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ESSENTIALS Musculoskeletal symptoms can occur in a variety of diseases, or as drug side effects. Presentations and conditions discussed in this section include: Multisystem diseases—adult-onset Still’s disease (including macrophage activation syndrome as sequelae), acute sarcoid arth- ritis, amyloidosis Paraneoplastic syndromes—hypertrophic pulmonary osteoarthro pathy, remitting seronegative symmetrical synovitis with pitting oe- dema, tumour-induced osteomalacia Skin manifestations of rheumatic disease—panniculitis, neutrophilic dermatoses, multicentric reticulohistiocytosis Primary joint pathology and synovial disorders—pigmented vilonodular synovitis, synovial osteochondromatosis, Charcot
joint Rheumatic manifestations of haematological disease— haemophilia, sickle cell disease, leukaemia, lymphoma, and poly- neuropathy, organomegaly, endocrinopathy, M-protein, and skin abnormalities Rheumatic manifestations of metabolic disease—hereditary haemo- chromatosis, Wilson’s disease Disorders of the spine and axial skeleton—Tietze’s syndrome, diffuse idiopathic skeletal hyperostosis, and alkaptonuria Drug-induced rheumatic syndromes—statin-induced myop- athy, drug-induced tendinopathy, drug-induced lupus, allopurinol hypersensitivity Multisystem diseases Adult-onset Still’s disease Adult-onset Still’s disease (AOSD) is a rare, idiopathic, multisystem inflammatory disorder characterized by quotidian fever, evanescent rash, and inflammatory arthritis. The condition was first proposed as a separate disease entity by Eric Bywaters in 1971, who described the clinical syndrome in 14 adult patients, and named it adult-onset Still’s due to similarities with paediatric Still’s disease, described by George Still in 1897 and now known as systemic onset juvenile idiopathic arthritis. Adult-onset Still’s disease effects approximately 0.1 to 1 per 100 000 population. It is more common in females than males, and is most frequent in younger age groups, with 75% of patients with disease onset between the ages of 16 and 35 years. There appears to be no ethnic predisposition and there are no known human leuko- cyte antigen (HLA) associations. Adult-onset Still’s disease is often classified under the

spectrum of autoinflammatory disease, as an idiopathic febrile syndrome, but unlike other diseases in this category an underlying molecular mechanism has not been clearly defined. It is clear that macrophage activation is prominent in the immunopathogenesis, and patho- genic roles of inflammatory cytokines IL-1β, IL-6, IFN-γ, TNFα, and IL-18 have been demonstrated. Adult-onset Still's disease is a clinical diagnosis and can be as- sisted by Yamaguchi 1992 and Fautrel 2002 criteria (Table 19.12.1). The fever, which for diagnosis must rise to more than 39oC, typically appears in the evening (Fig. 19.12.1). The articular manifestations most frequently involve symmetrical inflamma- tory arthritis affecting the knees, wrists, and ankles, however small joint polyarthritis involving the proximal interphalangeal or metacarpophalangeal joints has frequently been described. Compared to other inflammatory arthropathies there is more fre- quent structural damage in the carpus, including pericapitate joint space narrowing and ankylosis. The skin eruption in adult-onset Still's disease is transient, hence called evanescent, and is usually present in the evening accom- panying febrile periods. It typically affects the trunk and proximal limbs, is nonpruritic, 'salmon pink', maculopapular, and may display Koebner's phenomenon (Fig. 19.12.2). In large case series organ manifestations include splenomegaly in 44%, pleuritis in 26% and pericarditis in 24%. Large pleural effu- sions and cardiac tamponade have been reported. Laboratory features in adult-onset Still's disease reflect sys- temic inflammation, with anaemia of chronic disease, reactive thrombocytosis, high C-reactive protein and erythrocyte sedimen- tation rate (ESR). There is usually a marked neutrophil leucocytosis and mixed derangement in liver function tests. There are no specific autoimmune tests, but negative antinuclear antibodies (ANA) and rheumatoid factor (RF) form part of the historical diagnostic criteria to ensure exclusion of alternative diagnoses such as systemic lupus erythematosus (SLE) and systemic rheumatoid arthritis (RA). 19.12 Miscellaneous conditions presenting to
the rheumatologist Stuart Carter, Lisa Dunkley, and Ade Adebajo

 The mechanism for marked hyperferritinaemia is unclear, al- though it is likely driven by macrophage activity and inflammatory cytokines. It is usually more than five times the upper limit of normal laboratory measurements. This is not specific to the condition and hence not a diagnostic test alone, but is a useful biomarker during treatment as levels normalize with remission. In health 50–80% of ferritin is glycosylated, a mechanism that appears to be impaired in adult-onset Still's disease, producing glycosylated ferritin levels below 20%. The combination of serum ferritin more than five times upper limit of normal laboratory measurements and glycosylated ferritin less than 20% has a specificity of 93% for adult-onset Still's disease, although the test is not widely available. Macrophage activation syndrome is a well-recognized life threatening manifestation of adult-onset Still's disease, affecting 12–15% of cases and carrying a significant mortality, reported between 10–22%. In this condition activated tissue macrophages phagocytose haemopoetic cells in bone marrow and the reticulo-endothelial system. Macrophage activation syndrome can be a presenting feature of adult-onset Still's disease, making diagnosis challenging as sec- ondary haemophagocytic lymphohistiocytosis caused by other conditions (including malignancy, infection, and systemic lupus erythematosus) has common clinical and laboratory abnormal- ities to adult-onset Still's disease, including high spiking fever, hyperferritinaemia, and liver dysfunction. Clinicians should be alerted to the condition if a patient develops a nonremitting fever, neurological dysfunction, hepatosplenomegaly, lymphadenop- athy, accompanied by pancytopenia (or normalization from a pre- vious high level), falling ESR (caused by hypofibrinogenaemia), hypertriglyceridaemia, hyponatraemia, hypoalbuminaemia, and worsening liver dysfunction. Treatment of adult-onset

Still’s disease is dependent upon disease manifestations and severity. While nonsteroidal anti-inflammatories have been used as first-line historically, only 20% of patients re- spond, and corticosteroids are usually required. Combination methotrexate and corticosteroids is an effective first-line treatment and steroid-sparing strategy. In recent years, anti-TNF antagonists (etanercept, adalimumab, infliximab), IL-1 antagonists (anankinra, canakinumab, rilonacept) and IL-6 antagonists (tocilizumab) are now recommended ahead of alternative treatments such as leflunomide, azathioprine, ciclosporin, cyclophosphamide, or intra- venous immunoglobulins in severe or methotrexate refractory cases. In cases of macrophage activation syndrome there is no defined treatment protocol, but aggressive immunosuppression is needed, commonly with high dose intravenous glucocorticoids, intravenous immunoglobulins and immunosuppression with ciclosporin and/or biologic agents anakinra or tocilizumab. Table 19.12.1 Yamaguchi 1992 and Fautrel 2002 diagnostic criteria for adult-onset Still’s disease Yamaguchi, 1992 Fautrel, 2002 ≥5 (2 must be major) ≥4 major criteria, or 3 major
and 2 minor Major Major • Fever >39°C ≥1 week • Spiking fever ≥39°C • Arthralgia ≥2 weeks • Arthralgia • Typical rash • Transient erythema • Leukocytosis >10 000/mm3, >80% • Pharyngitis polymorphs • Polymorphs ≥80% Minor • Glycosylated ferritin ≤20% • Sore throat • Lymphadenopathy Minor • Hepatomegaly or splenomegaly • Maculopapular rash • Abnormal liver function tests • Leukocytosis >10 000/mm3 • Negative antinuclear factor and rheumatoid factor Exclusion criteria • Infection • Malignancy (lymphoma) • Other rheumatic disease (systemic vasculitis) AM PM AM PM AM PM AM PM AM PM AM PM 39 38 37 36 Time Temperature °C
Fig. 19.12.1 Quotidian fever typical of adult-onset Still’s disease consisting of daily spiking temperatures above 39°C in the evening, returning to baseline levels in the morning. Fig. 19.12.2 The rash of adult-onset Still’s disease. © American College of Rheumatology.

