19.2 Clinical presentation and diagnosis of rheuma

19.2 Clinical presentation and diagnosis of rheumatological disorders 4386 Christopher Deighton and Fiona Pearce

ESSENTIALS Most rheumatological diagnoses are made through effective history taking and physical examination rather than investigation. Systemic symptoms, such as weight loss, anorexia, and fever, point to systemic diseases such as rheumatoid arthritis, other polyarthritides, systemic lupus erythematosus, polymyalgia, and vasculitides. Swelling of joints is a symptom commonly reported by patients with no objective evidence of this on examination. Inflammatory arthropathies should not be diagnosed unless the physician is able to identify objective swelling, if necessary by arran- ging a prompt review during an active episode. Diagnostic criteria for the systemic rheumatic diseases are useful in directing the history taking to verify a suspected diagnosis. Investigations are best used to confirm a strongly suspected diag- nosis, already made on the basis of history and examination, not as a screening tool for rheumatic disease. What are rheumatological disorders? Rheumatological disorders include arthritis and other conditions where musculoskeletal symptoms and signs are prominent. They include inflammatory arthritis and other systemic autoimmune dis- orders (connective tissue diseases and vasculitis) as well as soft tissue conditions, osteoarthritis, and spinal pain. Many rheumatology de- partments also provide expertise in metabolic bone disease. All to- gether rheumatological disorders incorporate over 200 conditions affecting joints, bones, muscles, and soft tissues. A significant pro- portion of these also affect other organ systems directly (e.g. glom- erulonephritis in vasculitis) or indirectly (e.g.

cardiovascular disease in rheumatoid arthritis). How do rheumatological disorders present? Most patients presenting with rheumatological disorders present with pain, but occasionally other symptoms suggest underlying auto- immune rheumatic disorders (e.g. Raynaud's phenomenon). A chief task in the history is to determine whether the pain that the person presents with is inflammatory, mechanical, or sinister. To deal with the latter category first, it is important that patients with significant systemic symptoms and musculoskeletal pain have a history taken carefully, thorough general medical examination, and appropriate investigations. Life-threatening disease such as infection and malig- nancy can present with musculoskeletal symptoms, and this needs to be considered primarily. A good example is back pain, where 'red flag' signs should alert the clinician to the possibility of infection or malignancy until proven otherwise (Table 19.2.1). Similar prin- ciples can be applied to limb musculoskeletal symptoms. Once sinister disease has been considered and seems unlikely or preferably excluded, the authors consider it is helpful to categorize 19.2 Clinical presentation and diagnosis of rheumatological disorders Christopher Deighton and Fiona Pearce Table 19.2.1 Red flags for back pain Features • Previous history of malignancy (however long ago) • Age <16 or >50 with NEW onset pain • Weight loss (unexplained) • Previous or current longstanding steroid use • Recent serious illness • Recent significant infection Signs • Saddle anaesthesia • Reduced anal tone • Hip or knee weakness • Generalized neurological deficit • Progressive spinal deformity • Urinary retention Symptoms • Nonmechanical pain (worse at rest) • Thoracic pain • Fevers/rigors • General malaise • Urinary retention

19.2 Clinical presentation and diagnosis of rheumatological disorders 4387 rheumatological disorders into four main groups: inflamma- tory arthritis; autoimmune rheumatic diseases and vasculitis; noninflammatory musculoskeletal pain and pain syndromes; and bone disease (Table 19.2.2). A general approach in the history Key considerations in the history of a patient with musculoskeletal pain that influence the differential diagnosis are: • How many joints or regions are affected? Is it a monoarthritis, oligoarthritis (two to four joints), or a polyarthritis? Is it periarticular (structures around joints but not in them)? Are there any axial symptoms? • How quickly did it come on? Was it acute, or insidious, or waxing and waning? • Is there anything to suggest ■ Any sinister features? ■ Inflammatory features? ■ Multisystem autoimmune disease (Table 19.2.3)? ■ Other local or general musculoskeletal disorders? ■ Bone disease? • Are there any other clues on systematic enquiry (e.g. recent gastroenteritis, psoriasis, iritis, and so on?) (Table 19.2.3) Table 19.2.2 A clinical classification of rheumatological disorders Inflammatory arthritis — Rheumatoid arthritis — Spondyloarthropathies: ankylosing spondylitis, psoriatic arthritis, reactive arthritis, enteropathic arthritis — Juvenile idiopathic arthritis (JIA) — Crystal arthropathies: gout, pseudogout — Septic arthritis Multisystem autoimmune rheumatic disease — Systemic lupus erythematosus — Sjögren's syndrome — Scleroderma (systemic sclerosis) — Polymyositis — Dermatomyositis — Polymyalgia rheumatica — Mixed connective tissue disease — Polychondritis — Sarcoidosis — Vasculitis: Granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), Microscopic Polyangiitis, Eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg-Strauss syndrome), Polyarteritis nodosa, IgA nephropathy (formerly known as Henoch–Schönlein purpura), Takayasu's arteritis, Behçet's syndrome, Kawasaki's disease (mucocutaneous lymph node syndrome), Buerger's disease (thromboangiitis obliterans) Noninflammatory musculoskeletal pain and pain syndromes — Local (diseases affecting the joints and structures around the joints including tendons, ligaments capsules, bursae, stress fractures, muscles, nerve entrapment, vascular lesions, and ganglia). For example: — Low back pain — Tennis elbow — Plantar fasciitis — Olecranon bursitis — General — Osteoarthritis — Fibromyalgia

