseline and monthly laboratory testing should be assessed until it is clear the medication is safe and well tolerated. If laboratory studies are stable, blood counts and liver enzymes can be reduced to every 3 months. Daily folic acid supplementation reduces the risk of side-effects with methotrexate and should routinely be prescribed for patients on long-term methotrexate. Leflunomide

is increasing used as an oral treatment for RA and may be used cautiously in combination with methotrexate or other DMARDs. Laboratory monitoring of leflunomide is similar to methotrexate. While methotrexate is relatively inexpensive, a prescription for leflunomide in the United States is several hundred dollars per month.

The clinical skills necessary to safely and effectively treat patients with rheumatoid arthritis require a familiarity with the costs and potential side-effects of each drug. However, the rewards are high for both the patient and clinician. Control of pain, preservation of function, and prevention of damage are possible for nearly all patients with RA.

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