Viral and retroviral myositis

Introduction

Overview

Viruses are important causes of viral myositis. In addition to myriad other infections, both viruses and retroviral contributions to retroviruses are well-known human pathogens that can be associated with an inflammatory myopathy. Either by direct infection of muscle or the ensuing inflammatory response, viruses are associated clinically with myositis. Advances in humans have important clinical, antiretroviral, and theoretical implications. The theoretical implications especially stem from the possibility that antiretroviral treatment myositis may also occur as a result of treatment of the initial infection. Theoretically, certain infectious agents could trigger certain “idiopathic” chronic inflammatory myopathies, or their occasional association might shed light on pathogenesis and offer practical treatment strategies for these classic neuromuscular diseases. This became especially important in the 1990s when HIV and other retroviruses as well as hepatitis C virus were investigated for their role in polymyositis and inclusion body myositis (among many other neurologic diseases). In this article, the authors discuss the clinical manifestations, pathogenesis, and diagnoses of viral and retroviral myositis.

Key points

• Viral myositis manifests with myalgia, weakness, and, rarely, rhabdomyolysis.
• Although virtually any virus can cause an acute myositis, influenza virus and enterovirus are most common in North America and Northern Europe.
• Acute and subacute viral myositis is mostly benign and self-limited.
• Chronic viral myositis is associated with retroviruses and hepatitis viruses.
• Basic evaluation of viral myositis is warranted in all patients, but further studies for underlying hereditary myopathies is indicated in certain cases.

Historical note and terminology

The rather broad topic of viral and retroviral contributions to inflammatory myopathy in humans has important clinical and theoretical implications. The theoretical implications especially stem from the possibility that certain infectious agents could be the root cause of certain “idiopathic” chronic inflammatory myopathies or that their occasional association might shed light on pathogenesis and offer practical treatment strategies for these classic neuromuscular diseases. This became especially important in the 1990s when HIV and other retroviruses as well as hepatitis C virus were investigated for their role in polymyositis and inclusion body myositis (among many other neurologic diseases).

The first recognition of a connection between viruses and human muscle disease occurred with coxsackieviruses in 1934 with the epidemic pleurodynia, an ill-defined, self-limited, acute febrile illness with painful thoracic and abdominal muscles (Sylvest 1934).

Viral myositis. The word myalgia comes from the Greek mys (“muscle”) and algos (“pain”). One of the first physicians to describe myalgia specifically as muscle pain distinct from neuralgia was Dr. Thomas Inman in a book written in 1860 titled On Myalgia. Descriptions of myalgia in journal articles first began to appear in the early 20th century, and again the focus was on muscle-specific pain and differentiation from other causes of pain (Keith 1908).

The word virus originates from Latin meaning “poison.” Diseases caused by viruses (such as poliomyelitis and smallpox) have been recognized since ancient Egypt, yet the discovery and definition of viruses did not occur until the
latter half of the 19th century. As early as 1840, German anatomist Jacob Henle of Gottingen posited the existence of agents too small to be seen by the light microscope but able to cause disease. Multiple simultaneous discoveries by Chamberland and Pasteur, Iwanowski, and Beijerinck and Mayer led to the knowledge that living agents smaller than all known bacteria and capable of causing disease in both plants and animals could be transmitted through bacteria-free filtrates (Fields et al 2007; Collier et al 2011).

Myositis comes from the Greek *myo* ("muscle") and *itis* ("inflammation"). The first description of what was most likely a viral myositis was by Dabney in 1888. He described an epidemic in Charlottesville, Virginia, which he likened to dengue and was characterized by acute severe pleuritic chest pain, also called epidemic pleurodynia, and nicknamed “Devil’s Grip” in the setting of fever and systemic symptoms. In the summer of 1923, an epidemic of likely viral myositis consisted of an acute febrile disease and severe, transient epigastric pain, thought to be diaphragmatic spasm at the Presbyterian Hospital in New York (Anonymous 1924). In the 1930s, Dr. Ejnar Sylvest of Denmark described “myositis acute epidemica” and posited that there was an infiltration of the muscles and noted the increased frequency in the summer and autumn months (Sylvest 1934). Dr. Thomas Pickles called a similar phenomenon Bornholm disease (named after an island in the Baltic where many cases were seen) and “epidemic myalgia” and even Sylvest disease, whereas others described it as “epidemic pleurodynia.” The localization to the muscle (in particular the diaphragm) was hypothesized given the absence of pleuritic rub or pulmonary findings.

An association between epidemic pleurodynia and a causative viral agent was first found in the late 1940s, and in 1950 the isolation of coxsackievirus from throat washings from prior epidemics as the causative agent (Weller et al 1950). This observation was expanded over the ensuing years to patients with inflammatory myopathies who had serological evidence of high viral antibody titers (Tang et al 1975; Travers et al 1977; Christensen et al 1986). The saga re-emerged when antibodies to the Jo-1 antigen, a histidyl-transfer RNA synthetase (Targoff 1990), were found in up to 10% of patients with myositis (Dalakas 1989). Jo-1 antigen shares structural homology with the genomic RNA of an animal picornavirus, the encephalomyocarditis virus, which suggested a possible molecular mimicry phenomenon. Strengthening the association of viral infection and inflammatory myopathy, enteroviral RNA was found in some cases by in situ hybridization in muscle fibers of some myositis patients (Rosenberg et al 1989; Youse et al 1990), but this could not be verified.

Influenza-associated myositis was first described in 1950s as “myalgia cruris epidemica,” proven to be confirmed with polymerase chain reaction studies (Leff et al 1992; Leon-Monzon and Dalakas 1992). The idea of entervirus replication within the myocytes of chronic inflammatory myopathies fell from favor as studies began focusing on HIV, other retroviruses, and hepatitis C due to influenza virus. in 1970.

Retroviral myositis. The first report of a retrovirus associated with inflammatory myopathy came in the 1980s with monkeys infected with simian immunodeficiency virus (Dalakas 1986; Dalakas et al 1986), followed closely by human cases associated with HIV (Dalakas 1986; Dalakas et al 1986) and later HTLV-I (Morgan et al 1989).

Other viruses. Hepatitis C virus-associated polymyositis or myositis was first reported in 1994 (Matsuya et al 1994), with numerous subsequent reports (Horsmans and Geubel 1995; Ueno et al 1995; Weidensaul et al 1995; Saperstein et al 1999) including 2 cases in which hepatitis C virus RNA was detected in muscle biopsies using polymerase chain reaction (Sola et al 1999; Villanova et al 2000). There were next several case reports of inclusion body myositis co-occurring with hepatitis C virus infection (Alexander and Huebner 1996; Saperstein et al 1999; Yakushiji et al 2004), and in one case reverse transcriptase polymerase chain reaction revealed hepatitis C virus RNA in muscle samples (Yakushiji et al 2004). This led to a Muscle Study Group investigation into interferon beta as a treatment for seronegative inclusion body myositis patients. Unfortunately, this was not found to be effective in 2 randomized controlled trials (Muscle Study Group 2001; Muscle Study Group 2004; Yakushiji et al 2004).