section 19 Rheumatological disorders 4600 Acute sarcoid arthritis Löfgren described a unique presentation of acute sarcoid arthritis in 1953, with a triad of bi-hilar lymphadenopathy, arthritis and ery- thema nodosum (Fig. 19.12.3), now known as Löfgren’s syndrome, which is considered pathognomonic of the condition, making tissue biopsy to secure a diagnosis redundant, unlike many other mani- festations of sarcoidosis. Tissue biopsy should be sought if there are atypical features, to exclude alternative diagnoses such as lymphoma and tuberculosis. Epidemiological studies in sarcoidosis have described articular symptoms in up to 25% of cases, most frequent among Caucasians and rare in Japanese populations. Typical Löfgren’s syndrome presents with lower limb oligoarthro pathy, most frequently with diffuse ankle swelling, although peri- articular inflammation where joint range of motion is maintained and ultrasound demonstrates no intra-articular abnormality is a well-recognized variant. Tenosynovitis is often frequently encoun- tered in ultrasound studies. Other joint involvement in order of fre- quency includes the knee, wrist, and metacarpophalangeal joints. The most frequent skin abnormality in acute sarcoid arthropathy is erythema nodosum, but this is not present in all cases, and was only present in 53% of Löfgren’s original cohort. Lupus pernio, granulomatous skin lesions, and inflammatory papules developing within scars and tattoos have also been reported. Additional features in Löfgren’s syndrome may include fever in up to two-thirds. A few patients display respiratory symptoms including cough and dyspnoea, hepatomegaly, inflammatory eye disease, and rarely peripheral lymphadenopathy, splenomegaly, hypercalcaemia, and salivary gland hypertrophy. Serum angiotensin converting en-zyme levels are elevated in 50% of patients. Most patients with Löfgren’s syndrome improve rapidly with nonsteroidal anti-inflammtory drugs (NSAIDs) or oral cortico- steroid treatment. Long-term prognosis is good, with most achieving treatment free remission within the first year of

diagnosis. Only a few patients progress to chronic arthropathy in which methotrexate is the first-line recommended disease-modifying antirheumatic drug (DMARD). Predictors of poor prognosis and disease persistence include absence of erythema nodosum, pulmonary infiltrates on chest X-ray, presence of splenomegaly, and absence of bi-hilar lymphadenopathy on chest X-ray. Amyloidosis Systemic amyloidosis consists of a group of conditions causing extracellular deposition of insoluble fibrillar proteins in the extra- cellular space, including in joints and periarticular tissue. The conditions are categorized depending on the fibril precursor re- sponsible for the amyloid protein deposition, which produce a recognizable clinical syndrome and set of complications, al-though there is considerable overlap. The precursors responsible in nonhereditary amyloidosis are serum amyloid A in secondary (AA) amyloidosis, immunoglobulin light chains in amyloid light-chain (AL) amyloidosis, and dialysis-associated β-2 microglobulin in β-2M amyloidosis. Secondary (AA) amyloidosis The most frequent causes of secondary amyloidosis are chronic inflammatory diseases, chronic infections and malignancies, in cases where inflammatory disease is poorly controlled and there is a persistent acute phase response. Rheumatic disease including rheumatoid arthritis, juvenile idiopathic arthritis, and ankylosing spondylitis account for 70% of cases, with a reported prevalence of 3–6% in all inflammatory arthropathies. Other important condi- tions which cause amyloidosis that is seen in the rheumatology clinic include autoinflammatory syndromes and systemic vasculitides. Secondary amyloidosis should be considered in patients with rheumatic disease with evidence of longstanding uncontrolled in- flammatory activity. The combination of renal dysfunction and proteinuria is found in 97% of patients at diagnosis, and the renal prognosis is poor, with 40% progression to end-stage renal failure requiring renal replacement therapy. Alongside renal abnormalities hepatosplenomegaly is common. Gastrointestinal involvement oc-curs in advanced disease and manifests as malabsorption, pseudo- obstruction, or nausea and vomiting from mucosal infiltration. Amyloid light-chain (AL) amyloidosis In amyloid light-chain (AL) amyloidosis, rheumatic manifestations are uncommon. The principle causes of morbidity are renal dysfunc- tion with nephrotic syndrome, congestive cardiac failure, painful sensory peripheral neuropathy, and hepatomegaly. However, pa- tients can present to the rheumatology clinic in a variety of ways. A classical presentation is ‘shoulder pad sign’, caused by infiltration of the glenohumeral joint and capsule, causing pain, stiffness, swelling, and limitation. In combination with macroglossia and ‘racoon eyes’, caused by periorbital ecchymosis, this triad is considered pathog- nomonic of amyloid light-chain amyloidosis. Peripheral articular symptoms occur in 9% of patients, which may produce inflamma- tory joint stiffness mimicking rheumatoid arthritis. Infiltration of muscles of mastication can cause jaw claudication mimicking tem- poral arteritis. Infiltration of exocrine glands can lead to sicca symp- toms mimicking Sjogren’s syndrome. Carpal tunnel syndrome is also common. β-2M amyloidosis Historically, this condition caused substantial morbidity in long- term haemodialysis patients, but it is no longer seen with use of Fig. 19.12.3 Erythema nodosum on the shins. Reproduced from Watts RA et al. (eds) (2013). Oxford Textbook of Rheumatology, 4th edn, by permission of Oxford University Press.

 modern high flux dialysis membranes that clear β-2 microglobulin from the circulation more effectively. In contrast to AL and AA amyloidosis, in dialysis-related amyloidosis β-2 microglobulin de- position outside of the musculoskeletal system is rare. Involvement of the musculoskeletal system caused a persistent, erosive, sym- metrical large and small joint polyarthropathy, and tenosynovitis. Carpal tunnel syndrome was common and often a presenting fea- ture. Deposition in periarticular bone manifested as erosive disease in both the axial and appendicular skeleton, leading to pathological

