THE NORTHERN HOSPITAL

RHEUMATOID ARTHRITIS

"The Picture of Dorian Grey", Vanity Fair, Lithographic Print, 1913

"How sad it is!" murmured Dorian Gray, with his eyes still fixed upon his own portrait. "How sad it is! I shall grow old, and horrid, and dreadful. But this picture will remain always young. It will never be older than this particular day of June. . . . If it was only the other way! If it was I who were to be always young, and the picture that were to grow old! For this–for this–I would give everything! Yes, there is nothing in the whole world I would not give!"

Oscar Wilde, The Picture of Dorian Gray, 1891.

Dorian Grey expresses the age old yearning, the yearning for eternal youth. Our time on Earth is so very short, almost before we know it our youth is gone forever, we become old, crippled with the irreversible infirmities of old age. The young and most handsome Dorian Grey comes to this realization one afternoon. He would give anything…anything at all to remain young. The shear force of his desire to remain young forever induces a miraculous spell over his portrait standing at the end of the hall. The portrait somehow takes on the natural ageing process itself, in order to spare Dorian of it.

The portrait begins to age, yet he does not. The portrait however has a dark aspect to it. It also somehow seems to reflect the sinister inner defects in his personality… vanity, callousness, superficiality, a horrible and ageing picture emerges over the years. Dorian becomes increasingly tormented as he is reminded constantly of his own defects. So grotesque does the portrait eventually become, there comes a point when he can no longer bear to look at it and destroys it, but in so doing he breaks the spell and reverts to his correct age and dies instantly, a broken and hideous cripple. We learn the lesson from Dorian Grey, that the "quantity" of our lives is ultimately not so important as is its "quality".

One of the innate yearnings of the human condition is to remain forever young. Many including Dorian, have sought the "fountain of youth". In the 21st century a major advance has occurred in this quest in the form of disease modifying anti-rheumatic drugs. Whilst not providing eternal youth, they do significantly modify one of the major crippling infirmities of the passing years, that of rheumatoid arthritis. Dorian payed the price for remaining young by being constantly confronted with the darker aspects of his personality reflected in his portrait, until he could no longer bear to live with it. Like the portrait of Dorian Grey, our disease modifying anti-rheumatic drugs are quite miraculous in what they can do, however like the portrait of Dorian they also have a dark aspect to them. This dark aspect comes to us in the form of their not insignificant potential for toxicity, a price we must pay in the eternal quest to stay young. Most are willing, like Dorian to accept some price, "…for this I would give everything", however in some cases the price may also eventually become too high with regard to particular agents and alternatives will need to be sought.

Like Dorian some will actually have the quantity of their life span significantly increased, but unlike Dorian it can be expected that the quality of that life will also be increased, providing the "dark aspects" can be kept to a minimum.

RHEUMATOID ARTHRITIS

Introduction

- Rheumatoid arthritis is a systemic inflammatory disease that, initially, affecting synovial joints, that may progress to a multi-system systemic process.

- There are no current specific tests, hence the diagnosis remains essentially a clinical one.

- The prognosis of treated rheumatoid arthritis has vastly improved in the last 20 years, with the use of disease-modifying anti-rheumatic drugs, (DMARDs) resulting in better control of inflammation and less long term complications. Most people presenting with rheumatoid arthritis today can expect to achieve disease suppression and can avoid or substantially delay joint damage and deformities, and can maintain a good quality of life. This is in stark contrast to previous times when long term consequences for many where devastating.

- The key to these much improved outcomes lies in early diagnosis and management with combinations of "conventional" disease modifying antirheumatic drugs (DMARDs). If these do not effect remission, newer "biological" DMARDs are now a further option.

- It is important to appreciate that lack of recognition of the early signs of rheumatoid arthritis, ignorance of the benefits of early application of modern treatment regimens, and avoidable delays in securing specialist appointments may hinder achievement of best outcomes for many patients.

From an ED perspective important issues include:

1. Recognition of possible first presentations with early specialist Rheumatological referral especially in view of the effectiveness of early treatment.

2. Recognition and awareness of the important possible complications that are associated with anti-rheumatic drugs, in particular:

    - The potential for NSAIDS to cause **GIT bleeding.**

    - The potential of the DMARD agents for **immunosuppression.**

    - With the greatly increased use of methotrexate emergency department staff need to be familiar with the management the deliberate self harm overdose of this agent.

