Chronic Progressive Lymphedema in Draft Horses

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KEYWORDS

• Lymphedema • Draft horses • Legs • Combined decongestive therapy
• Compression bandages • *Chorioptes bovis*

KEY POINTS

- Chronic progressive lymphedema (CPL) is an ultimately debilitating condition in draft horses.
- Although no permanent treatment is known, diligent management can improve the horses' conditions and prolong their use and life.
- Several factors contribute to this process.
- The high incidence within affected breeds highlights the importance of identifying underlying genetic factors in order to have a fair chance of winning the battle against CPL.

INTRODUCTION

Chronic progressive lymphedema (CPL) is a disabling disorder of many draft horse breeds, including Shires, Clydesdales, Belgian draft horses, Gypsy Vanners, English Cobs, several German draft horse breeds, and Friesians.[1–4] It also has been observed in Percherons in Europe. The clinical presentation resembles primary lymphedema in humans, also referred to as elephantiasis verrucosa nostra.[5–8] The clinical manifestations, etiopathogenesis, diagnostics, and therapies for primary lymphedema in humans have been addressed in several publications.

The horses present with progressive swelling of the distal portions of their legs, which is associated with scaling, marked dermal fibrosis, and the development of skin folds and nodules.[1] Typically, secondary recurrent bacterial and parasitic infections complicate these lesions and contribute to the aggravation of the lymphedema.[4] CPL is likely a multifactorial process with an underlying genetic component. It results in marked disfigurement of the distal extremities and, as such, often leads to lameness and premature euthanasia. Chronic progressive lymphedema has often erroneously been referred to as "chronic pastern dermatitis". The use of this term is discouraged,

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Vet Clin Equine 29 (2013) 589–605
http://dx.doi.org/10.1016/j.cveq.2013.08.007 **vetequine.theclinics.com**
0749-0739/13/$ – see front matter

as it does not take into consideration that the inflammatory changes are secondary to the underlying disturbed lymph drainage. The clinical manifestations, etiopathogenesis, diagnostics, and therapies for CPL have also been addressed in several publications.

CAUSE AND PATHOGENESIS

The exact cause of equine CPL still needs to be elucidated.[6–11] Several studies indicate an altered elastin metabolism that results in an impaired function of the lymphatic system in the distal extremities. Given the high incidence of CPL in certain breeds, a genetic component likely contributes to the development of CPL. Several studies have elucidated that various additional factors contribute to the development of CPL. In summary:

1. Radiographs identify the soft tissue folds and nodules (**Fig. 1**).
2. Lymphangiography illustrates the tortuous and dilated lymphatic vessels in legs of horses with CPL (**Fig. 2**).[1]
3. Lymphoscintigraphy reveals significant accumulation of interstitial fluid and a slower clearance of a particular radiopharmaceutical in legs of horses with CPL, when compared with normal horses (**Fig. 3**).[12]
4. The amino acid desmosine cross-links elastin fibers; its concentration in tissues reflects the amount of elastin. Desmosine within the skin of the neck and distal legs of clinically healthy horses of affected breeds are decreased when compared with other breeds.[13] Once the lesions develop the levels increase.[13]
5. Although elastin levels are generally low in the skin of healthy horses of affected breeds, the clinical lesions are mostly limited to the legs. Occasionally, there may be slight folding of the skin in the neck region. Hydrostatic pressure is considered an important contributing factor to the edema in the distal legs.[13] A higher risk for microtrauma and infections in this area enhances the lymphedema.

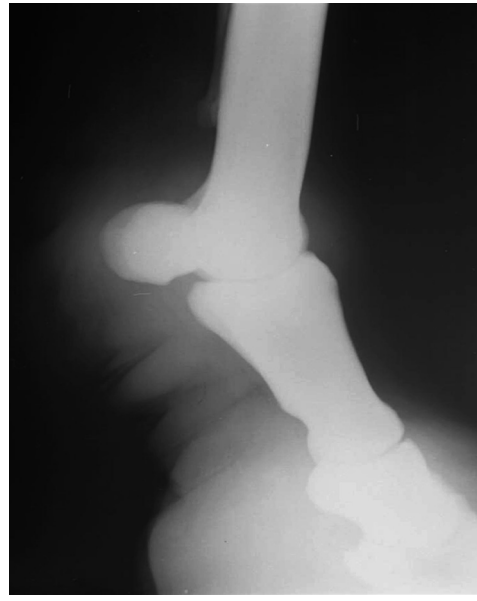

Fig. 1. Radiograph of the lower leg in a horse with CPL identifying the marked soft tissue swelling and formation of folds.

