Rheumatoid arthritis: acute presentations and urgent complications

Rheumatoid arthritis is a common chronic disorder. Its many complications, comorbidities and adverse effects of treatment often involve general physicians. Particular risks are septic arthritis, systemic infections, upper gastrointestinal ulcers and systemic vasculitis. Delayed diagnosis will result in poor outcomes.

Rheumatoid arthritis (RA) is the commonest chronic inflammatory disease in the UK and most Western countries. It is characterized by persisting inflammation that involves most peripheral joints. The end result of this inflammation is joint damage and eventual failure. Because of the combination of joint inflammation and damage patients become increasingly disabled over time and have a reduced quality of life. Many patients become unable to work because of their arthritis. It also results in high medical and social costs.

The cause of RA is unknown. Genetic factors are, however, important, and it affects three times as many women as men. It is associated with disturbed immunity, classically shown by the presence of rheumatoid factor. Some environmental factors are also important in triggering the disease, particularly cigarette smoking.

Patients are treated with symptom relieving drugs – analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). In addition, they usually receive disease-modifying drugs, such as methotrexate and sulfasalazine. Many patients receive systemic steroids and a growing minority receive biologics, particularly tumour necrosis factor inhibitors, which are probably the most powerful immunosuppressive drugs currently available.

RA is a systemic disease and has many extra-articular features. Its systemic features can result in malaise, weight loss and an elevated acute phase response with a high erythrocyte sedimentation rate (ESR), high C-reactive protein level and normochromic normocytic anaemia. The most classical extra-articular feature is the presence of rheumatoid nodules, although there are many others including vasculitis and pleural inflammation. In addition to specific extra-articular features of RA, patients often have comorbidities, such as hypertension and diabetes. The frequencies of such comorbidities from one North American series of 603 RA patients (Maradit-Kremers et al, 2005) are summarized in *Figure 1*.

Acute problems in RA can be a result of the disease itself, its extra-articular features, the effects of systemic inflammation, and the adverse effects of treatment. Sometimes these can interact; for example systemic inflammation and immunosuppressive drugs will both increase the risk of severe infection.

An unseen disease

Many clinicians outside the confines of rheumatology will see patients with RA. Unfortunately a large number, if not the majority, will overlook its presence and not consider its impact on patients. In this sense arthritis remains all too often a medically unseen disease. An audit of 200 general medical inpatients in a teaching hospital undertaken some years ago showed that about half of the patients had evidence of musculoskeletal disease, but 92% of rheumatic disorders were not recorded in the case notes (Doherty et al, 1990). Despite intensive efforts the situation remains unchanged and in 2003 musculoskeletal symptoms were still only recorded in general medical notes in half of patients in whom they were present and only one third of musculoskeletal physical findings were noted (Lillicrap et al, 2003).

It is very important for clinicians in general medical and other specialities to recognize that patients have musculoskeletal problems, and to consider that some general disorders can occur as a result of RA and other rheumatic disorders (*Table 1*).

Acute RA

The onset of RA is usually but not always gradual. In its early stages RA is characterized by joint pain and swelling, which is usually symmetrical and generally involves

Figure 1. Comorbidities in rheumatoid arthritis.

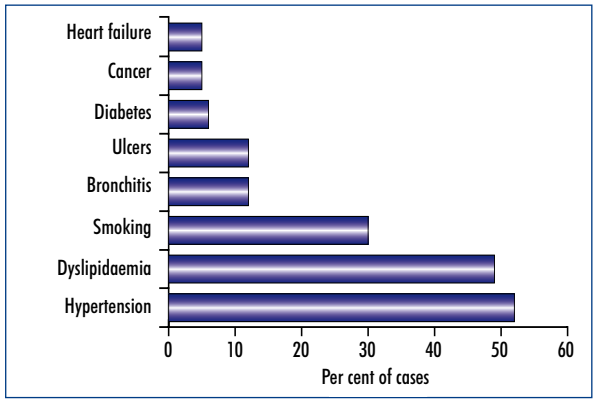

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Table 1. Acute problems in rheumatoid arthritis

System	Problem
Musculoskeletal	Acute onset
	Septic arthritis
	Joint failure
	Osteoporotic fracture
General	Systemic infection
Respiratory	Interstitial lung disease
	Pleurisy
Cardiac	Pericarditis
Gastrointestinal	Upper gastrointestinal ulceration
	Small bowel enteropathy
	Colitis
Neurological	Cervical myelopathy
	Neuropathy
Renal	Impaired renal function
Vascular	Vasculitis
Skin	Drug rash
	Ulceration
Eye	Scleritis

the hands, together with marked morning stiffness that usually lasts more than 1 hour. Occasionally the onset can be abrupt and unexpected (Eberhardt et al, 1990).

