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Neurologic Manifestations of Systemic Disease (David Lapides, Section Editor)

Secondary Causes of Myositis

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Abstract

Purpose of review The purpose of this paper is to comprehensively evaluate secondary causes of inflammatory myopathies (myositis) and to review treatment options.
Recent findings This review highlights recent advancements in our understanding of known causes of myositis, including newer drugs that may cause myositis such as checkpoint inhibitors and viruses such as influenza, HIV, and SARS-CoV2. We also discuss treatment for malignancy-associated myositis and overlap myositis, thought to be a separate entity from other rheumatologic diseases.
Summary Infections, drugs, rheumatologic diseases, and malignancies are important causes of myositis and are important to diagnose as they may have specific therapies beyond immunomodulatory therapy.

Introduction

The term "myositis" is often used interchangeably with "idiopathic inflammatory myopathy" (IIM), referring to primary autoimmune diseases of muscle including dermatomyositis, inclusion body myositis (IBM), antisynthetase syndrome, and necrotizing autoimmune myopathy [1–6]. However, there are also known causes of inflammatory myopathies which must be considered in the evaluation of patients with acute or subacute myopathy, including infections, drugs, mixed connective tissue disease, and malignancies. Furthermore, while polymyositis is classically included in IIMs, most cases are now thought to either be early IBM or secondary to another disease such as those covered here. As several excellent recent reviews have covered treatment of IIM [6,7••,8], this review will focus on known, or secondary, causes of myositis.

Infectious myositis can occur with bacterial, viral, fungal, or parasitic infections. Bacterial myositis, which is typically focal, can occur via hematogenous spread (pyomyositis) or via spread from contiguous infection or trauma [9]. While a range of bacteria can cause pyomyositis, the most common is *Staphylococcus aureus*, which causes up to 90% of cases in tropical regions and up to 70% in the USA [10, 11]. The most common cause of bacterial myositis not due to

hematogenous spread is *Streptococcus*, whereas myositis in the setting of trauma is typically due to polymicrobial infection [9]. Viral myositis is most commonly caused by influenza and enterovirus but can be caused by many different classes of viruses [12], and clinical presentations range from myalgias to focal myositis to rhabdomyolysis. Myalgias are typically an initial presenting symptom of influenza, whereas myositis usually follows days of illness and is marked by pain and swelling. In progression to rhabdomyolysis, muscle pain and weakness typically become diffuse and are accompanied by a marked increase in serum creatine kinase (CK) enzyme level and myoglobinuria. A recent retrospective case study from Wuhan on neurologic complications of SARS-CoV-2 indicates that infectious myositis may also be a complication of SARS-CoV-2, as close to 10% of patients had muscle injury as defined by the presence of myalgias and CK > 200 units per liter (U/L) [13•]. Typically, viral myositis is treated symptomatically and resolves within days. An exception to this is HIV-associated myositis which presents with both proximal and distal weakness progressing over weeks to months that clinically and pathologically overlaps with inclusion body myositis (IBM) [14•]. Finally, fungal and parasitic infections have been reported to cause myositis. Fungal myositis is rare and usually occurs in immunocompromised hosts, whereas parasitic myositis occurs in endemic regions; the most common causes include *Trichinella*, *Taenia solium*, and *Toxoplasma gondii* [9].

Medications have also been linked to myositis. Statins commonly cause myalgias, but are also rarely associated with an autoimmune necrotizing myopathy and autoantibodies to 3-hydroxy-3 methylglutaryl-coenzyme A reductase (HMGCR) [15]. Most (63%) patients with anti-HMGCR myositis were previously exposed to statins [16], though anti-HMGCR myositis can also present in statin-naïve patients. Immune checkpoint inhibitors (ICI) are a class of drugs recently developed for cancer treatment, for which myositis has been recognized as an immune-related adverse event. Myositis in these patients can occur along with other autoimmune syndromes, most commonly myasthenia gravis or myocarditis [17]. Myositis typically occurs early in the course of treatment, with one study showing median onset 25 days after initiation of ICI [18]. Other medications that have been linked to myositis include penicillamine [19, 20], interferon beta [21], and TNFα inhibitors [22]. In this era of COVID-19, it is important to note that chloroquine and hydroxychloroquine, used to treat or prevent SARS-CoV-2, can cause a progressive myopathy characterized by autophagic vesicles [23•].

