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Serum Hepatitis Associated with Commercial Plasma Transfusion in Horses

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This report describes 4 fatal cases of serum hepatitis associated with the administration of commercial plasma in the horse. Serum hepatitis in the horse is characterized by acute hepatic central lobular necrosis, and it has been associated with the administration of biological products of equine origin. None of these horses had a recent history of equine biologic-origin vaccination; however, they had received 1.5–5 L of commercial plasma, and in 1 horse, an additional 8 L of fresh blood. Acute, severe colic unresponsive to medical therapy, lethargy, or sudden death developed in these 4 horses 41 to 60 days later. Two of the horses developed encephalopathy, confirmed in 1 horse by the presence of severe diffuse Alzheimer type II astrocytes in the brain. Although the prevalence of serum hepatitis associated with the administration of commercial plasma appears to be low in the horse, it should be considered an uncommon but potentially fatal risk factor.

Key words: Encephalopathy; Horse; Plasma transfusion; Serum hepatitis.

Serum hepatitis in horses is also known as Theiler's disease, acute hepatic necrosis, or postvaccination hepatitis. Postvaccination hepatitis was 1st described in South Africa when hyperimmune antiserum of equine origin was used in combination with live virus vaccine for African horse sickness.[1] Acute hepatic necrosis has been reported 4–12 weeks after the administration of tetanus antitoxin (TAT)[2,3]; antiserum for anthrax,[4] strangles, influenza,[5] and equine encephalomyelitis[6]; and active vaccination of equine encephalomyelitis and rhinopneumonitis prepared from equine fetal tissues.[6] Most cases were reported during the summer and fall.[3] Dietary and vaccination practices, pregnancy, lactation, and toxic and infectious agents have been suggested as possible factors in the apparent seasonality.[4] The disease affects adult horses, but cases in horses as young as 1 year of age have been reported.[7] Clinical signs include lethargy, anorexia, profound icterus, decreased borborygmi, and variable central nervous system signs. The prognosis is poor if signs of liver failure with severe progressive neurological signs develop. Plasma has been advocated for the treatment of horses with endotoxemia, neonatal failure of passive transfer, hypoproteinemia, and antibody-specific products such as commercial botulism antiserum and *Rhodococcus equi* hyperimmune plasma. We report 4 horses that developed serum hepatitis after commercial plasma[a] administration from different batches at the Veterinary Medical Teaching Hospital (VMTH) of the University of California at Davis from 1992 to 1998.

Horse 1

A 13-year-old Arab mare was presented for stallion-like behavior of 7 months duration. A diagnosis of granulosa-theca cell tumor was made. Her initial PCV was 29.7% (reference range 32–46%). On opening the abdomen at surgery, several liters of hemorrhagic fluid with a PCV of 4% were found. The source of the fluid was not determined. During surgery, the mare received 5 L of commercial plasma and 8 L of fresh blood. At the end of the surgical procedure, the mare's peripheral PCV increased from 23 to 31%, and the abdominal fluid PCV increased to 15%. The mare was treated with procaine penicillin (22,000 IU/kg IM q12h), gentamicin (2 mg/kg IV q8h), flunixin meglumine (0.5 mg/kg IV q8h), and tranexamic acid (50 mL IV once). The mare's condition and blood work improved, and she was discharged 6 days later. Forty-one days after discharge, a referring veterinarian diagnosed acute liver failure and euthanized the mare because of a poor prognosis. The liver was reported to be small, and several tissues were collected and sent to our institution for histopathologic examination. The liver had marked bile duct hyperplasia with moderate numbers of peribiliary lymphocytes. Many hepatocytes were missing and had undergone necrosis previously. The remaining hepatocytes were enlarged with irregular vacuoles containing fat. Most of the lobular architecture was composed of macrophages, erythrocytes, and few neutrophils. The histopathologic diagnosis was severe diffuse acute hepatic necrosis consistent with serum hepatitis.

