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96 Myositis and Myonecrosis

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SHORT VIEW SUMMARY

Definition

- Myositis is an inflammatory and generally necrotizing process primarily due to hematogenous seeding of muscle with subsequent bacterial invasion. Direct inoculation of muscle as the result of penetrating trauma is also an important mechanism of infection (associated with clostridial myonecrosis). More generalized muscle inflammation may also accompany a variety of acute and chronic viral and parasitic disorders.

Epidemiology

- Pyomyositis occurs across the age spectrum in temperate regions and may occur in previously healthy as well as immunocompromised individuals; in warm climates, infections in children predominate (i.e., tropical pyomyositis). Clostridial myonecrosis most commonly complicates penetrating trauma (e.g., vehicular accidents, war, natural disasters), especially in resource-limited settings.

Microbiology

- *Staphylococcus aureus* is the classic cause of pyomyositis, but similar illnesses have been associated with a wide variety of bacterial pathogens, particularly in compromised hosts. *Clostridium perfringens* myonecrosis complicates penetrating trauma, but nontraumatic clostridial myonecrosis may develop after hematogenous dissemination of more aerotolerant species (e.g., *C. septicum, C. sordellii*). Group A streptococci can also cause severe myonecrotic infection, which is a true medical emergency. Acute generalized muscle inflammation occurs after influenza and dengue virus infections, but a wide variety of viral pathogens have sporadically led to significant muscle injury and even severe rhabdomyolysis.

Diagnosis

- Consideration of these uncommon processes is the first step toward the proper diagnosis, because the focal progressive pain of pyomyositis mimics a variety of disorders. Blood cultures and (percutaneous) drainage based on the findings of cross-sectional imaging confirm the diagnosis and guide therapy. Pyomyositis may accompany toxic shock, and investigation of a focal process responsible for fulminant systemic illness is essential. Gas production in muscle and soft tissue in the setting of a rapidly progressive illness occurs in clostridial myonecrosis and related infections; this is a surgical emergency and exploration for débridement of nonviable tissue and appropriate cultures is critical.

Therapy

- Ideally, after expedited imaging and drainage, empirical broad-spectrum antibacterial therapy effective against *S. aureus* (including methicillin-resistant *S. aureus*) and gram-negative bacilli as well as anaerobes should be administered. The findings of associated toxic shock mandate the addition of a protein synthesis inhibitor (e.g., clindamycin) and possibly intravenous immunoglobulin therapy. Narrow-spectrum therapy is appropriate after identification and sensitivity testing of the isolated pathogen. Patients presenting with the clinical findings of gas gangrene (clostridial myonecrosis) require immediate high-dose penicillin and clindamycin and urgent surgical exploration.

Prevention

- Because most episodes of pyomyositis develop after transient bacteremia, prevention is not practical. Prompt débridement of devitalized tissue after penetrating injury is highly effective at preventing clostridial myonecrosis.

Infection of skeletal muscle (infectious myositis) is uncommon. When it occurs, a wide range of organisms may be responsible: bacteria, mycobacteria, fungi, viruses, and parasitic agents.[1] Bacteria invade muscle either from contiguous sites of infection (e.g., skin and subcutaneous abscesses, penetrating wounds, decubitus ulcers, osteomyelitis) or by hematogenous spread from a distant focus. It is helpful to categorize infectious myositis on the basis of clinical manifestations. These may be very distinctive, as in clostridial gas gangrene, and suggest the specific etiologic agent, or they may be very nonspecific, as in the myalgias of viral infections and infective endocarditis (Table 96-1). In certain instances (e.g., psoas abscess), it is the anatomic location rather than the morphologic characteristics of the lesion or the nature of the infecting agent that distinguishes the particular type of muscle infection.

PYOMYOSITIS

Pyomyositis is an acute bacterial infection of skeletal muscle that is most commonly caused by *Staphylococcus aureus*. Pus accumulates within muscles initially; the muscle infection is not usually due to primary infection of adjacent skin, soft tissue, or bone. Clinically, pyomyositis is characterized by fever, localized muscle pain and stiffness, swelling, and tenderness.

Pathogenesis and Pathologic Characteristics

Bacterial infections of muscle usually occur after a penetrating wound, prolonged vascular insufficiency in an extremity, or a contiguous infection. Bacteremic spread of infection to skeletal muscle is extremely uncommon. Among fatal cases of staphylococcal septicemia, abscesses in skeletal muscle are found in less than 1%.[2] Pyomyositis (primary muscle abscess) is a bacterial infection of muscle that occurs in the absence of a predisposing site of infection. *S. aureus* is the most common cause.[3,4] Blood cultures are positive in 5% to 35% of the cases in most series at the time of presentation; metastatic infections in tissue other than muscle are rare, although the development of venous thrombosis and septic pulmonary emboli has been reported.[5] In individual patients with multifocal infections or associated endocarditis, it may be challenging to clarify whether sustained bacteremia was the primary process or the result of progressive pyomyositis.[6]

Most cases of pyomyositis occur in the tropics, hence the term *tropical pyomyositis*. Historically, it accounted for 1% to 4% of hospital admissions in some tropical areas,[7] although recently in northern India pyomyositis accounted for only 0.03% of admissions.[8] In more temperate areas, pyomyositis is very uncommon, with approximately 330 reported cases in the United States between 1981 and 2002[4] and a reported incidence of 0.5/100,000 annually in Australia.[6] Pyomyositis occurs at all ages, in the tropics more frequently among children, but in North America more often in adults and the elderly.[4,9] No convincing evidence relates pyomyositis causally to predisposing

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KEYWORDS

clostridial myonecrosis (gas gangrene); group A streptococcal necrotizing myositis; myalgia; nonclostridial myositis; parasitic myositis; pyomyositis; psoas abscess; rhabdomyolysis

TABLE 96-1 Classification of Infectious Myositis

TYPE OF PROCESS	CLINICAL PATTERN	SPECIFIC CAUSES
Pyogenic and predominantly localized (spreading by contiguity)	Pyomyositis	*Staphylococcus aureus*
		Group A streptococcus (occasionally)
		Other gram-positive cocci (rarely)
		Group B, C, or G streptococci
		Streptococcus pneumoniae
		Gram-negative bacilli (rarely)
		Anaerobic bacteria (rarely)
		Fusobacterium necrophorum
		Clostridia
		Mycobacteria (rarely)
		Mycobacterium tuberculosis
		Mycobacterium avium-intracellulare
		Fungi (rarely)
		Cryptococcus neoformans
	Gas gangrene	*Clostridium perfringens;* occasionally other histotoxic clostridial species
	Nonclostridial (crepitant) myositis	
	Anaerobic streptococcal gangrene	*Peptostreptococcus* (plus group A streptococci or *S. aureus*)
	Group A streptococcal necrotizing myositis	Group A streptococcus
	Synergistic nonclostridial anaerobic myonecrosis	Mixed infections: *Bacteroides* and other anaerobic non–spore-forming gram-negative bacilli; *Peptostreptococcus* and various streptococci; *Escherichia coli; Klebsiella; Enterobacter*
	Infected vascular gangrene	Same as for synergistic nonclostridial anaerobic myonecrosis
	Aeromonas hydrophila myonecrosis	*A. hydrophila*
	Psoas abscess	Gram-negative bacilli; *S. aureus;* mixed infections; *M. tuberculosis*
Nonpyogenic and predominantly generalized	Myalgias	Viral infections (e.g., influenza, dengue); infective endocarditis; bacteremias (e.g., meningococcemia); rickettsioses (e.g., Rocky Mountain spotted fever); toxoplasmosis
	Pleurodynia	Coxsackievirus B
	Myalgias with eosinophilia	
	Trichinosis	*Trichinella spiralis, Trichinella pseudospiralis*
	Cysticercosis (also subcutaneous nodules)	*Taenia solium*
	Muscle degeneration and destruction associated with infections elsewhere	
	Acute rhabdomyolysis	Influenza viruses, dengue virus, echoviruses, coxsackieviruses, Epstein-Barr viruses, *Legionella,* and others (see text)

circumstances peculiar to the tropics (e.g., malaria, filariasis, arbovirus infection). However, an association between *Toxocara canis* infection (visceral larva migrans) and staphylococcal pyomyositis has been proposed.[10] Migration of the guinea worm *Dracunculus medinensis* in the deep connective tissues of the lower extremities may be complicated by staphylococcal abscesses, but these are located between muscle groups and are not the intramuscular abscesses typical of pyomyositis. Approximately 40% of cases in temperate climates lack any relevant underlying disease, but the remainder have possible predisposing risk factors such as intravenous drug abuse and systemic conditions including human immunodeficiency virus (HIV) infection, diabetes mellitus, alcoholic liver disease, corticosteroid therapy, hematologic malignancies (e.g., leukemia, lymphoma, or multiple myeloma), other hematologic processes (e.g., Felty's syndrome, myelodysplasia, sickle cell disease, cyclic neutropenia, chronic granulomatous disease) and/or their cytotoxic therapies, and rheumatologic diseases (particularly rheumatoid arthritis and systemic lupus erythematosus).[4,9] The postpartum,[11] postabortion,[12] and postoperative states, as well as deep acupuncture,[13] are rare predisposing risk factors for the development of pyomyositis.

