Title of the article: Rheumatological manifestations of haematological diseases.

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ABSTRACT:
Rheumatologic 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, thalassemia, leukaemia, lymphoma, myelodysplastic syndromes, multiple myeloma and cryoglobulinemia and rheumatic manifestations.
INTRODUCTION:

Haematological diseases predispose to a variety of musculoskeletal manifestations [1, 2]. Since our last review [2] of these issues, twenty years ago, advances in imaging, improved understanding of their aetiology and a better appreciation of the complex interaction between hematologic and rheumatologic disease have occurred. This review focuses on these advances. Details of the major clinical features including musculoskeletal problems and some practical management advice 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 as 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 metacarpophalangeal (MCP) joints causing the “pain at the handshake” sign [5]. Proximal interphalangeal (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]. 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 synovial fluid are increased in HH patients with osteoarthritis [5, 7]. Ferritin acts as a proinflammatory cytokine (acting as a potent and rapid inducer of interleukin-1 gene expression). It could contribute directly to joint injury in HH arthropathy [11]. Hemosiderin deposits occur particularly in the synovial lining cells as opposed to secondary forms of hemochromatosis, such as thalassemia, where the deposition occurs in the sublining layers or synovial stroma [5, 7].

Imaging:

Radiographic features are similar to those found in osteoarthritis, and include joint space narrowing, subchondral cyst and osteophyte formation [6]. However, in contrast to osteoarthritis there is a predilection for the the 2nd – 4th 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]. Removing 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, nonsteroidal anti-inflammatory drugs (NSAID’s), and coxibs, 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 resulting in joint replacement surgery, especially of the hips, knees and ankles [6, 12].

**Haemophilia: Pathogenesis:**
Hemophilia is a hereditary disease associated with a defect on 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 1:5,000 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 concentrations - VIII or IX - <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 only develops after major trauma or surgery [13, 15, 19].

Three stages of joint damage are recognised: 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 hemosiderin 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 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, eg 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) due to 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 as early symptoms are often misdiagnosed as haemarthrosis [23]. After orthopedic surgery the risk of infection is considerably increased; arthroplasty has a 10x 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 bone mineral density (BMD) of 70% in adults [18]. The mechanism of low BMD is not completely understood, though, decreased mobility, [24] malnutrition, chronic inflammation, vitamin D deficiency and hypercalciuria probably contribute [25].
Uncommon musculoskeletal manifestations, such as muscle hematomas and/or pseudotumors (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.2 a and b). Early in the disease x-rays of the affected joint may demonstrate the presence of an effusion, periarticular osteopenia and epiphyseal overgrowth. Late changes resemble severe osteoarthritis [16]. Ultrasound imaging is useful to diagnose and follow-up haemarthroses and haematomas [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 hematological treatment (commonly 20–30U/kg IV 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 (either chemical, radioactive, or surgical - open or arthroscopic), reduces the bleeding cycle, delaying the onset of chronic hemophilic 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, approximately 90% of patients with severe hemophilia develop severe articular destruction (advanced hemophilic arthropathy) [15, 17, 20]. In addition, patients may experience contractures, angular deformity and loss of bone tissue due 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, 2 molecular ‘scissors’ (iRhom2 and TACE) are activated to release TNFα which induces a persistent inflammatory response and could promote the development of haemophilic arthropathy [28]. Melchiorre et al have shown that in patients with Haemophilia A and concomitant auto-immune disease treated with adalimumab, the anti-TNFα therapy has prevented the recurrence of joint bleeding. [29].

**Sickle cell diseases:**

**Pathogenesis:**

Sickle cell diseases (SCD) are a group of genetic haemoglobin disorders including sickle cell anaemia (haemoglobin SS), haemoglobin SC, haemoglobin Sβ-thalassemia, and other heterozygous conditions [30, 31]. They result from a mutation in the gene coding the β-globin chain of the haemoglobin molecule [31, 32]. If it occurs on both chromosomes (homozygosis), sickle cell anaemia (SCA) develops but if only one chromosome is involved (sickle cell trait) the individual
is a carrier (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 ischemia, 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 minutes 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 osteoarthritic change [32] and synovial effusions may develop.

The first clinical manifestations usually appear between 6 months to 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.3 a and b) and humeral heads causing pain and reduced joint movement [32, 36].

