REVIEW

Rheumatological manifestations of haematological diseases

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In a review published in 1983, an attempt was made to highlight the rheumatological aspects of diseases generally regarded as haematological in origin.¹ Since then, a variety of reports have served to strengthen the links between these two areas of medicine. In this review, we consider these more recent reports and focus on patient presentation, advances in treatment, and knowledge of underlying mechanisms. Epidemiological data are reviewed and, in particular, we speculate on the possible immunological mechanisms common to lymphoproliferative malignancy and autoimmune disease.

Haemoglobinopathies and iron storage disease

SICKLE CELL DISEASE

Homozygous (SS) sickle cell disease, heterozygous (SC) sickle cell disease, and the overlap sickle S/β thalassaemia cause major morbidity and mortality. Sickle haemoglobin polymerises when deoxygenated and red cells distort and block small vessels but, nevertheless, the sickle cell gene persists by conferring to heterozygotes resistance against malarial infection.

Sickle cell disease typically presents in childhood with haemolytic anaemia and intermittent crises, during which acute phase reactants such as C reactive protein are increased² and it is important to achieve pain control, using opioids and possibly intravenous methylprednisolone.³ Severe oligo- or polyarthralgia may develop and transient joint swelling lasting for up to three weeks may occur.⁴ The joints feel warm and tender, and septic arthritis, acute gout, and haemarthrosis should be excluded. Joint aspirate is typically yellow, non-inflammatory, sterile, and free of urate crystals. Ankle arthritis is occasionally associated with vaso-occlusive leg ulceration, implying that joint effusion is secondary to synovial and bone ischaemia or infarction.⁴

Osteonecrosis contributes significantly to the disabling skeletal manifestations of sickle cell disease and by 2 years of age, up to 45% of children have dactylitis with recurrent, painful swelling.⁵ This 'hand-foot' syndrome is caused by bony infarction and digits are permanently shortened after epiphyseal plate damage. Sickle cell disease is probably the commonest cause of avascular necrosis world wide, with 150 000 estimated cases in Zaire alone.⁶ Most reports describe femoral head involvement (fig 1) with an incidence of 5-33% in large series;⁷ other

sites include the humeral head (2-17%),^{8,9} distal femur, calcaneum, and ribs.

Bone¹⁰ and magnetic resonance¹¹ scanning are sensitive early methods of detecting necrosis, particularly of the spine and pelvis, as nearly 25% of radiographs may be normal at presentation.¹² In the hip, sclerosis and patchy lucency are seen, and the femoral head subsequently flattens and collapses. Treatment requires bed rest initially, and surgery ranges from osteotomy and arthrodesis to various forms of arthroplasty. However, most approaches have met with little success, and replacement surgery is often required. Post-operative complications include haematological crisis,⁹ infection, loosening of the prosthesis, and fractures at the level of the femoral stem.^{13,14} Revision may be necessary,⁸ and a mean survival of 5.4 years has been estimated for replacement arthroplasty.¹⁴

Polyarticular chondrolysis has been reported in a patient who required bilateral hip arthroplasties.¹⁵ Light microscopy showed eroded cartilage with congested vessels and mononuclear cells in the synovium. Electron microscopy found occluded synovial blood vessels,

Figure 1 Sickle cell disease. Avascular necrosis, resulting in collapse and sclerotic appearance of the femoral head. Fissuring of the subcortical bone is also evident.

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and phagocytic cells containing crystalline debris. This implies a role for both phagocytic cells and vessel obstruction in joint destruction. A variety of mechanisms, common to any inflammatory arthritis, may also contribute to cartilage breakdown, and these include release of lytic enzymes, oxygen free radicals, or both, during phagocytosis,¹⁶ hydrogen peroxide generation,¹⁷ and the release of cytokines by phagocytes, which promote the production of collagenase¹⁸ and neutral proteases¹⁹ by chondrocytes.

Despite the increased risk of serious bacterial infections in sickle cell disease, osteomyelitis is uncommon,²⁰ with *Salmonella* as the reported pathogen in the majority of cases.^{9, 20} Osteomyelitis is multifocal in 40% and the tibia, femur, and humerus are affected most often.²¹ The infection starts in the medullary cavity and is later complicated by sinus formation and pathological fracture.

