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19.11.5 Inflammatory myopathies 4537 gland swellings, constitutional symptoms), which should prompt them to seek medical attention. Investigation when lymphoma is possible or suspected should include MRI or computed tomography (CT) of neck, chest, abdomen and pelvis, and blood tests including full blood count, biochemistry, lactate dehydrogenase, immuno- globulins, serum protein electrophoresis, serum complements, and cryoglobulins. Other investigations may be required in selected cases, including bone marrow aspiration and biopsy, and oesopha- geal-gastro-duodenal endoscopy and H. Pylori testing. Pulmonary opacities should be investigated for bronchial mucosal-associated lymphoma. Treatment is usually coordinated by haemato-oncologists and tailored to the individual patient based on symptoms, site, grade, stage, extent of the lymphoma, and coexisting Sjögren’s syndrome manifestations. Prognosis Contrary to the common belief that Sjögren’s syndrome is a benign condition, except among those with lymphoma, a recent study has demonstrated that Sjögren’s syndrome has an overall adjusted stand- ardized mortality ratio of 4.7, with the leading causes of death being cardiovascular disease, haematological malignancies, infections, and systemic disease. Special circumstances Pregnancy Patients with anti-Ro (especially anti-Ro52) antibodies are at risk of recurrent miscarriage as well as fetal complete heart block and neo- natal lupus syndrome in the newborn. Their pregnancies should be closely monitored by obstetric ultrasound scanning and echocardi- ography between 12 and 30 weeks of gestation,

when complete heart block most commonly develop. Neonates should be delivered in a tertiary centre with cardiac pacing facilities. Treatment with high dose dexamethasone or betamethasone in early pregnancy may re- duce the risk of complete heart block developing. Future developments Several biological therapies targeting the dysregulated biological pathways in Sjögren's syndrome (e.g. B cells, T cells, type I inter- ferons, interlukin-6, co-stimulation molecules, kinases) are in early to late phases of development. FURTHER READING Brito-Zerón P, et al. (2016). Systemic activity and mortality in primary Sjögren syndrome: predicting survival using the EULAR-SS Disease Activity Index (ESSDAI) in 1045 patients. Ann Rheum Dis, 75, 348–55. Seror R, et al. (2015). Validation of EULAR primary Sjögren's syn- drome disease activity (ESSDAI) and patient indexes (ESSPRI). Ann Rheum Dis, 74, 859–66. 19.11.5 Inflammatory myopathies Ingrid E. Lundberg, Hector Chinoy, and Robert Cooper ESSENTIALS The idiopathic inflammatory myopathies are a heterogenous group of disorders characterized by muscle weakness, inflamma- tion in muscle tissue, and with frequent extramuscular involvement. Autoantibodies are common, supporting the notion of these dis- orders being autoimmune. Clinical features—Dermatomyositis is characterized by sym- metrical, proximal muscle weakness that develops slowly, with various cutaneous manifestations including heliotrope rash. The muscle weakness of polymyositis is clinically indistinguishable. Extramuscular features are common in both conditions and include interstitial lung disease, aspiration pneumonia, arthritis, and dys- phagia. There is an association with malignancy, particularly in pa- tients with dermatomyositis. Investigation and diagnosis—Diagnosis is based on clinical fea- tures in combination with elevated serum levels of muscle enzymes (creatine kinase), myositis-specific autoantibodies, and muscle bi- opsy. Particular autoantibodies are associated with particular dis- ease phenotypes. Novel clinical phenotypes include amyopathic dermatomyositis, antisynthetase syndrome, and immune-mediated necrotizing myopathy (sometimes associated with statin treatment). Magnetic resonance imaging can demonstrate muscle involvement, be repeated as a method of evaluating response to therapy, and be useful in selecting a muscle group for biopsy. Management and prognosis—treatment is with glucocorticoids, usually beginning with 0.75–1 mg/kg/day of prednisone. Second- line agents, usually azathioprine or methotrexate, are recommended as steroid sparing. Biologics are likely to be increasingly used in the future. Five-year survival rate is greater than 80%, but morbidity from both the diseases themselves and their treatments is high. Introduction The idiopathic inflammatory myopathies, collectively named myo- sitis, are a group of rare diseases that are characterized clinically by insidious onset of muscle weakness and muscle fatigue, mainly af- fecting proximal muscles with a symmetric distribution. Typically, inflammatory cell infiltrates are found in muscle biopsies. Other or- gans are frequently involved such as skin, lungs, joints, gastrointes- tinal tract, and the heart. These heterogenous disorders can be subclassified based on clinical and histopathological features, or by autoantibody specificities. The idiopathic inflammatory myopathies have traditionally comprised polymyositis (PM), dermatomyositis (DM), juvenile dermatomyo- sitis, polymyositis/dermatomyositis overlapping with another con- nective tissue disease, and inclusion body myositis. More recently a subgroup with similar clinical features but with no or scarce inflam- mation and with pronounced muscle fibre necrosis has been identi- fied and termed immune-mediated necrotizing myopathy.

