Review Article

Secondary myopathy due to systemic diseases

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Background – Some systemic diseases also affect the skeletal muscle to various degrees and with different manifestations. This review aimed at summarizing and discussing recent advances concerning the management of muscle disease in systemic diseases. Method – Literature review by search of MEDLINE, and Current Contents with appropriate search terms. Results – Secondary muscle disease occurs in infectious disease, endocrine disorders, metabolic disorders, immunological disease, vascular diseases, hematological disorders, and malignancies. Muscle manifestations in these categories include pathogen-caused myositis, muscle infarction, rhabdomyolysis, myasthenia, immune-mediated myositis, necrotising myopathy, or vasculitis-associated myopathy. Muscle affection may concern only a single muscle, a group of muscles, or the entire musculature. Severity of muscle affection may be transient or permanent, may be a minor part of or may dominate the clinical picture, or may be mild or severe, requiring invasive measures including artificial ventilation if the respiratory muscles are additionally involved. Diagnostic work-up is similar to that of primary myopathies by application of non-invasive and invasive techniques. Treatment of muscle involvement in systemic diseases is based on elimination of the underlying cause and supportive measures. The prognosis is usually fair if the causative disorder is effectively treatable but can be fatal in single cases if the entire musculature including the respiratory muscles is involved, in case of infection, or in case of severe rhabdomyolysis. Conclusion – Secondary muscle manifestations of systemic diseases must be addressed and appropriately managed. Prognosis of secondary muscle disease in systemic diseases is usually fair if the underlying condition is accessible to treatment.

Introduction

Systemic diseases are characterized by involvement or affection of the entire organism and contrast focal diseases, in which only a single organ or part of it is affected [1a]. Systemic diseases are also those affecting a system which is distributed all over the body, such as the nervous system (CNS), the vascular system, or the blood. Systemic diseases include for example leukemia, anemia, central nervous systemic diseases, vasculitis, diabetes, thyroid dysfunction, hemochromatosis, rheumatological disorders, psoriasis, sarcoidosis, systemic lupus erythematosus, scleroderma, or mucoviscidosis (1). Some of these disorders secondarily affect the skeletal muscle, manifesting as myositis, muscle abscess, endocrine or metabolic myopathy, rhabdomyolysis, or myasthenia. The following review aims at summarizing and discussing recent advances concerning the management of muscle disease in systemic diseases, including infectious diseases, endocrinological disorders, metabolic...
disorders, immunological disorders, vascular disorders, and hematological disorders.

**Methods**

Data for this review were identified by searches of MEDLINE, Current Contents, for references of relevant articles using the search terms ‘infection’, ‘infectious’, ‘viral’, ‘bacterial’, ‘protozoal’, ‘helminthic’, ‘leukemia’, ‘anemia’, ‘diabetes’, ‘thyroid’, ‘hemochromatosis’, ‘rheumatological’, ‘psoriasis’, ‘lupus’, ‘scleroderma’, ‘sarcoidosis’, ‘mucoviszidosis’, ‘vasculitis’, and ‘vascular’ in combination with ‘skeletal muscle’, ‘myopathy’, ‘myositis’, ‘myasthenia’, ‘neuromuscular transmission’, and ‘rhabdomyolysis’. Randomized (blinded or open label) clinical trials, longitudinal studies, case series, and case reports were considered. Abstracts and reports from meetings were not included. Only articles published in English, French, Spanish, or German between 1966 and 2015 were included. Appropriate papers were studied and discussed for their suitability to be incorporated in this review. Due to limitations of space not all systemic diseases with muscle involvement could be discussed. Only the clinically most relevant were included.

**Results**

Classification of muscular manifestations of systemic diseases

Muscular manifestations in systemic diseases may be classified as acute, subacute, or chronic. Acute muscle manifestations include pathogen-caused myositis, muscle infarction, or rhabdomyolysis. Subacute or chronic muscular manifestations of systemic diseases include secondary endocrine or secondary metabolic myopathy, myasthenia, immune-mediated myositis, muscle abscess, or vasculitis with secondary myopathy (2). They may be further classified as transient or permanent, as mild or severe, as dominating or not dominating the clinical presentation, or as affecting a single muscle, a group of muscles, or the entire musculature.

Infectious diseases

**Viral infections** – Systemic viral infections may manifest in the muscle as myositis, rhabdomyolysis, or myasthenia. The most frequent among the muscle manifestations is myositis with a self-limiting course. More rarely, viral infections may manifest with rhabdomyolysis. Myasthenia due to viral infections is only reported in single cases.