Myositis has also been associated with connective tissue diseases, including systemic sclerosis, systemic lupus erythematosus (SLE), mixed connective tissue disease, and Sjögren's syndrome. Recent studies suggest that myositis in patients with systemic sclerosis confers a worse prognosis than those without myositis [24, 25], suggesting that overlap myositis should guide treatment decisions in these patients.

Finally, myositis can also be secondary to underlying malignancy. Autoimmune necrotizing myopathy, dermatomyositis, and polymyositis have all been associated with malignancies [26, 27]. Risk of malignancy is highest in the year prior to and following diagnosis [28–34], and it is associated with older age [33, 35, 36], male sex [37], cutaneous necrosis [37, 38], rapid onset of disease [38], high inflammatory markers [38, 39], and resistance to treatment [29]. In dermatomyositis, the presence of NXP-2 and TIF-1γ antibodies are also associated with an increased risk of malignancy [40]. Of note, myositis can be a rare feature of chronic graft versus host disease (cGVHD), a complication of allogeneic stem cell transplantations [41–43].

Treatment of secondary myositis

For an overview of commonly used medications to treat myositis, see Table 1. While these are the most common medications used to treat both primary (IIM) and secondary causes, this is not a comprehensive list, and the use of these and other medications is discussed in detail elsewhere [6–8].

Table 1. Commonly used immunomodulatory treatment of inflammatory myopathies

Medication	Standard Dose	Relative Contraindications	Main drug interactions	Main side effects	Special points	Cost/cost-effectiveness
Prednisone [44]	0.5–1 mg/kg/d	Dose-dependent with live or live-attenuated vaccines [45], systemic fungal infections	-Minor substrate of CYP3A4; use with caution with other drugs interacting with CYP3A4 metabolism	Hypertension, hyperglycemia, psychiatric disturbances, osteoporosis, weight gain, fluid retention, cataracts, acne, skin fragility.	-Administer age-appropriate live-attenuated vaccinations prior to initiation -May cause myopathy -Use with caution in patients with diabetes, hypertension, renal impairment, ocular disease, osteoporosis, and seizure disorders -May cause adrenal suppression; taper slowly - consideration of PCP prophylaxis - calcium (1200 mg/daily) and vitamin D (at least 1000 IU) for bone protection - Consider prophylactic bisphosphonate for prolonged use (> 3 months) of prednisone >7.5 mg daily	Tablets (per each): $0.16–$1.50 each
IV methylprednisolone [46]	Up to 1 g/dose for 3–5 days for high dose "pulse therapy"	Live or live attenuated vaccines, systemic fungal infection,	-Major substrate of CYP3A4; use with caution with other drugs interacting with CYP3A4 metabolism	Hypertension, hyperglycemia, psychiatric disturbances, osteoporosis, weight gain, fluid retention	-Administer age-appropriate live-attenuated vaccinations prior to initiation -May cause myopathy -Use with caution in patients with diabetes, hypertension, renal impairment, ocular disease,	Solution (injection): 1000 mg: $36.00–$50.27

Table 1. (Continued)