Horse 2

An apparently healthy 12-year-old research Quarter Horse mare was found dead in a paddock. The mare had no known medical problems before her death. Five other horses shared the paddock with the mare, but none of them appeared to be ill. The mare received 2 L of commercial plasma as part of a research protocol 6 weeks before her death. Other research horses received the same batch of plasma and looked healthy. The carcass was sent to the VMTH for postmortem examination. The liver was characterized by massive zonal hepatic necrosis involving the majority of the periacinar and midzonal regions. There were occasional thin rims of hepatocytes around the portal areas and scattered intact hepatocytes within the midzonal and periacinar regions. The portal areas were characterized by biliary hyperplasia and accumulations of lymphocytes, plasma cells, and occasional neutrophils. Occasional scattered hepatic megalocytes with enlarged nuclei were pre-

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sent within the periportal areas. The midzonal and periacinar regions were replaced by large numbers of erythrocytes and scattered accumulations of granular golden brown pigment. Numerous Kupffer cells within the portal regions contained similar pigment. There were also scattered syncytial hepatocytes present throughout the periportal regions. The histopathologic diagnosis was severe: massive acute hepatic necrosis, consistent with serum hepatitis, as well as megalocytosis and biliary hyperplasia with portal accumulations of plasma cells. The megalocytosis was considered an incidental finding, representing an earlier exposure to pyrrolizidine alkaloid–containing plants, which are common feed contaminants in our area.

Horse 3

An 18-year-old Arab mare was presented with profuse diarrhea after an uneventful parturition. The clinical signs included tachycardia (100 beats/min, bpm), dehydration, toxic mucous membranes, and profuse diarrhea. The significant clinicopathologic findings were PCV 51%, WBC 3,200 cells/μL, slightly toxic neutrophils 832 cells/μL, bands 1,056/μL (reference rare), fibrinogen 700 mg/dL, chloride 84 mmol/L (reference range 96–107 mmol/L), total bilirubin (TB) 4.4 mg/dL (reference range 0.5–2.3 mg/dL), indirect bilirubin (IB) 4.2 mg/dL (reference range 0.3–1.7 mg/dL), creatinine 2.3 mg/dL (reference range 0.9–2.0 mg/dL), and blood urea nitrogen (BUN) 34 mg/dL (reference range 12–27 mg/dL). The mare was hospitalized and treated with IV fluids, 1.5 L of commercial plasma, flunixin meglumine (0.25 mg/kg IV q8h), and cimetidine (6 mg/kg PO q8h). Fecal culture was negative for *Salmonella* spp. and *Clostridium difficile.* The mare's condition and blood work improved, and she was discharged on day 5. Two months later, the mare was referred to our clinic for severe colic unresponsive to medical therapy. On presentation, the clinical findings were hypothermia (35°C), pale mucous membranes with a toxic line, abdominal distension, absent borborygmi, colic, profound sweating, cold extremities, ataxia, disorientation, and large colon distension. No reflux was obtained via nasogastric tube (NGT). Initial blood work indicated dehydration, acidosis, and electrolytes abnormalities that were managed with IV fluids. A complete blood work was not available at the time, and an abdominocentesis was not performed because of the mare's violent colic signs, which were unresponsive to sedation. Presurgical medication included potassium penicillin G (22,000 IU/kg IV), gentamicin (6 mg/kg IV), and flunixin meglumine (1 mg/kg IV). A celiotomy indicated generalized intestinal distension. The mare remained in lateral recumbence after surgery, and supportive therapy was initiated.