Patients are occasionally seen by general physicians in emergency units, either because their RA has started very suddenly, or because they have been uncertain about what is happening and have delayed seeking routine medical advice from their GP.

In such circumstances patients need to have symptomatic treatment with analgesics and NSAIDs, and to be referred for specialist rheumatologist advice. Although it is important to start disease-modifying drugs as soon as possible, treatment is invariably best organized after assessment in a specialist rheumatology unit. In this setting patients can be fully informed about the benefits and limitations of different treatment approaches and treatment can be tailored to meet patients' individual needs.

Septic arthritis complicating RA

One of the more difficult clinical assessments is when patients with established RA present with a single active joint. Usually this represents incompletely controlled disease. Occasionally it can be the result of infection in a joint previously damaged by RA.

Septic arthritis can be a rapidly destructive joint disease (Goldenberg, 1998). In the general population it is seen in 2–10 per 100 000 adults. However, it is far more common in RA, with an estimated incidence of 30–70 per 100 000 patients. It often causes irreversible loss of function and can prove fatal unless adequately treated. About 10–20% of cases are polyarticular when septic arthritis develops in RA.

Usually the onset is sudden with pain and swelling in a single joint. In some cases with RA its onset is insidious. Most patients have an associated fever. Diagnostic delay is an important contributor to the poor outcome of septic arthritis in RA, which has a high mortality, sometimes reaching 30–50%. If one or two joints are suddenly inflamed in a RA patient, it is prudent to assume the joint is septic until proven otherwise. Definitive diagnosis depends on culturing synovial fluid and blood and finding the causative bacteria. There is an accompanying leucocytosis in most cases.

Patients need rapid and effective antibiotic treatment. Antibiotics are usually given parenterally for some weeks, but there are no absolute time requirements. The initial antibiotics used should be chosen empirically, helped by the type and sensitivity of bacteria in the community and any information from blood and synovial fluid cultures. Many patients require combinations of penicillin or later generation cephalosporins. In addition to antibiotic treatment, it is common practice to drain the joint either by repeated aspiration or surgically.

Infection

As well as occasionally presenting with septic arthritis, RA patients also have increased risks of developing systemic infections at other sites. Part of this risk comes from the disease itself and part is attributable to treatment with steroids and immunosuppressive disease (Mikuls, 2003). Before the use of steroids there was a marked increase in deaths in RA as a result of infection and this propensity to infections has continued with modern drug therapy. As immunosuppressive drugs are given to patients with severe RA it can be difficult to distinguish between the impact of the disease and the impact of its treatment.

RA patients are especially susceptible to chest infections. The reasons for this are uncertain, but may include subclinical pulmonary disease, as an extra-articular feature of RA weakens local airway host defenses, rendering patients susceptible to pneumonia, bronchitis and other respiratory-related infections. The infections in RA are usually similar to those in non-rheumatoid patients. They require conventional treatment with antibiotics and supportive care.

One exception is the infections that occur in patients taking biologic treatment, particularly tumour necrosis factor inhibitors (Cunnane et al, 2003). These therapies increase susceptibility to tuberculosis and other intracellular pathogens. A wide variety of less common infections have been seen in these patients, including *Pneumocystis carinii* pneumonia, coccidiomycosis, histoplasmosis, listeriosis and cryptococcal infections. These all require conventional treatment for the specific infective agent and treatment needs to be stopped. However, in the immunosuppressed the clinical features can be masked and therefore considerable care and vigilance is needed when they are assessed.