 Patients are often referred to rheumatology clinics as presenta- tion of symptoms often include muscle weakness together with pain in joints and muscle, general symptoms of inflammation, as well as symptoms from other organs. Awareness of the multiorgan in- volvement together with muscle weakness and muscle fatigue, and the frequent presence of autoantibodies, should guide clinicians to- wards a myositis diagnosis. Aetiology Both

genetic and environmental risk factors are likely to con- tribute to the risk of developing polymyositis and dermatomyositis. Based on the first genome wide association studies, a strong asso- ciation with the human leukocyte antigen (HLA) region was de- termined. There were also associations with other genes involved in the immune system, supporting the notion of polymyositis/ dermatomyositis being autoimmune diseases (Box 19.11.5.1). Genes are likely to contribute to the risk of developing poly- myositis and dermatomyositis in the context of environmental exposures. The most clear environmental risk factor for devel- opment of dermatomyositis is exposure to ultraviolet light, with the dermatomyositis/polymyositis ratio highest in countries closer to equator. The role of infections to trigger onset of myo- sitis is less clear. Smoking is a risk factor to develop Jo-1 posi- tive myositis in patients with HLA-DRB1*0301 genotype. The immune-mediated necrotizing myopathy clinical phenotype, as- sociated with statins, is strongly associated with HLADRB1*11:01 genotype. For future studies on etiology in myositis it will be im- portant to collect information on both genetics and environmental exposures. Inclusion body myositis is clinically different from polymyositis and dermatomyositis in that it mainly affects persons over the age of 50 years, by muscle biopsy features suggesting a degenerative component of the disease, and by being resistant to immunosup- pressive treatment. Less is known about the aetiology of inclusion body myositis. Epidemiology The female to male incidence rate ratio in polymyositis/dermato- myositis varies between 1.5 and 2.4, although during childbearing age this ratio increases to over 5:1. The frequency of inclusion body myositis is generally higher in men compared to women, the gender ratio varying from 0.5–1:1 (Box 19.11.5.2). Overall annual incidence rates indicate that idiopathic inflamma- tory myopathies are rare diseases, at 8/million, ranging from 1.2 to 19/million. Overall prevalence rates are estimated at 14–87/million. Higher myositis incidence has been reported in black compared to white populations. Reported increased incidence rates over time may in part be due to better diagnostics and increased physician awareness. The median time to diagnosis of overall idiopathic inflammatory myopathies varies between 3–6 months, but is higher for inclusion body myositis, where the mean duration of symptoms prior to diag- nosis is 4.1–8 years. The peak age of disease diagnosis for idiopathic inflammatory myopathies overall is 55 years. The age of diagnosis for dermatomyositis has two peaks, at 5–15 years and 45–65 years. Mean age at onset of inclusion body myositis ranges from 60 to 64 years. Pathogenesis/Pathology An autoimmune component in the disease mechanism is suggested by infiltrates of T and B cells in the skeletal muscle tissue and by fre- quent presence of autoantibodies (Box 19.11.5.3). There are two main patterns of the inflammatory cell infiltrates; one with predominating perivascular and perimysial infiltrates composed mainly of CD4+ T lymphocytes, macrophages and B lymphocytes; and another with predominating endomysial infil- trates surrounding muscle fibres, mainly composed of CD8+ T lymphocytes, but where CD4+ T lymphocytes and macrophages are often present (Fig. 19.11.5.1). In both type of infiltrates dendritic cells may be present. These two different patterns of inflammatory cell infiltrates suggest that there are different molecular pathways in- volved in pathogenesis: the first pattern with perivascular infiltrates suggests that blood vessels are targets of the immune reaction, and Box 19.11.5.1 Aetiology of myositis • Genetic and environmental factors are likely to contribute to risk of developing myositis • There is a strong association between myositis and HLA region • Different myositis-specific autoantibodies are associated with dif- ferent HLA-DR genotypes • There are seasonal and regional variations in onset, suggesting envir- onmental factors to be important risk factors for myositis • Statin use may induce a necrotizing myopathy Box 19.11.5.2 Epidemiology of myositis • More common in women than in men, except inclusion body myositis • Overall incidence rate 8/million/year, prevalence