Myositis – In a retrospective study of 35 patients with viral myositis, muscle manifestations included localized pain of the calves (80%), lower limb weakness (71%), impaired ambulation (57%), and gait disturbance (40%) lasting on the average 3.6 days (3). Symptoms were associated with elevated muscle enzymes (3). Myositis may affect all muscles, a group of muscles (4, 5), or a single muscle (6). In a study of 355 pediatric patients with laboratory-confirmed influenza-B, 17.9% developed myositis (7). During the influenza pandemic in 2009, children developed more frequently myositis as compared to adults (8). Infections with human T-cell lymphotropic virus (HTLV-1) may manifest as axial myositis (4). Some of the viral infections may also cause orbital myositis, such as infections with the chickenpox virus (5). Rarely, a single muscle like the serratus anterior may be affected during flu (6).

Concerning the causative agents, viral myositis has been reported following infections with influenza-B (7), influenza-A (8), parainfluenza-1 (9), parvoviruses (10), HTLV-1 (11), Epstein-Barr virus (12), arboviruses (e.g., dengue myositis) (13), adenovirus (14), coxsackie (15), herpes (16), human immunodeficiency virus-1 (HIV-1) (17), or chickenpox (5). Most frequently myositis is due to infection with the influenza (7) or parainfluenza virus (9). These patients may present with acute onset calf pain, tenderness, or gait disturbance (9). Myositis in dengue infection can be fulminant and affect the respiratory muscles requiring artificial ventilation (18). Only rarely is myositis due to infection with parvovirus-B19 (10), HCV (19), or the West Nile virus (20). Chronic HCV infection may be also associated with dermatomyositis (21) or inclusion body myositis (22). Infection with the New Jersey polyomavirus NJPyV-2013 may cause vasculitic myopathy (2). Muscle-tropic viruses often spread to the CNS, which may dramatically increase morbidity and mortality (23). Whether patients with an underlying subclinical primary or secondary myopathy or those taking muscle-toxic drugs are particularly prone to develop viral myositis is unknown. Infection with HIV-1 may be associated with polymyositis, dermatomyositis, or inclusion body myositis (17). Polymyositis from HIV-1 may be complicated by the development of muscle abscesses (24). HIV-myositis may be even the initial manifestation of acquired immunodeficiency syndrome (AIDS) (25).
Rhabdomyolysis – Viral infections, particularly dengue and influenza-A, have been recognized as cause of rhabdomyolysis with considerable morbidity and mortality (26). Rhabdomyolysis as a complication of a viral infection occurs particularly in children and usually has a benign course (27). The main complication of rhabdomyolysis is acute renal failure, often requiring hemofiltration or hemodialysis (28). Rhabdomyolysis occurs in 1% of the patients with dengue infections. Risk factors for developing rhabdomyolysis include myalgia, arterial hypertension, and acute renal failure (29). More rarely rhabdomyolysis may be triggered by infections with influenza-A (30), influenza-B (31,32), parainfluenza (33), herpes-6 (34), varicella zoster (35), cytomegaly virus (CMV) (36), coronavirus-NL63 (37), chikungunya (38), Alkhurma hemorrhagic fever virus (39), or HIV-1 (40). Rhabdomyolysis in dengue fever infections can be life-threatening in some cases (41–43).

Myasthenia – Whether viral infections cause myasthenia is under debate. Well-known, however, is that infections may deteriorate myasthenia. There are, however, some reports indicating that a causal relation between a viral infection and the development of myasthenia may exist. In six Chinese patients with a West Nile virus infection, myasthenia developed 3–7 months after the infection (44). Further evidence for an association between viral infections and myasthenia are results of single-fiber EMG investigations in patients with influenza or echovirus infection showing a neuromuscular transmission defect (45).

Bacterial infections – Systemic bacterial infections manifest in the muscle as myositis or rhabdomyolysis.

