

Intermittent hypoglycemia in a horse with anaplastic carcinoma of the kidney

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- ▶ Clinically apparent hypoglycemia is rare in adult horses.
- ▶ Hypoglycemia is a well-recognized paraneoplastic syndrome in humans and dogs with non-insulin-secreting tumors and may occur in horses as well.
- ▶ Hypoglycemia associated with non-insulin-secreting tumors is believed to result from production of an abnormal form of insulin-like growth factor II.
- ▶ Neoplasia should be considered in the differential diagnosis for adult horses with hypoglycemia.

A 14-year-old Mustang gelding was referred to the University of California, Davis, Veterinary Medical Teaching Hospital for evaluation of a suspected episode of hypoglycemia and collapse. The horse had a 5-day history of mild colic and partial anorexia, chronic diarrhea of unknown duration, and a 2- to 3-week history of weight loss despite an increase in the amount of feed. On the morning of referral, the horse was examined by the referring veterinarian who reported that the horse was recumbent with hypoglycemia. At that time, the horse responded to IV administration of flunixin meglumine and dextrose and was standing and eating within a few minutes after treatment.

On initial examination at the veterinary teaching hospital, the horse was observed to be moderately thin and appeared slightly weak with noticeable muscle tremors. Temperature, heart rate, and respiratory rate were normal, and the horse passed soft formed feces followed by fluid feces during the examination. Examination per rectum did not reveal any clinically important abnormalities. Blood glucose concentration was 185 mg/dl (reference range, 59 to 122 mg/dl). Urine glucose concentration was initially estimated to be 250 mg/dl by use of a dipstick test, but results of a follow-up test approximately 24 hours later were negative. Total WBC count, PCV, and serum total protein, sodium, potassium, ionized calcium, and bicarbonate concentrations were within reference limits.

Abdominocentesis yielded a hazy yellow fluid with a total protein concentration of 1.2 g/dl and WBC count of 690 cells/ μ l. Evaluation of blood samples collected on days 3, 4, and 10 of hospitalization revealed moderate anemia (PCV = 22.5, 28.6, and 24.9%, respectively) and mild thrombocytopenia (98,000 platelets/ μ l) on day 3. Serum glucose, electrolyte, urea nitrogen, creatinine, total bilirubin, albumin, and globulin concentrations and sorbitol dehydrogenase, γ -glu-

tamyltransferase, aspartate aminotransferase, alkaline phosphatase, and creatine kinase activities were within reference ranges the morning following admission.

Initially, financial constraints of the owner prevented thorough diagnostic evaluation, and the horse was treated conservatively on the basis of an assumption that it had colic of an unknown cause that was resolving. On the third day of hospitalization, the horse developed a large abscess on the left side of the neck consistent with infection of the site where the owner had injected flunixin meglumine multiple times during the week prior to admission. Bacterial culture of material from the abscess yielded *Bacillus cereus*, which was resistant to penicillin but susceptible to gentamicin. The abscess responded to treatment with gentamicin IV, hot packing, and drainage by needle aspiration and decreased in size considerably during the remaining 14 days of treatment. As the horse did not initially have any signs of acute illness following admission, treatment of this abscess was the reason for the prolonged hospitalization.

On the eighth day of hospitalization, the horse was found to be nonresponsive. It was standing but would not move, even when encouraged, or respond when offered food. Its pupils were dilated and did not respond to light, and its ears were twitching repetitively. Heart and respiratory rates were within reference limits. Blood glucose concentration was 13 mg/dl. The horse collapsed during examination, and 5 L of lactated Ringer's solution with 10% dextrose was administered IV. The horse responded almost immediately and was standing and eating within 10 minutes after initiation of IV treatment. Blood glucose concentration was 296 mg/dl following administration of 5 L of lactated Ringer's solution with 10% dextrose.

Blood glucose concentration was monitored 1 to 3 times daily for the remaining 8 days of hospitalization. Nine of 12 samples had a blood glucose concentration between 63 and 136 mg/dl, and 3 had a concentration between 37 and 53 mg/dl. Blood glucose concentration was not obviously associated with time of blood sample collection or time since the horse was fed. For 3 samples, serum insulin concentration was measured at the same time blood glucose concentration was measured. For the first sample, insulin concentration was < 1.5 μ U/ml (reference range,¹ < 300 μ U/ml), and glucose concentration was 37 mg/dl. For the second sample, insulin concentration was 65.6 μ U/ml, and glucose concentration was 136 mg/dl. For the third sample, insulin concentration was 14.6 μ U/ml, and glucose concentration was 37 mg/dl. Insulin-to-glucose ratios for samples 1, 2, and 3 were 0.4, 0.48, and 0.4, respectively, which were within the range previously documented for healthy adult horses.² Other than the episode of hypoglycemia on the eighth day of hospital-

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ization and the episode described by the referring veterinarian, clinical signs of hypoglycemia, other than lethargy, were not observed at any time.

Ultrasonography of the liver performed on day 8 revealed hyperechoic areas with shadow lines consistent with calcification. The right kidney was found to contain a mass that extended to the liver and had many hyperechoic and hypoechoic areas. A follow-up examination per rectum at this time revealed that the right kidney was larger than normal but firm and smooth. The left kidney was palpably normal.

Fine-needle biopsy specimens of the right kidney and liver were submitted for histologic evaluation on day 8. Evaluation of the kidney specimen revealed cells suggestive of anaplastic carcinoma; evaluation of the liver specimen revealed diffuse vacuolar hepatopathy. Because of the grave prognosis, the owners elected to have the horse euthanized.

