PEER REVIEWED

Caseous lymphadenitis: Realities in treatment and prevention

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Abstract

Caseous lymphadenitis, caused by the bacterium *Corynebacterium pseudotuberculosis*, is of importance to small ruminant producers worldwide. The chronic persistent nature of the disease process makes it challenging to effectively treat or control once endemic in a herd or flock. This article discusses the recent advances and time-honored methods utilized in the management of caseous lymphadenitis in sheep and goats, as well as the associated advantages and disadvantages of each.

Key words: caseous lymphadenitis, *Corynebacterium pseudotuberculosis*, small ruminants

Résumé

La lymphadénite caséeuse, provoquée par la bactérie Corynebacterium pseudotuberculosis, affecte les élevages de petits ruminants du monde entier. Une fois devenue endémique dans un troupeau, le traitement et la lutte contre cette maladie sont un réel défi, en raison de sa nature chronique et persistante. Dans cette communication, nous décrirons les progrès récents et les méthodes éprouvées pour la gestion de la lymphadénite chez les ovins et les caprins, ainsi que les avantages et les désavantages de chacune de ces méthodes.

Introduction

Caseous lymphadenitis (CLA) affects a variety of species, and is of particular interest in small ruminants. It has been suggested as the third leading cause of economic loss to the sheep industry in the western US;[44] the prevalence of CLA in mature culled US sheep presented to an abattoir from nine western states was 42.41%.[50] While economic and prevalence studies in US goats are lacking, the goat populations in North America continue to increase, making CLA an important health concern in both species.[53] Because of the chronic persistent nature of the disease process and the frequency of subclinical infections, CLA can be very difficult to treat and control.

Causative Agent

The etiologic agent for caseous lymphadenitis is *Corynebacterium pseudotuberculosis*, an actinomycete.[48] This family also contains the *Rhodococcus* genus, and similarities between the disease processes caused by *R. equi* and *C. pseudotuberculosis* in their respective hosts are apparent. *C. pseudotuberculosis* is a non-motile, pleomorphic, gram-positive facultative intracellular rod.[7] The bacteria can grow under either anaerobic or aerobic conditions at 98.6°F (37°C), and when viewed under the microscope groups of the bacteria show 'picket fence' or 'Chinese letter' configurations.[10]

Virulence factors of *C. pseudotuberculosis* most widely recognized as contributing to the disease process are phospholipase D, an exotoxin, and the mycolic acid, present on the bacterial cell wall.[7,34] Phospholipase D cleaves sphingomyelin in endothelial cell membranes resulting in increased vascular permeability, and is integral to CLA pathogenesis.[14,56] Without this exotoxin the bacterium is incapable of dissemination, and its ability to cause lymph node abscessation is significantly diminished.[7,27,33] The presence of antibody towards this virulence factor limits clinical disease progression substantially.[7] Mycolic acids provide a lipid layer on the surface of the cell wall,[10,13] have cytotoxic capabilities,[8] and have been postulated to allow survival in the environment for extended lengths of time under certain conditions.[7] Additionally, mycolic acid provides the bacterium protection from lysosomal enzymes, allowing the organism to survive phagocytosis but remain

intracellularly to be disseminated to secondary sites, particularly within macrophages.[7,23,28,55]

Naturally occurring routes of inoculation include the cutaneous route (either through broken or intact skin),[37] access via mucous membranes (particularly in the oral cavity),[5,29] or perhaps inhalation.[37] Once *C. pseudotuberculosis* gains entry to the host through skin or mucous membranes, it spreads initially to lymph nodes where it causes microabscesses[39] within the cortex that coalesce to form larger encapsulated abscesses.[29] In some animals this is followed by extension of the infection hematogenously or via lymphatics, and can cause comparable lesions in other visceral organs or lymph nodes.[7]

Cross-Species Transmission and Zoonotic Potential

While clinical infection with *C. pseudotuberculosis* most commonly occurs in sheep and goats, horses, cattle, camelids, camels, deer, pigs, and humans can also be affected.[2,3,22,31,35,42,49,57-60] In horses, three main forms have been described and include ulcerative lymphangitis, external abscesses, and internal abscesses.[1] In cattle, infection with *C. pseudotuberculosis* is uncommon but may occur sporadically or as a herd outbreak.[57,60,61] Clinical signs usually manifest as cutaneous ulcerative granulomatous lesions; visceral,[60] mastitic, or mixed infections may also occur.[61] Necrotic and ulcerative dermatitis of the heels from CLA has also been reported in dairy heifers.[59]