14–87/million • Peak age of disease diagnosis for idiopathic inflammatory myop- athies overall is 55 years • The age of disease diagnosis of dermatomyositis has two peaks, at 5–15 years and 45–65 years Box 19.11.5.3 Pathogenesis/pathology of myositis • There are at least four distinct histopathological features of muscle bi- opsies of patients with myositis, suggesting at least four different mo- lecular pathways leading to muscle weakness and loss of muscle mass. • The pathophysiology leading to muscle weakness is complex and involves both the adaptive immune system and the nonimmune or innate immune system. • T cell mediated muscle fibre cytotoxicity leading to muscle atrophy is one molecular mechanism leading to muscle weakness. • Another molecular pathway is the so-called endoplasmic reticulum (ER) stress affecting muscle fibre phenotype, including expression of major histocompatibility complex (MHC) class I leading to impaired muscle function.

19.11.5 Inflammatory myopathies 4539 the second pattern that muscle fibres are the target. However, some- times these biopsy features may occur together, emphasizing the complexity of the pathology of myositis. Perivascular inflammatory infiltrates are predominantly ob- served in patients with skin rash typical of dermatomyositis, but may occasionally be seen in patients with other clinical myositis subphenotypes. The endomysial pattern is mainly seen in patients without skin rash, thus in patients with polymyositis or patients with inclusion body myositis. Patients with inclusion body myo- sitis may, in addition, have rimmed vacuoles, which are not specific but suggestive of this condition in a typical clinical context (Fig. 19.11.5.2). Nuclear or cytoplasmic inclusions often require electron microscopy to be detected. Protein accumulation in muscle fibres is a characteristic finding in inclusion body myositis, suggesting a disturbed protein machinery in the muscle fibres. The presence on immunostaining of p62 or TDP43 accumulations, two proteins involved in the protein degradation pathways, is a sensitive patho- logical finding of inclusion body myositis. A fourth muscle biopsy pattern is dominated by necrotic muscle fibres with no or sparse in- flammation typically, seen in the subset called immune-mediated necrotizing myopathy. Importantly, normal muscle histopathology does not exclude myositis. Although not very common, this observation tells us that mechanisms other than T lymphocyte mediated muscle necrosis may lead to muscle weakness. In muscle biopsies with out inflammatory infiltrates and without signs of muscle fibre degeneration, a phenotypic change of muscle fibres can be detected by immunostaining, namely expression of major histocompatibility complex (MHC) class I in the muscle fibres, which normally do not express MHC class I molecules. Even though this is not specific for myositis, it is a support for a myositis diagnosis in the relevant clin- ical context, hence it is included as a routine stain in many muscle laboratories. In experimental models it has been demonstrated that up-regulation of MHC class I molecules in muscle fibres may lead to muscle weakness. Another mechanism that may be involved in the pathogenesis of myositis is metabolic disturbance, including a reduced mitochon- drial activity in muscle fibres. Clinical features The main clinical features and clinical subgroups of myositis are shown in Box 19.11.5.4 and Box 19.11.5.5. Patients can present with acute or subacute onset of proximal, bilateral, symmetrical muscle weakness affecting the shoulder and/ or pelvic girdle. Myalgia is present in about 25% of cases. Upper limb symptoms can include difficulty combing hair, or reaching up for objects above their head. Lower limb symptoms related to weakness include difficulty rising to a standing position and diffi- culty climbing steps. Abdominal musculature weakness may cause difficulty sitting up from a supine position. Pharyngeal weakness (a) (c) (d) (b) Fig. 19.11.5.1 Polymyositis.
(a) Inflammation in the endomysium surrounding individual muscle fibres, some of which appear vacuolized and invaded by inflammatory cells. (b) Immunocytochemistry for CD8 showing

predominant CD8 cytotoxic lymphocytes within the inflammatory infiltrate.
(c) Immunocytochemistry for MHC class 1 showing widespread expression by muscle fibres.
(d) Lymphocytic vasculitis in a case of polymyositis associated with lupus. Reproduced from Gray F et al. (eds) (2013). Escourolle and Poirier's Manual of Basic Neuropathology, 5th ed, by permission of Oxford University Press.