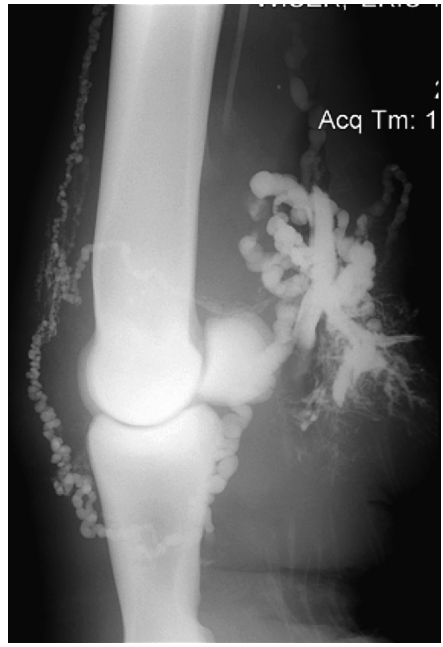

Fig. 2. Lymphangiography of a horse with severe CPL showing tortuous and dilated lymphatic vessels in the distal leg. (*From* De Cock HE, Affolter VK, Wisner ER, et al. Progressive swelling, hyperkeratosis, and fibrosis of distal limbs in Clydesdales, Shires, and Belgian draft horses, suggestive of primary lymphedema. Lymphat Res Biol 2003;3:193; with permission.)

6. Elastin repair and regeneration in adult tissues tends to result in a visually and functionally inappropriate fiber network.[10,14,15] The altered elastin network in affected horses can be visualized with special stains (acid-orcein Giemsa) or by immunohistochemistry using antielastin antibodies.[1,16] There is an increase of morphologically altered elastin fibers in a prominent disturbed arrangement within the superficial and middermis of affected horses when compared with clinically normal horses of affected breeds and horses of other breeds (**Fig. 4**). Dermal lymphatic vessels lack the normal concentric ring of elastin fibers observed in nonaffected breeds (**Fig. 5**).[1,16]
7. Horses with CPL have higher circulating antielastin antibody levels compared with clinically normal Belgian draft horses or healthy Warmblood horses.[17] This indicates tissue damage. Correlation of antibody levels with severity of disease is controversial.[17,18]
8. The high incidence of CPL and the challenge to find unaffected middle-aged or older horses within these breeds clearly indicates a genetic background to this disorder. In Belgian draft horses, CPL occurs after prolonged selected breeding with emphasis for dense feathering and heavier legs; this further suggests a genetic background for CPL. Moreover, certain familial lines of draft horses are more affected than other lines. The genetic predisposition of equine CPL, however, has not been characterized to date. None of the studies have identified a specific genetic marker and or mutation correlated with CPL. The studies performed to date include (1) forkhead transcription factor 2 gene (FOXC2)[19]

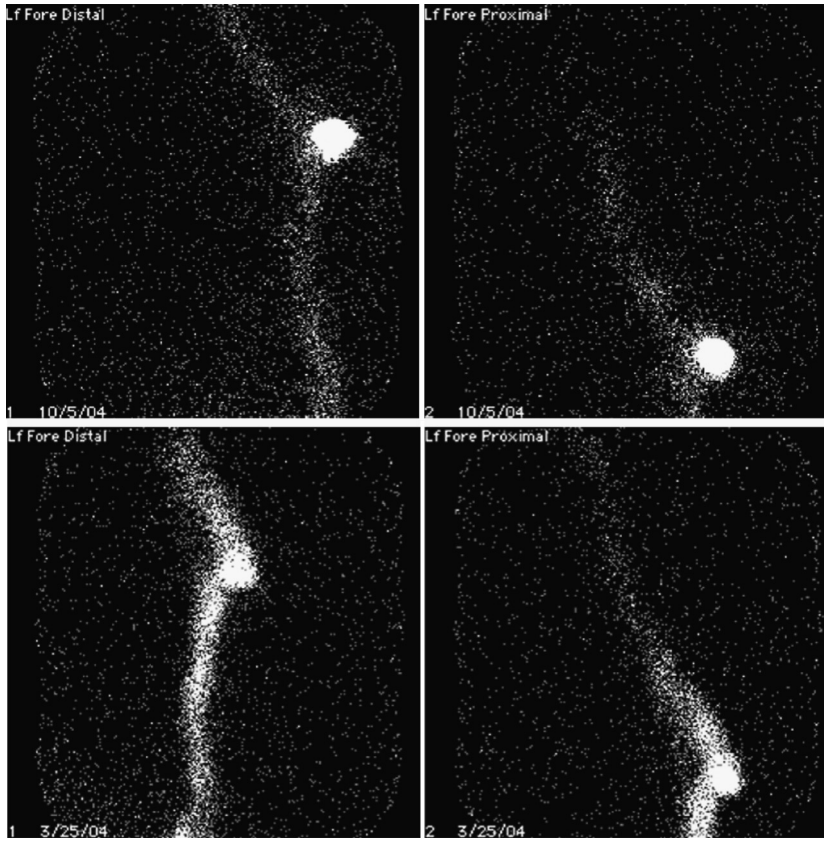

Fig. 3. Lymphoscintigraphy of the distal (*left*) and proximal (*right*) leg. Areas of external activity are added at the level of the accessory carpal bone as an anatomic reference point. In a normal horse there is weak to moderate staining of the contrast media left 30 minutes after injections (*top*) in comparison with a horse with mild CPL (*bottom*). (*From* De Cock HE, Affolter VK, Wisner ER, et al. Lymphoscintigraphy of draught horses with chronic progressive lymphoedema. Equine Vet J 2006;38:150; with permission.)