**Clinical manifestations**

**Presentation and course**

Identifying the clinicopathologic syndrome is important to narrow the etiologic differential diagnosis and guide treatment and prognosis. Parainfectious viral myositis may present as several distinct syndromes: diffuse myalgias (often with little or no weakness), segmental myalgias, polymyositis, inclusion body myositis, rhabdomyolysis, and rarely dermatomyositis, granulomatous myositis, or necrotizing myopathy. Elevations of creatine kinase as well as aldolase, lactate dehydrogenase, and the aminotransferases would be expected in many cases of myalgias, most
cases of polymyositis and dermatomyositis, inclusion body myositis, and all cases of rhabdomyolysis. For most cases of inflammatory myopathy, the electromyogram shows irritability (fibrillations, positive sharp waves) and low-amplitude, short-duration (“myopathic”) motor units.

A syndrome of acute-onset diffuse myalgias may precede, accompany, or follow infection with various viruses. This association is especially strong for coxsackieviruses and influenza viruses but probably also occurs with various other common human viruses. Sometimes the myalgias may be more restricted, at which point "epidemic pleurodynia" or "Bornholm’s disease" may be applied (Sylvest 1934). Diffuse myalgias also occur in many HIV patients treated with zidovudine and in hepatitis C virus patients treated with interferon-alpha (see below).

A more specifically defined syndrome with segmental myalgias, sometimes termed “benign acute childhood myositis” or “myalgia cruris epidemica,” can follow infection with influenza A or B viruses (Mackay et al 1999; Agyeman et al 2004; Crum-Cianflone 2008). This disease characteristically occurs about 3 days (range 0 to 18 days) after the initial manifestations of influenza (ie, fever, headache, cough, rhinorrhea). Benign acute childhood myositis has a strong predilection for school-aged children, though it has been reported in adults including the elderly. Characteristically, the child experiences acute onset of calf pain and difficulty walking. Examination usually reveals only tenderness to palpation of the calf muscles and abnormal gait. Diagnosis rests mostly on finding the appropriate history and examination in a child with influenza A or B proven by nasopharyngeal swab or residing in an influenza-afflicted community. Also, creatine kinase elevation and a myopathic EMG may be useful to narrow the differential diagnosis or to confirm prior suspicions. Musculoskeletal MRI may show T2 and STIR hyperintensity and contrast enhancement (Panghaal et al 2008). In cases that have gone to biopsy, there is degeneration and necrosis with surprisingly little inflammatory infiltrate. The prognosis is excellent as the disease is self-limited over about 3 days (range 1 to 30 days). Neuraminidase inhibitors, which are useful in influenza only within the first 36 hours of symptoms, have not been studied in benign acute childhood myositis and are not likely to be useful because presentation is usually outside this window. Some studies suggest benign acute childhood myositis may occur in 6% to 34% of childhood cases of influenza A or B. Most commonly, patients with virus-associated myositis will present with diffuse myalgias, although multifocal myalgias, muscle weakness, and rhabdomyolysis are also possible. There is often muscle tenderness to palpation or with movement, and occasionally there is muscle edema. Most commonly, the large muscles in the legs are affected (quadriceps, calf, gluteus muscle groups) (Crum-Cianflone 2010). The clinical presentation depends on a number of factors, including which muscles are involved, host characteristics, and virus-specific features. The clinical course of viral myositis may be acute, subacute, or chronic. Myositis associated with influenza and enterovirus infection is often acute or subacute, whereas that associated with retroviruses and hepatitis is often chronic. Secondary complications, such as rhabdomyolysis, are rare but can occur with any viral myositis.

**Influenza virus.** In the case of influenza A or B virus, additional nonspecific systemic symptoms are fever, headache, cough, and rhinorrhea; in most patients who experience myalgias, these are diffuse and self-limited. However, in a subset of patients (from 5.5% to 33.9% of children) a specific syndrome sometimes referred to as “benign acute childhood myositis” will develop, which is distinct from the initial myalgias in that symptoms are more severe, can be focal, and occur later in the course of infection (more than 3 days later). It is more common in school-aged children with a male predominance (2:1), and 75% are associated with influenza B virus. Children may exhibit sudden-onset calf pain and difficulty walking. There may be tenderness, swelling of gastrocnemius muscles, soleus, or other muscles. Calf muscles are usually involved and in two thirds of cases are the only muscle group involved. These features were shown to be prominent in a 2007-2008 outbreak in the pediatric population in Germany of influenza B-associated benign acute childhood myositis (Mall et al 2011).

A retrospective study in Austria of 375 cases of influenza A H1N1 during the 2009 pandemic demonstrated that a greater proportion of children had serum elevations of creatine kinase (almost 50%) whereas this proportion was much lower in adults (approximately 25%) (Redlberger-Fritz et al 2014). Meanwhile, myalgias were more often experienced in the group with constitutional symptoms (both adult and children) and were also more common in adults compared to children (all symptom groups). Retrospective analysis of emergency department cases of suspected acute viral myositis in Brazil found that symptoms were most often localized to the legs and in particular the calves with elevated muscle enzymes and leukocytosis (Cardin et al 2015). During the 2009 pandemic, several cases of acute viral myositis with myalgias, weakness, and elevated CK were reported, all of which recovered within a week with supportive care (Gibson et al 2013).

Myocarditis associated with influenza infection usually develops within the first week of infection. Patients may be
asymptomatic or have chest pain, shortness of breath, or signs and symptoms of acute congestive heart failure.

Rhabdomyolysis is a rare but potentially fatal syndrome due to the breakdown of skeletal muscle with the release of skeletal muscle cell contents, including proteins and electrolytes, in the systemic circulation. The rapid release of large quantities of potassium, calcium, organic acids, and myoglobin can lead to renal tubular toxicity and acute renal failure as well as cardiac arrhythmias and compartment syndrome. Numerous viruses have been associated with rhabdomyolysis, including: influenza, parainfluenza, enteroviruses, adenovirus, SARS-coronavirus, HIV, herpes viruses, parvovirus, dengue virus, and West Nile virus. Of all rhabdomyolysis associated with viral infection, the most common etiology is influenza virus (42%), followed by HIV and enterovirus. However, a review of 300 cases of influenza-associated myositis found that only 3% developed rhabdomyolysis (Agyeman et al 2004).

