Immune-Mediated Myopathies

Stephanie J. Valberg, DVM, PhD, Diplomate ACVIM

Immune-mediated myopathies in horses can present as signs of acute rhabdomyolysis, multifocal muscle swelling, and infarction or acute muscle atrophy. Some but not all myopathies are associated with *Streptococcus equi* infection. A diagnosis can be made by histopathologic evaluation of the affected muscle group. Successful treatment requires early recognition and a combination of antibiotic and corticosteroid therapy. Author’s address: Department of Veterinary Population Medicine, College of Veterinary Medicine, University of Minnesota, 1365 Gortner Avenue, St. Paul, MN 55108; e-mail: valbe001@umn.edu. © 2006 AAEP.

1. Introduction

Three distinct myopathies with an apparent immune-mediated etiology are currently recognized in horses. The first myopathy manifests as acute, severe rhabdomyolysis. The second presents as focal severe muscle swelling caused by infarction. The third myopathy is characterized by rapid muscle atrophy. Many but not all of the cases of immune-mediated myositis seem to be a sequella to infection with *Streptococcus equi* subspecies *equi*. *S. equi* infection (strangles) typically has a low level of mortality (2.6%); however, a complication rate of 20.3% has been reported in some outbreaks. Reported complications of strangles include purpura hemorrhagica, gullett pouch empyema, upper respiratory tract obstruction, bastard strangles, pneumonia, pleuritis, agalactia, and peri orbital abscess. In some horses, a further complication of *S. equi* infection is the development of an immune-mediated myopathy.

2. Acute Rhabdomyolysis Caused by *S. equi*

Prevalence

There are only a small number of cases discussed in the literature, and they describe Quarter Horses <7 yr of age. This may not reflect the prevalence of the disease, because many cases may not present to university hospitals or diagnostic laboratories.

Clinical Signs

Affected horses usually have evidence of submandibular lymphadenopathy and/or guttural pouch empyema caused by *S. equi*. Owners notice that horses develop a stiff gait that progresses rapidly to markedly firm, swollen, and painful epaxial and gluteal muscles. Muscle pain becomes severe in spite of aggressive antimicrobial and anti-inflammatory treatment. The majority of reported cases became recumbent, were unable to rise, and developed unrelenting pain that necessitated euthanasia within 24–48 h of hospitalization.

Hematological abnormalities include mature neutrophilia, hyperfibrinogenemia, and marked elevations in creatine kinase (CK; 115,000–587,000 U/l) and aspartate aminotransferase (AST) activities (60–14,500 U/l). Titors to the M protein of *S. equi* are low in affected horses unless horses are recently vaccinated for strangles. Titors to another protein called myosin-binding protein were high in a small number of horses that were tested.
At post-mortem examination, large, pale areas of necrotic muscle are evident in hindlimb and lumbar muscles. The histopathologic lesions are characterized by severe acute myonecrosis with a degree of macrophage infiltration. Sublumbar muscles often show the most severe and chronic necrosis that is indicated by greater macrophage infiltration of myofibers.1

Pathogenesis
In human medicine, β-hemolytic streptococci of Lancefield groups A, B, C, and G can cause severe myonecrosis manifested by severe myalgia, muscle swelling, and sometimes toxic shock.8 Toxic shock arises as a result of profound non-specific T-cell stimulation by streptococcal superantigens with the release of high levels of inflammatory cytokines9,10 Genes for four superantigens have recently been identified in S. equi, and it is possible that horses with S. equi rhabdomyolysis also develop a toxic shock-like syndrome.11,12 An alternative explanation for rhabdomyolysis may be a bacteremia with local multiplication and production of exotoxins or proteases within skeletal muscle. S. equi virulence factors that may account for muscle necrosis include an unidentified cytotoxic protein, several proteases, streptokinase, and streptolysin S.1,5 Although S. equi has not been cultured in skeletal muscle from horses with rhabdomyolysis, S. equi bacteria have been identified in affected muscle using immunofluorescent stains for both Lancefield group C carbohydrate and S. equi M protein.1 There is currently no evidence that the S. equi involved is an atypical genetic strain of S. equi.1,13

Treatment
A high mortality rate has been reported in horses receiving IV penicillin therapy when clinical signs of strangles and myopathy were well established.1 It is possible that early recognition of the signs of muscle stiffness in horses with S. equi infections and prompt aggressive treatment may be required for a successful outcome. Although streptococcal species are very susceptible to β-lactam antibiotics, a mortality rate of 85% has been reported in human group A streptococcal myositis despite penicillin treatment.14 An antimicrobial that inhibits protein synthesis, such as rifampin, combined with IV penicillin might enhance survival rates in horses with S. equi rhabdomyolysis. In addition, flushing infected guttural pouches and draining abscessed lymph nodes will diminish the bacterial load. Non-steroidal anti-inflammatories and possibly high doses of short-acting corticosteroids may assist in diminishing the inflammatory response. Control of unrelenting pain is a major challenge in horses with severe rhabdomyolysis. Constant-rate infusion of lidocaine, detomidine, or ketamine may provide better anxiety and pain relief than periodic injections of tranquilizers.15–17 Horses should be placed in a deeply bedded stall and moved from side to side every 4 h if they are unable to rise. Some horses may benefit from a sling if they will bear weight on their hindlimbs when assisted to stand.

