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# Litrature Review on Epizootic Lympangentis of Equine

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**Abstract:** Epizootic lymphangitis is a relatively common infectious disease of horses and other equids in certain parts of the world. The infection rate varies according to the geographic area and the age of the animal. The disease is most commonly characterized by a cord-like appearance of the subcutaneous lymphatic and cutaneous pyogranulomas, the discharge from which contains spherical or pear-shaped bodies of the causal agent, *Histoplasma farciminosum that* is seen particularly in the neck, legs and chest. It can also present as an ulcerating conjunctivitis, or rarely a multifocal pneumonia. Transmission is by contact of infected material with traumatised skin, by biting flies, ticks or inhalation. The causative agent, Histoplasma capsulatum var. farciminosum, is a thermally dimorphic, fungal soil saprophyte. Diagnosis can be made by the demonstration of typical organisms in stained smears, culture and tissue sections. Serological tests and a skin hypersensitivity test have been described. Differential diagnoses include glanders (Farcy), caused by Burkholderia mallei, ulcerative lymphangitis due to Corynebacterium pseudotub erculosis, sporotrichosis caused by Sporothrix schenckii and the skin lesions of histoplasmosis caused by H. capsulatum var. capsulatum. Amphotericin B is the drug of choice for the treatment of clinical cases. An attenuated vaccine and a killed formalized vaccine are available and can be used in endemic areas to control the disease.

**Key words:** Epizootic Lymphangitis · Epidemiology · Diagnosis · Treatment · Control

## INTRODUCTION

Epizootic lymphangitis is a contagious, chronic disease of horses, mules and donkeys. The disease is characterised clinically by a suppurative, ulcerating and spreading pyogranulomatous, multifocaldermatitis and lymphangitis [1]. It is seen most commonly in the extremities, chest wall and the neck,butit can also be present asan ulcerating conjunctivitis of the palpebral conjunctiva, or rarely as a multifocalpneumonia [2]. The organism may also invade open lesions including ruptured strangles abscesses and castration wounds. It has also been called pseu dofarcy or pseudoglanders. Another synonym is equine histoplasmosis, which may be a more accurate name for the disease, as not all clinical cases present obvious lymphangitis. The form that the disease takes seems to depend primarily on the route of entry [3]. The traumatised skin is either infected directly by infected pus, nasal or ocular excretions or indirectly by soil or contaminated harnesses, grooming equipment, feeding and watering utensils, wouddressings or flies. It is also believed that ticks may play a role in the transmission of this agent [4].

Epizootic lymphangitis is a debilitating fungal disease seen mainly in equids [5]. The most common form of this disease is an ulcerative, suppurative, spreading dermatitis and lymphangitis; however, otherforms including pneumonia or ulcerative conjunctivitis also occur. Epizootic lymphangitis spreads most readily where large numbers of animals are assembled and it was a serious problem during the early twentieth century when large numbers of horses were stabled together [6]. This disease continues to be a significant concern in some countries such as Ethiopia, where the prevalence in carthorses is nearly 19% and economic lossesfrom this disease are high [7]. The causative agent, *Histoplasma capsulatum* var. *farciminosum*, is a thermally dimorphic fungus. The mycelial form is present in soil; the yeast form is usually found in lesions. *Histoplasma farciminosum* was formerly described as an independent species, but this assessment has been changed and it is now considered to be avariety of *H. capsulatum* due to the close morphological similarities of both the mycelial and yeast forms [8]. Antigenically, *H. capsulatum* var. *farciminosum* and *H. capsulatum* var. *capsulatum* are indistinguishable, however the latter is the cause of disseminated

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histoplasmosis, is endemic in North America and has a wide host range [9]. DNA sequences of four protein coding genes have been analysed to elucidate the evolutionary relationships of *H. capsulatum* varieties [10]. This indicated that *H. capsulatum* var. *farciminosum* is deeply buried in the branch of SAm Hcc group A, (H60 to 64, 67, 71, 74 and 76), looking as if it were an isolate of South American *H. capsulatum* var. *capsulatum* [11].