Enterovirus. Infection with coxsackievirus, an enterovirus, is associated with the syndrome of epidemic myalgia or epidemic pleurodynia. Epidemic myalgia manifests as paroxysmal sharp pain in the thoracic and upper abdominal muscles and intercostal regions and is associated with localized muscle tenderness and fever. The pain is worse with cough or deep breathing, and there may be an associated headache and sore throat. Correlating with common times of coxsackievirus infection, this is most often seen in the summer and fall months. A study in Yunnan province in China identified 98 cases of enterovirus-associated acute flaccid paralysis. Most cases occurred in young children; two thirds had fever at onset, one third had myalgias, and lower numbers had diarrhea or neck stiffness or upper respiratory symptoms (Tang et al 2014). Group B coxsackievirus can also cause myocarditis and pericarditis.

Retroviruses. The human immunodeficiency virus (HIV) is associated with a more chronic polymyositis-like syndrome. Symptoms include slowly progressive, proximal, and symmetrical weakness and myalgias. It appears to be more common with influenza B and has a 2:1 male predominance. Benign acute childhood myositis must be distinguished from the more common diffuse myalgia syndrome that precedes or co-occurs with the usual influenza symptoms: (1) benign acute childhood myositis onset is later, after onset of usual symptoms; (2) benign acute childhood myositis is more focal (2/3 of cases involve only the calves), and (3) benign acute childhood myositis affects the patient more severely. Up to 3% of cases of influenza-associated myositis are accompanied by rhabdomyolysis; interestingly, this complication is seen more often in girls with influenza A (contrary to the epidemiological tendencies for benign acute childhood myositis).

Polymyositis as defined clinicopathologically likely represents the final common pathway of various myopathies, especially infectious and autoimmune varieties. HIV, HTLV-1, and hepatitis C virus have been studied extensively to clarify their roles in polymyositis. HIV myositis presents as a subacute-onset, slowly progressive, proximal, often symmetrical, muscle weakness of the arms and legs; this closely parallels the presentation of autoimmune polymyositis. The serum CK can elevate as much as 10 to 15 times normal; however, it may also be normal. Although rare, this can be the first presenting symptom of HIV. HIV-associated myositis may occur with seroconversion, as the only indication of a chronic silent HIV infection, or in a known HIV-infected patient. HIV patients are also at risk of medication-induced mitochondrial myopathy and associated myalgias. In addition, myopathy can occur from the use of antiretroviral therapy, such as in nucleoside-related mitochondrial myopathy. HIV is also associated with subacute proximal limb weakness due to a nemaline myopathy or even an inclusion-body myositis clinical picture. There are case reports of dermatomyositis as a rare presentation of HIV seroconversion (Rajadhyaksha et al 2012).

Human T-cell lymphotropic virus type 1 (HTLV-1) can induce an inflammatory myopathy clinically and pathologically indistinguishable from sporadic polymyositis. This presentation may coexist with the more common HTLV-associated myeloneuropathy/tropical spastic paraparesis or may be the only clinical manifestation of HTLV-1 infection. The association of HTLV-1 with polymyositis is highlighted by studies in 2 areas where HTLV-1 is endemic: (1) in Jamaica, 7% to 18% of healthy normals are seropositive compared to 85% of polymyositis patients; and (2) in Kagoshima, Japan, 11.6% of the population is seropositive compared to 27.5% of polymyositis patients. Cases of localized axial (paraspinal muscle) myopathy due to HTLV-1 have been reported (Matsuura et al 2015).

Chronic hepatitis C virus inclusion-body myositis has been associated with HIV and HTLV-1, although not nearly as often as polymyositis. The first reports demonstrated the histopathological and immunopathological similarities between sporadic and retroviral-associated inclusion-body myositis (Cupler et al 1996).

Hepatitis viruses. Hepatitis B virus and hepatitis C virus can be associated with a polymyositis but also with polyarthritis or polymyalgia rheumatica. Chronic hepatitis C virus infection has been associated with polymyositis (Horsmans and Guebel 1995; Ueno et al 1995; Weidensaul et al 1995; Saperstein et al 1999; Sola et al 1999; Villanova
et al 2000; Di Muzio et al 2003). Patients may have myalgias for some time before the inflammatory myopathy is diagnosed. Chronic hepatitis B virus infection has also been associated with myositis in several cases (Mihas et al 1978; Pittsley 1978; Nojima et al 2000; Capasso et al 2006). In one case, lamivudine (an antiviral therapy used in hepatitis B) normalized symptoms and electromyography in a steroid-refractory patient (Gruber-Wackernagel et al 2008).

Inclusion body myositis has been associated with HIV, HTLV-1, and hepatitis C virus, although not nearly as often as polymyositis. Cupler and colleagues reported inclusion body myositis in patients with HIV and 1 patient with HTLV-1 (Cupler et al 1996). They developed all the usual clinical and histological features with the exception of high (up to 1000-fold) elevation of serum creatine kinase. At least 7 more cases have been reported (Ozden et al 2001; Ozden et al 2004; Loutfy et al 2003; Dalakas et al 2007). Matsuura and colleagues identified positive HTLV-1 serology in 11 of 21 sporadic inclusion body myositis patients in an endemic area of Japan, suggesting that HTLV-1 may be associated with either polymyositis or inclusion body myositis (similar to HIV) (Matsuura et al 2008). Yakushiji and colleagues found incapacitating inclusion body myositis in a hepatitis C virus carrier and obtained significant improvement using interferon-beta therapy at doses higher than those used by the Muscle Study Group in sporadic inclusion body myositis--250 MIU over 10 weeks compared to 144 MIU over 24 weeks (Yakushiji et al 2004). There are several other case reports of inclusion body myositis occurring in the setting of hepatitis C virus infection (Alexander and Huebner 1996; Saperstein et al 1999).

Dermatomyositis and granulomatous myositis have not convincingly been attributed to any viral or retroviral etiology. In 2 HIV patients, a facial rash raised suspicion of dermatomyositis, but classic skin lesions and histologic signs of dermatomyositis were absent (Baguley et al 1988; Gresh et al 1989). There are 2 reports of dermatomyositis occurring in hepatitis C virus-infected patients (Nishikai et al 1994; Fiore et al 1996).

Inclusion-body myositis has long been associated with hepatitis C virus, as evidenced in numerous case reports and series. The clinical presentation and course, histopathological findings on muscle biopsy, and prognosis in patients with sporadic inclusion-body myositis and HCV-associated inclusion-body myositis are virtually indistinguishable. One study quantified the increased prevalence of positive HCV serologies in patients with inclusion-body myositis (28%) compared to matched controls with polymyositis (4.5%), whereas both groups had similar prevalences of positive serologies for HTLV-1, HIV, and hepatitis B virus (Uruha et al 2016).