associated with primary lymphedema and distichiasis in humans, (2) ATP-ase Ca++316-transporting cardiac muscle slow twitch 2 isoform 2 gene (*ATP2A2*) associated with autosomal dominant inherited Darier-White disease, characterized by warty proliferations.[20,21] Four different quantitative trait loci were identified in the German draft horse. Some candidate genes were suggested within four different quantitative loci, but further studies are required.

9. Recurrent and persistent bacterial (*Staphylococcus* sp and *Dermatophilus congolensis*) and/or parasitic (*Chorioptes bovis*) infections are a typical event in horses with CPL.[1–4,22] Similar to primary lymphedema in humans, equine CPL is characterized by impaired circulation and lymph drainage.[7,8] This results in impaired skin barrier function and impaired function of the skin immune system. In addition, the heavy feathering leads to an occlusive environment supporting bacterial growth. With each bout of infection and inflammation, the lymph flow is increasingly impaired similar to the situation in humans with primary lymphedema.

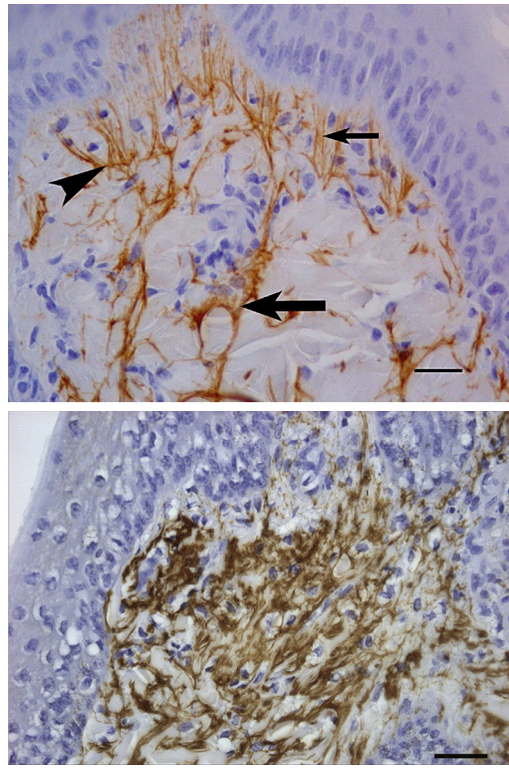

Fig. 4. Immunohistochemistry of elastin fibers using an antielastin antibody (NCL-Elastin, Novocastra, Illinois, USA) and diaminobenzidine as chromogen. Normal dermal elastin network (*top*) is characterized by oxytalan fibers (*small arrow*), the elaunin plexus (*arrowhead*) and the elastic fibers (*broad arrow*). The dermal elastin network of a horse with marked CPL (*bottom*) is disturbed; a dense band of clumped, distorted, and thickened elastin fibers is observed. (*From* De Cock HE, Van Brantegem L, Affolter VK, et al. Quantitative and qualitative evaluation of dermal elastin of draught horses with chronic progressive lymphoedema. J Comp Pathol 2009;140:136–7; with permission.)

10. The epidermal keratinocytes of lesional skin have altered expressions of cytokeratin 5, 6, 4, 10, and 14.[3] Increasingly evident in severe lesions, it is more consistent with a secondary phenomenon rather than the cause of the secondary infections.
11. Environmental factors influence the severity of CPL. With clean rubber flooring the lesions can be better controlled when compared with a sandy or muddy environment. Horses with regular exercise and turn out are less severely affected.

CLINICAL PRESENTATION

The lesions of CPL tend to be more pronounced in the hind legs, but both front and hind limbs can be affected.[1–4] Clinical signs become more evident as disease progresses. The presence of secondary infections markedly enhances the associated skin lesions. **Table 1** summarizes lesions observed and their correlation with severity of disease.

Mild and/or Early CPL

It is very difficult to palpate the early, mild thickening of the legs because heavy feathering obscures the early pitting edema. As a result, early signs of edema and mild