section 19 Rheumatological disorders 4540 may lead to dysphonia and dysphagia. The facial musculature is generally spared. Dermatomyositis is defined by characteristic rashes, including the heliotrope rash and Gottron's papules and signs (Fig. 19.11.5.3). Patients may present without muscle weakness, so-called amyopathic dermatomyositis. 'Mechanics hands' refers to hyperkeratosis, scaling and fissuring of the skin in the tips and sides of the fingers (Fig. 19.11.5.4). Other rashes include anterior chest macular erythema in a 'V' distribution (V-sign), or on the back in a shawl- like distribution (shawl sign) or over the hips (holster sign) and periungual erythema (Fig. 19.11.5.5). Skin vasculitis is a recognized feature of juvenile dermatomyositis. Interstitial lung disease occurs in 5–40% of idiopathic inflam- matory myopathies patients, more commonly in antisynthetase or polymyositis-Scl positive patients. Clinical signs may range from asymptomatic disease to acute respiratory distress syndrome. Aspiration, due to weakness of pharyngeal musculature, may lead to aspiration pneumonia. Anti-synthetase syndrome is defined by the presence of an antisynthetase antibody and ≥1 of the following: myo- sitis, interstitial lung disease, Raynaud's phenomenon, mechanics' hands, arthritis, and fevers. Dysphagia is the most common gastrointestinal symptom in the idiopathic inflammatory myopathiess, due to weakness of the tongue and/or pharynx, or disordered upper oesophageal motility. Dysphagia is common in inclusion body myositis and the pres- ence of this symptom in a patient without a skin rash should raise suspicion of this diagnosis in a clinical context with thigh muscle atrophy or finger flexor weakness. Cardiac manifestations may manifest as subclinical electro- cardiogram (ECG) abnormalities, including arrhythmias and (a) (b) (c) Fig. 19.11.5.2 (a) Muscle biopsy (haematoxylin–eosin stain) of a patient with sporadic inclusion body myositis (sIBM) showing endomysial collections of mononuclear cells surrounding and sometimes invading nonnecrotic muscle fibres. (b) Muscle biopsy of a patient with IBM showing a muscle fibre with rimmed vacuoles. (c) Muscle bopsy (succinate dehydrogenase–cytochrome c oxidase stain) of a patient with sIBM showing an increased number of cytochrome c oxidase-negative muscle fibres which stain blue. Reproduced from Hilton-Jones D and Turner MR (eds) (2014). Oxford Textbook of Neuromuscular Disorders, by permission of Oxford University Press. Box 19.11.5.4 Clinical features of myositis • Typical presentation of proximal muscle weakness, sometimes with myalgia • Characteristic rashes observed in dermatomyositis • Extramuscular manifestations, include skin, lung, cardiac, joint, and gastrointestinal • Link with malignancy Box 19.11.5.5 Main clinical subgroups of myositis Polymyositis (PM) Dermatomyositis (DM) Inclusion body myositis (inclusion body myositis) Antisynthetase syndrome Immune-mediated necrotizing myopathy Myositis associated with other connective tissue disease Juvenile dermatomyositis

19.11.5 Inflammatory myopathies 4541 conduction defects. Myocarditis is an under-recognized feature in more severe cases. Articular manifestations occur early in idiopathic inflammatory myopathies, in a mild, rheumatoid-like distribution, most com- monly in patients with antisynthetase antibodies (e.g. anti-Jo-1) or myositis/connective tissue disease-overlap patients. Arthritis may be a presenting symptom in patients with antisynthetase syndrome. Malignancy and myositis There is a well-described association between malignancy and dermatomyositis, where

the reported frequency of cancer is (a) (b) Fig. 19.11.5.3 (b) Heliotrope rash, confluent macular erythema confined to the upper eyelid. (b) Gottron’s papules, symmetric erythematous to violaceous papules overlying the metacarpal and interphalangeal joints. From Dugan E et al. (2009). Photoessay of the cutaneous manifestations of the idiopathic inflammatory myopathies. Dermatology Online Journal, 15(2): 1. Fig. 19.11.5.4 ‘Mechanics’ hands’. Fig. 19.11.5.5 Periungual abnormalities in dermatomyositis.

