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Polysaccharide storage myopathy in two Percheron horses

Miopatia por acúmulo de polissacarídeo em dois equinos da raça Percheron

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ABSTRACT

Polysaccharide storage myopathy (PSSM) is a genetic disorder or by undetermined cause characterized by the abnormal accumulation of glycogen and polysaccharides in skeletal muscle fibers. The present report describes two Percheron horses, from different properties in the municipality of Pouso Redondo - SC, with locomotor clinical signs that started after work. The clinical signs observed were rigid gait, mainly of the pelvic limbs, muscle weakness, and recumbency. In the first case, the animal was diagnosed with severe multifocal rhabdomyonecrosis, moderate multifocal myoglobin nephrosis and severe diffuse transmural fibrinonecrotic gastritis. PSSM was confirmed by the presence of polysaccharide inclusions in myofiber sarcolemma visualized by periodic acid-Schiff (PAS) staining. In the second case, the horse presented two episodes of muscle disorder after work. The therapeutic protocol was based on penicillin, flunixin meglumine and fluid therapy with ringer lactate. An increase in creatine kinase (669.0 UI/L) and aspartate aminotransferase (669.0 UI/L) was observed in the serum biochemical evaluation. Research for mutation in the GYS1 gene was performed, with a positive heterozygote result. After rest and gradual recovery, the horse was only submitted to light work, with no return of the clinical condition since then. Thus, this report describes two cases of PSSM with distinct clinical evolution and diagnostic methods.

KEYWORDS: equine; pathology; rhabdomyonecrosis; myopathy; GYS1 gene.

RESUMO

A miopatia por acúmulo de polissacarídeos (PSSM) é uma desordem genética ou de causa indeterminada caracterizada pelo acúmulo anormal de glicogênio e polissacarídeos nas fibras musculares esqueléticas. O presente relato descreve dois cavalos Percheron, oriundos de diferentes propriedades do município de Pouso Redondo – SC, com sinais clínicos locomotores que iniciaram após o trabalho. Os sinais clínicos observados foram marcha rígida, principalmente dos membros pélvicos, fraqueza muscular, e decúbito. No primeiro caso, o animal foi diagnosticado com rabdomionecrose multifocal acentuada, nefrose mioglobínica multifocal moderada e gastrite fibrinonecrótica transmural difusa acentuada. A PSSM foi confirmada pela presença de inclusões polissacarídicas no sarcolema de miofibras visualizadas pela coloração com ácido periódico de Schiff (PAS). No segundo caso, o equino apresentou dois episódios de disfunção muscular após o trabalho. O protocolo terapêutico foi baseado em penicilina, flunixin megluminee fluidoterapia com ringer lactato. Um aumento de creatina quinase (669,0 UI/L) e aspartato aminotransferase (669,0 UI/L) foi observado na avaliação bioquímica sérica. Foi realizada pesquisa de mutação no gene GYS1, com resultado heterozigoto positivo. Após repouso e recuperação gradual, o cavalo foi submetido apenas a trabalhos leves, sem retorno do quadro clínico desde então. Assim, este relato descreve dois casos com PSSM com evolução clínica e métodos diagnósticos distintos.

PALAVRAS-CHAVE: equino; patologia; rabdomionecrose; miopatia; gene GYS1.

INTRODUCTION

Polysaccharide storage myopathy (PSSM) was first described in 1992, characterized as an abnormal accumulation of glycogen and glycogen-linked polysaccharides in skeletal muscle fibers (VALBERG et al. 1992, VALENTINE 2005, DE LA CORTE et al. 2002). PSSM is classified into PSSM type 1 (PSSM1) and PSSM type 2 (PSSM2). Type 1 is caused by a genetic mutation in the glycogen syntax 1 gene (GYS1)

(MCMUE et al. 2008a). PSSM type 2 (PSSM2) represents the form of muscle disease where the cause is undetermined, with no mutation in the GYS1 gene (MCMUE et al. 2008b, MCMUE et al. 2009, SÖDERQUIST et al. 2013). The mutation that occurs in the GYS1 gene, which causes a gain of function in the glycogen syntax enzyme (GS), is an autosomal dominant mutation of the conformational type (MCMUE et al. 2008a, MCMUE et al. 2008b, COOPER & VALENTINE 2016). Substitution in a single base pair causes an amino acid change from arginine to histidine, thus altering the activity of the GS enzyme in skeletal muscle, making it more active and resulting in glycogenosis with excessive accumulation of glycogen (MCMUE et al. 2008b, MAILE et al. 2017).

