Rheumatological and immunological disorders

Edited by Paul Bacon MB, FRCP
ARC Professor of Rheumatology, University of Birmingham

Core knowledge in rheumatology: what does a general physician need to know?

Deva Situnayake FRCP,
Consultant Rheumatologist, *Department of Rheumatology, City Hospital NHS Trust, Birmingham*

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Rheumatological disease constitutes a small but challenging proportion of the emergency medical workload presenting to general physicians. The timely diagnosis and effective management of such emergencies are often crucial to optimal outcomes, since there is a growing understanding of the link between rapid control of inflammatory disease and the sparing of irreversible damage. This is particularly relevant in multisystem vasculitic and connective tissue disease, but it is also pertinent in the assessment and therapy of other disorders such as giant cell arthritis (GCA), bacterial arthritis and avascular necrosis. The knowledge required to perform this function spans skills in areas such as clinical examination, joint aspiration, interpretation of diagnostic information, and therapeutics. An awareness of atypical presentations of rheumatological disease and a willingness to seek multidisciplinary advice is vital, as is an understanding of when to refer for specialist rheumatological management. The assessment of patients presenting acutely with clinical features suggestive of rheumatological disease by the appropriate use of history, clinical examination and investigations is fundamental to forming an appropriate differential diagnosis.

Key Points

- **Urgent joint aspiration prior to antibiotic therapy in suspected septic arthritis, inoculating blood culture bottles with synovial fluid, as well as routine bacteriology, is vital for optimal outcome**
- **Delay in effective therapy in systemic vasculitic syndromes can have profound and irreversible effects on organ function**
- **In the context of systemic disease and pulmonary/renal dysfunction, antineutrophil cytoplasmic antibodies (PR3/myeloperoxidase specificity) have high sensitivity for systemic vasculitic disease**
- **Pulmonary haemorrhage typically presents with respiratory failure associated with haemoptysis, and falling haemoglobin associated with diffuse bilateral alveolar infiltrates**
- **In the context of established connective tissue disease, bronchoalveolar lavage may be required to confirm pulmonary haemorrhage and rule out opportunistic pulmonary infection**
- **A preceding history of knee pain and swelling is almost always present before the onset of ruptured popliteal cyst**
- **Cervical cord compression should always be considered when the patient with established rheumatoid arthritis becomes immobile**
- **Infection and active disease may coexist in systemic lupus erythematosus. A very high C-reactive protein is a useful pointer to infection**

The acute hot joint: septic arthritis, crystal arthropathy, reactive arthritis

In addition to bacterial infection, an inflamed joint can reflect a wide variety of internal diseases, all of which can present with a monoarthritis:

- crystal arthropathies
- seronegative arthropathies
- Reiters syndrome
- connective tissue disease
- inflammatory bowel disease
- sarcoidosis
- vasculitis.

Apart from post-dysenteric and sexually acquired reactive arthropathies, non-specific reactive monoarthritis may be a feature of a wide variety of infections including brucellosis, Lyme disease and leptospirosis, and tuberculosis should not be forgotten. The ability of the joint to reflect multisystem disease necessitates close liaison with other specialists. A multidisciplinary approach to the management of these patients is strongly encouraged, as some will have unusual diseases that require specialist advice[1].

At its inception, bacterial infection of joints most often results from haematogenous seeding of the synovium, ultimately spreading to the joint space. If antibiotics are started before extension to the joint space, synovial fluid cultures will be negative. Thus, the initial synovial fluid culture may yield no growth, and subsequent cultures ultimately become positive. The skills for large joint aspiration are readily learned and are associated with minimal risk.

Despite advances in antimicrobial therapy, septic arthritis may frequently be responsible for permanent functional impairment and mortality. Risk factors include:

- older age
- diabetes mellitus
- rheumatoid arthritis (RA)
- immunodeficiency
- pre-existing joint disease.

Urgent joint aspiration, seeding the fluid on blood culture flasks immediately after aspiration, increases the yield of microbiology. Samples should also be submitted for polarising light microscopy since gout and pseudogout may present in a similar way.

