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Chronic progressive lymphoedema in a Friesian horse: clinical aspects and diagnostic approach – case report

[*Linfedema progressivo crônico em um cavalo Friesian: aspectos clínicos e abordagem diagnóstica – relato de caso*]

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ABSTRACT

Chronic Progressive Lymphoedema (CPL) is a disabling disease of draft horses that affects lymphatic system function typically in the distal limbs. Deformities of distal limbs, especially of the pastern, with fibrosis and skin nodular lesions are consequences of disease progression. A 15-year-old Friesian stallion presented for evaluation with history of forelimb enlargement and nodule formations distal to the carpus for four years. Simple radiographs showed soft tissue nodular lesions and venous contrasted radiography showed intense enlargement of II common digital palmar vein of both forelimbs. Tissue culture tests revealed *Streptococcus equi* and *Proteus mirabilis* isolation and skin scraping test identified *Chorioptes bovis* mites. Histological examination revealed perivasculitis and lymph vessels distention. History, clinical and histological findings, and complementary exams suggested CPL diagnosis. We were unable to find previously published cases describing this disease in Brazil, where the increasing number of draft horses requires attention to this problem. The correct and early diagnosis substantially delays disease progression. Therefore, we highlight the need for nationwide propagation of these data to ensure better diagnosis and early treatment of future CPL cases.

Keywords: lymphatic system, draft horses, pastern dermatitis

RESUMO

O linfedema crônico progressivo (LCP) é uma enfermidade incapacitante de cavalos de tração que afeta o sistema linfático e se manifesta especialmente na região distal dos membros. A progressão da doença resulta em deformações na região distal dos membros, especialmente na quartela, com fibrose e lesões nodulares na pele. Foi atendido um garanhão da raça Friesian, de 15 anos de idade, com histórico de aumento de volume, nodulações e deformações na região distal dos membros torácicos, com início há aproximadamente quatro anos. Ao exame radiográfico simples, foram identificadas nodulações na pele e no subcutâneo e, ao exame venoso contrastado, identificou-se marcante dilatação II veia digital palmar comum em ambos os membros torácicos. Foi isolado Streptococcus equi *e* Proteus mirabilis *ao cultivo tecidual e identificou-se sarna do tipo corióptica ao raspado de pele. No exame histopatológico, foram identificadas perivasculite e dilatação de vasos linfáticos. Os achados clínicos, histórico, de raça do animal e os exames complementares direcionaram o diagnóstico para o LCP. A pesquisa da literatura nacional não revelou descrições clínicas dessa enfermidade, mas, devido ao aumento do número de animais de tração no país nos últimos anos, a descrição dessa enfermidade se torna importante. O diagnóstico correto e precoce é necessário para retardar a progressão da doença. Nesse sentido, ressalta-se a relevância da divulgação nacional desses achados, a fim de contribuir para o diagnóstico precoce e permitir o retardo da evolução da doença.*

Palavras-chave: sistema linfático, cavalos de tração, dermatite de quartela

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INTRODUCTION

Lymphatic system functions include maintaining tissue fluid homeostasis and removing cellular debris. Lymph is a protein-rich fluid that occupies lymphatic capillaries and is passively transported through the lymphatic system to blood capillaries by muscle contraction. The capillary filtration dysfunction between blood vessels, lymphatic vessels and interstitium results in lymph stasis or lymphoedema. Lymphoedema reduces tissue perfusion and oxygenation ending in metabolic waste augmentation that compromises immunity and skin barrier integrity (Skobe and Detmar, 2000; Keyser, 2014).

A chronic condition affecting the lymphatic system, called chronic progressive lymphoedema (CPL), clinically manifests in distal limbs of draft horses, especially, Gypsys, Clydesdales, Shires, (Cock *et al*., 2003; Affolter, 2013; Keyser *et al*., 2014; Affolter *et al*., 2020). CPL results in skin and subcutaneous fibrosis with skin fold formation and nodular lesions as consequences of lymph stasis and poor-quality elastic content of dermal lymphatic vessels (Keyser *et al*., 2014), similar to what occurs in human elephantiasis nostras verrucosa (Richards, 1981). Typically, CPL presents with secondary bacterial or parasitic infection (*Chorioptes bovis)* and has multifactorial etiology and genetic content. Disease progression frequently leads to permanent limb distortion, lameness, and early euthanasia (Affolter, 2013; Keyser *et al*., 2014; Affolter *et al*., 2020).

