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Brain Pathology

MINI-SYMPOSIUM

Infective myositis

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Abstract

Myositis is inflammation especially of the voluntary muscles, characterized by localized or diffuse pain, tenderness on movement or palpation, swelling, and/or weakness. The two main categories of myositis include non-infectious and infectious. Infective myositis may be due to a wide variety of pathogens, including bacteria, fungi, viruses, and parasites. A brief account of the various pathogens causing infective myositis is discussed.

KEYWORDS
fungal, infective myositis, parasitic, pyomyositis, viral

1 | INTRODUCTION

Infective myositis, an uncommon group of inflammatory myopathies caused by a wide range of infective agents such as viral, bacterial, fungal, and parasitic, is a potentially treatable entity. Infective myositis, though confined to particular geographic regions is related to socioeconomic, sanitary conditions, cultural and dietary habits. Increased travel in the recent past has resulted in transmission to other countries, where it is seldom known.

Clinically, infective myositis may display an acute, subacute, or chronic course marked by pain, tenderness, swelling, and /or weakness. Some idiopathic cases of polymyositis are suspected to be due to underlying viral infection. The standard of care depends on establishing the diagnosis based on clinical, culture or serological testing and muscle biopsy findings. Albeit molecular genetics sequencing is available for some infectious agents, it is not used routinely as a diagnostic tool.

It is noteworthy that some clinical findings point toward the general category of an infective agent. Bacterial myositis presents as focal muscle infection, while viruses and parasites are more diffuse leading to generalized myalgia or multifocal myositis.

2 | BACTERIAL INFECTIONS

Skeletal muscle is resistant to bacterial infection. Invasion occurs due to injury, surgery, or ischemia and a higher risk of bacterial infection in immunocompromised individuals. Myositis due to bacterial infection often results from contiguous spread from adjacent sites of infection, penetrating injury, ischemia, foreign body, and hematogenous spread. *Staphylococcus aureus* often spreads through the hematogenous route. Infection related to penetrating and ischemic injury involves multiple organisms (polymicrobial). Microbiological typing of these organisms with information on their drug sensitivity is essential for providing specific treatment. Some of the critical pathogenetic / virulence factors implicated in bacterial infections include adhesins, cytotoxins, superantigens, and immunomodulatory proteins (1, 2). The pathogenic bacteria include gram-positive, gram-negative bacteria, anaerobic bacteria, mycobacterial organisms, and some atypical bacteria. Table 1 shows a short list of pathogenic bacteria that are implicated in myositis.

2.1 | Pyomyositis

Pyomyositis, also called "tropical pyomyositis," Myositis purulent atropica, Pyogenic myositis or Suppurative

TABLE 1 Some of the Important microorganisms causing myositis

Bacteria	**Gram-positive bacteria**
	Staphylococcus aureus
	Streptococcus (groups A, B, C, and G, *S. pneumoniae, S. anginosus*)
	Gram-negative bacteria
	Aeromonas hydrophila
	Burkholderia mallei, B. pseudomallei
	Citrobacter freundii
	Enterobacter spp.
	Escherichia coli
	Haemophilus influenzae
	Klebsiella oxytoca, K. pneumoniae
	Morganella morganii
	Neisseria gonorrhoeae
	Pasteurella spp.
	Proteus spp.
	Pseudomonas spp.
	Salmonella spp.
	Serratia marcescens
	Vibrio vulnificus
	Yersinia enterocolitica
	Anaerobic bacteria
	Bacteroides spp.
	Clostridium spp.
	Fusobacterium necrophorum and F. nucleatum
	Streptococcus spp. (anaerobic, e.g., Peptostreptococcus)
	Villanelle spp.
	Mycobacterium spp.
	Mycobacterium tuberculosis
	Mycobacterium avium complex
	Mycobacterium bovis
	Mycobacterium haemophilum
	Mycobacterium leprae
	Atypical bacteria
	Actinomyces spp.
	Bacillus spp.
	Bartonella spp.
	Borrelia burgdorferi
	Brucella spp.
	Coxiella burnetii
	Francisella tularensis
	Legionella pneumophila
	Leptospira spp.
	Mycoplasma pneumoniae
	Nocardia spp.
	Rickettsia rickettsii and R. conorii
	Treponema pallidum
Fungi	*Aspergillus* spp.
	Blastomyces dermatitidis
	Candida spp.
	Coccidioides spp.
	Cryptococcus neoformans
	Fusarium spp.
	Histoplasma capsulatum
	Pneumocystis jiroveci
Parasites	*Entamoeba histolytica*
	Echinococcus spp.
	Microsporidial spp. (Brachiola, Trachipleistophora, Pleistophora)
	Onchocerca volvulus
	Plasmodium spp
	Sarcocystis spp.
	Schistosoma spp.
	Spirometra mansonoides
	Taenia solium
	Toxocara canis
	Toxoplasma gondii
	Trichinella spp.
	Trypanosoma cruzi
Viruses	Adenovirus
	Cytomegalovirus
	Dengue virus
	Enteroviruses (Coxsackie B virus and ECHO virus)
	Epstein-Barr virus
	Hepatitis B and C viruses
	Herpes simplex virus 2
	Human immunodeficiency virus (HIV)
	HTLV-1
	Influenza A and B viruses
	Mumps virus
	Parainfluenza virus
	Parvovirus B19
	Varicella zoster virus

Note: The table includes only the common infective agents and not the rare ones.
Adapted from Crum-Cianflone (1).

myositis is an acute inflammation characterized by neutrophil-rich infiltrates (3). It is commonly observed in the tropical regions infecting healthy individuals, including children (1, 4). However, with an increase in travel, change in the geographical and demographic factors, many cases are being detected in temperate regions as well. One-third of the patients in temperate zones reported a travel history to the tropics (5). In general, men are more affected than women, especially those with comorbidities, chronic diseases associated with immunosuppression, and immunocompromised state (6–10). The infections have hematogenous spread by a breach in the

anatomical and physiological integrity such as injury, surgery, ischemia, or foreign body. Besides, host immune factors also contribute to the development and progression of the infection (8). Some refer to this hematogenous origin of inflammation as primary, while those that occur due to extension from an adjacent infective process as secondary (11, 12). *Staphylococcus aureus* is implicated in 90% of cases. Also, *Streptococcus pyogenes, Salmonella, Escherichia coli*, and pneumococci are known to cause pyomyositis (4, 5). Pyomyositis due to trauma is observed in 25 to 40% of the patients (13). Intravenous injections pose significant risk mainly due to pre-existing surface colonization of the bacteria, neutropenia, neutrophilic functional defects, defective cell-mediated immunity, and others (14–16). Other predisposing factors include concurrent skin infection and viral infections. Pyomyositis has been observed to be associated with thiamine deficiency, scurvy, and beriberi (6).The exact prevalence of pyomyositis though not clear, it is not uncommon.

Clinically, three stages of the evolution of pyomyositis have been described (5). The first stage (subacute) referred to as the invasive stage, occurs over 1 to 3 weeks characterized by swelling, variable texture with pain (often dull and crampy) associated with low-grade fever and malaise. This stage may be mistaken for thrombotic conditions, hematoma, muscle strain/tear, osteomyelitis, or trauma (contusion). In the second stage, the suppurative phase develops between ten to twenty-one days characterized by prominent tenderness, swelling, and severe myalgia (1). Diagnosis is often made at this stage since a definite abscess is recognized by imaging or by the pathological study. Muscle from the affected region histologically shows suppuration with numerous degenerating polymorphonuclear leukocytes admixed with necrotic cellular debris. A rim of histiocytes along with peripheral neovascularization, perivascular inflammation forming granulation tissue, fibrosis, and scarring is seen (17). Since the pathological changes are within the muscle, the overlying skin may not show erythema commonly noted with soft tissue infections. The third stage is a severe stage with evidence of sepsis and fever. The tenderness may be severe with apparent fluctuating character. The mean age at diagnosis ranges from 2 weeks to 92 years with male preponderance both in tropical and temperate regions. Usually, a single muscle group is involved, while it may be diffuse in around 10-20% of cases (1, 6). The lower limb muscles with large bellies (e.g., quadriceps and gluteus group, calf muscles) are commonly affected due to their proneness to injury and constant stress and strain. The other muscle groups that can also be affected are psoas muscles, iliacus, pectoralis major followed by sternocleidomastoids, and upper extremity muscles (8). The lesion may be solitary (seen in a quarter of cases), or multiple (18).