fractures. Paraneoplastic syndromes Hypertrophic osteoarthropathy Hypertrophic osteoarthropathy (HOA) is a syndrome caused by periostosis and soft tissue hypertrophy at the distal extremities, causing a combination of finger clubbing, bone and joint pain, and synovial effusions. It is a well described indicator of serious underlying pathology, including lung cancer, and can precede the secondary cause by several years. The condition was initially called hypertrophic ‘pulmonary’ osteoarthropathy due to its association with pulmonary malig- nancy (predominantly squamous cell carcinoma), bronchiectasis, cystic fibrosis, and lung abscess. However, the ‘pulmonary’ was re- moved with recognition that hypertrophic osteoarthropathy could be caused by extrapulmonary conditions including congenital heart disease, inflammatory bowel disease, and head and neck cancers. Although there is a spectrum of severity, clubbing is usually ob- vious and bone pain can be elicited by palpation of the affected areas. Periosteal reaction is often visible on plain radiographs and uptake in bone scintigraphy can be seen in a periosteal distribution in distal long bones (Fig. 19.12.4). Hypertrophic osteoarthropathy can also be associated with acanthosis palmaris, a hyperkeratoic condition affecting the palm, causing accentuation of the dermatoglyphic lines and leading to a velvety, ridged appearance described as ‘tripe palms’. Acanthosis palmaris alone is a paraneoplastic sign, often found in lung or gas- tric malignancy. Management involves seeking and treating the underlying diag- nosis, which may cause hypertrophic osteoarthropathy to remit. It responds well to NSAIDs as first-line agents. Refractory cases have been successfully treated with the bisphosphonates pamidronate and zolendronate, and with the somatostatin analogue octerotide. Remitting seronegative symmetrical synovitis with pitting oedema Remitting seronegative symmetrical synovitis with pitting oedema is descriptive of a clinical presentation of acute polyarthritis de- scribed in 1985. Patients present with a symmetrical small joint polyarthritis, with gross swelling and pitting oedema in the dorsum of the hands and/or feet. The condition is nonerosive, autoantibody negative, and responds well to low dose corticosteroid, typically 10 mg daily. Malignancy was reported in 25% of 89 patients in five case series, with a mixture of solid and haemopoeitic malignancy, suggesting overrepresentation of malignancy in this condition, al- though it does tend to occur in older age groups (over 70 years) and is more common in men. Tumour-induced osteomalacia Tumour-induced osteomalacia is caused by occult tumours with relatively heterogeneous histopathology usually found in bones in the lower extremities or peripheral soft tissues. The tumours secrete fibroblast growth factor-23 (FGF-23, also known as phosphatonin), which causes excess secretion of phosphate from the proximal tu- bule of the kidney. The diagnosis is challenging as tumour sites may be asymptom- atic, with most symptoms mediated by ectopic hormone production and progressing gradually, often leading to diagnostic delay by sev- eral years. Symptoms are often nonspecific, including malaise and myalgia, but presence of bone pain and low trauma fracture prompts further investigation. Biochemical analysis shows hypophosphataemia, inappropriately low or normal 1, 25 dihydroxyvitamin D, hyperphosphaturia, and elevated levels of FGF-23. Plain radiographs reveal features of osteomalacia with cortical thinning, coarsened trabeculae, and pseudofractures. To locate le- sions octreotide scintigraphy or positron emission tomography (PET) is required, followed by structural imaging with CT or MRI to characterize the lesion. Other causes of genetic and acquired hypophosphataemia should be excluded. Complete excision of the tumour allows resolution of the bio- chemical abnormalities, and provides excellent long-term prog- nosis. If surgery is not possible due to lesion location or inability to locate the lesion, medical treatment is indicated. This includes high dose phosphate and 1,25 dihydroxyvitamin D replacement, with regular monitoring of serum calcium levels. Subcutaneous adminis- tration of octreotide is successful in some cases.
Fig. 19.12.4 Radiography of distal tibia showing the periosteal reaction (arrow). Reproduced from

Rosencow, III EC (2010). Mayo Clinic Challenging Images for Pulmonary Board Review. © Mayo Foundation for Medical Education and
Research, by permission of Oxford University Press.

section 19 Rheumatological disorders 4602 Skin manifestations of rheumatic disease Panniculitis Panniculitis describes a heterogeneous group of conditions character- ized by inflammatory lesions affecting subcutaneous adipose tissue. They are subcategorized into four histological subtypes, mostly septal or mostly lobular, with or without vasculitis. The range of possible diagnoses includes leukocytoclastic vasculitis, erythema nodosum, rheumatoid nodules, cutaneous polyarteritis nodosa, gout panniculitis, subcutaneous sarcoidosis, and lupus erythematosus profundus. The most common panniculitis is erythema nodosum (mostly septal without vasculitis). This is characterized by painful, symmet- rical subcutaneous nodules usually over 1 cm affecting the lower extremities and more uncommonly the forearms (see Fig. 19.12.3). They appear as bright red nodules, progressing to purple, followed by yellow/green colouration, spontaneously resolving over 3–6 weeks without a scar. The skin lesions are frequently accompanied by fever, arthralgia and fatigue, and may be accompanied by abdom- inal pain and diarrhoea. It is most common in females between the second and fourth decades of life. In children erythema nodosum is most commonly associated with streptococcal infection, but in adults medications, sarcoid- osis and inflammatory bowel diseases are the most common causes (Table 19.12.2). The rheumatic diseases most frequently associated with the condition are sarcoidosis (in Löfgren’s syndrome), Behçet’s disease, and Takayasu’s arteritis. Important differentials to con- sider are Mycobacterium tuberculosis, Mycoplasma pneumonia, Hodgkins and non-Hodgkin’s lymphoma. Neutrophilic dermatoses Neutrophilic dermatoses are characterized by skin infiltration by polymorphonuclear leukocytes. The archetypal conditions presenting to rheumatology are pyoderma gangrenosum and Sweet’s syndrome, disease associations of which are shown in Table 19.12.3. Pyoderma gangrenosum Pyoderma gangrenosum is a rare disease with a UK incidence of 0.63 per 100 000 person-years. It has a variety of clinical presenta- tions including classical ulcerating lesions and atypical bulbous, pustular and granulomatous subtypes (Figs. 19.12.5 and 19.12.6). Table 19.12.2 Conditions associated with erythema nodosum Infections • Streptococcus sp. • Tuberculosis • Yersinia sp. • Atypical pneumonia — Mycoplasma pneumonia — Chlamydia psitacci • Infectious mononucleosis Malignancy • Hodgkin’s lymphoma • Non-Hodgkin’s lymphoma • Leukaemia Autoimmune conditions • Ulcerative colitis • Crohn’s disease • Behçet’s disease • Reactive arthritis Miscellaneous • Sarcoidosis Drugs • Sulfonamides, e.g. sulphasalazine • Celecoxib • Furosemide • Bumetanide • Gliclazide • Penicillin • Oral contraceptives Table 19.12.3 Disease associations of Pyoderma gangrenosum and Sweet’s syndrome Pyoderma gangrenosum Sweet’s syndrome Rheumatic disease • Rheumatoid arthritis • Ankylosing spondylitis • Systemic lupus erythematous • Behçet’s disease • Relapsing polychondritis • Systemic lupus erythematous Gastrointestinal • Inflammatory bowel disease (Ulcerative colitis > Crohn’s disease) • Inflammatory bowel disease (Crohn’s disease > Ulcerative colitis) Infections • HIV • Hepatitis B • HIV Haematological • Monoclonal gammopathy of uncertain significance (MGUS) • Waldenstrom macroglobulinaemia • Myelofibrosis • Non-Hodgkin’s lymphoma • Acute myeloid leukaemia • Chronic lymphocytic leukaemia • Non-Hodgkins lymphoma • Multiple myeloma • Myelodysplastic syndrome • Hairy cell leukaemia • Mixed cryoglobulinaemia Solid tumours • Prostate • Colon • Bladder • Breast • Lung • Ovary • Prostate • Colon • Renal • Lung Endocrine • Pregnancy • Pregnancy • Hashimoto’s thyroiditis Drug-induced • Granulocyte colony stimulating factor (G-CSF) • All-trans retinoic acid • Granulocyte colony stimulating factor (G-CSF) • Bortezomab • Imatinib • Co-trimoxazole

Miscellaneous • Sarcoidosis • Pyoderma gangrenosum and acne (PAPA) syndrome • Takayasu's arteritis • Relapsing polychondritis

