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Immune-Mediated Myositis and Emerging Myopathies

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Immune Mediated Myopathies

There are 3 newly recognized myopathies with an apparent immune-mediated origin that have recently been recognized in horses. The first myopathy manifests as acute, severe rhabdomyolysis the second presents as focal severe muscle swelling due to infarction; and the third myopathy is characterized by rapid muscle atrophy. Many, but not all, of the cases of immune-mediated myositis appear to be a sequela to infection with Streptococcus equi subspecies equi.

Acute rhabdomyolysis due to S. equi

The small numbers of cases described in the literature are Quarter Horses less than 7 years of age. This may not reflect the prevalence of the disease, however, as 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 due to S. equi. Owners notice that horses develop a stiff gait which progresses rapidly to markedly firm, swollen, 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, was unable to rise, and developed unrelenting pain necessitating euthanasia within 24-48 hours of hospitalization.

Hematological abnormalities include mature neutrophilia, hyperfibrinogenemia, and marked elevations in creatine kinase (115,000 – 587,000 U/L), and aspartate aminotransferase activities (600- 14,500 U/L). Titers to the M protein of S. equi are low in affected horses, unless horses are recently vaccinated for strangles. Titers to another protein called myosin binding protein were high in a small number of horses that were tested.

At postmortem 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 as indicated by greater macrophage infiltration of myofibers.

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. Toxic shock arises as a result of profound non-specific T cell stimulation by streptococcal superantigens with the release of high levels of inflammatory cytokines. It is possible that horses with *S. equi* rhabdomyolysis also develop a toxic shock like syndrome as genes for four superantigens have recently been identified in *S. equi*. 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. 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. There is currently no evidence that the *S. equi* involved is an atypical genetic strain of *S. equi*.

*Treatment:* A high mortality rate has been reported in horses receiving intravenous penicillin therapy once clinical signs of strangles and myopathy were well established. 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 exquisitely susceptible to β-lactam antibiotics, a mortality rate of 85% has been reported in human group A streptococcal myositis despite penicillin treatment. An antimicrobial that inhibits protein synthesis, such as rifampin, combined with intravenous 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. Nonsteroidal antiinflammatories and possibly high doses of short acting corticosteroids may provide better anxiety and pain relief than periodic injections of tranquilizers. Horses should be placed in a deeply bedded stall moved from side to side every 4 hours if they are unable to rise. Some horses may benefit from a sling if they will bear weight on their hind limbs when assisted to stand.

**Infarctive Purpura Hemorrhagic**

*Prevalence:* The prevalence of infarctive Purpura Hemorrhagica (PH) in one study was three out of a total of 53 PH cases reviewed. Five other cases of infarctive PH have been described in horses that were either exposed to *S. equi* within three weeks of presentation and or had markedly elevated serum ELISA M protein titers. Although horses with classic PH usually have a good prognosis, infarctive PH has a high fatality rate.

*Clinical signs:* The primary presenting complaint for horses with infarctive PH is often painful lameness, muscle stiffness and/or colic. Careful physical examination reveals classic signs of PH such as petechia and moderate well demarcated limb edema, however, in addition, horses with infarctive PH will have focal firm intramuscular swellings (figure 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, hyperproteinemia, hypoalbuminemia and marked elevations in CK (47,000-280,000 U/L) and AST (960-7,000 U/L) activities. Peritoneal fluid obtained by abdominocentesis may be normal or may have an increased total protein, nucleated and red blood cell counts if gastrointestinal infarction is present.

Ultrasonographic examination of swollen muscle reveals focal hypoechoic lesions within muscle tissue. 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 (figure 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 due to IgA immune complex deposition. Immune complexes are present in the sera of horses with PH that appear to primarily be 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 intravenous pulse therapy with methylprednisolone (1000mg/m^2 every other day for three treatments) followed by oral corticosteroids plus immunosuppressive agents such as cyclophosphamide and azathioprine. One horse with infarctive PH was successfully treated with penicillin, nonsteroidal antiinflammatories and three weeks of dexamethasone (0.1- 0.07mg/kg) followed by a ten week tapering course of oral prednisolone (2 mg/kg initially).

Immune-mediated polymyositis

Prevalence: Immune-mediated polymyositis (IMM) has recently been reported in horses. The affected horses are primarily of Quarter horse related bloodlines, although two ponies, one Icelandic horse and a Thoroughbred have been described with IMM. A bimodal age distribution seems to occur in affected horses with all horses identified to date either ▪ 8 yrs of age or ▪ 16 yrs of age. In approximately 1/3 of horses with IMM a triggering factor appears to have been exposure to S. equi or a respiratory disease.

Genetics: IMM in humans is believed to have a nonMendelian polygenic pattern of
inheritance. The high prevalence of the disorder in Quarter horse 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 (figure 3), accompanied by stiffness and malaise. Atrophy may progress to involve 50% of the horses' muscle mass within a week 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. However, 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 inflammatory infiltrates in epaxial muscles is such that a diagnosis can often be established from several formalin fixed Trucut samples.

Pathogenesis: The lymphocytic infiltrate seen in muscle samples from horses with IMM is distinct from that found in dogs and humans with immune-mediated polymyositis, in that the CD4:CD8 ratio in horses appears higher. In contrast to immune-mediated masticatory muscle myositis which does have a higher CD4:CD8 ratio, the specific binding of IgG to myofibers seen in canine masticatory muscle is not a feature of equine IMM. The reason why specific muscle groups are affected in horses with immune mediated polymyositis is unclear.