Myositis – Bacterial infections associated with myositis usually manifest as bacterial polymyositis (46). Commonly, bacterial polymyositis is a purulent infection accompanied by muscle abscesses (pyomyositis) (46). The main etiologic agent of bacterial polymyositis is Staphylococcus aureus (46). Staphylococcal pyomyositis is a severe infection with high mortality being increasingly recognized in temperate climates (47). Pyomyositis may originate from a focal infection such as arthritis, sacroiliitis, a spinal abscess, or from bacteremia or sepsis. Pyomyositis may develop after trauma, may remain focal, and may resolve upon a nonsurgical approach (48). Pyomyositis may affect a single muscle, such as the rectus femoris muscle (49), or may affect all muscles resulting in quadripleasis, as described in a patient after induction of chemotherapy for lymphoblastic leukemia (50). Pyomyositis may be diagnosed with ultrasound and culture of the aspirate (51). Pyomyositis of the iliopsoas muscle may be complicated by septic pulmonary embolism (47). These patients may require abscess drainage under CT-guidance (47). Presence of intramuscular hemangiomias seems to predispose for pyomyositis, as reported in a 4-year-old child with fatal meningitis (46). Sepsis from streptococcus group-G originating from arthritis may cause diffuse polymyositis without skin lesions or toxic shock syndrome (52). A severe form of bacterial myositis is streptococcal necrotizing myositis, which is often fatal (53). Muscle abscesses may also result from infection with Klebsiella pneumoniae (49) or mycobacterium tuberculosis (54). A rare cause of systemic myositis may be infection with campylobacter jejuni (55). Predisposing factors include skin penetration or impaired host immunocompetence (HIV-1, transplant recipient) (47).

Rhabdomyolysis – Occasionally, rhabdomyolysis may be a manifestation of a bacterial infection. Rhabdomyolysis has been particularly reported during infections with Staphylococcus aureus (56), Salmonella (57), brucella (58), mycoplasma pneumoniae (59), tuberculosis (60), tetanus (61), Legionella (62), or bacillus cereus (63). In a 6-year-old girl, life-threatening rhabdomyolysis was triggered by streptococcus bovis sepsis (27).

Protozoal infections – Muscle manifestations of protozoal infections include myositis or rhabdomyolysis.

Myositis – Protozoal infections are a frequent cause of myositis. In some of these cases, myositis may be the dominant feature of the infection, such as in muscular sarcocystis (64). Causative agents include sarcocystis, plasmidium falciparum, toxoplasma gondi, neospora, microspora, borrelia, pleistophora, babesia, ehrlichia, or trypanosoma. Muscular sarcocystis is clinically characterized by myalgia with or without fever, and delayed onset of hyper-CKemia and eosinophilia with the possibility of relapses (65). Muscular sarcocystis is particularly prevalent in Malaysia (65). Other frequent protozoal infections with muscular involvement include toxoplasmosis (66) and malaria (67). In toxoplasmosis, severe polymyositis may be even the presenting manifestation (66). In a patient with AIDS, myositis due
Helminthic infections – Helminthic infestations are frequently associated with muscle disease. Helminthic infestations manifest in the muscle predominantly as myositis. Helminthes potentially affecting the muscle include Toxocara (toxocarosis) (83), Echinococcus granulosus (hydatidosis) (84), Cysticercus (cysticercosis) (85), Trichinella (trichinosis) (86), Strongyloides (strongyloidiasis) (87), Haycocknema perplexum (88), Spirometra (sparganosis) (89), Fasciola (fasciolosis) (90), or Filaria (filariasis). Toxocara infection may go along with lumbar myositis (83). In the tropics, visceral larva migrans (toxocarosis) may manifest as tropical pyomyositis requiring repeated debridement (91). Hydatid cysts from infestation with Echinococcus may rarely occur in a single muscle as the initial manifestation (84,92). Most commonly, liver and lung are affected (92). Hydatid cysts of the muscle have been occasionally observed in patients with primary muscle disease (93). Cysticercosis may initially manifest as ptosis if the lid elevator is affected (94). Cysticercosis may also manifest as ocular myositis (95). Focal cisticercal myositis may be diagnosed with muscle ultrasound or MRI (85). Trichinosis manifests clinically in the muscle as myalgias due to dermatopolymyositis (86, 96). Trichinella has a unique relation to the muscle as it is located intracellularly. Patients may present with myalgia and fever, and elevated muscle enzymes (97). Rarely, trichinosis may go along with muscle weakness (98). In case of focal necrosis due to trichinosis, EMG may show profuse fibrillations (99). Later in the course, fibrosis and contractures may develop (99). Strongyloides rarely affects the muscle. Occasionally, patients taking steroids or immuno-suppressants may develop polymyositis from strongyloides infestation (87). In Australia, myositis may be due to infestation with the nematode Haycocknema perplexum (88). In single cases, sparganosis may manifest as ocular myositis (89). Rarely, cutaneous fasciolasis may cause myositis of the intercostal muscles (90). Filariasis rarely manifests as myositis with muscle swelling (100).

