Musculoskeletal complications of haematological disease

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Abstract

Rheumatological manifestations complicate many benign and malignant blood disorders. Significant advances in haematology, with improved diagnostic techniques and newer musculoskeletal imaging, have occurred in the past two decades. This review focuses on the interrelationship between the major haematological diseases (haemochromatosis, haemophilia, sickle cell disease, thalassaemia, leukaemia, lymphoma, myelodysplastic syndromes, multiple myeloma and cryoglobulinaemia) and rheumatic manifestations.

Key words: haematological diseases/complications, rheumatic diseases/aetiology, rheumatic diseases/radiography, humans.

Rheumatology key messages

- Most haematological diseases are associated with rheumatological manifestations.
- On occasion, muscular features are the first clue to the presence of an underlying haematological disorder.
- Rheumatologists need to be aware that joint problems may be the hallmark of an underlying serious haematological disorder.

Introduction

Haematological diseases predispose to a variety of musculoskeletal manifestations [1, 2]. Since our last review of these issues [2], 20 years ago, advances in imaging, improved understanding of their aetiopathogenesis and a better appreciation of the complex interaction between haematological and rheumatological disease have occurred. This review focuses on these advances. Details of the major clinical features, including musculoskeletal problems and some practical advice on management, are shown in Tables 1 and 2.

Benign haematological diseases

Haemochromatosis

Pathogenesis

Hereditary haemochromatosis (HH) comprises a group of inherited iron-storage diseases. The HH type 1 is autosomal recessive and the commonest variant in Caucasians. It is usually caused by homozygous C282Y mutations (90%), or occasionally, by compound heterozygous C282Y/H63D mutations (5%) on the HFE gene at chromosome 6 [3-5]. For unexplained reasons, only a low proportion of those homogenous for HFE mutations become iron overloaded [3].

Clinical aspects

Diagnosis is often delayed because early symptoms are non-specific, notably fatigue, arthralgia and abdominal pain. Disease progression leads to cirrhosis, hepatocellular carcinoma, diabetes mellitus, impotence, skin pigmentation, cardiomyopathy and hypogonadism [6].

Up to 80% of HH patients develop a chronic progressive non-inflammatory arthropathy, which is usually the presenting symptom [7]. It affects the second and third MCP joints, causing the pain at the handshake sign [5]. PIP joints, the knees, wrists and distal radioulnar joints, hips, shoulders, ankles and elbows are often involved [5-7]. In type 1 and in juvenile HH (HH type 2), which has a different genetic basis from HH type 1 (linked to chromosome 1q21) [8], progressive stiffness and swelling may occur [6, 7, 9].
**TABLE 1** Description of the major clinical features of benign haematological conditions and bone marrow transplantation, including rheumatological manifestations and some advice for practical management