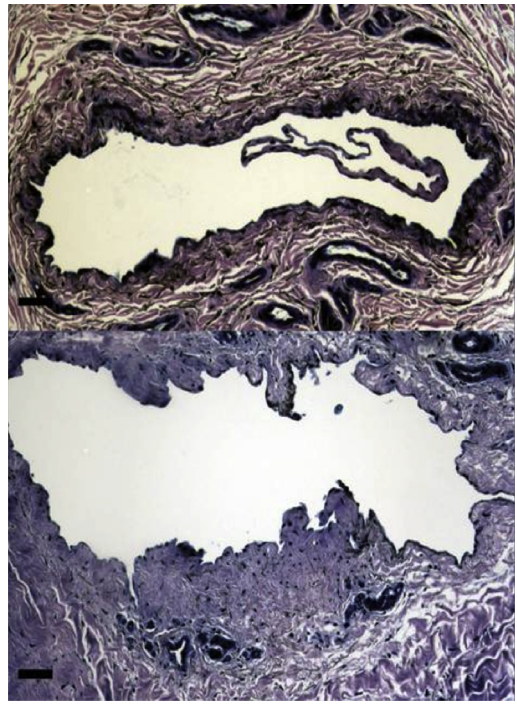

Fig. 5. Elastin network around lymphatic vessels of the deep soft tissues in a normal horse (*top*) using acid-orcein Giemsa. The concentric elastin network is missing in this lymphatic vessel of a horse with CPL (*bottom*). (*From* De Cock HE, Affolter VK, Wisner ER, et al. Progressive swelling, hyperkeratosis, and fibrosis of distal limbs in Clydesdales, Shires, and Belgian draft horses, suggestive of primary lymphedema. Lymphat Res Biol 2003;3:197; with permission.)

hyperkeratosis remain unnoticed. However, careful palpation can identify the lack of clear definition of the cannon bone, flexor tendons, and fetlock. Small ripples, a preliminary sign of subsequent skin folds, can be detected in horses as young as 2 years of age. The skin surface is scaly and often slightly greasy. Clipping of the feathering allows for the detection of early pitting edema and mild skin rippling, in particular in the fetlock and pastern areas (Fig. 6). Typically, owners become aware of the lesions at times of secondary parasitic and/or bacterial infections. Leg stomping and scratching associated with chorioptic mange, as well as oozing and crusting due to bacterial infections, initiate the more careful evaluations of the skin hidden below the dense feathering. Each bout of infection and inflammation will further disrupt lymph flow and increase the lymphedema.[1–4]

Moderate to Severe Chronic CPL

Typically, the lower extremities become more cone-shaped as clear definition of the cannon bone, flexor tendons, and the fetlock joint contours are lost. Prolonged pitting edema results in fibrosis of the skin and subcutis. As a result, the swollen, enlarged legs palpate as being very firm. The progressing fibrosis further impairs lymph flow. In addition to the increased circumference, the number, size, and depth of folds and nodules increases and may measure up to several centimeters (Fig. 7). This is

Table 1
Guidelines to categorize clinical evaluation of CPL using palpation and visual evaluation of skin surface; contour of lower legs; and presence of folds, nodules, and signs of secondary infection

Mild CPL	Moderate	Severe	Extreme
Slight skin thickening Scaling Pitting edema Normal limb diameter Leg definition slightly blurred 1–2 small folds of the pastern (P and PL)	Moderate skin thickening Prominent scaling Exudate, possible erosions, ulcers Increased leg diameter Cone shape of lower leg Firm swelling (brawny edema) Multiple folds, nodules in pastern and fetlock (D, P, PL)	Severe skin thickening Severe scaling Marked exudation, erosions, ulcers Increased limb diameter Firm swelling (brawny edema) Complete lack of leg definition Multiple skin folds, nodules ascending toward carpus or tarsus (D, P, PL) Possible mechanical disturbances	Severe skin thickening Severe scaling Marked exudation, erosions, ulcers Feathering broken Large limb diameter Firm swelling (brawny edema) Complete lack of leg definition extending above carpus, tarsus Numerous skin folds, nodules ascending to and above carpus or tarsus; circumferential Folds and nodules alopecic and ulcerated Severe mechanical impairment Possible secondary lymphangitis
Slight skin thickening Scaling Pitting edema Normal limb diameter Leg definition slightly blurred 1–2 small folds of the pastern (P and PL)			

Abbreviations: D, dorsal; P, palmar; PL, plantar.

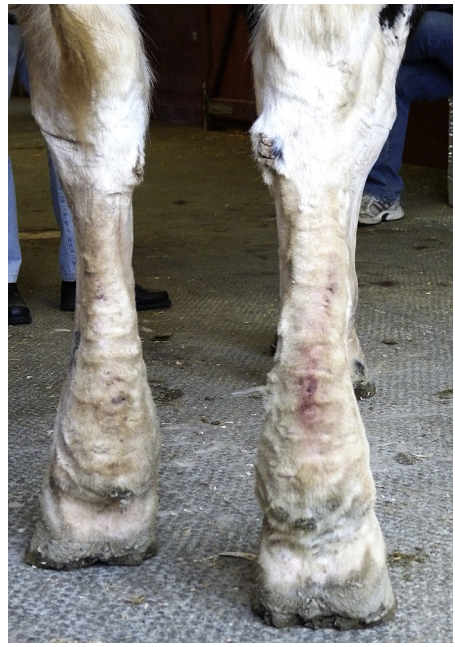

Fig. 6. Gypsy Vanner mare, 6 years old, with mild CPL. After clipping the feathering, it is evident that there is swelling of the pasterns, fetlocks, and lower areas of the cannon bones resulting in a slight cone shape of the lower extremity. The skin is slightly rippled and there are small folds in the pastern.