Approximately 50% of sickle cell patients experience orofacial pain and 3/4 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, impaired complement function [36] and deficiency in IgG 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, 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 to 20%, usually affecting long bones [38, 40].

The most common organisms are *Salmonella* species, especially the nontypical serotypes, followed by *Staphylococcus aureus* and others including tuberculous osteomyelitis [38, 40, 41].

Hyperuricemia is a common feature occurring in 32 to 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, “hair-on-end” appearance of the skull [31, 32] as a result of diploic space widening. Imaging is used to identify and characterise sites of bone infarction, see fig.3 a-d [32, 33, 36, 39]. MR imaging is the most sensitive imaging modality [31, 32].

**Treatment:**
The main management of 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 IV 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].

Thalassemia:
Pathogenesis:
The thalassemias 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 due to a reduced or absent rate of synthesis of one or more of the globin chains (α or β) [32, 43-45]. Several risk factors are implicated in the pathogenesis of thalassemia-induced bone mineral damage, including, two genetic factors, namely, the polymorphism at the Sp1 site of the collagen type la1 (COLIA 1) gene [45, 46] and the vitamin D receptor (VDR) BsmI and FokI polymorphisms [45, 47].

Clinical aspects:
Thalassemia is the most common monogenic disease worldwide, [45] causing hypochromic and microcytic anemia, hepatosplenomegaly, and extramedullary hematopoiesis with secondary skeletal deformities [32]. In untreated thalassemia, skeletal changes are related to ineffective erythropoiesis (and consequent chronic anaemia) causing marrow hyperplasia [32, 48]. In severe cases marrow expansion a loss of the normal concave outline of the long bones occurs; an abnormality commonly seen in the humerus and femur [48]. In untreated thalassemia 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 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 distinguishes skeletal dysplasia, reflecting chelator toxicity, and iron deposition in the skeleton and soft tissues [48].

Treatment:
Severe forms of thalassemia 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 thalassemia 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 (due to regular transfusion), adequate hormone replacement, and effective iron chelation therapy patients with β-thalassemia
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 under 3 years and at higher doses [48]. Patients with transfusion-dependent thalassemia 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 the normal haematopoiesis and immunity [51]. Leukaemias are classified into 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 leukemic cells infiltrating the intramedullary bone marrow space [55] and the joints. These cells may cause a synovial reaction secondary to periosteal capsular infiltration [36, 56, 57]. In addition there may be intra- or periarticular hemmorhages or paraeoplastic effects likely to be due to humoral factors (eg local osteolytic hypercalcaemia, increased parathormone-related peptide or some pro-inflammatory cytokines, secreted by the malignant clone eg TNF-alpha or interleukin-6) [57].
Leukemic 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 adults (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, erythematos 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 leukemic 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 (NSAID or corticosteroids), [58] and early significant osteopenia or lytic bone lesions [63].
Although, synovial biopsy is regarded as the gold standard for a leukemic arthritis diagnosis, the infiltration is usually focal and can be missed [56]. The average rheumatic prodome is 3 to 7 months before the correct diagnosis is made [56, 57, 63]. Leukemic 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 septicaemia [36]. Secondary gout rarely occurs 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 to 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 infiltration may be assessed by bone scintigraphy [57]. In regions of leukemic 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]. If necessary, 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, hepatosplenomegaly, raised ESR and lactate dehydrogenase level, weight loss, nocturnal sweating, pruritus and abnormalities of white blood cells [34]. The most common musculoskeletal feature in patients with Hodgkin and non-Hodgkin’s lymphomas is bone involvement (supplementary figure A), [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 worst prognosis [72]. Synovial biopsy is usually recommended for the definitive diagnosis of intraarticular tumours [76, 79]. 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].
Synovial fluid examination may reveal a sterile inflammatory fluid without crystal deposition but in almost 60% atypical lymphoid cells have been reported [68, 69]. In intraarticular lymphoma mild leucocytosis with lymphocyte predominance is often present in synovial fluid 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 rheumatologic features improve or disappear with the treatment of the lymphoma consistent with their paraneoplastic 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 paraprotein or an immunoglobulin free light chain [75, 76]. It accounts for 10% of haematological malignancies and about 1% of all human malignant diseases [76].