Pyomyositis has been reported repeatedly in patients with HIV infection, with or without acquired immunodeficiency syndrome (AIDS) (including one neonate); in the majority of these patients, it was caused by *S. aureus*.[4,14] The predisposition to pyomyositis in AIDS patients probably relates to granulocyte dysfunction,[15] progressive cell-mediated immunodeficiency,[16] and possible muscle injury (e.g., HIV myopathy, zidovudine-associated mitochondrial myopathy, myositis from parasitic disease, *Mycobacterium avium* complex infection). Although *S. aureus* is the etiologic agent in the majority of HIV-associated cases, *Salmonella* accounts for as many as 10% and streptococci for 5% of pyomyositis episodes in this population[4,14]; pneumococci, enterococci, and granulomatous infections due to *Mycobacterium tuberculosis* and *Sporothrix schenckii* have also been reported. Pyomyositis has been reported in growing numbers of intravenous drug abusers (with or without HIV infection) caused primarily by *S. aureus* but also by streptococci, gram-negative bacilli, or multiple organisms (including anaerobes).[17] Pyomyositis is a rare complication of bacterial endocarditis and has been reported in an intravenous drug abuser who had left-sided *S. aureus* endocarditis.[6,18]

The presumed pathogenesis of (primary) pyomyositis involves previous bacteremia, commonly asymptomatic and transient. Because muscle trauma (locus minoris resistentiae) is necessary to produce pyomyositis in experimental animals after intravenous injection of *S. aureus,*[19] a role for local mechanical injury has been hypothesized. Secondary pyomyositis reflects spread of infection from a contiguous source, typically a site of hematogenous osteomyelitis. The frequency of pyomyositis complicating staphylococcal osteomyelitis may be increased in community-acquired methicillin-resistant *S. aureus* strains expressing Panton-Valentine leukocidin[20] and, in general, molecular features of distinct *S. aureus* clones correlate with superficial or invasive clinical syndromes.[21]

Clinical Manifestations

In 20% to 50% of cases there has been recent blunt trauma to or vigorous exercise of the involved area or a local primary dermatologic process.[4,6] The clinical picture often involves three stages. In the first, or invasive, stage, the onset is subacute with variable fever, local swelling with or without erythema, mild pain, and minimal tenderness. The

area is indurated or has a wooden consistency. This stage is often overlooked. Because the initial swelling is firm and pain is not striking, and/or involves deep muscles not easily assessed at the bedside, attention is directed away from an infectious cause. Aspiration, if attempted, yields no pus. The second, or suppurative, stage occurs 10 to 21 or more days later, and this is the time when most patients are diagnosed. The patient is febrile, and distinct muscle tenderness and swelling (conforming to the involved muscle) are present. The overlying skin is intact and warm, and erythema is commonly absent. At this point, pus can be aspirated from the involved muscle. In the third stage, systemic manifestations of sepsis and local findings of erythema, exquisite tenderness, and fluctuance are striking. If untreated, the infection can progress to metastatic abscesses, shock, renal failure, and death[22]; the overall mortality rate is approximately 5%[4] and is largely associated with the presence of severe sepsis and septic shock.[4] The progression of pyomyositis from the initial invasive stage, associated with muscle inflammation and swelling, to the suppurative stage, with focal abscess formation, was documented by serial imaging in a patient whose infection was initially managed with antibiotic therapy.[23]

Occasionally, the onset is acute rather than subacute, with malaise, chills, and high fever. Rarely, the clinical picture is combined with that of toxic shock syndrome.[24,25] This is a particular risk of myositis caused by group A β-hemolytic streptococci (see later discussion). Because the muscle abscesses are contained by the overlying fascia, local erythema and warmth may be minimal and the severity of the process not appreciated until the infection extends to the subcutaneous tissues some days to weeks later. Regional lymphadenitis is not a feature. Usually only a single muscle group is involved, but multiple muscle abscesses may be present at presentation[26] or develop after contiguous spread (e.g., from the psoas to the thigh adductors[27]). The most frequent sites of involvement are the large muscles of the lower extremities (e.g., quadriceps femoris, gluteus group) and the trunk muscles, but a variety of other muscles can be involved (Fig. 96-1). Involvement of the abdominal muscles is uncommon but noteworthy because it may mimic an acute abdomen.[28] Even in fatal cases, the diagnosis may be overlooked and involvement of superficial muscles may be missed at autopsy.[22]

Leukocytosis is prominent; eosinophilia is common in patients with tropical pyomyositis (even in the presence of a prominent granulocytosis) and may simply reflect concomitant parasitic infestation. Serum muscle enzyme levels may be elevated, particularly with severe streptococcal disease, but they frequently are normal despite gross muscle destruction. However, marked rhabdomyolysis with myoglobinuria and acute renal failure, more commonly seen in viral myositis, was reported in a patient with pyomyositis.[29]

Etiologic Agents

S. aureus is responsible for 95% of tropical pyomyositis cases while in temperate areas, *S. aureus* is the cause of 66% to 70% of cases.[4,9] Group A streptococci account for 1% to 5% of the cases. Other gram-positive organisms uncommonly implicated in pyomyositis include various streptococci (groups B, C, and G), *Streptococcus pneumoniae,*[30] *Enterococcus faecalis,*[31] and *Streptococcus anginosus.*[32] Myositis due to viridans streptococci complicating the viridans streptococcal sepsis syndrome in acute myelogenous leukemia has been reported.[33] Other very rare causes include Enterobacteriaceae[1] (*Escherichia coli* [particularly in neutropenic patients with hematologic malignancy[34]], *Klebsiella oxytoca, Klebsiella pneumoniae, Serratia marcescens, Morganella morganii, Citrobacter freundii, Enterobacter* spp., *Salmonella* spp.[35]), *Yersinia enterocolitica, Neisseria gonorrhoeae, Haemophilus influenzae, Pseudomonas aeruginosa, Burkholderia cenocepacia,*[36] and *Aeromonas hydrophila.* Anaerobes (*Fusobacterium nucleatum, F. necrophorum,*[37] *Veillonella* spp., oral anaerobic streptococci,[38] *Capnocytophaga sputigena,*[39] actinomycetes, and *Clostridium septicum*) have been the cause in several cases. Pyomyositis may be caused by mixed pathogens, especially in patients with diabetes in whom, in addition to *S. aureus,* gram-negative or anaerobic pathogens, or both, were recovered in approximately 35% of episodes.[40] In the past, *Burkholderia mallei* and *Burkholderia pseudomallei* have very rarely caused muscle abscesses in the septicemic or chronic suppurative forms of glanders and melioidosis, respectively. *Aspergillus fumigatus* has caused a localized muscle abscess in rare patients with myelodysplasia or AIDS and in patients who have received corticosteroids. Pathogenic yeasts can cause myositis on rare occasions. Pyomyositis due to *Cryptococcus neoformans* was reported in an immunocompromised host,[41] and multifocal *Histoplasma capsulatum* nodular myositis was identified in an HIV-infected patient.[42] Hematogenously disseminated candidiasis in neutropenic

