Histophilus somni – Unique Features, Pathogenesis and Lesions Update

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Abstract

Haemophilus somnus has recently been renamed *Histophilus somni* and it has been proposed this name also includes *Haemophilus agni* and *Histophilus ovis*. The organism occurs in all management systems of the cattle industry, but the most serious losses occur in beef feedlots where co-mingling of cattle from numerous farms occurs. The disease in feedlots most often manifests as the septicemic form and is known as the *Histophilus somni* disease complex (HSDC), but pleuritis and bronchopneumonia are two other very common causes of disease or death. Despite effective vaccines and antibiotics, sudden losses from 30 to 90 days after arrival at feedlots continue to occur in significant numbers, especially in certain geographical areas of North America and Europe. There undoubtedly remains much to be learned about predisposing factors to histophilosis and how this organism avoids natural body defense mechanisms.

Introduction

For nearly five decades *Histophilus somni* (recently renamed from *Haemophilus somnus*) has been considered as part of the bovine respiratory disease complex (BRDC), as a cause of septicemia and its sequelae (the HSDC) and also a cause of reproductive losses in cattle. Despite bacterins being available for many years and several antibiotics showing good *in vitro* sensitivity patterns for *H. somni*, significant losses in beef cattle feedlots, cow-calf operations and dairy cattle continue to be highly significant problems in Canada, the United States, Germany, the United Kingdom, Switzerland and Israel. The organism also causes significant losses in sheep, bighorn sheep and bison. *H. ovis* and *H. agni* are common in Australia, New Zealand and Canadian sheep flocks. Serum titres reach high levels in most feedlot cattle 14 to 21 days after arrival but the organism has many unique characteristics and virulence factors that allow it to not only colonize airways of the lung parenchyma but also invade the bloodstream, which in turn results in a variety of clinical conditions and lesions at post mortem.[4,5]

Classification, Virulence Factors and Special Features of *H.somni*

Histophilus somni, *Histophilus ovis* and *Haemophilus agni* are now considered to be the same organism and *H. somni* is the only member of the genus *Histophilus* in the Pasteurellaceae family. Microbiologists have never been happy with *H. somni* being classified as a *Haemophilus* genus member due to the lack of "X" and "V" factors for *in vitro* growth. Recent phylogenetic studies has resulted in the now accepted new name *Histophilus somni* based on sequence analysis of the 165-rDNA and rpoB genes.[1]

H. somni is a gram negative, nonmotile, pleomorphic and nonencapsulated bacterium with common surface antigens for all strains of the organism. Nonclinical carriers make up 3.2 to 8.0% of cattle entering feedlots, and the organism can be isolated from upper and lower respiratory tracts and urogenital tracts, and most commonly from the preputial cavity of rams and bulls. The organism is therefore a commensal in these sites. Simple isolation of the organism, therefore, does not necessarily confirm an etiologic diagnosis, and antibiotic therapy prior to death easily interferes with laboratory isolation of the organism so do not rule it out based on simple culture results. Therefore, as with *Mycoplasma bovis*, typical histologic lesions and immunohistochemical (IHC) demonstration of the organism relative to the lesions are very important to confirm the diagnosis.

Many different strains of the organism with different tissue tropisms and therefore a variety of disease manifestations occurs, but in feedlot cattle the organism most commonly causes pneumonia or a septicemia. Septicemic histophilosis in tissue can result in pleuritis, myocarditis, thrombotic meningoencephalitis (TME) or polyarthritis, and the septicemic forms are referred to as the *H. somni* disease complex or HSDC.

Thoracolumbar myelitis, otitis media, laryngeal necrosis, conjunctivitis and retinal hemorrhages are also not uncommon feedlot cattle clinical or lesional manifestations.

A particularly unique feature of *H. somni* is its ability to invade into the bloodstream (likely via the

respiratory tract), even in the presence of high circulating antibody titers, and to avoid being killed despite being phagocytosed by neutrophils, circulating monocytes and tissue macrophages. This intracellular survival allows it to continue to replicate. This feature is due to immunoglobulin binding proteins (IgBPrs) on the surface of the organism that prevents complement-mediated destruction. Normally, in conjunction with organism-specific antibodies, this would result in phagocytosis and intracellular death, commonly referred to as opsonization. Also, outer membrane proteins (OMPrs) have been demonstrated in virulent strains, and rapid phase variation of these proteins result, in part, in the organism's avoidance of the normal host defenses both within the bloodstream and after localization in tissues.

