Relationship of Polyarthritis and Respiratory Disease in Cattle

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Abstract

Nearly 15 years' experience with a chronic pneumonia and polyarthritis syndrome (CPPS) in western Canadian feedlots is described. Emphasis in this presentation is on the postmortem and laboratory diagnosis of CPPS. *Mycoplasma bovis* is the most consistent etiologic agent isolated, but in the author's experience and opinion, chronic primary BVDV infection likely plays a significant role in predisposing to this antibiotic-unresponsive infectious disease problem. The syndrome appears to be a problem throughout North America and is an increasing problem in some dairy herds as well. The *Haemophilus somnus* disease complex (HSDC) is a less-common cause of concurrent respiratory and joint infections and is much simpler to diagnose.

Introduction

For many years, field service veterinarians of the Western College of Veterinary Medicine (WCVM) have been doing postmortem examinations of all dead and chronic feedlot cattle at several multi-source feedlots in the Saskatoon region with hundreds of submissions made to the diagnostic laboratory, and a tremendous amount of data and experience has thus been obtained.

Two syndromes are responsible for at least 99% of the cases where arthritis and pneumonia in combination are seen. The most common of these we refer to as the chronic pneumonia/polyarthritis complex (CPPS), with *M. bovis* as the principal pathogen. However, ongoing work by our group shows that primary bovine virus diarrhea virus (BVDV) infection is probably important in this disease complex, likely because of its immunosuppressive effects. When mycoplasma lung lesions are obvious at postmortem, about 10% of these cases will also have a mycoplasma arthritis and tenosynovitis / peritendinitis in one or more large joints. The stifle joint is very commonly involved. Conversely, if mycoplasma arthritis was the most obvious clinical problem and the associated lesions were the most outstanding feature at postmortem, at least 95% of such cases will also have a mild, localized to extensive mycoplasma pneumonia, suggesting that the mycoplasma infection begins in the lung with hematogenous spread to one or more joints. Diagnostic laboratory support is always needed to confirm that mycoplasma sp is involved until a lot of postmortem experience with CPPS is obtained. Diagnostic laboratory support to confirm the co-existence of BVDV is always required, since there are no primary BVDV grossly visible lesions in any tissue in these cases.

The second most important organism in pneumonia and arthritis in feedlot cattle is *Haemophilus somnus*, referred to as the Haemophilus somnus disease complex or HSDC. I am not a believer, however, that *H. somnus* has anything to do with the chronic arthritis cases that feedlots throughout North America have recognized as a major problem during the last one to two decades. Arthritis seen in the HSDC is always a polyarthritis, and is usually peracute due to *H. somnus* septicemia, or at least bacteremia, with increased fibrin and joint fluid being a consistent finding at postmortem. As in other tissues, damage to endothelial cells of tiny blood vessels in the synovial membranes of the joints results in the exudation of fibrin into the joint fluid. If examined by histopathology, the brain, lung, heart and various other tissues will also have evidence of thrombophlebitis, the hallmark histologic lesion of *H. somnus* septicemia. In some cases of infectious thrombotic meningoencephalitis (ITME), there will be no thrombophlebitis in tissues other than the brain, especially when there has been time for antibiotic therapy.

Other disease entities within the HSDC include myocarditis/myocardial infarction, fibrinous pleuritis and chronic suppurrative bronchopneumonia. The myocardial lesions can vary tremendously in their gross appearance, and may include sequestration of necrotic myocardial tissue, and endocarditis of both valvular and mural types. Subacute to chronic passive congestion of the lung is a common feature when there is myocardial
involvement. The fibrinous pleuritis cases usually are restricted to the visceral and parietal pleural tissue, with interlobular thrombolympangitis of the lung often present, but no pneumonia exists. Suppurative bronchopneumonia cases, where H. somnus can be demonstrated in airway lumens by immunohistochemistry (IHC) or culture, is also not uncommon. This condition is not accompanied by pleuritis and, in my opinion, is a superimposed infection in bronchioles previously damaged by a respiratory virus. These bronchopneumonia cases will sometimes co-exist with myocardial lesions of H. somnus, and may be the source of embolic lesions in the myocardium.

**CPPS Investigations and Research Summaries**

We have recognized M. bovis as being an important joint and lung pathogen for nearly 15 years, and several publications from western Canada have been published or submitted for publication on this topic.