Endocrinological disorders

Diabetes – Diabetes is a catabolic condition which manifests in the muscle as diabetic myopathy (101). Diabetic myopathy encompasses a spectrum of abnormalities, including wasting, muscle inflammation, ischemia, infarction, hemorrhage, necrosis, fibrosis, or fatty atrophy (101). Clinical manifestations vary depending on the underlying abnormality. The most frequent muscle manifestation in diabetes is painless muscle wasting (diabetic amyotrophy), which is either due to a diabetic plexus lesion (102) or due to affection of satellite cells by the diabetes (103). A further frequent manifestation of diabetic myopathy is diabetic myonecrosis presenting as self-limiting condition with acute onset of swelling and severe muscle pain (104). Typically, patients have no fever, normal white blood cell count, normal blood sedimentation rate, but elevated C-reactive protein (104). Usually, myonecrosis occurs in poorly controlled diabetes (105). The diagnosis is established by muscle MRI, and the treatment of choice is bed rest and analgesics (104). An increasingly recognized manifestation of diabetic myopathy is diabetic muscle infarction, which is regarded as rare and occurs in long-standing diabetic patients (106). Clinical manifestations of muscle infarction include acute onset local pain, together with a focal, palpable mass lesion. The diagnosis is established by muscle MRI (106). Additionally, the expression level of Pax7, MyoD, myogenin, and fatal myosin-heavy-chain (MHC) is significantly decreased in diabetic myopathy (102).

Thyroid dysfunction – Hypothyroidism – Hypothyroidism is a well-known cause of muscle disease (hypothyroid myopathy) (107). In contrast to hyperthyroid myopathy, CK is usually elevated,
pain is frequent, and muscles can be swollen. Additionally, hypothyroidism due to autoimmune disease may be associated with dermatomyositis (108) or polymyositis (109, 110). Rarely, hypothyroidism may also go along with rhabdomyolysis (111). In infancy or childhood, hypothyroidism may manifest as Kocher–Debré–Semelaigne syndrome, characterized by lower limb or generalized muscle hypertrophy, myxedema, short stature, and cretinism. In adults, hypothyroidism may manifest as Hoffmann’s syndrome, characterized by muscle stiffness and muscle pseudo-hypertrophy. Muscle enzymes are generally elevated in hypothyroid myopathy. The EMG may show a myopathic, neuropathic, or a mixed pattern. Clinical manifestations of hypothyroid myopathy return to normal with hormone replacement therapy.

Hyperthyroidism – Graves’ disease may manifest in the skeletal muscle as mild and usually painless proximal weakness or as idiopathic ocular myositis (112). Myositis may respond favorable to thiama- zole without adding steroids (113). Thyrotoxicosis may go along with episodic muscle weakness due to polymyositis (113). Thyrotoxicosis may also manifest as acute or chronic bulbar muscle dysfunction (bulbar myopathy). If thyrotoxicosis leads to hypokalemia, generalized muscle weakness may ensue (thyrotoxic periodic paralysis). A rare manifestation of hyperthyroidism or thyreotoxicosis may be myokymia.

Hyper-/hypoparathyroidism – Hyperparathyroidism may cause muscle weakness (dropped head syndrome), muscle pain, or ischemic, calcifying myopathy (114, 115). Hyperparathyroidism may also go along with spontaneous rupture of the Achilles tendons. Rarely, the initial manifestation of hyperparathyroidism may be dysphagia. FDG-PET in hyperparathyroidism may show tumors mimicking muscular metastases. Affection of the muscle in hyperparathyroidism may present as myopathy, neuromyotonia, or rhabdomyolysis (116).

Other endocrinopathies – Hypoadrenalism as well as hyperadrenalism may be complicated by generalized muscle weakness. In case of acromegaly, the muscles may be hypertrophic and stronger than normal, but later in the course proximal weakness may become evident.

**Metabolic disorders**

Various metabolic disorders secondarily affect the muscle. The most well-known are hemochromatosis, amyloidosis, and porphyria.
Porphyria may go along with rhabdomyolysis (132). There are also reports about transient muscle weakness and muscle contractures in acute intermittent porphyria (133). Acute intermittent porphyria may also manifest as acute myalgias or muscle weakness (134).

**Immunological disorders**

A number of immunological disorders may involve the skeletal muscle presenting as polymyositis, dermatomyositis, rarely as inclusion body myositis, or as ocular myositis. The most important among these disorders are systemic lupus erythematosus (SLE), Sjögren syndrome, rheumatoid arthritis, systemic sclerosis, psoriasis, and the antisynthetase syndrome (ASS).