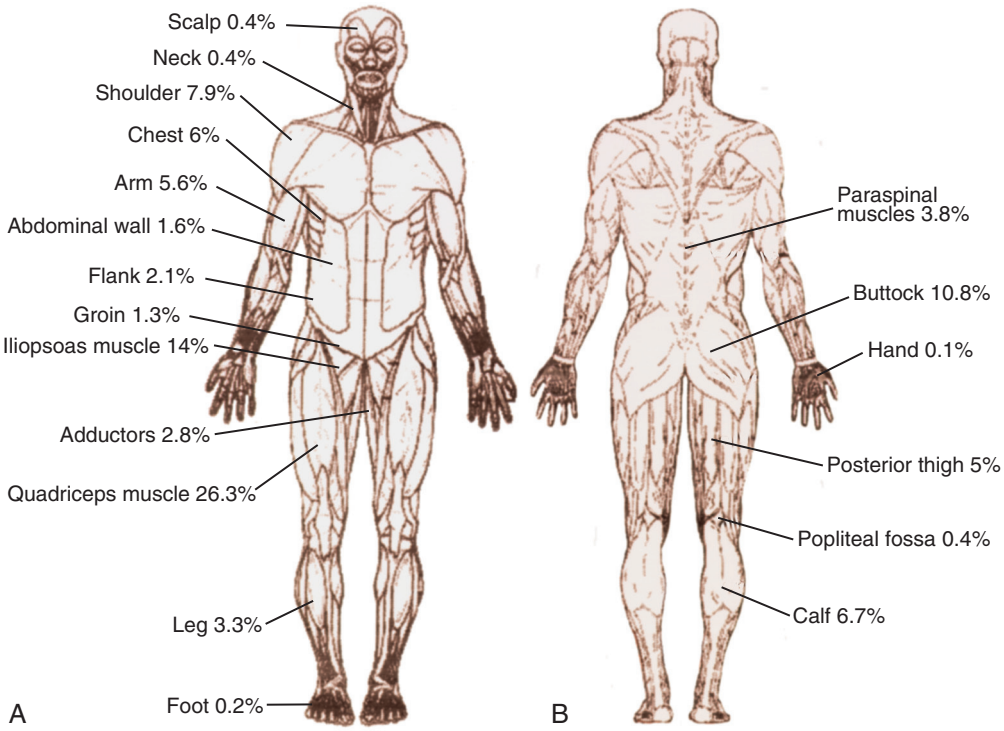

FIGURE 96-1 Distribution of sites of pyomyositis. A, Anterior view. **B,** Posterior view. *(Adapted from Bickels J, Ben-Sira L, Kessler A, et al. Primary pyomyositis.* J Bone Joint Surg Am. *2002;84:2277-2286.)*

patients can manifest as fever and muscle pain. The scattered *Candida* abscesses in the muscle are generally too small to localize by symptoms and physical examination, but myositis in these patients is often accompanied by small, tender, erythematous, hematogenously disseminated skin lesions. Punch biopsy of a skin lesion shows numerous *Candida* organisms in the dermis. Larger candidal lesions may be identified and managed using conventional imaging approaches.[43] Tuberculous pyomyositis is a rare form of extrapulmonary tuberculosis recognized in both competent[44] and immunocompromised[45] hosts and can present with or without features of disseminated disease.[44] Pyomyositis due to *M. avium* complex is occasionally diagnosed in HIV-infected patients, sometimes as part of the immune reconstitution syndrome,[46] and *Mycobacterium haemophilum* pyomyositis was observed in a renal transplant recipient.[47] Extrapulmonary *Pneumocystis jirovecii* infection is relatively uncommon in patients with AIDS, but in one patient it manifested as an intramuscular, localized, painful thigh swelling with typical granulomatous histopathology.[48]

Differential Diagnosis

Early in the course of pyomyositis, other diagnoses may be suspected, particularly in nontropical areas: fever of obscure origin (in the early phase, when localizing findings may be minimal or absent), osteomyelitis, septic arthritis, appendicitis or diverticulitis, muscle strain, contusion or hematoma, muscle rupture, and thrombophlebitis. Iliopsoas myositis has mimicked appendicitis[49]; obturator internus, iliacus, and rarely obturator externus pyomyositises have mimicked septic arthritis of the hip[50]; and pyriformis muscle pyomyositis has simulated an epidural abscess because of severe back and radiating (sciatic) leg pain.[51] Pyomyositis involving these deep pelvic muscles may be difficult to diagnose in patients with active joint disease such as rheumatoid arthritis in whom symptoms may readily be attributed to the primary disease. Muscle infarction is an uncommon condition that occurs most frequently in the quadriceps muscle in patients with poorly controlled diabetes with nephropathy, neuropathy, and hypertension. It may suggest pyomyositis because of the acute onset of pain and presence of tender local swelling, but, in contrast to pyomyositis, fever is absent.[52] In the patient with multiple sites of muscle involvement and eosinophilia (from incidental parasitic infestation), the picture may initially suggest trichinosis. Rupture of the muscle abscess through the fascia into subcutaneous tissues may suggest the diagnosis of cellulitis. The presence of a slowly enlarging, painful mass in an extremity of a patient with only low-grade fever may suggest the diagnosis of sarcoma. Pyomyositis of the pectoral muscle can pose a particular diagnostic problem because it must be distinguished not only from muscle rupture, hematoma, and sarcoma but also from cryptic abscessed subpectoral nodes complicating infection of the ipsilateral thumb or index finger. Streptococcal necrotizing fasciitis, like gangrenous streptococcal myositis, manifests initially as local pain disproportionate to any physical findings. Localized swelling, tenderness, and erythema ensue, but only in advanced stages are the characteristic violaceous skin changes, bullae, and frank skin necrosis seen overlying areas of fascial necrosis. Rapid frozen-section biopsy or surgical exploration may be needed to distinguish among these processes.

Diagnosis

Prompt imaging is essential in the evaluation of patients with focal soft tissue pain and fever because the possible need for surgical exploration must be assessed urgently. Plain radiographs can demonstrate focal soft tissue swelling, the presence of gas in the soft tissues, and any primary skeletal abnormalities (e.g., osteomyelitis, osteosarcoma). Ultrasonography is readily accessible and can demonstrate muscle enlargement in the initial stage of pyomyositis; it can also show the presence of focal abscess formation in the suppurative stage of disease, revealing hypoechoic areas with internal echoes,[53] especially if symptoms are localized in an extremity. Ultrasound assessment of the hip can detect the presence of a joint effusion, but it may be less sensitive in assessing the deep pelvic musculature. Ultrasonography is usually followed by cross-sectional imaging to gain greater anatomic detail and should not delay definitive imaging studies in acutely ill patients.

Magnetic resonance imaging (MRI) has proved invaluable in the assessment of patients with pyomyositis because it identifies focal muscle edema and localizes the presence of focal abscess formation with great precision. MRI can demonstrate enlargement of involved muscles and a slight increase in signal intensity on T1-weighted images in the involved area, with a hypointense central area and a surrounding gadolinium-enhanced rim. It also shows a diffuse increase in signal intensity on T2-weighted images, with a central high-signal-intensity fluid collection surrounded by a low-intensity rim.[54] Computed tomography (CT) is a more readily available cross-sectional modality, often performed during emergency department evaluation that provides less anatomic detail at the inflammatory stage of myositis but is helpful when used to guide percutaneous drainage of an established muscle abscess. CT can reveal low-density areas with loss of muscle planes, central fluid collection, and a surrounding rim of contrast enhancement characteristic of pyomyositis.[53] Enlargement of the involved muscle is usually evident. Superimposed cellulitis may sometimes be evident on CT, namely, skin thickening, stranding of subcutaneous fat with blurring of fat and fascial planes, and subcutaneous venous distention. Radionuclide imaging using indium 111–labeled leukocytes, sometimes performed as dual SPECT (single-photon emission CT)/CT, provides functional and anatomic detail but has not been compared directly with MRI regarding predictive value or cost.[55]