The cutaneous form of the disease may be confused with farcy (The skin form of glanders), which is caused by *Burkholderia mallei*, ulcerative lymphangitis, which is caused by *Corynebacterium pseudotuberculosis*, indolent ulcers acaused by *Rhodococcus equi*, sporotrichosis caused by *Sporothrix schenckii* and histoplasmosis caused by *H. capsulatum* var. *capsulatum*, cryptococcosis, strangles sarcoids and cutaneous lymphosarcomas [12]. The disease is more common in the tropics and subtropics and is endemic in north, east and northeast Africa and some parts of Asia, including some countries bordering the Mediterranean Sea, India, Pakistan and Japan [13].The disease is common in Ethiopia, especially in cart horses, affecting an average of 18.8% of horses in warm, humid areas between 1500 and 2300 metres above sea level [14]. Reports from other parts of the world are sporadic and all cases must be verified by laboratory testing. The prevalence of the disease increases with assembling of animals; it was much more common, historically, when large numbers of horses were stabled together for cavalry and other transportation needs. Mainly, it is horses, mules anddonkeys that are affected by the disease, although infection may occur in camels, cattle and dogs [15]. Experimentally, other animals are refractory to infection subsequent to inoculation, with the exception of certain laboratory animal species such as mice, guinea pigs and rabbits [7]. Infection in humans has alsobeen reported [16].

The disease is eradicated by the humane slaughter of infected horses, disinfection of infected premises and restricting the movement of equids from infected premises [17]. In endemic areas where eradication is not possible, inorganic iodides can be used for therapy in early cases [18]. Localised nodules can also be lanced, the pus drained and the nodules packed with a 7% tincture of iodine. If affordable, amphotericin B can be used. As the clinical signs of epizootic lymphangitis can be confused with those of other diseases in the field, definitive diagnosis rests on laboratory confirmation [19].

**Etiology:** Epizootic lymphangitis results from infection by adimorphicfungus, *Histoplasma capsulatum* var. *farciminosum* [20]. This organism has also been known as *Histoplasma farciminosum*, *Cryptococcus farciminosis*, *Zymonema farciminosa* and *Saccharomyces farciminosus* [21]. *H. capsulatum* var. *farciminosum* exists as a yeast in animal tissues and a saprophytic mycelium in the environment. Recent genetic evidence suggests that the isolates causing epizootic lymphangitis originated independently from different geographical clades of *Histoplasma capsulatum.* Based on this evidence, some authors question the existence of the variety *H. capsulatum* var. *farciminosum* and consider epizootic lymphangitis to be aform of histoplasmosis, caused by *H. capsulatum,* that occurs in horses [22].

**Epidemology**

**Species Affected:** Epizootic lymphangitis mainly affects horses, donkeys and mules. *H. capsulatum*var. *farciminosum* has also been reported in camels, cattle and dogs and experimental infections have been established in mice, guinea pigs and rabbits [23].

**Geographic Distribution:** Epizootic lymphangitis is more common in tropical and subtropical regions than in temperate zones [24].

Currently, *H. capsulatum* var *farciminosum* is endemic in somecountries in the Mediterranean region and in parts of Africa and Asia including India,Pakistan and Japan. Sporadic cases have been reported from other parts of the world [25].

**Transmission:** *H. capsulatum* var. *farciminosum* infects animals through wounds. Both the yeast form found in animals and the mycelial form in the environment can produce epizootic lymphangitis after experimental inoculation [3]. The source of the organisms can be the skin lesions and nasal and ocular exudates of infected animals, or the soil.In its saprophytic mycelial phase, *H. capsulatum* var. *farciminosum* can survive for many months in warm, moist environments.This organism can also be spread on fomites such as grooming or harness equipment. Biting flies in the genera *Musca* and *Stomoxys* are thought to spread the conjunctival form [26]. Flies may also transmit the skin form mechanically when they feed on lesions and exudates [27]. Ticks might be involved in transmission; in a recent study, tick bites appeared to be a predisposing factor for epizootic lymphangitis in mules.

The pulmonary form, which is rare, probably develops when an animal inhales theorganism [28].