**Systemic lupus erythematosus (SLE)** – SLE is a chronic inflammatory, multisystem disease with a broad spectrum of clinical and serological abnormalities (135). SLE has been repeatedly reported to manifest with muscle disease. Muscle manifestations of SLE include polymyositis or rhabdomyolysis (Table 1). Some patients with SLE may even develop myositis together with rhabdomyolysis (136). Myositis is much more frequent than rhabdomyolysis. In a study of 15 SLE patients, 9% had developed clinical myositis (137). However, histopathological evidence of myositis was seen in 47% of these patients (137). Type-2 atrophy was the predominant histopathological finding. Occasionally, myositis may be the initial manifestation of SLE (138). Rarely, SLE may manifest as ocular myositis (139). Muscle involvement in SLE may also manifest as necrotizing autoimmune myopathy with muscle weakness and rhabdomyolysis (140). Polymyositis is also a feature of mixed connective tissue disease, including clinical and laboratory manifestations of SLE, scleroderma, and polymyositis along with high titeres of anti-U1 and anti-U2-nRNP antibodies (141). Myositis may also occur in patients with SLE/polymyositis or SLE/dermatomyositis overlap syndrome (142). Rhabdomyolysis in SLE may be fatal in some cases (143).

**Sjögren syndrome** – The skeletal muscle is frequently affected in Sjögren syndrome usually manifesting as myalgia or weakness (144). In 3% of the patients, myositis has been described (144). In a study of 573 patients with Sjögren syndrome, myositis was found in 4.9% of them (145). Occasionally, muscle affection manifests as ocular myositis (146). Rarely, dermatomyositis may occur (147). Occasionally, Sjögren syndrome may be also associated with polymyositis (148). In some patients, Sjögren syndrome was even associated with inclusion body myositis (149). The latter patients usually carried the HLA-DRB1 allele or its equivalent HLA-DR3 or the MHC ancestral haplotype. This is why the association of Sjögren syndrome and sporadic inclusion body myositis was assumed due to a genetic predisposition linked to MHC (150).

**Rheumatoid arthritis** – Affection of the skeletal muscles in rheumatoid arthritis manifests as rheumatoid myositis (151). Causes of rheumatoid arthritis are variable and include inflammation, drugs, impaired joint flexibility, or sedentarism (151). Muscle enzymes are usually highly elevated. Electromyography (EMG) may show short duration, low-amplitude, polyphasic motor unit action potentials (151). Active inflammation can be found on both muscle ultrasound and MRI.

**Myopathy in systemic disease**

*Table 1 Muscle manifestations of systemic diseases*

| Disorder                             | MP | FMS | PM | DM | IBM | MG | RM |
|--------------------------------------|----|-----|----|----|-----|----|----|
| Infectious disease                   |    |     |    |    |     |    |    |
| Viral infections                     | +  |     | +  |    |     | +  |    |
| Bacterial infections                 |   - | +  |    |    |     |    |    |
| Protozoal infections                 | -  | +  | +  |    |     | +  |    |
| Helminthic infections                | -  | +  | +  |    |     | +  |    |
| Endocrinological disorders           |    |     |    |    |     |    |    |
| Diabetes                             |    |     |    |    |     |    |    |
| Hypothyroid dysfunction              |    |     |    |    |     |    |    |
| Hyperthyroid dysfunction             |    | +  | +  |    |     |    |    |
| Hypoparathyroidism                   |    | +  |    |    |     |    |    |
| Hypoparathyroidism                   |    | +  |    |    |     |    |    |
| Hypo-hyperadrenalism                 |    | +  |    |    |     |    |    |
| Metabolic diseases                   |    |     |    |    |     |    |    |
| Hemochromatosis                      |    | -  | +  |    |     |    |    |
| Amyloidosis                          |    | +  | -  |    |     |    |    |
| Porphyria                            |    | +  |    |    |     |    |    |
| Immunological disorder               |    |     |    |    |     |    |    |
| Systemic lupus erythematosus         |    | +  | +  |    |     | +  |    |
| Sjögren syndrome                     |    | +  | +  |    |     | +  |    |
| Rheumatoid arthritis                 |    | +  |    |    |     |    |    |
| Systemic sclerosis                   |    | +  | +  |    |     |    |    |
| Psoriasis                            | +  | +  |    | +  |     |    |    |
| Antisynthetase syndrome              |    | +  |    |    |     |    |    |
| Sarcoidosis                          |    | +  |    |    |     |    |    |
| Vascular diseases                    |    |     |    |    |     |    |    |
| Behcet disease                       |    | +  |    |    |     |    |    |
| Wegener                              |    | -  | +  |    |     |    |    |
| Churg-Strauss syndrome               |    | +  | +  |    |     |    |    |
| Hematological disease                |    |    |    | +  |     |    |    |
| Sickle cell anemia                   |    |    |    | +  |     |    |    |
| Neoplasms                            |    |    |    |    |      +|    |    |
| Leukemia                             |    | +  | +  |    | +  | +  |    |
| Lymphoma                             | +  | +  |    | +  | +  | +  |    |
| Breast, lung, gastrointestinal       | +  | +  | +  | +  | +  | +  |    |
| Bladder tumor                        |    |    |    |    | +  | +  |    |