Unlike other Pasteurellaceae family members an exotoxin of *H. somni* has not been convincingly demonstrated, but a lipooligosaccharide (LOS) has been clearly shown with *H. somni*. This LOS has been shown to be capable of undergoing structural and antigenic variation, and by so doing allows the organism to mimic host antigens and thus evade immune mechanisms. The LOS is also partially responsible for adherence of the organism to epithelial cells of airways and endothelial cells lining blood vessels. The lipid A content of LOS also has an endotoxin-like effect on host tissues by inducing pro-inflammatory IL-1 and tumor necrosis factor (TNF) from macrophages.

Lesions produced by the HSDC or septicemic form of *H. somni* requires that the organism first colonize the respiratory tract tissues, then adhere to and damage endothelial cells that line blood vessels. Once intravascular, the organism can evade host defenses as mentioned above. In addition, as with *Pseudomonas aeruginosa*, virulent *H. somni* bacteria produce a biofilm at sites of colonization which promotes epithelial cell adherence and allows for bacterial inter-communication, which is important for replication. Stressors such as transport, overcrowding, changes in feed and adverse weather conditions appear to precipitate disease outbreaks and damage to the mucociliary apparatus, especially of the lower respiratory tract (lung), which promotes colonization of airway epithelium. Several respiratory viruses commonly seen in feedlots are significant contributors to initiating airway epithelial damage, but especially BRSV, PI3, BVD and IBR. Depending on the strain of the organism, many of these lower respiratory *H. somni* infections remain confined to the lung as a bronchopneumonia or invade into the vascular system as described above and result in a septicemia. Less common cases of otitis media, conjunctivitis and some cases of arthritis appear to occur coexistent with or following several weeks of suppurative bronchopneumonia. Occasionally suppurative bronchopneumonia and myocarditis occur at the same time so the lung may be the source of the organism for the myocarditis.[3]

Gross Post Mortem and Histopathologic Lesions of Histophilosis

I have had no experience with the lesions of *H. somni* placentitis, aborted fetuses, endometritis, vaginitis, vulvitis, balanoposthitis, orchitis, seminal vesiculitis or mastitis, but all of these are reported to occur in both beef and dairy cattle. None of the above, except perhaps the disseminated lesions in multiple tissues of aborted fetuses, are considered part of the HSDC.

The lesions of the HSDC are a result of a septicemia and the hallmark histopathologic lesions, which may or may not be seen as visible gross lesions, include fibrinous thrombi, clumps of bacteria in or around small vessels and large numbers of neutrophils in these foci of vasculitis. A vasculitis and "microabscesses" are therefore usually described and often, especially in the brain and meninges, the vasculitis is more specifically a thrombophlebitis since small veins and venules are clearly involved. L0S-induced production of TNF and IL-1 are thought to play a role in the vasculitis lesions and immune complexes, and may be partially responsible for the vasculitis seen histologically.

Reflecting the not-yet-totally understood and peculiar tissue tropisms of different strains of *H. somni*, it is not uncommon to see gross lesions in only one organ or body system in the HSDC. The brain was the first to have *H.somni* lesions described where it was named ITEME, but it is now recognized that 'embolism' *per se* does not occur so the disease is simply referred to as thrombotic meningoencephalitis or TME. One tissue where embolism might occur, however, is the spinal cord and cases of sudden onset posterior paralysis can be due to *H. somni* embolic myelitis and can exist with or without concurrent brain involvement. A formalin fixative-immersed short segment of lumbar spinal column removed with a handsaw is a useful specimen to submit to a diagnostic lab in such cases. The brain lesions are usually seen grossly as focal brown to red lesions visible on the outer or cut surfaces of the brain, but if animals were treated with antibiotics while sick, in our experience many cases will be missed if multiple sections of brain are not examined histopathologically.

The heart lesions are usually seen as a myocarditis and, except for a few cases thought to arise secondary to *H. somni* suppurative bronchopneumonia, are thought to occur from a "silent" septicemia or bacteremia. Lesions are not usually seen concurrently in any other tissues. In the peracute to acute cases dark red hemorrhagic lesions may occur, especially in the left