Undue delay in diagnosis and blind antibiotic therapy may increase mortality and be associated with irreversible cartilage loss, particularly in children. Early and aggressive therapy is therefore imperative to prevent joint destruction and mortality, particularly in elderly patients with RA or diabetes.

Management

Age and underlying diseases will determine the choice of antibiotic therapy. *Staphylococcus aureus* and other Gram-positive cocci are common in RA, while *Haemophilus influenzae* is more common in children below three years of age with acute arthritis. Gram-negative infection becomes more common in the elderly with predisposing diseases.

When aspiration is difficult or inaccessible (eg the hip), X-ray or ultrasound-guided aspiration may be necessary, and the support of the orthopaedic team for arthroscopic lavage or arthrotomy may be required. Partially treated septic arthritis, resulting from blind antibiotic therapy before appropriate bacteriological specimens have been obtained, presents a difficult management challenge, with antibiotic choice preferably determined after microbiological advice. Polymerase chain reaction may detect bacterial DNA in culture-negative cases[2]. Once microbiological specimens have been obtained, empirical parenteral antibiotic therapy should not be delayed – though this will be guided later by the culture results. The joint should be splinted in a position of function and antibiotic therapy continued for a minimum of 4-6 weeks, switching to the oral route approximately one week after clinical response. The joint should be protected from weight-bearing for an average of six weeks, but the patient is normally mobilised as soon as the pain has subsided. Laboratory variables such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) should be monitored. Normalisation of these variables may be interpreted as evidence of the effectiveness of the antibiotic treatment. The evaluation of early anti-inflammatory therapy is currently in an experimental phase.

Acute crystal arthropathy (gout or pseudogout) is usually clinically evident, but can be confidently diagnosed only by finding crystals on polarising microscopy of synovial fluid (serum urate may be normal in an acute attack of gout). Once gout (or pseudogout) has been ruled in and infection ruled out, prompt response can usually be achieved either by use of non-steroidal anti-inflammatory drugs or, if contra-indicated, colchicine or intra-articular steroid injection. Such patients may not require admission. Decisions on urate lowering therapy can be delayed until outpatient assessment. Its introduction is usually delayed for at least one month following an acute attack (although it is not necessary to discontinue therapy during an attack).

Primary systemic vasculitic syndromes

The general physician may infrequently encounter these syndromes in the context of an acutely ill, febrile patient with multisystem disease, often with a very high CRP, in whom infection has been suspected but not confirmed. The consequences of delaying effective therapy are frequently profound, and irreversible organ damage is common.

Diagnosis and classification of vasculitis have been revolutionised by the discovery and characterisation of serum antineutrophil cytoplasmic antibodies (ANCA). ANCA are detected in serum by indirect immunofluorescence using ethanol-fixed human polymorphs, though confirmatory testing using solid-phase ELISA assays for defined target antigens is available. Cytoplasmic (cANCA) and perinuclear (pANCA) staining patterns for ANCA can be identified. They are highly specific markers for the systemic vasculitides including:

- Wegener's granulomatosis (WG) (Table 1)
- polyarteritis nodosa (microscopic polyangiitis)
- Churg-Strauss syndrome
- idiopathic pauci-immune necrotising and crescentic vasculitis, with or without pulmonary haemorrhage.

Sensitivity is high when there is systemic involvement, as defined by renal involvement. The antibodies are only moderately sensitive markers in limited or localised disease[3]. The American College of Rheumatology proposed a system for classification and nomenclature for the systemic vasculitides which is now widely adopted[4]. Diagnosis still rests heavily on clinical criteria and the use of tissue biopsy/angiography.

Delineation of subsets of humoral ANCA by solid-phase ELISA assays using purified neutrophil proteins has allowed further definition of antigen specificity of ANCAs. The cANCA pattern (diffuse granular cytoplasmic staining) correlates closely with proteinase 3 specificity. This pattern of staining is most frequently observed in patients with WG, with a higher sensitivity for active WG (90%) depending on the extent of disease. Specificities above 90% have been achieved. Some cANCA-positive patients may have other forms of systemic vasculitis such as microscopic polyangiitis, Churg-Strauss syndrome and primary necrotising and crescentic glomerulonephritis, with or without pulmonary haemorrhage, though a pANCA pattern (anti-myeloperoxidase (MPO)) is more frequently found. In the setting of rapidly progressive glomerulonephritis, the positive predictive value

Table 1. Clinical manifestations of Wegener's granulomatosis.