MP, myopathy; FMS, focal myositis; om, orbital myositis; PM, polymyositis.

*Pyomyositis, abscess; IBM, inclusion body myositis; RM, rhabdomyolysis; necrotizing myopathy.*
Muscle biopsy may show nonspecific findings, such as changes in fiber size or internal structure, pleomorphic mitochondria, dilated sarcotubular system, multiple internal or subsarcolemmal nuclei, a trend toward type-II-fibers, fiber atrophy, degenerative/regenerative modifications, and inflammatory features such as patchy B- or T-cell infiltrates, mainly perivascularly or endomysially, but also in the perimysial compartment (151). In rare cases, rheumatoid myositis may be complicated by compartment syndrome (152) or may affect the extraocular muscles (ocular myositis) (153, 154). Adalimumab has been reported to induce myositis in rheumatoid arthritis. Eosinophilic myositis has been reported in a patient with myotonic dystrophy-1 and rheumatoid arthritis (155).

Systemic sclerosis – Systemic sclerosis is characterized by arthralgia, synovitis, contractures, tendon friction rubs, tenosynovitis, and muscle disease (156). Muscle involvement in systemic sclerosis is frequent (156). Muscular manifestations of systemic sclerosis include myositis with myalgia and weakness (156). Rarely, patients with systemic sclerosis may develop inclusion body myositis (157). In a study of 1145 patients with systemic sclerosis, 5.6% had elevated CK. This subset of patients had a poor prognosis impacting survival, particularly in male with early onset, topo1 and RNP autoantibodies, and interstitial lung disease (158). If muscle weakness includes the head extensor muscles, dropped head syndrome may ensue (159). Muscle MRI is an appropriate tool to support the diagnosis of muscle involvement in systemic sclerosis (160). In some patients, myositis responded favorably to immunoglobulin (161).

Psoriasis – Psoriasis is a noninfectious, inflammatory dermatological disorder, which presents as systemic disease if joints, bands, eyes, arteries, or the heart are additionally involved. Psoriasis is associated with an increased risk of diabetes and ischemic stroke. Only rarely muscle involvement has been reported. In a study of 11370 patients with psoriasis, 13 had a pathologically confirmed myopathy (0.11%) (162). Eleven had generalized inflammatory myopathy and 2 had focal muscular inflammation (162). In two-thirds of these patients, onset of psoriasis preceded that of myopathy. Patients receiving a TNF-alpha blocker had an increased risk of developing myositis (162). Rarely, orbital myositis has been reported (163). FDG-PET may show an increased tracer-uptake in affected muscles (164). In a single case, psoriasis was associated with dermatomyositis and antibodies against the glomerular basement membrane (165).

Antisynthetase syndrome (ASS) – ASS is due to auto-antibodies directed against aminoacyl-transfer ribonucleic acid (tRNA) synthase enzymes such as anti-Jo1, anti-PL7, or anti-PL12 (166). Clinical manifestations include fever, nonerosive polyarthritis, Raynaud phenomenon, mechanic’s hands, myocarditis (42% of patients), interstitial lung disease, which is frequently associated with anti-Jo1 antibodies, pulmonary hypertension, progressive multifocal leucoencephalopathy, or myositis with myalgias (166, 167). Presence of interstitial lung disease is a major prognostic factor (168). Treatment of choice is the application of corticosteroids with or without immunosuppressive agents (168).