Due to the scarcity of draft breeds in Brazil, equine veterinarians are frequently unfamiliar with CPL, which can result in misdiagnosis and retard correct support treatment. Therefore, this study aims to report for the first time detailed clinical and complementary findings of a CPL case in a draft horse in Brazil.

CASUISTRY

A 15-year-old Friesian stallion weighing 450 Kg presented with a history of lameness and chronic lesions in both forelimbs first observed four years previously. The horse had already been admitted at other facilities and after radiographic and histological exams the final diagnosis was not stated. The horse had been treated for habronemosis with ivermectin- and trichlorfon-based products; furthermore, ozone therapy, antibiotic and non-steroidal anti-inflammatory drugs were unsuccessfully used. Due to the lack of diagnosis and progression of disease with intense lameness and severe weight loss, the horse was referred to our facility.

At admission the clinical evaluation revealed a heart rate of 44 bpm, respiratory rate of 19 mpm, pale pink mucous membrane, 37.7°C rectal temperature and normal gut motility. The musculoskeletal evaluation revealed severe fibrous tissue deposition at distal limbs ranging from pastern to carpus. Multiple ulcerated or non-nodular lesions, skin folds and subcutaneous tissue were visible under the hair (Fig. 1). Lesions were firm in consistency and unpainful when palpated. The same nodular aspect and skin folds were observed when hind limbs were examined except for the ulcerative lesions that were absent in hind limbs. Additionally, all four limbs showed skin crusts along the lesions and hair loss dorsal and caudal to carpus joints (Fig. 2) Occasionally, discrete itching was observed when the horse scratched the lesions against objects.

The horse presented left forelimb lameness (score 4 to 5/5 according to AAEP), alternating from severe lameness to complete limb dysfunction. Additionally, the left forelimb hoof showed chronic deformity with overgrown heels. Based on CPL suspicion, lesions were biopsied for histopathological exam, bacterial and fungal culture of deep tissue. Skin scraping, contrasted (venography) and simple radiograph were obtained, in addition to complete blood count, hepatic and renal blood tests.

The blood tests revealed hyperfibrinogenemia, normal erythrogram and leukogram, low levels of creatinine (1.08 mg/dL), hypoalbuminemia (2 mg/dL) and hyperglobulinemia (5.9 g/dL) (Kaneko *et al.*, 1997). Tissue culture was negative for fungus, whereas the aerobic culture found growth of *Streptococcus equi* and *Proteus mirabilis*, both sensitive to cephalosporins. From the skin scraping test, *Chorioptes bovis* was identified.

Figure 1. Lesion aspect of chronic progressive lymphoedema in a Friesian stallion: Lateral aspect of left forelimb during admission (A) and same limb after clipping (B); In a closer approximation, respectively, after admission (C) and after clipping (D). Observe deformities, nodulations, and granulomatous wounds where ulceration has occurred. Cranial and medial aspects of forelimbs after hair removal indicate multiple nodulations (E).