The clinical differentials include osteomyelitis, infective (septic) arthritis, cellulitis, vascular thrombosis, muscular tear/rupture, and hematoma. If abdominal muscles are involved, they may mimic visceral pathologies like psoas muscle involvement masquerading as appendicitis and iliac muscle involvement mimicking septic hip arthritis (19, 20). In a case with fever of unknown origin, pyomyositis is one of the differentials to be considered.

Staphylococcus aureus is implicated in 90% of cases with pyomyositis (1, 21). Community-acquired methicillin-resistant *Staphylococcus aureus* [MRSA] is high (22–24).The virulence in MRSA may be due to expression of core genome encoded virulence factors that include alpha-toxin, phenol soluble modulins, and phage-encoded Panton-Valentine leukocidin (PVL) gene (23). Some of these are associated with large suppurative exudates and risk for septicemia and other complications.

The other organisms implicated include: group A Streptococci followed by group B, group C, group G Streptococci, *Streptococcus pneumoniae*, Salmonella species, *Neisseria* spp., *Haemophilus* spp., *Aeromonas* spp., *Klebsiella* spp., *Yersinia* spp., *Pseudomonas* spp., and *Escherichia* spp.(25, 26). *Salmonella enteritidis* is one of the common causes of focal myositis (27). Salmonella and Streptococci induce muscle damage by reducing the oxidative and glycolytic enzyme activity and activating the lysosomal enzymes. *S. agalactiae*, an important member of group B Streptococci causes opportunistic infections that can develop due to diabetes or necrotizing fasciitis. The less common causes of pyomyositis include gram-negative bacilli and anaerobe bacteria such as Clostridia, Mycobacteria, and *Fusobacterium necrophorum*. Among atypical infections, Actinomycosis (Figure 1) occurs as a spread from the cervicofacial forms and in the context of alcoholism (1).

The diagnosis of pyomyositis relies on imaging. Although soft tissue swelling can be detected on plain films, their diagnostic yield is limited. Ultrasounds, computed tomography (CT), magnetic resonance imaging (MRI) scans are more sensitive. Since CT is more accessible, most cases are diagnosed using CT scans. A low-density area with a central fluid collection and surrounding rim of enhancement suggests focal abscess formation within the muscle. For axial lesions, MRI is the test of choice due to high specificity. The lesion harbors a hypointense central area with a gadolinium-enhanced rim.

Laboratory investigations reveal raised ESR, neutrophilic leucocytosis with a left shift in all cases. White blood cell count is elevated in only 19%in immunocompromised states. Eosinophilia is seen concurrent to parasitic infection. Creatine kinase and aldolase levels are normal or only minimally elevated. Optimizing treatment depends on identifying the causative agent. The exudate is obtained either by imaging or open procedure. The abscess material thus obtained is subjected to routine gram stain and Ziehl–Neelsen (acid-fast bacilli stain-AFB) stain. When fungal, parasitic, or atypical bacterial agents are suspected, other microbiologic stains [Grocott-Gomori's methenamine silver (GMS) stain or Periodic acid-Schiff (PAS) stain], may be performed.

Bacterial infection -Actinomycosis

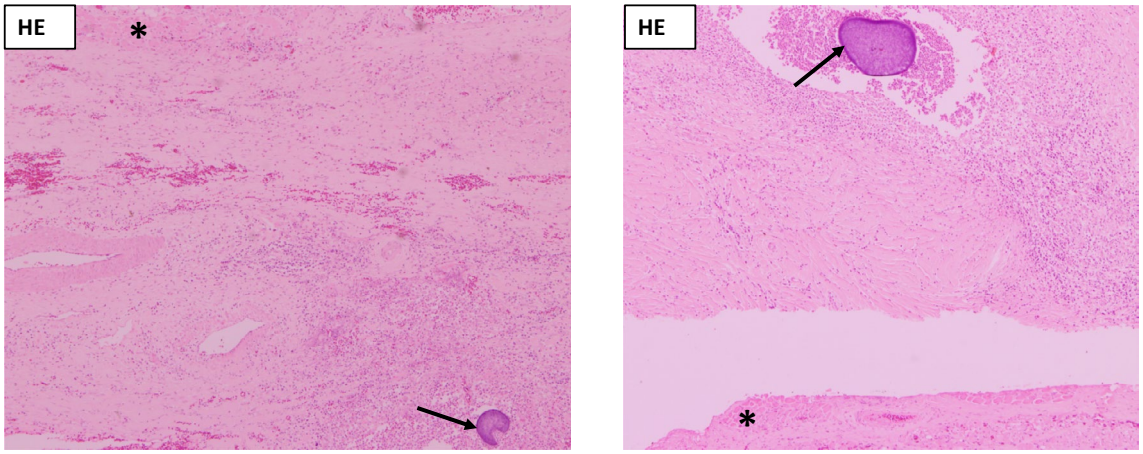

FIGURE 1 A case of actinomycosis of the temporal scalp region in a previously operated case of extradural hematoma (post-road traffic accident). Hematoxylin and eosin-stained section shows slender filamentous actinomycotic colony (†) surrounded by suppurative granulomatous inflammation. Skeletal muscle fibers (*) is seen

Blood cultures are positive in only 5 to 35% of cases since bacteremia is often transient. It is imperative that aerobic and anaerobic wound cultures be performed along with antibiotic sensitivity testing for optimizing treatment. In an immunocompromised host, cultures for *Mycobacterium* spp., *Nocardia* spp., and fungi should be considered.

2.2 | Bacterial myositis

Myositis, due to diffuse involvement of the muscle by bacteria without abscess formation, is referred to as bacterial myositis and less common than pyomyositis. Adults are more frequently affected than children. Similar to pyomyositis, the other types of bacteria, chiefly gram-positive organisms such as *Staphylococcus aureus* and Group A Streptococci (GAS), cause myositis. GAS causes myositis of varying severity ranging from acute, subacute to "malignant" (severe) myositis. The most severe form and less common as compared to pyomyositis is GAS necrotizing myositis, also known as streptococcal myonecrosis or spontaneous streptococcal gangrenous myositis. It is a more aggressive and fatal infection (1, 28).

Some patients may have a preceding infection like pharyngitis or other risk factors. Both necrotizing myositis and necrotizing fasciitis may be caused by Group A Streptococci and may also be associated with toxic shock syndrome. Bacteremia and toxemia are prominent and associated with high mortality, accounting for 85% of cases.

GAS necrotizing myositis can evolve very rapidly within two to three days leading to multiorgan failure. Clinically, an initial prodromal stage with flu-like symptoms may be associated with rash and myalgias, followed by intense local muscle pain, local tense swelling, and fever. Multiple muscle sites are involved. Intramuscular pressure increases, which may lead to compartment syndrome due to the fulminant nature of this infection.

Lab findings are similar to those pyomyositis with elevated ESR and neutrophilic leucocytosis. Because of the necrosis, muscle enzymes may be elevated. Histopathologically, muscle necrosis with gram-positive cocci in chains can be identified between the muscle fiber bundles. Since these are associated with bacteremia, blood culture will often be positive. The important differential diagnosis is necrotizing fasciitis. However, necrotizing fasciitis is marked by a violaceous skin appearance and formation of bullae. MRI is useful in differentiating. The standard of care includes surgical exploration and debridement.

Myositis due to Group B Streptococci is mainly due to *S. agalactiae*. This can cause pyomyositis or myositis. This infection often occurs in association with underlying diabetes mellitus, peripheral vascular disease, malignancy, alcoholism, malnutrition, or other immunocompromising situations (29, 30). One case with a foot ulcer who subsequently developed bacteremia probably due to seeding to the musculature, and one case of myositis developing in the context of endocarditis has been reported (1).