Septic arthritis remains infrequent^{9, 20} and predominantly a disease of childhood. Multiple joints are involved in up to 40% of cases, and osteomyelitis is also present in up to 84%.¹² Unfortunately, many patients present late, with only 30% seen within the first week of illness in Nigeria.¹² The commonest joints affected are knees, hips, ankles, and shoulders, and it is usually gram negative bacilli (primarily *Salmonella*) that are responsible. There are several possible reasons why sickle SS patients are prone to infection: multiple splenic infarction leads to atrophy of the spleen, and there is evidence of impaired opsonisation,²² and defective functioning of the alternative complement pathway.²³

THALASSAEMIA

The thalassaemias are a group of congenital disorders in which synthesis of one or other of the globin chains is reduced. The β -thalassaemia trait is found in up to 10% of the population in Turkey,²⁴ and in the homozygous individual severe anaemia is apparent by six months after birth. Management has improved considerably in the past 15 years (for example with changes in transfusion policies and the availability of intramuscular and subcutaneous desferrioxamine), with a striking improvement in survival, which is now 95% at 15 years of age.²⁵ Nevertheless, large doses of desferrioxamine can cause growth failure, and a variety of bony changes in the lower thoracic and lumbar vertebrae.²⁶ The new experimental oral iron chelator 1,2 dimethyl-3-hydroxypyrid-4-one (L_1) is reported to produce arthralgias and joint swelling, but this improves after reduction of the dose or temporary discontinuation.²⁷

As a consequence of the improved management, more β -thalassaemia major patients survive to adulthood, but those with sub-optimally treated disease may have significant joint pathology.²⁸ Medullary expansion gives long bones a characteristic squared appearance, there is coarsening of the trabecular pattern of bone (fig 2), and osteoporosis and cortical thinning are common.²⁹ Fractures are

most frequently seen in the long bones of the lower limb, particularly the femur,³⁰ and may be present in 30% of patients. Profound growth disturbance from premature fusion of the growth plate (particularly of the proximal humerus and distal femur) occurs in 10–15% of patients, but is significantly reduced with regular transfusions, which suppress ineffective erythropoiesis. However, some patients develop hyperuricaemia and gout, and also secondary haemochromatosis.³¹

Heterozygous thalassaemia (minor) remains a common and usually silent disorder. In a blind study comparing 80 cases of thalassaemia minor with control patients, 55% of cases had musculoskeletal symptoms compared with 54% of controls.³² Arthralgia of the wrist and shoulders was most common, and three patients had a short lived arthritis. In consequence, the authors concluded that no specific form of chronic arthritis occurs.

HEREDITARY (PRIMARY) HAEMOCHROMATOSIS

In the classical inherited form, increased intestinal iron absorption results in excess iron deposition throughout the body. The liver, pancreas, and heart are commonly affected³³ with fibrosis and subsequent organ malfunction, and the diagnosis is made by blood tests showing characteristic iron studies and liver biopsy specimens demonstrating iron deposition.³⁴

Haemochromatosis is five to 10 times more frequent in males than females, and 70% of patients develop their first symptoms in middle age.³⁵ An association has been described with the HLA-A3 which is found in 70% of patients (compared with 28% of the general population), and the mode of inheritance is usually autosomal recessive.³⁶

Arthritis occurs in about 50% of cases³⁴ and is most severe in those over 50 years of age. Both acute and chronic arthropathies are well described and the manifestations are diverse. Acute episodic synovitis, especially in the knees and wrists, is probably the result of calcium pyrophosphate dihydrate deposition, which is found in 67% of patients.³¹ Chronic arthropathy begins in the small joints of the hand, particularly the second and third metacarpophalangeal joints³⁷ with acute attacks of synovitis, stiffness, pain on flexion, and impaired movement. Thereafter the arthritis spreads to the large joints, involving the shoulders, elbows, hips, and knees.³⁸

On joint imaging (fig 3), chondrocalcinosis, loss of articular cartilage, sclerosis, and joint narrowing are seen. Small cysts 1–3 mm in diameter affect the metacarpal heads, which sometimes bear characteristic hook like osteophytes.³⁴ There is usually asymptomatic osteoporosis localised to the hands. Macroscopically, synovial tissue is brown as a result of iron deposition; microscopically, iron is found in intimal and phagocytic cells with little or no signs of synovial inflammation.³⁷

The precise relationship between iron deposition and arthritis remains obscure and there is no direct relationship between the

Figure 2 Thalassaemia. The bones are expanded and marrow spaces enlarged. Residual trabeculae appear more prominent.