The clinical signs of PSSM are related to muscle dysfunction (VALENTINE et al. 2001), including abnormal gait of the pelvic limbs, poor performance, exercise intolerance, severe rhabdomyolysis, spontaneous decubitus with difficulty in standing (VALENTINE 2005), muscle pain, and myoglobinuria (MCMUE et al. 2008b). The main clinical and pathological findings are related to the mild to moderate increase in creatine kinase (CK), amino aspartate transferase (AST), and lactate dehydrogenase (LDH) in samples obtained from four to six hours after physical exercise (VALENTINE 2005). However, given the short half-life of CK, the most pronounced finding of AST and LDH, even with a slight increase in any enzymes, may suggest PSSM (BIRD et al. 2001).

Clinical signs and laboratory tests, especially biochemical profiles and urinalyses may not be specific for diagnosing the disease. However, muscle biopsy (VALBERG et al. 1992, MCMUE et al. 2006) and the molecular identification of the GYS1 gene mutation can confirm the clinical suspicion (MCMUE et al. 2008b, COOPER & VALENTINE 2016). The skeletal muscle biopsy shows abnormal staining for amylase-sensitive glycogen, subsarcolemmal vacuoles, necrosis, atrophy and evident regeneration in skeletal muscle fibers (VALBERG et al. 1992, BIRD et al. 2001, QUIROZ-ROTHE et al. 2002). Histological diagnosis for PSSM is determined by the presence of abnormal amylase-resistant polysaccharide inclusions stained with the periodic acid-Schiff (PAS) technique in skeletal muscle sections (VALBERG et al. 1992, VALENTINE et al. 1997, QUIROZ-ROTHE et al. 2002, FIRSHMAN et al. 2003, LEDWITH & MCGOWAN 2004). Treatment can be based on relieving clinical signs and preventing recurrence. The disorder is progressive, and early diagnosis combined with therapy is essential (VALENTINE 2005). The present work aims to report two cases of myopathy due to polysaccharide accumulation in two Percheron horses, considering the clinicopathological findings.

CASE DESCRIPTION

Case 1

Case history

A 20-year-old Percheron horse, from city of Pouso Redondo, Vale do Itajaí, Santa Catarina state, Brazil, presented muscle disorder, with previously treated by field veterinarians, with the initial clinical suspect of allergic reaction to insect bites. The horse received therapy with non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, and diuretics in unknown dosages, but lasting one week.

The horse received food based on the supply of corn as the primary energy source and was kept in native pasture and with mineral supplementation, with no other contacts of the same species and no history of previous diseases.

Clinical findings

During clinical care, reluctance to exercise, rigid walking associated with marked dragging of the pincers on the pelvic limbs, muscle weakness, able to remain stationary, but preferentially remaining in sternal decubitus with difficulty in standing was observed. Furthermore, the horse presented intense edema in the cranioventral pectoral region (Figure 1, A-B), thoracic and pelvic limbs, and left unilateral eyelid, and brownish urine.

Treatment and outcome

The wide range of measurements previously used showed no therapeutic efficiency. Therefore, all previously instituted protocols were immediately discontinued. Adjuvant therapy was established based on the massage the muscle groups using warm water, which promoted an initial improvement in the clinical condition, but the patient but the patient got progressively worse. The patient died due to the worsening of the prognosisand necropsy was performed. Samples of skeletal muscle, stomach, spleen, lungs, liver, kidneys, brain, cerebellum, adrenal, thyroid, pituitary gland, heart, small and large intestine were collected. The samples were stores in 10% buffered formalin for routine histological processing, stained with hematoxylin and eosin (HE). Additionally, skeletal muscle sections were submitted to histochemical reaction with periodic acid Schiff (PAS).

Postmortem findings

At necropsy, there was moderate to severe and diffuse edema in the pelvic, thoracic, and pectoral limbs, and face. The skeletal muscles of the thoracic and pelvic limbs, masseter, temporal, and intercostal muscles showed dark red areas, focally extensive and marked (Figure 1, C).

Suffusions in cartilage-support muscles were observed in the larynx, in addition to petechiae in the glottis. The stomach was markedly thickened with diffuse transmural edema associated with hemorrhages in the pyloric and non-glandular region. A marked dark red to diffuse brownish color was observed in the kidneys.