2.3 | Clostridia myositis

Clostridial myositis, popularly known as gas gangrene is commonly caused by *C. perfringens*. Infection occurs in traumatic wounds with soil contamination, compound fracture, penetrating wounds, gastrointestinal

(GI) surgery, septic abortions, parenteral drug abuse, and peripheral arterial disease of limbs, devitalized tissue and foreign body (containing spores of *C. perfringens* or other histotoxic clostridial species). Clostridial myositis is a rapidly progressive necrotizing inflammation of the skeletal muscle. Rarely, clostridial myonecrosis caused by *C. septicum* can occur spontaneously even in the absence of an injury (spontaneous non-traumatic gas gangrene). Usually, these are cases with underlying GI pathology (cancer, infarction, enterocolitis, diverticulitis, volvulus) (31). It may also be associated with neutrophilic dysfunction (primary/secondary) and hematological malignancies.

The clinical features include pain, edema, sweet odorous discharging from paranasal sinus, and most importantly presence of gas, which can be identified on imaging or examination (crepitus/gas bubbles). The toxins released (mainly alpha toxins) cause hypotension. The involved area is tense, edematous, and tender. The muscle will be swollen, and crepitus may be observed with gas bubbles. The overlying skin maybe discolored with blebs.

Lab findings include leukocytosis and hemolysis with decreased hematocrit. The lysolecithinase activity of the alpha (phospholipase C) toxin is implicated in haemolysis (1). The muscle on gross examination show pallor, edema, loss of elasticity, discoloration (reddish-purple to greenish purple), and becomes friable, heralding disintegration (31). Histologically, prominent coagulative necrosis and cavities that represent gas formation are observed. Connective tissue disintegration, gram-positive bacilli, and thrombosis may occur. The inflammation is disproportionately less with few inflammatory cell infiltrations. These cases require surgical management with debridement, excision of the infected tissues, and fasciotomy along with antibiotic coverage (32).

2.4 | Non-clostridial myositis

This category includes anaerobic streptococcal myositis, synergistic non-clostridial myonecrosis, *Aeromonas hydrophila* myonecrosis, and vascular (infected) gangrene (14, 31, 33).

Anaerobic streptococci predominated by Peptostreptococci cause myositis similar to clostridial myonecrosis with the presence of gas, prominent necrosis, and foul-smelling exudate. Numerous streptococci and polymorphonuclear leukocytes are present in the exudate (31). Synergistic nonclostridial myonecrosis mainly involves the subcutaneous tissues and fascia that extend to the muscle and the overlying skin. Multiple aerobic and anaerobic organisms may cause this. Streptococci, Bacteroides, *E. coli*, Enterobacter, Klebsiella, and *Bacillus cereus* are some of the causative microbes. These are often associated with immunocompromised state, particularly diabetes and neutropenia (31).

Aeromonas hydrophila, a facultative anaerobic gram-negative bacillus, causes Aeromonas myonecrosis usually associated with penetrating injury in a freshwater environment or in contact with aquatic animals. It progresses rapidly and may form a gas (31). While myositis from *Vibrio vulnificus* is often linked to salt-water exposure, and a predilection to occur in patients with liver disease, infection may also occur in immunocompetent hosts.

Vascular gangrene is due to compromise in the arterial blood supply, post-injury or in diabetics. Several organisms (mixed infection that includes *Proteus* spp., *Bacteroides* spp., and anaerobic streptococci) may be involved(34). Gas formation and foul-smelling exudate are commonly seen.

2.5 | Other bacterial myositides

Bacteria other than those mentioned in the previous section can cause myalgia, myositis, myopathy, or acute rhabdomyolysis. Rickettsia and Borreliacan cause localized myositis. Some bacteria like Legionella cause acute rhabdomyolysis by the generation of endotoxins or by direct invasion (1).

Mycobacterial species can also cause myositis but less common as compared to other tissues in the body. They usually involve muscle by extension from an adjacent site of infection (bone, abscess, joints) and rarely by hematogenous spread (35). The best example is the psoas muscle involvement by extension from Potts spine lesion, the extension of pulmonary infection to the intercostal muscles, and involvement of leg muscles from tuberculous (TB) arthritis (36). In general, the involvement of muscle by TB is rare (1%) and has a prolonged chronic course with swelling or mass-like appearance (1). There can be "discharging sinus" with sinus tracts and calcification. Histopathological examination and microbiological studies will be necessary for a definitive diagnosis. On histological examination, the tissue response shows granulomatous inflammation comprising **epithelioid** cells with Langhans-type giant cells and caseous necrosis. Ziehl–Neelsen stain demonstrating the acid-fast bacilli is the gold standard for diagnosis. However, the yield of AFB in the excised tissue may be low, and a typical granulomatous response supported by microbiological studies will guide the diagnosis and management. TB pyomyositis is a rare form of extrapulmonary complication that can occur in immunocompromised patients and with Mycobacterium avium complex.

2.6 | Leprosy and Lyme myositis

Leprosy, a chronic infection caused by *Mycobacterium leprae*, is the commonest infective and treatable cause of peripheral neuropathy. It is endemic in many parts of the world (37, 38). The skeletal muscles may be involved

because of peripheral neuropathy with subsequent muscular denervation or as a primary muscle disease eliciting an inflammatory reaction, giving rise to leprous myositis, also referred to as lepromatous myositis, leprous interstitial myositis, or leprous nodular interstitial myositis (37–43). Subclinical muscle involvement in leprosy is common and does not influence the prognosis (44). The exact incidence of leprous myositis is not known. The muscle biopsy may show variation in fiber size, type1 and/or type 2 fiber atrophy, type 1 fiber predominance and grouping. These changes are consequent to mononeuropathy, multiplex neuropathy or polyneuropathy. Also noted is the subsarcolemmal accumulation of reaction products on oxidative stains along with the presence of acid and alkaline phosphatase positive fibers. The presence of ring fibers and moth-eaten fibers is reported (45). Inflammation is prominent in the perimysium and may extend into the muscle along the interstitial connective tissue. Collection of foamy macrophages with clumps of lepra bacilli may be noted around necrotic and non-necrotic fibers (Figure 2), and in the perivascular regions involving several vessels in epi- and perimysium. In some instances, lepra bacilli may be detected within relatively well-preserved skeletal muscle fibers. The inflammation may involve the nerve twigs present in the perimysium. Myonecrosis and myophagocytosis may rarely be seen. Variably distinct granulomas may be present (44). Acid-fast bacilli (Wade Fite Faraco staining) may be detected in the macrophages, interstitium, endothelial cells, and intramuscular nerve twigs, especially in lepromatous leprosy type (41, 45). Three stages may develop, an initial stage of invasion and proliferation of the *M. leprae* inside muscle fibers, followed by muscle fiber degeneration and infiltration by polymorphonuclear leukocytes, lymphocytes, macrophages, and the bacilli fragmentation, and last, muscle fiber destruction, fibrous tissue replacement, vacuolation of the macrophages, and complete disappearance of the bacilli (42). That muscle involvement in leprosy maybe consequent to systemic spread of bacilli has been reported (46).

Myositis can rarely be a part of Lyme's disease and can occur with other symptoms like arthritis and skin lesions. Generalized myositis and the complication of rhabdomyolysis have been described. CK is usually normal or mildly elevated (47). The muscle histology may show interstitial macrophages and $CD4^+$ cells around the blood vessels accompanied by myopathic changes. Spirochetes are rarely detected in the tissue and require silver stains for identification.

3 | FUNGAL MYOSITIS

Fungi are an important, but uncommon cause of myositis (Fungal myositis). It is often associated with immunocompromised states and rarely affects immunocompetent individuals. It involves one muscle or muscle group due to abscess formation. The clinical presentation is similar to bacterial myositis. The spread of the rhinocerebral form of mucormycosis into ocular muscles results in ophthalmoplegia, proptosis, edema of eyelids, and rarely blindness. Candida, *Cryptococcus neoformans*, Histoplasma, Coccidioides, Aspergillus, may all cause fungal myositis (1). Histopathological examination supported by microbiological culture is necessary for a definitive diagnosis.