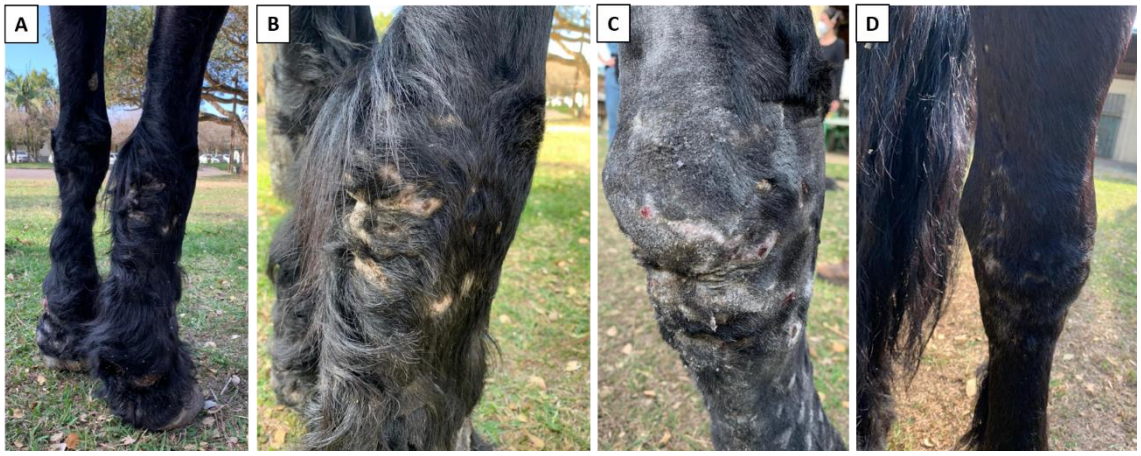

Figure 2. Lesion aspect of chronic progressive lymphoedema in a Friesian stallion: Caudal aspect of forelimbs (A) Detailed caudal view of the right hind limb evidencing caudal tarsus with intense fibrous tissue and alopecia before clipping (B) and after clipping (C), respectively; and cranial view of left tarsus, showing alopecic area (D).

The histology of tissue biopsies showed large epidermal and superficial dermic erosion areas with ulceration and necrosis associated with polymorphonucleated (neutrophil and eosinophil) infiltrate. Bacterial myriads and serocellular scabs were also observed. When epidermic tissue was integrated, acanthosis was observed, as well as multifocal dermal fibroplasia associated with neovascularization, mild edema, and lymphocytic infiltrate with perivascular pattern on blood and lymphatic vessels and with stasis of deep lymphatic vessels (Fig. 3).

Radiograph exams revealed multiple soft tissue nodulations and skin folds in all limbs. On the left forelimb we observed exostosis on the dorsal aspect of the distal phalanx, distal interphalangeal joint osteoarthritis and enthesophytes on common digital extensor tendon insertion with osseous proliferation and remodeling of the distal phalanx extensor process. Venography showed severe dilatation of digital palmar vein (Fig. 4).

To identify and treat skin lesions, both forelimbs were shaved from the carpus to the hoof and a compressive bandage was applied on the area. Additionally, Firocoxibe (0.1mg/Kg IV SID), intravenous regional perfusion with ceftriaxone was started in left forelimb (2g IV, every other day) and doramectin 0.3mg/kg SC (Dectomax®, doramectin, Zoetis Brazil, Brazil) was administered. For topical use, selenium sulfate

1.5% shampoo and fipronil 0.25% (Frontline®, fipronil, Merial, France) for limbs were indicated. Two days after the beginning of treatment, lameness score for the left forelimb improved but worsened again a few days later, alternating between mild (3/5) to severe lameness (4/5).

Five days after admission the horse developed a surgical colic syndrome with large colon impaction with a fecalith in small colon. After surgery the clinical parameters deteriorated, and the horse died because of postoperative complications.

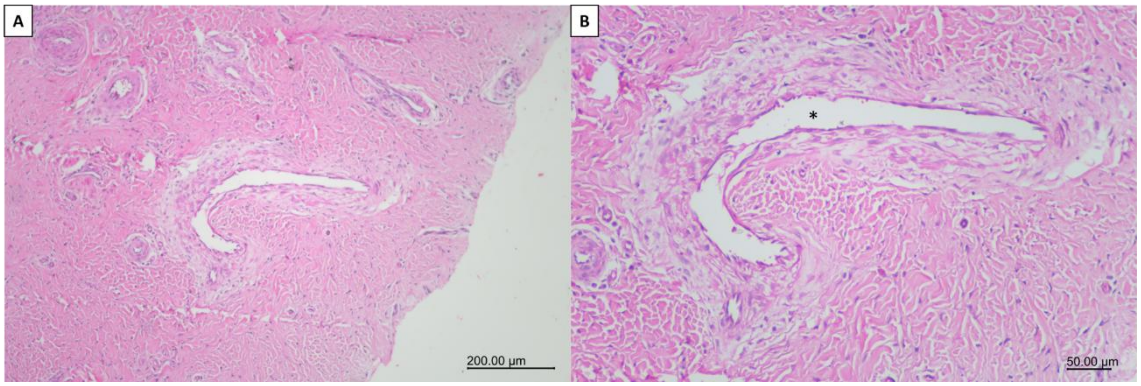

Figure 3. Histologic micrography harvested within 1.5 cm depth from a Friesian horse with suspected CPL lesions. A. Dermal fibroplasia, neovascularization and perivascular inflammatory infiltrate on blood and lymphatic vessels (200.00 µm); B. Perilymphatic severe fibrosis with lymphatic vessel enlargement (asterisk) (50.00 µm). Hematoxilin and eosin.