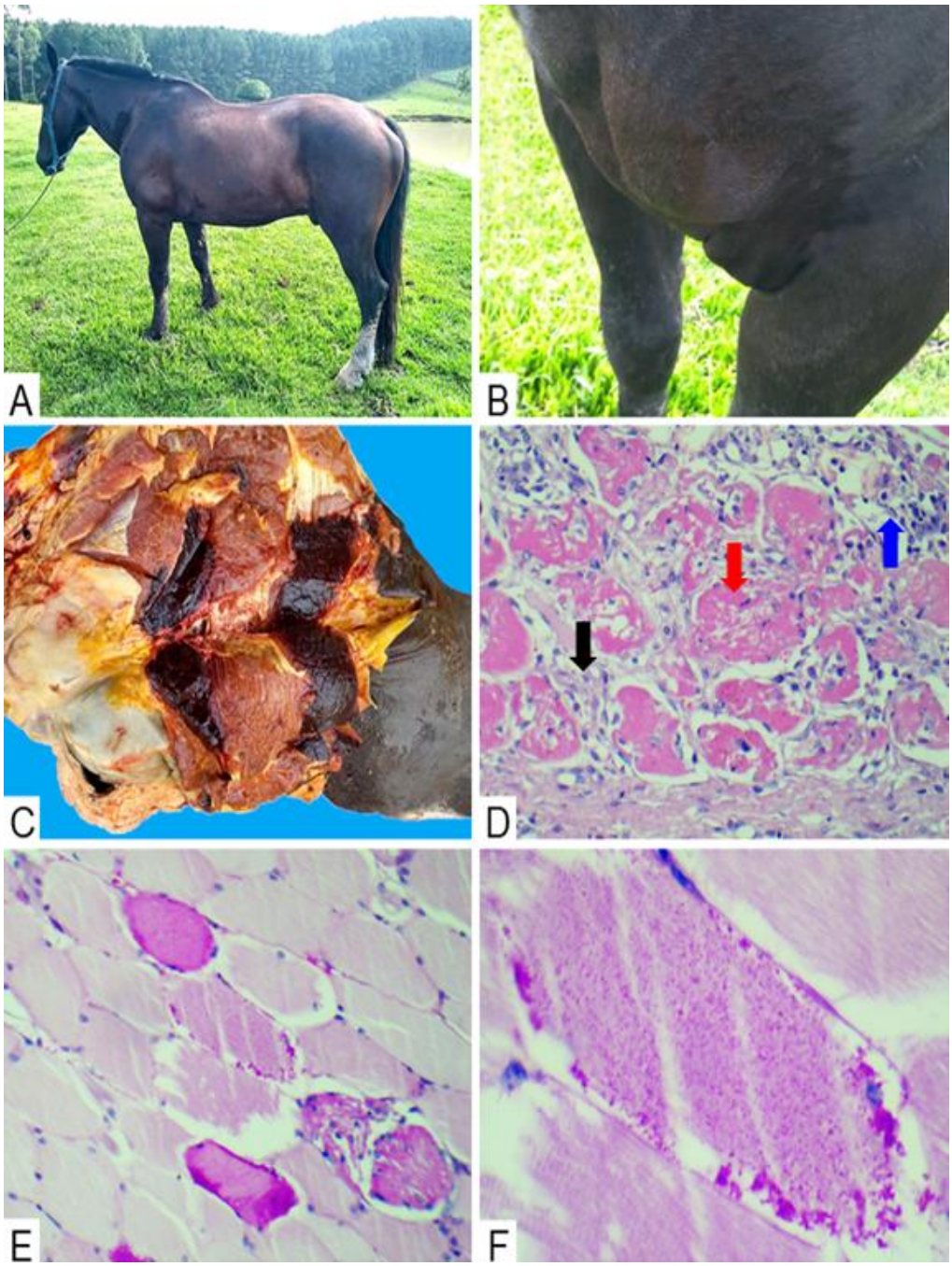

Figure 1. Percheron horse (case 1), with PSSM. A. General appearance of the patient during the first visit. B. Subcutaneous edema in the cranioventral and axillary pectoral regions. C. Muscle groups of the right pelvic limb, demonstrating marked multifocal darkened red areas. D. Microscopic lesions of the skeletal musculature of the right pelvic limb demonstrating intensely eosinophilic, flocculated rhabdomyocytes, often with discontinuity of the sarcoplasmic membrane (red arrow), and moderate, multifocal lymphoplasmocytic, macrophagic (blue arrow), and proliferation of multiple active fibroblasts (black arrow) (HE, x40). E. Periodic acid Schiff histochemical technique in sections of skeletal muscle that show accumulation of intensely pink granulation diffusely distributed in the sarcoplasm (PAS, x40) F. Close-up anterior image to demonstrate polysaccharide sarcoplasmic granulation, sometimes forming clumps adjacent to the inner surface of the sarcoplasmic membrane (PAS, x100).