Lung disease

RA patients often have lung disease, mainly as an extra-articular feature of their arthritis. The frequency of lung disease in RA depends on the methods used to evaluate its presence. RA patients can have pleural involvement with features of pleurisy or a pleural effusion. They can have nodules within the lungs and they can have interstitial lung disease. They can also have bronchiectasis. Finally the increased susceptibility to pneumonia has been considered above. Some of these problems, particularly interstitial changes, can be caused by drug therapy, particularly methotrexate. Although RA is more common in women, rheumatoid lung disease occurs more frequently in men, particularly those with long-standing disease, who are also positive for rheumatoid factor and have nodules.

The clinical features and course of interstitial lung disease and pulmonary fibrosis in RA are similar to those of idiopathic disease. The diagnosis can be confirmed with plain chest X-rays, lung function tests and high-resolution computed tomography. Biopsy or bronchial lavage are indicated in a small minority of cases. RA patients presenting with cough and increased breathlessness need to be investigated urgently with this diagnosis in mind. In particular, patients taking methotrexate need to have such symptoms evaluated with alacrity. Methotrexate should be stopped. Treatment of lung disease in RA is empirical. Corticosteroids are usually given and immunosuppressive drugs like azathioprine are often added.

Cardiac disease

Patients with RA have increased risks of atherosclerotic cardiovascular events. Traditional risk factors for atherosclerosis, such as hypertension, hyperlipidaemia and sedentary lifestyle, account for some of the excess burden of cardiovascular disease in RA. Drug therapy, particularly NSAIDs, may increase these risks or change their expression. There is also increasing evidence that RA itself results in accelerated atherosclerosis, possibly as a consequence of chronic systemic inflammation (Wasko, 2004). There is evidence for a 30–60% excess of cardiovascular events in RA. The features of myocardial infarctions are no different in RA from other cases, but the increase in incidence merits careful vigilance. RA patients presenting with chest pain need careful evaluation before deciding that they do not have a myocardial infarction.

Pericardial disease is an occasional occurrence in RA and in some cases can cause overt cardiac disease. Its rarity is shown in a series of 204 effusions of patients with pericarditis in which seven were attributed to RA (Levy et al, 2003). In most cases no specific treatment is needed. There are reports of large effusions impairing cardiac function in occasional cases and these may need surgical intervention.

Gastrointestinal problems

RA does not usually cause gastrointestinal problems as part of the disease process itself, with the exception of rare cases of vasculitis affecting the bowel. However, serious gastrointestinal adverse effects can result from anti-rheumatic drugs. In the 1990s upper gastrointestinal ulceration as a result of NSAIDs was considered a major health problem, on a par with cancer of the cervix and deaths from melanoma. However, its frequency has fallen by two thirds because lower doses of safer drugs are now used, with a decline in the use of more toxic NSAIDs and increasing use of proton-pump inhibitors (Fries et al, 2004). These declines seem likely to continue. Nevertheless it remains commonplace for RA patients to present with an acute complicated upper gastrointestinal ulcer because of the effect of NSAIDs. Sometimes the use of steroids can mask the severity of the ulcer disease.

In addition to upper gastrointestinal disease, a substantial minority of patients with RA who are taking anti-inflammatory drugs have small bowel disease. This usually presents as anaemia, often with features of iron deficiency. There can also be increased permeability of the small bowel (Sigthorsson et al, 1998). Just as upper gastrointestinal endoscopy revolutionized the medical management of upper gastrointestinal ulcers as a result of anti-rheumatic drugs, it is likely that the growing use of capsule enteroscopy will have a similar effect on small bowel disease (Carey and Fleischer, 2005).

Neurological

The cervical spine often becomes involved early in the course of RA, with three different patterns of instability: atlantoaxial subluxation, atlantoaxial impaction, and subaxial subluxation (Kim and Hilibrand, 2005). Although X-ray changes are common, neurological damage is infrequent. The key aim is to avoid permanent neurological injury while avoiding unnecessary surgery. When there are concerns about possible cervical cord damage, magnetic resonance imaging is indicated. Surgery may be needed in such cases, and should be undertaken in highly specialized units. Neck pain itself should not be a matter of concern but evidence of instability in the cervical spine or any clinical features of cord damage need urgent assessment.