Two biovars of *C. pseudotuberculosis* have been described based on their ability to reduce nitrate.[9,47] Most isolates obtained from horses and cattle were able to reduce nitrate to nitrite,[9] referred to as 'nitrate-positive' and later designated biovar *equi*.[47] The majority of isolates obtained from sheep and goats were incapable of nitrate reduction,[9] referred to as 'nitrate-negative' and later designated biovar *ovis*.[47] Songer *et al* subsequently determined that the host preference displayed by the two biovars did not exist in cattle;[47] which directly contrasts a later report where all isolates obtained from dairy cattle with clinical *C. pseudotuberculosis* infection were nitrate-negative.[60] Baird *et al* suggested classification based on nitrate reduction may not be satisfactory.[7] Regardless, in reference to species-to-species transmission, experimental intradermal infection of goats with an equine-origin strain resulted in abscesses at injection sites and in the draining lymph nodes.[11] Although natural cross-species transmission of *C. pseudotuberculosis* has not been documented,[1] strict biosecurity measures are recommended if clinical signs of infection with *C. pseudotuberculosis* become apparent, regardless of species affected.

Human infection with *C. pseudotuberculosis* primarily results in granulomatous lymphadenitis.[20,21,25,26,38] Eosinophilic pneumonia has also been reported.[30] The majority of human cases of *C. pseudotuberculosis* have occurred in people occupationally exposed to sheep,[38] including farm workers, shepherds, meat inspectors, butchers, abattoir workers, sheep shearers, and a veterinary student.[30] It is therefore largely considered an occupational disease,[25] although drinking infected unpasteurized milk or milk products is another risk factor.[20] In addition to bovine mastitis, the bacterium has been isolated from milk from CLA-affected goats.[45] Veterinarians should take precautions when working with infected animals and inform clients of the zoonotic potential of this bacterium.

Clinical Manifestations

Clinical features of CLA in small ruminants include pyogranulomatous lesions in two main forms, the external form and the internal form. The external form, also known as the superficial or cutaneous form of CLA, is characterized by abscess formation in externally palpable lymph nodes.[7] The internal or 'visceral' form of the disease is characterized by abscessation of internal lymph nodes and other visceral organs.[7] Both forms may exist simultaneously in the same host.[41] Additionally, the bacterium can cause a purulent infection or abscessation of the skin and/or subcutaneous tissue without apparent lymph node involvement or, in some cases, bronchopneumonia.[56]

In goats, the most common form of CLA is the external form, characterized by superficial lymph node abscesses with diameters of 1.2 inches up to 6.8 inches (3 cm to 15 cm; Figure 1).[52] Lymph nodes of the head

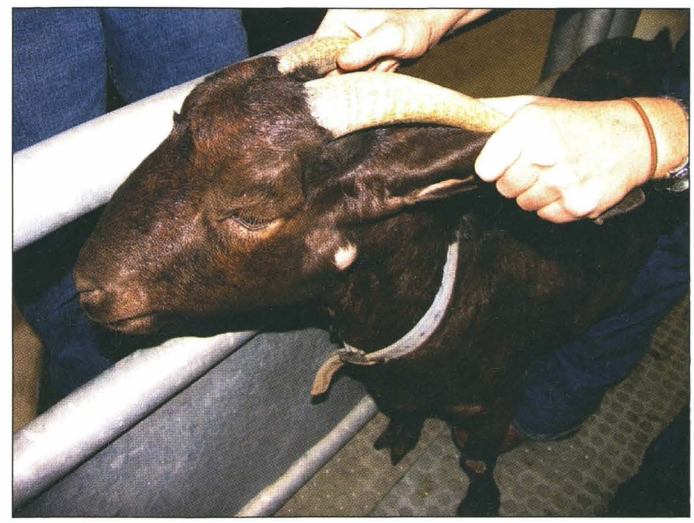

Figure 1. External CLA abscess in the parotid lymph node of a Boer goat.

and neck are predominantly affected in goats,[5,6,10,29,55] with the submandibular, parotid, and prescapular lymph nodes being the most commonly affected.[5] In sheep, the external form of CLA most commonly affects lymph nodes of the torso, namely the prefemoral and/or prescapular lymph nodes.[6,10,36,37] It cannot be emphasized enough, however, that any external lymph node can be affected in either species.