Medication	Standard Dose	Relative Contraindications	Main drug interactions	Main side effects	Special points	Cost/cost-effectiveness
					osteoporosis, and seizure disorders - May cause adrenal suppression; taper slowly	
Azathioprine [47]	50 mg/day; increase by 50 mg/week to total dose of 2 to 3 mg/kg/day	contraindicated with allopurinol	Use with caution with pregnancy (category D), other immunosuppressive drugs; contraindicated with allopurinol, aminosalicylates, other drugs affecting myelopoiesis, ACE-inhibitors, warfarin, ribavirin	-Malaise, fever -Nausea and vomiting Adverse effects: hematologic toxicity, hepatotoxicity, increased risk of infections, rare pancreatitis, chronic treatment increases malignancy risk, PML has been reported -Hypersensitivity reaction with fevers and rash is a rare side effect	-Administer age-appropriate live-attenuated vaccinations prior to initiation -Screen for TB, HBV, HCV, HIV before initiation -May take 2–3 months to show an effect - Monitor CBC with differential and platelets weekly during the first month, then twice a month for 2 months, then monthly -Check TPMT prior to initiation	Tablets (per each): Azathioprine oral: 50 mg: $2.11–$6.81 Imuran oral – 50 mg: $9.07
Methotrexate [48]	15 mg once weekly; may increase the dose slowly in 2.5 mg/week increments to 25 mg once weekly	Pregnancy, breastfeeding	-use with caution with other immunosuppressive agents -Use with caution with NSAIDs and salicylates, drugs that could displace methotrexate from albumin, certain antibiotics, hepatotoxins, nitrous oxide anesthesia	Alopecia, skin photosensitivity, diarrhea, nausea and vomiting, stomatitis, increased liver enzymes Adverse effects: acute renal failure, bone marrow suppression (especially with NSAIDs), severe skin reactions, GI toxicity, hepatotoxicity, increased risk of infections, pneumonitis, risk of secondary malignancy -Linked to impaired fertility, embryotoxicity, and fetal defects	-Administer age-appropriate live-attenuated vaccinations prior to initiation --Screen for TB, HBV, HCV, HIV and with chest X-ray before initiation -Give concomitant folic acid to reduce side effects - Monitor CBC with differential and platelets, serum creatinine, and LFTs: Baseline and every 2 to 4 weeks for	Tablets (per each) 2.5 mg: $3.56–6.24)

Table 1. (Continued)

Medication	Standard Dose	Relative Contraindications	Main drug interactions	Main side effects	Special points	Cost/cost-effectiveness
					3 months after initiation or following dose increases, then every 2–3 months during 3 to 6 months of treatment, then every 3 months beyond 6 months of treatment -Caution in renal dysfunction (renally cleared, dose reductions mandated)	
Mycophenolate [49]	500 mg twice daily; increase to a maintenance dose of 1 g to 1.5 g twice daily	Pregnancy, risk of fetal malformations. Must use at least 2 forms of contraception	Use with caution with other immunosuppressive agents -Use with caution with acyclovir, antacids, cholestyramine, cyclosporine, ganciclovir, oral contraceptives, sevelamer, trimethoprim/sulfamethoxazole, norfloxacin, and metronidazole	Nausea, diarrhea, abdominal cramping, Adverse effects: bone marrow suppression, infections, PML, increased malignancy risk -Teratogenic	--Administer age-appropriate live-attenuated vaccinations prior to initiation --Screen for TB, HBV, HCV, , HIV before initiation -may decrease serum concentration of estrogen or progestin contraceptives Use with caution in patients with active GI disorders or renal impairment Monitor CBC (weekly for first month, twice monthly during months 2 and 3, then monthly through the first year	Tablets (per each) Mycophenolate mofetil 500 mg: $7.85–7.95 Cellcept 500 mg: $21.59 Capsules (per each): Mycophenolate mofetil 250 mg: $3.93–3.99 Cellcept 250 mg: $10.80
IVIG [50]	2000 mg/kg per treatment course administered in divided doses over 2	Caution with IgA deficiency (with antibodies against IgA and history of hypersen-sitivity)	Estrogens may increase thrombotic risk	Hypersensitivity and anaphylactic reactions (greater risk with IgA antibodies), aseptic meningitis, hemolysis, infusion reactions,	--Screen for TB, HBV, HCV, HIV before initiation -Use with caution in elderly patients due to risk of renal failure	Solution (intravenous) 5 g/50 ml (per mL): $11.31–$109.08

Table 1. (Continued)