most evident in the palmar and plantar area of the pastern region, but extends proximally to the fetlock and, eventually, up to carpus and tarsus (**Fig. 8**).[1–4]

The skin surface is extremely scaly, often moist, and occasionally greasy. Unattended legs routinely have evidence of secondary infections: staphylococcal species

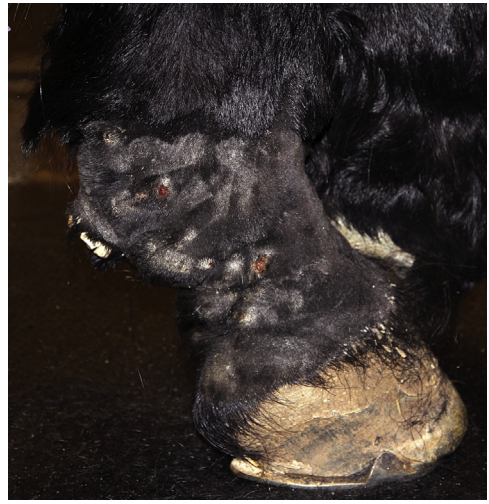

Fig. 7. Friesian mare, 8 years old, with moderate CPL. In addition to the swelling of the lower extremity, there are numerous firm skin nodules and folds, some of them eroded and ulcerated.

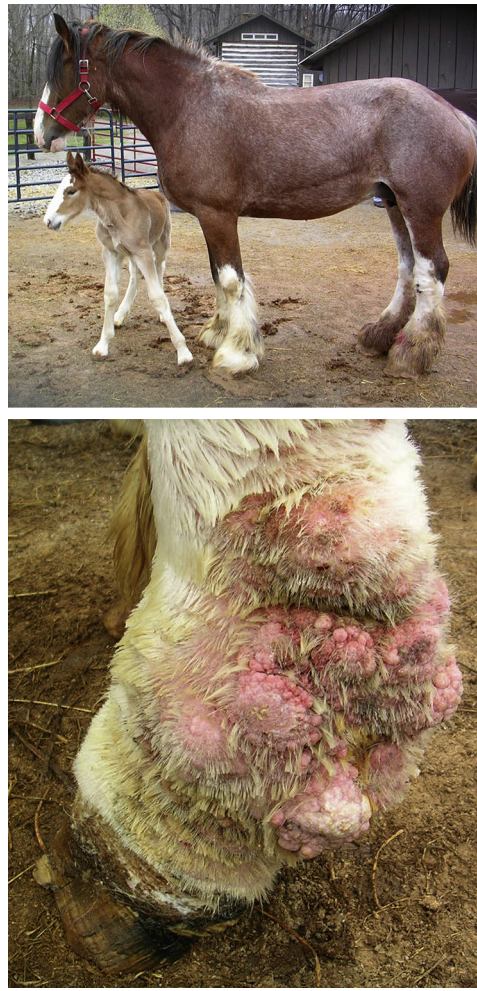

Fig. 8. Clydesdale mare, 13 years old, with severe CPL (*top*). The feathers are clumped and partially blood stained from the oozing skin lesions and both hind legs are swollen to the hock joints. Milder discoloration of the feathers is seen on the palmar region of both front legs and the swelling of the pastern area is still hidden by the feathering. After clipping of the feathers, the hind legs (*bottom*) reveal severe swelling, thick folds, and nodules with markedly irritated, erythematous skin surfaces. The coronary band is irregular and bulging.

and/or *C bovis* mites are the most common pathogens observed. Occasionally, *D congolensis* or other bacteria are isolated from the lesions. *C bovis* infections elicit marked pruritus, clinically evidenced by stomping the feet or rubbing the legs.

Many nodules, folds, and (occasionally) the skin in between become eroded and ulcerated (Fig. 9), either due to the trauma induced by constant scratching, interference with the gait, and/or impaired tissue perfusion.

By the time owners become overly concerned about the changes, the lesions have significantly progressed. The lesions may not be only pruritic but also painful, and many horses become very reluctant to have their legs touched. The periods between recurrent infections become shorter due to severely impaired lymph drainage and

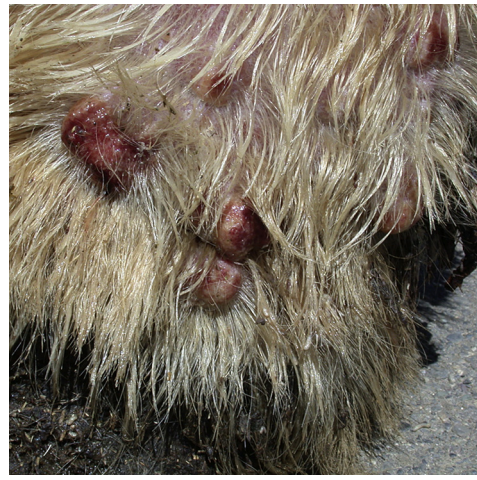

Fig. 9. Shire, 13 years old, with severe CPL. The fibrotic nodules are ulcerated.

tissue perfusion. Despite appropriate antibiotic and antiparasitic therapy, the erosions and the chronic dermatitis persist. The skin surface oozes, bleeds, and is covered with crusts. Persistent infections may affect deeper tissues and induce lymphangitis and swelling of the entire leg. The deep skin folds with the oozing surface are ideal niches for maggot infestation.