The tissue response is a suppurative granulomatous inflammation with prominent giant cell response often with eosinophils. The density of inflammatory cells may vary, and some show prominent fibrosis and calcification, especially with chronic infections. In addition to the usage of antifungal drugs for treatment, some may need surgical debridement.

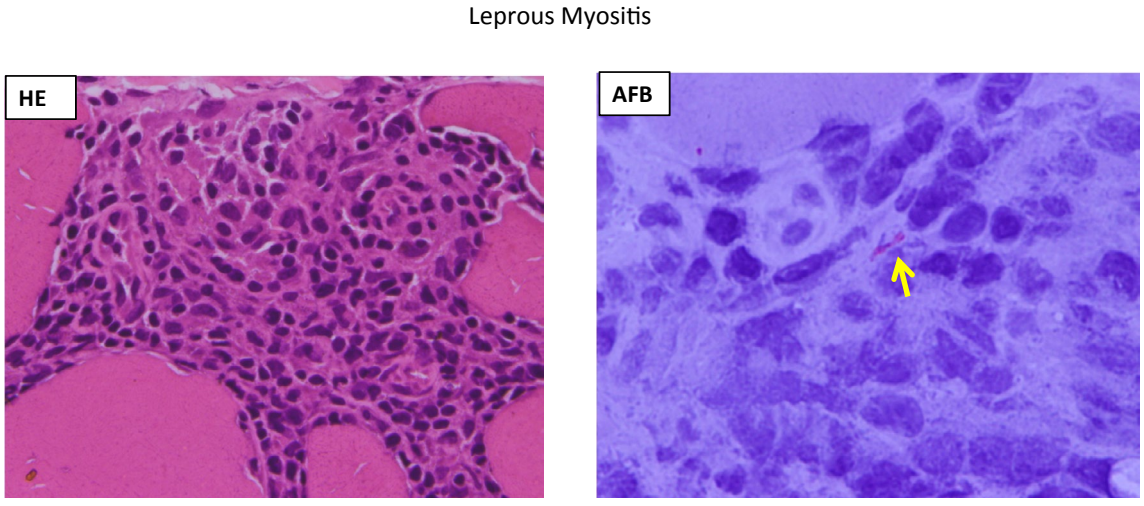

FIGURE 2 A case of Leprous myositis with granulomatous inflammation in the endomysium comprising of epithelioid cells, macrophages and lymphocytes. AFB stain (modified Wade Fite Faraco) showing acid-fast Lepra bacillus (↑)

3.1 | Candidiasis

Candida species form the common fungal microbes causing myositis and are most often part of a systemic infection important risk factors being severe neutropenia, extensive use of broad-spectrum antibiotics, and immunosuppressive drugs. Generally, there is diffuse muscle involvement associated with tenderness, fever, and rash (48). Disseminated candidiasis with a localized muscle mass progressing to a candida abscess has been reported. The muscle may also show microabscesses, which may coalesce to form larger abscesses (49, 50). Budding yeast forms and pseudohyphae are noted on histological examination using special stains. Culture would show the growth of the fungal organism (1). Blood culture may be positive in systemic infection. Mortality is high. Hence, early diagnosis and treatment are crucial. Imaging often plays an essential role in diagnosing, defining the extent of involvement, directing tissue sampling, and monitoring treatment response.

3.2 | Cryptococcosis

Cryptococcal infection is one of the rare causes of myositis. Similar to candida, cryptococcal myositis is a disseminating disease, although localized muscle infection can also occur. Histopathology reveals typical intracytoplasmic yeasts with a mucopolysaccharide capsule that is easily recognized with mucicarmine or Alcian blue stains. Serology and blood culture is useful and supportive in diagnosis. *C. neoformans* infections occasionally present with infectious myositis. It is generally seen in immunocompromised and diabetic patients with disseminated cryptococcal disease. Successful treatment is achieved with surgical drainage and systemic antifungal agents. Molecular identification with DNA sequence analysis helps in confirming the diagnosis (1).

3.3 | Other fungi

Histoplasmosis and Coccidioidomycosis are caused by dimorphic fungi that rarely affect muscle post-dissemination from the lungs. Histopathologically, typical ovoid yeast forms of Histoplasma can be detected on GMS (Gömöri's methenamine silver) stain and fungal culture. The biopsy of the muscle involved by *Coccidioides* spp. shows changes in abscess with the organisms appearing as spherules filled with endospores (1). Fungal culture and serology are helpful for identification.

Aspergillosis rarely involves the muscle as part of a disseminated disease or a focal infection in an immunocompromised situation.

4 | MYOSITIS DUE TO PARASITIC INFECTIONS

A wide range of parasites can involve the muscle. Consequent to infection, the tissue response may be focal or diffuse, suppurative to suppurative granulomatous inflammation with eosinophilia. Besides, each parasite displays unique features. While the protozoa occur within the muscle fiber, nematodes and cestodes are seen within or between the myofibers. The common parasitic infections are due to *Trichinella spiralis*, *Taenia solium*, and *Toxoplasma gondii*, followed by the less common ones that include *Trypanosoma cruzi* causing Chagas disease, *Toxocara canis*, Schistosoma, Echinococcus, *Entamoeba histolytica*, Spirometra, mansonoides causing Sparganosis, *Plasmodium falciparum*, and others (*Sarcocystis* spp., *Schistosoma* spp., *Echinococcus* spp., and *Microsporidia* spp.) (1).

4.1 | Trichinosis

Trichinella organisms cause trichinosis which is an important parasitic infection that involves the muscle. An autopsy study detected Trichinella cysts in >4% of diaphragmatic muscle (51), hence humans are incidental hosts. *Trichinella spiralis* is the most common organism that affects humans subsequent to the consumption of undercooked pork meat infected with Trichinella. The larva reaches the stomach on consumption and gets released in the gastric cavity following the digestion of the larva's outer coverings by the gastric enzymes. Since the larvae are resistant to gastric acid, they easily pass into the small intestine, pierce through the epithelium, reach the subepithelial lamina propria and develop into adult forms, thus forming new larvae that disseminate via the lymphatic and hematogenous routes to reach the muscle and encyst. These larvae often remain viable without eliciting any tissue response and clinical manifestation. Other species that cause human infection are *Trichinella nativa, Trichinella britovi, Trichinella pseudospiralis*, and *Trichinella nelson* (52). Clinical presentation depends on the larval density, size, also on the age of patients, and their co-morbidities. The larger the number of larvae, the shorter is the incubation period. Gastrointestinal symptoms may be observed between 2 and 7 days of ingestion. Systemic manifestations commence between 9 and 28 days following larval penetration into the abdominal wall and dissemination all through the body, causing fever, myalgia, conjunctival hemorrhage, and periorbital edema (1). Most cases remain asymptomatic. Trichinella larvae invade the muscle (Figure 3), causing disruption and disintegration of the myofibrillar network that activates the satellite cells to proliferate and differentiate (53, 54). Often necrosis occurs