ventricle papillary muscles (very similar to Blackleg), but more often chronic infarcted lesions are seen and most often as sequestra in the papillary muscles of the left ventricle. Sequestra are not true abscesses as they are often described, but pale and dry central masses of necrotic (infarcted) myocardium with outer zones of white fibrosis, although some may have intervening zones of purulent material where the body is trying to rid itself of the central necrotic tissue (the process is called sequestration). This is very similar to the sequestra that occur in *Mycoplasma bovis* in the lung. Scattered smaller fibrotic (healed) foci may be present throughout both ventricles, mural or vegetative endocarditis may also be present, and sometimes subacute to chronic fibrinous pericarditis co-exists along with myocardial lesions. We have seen cases where an entire necrotic papillary muscle is suddenly pulled away peracutely into the ventricle in the live animal because of the chordae tendinae attachments of the papillary muscles to the mitral valve leaflets. Feedlot cattle that die of congestive heart failure due to *H. somni* myocarditis typically have passive congestion of the lung characterized by heavy, non-collapsed lungs with interlobular edema and a finely mottled hemorrhagic appearance throughout both pleural and cut surfaces due to intra-alveolar hemorrhage. The cut surfaces of these lungs, and especially in the caudal lung lobes, will sometimes reveal round interlobular lymphatics distended with dark blood that is trying to exit the lung parenchyma.

Currently, the most common manifestation of *H. somni* in western Canada feedlots is acute fibrinous pleuritis. These occur 30-90 days after arrival at the feedlot. Rarely are lesions seen in any other organ, even histologically. These animals usually are sudden death cases, the parietal pleura on both sides of the chest are covered in a thick sheet of fibrin and the lungs are often remarkably collapsed. Abundant straw-colored fluid is invariably present in the chest surrounding both lungs. The cut surfaces of the lung either show simple compression collapse and congestion, or there may be yellow fibrin-distended interlobular septae, giving a "marbled" appearance to the cut surfaces. Airway exudates are not a feature of these cases, and in fact rarely can a pneumonic process be demonstrated at all, grossly or histologically. These marbled lungs with interlobular lymphatics plugged with fibrin and bacteria are easily confused with acute mannheimiosis cases. Histologically thrombolymphangitis is the hallmark lesion of both the visceral pleura and the interlobular lesions, and organisms are easily demonstrated by IHC confined to the pleural and interlobular lesions.

Pneumonic histophilosis is usually a subacute to chronic, cranial-ventral suppurative bronchopneumonia. Typically seen is diffuse dark red and consolidated cranial, middle, accessory and cranial portions of caudal lung lobes. The cut surfaces show variable amounts of purulent exudates in small airways, but unless *M. haemolytica* or *Mycoplasma bovis* are co-existent areas of necrosis or interlobular fibrin are not seen. A *Pasteurella multocida* bronchopneumonia looks identical to these *H. somni* bronchopneumonia cases in my opinion. Histologically and by IHC neutrophils and *H. somni* bacteria are within airway lumens and less commonly in small patches of surrounding alveoli as well. In the bronchioles the bacteria are mixed with neutrophils, reflecting the organism's ability to be engulfed by but not killed by neutrophils. It is also not uncommon to have feedlot interstitial pneumonia ("AIP") lesions in the caudal lung lobes and *H. somni* bronchopneumonia cranial-ventrally, and this combination of lung lesions is often referred to as "upstairs-downstairs" pneumonia.

In HSDC cases, if the larynx is routinely opened at necropsy, bilateral tiny focal to large bilateral caseopurulent ulcerative lesions of the vocal folds and/or arytenoid cartilages and laryngeal mucosa are often seen. A histologic and IHC workup will often show *H. somni* in these lesions, but *Mycoplasma bovis*, *Fusobacterium necrophorum* and *Arcanobacterium pyogenes* may be present secondarily as well. Vasculitis due to *H. somni* is often found histologically in the mildest laryngeal cases, but usually in combination with septicemic lesions in other organs or in cases of suppurative bronchopneumonia.

When a variety of other organs and tissues of suspect *H. somni* septicemic cases are examined grossly and/or histologically, lesions are often found. Fibrinous arthritis is consistently found if looked for and the amount of joint fibrin is much less than in *Mycoplasma bovis* cases in my opinion. Also all large joints will show this fibrinous arthritis, unlike *Mycoplasma bovis* cases where only one or two joints are more commonly involved. Skeletal muscle, renal and intestinal vasculitis lesions are often found histologically, but severe and obvious gross lesions of these tissues are occasionally seen as well.[2]

Conclusions

Histophilus somni can cause a wide variety of clinical diseases and pathologic lesions and reliance on cultures alone, especially if there was antibiotic therapy, commonly fails. There are many strains of the organism that result in the different diseases, but pleuritis, the HSDC and its sequelae (TME, myocarditis, arthritis, myelitis, laryngitis) and suppurative subacute to chronic bronchopneumonia are by far the majority of cases seen in beef cattle feedlots.

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