System	Clinical manifestation
Upper airway	nasal mucosal ulceration epistaxis nasal septal perforation/collapse and deformity sinusitis
Lower airway	subglottic stenosis tracheal inflammation cough haemoptysis pleurisy pulmonary infiltrates or nodules
Renal	glomerulonephritis renal failure
Ophthalmological	conjunctivitis dacrocystitis scleritis proptosis eye pain visual loss retinal or corneal disease
Musculoskeletal	arthralgia arthritis myalgia
Dermatological	subcutaneous nodules palpable purpura ulcers vesicles and papules
Neurological	mononeuritis multiplex stroke cranial nerve disease diabetes insipidus
Cardiac	pericarditis myocardial or coronary artery involvement
Non-specific	fever weight loss anaemia

of either type of ANCA for pauci-immune necrotising and crescentic glomerulonephritis is high. Most patients with ANCA-related disease have a prodrome of often non-specific symptoms, including persistent sinus, nasal or otological disease, and progress to systemic involvement. Since ANCA-related diseases are associated with high morbidity and mortality, early diagnosis and effective therapy is the key to improved outcomes. Such patients require prompt and systematic assessment and referral to the appropriate specialist[5].

Diagnostic laboratory and imaging techniques

Scintigraphy

Intravenous radioisotopes such as Technetium 99m methylene diphosphonate detect areas of increased bone turnover, and can be usefully employed for the detection of bone infection (Fig 1), secondary deposits and metabolic bone disease, stress or osteoporotic fracture. Isotope bone scans may become abnormal prior to radiological changes in avascular necrosis, though magnetic resonance imaging (MRI) remains the procedure of choice in this situation. The use of rapid tests for D-dimers (a product of fibrinuge degradation), together with ultrasound and Doppler flowmetry, is vitally important in the assessment of the painful calf where differentiation between deep venous thrombosis (DVT) and ruptured popliteal cysts continues to present a challenge to the physician. Almost always, there is a preceding history of knee disease and/or swelling in patients who develop a ruptured popliteal cyst. Prompt investigation is vital to facilitate appropriate management. In those subjects in whom calf pain is most probably due to popliteal cyst, early anti-coagulation (to cover DVT) before investigation is inappropriate and can lead to devastating haemarthrosis and the need for prolonged rehabilitation. Early discharge following ruptured popliteal cyst can be achieved using intra-articular cortico-steroid injection.

Radiology

MRI is the imaging modality of choice in the evaluation of the unstable cervical spine in RA. 'Red flags' suggesting the need for further evaluation are outlined in Table 2. Cervical cord compression

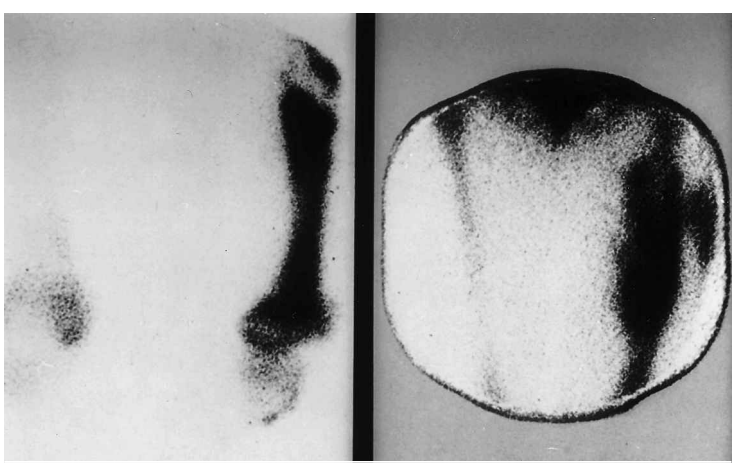

Fig 1. Osteomyelitis of the left femur showing abnormal technetium bone scan (left) and gallium scan (right) with soft tissue collection.

should always be considered in the differential diagnosis when an established RA patient becomes less mobile or incontinent (Fig 2). Other rheumatological diseases which can cause spinal cord compression include cervical spondylosis, spondylolisthesis (cauda equina syndrome), central disc prolapse, Paget's disease, spinal tuberculosis and staphylococcal discitis.