19.12 Miscellaneous conditions presenting to the rheumatologist 4603 Ulcerative or classical lesions may develop after minor trauma or surgery, a phenomenon known as pathergy, which produces a small red-blue pustule, which then enlarges and ulcerates. The ul- cers classically have a raised edge with a blue or violaceous border, a steep and undermined internal margin with purulent exudates. Elliptical tissue biopsies which include the floor and margin of the lesions are recommended for diagnostic purposes. Histopathology demonstrates destruction of adnexal glands and follicular units by neutrophillic inflammation with haemorrhage and necrosis. Folliculitis and granulomas may be found in pustular and granu- lomatous variants respectively. Topical treatment for mild lesions includes potent steroid pre- parations and tacrolimus, but systemic treatment is usually re- quired: high dose oral prednisolone (1–2 mg/kg/day) and ciclosporin are used most frequently, with mycophenolate mofetil, azathioprine, and tacrolimus commonly used alternatives. Patients with coex- istent inflammatory bowel disease and rheumatoid arthritis can be successfully treated with anti-TNF agents. Sweet's syndrome Robert Sweet described the syndrome, otherwise known as acute fe- brile neutrophilic dermatosis, in 1964. It is characterized by acute onset fever, peripheral neutrophilia and painful erythematous, ir- regular papules or plaques, the histology of which demonstrates neutrophilic inflammation in the papillary dermis. Skin lesions are accompanied by dermal oedema and are distributed most frequently on the face, neck, upper limbs and trunk (Fig. 19.12.7). Lesions may also occur on the lower limb indistinguishable from erythema nodosum. Arthralgia, myalgia, lethargy, and painful red eyes are commonly reported. Treatment for Sweet's syndrome importantly includes treatment of underlying disease (Table 19.12.3), which may drive activity of skin lesions. Given the many disease associations, the diagnostic work-up includes seeking an underlying cause and exclusion of malignancy, before proceeding with empirical treatment. However, Sweet's syndrome responds very well to high dose oral corticoster- oids (prednisolone 1 mg/kg/day), which is first-line therapy. A third of patients show persistent disease after corticosteroid tapering at 4–6 weeks, requiring second-line, steroid-sparing treatment. If pa- tients have underlying inflammatory bowel disease or rheumatoid arthritis, anti-TNF agents should be considered. Dapsone, colchi- cine, NSAIDs, and ciclosporin are alternative agents, which are used second line in idiopathic cases. Case reports have demonstrated benefit with anakinra and rituximab in refractory disease. Multicentric reticulohistiocytosis Multicentric reticulohistiocytosis is a rare disease of unknown aeti- ology presenting most commonly in women in the fourth decade, with an erosive and destructive symmetrical small joint polyarthritis and progressive papulonodular skin lesions. Joint disease com- monly affects the distal interphalangeal joint, distinguishing it from rheumatoid arthritis. It may produce a rapidly progressive arth- ritis mutilans, and juxta-articular erosion which can mimic gout radiographically. A wide variety of malignancies, both solid and haemopoeitic, have been identified in up to 25% of patients in some case series, raising the possibility of paraneoplastic pathogenesis. Fig. 19.12.5 Pyoderma gangrenosum. Fig. 19.12.6 Ulcerating pyoderma gangrenosum. Reproduced from Watts RA et al. (eds) (2013). Oxford Textbook of Rheumatology, 4th edn, by permission of Oxford University Press. Fig. 19.12.7 Rash of Sweet's syndrome. Reproduced from Watts RA et al. (eds) (2013). Oxford Textbook of Rheumatology, 4th edn, by permission of Oxford University Press.

section 19 Rheumatological disorders 4604 Nodules and arthritis present simultaneously in approximately 20% of patients, but there may be an interval between arthritis onset and skin

disease of a few years. Skin nodules occur most fre- quently on the face and dorsum of the hand. Distal limb nodules can occur in a periungual distribution, causing a ‘coral bead’ ap- pearance of the nail bed (Fig. 19.12.8). In addition to the skin, papulonodular lesions frequently affect the oropharyngeal and nasal mucosal. Constitutional symptoms such as fever, malaise, and weight loss are often present. Major organ disease is infre- quent, but most commonly affects the heart and lungs, manifesting as pericardial effusion, pleural effusion, or pulmonary fibrosis. Diagnosis can be achieved by skin or synovial biopsy, clas- sically revealing a multinucleated giant cell inflammation with eosinophilic periodic acid–Schiff (PAS) positive ‘ground glass’ cytoplasm. There is no treatment consensus because the rarity of multicentric reticulohistiocytosis prevents rigorous clinical trials. Modern approaches mimic ‘treat to target’ rheumatoid arthritis regimen, with first-line use of corticosteroids and disease-modifying antirheumatic drugs, in which methotrexate, hydroxychloroquine, and azathioprine have been most commonly used with variable success. Likewise, both joint and skin disease, refractory to cor- ticosteroid and disease-modifying antirheumatic drugs, have been successfully treated with anti-TNF agents etanercept, adalimumab and infliximab, and IL-6 blockade with tocilizumab in case reports and small case series. Bisphosphonates including alendronic acid, pamidronate, and zolendronate have also shown benefit. Primary joint pathology and synovial disorders Pigmented villonodular synovitis Pigmented vilonodular synovitis is an aggressive and locally in- vasive synovial proliferation of unknown aetiology, considered to have both inflammatory and tumour-like characteristics. The hyperplastic synovium is pigmented due to haemosiderin con- taining multinucleated giant cells and macrophages, which are thought to mediate joint destruction by local metalloproteinase and cytokine production. Diffuse, localized, and extra-articular subtypes have been described, with diffuse and localized forms affecting all or part of the contiguous synovium respectively, and the extra-articular subtype commonly causing tenosynovitis or bursitis. In extra-articular manifestations, nodular tendon lesions com- monly affect the extensor tendons of the wrist and—although painless—may restrict movement. Treatment is by surgical ex- cision, which allows histological confirmation of the diagnosis. Recurrence is rare. Diffuse and localized intra-articular lesions occur most com- monly as a monoarthritis of the knee, hip, or ankle of adult men aged between 20 and 50 years. Slow evolution of pain, swelling, and a gradual reduction in the range of movement can lead to diagnostic delay. Aspiration of serosanguineous fluid in the absence of trauma should raise the suspicion. MRI is the optimal imaging study, cap- able of demonstrating synovial proliferation in some cases. Intra-articular steroid administration gives only short-lived re- lief, and surgical excision is the treatment of choice. In the event of a recurrence (40% in diffuse cases), radioisotope synovectomy with Yttrium may be used. Joint replacement may be required in advanced cases. Primary synovial osteochondromatosis This is a rare condition with an incidence of 1 in 100 000, occurring most commonly in men between the ages of 30 and 50 years, in an otherwise normal joint. It is a benign neoplastic process involving subsynovial cartilage and synovial hyperplasia. The process leads to formation of hyaline cartilage chondromas, which may detach from the synovium and ossify, forming intra-articular loose bodies. Usually multiple calcified periarticular bodies are formed, ranging from 1 mm to 3 cm in size (Fig. 19.12.9). The condition can also be extra-articular, affecting bursae and tendon sheaths. Intra-articular disease is typically monoarticular, with the knee affected in 50% of cases, but other commonly affected sites include (a) (b) (c) Fig. 19.12.8 Smooth, reddish brown papules and nodules on the ear (a) and fingers (b, c) in multicentric reticulohistiocytosis. Reproduced from Burge S et al. (2016). Oxford Handbook of Medical Dermatology, 2nd edn, by permission of Oxford University Press.