In 1988, WCVM personnel investigated large numbers of chronic arthritis cases from a large Alberta feedlot and were able to recover M. bovis by culture from the joint exudates. In 2000, Dr. Njaa et al published an article showing that IHC on skin biopsies collected from anywhere on the body could be used to detect persistently BVDV-infected (PI) cattle. This tool has been invaluable in our ongoing studies of CPPS and we are able to show that primary BVDV infection is probably very important in the pathogenesis of the CPPS.

Our immunohistochemistry laboratory now finds itself very busy doing IHC on large numbers of cattle skin biopsies in an effort to detect and eliminate PI animals from western Canada beef and dairy herds. In the November 2001 *Canadian Veterinary Journal*, we published an article on IHC results from chronic arthritis cases that Dr. Eugene Janzen euthanized and necropsied in a large Alberta feedlot. In the 49 cases, M. bovis was identified in 71% of the lung samples and 45% of the joint samples. H. somnus was negative in all joint samples, but was identified in 14% of submitted lung samples. Mannheimia hemolytica was identified in 23% of the lungs, but was usually combined with other infectious agents. BVDV was present in 40% of the cases, but in a pattern consistent with a primary infection, and none of the 49 animals were shown to be PI individuals. The conclusion on this series of cases was that BVDV and M. bovis were the most consistent pathogens persisting in feedlot cattle that failed to respond to therapy.

A graduate student of mine, Dr. Farshid Shahriar, has a paper accepted for publication on mycoplasma lung cases. It was a combined retrospective and prospective IHC study to determine how many of the cases had evidence of primary BVDV infection, based on cultural and IHC tests. In the retrospective group, 44 of 48 mycoplasma pneumonia cases were positive by IHC tests for M. bovis, and 31 were also positive for BVDV in the lung or heart. Thirteen were also positive for H. somnus, usually combined with other pathogens. In the prospective group, he was only able to culture BVDV in 4 of 16 cases, but an additional 5 cases were also positive by IHC. Fifteen out of the 16 cases were culture and IHC positive for M. bovis.

Dr. Colleen Pollock has also submitted a paper for publication on an epidemiologic study of CPPS. This study utilized some IHC testing but was mainly a serologic and cultural study. The results clearly showed that *Mycoplasma bovis* was the principal pathogen involved, and serologically BVDV infection was also closely associated with the syndrome. The study revealed that PI animals were not directly involved, but it is proposed that they were likely the source of the primary BVDV infections.

**Pathology Summary**

We rely heavily on IHC in our studies of feedlot cattle diseases and believe it has many advantages over culture results for both bacterial and viral agents. Most important is the fact that positive staining only occurs in the histologic lesions, confirming the significance of the infectious agents. The stains are done only on formalin-fixed tissues and not only is this convenient for the veterinarian submitting tissues to the lab, it makes possible retrospective studies of cases stored in diagnostic laboratory files. The IHC stains are permanent and are therefore stored in the laboratory histologic slide files along with the routine H and E stained slides. An ordinary light microscope is used to examine the IHC slides, which is convenient for the diagnostic pathologist. Direct immunofluorescence stains, on the other hand, require a fluorescence microscope and the stains are not permanent. Communications via digital imaging is another advantage of IHC. We have clients that sometimes request digital pictures of positive results. This is easily done with digital camera images of IHC slides sent as attachments by e-mail.

In the lung and heart, the lesions of primary BVDV infection are principally a necrotizing and lymphocytic vasculitis and associated with proliferative changes in vessel walls. It is usually only in these vessel walls that positive IHC staining for BVDV occurs. Most often, we see these BVDV lesions in animals with concurrent *Mycoplasma bovis* lesions in the lung and/or joints with fibrinous arthritis. Primary BVDV lesions can only be diagnosed or suspected by histopathology and IHC, and not by any specific gross lesions. Cultures for the virus are usually negative. Most consistently, the vasculitis is seen throughout all areas of the myocardium, includ-
lesions may have ruptured onto the pleural surface. On cut surfaces, these lesions are usually delineated by thin white lines similar to old myofibers and Purkinje fibers often stain positive for BVDV. Similar vascular lesions are seen in lung areas where M. bovis lesions are common, but they are less obvious in lung tissue because of the common co-existence of inflammatory changes due to other bacterial agents. Occasionally vasculitis lesions associated with primary BVDV infection is also seen in kidneys, intestines and joint capsules. Recently, we have seen a few cases in the leptomeninges that were associated with neurologic clinical signs.

The other histologic lesion we associate with primary BVDV infection is complete, severe atrophy and depletion of Peyer’s patches (PP) lymphoid follicles in the ileum and distal jejunum. The degree of PP atrophy and depletion is much more complete and diffuse than that co-associated with other disease processes, where they are considered a result of endogenous corticosteroid output due to stress. Often these atrophic PP follicles will stain mildly positive for BVDV, with negative staining elsewhere in the gastrointestinal tract tissues, including the mucosa.