and regional pain syndromes Bone disease — Osteoporosis — Osteomalacia — Paget’s disease — Rare metabolic bone disorders Table 19.2.3 Extra-articular manifestations of rheumatological disorders Clinical feature Causes Mucocutaneous Photosensitivity Raynaud’s phenomenon Mouth ulcers Subcutaneous nodules Erythema nodosum Nail dystrophy Cutaneous vasculitis Systemic lupus erythematosus (SLE), dermatomyositis, Sjögren’s syndrome SLE, scleroderma, dermatomyositis SLE, Behçet’s syndrome, spondyloarthropathies (particularly reactive arthritis and IBD-related) Rheumatoid arthritis (RA), tophaceous gout, acute rheumatic fever Sarcoidosis, Behçet’s syndrome, spondyloarthropathies, SLE Spondyloarthropathies (particularly psoriatic arthritis, and reactive arthritis) Systemic vasculitis, SLE, RA, dermatomyositis, Behçet’s syndrome Ocular Keratoconjunctivitis sicca Conjunctivitis Scleritis Uveitis Retinal vasculitis Primary: Sjögren’s syndrome. Secondary: RA, SLE, scleroderma Spondyloarthropathies (particularly reactive arthritis) RA, Granulomatosis with polyangiitis Spondyloarthropathies (particularly ankylosing spondylitis and IBD-related), juvenile idiopathic arthritis, Behçet’s syndrome, sarcoidosis SLE, Behçet’s syndrome Renal Acute kidney injury Glomerulonephritis Renal calculi Scleroderma (renal crisis), SLE, systemic vasculitis SLE, ANCA-associated vasculitis Gout Pulmonary Serositis (pleuritis, pericarditis, peritonitis) Interstitial lung disease Nodules Pulmonary hypertension SLE, systemic juvenile arthritis (Still’s disease), rheumatoid arthritis, acute rheumatic fever Scleroderma, antisynthetase syndrome (myositis), SLE, RA Sarcoidosis, RA, granulomatosis with polyangiitis Scleroderma, SLE Cardiac Valvular heart disease (mitral regurgitation, aortic regurgitation) Myocarditis Acute rheumatic fever, Ankylosing spondylitis, RA, SLE, reactive arthritis, systemic vasculitis, scleroderma, sarcoidosis SLE, mixed connective tissue disease, scleroderma Neurological Mononeuritis multiplex Stroke Systemic vasculitis, RA, SLE Antiphospholipid syndrome, Behçet’s syndrome, Takayasu’s arteritis ANCA, antineutrophil cytoplasmic antibody; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus;

