Epizootic Lymphangitis

Pseudoglanders,
Pseudofarcy,
Equine Histoplasmosis,
Histoplasmosis Farciminosi,
African Farcy,
Equine Blastomycosis,
Equine Cryptococcosis

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Importance

Epizootic lymphangitis is a debilitating fungal disease, caused by some isolates of *Histoplasma capsulatum*, which mainly occurs in equids. Its most common form is an ulcerative, suppurative, spreading dermatitis and lymphangitis; however, some animals can develop lesions in other organs, particularly the respiratory tract or eye. 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. This disease has now become uncommon in most countries, though it can still be a significant concern in some areas. Most recent descriptions are from Ethiopia, where equids are widely employed as work animals, epizootic lymphangitis is common, and effective treatment can be unaffordable, leading to uncontrolled spread of the organism and significant economic losses. Rare clinical cases that appear to be caused by the same organism have also been reported sporadically in other species such as dogs, cats and badgers. Some of these cases were recognized in countries thought to be free of epizootic lymphangitis.

Etiology

Epizootic lymphangitis results from infection by a dimorphic fungus, *Histoplasma capsulatum*, which exists as a yeast in animal tissues and a saprophytic mycelium (mold) in the environment. This organism is a member of the family Ajellomycetaceae and order Onygenales. Its teleomorph stage is called *Ajellomyces capsulatus*. Traditionally, *H capsulatum* has been divided into three subspecies: *H. capsulatum* var. *capsulatum*, which causes most cases of histoplasmosis, especially in the Americas; *H. capsulatum* var. *duboisii*, which occurs in Africa and has mainly been reported in humans; and *H. capsulatum* var. *farciminosum*, which causes epizootic lymphangitis. Some former names for *H. capsulatum* var. *farciminosum* include *Histoplasma farciminosum*, *Cryptococcus farciminosis*, *Zymonema farciminosa* and *Saccharomyces farciminosus*.

Whether these three subspecies are still valid is unclear. Some genetic studies suggest that some *H. capsulatum* var. *farciminosum* and *H. capsulatum* var. *capsulatum* isolates belong to the same clade, and some authors now consider epizootic lymphangitis to be a form of histoplasmosis, caused by *H. capsulatum*, that occurs in horses. However, *H. capsulatum* var. *farciminosum* does seem to be associated with a distinct, mostly cutaneous, clinical syndrome in equids and other species, and some research papers and reviews continue to use the subspecies names. At present, there does not seem to be a useful alternative until the status of this organism is resolved.

Species Affected

Epizootic lymphangitis mainly affects horses, donkeys and mules. There do not seem to be any reports of this disease in zebras or other wild equids. *H. capsulatum* var. *farciminosum* has also been found in camels, cattle, dogs, cats and at least one wild badger (*Meles meles*), and experimental infections have been established in mice, guinea pigs and rabbits.

Zoonotic potential

Whether *H. capsulatum* var. *farciminosum* is zoonotic is still uncertain. This organism has been reported from only a few clinical cases in people, and some identifications were later found to be unsubstantiated. *H. capsulatum* var. *capsulatum*, which causes most human cases of histoplasmosis, is normally acquired by inhaling microconidia from its saprophytic form in the environment, and zoonotic or person-to-person transmission of this subspecies has not been reported. *H. capsulatum* var *duboisii* is poorly understood, but it is also thought to be acquired from the environment. However, *H. capsulatum* var. *farciminosum* often spreads as a yeast between horses, with large numbers of organisms in some exudates, and it might be more likely to infect susceptible humans (especially those who are immunosuppressed) than the other two subspecies.

Geographic Distribution

The distribution of *H. capsulatum* var *farciminosum* is unclear; however, it seems to occur mainly or exclusively in the Eastern Hemisphere, and it is most common in tropical and subtropical regions. In the past, epizootic lymphangitis was reported to be endemic in the Middle East, some countries in southern Europe (e.g., Italy, southern France), certain regions in sub-Saharan Africa, and parts of Asia including Russia, India, Pakistan, China and Japan. Historically, clinical cases also occurred in other countries, such as the U.K. and Ireland, and some *H. capsulatum* isolates from Poland in the 1960s were identified as *H. capsulatum* var. *farciminosum*. Epizootic lymphangitis is no longer reportable to the World Organization for Animal Health (OIE), but case reports have documented infections in some of the regions where *H. capsulatum* var. *farciminosum* was formerly endemic. The vast majority of these reports describe cases in Ethiopia, but the organism has also been detected in some other countries, including Japan and Thailand. Unusually, several indigenously acquired clinical cases occurred in small animals and wildlife in European nations including France, Germany and Switzerland.