19.12 Miscellaneous conditions presenting to the rheumatologist 4605 hip, shoulder, elbow, and ankle. The symptoms include joint pain, swelling, restricted range of motion, and locking suggestive of intra- articular loose bodies. The current treatment of choice is surgical synovectomy and removal of loose bodies. Malignant transform- ation to chondrosarcoma is rare. Charcot joint Charcot's osteoarthropathy is a deformity of the foot and ankle re- sulting from peripheral neuropathy (Figs. 19.12.10 and 19.12.11). Originally described by Charcot in tabes dorsalis, the most common cause today is diabetes mellitus type 1 and 2, occurring in type 1 diabetes most commonly in the fifth decade, and in type 2 the sixth decade. Leprosy is a frequent cause in endemic areas. Charcot joints commonly present with a unilateral, erythema- tous, swollen foot, with pain in only 30% at presentation and recent trauma reported by up to 53% of patients. There are five anatom- ical classifications, describing the clinical patterns and distribution of bones and joints affected (Table 19.12.4). Types 2 and 3 are most common; hindfoot involvement (Type 4 and 5) is associated with poorer prognosis. The natural progression of disease can be described in four stages. Stage 0 is characterized by inflammatory foot oedema and erythema with normal plain radiographs; stage I by bone dis- solution; stage II by bone coalescence; and stage III by bone re- modelling. In early disease (stage 0), MRI is the most sensitive imaging modality to detect changes such as soft tissue oedema, joint effusions, subchondral bone marrow oedema, and to exclude osteomyelitis. The mainstay of Charcot joint management is offloading with casting therapy, which has been shown to limit bone and joint destruction and reduce progression to deformity. Gradual and Fig. 19.12.9 Osteochondromatosis: lateral radiograph of the knee showing extensive periarticular chondral-type soft tissue calcifications (arrows) typical of synovial osteochondromatosis. Reproduced from Watts RA et al. (eds) (2013). Oxford Textbook of Rheumatology,
4th edn, by permission of Oxford University Press. Fig. 19.12.10 Charcot ankle joint. Reproduced from Jolly E et al. (eds) (2016). Training in Medicine, by permission of Oxford University Press.
Fig. 19.12.11 Charcot foot. There is marked disruption of the midfoot in this patient with diabetes. There is a divergent Lis Franc dislocation and fragmentation of the midfoot bones. Reproduced from Watts RA et al. (eds) (2013). Oxford Textbook of Rheumatology, 4th edn, by permission of Oxford University Press. Table 19.12.4 Anatomical subtypes of Charcot osteoarthropathy Subtype Joints/bones involved Type 1 Metatarsophalangeal and interphalangeal joints Type 2 Tarsometatarsal joints Type 3 Naviculocuneiform, talonavicular, and calcaneocuboid joints Type 4 Ankle and subtalar joints Type 5 Calcaneum

section 19 Rheumatological disorders 4606 smooth transition to footwear and rehabilitation to progressive weightbearing is important to prevent further damage. Evidence for bisphosphonate and calcitonin use is weak. They have been success- fully used to reduce bone turnover, but this does not appear to trans- late into improved clinical outcomes. Teriparatide use is currently being evaluated in a randomized controlled trial. Rheumatology and haematology Haemophilia Haemophilias are a group of X-linked recessive disorders, re- sulting in factor VIII deficiency in haemophilia A and factor IX in haemophilia B (Christmas disease). Haemarthrosis is the main musculoskeletal manifestation, occurring spontaneously in major forms (factor VIII levels <1% of normal), minor trauma in mod- erate forms (1–5% of normal) and major trauma in mild forms (>5% of normal). Symptoms of haemarthrosis include rapid swelling of the in- volved joint, usually preceded by tingling or burning and joint stiffness. It most commonly occurs in knees, ankles, and elbows. Presence of iron and haemosiderin deposition in synovium results in proliferation of synovial fibroblasts, neovascularization, and activation of inflammatory cytokines, leading to joint

damage. Prophylactic factor replacement between 2 and 18 years of age prevents disabling joint complications. Without this, acute haemarthroses begin from around five years of age. In acute haemarthrosis ultrasonography is useful to differen- tiate haemarthrosis from soft tissue or subperiosteal haemorrhage. Management of acute haemarhroses includes rest, ice, and immo- bilization, factor replacement, followed by joint aspiration in large, tense joint effusions. Synovial fluid should be sent for microscopy, culture, and sensitivity to exclude septic arthritis, the incidence of which is 40 times higher in haemophilia than the general popula- tion. After adequate factor replacement, physiotherapy aids restor- ation of normal range of motion and prevents joint contractures. Systemic or intraarticular steroid are not recommended. Analgesics including NSAIDs, COX-2 inhibitors, and opiates in severe cases are helpful to manage pain. Advanced haemophilic arthropathy may develop in severe cases requiring early joint replacement. In selected patients with trouble- some, recurrent haemarthrosis, synovectomy or angiographic em- bolization may be considered to prevent severe joint damage. Sickle cell disease Sickle cell disease encompasses a group of inherited haemo globinopathies characterized by abnormal β-globin chain produc- tion, resulting in structurally abnormal, sickled red blood cells. Musculoskeletal pain is very common as a consequence of self- limiting vaso-occlusive episodes, causing tissue ischaemia, which may manifest between six months and four years with sickle cell dactylitis or hand-foot syndrome, caused by infarction of diaphyses in the bones of the hands and feet. Avascular necrosis of the fem- oral head or humeral head can also occur in up to one-third of pa- tients, manifesting during painful vaso-occlusive crises affecting the epiphyses. Management of mild cases includes oral hydration and NSAIDs, with severe cases requiring intravenous fluids, NSAIDs, and opiate analgesia. Osteomyelitis is 100 times more prevalent than the general population due to a combination of medullary bone infarction, hyposplenism and impaired humoral immunity. This should be considered in the presence of bone pain or prolonged pain crises (>2 weeks) accompanied by fever. Frequently encountered organ- isms include Salmonella sp. and Staphylococcus aureus, typically affecting femoral, tibial, and humeral shafts. Septic arthritis may complicate up to 20% of cases of osteomyelitis. Hyperuricaemia occurs in up to 40% of patients and may result in clinical gout. Leukaemia Arthritis is common in leukaemia, particularly in childhood leu- kaemia. It occurs due to bone marrow and joint infiltration by leu- kaemic cells, and may lead to a misdiagnosis of juvenile idiopathic arthritis. Rarely, a frank inflammatory leukaemic arthritis can de- velop. Clinical patterns of arthritis include asymmetrical large joint oligoarthritis or distal, symmetrical polyarthritis. It is well recognized that musculoskeletal involvement may pre- cede the diagnosis of leukaemia by weeks to months, requiring a high index of suspicion and vigilance during treatment of the ini- tial arthritis. Diagnostic clues indicating leukaemia include a dis- proportionate amount of pain to clinical findings, nocturnal pain, fever, cytopenia, lytic lesions, and a poor response to NSAIDs and corticosteroids. Lymphoma Arthritis is an uncommon feature of lymphomas, but may be a presenting feature in non-Hodgkin’s lymphoma in absence of other symptoms. This can mimic rheumatoid arthritis with a small joint polyarthritis, and some patients are found to be rheumatoid factor and anticyclic citrullinated peptide antibody positive. Atypical lymphocytes are detectable in synovial fluid in up to 60%. POEMS POEMS refers to an uncommon disorder that may present to any specialty, depending on the dominant feature in the spectrum of polyneuropathy, organomegaly, endocrinopathy, M-protein (i.e. a monoclonal paraproteinaemia), and skin abnormalities. Papilloedema, extravascular volume overload (peripheral oedema, pleural effusion, ascites, pericardial effusion), sclerotic bone lesions, and thrombocytosis are also well recognized features. Neuropathy is the most common manifestation, classically a symmetrical sensorimotor demyelinating peripheral neuropathy. Osteosclerotic bone lesions occur in most