<table>
<thead>
<tr>
<th>Condition</th>
<th>Major clinical manifestations</th>
<th>Rheumatological manifestations</th>
<th>Some practical management advice</th>
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<tbody>
<tr>
<td>Haemochromatosis</td>
<td>Non-specific early symptoms of fatigue, arthralgia or abdominal pain. Progression to cirrhosis, hepatocellular carcinoma, diabetes mellitus, impotence, skin pigmentation, cardiomyopathy and hypogonadism</td>
<td>Chronic progressive non-inflammatory arthropathy; ↑ ferritin concentrations in SF. Affected joints: second and third MCP joint (pain at the handshake sign), PIP joint, knees, wrists and distal radioulnar joints, hips, shoulders, ankles and elbows. Chondrocalcinosis of the knee, wrist, symphysis pubis and spine.</td>
<td>Permanent articular damage because synovial hemosiderin deposits are not removed by venesection. Medical treatment: for acute symptoms requiring analgesics, NSAIDs, cyclooxygenase selective inhibitors. Additionally, colchicine (0.5-1 mg daily), intra-articular steroids. Treatment of severe arthropathy: joint-replacement surgery (major joints).</td>
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<td>Haemophilia</td>
<td>Related to bleeding, mostly affecting the musculoskeletal system. Uncommon musculoskeletal manifestations: muscle haematomas and pseudotumours. Acute haemarthrosis: swollen, warm and painful joint. Mainly large joints. Chronic haemophilic arthropathy, generally accompanied by severe contractures, angular deformity and loss of bone tissue. Increased incidence of septic arthritis and osteoporosis/low BMD.</td>
<td></td>
<td>Treatment of acute haemarthrosis: 20-30 U/kg i.v. coagulation factor, joint aspiration, physiotherapy (after acute phase), avoid rebleeding. Treatment of chronic proliferative synovitis: factor replacement, physiotherapy and pain management. If necessary, synovectomy [chemical, radioactive or surgical (open or arthroscopic)] Treatment of chronic haemophilic arthropathy: total joint arthroplasty, resection of the radial head or ankle arthrodesis, joint debridement or angiographic embolization. Treatment of septic arthritis: antibiotics against Gram-positive bacteria.</td>
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<tr>
<td>Sickle cell diseases</td>
<td>Frequently, orofacial pain and headaches. Rarely, neuropathy, fibrous ankyloses and inflammation, oedema and necrosis of muscles. Sickle cell dactylitis (in children), bone infarction, AVN, vertebral collapse, secondary OA. Non-inflammatory synovial effusions. Frequently, osteomyelitis of femoral, tibial or humeral shafts and septic arthritis of long bones. Symptoms of bone pain, fever, localized swelling/erythema. High suspicion index as symptoms are similar to SC crisis. Rarely, mandibular osteomyelitis and pathological fracture.</td>
<td></td>
<td>Treatment of mild acute pain (managed at home): ↑ fluid intake, analgesics, NSAIDs, mild opiates and sedatives. Treatment of severe acute pain (hospitalization): i.v. fluids and parenteral anti-inflammatory drugs and opiates. Treatment of AVN (femoral head): bed rest; if necessary, core decompression or autologous bone marrow grafting. Treatment of osteomyelitis: antibiotics against <em>Salmonella</em> species and <em>Staphylococcus aureus</em>.</td>
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<tr>
<td>Thalassaemia</td>
<td>Hypochromic/microcytic anaemia, extramedullary haematopoiesis with secondary skeletal deformities (leading to skeletal</td>
<td>Untreated patients: multiple and recurrent spontaneous pathological fractures of the long bones. Sites of bone involvement: skull/facial, the spine.</td>
<td>Treatment of severe forms: transfusion therapy (to haemoglobin levels &gt;9-10g/dl). Important: chronic transfusions result in iron</td>
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</table>
Chondrocalcinosis is reported [7, 10], commonly involving the meniscal and articular cartilage in the knee, wrist (Fig. 1), symphysis pubis and spine [7]. Interestingly, ferritin concentrations in the SF are increased in HH patients with OA [5, 7]. Ferritin acts as a pro-inflammatory cytokine (acting as a potent and rapid inducer of IL-1 gene expression). It could contribute directly to joint injury in HH arthropathy [11]. Haemosiderin deposits occur particularly in the synovial lining cells as opposed to secondary forms of haemochromatosis, such as thalassaemia, where the deposition occurs in the sublining layers or synovial stroma [5, 7].

**Imaging**

Radiographic features are similar to those found in OA, and include joint space narrowing and formation of subchondral cysts and osteophytes [6]. However, in contrast to OA there is a predilection for the second-fourth MCP joints. The formation of hook-like osteophytes at MCP joints is characteristic of the disease. Chondrocalcinosis is a common feature; osteopenia and osteoporosis (prevalence 25–35%) are also described [6, 9, 10].

**Treatment**

The main treatment of HH is phlebotomy; most clinical manifestations respond to iron depletion. The patients’ quality of life is often adversely affected by the rheumatological complications [5]. Removal of iron has no effect on structural progression of the joint disease, which is progressive and irreversible. The arthropathy is the main cause of morbidity [5, 7].

Other forms of medical treatment for HH arthropathy include analgesics, NSAIDs and cyclooxygenase selective inhibitors, which can produce acute symptomatic relief but lack disease-modifying effects [5, 7]. Colchicine at low doses (0.5–1 mg daily) or intra-articular glucocorticosteroids are also effective [5]. The progression of the arthropathy can lead to severe joint damage, necessitating joint-replacement surgery, especially of the hips, knees and ankles [6, 12].

**Haemophilia**

**Pathogenesis**

Haemophilia is a hereditary disease associated with a defect on the X chromosome, leading to absence or deficiency production of coagulation factor VIII in haemophilia A (85% of cases) and factor IX in haemophilia B [13]. It has an incidence of 1:5000 male births [14] and a prevalence of 1:10'000 individuals [15].

**Clinical aspects**

The symptomatology is generally secondary to bleeding [16]; the musculoskeletal system being the most frequently involved (>80% of haemorrhages) [17]. Bleeding symptoms appear early in life [16, 18]. When the disease is severe (plasma factor VIII or IX concentrations <1% of normal), muscle and joint bleeding may appear spontaneously. In moderate disease (1–5%), haemorrhage is usually preceded by a minor trauma. In the minor form (>5%), bleeding develops only after major trauma or surgery [13, 15, 19]. Three stages of joint damage are recognized: acute haemarthrosis, chronic proliferative synovitis and chronic haemophilic arthropathy [13, 15, 20].