Table 2. 'Red flags' suggesting cord compression in rheumatoid arthritis.

- Severe neck pain radiating to the occiput associated with occipital numbness
- Diminished power in arms and legs or loss of mobility
- Numbness or tingling in the hands or feet
- Lhermitte sign
- Involuntary movements of the limbs
- Disturbed bladder or bowel function

Distinguishing infection from disease activation in systemic lupus erythematosus

Fever is a common complication in systemic lupus erythematosus (SLE) and may occur as a disease manifestation or from intercurrent infection. In some circumstances, both factors may be operating since infection-driven apoptosis may lead to SLE disease activation through impaired clearance of apoptotic fragments and nucleosomal cleavage products which are now thought likely to lead to the generation of anti-dsDNA antibodies[6]. It is in this context that the physician must determine whether fever represents active lupus or infectious process. In the very sick lupus patient, these decisions must be made promptly, and appropriate evaluation and treatment begun. This process may be challenging, particularly when there are clinical signs of active lupus. Rigors tend to occur more commonly in infection, and fever will usually respond poorly to modest increases in steroid dose in contrast to disease-related fever. Leukopenia (white cell count $<4{,}000/mm^3$) and marked elevation of CRP (>20 mg/l) are suggestive of infection in lupus; raised CRP occurs infrequently unless there is major serositis or synovitis. Whilst lupus itself may be associated with increased infection risk (bacterial endocarditis, pneumococcal septicaemia, and disseminated neisseria and salmonella infection are well described), factors associated with enhanced risk of opportunistic infection include renal disease, hyposplenism, hypogammaglobulinaemia, hypocomplementaemia/complement deficiency and high-dose corticosteroid and immunosuppressive therapy.

It is usual practice to perform a comprehensive infection screen on all such patients. Since the risks attendant on delay in appropriate antimicrobial therapy are great in the very sick, broad spectrum antibiotic therapy should be started guided by the clinical context.

Giant cell arteritis and polymyalgia rheumatica

Polymyalgia rheumatica (PMR) is 2–3 times more common than GCA, but targets the same elderly population. Polymyalgic symptoms are present in 50–90% of patients with GCA, but a polymyalgic presentation can herald RA, SLE, carcinoma or lymphoma. Histological evidence of GCA in temporal artery biopsies may be observed in up to 20% of PMR patients, and recent evidence suggests that subclinical arteritis in large vessels may be quite common[7]. Anterior ischaemic optic neuropathy may cause irreversible blindness, a most feared complication, due to vascular occlusion in response to vasculitis, resulting in central retinal artery thrombosis. Doses of corticosteroid required to induce remission of symptoms and control of the acute-phase response in PMR are usually lower than for GCA. Corticosteroids prevent the majority of ischaemic complications, and 50% of GCA patients are able to withdraw corticosteroids within two years without recurrence[8], though there is no proof that corticosteroids influence the course of disease. A subset of patients with PMR requires long-term therapy. Persistent suppression of CD8 lymphocyte counts[9] and elevated von Willebrand factor may predict subjects at greater risk of relapse[10]. Treatment

Fig 2. X-rays of the cervical spine showing atlantoaxial subluxation in rheumatoid arthritis. The distance between the anterior arch of the atlas and the odontoid peg should not normally exceed 3 mm. It is best demonstrated with the neck in flexion.