On gross postmortem examination, a large mass involving the right kidney that was firmly attached to the right mid-abdominal aspect of the peritoneum was found. The right kidney contained a single localized area of normal-appearing tissue; the remainder of the kidney consisted of a soft multilobulated mass. The left kidney appeared grossly normal. The liver was found to have numerous nodules on the capsular surface and within the parenchyma consistent with parasitic migration but, otherwise, appeared grossly normal.

The postmortem histologic diagnosis was anaplastic carcinoma of the right kidney. Other findings included myonecrosis and bacterial infection of the neck secondary to multiple IM injections. Gastrointestinal tract lesions included chronic lymphoplasmacytic enterocolitis, chronic gastric ulceration, moderate multifocal hepatocellular necrosis, and biliary hyperplasia.

Primary renal neoplasia is rare in horses, and the most common primary renal neoplasm in horses is renal cell carcinoma.³ Hypoglycemia associated with nonislet cell neoplasia in humans^{4,5} and dogs⁶⁻¹⁰ is well-documented, but to our knowledge, persistent hypoglycemia associated with nonislet cell neoplasia in a horse has been reported only once previously.¹¹ That case involved a yearling filly with persistent hypoglycemia associated with hepatocellular carcinoma.

Hypoglycemia is rare in adult horses, and unlike most other species of domestic animals, no reported condition of adult horses is regularly associated with hypoglycemia. This is apparently not attributable to the unique carbohydrate metabolism in horses; rather, it seems that few of the diseases known to induce hypoglycemia in other species affect adult horses. As with most species, glucagon, growth hormone, epinephrine, and cortisol usually maintain blood glucose concentrations at or above the minimum physiologically normal concentration, preventing fasting hypoglycemia in adult horses.

Although rare, hypoglycemia reportedly can develop in horses that are exhausted following extensive and prolonged exercise, in horses with acute toxic enteritis or acute endotoxemia, and in ponies with hyperlipidemia syndrome or in the terminal stages of starvation.¹² Hypoglycemia in horses with colic associ-

ated with strangulating lesions of the intestine has also been reported.^{13,14} Hypoglycemia associated with excessive secretion of insulin from an islet cell tumor in a pony has been reported¹⁵ but, otherwise, is an unusual finding in horses.

In dogs, several non-insulin-secreting tumors, including leiomyoma, leiomyosarcoma, hepatoma, lymphocytic leukemia, plasma cell myeloma, malignant melanoma, salivary adenocarcinoma, hemangiosarcoma, and malignant lymphoma, have been associated with hypoglycemia.^{6-10,15,16} Most of these tumors have been malignant and associated with short survival times.¹⁰ In many affected dogs, hypoglycemia resolved following complete removal of the tumor.⁶

It is currently thought that hypoglycemia associated with non-insulin-secreting tumors in dogs and other species is associated with production of an abnormal form of **insulin-like growth factor (IGF)-II**, referred to as "big IGF-II," and an alteration of its interactions with other substances.¹⁷ In humans with hypoglycemia secondary to non-insulin-secreting tumors, there is impaired formation of serum complexes of IGF, IGF-binding protein, and the acid-labile subunit.⁵ These patients have high circulating concentrations of big IGF-II (which has insulin-like activity), may have normal or high concentrations of normal IGF-II, and have normal or low insulin concentrations. The result is increased insulin-like activity and uptake of glucose into tissues, primarily muscle, resulting in hypoglycemia. Serum big IGF-II concentration returns to normal and, as in dogs, hypoglycemia resolves following complete surgical removal of the tumor.¹⁸ Other proposed causes of tumor-associated hypoglycemia include increased metabolic demand for glucose by the tumor itself, stimulation of increased glucose uptake by tumor necrosis factor,¹⁹ and in the case of neoplasia involving the liver, decreased hepatic gluconeogenesis because of a decrease in the total number of functional hepatocytes.

It is possible that hypoglycemia in the horse described in the present report resulted from tumor-related production of big IGF-II. Although the horse had intermittent signs of mild colic and diarrhea, there was no evidence of endotoxemia, strangulation of the intestines, starvation, excessive exercise, or hyperlipidemia. Histologic examination of the tumor, serum insulin concentration, and the insulin-to-glucose ratio, which was evaluated on 3 separate occasions, did not support a diagnosis of an insulin-secreting islet cell tumor.

The horse did have moderate multifocal hepatocellular necrosis and biliary hyperplasia, but most of the liver was unaffected histologically. Serum albumin and bilirubin concentrations and hepatic enzyme activities were normal, and the horse did not have any other clinical or laboratory evidence of compromised liver function. In addition, episodes of hypoglycemia were sporadic, and the horse had blood glucose concentrations within reference limits most of the time. Thus, it is unlikely that persistent hepatic disease or dysfunction was a major contributor to the hypoglycemia. Rather, the rapid decrease in blood glucose concentration, coupled with the apparent lack of an

association between blood glucose and insulin concentrations, was suggestive of intermittent action of a substance with hypoglycemic or insulin-like activity in this horse.

To our knowledge, there has been only 1 other report of hypoglycemia associated with a nonislet cell tumor in a horse.¹¹ This paraneoplastic condition may be more common in horses than presently recognized, and neoplasia should be included in the differential diagnosis for horses with hypoglycemia.

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