Postsurgical blood work indicated PCV 47.6%, sodium 150 mmol/L, T_{CO_2} 24 mmol/L (reference range 28–36 mmol/L), calcium 8.3 mg/dL, BUN 6 mg/dL (reference range 12–27 mg/dL), amino aspartate transferase (AST) 2,376 IU/L (reference range 138–409 IU/L), gamma glutamyl transferase (GGT) 74 IU/L (reference range 8–22 IU/L), sorbitol dehydrogenase (SDH) 308 IU/L, TB 15.5 mg/dL, IB 14.2 mg/dL, bile acids (BA) 103 μmol/L (reference range 0–15 μmol/L), and serum ammonia 751 μg/dL (control horse 10 μg/dL). The urine was positive for protein, myoglobin, and glucose and had a specific gravity of 1.009 (reference range 1.020–1.050). Hepatic ultrasound was attempted, but the presence of air as the result of surgery precluded the examination. A liver biopsy was performed for histopathologic analysis. The mare developed bilateral rotatory nystagmus and loss of deep pain perception. A clinical diagnosis of acute hepatic disease and encephalopathy was made. Because of the poor prognosis, and for humane reasons, the owner elected euthanasia. An atlantooccipital spinal fluid sample collected immediately after her death had a normal cytology but appeared slightly xanthochromic and had an ammonia concentration of 294 μg/dL (control horse 0 μg/dL). At postmortem examination, marked icterus was observed in mucous membranes, serosa, and fat. The liver had a smooth capsular surface with irregular firm depressed areas throughout. There were also several irregular pale red to tan areas on the capsular surface that did not extend to the parenchyma, multiple areas of fibrosis, and an enhanced lobular pattern throughout the parenchyma. The histopathologic diagnosis was severe diffuse subacute midzonal hepatic necrosis consistent with serum hepatitis and hemorrhage with mild periportal lymphoplasmacytic hepatitis. The brain had severe diffuse Alzheimer's type II gliosis consistent with hepatic encephalopathy.

Horse 4

A 4-year-old Paint gelding was presented with a history of colic of 7 hours duration that had been treated with mineral oil via NGT and sedation for pain control. On physical examination, the horse had bradycardia (27 bpm), lethargy, dehydration, hypovolemia, and severe pain. No reflux was obtained via NGT, and rectal examination was difficult because of the horse's violent colic. The horse received IV fluids, potassium penicillin G (22,000/kg IV), gentamicin (6 mg/kg IV), and flunixin meglumine (1 mg/kg IV) and underwent an exploratory celiotomy. A colon torsion was found and corrected. The horse was treated with polymixin B, dimethyl sulfoxide, 2 L of commercial plasma, IV fluids, systemic antibiotics and flunixin meglumine. The day after surgery, the horse's blood work results were a total protein (TP) of 4.4 g/dL (reference range 5.8–7.7 g/dL), albumin 1.9 g/dL (reference range 2.3–3.6 g/dL), sodium 142 mmol/L (reference range 132–140 mmol/L), calcium 8.9 mg/dL (reference range 11.0–13.0 mg/dL), phosphorus 5.7 mg/dL (reference range 2.1–4.7 mg/dL), creatine kinase (CK) 922 IU/L (reference range 119–287 IU/L), SDH 14 IU/L (reference range 0–8 IU/L), TB 3.0 mg/dL, and IB 1.9 mg/dL. The horse improved and was discharged on day 5. At home, the horse appeared to be healthy until week 6, when the horse developed lethargy, tachycardia, and mild colic of 24 hours duration. On physical exam, the horse had tachycardia (72 bpm), dehydration, lethargy, moderate ataxia, icterus, toxic mucous membranes, decreased borborygmi, and small intestinal distension. The horse became aggressive and developed mydriasis, loss of menace reflex, compulsive circling, and appeared acutely shocky. The horse was given hydrocortisone (600 mg IV) and IV fluids with dextrose.