Haemophilic arthropathy is triggered by blood entering the joint space [13, 21]. The iron component of haemoglobin affects the cartilage, leading to the formation of destructive oxygen metabolites, subsequently affecting the synovium [13, 21]. An inflammatory reaction is initiated by synovial macrophages, resulting in progressive haemosiderin deposition, synovial hypertrophy and neovascularization of the subsynovial layer, which causes fibrosis and joint destruction [13, 21].

Acute haemarthrosis develops quickly. Before the intra-articular bleeding occurs, patients commonly describe a tingling sensation (the aura) and, subsequently, the joint

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<tr>
<td>Bone marrow transplantation</td>
<td>Growth abnormalities in children</td>
<td>(vertebral compression fractures leading to scoliosis/kyphosis), the ribs and metaphyses of long bones</td>
<td>Removal of iron has no effect on structural progression of the joint disease, which is progressive and irreversible. The arthropathy is the main cause of morbidity [5, 7].</td>
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†: high/increase; AVN: avascular necrosis; BMT: bone marrow transplantation; GVHD: graft-vs-host disease; SC: sickle cell.
Table 2: Description of the major clinical features of malignant haematological conditions, including rheumatological manifestations and some advice for practical management

<table>
<thead>
<tr>
<th>Condition</th>
<th>Major clinical manifestations</th>
<th>Rheumatological manifestations</th>
<th>Some practical management advice</th>
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<tbody>
<tr>
<td>Leukaemias</td>
<td>Anorexia, fatigue, fever, pallor, purpura, hepatosplenomegaly, lymphadenopathy, anaemia, thrombocytopenia, neutropenia and lymphocytosis</td>
<td>Commonly, diffuse osteopenia, osteolytic lesions mainly in the metaphysis of long bones, pathological fractures and AVN</td>
<td>Treatment of the underlying leukaemia; if necessary, adjunctive radiotherapy of the affected joints</td>
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<td></td>
<td></td>
<td>Leukaemic arthritis: inflamed, erythematous and tender joints; mainly distal large joints. Frequently, fever and severe nocturnal pain (in an atypical location, poorly responsive to conventional anti-rheumatic treatment); associated with early significant osteopenia or lytic lesions</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Rarely, intra-articular haemorrhage, septic arthritis, secondary gout</td>
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<tr>
<td>Myelodysplastic</td>
<td>Peripheral cytopenias Progression: ↑ weakness, dyspnoea, recurrent serious infections and/or bleeding problems</td>
<td>Frequently, arthralgia, non-erosive acute symmetrical polyarthritis</td>
<td>Treatment: steroids; DMARDs not recommended</td>
</tr>
<tr>
<td>syndromes</td>
<td></td>
<td>Rarely, monoarthritis or spinal cord compressive symptoms</td>
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<tr>
<td></td>
<td></td>
<td>Children/adolescents may develop chronic recurrent sterile osteomyelitis of multiple bone sites.</td>
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<tr>
<td>Lymphomas</td>
<td>Fever, lymphadenopathy, hepatosplenomegaly, ↑ ESR and lactate dehydrogenase level, ↓ weight, nocturnal sweating, pruritus and white blood cell abnormalities RF and anti-CCP (+) may occur</td>
<td>Rarely, poly- or monoarticular arthritis, involving the knee, shoulder, sternoclavicular or elbow joints Sterile inflammatory SF, with atypical lymphoid cells in 60%; mild leucocytosis with lymphocyte predominance in intra-articular lymphoma Occasionally, septic arthritis, secondary gout or hypertrophic pulmonary osteoarthropathy</td>
<td>Treatment of the underlying lymphoma Important: osteonecrosis is a complication of lymphoma treatment Treatment of septic arthritis: antibiotics against Salmonella species</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Anaemia, hypercalcaemia, renal failure, recurrent infections or bony lytic lesions</td>
<td>Osteoporosis/osteopenia, bony pain, osteolytic bone lesions and pathological fractures, mainly of the vertebrae, ribs, skull, shoulders, pelvis and long bones Symmetrical or asymmetrical polyarthritis of knee, hands and feet joints Inflammatory arthritis with polymorphonuclear leucocytes in SF, no crystals, sometimes with amyloid infiltration Complications: spinal cord compression secondary to vertebral body collapse or pathological fractures Occasionally, articular manifestations related to amyloidosis or metabolic complications or Ig deposit</td>
<td>Management of myeloma bone disease: bisphosphonates Treatment of inflammatory arthritis: anti-myeloma treatment Treatment of spinal cord compression: radiotherapy</td>
</tr>
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</table>

(continued)
becomes swollen, warm and painful [16, 20]. Patients may experience functional loss, adopting an antalgic position in flexion, and fever can develop [16, 20].