Treatment: Horses with concurrent evidence of streptococcal infection should be treated with antibiotics. It is likely prudent to avoid intramuscular injections. Administration of corticosteroids appears to immediately improve signs of malaise and inappetence and prevented further progression of muscle atrophy. Recommended dosages are: dexamethasone (0.05 mg/kg) for three days, followed by prednisolone (1 mg/kg for 7 to 10 days) tapered by 100 mg/week over one month. Serum CK activity often normalizes after 7 – 10 days. Muscle mass will usually gradually recover over two-to-three months.

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.

Seasonal Pasture Myopathy in the Midwestern USA
A retrospective case series (14 horses) was recently performed in Minnesota that described clinical signs, diagnostic findings, tissue tremetone concentrations, and clinical outcome or postmortem findings of horses evaluated for acute severe nonexertional rhabdomyolysis initially attributed to white snakeroot toxicosis.5

Clinical signs: The most common clinical signs of this myopathy were myoglobinuria, generalized weakness, muscle fasciculations, lethargy, and prolonged recumbency. Elevated heart and respiratory rates were present and most horses were initially thought to have colic. Horses did not have firm painful muscles typical of exertional myopathies. Serum CK activity ranged from 46,487 to 959,499 U/L (reference range 82-449 U/L) and aspartate transaminase activity was >1,500 U/L (reference range 162-316 U/L). While all horses suffered from skeletal muscle necrosis, 50% were also found to have myocardial degeneration. All horses were kept on pasture >12 h a day without snow cover when minimum daily temperatures were from 29°F to 56°F and weather was often inclement. Thirteen of 14 horses developed the disorder in the fall and many farms had a history of horses previously dying from similar clinical signs.

Post mortem findings: Only two horses survived with aggressive antioxidant and anti-inflammatory treatment. Postmortem examination revealed acute severe myonecrosis primarily in neck, proximal fore and hind limb, intercostal, and diaphragm muscles. Frozen intercostal, diaphragm or muscles surrounding the hip joint stained darkly for the presence of lipid (oil red O stain), which was an unusual common finding suggesting a similar underlying mechanism for necrosis.

Pathophysiology: Vitamin E and selenium concentrations were within reference range in all horses evaluated suggesting that the myopathy was not related to nutitional myodegeneration. Clinical signs were similar to those reported for monensin toxicosis in horses, however, none of the horses received significant supplemental grain (the usual source of monensin). The seasonal occurrence of the myopathy as well as the acute clinical signs of muscle fasciculations, weakness, esophageal obstruction, colic, and pigmenturia were consistent with white snakeroot toxicosis. However, the toxic component of white snake root, tremetone, was not detected in liver or urine samples of any horses. Weather conditions, seasonality, clinical signs, clinicopathologic findings, mortality rate, and postmortem findings of minnesota cases closely resembled those associated with atypical myopathy (AM) reported in European countries where white snakeroot does not grow. Atypical myopathy affects postural and respiratory muscles as well as the myocardium and produces lipid accumulation in these muscles, In Minnesota, the majority of affected horses are isolated cases, whereas as many as 115 horses in a pasture may be affected in an outbreak of AM. The cause of AM is suspected to be an ingested or enterically produced toxin (eg, bacterial toxin, mycotoxin, or phytotoxin). AM was reported to cause 51 deaths in horses in Europe this fall.

Treatment: Impaired antioxidant capacity may play a role in the pathogenesis of AM since the primary muscles affected by the disorder are highly oxidative and develop marked lipid accumulation. In our study, of the 2 horses that survived, both presented within 4 h of
clinical signs developing. One of these horses was treated with phenylbutazone (2.2 mg/kg [1 mg/lb], PO, q12h) and vitamin E (5,000 U, PO, q24h). Serum CK activity in that horse decreased during a period of 5 days (serum CK activity at admission, 46,487 U/L; 1 day after admission, 29,842 U/L; 5 days after admission, 1,426 U/L). A follow-up examination performed in that horse 6 months after discharge revealed no residual clinical signs. The other horse responded to treatment with vitamin E and selenium (0.02 ml/kg [0.01 ml/lb], IM) once followed by administration of vitamin E (5,000 U, PO q24h), vitamin C (5,000 mg in 5 L of lactated Ringer’s solution given IV over 12 hours q24h), 2.5% solution of dimethyl sulfoxide in lactated Ringer’s solution given IV over 4 hours q24h for 3 days), flunixin meglumine (1.1 mg/kg [0.5 mg/lb], IV, q12h), and balanced polyionic fluids (2.2 mg/kg/h [1.1 mg/lb/h], IV). Serum CK activity in this horse increased from 256,103 U/L at admission to 264,359 U/L one day after admission, then subsequently decreased to 31,524 U/L three days after admission.

Clinical Relevance: Cases of rhabdomyolysis have been attributed to the toxin trematone in white snakeroot; however, trematone was not identified in our study of horses with a pasture myopathy. A seasonal myopathy, characterized by primary acute severe skeletal muscle necrosis and, in many cases, myocardial degeneration exists in Minnesota. Numerous similarities exist among cases of seasonal pasture myopathy and AM in Europe.7

References