Empirical Therapy

Drainage of all established abscesses is essential, and selection of open or percutaneous drainage via ultrasound or CT guidance depends on the abscess location, size, and complexity and the available expertise. Initial antibiotic therapy should consist of empirical intravenous vancomycin because of the preponderance of *S. aureus* isolates from these abscesses and the frequent and increasing incidence of methicillin-resistant *S. aureus*. In compromised hosts or patients with severe disease, empirical high-dose broad-spectrum therapy effective against gram-negative pathogens and anaerobes should be added initially (e.g., β-lactam/β-lactam inhibitor combination such as piperacillin-tazobactam or a carbapenem such as meropenem). Early modification of initial antimicrobial therapy is based on interpretation of a Gram stain of pus and subsequent cultures and susceptibility testing. If a group A streptococcus is isolated, treatment should be changed to high-dose penicillin G and clindamycin (see later discussion). Continued fever after surgical or percutaneous needle drainage of a muscle abscess while the patient is receiving appropriate antimicrobial therapy suggests the presence of other undrained suppurative foci; relapsing or recurrent pyomyositis is frequent among patients with advanced HIV infection.[4] Pyomyositis may be complicated by a compartment syndrome, particularly if it occurs in the forearm[56] or anterior tibial compartments,[57] and may require surgical drainage, fasciotomies, and débridement beyond simple percutaneous drainage.

The prognosis after definitive treatment of pyomyositis is excellent, unless staphylococcal or streptococcal infection is complicated by the presence of toxic shock syndrome.[24,25] The multiorgan failure associated with established toxic shock carries a disturbingly high mortality rate. In the absence of toxic shock, definitive drainage accompanied by prolonged effective antibiotic therapy usually leads to complete resolution of infection with little or no long-term morbidity, even in immunocompromised individuals. Delays in diagnosis and definitive drainage (when drainage is necessary) have led to muscle fibrosis, with the need for widespread excision, and subsequent functional disability.

GROUP A STREPTOCOCCAL NECROTIZING MYOSITIS

In addition to producing an occasional case of typical pyomyositis with abscess formation, on rare occasions group A streptococci cause a fulminant form of myositis, which is a true medical emergency, referred to as peracute streptococcal pyomyositis, streptococcal necrotizing myositis, streptococcal myonecrosis, or spontaneous streptococcal gangrenous myositis.[58,59] Both necrotizing myositis and necrotizing fasciitis are frequently associated with group A streptococcal toxic shock syndrome.[59] The entire clinical course may occur in 2 to 3 days, with intense pain, boardlike swelling of the affected muscle, and fever. The overlying skin may be uninvolved, or it may become erythematous or violaceous and contain petechiae and bullae.[59] Most cases involve

the extremities and appear to develop spontaneously without antecedent pharyngitis or tonsillitis. Bacteremia and toxemia are prominent features and contribute to the very high mortality rate (80% to 100%).[59] The rapid spread of infection in a closed compartment of muscles can markedly increase intramuscular pressure, resulting in further necrosis of muscle.[60] However, both processes can be simultaneously present in the same area. The compartment syndrome with group A streptococcal myositis (e.g., a tibial compartment syndrome) may develop in the absence of frank fascial and muscle necrosis with muscle bulging and increased pressure secondary to edema and serosanguineous exudate.[61] The clinical features of such a syndrome include weakness of the compartment muscles, which are swollen and tender, severe pain on movement of the lower leg, and overlying cutaneous hyperesthesia.

Streptococcal necrotizing fasciitis may resemble streptococcal myositis clinically, although the presence of tense bullae and focal skin necrosis is more suggestive of the former; often both conditions are present. MRI may disclose the predominantly involved structure, but urgent surgical exploration, always necessary in the setting of suspected toxic shock associated with focal pain and swelling, should provide a clear answer. Rarely, acute streptococcal myositis with toxic shock syndrome is caused by non–group A streptococci.

Laboratory findings include leukocytosis and an elevated serum creatine phosphokinase level, in marked distinction to nonstreptococcal forms of pyomyositis, in which little, if any, creatine phosphokinase elevation occurs. This medical emergency requires prompt clinical diagnosis with verification at surgery. Distinguishing group A streptococcal necrotizing myositis from streptococcal necrotizing fasciitis and spontaneous clostridial myonecrosis may be difficult clinically, but gas in the tissue suggests spontaneous clostridial myonecrosis. In any case, all three diseases require prompt surgical exploration. Ultrasonography, CT, or MRI usually reveals muscle swelling and fluid collection in muscle compartments. If prolonged delays are encountered in the pursuit of imaging studies, proceeding directly to surgical exploration with an initial limited surgical approach for diagnostic purposes is justified. Early aggressive surgical intervention with fasciotomy and débridement of necrotic tissue is indicated; in some instances, amputation is required. If the operative Gram stain suggests streptococcal infection, antibiotic therapy should consist of high doses of penicillin G (3 million units IV every 3 hours or 4 million units every 4 hours or adjusted appropriately for renal insufficiency) along with clindamycin (600 mg IV every 6 to 8 hours).[62] Clinical experience suggests that clindamycin has greater efficacy against group A streptococci in this life-threatening infection (Eagle effect) because of its greater activity against large bacterial populations in stationary phase growth, its more sustained postantibiotic effect, and its suppression of the production of toxins and other virulence factors through its inhibition of bacterial protein synthesis.[59] The use of intravenous immunoglobulin G as an adjunct in the treatment of streptococcal toxic shock to neutralize streptococcal exotoxins and perhaps to modulate the host immune response has gained popularity based on retrospective studies and one small prospective, randomized trial,[63] but conclusive evidence supporting its use remains limited.[64]

GAS GANGRENE (CLOSTRIDIAL MYONECROSIS)

Gas gangrene is a rapidly progressive life-threatening infection of skeletal muscle caused by clostridia (principally *Clostridium perfringens*). It usually occurs after muscle injury and contamination (as in a dirty traumatic wound) or rarely postoperatively. Nontraumatic gas gangrene, usually caused by *Clostridium septicum,* is a complication of bacteremia often arising from an occult gastrointestinal mucosal lesion such as an adenocarcinoma or as a complication of neutropenic colitis (also see Chapter 248).

Pathogenesis and Pathologic Characteristics

Gas gangrene occurs in settings that have in common muscle injury and contamination with soil or other foreign material containing spores of *C. perfringens* or other histotoxic clostridial species. Classic scenarios include (1) accidental traumatic civilian injuries such as compound fracture; (2) penetrating war wounds[65]; (3) surgical wounds, particularly after bowel or biliary tract surgery[66] or septic abortion; and (4) arterial insufficiency in an extremity.[67] Rare cases of gas gangrene have occurred after parenteral injection of medication, including aqueous epinephrine[68]; subcutaneous insulin administration[69]; and parenteral injection of methamphetamine or heroin.[70] Fulminant gas gangrene has complicated routine venipuncture[67] or platelet infusions[71] in patients with granulocytopenia. *C. perfringens* organisms usually are present in large numbers as normal flora in human feces and therefore can endogenously contaminate skin surfaces. Despite a high frequency (as high as 88%) of clostridial contamination of major traumatic open wounds, the incidence of gas gangrene in this setting is only 1% to 2%,[72] emphasizing the importance of devitalized tissue and the presence of foreign bodies in the pathogenesis of gas gangrene. The minimal dose of *C. perfringens* needed to produce fatal gas gangrene in experimental animals is reduced by a factor of 10^6 if the organism is injected into devitalized muscle contaminated with sterile dirt rather than into normal muscle. The policy of prompt, thorough débridement and of leaving wounds open has decreased the incidence of gas gangrene in wartime injuries; only 22 cases among 139,000 combat casualties in Vietnam were reported.[73]