RA patients often have compression neuropathies, such as the carpal tunnel syndrome, as a result of compression of the median nerve. They occasionally have peripheral neuropathies, which are sometimes a result of the disease itself, but may also be the result of RA vasculitis or an unusual adverse reaction to drug therapy.

Finally RA is one of the disorders in which a vasculitis can cause neural damage and patients develop mononeuritis multiplex in which several peripheral nerves are

damaged because of inflammation of their blood vessels. The management of these neuropathies depends on circumstances. Ideally the diagnosis should initially be confirmed by nerve conduction tests. Compression neuropathies like carpal tunnel syndrome may respond to local steroids but usually require surgical intervention. A peripheral neuropathy usually has no specific treatment, but if drugs are implicated treatment needs changing and the likely causative drug should be stopped. If there is a mononeuritis multiplex in the setting of RA vasculitis, the treatment is that of the vasculitis, which usually means steroids or cytotoxic drugs.

Renal

Renal problems are uncommon as a consequence of RA. They usually represent either drug toxicities or amyloidosis. Occasionally RA vasculitis can present with renal problems. Some diagnostic caution is needed as sometimes it can be difficult to differentiate RA from connective tissue disorders, particularly systemic lupus erythematosus, and in this situation the connective tissue disorder can result in renal involvement unexpectedly.

When injectable gold and penicillamine were often used to treat RA, renal involvement was relatively common. Pencillamine caused a range of renal problems including the sudden development of nephritic syndrome. Gold injections are often nephrotoxic, and proteinuria and haematuria can be found in up to 10–20% of cases. Both drugs needed careful monitoring for renal toxicity and when there was any indication it was developing they had to be stopped. Even so, nephritic syndrome could develop despite their cessation. Now that they are rarely used, renal toxicity from drugs has markedly declined (Schiff and Whelton, 2000). Cyclosporin is still used in some cases of RA and can cause renal toxicity with increases in plasma creatinine levels and subsequent decline in creatinine clearance. This usually returns to normal when the cyclosporin is stopped. The reduced creatinine clearance may be attributable to cyclosporin-induced renal afferent arteriolar vasoconstriction with a resultant reduction in renal blood flow. Creatine levels need careful monitoring when using cyclosporin. Occasionally patients with RA treated in this way will present with major impairments in renal function that should respond to cessation therapy. Other disease-modifying drugs, like methotrexate, do not cause significant renal toxicity.

NSAIDs can also cause renal problems. These are relatively uncommon and very diverse in type. Acute interstitial nephritis, in which there is proteinurina and eosinophilia, is one example; in addition NSAIDs often result in fluid retention as they impair renal physiology. When RA patients develop renal disorders it is prudent to stop NSAIDs, as these are always a potential causal agent.

The other renal complication of RA that may result in an acute problem is secondary amyloidosis, with deposition of AA amyloid in the renal tissue (Boers, 1990). Patients usually present with progressive proteinuria that ends in renal failure. Up until 20 or 30 years ago amyloidosis was common in RA, and involved 10% of cases or more. Nowadays it is exceedingly rare. The reasons for this decline are uncertain, but are usually attributed to the improvements in disease control in RA and the widespread use of disease-modifying drugs.

Vasculitis

Vasculitis is an inherent component of all connective tissue diseases, including RA. It is common to develop small areas of vasculitis in the skin overlying subcutaneous nodules, suggesting nodulosis and vasculitis may be closely related (Luqmani et al, 2005).

Some components of RA vasculitis, such as nail edge infarcts and splinter haemorrhages, are common and relatively trivial. However, they may indicate underlying major vessel involvement, and it is unwise to dismiss them as irrelevant. Systemic RA vasculitis used to affect about 12–16 cases per million each year, although there are suggestions that it is declining. Its clinical presentations are variable depending on which organ or organs are involved. In some cases it can result in gangrene as a result of obstruction of peripheral blood vessels. Some patients with RA leg ulcers have an underlying vasculitis, and in others there can be CNS vascular inflammation or renal disease.

It is preferable to have histological confirmation of RA vasculitis. In many cases this is impractical and patients have to be treated on clinical grounds. Immunosuppressive drugs like azathioprine and cyclosporin, steroids and, in severe vasculitis, pulse cyclophosphamide, are all used in RA vasculitis, and treatment needs to be individualized for specific patients.