section 19 Rheumatological disorders 4542 7–30%. The risk is greatest for the first three years after disease onset. Increased pick-up in the first year may be due to surveil- lance bias, but undoubtedly also suggests that in some patients dermatomyositis represents a paraneoplastic phenomenon. Risk factors for malignancy include male gender, older age at disease onset, more severe skin or muscle disease, elevated inflammatory markers, low serum albumin, and a positive antitranscription intermediary factor-1 (TIF-1γ) antibody. The clinical conse- quence is that for patients with dermatomyositis, following de- tailed history-taking and examination, laboratory evaluation should include full blood count, inflammatory markers, routine biochemistry, chest radiography, urinalysis, and chest/abdomen/ pelvis computed tomography scans. Mammography and gynaeco- logical examination are recommended in women, and testicular examination in men. Faecal occult blood testing and gastros- copy/colonoscopy should be considered, particularly in patients with microcytic anaemia. The use of FDG-PET scanning ap- pears comparable to conventional screening for detecting occult malignancy. Autoantibodies and clinical features In idiopathic inflammatory myopathies, an individual patient’s antibody is predictive of their disease-phenotype. Autoantibodies against nuclear or cytoplasmic antigens can be detected in 80–90% of cases. Myositis-specific autoantibodies are specific for inflam- matory myositis, while myositis-associated autoantibodies may also be detected in other rheumatic disorders without signs of in-flammatory muscle disease, hence they are not specific to myositis (Table 19.11.5.1). Differential diagnosis Patients with myositis may present with muscle weakness and myalgia, or with skin rash, or with other organ manifestations such as interstitial lung disease or arthralgia/arthritis, so the potential for misdiagnosis is considerable and depending on the presenting features a variety of other diseases need to be considered. Concerning muscle weakness as a predominating symptom, there are several myopathies and other conditions that need to be excluded (Table 19.11.5.2). In patients presenting with hallmark dermatomyositis (i.e. with violacious Gottron’s papules and periorbital oedema and erythema- tous shawl and V-sign changes), these changes are so specific that a dermatomyositis diagnosis should be only rarely missed. However, in some patients, skin changes are not so dermatomyositis-specific, regarding their distribution and/or colour, so misdiagnoses can arise, including erythrodermic psoriasis, SLE, systemic Sjögren’s, and paraneoplastic syndromes. Clinical approach and investigations In patients with muscle weakness or myalgia a medical history should include family history for muscle disorders. It is vital to also obtain an accurate drug history. Similarly, alcohol misuse is a cause of acute and chronic myopathy. Patients may fail to volunteer symp- toms suggestive of dysphagia or dysphonia, unless specifically asked about these aspects, yet these can be early symptoms in idiopathic inflammatory myopathies. The general examination should include examination of muscle strength. Using the manual muscle testing in eight muscle groups is recommended (see IMACS website for instructions). One grading scale is the Medical Research Council (MRC) scale of 0–5, where 0 = no flicker of contraction visible, 1 = flicker of contraction vis- ible, 2 = muscle contraction obvious and can lift somewhat against gravity, but unable to hold against gravity, 3 = contraction held against gravity but unable to sustain with any extra load, 4 = good contraction and can sustain against

gravity with extra load applied, but not normal and 5 = normal contraction. Investigation should include signs of extramuscular involvement such as skin, lungs, heart, and joints. Investigations should include serum levels of muscle enzymes such as creatine kinase (CK), alanine aminotransferase (ALT), aspartate aminotransferase (AST), aldolase, and lactate de- hydrogenase (LDH). All could be used to monitor myositis ac- tivity, although creatine kinase has become the preferred option. Creatine kinase is not always elevated in active myositis, hence normal levels do not exclude this diagnosis, and moreover there are many causes of creatine kinase elevations other than myositis (Table 19.11.5.3). Muscle biopsy is one of the corner stones in the diagnostic work up of inflammatory myopathies, both to confirm inflam- mation and to exclude other noninflammatory myopathies. Histology characteristically shows infiltrations of inflamma- tory cells with different patterns as described here under path- ology. Notably the inflammatory cell infiltrates may be patchy, and not always present, hence normal histopathology does not exclude myositis. It is vital that attending laboratories have the full immunohistochemistry capability required to appropriately interrogate for the full range of other myopathies which could mimic myositis, especially in the absence of a dermatomyositis rash. It is recommended that proximal myopathy cases should be diagnostically worked up in tertiary referral centres if misdiag- noses are to be avoided. As outlined in Table 19.11.5.1, there are a growing number of myositis-specific and associated autoantibodies (MSA/MAA), and these very strongly predict clinical phenotypes. Muscle MRI scanning allows for detection of muscle oedema on fat-suppressed short tau inversion recovery (STIR) images (i.e. to suggest active myositis), and comparison of T1 and short tau inversion recovery images permit detection of fatty replacement and scar tissue (i.e. to suggest irreversible muscle damage; see Fig. 19.11.5.6). It should be noted, however, that oedema on short tau inversion re- covery is not specific for myositis, as it can also occur with denerv- ation (e.g. as in motor neuron disease). Needle electromyography (EMG) testing characteristically shows low voltage polyphasic (i.e. so-called myopathic) potentials in the chronic phase, with fibrillation changes also present in the acute phase. There are no EMG features that are specific for inflammatory myopathies, and it is important to remember that EMG interpret- ation is operator-dependant. Involvement of lungs should be investigated for by pulmonary function tests and (when appropriate) by high resolution compu- terized tomography,and cardiac involvement should be checked for by ECG and (when appropriate) echocardiography. Lung and heart