 There are some typical patterns that suggest a likely diagnosis; for example, acute monoarthritis in a systemically unwell 17-year- old woman with a vaginal discharge returning from a holiday in Majorca (gonococcal septic arthritis); a 54-year-old publican with a red hot swollen big toe (gout); insidious onset of symmetrical peripheral joint inflammation in a 63-year-old woman (rheuma- toid arthritis); recent onset of severe Raynaud’s phenomenon with arthralgias, myalgias, pleurisy, and a rash on sun exposure (sys- temic lupus erythematosus). However, most patients do not fit into straightforward caricatures, and the diagnosis is determined by using traditional medical skills in history and examination findings, and may then be confirmed on blood tests, aspirates, imaging, or biopsies. Suggested initial screening tests and some diagnostic tips are included in Tables 19.2.4 and 19.2.5. Inflammatory arthritis
A common challenge in a patient with arthralgias is whether the patient has inflammatory or noninflammatory joint symptoms. Features of inflammatory versus noninflammatory symptoms (e.g. osteoarthritis) are listed in Table 19.2.6. The examination finding of synovitis may be difficult to elicit, and may not be present in all types of inflammatory arthritis (e.g. enthesitis-related arth- ritis) and ultrasound or MRI imaging can be helpful in equivocal cases. Once an inflammatory arthritis is suspected, the number and pattern of joint involvement, along with presence or absence of extra-articular features, suggests likely diagnoses (see Figs. 19.2.1 and 19.2.2). These are considered next. Monoarthritis Monoarthritis is septic arthritis until proven otherwise. A history and examination must be followed by joint aspiration, and certainly before commencing empirical antibiotics. Analysis of the joint fluid suggests likely causes (Table 19.2.7), but these are a guide only and septic arthritis may occur with ‘normal’ or ‘inflammatory’-looking Table 19.2.4

Screening tests In all cases consider Acute polyarthritis Chronic polyarthritis Diffuse arthralgias/ myalgias FBC, ESR Blood cultures TSH CRP ASOT Uric acid Creatinine kinase Rheumatoid factor (RF) Parvovirus B-
19 IgG & IgM Urinalysis U&E, calcium, phosphate, glucose, Anti-CCP (if RF negative) Hepatitis B TSH Vitamin D ANA, HIV Serum and urine protein electrophoresis Rubella ACE, CXR ANCA ANA, antinuclear antibody; Anti-CCP, anticitrullinated peptide; ASOT, antistreptolysin O titre; ACE, angiotensin converting enzyme; ANCA, antineutrophil cytoplasmic antibody; TSH, thyroid-stimulating hormone Table 19.2.5 What to look for: diagnostic tips Rheumatoid arthritis (RA) Spondyloarthropathies (e.g. reactive and psoriatic arthritis) Gout Connective tissue disease Osteoarthritis (OA) Fibromyalgia Polymyalgia rheumatica Onset Usually subacute or acute Acute/subacute/ chronic Usually Acute Subacute Chronic Chronic Usually within a few weeks Typical age and gender Female: male 3:1 Any age Any age Female: male
1:3 Very rare in pre- menopausal women Female: male 10:1 Typically pre- menopausal Hand OA more common in females Usually age ≥45 Female:male 7:1 Age 30–50 Female:male 2:1 Pattern of joint involvement Usually symmetrical hands and feet Can be monoarthritis or asymmetrical oligo/ polyarthritis Monoarthritis most commonly—1st metatarsophalangeal joints, ankle, or knee Can be symmetrical Any, may be flitting Hands, knees, hip, and feet most common Widespread Usually shoulder and pelvic girdle Other clues 15–30% of patients are rheumatoid factor negative—this does not exclude the diagnosis May be associated with inflammatory back pain, Psoriasis, Inflammatory bowel disease or Uveitis Risk factors: diuretic treatment, obesity, alcohol Raynaud’s phenomenon, mouth ulcers, rashes (butterfly or vasculitic), Systemic features, Pleuritic chest pain Heberden’s or Bouchard’s nodes Crepitus Poor quality of sleep Tender soft- tissue ‘trigger points’ on examination Multiple symptoms Overlap with temporal arteritis—ask about headache, visual symptoms and jaw claudication Table 19.2.6 Features of inflammatory versus noninflammatory arthralgias Favours noninflammatory disease Favours inflammatory disease Pain after activity/at end of day Pain worse after rest and on waking in the morning Morning stiffness for <30 minutes Morning stiffness for >30 minutes No night-time pain Night-time paina No systemic symptoms Systemic symptoms presenta Chronic symptoms Acute/subacute presentation a Night pain and systemic symptoms indicate other serious pathology including cancer, or infection (see above).

 joint fluid, and gram stain and culture are essential. For example, patients who are on steroids or who are immunocompromized may not mount an inflammatory response and have synovial fluid that looks benign but is infected. It is common for those with a septic joint to have fever, neutrophilia, and raised inflammatory markers. But as with joint fluid that appears unremarkable, it is also possible for these features to be completely normal in patients who are on steroids or immunocompromized, or on biological therapies such as anti-TNF or tocilizumab. Septic arthritis is more common in abnormal joints, and is usually spread haematologically. Bear in mind that prosthetic joints may have no signs (only symptoms), and are more prone to infection than native joints. Staphylococcus and Streptococcus are the most common or- ganisms, but atypical organisms should be covered in certain groups (e.g. sickle cell—salmonella; intravenous drug abusers—gram nega- tive or fungal organisms). Gout typically has an acute onset over hours, and a natural history of resolution over three to four days in early attacks. Pyrophosphate can come on more insidiously and last longer. The joint may be very erythematous and hot, as well as swollen, and the appearance may be confused with cellulitis. The key differentiator between intra-articular inflammation and cellulitis is the global painful loss of movement in the affected joint. Joint fluid