A case report of hepatitis E virus-induced severe myositis was reported, with flaccid tetraparesis, acute hepatitis, and renal failure (Mengel et al 2016).

Other viruses. Alphaviruses (including Ross River virus, Barmah Forest virus, Chikungunya virus) are positive-sense single-stranded RNA viruses of the family Togaviridae. Manifestations in humans include arthritis and arthralgia and myalgias.

A new polyomavirus was identified as a cause of a vasculitic myopathy in a transplant patient. Polyomaviruses are small, double-stranded DNA viruses that are widespread. Most often they cause mild respiratory symptoms or are asymptomatic in humans; however, the two most often associated with human disease are the BK and JC viruses. Mishra and colleagues reported a patient who was on immunosuppression and developed fatigue, myalgias, weakness, and loss of visual acuity (Mishra et al 2014). Serum CK was initially normal but then elevated to a peak of 8,000 U/L. EMG showed widespread myopathy, and muscle biopsy of the biceps brachii showed vasculitis, microthrombosis of capillaries, myonecrosis, myositis, and atrophy.

Parvovirus B19 can cause a myositis with associated fever and diffuse rash (slapped cheeks). Parvovirus B19 infection is usually asymptomatic but may cause aplastic anemia, erythema infectiosum (diffuse rash with “slapped cheeks” appearance and fever), hydrops fetalis, or chronic red cell aplasia. A case of myositis (in the setting of fever, rash, and acute B19 infection) in an adult was described (Cakirca et al 2015).

Adenovirus has been associated with myocarditis, myositis, and rhabdomyolysis. Although herpes zoster ophthalmicus is known to cause ophthalmoplegia, varicella zoster virus and orbital myositis causing ophthalmoplegia in an adult has been reported (Kim et al 2014).

Dengue infections occur globally, and symptoms can range from asymptomatic to severe with multiorgan impairment and bleeding. Classic symptoms include rapid onset fever, headache, retro-orbital pain, arthralgia, and severe myalgia.
Both direct viral infection and indirect host immune responses are important for the neurologic manifestations of dengue infection. Myalgia is very common, but myositis and weakness are rare and usually severe, accompanied by respiratory muscle involvement, elevated CK, and myopathic findings on EMG.

Chikungunya was first identified in 1952 in Tanzania and named by the Makonde people for the painful arthritis that it causes (chikungunya roughly translates as “the disease that bends up the joints”) (Ross 1956). It is re-emerging in Africa, Asia, South America, and the Caribbean, and more recent outbreaks have been more clinically severe and fatal, due in part to new virus mutations. Chikungunya virus causes fever, rash, arthralgias, and myositis. Symptoms are usually self-limited and resolve within 3 to 4 days.

**Prognosis and complications**

Prognosis for viral myositis depends to some degree on which virus is involved and the temporal course of the myositis. Most viral myositides are self-limited and benign with prognosis for full recovery.

Influenza-associated myositis is usually self-limited, and full recovery is expected. Potential complications include the development of rhabdomyolysis (as described in clinical features above) and the ensuing associated issues. Symptoms often last a week but may last up to a month.

The clinical course of Coxsackievirus-associated myositis is self-limited, lasting approximately 5 days, but up to 25% will experience a recurrence of pleurodynia symptoms.

Myositis occurring in the course of a chronic infection such as HIV, HTLV-1, hepatitis C virus, or hepatitis B virus is usually chronic and will increase the patient's disability. Early diagnosis and effective management may prevent further disability. Nevertheless, there is concern that using immunosuppression may enhance the severity of the underlying disease and cause more systemic complications or, in the case of AIDS, co-infections. There are a few anecdotal reports that patients with HIV-associated myopathy may improve spontaneously, but it is not known whether this is related to better nutrition, medical care, or other types of supportive therapy. In general, the inclusion-body myositis associated with HIV, HTLV-1, and hepatitis C virus are similar to the sporadic form and follow a similar clinical course, with limited response to immunotherapy.

Myopathies associated with acute viral infection are generally self-limited with good prognosis for return to previous level of function. Myositis associated with HTLV-1 infection seems to be clinically indistinguishable from sporadic polymyositis and would, therefore, follow a similar natural history.

**Clinical vignette**

A 32-year-old man presented with several days of proximal leg and arm muscle weakness, calf cramping, and myalgias. He reported low-grade fevers at home but no cough, rhinorrhea, nausea, diarrhea, or rash. Neurologic examination was notable for mild proximal weakness (deltoids 4+/5 and hip flexors 4+/5), but otherwise strength was full throughout. Reflexes were 2+ and symmetrical throughout, and sensation was intact to all modalities.

Laboratory findings were notable for elevated creatine phosphokinase at 1120 units/L (upper limit of normal 225 units/L), aldolase 17.7 units/L (upper limit of normal 8.1 units/L), and positive IgM and IgG for the Epstein Barr virus. Sedimentation rate was normal and C-reactive protein was elevated at 0.72mg/dL (upper limit of normal 0.5mg/dL). A myositis serology panel was negative (including: Mi-2, PL-12, PL-7, Ej, Oj, SRP, Ku, U2 snRNP, PM/SCL, Jo-1). Other findings included: low-level cryoglobulinemia, polyclonal immunoglobulin pattern on serum protein electrophoresis, normal white blood cell count, mildly positive ANA at 1:160, normal TSH, and serologies for E. Chaffeensis negative (IGG, IGM), RMSF/Rickettsia, C. pneumoniae IGG positive, IGM negative, HHV6 IGG positive, IGM negative, Babesia duncani IGG negative, parvovirus B19 IGG positive, IGM negative, and Lyme western blot negative.

Electrodiagnostic studies revealed normal motor and sensory nerve conduction studies, but on needle electromyography a myopathic pattern without active myonecrosis was seen in several muscles in the arm and leg.

He was treated symptomatically, and weakness resolved within days; myalgias and cramps resolved within 6 weeks. Creatine phosphokinase returned to normal. Repeat electrodiagnostic study after 3 months was normal. Muscle biopsy was not performed due to full recovery.
Biological basis

Etiology and pathogenesis

Human viruses associated with inflammatory myopathy include coxsackieviruses, influenza A and B viruses, HIV, HTLV-I, hepatitis C virus, and hepatitis B virus. Rare cases have been associated with cytomegalovirus (Maeda et al 2000), Epstein-Barr virus (Uchiyama et al 2005), and West Nile virus (Smith et al 2004). The specific clinicopathological syndrome may narrow the likelihood of a viral etiology.