Bleeding occurs more frequently in large synovial joints, for example, the knee or hip [13]. The incidence of septic arthritis among patients with haemophilia is increasing (being up to 40 times higher than in the general population) because of increasing age, high prevalence of concomitant HIV infection and an increased use of central venous access devices for prophylaxis [22]. The knee is the most commonly affected joint (about 2/3 of cases) [22]. The diagnosis in these patients is frequently delayed because early symptoms are often misdiagnosed as haemarthrosis [23]. After orthopaedic surgery, the risk of infection is considerably increased; arthroplasty has a 10 times greater risk of infection than other procedures [13]. Common microorganisms isolated are Gram-positive bacteria (76.7%); in particular, *Staphylococcus* (50%) and *Streptococcus* (23%) [22].

Haemophilic patients have a higher risk of osteoporosis [24], with a reported prevalence of low BMD of 70% in adults [18]. The mechanism of low BMD is not completely understood, although decreased mobility, [24] malnutrition, chronic inflammation, vitamin D deficiency and hypercalciuria probably contribute [25].

Uncommon musculoskeletal manifestations, such as muscle haematomas and/or pseudotumours (Fig. 2D), also occur, usually associated with direct trauma [20].

**Imaging**

The changes on imaging in haemophilic arthropathy are complex. Recurrent episodes of haemarthrosis cause synovial inflammation and degeneration of the cartilage and subchondral bone, culminating in severe secondary degenerative disease (Fig. 2A and B). Early in the disease, X-rays of the affected joint may demonstrate the presence of an effusion, periarticular osteopenia and epiphysial overgrowth. Late changes resemble severe OA [16]. US imaging is useful to diagnose and follow up haemarthroses [26].

MRI is considered the gold standard imaging technique for the evaluation of synovium and cartilage, enabling the early identification of changes that may culminate in haemophilic arthropathy [18, 23, 26]. Gradient echo sequences are useful to detect the presence of haemosiderin in a joint (Fig. 2C) [26].

**Treatment**

Treatment includes adequate haematological treatment (commonly 20–30 U/kg i.v. of the deficient coagulation...
factor), joint aspiration, physiotherapy and avoidance of rebleeding [20]. Early treatment significantly reduces joint damage and functional deterioration [27]. However, the use of factor VIII concentrate prophylaxis may not stop continuous joint deterioration [18].

Despite prompt and adequate treatment, the development of chronic proliferative synovitis seems inevitable [20]. It needs to be treated early and aggressively so that the vicious cycle of haemarthrosis–synovitis–haemarthrosis is broken [20]. Standard conservative measures (factor replacement or physiotherapy) [20] and pain management are helpful [18]. However, an invasive approach may be considered [20]. Commonly, under these circumstances synovectomy [(chemical, radioactive or surgical (open or arthroscopic)] reduces the bleeding cycle, delaying the onset of chronic haemophilic arthropathy [20]. These procedures have side effects, and a balanced decision, aided by a consultation between a rheumatologist and a haematologist, is beneficial.

Between the second and fourth decades of life, ~90% of patients with severe haemophilia develop severe articular destruction (advanced haemophilic arthropathy) [15, 17, 20]. In addition, patients may experience contractures, angular deformity and loss of bone tissue owing to mechanical abrasion and bone cysts [13, 19]. Appropriate surgical procedures include total hip or knee arthroplasty, resection of the radial head or ankle arthrodesis [17, 20], joint debridement or angiographic embolization [13, 14].

An ongoing study is testing the hypothesis that once blood enters the joint, two molecular scissors (iRhom2 and TACE) are activated to release TNF-α, which induces a persistent inflammatory response and could promote...
the development of haemophilic arthropathy [28]. Melchiore et al. [29] have shown that in patients with haemophilia A and concomitant autoimmune disease treated with adalimumab, the anti-TNF\(a\) therapy has prevented the recurrence of joint bleeding.

**Sickle cell diseases**

**Pathogenesis**

Sickle cell diseases (SCD) are a group of genetic haemoglobin disorders including sickle cell anaemia (haemoglobin SS), haemoglobin SC, haemoglobin S\(\beta\)-thalassaemia and other heterozygous conditions [30, 31]. They result from a mutation in the gene coding the \(\beta\)-globin chain of the haemoglobin molecule [31, 32]. If it occurs on both chromosomes (homozygosis) sickle cell anaemia develops, but if only one chromosome is involved (sickle cell trait) the individual is a carrier [haemoglobin SA (HbSA)] [31, 32]. Interestingly, individuals with HbSA have greater protection against malaria infection [30, 31].