Parasitic infection - Trichinellosis

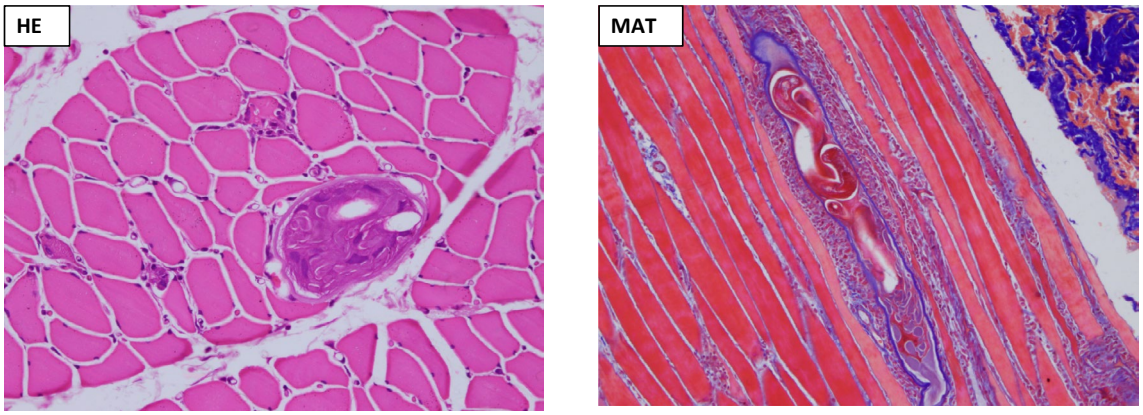

FIGURE 3 A case of Trichinella infection showing larvae of *Trichinella spiralis* within the muscle fiber

when regeneration is less effective (55). The viable area is separated from the affected zone by a septum that appears basophilic and subsequently results in larval calcification(53, 56). Signs of myalgia, swelling, and weakness indicative of muscle involvement are seen between 5 and 6 weeks after infection and subside once the larvae are encapsulated and calcified within the muscles. Extraocular muscles may be involved early, followed by masseters, diaphragmatic, neck, laryngeal, and limb muscles. The symptoms depend on the muscles involved and consequent tissue inflammation. The severity is related to larval density. A capsule of fibrocollagenous tissue formed around the Trichinella larvae and nurse cells represents the muscle cells' reparative response (55). Though the prognosis is good, life-threatening complications are reported in less than 2% of cases when the larvae reach vital organs(heart, lung, and brain) with consequent inflammation and its corresponding lethal effects depending on the organ involved. Eosinophilia, an important clue, is detected in the second week and correlates well with the degree of myalgia (1).

In a situation with multiple muscle involvement and eosinophilia, the possibility of a parasitic infection, especially trichinosis, should be considered. This may accompany increased WBC count, IgE levels, and muscle enzymes. Serologic testing of anti-Trichinella antibodies is useful for diagnosis as the antibodies can be detected 2 to 4 weeks post-infection with raising titers (1). Histopathological examination of muscle is useful and confirmatory especially when sampled from the swollen, tender region of the muscle, which may be superficial or near the insertion commonly in the deltoid or gastrocnemius muscle. Muscle fibers showing basophilic transformation are an important clue for the diagnosis of Trichinella invasion, even in situations where the larvae may not be detected (57, 58). The earlier the therapy with antihelminthic drugs, the better is the responses as larva remain viable even after starting the treatment. Important antihelminthic drugs are albendazole/mebendazole/thiabendazole supported with analgesics against myalgia. Corticosteroids are instituted if severity increases or vital organs are involved.

4.2 | Cysticercosis

Cysticercus cellulosae, the larval form of the pork tapeworm *Taenia solium* causes cysticercosis and is endemic in several countries, mainly affecting individuals of low socioeconomic status, accounting for 1.2–25% of all intracranial space-occupying lesions seen in specialized centers in India and 2.2–18.6% of unselected cases of seizures from the epilepsy clinics in the country (1, 2). Invasion to the brain parenchyma by this larval form of cestode occurs in 60% of cases, skeletal muscle in 5%, and the eye in nearly 3% of cases (59). The coincidence of taeniasis (infestations by the adult worm) and cysticercosis in the same patient is rare. It is encysted in the subcutaneous tissue, skeletal and cardiac muscle, eye, and brain and is a major cause of adult-onset seizures. Humans, the intermediate hosts acquire infection by consuming food, including vegetables contaminated by ova excreted in the feces either from another person infected with tapeworms or fecal-oral autoinfection in patients with a gastrointestinal infection. People living in the same household with one person infected with tapeworm have a much higher risk of cysticercosis. Ingested eggs after activation by the gastric fluid develop into larvae within the GI tract. The larva is invasive, and penetrates the intestinal wall and disseminates hematogenously to different regions of the body. Infection also occurs on the consumption of undercooked meat that contains the larvae. The larva has tissue tropism, especially for the CNS, eyes, and those organs with rhythmic pulsatile or contractile properties like skeletal muscle,

diaphragm, heart, peritoneum, pleura, and subcutaneous tissue. These tissues, in addition to rich lymphatic and vascular plexus with a high degree of permeability, are rich in cholinergic innervation (60). Muscle involvement is common in 75% of patients with neurocysticercosis. Most cases of muscle cysticercosis are asymptomatic except when extraocular muscles are involved. The larvae tend to remain intact with suppressed immune and inflammatory response in its vicinity. However, with the degeneration of cysticerci, a variable amount of inflammatory response may be elicited. Others include retinitis and subcutaneous nodules. The involvement of the musculature during the acute phase is asymptomatic, myalgia and one or more subcutaneous nodules are seen. Asymmetric pseudohypertrophy of muscle without weakness associated with seizures and dementia is noted in disseminated cysticercosis (61, 62).

In due course, the cysts degenerate and become fibrotic with calcification that can be detected on imaging, especially by CT scans. The death, degeneration, and calcification occur earlier after infection within striated muscles than in the brain. Viable cysts with scolex can be diagnosed on MRI, CT, and ultrasound. This is supported by serology testing like ELISA and histopathological examination is useful in confirming the diagnosis. Post-detection of the cyst in muscle, a concomitant presence of cysts in vital organs needs to be investigated. Histopathologically, encysted larvae are 3-4 cm in diameter consisting of a thin wall having an outer folded eosinophilic cuticular layers (Figure 4), with bundles of muscle fibers abutting covered with microtrichia, a middle cellular layer, and internal reticular layer of fibrous network with a few calcareous bodies. The inflammatory response following the degeneration of the parasite due to cyst fluid permeation includes lymphocytes, plasma cells, eosinophils, and foreign body giant cells. Muscle involvement with viable cysts is treated with albendazole/praziquantel.

4.3 | Protozoal infections

4.3.1 | Toxoplasmosis

Toxoplasmosis is caused by *Toxoplasma gondii*, an intracellular protozoan that enters the body through the ingestion of food contaminated with sporozoites from feline feces or consumption of undercooked pork and lamb meat contaminated with Toxoplasma yeasts. The infection increases steadily with age. The prevalence varies geographically. Immunocompetent patients remain asymptomatic or may develop nonspecific self-limiting prodromal symptoms. However, in immunocompromised circumstances, the acute infection may be severe, or reactivation may occur that involves tissues like CNS, eyes, lungs, and muscles (63). The myositis can be acute that often responds to anti-protozoal therapy or chronic that requires steroids due to an altered immune response (64).

Clinical signs of myalgia, weakness, and wasting indicate muscle involvement. A progressive myositis can also occur. Systemic signs noted in many immunocompromised patients include fever, encephalitis, and multiorgan dysfunction. Detection of IgM antibodies by ELISA / immunosorbent agglutination indicates acute infection (65). IgG appears in the first two weeks of infection and persists throughout life (53). Rising IgG titers indicate reactivation (63). *Toxoplasma* can be identified histologically or isolated in tissue cultures. Isolation of *T. gondii* from muscle tissue in cases of myositis has been reported (66). The immunohistochemistry using antisera to *T. gondii* is both a sensitive and specific diagnostic marker (67).