Viral contributions to inflammatory myopathy are postulated to occur via several mechanisms. The mechanisms of viral myositis are not fully elucidated, but there is evidence for several pathophysiological mechanisms. Broadly speaking, direct viral invasion of skeletal muscle cells is one possible process, and the inflammatory and cytokine response is a second. The virus-host interactions that contribute to myositis include: (1) direct infection (acute or chronic) or host response to viral antigens, (2) molecular mimicry, and (3) immune dysregulation. This section covers the host and pathogen contributors to the pathogenesis of viral myositis.

In inoculated mice, coxsackieviruses can cause acute and chronic myositis (Kibrick 1964; Favara et al 1967; Ginsberg 1990; Sandager et al 2008). Furthermore, muscle cultures (especially immature myotubes) can be directly infected with coxsackieviruses. Nevertheless, the role of coxsackieviruses in human polymyositis has been unconvincing, with some reports of high antibody titers in chronic inflammatory myopathies (Tang et al 1975; Travers et al 1977; Christensen et al 1986). Similarly, there has not been any clear evidence that influenza virus causes sporadic polymyositis in humans although in 2 well-studied cases, viral particles were seen in muscle biopsy by electron microscopy (Gamboa et al 1979; Kessler et al 1990). Maeda and colleagues reported a single case of polymyositis occurring in the setting of acute cytomegalovirus infection (Maeda et al 2000). In 2 cases, hepatitis C virus RNA was detected in muscle biopsies using polymerase chain reaction (Sola et al 1999; Villanova et al 2000). Mumps virus was once considered a candidate for causing inclusion body myositis because the 15-nm to 20-nm microtubular filaments in inclusion body myositis resemble mumps virus nucleocapsids (Chou 1967), but the search for mumps virus via polymerase chain reaction has been negative (Nishino et al 1989; Leff et al 1992; Fox et al 1996). Leff and colleagues also thoroughly searched for nucleic acids of encephalomyocarditis virus (see below), adenovirus, HIV, HTLV-I, and HTLV-II in 44 polymyositis patients; all were negative (Leff et al 1992). Electron microscopy, immunocytochemistry, in situ hybridization, cultures, and polymerase chain reaction of muscle biopsy in patients with inflammatory myopathy and HIV, HTLV-I, or hepatitis B virus infection have failed to reveal evidence of virus (Chad et al 1990; Illa et al 1991; Dalakas et al 1992; Leon-Monzon and Dalakas 1994; Gruber-Wackernagel et al 2008). However, in 2 cases of inflammatory myopathy associated with chronic hepatitis B infection, hepatitis B virus DNA and viral antigens were found inside intact muscle fibers (Capasso et al 2006).

Molecular mimicry was first studied as a possible mechanism of inflammatory myopathy when antibodies to the Jo-1 autoantigen were discovered in up to 10% of myositis patients (Dalakas 1989). Jo-1 autoantigen, part of a histidyl-tRNA synthetase (Targoff 1990), has structural homology with the genomic RNA of encephalomyocarditis virus, an animal picornavirus related to coxsackieviruses and enteroviruses. This association was strengthened when enteroviral RNA was found by in situ hybridization in muscle fibers from patients with myositis (Rosenberg et al 1989; Youse et al 1990). However, polymerase chain reaction studies have repeatedly failed to confirm the presence of enterovirus in muscle biopsies of inflammatory myopathy (Leff et al 1992; Leon-Monzon and Dalakas 1992). Nevertheless, a French study using reverse transcriptase PCR found enterovirus RNA in 3 of 20 muscle biopsies of inflammatory myopathy patients, compared with 0 of 29 controls (Douche-Aourik et al 2003). In HIV, gag and pol genes share antigens with human ribonucleoproteins, which are the target of circulating autoantibodies in some sporadic polymyositis cases (Rucheton et al 1985).

Retroviruses including HIV and HTLV-I as well as hepatitis viruses might act via immune dysregulation. There are clinical and histological similarities between HIV or HTLV-I myopathy and sporadic polymyositis (Arahata and Engel 1984; Engel and Arahata 1984), leading Dalakas and colleagues to perform comparative immunohistological studies in patients with HIV myositis, HTLV-I myositis, and sporadic polymyositis (Illa et al 1991; Leon-Monzon et al 1994). The predominant inflammatory cells within the endomysial infiltrates were CD8+ T cells (49% of the total cells) and macrophages (38%), which surrounded or invaded non-necrotic muscle fibers. More recently, in 4 patients with inclusion body myositis and HIV, it was shown that a percentage of the autoinvasive CD8+ T cells showed clonal restriction specific for HIV virus antigens (Dalakas et al 2007). These findings suggest that chronic infection may
trigger a T cell-mediated inflammatory process (Ytterberg 1996), and studies have begun uncovering the genetic mechanisms by which this might occur with coxsackieviruses in mice (Sandager et al 2008).

**Virus-host interactions.** Influenza viruses are the most common infectious agents responsible for viral myositis. Influenza viruses are members of the Orthomyxoviridae family and are single-stranded negative-sense RNA viruses. The actual pathogenesis of the symptoms of influenza-associated myositis is unknown but may be in part related to elevated levels of circulating cytokines. Transient viremia allows access to muscle cells by the virus, and there may be a predilection for the calf muscles in “benign acute childhood myositis.” Muscle biopsy shows degeneration or rhabdomyolysis with or without inflammation, which is focal and patchy. Mouse models have shown infection of myocytes with influenza virus. There are variable reports of isolating influenza virus and detecting antigens from human muscle biopsy samples. That the myositis more often occurs in children is postulated to be because young muscle is more permissive to infection. Influenza B is more often associated with myositis, and that may be due to certain myotropic glycoproteins in its structure. Myocarditis from influenza may be due to the direct effects of virus on the myocardium, or exacerbation of underlying coronary artery disease. Rhabdomyolysis in the setting of influenza infection is proposed to be due to several possible factors: direct viral invasion of myocytes, cytokine storm from the immune response, or toxicity of circulating viral factors. Viral isolates from the 2009 influenza A pandemic compared to a seasonal influenza A (both H1N1) were studied. One group found that the influenza A virus can directly infect human muscle cells in vitro, and in this model, levels of inflammatory cytokines were not increased after infection (Desdouits et al 2013). In addition, this group shows that the pandemic virus replicated at higher titers than the seasonal virus and had a lytic effect on the muscle cells. Interestingly, the authors also detected on the surface of human primary muscle cells, sialic acid receptors, which are the same as those on respiratory epithelium and which serve as the receptors to which the influenza virus binds.