Medication	Standard Dose	Relative Contraindications	Main drug interactions	Main side effects	Special points	Cost/cost-effectiveness
	to 5 consecutive days every 4 weeks			pulmonary edema, acute renal failure, thromboembolic events	and thromboembolic events -Monitor renal function -Majority of side effects are dose and rate-dependent	
Plasmapheresis [51,52]	One exchange of 1–1.5 plasma volumes every second or third day for a total of three to five procedures.	–	Plasmapheresis may remove therapeutic antibodies or medications that are highly protein-bound or with small amount of vascular distribution. If given after IVIG, may remove IVIG. For non-plasma replacement fluids, patients on ACE-inhibitors are at increased risk of symptoms similar to anaphylaxis.	Hypotension, pulmonary edema, catheter complications. Non-plasma replacement fluids: hypocalcemia, hypokalemia, coagulation factor or immunoglobulin depletion. Donor plasma/red blood cells: hives, anaphylaxis, TRALI.	-If using non-plasma replacement fluids, hold ACE inhibitor for 24 h prior to pheresis. -Care should be taken with dosing timing of certain medications (i.e. small vascular distribution, protein-bound, or antibodies), as plasmapheresis may remove these medications	Variable
Rituximab [53]	1 g once every 2 weeks for 2 doses		-Use with caution with other immunosuppressive agents	Hypertension, edema, sweating, night sweats, pruritis, increased LFTs, increased risk infections, chills, fatigue, headaches, asthenia, cough diverse events: Bowel obstruction/perforation, cardiac events, cytopenias, hepatitis B virus or TB reactivation, infections, infusion-related reactions, mucocutaneous reactions, PML	-Administer age-appropriate live-attenuated vaccinations prior to initiation -Screen for TB, HBV, HCV, HIV before initiation - Obtain CBC with differential and platelets prior to treatment and prior to each treatment course, and at 2–4 month intervals -Avoid in pregnancy: women of reproductive potential during	Solution (Intravenous) 500 mg/50 mL (per mL): $86.02–112.74

Table 1. (Continued)

Medication	Standard Dose	Relative Contraindications	Main drug interactions	Main side effects	Special points	Cost/cost-effectiveness
					therapy and for at least 12 months following the last rituximab dose should be using contraception. -Premedicate with IV steroids, antihistamine and acetaminophen before infusion	

Infectious myositis

For viral infectious myositis, patients are treated with hydration, rest, and analgesics, and symptoms usually resolve within days [12]. For HIV-associated myositis, one study of 11 patients showed patients treated with immunosuppressive medications had improvement in proximal weakness despite the progression of distal weakness, though it is unclear if this improvement may be due to the natural progression of disease [14•]. In this case series, several patients improved with initial treatment of prednisone transitioned to steroid-sparing agents such as mycophenolate or azathioprine. In our opinion, it is reasonable to initiate a trial of immunosuppressive therapy in HIV-associated myositis with consultation of an infectious disease physician. Treatment of bacterial, fungal, or parasitic myositis will require antibacterial, antifungal, or antihelminthic therapy, respectively [9].

Medication-induced myositis

HMGCR antibodies associated with statin use

For patients with anti-HMGCR antibodies, cessation of statin therapy is important [54]. For patients that require cholesterol-lowering medication, proprotein convertase subtilisin/kexin type 9 (PCSK9) can be considered, as these medications were shown to be safe in a case series of 8 patients with HMGCR antibody-positive necrotizing myopathies [55]. In rare mild cases, further treatment beyond statin cessation may not be necessary [54]. For immune treatment, expert consensus recommends initial treatment with steroids (oral steroids at 1 mg/kg/day or IV steroids 0.5–1 g/day for 3–5 days) with initiation of azathioprine, methotrexate, mycophenolate, or intravenous immunoglobulin (IVIG) [2]. IVIG monotherapy may be considered in patients with comorbidities that could be worsened with steroids, such as diabetes mellitus or osteoporosis [56]. In refractory or relapsing patients, rituximab may be considered [2, 57, 58].