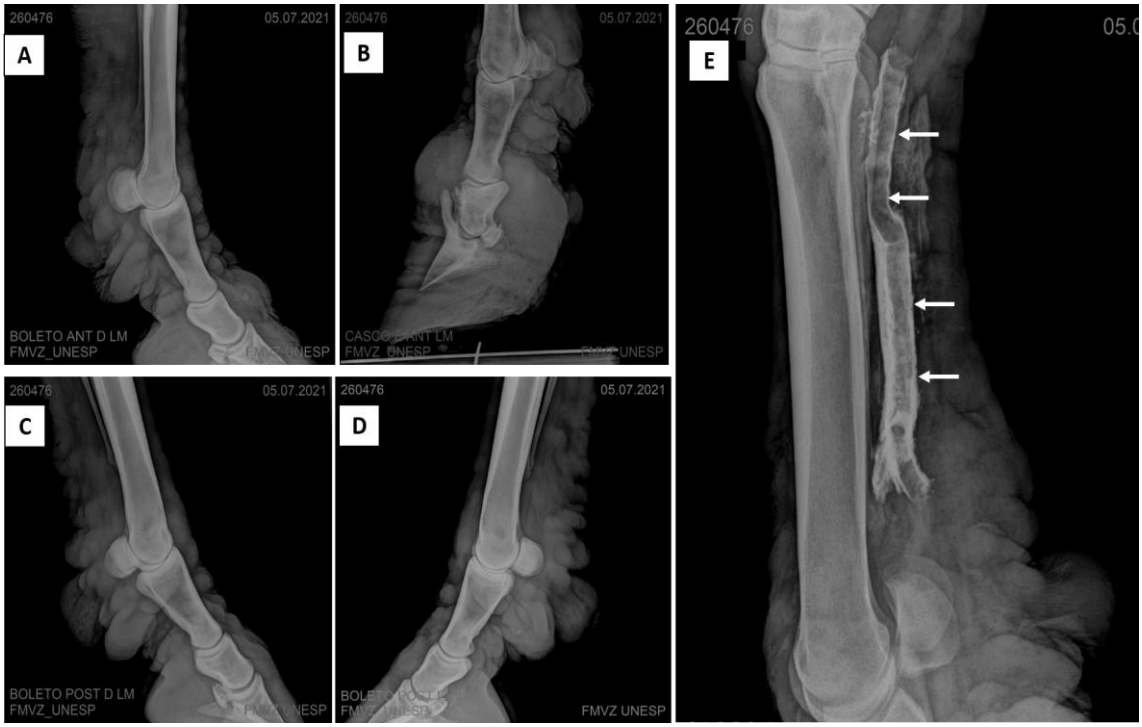

Figure 4. Radiographic images of Friesian horse showing CPL: Simple latero-medial radiography of right and left forelimbs (A and B), and right and left hind limbs (C and D), respectively. And contrasted radiograph in latero-medial left forelimb (E) demonstrating II common digital palmar vein enlargement (arrows).

DISCUSSION

CPL has high occurrence in draft horse breeds, especially, Clydesdales, Shires, and Belgians (Cock *et al*., 2006a) and, recently, Friesian was included as a susceptible breed, thus suggesting genetic content for disease development (Cock *et al*., 2003; Affolter, 2013; Keyser *et al*., 2014; Affolter *et al*., 2020). A previous study observed minor elastin content in dermis biopsies of susceptible draft horse breeds when compared to other draft horse breeds with no previous reports of CPL, such as Percheron (Cock *et al*., 2006b). In this study, the stallion was a Friesian horse, previous reported as a susceptible breed. The gender is not related to disease manifestation, although male horses frequently develop disease when they are older, with accelerated progression (Keyser *et al*., 2014).