4.3.2 | Trypanosomiasis

Rare cases of myositis in Chagas disease caused by *Trypanosoma cruzi* transmitted by a reduviid bug bite,

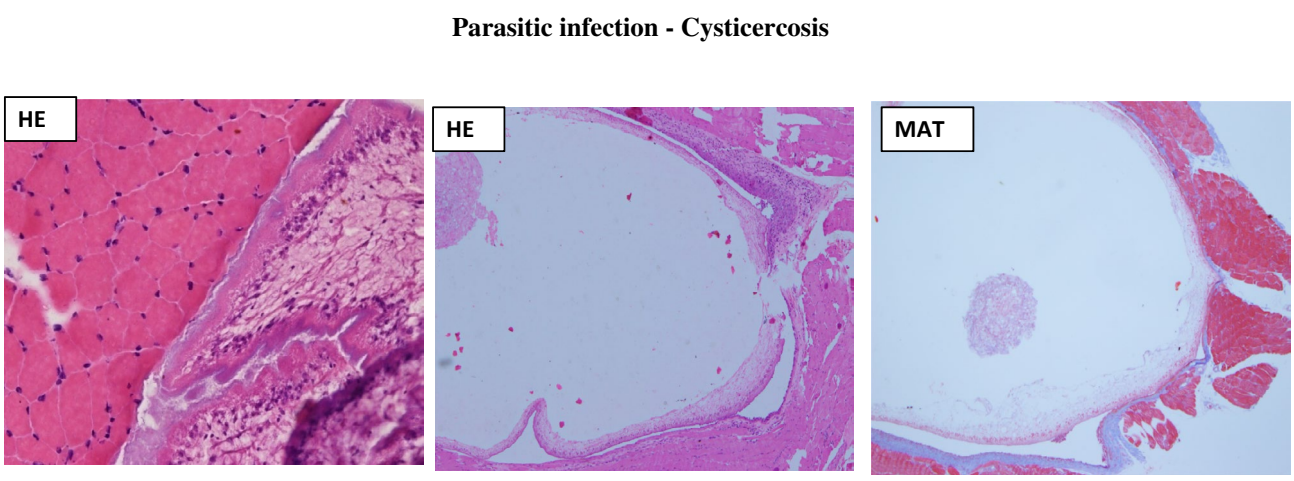

FIGURE 4 A case of Cysticercal infection shows cyst consisting of a thin wall having an outer folded eosinophilic cuticular layer with bundles of muscle fibers abutting, a middle cellular layer, and internal reticular layer of fibrous network

blood transfusion, or congenitally has been reported (68, 69). Myositis can occur during any disease phase (acute/chronic) with a variable degree of inflammation and clinical manifestations (68). Muscle biopsy reveals amastigotes forming a pseudocyst or cavity without distinct wall and perivascular inflammation. With ongoing degeneration, inflammation develops with variable myopathic changes. The parasite affects the myocardium and the smooth muscle cells. Myocardial affection results in myofibrillar inflammatory lesions with or without fibrosis that can complicate as heart failure. In an immunocompromised state, reactivation of Chagas disease may occur and cause myositis.

In acute cases, blood examination (peripheral blood smear for Trypomastigotes) may be useful, but maybe negative in later phases of infection, during which serology (IHA and ELISA) is helpful (70). Studies on the use of biomarkers have demonstrated both increased titers of s-VCAM-1 and s-P-selectin and a positive association between disease severity and levels of s-P-selectin in chronically infected patients.

4.3.3 | Sarcocystosis

Sarcocystosis, a rare protozoal infection caused by *Sarcocystis* spp., can affect the muscle. Infection in humans is incidental and caused due to the ingestion of undercooked meat or food contaminated with carnivorous animal feces carrying sporocysts. Muscle involvement may show changes due to parasites directly reacting with the muscle or due to unregulated immune response and manifests as episodic painful muscle swelling, myalgia (chronic/ relapsing), weakness, tenderness, and fasciculations along with fever, rash, bronchospasm, and subcutaneous nodules (1). The formation of muscle cysts is seen in a disseminated state. As the cysts disintegrate, myositis develops and termed as sarcosporidiosis (71, 72). Several muscles (tongue, esophagus, pharynx, larynx, diaphragm, and cardiac) can show the sarcocysts, and clinical signs can occur in the pre-cystic stage (72). Lesions depend on the sarcocyst density. Histologically, hemorrhage, vasculitis, and myocyte necrosis are seen subsequent to muscle invasion by merozoites. Consequent to sarcocystis degeneration, a dense inflammation comprising mononuclear cells, neutrophils, eosinophils, and giant cells may occur. Diagnosis is made by peripheral eosinophilia and elevated CK levels. Sarcocysts are highlighted by PAS stain (73).

4.3.4 | Microsporidiosis

Microsporidiosis though rare is increasingly recognized among immunosuppressed individuals since the HIV epidemic (74). The infection in humans is by the ingestion or inhalation of the spores, or through direct contact, trauma, or via insect bites, clinically manifesting with myalgia, weakness, arthralgia, fatigue, contractures, fever, and wasting often accompanied by elevated CK levels (74–76). Five important Microsporidial species (*Brachiola vesicularum, Trachipleistophora hominis, Pleistophoraronneafiei, Anncaliia (Brachiola) algerae*, and *Tubulinosema* spp.) are implicated in myositis (76). Often white patches may be detected in the affected muscles, and the biopsy shows disrupted myofibers, necrosis, neutrophil-rich inflammatory cell infiltrate, and extracellular organisms (69). Microsporidia are easily identified as ovoid and refractile spores (<4 microns) within the myofibers by modified Gömöri trichrome stain (69) (Figure 5). Definitive diagnosis is by transmission electron microscopy (Figures 6 and 7) that helps in species identification and the presence of polar filaments (77). Other methods include immunofluorescence antibody staining methods/serological tests (IFA, ELISA, and immunoblot) and PCR (78).

4.4 | Echinococcosis

Echinococcosis (Hydatid Cyst), commonly caused by *Echinococcus granulosus* can involve multiple organs forming cysts and rarely involves muscle (<1% to 4%). Among muscles, the thigh muscles are commonly involved, followed by paraspinal, pelvic, deltoid, and psoas muscles (1). Transmission is by the consumption of food contaminated with eggs. It presents as an incidentally detected lesion (often calcified) on radiology or a slowly growing mass or acute onset if associated with cyst rupture. Rupture of the cysts can pose a severe allergic response (anaphylactic reaction). Though imaging is useful, confirmatory diagnosis is by histopathology, which reveals cysts with outer multilaminar (ectocyst) wall and inner germinal layer (1). Aspirated cyst fluid show protoscolices, rostellar hooks, antigens or DNA (79).

5 | VIRAL MYOSITIS

Though several microbial organisms are known to cause myositis, viruses easily involve the muscle and are the most common cause for infectious myositis leading to myalgia, polymyositis, or associated rhabdomyolysis. The common ones include influenza (A and B) group of viruses, parainfluenza, enteroviruses (Coxsackievirus and Echovirus), adenovirus, severe acute respiratory syndrome, coronavirus, retroviruses, herpesviruses (Varicella, Herpes simplex, Epstein–Barr, and cytomegalovirus), parvovirus B19, dengue, and hepatitis viruses (B and C) (80). The viral infection mechanisms include direct cytopathic/ cytolytic effect, molecular mimicry, immune complex formation, immune dysregulation, and others. However, direct myotoxic effect and immune-mediated mechanisms are the main causes of muscle damage. There is usually