3. Recognition of the potential for cervical spine injury in patients with advanced disease in this region.

4. Recognition that there is an increased risk of atherosclerotic disease.

5. Recognition of the importance of the role of allied health and care- coordination input into these patients.

These guidelines relate primarily to the initial presentation of a patient with an acute polyarthritis, in which it is suspected the diagnosis is Rheumatoid arthritis, though an extensive list of possible secondary and long term complications in established disease is also included.

Pathophysiology

Incidence

- The prevalence of rheumatoid arthritis is about 1%.
- Women are more commonly affected than men.

Pathology

- Rheumatoid arthritis is best characterised as a lymphocyte-mediated inflammatory disease.
- The stimulating antigen(s) are unknown, but pro-inflammatory mediators including cytokines, chemokines and prostanoids, exist in the joint, resulting in cellular activation, migration and proliferation.
- The cytokines tumour necrosis factor (TNF) and interleukin 1 (IL-1) appear to be key factors, although others are also involved.
- This pro-inflammatory milieu results in joint destruction, with both erosions and cartilage loss.

Risk Factors

- Between 15% and 70% of the risk of developing rheumatoid arthritis may be due to genetic factors.
- Patients with rheumatoid arthritis express a "shared epitope" in leucocyte antigens including HLA-DR1, HLA-DR4 and HLA-DR10, at a higher rate than in the general population, and patients doing so have more severe disease. Nonetheless, HLA typing is not used for prognostication in the routine management of patients with rheumatoid arthritis.
- Putative environmental factors include smoking and viral infections.

Complications

The list of possible local secondary and systemic complications is extensive and may include the following:

Joint and tissue destruction

Joint and adjacent tissue destruction can be extensive in the long term if not adequately treated.

This can be particularly devastating in the hands, where a wide range of deformities may occur.

Useful functional assessments for the hands include:

- Grip strength
- Opposition, (thumb and fingers)
- Simple "every day" tasks, (eg writing, undoing a button)

Cervical spine

TMJ involvement may restrict jaw movement, making intubation more problematic.

Atlanto-axial subluxation may occur with erosion of the transverse ligament and the odontoid peg may occur.

Care needs to be exercised when intubating patients with advanced disease involving the upper cervical spine.

Nodules

Skin nodules, usually seen on the extensor surfaces, especially the ulnar border of the forearm and elbow, within the walls of bursae, occasionally on the eye.

Vascular

1. Raynaud's phenomenon.
2. Nail fold or digital (pulp in particular) infarcts
3. Chronic leg ulceration, due to vasculitis.
4. Rarely a vasculitis of small arteries and venules.

CVS

1. **Accelerated atherosclerosis (due to vascular inflammation) is an important complication, as the major cause of premature death in patients with rheumatoid arthritis.**
2. Pericarditis, (not usually clinically significant)
3. Valvular lesions, (AI, MI)

Ocular

Uncommon associations include:

1. Sjogren's syndrome.

2. Iritis.

3. Episcleritis/ scleritis.

4. Scleromalacia perforans, (perforation of a rheumatic nodule on the sclera)

Haematological

1. Anaemia

    - May be seen due to the anaemia of chronic disease, or possibly from chronic NSAID use.

2. Felty's syndrome, (rare)

    This consists of the triad of:

    - Rheumatoid arthritis
    - Splenomegaly
    - Neutropenia

3. A generalized reactive lymphadenopathy may occur.

Neurological

1. Peripheral neuropathy, (mainly sensory)

2. Mononeuritis/ Mononeuritis multiplex.

Lungs

Lung involvement is uncommon.

Occasionally:

1. Pleural effusions.

2. Pulmonary fibrosis, (predominantly in the lower lung fields, as opposed to the upper)

3. Rheumatoid nodules, ("Caplan's syndrome" are large nodules up to 5 cm in association with pre-existing pneumoconiosis)

Renal

Possible impairment secondary to vasculitis

Skeletal

1. Significant bony erosions

2. Secondary degenerative changes

3. Secondary (disuse) osteoporosis

Clinical Features

The key diagnostic feature in **early disease** is the presence of **synovitis**, which is manifest as soft tissue swelling or an effusion of the affected joint.

Tenderness of the joint line *alone is insufficient* to demonstrate synovitis.