Skin

Many skin reactions occur as adverse reactions to antirheumatic drug therapy. Their appearances vary greatly, they are usually mild but can be severe, and most settle when treatment is stopped. There are also skin problems as a result of the underlying disease process. Some of these are because of vasculitis, including leg ulcers and leucocytoclastic vasculitis with a rash.

Pyoderma gangrenosum is a specific cutaneous problem that can complicate RA. It begins with a tender, erythematous area on the lower portions of the legs. It rapidly matures into a purulent necrotic ulcer with ragged oedematous edges. There are often multiple lesions, typically less than 10 cm in diameter. Ulcers tend to last months to years and resolve with scarring (Sayah and English, 2005). It often requires cytotoxic drugs or high-dose steroids.

Eye problems

RA patients often have eye problems, which are mainly long-standing and attributable to reduced tear production on account of Sjögren's syndrome. This results in dryness, irritability and variable redness. In addition some patients on long-standing steroid therapy may develop cataracts as an adverse effect.

The most important eye complication of RA is the development of scleritis, which can also complicate other inflammatory rheumatic disorders (Akpek et al, 2004). Most scleritis has a diffuse and anterior pattern. A minority of patients have necrotizing scleritis, and in less than 1% of cases there is scleromalacia perforans. Scleritis gives a characteristic clinical picture of inflammation and oedema of the episcleral and scleral tissues. It is usually, but not invariably, accompanied by pain and tenderness. Scleritis is sometimes accompanied by ulcerative keratitis, interstitial keratitis or uveitis. Its evaluation and treatment needs to be undertaken by ophthalmologists.

Osteoporosis

Reduced bone mass, which is the key feature of osteoporosis, occurs in RA patients with marked systemic inflammation. It can also occur as an adverse effect of steroid therapy. Many patients take bone-protecting drugs including vitamin D and calcium supplements and bisphonates. Preventive measures are important and dual-energy X-ray absorptiometry screening should be undertaken if there are any indications of osteoporosis or other risk factors. Despite these measures there are increased rates of spinal fracture and fractures of the long bones. When RA patients sustain a fracture it is important to check their bone density as part of their post-fracture management.

Conclusions

RA is a common chronic disorder that affects in the region of 1% adults. Although its care is the primary responsibility of rheumatologists, its direct complications, associated comorbidities and the adverse effects of the many drugs used in its treatment mean that many members of the general medical staff will be involved in a patient's care. The most important treatable problems are septic arthritis, systemic infections as a result of either the disease itself or the effects of immunosuppressive therapy, upper gastrointestinal ulceration as a result of the unwanted effects of NSAIDs and systemic vasculitis. Delays in making an accurate diagnosis in any of these conditions can have significant deleterious effects and, in the case of infections, can increase the likelihood of fatal outcomes.

When RA patients have other clinical problems it can be difficult to reach a definitive diagnosis in a timely fashion, because of the patient's widespread pain from arthritis, and the raised ESR and C-reactive protein owing to the systemic inflammatory nature of the disease. In particular the increasing use of new biological treatments – tumour necrosis factor inhibitors – not only make infections more likely but also mask the features of sepsis. **BJHM**

Conflict of interest: Professor Scott has served as a consultant for Novaratis and Sumitomo and has been paid lecture fees by Wyeth, Sanofi Aventis, Merk Sharp and Dohme and Novartis. His department has received funding for clinical trials from Pfizer, O-Med, Astra-Zeneca, Sumitomo and Roche and unrestricted clinical research grants from Amgen, Schering-Plough and Aventis. His department has aso received grants from ARC, MRC, Nuffield Foundation and Myositis Support Group. He acts as an advisor for Arthritis Care, the Arthritis and Musculoskeletal Alliance and the Myositis Support Group.

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KEY POINTS

- Rheumatoid arthritis (RA) is a common chronic disorder with many complications and comorbidities.
- Septic arthritis, other systemic infections, gastrointestinal ulcers and vasculitis are major problems.
- Immunosuppression in RA can mask life-threatening infections.
- A single active joint in a patient with established RA might be the result of infection.