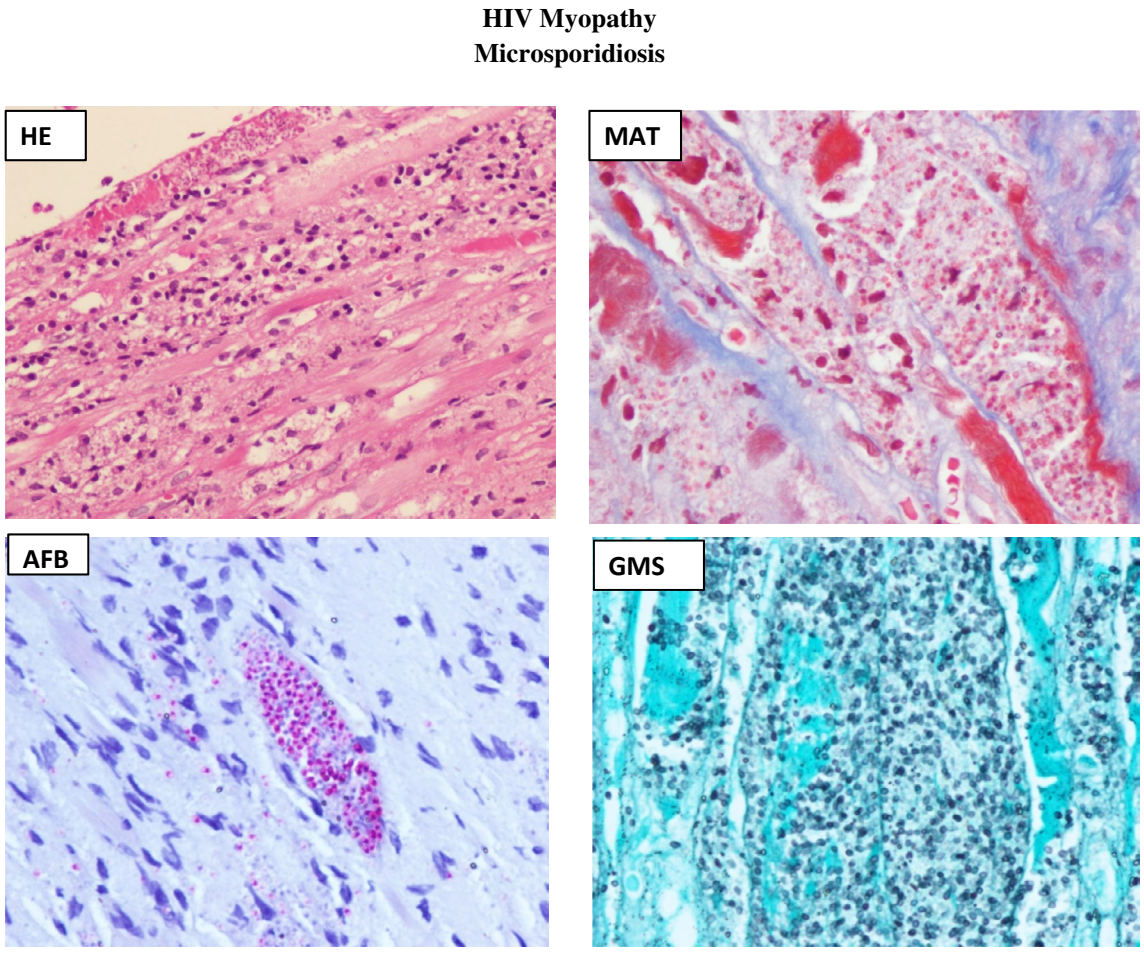

FIGURE 5 A case of microsporidial myositis in HIV infected patient showing dense proliferations of multiple ovoid spores totally replacing the myofibers

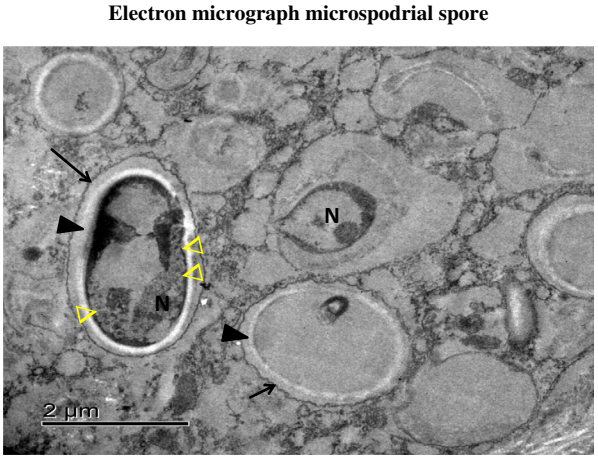

FIGURE 6 Electron micrograph of the microspodrial spore shows electron-dense exospore (↑), electron-lucent endospore (►), polar tubules (▽) arranged in a single row, spore nucleus (N), and degenerated spores Bar 2 µm

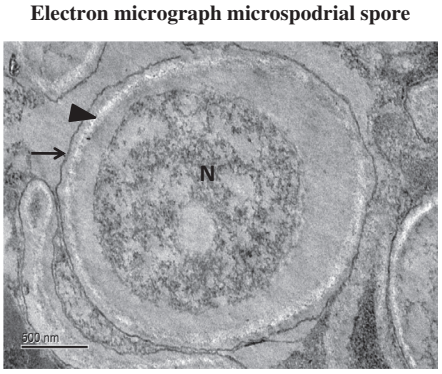

FIGURE 7 Ultrastructural features of the mature microspodrial spore shows electron-dense exospore (↑), electron-lucent endospore (►), and spore nucleus (N) Bar 500 nm

spontaneous recovery except in some who develop complications of rhabdomyolysis, myoglobinuria, acute renal failure, cardiac arrhythmias, and compartment syndrome.

The common viruses that cause rhabdomyolysis include Influenza, enteroviruses (Coxsackie A & B) followed by Epstein-Barr virus (EBV), Human immunodeficiency virus (HIV), and Herpes simplex virus (81, 82).

The muscle damage caused by viruses may be exaggerated or triggered by exercise. Normalization of muscle enzymes (e.g., CK levels) precedes functional recovery.

Viral myositis is relatively more common in children because of viruses' trophic property to immature muscle cells (83, 84). Clinically, viral myositis is often mistaken with idiopathic "polymyositis" or dermatomyositis when skin rashes exist. A severe form of viral myositis with extensive necrosis may mimic necrotizing myopathy, drug-induced myopathy, metabolic crisis, or vasculitis.

The biochemical parameters, EMG, and muscle biopsy findings may be similar in both viral myositis and idiopathic inflammatory myopathies. Viruses can rarely be isolated from muscle biopsy specimens. Clinical evaluation and corroborative evidence from all the ancillary tests are needed for a definitive diagnosis. However, suspicion of viral etiology increases when muscle symptoms (weakness) develop acutely or subacutely following an antecedent respiratory or gastrointestinal infection (85).

5.1 | Influenza A and B viruses

Influenza A and B viruses cause myalgia as a part of the initial viral prodrome accompanied by fever, malaise, and other generalized symptoms. Most cases manifest with respiratory tract infection. However, other complications include myositis, myocarditis, and meningoencephalitis (86). It is prevalent in children and in adults with a relative male preponderance (83, 84). Myositis is more common with Influenza B infection due to the presence of a unique type III integral membrane protein, the NB protein expressed abundantly on the surface of virus-infected cells thus mediating its entry (84, 87, 88). Clinically, calf muscles are frequently affected with tenderness and gait abnormalities (83). In some patients, several muscles may be affected. Muscle enzymes (CK, LDH, and aminotransferases) are elevated, and EMG shows myopathic potentials. Clinical evaluation and nasopharyngeal specimen testing are more useful than biopsy. Muscle involvement may be focal or patchy with variable myopathic changes ranging from myositis with mild inflammation to severe myonecrosis, mimicking immune-mediated necrotizing myositis. Infection, in general, is self-limited; however, antiviral drugs are used to manage respiratory and systemic pathology. As a rare complication, rhabdomyolysis can occur, leading to renal failure. Interestingly rhabdomyolysis is more common with type A than type B viruses and is more common in girls. In adults, acute neurological symptoms associated with muscle involvement are seen with Influenza A (H1 N1)virus(2). Recently, as a complication with renal failure, rhabdomyolysis has been reported in pediatric and adults infected with Covid-19 (89, 90). Myotoxic cytokines are implicated in pathogenesis. A benign acute childhood myositis (BACM), an uncommon self-limiting muscle disorder, commonly affects school-going boys. They present with acute onset bilateral muscle pain and tenderness, affecting mainly the gastrocnemius and soleus following a bout of viral prodromal symptoms (fever, malaise, cough, sore throat, and rhinorrhea) and raised serum CK levels (91, 92). The patients' myositis recovers spontaneously within one week without any complications like rhabdomyolysis.

5.2 | Enteroviruses

Acute Coxsackie, particularly group B5 serotype and enteric cytopathogenic human orphan virus, can rarely cause myositis (93, 94). Children are more commonly affected and present with chest pain and costochondral muscle tenderness. As a complication, they can rarely cause rhabdomyolysis (93, 94). In general, a muscle biopsy is not recommended.

5.3 | Human immunodeficiency virus (HIV)

Capable of involving multiple organs, retroviruses affect through multiple mechanisms. As part of neurological manifestations, myopathy is common in patients with HIV infection or associated with antiretroviral (ARV) therapy use. Secondary myopathy due to vasculitic, metabolic, opportunistic infections or neoplastic causes, though occur, but are relatively rare in HIV-infected individuals (95, 96). The other clinical conditions associated include inclusion body myositis, myopathy with nemaline rods, HIV-wasting-syndrome, myasthenic syndromes, chronic fatigue syndrome, and diffuse infiltrative lymphocytosis syndrome.