 involvement may be clinically asymptomatic, particularly in patients with low grade of physical activity due to muscle weakness. Treatment The usual approach is to combine immunosuppressive treatment with physical exercise. Pharmacological treatment is aimed at suppressing muscle inflammation. There are few randomized con- trolled trial in myositis, hence recommendations are based mainly on case series and clinical experience. Most clinicians would use high doses of glucocorticoids, alone or in combination with a traditional steroid-sparing agent (e.g. methotrexate, azathioprine, ciclosporin, mycophenylate mofetile), but none of these agents or their combinations is assured of a successful outcome. Some pa- tients respond well to glucocorticoids, alone or in these various Table 19.11.5.1 Autoantibodies associated with myositis Autoantibodies Target autoantigen and function Clinical phenotype Frequency in adult IIM (%) A. Myositis-specific antibodies Anti-aminoacyl-tRNA synthetases—associated with antisynthetase syndrome Anti-Jo-1 Histidyl Myositis, mechanics' hands, Gottron's papules, arthritis, Raynaud's phenomenon, interstitial lung disease 11–20 Anti-PL-7 Threonyl 2 Anti-PL-12 Alanyl 1 Anti-EJ Glycyl 1–3 Anti-OJ Isoleucyl 1 Anti-KS Asparaginyl <1 Anti-Ha Tyrosyl <1 Anti-Zo Phenylalanyl <1 Anti-Ha Tyrosinyl <1 Antibodies associated with acute

necrotizing myopathy Anti-SRP Ribonucleoprotein complex comprising 6 polypeptides and 7SL RNA (intracytoplasmic protein translocation) Acute necrotizing myopathy, high creatine kinase (up to 25 000), severe weakness, may be refractory to treatment. Usually respond well to steroids, but may flare on tapering thus requiring long-term immunosuppression 5 Anti-HMGCR HMG-CoA reductase Acute necrotizing myopathy, associated with statin use. Proximal weakness despite statin cessation. CK 2–35 000 unknown Antibodies associated with adult dermatomyositis Anti-Mi-2 Nucleosome remodelling histone deacetylase complex (nuclear transcription) Cutaneous disease, milder muscle disease, acute onset, good response to treatment, lower mortality rates 5–10 (10–20% adult DM) Anti-TIF1-γ Transcription intermediary factor 1-γ (nuclear transcription and cellular differentiation) Severe cutaneous disease, cancer-associated myositis 5–10 (13–21% adult DM) Anti-NXP-2 Nuclear matrix protein 2 (p140) (nuclear transcription and RNA metabolism) Cutaneous disease, systemic features, ILD (calcinosis more common in juveniles) 3 Antibodies associated with amyopathic dermatomyositis Anti-SAE Small ubiquitin-like modifier activating enzyme (post-translational modification) Cutaneous disease precedes muscle disease 5 Anti-MDA5 Melanoma-differentiation associated gene 5 (innate immune responses against viral infections) Ulcerating skin lesions, amyopathic dermatomyositis, rapidly progressive interstitial lung disease Unknown B. Myositis-associated antibodies Anti-PM-Scl Nucleolar protein complex (human exosome) SSc overlap, Raynaud’s phenomenon, interstitial lung disease 8–10 (50% myositis-scleroderma overlap syndrome) Anti-U1 RNP U1 small nuclear RNP Mixed connective tissue disease 10 Anti-Ku DNA-PK regulatory subunit SSc overlap, interstitial lung disease 20–30 Anti-Ro Y1-Y5 RNP Sjögren’s overlap, frequently associated with Jo-1 10–20 Anti-La RNA polymerase III termination factor Sjögren’s overlap 5 Adapted from Chinoy H., Cooper, R. G. Polymyositis and Dermatomyositis in adults. Oxford Textbook of Rheumatology, 4th edition, ed Watts R., Conaghan P., Denton C., Foster H., Isaacs J., Müller-Ladner U. (Oxford) 2013.