3. Infarctive Purpura Hemorrhagic

Prevalence
The occurrence of infarctive purpura hemorrhagica (PH) in one study was 3 of 53 PH cases reviewed.18 Five other cases of infarctive PH have been described in horses that were either exposed to S. equi within 3 wk of presentation and/or had markedly elevated serum enzyme-linked immunosorbent assay (ELISA) M protein titers.2 Although horses with classic PH usually have a good prognosis, infarctive PH has a high fatality rate.2,7,18

Clinical Signs
The primary presenting complaints for horses with infarctive PH are painful lameness, muscle stiffness, and/or colic.2 Careful physical examination reveals classic signs of PH such as petechia and well-demarcated limb edema. Additionally, horses with infarctive PH will have focal firm IM swellings (Fig. 1). Horses with evidence of colic may have markedly decreased borborygmia and hemorrhagic gastric reflux.

Hematologic abnormalities usually include a leukocytosis characterized by a neutrophilia with a left shift and toxic change, hyperproteinaemia, hypoalbuminemia, and marked elevations in CK (47,000–280,000 U/l) and AST (960–7000 U/l) activities.2,7 If gastrointestinal infarction is present, peritoneal fluid obtained by abdominocentesis may be normal or may have an increased total protein, nucleated, and red blood cell counts.

Ultrasonographic examination of swollen muscle reveals focal hypoechoic lesions within muscle tis-
sue. Biopsies of abnormal muscle show diffuse acute coagulative necrosis, whereas samples from palpably normal muscle tissue show no pathological abnormalities.

Post-mortem findings of horses with infarctive PH show extensive infarction of the skeletal musculature (Fig. 2), skin, gastrointestinal tract, pancreas, and lungs and S. equi abscessation of a lymph node. Definitive histopathologic findings include leukocytoclastic vasculitis and acute coagulative necrosis resembling infarction in numerous tissues.  

Pathogenesis
Infarctive PH resembles Henoch-Schönlein purpura in humans, which is characterized by infarctive vasculitis of the skin, kidneys, and gastrointestinal tract caused by IgA immune-complex deposition. Immune complexes are present in the sera of horses with PH and seem to be primarily composed of IgM or IgA and streptococcal M protein. Deposition of complement near immune complexes in vessel walls may result in cell-membrane destruction, cell death, and vascular occlusion. The distinctive feature of infarctive PH in horses is the extensive infarction of skeletal muscle and consequently marked elevation in serum CK and AST activity.

Treatment
Early recognition of focal muscle swelling, abdominal discomfort, neutrophilia, hypoalbuminemia, and marked elevations in CK activity combined with aggressive antibiotic and corticosteroid treatment may enhance the likelihood of a successful outcome. Treatment of Henoch-Schönlein purpura in humans, including cases with intestinal infarctions, involves high-dose IV pulse therapy with methylprednisolone (1000 mg/m² every other day for three treatments) followed by oral corticosteroids and immunosuppressive agents such as cyclophosphamide and azathioprine. One horse with infarctive PH was successfully treated with penicillin and non-steroidal anti-inflammatories as well as 3 wk of dexamethasone (0.1–0.07 mg/kg) followed by a 10-wk tapering course of oral prednisolone (2 mg/kg to start).

4. Immune-Mediated Polymyositis

Prevalence
Immune-mediated polymyositis (IMM) has recently been reported in horses. In the largest retrospective study, 31 of 1350 horses that received a muscle biopsy for evaluation of neuromuscular disease were diagnosed with IMM. The breed and age of all horses identified to date include 32 horses with Quarter Horse bloodlines and four other breeds including two ponies, one Icelandic horse, and one Thoroughbred. A bimodal age distribution seems to occur in affected horses with all horses identified to date being either ≥8 yr of age or ≥16 yr of age.

In approximately one-third of horses with IMM, exposure to S. equi or a respiratory disease seems to be a triggering factor.

Genetics
IMM in humans is believed to have a non-Mendelian polygenic pattern of inheritance. The high prevalence of the disorder in Quarter Horses suggests that there is the potential for a polygenic mode of inheritance in this breed.

Clinical Signs
The most prominent clinical sign of IMM in Quarter Horses is rapid onset of muscle atrophy, particularly affecting the back and croup muscles (Fig. 3), accompanied by stiffness and malaise. Atrophy may progress to involve 50% of the horse’s muscle mass within 1 wk and may lead to generalized weakness. Focal symmetrical atrophy of cervical muscles has been reported in a pony with IMM.

Hematologic abnormalities are relatively minor in affected horses and are usually restricted to mild to moderate elevations in serum CK and AST activity. In some cases, serum muscle-enzyme activities are normal.

Diagnosis
Muscle tissue obtained from the epaxial and gluteal muscles contains many of the following abnormalities: lymphocytic vasculitis, anguloid atrophy, lymphocytic myofiber infiltration, fiber necrosis with macrophage infiltration, and regeneration. Biopsies of semitendinosus or membranous muscles may show some evidence of atrophy and vasculitis, but significant inflammatory infiltrates may be absent in these tissues. The extent of the inflammation that infiltrates into the epaxial muscles is such that a diagnosis can often be established from several formalin-fixed Trucut samples.
Horses that are not treated with corticosteroids may develop extensive muscle atrophy, but in many cases, muscle mass will gradually recover. Recurrence of atrophy in susceptible horses is common and may require reintroduction of corticosteroid therapy. Some horses develop focal residual muscle atrophy.4

References