Histopathology showed marked diffuse rhabdomyonecrosis (Figure 1, D) and multifocal hemorrhage associated with diffuse marked neutrophil, lymphocyte, plasma cell, and macrophage infiltration in the skeletal striated muscle, in addition to the moderate multifocal proliferation of fibrous connective tissue. Marked necrosis and transmural edema associated with hemorrhage, fibrinous exudation, and marked diffuse infiltrate of neutrophils, lymphocytes, plasma cells, and macrophages were observed in the stomach. There was a deposition of amorphous eosinophilic material in the lumen of tubules of the cortical region in the kidneys, characterized as hyaline casts, and discrete eosinophilia of the cells of the proximal and distal tubules, in addition to discrete multifocal infiltrates of lymphocytes and macrophages in the interstitium.

The skeletal muscle submitted to a histochemical reaction by PAS showed accumulations of discrete multifocal intracytoplasmic pink granulation (polysaccharide inclusions), isolated or in groups, in multiple rhabdomyocytes sarcolemmas (Figure 1, E-F), considered consistent for the diagnosis of PSSM. No lesions were observed in the other organs, ruling out the presence of other diseases.

Case 2

Case history

A 4-year-old mare, the Percheron breed, unrelated to the horse in the first case, from another property located in the city of Pouso Redondo, Vale do Itajaí, Santa Catarina, Brazil. The initial clinical condition show a muscle disturbance during locomotion, which began after the first 30 minutes of work. Feeding consisted mainly of corn grains, which were supplemented only with minerals, and kept in native pasture. No history of illnesses previously on the property.

Clinical findings

During care, the clinical condition observed was reluctance to exercise, rigid walking, especially of the pelvic limbs, muscle weakness, and difficulties in locomotion.

Diagnosis

Blood samples were collected through jugular puncture, placed in tubes with and without ethylenediaminetetraacetic acid (EDTA). The samples were sent to measure the muscle enzyme creatine kinase (CK) according to the methodology determined by the IFCC (International Federation of Clinical Chemistry) using the CK-NAC Liquiform reagent (Labtest®, Lagoa Santa, Minas Gerais, Brazil, Lagoa Santa, Minas Gerais, Brazil). Aspartate aminotransferase (AST) was measured using the UV-IFCC kinetics methodology from the AST/GOT Liquiform reagent (Labtest®, Lagoa Santa, Minas Gerais, Brazil). Both enzymes were analyzed in the Labmax Plenno automatic biochemical analyzer (Labtest®, Lagoa Santa, Minas Gerais, Brazil). The results were values of 669.0 UI/L CK (IR 2.4-23.4 UI/L, KANEKO et al. 2008) and 600.0 IU/L for AST (IR 226-366 IU /L, KANEKO et al. 2008).

Aliquots of whole blood with EDTA were separated to perform polymerase chain reaction (PCR) for *Trypanosoma evansi* and *Trypanosoma vivax*. The DNA was extracted employing the standard phenol-chloroform method, using primers and amplification conditions according to CLAES et al. (2004), presenting negative results for both *Trypanosoma*.

An aliquot of whole blood with EDTA was sent to search for a genetic mutation in the GSY1 gene (glycogen syntax 1), performed by automatic sequencing of PCR products by capillary electrophoresis in the ABI 3500 Genetic Analyzer equipment (Life Technologies®, Carlsbad, California, USA) and subsequent analysis of the region in which the c.926G>A mutation is located in the GYS1 gene (MCMUE et al. 2008b). The result was the presence of the mutation, being positive heterozygote, having an allele mutated to PSSM.

Treatment and outcome

Penicillin (Pencivet Plus PPU®, Kenilworth, New Jersey, USA) 10,000 IU/Kg IM was administered once a day for two days, flunixin meglumine (Banamine®, Kenilworth, New Jersey, USA) 1.1mg/Kg, IV, once a day, for two days, in addition to IV ringer lactate fluid therapy. Two days after the beginning of the treatment, the horse already showed improvement in the clinical condition. However, the areas of intramuscular application were enlarged and with painful sensitivity. The treatment with penicillin was maintained, but every 48 hours, totaling five doses. Flunixin Meglumine was replaced by Meloxican (Maxican® 2%, Ourofino, Cravinhos, São Paulo, Brazil) 0.6mg/Kg IM, SID, for four days. Fluid therapy with ringer lactate, IV was also administered.