**Clinical aspects**

Clinical presentation is characterized by recurrent microvascular occlusion with subsequent tissue ischaemia, leading to painful vaso-occlusive crises [30–32]. The associated risk factors are cold exposure, intense physical effort, hypoxia, dehydration, infections and general trauma [33].

Painful crises last from 30 min to a few weeks, but if >2 weeks the probability of a complication [osteomyelitis or avascular necrosis (AVN)] must be considered [34].

In the musculoskeletal system, vaso-occlusive-related complications mainly include sickle cell dactylitis (in children), bone infarction, AVN or vertebral collapse [30, 32, 35]. Non-inflammatory [34] and secondary osteoarthritis change [32] and synovial effusions may develop.

The first clinical manifestations usually appear between 6 months and 4 years. Children are susceptible to infarction in the diaphysis of the small tubular bones of the hands and feet (dactylitis) [32].

Up to 30% of the SCD population develops infarction of the epiphyses, leading to AVN usually in the femoral (Fig. 3A and B) and humeral heads that causes pain and reduced joint movement [32, 36]. Approximately 50% of sickle cell patients experience orofacial pain, and three-quarters complain of headaches [35]. Complications such as mandibular osteomyelitis, neuropathy and fibrous ankylosis may occur [35].

Infarction and necrosis of the medullary bone encourages bacterial growth. Factors responsible for the high incidence of bone and joint infections include hyposplenism [36], impaired complement function [36] and deficiencies in IgG and IgM antibodies [37].

Osteomyelitis is one of the most common infectious complications in SCD patients [100 times more prevalent (12–49%) than in the general population] [32]. The most commonly infected sites are the femoral, tibial and humeral shafts [32, 38]. A high index of suspicion is needed in SCD patients with joint pain and fever, in order to prompt rapid investigation [36, 37, 39–41]. Failure to treat osteomyelitis leads to chronic bone damage, deformity or sepsis [41]. Septic arthritis, a serious complication of the disease, develops in 7–20%, usually affecting long bones [38, 40].

The most common organisms are *Salmonella* species, especially the non-typical serotypes, followed by *Staphylococcus aureus* and others, including tuberculous osteomyelitis [38, 40, 41]. Hyperuricaemia is a common feature, occurring in 32–41% of sickle cell patients [42]. Other less common musculoskeletal manifestations include pathological fracture, inflammation, oedema and necrosis of the muscles [36].

**Imaging**

Radiographic features reflect the underlying processes of marrow hyperplasia and osteonecrosis. X-Rays demonstrate changes compatible with the expansion of the medullary space, such as a hair-on-end appearance of the skull [31, 32] as a result of diploic space widening. Imaging is used to identify and characterize sites of bone infarction (see Fig. 3) [32, 33, 36, 39]. MRI is the most sensitive imaging modality [31, 32].

**Treatment**

The main management for severe pain is opiate analgesia [30]. A mild pain crisis may be managed at home with increased fluid intake, analgesics, NSAIDs, mild opiates and sedatives; however, a severe crisis requires i.v. fluids and parenteral anti-inflammatory drugs and opiates [30, 34, 35].

For complications of SCD such as AVN of the femoral head, bed rest is recommended [31]. However, treatment options include core decompression or autologous bone marrow grafting [30].

**Thalassaemia**

**Pathogenesis**

The thalassaemias are a group of inherited blood disorders characterized by the acquisition of a gene mutation or deletion in the haemoglobin gene on the short arm of chromosome 11. Abnormal haemoglobin molecules are formed because of a reduced or absent rate of synthesis of one or more of the globin chains (\(\alpha\) or \(\beta\)) [32, 43–45]. Several risk factors are implicated in the pathogenesis of thalassaemia-induced bone mineral damage, including two genetic factors, namely, the polymorphism at the Sp1 site of the collagen type la1 gene [45, 46] and the vitamin D receptor polymorphisms at exon 2 (FokI) and intron 8 (BsmI) [45, 47].

**Clinical aspects**

Thalassaemia is the most common monogenic disease worldwide [45], causing hypochromic and microcytic anaemia, hepatosplenomegaly and extramedullary haematopoesis, with secondary skeletal deformities [32]. In untreated thalassaemia, skeletal changes are related to ineffective erythropoiesis (and consequent chronic anaemia), resulting in marrow hyperplasia [32, 48]. In severe cases of marrow expansion, a loss of the normal...
In untreated thalassaemia patients, spontaneous pathological fractures may develop in almost a third of cases, being multiple, recurrent and commonly involving the femur, tibia and fibula [32]. Generalized pain (which increases with age) occurs in 69% of adults/adolescents, many describing moderate pain [49]. Fractures are more frequent in adults, mainly attributed to vitamin D deficiency and low BMD [45] and are reported in 11.6% of transfusion-dependent patients [44].