cases. Hepatomegaly is found in up to 78% and splenomegaly in up to 70%. Endocrine abnormalities include hypogonadism, thyroid disorders, diabetes mellitus, hyperprolactinaemia, and adrenal insufficiency. The paraprotein is almost exclusively a lambda monoclone. Skin changes may manifest as hyperpigmentation, new haemagioma formation, telangiectasia, flushing, thickening (which may resemble sclero- derma) and acryocyanosis. Serum vascular endothelial growth factor (VEGF) levels are markedly elevated in POEMS. Radiographs may show single or multiple osteosclerotic lesions with unusual patterns of proliferative change, both of which are unexpected in myeloma. Bone marrow bi- opsy demonstrates megakaryocyte hyperplasia and clustering, with

 two-thirds having plasma cell clonal expansion with lambda expres- sion in over 90%. Treatment is directed at the principal presenting features. The paraproteinaemia may require melphalan and corticosteroid. Serum levels of VEGF correlate with clinical course and response to therapy. Remission in POEMS has been reported after treatment with a VEGF-blocking monoclonal antibody, bevacizumab. Rheumatology and metabolic disorders Hereditary haemochromatosis This is a group of inherited iron storage disorders, most commonly involving autosomal recessive inheritance of a C282Y mutation, with the remaining 5% of cases involving a heterozygous C282Y/H63D mutation. 80% of patients develop a progressive, noninflammatory arthropathy, typically mimicking the distribution of calcium pyro- phosphate arthritis, with second and third metacarpophalangeal joints affected most frequently (Fig. 19.12.12). The proximal interphalangeal joints and wrists are also frequently affected, with shoulders, knees, ankles, elbows also involved. Nonspecific symptoms at onset including fatigue and abdominal pain lead to diagnostic delay. The classical radiographic features are those of calcium pyrophos- phate arthritis with hook-like osteophytes and chondrocalcinosis, which may be detectable in knee meniscal cartilage, the triangular ligament of the wrist, pubic symphysis, and spine. The joint disease is irreversible, with no impact from serum iron reduction following phlebotomy. NSAIDs, COX-2 inhibitors, colchicine, and intra- articular steroids give short-term relief. Wilson’s disease A rare genetic disorder of copper metabolism, Wilson’s disease typically presents between the second and third decades of life with three neurological presentations: a dystonic syndrome, an ataxic syndrome, or a Parkinsonian syndrome. Most patients pre- senting with neurological symptoms have asymptomatic liver disease. Musculoskeletal involvement is present in two-thirds of patients, and typically manifests as development of early degen- erative arthritis due to copper deposition in the synovium or sec- ondary chondrocalcinosis. Hypermobility and osteopenia are also frequently reported. Characteristic radiological features include fluffy periostitis at the greater trochanter and inferior aspect of the calcaneus, and cor- ticated ossicles near affected joints. Diagnosis requires measuring urinary 24 hour copper excretion, serum caeruloplasmin, slit lamp examination for Kayser-Fleischer rings (present in 98% of patients with neurological disease), and genetic testing for ATP7B mutations. Treatment includes using copper chelators penicillamine or trientine, which increase copper excretion. These can be used in combination with zinc which inhibits intestinal copper absorption. Disorders of the spine and axial skeleton Tietze’s syndrome Tietze’s syndrome is a rare benign condition, also known as chondropathia tuberosa, affecting middle-aged men and women, characterized by anterior chest pain associated with focal tender- ness and swelling over the second or third sternocostal joint. Pain is typically exacerbated by coughing and deep inspiration. It is differ- entiated from costochondritis by the presence of swelling. Tietze’s syndrome is a diagnosis of exclusion, and imaging must be performed to exclude serious underlying pathology. Plain radio- graphs are

insufficient to assess the sternocostal joint, even on ob- lique views, due to the overlying structures. A combination of CT and MRI imaging helps identify serious differentials such as osteo- myelitis and bone tumours, including primary chondrosarcomas and metastases from bronchogenic or breast carcinoma. Anterior chest wall pain is present in up to one-third of patients (of which a proportion have swelling) with early seronegative spondyloarthropathy and may predate onset of spinal pain and stiff- ness. Rarer conditions such as SAPHO should be considered in cases of multiple swellings and presence of hyperostosis and osteitis on imaging (see next section). Tietze's is commonly self-limiting, requiring symptomatic treat- ment with NSAIDs, but in some cases the condition may last for years, when local injection with lidocaine or corticosteroid may pro- vide symptomatic relief. Diffuse idiopathic skeletal hyperostosis Diffuse idiopathic skeletal hyperostosis (DISH) is an idiopathic condition which is commonly asymptomatic, twice as common in males, and has increasing prevalence with age. It is characterized by ossification of ligaments and entheses in the axial skeleton and peripheral sites. The spine is principally affected, leading to bony bridges (entheso phytes) between adjacent verterbrae, most commonly in the lower thoracic and upper lumbar verterbrae. Cervical spine involvement is well described and can lead to large osteophytes capable of causing dysphagia and airway obstruction requiring surgery. Spinal symp- toms include pain and restriction, which may mimic seronegative spondyloarthropathy. Fig. 19.12.12 Iron fist sign in hereditary haemochromatosis. Contrast the normal clenched fist on the left with the abnormal fist on the right, caused by arthritis of the second and third metacarpophalangeal joints. Reproduced from Watts RA et al. (eds) (2013). Oxford Textbook of Rheumatology, 4th edn, by permission of Oxford University Press.

 Peripheral ossification can also occur in peripheral joints, ligaments and entheses, including the shoulder, elbow, knee, metacarpophalangeal joints, and calcaneus. Phalangeal tufting and an increase in the cortical thickness of the tubular bones of the hand is recognized. Articular osteophytes are classically para-articular and distinguishable from osteoarthritic osteophytes. Classical radiographic changes include ossification of the anterior longitudinal ligament, visible as ossifications on lateral radiographs, likened to 'flowing candle wax'. There is preservation of the vertebral cartilage and vertebral disc height (Fig. 19.12.13). Diffuse idiopathic skeletal hyperostosis is distinguishable from ankylosing spondylitis by the age of the patient at symptom onset, by typical radiographic features (Table 19.12.5), and the lack of as- sociation with HLA-B27. There is no specific treatment for diffuse idiopathic skeletal hyperostosis. The natural history is similar to ankylosing spondylitis in terms of progression, reaching advanced disease after ten years. Treatment strategies are similar to those for osteoarthritis, including physiotherapy, topical NSAIDs, and analgesia. Corticosteroid injec- tion can be considered for painful peripheral entheseal involvement. Diffuse idiopathic skeletal hyperostosis is associated with obesity, dyslipidaemia, hypertension, impaired glucose tolerance, hyperuricaemia, and hyperinsulinaemia, hence management in- cludes testing for these known metabolic associations and instigating secondary prevention measures. Alkaptonuria Alkaptonuria is a Mendelian autosomal recessive disorder resulting from absence of homogentisate 1,2 dioxygenase, which is important in the metabolism of phenylalanine, leading to accumulation of homogentisic acid in tissues. It is rare worldwide with an estimated prevalence of 1 in 250 000–1 000 000, but it is more common in the Dominican Republic, India, Jordan and most prevalent in Slovakia (1 in 19 000). Deposition of homogentisic acid occurs in bone, joints, ten- dons, cartilage and heart valves, and accumulation in urine leads to dark urine, which turns to black on standing. Although urine discolouration is evident from birth, its significance is rarely rec- ognized, leading to delay in