Coxsackieviruses A and B are enteroviruses, which are single-stranded positive-sense RNA viruses in the Picornaviridae family and include polioviruses and echoviruses. Enteroviruses are transmitted via the fecal-oral route and include an ever-enlarging number of serotypes. Most epidemic pleurodynia is caused by group B Coxackieviruses and only infrequently by group A 4, 6, 9, 10, or the enteric cytopathogenic human orphan (ECHO 1, 6, 9, 16, 19) viruses. A study in Yunnan province in China assessed 98 cases of enterovirus-associated acute flaccid paralysis; the researchers identified 33 particular serotypes of enterovirus and characterized their phylogenetic relationship to the prototype and molecular evolution compared to strains in other parts of the world (Tang et al 2014). In inoculated mice, Coxsackieviruses can cause acute and chronic myositis.

Polymerase chain reaction studies in muscle biopsy specimens have been inconclusive for confirming the presence of enteroviruses (both positive and negative results), and attempts to isolate retroviruses have been negative.

The hepatitis C virus RNA and antigen were detected in the inflammatory cells attacking muscle fibers in a case of hepatitis C virus-associated inflammatory myopathy (Di Muzio et al 2003); and HTLV-1 proviral DNA was detected in CD4+ T cells around but not in myofibers in a case of inclusion body myositis (Matsuura et al 2008). Although HIV, HTLV-I, and hepatitis C virus do not seem to cause persistent muscle infection, they do persist in many cells of the body and may cause muscle inflammation via several mechanisms: (1) immune cell activation, leading to cytokine and lymphokine release that may induce the expression of nontolerant antigens on muscle cells or (2) molecular mimicry (discussed above). However, in two cases of inflammatory myopathy associated with chronic hepatitis B infection, hepatitis B virus DNA and viral antigens were found inside intact muscle fibers (Capasso et al 2006).

Alphaviruses (including Ross River virus, Barmah Forest virus, Chikungunya virus) are positive-sense single-stranded RNA viruses of the family Togaviridae. In a mouse model, the Ross River virus causes an upregulation of inflammatory cytokines and causes severe myositis, whereas Barmah Forest virus did not cause this upregulation and is not associated with replication in myocytes (Herrero et al 2014). In vitro studies of muscle cells infected with Chikungunya virus show upregulation of many proteins involved in metabolism, cell signaling, and notably the cytoskeleton (Issac et al 2014). Mouse models infected with Chikungunya virus show development of edematous muscles, viral antigen detected in muscle connective tissue fibroblasts and satellite cells (Ozden et al 2007), myoblasts and muscle fibroblasts (Couderc et al 2008), and upregulation of proinflammatory cytokines that correlates with severity of disease (Ng et al 2009; Dhanwani et al 2014). An elegant study of the pathogenic mechanisms of the epidemic strains from the La Reunion outbreak in 2006 was analyzed compared to a strain from 1983 outbreak in Senegal, and both were able to infect muscle connective tissue fibroblasts, yet only the La Reunion strain directly infected the myofibers with high viral titers in muscle leading to myonecrosis. The reason for this difference is unclear as tropism was similar, and
induced cytokine and chemokine profiles were also similar (Rohatgi et al 2014).

Polyomaviruses are small double-stranded DNA viruses that are widespread. Most often they cause mild respiratory symptoms or are asymptomatic in humans; however, the two most often associated with human disease are the BK and JC viruses. A novel polyomavirus has been identified in endothelial cells causing vasculitic myopathy and retinal blindness in a pancreatic transplant recipient. A double-stranded DNA virus was isolated from muscle tissue with greatest homology to chimpanzee polyomaviruses (tentatively named New Jersey polyomavirus 2013) (Mishra et al 2014).

Retroviruses are single-stranded positive-sense RNA viruses that replicate by reverse transcription of the RNA genome into a double-stranded DNA molecule that integrates into the host genome. HIV and HTLV are human retroviruses that have been associated with inclusion-body myositis. Muscle biopsy of HIV patients with inclusion-body myositis show similar pathology to idiopathic inclusion-body myositis with endomysial infiltration with CD8 cytotoxic T cells and macrophages, which invade non-necrotic muscle fibers that are MHC Class I antigen expressing. Through a variety of molecular and biochemical techniques, viral antigens were not detected in the muscle fibers and only at times in the surrounding macrophages. Instead, in HIV- and HTLV-associated inclusion-body myositis, the underlying pathophysiology is thought to be driven by clonal-activated T-cells that attack MHC-class I expressing myofibers. Myotoxicity may be enhanced by increased secretion of cytokines and chemokines (Dalakas 2006). Clonal expansion of viral-specific T-cells surrounding muscle fibers was found in patients with HIV-associated inclusion-body myositis. A significant proportion of the autoinvasive CD8+ cells invaded myofibers expressing a particular human leukocyte antigen-A allele (Dalakas et al 2007; Dalakas 2012). In HIV, gag and pol genes share antigens with human ribonucleoproteins, which are the target of circulating autoantibodies in some sporadic polymyositis cases.

There are 4 HTLV-1 subtypes, A-D according to geographical origin. Most persons are asymptomatic lifelong carriers, but HTLV-1 can cause severe adult T-cell leukemia or HTLV-1 associated myelopathy (tropical spastic paraparesis) and is associated with several inflammatory disorders, including myopathy.

Dengue virus is a member of the single-stranded RNA Flaviviridae family, transmitted by mosquitos of the Aedes genus. Muscle biopsy has not shown myocyte invasion by dengue virus, with lymphocytic infiltrates at foci of myonecrosis (Verma et al 2014).

Toscana virus (Bunyaviridae family) is a Mediterranean arbovirus transmitted by sandflies. Infected patients are usually asymptomatic or present with fever and myalgia. Two cases of myositis and fasciitis have been reported (Mosnier et al 2013).

Genetics. There are no known definite genetic predispositions to viral myositis in humans. In a mouse model of viral myositis, innate immune pathways are being investigated. SHP-1 normally suppresses macrophage-mediated inflammation and contributes to muscle disease. In SHP-1 knock-out mice, although there is still myofiber infection and inflammation with the TMEV virus, the mice do not develop myonecrosis and retain ambulation. This correlated with immature macrophages in the SHP/- mice compared to the mature macrophages in the wild-type mice. This suggests that SHP-1 promotes inflammation through maturation of macrophages and, thus, is necessary for virus-induced myonecrosis with clinical consequences (Watson et al 2015).

Patients with underlying hereditary myopathies or muscular dystrophies are at higher risk of more severe myositis during viral infection. In particular, patients with dysferlinopathies may be especially at risk for Coxsackie B virus infection (Wang et al 2015). In certain cases, a viral infection and myositis may be the first presenting sign of a hereditary myopathy. Appropriate cases should be screened when clinically indicated.

Molecular mimicry. Molecular mimicry was first studied as a possible mechanism of inflammatory myopathy when antibodies to the Jo-1 autoantigen were discovered in up to 10% of myositis patients. Jo-1 autoantigen, part of a histidyl-transfer RNA synthetase, has structural homology with the genomic RNA of encephalomyocarditis virus, an animal picornavirus related to coxsackieviruses and enteroviruses.