Because culture and definitive identification is not always done, the identification of *H. capsulatum* var *farciminosum* is complicated by its co-circulation with .*H. capsulatum* var *capsulatum* in some regions. All three subspecies occur in Africa, and possibly in India.

Transmission

Both the yeast form of *H. capsulatum* var. *farciminosum*, found in animals, and its saprophytic mycelial form (mold) in the environment can infect animals. Most animals are thought to be infected by direct contact with yeasts, which occur in exudates from skin lesions, nasal and ocular secretions and other affected sites. One study found evidence for nucleic acids in the blood, including samples collected from some asymptomatic animals, though the significance of this finding is still unclear.

Most animals are thought to become infected through breaks in the skin, but *H. capsulatum* var. *farciminosum* can also invade mucous membranes (e.g., the conjunctiva or nasal mucosa), and some cases affecting the respiratory tract are thought to be acquired by inhalation. Apparent sexual transmission was described from stallions to mares. *H. capsulatum* var. *farciminosum* can be spread on fomites such as grooming or harness equipment, and biting flies, e.g., members of the genera *Musca* and *Stomoxys*, appear to transmit it mechanically. Flies may be particularly important in contaminating the eye. One study found an association between tick bites and epizootic lymphangitis in mules, raising the possibility that ticks might also play some role.

Few studies have investigated the life cycle or persistence of *H. capsulatum* var. *farciminosum* in the environment; however, it is reported to remain viable for at least a month in the dust of stables or kraals, for up to 10 weeks in non-sterile water (26°C/79°F), and for at least 2 years desiccated in the laboratory. It is said to survive for many months in warm, moist environments. Its environmental stage is probably very similar to that of *H. capsulatum* var *capsulatum*, which is a saprophyte that mainly occurs in the soil. *H. capsulatum* var *capsulatum* grows best in moist, acidic soils that are rich in nitrogen (e.g., soils enriched with feces from birds and bats), such as those in caves, hollow trees and chicken pens. Studies have found that this subspecies can survive for more than 10 years in soil, and it can probably grow indefinitely in suitable environments.

Disinfection

H. capsulatum is reported to be susceptible to 1% sodium hypochlorite, peracetic acid, at least one iodophor, glutaraldehyde, formaldehyde, 70% ethanol and phenolic disinfectants. It can be killed by autoclaving (moist heat of 121ºC/ 250ºF for at least 15 minutes), and burning has been recommended for destroying bedding from infected animals. *H. capsulatum* spores and yeast cells are reported to be inactivated by prolonged exposure to temperatures higher than 40ºC (104ºF).

Incubation Period

The incubation period is usually several weeks to 2 months, with some sources describing incubation periods up to 6-7 months or even a year. One study, which used only two horses, suggested that clinical cases appear much sooner in animals inoculated with yeasts than the saprophytic environmental form.

Clinical Signs

Epizootic lymphangitis can affect many organs and tissues, but most cases in equids involve the skin and lymphatics, underlying bones and joints, respiratory tract and/or conjunctiva. This disease mainly results in pain and debilitation; however, extensive lesions can be fatal, especially if animals are in poor condition and veterinary care is limited or absent, or when the respiratory tract is affected.

Cutaneous disease is the most commonly reported syndrome, with or without ocular signs and respiratory involvement. Skin lesions can develop wherever the organism is inoculated into a wound. In working carthorses in Ethiopia, lesions tend to be found on the legs, chest wall, face and neck, a distribution that probably reflects sites of contact with harnesses. The first sign is a painless, freely moveable small skin nodule or skin papule, which enlarges and eventually bursts, becoming an ulcer with a thick, purulent exudate that may sometimes be bloody. In some cases, the initial lesions can be small and inconspicuous, and heal spontaneously. More often, they grow and spread, with cycles of granulation and partial healing followed by new pyogranulomatous eruptions. Many infections also spread along the lymphatics, causing new nodules, cord-like thickening of the lymphatics, and further skin involvement. In some cases, the skin lesions remain localized to one area

of the body; in others, they spread more widely. In extreme cases, they may affect most of the body. The skin surrounding the lesions is edematous at first, and later becomes thickened, hard and variably painful, and may become fixed to the underlying tissues. The regional lymph nodes are often enlarged, but fever is uncommon. Sometimes the infection also invades the underlying joints, resulting in severe arthritis. In some animals, the cycles of exacerbation and partial healing gradually resolve, usually within 2-3 months, leaving only a scar. However, other cases may become chronic. Animals with severe, non-resolving skin lesions lose condition, eventually becoming debilitated and anorectic.