Gas gangrene may occasionally develop in the absence of an obvious external wound. This form of clostridial myonecrosis is designated spontaneous, nontraumatic gas gangrene. Its principal cause is *C. septicum,* a relatively aerotolerant species that spreads by the bacteremic route and is more capable of establishing infection without significant antecedent tissue injury than other clostridia. Intestinal tract abnormalities (colon cancer, diverticulitis, bowel infarction, necrotizing enterocolitis, volvulus) are the major predisposing conditions.[74] Colon cancer, often cryptic, is the most common of these, occurring in as many as 88% of patients with *C. septicum* bacteremia. Other predisposing disorders include leukemia, other causes of neutropenia, and diabetes mellitus. The primary source of infection is probably mucosal ulceration or perforation of the intestinal tract. The spread by the bacteremic route probably accounts for the bilateral multifocal involvement observed in a few patients with spontaneous gas gangrene.[75] However, it may also manifest in the buttocks or flanks after an intra-abdominal catastrophe, with rapid extension of infection along the iliopsoas or other deep muscle groups. The progression of *C. septicum* spontaneous gas gangrene may be even more fulminant than that of traumatic *C. perfringens* gas gangrene; the mortality rate of the former is 67% to 100%, with most patients dying within 24 hours after onset.[74]

The involved muscle undergoes rapid disintegration. Initially, it may exhibit only pallor, edema, and loss of elasticity. When examined at surgery, it fails to contract on stimulation and does not bleed from a cut surface. Later it becomes discolored (reddish purple, then greenish purple and gangrenous) and friable. Histologically, the muscle fibers show coagulation necrosis, cavities caused by gas production, and a loss of supporting connective tissue; numerous gram-positive bacilli are present. Few, if any, inflammatory cells are present. Evidence suggests that the α- and θ-toxins of *C. perfringens* are major virulence factors that lead to myonecrosis and apparent lack of inflammation at the site of infection through cytolysis.[76] Intravascular thrombosis due to the local effects of α-toxin on platelets and granulocytes appears to be responsible for the severe herald pain (which may be ischemic) and extensive myonecrosis.[77] In addition to these local effects, the α-toxin provokes systemic hypotension by directly suppressing myocardial contractility and triggering the release of endogenous inflammatory mediators.[78]

Clinical Manifestations

The usual incubation period between injury and the development of clostridial myonecrosis is 2 to 3 days, but it may be as short as 6 hours. The onset is acute. Pain is the earliest and most important symptom, although on occasion a sense of heaviness may be the only initial symptom. Pain rapidly increases in intensity, beyond what would generally be associated with the preceding injury or surgical procedure, and may become excruciating. The patient soon appears severely ill, pale, and sweaty. Hypotension, tachycardia, shock, and renal failure follow. The patient may be apathetic or may be apprehensive and restless but mentally clear. Delirium, stupor, and unconsciousness may

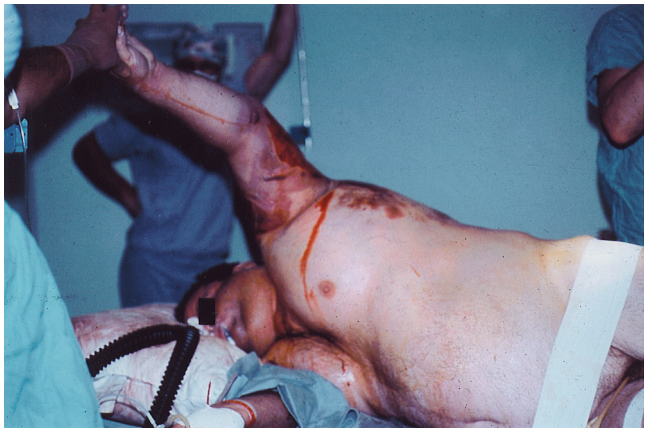

FIGURE 96-2 Clostridial gas gangrene of the left upper extremity. There is prominent characteristic bronze discoloration of the skin extending over the shoulder. Crepitus could be palpated beyond the area of discoloration onto the back.

supervene. Low-grade fever is frequently present, often with a temperature below 38.3° C (101° F); hypothermia is a poor prognostic sign and is usually associated with shock. Jaundice may become evident. The process may rapidly progress over a period of hours, with a fatal outcome if not treated aggressively.

Initially, tense edema and local tenderness may be the only local findings. Swollen muscle may herniate through an open wound. A serosanguineous, dirty-appearing discharge containing numerous organisms but few leukocytes escapes from the wound and has a peculiar foul odor. Gas bubbles may be visible in the discharge. Crepitus is usually present, but not prominent; sometimes it is completely obscured by very marked edema. The skin adjacent to the wound is initially swollen and white but rapidly takes on a yellowish or bronze discoloration (Fig. 96-2). Tense blebs containing thin, serosanguineous or dark fluid develop in the overlying skin, and areas of green-black cutaneous necrosis appear. In fulminant cases, this progresses visibly over 2 to 4 hours, as indicated by advancing edema and crepitation.

Laboratory Findings

The hematocrit is usually decreased, despite progressive local edema and expected hemoconcentration, because of the lysolecithinase activity of clostridial α-toxin and acute hemolysis. Initial leukocytosis is common. *C. perfringens* bacteremia occurs in about 15% of patients with gas gangrene.[79] Intense bacteremia (with associated intravascular hemolysis) occurs more frequently after uterine infection.[80]

A Gram-stained smear of the wound exudate or an aspirate from a cutaneous bleb reveals many large, gram-positive bacilli with blunt ends but few polymorphonuclear leukocytes (see Chapter 248).[75] In almost all cases spores are not evident. The presence of subterminal spores suggests *C. septicum*. Not infrequently, scattered gram-negative bacilli are also present, particularly in grossly contaminated wounds. The growth of *C. perfringens* in culture can be extraordinarily rapid (generation time as little as 8 minutes), paralleling the rapid advance of the infection in devitalized tissue. Examination of liquid anaerobic cultures for gas production ("stormy fermentation") and subsequent Gram stain examination as early as 6 hours after inoculation may provide an early presumptive diagnosis of the infecting species. Radiographs as well as CT scans of the involved areas show extensive and progressive gaseous dissection of muscle and fascial planes.

Etiologic Agents

C. perfringens is most commonly isolated from the lesions of gas gangrene (80% to 95% of the cases).[65,73] *Clostridium novyi* is involved in 10% to 40% of the cases and *C. septicum* in 5% to 20%. Other clostridial species (e.g., *C. bifermentans, C. histolyticum, C. fallax, C. ramosum,* and *C. sordellii*) have been implicated on rare occasions. In addition to clostridia, other organisms (e.g., *E. coli, Enterobacter* spp., enterococci) are sometimes isolated from the lesions of gas gangrene, reflecting the contaminated character of the initiating trauma or lesion.[79]

Differential Diagnosis

The major differential diagnostic considerations are other gas-forming infections of the soft tissues (clostridial anaerobic cellulitis, nonclostridial crepitant myositis, nonclostridial crepitant cellulitis). Clostridial anaerobic cellulitis (see Chapter 95) is more gradual in onset and progression, and the systemic manifestations of illness are much milder than in gas gangrene. Local pain is relatively mild, and the skin lesions of gas gangrene (bronzing, dark blebs) do not develop. Paradoxically, gas formation is often much more extensive in clostridial cellulitis than in gas gangrene. Clinically, it is often difficult to distinguish between early clostridial cellulitis and myonecrosis. Definitive evaluation requires examination in the operating room for the characteristic changes of myonecrosis described earlier. The clinical picture of nonclostridial crepitant cellulitis is very similar to that of clostridial cellulitis. Although contamination of a surgical or traumatic wound may be the source of infection in both types of cellulitis, nonclostridial crepitant cellulitis frequently develops in the setting of vascular insufficiency or perirectal infection. Bacteria isolated from nonclostridial crepitant cellulitis include facultative species (e.g., *E. coli, Klebsiella*, various streptococci) and anaerobic bacteria (e.g., *Bacteroides, Peptostreptococcus*). Commonly, these are present in mixed culture and can be seen on the Gram-stained smear of a wound aspirate.