The internal form of CLA is arguably less common, and is much more common in sheep.[24,43] The internal form usually results in chronic weight loss and ill-thrift, sometimes known as 'thin ewe syndrome'. The primary organs involved in sheep include the lung parenchyma and thoracic lymph nodes,[50] but the liver, kidneys, spleen, mammary gland, testis, scrotum, eyes, joints, bones, brain, and spinal cord can all be affected[32,54] in both sheep and goats. Any organ or tissue is susceptible to CLA.[32] In goats, the abscesses often have a uniform, pasty green-tinged content, whereas in sheep the abscesses tend to have a caseated, laminar or 'onion-layer' appearance.[10,29]

Disease Transmission

Transmission of CLA in the external form is by rupture of superficial abscesses that subsequently contaminate the environment for extended periods, and can infect other animals either by direct contact or via fomites.[19] In the internal form, lung lesions may allow the bacteria to be discharged into the airways[50] and then aerosolized.[18] In flocks or herds previously free of CLA, the usual method of disease introduction is a clinically or subclinically infected carrier animal.[6] However, fomites may also introduce the disease, including shearing equipment, shearers, farm workers, and portable equipment used for restraint.[7] Milk or colostrum from infected does or ewes may be a risk factor for neonatal transmission. The organism has also been isolated from the semen of an infected ram,[12] but the role of semen in disease transmission is unknown.

Diagnostic Tests

Definitive diagnosis of CLA in an animal is based on culture and isolation of *C. pseudotuberculosis*. The bacterium can typically be isolated from abscesses regardless of chronicity, although lower numbers of viable bacteria may be present in aged lesions.[7] Polymerase chain reaction has been utilized to identify the organism as well, and may provide a more rapid diagnosis compared to culture.[15] Serology has also been used to attempt diagnosis, although serologic tests do not differentiate between exposure, past infection, current external or internal infection, maternal antibody, or vaccinated animals.[10,16,41,55] The synergistic hemolysin inhibition (SHI) test is probably the most commonly used and readily available serologic diagnostic, and recent findings by Washburn *et al* suggest the sensitivity of the test for external infection with CLA was 81% and the specificity was 40%.[53] A major disadvantage to this test is that no titer or a low titer does not rule out infection. This is believed to result from encapsulation of the abscess which prevents antibody response, acute onset of disease with rapid abscess maturation prior to the immune system being able to mount a serologic response, or potentially antibody consumption during the active disease process.[2,16]

Diagnosis of the Visceral Form of CLA

In animals with external abscesses, culture of the lesion content is recommended for diagnostic confirmation of CLA; in animals suspected of having internal CLA, definitive antemortem diagnosis can be challenging. The authors recommend thoracic radiography and/or ultrasonography if intrathoracic CLA is suspected. In valuable animals, computed tomography (CT) or magnetic resonance imaging (MRI) can also be performed. If pulmonary abscesses are confirmed, transtracheal wash (TTW) with subsequent cytology and aerobic culture should be performed. Positive culture for *C. pseudotuberculosis* confirms the diagnosis, while absence of the bacterium on TTW does not rule it out. Alternatively, the SHI test can be performed in animals with intra-thoracic abscesses with the understanding that a negative or low titer also does not definitively rule out the disease; a positive titer in such a case is strongly suggestive of CLA. However, readers should be aware that high CLA titers may also occur in animals that do not display any overt clinical signs of disease.

If intra-abdominal CLA is suspected, ultrasonography is the initial imaging modality of choice (Figures 2 and 3) and may be followed by CT or MRI. Intra-abdominal abscesses in a location amenable to needle aspiration, including hepatic or splenic abscesses, may be aspirated and cultured. Presence of any internal abscesses, combined with either clinical evidence of current or previous external abscess formation, or a positive SHI test in an unvaccinated animal, should strongly increase suspicion of CLA.

Treatment and Control

Treatment and control options for the external form of CLA have consisted of parenteral antimicrobial therapy; intralesional antimicrobial therapy; isolation of affected animals; culling infected animals; and opening, draining, and flushing active lesions.[55] Pharmacological treatment has proven difficult, and has not yet been reported to result in bacteriologic cure. In a

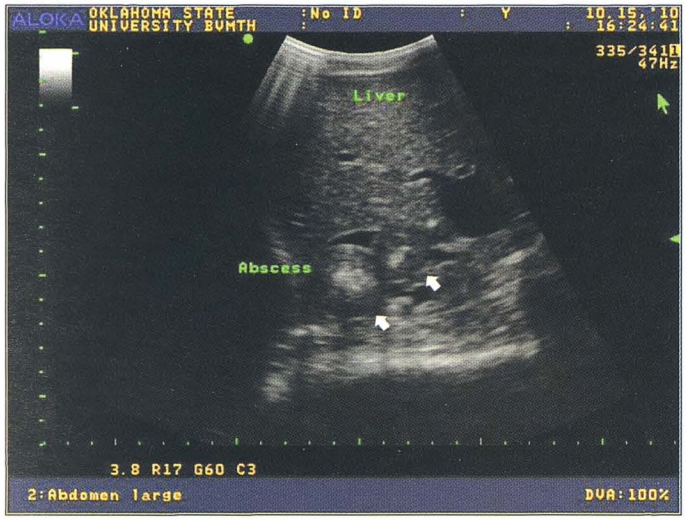

Figure 2. Ultrasonographic image of internal CLA abscesses (white arrows) in the hepatic parenchyma of a goat.