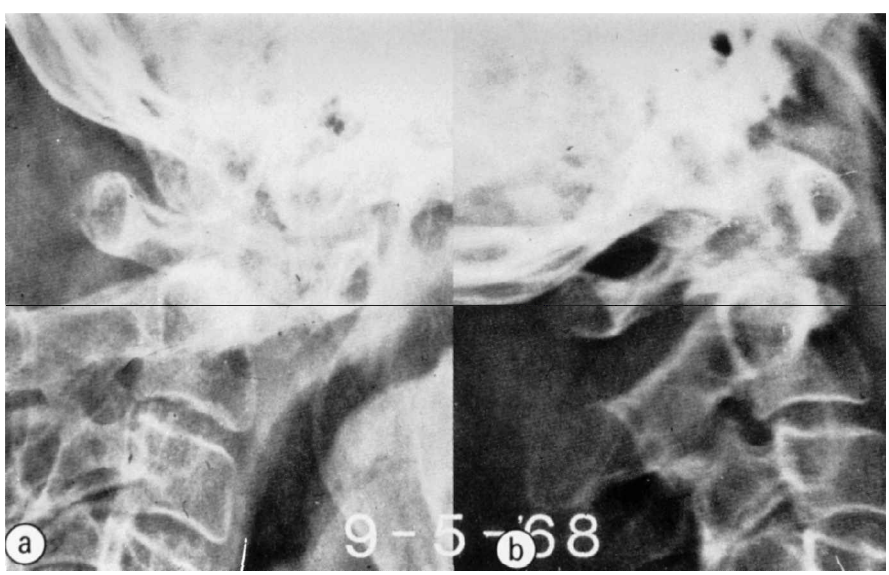

Table 3. Key points in giant cell arteritis (GCA)/polymyalgia rheumatica (PMR).

Age >50	Examine arteries in head, neck & upper limbs
Recent headache	(bruits, tenderness, blood pressure)
Transient visual loss	Biopsy abnormal segment of temporal artery
Myalgia	Skip lesions characteristic
Fever	Panarteritis with giant cell granulosa
Weight loss	PMR: prednisolone 15 mg/day, reducing to 7.5–10 mg by 6–8 weeks
Anaemia	GCA: 40 mg daily for the first month (if visual
Raised ESR	symptoms persist, 60–80 mg), 20 mg daily by
Raised alkaline phosphatase	8 weeks, then gradual reduction by 1 mg every 2–3 months
Granuloma on liver biopsy	Possible withdrawal of steroids by 18 months to 2 years

ESR = erythrocyte sedimentation rate.

strategies employ adequate doses of prednisolone for the first month to obtain good symptomatic control with a fall in ESR, aiming for maintenance with doses of less than 10 mg after six months (Table 3). Corticosteroid-dependent patients may require a steroid sparing agent such as azathioprine or methotrexate. Since corticosteroid-induced bone loss occurs early, adequate consideration should be given for osteoporosis prophylaxis with bisphosphonates[11].