ICI-associated myositis

Expert guidelines recommend the treatment of ICI-associated myositis tailored to severity [59••]. For mild weakness without CK elevation, patients may be offered analgesia, and ICI may be continued with careful monitoring of CK. For mild or moderate weakness with CK elevation, it is recommended for ICIs to be held, and prednisone can be initiated at 0.5–1 mg/kg. These cases may require permanent discontinuation. For severe weakness limiting activities of daily living, cessation of ICI and referral to a neurologist or rheumatologist with expertise in managing myositis are recommended. In this case, patients can be treated with 1–2 mg/kg prednisone (use higher dose if weakness is severely limiting mobility or if there is dysphagia or cardiac or respiratory involvement), with consideration of plasmapheresis or IVIG treatment. If there is no improvement in 4–6 weeks, transition to immunosuppression therapy such as azathioprine, methotrexate, or mycophenolate may be considered. With myocardial involvement, it is recommended that ICIs be permanently discontinued [59••]. It is unclear if rechallenge of severe ICI-associated myositis with ICI is safe, although one report examining two patients re-challenged 7 or 9 months after myositis resolution did not see a reoccurrence of ICI-associated myositis [60]. In

a systematic review of ICI-associated neuromuscular complications, 20 of 29 ICI-associated myositis patients improved with immunosuppression [17].

Other medications

For myositis related to penicillamine, TNFα inhibitors, and interferon beta therapy, cessation of these medications led to improvement in symptoms [19, 21, 22]. Caution is recommended with re-challenge of penicillamine and TNFα inhibitors, as re-challenge has been reported to be associated with relapse for both penicillamine-associated myositis [61, 62] and TNFα inhibitor-associated myositis [22, 63].

Overlap myositis

There is limited data for treatment of overlap myositis, but the general principle is to use immunosuppression therapy that also targets the associated rheumatic disease. Systemic sclerosis is the most common rheumatologic disease that overlaps with myositis [64, 65]. Although there is limited data for immunosuppressive treatment, our center prefers to start with a steroid-sparing agent such as mycophenolate which is commonly used to treat systemic sclerosis, as glucocorticoid treatment is a risk factor for renal crisis [66]. For myositis associated with systemic lupus erythematosus (SLE), patients typically respond well to glucocorticoid treatment; resistant myositis can be treated with additional immunosuppression such as methotrexate [67, 68]. IVIG is usually avoided in patients with systemic lupus erythematosus with antiphospholipid antibodies due to the risk of thromboses. In myositis associated with mixed connective tissue disease, known to respond well to steroids, treatment with increased doses of glucocorticoids usually provides a good response [69]. Rheumatoid arthritis rarely is associated with myositis [70], and myositis is usually initially treated with glucocorticoids with consideration of transition to steroid-sparing agents [71].

Sjogren's syndrome and inclusion body myositis

Sjogren's syndrome is rarely associated with inclusion body myositis (IBM) [72, 73]. Although IBM is refractory to treatment [74–76], patients with IBM and Sjogren's syndrome have been reported to respond to treatment with immunosuppression [72, 73, 77, 78]. Thus, it is our practice to treat Sjogren's syndrome patients with new diagnosis of IBM with immunosuppression, starting with prednisone 1 mg/kg/day for 2–3 months. If patients respond to glucocorticoids, we initiate steroid-sparing agents such as methotrexate or azathioprine for a trial period while tapering glucocorticoids. Steroid-sparing agents are selected due to side effect profile (Table 1) [79]. However, in our clinical experience, we have seen little response to immunosuppression in these patients.

Myositis associated with malignancy

When myositis is discovered to be associated with malignancy, a guiding principle is to treat the underlying malignancy, which in some cases has been shown to cure myositis [80–83]. However, this should not preclude the treatment of myositis with immunosuppression. Corticosteroids and IVIG are commonly used to avoid side effects and interactions with chemotherapeutic agents.

Glucocorticoid treatment should be coordinated around possible surgery, since glucocorticoids can delay wound healing. Prognosis tends to be worse than in idiopathic inflammatory myositis, but depends on the treatment of the underlying malignancy [33, 84].

Myositis associated with cGVHD

In a study examining polymyositis in the setting of cGVHD, 12 patients were treated with either prednisone monotherapy or a combination of prednisone with either azathioprine or cyclosporine, and all showed improvement [42]. Another case series of three patients with dermatomyositis-associated cGVHD showed improvement with immunosuppression via combination treatment of corticosteroids, tacrolimus, rituximab, mycophenolate mofetil, and/or IVIG [43]. Given these results, we recommend steroids with additional immunosuppressive agents if necessary for cGVHD-associated myositis.