viewed under polarized light microscopy shows needle shaped negatively birefringent monosodium urate crystals in gout, and rhomboid weakly positively birefringent crys- tals in pseudogout (acute calcium pyrophosphate arthritis). Oligoarthritis (2–4 joints) and spondyloarthritis An oligoarthritis is most commonly one of the spondyloarthro pathies (SpA) which include ankylosing spondylitis and psoriatic arthritis. These conditions (Table 19.2.8) share several common features which are set out in Table 19.2.9. Clinically, SpA should be suspected whenever a young patient (<40 years) presents, with inflammatory low back pain, and/or asymmetrical involvement of knees or ankles. These may be associated with psoriasis, uve- itis, inflammatory bowel disease, and recent gastroenteritis or urethritis. Polyarthritis (five or more joints) Rheumatoid arthritis Rheumatoid arthritis (RA) should be considered in patients pre- senting with symmetrical, inflammatory, polyarthritis affecting the hand joints. The longer the duration of symptoms, the more likely it is to be rheumatoid arthritis. Key points are as follows: • Rheumatoid arthritis is a diagnosis that can confidently be made on clinical grounds. Only 70–85% of patients are rheuma- toid factor seropositive. Rheumatoid arthritis is typically sym- metrical: asymmetrical or unilateral involvement should arouse suspicion of other arthritides such as psoriatic or other spondyloarthropathy. • Do not diagnose rheumatoid arthritis unless hands are involved. Distal interphalangeal joint involvement is uncommon in rheuma- toid arthritis. If distal interphalangeal joints are involved, suspect psoriatic arthropathy, scleroderma, or osteoarthritis. • The lumbar spine is not involved in rheumatoid arthritis. The pres- ence of inflammatory low backache with mono or oligoarticular involvement, especially in lower limbs, should arouse suspicion of a spondyloarthropathy. Table 19.2.7 Analysis of joint fluid Normal Non- inflammatory Inflammatory Septic Haemorrhagic Colour Clear Yellow Yellow to opalescent Yellow- green Red White blood cells/mm3 <200 200–2000 2000–75 000

> 50 000 Similar to blood level Neutrophils (%) <25 <25 50–70 70 Similar to blood level Viscosity Normal Normal Decreased Decreased Decreased Table 19.2.8 Spondyloarthropathies (SpA) • Ankylosing spondylitis • Reactive arthritis • Psoriatic arthritis • Inflammatory bowel disease related (Enteropathic spondyloarthropathy) Joint pain Noninflammatory Inflammatory Monoarthritis Oliogoarthritis Polyarthritis Septic arthritis Crystal arthritis Haemarthrosis Spondyloarthritis Psoriatic arthritis Enteropathy arthritis Crystal arthritis Acute sarcoid Rheumatoid arthritis Psoriatic arthritis SLE or other CTD Fig. 19.2.1 Patterns of inflammatory joint pain, and likely diagnoses. Fig. 19.2.2 Symmetrical swelling of the metacarophalangeal joints and proximal iinterphalangeal joints characteristic of rheumatoid arthritis, with some nodal osteoarthritis in the distal interphalangeal joints and possible nail dystrophy in the left ring finger nail. Reproduced with permission from Chapel H, et al. (2014). Essentials of Clinical Immunology, 6th edn. Blackwell Publishing, Oxford.

 • Mere presence of rheumatoid factor in blood is not enough to make a diagnosis of rheumatoid arthritis. It is also seen in 5% of elderly people who are well, and in other conditions see Table 19.2.10. • The presence of extra-articular features like fever, oral ulcers, malar rash, and alopecia, should alert the clinician to the pres- ence of lupus or