**Clinical aspects:**
The clinical presentation of MM is diverse, common complications including anaemia, hypercalcaemia, renal failure, recurrent infections or bony lytic lesions [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 severe impaired bone formation and the development of osteoporosis/osteopenia or osteolytic bone lesions (Supplementary figure B i and ii) [77,78]. Pathological fractures (Supplementary figure B iii) 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 receptor activator of nuclear factor-kappa B (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 occur in 10 to 15% of patients at diagnosis [77, 78]. Bony pain is a common symptom, particularly back pain, (up to 58% of patients) [75].

Rheumatologic 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 [36] arthritis have also been reported, the former in most cases, improves with antimyeloma treatment [81]. Articular manifestations have been related to amyloidosis [81,82] (amyloidosis arthritis being described in 0.1 to 6% of patients [82]), metabolic complications, and sometimes, immunoglobulin deposit [91].

Joint involvement includes a symmetrical or asymmetrical polyarthritis, [91] involving the knees, hand and feet joints in particular [83]. Synovial fluid analysis may show leukocytes (mainly polymorphonuclear leukocytes) 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:**

Musculoskeletal radiographic findings include lytic and sclerotic lesions and soft tissue masses [66, 69]. MRI can be used to demonstrate marrow infiltration [68, 69].
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% [78, 84]. The vertebrae, ribs, skull, shoulders, pelvis and long bones are the most frequent sites of skeletal involvement [78, 84].

20% of patients with MM have a normal skeletal survey at diagnosis [84]. MRI is more sensitive for assessing bone marrow infiltration (Supplementary figure B iv), notably in the spine, predicting the risk of vertebral fractures [78]. Bone deposits have been demonstrated on MRI in about 50% of asymptomatic myeloma patients with normal x-rays [78].

**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, cryoglobulinaemia and bone marrow transplantation are provided in a separate supplement.

**CONCLUSIONS:**

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


FIGURES AND LEGENDS:

Figure 1. X-rays of the wrist demonstrating chondrocalcinosis of the triangular fibrocartilage.

Figure 2. a and b) X-rays of the elbow and knee. There is advanced haemophilic arthropathy with erosive change, subchondral cyst formation and gross joint deformity.

c) MRI elbow joint, gradient echo sequences. Images demonstrate synovial haemosiderin deposits, characterized by low signal intensity and ‘blooming’ artifact on gradient echo sequences.

d) MRI pelvis demonstrating intramuscular haematoma within the left gluteus muscles (arrow), which is of low signal intensity and mimics a mass lesion. Pseudo tumor formation is a rare complication that occurs in 1-2% of patients with severe haemophilia [15, 20], and reflects recurrent intramuscular haemorrhage.

Figure 3. a) Coronal CT pelvis. Bilateral avascular necrosis of the femoral heads with secondary advanced osteoarthritic change.

b) Chest radiograph exhibiting ‘H shaped’ vertebral bodies, a characteristic deformity of sickle cell disease which results from bone infarction of the central regions of the vertebral plateaus causing excessive growth in adjacent regions and a depression of the central plateaus [32, 39].

c) Proton density and d) STIR (fat suppression) weighted MRI of the pelvis of a patient with bilateral AVN of the femoral heads, demonstrating different stages of disease progression. Patients with sickle cell disease are prone to bilateral disease. There is early AVN of the right femoral head, involving approximately 90% of the weight-bearing surface. The morphology of the femoral head is maintained. A characteristic serpiginous band (arrow), delineates the interface between normal marrow and the ischemic epiphyseal marrow. There is advanced AVN of the left femoral head with evidence of subchondral fracturing and collapse. There is secondary degenerative change in the left hip joint and a joint effusion.

Figure 4. Lateral skull radiograph demonstrating expansion of the diploic space within the skull vault, secondary to marrow hyperplasia. Perpendicular orientated trabeculae transversing the diploic space give the classic ‘hair-on-end’ appearance.

Supplementary figure A. T2 weighted MRI of the lower spine. There is generalized abnormal heterogeneous marrow signal within the osseous spine, reflecting lymphomatous infiltration of multiple vertebral levels.