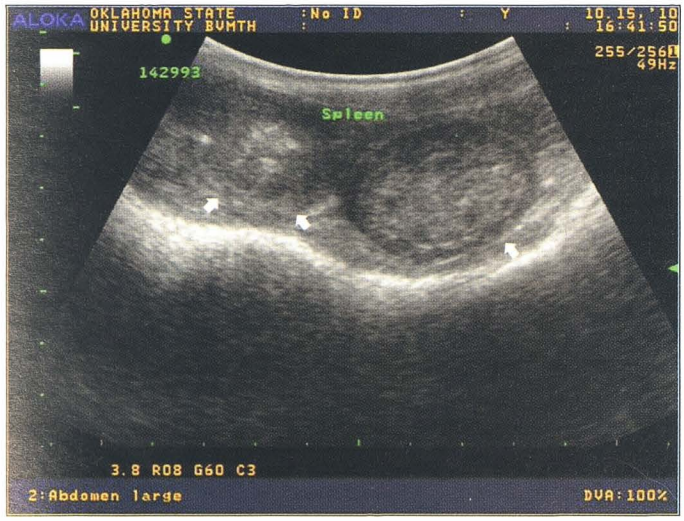

Figure 3. Ultrasonographic image of internal CLA abscesses (white arrows) in a caprine spleen.

recent study, numerous isolates of *C. pseudotuberculosis* demonstrated in vitro susceptibility to ceftiofur, florfenicol, oxytetracycline, penicillin, and tulathromycin, among others. The bacterium was resistant only to sulfadimethoxine (Washburn, Libal, Fajt, unpublished data). Lack of antimicrobial efficacy in vivo is likely due to the thick encapsulation of the abscess which deters drug penetration,[41] and the intracellular location of the bacteria limits the utility of some antibiotics. The best outcome expected from antimicrobial treatment alone would be decreased abscess size and non-recurrence of the lesion. The worst possible outcome would be an abscess that ruptured and drained, regardless of treatment, resulting in environmental contamination and exposure of potentially non-infected herdmates.[53]

Opening, flushing, and draining lesions is a modality used with most abscesses; however, in CLA lesions, this practice is not without potential long-term hazards. If performed in a clinic, this is ideally done over a drain or else all exudates are immediately collected, discarded, and the treatment area thoroughly disinfected if contamination occurs. Treatment of cellulitis, if present, would also be indicated and might include antimicrobials and anti-inflammatory drugs. The disadvantage to this therapeutic approach is discharge of abscess content into the environment during the convalescent period with subsequent exposure and infection of naïve animals.

Surgical excision of an abscess/affected lymph node is one method of minimizing spread and contamination, albeit a more expensive method, and does not address the potential for recurrence of external lesions or development of the internal form of CLA.[53] Some authors recommend antimicrobial therapy for four to six weeks post-surgery to minimize likelihood of recurrence.[7]

Another control measure is to split the herd/flock into 'infected' and 'clean' groups with no sharing of feeders, water troughs, or grazing areas. Animals with external abscesses can be treated, and those with actively draining lesions should be isolated until lesion resolution. Kids or lambs may be removed from the dam and fed heat-treated colostrum and pasteurized milk or milk replacer to prevent CLA exposure.

Intralesional injection of 10-25 mL of 10% formalin has been successfully utilized as a treatment,[4] but formalin has no established meat or milk withdrawal time, possesses carcinogenic properties, and may be negatively viewed by the general public.[53,55] If used intralesionally at the aforementioned dose, the Food Animal Residue Avoidance Databank (FARAD) recommends a meat withdrawal of 30 days and a milk withdrawal of three days in goats (FARAD, personal communication).

A recent study by Washburn *et al* described a closed-system lavage of external abscesses with a large-bore needle and saline, followed by intralesional or subcutaneous tulathromycin administration (1.1 mg/lb or 2.5 mg/kg one time, by either route).[53] The majority of those abscesses resolved and did not return within one month.[53] From a biosecurity standpoint, this treatment approach is intuitively more defensible than opening and draining the abscesses. Meat withdrawal times for goats using a single injection of tulathromycin subcutaneously at this dose was 23 days in a recent pharmacokinetics study by Young *et al*;[62] FARAD has recommended a milk withdrawal of 50 days in both sheep and goats (FARAD, personal communication).