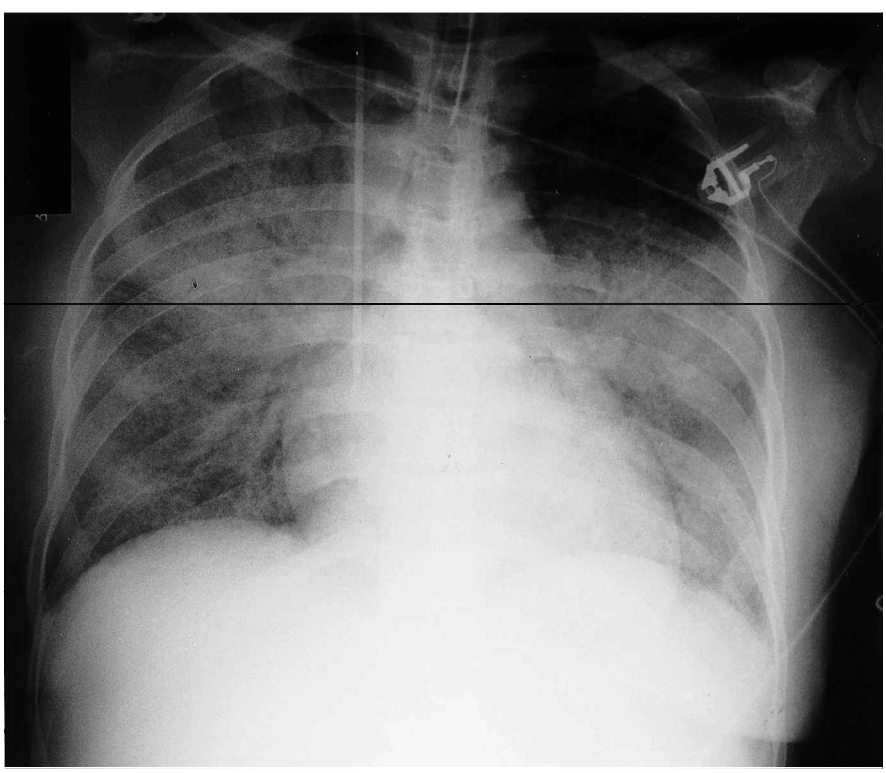

Fig 3. Chest X-ray findings showing diffuse bilateral alveolar infiltrates in a young woman with established systemic lupus erythematosus. She presented with falling haemoglobin, haemoptysis and respiratory failure, and required ventilation due to alveolar haemorrhage. Plasmapheresis was given, followed by pulsed steroid/cyclophosphamide therapy.

Alveolar haemorrhage and critical illness in rheumatic disease

Admission to the ITU is infrequently required for patients with rheumatic disease, but may be necessary when critical pulmonary, renal or haemodynamic disease occurs. These complications most commonly present in the context of established connective tissue or vasculitic disease, only occasionally occurring as a *de novo* presentation. Respiratory failure (atypical pneumonia, left ventricular failure, cardiac tamponade, pulmonary embolism, acute respiratory distress syndrome and pulmonary haemorrhage) and overwhelming sepsis are common causes. They occur in the context of:

- ANCA-associated vasculitis (pulmonary haemorrhage and pulmonary renal syndrome)
- SLE (acute nephritis, pneumonitis, pulmonary haemorrhage, catastrophic antiphospholipid syndrome)
- interstitial lung disease (RA, SLE, antisynthetase syndrome and scleroderma).

Pulmonary haemorrhage typically presents with respiratory failure associated with haemoptysis, and a falling haemoglobin associated with bilateral diffuse alveolar infiltrates (Fig 3). Renal function may be disturbed at presentation or dysfunction become apparent later[12–14].

In addition to supportive measures, rapid diagnostic evaluation using bronchoscopy with bronchoalveolar lavage (BAL) is required to confirm pulmonary haemorrhage and rule out opportunistic lung infection. In this context, other possible causes of pulmonary failure in patients with rheumatological disease include pneumocystis infection, associated with methotrexate therapy for RA. BAL may help to distinguish this from methotrexate pneumonitis. Pulmonary pneumocystis may also occur in WG, and

may be particularly associated with combinations of corticosteroid and immunosuppressive therapy and low CD4 counts[15]. Infection with intracellular pathogens such as aspergillus, nocardia, mycobacteria and cytomegalovirus will also be more readily disclosed by BAL (comprehensively reviewed in Ref 16).

In the context of suspected or established connective or vasculitic diseases, pulmonary haemorrhage may occur due to:

- Goodpasture's syndrome
- microscopic polyangiitis
- WG
- SLE
- antiphospholipid syndrome (rarely)[14].

Urgent serological testing for ANCA (anti-MPO or PR3), and anti-glomerular basement membrane (GBM) antibodies will provide supportive evidence, though renal or other tissue biopsy may be necessary to establish the histopathological lesion. Open lung biopsy or thoracoscopic biopsy may occasionally be required if renal or nasal tissue are unlikely to provide the diagnosis. Treatment with high-dose corticosteroid therapy and cyclophosphamide is indicated in the systemic vasculitides (following plasmapheresis in those with anti-GBM disease and SLE). The mortality rate remains high, with better prognosis in those who possess anti-MPO ANCA in contrast to anti-PR3[17]. Such patients will require early specialist referral and multidisciplinary management.

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Address for correspondence:
Dr R D Situnayake, City Hospital NHS Trust, Birmingham B18 7QH.