Physical/speech therapy and exercise

Physical therapy and exercise

We recommend that all patients with myositis be evaluated by a physical therapist that specializes in neuromuscular disease to develop an exercise program. Exercise in myositis has been shown to be safe and effective at improving endurance and strength [85–88]. Patients with polymyositis or dermatomyositis that underwent intensive aerobic exercise combined with resistance training in a randomized controlled trial have improved muscle function, quality of life, and possible reduced disease activity [89]. In fact, a subset of dermatomyositis and polymyositis patients undergoing resistance training showed decreased disease activity [90]. A recent randomized, single-blinded crossover trial examining aerobic training with exercise bicycles showed safety and improved aerobic capacity in patients with inclusion body myositis, providing class II evidence for aerobic training improving cardiopulmonary fitness [91]. We recommend combined aerobic and strength training [86], with avoidance of high-impact and eccentric exercises. Additionally, passive range of motion exercises is useful for extremely weak muscles to prevent contractures. Physical therapists should also work with patients to prevent falls and evaluate patients for assistive devices for ambulation.

Speech therapy

We recommend referring patients with dysphagia to speech therapy for a swallow evaluation. Oropharyngeal dysphagia may be addressed with diet modifications and head positioning maneuvers. For refractory dysphagia, patients may require percutaneous endoscopic gastrostomy to maintain nutrition.

Emerging therapies

Rituximab

Attention has turned to using rituximab for refractory myositis, for which several studies have shown positive effects for patients with myositis or necrotizing myopathies [57, 92–94]. A randomized, double-blind placebo-controlled trial examining rituximab in myositis did not reach its primary endpoint,

but most patients had clinical improvement [95•]. These studies support an off-label use for rituximab in patients with refractory myositis, although additional rigorous studies are needed to evaluate its effectiveness.

Other emerging therapies

Several new medications for IIM are currently undergoing clinical trials. If they are found to be effective, further evaluation in treatment of secondary causes of myositis will be warranted. Some of the most promising ones are commented on below.

Abatacept is a fusion protein of F_c region of IgG1 and CTLA-4 designed to prevent T cell activation that is currently FDA-approved to treat rheumatoid arthritis. There have been case reports of abatacept successfully used to treat refractory overlap myositis [96] and refractory ICI-associated myositis [97]. A pilot study of 20 patients with refractory dermatomyositis or polymyositis using abatacept found that almost half of their patients showed reduced disease activity and improved muscle performance after treatment for 6 months [98], and there is now a phase III, randomized, double-blind trial to further evaluate abatacept for myositis treatment (ClinicalTrials.gov identifier: NCT02971683).

JAK inhibitors, designed to prevent interferon-induced activation of cytokine receptors, have also been tested in pilot studies for refractory dermatomyositis with promising results, including improved weakness and skin lesions [99–101]. The JAK inhibitor tofacitinib is under investigation in the open-label pilot STIR trial (ClinicalTrials.gov identifier: NCT03002649).

Another drug currently under investigation is tocilizumab, a monoclonal antibody directed against interleukin 6. A case report found normalization of CK in two patients with refractory polymyositis treated with tocilizumab [102], and another showed improvement of both arthritis and weakness in a patient with overlap myositis with rheumatoid arthritis [103]. A randomized controlled phase II trial is underway examining tocilizumab treatment of myositis patients (ClinicalTrials.gov identifier: NCT02043548).

Conclusion

Secondary myositis has several underlying triggers. Here, we have highlighted myositis in the setting of infections, medications, systemic rheumatologic disease, and malignancies. A careful history and workup will detect these underlying causes, for which treatment can be modified accordingly. Severe and persistent cases of secondary myositis require an integrated approach of treating the underlying systemic cause, immunosuppression, and physical therapy.

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Compliance with Ethical Standards

Conflict of Interest

Sarah H. Berth declares that she has no conflict of interest. Thomas E. Lloyd declares that he has no conflict of interest.

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