amount of iron and joint symptoms.³⁷ Studies of ferritin induced arthritis in animals suggest iron deposition plays a role^{39 40} and may trigger a number of pathological events such as free radical generation and crystal formation. Treatment of the arthropathy is palliative only with non-steroidal anti-inflammatory drugs (NSAIDs); the arthropathy is likely to be

Figure 3 Haemochromatosis. Chondrocalcinosis and advanced degenerative changes are seen in the metacarpophalangeal joints. Marginal osteophytes are also present.

irreversible and crystal deposition, once initiated, does not decrease.³⁷

Malignant disorders of white cells and their precursors

ACUTE LEUKAEMIAS

In both acute and chronic leukaemias, bone and joint problems can precede other leukaemic manifestations, and may occasionally mimic juvenile arthritis or rheumatic fever;⁴¹ in one group of children diagnosis was delayed up to 22 months.⁴² Fever, arthralgia or arthritis, hepatosplenomegaly, lymphadenopathy, and cardiac involvement may predominate early on, and therefore even for those fulfilling criteria for rheumatic diseases, diagnosis should be made cautiously.⁴² Rheumatoid factor, antinuclear and double stranded DNA antibodies are occasionally present,⁴³ but initial blood count, radiographs, synovial biopsy specimens, and marrow examination may be normal. Moreover, arthrocentesis can show normal values for cell count, protein and glucose, and the synovium may exhibit non-specific changes. Clues to the correct diagnosis are a failure to improve with antirheumatic treatment, progressive anaemia, thrombocytopenia, and leucopenia.

At presentation with acute leukaemia, 25% of children have bone pain, compared with 5% of adults, and similar percentages are found for joint symptoms.⁴⁴ Subsequently, 50% of children can develop joint pain in the first two years.⁴⁴ Acute lymphoblastic leukaemia is predominantly responsible for osteoarticular symptoms, although a few cases occur with acute myeloid leukaemia. Bone pain is sharp and episodic, and joint involvement is associated with effusion. The arthritis affects more than one joint, particularly the knees, and the pain can be remittent or recurrent.⁴⁴ Spinal involvement is rare, but 1.6% of 1466 children presented in Memphis with vertebral compression fractures,⁴⁵ with diagnosis delayed in 25% of them because of the atypical presentation.

In adults, acute leukaemia can present with arthritis that is polyarticular and asymmetrical⁴⁶ and, again, the knees are affected most often. Even patients in remission may continue to have bone pain, with limping and occasional fractures. In addition, patients are more vulnerable to infection, although osteomyelitis and septic arthritis are rare—nine cases in 673 patients over 11 years⁴⁷ have been reported.

Bone pain is produced by multiple factors including osteoporotic fracture, periosteal infiltration (fig 4), osteolytic lesions and bone infarction. Joint disease also has a heterogeneous pathogenesis and may be associated with gout, pseudogout, synovial infiltration, and haemorrhage. Sympathetic joint effusion results from involved synovium or adjacent bone or marrow. Synovial fluid may be mildly inflammatory, and monoclonal and polyclonal antibodies have been used to identify early leukaemic antigens in the synovial fluid.^{48 49} However, normal synovial fluid has been found after mononuclear cell infiltration of synovial

Figure 4 *Leukaemia. There is generalised demineralisation in this child, accentuated in subcortical and metaphyseal regions. Periostitis results from bone cortical infiltration by tumour.*

tissue has already occurred.⁵⁰ Children do not appear to develop gout, even with high serum urate concentrations,⁵¹ but adults do, particularly during treatment. Radiological abnormalities include osteoporosis (fig 4) and osteolysis. In children, osteosclerosis, osteolysis, subperiosteal new bone formation and radiolucency at the metaphyses of long bones are recognised in 20–91%.⁵²

In children, NSAIDs have partial or no effect,⁵³ but osteoarticular symptoms may respond to antileukaemic treatment.⁵⁴ The recurrence of symptoms should raise the possibility of relapse; aseptic necrosis has been linked to malignant recurrence⁵⁵ and also to treatment with steroids.⁵⁶