Ocular disease usually appears as ulcerative conjunctivitis or keratoconjunctivitis, with papules and button ulcers on the conjunctiva and/or nictitating membranes. Some animals may develop secondary bacterial infections or invasive lesions such as corneal ulcers or panophthalmitis. Ocular lesions occasionally spread to the lacrimal duct (which may become occluded), periorbital tissues and/or the skin of the face.

Respiratory involvement can occur alone or with other signs, including as a late complication of skin lesions. Respiratory signs were relatively common in historical outbreaks but seem to be infrequent in recent reports. The lesions mainly involve the upper respiratory tract, and are characterized by yellowish, ulcerating papules and nodules on the mucosa. They occasionally affect the lungs, and pneumonia is possible.

H. capsulatum var. *farciminosum* has been found in a few clinical cases in other species, including dogs, cats and at least one wild badger. Most cases resembled the cutaneous form of epizootic lymphangitis in equids, with skin ulcers, nodules and granulomatous lesions. The gingiva was also affected in some dogs. Unlike histoplasmosis caused by *H. capsulatum* var *capsulatum* in the Americas, the internal organs were not affected in most animals. Nevertheless, there was at least one case of disseminated disease in a dog, and the full clinical picture might not be apparent with the limited number of cases reported to date.

Post Mortem Lesions

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At necropsy, areas of the skin and subcutaneous tissues are thickened and fibrotic, and contain nodules, ulcers and thickened lymphatics. Cutaneous nodules have a thick, fibrous capsule, and both nodules and lymphatics contain purulent exudates. In some cases, there may be arthritis, periarthritis or periostitis in the underlying joints and bones. The regional lymph nodes are usually enlarged, and may contain purulent foci, which are sometimes encapsulated, or ulcerated lesions. In some animals, papules or button ulcers may be detected on the conjunctiva, nictitating membrane or cornea. Multiple small, gray–white or yellowish papules, nodules or ulcers with raised borders and granulating bases are sometimes apparent in the nasal cavity, nasal sinuses, pharynx, larynx and/or bronchi. Purulent lesions and nodules are occasionally found in the lungs. Other internal organs, such as the spleen, liver or testes, may also contain nodules or abscesses, though this does not seem to be common.

Diagnostic Tests

A definitive diagnosis of epizootic lymphangitis requires isolating *H. capsulatum* var. *farciminosum* from lesions or detecting its nucleic acids in clinical samples. To avoid contamination by environmental fungi, samples from skin lesions should be collected by aspiration of unruptured nodules whenever possible. *H. capsulatum* var. *farciminosum* from clinical samples will grow as a mycelium on various fungal media (e.g., mycobiotic agar, enriched Sabouraud's dextrose agar, brain–heart infusion agar with 10% horse blood, PPLO dextrose glycerol agar) at room temperature. Mycelial colonies grow slowly, appearing in about 2-8 weeks at 26°C (79°F). They are dry, granular, wrinkled and whitish to tan, becoming brown as they age. Aerial growth is usually scant. *H. capsulatum* var. *farciminosum* can produce chlamydospores and arthroconidia (and blastoconidia in the yeast form), but large, round, double-walled macroconidia, which are common in cultures of *H. capsulatum* var. *capsulatum*, seem to be absent. *H. capsulatum* var. *farciminosum* may difficult to culture, with isolation failing in up to half of all clinical cases.