Associated Lesions of the Hooves

The coronary band is markedly hyperkeratotic and hyperplastic, which results in broad and deformed hooves of poor quality. The hoof walls are brittle and chipped with splits and cracks. Repeated bouts of thrush and deep hoof abscesses are commonly seen, and some horses develop laminitis.

Ergots and Chestnuts

Usually, CPL-affected horses have irregular, misshapen chestnuts and ergots.

HISTOPATHOLOGY

Diagnostic morphologic lesions are typically seen in hematyoxylin-eosin stained tissue sections of the deep dermis and subcutis.[1] The markedly dilated lymphatics are surrounded by edematous connective tissue that, eventually, transition to severe fibrosis (**Fig. 10**). There are increased numbers of vascular structures. For instance, many arteries have increased numbers of vasa vasorum (see **Fig. 10**). Mild inflammation may surround the lymphatics and vessels. Within the dense fibrosis, there may be encapsulated small abscesses. The inflammation may progress in to the deeper tissues and be associated with lymphangitis. The morphologic changes of superficial biopsy specimens tend to have lesser diagnostic value. There is marked acanthosis and hyperkeratosis. Intraepidermal pustules, erosions, ulcerations, crusts, and luminal folliculitis are observed with secondary infections (see **Fig. 10**). There may be microhemorrhage due to compromised vascular walls.

Acid-orcein Giemsa stains highlight the disturbed elastin network within the superficial dermis. The large, dilated lymphatics in the deeper tissues lack the supportive circular elastin network (see **Fig. 5**).[1,4]

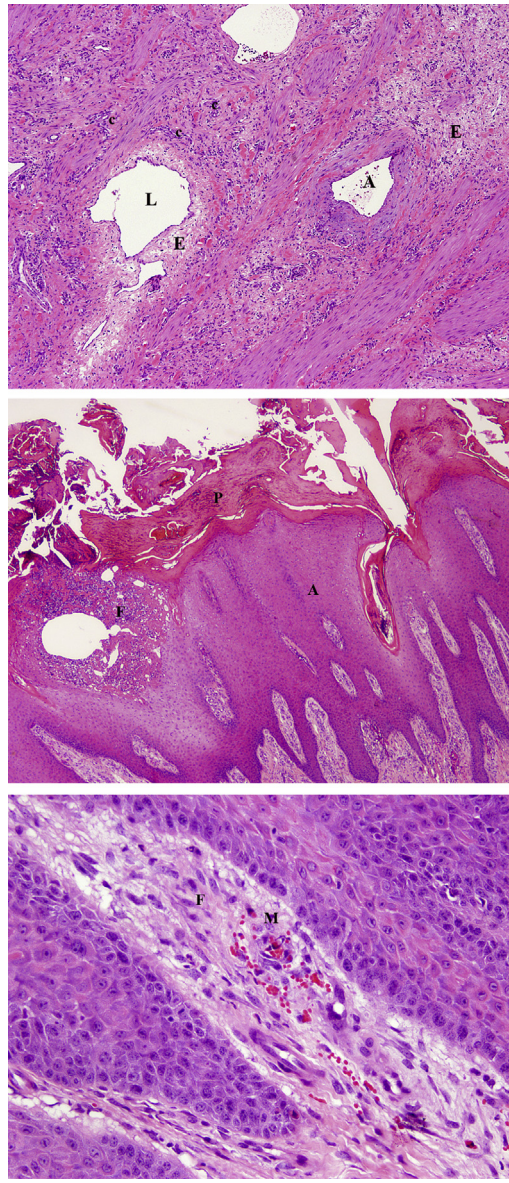

Fig. 10. Histology of skin with CPL. H&E staining. Deep dermis (*top*) of affected horse is characterized by dilated lymphatic vessels (L) with marked subacute edema with early fibrosis (E), increased numbers of small capillaries (C) and occasional arterial wall hyperplasia (A). Secondary infections (*middle*) is associated with a marked acanthosis (A), a thick layer of parakeratosis (P) and a pustule in the infundibular area of the follicle, indicating superficial folliculitis (F). The superficial dermis (*bottom*) may have variable degrees of fibrosis (F) and microhemorrhage (M) indicating vascular wall compromise.