Empirical Therapy

Treatment includes emergency surgical exploration, both to define the nature of the process (gas gangrene vs. crepitant cellulitis) by direct muscle examination at the site of infection and to perform appropriate débridement. Prompt and extensive surgery is the principal element in the treatment of gas gangrene. This includes excision of involved muscles (or amputation if necessary) and fasciotomies to decompress and drain the swollen fascial compartments. Antibiotic therapy is an important adjunct to surgical management. Penicillin G, the traditional antibiotic of choice, is administered in a dose of 2 million units IV every 2 hours or 3 million units IV every 3 hours (24 million units/day) (or adjusted for acute renal insufficiency) for an adult. Currently, combined penicillin and clindamycin (600 mg IV every 6 to 8 hours) is widely used in treatment. The addition of clindamycin is based on results of experimental studies of fulminant clostridial myonecrosis in mice, in which clindamycin, metronidazole, and tetracycline were each more effective than penicillin.[81] In vitro, the addition of penicillin to metronidazole antagonizes the activity of the latter; in contrast, the combination of penicillin with clindamycin provides slightly greater efficacy than clindamycin alone but significantly enhanced efficacy over that of penicillin alone.[82]

An additional antimicrobial agent (e.g., ciprofloxacin, a third- or fourth-generation cephalosporin, or a carbapenem agent) may be used initially if Gram-stained smears of the wound exudate show gram-negative bacilli as well as the predominant gram-positive bacilli. Patients who are highly penicillin allergic may be treated with clindamycin; plasmid-mediated resistance to tetracycline and erythromycin is now common among clostridia. Although the majority of *C. perfringens* isolates are susceptible in vitro to cephalosporins, the second-generation agents cefotetan and cefoxitin appear to have more favorable minimal inhibitory concentrations than the third-generation agent ceftriaxone.[83] *C. perfringens* is highly susceptible in vitro to the carbapenems, as well as metronidazole[83] and linezolid, but experience with the use of these drugs in clostridial myonecrosis is limited.

The role of hyperbaric oxygen therapy is still debated (see Chapter 49).[84,85] Elevated partial pressures of oxygen are thought to reduce the rate of clostridial replication and to suppress toxin expression.[84] The rarity of clostridial myonecrosis and the limited availability of hyperbaric oxygen facilities has made prospective, controlled clinical trials impractical. Its use should never delay immediate surgical débridement if possible. Its most appropriate role at present seems to be in the management of extensive truncal involvement, for which complete surgical excision would be impossible (paraspinal sites) or mutilating. In a murine model of *C. perfringens* myonecrosis initiated with a high inoculum, clindamycin therapy was more effective than hyperbaric oxygen and the addition of the latter provided no more efficacy than clindamycin alone.[86] Initial hyperbaric oxygen therapy may decrease the extent of débridement that is necessary under these circumstances.

The efficacy of intravenously administered polyvalent gas gangrene antitoxin has never been established clinically, and it is no longer available. Comprehensive ancillary therapy in the intensive care unit is essential in the management of gas gangrene, including attention to fluid and electrolyte replacement and maintenance of adequate hematocrit levels through transfusion.

NONCLOSTRIDIAL (CREPITANT) MYOSITIS

Nonclostridial (crepitant) myositis includes four relatively distinct entities that differ from gas gangrene in their clinical picture and bacteriologic characteristics: (1) anaerobic streptococcal myonecrosis, (2) synergistic nonclostridial anaerobic myonecrosis, (3) infected vascular gangrene, and (4) *A. hydrophila* myonecrosis.

Anaerobic Streptococcal Myonecrosis

Anaerobic streptococcal myonecrosis is an acute interstitial myositis that clinically resembles subacute clostridial gas gangrene. The initial manifestations are swelling and a copious seropurulent exudate occurring 3 to 4 days after an injury. Pain develops later, unlike the early occurrence of pain in gas gangrene. Tissue gas is present in muscle and fascial planes but is not extensive. The wound has an unpleasant sour odor. The involved muscles are discolored but do react to stimulation. In contrast to gas gangrene, early cutaneous erythema is prominent. If it is not adequately treated, the infection progresses, with the development of toxemia, frank gangrene, and shock.

Numerous streptococci and polymorphonuclear leukocytes are present in the exudate. The infection is usually mixed (anaerobic streptococci with group A streptococci or *S. aureus*). A mixed infection of muscle with both *Finegoldia magna* and *Bacillus subtilis* has been observed on several occasions in the setting of vascular injury. The clinical picture, along with the appearance of the Gram-stained smear, initially might suggest the diagnosis of clostridial myonecrosis.[87] Treatment involves the use of large doses of penicillin and initial antistaphylococcal therapy such as vancomycin if indicated by initial Gram stain along with surgical débridement.

Synergistic Nonclostridial Anaerobic Myonecrosis

Synergistic nonclostridial anaerobic myonecrosis, a severe infection seen particularly in patients with diabetes and those with neutropenia, is also known as synergistic necrotizing cellulitis (see Chapter 95). It involves skin, subcutaneous tissue, fascia, and muscle. The most extensive involvement is in the subcutaneous tissues and fascia; changes in overlying skin and underlying muscle are usually secondary. Although a mixture of anaerobic and facultative organisms is commonly recovered at surgical exploration, on rare occasions crepitant myonecrosis may be caused by *K. pneumoniae,*[88] *Enterobacter cloacae,*[89] or *Bacillus cereus*[90] unaccompanied by other organisms (aerobic or anaerobic) in high-risk patients. The clinical course is rapidly progressive, often leading to a fatal outcome despite emergency surgical exploration and débridement of necrotic tissue.

Infected Vascular Gangrene

Infected vascular gangrene is a mixed infection that develops in a group of muscles or in a limb that is devitalized as a result of arterial insufficiency, particularly in patients with diabetes mellitus. *Proteus* spp., *Bacteroides* spp., and anaerobic streptococci are among the bacteria found in such lesions. Gas formation and foul-smelling pus are prominent. The infection does not extend beyond the area of vascular gangrene to involve healthy muscle. *Bacillus cereus* infection has been associated with myonecrosis with slight crepitus after thrombosis of arterial grafts in addition to more aggressive post-traumatic infections.[90]

Aeromonas hydrophila Myonecrosis

Rapidly progressive myonecrosis caused by *A. hydrophila,* a facultatively anaerobic gram-negative bacillus, may occur after penetrating trauma in a freshwater environment or in association with fish or aquatic animals.[91,92] Although *Aeromonas* was associated with pyomyositis and a compartment syndrome in neutropenic patients,[93] spontaneous (nontraumatic) myonecrosis due to *Aeromonas* has not been reported in other settings. In a few instances, myonecrosis has been accompanied by gas spreading extensively in soft tissue planes. The rapid onset (24 to 48 hours) and rapid progression after trauma resemble those of clostridial gas gangrene. The prominence of pain, marked edema, serosanguineous bullae, and toxicity, in addition to the presence of gas in fascial planes, adds to the similarity of these conditions, and elicitation of freshwater exposure supports the diagnosis of *Aeromonas* infection. Bacteremia is frequently present. Treatment consists of extensive surgical débridement and prompt initiation of antimicrobial therapy. Most isolates of *Aeromonas* are susceptible in vitro to gentamicin, tobramycin, carbapenems, and ciprofloxacin.[91] Third- and fourth-generation cephalosporins, trimethoprim-sulfamethoxazole, and aztreonam also appear to be active, although individual strains may express β-lactamases that selectively hydrolyze cephalosporins or carbapenems.

PSOAS ABSCESS

Infection of the psoas muscle takes the form of either an abscess or a phlegmon, similar to the progression seen in primary pyomyositis. Unlike pyomyositis of other sites, psoas infections in temperate regions most commonly develop after the spread of infection from an adjacent structure (secondary psoas abscess)[1]; in tropical areas primary psoas abscesses, which develop by the hematogenous route, dominate, and *S. aureus* is the most common cause in this setting.[1,94,95] In adult women, hematogenous psoas abscesses have been observed as a complication of spontaneous vaginal delivery.[11,96] A psoas abscess usually is confined within the psoas fascia, but, occasionally, because of anatomic relationships, infection extends to the buttock, hip, or upper thigh.[27] A psoas abscess may complicate pyogenic, tuberculous, or fungal vertebral osteomyelitis. Tuberculosis was formerly the principal cause of psoas abscesses; now they most commonly result from direct extension of intra-abdominal infections (e.g., diverticulitis, appendicitis, Crohn's disease)[94] or from vertebral infection.[95] Occasionally, a psoas abscess results from extension of a perinephric abscess or from secondary infection of a retroperitoneal hematoma. The organisms involved in the spread of infection from an intestinal site are usually members of the aerobic and anaerobic bowel flora. *S. aureus* is the most common cause of psoas abscess secondary to vertebral osteomyelitis.