A number of clinical features in *early* inflammatory arthritis suggest a diagnosis of rheumatoid arthritis. These include: [1]

1. Symptom duration of >6 weeks.

2. Early morning stiffness of >1 hour, (stiffness after inactivity, hence early morning)

3. Arthritis in 3 or more regions.

4. Bilateral squeeze tenderness of the metacarpophalangeal or metatarsophalangeal joints.

5. Symmetry of the areas affected.

6. Rheumatoid factor positivity.

7. Anti-cyclic citrullinated peptide (anti-CCP) antibody positivity.

8. Bony erosions evident on radiographs of the hands or feet, although these are uncommon in early disease.

Prognostic factors [1]

Once a diagnosis of rheumatoid arthritis has been established, it is important to establish the likely prognosis of the disease to allow rational therapeutic planning.

The factors listed in below indicate a poorer prognosis which supports a more intensive approach to disease-modifying antirheumatic drug (DMARD) therapy.

Unfortunately however no single prognostic factor is entirely reliable in an individual rheumatoid arthritis patient

These prognostic factors include:

1. Socio-demographic

    - Onset in early adulthood
    - Female

- Elderly-onset male
- Adverse socioeconomic circumstances
- Smoking

2. Clinical

- **Greater number of swollen joints (>20)**
- Insidious onset
- Longer duration of disease at presentation
- Involvement of small joints of hands and feet
- Extra-articular features (eg nodules)
- Impaired physical function

3. Laboratory features at onset

- **High rheumatoid factor titre**
- **Elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).**
- Presence of anti-CCP antibodies
- Erosions on imaging
- Certain HLA-DR types (HLA-DR1 +/- HLA-DR4 +/- HLA-DR10). HLA typing is not routinely done.

The most important factors are a positive rheumatoid factor, sustained raised measures of inflammation (CRP or ESR), and a high number of swollen joints.

Investigations

Blood tests:

1. Inflammatory markers of disease activity:

- ESR
- CRP

2. Diagnostic immunological markers:

- Rheumatoid factor is present in about 70% of established rheumatoid arthritis patients but is detected less frequently in early disease. Note

that as a diagnostic test for RA, rheumatoid factor is neither very sensitive nor specific

- The presence of **anti-cyclic citrullinated peptide** (anti-CCP) antibodies is much more specific for rheumatoid arthritis, but a little less sensitive.

3. FBE

   - Look for anaemia.

4. U&Es

   - Look for renal impairment and/ or drug toxicity

5. LFTs

   - If drug toxicity is suspected

Ultrasound and MRI:

- In specialist clinical settings, magnetic resonance imaging and ultrasonography can confirm the presence of joint synovitis when there is clinical uncertainty, and detect joint erosions well before they are visible on radiographs.

Radiology:

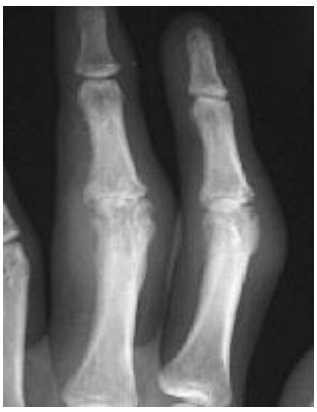
Radiology of the hands and wrists may demonstrate:

Early changes including:

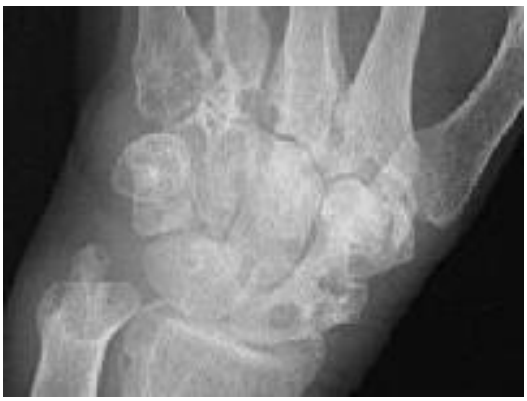
- Soft tissue swelling.
- Peri-articular osteoporosis.
- Bone erosions, which tend to be more marginal (ie the center of a circular lesion is located outside the bony margin) when compared to gout erosions, where the lesions tend to be deeper set, ie the center of a circular lesion is located within the bony margin)

Late Early changes including:

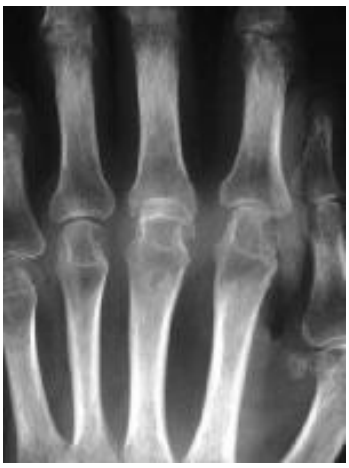
- Loss of joint space
- Joint subluxation/ dislocation.
- Extensive erosion, leading to bony destruction, in the wrist ankylosis may be seen within the carpus as well as secondary degenerative changes.



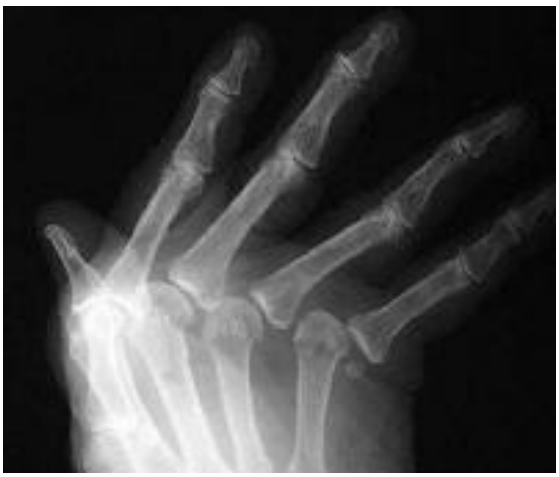
Soft tissue swelling



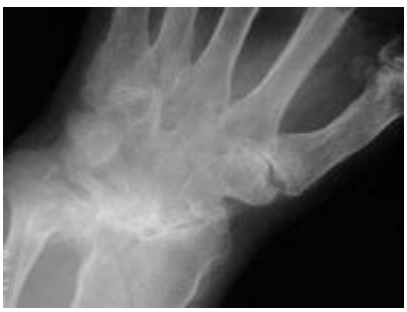
Bony erosions

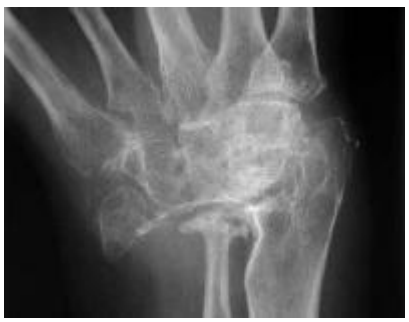


Periarticular osteopenia



Ulnar deviation with extensor tendon disruption





(L) Marked ankylosis of most of the carpal bones and(R) partial collapse of fused carpal bones in advanced disease.

Management

The Aims of Management

The aims of current rheumatoid arthritis therapy have radically shifted from "palliation" to early induction of disease remission, to prevent joint damage.

1. The key elements of the current approach to rheumatoid arthritis are:

2. Rheumatoid arthritis should be diagnosed and treatment commenced with disease-modifying antirheumatic drugs (**DMARDs**) as **early** as possible.

3. DMARD and other therapies should be used to **induce** an inflammatory **remission** and thus prevent joint damage.

4. Rheumatoid arthritis patients need to be **regularly monitored** for drug toxicity and to minimise rheumatoid arthritis co-morbidities such as osteoporosis and atherosclerosis.

5. All patients with rheumatoid arthritis should be **educated** about their disease, and participate actively in its management.

Initial Presentation of Undifferentiated Inflammatory Arthritis

The nature of the treatment provided while waiting for investigations to be performed, or for a specialist consultation to occur, in order to establish the diagnosis, will depend on the severity of the symptoms, the age of the patient and their co-morbidities. Initial treatment from the ED in the suspected but as yet rheumatologist undiagnosed patient will include the following drug options:

NSAIDS

In a patient with mild to moderate symptoms but who is otherwise in good health, the best initial "empiric" treatment will be NSAIDS, providing there are no significant contra-indications.

Fish oil

Fish oil in doses sufficient to deliver 3 to 4 g of long chain omega-3 fats daily has been shown to reduce *symptoms* and recourse to NSAIDs in rheumatoid arthritis, and to reduce production of pro-inflammatory eicosanoids and cytokines.