After beginning treatment, the horse showed a significant improvement in the clinical condition. However, it was used again for work and, consequently, presented the same clinical condition, with a therapeutic protocol based only on fluid therapy and NSAID being instituted, with an improvement in the clinical condition in the first days. Finally, an eight-month rest period was chosen, with the horse used only for light work, with no further clinical changes.

DISCUSSION

In both cases, the clinical history characterized by the sudden onset of exhaustion at the beginning of physical exercise, associated with a characteristic muscular disorder and Percheron breed predisposition, are consistent with studies previously conducted by VALENTINE et al. 2001, VALENTINE 2005 and MCCUE et al. (2008b) since the horses presented the clinical picture of muscle dysfunction, where animals used for traction developed severe myopathy (COOPER & VALENTINE 2016).

An 80% prevalence of PSSM was observed in a study conducted with crossbred Percheron horses (MCCUE et al. 2008b) and in a similar case using the Percheron breed described by FREDO et al. (2018). PSSM is described as a hereditary predisposition, especially in Percheron. Animals historically used for traction also tend to inherit this type of genetic mutation (VALENTINE 2005, and COOPER & VALENTINE 2016).

The horse from the first case presented acute kidney failure concomitant with the muscle injury. This case is attributed to two important factors, the nephrotoxicity induced by myoglobin released by necrotic muscle fibers and the history of NSAID-mediated therapy. The nephrotoxicity of heme pigment present in myoglobin is still poorly understood, but it is commonly related to reduced renal blood flow, oxygen privation and consequent ischemic injury. It is important to consider that the formation of intratubular hyaline cylinders by heme group protein deposits, such as observed in the kidneys of this patient, can also have strongly contributed to the occurrence of tubular lesions (GEOR 2007). NSAIDs, in turn, directly interfere in the autoregulation of renal blood flow (GAMBARO & PERAZELLA 2003, D'ANDRETTA & BARROS 2018). This condition, in synergy with the lesions already caused by the deposition of myoglobin in the patient, significantly worsened the patient's clinical status, accentuating the renal failure.

As noted in this report, animals with PSSM are more likely to develop exertional rhabdomyolysis since it also affects horses with a high grain diet (COOPER & VALENTINE 2016), and dysfunction in the metabolism of glycogen that is deposited in the muscle fibers (VALBERG et al. 1999).

Furthermore, horses with PSSM are more prone to develop post-anesthetic myopathy, such as the case described by FREDO et al. (2018) in which the equine had homozygous dominant characteristics for the GYS1 gene. This case was similar to the first report of this study, where the horse developed rhabdomyolysis injuries secondary to PSSM, evidenced during necropsy in different muscle groups, especially those related to appendicular movement, and finally confirmed by histopathology and myoglobin nephrosis.

Additionally, factors such as diet composition, frequency of physical activities and breed predisposition, especially regarding food since carbohydrate-rich foods, such as corn, are strongly related to the intensity of PSSM clinical signs (VALENTINE et al. 2001, MCMUE et al. 2008b, FREDO et al. 2018). This corroborates both cases presented here since the primary source of energy was corn, given that the animals were on native pasture, thus favoring the clinical condition of PSSM.

Laboratory results of AST and CK in animals with PSSM found in other studies corroborate the serum biochemistry results founded in the second case of this study, where the levels of CK and AST were high due to muscle damage caused by the excessive accumulation of glycogen in muscle fibers (VALENTINE 2005, VALBERG et al. 2008, TOSI et al. 2014). However, the significant increase in CK only demonstrates severe muscle damage and given that the half-life of the CK enzyme is short (BIRD et al. 2001), it is suggested that the levels were higher at the beginning of the signs.

Compared with other studies of animals of the same breed (FREDO et al. 2018, FIRSHMAN et al. 2006) the histochemical findings by PAS shows a difference in marking since this study presented a slight marking in polysaccharide inclusions in the sarcolemma. This is explained by the critical condition in which the first horse was found due to the excessive muscle necrosis that made it difficult to visualize the accumulation of polysaccharides in the sarcolemma. Furthermore, there is a greater probability of necrosis accompanied by macrophage infiltration in animals diagnosed with PSSM compared to that found in horses without this disease (FIRSHMAN et al. 2006).