section 19 Rheumatological disorders 4544 combinations; others respond poorly or not at all, and so progress to suffer irreversible disability. Biological agents have been used with limited success so far, but with some patients responding favourably to rituximab. Presence of anti-Jo-1 or anti-Mi-2 antibodies seems to predict response. High doses of intravenous immunoglobulins Table 19.11.5.2 Causes of proximal muscle weakness other than idiopathic inflammatory myopathies Inherited myopathies Muscular dystrophies: Duchenne, fascioscapulohumeral, limb girdle, Becker, Emery-Dreifuss, distal ocular Congenital myopathies: nemaline, mitochondrial, centronuclear, central core Neurologic Denervating conditions: spinal muscular atrophies, amyotrophic lateral sclerosis Neuromuscular junction disorders: Eaton-Lambert syndrome, myasthenia gravis Myotonic disease: dystrophia myotonica, myotonia congenita Other: Guillain-Barre syndrome, chronic autoimmune polyneuropathy (e.g. Sjögren’s type) Metabolic Glycogen storage diseases: acid maltase deficiency, McArdle’s disease Lipid storage myopathies: carnitine/carnitine palmityltransferase deficiency Nutritional: vitamin E deficiency, malabsorption Other: uraemia, hepatic failure, alcoholism, acute intermittent porphyria, diabetic plexopathy Endocrine myopathies Hyper/hypothyroidism, acromegaly, Cushing’s syndrome, Addison’s disease, vitamin D deficiency, hyper/hypocalcaemia, hypokalaemia Drug-induced myopathies Lipid-lowering agents, e.g. statins, and clofibrate; D-penicillamine, chloroquine, amiodarone, vincristine, zidovudine Infections Acute viral: influenza, hepatitis B, echovirus, rickettsia, coxsackievirus, rubella, vaccine-associated Bacterial pyomyositis: staphylococcus, streptococcus, clostridium perfringens, leprosy Parasites: toxoplasma, trichinella, schistosoma, cysticercus Myositis/CTD overlap Myositis—Overlapping with systemic sclerosis, mixed CTD, Sjögren’s syndrome, systemic lupus

erythematosus, and rheumatoid arthritis Miscellaneous Periodic paralyses, carcinomatous neuromyopathy, acute rhabdomyolysis, myositis ossificans, microembolization by atheroma or carcinoma, sarcoidosis with myopathy Adapted from Oddis CV (2002). Idiopathic inflammatory myopathy: management and prognosis. Rheum Dis Clin North Am, 28: 979–1001, copyright 2002, with permission from Elsevier. Table 19.11.5.3 Causes of elevated creatine kinase other than active idiopathic inflammatory myopathy

1. Muscle trauma a) Muscle injury b) Needle stick c) EMG d) Surgery e) Convulsions, delirium tremens
2. Diseases affecting muscle a) Myocardial infarction b) Rhabdomyolysis c) Metabolic or mitochondrial myopathies d) Muscular dystrophy e) Infectious myositis g) Amyotrophic lateral sclerosis
3. Drug/toxin-induced myopathy a) Lipid-lowering agents, especially HMG-CoA-reductase inhibitors b) Alcoholic myopathy c) Drugs of abuse: e.g. cocaine, amphetamines, phencyclidine d) Malignant hyperthermia and neuroleptic malignant syndrome e) Other medications: e.g. zidovudine, colchicine, chloroquine, ipecac
4. Drug-induced myositis a) D-penicillamine b) Interferon
5. Drug-induced creatine kinase elevation Inhibition of excretion: e.g. barbiturates, morphine, diazepam
6. Endocrine and metabolic abnormalities a) Hypothyroidism b) Hypokalaemia c) Hyperosmolar state or ketoacidosis d) Diabetic nephrotic syndrome with oedema e) Renal failure
7. Elevation of CK–BB a) CNS disease b) Tumours (GI, bronchial, other)
8. Elevation without disease a) Strenuous, prolonged, and/or unaccustomed exercise b) Ethnic group (black > white) c) Increased muscle mass Adapted from Targoff IN (2002). Laboratory testing in the diagnosis and management of idiopathic inflammatory myopathies. Rheum Dis Clin North Am, 28: 859–890, copyright 2002, with permission from Elsevier. Fig. 19.11.5.6 MRI of the thighs in polymyositis: T1 (upper) and short tau inversion recovery (lower) sequencing demonstrates oedema in the anterior compartment of the muscles on the short tau inversion recovery sequences, which is compatible with active muscle inflammation. (Courtesy of Dr Lisa Christopher.)

