CASE ONE

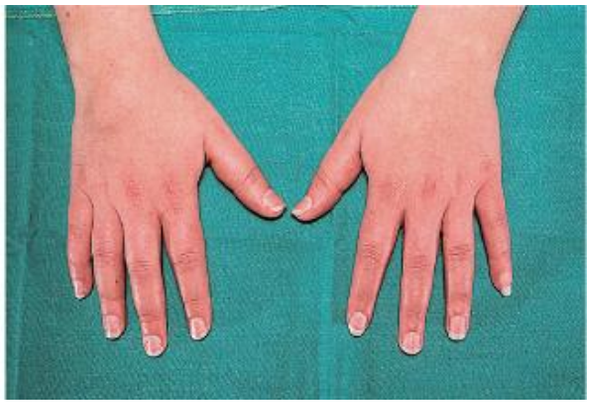
Short case number: 3_26_1
Category: Musculoskeletal System & Skin
Discipline: Medicine
Setting: General Practice
Topic: Joint Pain_Rheumatoid Arthritis.

Case

Felicity Masters is 35 years old, she presents worried about her aching joints. She has suffered with pains in her hands for 9 months, initially it would come and go and she thought it was due to her work as a florist. Lately however her hands have become quite stiff and take a while to 'warm up' in the morning. She has also been feeling very tired and run-down and she has recently noticed that her fingers appear to be swollen.

Questions

1. In your assessment of Felicity outline the key features of her history and examination that would suggest a diagnosis of rheumatoid arthritis compared with other types of arthritis



2. On examination you note the appearance of Felicity's hands. Describe the clinical features seen and the underlying pathophysiology.
3. You explain to Felicity that she may have rheumatoid arthritis, she informs you that her mother has osteoarthritis and asks if this is the same. What would you explain to her about rheumatoid arthritis and how it differs from osteoarthritis?
4. What investigations would you undertake to confirm the diagnosis and what results would support the diagnosis?
5. What are the radiological features of rheumatoid arthritis?
6. Felicity returns for her results a week later and she has done some reading on rheumatoid arthritis, she is quite concerned about all the complications that can occur and is worried about deformities that can occur with her hands, as this would impact on her work. Outline the articular and non-articular complications of rheumatoid arthritis.
7. Felicity would like to commence treatment as soon as possible as she wants to avoid the complications and deformities developing, summarise the medications that can be used in Rheumatoid arthritis outlining the mechanism of action, the indications, side effects and special precautions.

Suggested reading:

- Kumar P, Clark ML, editors. Kumar & Clark's Clinical Medicine. 8th edition. Edinburgh: Saunders Elsevier; 2012.
- Colledge NR, Walker BR, Ralston SH, Penman ID, editors. Davidson's Principles and Practice of Medicine. 22nd edition. Edinburgh: Churchill Livingstone; 2014.

ANSWERS

1. In your assessment of Felicity outline the key features of her history and examination that would suggest a diagnosis of rheumatoid arthritis (RA) compared with other types of arthritis:

   The diagnosis of RA can only be established by an accurate and careful history and physical examination. Laboratory tests are of secondary importance, although seropositive status (Rheumatoid Factor and/or anti-CCP) and elevated inflammatory markers (CRP and/or ESR) add to the likelihood of the diagnosis, and are predictors of a poorer prognosis. Risk factors for developing rheumatoid arthritis include family history, smoking, female gender and HLA-DRB1 "shared epitope".
   The clinical hallmark of inflammatory joint disease is persistent synovitis, characterised by soft tissue swelling of the joint, which must persist beyond 6 weeks. Other diagnostic criteria include:
   - Morning stiffness (> 1 hour)
   - Arthritis of three or more joint areas
   - Arthritis of hand joints
   - Symmetrical arthritis
   - Rheumatoid nodules
   - Positive rheumatoid factor and or anti-CCP
   - Radiological changes (in later stages of the disease)

2. On examination you note the appearance of Felicity's hands. Describe the clinical features seen and the underlying pathophysiology.

   Symmetrical swelling of the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints. The changes that underlie this are swelling and congestion of the synovial membrane and the underlying connective tissues, which become infiltrated with lymphocytes (especially CD4 T cells), plasma cells and macrophages.
   Joint erosions occur where the inflamed hypertrophic synovium is in contact with, and invades, the adjacent bone. This is mediated by osteoclasts at the bone-synovium interface, and is consistent with the clinical observation that the volume of synovitis correlates with the rate of joint erosion. The long term outcome of untreated RA is destruction of the joint, leading to deformity and subsequent disability.

3. You explain to Felicity that she may have rheumatoid arthritis; she informs you that her mother has osteoarthritis and asks if this is the same. What would you explain to her about rheumatoid arthritis and how it differs from osteoarthritis?