CPL symptoms frequently begin at the age of two years; however, long hair in limb extremities of draft horses hamper early detection of disease signs and the lesions are identified when itching starts during secondary infection (bacterial or parasitic) (Affolter, 2013; Affolter *et al*., 2020). In the present case report the late manifestation or identification may be a consequence of intense hair coverage on distal limbs or late manifestation in males, both of which are associated with lack of knowledge about this disease in Brazil (Keyser *et al*., 2014).

Chronic and progressive, as the name suggests, CPL affects distal limbs causing progressive enlargement, soft tissue deformation and aberrant skin aspect. When the disease progresses and affects dermis, subcutaneous and adjacent tissues, the entire limb can lose its original shape (Keyser *et al*., 2014). In the late stages the disease culminates in fibrosis, skin nodulations and folds, first on the pastern, then can ascend to the carpus or tarsus (Affolter, 2013). We found, in this case, macroscopic findings compatible with late-stage CPL.

Forelimbs presented more evolved lesions reaching the carpus region whereas in the hind limbs, nodulation and fibrosis were palpated, but restricted to half to distal metatarsus. The grade of previously proposed lesion ratings varies according to the number and thickness of skin folds, limb enlargement and number and region of fibrous nodulations (Cock *et al*., 2006a). All four limbs of the presented horse fitted into the most severe grade (grade 4), according to the authors above.

CPL is a multifactorial disease that covers genetic and environment interaction (Keyser *et al*., 2014). Before CPL was accepted as a syndrome, uncured distal-limb lesions in horses were diagnosed as chronic pastern dermatitis, which is characterized by crusty, hyperkeratotic-hyperplastic, nodular, or warty dermatitis. Currently, the term CPL is correctly used given the lymphatic compromise in this disease (Keyser *et al*., 2014). In our case, pastern dermatitis was first suspected. However, the lack of response to conventional treatment highlighted the possibility of some unknown components.

Ulceration observed on skin folds was associated with skin trauma resulting in erosion, ulceration, and hemorrhaging. The integrity loss of skin barrier perpetuates the inflammation, impedes lymph drainage, and contributes to secondary infection and lymphoedema progression (Affolter *et al*., 2020).

The left forelimb lameness may have more than one cause, since there was deep soft tissue infection and osteoarthritis signs in distal interphalangeal joint, with bone remodeling of the second phalanx and a large enthesophyte on a common extensor tendon insertion of the distal phalanx (Ramos *et al*., 2020). Mechanical movement restriction was also described as a consequence of intense fibrosis of the limb, nodulation and skin folds, which when surrounding the entire region, can restrict movement and result in lameness (Keyser *et al*., 2014). Although, functional lameness is described as caused by fibrosis, the same lesion grade was observed in other limbs without apparent lameness, suggesting that fibrosis was not the main cause in our case.

Fibrinogen is an unspecific acute phase protein that guides the diagnosis and prognosis of inflammatory process in horses, and its elevation is associated with tissue lesion of either infectious or inflammatory cause (Campbell *et al*., 1981; Alonso *et al*., 2020). The related horse had marked hyperfibrinogenemia (800mg/dL) caused by the chronic inflammatory condition associated with CPL.

In the absence of hepatic lesion observed by the normal range for liver enzymes in blood tests, we attribute the hypoalbunemia (Muñoz *et al*., 2010), lower creatinine values (Diago and Señaris, 2020) and hyperglobulinemia (Crisman *et al*., 2008; Muñoz *et al*., 2010) to malnutrition and chronic inflammation. Low creatinine levels are associated with an excessively catabolic muscle state in situations such as intense inflammatory response, malnutrition, and lack of physical activity (Diago and Señaris, 2020). The weight loss marker is associated with lameness severity, since chronic pain results in movement restriction and consequently limits food intake (Tamzali, 2006).

Although *Staphyloccus sp*. and *Dermatophilus congolensis* are the most common agents isolated from CPL skin lesions (Affolter, 2013), in the present study *Streptococcus equi subsp. zooepidemicus* and *Proteus mirabilis* were isolated. These findings did not indicate climatic or environmental interference, given that all the agents cited above are opportunistic pathogens and are found in healthy skin microbiota (Timoney, 2004; Barracco and Bisno, 2006; Westgate *et al*., 2011; Weese and Yu, 2013; Drzewiecka, 2016; Haag *et al*., 2019). Considering the characteristics of secondary infection and the commensal presence of these agents in microbiota, our findings are justified despite the less usual isolation.