Epidemiology"

Benign acute childhood myositis is overwhelmingly a pediatric disease, though there are reports of adults including the elderly being affected as well. Some studies suggest benign acute childhood myositis may occur in 6% to 34% of childhood cases of influenza A or B. It appears to be more common with influenza B and has a 2:1 male predominance.
Up to 3% of cases of influenza-associated myositis are accompanied by rhabdomyolysis; interestingly, this complication is seen more often in girls with influenza A (contrary to the epidemiological tendencies for benign acute childhood myositis).

The factors that predispose a patient with hepatitis C virus, HIV, or HTLV-I infection to develop a myopathy are unknown. The use of zidovudine in HIV has increased the incidence of myopathy in HIV patients, but this myopathy is different from HIV-associated myositis. The frequency of HTLV-I-related myopathy in the United States is unknown but may be expected to gradually increase with globalization and exposure to endemic areas (Carribean, Africa, Japan). HTLV-1 may be endemic to the southern United States (Crum-Cianflone 2008).

Benign acute childhood myositis is overwhelmingly a pediatric disease, though there are reports of adults including the elderly being affected as well (Yoshino et al 2000).

**Prevention**

There are no specific measures to prevent the development of an inflammatory myopathy once viral infection has occurred.

Primary prevention of myriad viruses discussed is the only sure method to prevent viral myositis.

Whether or not neuraminidase inhibitors can prevent the development of benign acute childhood myositis following influenza A or B exposure or infection is unstudied.

**Differential diagnosis**

Viral-associated myositis should be distinguished from other acquired myopathies occurring in noninfected populations. Metabolic, hereditary, endocrine, or toxic causes should be excluded. Systemic and infectious symptoms (such as fever, upper respiratory symptoms, or gastrointestinal symptoms) will often distinguish viral myositis from other causes. Myotoxic factors, such as drugs, medications, illicit drug use, other co-infections, and the consequences of multiple organ failure that occur in HIV-positive patients with AIDS should also be considered. Interferon may play a role in some patients with hepatitis C virus infection (Matsuya et al 1994; Arai et al 1995).

Other causes of infectious myositis (bacterial, fungal, or parasitic) should also be considered.

Underlying hereditary myopathy may predispose persons to viral myositis and in the appropriate clinical setting should be excluded.

Myopathy with the features of a mitochondrial disease at biopsy can occur in the setting of zidovudine or didanosine therapy for HIV; in fact, this is the most common myopathy in HIV patients (Dalakas et al 1990; Mhiri et al 1991). This is not a parainfectious process, per se, but deserves mention as it would feature prominently in the differential diagnosis of any HIV patient with neuromuscular weakness. The clinical presentation is indistinguishable from HIV-associated myositis. The distinction is made via muscle biopsy showing ragged-red fibers, subsarcolemmal red-rimmed cracks or pale granular washed-out staining, lipid accumulation, and focal depletion of cytochrome c oxidase (COX); and electron microscopy showing accumulation of abnormal mitochondria with paracrystalline inclusions and excessive amounts of lipid droplets (Dalakas et al 1990; Dalakas et al 1994; Mhiri et al 1991). This probably results from depletion of mitochondrial DNA (mtDNA), as shown by genetic analyses (Arnaudo et al 1991). Notably, up to 8% of all HIV patients on zidovudine will develop diffuse myalgias. Whether this is a prodrome to zidovudine-associated mitochondrial myopathy is not known. However, antiretroviral drugs (nucleoside analog reverse transcriptase inhibitor, NRTI) used to treat human HIV patients, lead to mitochondrial myopathy, with COX-negative fibers and with evidence of multiple mtDNA deletions (Payne et al 2015). In both cases, it seems clear that the effects of NRTI drugs damage the maintenance of mtDNA.

Pyomyositis bacteria myositis should also be considered in AIDS and immunocompromised patients. This focal infection is usually due to *Staphylococcus aureus* or rarely to Gram-negative organisms (Schwartzman et al 1991; Widow et al 1991). Pyomyositis is suspected when patients have low-grade fever, localized pain, and swelling in a large muscle group; leukocytosis and creatine kinase elevation may or may not occur. Imaging with ultrasound, MRI, or CT will show some combination of edema, fluid density, and contrast enhancement. Risk factors include underlying muscle abnormalities, local trauma, exercise, and hematogenous spread of a systemic bacterial infection.
Other factors that might contribute to the development of a myopathy in AIDS (and possibly chronic hepatitis B and C) patients include vitamin deficiencies, disuse atrophy, chronic wasting syndrome, and myocytotoxicity caused by septicemia, bacteriotoxins, and antimicrobial drugs.

Although rhabdomyolysis is a rare complication of viral myositis, the differential diagnosis for rhabdomyolysis includes: trauma, prolonged immobilization, excessive muscle activity, compartment syndrome, heat exposure, drugs of abuse (cocaine, heroin, amphetamine), alcohol, medications (statins, fibrates, salicylates, steroids), and idiopathic inflammatory myopathies.

**Diagnostic workup**

As with any other acquired form of inflammatory myopathy, the laboratory tests that complement the clinical examination in viral myositis may include:

1. Determination of serum muscle enzymes (CK, AST, ALT, LDH, aldolase)
2. Electromyography. Electromyography in an inflammatory myopathy usually shows spontaneous activity (fibrillation potentials, positive sharp waves) and myopathic motor unit potentials (short-duration, low-amplitude, polyphasic), and an early recruitment pattern
3. Muscle biopsy. Muscle biopsy is not needed in all cases of suspected viral myositis. If a self-limited and acute viral infection with associated myositis is suspected (such as with influenza or coxsackievirus infection), it is advisable to wait a few weeks before considering muscle biopsy as symptoms may completely resolve. Muscle biopsy is especially important in HIV as it is the critical test to distinguish HIV-associated myositis from medication-induced myopathy. Diagnostic evaluation must be tailored to the individual presentation and history.

In the case of specific viruses, additional diagnostic considerations are in order.

Influenza infection is often diagnosed clinically, based on activity in the community, but also by polymerase chain reaction (PCR) of nasal swabs. Muscle enzymes are often elevated (CK, LDH, AST). EMG shows myopathic changes, and in cases where muscle biopsy was performed, there is degeneration and necrosis with minimal inflammatory infiltrates. In cases with myocardial involvement, the EKG may show nonspecific tachycardia, ST elevation, Q waves, or left bundle branch block. Transthoracic echocardiogram may show left ventricular dysfunction, wall motion abnormalities, and reduced ejection fraction. Cardiac MRI may show focal left ventricular edema and contrast enhancement. Myocardial biopsy at this stage will show foci of active inflammation, edema, degeneration, and necrosis, and influenza virus can be detected by PCR.