LYMPHOMA

Approximately 7–25% of patients with non-Hodgkin's lymphoma develop skeletal manifestations.⁵⁷ Lymphomas can present with musculoskeletal symptoms such as bone pain from metastases. True articular symptoms are less frequent, although monoarticular^{58 59} or polyarticular⁵⁷ presentation, without lymphadenopathy or hepatosplenomegaly, has been reported. Synovial biopsy may be revealing if a patient has disproportionately severe constitutional disturbance or anaemia.⁵⁷ However, T cell lymphomas can provoke a reactive arthritis in which there is no direct infiltration of the synovial membrane, and biopsy specimens show non-specific chronic inflammatory changes.⁶⁰ Other symptoms may include hypertrophic osteoarthropathy,⁶¹ secondary gout, and synovial effusions. Joint symptoms and frank arthritis (seronegative, non-erosive, symmetrical, and peripheral) are also found in approximately 7% of patients with angio-

immunoblastic lymphadenopathy, which is an uncommon lymphoproliferative disorder in which lymphadenopathy, fever, and hepatomegaly are seen.⁶²

Negative radiological findings do not exclude non-Hodgkin's lymphoma. However, the presence of mixed osteolytic and osteosclerotic lesions with anterior marginal erosions of vertebral bodies is highly characteristic (fig 5), and indicates a poor prognosis and mean survival of less than two years.⁶³

MYELOMATOSIS (MULTIPLE MYELOMA)

The diagnosis of myeloma is now generally made earlier than hitherto, and consequently at presentation fewer patients have spontaneous bone pain—37% compared with more than 60% previously.⁶⁴ This parallels a lower incidence of advanced bone disease (osteoporotic or osteolytic changes (fig 6), and pathological fractures), although secondary gout or hypercalcaemia at presentation is not unusual. Pain from involved vertebrae and ribs is most common and the incidence of paraparesis is 10%.⁶⁵ Surgery of the spine involving stabilisation, evacuation of tumour, and reconstruction of vertebrae, reduces pain^{65 66} and has been reported to improve paraparesis.⁶⁵ The use of etidronate, however, does not appear to influence bone pain, hypercalcaemia, or the development of pathological fractures.⁶⁷ Internal fixation for fractures elsewhere is well documented,^{68 69} and total knee replacement for metastatic destruction of the proximal tibia has been performed.⁶⁸

Magnetic resonance imaging of the spine appears to be helpful in detecting spinal involvement; the technique recognised 30 of 32 recently diagnosed patients with back pain and biopsy proven myeloma,⁷⁰ particularly with fat suppressed or T2 weighted images.^{70 71} It may also prove a useful tool in monitoring the treatment of focal bone lesions.⁷²

No specific arthritis is recognised, although amyloid arthropathy is a complication and can resemble rheumatoid arthritis. It is, however, resistant to usual treatment options such as NSAIDs and intra-articular steroids, though radiosynovectomy of the knees may lead to a profound and long lasting improvement in symptoms and function.⁷³ Septic arthritis with *Streptococcus*,^{74 75} *Haemophilus*,⁷⁶ and *Neisseria*⁷⁷ has been reported to occur mainly in the knees of patients, but as nearly 70% of myeloma patients die from infection,⁷⁶ it is perhaps surprising that only a few cases have been reported in the literature.

Defects of coagulation

HAEMOPHILIAS

Haemophilia is relatively rare (10 per 10 000 population⁷⁸) and is caused by both absolute and functional deficiencies of clotting factor VIII (classic haemophilia A) or factor IX (haemophilia B or Christmas disease).⁷⁹ The frequency of bleeding episodes parallels plasma factor concentrations such that severe defects (factor VIII concentrations less than 1% of

Figure 5 *Lymphoma.* The initial radiograph shows anterior scalloping and collapse of L1. Subsequently, L1 is almost totally destroyed, and adjacent vertebrae also show progressive changes.

normal values) are characterised by spontaneous bleeding.

Joint disease is the major cause of morbidity in haemophiliacs and is found in up to 90% of severely affected patients.⁸⁰ However, even with mild or moderate disease (6–60%) haemarthrosis affects more than 67%.⁸¹ Mechanical factors are clearly important, with knees, elbows, and ankles most often affected. The dominant side is more severely affected, and haemarthrosis sometimes first begins with weight bearing.