The identity of a *H. capsulatum* colony is usually confirmed by traditional morphological methods, including conversion to the yeast phase on suitable media (e.g., brain–heart infusion agar with 5% horse blood or Pine's medium at 5% CO2) at a temperature of 35-37°C. Complete conversion occurs only after repeated serial transfers to fresh media. Molecular methods, including PCR or MALDI-ToF, can identify cultured *H. capsulatum* var. *capsulatum*, but they do not seem to be in widespread use yet in clinical laboratories. Whether these PCR tests can detect *H. capsulatum* var *farciminosum* does not seem to have been evaluated. A MALDI-ToF assay could identify both the yeast and mycelial stages of *H. capsulatum*, including *H. capsulatum* var *farciminosum*, but did not distinguish the three subspecies of *H. capsulatum*. There are, however, occasional reports of research groups using PCR, in conjunction with DNA sequencing, to identify *H. capsulatum* var. *farciminosum* in clinical cases, especially in unusual hosts such as small animals. A PCR test reported to be specific for *H. capsulatum* var. *farciminosum* was published in 2016, and could detect this organisms directly in clinical samples from horses, including exudates from skin lesions and nasal discharges.

An antigen detection kit has been produced for *H. capsulatum* var *capsulatum*. It cross-reacts with some other fungi, and might detect *H. capsulatum* var. *farciminosum*, though this has not been investigated. Animal inoculation into immunosuppressed mice or other laboratory animals can also be used to diagnose epizootic lymphangitis, though it should be avoided, if possible, for animal welfare reasons.

A presumptive diagnosis of epizootic lymphangitis can be established by cytology or histopathology. *H. capsulatum*

can be visualized with various stains including hematoxylin and eosin, Diff-Quik®, Giemsa, or specific fungal stains such as periodic acid–Schiff or Gomori methenamine–silver. Immunofluorescent staining may also be available. In exudates or tissues, *H. capsulatum* var. *farciminosum* is a Gram–positive, pleomorphic, ovoid to globose yeast, approximately 2–5 µm in diameter. It is usually surrounded by a capsule, which does not stain and appears as a halo. The organisms can occur singly or in groups, and may be found extracellularly or in macrophages. Some resource-poor countries diagnose most clinical cases of epizootic lymphangitis entirely by cytology or histopathology, combined with clinical signs. However, these techniques are insufficient for a definitive diagnosis: the yeast form of *H. capsulatum* var. *farciminosum* is indistinguishable from *H capsulatum* var *capsulatum*, and it may also be confused with other yeasts such as *Candida*, *Cryptococcus* or members of the *Sporothrix schenckii* complex, or even with some protozoa such as *Leishmania*. The larger size of its yeasts was thought to distinguish *H. duboisii* from *H. capsulatum* var *farciminosum* and *H. capsulatum* var. *capsulatum;* however, a recent analysis suggests that the sizes of these organisms may overlap.

Serological reactions can also be used as an aid in diagnosis. Antibodies can usually be found in equids with clinical signs, though they can also occur in asymptomatic animals and those with healed lesions. Serological tests for epizootic lymphangitis include fluorescent antibody tests, ELISAs, passive hemagglutination and tube agglutination. Cross-reactions can occur with other organisms. An intradermal hypersensitivity test (histofarcin skin test) can detect cell-mediated immune responses in some equids. This test has not yet been validated in donkeys.

Treatment

In developed countries, histoplasmosis in people and animals is usually treated with azoles (e.g., itraconazole, fluconazole, voriconazole) or amphotericin B.

Amphotericin B has been used in some cases of epizootic lymphangitis in equids, but in the impoverished countries where this disease is most common, treatment may be limited to inexpensive drugs such as iodides. Early cases are treated with intravenous sodium iodine or oral potassium iodide, sometimes in conjunction with topical iodide applied to lesions and/or surgical excision. Even successfully treated lesions sometimes recur, and iodide is reported to have limited efficacy in moderate to severe cases. Griseofulvin combined with topical treatment has also been used, and *H. capsulatum* var. *farciminosum* is reported to be sensitive to other drugs (e.g., nystatin) *in vitro*. Azoles have not yet been evaluated in clinical cases, but are likely to be effective.

Control

Disease reporting

Veterinarians who encounter or suspect epizootic lymphangitis should follow their national and/or local guidelines for disease reporting. Epizootic lymphangitis is no longer reportable to the OIE, and in the U.S., state or federal authorities should be consulted for the most recent reporting requirements. The current federal list of reportable diseases is available at:

https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/monitoring-and-surveillance/sa_disease_reporting/voluntary-reportable-disease-list. In 2019, it did not include epizootic lymphangitis.

Prevention

In the past, outbreaks of epizootic lymphangitis were controlled or eradicated by quarantines and the euthanasia of infected animals. Infected premises and equipment must be thoroughly cleaned and disinfected. Organisms that contaminate the soil may survive for long periods. Screening with serological tests or the histofarcin skin test might help identify infected animals, but the false positive rate might be high.