other multisystem autoimmune rheumatic dis- ease (see ‘Autoimmune rheumatic diseases and vasculitis’, next). The presence of prominent Raynaud’s phenomenon in a patient with joint pains should alert the physician to the possibility of scleroderma. A history of bloody diarrhoea may be a pointer towards enteropathic arthritis. Autoimmune rheumatic diseases and vasculitis Autoimmune rheumatic diseases and vasculitis range from mild presentations of fatigue and arthralgias, to severe, rapidly progres- sive organ- or life-threatening diseases. Diagnosis requires a full his- tory and a high level of suspicion, as presenting symptoms are often nonspecific, and the key to not missing a diagnosis is considering it whenever multiple organ systems are affected. The assumption must always be that the patient has a sinister disease (such as infection or malignancy) or life-threatening autoimmune disease until fully as- sessed and proven otherwise. Onset is usually subacute or chronic, patients usually feel unwell, and inflammatory markers are often raised. Presenting symptoms are very variable, such as fatigue, joint pain, shortness of breath, rash, abdominal pain, and paraesthesia. Systemic symptoms such as weight loss, fever, fatigue, and lymph- adenopathy are common. More specific are new onset or worsening Raynaud’s phenomenon (Fig. 19.2.3) or typical rashes which are strongly suggestive of a connective tissue disease (see Table 19.2.2 for extra-articular manifestations of rheumatic diseases and Table Table 19.2.10 Diseases associated with a positive rheumatoid factor Condition Prevalence (%) Rheumatoid arthritis 70–85 Elderly people 5 Other rheumatological disorders — Mixed cryoglobulinaemia 90–100 — Primary Sjögren’s syndrome 75–90 — Mixed connective tissue disease 50–60 — Systemic lupus erythematosus 20–30 — Systemic sclerosis 20–30 Chronic bacterial infections — Subacute bacterial endocarditis 25–50 Miscellaneous conditions — Interstitial pulmonary fibrosis 10–50 — Chronic active hepatitis 25–40 — Sarcoidosis 5–30 Table 19.2.9 Key features of spondyloarthropathies • Usual age <40 years • Male preponderance • Involvement of sacroiliac joints is a cardinal feature • Affects the axial skeleton; inflammatory low back pain is common • Peripheral joint involvement is usually asymmetrical, oligoarticular, below waist • Enthesopathy (pain along soft tissue insertion sites into bone (e.g. tendons, ligaments, fascia) is characteristic) • Seronegative for rheumatoid factor • Usually associated with HLA-B27 Fig. 19.2.3 Persistent acrocyanosis suggesting secondary Raynaud’s. Reproduced with permission from Ball GV, et al. (eds) (2014). Oxford Textbook of Vasculitis, 3rd edn. Oxford University Press, Oxford. © Oxford University Press 2014. Table 19.2.11 Typical skin manifestations of connective tissue diseases and vasculitis SLE Photosensitive (often malar or ‘butterfly’) rash Diffuse alopecia Mouth ulcers Antiphospholipid syndrome Livedo reticularis Scleroderma Sclerodactyly and Raynaud’s Digital pitting/ulceration Telangiectasia Calcinosis Dermatomyositis Facial rash (‘heliotrope’) with periorbital oedema Gottron’s papules Periungal erythema Vasculitis Splinter haemorrhages and nailfold infarcts Purpuric rash (often ‘palpable purpura’) Oral and genital ulcers in Behçet’s syndrome Cutaneous ulcers

 19.2.11 for typical skin manifestations). If an autoimmune connective tissue disease or vasculitis is a possibility, urinalysis, blood pressure, and urea and electrolytes must be performed, as renal disease may be silent. Persistent symptoms in other organ systems (e.g. shortness of breath or cough, blocked nose/epistaxis/hearing loss, skin rashes/ photosensitivity) require assessment by the appropriate specialty. Autoimmune rheumatic diseases are often associated with specific autoantibodies that can assist with diagnosis, see Table 19.2.12. Autoimmune rheumatic diseases Systemic lupus erythematosus typically affects women in their childbearing years, and is more common in those of Afro- Caribbean, Asian, or Chinese origin. It covers a spectrum of disease from mild rashes, mouth