The iliacus muscle, applied to the ilium in the iliac fossa, forms a conjoined tendon with the lower portion of the psoas muscle. Osteomyelitis of the ilium or septic arthritis of the sacroiliac joint can penetrate the sheaths of either or both muscles in this location, producing an iliacus or psoas abscess.[97]

Clinical manifestations of a psoas abscess include fever, lower abdominal or back pain, or pain referred to the hip or knee. A limp may be evident, and flexion deformity of the hip may develop from reflex spasm, suggesting septic arthritis of the hip. The psoas sign is evident. Often a tender mass can be palpated in the groin.

Radiographs may show a bulge produced by a psoas muscle abscess or the presence of gas within the psoas sheath. Calcification in a psoas abscess strongly suggests tuberculosis. CT is the most rapid and sensitive noninvasive imaging technique to assess the psoas and iliacus muscles.[98] Ultrasonography is less reliable for detecting small lesions or a phlegmon. Radionuclide imaging is no longer widely used in this situation. CT may show diffuse enlargement of the psoas (phlegmon), a sharply circumscribed, low-density fluid collection (abscess) within the muscle, or the presence of gas within the muscle (indicative of abscess).[98] MRI of the pelvis can reveal enlarged psoas and iliacus muscles displaying grossly abnormal signal intensities.

Pyogenic psoas abscesses require drainage and initial empirical antibiotic therapy based on knowledge of the origin of the infection. CT is often quite valuable for abscess visualization and catheter drainage,[99] with direct surgical drainage reserved for unsuccessful interventional radiologic attempts and instances of inadequate catheter access. Although culture-negative psoas abscesses can be seen when drainage procedures follow an initial course of empirical antibiotic therapy, sterile pseudopsoas abscesses associated with erosive discitis due to calcium pyrophosphate deposition have been reported.[100] If the process appears to be a phlegmon, repeat CT during the course of antibiotic therapy can confirm resolution of the anatomic changes.

OTHER SPECIFIC SITES OF MUSCLE ABSCESSES

Infective myositis or pyomyositis may occasionally occur in less common anatomic areas and mimic other more common infections; deep pelvic muscle infections are relatively more common in children. Iliacus pyomyositis[50] and pyomyositis of the adductor muscles or the obturator internus muscle[101] may mimic septic arthritis of the hip; pyriformis pyomyositis may suggest a spinal epidural abscess[51] or pelvic osteomyelitis[102]; and iliopsoas myositis[49] may mimic appendicitis. On occasion, the primary myositis may actually progress to involve adjacent joints, resulting in adjacent septic arthritis.

MYALGIAS

Myalgias are prominent features of a variety of infections, such as dengue, influenza, and Rocky Mountain spotted fever, and are often associated with mildly to moderately elevated levels of creatine phosphokinase.[103] Histologic changes include the presence of virions and variable patchy myonecrosis, often with a paucity of inflammation.[104,105] Clinically significant muscle weakness is occasionally present, often in association with severe rhabdomyolysis (see later discussion).[104,106-108] In addition to the focal myositis syndromes discussed earlier, a variety of pathogens are associated with acute diffuse muscle injury (culminating in rhabdomyolysis) or with chronic diffuse muscle injury, mimicking autoimmune polymyositis (see Table 96-1). The histopathologic similarities observed between autoimmune muscle injury and the polymyositis associated with certain infectious processes and the demonstration of pathogen-specific antigen recognition by infiltrating lymphocytes suggest that infection may trigger an autoimmune attack on myocytes in at least some instances.[109,110]

Influenza

Muscle aches are common early in the course of influenza. Occasionally, severe bilateral muscle pains in the lower limbs may develop in the recovery phase of influenza A or B, particularly in young children, which has been termed *acute benign myositis*.[111] Although influenza B is less common than influenza A, the rate of influenza B–associated myositis greatly exceeds that of influenza A.[106,107] Muscle tenderness is demonstrable, principally in the gastrocnemius and soleus muscles, and calf swelling may be present. Deep tendon reflexes and muscle strength are normal, but there is considerable difficulty in walking. The leg pains and muscle tenderness subside in less than 1 week. Mild increases in serum concentrations of aldolase and creatine phosphokinase occur. The specimens from the few biopsies performed have shown either nonspecific degenerative changes or muscle necrosis with polymorphonuclear leukocytic infiltration. Whether this myositis is generally caused by direct viral invasion or by some immunologic or other response is unknown. Direct viral replication within skeletal muscle has been demonstrated in fatal cases of influenza A.[105] Life-threatening rhabdomyolysis with extreme increases in creatine phosphokinase and myoglobin-induced acute renal failure are rarely seen after influenza A infection; the prognosis is favorable but may require short-term dialysis[108] or even extracorporeal membrane oxygenation if myocardial dysfunction is present. Isolated influenza myocarditis, sometimes quite severe, can occur in the absence of generalized rhabdomyolysis (see Chapter 167).[112]

Infective Endocarditis

Prominent myalgias occur in about 15% of patients with infective endocarditis.[113] They may be either diffuse or localized. The pathogenesis is not known, but in one instance muscle biopsy specimens showed a small focus of muscle fiber destruction and leukocytic infiltration consistent with embolization to a small artery. On rare occasions, infective endocarditis may lead to frank pyomyositis[18] or rhabdomyolysis.[114]

Toxoplasmosis

The major features of acute acquired disseminated toxoplasmosis are those of meningoencephalitis, myocarditis, pneumonitis, lymphadenitis, rash, and occasionally hepatitis (see Chapter 280). In rare instances, particularly (but not exclusively[115]) in immunocompromised hosts (e.g., HIV infection,[116] chronic immunosuppressive therapy after organ transplantation, CD4 lymphopenia[117]), polymyositis may be a prominent clinical manifestation resembling autoimmune polymyositis. Marked myalgias, muscle weakness and swelling, and fasciculations occur in such patients. Muscle biopsy specimens show interstitial myositis with destruction of muscle fibers, and pseudocysts of *Toxoplasma gondii* can be found in areas of muscle that are free of inflammatory reaction.[116]

Other Causes

Occasionally, the only clinical manifestations of initial infection with HIV type 1 (HIV-1) are those of polymyositis (myalgias, muscle weakness, and increased serum levels of muscle enzymes). HIV-1 viral antigens can be found in $CD4^+$ T lymphocytes in areas of muscle fiber inflammation and necrosis.[118] During the subsequent course of HIV-1 infection, various forms of muscle disease may develop,[118] including generalized or localized myalgias, HIV myopathy (polymyositis), inclusion body and nemaline myopathies, muscle atrophy accompanying AIDS wasting syndrome or vasculitis, opportunistic infectious myositis, and mitochondrial myopathy related to antiretroviral therapy (see Chapter 130). The clinical presentation of HIV-1 myopathy (inflammatory polymyositis) is that of progressive proximal muscle weakness. Increased levels of serum creatine phosphokinase and electromyographic changes assist in diagnosis. Muscle biopsy can help resolve this rather long differential diagnosis and guide specific therapy.[118] The inflammatory myopathy may represent primarily an HIV-associated autoimmune process and may respond clinically to prednisone.