**Incubation Period:** The incubation period is usually several weeks to 2 months [25]. In a recent study, the incubation period was much longer in a horse inoculated with mycelialorganisms than in a horse inoculated with the yeast form Ameni *et al*. [29].

**Morbidity and Mortality:** Epizootic lymphangitis is more common in the tropics and subtropics than in temperate areas. Warm, moist conditions allow the organism to survive in the soil formonths [30]. The incidence of this disease is much higher when large numbers of animals are gathered together than when populations are less dense. The prevalence can be high in some areas [31].In Ethiopia, nearly 19% of thecarthorses in warm, humid areas are affected and theoverall prevalence was 21% among mules in two towns.Death is uncommon if an animal is in good condition and receives good care, but animals with extensive lesions may die [32].

**Pathogenesis:** The incubation period ranges from several weeks to six months [33]. Following the initial invasion of the skin, the organism spreads through the lymphatic vessels to the regional lymph nodes and in more advanced cases involves the internal organs. Nodular and chronic suppurating lesions are evident in the skin overlying lymph vessels and nodes [34]. When mucosal lesions occur, most are confined to the upper respiratory tract and eyes [35]. The nasal infection is usually accompanied by mucopurulent discharge containing large numbers of the fungus. In the Sudan, *H. farciminosum* has been isolated from granulomatous lung lesions of two horses suffering from pneumonia [3, 36[. A fatal pneumonia due to *H. farciminosum* has been reported in an immunosuppressed foal [37].

**Clinical Signs:** The most common form of epizootic lymphangitis affects the skin and lymphatics [38]. It often occurs on the extremities, chest wall, face and neck, but can beseen wherever the organism is inoculated into a wound.The first symptom is apainless, freely moveable intradermal nodule, approximately 2 cm in diameter [39]. This nodule enlarges and eventually bursts. In some cases, the lesions may be small and inconspicuous and heal spontaneously. More often, the skin ulcers grow, with cycles ofgranulation and partial Healing followed by new eruptions [40]. The surrounding skin is edematous at first and later becomes thickened, hard and variably painful. The skin over the nodules may be fixed to the underlying tissues [33].

The regional lymph nodes can be enlarged, but fever is uncommon. The infection also spreads along the lymphatics, causing cord like thickening And further skin involvement. These cycles of exacerbation and partial healing gradually resolve, leaving only ascar.The process usually takes about 2 to 3 months. Epizooticlymphangitis sometimes spreads to the underlying joints and results in severe arthritis [41]. Occasionally, there may be ulcerative conjunctivitis, keratoconjunctivitis, a serous or purulent nasal discharge, or pneumonia. Extensive lesionscan end in death; this usually occurs in areas where animals are in poor condition and veterinary care is limited.In dogs, both cutaneous infections and infections that disseminate to internal organs have been reported [36].

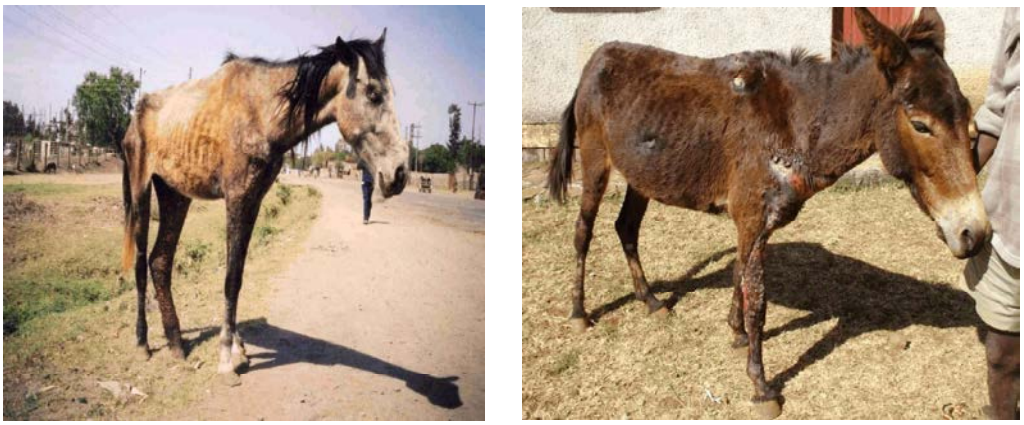

Fig. 1: Infected equine shows cord like lesion, source [42].