ulcers, and flitting joint aches to severe life-threatening multiorgan disease including immune-complex glomerulonephritis, serositis (pleural effusion, pericarditis, or abdominal pain), and cytopaenias. Renal disease when present is usually silent, and urinalysis must be performed. Occasionally inflammation of the brain can cause epilepsy, headaches, and mi- graines, but usually neurological symptoms are caused by an as- sociated antiphospholipid syndrome causing arterial or venous thrombosis. The presence of antinuclear antibodes is almost uni- versally positive and often typical extractable nuclear antigens are seen (Table 19.2.12). ESR is raised but C-reactive protein usu- ally normal unless there is serositis or superimposed infection. Appearances of severe disease are often similar to infection and specialist management is required. Scleroderma (systemic sclerosis) is characterized by hardening of the skin caused by increased deposition of collagen in skin and to a variable extent in internal organs. It is subdivided into limited (skin thickening limited to distal to the elbow and face) and diffuse (skin thickening proximal to the elbow) with typical antibody as- sociations (Table 19.2.12), and association of limited disease with pulmonary arterial hypertension, and diffuse with interstitial lung disease. Scleroderma renal crisis causing severe hypertension and renal dysfunction may be precipitated by steroids: diagnosis de- pends on urinalysis, blood pressure, and renal function. Other connective tissue diseases are briefly described in Table 19.2.13. All of the connective tissue diseases can overlap, and mani- festations can include inflammatory arthritis, myositis, interstitial lung disease, or glomerulonephritis. Vasculitis The vasculitides cover a collection of disorders caused by inflam- mation within blood vessels. The commonest vasculitis is giant cell arteritis (temporal arteritis) which causes temporal headaches and tenderness, and can cause blindness due to anterior ischaemic optic neuropathy. Risk of blindness is increased in patients with symp- toms of tongue or jaw claudication. It affects people aged above 50, and diagnosis is supported by a typical history, tender temporal ar- teries on palpation, and an abnormal temporal artery biopsy. Less invasive imaging techniques (e.g. ultrasound) are entering clinical use, having recently completed clinical trials. The vasculitides were classified by the Chapel Hill consensus con- ference in 2012 according to the vessel size predominantly affected (Table 19.2.14). Noninflammatory musculoskeletal pain and pain syndromes Most self-limiting noninflammatory disorders and exacerbations of chronic degenerative disease such as osteoarthritis and back pain are managed in primary care and physiotherapy, with more severe conditions referred to orthopaedics. While most back pain does not reflect serious underlying pathology, the suspicion of fracture, infection, or malignancy are raised by the ‘red flags’ discussed pre- viously (Table 19.2.1). Fibromyalgia syndrome Fibromyalgia and other chronic pain syndromes are also mainly managed in the community, but patients often attend rheumatology clinics if there is diagnostic uncertainty, significantly uncontrolled symptoms, or patient request for specialist opinion. Fibromyalgia syndrome is the presence of chronic widespread pain, often combined with other multiple symptoms, in the absence of any demonstrable explanatory pathology. Symptom clusters asso- ciated with fibromyalgia syndrome include irritable bowel syndrome, dysmenorrhoea, premenstrual syndrome, headaches, atypical facial pain, noncardiac chest pain, and chronic fatigue syndrome. While there are diagnostic criteria for fibromyalgia syndrome, it is essential to rule out other causes of widespread musculoskel- etal pain, such as those listed in Table 19.2.15. Serious illness such Table 19.2.12 Autoimmune rheumatic diseases associated with specific autoantibodies that can assist with diagnosis Disease Antibody Frequency Systemic lupus erythematosus Anti-DsDNA) Anti-Sm Anti-RNP Anti-Ro Anti-La 70% 10–25% 30% 40% 15% Drug induced Lupus Antihistone Drugs associated are: isoniazid, phenytoin, hydralazine, methyldopa, chlorpromazine, penicillamine, and minocycline Sjögren’s syndrome Anti-RNP Anti-Ro Anti-La 15% 60–90% 35–85% Scleroderma Centromere pattern ANA

Anti-Scl-70 20–30% 40% of diffuse, 10% of limited Dermato/polymyositis Anti-Jo-1 & other antisynthetases Anti-SRP Anti-Mi2 myositis, fevers, interstitial lung disease and ‘mechanic’s hands’ Severe myositis Dermatomyositis Mixed connective tissue disease Anti-RNP 100% Table 19.2.13 Other connective tissue diseases Sjögren’s syndrome Dry eyes and a dry mouth predominate (keratoconjunctivitis sicca) Polymyositis Inflammation of muscles, causing weakness which may include bulbar and respiratory muscles Dermatomyositis Muscle inflammation and a typical rash Mixed connective tissue disease Overlapping clinical features of SLE, scleroderma and myositis