HIV myositis is reported at all stages of infection, presenting with proximal muscle weakness, myalgia, and elevated serum kinase (1). Muscle biopsy may show necrosis, myophagocytosis, inflammatory infiltrates in the epimysium, perimysium, interstitial and interfascicular zones (97). The inflammatory cell infiltrate consists predominantly of $CD8^+$cells and macrophages with significantly fewer $CD4^+$ cells (98). Loss of thick filaments and cytoplasmic microvesiculation can be detected on electron microscopy. The pathogenesis is considered to be immune-mediated. HIV-associated myopathy with nemaline rods reveals rod-like structures and cytoplasmic bodies on MGT stains and basophilic granular material. HIV infection can be a triggering factor of amyotrophic lateral sclerosis, brachial amyotrophic diplegia, and inflammatory muscle diseases like IMNM(Immune-mediated necrotizing myopathy)(99). Antiretroviral drugs (especially zidovudine, didanosine) and opportunistic infections can add to the pathology or cause new lesions in the muscle. Zidovudine is associated with secondary mitochondrial myopathy (100, 101). AZT-induced myositis is dose-related, and cessation of therapy provides improvement (102). The pathogenesis includes an autoimmune phenomenon as well, with the presence of tubuloreticular inclusions recognized by EM

in the capillary endothelial cells(103). In the setting of IRIS (immune reconstitution inflammatory syndrome), myopathy can occur, indicating an immunological mechanism.

HIV myositis is typically symmetric with bilateral involvement as compared to pathology due to other infections (opportunistic infections like mycobacterial infections including atypical mycobacteria, microsporidia, Cryptococcus, CMV, and Toxoplasma), which are often asymmetric. Tendon reflexes in HIV-myopathy may be depressed, and there may be fasciculations. CK may be normal, and monoclonal or polyclonal hypergammaglobulinemia is often observed that normalizes with highly active antiretroviral therapy (HAART). HIV-associated neuromuscular weakness syndrome can occur, which includes subacute progressive myopathy, rapidly progressive sensorimotor polyneuropathy with inflammation in the muscle, ragged red fibers, abnormalities in respiratory chain enzymes, and mitochondrial DNA depletion (60, 97). Patients with HIV infection can also clinically present as Inclusion body myositis(IBM) or polymyositis, both being T - cell-mediated inflammatory myopathies (104). These patients present with early age of onset with proximal muscle weakness and elevated CK levels mimicking polymyositis and eventually progress to overt inclusion body myositis with rimmed vacuoles and wrist flexor weakness (105, 106). Muscle biopsy shows features of both polymyositis -like endomysial inflammation with MHC-I/CD8 complex and degenerating features seen in IBM such as fiber atrophy, red-rimmed vacuoles, eosinophilic inclusions, and amyloid deposits. That retroviral antigens have been detected only on endomyseal macrophages and not within the muscle fibers, suggests that retroviruses do not directly infect the muscle but trigger an immune response identical to sporadic IBM (107).

5.4 | HTLV-1

Infection causes myositis either alone or as a complication of tropical spastic paraparesis through an immune-mediated mechanism, mainly by $CD4^+$ lymphocytes. Initial symptom include muscle weakness and elevated CK followed by respiratory failure. Muscle biopsy shows myophagocytosis and inflammatory infiltrates predominantly $CD8^+$ lymphocytes in endo- and perimysium, perivascular region and around necrotic fibers. There is an upregulation of the MHC class 1 antigen.

5.5 | Hepatitis viruses

Especially B and C causes polyarthritis, cryoglobulinemia, and polymyalgia rheumatica. They rarely cause myositis *per se* and present as myalgia and proximal muscle weakness. This can accompany hepatitis and can show fluctuation similar to and along with hepatitis (1).

5.6 | Other viruses

Other viruses that include parainfluenza viruses, adenoviruses, and respiratory syncytial viruses may cause myositis of variable severity with or without rhabdomyolysis. Muscle involvement is along with other organ infections especially respiratory or gastrointestinal. Muscle pathology may be due to a direct viral cytopathic/cytolytic effect or an indirect immune-mediated (humoral / cell-mediated) mechanism. A special mention is required for myositis due to arboviruses, which can present as "dengue-like syndrome" with fever, rash, conjunctivitis, arthralgia, myalgia, myositis, and rhabdomyolysis (108).

The arboviruses, which are arthropathic-associated, include Chikungunya viruses (CHIKV). CHIKV often affects the muscle along with the joints (40 − 90%)(108, 109). These symptoms can persist. CHIKV is endemic in some areas of the world. A massive global re-emergence of CHIKV in 2004, initiated with the Kinshasa (Kenya) outbreak, which subsequently invaded the Indian Ocean islands, significantly affecting La Réunion and ultimately affecting the Indian subcontinent and other southeast Asian countries (110, 111).

Transmitted by *Aedes* mosquitoes, the virus causes Chikungunya fever characterized by rheumatic manifestations along with myalgia. Rhabdomyolysis has been rarely reported. Serology is most useful for diagnosis, and for those with respiratory involvement, nasopharyngeal specimen culture will be essential; for viruses affecting gastrointestinal organs, stool culture will be helpful for the diagnosis.

The other viruses that rarely affect muscles include Dengue, Mumps, and parvovirus B19. Overactive immune response by a range of antigenic stimuli is involved in the pathophysiology of the myositis associated with these infections. The muscle may show myonecrosis and myotoxic cytokines, and in particular, tumor necrosis factor is involved in the pathogenesis.

6 | CRITICAL ILLNESS MYOPATHY

Some of the viruses and bacteria can cause a severe form of pathology that necessitates ICU care and extended hospital stay, posing a risk for complications including critical illness myopathy (CIM) (112, 113). The exact pathophysiology is unclear, but complex structural/functional alterations within myofibers and neurons affecting the excitation-contraction coupling, microcirculatory disturbance, metabolic, electrical muscle alterations, and mitochondrial dysfunction have been reported (114). Some of the suspected risk factors for CIM include sepsis, hyperglycemia, administration of neuromuscular blocking agents, prolonged mechanical ventilation, and ICU admission (115).

7 | CONCLUSION

Infectious myositis is an important cause of inflammatory myopathy, especially in tropical countries, and poses clinical challenges in differentiating from other inflammatory myopathies, thus increasing the diagnostic investigations and delaying the diagnosis. Infectious myositis is caused by various pathogens, including bacteria, viruses, parasites, and fungi. Often, bacterial myositis presents as focal muscle infection, and viruses tend to cause a diffuse disease. Prevention, improving sanitary conditions, and medical care are essential to control the prevalence of infection. The muscle pathology and the clinical presentation may vary ranging from localized pathology to severe forms with rhabdomyolysis. Some microbes may form gas, while others may be associated with eosinophilia, which serves as a diagnostic clue. Atypical findings allow one to suspect rarer infections and guide toward evaluation and management. A prompt and early treatment with appropriate antibiotics is necessary for complete recovery, while an incomplete or delay in treatment may cause complications that include sepsis. The use of antiretroviral agents and vaccination reduce the number of infected patients. New technology has paved way for identifying the pathogen and gene expression of the pathogens in tissue. Molecular genetics sequencing for some infectious agents serves as a diagnostic tool. Proteomics-based mass spectrometry and bioinformatics are now used as a potent method to elucidate post-translational modifications such as glycosylation or proteolysis and complement genetic studies. Application of improved and novel technologies will unravel the pathomechanisms of infections ultimately leading to therapeutic and preventive measures.

AUTHOR CONTRIBUTIONS

Dr. Gayathri N. and Dr. Nandeesh B.N. have contributed in preparing the article, putting the microphotographs together, reviewed and discussed.

DATA AVAILABILITY STATEMENT

The data and the references provided by the authors are checked. All references quoted are from the pubmed.

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