Histopathologic findings characterize the presence of bacterial dermatitis and fibrous dermatitis and support the suspicion of CPL with the presence of perivasculitis and enlarged lymphatic vessels (Cock *et al*., 2003; Affolter, 2013). Complementary exams assist in finalizing the diagnosis, but predominantly based on history, breed, and clinical findings. The initial symptoms can be confused with other pastern dermatitis caused by mites, fungi and/or bacterial infections; nonetheless, these infections cannot cause severe symptoms as observed in CPL (Keyser *et al*., 2014).

Radiographic exams permit early detection of skin thickness, tissue folds and nodulations (Keyser *et al*., 2014). In this case, due to advanced disease, nodulations were easily identified. Severe fibrosis resulted in lymph stasis and lymphatic vessel dilatation, usually observed by contrasted radiography of limb lymphatic vessels. Unfortunately, since we could not accomplish this exam, sedation was prioritized for regional perfusion of antibiotics. Before regional antibiotic perfusion, angiography was performed and revealed intense blood vessel enlargement. Similar to what happens to the lymphatic vessels, limb enlargement and fibrosis reduce blood return resulting in vessel dilatation (Cock *et al*., 2003). Angiographic findings support CPL diagnosis.

Previous studies raised the possibility that affected horses could have higher levels of anti-elastin antibodies, which in humans are quantified using an enzyme-linked immunosorbent assay (ELISA) and are important for monitoring severe connective tissue disorder. The ELISA for anti-elastin antibodies was already described for horses (Keyser *et al*., 2012); however, more recently, the real importance of the anti-elastin quantification for CPL diagnosis was not sustained (Keyser *et al*., 2015).

The genetic content of the disease is highly suspected; however, this hypothesis is yet to be proven. Recently, genomic associations were evaluated to investigate CPL in Friesians. The results of the genomic study suggest high complexity and other than the studied nucleotide polymorphisms (Affolter *et al*., 2020). The absence of specific tests for CPL diagnoses highlights the importance of clinical and radiographic findings to identify the disease.

CPL is an incurable disease whose treatment involves intense management changes to detain disease progression. There are three major principles: to treat the secondary infection, to take care of the skin, and to promote lymph transport. Even achieving the three steps, treatment can be disappointing with frequent infection recurrence (Keyser *et al*., 2014). Despite the bad prognosis, in our case, the owner chose to maintain animal's life and institute the support treatment. To contain bacterial infection and parasitic infestation, regional perfusion was started in the cephalic vein with ceftriaxone, and to minimize lymphedema the limbs were bandaged. The severe lameness precluded controlled exercise, which is essential to improve lymphatic circulation. Muscle activity acts as a pump to propel lymph through lymphatic vessels, so the combination of compressive

bandaging, massage and exercise is imperative to improve lymph drainage in horses (Affolter, 2013), resulting in reducing limb enlargement and improving movement (Keyser*et al*., 2014).

Clipping the limb enables visualization of lesions covered by hair and improvement of topical treatment contact. There are frequent descriptions of an owner's reluctance to clip a draft horse's distal limb hair given its importance as a breed characteristic. We highlight the necessity of clipping the affected area to improve diagnoses and lesion treatment (Affolter, 2013). For parasite control two doramectin doses were planned at a 14-day interval as described by Rendle *et al*. (2007) and topical administration of fipronil (Littlewood, 2000; Rendle *et al*., 2007; Affolter, 2013) with routine bathing with selenium-sulfate-based shampoos acting as a keratolytic (Affolter, 2013; Keyser *et al*., 2014). Unfortunately, due to the colic episode with unfavorable progression we could not evaluate the treatment's effectiveness in controlling CPL. Although the animal's death prevented the treatment follow-up, we emphasize the importance of this case description, given the lack of CPL records in Brazil and the difficulty in diagnosing the disease for lack of CPL knowledge by local equine veterinarians. Describing clinical findings along with diagnostic strategies can facilitate early disease detection.

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