Coxsackievirus infection can be assessed by serological testing and culture of both pharyngeal and fecal specimens. Although it is not generally recommended for diagnosis, muscle biopsy may reveal detection of viral antigens.

In the case of a hepatitis (B or C) patient who has symptoms and signs of myositis, gamma-glutamyl transeptidase (GGT) should be checked in addition to the transaminases, as GGT is specific for liver injury whereas AST and ALT may be elevated in muscle or liver diseases. Conversely, a polymyositis patient with GGT elevation should be investigated for a chronic hepatitis virus infection.

Muscle biopsy in myositis associated with HIV and HTLV-1 is often indistinguishable from sporadic polymyositis. Rarely, a few cytoplasmic bodies and rods can be seen. Occasionally, myofiber degeneration predominates and endomysial inflammation is sparse. Scattered angular fibers, if present, suggest the co-occurrence of an axonal neuropathy. Vacuoles have been described in HTLV-1-associated myositis (Wolfe et al 1998).

Muscle is often affected in patients with HIV or AIDS. In a prospective clinicopathological study, 60% of untreated HIV-positive patients without neuromuscular symptoms, and seemingly with normal strength, had histological abnormalities in muscle, such as mild inflammation, type II fiber atrophy, or denervation (Gabbai et al 1990). In another study of 50 untreated patients without neurologic deficits but with some degree of muscle wasting, 96% had histological abnormalities consisting of denervation (76%), type II atrophy (58%), endomysial inflammation (36%), and necrosis with phagocytosis (30%). These changes are probably multifactorial in origin and may be the histological correlates of the myalgia, fatigue, diminished endurance, or transient CK elevation noted in AIDS patients without weakness. Likely patients with this disease are underevaluated, and the true burden of disease is unrecognized.

Suspected myositis in a patient with HIV will often require muscle biopsy. Serum elevation of muscle enzymes and myopathic pattern on EMG support the diagnosis. Muscle biopsy will show inflammatory infiltrates of T-cells and
macrophages in the endomysium, with or without necrosis. Biopsy can help distinguish HIV-associated myositis from other myopathies associated with HIV, such as that from ART (nucleoside-related mitochondrial myopathy), nemaline myopathy, and inclusion-body myositis.

Management

In the case of acute viral myositis, most treatment is symptomatic and supportive. Patients with mild myopathic symptoms and signs that are not functionally limiting can be monitored with serial examinations and CK levels. Many of these patients remain stable and do not require specific therapy. Nonsteroidal anti-inflammatory drugs may be useful in managing myalgias.

Patients with HIV-associated myositis may benefit from HIV-specific antiviral therapy, including zidovudine and other medications that may cause a distinct myopathy. However, there is one report of zidovudine worsening an HIV-associated myopathy (Berger et al 1991). Treatment with antivirals for other viruses, such as Epstein Barr virus, should be considered on a case-by-case basis and treatment individualized.

With the chronic myositis associated with HIV, patients may respond to immunotherapy. Treatment with prednisone (as in sporadic polymyositis) may be considered and does not seem to worsen HIV or immunocompromised status (Johnson et al 2003). Nevertheless, intravenous immunoglobulin is an attractive alternative because it is well tolerated and immunoenhancing rather than immunosuppressive. The largest case series suggests that 50% of patients will achieve remission after 9 months (Robinson-Papp and Simpson 2009). Other immunotherapies, such as IVIG and immunosuppressants, have been evaluated in HIV-associated myositis, but there are no definitive data, and there is concern over further immunosuppression in patients with HIV-associated myositis.

Zidovudine-associated myopathy (a mitochondrial myopathy distinct from HIV-myositis) will often improve if the dose is reduced, with or without a drug holiday. Improvement generally begins within 1 to 2 months and may be incomplete, even if the offending drug is stopped permanently. A wide array of effective antiretroviral alternatives is now available to the HIV-positive patient.

HTLV-1-associated polymyositis is treated the same as sporadic autoimmune polymyositis, with less concern for immunosuppression complications than with HIV infection. Myositis does not appear to be due to direct, persistent retroviral infection of myofibers but, rather, an inflammatory reaction induced by the HTLV-1 infected monocytes. Two patients with HTLV-1 associated myositis were treated with alemtuzumab, a monoclonal antibody against the CD52 molecule on B and T cells, monocytes, macrophages, and eosinophils. HTLV-1-associated polymyositis is typically refractory to multiple immunotherapies. Two patients with refractory HTLV-1-associated polymyositis were treated with alemtuzumab and showed clinically meaningful improvement in muscle strength, reduction in CK to normal, and normalization of myopathic EMG findings (Cochereau et al 2014).

Special considerations

Pregnancy

Though HIV-associated myositis could certainly occur in a pregnant woman, to our knowledge there are no reported cases of this or other virus-associated myopathies in this population.

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**References especially recommended by the author or editor for general reading.**

**Former authors**

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**ICD and OMIM codes**

**ICD codes**

ICD-9:
- Acquired immunodeficiency syndrome with or without other conditions: 042.9
- Asymptomatic human immunodeficiency virus (HIV) infection status: V08
- HTLV-III/LAV infection, not otherwise specified: 044.9
- Myalgia and myositis unspecified: 729.1
- Infective myositis: 728.0

ICD-10:
- Unspecified human immunodeficiency virus [HIV] disease: B24
- HIV disease resulting in infection NOS: B20.9
- Myalgia: M79.1
- Infective myositis: M60.0

**Profile**

**Age range of presentation**

- 0-01 month
- 01-23 months
- 02-05 years
- 06-12 years
- 13-18 years
- 19-44 years
- 45-64 years
- 65+ years

**Sex preponderance**

- male>female, >2:1
- male>female, >1:1

**Family history**

- none

**Heredity**
Population groups selectively affected

none selectively affected

Occupation groups selectively affected

none selectively affected

Differential diagnosis list

- metabolic myopathies
- endocrine myopathies
- hereditary myopathies
- toxic myopathies
- consequences of multiple organ failure in AIDS
- hepatitis C virus infection
- AZT myopathy
- coinfection with other viral or bacterial agents
- type II muscle fiber atrophy
- pyomyositis
- vitamin deficiencies
- disuse atrophy and muscle wasting
- myocytotoxicity from septicemia
- myocytotoxicity from bacteriotoxins
- mycotoxicity from antimicrobial drugs

Associated disorders

- HIV myelopathy
- HIV peripheral neuropathy
- HIV wasting syndrome
- Zidovudine-induced myopathy

Other topics to consider

- Dermatomyositis
- Inclusion-body myositis