**Post Mortem Lesions:** At necropsy, areas of the skin and subcutaneous tissueare thickened and the skin may be fused to the underlying tissues. The regional lymph nodes maybe enlarged andinflamed [43]. Nodules in the skin have a thick, fibrous capsuleand the affected lymphatic vessels are usually thickenedor distended. Both nodules and lymphatics containpurulent exudates. In some cases, the lesions may extendto the underlying joints, resulting in arthritis, periarthritis or periostitis [44]. Multiple, small, graywhite nodules orulcers with raised borders and granulating bases may be apparent on the nasal mucosa and lesions may be foundon the conjunctiva and cornea [45]. The lungs, spleen, liver, testes and other internal organs may alsocontain nodulesand abscesses [46].

**Diagnosis**

**Clinical:** The symptoms are highly suggestive in cases with skin lesions [47]. Epizootic lymphangitis should be suspected in horses, mules or donkeys with skinnodules or ulcers that follow a pattern of partial healing followed by renewed eruption. This disease must be differentiated by laboratorytests from other conditions such as glanders [48].

**Samples to Collect:** Before collecting or sending any samples fromanimals with a suspected foreign animal disease, the proper authorities should be contacted. Samples should only be sent under secure conditions and to authorized laboratories to prevent the spread of the disease [49]. Rare human infections with *H. capsulatum var farciminosum* have been reported and pre cautions should be taken to prevent zoonotic disease. Samples should be collected from unruptured nodules for culture. These samples should be placed in a liquid nutrient medium that contains antibacterials. They should be kept refrigerated and sent to the laboratory on wet ice as soon as possible [50]. Airdried smears from exudates should be prepared on glass slides and fixedimmediately for direct examination. Samples of lesions that include both viable and nonviable tissue should be collected in 10% neutral Buffered formali for histopathology. Serum samples should also be submitted for serology [51].

**Laboratory Tests:** Epizootic lymphangitis can be diagnosed by detecting *H. capsulatum* var. *farciminosum* in lesions. Histopathology or the direct examination of smears from exudates is helpful in diagnosis. In established lesions, the organisms may be numerous [52]. Tissue sections can be stained with hematoxylin and eosin, periodic acid Schiff or Gomori methenamine silver staining [23]. In a Gram stained preparation *H. capsulatum*is a Gram positive, pleomorphic, void to globose structure that is approximately 2-5 µm in diameter.

Organismsare found extracellularly or in macrophages and can be seen singly or in groups. Each yeast isoften surrounded by a capsule, which does not stain and appears as a halo [53]. An immunofluorescent technique to demonstrate *H. capsulatum* has also beendeveloped [54]. Electron microscopy may be used on skin biopsy samples. *H. capsulatum* var *farciminosum* can be cultured on avariety of fungal media including mycobiotic agar, enriched Sabouraud's dextrose agar with 2.5% glycerol, brain heart in fusion agar with 10% horse blood and pleuropneumonia like organism (PPLO) nutrient agar with 2% dextrose and 2.5% (pH 7.8) [55].This organism grows as amycelium at cooler temperatures. These colonies growslowly and develop in approximately 2 to 8 weeks at 26°C.They aredry,granular, wrinkled and grayish-white, becoming brown as they age [56].

Aerial forms are rare. On microscopic examination, the hyphae are hyaline, septate,branched, Pleomorphic and Gramstain variable [57]. A variety of conidia including chlamydospores, arthroconidia and blastoconidia may be found, but *H. capsulatum*var *farciminosum* does not produce the large, round, double walled macroconidia often seen in *H.capsulatum* var.*capsulatum* cultures [58]. Isolation may fail in up to half of the cases. Conversion to the yeast form can be demonstrated35 37°C bysubculturing the mycelium into brain heart infusion agar containing 5% horse blood, or by growing the organism in Pine's medium in 5% CO2[59]. The yeast phase forms colonies that are flat, raised, wrinkled, white tograyish brown and pasty. Complete conversion occurs only after repeated serial transfers to fresh media. Animal inoculation into immuno suppressed mice or other laboratory animals has also been used for diagnosis [60]. Antibodies can usually be found in animals with clinical signs. Serological tests include fluorescent antibody tests, enzyme linked immunosorbent assays (ELISA) and passive hemagglutination. Skin hypersensitivity tests can be used to detect cell-mediated immune responses [61].