Supplementary figure B i) Lateral radiograph of the skull demonstrates multiple ‘punched-out’ lesions with absent reactive sclerosis of the surrounding bone.

ii) Plain radiograph of the humerus. Lytic lesion in the diaphysis of the humerus with endosteal scalloping.
iii) Plain radiograph. There is a large destructive lesion involving the proximal right humerus with evidence of pathological fracture (arrow).

iv) T1 weighted MRI of the cervical and thoracic spine. Multiple focal areas show loss of the normal bright fatty marrow signal due to myelomatous infiltration of the vertebral column. The largest deposit is seen within the T3 vertebral body. Myelomatous infiltration results in a reduction in signal intensity on T1 weighted imaging because MM usually has increased cellularity (e.g. plasma cells) and decreased fatty components [87, 88].
Table 1: Description of the major clinical features including rheumatological manifestations and some practical management advices of benign haematological conditions and bone marrow transplantation.

<table>
<thead>
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<th>Major Clinical Manifestations</th>
<th>Rheumatological Manifestations</th>
<th>Some practical management advice</th>
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<td>Haemochromatosis</td>
<td>Non-specific early symptoms of fatigue, arthralgia or abdominal pain. Progression to cirrhosis,</td>
<td>Chronic progressive non-inflammatory arthropathy; ↑ ferritin concentrations in synovial fluid.</td>
<td>Permanent articular damage as synovial hemosiderin deposits not removed by venesection. Medical treatment: For acute symptoms requiring analgesics, NSAID’s, coxibs. Additionally, colchicine (0.5-1mg daily), intra-articular steroids. Treatment of severe arthropathy; joint replacement surgery (major joints).</td>
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<td></td>
<td>hepatocellular carcinoma, diabetes mellitus, impotence, skin pigmentation, cardiomyopathy and</td>
<td>Affected joints: 2nd and 3rd MCP (pain at the hadshake sign), PIP, knees, wrists and distal radioulnar joints, hips, shoulders, ankles and elbows. Chondrocalcinosis of the knee, wrist, symphysis pubis and spine.</td>
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<td></td>
<td>hypogonadism</td>
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<td>Haemophilia</td>
<td>Related to bleeding, mostly affecting the musculoskeletal system. Uncommon musculoskeletal</td>
<td>Acute haemarthrosis: swollen, warm and painful joint. Mainly large joints. Chronic hemophilic arthropathy generally accompanied by severe contractures, angular deformity and loss of bone tissue. Increased incidence of septic arthritis and osteoporosis / low BMD.</td>
<td>Treatment of chronic synovitis: Factor replacement, physiotherapy and pain management; If need synovectomy (chemical, radioactive or surgical - open or arthroscopic). Treatment of chronic haemophilic arthropathy: total joint arthroplasty, resection of the radial head or ankle arthrodeseis, joint debridement or angiographic embolization. Treatment of septic arthritis: antibiotics against gram positive bacteria.</td>
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<td>manifestations: muscle hematomas and pseudotumors.</td>
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<td>Sickle cell diseases</td>
<td>Frequently, orofacial pain and headaches. Rarely, neuropathy, fibrous ankyloses and inflammation,</td>
<td>Sickle cell dactylitis (in children), bone infarction, AVN, vertebral collapse, 2nd osteoarthritis. Non-inflammatory synovial effusions. Frequently, osteoarticial 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>Treatment of acute haemarthrosis: 20-30U/kg IV coagulation factor, joint aspiration, physiotherapy (after acute phase), avoid rebleeding. Treatment of chronic proliferative synovitis: Factor replacement, physiotherapy and pain management; If need synovectomy (chemical, radioactive or surgical - open or arthroscopic). Treatment of chronic haemophilic arthropathy: total joint arthroplasty, resection of the radial head or ankle arthrodeseis, joint debridement or angiographic embolization. Treatment of septic arthritis: antibiotics against gram positive bacteria.</td>
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<td>oedema and necrosis of muscles.</td>
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<td>Thalassemia</td>
<td>Hypochromic/microcytic anemia, extramedullary hematopoesis with 2nd skeletal deformities (leading to</td>
<td>Untreated patients: multiple and recurrent spontaneous pathological fractures of the long bones. Bone involvement sites: skull/facial, the spine (vertebrae compression fractures leading to scoliosis/kyphosis), the ribs and metaphyses of long bones.</td>
<td>Treatment of severe forms: transfusion therapy (to haemoglobin levels &gt;9-10g/dL) Important: Chronic transfusions leading to iron overload leading to consequent 2nd synovium and articular cartilage abnormalities. Iron chelating therapy: desferrioxamine or deferiprone.</td>
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<td>skeletal dysplasia and growth retardation) and hepatosplenomegaly. Frequently, generalized pain.</td>
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<tr>
<td>Bone Marrow Transplantation</td>
<td>Growth abnormalities in children.</td>
<td>Following BMT: frequently arthralgia. Lower limbs commonly affected. Sickle arthrits or osteomyelitis are rare. In chronic GVHD: AVN or severe osteoporosis; rarely, transitory or chronic non-erosive arthrits.</td>
<td>Treatment of chronic arthritis: partial response to NSAID’s and steroids requiring treatment of GVHD. Treatment of acute bacterial arthritis: antibiotics against Streptococcus and Salmonella species and joint drainage.</td>
</tr>
</tbody>
</table>