 (IVIG) are expensive but may have a therapeutic effect in some otherwise drug-resistant cases. In patients who are completely nonresponsive to immunother- apies, a careful review of the diagnosis may disclose a misdiagnosis (e.g a nonresponsive polymyositis may in fact be a covert inclusion body myositis, which may only be disclosed by a repeat muscle biopsy). Even patients who respond to immunosuppressive treatment with suppression of inflammation may be left with impaired muscle performance due to persisting muscle weakness and low muscle en- durance. Combining immunosuppressive treatment with physical exercise has been shown to be both safe and effective in restoring physical function. Prognosis/outcome The most useful outcome measure in patients with idiopathic in- flammatory myopathies is physical function, although patients with prominent extramuscular symptoms, such as interstitial lung dis- ease, may require more specific assessments. Manual muscle testing is the most often used test of muscle strength and can be easily per- formed in clinical practice. To direct treatment decisions it is im- portant to be able to distinguish whether poor muscle performance and other organ involvement is due to active inflammatory dis- ease or instead due to irreversible organ damage. The International Myositis Assessment and Clinical Studies Group (IMACS) has de-

veloped core set activity and damage measures in idiopathic inflam- matory myopathies (http://www.niehs.nih.gov/research/resources/ imacs/diseaseactivity/index.cfm). Most patients suffer with mild to moderate degrees of disabil ity, with impact on quality of life. Disease progression may be monophasic, relapsing-remitting, chronic progressive, or remitting. Lung involvement and paraneoplastic involvement are major con- tributors to comorbidity. Comorbidities associated with treatment include Cushingoid appearance, osteoporosis, and infections. Up to 50% of patients remain out of employment due. Idiopathic inflammatory myopathies are associated with in- creased mortality: survival rate at two years ranges from 72% to 85%, at five years 34% to 75%, and at 10 years 42% to 85%. There may be a bimodal distribution of deaths: in the first year after onset, and 5–10 years later. Cancer, lung, and cardiac complications, and infection are the most common causes of death. Demographic and clinical features associated with worse survival include male gender, diagnostic delay, older age at onset of disease, associated malignancy, calcinosis, and oesophageal, cardiac or respiratory involvement. Special circumstances/complications Inclusion body myositis There is ongoing debate regarding whether inclusion body myo- sitis is an idiopathic inflammatory myopathies subgroup member. Patients exhibit quadriceps weakness and inflammatory cell in- filtrations in muscle biopsies, thus mimicking polymyositis, but in ‘classic’ inclusion body myositis patients also have the specific clinical features of distal muscle weakness selectively affecting the finger flexors and tibialis anterior muscles, and muscle involve- ment may be asymmetrical. Affected patients may experience loss of grip and report falls. In classic inclusion body myositis, patients can also demonstrate dramatic wasting of the quadriceps and the finger flexor muscles, which are not typical features of polymyositis. However, discriminating inclusion body myositis from polymyositis is vital as, unlike in polymyositis, inclusion body myositis does not improve with immunosuppression. Some inclusion body myositis cases do not exhibit peripheral weakness at disease onset, and such cases are misdiagnosed as ‘drug-resistant polymyositis’ for years, until an inclusion body myositis diagnosis is disclosed by the development of an inclu- sion body myositis pattern of peripheral weakness, and/or re- peat muscle histology confirms development of inclusion body myositis-specific features, including inclusion bodies and rimmed vacuoles. Statin-induced myopathies Statin-induced myopathies are an increasing problem with the increasing use of these drugs. A common problem is muscle cramps and myalgias, symptoms which may be associated with elevated serum levels of creatine kinase. In rare individuals a severe rhabdo- myolysis may develop. These conditions are usually reversible if statins are stopped, although improvement may take months. The other myopathy associated with statins is a so-called immune- mediated necrotizing myopathy with very high serum creatine kinase-levels and a newly identified autoantibody: anti-HMG-CoA reductase (HMGC-CR), which is the target of statins. This condi- tion requires immunosuppressive treatment, to which patients usu- ally respond well. Areas of uncertainty, controversy, and future developments The results of treatment of patients with myositis is often disappointing, hence there is an unmet need for new therapies. In order to develop more effective treatments with fewer side-effects we need to achieve a better understanding of the molecular pathways that are involved in myositis. To accomplish this we need to follow our patients systematically and record the response to treatment in relation to clinical subgroups where the pathophysiology is likely to be shared by particular groups of patients. One such way forward could be to study the effects of different targeted therapies in sub- groups based on autoantibody profile. Clinical longitudinal studies combined with experimental studies in which new compounds can be tested are strongly needed. FURTHER READING Ibrahim F, et al. (2015). Second-line agents in myositis: 1-year

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