Three stages of joint damage (fig 7) are recognised:⁸² acute haemarthrosis, chronic synovitis, and degenerative arthritis. Once a bleed has occurred the joint becomes tense, painful, and flexed, and one joint may become a focus for recurrent bleeding. Later, the patient develops persistent and often painless joint swelling as a result of synovial hyper-

Figure 7 *Haemophilia.* There is generalised muscle atrophy and osteoporosis. Overgrowth is seen in the right knee, and the epiphyses are markedly enlarged and misshapen. Growth arrest lines are demonstrated, indicating that the patient has been bedridden on numerous occasions.

trophy. Finally, degenerative arthritis supervenes, with coincident muscle atrophy, unstable weight bearing joints and loss of movement because of flexion contracture. These changes are reflected radiologically by joint space narrowing, marginal spurring, bone sclerosis, and frequently bone cysts.⁸³

The mechanism by which joint tissues respond to intra-articular blood is not fully understood. Animal experiments suggest that, initially, intra-articular bleeding stimulates a non-specific inflammatory response.⁸⁴ Macrophages accumulate around synovial iron deposits and collagenases and prostaglandins are released by the synovium, which proliferates with repeated bleeding episodes and eventually forms pannus.

The treatment of haemophilic arthritis is based on early efforts to limit the effect of chronic synovitis. Acute haemarthrosis should be treated by bed rest, elevation of the affected limb, ice packs, and the prompt use of clotting factor concentrates, which remains paramount. The early use of clotting factor concentrates delays the onset of haemophilic arthritis, which is directly related to the frequency of joint bleeding, and the current opinion is that treatment with dose regimens of greater than 1000 U/kg/yr is likely to confer protection against progression of arthropathy.⁸² Approximately 15% of patients develop inhibitor antibodies against factor VIII/IX⁸⁵ and their treatment has become a major challenge. Porcine FVIII⁸⁶ and factor VIII bypassing agents such as recombinant activated factor VII⁸⁷ are treatment modalities with reported success.

Unfortunately, in the past 10 years, the major impact on haemophilia has been infection with HIV-1 virus. This is responsible for considerable morbidity and early death in severe haemophiliacs. In particular, before HIV infection, septic arthritis was rare, estimated to occur in fewer than 0.15% of patients.⁸⁸ Since HIV infection became widespread, several reports^{89–91} describe septic

Figure 6 *Myeloma.* Multiple focal areas of demineralisation are demonstrated throughout the skull vault.

arthritis, predominantly of the knee, caused by *Staphylococcus*, *Streptococcus*, and *Salmonella*.

Consequently, while arthrocentesis is not routinely recommended, it should be considered if sepsis is suspected or for large tense haemarthroses. Haemarthrosis and pyarthrosis have similar features, though the latter is likely if there is fever $>39^{\circ}\text{C}$, concurrent involvement of more than two joints, a coexistent coagulopathy, and persistent pain despite clotting factor replacement.⁸⁸ The leucocyte count may be normal in infections⁸⁹ and therefore clinicians should have a low threshold of suspicion when a swollen joint is slow to respond.

In treating patients with either degenerative arthritis or chronic synovitis, ibuprofen has been effective in controlled trials, with no adverse effects,⁹² and may be used cautiously with simple analgesics and physiotherapy. Intra-articular corticosteroid treatment produces subjective diminution of intensity and duration of synovitis,⁸² and surgical or arthroscopic⁹³ synovectomy may be considered for persistent synovitis. Major joint surgery such as hip arthroplasty and total knee replacements⁹⁴ have been widely performed, though post-operative complications, for example haemarthrosis, are more likely. Revision rates between 9–34% have been reported for hips⁹⁵ and, despite complications in more than 50% of patients with knee surgery, excellent results were obtained in nine of 11 knees.⁹⁴ Patients younger than 50 years and those with severe haemophilia have earlier loosening of the prosthesis, possibly because of greater activity and as a result microhaemorrhages at the bone-cement interface when factor concentrations subsequently decrease.⁹⁵

Autoimmune disease and lymphoproliferative malignancy

Of major current interest is the evidence of a strong link, particularly, between lymphoreticular malignancy and autoimmune disease, which may throw some light upon the aetio-pathogenesis of disease in these conditions. The epidemiological evidence is well established, and reports in the past 10 years seem to confirm earlier observations.