Vascular disorders

Muscle function not only depends on appropriate innervation and energy production, but also on sufficient blood perfusion. Muscle perfusion may depend not only on cardiac function but also on muscle artery contractility. Physiologically, endothelial cells produce basal and stimulated nitric oxide (NO). During exercise, NO production is stimulated, which contributes to exercise-induced muscle hyperemia. In patients with reduced NO production due to reduced activity of NO-synthetase (NOS), reduced microcirculation contributes to exercise-induced muscle fatigue. NO deficiency results in muscle hypoperfusion with decreased provision of nutrients and thus decreased protein production (169). Microvascular perfusion is particularly compromised in systemic vasculitis, which includes Behcet disease, Wegener’s granulomatosis, and Churg-Strauss syndrome.

Behcet disease – Behcet disease is a form of systemic vasculitis with the classical triad of oral ulcers, genital ulcers, and uveitis (152). Involvement of the skeletal muscle is rare (152). The most common muscle manifestation is myositis. Myositis usually shows a focal distribution (170). In single cases, orbital myositis has been reported (171). Only a single extra-ocular muscle may be affected (172). Only rarely may myositis dominate the clinical presentation (173). Development of myositis in Behcet disease may be triggered by stress such as surgery (174). Occasionally, myositis may be of the necrotizing type (175). Generalized myositis may be diagnosed by muscle ultrasound, CT, or MRI (152). Generalized
myositis in Behcet disease may occasionally respond favorably to cyclosporine (176).

Wegener’s granulomatosis – Wegener’s granulomatosis (granulomatosis with polyangiitis) is a systemic necrotizing vasculitis which is associated with granulomatous infection of the nasopharynx, the sinuses, the oropharynx, and the lower bronchial airways. Muscle involvement is infrequent and usually manifests as myositis. The most common type of myositis in Wegener’s granulomatosis is ocular myositis (177). If myositis predominantly affects the lower limb muscles, it may go along with muscle weakness and gait disturbance (178).

Churg–Strauss syndrome – Churg–Strauss syndrome, also known as eosinophilic granulomatosis with polyangiitis, is a granulomatous vasculitis of the small arteries accompanied by infiltrates of eosinophils. It manifests clinically in three stages, initially as allergic cold and asthma, followed by eosinophilic infiltration of the lung and intestines and systemic vasculitis. Myositis is a rare muscle manifestation of the disease and presents with myalgia, fever, and muscle weakness (179). Myositis in Churg–Strauss syndrome may not only concern all muscles resulting in polymyositis (180) but may occur focally as orbital myositis (181).

Hematological disorders

Hematological disorders are rarely associated with muscle disease. Muscle involvement has been particularly reported in sickle cell anemia (182). Muscle affection in sickle cell anemia includes myalgia, focal myopathy, focal myositis, pyomyositis, myonecrosis, fibrosis, fasciitis, or rhabdomyolysis. Muscle involvement is more frequent in hematological neoplasms, but they are described in more detail below.

Neoplasms

Muscle disease in neoplasms is a paraneoplastic phenomenon and includes focal or generalized myositis, polymyositis, dermatomyositis, or necrotizing myopathy. Neoplasms associated with muscle disease include leukemia, lymphomas, or other solid tumors.

Leukemia – Polymyositis/dermatomyositis are symmetric, proximal, paraneoplastic, inflammatory myopathies with or without distinct cutaneous eruptions (183). They have been long recognized in association with cancer (183). Only rarely may polymyositis/dermatomyositis be associated with acute myelocytic leukemia (183). In single cases, chronic lymphatic leukemia may go along with inclusion body myositis (184, 185). Pyomyositis may be the initial presentation not only of chronic myeloid leukemia (186) but also of acute lymphocytic leukemia (187). In a girl with secondary acute myelogenous leukemia following chemotherapy, tuberculous myositis developed (188). Chemotherapy for leukemia may occasionally induce pyomyositis (189).

Lymphoma – Lymphoma is frequently associated with muscle disease, particularly with polymyositis or dermatomyositis (190). B-cell lymphoma, T-cell-lymphoma, and Hodgkin’s lymphoma have been reported in association with dermatomyositis or polymyositis (191). In a study of 32 patients with polymyositis/dermatomyositis, 20 had B-cell lymphoma, four had T-cell lymphoma, and two had Hodgkin’s lymphoma (191). In single cases, B-cell lymphoma manifested with isolated myositis of a single extra-ocular muscle (192). Non-Hodgkin lymphoma may directly develop inside the muscle.

Other malignancies – Paraneoplastic myopathy has been reported also in a number of other neoplasms. Lung, gastrointestinal, and breast carcinomas are frequently associated with necrotizing myopathy. The bladder transitional cell tumor may cause necrotizing myopathy with pipecistem capillaries. Waldenström’s macroglobulinemia may go along with antidecorin (BJ) myopathy. Patients with thymoma may develop rippling muscle syndrome. Patients with paraproteinemia (M-protein, $\kappa > \lambda$ light chains, IgG) or carcinoids may present with scleromyxedema.