   Rheumatoid arthritis is an autoimmune inflammatory condition that involves hypertrophy of joint synovium, causing tender soft tissue swelling. It is progressive over time and may affect other organs. Rheumatoid arthritis tends to affect many of the small joints of the hands, wrists and feet, and may also involve large joints in the upper and lower limbs. There is usually involvement of the same joints on the left and right side, although this may not be apparent early in the disease when only a few joints are involved. The typical pattern of established RA is described as symmetrical, small joint polyarthritis (or polysynovitis).In contrast, osteoarthritis is characterised by cartilage loss with hard bony swelling due to osteophytes and minimal soft tissue synovial swelling. It frequently affects larger weight-bearing joints, such as the hips and knees. When OA is present in the hands, it most commonly affects the distal interphalangeal joints (DIPS) and the first carpometacarpal joint (1st CMC) at the base of the thumb, whereas RA most commonly affects the proximal interphalangeal joints (PIPs), metacarpophalangeal joints (MCPs) and the wrists.

4. What investigations would you undertake to confirm the diagnosis and what results would support the diagnosis?

   Positive anti-citrullinated peptide antibody (ACPA), usually detected in the laboratory as anti-cyclic citrullinated peptide (anti-CCP), has high specificity >90% and high positive predictive value for RA. Positive rheumatoid factor (RF) has lower specificity than anti-CCP, but is very useful in identifying some RA patients who are negative for anti-CCP.
   These auto-antibodies, anti-CCP or rheumatoid factors, are found in the serum of more than two-thirds of adults with the disease, characterising seropositive RA versus seronegative RA. Seropositive disease has a worse prognosis, with increased risk of joint erosions and extraarticular disease, especially with high titre auto-antibodies and most especially with high titre anti-CCP. Patients with nodules or vasculitis are almost always seropositive.
   Normochromic, normocytic anaemia is frequently present in active RA. The underlying disorder is thought to be ineffective erythropoiesis.
   The erythrocyte sedimentation rate (ESR) or C-reactive protein are increased in the majority of patients with active RA. Typically these acute phase reactants reflect disease activity.
   Synovial fluid aspiration is consistent with an inflammatory arthritis with no features that particularly suggest RA.

5. What are the radiological features of rheumatoid arthritis?

   Early in the disease, radiographic evaluation of joints is not useful to obtain a diagnosis. As the disease progresses, radiography is useful to define the patterns of joint destruction, the degree of cartilage loss and the severity of bone erosions.

6. Felicity returns for her results a week later and she has done some reading on rheumatoid arthritis. In addition to her pain and fatigue, she is quite concerned about all the complications that can occur and is worried about deformities that can occur with her hands, as this would impact on her work. Outline the articular and non-articular complications of rheumatoid arthritis.

Hand joint deformities	Ulnar deviation at metacarpophalangeal joints. Boutonniere deformity (flexed PIP and hyperextended DIP). Swan neck deformity (flexed DIP and hyperextended PiP) Thumb hyperextension
Other joint deformities	Frozen shoulder may develop; Shoulder subluxation and limited range of motion; Popliteal cysts can arise; Carpal tunnel syndrome.
Spinal cord compression	Tenosynovitis of transverse ligament can lead to instability of atlas on axis. Caution must be used during endotracheal intubation; may see loss of lordosis of the neck and decreased range of motion; C4–C5 and C5–C6 subluxations are possible and these may be seen as joint space narrowing on lateral cervical spine films. It is important to avoid flexion films until odontoid fracture ruled out if injury is suspected,
Cardiac problems Amyloidosis	Coronary artery disease, for which RA is an independent risk factor. Pericarditis occurs rarely. Up to one third of patients may have asymptomatic pericardial effusion at diagnosis; Other problems include atrioventricular block and myocarditis. This occurs in a small number of people with severe RA.
Vasculitis Cardiac problems	Subclinical vasculitis may be the cause of accelerated atherosclerotic disease, including CAD in later life.

	May present as distal arteritis, pericarditis, peripheral neuropathy, cutaneous lesions, arteritis of viscera, and coronary arteritis; There is an increased risk of developing this if male or high rheumatoid factor titres. .Pericarditis occurs rarely. Up to one third of patients may have asymptomatic pericardial effusion at diagnosis; Other problems include atrioventricular block and myocarditis.
Anaemia Vasculitis	This correlates with erythrocyte sedimentation rate and disease activity; Three fourths of patients have anaemia of chronic disease with one fourth of patients respond to iron therapy. May present as distal arteritis, pericarditis, peripheral neuropathy, cutaneous lesions, arteritis of viscera, and coronary arteritis; There is an increased risk of developing this if male or high rheumatoid factor titres. .
Septic arthritis Anaemia	Septic arthritis is a serious complication of RA that may be lead to serious morbidity and mortality. The most presentation is hot and swollen joint(s) associated with systemic manifestations of infection such as fever and malaise. The most likely organism involved in S. aureus. This correlates with erythrocyte sedimentation rate and disease activity; Three fourths of patients have anaemia of chronic disease with one fourth of patients respond to iron therapy.
Amyloidosis	This occurs rarely in a small number of people with severe RA.