In endemic areas, good cleaning and disinfection can help prevent the organisms from spreading between animals. Particular care should be taken to prevent transmission on grooming equipment or harnesses. Fly control is also expected to be useful. There are no known commercial vaccines for epizootic lymphangitis, although some reports suggest that live and inactivated vaccines have been tested (and possibly used) in some endemic regions (e.g., China), and appeared to be promising.

Morbidity and Mortality

Epizootic lymphangitis is more common in the tropics and subtropics than in temperate areas. This disease is reported to be seasonal in Ethiopia, where most cases occur between November and January. Cases are also reported to peak in fall and winter in Iran, and in January in Egypt. The incidence of epizootic lymphangitis is much higher when large numbers of animals are gathered together. In the past, it was reported to be common among horses used in military campaigns. Currently, most reports of clinical cases come from Ethiopia, where working equids are widely used, resources for veterinary care are limited, and control of this disease is poor. In Ethiopia, up to 39% of the horses in some warm and humid locations have lesions and cytology consistent with epizootic lymphangitis, but the incidence is low in very cold, or dry and windy, areas. The disease also seems to be common in mules in some parts of Ethiopia (e.g., 22-33% in three towns); however, donkeys may be more resistant to clinical signs. Reports of epizootic lymphangitis from other countries are uncommon. According to one review, epizootic lymphangitis was diagnosed in approximately 3% of 3000 horses at a large racing facility in Iraq over a 6 month period, but there are no further details. In the 1980s, a summary of fungal diseases in India found that epizootic lymphangitis seemed to be rare or absent, though underreporting could be an issue.

Clinical cases are more common in younger horses (e.g., < 6 years). Some equids have mild illnesses with limited skin involvement and often recover spontaneously; others have severe and widespread skin lesions that cause

significant debilitation. Recurrence has been seen horses up to a year after healing. Death is uncommon if an animal is in good condition and receives good care, but animals with extensive lesions may die. The estimated mortality rate is less than 10-15%. The true case fatality rate might be lower, as this estimate includes reports from some endemic areas where owners are often reluctant to rest affected animals; financial constraints may preclude treatment, even with relatively inexpensive agents; and it is apparently common to abandon equids that cannot work, to be killed by scavengers.

Some sources indicate that equids can become asymptomatic carriers of *H. capsulatum* var. *farciminosum*; however, this might need to be investigated further. Asymptomatic carriage has been defined as the presence of healed lesions, serological reactions and evidence for cell-mediated immune responses (positive intradermal skin tests), which could also occur in animals that have cleared the organism. A recently published study did find nucleic acids in the blood of some asymptomatic equids, but whether these animals were carriers or only transiently infected is not known. Animals that recover from epizootic lymphangitis are said to be resistant to reinfection for life, but there is little or no research to substantiate this.

Public Health

In most parts of the world, histoplasmosis in people is caused by *H. capsulatum* var. *capsulatum*. This organism tends to cause mild or asymptomatic infections in healthy humans who are not exposed to an unusually large infective dose. Serious illnesses mainly occur in immunocompromised patients, and usually affect the lungs and other internal organs. Skin disease seems to be an uncommon form of histoplasmosis in these areas. However, histoplasmosis often appears as cutaneous and/or bone lesions in some parts of Africa, and affects a significant number of patients without obvious immunosuppressive conditions. The causative agent is not identified beyond the species level in many cases in Africa, but it is generally assumed to be either *H. capsulatum* var. *capsulatum* or *H. capsulatum* var. *duboisii*. The latter organism is thought to be associated with most localized or disseminated cases involving the skin, lymphatic vessels or bones, though this has not been conclusively demonstrated.

Only rare illnesses caused by *H. capsulatum* var. *farciminosum* have been reported in humans, and some cases were later found to be unsubstantiated. There is little information about most of these cases, but some were cutaneous. In 2007, a genetic analysis found that a *H. capsulatum* isolate from a Thai patient with disseminated histoplasmosis and concurrent HIV infection seemed to be *H. capsulatum* var *farciminosum*, based on its similarity to isolates from dogs in Japan.

Internet Resources

The Merck Veterinary Manual

United States Animal Health Association. Foreign Animal Diseases

World Organization for Animal Health (WOAH)

WOAH Manual of Diagnostic Tests and Vaccines for Terrestrial Animals

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