**Imaging**

Skeletal imaging demonstrates exuberant expansion of bone marrow spaces. There is subsequent reabsorption of the cortex, rarefaction of cancellous bone with trabecular coarsening, and generalized loss of BMD [32, 48]. Common sites of bone involvement include the skull and facial bones, the ribs and the metaphyses of the long bones [32, 48]. In the spine, there is a high predisposition to compression fractures of the vertebrae and an increased incidence of scoliosis and kyphosis. Lateral X-rays of the spine may show a bone-within-bone appearance related to end-plate depression [32, 48], and skull X-rays may often show a hair-on-end appearance of the cranial vault (Fig. 4) [32]. MRI is sensitive and useful to distinguish skeletal dysplasia, reflecting chelator toxicity, and iron deposition in the skeleton and soft tissues [48].

**Treatment**

Severe forms of thalassaemia require transfusion therapy [43] to maintain haemoglobin levels above 9–10 g/dl [48]. However, chronic transfusion induces severe iron overload. The clinical course of transfusion-dependent thalassaemia patients is similar to those with other iron-overload diseases, with multiple organ involvement, including musculoskeletal complications [50]. High serum iron levels are associated with abnormalities of the synovium and
articular cartilage, and affect the large joints [48]. Typical radiological features include symmetrical loss of articular space, cystic lesions, collapse and flattening of the subchondral bone, osteophyte formation and even chondrocalcinosis [48]. Concomitant iron-chelating therapy, with desferrioxamine or deferiprone, prevents end-organ complications [50].

Even with normalization of haemoglobin levels (resulting from regular transfusion), adequate hormone replacement and effective iron-chelation therapy, patients with β-thalassaemia major continue to have an unbalanced bone turnover, with an increased resorptive phase causing seriously diminished BMD [43-45], (osteopenia/osteoporosis) and, subsequently, increased fractures, deformity and chronic bone pain [43, 45, 50].

Dysplastic changes commonly affect the spine and long bones, and growth retardation can develop. Dysplastic features are more common and severe in patients where iron-chelation therapy starts at <3 years and at higher doses [48]. Patients with transfusion-dependent thalassaemia have significant and continuous decline in BMD [43, 44, 50]; 50% develop osteoporosis [45].

**Malignant haematological diseases**

**Leukaemias**

**Pathogenesis**

The leukaemias are a group of neoplasms developing from the malignant transformation of haematopoietic cells [51]. Leukaemic cells proliferate primarily in the bone marrow and lymphoid tissues, interfering with normal haematopoiesis and immunity [51]. Leukaemias are classified as myeloid or lymphoid according to the cell type primarily involved and may be acute or chronic in onset [51].

**Clinical aspects**

Common clinical presentations of acute leukaemia include anorexia, fatigue, fever, pallor, purpura, hepatosplenomegaly, lymphadenopathy, anaemia, thrombocytopenia, neutropenia and lymphocytosis [52, 53]. Musculoskeletal manifestations are common [52-54], mainly due to leukaemic cells infiltrating the intramedullary bone marrow space [55] and the joints. These cells may cause a synovial reaction secondary to periosteal or capsular infiltration [36, 56, 57]. In addition, there may be intra- or periarticular haemorrhages or paraneoplastic effects, which are likely to be due to humoral factors (e.g. local osteolytic hypercalcaemia, increased parathormone-related peptide or some pro-inflammatory cytokines, secreted by the malignant clone, e.g. TNF-α or IL-6) [57]. Leukaemic arthritis is rare [56]. It can occur with all subtypes of leukaemia [56] and may parallel or antedate the course of the disease [58].

Arthritis in acute leukaemias usually presents early, whereas in chronic leukaemias it presents later and more symmetrically [51]. It complicates childhood leukaemias more frequently than adult leukaemias (14 and 4%, respectively) [34, 58], with bone pain being more severe in...
children [34], and often interferes with activities of daily living [56].

Up to 7% of children with acute lymphoblastic leukaemia have been reported to be misdiagnosed as having JIA [59]. The early initiation of steroids can further delay the diagnosis, compromising the subsequent response to chemotherapy [54, 57, 60].

Clinical examination may reveal inflamed, erythematous and tender joints. The pattern of involvement may be distal, with symmetric or asymmetric large joint involvement [56, 61]. Fever may develop. Effusions, usually small, may also be present, with the swelling being due to synovial hypertrophy [51, 56].