As observed in other cases, PSSM courses with macroscopic findings involving muscle pallor (FREDO et al. 2018), contrary to what was found in this horse. The intensely reddish color of skeletal muscle groups observed in the reported cases is associated with secondary rhabdomyolysis (VALENTINE & MCGAVIN 2013).

Although clinical signs are not specific for PSSM (VALBERG et al. 1992, MCMUE et al. 2006), the history and clinical signs demonstrate a disorder of muscle origin. When observing the clinical condition, it is necessary to exclude differential diagnoses that course muscular disorders, such as equine protozoal myeloencephalitis (VALENTINE 2005). Furthermore, trypanosomosis should also be considered in

differential diagnoses due to new reports in Santa Catarina state (RECK et al. 2020).

Equine trypanosomiasis, known as “surra”, “dourine” or “nagana”, is mainly caused by *Trypanosoma evansi*. It could also be a differential diagnosis since it also presents muscle disorders and subcutaneous edema (BRUN et al. 1998, RODRIGUES et al. 2005), as observed in the first case. Epidemiology must be considered additionally to the clinical condition since studies conducted by RECK et al. (2020) presented the first autochthonous case of trypanosomosis in horses from Santa Catarina, in the mesoregion of the Vale do Itajaí. However, other signs such as hyperthermia, jaundice, lymphadenomegaly, pale mucous membranes and skin eruptions (BRUN et al. 1998) should be observed in cases of trypanosomiasis, which were not found, corroborating the negative result of PCR.

According to the clinical presentation, another differential diagnosis would be ionophore poisoning, due to the locomotor alterations presented by the horses, as well as the serum biochemical alterations. However, as the epidemiology was not characterized by the consumption of ionophores by these animals and the lesions found during the necropsy are different from those observed in cases of ionophore poisoning, such as skeletal muscles with pale areas and in the histopathological evaluation, degeneration, and necrosis of myocytes (SOUSA et al 2019, SCHADE et al. 2022).

Equine protozoal myeloencephalitis (EPM) is an important differential for PSSM. However, muscle atrophy in this disease is predominantly asymmetrically distributed, and there is an important deficit of cranial nerves (COOPER & VALENTINE 2016, VALENTINE 2005). There is also a difference between the evolution of the diseases, where EPM has a chronic evolution and PSSM is super-acute to acute (VALENTINE 2005).

The definitive diagnosis of PSSM can be performed through muscle biopsy (VALBERG et al. 1992, MCCUE et al. 2006, VALBERG et al. 2020) and identifying the GSY gene mutation (MCMUE et al. 2008b, COOPER & VALENTINE 2016, VALBERG et al. 2020). However, the biopsy was not performed as the method of choice for diagnosing the second case, opting for molecular identification, also considering that the use of genetic tests has gained prominence in equine medicine in recent years and genetic testing for the GYS1 mutation is considering the gold standard for diagnosis of PSSM1 (COELHO & OLIVEIRA 2008, VALBERG et al. 2020). The identification of the mutation proved the clinical condition of the muscle disorder since PSSM has an autosomal dominant character (COOPER & VALENTINE 2016), requiring the presence of only one allele, as observed in the second case of this study, where the animal was heterozygous positive.

Due to the dominant autosomal character, one must consider the possibility of the mutation in the GSY1 gene in the offspring of positive animals, generating homozygous or dominant heterozygous offspring perpetuating the genetic mutation time (COOPER & VALENTINE 2016).

Regarding the limitations of the present work, the genetic evaluation and search for the mutation of the GSY1 gene in the horse in case 1 would be important to confirm the histopathological diagnosis since the gold standard for the diagnosis of PSSM1 is the genetic test for the GYS1 mutation performed on whole blood or hair root samples (VALBERG et al. 2020).

CONCLUSION

The clinical-pathological condition of PSSM due to dysfunction of muscle origin is characterized by reluctance and difficulty during movement, rigid walking, and dragging of pincers. The lesions found are based on the alteration of the musculature, such as a marked dark red color, especially of the movement muscles, originating from rhabdomyocyte necrosis when stained by HE, and characterized by polysaccharide inclusions in the sarcolemma of the muscle tissue observed with the use of PAS staining. The use of genetic mutation research associated with epidemiological and clinicopathological aspects, was essential for solving these cases.

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