Inflammatory myositis with a lymphoplasmacytic cellular response has been documented in patients with human T-cell lymphotropic virus-1 (HTLV-1)-associated polymyositis, and muscle-infiltrating lymphocytes specific for viral and class I major histocompatibility determinants were demonstrated.[109,119] There may be a direct toxic effect of HTLV-1 Tax-1 protein on myocytes, even in the absence of myocyte infection.[120] In addition, specific Tax-1 cytotoxic T-lymphocyte activity is present in HTLV-1–infected patients with muscle disease.[120] Inflammatory myositis is rarely a major feature in Lyme disease[121] and, if present, is often a focal process in relation to adjacent joint or skin involvement. Spirochetes consistent with *Borrelia burgdorferi* may be present on Dieterle's silver stain of muscle biopsy specimens, or the presence of *Borrelia* may be confirmed by polymerase chain reaction analysis.[121] Most cases have been reported from Europe, reflecting differences between European and American isolates. Rarely, infection by *Sarcocystis* (an intracellular sporozoan parasite) has been observed in histologic sections of muscle of individuals with muscle pain or weakness, mainly outside the United States.[122] Nematode myositis due to the minute nematode *Haycocknema perplexum* has been observed in Australia.[123] In addition to toxoplasmosis, HIV-infected individuals have developed protozoan myositis due to a variety of microsporidia,[124] including *Trachipleistophora hominis* (see Chapter 272).[125]

PLEURODYNIA SYNDROMES

Epidemic pleurodynia is an acute, febrile disease caused by group B (or rarely by group A) coxsackieviruses that is characterized by the sudden onset of sharp chest pain over the lower ribs or sternum (see Chapter 174). Paroxysms of knifelike pain are precipitated by voluntary or respiratory movements. Muscle tenderness may be present. Abdominal pain may also be present in some patients; in others, abdominal pain may be the sole manifestation, simulating intraperitoneal processes.

Group B coxsackieviruses produce visceral lesions and some focal myositis in experimental animals. Myositis has not been demonstrated as a feature pathologically, either in fatal cases of severe neonatal coxsackievirus B infection or in the few biopsy specimens obtained from affected muscles of patients with epidemic pleurodynia, but it has been associated with rhabdomyolysis complicating mild exercise in the recovery phase of illness.[126] A variety of other enteroviruses rarely provoke rhabdomyolysis.[1] Focal myositis with localized swelling and perivascular mononuclear cell infiltration sparing myocytes was observed in a patient with coxsackievirus A21 infection.[127]

MYALGIAS WITH EOSINOPHILIA (PARASITIC MYOSITIS)

Trichinosis

Trichinosis is acquired by ingestion of encysted larvae in insufficiently cooked pork or, less commonly, bear meat, wild boar meat, horse meat, or walrus meat. The prominent clinical manifestations of trichinosis include fever, myositis, periorbital edema, and eosinophilia. An initial intestinal phase (nausea, vomiting, nonbloody diarrhea) caused by larval release in the stomach, followed by larval maturation and copulation in the small intestine during the first week, is followed during the second week by release of progeny larvae, mucosal invasion, hematogenous dissemination, and invasion of skeletal muscle (see Chapter 289).[128] Serious complications in the form of myocarditis, meningoencephalitis, and pneumonitis can occur.[128] Myalgias, frequently accompanied by muscle swelling and weakness and occasionally associated with fasciculations, are present in most patients with the disease. Muscles commonly involved include the extraocular muscles, flexor muscles of the extremities, back muscles, and muscles used in chewing and swallowing. Periorbital edema, chemosis, and conjunctival hemorrhages are related to larval invasion of extraocular muscles. The inflammatory response in muscle produces increased serum levels of muscle enzymes and is associated with prominent eosinophilia.

Muscle biopsy specimens reveal encysted larval trichinae in necrotic muscle fibers, surrounded by inflammatory cells (predominantly eosinophils and neutrophils, but also lymphocytes). Severe skeletal muscle involvement reflects the burden of infection and possible host immunosuppression. Although granulomatous reactions have been observed in the heart and lungs in fatal cases, larval encystment does not take place in organs other than skeletal muscle.

Trichinella spiralis is the most common cause of human trichinosis, but multiple other species can infect humans.[128] Unlike *T. spiralis, Trichinella pseudospiralis* does not undergo encystment in skeletal muscle and leads to prolonged larval migration and clinical symptoms.

Diagnosis of trichinosis is made on the basis of the clinical picture, eosinophilia, elevated muscle enzymes, and compatible serologic findings (enzyme-linked immunosorbent assay, immunoblotting, and, if needed, muscle biopsy), and appropriate epidemiologic investigation.[128] Benzimidazole compounds (thiabendazole, mebendazole, albendazole), which kill mature worms, are the most effective therapies early in the illness; albendazole may have the advantage of being better tolerated. Short courses of systemic corticosteroid therapy ameliorate clinical symptoms and are administered in severe cases.[128]

Trichinosis should be distinguished from the eosinophilia-myalgia syndrome, which results from the ingestion of certain tryptophan products and is characterized by prominent myalgias, fatigue, and eosinophilia, followed, in some instances, by the development of neurologic and scleroderma-like skin changes.[129]

Cysticercosis (*Cysticercus cellulosae* Myositis)

Human cysticercosis is rare in the United States, but common in Latin America and Asia. It results from the ingestion and subsequent hatching of viable eggs of *Taenia solium* into the larval form (cysticercus) of the parasite (see Chapter 291). Eggs reach the upper intestinal tract in food contaminated by feces from a person parasitized by the adult worm. Autoinfection can occur through the fecal-oral route and possibly by reverse peristalsis transporting intestinal egg-laden proglottids back into the duodenum or stomach, where they hatch. From the stomach, they are widely distributed to the skeletal muscle, subcutaneous tissues, heart, eye, and central nervous system.

Symptomatic involvement of muscle is uncommon. Occasionally, the stage of invasion is characterized by fever, muscle tenderness, and eosinophilia. More characteristically, asymptomatic calcified cysts ("puffed rice" appearance) are detected in muscles on soft tissue radiographic films of patients with neurologic manifestations.

MUSCLE DEGENERATION ASSOCIATED WITH INFECTIONS AT OTHER SITES

Acute Rhabdomyolysis

Myoglobinuria occasionally occurs after an acute illness with symptoms suggesting an upper respiratory tract infection and has been associated with a variety of respiratory viral pathogens including influenza A and B, parainfluenza, adenovirus, and severe acute respiratory syndrome–coronavirus, as well as *Mycoplasma pneumoniae* and *Legionella pneumophila.* Rhabdomyolysis has also complicated systemic infections caused by HIV, Epstein-Barr virus, cytomegalovirus, human herpesvirus 6, measles virus, varicella virus, dengue virus, West Nile virus, rabies virus, and parvovirus B19. A variety of bacterial pathogens have led to rhabdomyolysis among critically ill patients with sepsis[130,131]; gram-positive pathogens including *S. aureus* and *S. pneumoniae* predominate, but *Salmonella* spp., *N. meningitidis,* and Enterobacteriaceae or nonenteric pathogens such as *P. aeruginosa* or *A. baumannii* may be responsible. Leptospirosis, brucellosis, and rickettsial infections can also trigger rhabdomyolysis. Diffuse muscle pains (especially in the extremities), weakness, swelling, and tenderness are prominent features, along with increased muscle enzyme (often striking), myoglobinuria, and even acute renal failure.

Muscle Proteolysis and Mediators of Fever in Patients with Sepsis

Muscle involvement in the form of myalgias and weakness is common in the course of systemic infections. Accelerated catabolism of skeletal muscle contributes to the marked weakness and muscle wasting that can be observed in systemic infections. This seems to be part of an acute phase host response to sepsis and trauma likely triggered by a variety of mediators, including interleukin-1, tumor necrosis factor, interferon-α, and interleukin-6, as well as endogenously and exogenously administered glucocorticoids. Detailed studies of myocyte mitochondrial number, protein synthesis and expression, mitochondrial enzyme activity, and messenger RNA levels (including microRNA) in muscle biopsy specimens from septic intensive care unit patients with multiorgan system failure demonstrate a loss of functional mitochondria with sustained but dysregulated mitochondrial protein expression and enhanced proteolytic activity. Transcriptional analysis demonstrated that several critical intracellular pathways (oxidative stress, apoptosis, proteasome function, ion homeostasis, and kinase signaling) are perturbed in these patients.[132] The intracellular events accompanying muscle catabolism involve prostaglandin E_2 synthesis, direct cleavage of actomyosin by caspase 3,[133] and subsequent degradation by proteasomes. Additional mechanisms also help regulate the process of muscle cachexia.[134] An important role of prostaglandin E_2 in the generation of myalgias and fever is consistent with the amelioration of these symptoms after administration of nonsteroidal anti-inflammatory prostaglandin synthesis inhibitors.

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