Several distinctive features suggest a leukaemic arthritis, notably severe pain disproportional to physical findings, in an atypical location (usually in the metaphyseal region), with significant nocturnal pain [54, 57, 62, 63], a poor response to conventional anti-rheumatic treatment (NSAIDs or corticosteroids) [58] and early significant osteopenia or lytic bone lesions [63].

Although synovial biopsy is regarded as the gold standard for a leukaemic arthritis diagnosis, the infiltration is usually focal and can be missed [56]. The average rheumatic prodrome is 3–7 months before the correct diagnosis is made [56, 57, 63].

Leukaemic patients become neutropenic as a consequence of profound myelosuppressive combination chemotherapy, causing a higher risk of septic arthritis [36]. Monoarticular involvement of a large joint is the most frequent form of presentation and may be associated with septicemia [36]. Secondary gout occurs rarely in leukaemia, particularly in chronic myeloid leukaemia [64]. It is induced by an overproduction of uric acid, and the treatment depends upon controlling the leukaemia [64].

**Imaging**

X-Ray is the primary imaging modality used to delineate bone involvement in children with leukaemia. The common radiographic features include diffuse osteopenia (16–41%; 10% at diagnosis), radiolucent metaphyseal bands, periosteal reaction, osteolytic lesions mainly localized in the metaphysis of long bones, osteosclerosis, permissive bone destruction, pathological fractures and AVN [52–54, 62, 65]. None of these is pathognomonic for leukaemia [53]. Leukemic bone marrow infiltration may be assessed by bone scintigraphy [57]. In regions of leukaemic bone marrow infiltration, MRI demonstrates loss of the normal marrow fat signal.

**Treatment**

Generally, treatment targeted to the underlying leukaemia improves the joint disease. The first sign of a response is often a rapid decrease in joint-related symptoms [52, 56, 58]. Adjunctive radiotherapy to the affected joints may be necessary [61].

**Lymphomas**

**Pathogenesis**

Non-Hodgkin’s lymphoma (NHL) is a haematological malignancy manifested by an uncontrolled proliferation of B lymphocytes [34, 66] and, occasionally, T lymphocytes or macrophages [34]. The mechanism of arthritis in NHL is poorly understood [67]. It may involve direct synovial invasion by lymphoma cells, as a result of direct extension from bone [68, 69]. Other plausible mechanisms include host response to tumour antigens [67] or cytokine-driven synovial inflammation [67, 70]. Lymphomas may secrete pro-inflammatory cytokines, explaining why the initial clinical presentation may mimic inflammatory rheumatological syndromes, with fatigue, arthralgia and fever [70]. The quantity and type of cytokine produced influences the presenting symptoms, with IL-6-producing tumours being particularly associated with pronounced systemic features [70].

**Clinical aspects**

The main features are fever, lymphadenopathy, hepatosplenoomegaly, raised ESR and lactate dehydrogenase concentration, weight loss, nocturnal sweating, pruritus and abnormalities of white blood cells [34]. The most common musculoskeletal feature in patients with Hodgkin and NHL is bone involvement (supplementary Fig. S1, available at Rheumatology Online) [34, 36], present in 20–30% of children and 10–20% of adults with NHL and in up to 25% of patients with Hodgkin’s lymphoma [36].

Arthritis is rare, but may be the presenting feature, especially in NHL [34, 67, 68] and <1% of Hodgkin’s lymphoma [71]. Secondary bone involvement occurs in up to 20% of patients and carries a worse prognosis [72].

Synovial biopsy is usually recommended for the definitive diagnosis of intra-articular tumours [66, 69]. A few cases are diagnosed by arthroscopy [69] or arthroplasty [66, 69].

A recent review reported that 29.4% of NHL patients with arthritis had polyarthritis simulating RA, and 35.3% had monoarticular involvement without other specific comorbidities or clear signs of NHL [72]. The knee joint is the most commonly involved site in systemic NHL [66, 72], although involvement of the shoulder [69], sternoclavicular or elbow joints [68, 73] also occurs. Occasionally, RF and anti-CCP antibody positivity may occur, leading to diagnostic confusion [74].

SF examination may reveal a sterile inflammatory fluid without crystal deposition, but in almost 60% atypical lymphoid cells have been reported [68, 69]. In intra-articular lymphoma, mild leucocytosis with lymphocyte predominance is often present in SF analysis [69]. Other types of rheumatic involvement include septic arthritis during the neutropenic phase, mainly caused by Salmonella species, secondary gout, mostly related to chemotherapy [34, 36], or hypertrophic pulmonary osteoarthropathy in cases of disease localization in the mediastinum [34].