**Gram Stain Smear:** Smears can be stained directly with Gram's stain and examined for the typical yeast form of the organism, Which appear as Gram positive, pleomorphic, ovoid to globose structures, approximately 2-5 µm in diameter [62]. They may occur singly or in groups and may be found either extracellularly or within macrophages. A halo around the organisms (Unstained capsule) is frequently observed [63].

**Histopathology:** In haematoxylin and eosin (H&E) stained histological sections, the appearance of the lesion isquite characteristic and consists of pyogranulomatous inflammation with fibroplasia [64]. Langhans giant cellsare common. The presence of numerous organisms, both extracellularly and intracellularly within macrophages or multinucleated giant cells in tissue sections stained wi H&E, Periodic acid–Schiff reaction and Gomori methenamine silver stain are observed [65]. There is some indication that the number of organisms increases with chronicity. The organisms arepleomorphic, often described as slightly lemon shaped basophilic masses, varying from 2 to 5 µm indiameter, that are surrounded by a 'halo' when stained with H&E or Gram's stain [37].

**Differential Diagnosis:** The differential diagnosis includes the skin form of glanders (Farcy), strangles, ulcerative lymphangitis, sporotrichosis, cryptococcosis, sarcoids and cutaneous lymphosarcoma [66]. Epizooticlympangitis are also resembles histoplasmosis,which is caused by *Histoplasma capsulatum* var. *capsulatum* [41].

**Treatment:** Epizootic lymphangitis is a chronic disease, although some cases may heal spontaneously a few weeks after the development of clinical signs [67]. Intravenous dosing of iodide may be used; this type of treatment is a satisfactory procedure, particularly in endemic areas. The intravenous injection of 100 ml of sodium iodide of a 10% solution, repeated weekly for four weeks, gives good results. Different antifungal drugs have also been used and successful treatment with amphotericin B has been reported [68]. The infected horses were treated with an intravenous injection of amphotericin B at a dose of 0.2 mg/kg body weight three times on alternate days. The scabs were removed and the areas cleaned daily with an iodine solution for seven days. The lesions should heal fully within four weeks. *In vitro* testing, at a concentration of 50 mol/ml to 100 mol/ml of amphotericin B inhibited strongly the growth of the yeast phase of *H. farciminosum* [42]. Administration of griseofulvin, repeated if necessary, has given good results when combined with iodides and local surgical treatment. The surgical treatment usually consists of opening the nodules and packing with gauze soaked in 7% tincture of iodine [69].

**Control:** Epizootic lymphangitis can be controlled or eradicated by quarantines and the euthanasia of infected animals. Screening may help identify cases. Infected premises and equipment must be thoroughly cleaned and Disinfected [70]. *H. capsulatum* can be inactivated by 1% sodium hypochlorite, glutaraldehyde, formaldehyde and phenolic disinfectants. Its susceptibility to 70% ethanol is questionable.This organism is also destroyed by moist heat of 121°C for at least 15 minutes. Bedding should be burned [71]. Organisms in the soil may survive for long periods. In endemic areas, good cleaning and disinfection can help prevent *H. capsulatum* var*farciminosum* from spreading between animals. Care should be taken to prevent transmission on grooming equipment or harnesse [72]. Early cases may be treated with Sodium or potassium iodide, but the lesions may later recur. Amphotericin B has also been used, but it is more expensive [73]. In some cases, nodules may be drained and packed with iodine, or excised surgically.Vaccines are not widely available; however, live and inactivated vaccines have been used in someendemicregions. Published reports suggest that some of these vaccines may be promising [72].

**Public Health:** Rare human infections by *Histoplasma capsulatum* var.*farciminosum* have been reported.

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