Immunohistochemistry with antielastin antibodies illustrates the disarray of the elastin network (see **Fig. 4**) and the lack of perilymphatic elastin.[4,16]

DIAGNOSIS

The clinical presentation is very diagnostic, particularly in advanced stages. Thorough palpation of the lower extremity is necessary to recognize the early stages of the disease. Often, clipping of the feathers is mandatory to identify the extent of the lesions. If the owner is reluctant to clip the feathers, radiographs can be used to outline clearly the marked soft tissue swelling and folds along with identifying underlying bone and joint lesions. Lymphangiograms illustrate the markedly dilated, tortuous lymphatics in the distal legs. Lymphoscintigraphy ultimately confirms the diagnosis of impaired lymph drainage.[1,12] Although these are effective diagnostic methods to identify even the early stages of the disease, both are not readily available and are very expensive.

Thorough and repetitive skin scraping and tape tests may be necessary to identify *C. bovis* mites. With persistent infections, culture and sensitivity testing is recommended. Regular skin punch biopsies may not always be helpful because diagnostic changes from the deep dermis and subcutis may not be represented. A double-punch biopsy technique is often more rewarding and illustrates the changes of lymphatic vessels and vasculature. The first step in this biopsy technique uses an 8 mm punch through superficial and middermal epidermis. The second step involves driving a 6 mm punch through the previous 8 mm biopsy site to harvest the deep dermis and subcutis.

Diagnostic threshold values of circulating antielastin antibodies have not been broadly established. In the initial study, a correlation between levels of circulating antibodies and severity of lesions was observed.[17] This could not be validated in a subsequent study.[18] Hence, ELISA will likely not offer a reliable screening tool for presence and severity of CPL.

Genetic studies to develop reliable diagnostic screening tests have been unrewarding to date.[19–21]

MANAGEMENT

It is important that owners understand that they are dealing with labor-intesive symptomatic management of a life-long disease and that there is no successful permanent treatment.[23–25] Lesions progress, even if secondary bacterial infections and mite infestations are treated appropriately. Diligent daily care, however, can drastically improve the condition, slow down progression, and help avoid recurrent infections.

The most crucial first step to successful management is clipping the feathers and keeping hairs short. Initially, owners tend to oppose this suggestion vigorously. Therefore, it is important to explain that the extent of the lesions hidden below the feathers can only be assessed accurately after removal of the feathering. Moreover, this will allow access to the skin surface for appropriate topical treatment. Owners can be reassured that feathering can grow back to original lengths in 10 to 12 months.

Treatment of Bacterial Infections

Topical treatment starts with careful, gentle washing (without scrubbing) and drying of the legs. Nonirritating sulfur-based shampoos are recommended. Blow-drying may be required to dry the skin surface completely. Bacterial infections of deep skin folds can be managed with topical antimicrobials. The periodic changing of antimicrobials and correct treatment is important to avoid the development of microbial resistance. With severe bacterial skin infections and evidence of possible lymphangitis systemic antibiotic therapy is indicated.[2]

Treatment of Chorioptic Mange

Topical application of fipronil spray (Frontline, Merial Limited, Duluth, GA, USA) has been used successfully to treat *C bovis* mite infestations. Its use in horses has not been approved by the Food and Drug Administration. It should also be avoided in pregnant and lactating mares. Lime sulfur has also been routinely used for treatment of *C bovis* mites. It is an economical and effective topical treatment and is safe to use in pregnant mares. Wettable sulfur powder ("flowers of sulfur") can be mixed with mineral oil to form a creamy paste and applied to the affected areas. Frequent topical or systemic macrocyclic lactone treatment (eg, eprinomectin, ivermectin) helps prevent reinfestation with mites.[2,26–28]

Environment

To help prevent constant reinfestation with mites, pesticide applications in barns may be necessary. Affected horses need to be kept in a dry environment to avoid prolonged wet and muddy skin.

Daily Exercise and Skin Care

The importance of exercise must be emphasized because it increases circulation as well as lymph flow. Light exercise can be performed with compression bandages. See later discussion on combined decongestive therapy (CDT).

Daily Skin Care

Any irritation to the skin surface must be avoided because it enhances the lymphedema. The use of drying soaps, alcohol, and vigorous scrubbing are contraindicated. Nonirritating sulfur-based shampoos can be used on a regular basis. Keeping the feathers short assists in maintaining cleanliness of the skin surface. Moreover, it is easier to identify new secondary infections earlier. Cold-water rinses are recommended on legs with clipped feathers, in particular after exercise. However, it is important to dry the legs carefully after each rinse. A blow dryer can be used, especially if the feathering is growing back.

Hydrotherapy

A special whirlpool has been designed to treat horses in Belgium (www.paardenjacuzzi.com). In addition to having a cleaning effect, the hydrotherapy will further enhance blood circulation. After treatment, the legs need to be dried very carefully and the horses should be kept on dry clean surfaces for a few hours to ensure complete drying of hair coat and skin surface. It has to be emphasized that the Jacuzzi could potentially harbor bacteria if not meticulously cleaned after each treatment, which, together with the whirling effect, could result in skin infections.