Patients should be advised that the symptomatic benefit of fish oils can be delayed for 6 to 12 weeks.

See Rheumatologic therapeutic guidelines for further information.

Prednisolone

Low dose oral prednisolone may be used when:

1. Symptoms are severe.

2. Symptoms are producing significant functional impairment.

3. The elderly, (with or without renal impairment)

4. In cases where there are significant contra-indications to NSAIDS

However, starting prednisolone before specialist review may delay diagnosis, though this may nonetheless be essential for rapid symptom relief or if significant contra-indications exist to NSAIDS

- Commence with oral prednisolone 5-10 mg daily.

Following specialist diagnosis patients will then in most cases be assessed for immediate DMARD therapy.

DMARDs

- The immediate or subsequent initiation of a disease-modifying antirheumatic drug (DMARD) should generally be on the advice of a specialist, who would also facilitate the withdrawal of the prednisolone.

- Disease-modifying antirheumatic drugs (DMARDs) reduce or eradicate synovial inflammation and thus prevent joint damage.

- NSAIDs are often continued even after the initiation of a DMARD.

- A response to DMARD therapy should be apparent within 12 weeks.

"Conventional" DMARDs

These agents include:

- **Methotrexate (with folic acid), usually given as low dose, once weekly.**

- Hydroxychloroquine

- Sulfasalazine

- In severe cases, leflunomide and cyclosporin

"Biological" DMARDs may be considered when "conventional" DMARDS are unsuccessful.

- These agents have added substantially to the range of effective agents for RA therapy but are expensive.

- They include a range of tumor necrosis factor (TNF) inhibitors.

As a general guide: [1]

- Mild rheumatoid arthritis, hydroxychloroquine or sulfasalazine may be considered.

- For mild to moderate rheumatoid arthritis in a patient with no contraindications, monotherapy with methotrexate may be sufficient.

- In very active rheumatoid arthritis with significant functional impairment, combination therapy (particularly methotrexate, hydroxychloroquine and sulfasalzine) should be considered.

- Steroid treatment, either as pulse or as intra-articular therapy, may be considered while awaiting response to the DMARDs.

Patients with Diagnosed Rheumatoid Arthritis

A management plan for each patient should be negotiated between the patient, the specialist, the general practitioner, and other health professionals.

The ultimate goal of therapy remains the prevention of joint damage and maintenance of quality of life.

The ongoing management of a patient with rheumatoid arthritis involves repeated:

1. Patient education.

2. Assessment of the current inflammatory activity of the arthritis (eg early morning stiffness, joint pain, swollen joint count, ESR or CRP)

3. Assessment of the degree of joint damage (eg physical examination or X-rays)

4. Adjustment of the DMARD and other therapy to induce and maintain an inflammatory remission in the arthritis, and then maintain therapy as necessary.

5. Assessment and management of the potential complications of rheumatoid arthritis (eg atherosclerosis, osteoporosis, vasculitis)

6. Assessment of the potential toxicity of the current pharmacological therapy (including appropriate blood test monitoring)

7. Referral to other allied health professionals as appropriate.

    - Physiotherapists

    - Occupational therapists

    - Social worker.

    - ED Care coordination.

Disease activity and outcome measurement

The key feature of the modern management of rheumatoid arthritis is that disease activity is measured and used to adjust therapy to attain remission.

Remission is defined as:

1. Symptomatic relief

PLUS

2. Normalisation of inflammatory markers

PLUS

3. The absence of joint swelling.

Notes:

- Induction of remission should always be the goal of the treatment of rheumatoid arthritis, and can be achieved in about 50% of cases.

- Decisions about the adjustment of DMARD therapy should be guided by measures that reflect inflammation.

- The presence of swollen joints and raised measures of inflammation such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are probably the most reliable.

- The absence of these objective measures of inflammation suggest that the patient's symptoms may be caused by joint damage, other painful processes or pain amplification.

- It is also important to assess the **functional consequences** of the arthritis on the patient's activities, both at home and at work. (There are formal questionnaires which assist in this assessment)

References

1. Rheumatology Therapeutic Guidelines, 1st ed 2006.

2. Roberts L.J Early combination disease modifying antirheumatic drug treatment for Rheumatoid arthritis. MJA vol 184, no (3) 6 February 2006, p. 122-125

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August 2007