diagnosis until on average the fourth decade, when patients typically present with musculoskeletal prob- lems including spinal deformity, presenting with back pain and restriction due to the development of ochronosis (darkening of con- nective tissue, from homogentisic acid deposition) and ochronotic osteoarthropathy. A large joint inflammatory arthritis affecting knees, shoulder, hips, elbows, and ankles occurs later in the disease process. Classical physical signs include evidence of homogentisic acid in tissues, which manifests as black, blue, or yellow pigmen- tation of ear cartilage and sclera. Valvular heart disease and renal stones are late complications. In those affected, homogentisic acid is measureable in urine, which is absent in healthy individuals. Radiographic features in- clude chondocalcinosis of intervertebral discs, ossification of liga- ments, and osteoporotic verterbral fractures. Although there is no cure, treatments can be targeted towards reducing the accumulation of homogentisic acid and its metabol- ites, including treatment with Vitamin C and Nitisone. Drug-induced rheumatic syndromes Statin-induced myopathy Statin-induced myopathy encompasses a spectrum of clinical prob- lems including asymptomatic rise in serum creatine kinase, myalgia, myositis, and rhabdomyolysis. In the United Kingdom, the inci- dence of statin-induced myopathy is 1.2 per 10 000 person-years, with incidence of rhabdomyolysis with simvastatin, atorvastatin, or pravastatin monotherapy 0.44 per 10 000 person-years. Symptoms include muscle aches, cramps, tenderness, or weak- ness, which usually develop after taking statins for six months and persist after withdrawal of the drug for an average of 2.3 months. Rarely, patients can have persistent myotoxicity after withdrawal of Fig. 19.12.13 Diffuse idiopathic skeletal hyperostosis. This lateral view of the lumbar spine reveals the classic flowing mature ossification of the anterior longitudinal ligament. Note the preservation of disc spaces. Reproduced from Watts RA et al. (eds) (2013). Oxford Textbook of Rheumatology, 4th edn, by permission of Oxford University Press. Table 19.12.5 Factors differentiating diffuse idiopathic skeletal hyperostosis from established ankylosing spondylitis Diffuse idiopathic skeletal hyperostosis Ankylosing spondylitis (Established disease) • Elderly males • Male 20–30 yrs • HLA-B27 negative • HLA-B27 80–85% • Anterior longitudinal ligament ossification—‘flowing candle wax’ • Romanus lesions—‘shiny corners’ • Squaring vertebral bodies • Preserved disc space • Disc space ossification • No sacroiliac joint abnormality • Bilateral sacroiliac abnormality (narrowing, sclerosis, erosion, fusion) • Nonmarginal osteophytes • Marginal osteophytes • Preserved facet joints • Facet joint erosion

 the statin, which raises the possibility of anti-HMG-CoA reductase associated immune-mediated necrotizing myopathy, which often requires immunosuppressive treatment. Risk factors that have been linked to development of statin- induced myopathy include female gender, advanced age, multiple comorbidities, impaired renal or liver function, and alcohol ex- cess. Untreated hypothyroidism, hyperthyroidism, hyperpara- thyroidism and vitamin D deficiency are known to cause myalgia and mildly elevated creatine kinase and need to be excluded. Important drug interactions with ciclosporin, amiodarone, macrolide antibiotics, and warfarin should be considered, which can cause elevated statin levels and myotoxicity by P450 cyto- chrome inhibition. It is recommended that hydrophilic statins (pravastatin, rosuvastatin and fluvastatin) are used in patients with existing muscle disease, rather than lipophilic statins (simvastatin, atorvastatin, lovastatin) which are more likely to penetrate muscle and produce myopathy. If serum creatine kinase is more than ten times the upper limit of normal, assessment of renal function, urine myoglobin, and urine output should be performed urgently to confirm or refute presence of rhabdomyolysis. If muscle symptoms and elevated creatine kinase persist despite withdrawal of the statin, or if muscle weakness pre- dominates,

further assessment is needed to exclude primary muscle disease or autoimmune myopathy, including serology, electromyog- raphy, and muscle biopsy. Drug-induced tendinopathy Drug-induced tendinopathy is caused by four main classes of drug: quinolones, statins, systemic glucocorticoids, and aromatase inhibitors. The most common site is the Achilles tendon, often presenting with abrupt onset localized pain, with warmth erythema and swelling. A positive Thompson's test (absent plantarflexion on squeezing the calf) identifies tendon rupture, which can be con- firmed by ultrasound or MRI imaging. The incidence of quinolone tendinopathy is estimated to be 0.5–2% of quinolone prescriptions. 90% of lesions effect the Achilles tendon (resulting in rupture in 41% of cases), with the remaining 10% of cases involving the rotator cuff, extensor tendons of the wrist, finger and thumb flexors, or quadricipital tendons. Risk factors in- clude age above 60 years, renal impairment, and concomitant gluco- corticoid treatment. Statin tendinopathy usually causes unilateral Achilles tendino pathy, of which one-third result in tendon rupture. Risk factors include advanced age and concomitant quinolone therapy. Systemic glucocorticoids may also result in Achilles, patellar, or quadricipital tendon rupture, which may be seen after just four months treatment, although thought to be a consequence of longer- term treatment affecting collagen integrity. Local steroid injections for the management of tenosynovitis can result in tendon rupture, although this is rare, occurring in only 0.1% of injections. Decreased collagen tensile strength in animal models after local injection sup- ports the recommendation of rest and avoidance of excess load bearing after a local injection. Aromatase inhibitors are capable of producing small joint syno- vitis and tenosynovitis of the wrist and hands, including both trigger finger and De Quervain's tenosynovitis, which may occur after just two weeks of treatment. Management includes withdrawal of the offending drug. In cases of Achilles tendinopathy without rupture, initial offloading may be achieved by activity modification and orthotic heel inserts. This should be followed by early physiotherapy guided rehabilitation, including eccentric exercises. Tendon rupture requires orthopaedic management, which may well be conservative in the first instance, with surgery reserved for isolated cases. Drug-induced lupus Drug-induced lupus is a well-recognized phenomenon reported in the treatment with over 80 different medications (Table 19.12.6). Securing the diagnosis is challenging, as there are many shared symptoms, signs, and laboratory parameters with idiopathic sys- temic lupus erythematosus. The risk of developing drug-induced lupus varies with drug, estimated to be less than 1% with most known associated medications, increasing to 5–8% with hydralazine and up to 20% per year with procainamide treatment. In contrast to idiopathic systemic lupus erythematosus, drug- induced lupus occurs more frequently in older patients, reflecting increased medication use in this population. The most common manifestations include serositis, fever, myalgia, and arthritis. Cutaneous involvement is atypical in drug-induced lupus, in con- trast to malar rash, discoid rash, photosensitivity, alopecia, and oral ulcers frequently encountered in idiopathic systemic lupus erythematosus. ANA antibodies are usually positive in drug-induced lupus, antihistone antibodies in more than 95%, but anti-dsDNA anti- bodies in less than 5%. In patients with drug-induced lupus and anti- dsDNA antibodies, the crithidia assay may be positive due to cross reactivity with antihistone antibodies. However, the presence of antihistone antibodies in drug-induced lupus is not a differentiating feature, as they are also present in up to 75% of cases of idiopathic systemic lupus erythematosus. More recently, the anti-TNF drugs infliximab, adalimumab and etanercept have also been shown to cause drug-induced Table 19.12.6 Medications reported to cause drug-induced lupus Commonly cause
drug-induced lupus • Procainamide • Hydralazine Less common causes Antibiotics • Isoniazid • Minocycline Anticonvulsants • Phenytoin, carbamazepine Antirheumatic drugs • Anti-