On the blood work, the significant findings were initial PCV 50%, WBC 14,550 cells/μL, and TP 8.5 g/dL (reference range 5.8–7.7 g/dL). The cytologic evaluation of the

abdominal fluid was within normal limits. The results of a CBC and chemistry panel were WBC 22,100 cells/μL with 18,122 neutrophils/μL, sodium 147 mmol/L, T_{CO_2} 16 mmol/L, calcium 9.0 mg/dL, BUN 9.0 mg/dL, AST 2,585 IU/L, GGT 57 IU/L, TB 14.6 mg/dL, IB 13.1 mg/dL, serum ammonia 433 μg/dL, and prothrombin time 24.0 seconds (reference range 14–17 seconds). Potassium penicillin G (22,000 IU/kg IV q6h), gentamicin (6 mg/kg IV q24h), flunixin meglumine (0.25 mg/kg IV q8h), lactulose (150 mL total per rectum), and dexamethasone sodium phosphate (0.08 mg/kg IV once) were initiated. The liver was not observed on ultrasonographic examination. On day 3, the horse's WBC increased to 26,400 cells/μL, with 22,440 slightly toxic neutrophils/μL and 528 bands/μL. The results of a biochemical profile were sodium 149 mmol/L, T_{CO_2} 20 mmol/L, BUN 8 mg/dL, AST 3,157 IU/L, creatine kinase (CK) 2,407 IU/L (reference range 119–287 IU/L), GGT 54 IU/L, SDH 363 IU/L, TB 22.8 mg/dL, IB 21.1 mg/dL, BA 104 μmol/L, and serum ammonia 618 μg/dL. The neurological signs progressed to head pressing and obtundation. A clinical diagnosis of hepatic encephalopathy was made, and the owner elected euthanasia because of a poor prognosis. The postmortem examination findings were a small firm liver (3.66 kg) with sharply defined lobular areas and enhanced diffuse reticular pattern. The histopathologic diagnosis was severe diffuse subacute midzonal to massive necrosis consistent with serum hepatitis and moderate multifocal lymphocytic, plasmacytic, and neutrophilic hepatitis. The brain was not examined.

Serum hepatitis is characterized by severe central lobular necrosis; a finding observed in all horses of the present report. Pregnant lactating mares that received TAT appear to be at higher risk of developing serum hepatitis.[5] None of these horses were pregnant, lactating, or had a recent history of vaccination. However, these horses had received between 1.5 and 5 L of commercial plasma, and in 1 horse, 8 L of fresh blood in addition to the plasma, some 41–60 days before the development of clinical signs. On reviewing the VMTH records from 1985 to 2003, 735 horses <1 year of age received plasma, and there were no reports of serum hepatitis. During the same years 1,260 horses older than 1 year of age received between 1 and 10 L of plasma. The prevalence of serum hepatitis associated with plasma transfusion in our institution was calculated to be 0.4% for horses older than 1 year of age. The prevalence was calculated by excluding horses euthanized ($n = 255$) for other reasons. The formula ($k = 100$) used was [Total number of cases/ Total number of horses that received plasma − horses euthanized]k.

Hepatic encephalopathy (HE) has been reported with severe chronic pyrrolizidine alkaloid toxicosis, serum hepatitis, and congenital or acquired portal systemic vascular shunts.[8] Hepatic encephalopathy associated with serum hepatitis usually occurs in mature horses and has a sudden onset of clinical signs. A complete history was available for 2 of the horses in this report, both of which developed neurological signs consistent with HE. Encephalopathy was confirmed by histopathologic examination by the presence of severe diffuse Alzheimer type II astrocytes in the brain of 1 horse. The brain was not examined in the other 3 horses. The pathophysiology of HE in the horse remains elusive, but one of the hypothesized mechanisms is the presence of high concentrations of ammonia in the brain.[8] One horse with HE had excessively high cerebrospinal fluid ammonia.

The majority of the reported cases of serum hepatitis in horses have been associated with the use of TAT; however, a wide variety of biological products of equine origin have been associated with this disease. Although the prevalence of serum hepatitis associated with the administration of commercial plasma appears to be low in the horse, it should be considered an uncommon risk, but one that can have a fatal outcome. Plasma should be added to the list of biological products of equine origin associated with the subsequent development of serum hepatitis.

Footnotes

[a] Polymune, Veterinary Dynamics Inc, Templeton, CA

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