Diagnosis

Methods to diagnose muscle manifestations of systemic disease are the same as those applied for diagnosing primary muscle disease. The basis is a thorough individual and family history and a thorough clinical exam. Determination of muscle enzymes, EMG, muscle imaging, and a muscle biopsy may be of additional help. FDG-PET may show increased muscular tracer-uptake in myositis (164) or tumors. Viral infections causing myositis may be diagnosed by detection of serum antibodies against viruses or by PCR. CK values may be higher during the acute stage of an influenza infection than during
the convalescence stage (193). Determination of various muscle-specific antibodies or auto-antibodies, such as anti-Jo1, anti-PL7, anti-PL12 (ASS) (166), anti-EJ, anti-OJ, anti-SRP, anti-Mi-2, anti-PM-Scl75, anti-PM-Scl100, and anti-Ku (overlap syndromes) may be necessary to establish the diagnosis of muscle disease in immunological disorders. U1-nRNP antibodies may be determined when suspecting SLE, scleroderma, or polymyositis overlap syndrome. Topo1 and RNP antibodies may be positive in myopathy from systemic sclerosis (158). Antidecorin antibodies (BJ antigen) may indicate Waldenström’s macroglobulinemia. Determination of ryanodine-receptor antibodies may be helpful for diagnosing myasthenia gravis or myotisitis, and determination of monoclonal antibodies (M-proteins) may suggest scleromyxedema. Single-fiber EMG may show a disturbed neuromuscular transmission during the acute stage of influenza or echovirus infections (45). Disturbed neuromuscular transmission may explain muscle weakness and fatigue during a viral infection (45). If muscle imaging reveals an enhancing lesion with a fluid density and needle aspiration shows pus, Staphylococcus aureus is growing in 85% of the cases (194). Before diagnosing a secondary myopathy, a primary myopathy needs to be excluded (195).

Treatment of muscle involvement in systemic diseases is mainly based on the treatment of the underlying disorder. Additionally, symptomatic measures for pain, muscle cramps, muscle stiffness, can be applied. Symptomatic measures for myositis may also include nonsteroidal analgesic drugs, steroids, immunoglobulin, or immunosuppressants. Diabetic myonecrosis responds favorably to bed rest and analgesics. In case of immune-mediated myasthenia, cholinergic drugs, steroids, or immuno-suppressants may be necessary. In case of vasculitis-related myopathy, immuno-suppression may be beneficial. Infectious myositis may respond to adequate antibiotic treatment. Helminthic infections may respond to anthelmintics with or without steroids. In case of abscess formation, puncture and drainage or resection may be indicated. In severe pyomyositis due to toxocarasis, repeated debridement may be inevitable (91). In a rare case of myopathy associated with Whipple disease antibiotics exhibited a beneficial effect on muscle manifestations (196). In case of severe rhabdomyolysis with renal insufficiency diuretics, hemofiltration or hemodialysis may beneficially influence the muscle pathology. Most cases of muscle involvement in systemic disease profit from physiotherapy.

Limitations
Systemic disease is not addressed in this review because of limited space, to few reports in the literature, or low frequency of muscle involvement, include aspergillosis, celiac disease (197), Henoch-Schoenlein purpura, Crohn’s disease, mucoviscidosis, sarcoidosis, AMPA-associated immune encephalitis (198), renal myopathy, and vitamin-D deficiency (199).

Clinical implications and summary
For treating physician, it is essential to know about muscular involvement in infectious, endocrine, metabolic, immunogenic, vascular, hematological diseases, or neoplasms. As soon as muscle involvement is suspected, referral to the neurologist is inevitable, and appropriate diagnostic measures as outlined above need to be initiated. In emergency cases due to renal or respiratory compromise, the treating neurologist must instantly manage and supervise the diagnostic procedures to initiate appropriate treatment in due time. In case of chronic muscle involvement, diagnostic steps may be taken more slowly but may be more invasive including abscess puncture or muscle biopsy. Particularly in infectious diseases, it is important to precisely determine the causative agent to apply the most specific antimicrobial agents with the highest effect. Muscle involvement in systemic diseases needs to be recognized and thoroughly investigated, as some cases may take a rapid or fulminant course with a high probability of an unfavorable or even fatal outcome.

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Conflict of interest
The authors have nothing to declare.

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