section 19 Rheumatological disorders 4392 as connective tissue diseases and vasculitis can also present with nonspecific widespread aches and pain and fatigue. The ACR 2010 diagnostic criteria for fibromyalgia syndrome require a combination of widespread pain and symptoms such as fatigue, waking unrefreshed, cognitive symptoms, and somatic symptoms for ≥3 months, with no alternative explanation for the pain. A suggested list of initial blood tests is given in Table 19.2.16. Regional pain syndromes Complex regional pain syndrome, formerly termed reflex sympa- thetic dystrophy, ‘causalgia’, or reflex neurovascular dystrophy, is a debilitating painful condition in a limb, associated with sensory, motor, and autonomic skin and bone abnormalities. It commonly arises after injury to a limb, but there is no relationship to severity of injury and in some cases no injury at all. The diagnosis is one of exclusion and made according to the ‘Budapest criteria’, which require (1) continuing pain disproportionate to the inciting event; (2) the patient has signs in two or more of the following four categories—sensory (heightened pain to a stimulus—allodynia or hyperalgaesia), vasomotor (symptoms of skin temperature or colour changes or asymmetry), ‘sudomotor/oedema’ (asymmetry of sweating or oedema), motor/trophic changes (weakness, tremor, or dystonia or trophic changes to hair, skin, or nails); (3) the patient re- ports at least one symptom in three or more of these four categories; (4) no other diagnosis provides better explanation for the patient’s symptoms and signs. Table 19.2.14 Chapel Hill consensus conference classification of vasculitides Vessel size Previous name Typical presentation Associated infection or autoantibody Small, ANCA-associated Granulomatosis with Polyangiitis (GPA) Wegener’s granulomatosis 50s, nasal crusting, deafness, SOB, and positive urinalysis PR3 (c-ANCA) Microscopic polyangiitis (MPA) N/A 60s, fatigue, arthralgia, myalgia, mononeuritis multiplex, and renal failure MPO (p-ANCA) Eosinophilic polyangiitis with Granulomatosis (EGPA) Churg-Strauss syndrome 50s, asthma, nasal polyps, lung infiltrates, mononeuritis multiplex, or cardiac involvement Often ANCA negative MPO (p-ANCA) Small, immune complex IgA vasculitis Henoch Schonlein purpura Children, purpuric rash on legs, can include abdominal pain, arthritis, and renal involvement IgA deposition Medium Polyarteritis nodosa (PAN) N/A Constitutional symptoms, deranged LFTs, aneurysms on renal angiogram Hepatitis B Kawasaki disease N/A Childhood disease, uncommonly affects 20s. Fever, conjunctivitis, lymphadenopathy, desquamation, risk of coronary artery aneurysms None Large Giant cell arteritis Temporal arteritis 70s, headache, temporal tenderness, possible jaw claudication, and sudden blindness None Takayasu’s Women 20s–30s Constitutional then claudicant symptoms Pulseless in later stages None N/A Behçet’s syndrome N/A Oral and genital ulceration, thrombosis, and vasculitis None N/A Thromboangiitis obliterans Buerger’s disease Ischaemia of extremities in a heavy smoker Angiogram may show ‘corkscrew’ arteries Smoking Table 19.2.15 Causes of diffuse or widespread musculoskeletal pain (differential diagnosis of fibromyalgia syndrome) • Inflammatory arthritis (including rheumatoid arthritis and spondyloarthropathies) • Hypermobility syndromes • Polymyalgia rheumatica • Polymyositis/dermatomyositis • Vasculitis • Hypo-/hyperthyroidism • Multiple sclerosis •

Neuropathies • Osteomalacia • Chronic fatigue syndrome/myalgic encephalomyelitis • Statin-induced myopathy Table 19.2.16 List of suggested blood tests in suspected fibromyalgia syndromeor other chronic pain syndrome Full blood count Erythrocyte sedimentation rate C-reactive protein Creatinine kinase Calcium and phosphate Alkaline phosphatase Blood glucose Thyroid-stimulating hormone Antinuclear antibody/rheumatoid factor Urinalysis for protein, blood, and glucose