**Imaging**

Musculoskeletal radiographic findings include lytic and sclerotic lesions and soft tissue masses [66, 69]. MRI can be used to demonstrate marrow infiltration [68, 69].
Treatment

Most rheumatological features improve or disappear with the treatment of the lymphoma, consistent with their para-neoplastic nature [34]. During lymphoma treatment, osteonecrosis may develop as a complication of steroids or radiation treatment [34].

Multiple myeloma

Pathogenesis

Multiple myeloma (MM) is a sinister plasma cell malignancy, characterized by a clonal population of bone marrow plasma cells which secrete a monoclonal para-protein or an immunoglobulin free light chain [75, 76]. It accounts for 10% of haematological malignancies and ~1% of all human malignant diseases [76].

Clinical aspects

The clinical presentation of MM is diverse, with common complications including anaemia, hypercalcaemia, renal failure, recurrent infections or bony lytic lesions (supplementary Fig. S2D, available at *Rheumatology* Online) [75, 76]

The increased bone destruction in MM results from an increase in osteoclast formation and activity, linked to suppressed or absent osteoblast differentiation and activity. These changes lead to severely impaired bone formation and the development of osteoporosis/osteopenia or osteolytic bone lesions (supplementary Fig. S2A and B, available at *Rheumatology* Online) [77, 78]. Pathological fractures (supplementary Fig. S2C, available at *Rheumatology* Online) and hypercalcaemia may develop. Growth factors released by the increased bone-resorptive process also induce MM cell growth, creating a vicious cycle of tumour expansion and bone destruction [79].

Biological pathways, including the RANK, its ligand (RANKL), osteoprotegerin (which is the decoy receptor of RANKL) [79] and activin A [80], exist that may explain the processes related to the increased osteoclast activity (osteoclastogenesis) observed in MM.

Bone disease is present in almost 80% of patients at diagnosis [75, 78] and in nearly all patients during the disease course [78]. In advanced disease, pathological fractures may occur following minimal trauma [75]. Osteopenia or osteoporosis occurs in 10–15% of patients at diagnosis [77, 78]. Bony pain is a common symptom, particularly back pain (up to 58% of patients) [75].

Rheumatological manifestations have been documented both at presentation and throughout the disease [36], with thoracolumbar spinal pain being the most common presentation [75]. Inflammatory [36, 81, 82] and septic arthritis [36] have also been reported; the former improves in most cases with antimalyeloma treatment [81]. Articular manifestations have been related to amyloidosis [81, 82] (amyloidosis arthritis being described in 0.1–6% of patients [82]), metabolic complications and, sometimes, immunoglobulin deposit [81].

Joint involvement includes a symmetrical or asymmetrical polyarthritis [81], involving the knee, hand and feet joints in particular [83]. SF analysis may show leucocytes (mainly polymorphonuclear leucocytes) without any crystals. Amyloid infiltration within and around the joint may be present [83]. A destructive arthritis, occasionally severe, has been described [81, 83].

Imaging

X-Ray remains the gold standard for diagnosis/stratification and follow-up of MM bone lesions [78, 84]. The characteristic patterns of bone involvement include an osteolytic type found in 70% of cases, an osteoporotic type found in 10–15% and a mixture of both osteoporotic and osteolytic pattern, found in 50% of cases [78, 84]. The vertebrae, ribs, skull, shoulders, pelvis and long bones are the most frequent sites of skeletal involvement [78, 84].

Twenty per cent of patients with MM have a normal skeletal survey at diagnosis [84]. MRI is more sensitive for assessing bone marrow infiltration (supplementary Fig. S2D, available at *Rheumatology* Online), notably in the spine, predicting the risk of vertebral fractures [78]. Bone deposits have been demonstrated on MRI in ~50% of asymptomatic myeloma patients with normal X-rays [76].

Treatment

In the management of myeloma bone disease, bisphosphonates are effective and may prevent skeletal related events and provide pain relief [85]. For complications of MM disease, such as spinal cord compression secondary to vertebral body collapse or pathological fractures, radiotherapy may be the treatment of choice [76]. An additional review of the musculoskeletal manifestations of myelodysplastic syndromes, cryoglobulinaema and bone marrow transplantation is provided in the supplementary data, available at *Rheumatology* Online.

Conclusion

In summary, most haematological diseases may be associated with rheumatic manifestations. In addition, musculoskeletal features are sometimes the first clue to the existence of a haematological disorder. Given that these patients may first present to the rheumatologist, awareness of the extent of these manifestations is important to facilitate earlier recognition, diagnosis and treatment.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.
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