TNF—infliximab, etanercept, adalimumab • Sulfasalazine • Penicillamine Cardiac drugs • Statins—simvastatin, lovastatin • β-blockers—propranolol, atenolol, metoprolol • Methyldopa • Hydrochlorthiazide • Quinidine Antipsychotics • Chlorpromazine

section 19 Rheumatological disorders 4610 lupus, with a phenotype more similar to idiopathic systemic lupus erythematosus than ‘classical drug-induced lupus’ (Table 19.12.7). It is thought that some of these cases may represent ‘unmasking’ of idiopathic systemic lupus erythematosus by anti-TNF therapy, and some cases of drug-induced autoimmunity. This phenom- enon is rare, however, with 0.2–0.4% of patients receiving anti- TNF treatment estimated to develop symptoms consistent with drug-induced lupus. Management for all drug-induced lupus involves withdrawal of the drug. Symptoms gradually improve over weeks. NSAIDs can be used to manage arthralgia. Corticosteroids are used in more severe manifestations, but are not required long term. Allopurinol hypersensitivity Allopurinol hypersensitivity is rare, with the incidence of severe cutaneous adverse reactions of 0.69 per 1000 person-years, but im- portant to recognize due to the severity of cutaneous manifestations that can result and the significant mortality (9–20%). Manifestations of allopurinol hypersensitivity include maculopapular eruptions, Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and allopurinol hypersensitivity syndrome. Allopurinol hypersensitivity syndrome is characterized by rash (including TEN, erythema multiforme, diffuse maculopapular or exfoliative dermatitis), eosinophilia, leucocytosis, fever, acute hepatocellular injury, and progressive renal failure. It typ- ically develops a month after allopurinol initiation, with most cases manifesting in the first six months of treatment. Risk fac- tors include higher starting dose, baseline renal impairment, concomitant diuretics and presence of HLA-B*58:01 allele, which is more prevalent in Asian populations. It is likely that all these factors contribute to sustained accumulation of the metabolite of allopurinol, oxypurinol, pre-disposing to development of allopur- inol hypersensitivity. The current recommendations to avoid adverse events with allo- purinol treatment include a maximum starting dose of 100 mg daily (reduced to 50 mg in patients with creatine kinased stage 4 = eGFR 15–30 ml/min/1.73 m2), careful monitoring of renal function after initiation and dose escalation to allow early detection of renal im- pairment, prompt dose reduction, and consideration of alternative urate lowering drugs. Miscellaneous infections Whipple’s disease Whipple’s disease, caused by Tropheryma whipplei, classically pre- sents in middle-aged men with a prodromal arthritis, before devel- opment of abdominal pain, diarrhoea, and weight loss. An acute or subacute migratory polyarthritis may precede bowel symptoms by years, and typically involves the ankles, knees, shoulders, and el- bows. However, a symmetrical small joint polyarthritis can mimic rheumatoid arthritis, leading to immunosuppressive treatment. Several cases have been reported where escalation to anti-TNF treat- ment has revealed bowel symptoms leading to the diagnosis, and the development of significant gastrointestinal symptoms during initiation of immunosuppression and poor response to treatment should prompt consideration of the diagnosis. The polymerase chain

Table 19.12.7 Differentiating features between classical drug-induced lupus, idiopathic systemic lupus erythematosus, and anti-TNF-associated drug-induced lupus

	Classical drug-induced lupus	Anti-TNF-associated drug-induced lupus	Idiopathic systemic lupus erythematosus
Demographics			
Mean age at onset	50–70 yrs	50 yrs	20–30 yrs
Gender distribution	Female = male	Female 5:1 Male	Female 9:1 Male
Clinical presentation			
Rash/cutaneous involvement	<5%	67–73%	54–70%
Arthritis	20%	31–52%	83%
Glomerulonephritis	<5%	7–9%	34%
Serositis	50%	12–18%	28%
Neuropsychiatric	<5%	3%	12%
Fever/constitutional	45%	23%	42%
Laboratory abnormalities			
ANA			

> 99% 79–100% 99% Crithidia ‘False positive’ due to antihistone antibodies – Positive Anti-DsDNA abs <5% 72–92% 50–70% Antihistone abs 95% 17–57% 75% Low complement <1% 59% 50% Leukopenia 15% 14% 56% Thrombocytopenia <5% 6% 31%

19.12 Miscellaneous conditions presenting to the rheumatologist 4611 reaction can detect bacteria in stool and saliva cultures, but duo- denal biopsy showing periodic acid–Schiff-staining macrophages is diagnostic. Treatment requires a long course of antibiotics, between one and two years’ duration. Chikungunya Chikungunya (‘to walk bent over’ in Kimakonde language) is a single stranded RNA alphavirus transmitted by Aedes mosquitos. Originally isolated in Tanzania, global expansion of disease has led to increasing cases in Africa, spread to Southeast Asia, the Pacific Islands, Europe, the Caribbean, northern South America, and the United States of America. Chikungunya presents with an acute phase of fever, severe arth- ralgia, myalgia, headache, and a maculopapular rash, which usually resolves within 14 days. Diagnosis is made by detection of chi- kungunya RNA by RT-PCR in the acute phase (days 0–7 post in- fection), with ELISA for IgM and IgG antibodies detectable in the subacute (days 7–14) and chronic phases of illness (day 14 onwards). Leukopenia (both lymphopenia and neutropenia), thrombocyto- penia, increased aminotransferases, and increased LDH may be present. Incapacitating arthralgia is found in 99% of patients in the acute phase of chikungunya, which usually develops within minutes to hours of a prodromal fever. After resolution of fever, headache, rash and myalgia, arthralgia may persist for up to several years, or re-emerge during the chronic phase. The arthritis may commonly mimic and even fulfil EULAR/ACR 2010 criteria for rheumatoid arthritis (with negative anticyclic citrullinated peptide and rheuma- toid factor antibodies), with a symmetrical small joint polyarthritis, capable of causing erosive damage in a minority. Involvement of the knees, hips, elbows, sternoclavicular, temporomandibular joints, and tenosynovitis have also been reported. There is no effective antiviral treatment. Initial treatment is supportive with rest and NSAIDs. In persistent inflammatory arthritis mimicking rheumatoid arthritis, a combination of intra- articular and oral steroids, disease-modifying antirheumatic drugs including methotrexate, sulfasalazine, and hydroxychloroquine have been used. FURTHER READING Gillmore JD, Hawkins PN (2013). Pathophysiology and treatment of systemic amyloidosis. Nat Rev Nephrol, 9, 574–86. Islam AD, et al. (2013). Multicentric reticulohistiocytosis: a rare yet challenging disease. Clin Rev Allergy Immunol, 45, 281–9. Kadavath S, Efthimiou P (2015). Adult-onset Still’s disease- pathogenesis, clinical manifestations, and new treatment options. Ann Med, 47, 6–14. Katz U, Zandman-Goddard G (2010). Drug-induced lupus: an update. Autoimmun Rev, 10, 46–50. Kirchgesner T, et al. (2014). Drug-induced tendinopathy: from physi- ology to clinical applications. Joint Bone Spine, 81, 485–92. Mader R, Verlaan JJ, Buskila D (2013). Diffuse idiopathic skeletal hyperostosis: clinical features and pathogenic mechanisms. Nat Rev Rheumatol, 9, 741–50. Manger B, Schett G (2014). Paraneoplastic syndromes in rheuma- tology. Nat Rev Rheumatol, 10, 662–70. Morais SA, et al. (2016). Musculoskeletal complications of haemato- logical disease. Rheumatology (Oxford), 55, 968–81. Perfetto F, et al. (2010). Systemic amyloidosis: a challenge for the rheumatologist. Nat Rev Rheumatol, 6, 417–29. Petrova NL, Edmonds ME (2013). Medical management of Charcot arthropathy. Diabetes Obes Metab, 15, 193–7. Phornphutkul C, et al. (2002). Natural history of alkaptonuria. N Engl J Med, 347, 2111–21. Puechal X (2013). Whipple’s disease. Ann Rheum Dis, 72, 797–803. Salles M, et al. (2011). The SAPHO syndrome: a clinical and imaging study. Clin Rheumatol, 30, 245–9. Sathasivam

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