19.2 Clinical presentation and diagnosis of rheumatological disorders 4393 Patients are often referred to rheumatology (among other spe- cialties) for exclusion of other conditions. Management is by a multidisciplinary pain management approach. Bone disease Bone disease includes malignant, metabolic, and genetic disorders of bone. Osteosarcoma is rare, usually presenting as bone pain in chil- dren. Leukaemia can also present with bone pain due to pressure within the bone marrow. In adults, cancer of bone is usually sec- ondary cancer. Red flags for bone cancer are listed in Table 19.2.17. Diagnosis is initially made on plain X-ray. Metabolic bone diseases are disorders of bone strength, usually caused by abnormalities of bone mass, bone mineralization, or bone structure. The most common metabolic bone disorders are osteo- porosis, osteomalacia, and Paget's disease, the pathologies of which are briefly characterized in Table 19.2.18. Rare genetic disorders are managed by metabolic bone specialists in tertiary centres (e.g. osteogenesis imperfect, x-linked hypopho sphataemic rickets or autosomal recessive hypophosphataemic rickets). Osteoporosis Osteoporosis is characterized by a decrease in bone mass and density which can lead to an increased risk of fracture, especially of wrist, hip, and vertebrae. Those at high risk for osteoporosis include pa- tients with older age, low BMI, personal or family history of fractures, steroid use, intestinal diseases, and kidney disorders. As it is asymp-tomatic, it must be suspected in at-risk individuals and investigated. Osteoporosis is defined by the World Health Organization (WHO) as a bone mineral density of 2.5 standard deviations or more below the mean peak bone mass (average of young, healthy adults) as meas- ured by dual-energy X-ray absorptiometry (T-score ≤–2.5); the term 'established osteoporosis' includes the presence of a fragility fracture. Osteomalacia/Rickets Osteomalacia is softening of the bones, due to defective mineraliza- tion. It is typically caused by deficiency of vitamin D (normally de- rived from sunlight exposure and, to a lesser extent, from the diet). More rarely it may be due to deficiency of phosphate or calcium, or overactive resorption of calcium from the bone secondary to hyper-parathyroidism or cancer. It causes the bones to become soft and weak. In children it is called Rickets, and can cause deformities in growing bones. Signs and symptoms of both can include diffuse body pains, muscle weakness, and fragility of the bones (Table 19.2.19). If meta- bolic derangement is very severe, it can be associated with hypocal- caemia and tetany. The most specific screening test for vitamin D deficiency in other- wise healthy individuals is a serum 25(OH)D level. Other investi- gations should include calcium, phosphate, alkaline phosphatase, parathyroid hormone, and x-rays of painful bones or joints. Paget's disease Paget's disease is a disorder of chronic, disorganized bone remod- elling. This causes affected bone to weaken, resulting in pain, mis- shapen bones, fractures, and arthritis in the joints near the affected bones. It most commonly affects the pelvis, femur, and lower lumbar vertebrae, and is often localized to a few bones. It can cause compli- cations such as uni/bilateral deafness or blindness from neural com- pression from bone overgrowth, and rarely it can undergo malignant transformation into Paget's sarcoma. Onset is usually over the age of 55 years, men are more commonly affected than women, and incidence is decreasing. An elevated level of alkaline phosphatase in the blood, in combination with normal Table 19.2.17 Red flags for bone cancer • History of malignancy • Weight

loss • Night sweats • Reduction in appetite • Night pain • Pain that is progressive or persistent • Pain in children Table 19.2.18 Comparison of bone pathology in common metabolic bone disorders Condition Calcium Phosphate Alkaline phosphatase Parathyroid hormone Comments Osteomalacia and rickets Decreased Decreased Elevated Elevated Soft bones Osteoporosis Unaffected Unaffected Normal Unaffected Decreased bone mass Paget's disease of bone Unaffected Unaffected Variable (depending on
stage of disease) Unaffected Abnormal bone architecture Table 19.2.19 Signs and radiographic findings in osteomalacia and rickets Osteomalacia Rickets Proximal weakness Costochondral swelling (aka 'rickety rosary') Waddling gait Greenstick fractures Looser's zones (pseudofractures) Toddlers: genu varum (bow legs) Older children: genu valgum (knock knees) Skull bossing or delayed fontanelle closure Pelvic deformity kyphoscoliosis or lumbar lordosis Harrison's sulcus (groove at costal insertion of diaphragm) Widening of wrist or double malleoli sign (due to metaphyseal hyperplasia)

section 19 Rheumatological disorders 4394 calcium, phosphate, and aminotransferase levels are suggestive of Paget's disease, as are 'hot spots' in typical locations on a bone scan. X-rays have a characteristic appearance, and a skeletal survey to as- sess extent is therefore indicated. FURTHER READING Arthritis Research UK (2012). The Approach to the Patient Presenting with Multiple Joint Pain. 'Hands on' series. http://www. arthritisresearchuk.org/shop/products/publications/information-for-medical-professionals/hands-on/ho1-series-7.aspx British Society for Rheumatology. Guidelines. https://www. Rheumatology.org.uk Coakley G, et al. (2006). BSR & BHPR, BOA, RCGP and BSAC guidelines for management of the hot swollen joint in adults. Rheumatology, 45, 1039–41. NICE guidance (CG79). Management of Rheumatoid Arthritis in Adults.
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