7. Felicity would like to commence treatment as soon as possible as she wants to avoid the complications and deformities developing, summarise the medications that can be used in Rheumatoid arthritis outlining the mechanism of action, the indications, side effects and special precautions.

The **objectives of management** are to **reduce the current symptoms,** particularly pain, stiffness and fatigue, and to **prevent the long term consequences** of the disease, particularly joint damage, disability and premature cardiovascular disease.

The **key principles of management** are, firstly, to **commence disease modifying anti-rheumatic drugs (DMARDs) as soon as possible** and then to continually adjust the DMARDs to achieve remission if possible. Early treatment with DMARDs can prevent erosive joint damage before its onset and may even improve the long term trajectory of the disease in years to come. Continual adjustment of DMARDs is done with a **"treat-to-target"** approach, targeting remission in:
- symptoms (no joint pain)
- physical signs (no soft tissue joint swelling/synovitis)
- inflammatory markers (normal ESR and CRP)

Note that RF and anti-CCP will likely remain positive, despite effective treatment.

Many patients will already be taking analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) prior to a diagnosis of rheumatoid arthritis. While these medications may reduce some of the symptoms, they are not disease modifying and can cause significant adverse effects. They should not be relied upon in the treatment of RA, and are preferably ceased when symptom control is achieved with DMARDs.

Corticosteroids relieve symptoms and signs quickly, effectively and reliably. They may be used in urgent situations when RA patients are severely distressed or disabled by inflammatory pain and stiffness. They can also keep a patient functioning while waiting for DMARDs to become effective. If possible, it is best to avoid corticosteroids, or if not, they should be used at the lowest dose and for shortest period of time possible. The long term adverse effects are well established and very significant.

When RA is suspected the patient should be promptly referred to a specialist rheumatologist, and if the diagnosis is confirmed the patient is likely to commence DMARDs as soon as possible. This often involves sensitive education of the patient, many of whom are reticent to commence DMARDs until they fully understand the risks and benefits.

Typically, patients start conventional synthetic DMARDS (csDMARDs). The most common csDMARD is methotrexate taken orally, usually up to 20mg once per week. Folic acid supplementation reduces the rate of methotrexate-related adverse effects. Other commonly used csDMARDs are sulfasalazine, leflunomide and hydroxychloroquine, each taken orally on a daily basis. When doing "treat-to-target" the dose of csDMARDs can be maximised and patients can have combination therapy with 2, 3 and sometimes 4 csDMARDs. The response time is slow for all of these drugs, typically taking 4 weeks for improvement to be evident and usually taking approximately 12 weeks (3 months) to achieve a full response. When starting a new csDMARDs the patient should be monitored with regular blood tests for safety (FBC, LFT & biochemistry) and for response (ESR & CRP).

Women of child bearing potential should use adequate contraception if taking methotrexate or leflunomide. Sulfasalazine and hydroxychloroquine and sometime used when there is a chance of pregnancy.

If patients fail to achieve remission with a combination of full dose csDMARDs, or if they must cease csDMARDs because of poor tolerability of adverse events, they may be considered for biological therapy (bDMARDs) or targeted synthetic therapy (tsDMARDs). The first anti-TNF bDMARDs became available in the late 1990s and subsequently there have been more bDMARDs and the tsDMARDs. These drugs have transformed the treatment of rheumatoid arthritis.

bDMARDs (SCI or IV)			**tsDMARDs (oral)**
TNF inhibitors	**IL-6R antagonist**	**T cell anti-CTLA4**	**JAK inhibitors**
etanercept	tocilizumab	abatacept	tofacitinib
infliximab			baricitinib
adalimumab		**B cell anti-CD20**	
golimumab		rituximab	
certolizumab			

The bDMARDs and tsDMARDs are associated with a small but significant increase risk of infection, including respiratory, skin and joint. There is a particular risk of activation of latent (asymptomatic) TB, so patients with RA are often screened for latent TB with CXR and IGRA (interferon gamma release assay, such as Quantiferon) in preparation for the possibility that they may subsequently need a bDMARD.

When applying a "treat-to-target" approach, a high proportion of seropositive patients, especially those with anti-CCP, will eventually require a bDMARD. Many patients require a combination of a csDMARD and a bDMARD.