Hoof Care

Routine foot trimming is essential because the hoof quality of horses with CPL is often impaired. Simultaneously, the ergots and chestnuts should be trimmed regularly, if necessary. Any inflammatory state enhances the progression of lymphedema. Daily careful hoof cleaning is important to address any flares of thrush immediately.

CDT

Combined decongestive therapy (CDT) is the most successful treatment of lymphedema in humans. In horses, this is achieved with a two-phase treatment plan that should be performed and overseen by an appropriately trained person. The treatment includes manual lymph drainage (MLD) and compression bandaging. MLD supports

and stimulates the lymphatic system to move accumulated proteins and water from the interstitium back to the circulation. The goal is to move lymph in a "transterritorial" fashion from affected areas to areas where the lymphatic system is functioning adequately. In addition, MLD induces breakdown of indurated fibrotic tissue, which is most prominent within the nodules and folds. Clipping the feathers will make the treatment considerably more effective. For subsequent compression, specialized multilayer short-stretch bandages (eg, Rosidal, Lohmann & Rauscher International GmbH & Co KG, Topeka, KS, USA and Wien, Austria) are applied over carefully padded limbs. The short-stretch bandages create a pressure gradient up the leg.[28–30]

Phase I of CDT

In phase I, daily MLD is followed by immediate specialized multilayer compression bandaging. Keeping bandages applied 24 hours per day and for at least 7 days of the week coincides with the best results. Light exercise such as walking is highly recommended while bandages are left on (**Fig. 11**). The massaging effect of the short stretch bandages during light exercise reduces the edema and swelling. During the early phases of this therapy, the lymphedema will ooze through the skin. This necessitates daily bandage changes. The skin needs to be dried, MLD repeated, and the compression bandage reapplied. This daily routine is repeated until no further reduction of the leg circumference, nodules, and folds is observed and the skin surface has improved.

Phase II of CDT

Phase II is the long-term management of the disease. Skin care is continued. Horses can go back to their regular exercise program. It is important to maintain an appropriate exercise program to support good circulation and lymph drainage. Specialized knitted cotton compression garments (Kerstin Gutberlet Strumpfproduktion u. Handel, Burghbaun, Germany) for horses are available to avoid prompt recurrence of the lymphedema (**Fig. 12**). Occasional, lymph drainage treatments can be applied as needed.

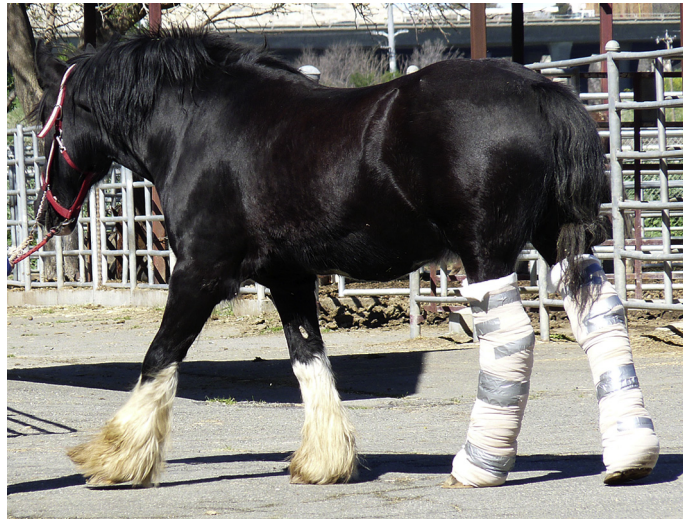

Fig. 11. Shire mare, 16 years old, with moderate CPL. After daily MLD and correctly applied compression bandaging, the mare is hand-walked (light exercise). During movement, the compression bandage has a massaging effect and assists in the movement of lymph from the lower legs back into the circulation.

Fig. 12. Shire mare, 16 years old, with moderate CPL. After completing the phase 1 of the CDT, which includes MLD and subsequent compression bandaging, compression garments (Kerstin Gutberlet Strumpfproduktion u. Handel, Burghbaun, Germany) is used to keep the recurrence of the edema under control.

Surgical Approach with Postsurgical Pressure Bandaging

Similar to techniques used in humans with lymphedema, surgical debulking of nodules or epidermal shaving with subsequent compression bandaging have been described as possible interventions for horses with CPL. However, each surgical intervention will disrupt the lymphatic vascular bed that is already challenged. Moreover, development of exuberant granulation tissue secondary to large wounds in lower extremities is a well-recognized sequela and therapeutic challenge in horses. Therefore, surgical intervention is not highly recommended.[31,32]

SUMMARY

CPL is an ultimately debilitating condition in draft horses. Although no permanent treatment is known, diligent management can certainly improve a horse's condition and prolong its use and life. The high incidence within affected breeds highlights the importance of identifying underlying genetic factors in order to have a fair chance of winning the battle against CPL.

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