Culling animals affected with CLA remains one of the most effective means of control and reduction of

incidence; however, this may mean eliminating genetically superior animals from the herd, which is often not ideal from an economic standpoint. Further, absence of external CLA lesions may make identification of infected carrier animals difficult, and may result in maintenance of CLA in herds thought to be "clean".

Control of CLA has been attempted with a variety of vaccination products including bacterins, toxoids, combined bacterin-toxoids, autogenous, and live vaccines. Currently in the United States, the only commercially available vaccine approved for use in sheep is a combined *C. pseudotuberculosis* bacterin-toxoid alone[a] or in combination with *Clostridium perfringens* type D toxoid and *C. tetani* toxoid.[b] Data from the manufacturer suggests that in sheep vaccinated prior to exposure to CLA, 90% are protected from the internal and 58% are protected from the external form.[40] Piontkowski *et al* reported that vaccination of sheep with this commercially available vaccine[b] could decrease both the number of sheep that developed abscesses and the number of abscesses formed.[41] Disadvantages to the vaccine are that it is not labeled in goats, animals must be vaccinated prior to exposure, mild post-vaccine lameness is expected, injection-site reactions can occur and may be worse if the animal is already infected, and serologic tests are rendered useless as they will be positive in vaccinated animals. However, failure of owners to comply with the recommended vaccine protocol of two initial vaccinations followed by yearly boosters may be partially responsible for a perceived lack of efficacy of toxoid vaccines by some herdsmen/shepherds.[56] Off-label use in goats does occur, but currently there are no efficacy or safety studies in this species. Owners should be made aware of the label claim and vaccine reaction concerns when utilizing these vaccines in goats; anecdotally, this vaccine does not appear to be as efficacious in caprines as it is in ovines (Lionel Dawson, personal communication). The vaccine manufacturer is actively pursuing research and development of a vaccine approved for use in goats with the intent of producing a fully licensed commercially available vaccine in the future (Randall Berrier, personal communcation). Recently, a Texas company[c] produced a new *C. pseudotuberculosis* bacterin conditionally licensed in goats and regulated by each state's veterinary agency.[51] Efficacy and safety studies for this vaccine have not yet been published in the peer-reviewed literature. Autogenous CLA vaccines have also been used in goats, and some producers believe they are very efficacious. However, these tend to be more costly than commercial vaccines unless utilized in large herds.

Management strategies to reduce the spread of CLA to uninfected animals in a herd/flock center predominantly around environmental control. Contaminated feeders and waterers may serve as a source of infection, as can shearing equipment in sheep flocks including shearer's clothing, vehicles, and footwear.[56] Grooming equipment and contaminated bedding or hay may also spread CLA.[17] Young sheep, especially those that have been recently shorn, should be separated from older sheep and should always be shorn first. Use of shower or plunge dips for ectoparasites should be minimized in the two weeks following shearing, as *C. pseudotuberculosis* can survive for up to 24 hours in these systems without loss of viability.[37] In goat herds, external parasites may result in the goats rubbing on posts, nails and the like, and ultimately result in bacterial spread.[46] All tattooers, tagging equipment, and surgical instruments should be sterilized between animals, needles should be discarded after a single use, and external wounds should be treated promptly. The umbilicus of all neonates should be dipped at birth, and all housing and facilities should be free of nails, wires, splintered wood, and other sharp projections that could penetrate the skin.[55] In herds with no previous cases of CLA, maintaining a closed herd and strict biosecurity protocols is highly recommended; in such a herd, vaccination against CLA is discouraged.

Unfortunately, there are no specific recommendations supported by the peer-reviewed literature regarding treatment or control measures for CLA in a given clinical scenario. Treatment and control measures may encompass a combination of the modalities described above and should be tailored to the specific herd or flock. Factors including herd/flock type (production, seedstock producers, pets), within-herd prevalence of CLA, economics, owner preferences, and available facilities should be considered when formulating recommendations for management of CLA.

Conclusions

CLA is a serious health concern in small ruminants worldwide. Treatment regimens that minimize environmental contamination are advantageous from a biosecurity perspective. Additionally, management strategies should be designed to decrease risk factors for CLA introduction and transmission. In conjunction with such control strategies, proper vaccine protocols should be considered in herds/flocks with endemic CLA.

Endnotes

[a]Case-Bac®, Colorado Serum Company, Denver, CO
[b]Caseous D-T®, Colorado Serum Company, Denver, CO
[c]Texas Vet Lab, Inc., San Angelo, TX

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