↑: high/increase; MCP: metacarpophalangeal; PIP: proximal interphalangeal; BMD: bone mineral density; AVN: avascular necrosis; SC: sickle cell; IV: intravenous; BMT: bone marrow transplantation; GVHD: graft-vs-host disease
### Table 2: Description of the major clinical features including rheumatological manifestations and some practical management advices of malignant haematological conditions.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Major Clinical Manifestations</th>
<th>Rheumatological Manifestations</th>
<th>Some practical management advice</th>
</tr>
</thead>
<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. Leukaemic arthritis: inflamed, erythematous and tender joints; mainly distal large joints. Frequently, fever and severe nocturnal pain (in an atypical location, poor responsive to conventional anti-rheumatic treatment); associated with early significant osteopenia or lytic lesions. Rarely, intra-articular haemorrhage, septic arthritis, 2nd gout.</td>
<td>Treatment of the underlying leukemia; if necessary, adjunctive radiotherapy of the affected joints.</td>
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<td>Myelodysplastic syndromes</td>
<td>Peripheral cytopenias. Progression: ↑ weakness, dyspnoea, recurrent serious infections and/or bleeding problems.</td>
<td>Frequently, arthralgia, non-erosive acute symmetrical polyarthritis. Occasionally, septic arthritis, 2nd gout or hypertrophic pulmonary osteoarthropathy.</td>
<td>Treatment: steroids; DMARDs not recommended.</td>
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<tr>
<td>Lymphomas</td>
<td>Fever, lymphadenopathy, hepatosplenomegaly, ↑ ESR and lactate dehydrogenase level, ↓ of weight, nocturnal sweating, pruritus and white blood cells abnormalities. RF and anti-CCP (+) may occur.</td>
<td>Rarely, poly- or monoarticular arthritis; involving the knee, shoulder, sternoclavicular or elbow joints. Sterile inflammatory synovial fluid, atypical lymphoid cells in 60%; mild leucocytosis with lymphocyte predominance in intra-articular lymphoma. Occasionally, septic arthritis, 2nd gout or hypertrophic pulmonary osteoarthropathy.</td>
<td>Treatment: of the underlying lymphoma. Important: Osteonecrosis as complication of lymphoma treatment. Treatment of septic arthritis: antibiotics against Salmonella species.</td>
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<td>Cryoglobulinemia: Monoclonal – type I Mixed – type II or III</td>
<td>Mixed: weakness, arthralgia and purpura. Serum autoantibodies (ANA and RF) may be present.</td>
<td>Type I: rarely musculoskeletal manifestations. Mixed: common arthralgia and myalgia are common. Type II: the MCP,PIP, knees and ankles frequently affected; often exacerbated by cold exposure. Generally, mild, non-erosive oligoarthritis.</td>
<td>Treatment: Mild symptoms → NSAIDs. Moderate symptoms → low-dose steroids ± HCQ. Treatment of severe disease: of the underlying disease. If consequent to haematological malignancies/lymphoproliferative disorders: chemotherapy and radiation therapy. If non-malignancy-related disease: O prednisolone 1-2mg/kg/day or plasmapheresis and IV cyclophosphamide 0.5-1.0g/m².</td>
</tr>
</tbody>
</table>

↑ - high/increase; ↓ - low/decrease; MCP: metacarpophalangeal; PIP: proximal interphalangeal; AVN: avascular necrosis; IV – intravenous; anti-CCP: anti-citrullinated protein antibody; ANA: antinuclear antibody; (+): positivity; Ig: Immunoglobulin; HCQ: Hydroxychloroquine; O: by mouth.