This association is particularly true for rheumatoid arthritis (RA), though a precise relative risk is difficult to assess. Prior *et al*⁹⁶ reviewed 489 RA patients and found a significant excess of tumours of the reticuloendothelial system, mainly attributable to six cases of lymphoma. From a registry of 46 101 RA patients, Hakulinen *et al*⁹⁷ confirmed a significant risk for Hodgkin's disease, non-Hodgkin's lymphoma (NHL), myeloma, and leukaemia, and in 11 683 Swedish patients with a hospital diagnosis of RA, the overall risk of lymphoma was doubled.⁹⁸

In 643 RA patients receiving immunosuppressive treatment, a 13-fold increase of NHL was noted;⁹⁹ others suggest lymphoma occurs five times more frequently in RA, but increases to 10 times when these patients are also given azathioprine.¹⁰⁰ Kinlen,¹⁰¹ when

examining all published cohort studies, found an overall increased risk of 2.5 without immunosuppressives, increasing to 10 times when they were used. Nevertheless, not all studies confirm an association, and two large studies report no cases of NHL in their cohorts of RA patients,^{102 103} others have found no link between lymphoproliferative malignancy and immunosuppressive therapy in these patients^{104 105} and a current European League Against Rheumatism (EULAR) study of 10 years follow up of more than 2500 RA patients (quoted by Donnelly *et al*¹⁰⁶) does not appear to show more cases of neoplasms of the immune system in those patients treated with immunosuppressives.

In the classical autoimmune rheumatic disease, systemic lupus erythematosus (SLE), numerous anecdotal reports are found in the literature, with more than 100 cases of co-incident SLE and lymphoma recorded,¹⁰⁷ of which notably only 12 or so are Hodgkin's lymphoma.¹⁰⁸ In a recent report of 205 patients,¹⁰⁹ NHL (and other solid tumours) occurred more frequently than expected, regardless of treatment. In the case of primary Sjögren's syndrome, it was estimated by investigators at the National Institutes of Health¹¹⁰ that patients had a 40-fold risk of developing lymphoma compared with age and gender matched controls; others, however, feel that this risk may have been overestimated.^{108 109 111}

Although the mechanism behind this link between RA and lymphoma is unknown, it seems to relate more to the duration of disease than to its severity, and there is little evidence to support either a common genetic linkage or an environmental factor. Natural killer cell activity is believed to have a role in immune surveillance against malignancy,¹¹² and is reduced in the blood and synovial tissue of patients with RA¹¹³ and SLE;¹¹⁴ however, this would predispose not only to lymphoma but also to an increase in all tumour types. In RA, abnormal lymphocyte function impairs the ability of T cells to prevent polyclonal proliferation of Epstein-Barr virus (EBV) infected B lymphocytes, with the subsequent overgrowth of one or several dominant clonal populations of transformed malignant cells. This impairment is associated with a reduction of lymphokines, interleukin-2, and interferon gamma production,¹¹⁵ and reflects selective immunodeficiencies in the immune system of rheumatoid patients, despite a general state of immune system hyperactivity.

EBV infection has been implicated in the development of Burkitt's lymphoma and other high grade lymphomas,¹¹⁶ though only 4% of lymphomas in the general population are associated with infection. In contrast, 30–50% of lymphomas in patients with AIDS contain EBV,¹¹⁷ and several reports describe EBV in lymphoproliferative lesions in patients with RA.^{117–119} In one report, 30% of lymphoid neoplasia in RA patients contained EBV genome and protein product and, of those, the majority had received immunosuppressive therapy.¹¹⁷ Several reports implicate the use of

methotrexate^{117 119-121} and cyclosporin¹¹⁸ and, notably, tumour regressed in two patients after methotrexate was discontinued.¹¹⁹

In Sjögren's syndrome, the salivary gland is infiltrated with lymphocytes bearing activation markers,¹²² and it is here that malignancies tend to develop. A change from polyclonal B cell infiltrate to a monoclonal one is associated with a proliferation of lymphoid tissue and indicated by immunocytochemistry (light chain restriction) or gene rearrangement studies.¹²³ This monoclonality has been interpreted as a prelymphomatous state or pseudolymphoma,^{124 125} and it is often many years later that the same clone is shown to be involved in disseminated disease. An association has also been noted with monocytoid B cell lymphoma that later progressed to higher grade lymphomas in five of 13 patients.¹²⁶ In RA the malignancies tend to occur in lymph nodes; at these sites there is also evidence of lymphocyte activation,¹⁰⁵ which suggests that chronic immune stimulation plays a part in the development of lymphoreticular malignancy in RA.

In summary, as we have discussed in this review, there are important associations between haematological and rheumatological diseases that rheumatologists should be aware of. The management of many haematological disorders requires an understanding of joint pathology, which may be the primary site of morbidity, and knowledge of the relevant investigations and available treatment.

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