M. bovis lesions of the lung vary considerably from case to case. Most show variable degrees of cranial-ventral chronic bronchopneumonia with nodular, firm yellow lesions within the lung lobes that often project prominently above the pleural surface. On cut surfaces, these lesions vary from very small miliary (1-2 mm) to large (often 1-2 cm or larger) areas of yellow, caseation-like necrosis, but usually not surrounded by fibrous tissue walls as in typical true abscesses. The exudate is never creamy like more typical purulent material of true abscesses. These are usually accompanied by dark red, firm collapsed lung, and the nodular mycoplasma lesions may be in small numbers or be randomly scattered and numerous through all lung lobes. Diffuse fibrinous pleuritis or chronic fibrosing pleuritis of one or both lungs is sometimes seen, and in these cases one of the nodular lesions may have ruptured onto the pleural surface. On the cut surfaces, the areas of yellow necrotic lung tissue are usually delineated by thin white lines similar to old M. hemolytica lesions of necrosis. Whole lung lobes may be diffusely involved. They may be yellow and necrotic and be accompanied by pleural and interlobular fibrosis. Linear yellow necrotic lesions of M. bovis are often seen in the interlobular spaces where the organism has gained access to the interlobular lymphatics, and the organism can be consistently isolated from the bronchial lymph nodes in such cases. It is my impression that the organism in lung tissue begins to proliferate within the luminal cell debris and exudates of small airways, then results in necrosis of the airway walls. It then continues to expand outward in a centrifugal-like fashion, coalesces with adjacent necrotic areas, and eventually invades into and spreads further via perivascular and interlobular lymphatics. It is not uncommon to have entire lobes or even one entire lung completely necrotic from M. bovis infection.

In cases where arthritis was the principal clinical and postmortem presentation, the lung lesions may be confined to the right middle lung lobe or perhaps only the accessory lung lobe of the right lung. We have seen cases with a single mycoplasma lung lesion, yet the arthritis lesions can be very extensive and seemingly more chronic. Histopathologically, the mycoplasma lesions are zones of diffuse hypereosinophilic, amorphous and necrotic lung tissue with no bacteria visible, even with standard bacterial histochemical stains. The outer edges of the necrotic zones often show lymphoid cells and some macrophages rather than neutrophils, but in small lesions some neutrophils are often seen and probably make up much of the necrotic cells in zones of necrosis. The Warthin-Faulkner silver stain is useful because it will stain the extremely tiny mycoplasma organisms black, but more importantly it stains any other types of bacteria that may be involved, helping to confirm whether or not pure mycoplasma is responsible. Large masses of mycoplasma are visible using this stain and the organisms are most numerous in the outer zones of the necrotic lesions and in the immediately adjacent viable lung tissue.

The joint lesions of CPPS show marked joint swelling and the presence of a non-odorous, yellow fibrinous exudate in the joint spaces, but quite frequently with necrosis extending into adjacent soft tissues. In the stifle in particular, invasion into and around the peronius tertius tendon, as it extends below and cranial to the stifle joint, is common. The long digital extensor muscle is thus often severely involved. Other joints not uncommonly involved include coxofemoral, tarsal, carpal and elbow joints. In very chronic arthritis cases, much of the exudate is replaced by fibrous connective tissue with fibrosis of the joint capsule, synovial membranes and intra-articular ligaments. The exudate within the joints contains massive numbers of mycoplasma organisms which are easily cultured or demonstrated by IHC or Warthin-Faulkner silver stains.
Other Diseases Secondary to Primary BVDV Infection

I do not want to leave the impression that *M. bovis* infection and CPPS are the only sequelae to primary BVDV infection that we see. Many submissions to our laboratory also include severe cases of mannheimiosis (classic shipping fever), IBR infection, bovine papular stomatitis, salmonellosis and mycotic hepatitis. In these cases, I can often demonstrate BVDV vasculitis and the presence of BVDV by IHC in the heart, lung, ileum and sometimes other tissues. Of particular importance is the fact that many of these cases occur in calves that have been on feed a month or more, rather than occurring during the first two weeks after arrival at the feedlot.

Another entity we are now seeing associated with vasculitis lesions of primary BVDV infection is digital necrosis, involving one or more distal limbs and sometimes ears and tail tips. Whether this is due to a direct viral vasculopathy in these tissues or to reduced myocardial output from viral damage to the myocardium has not been determined. Cold weather may be playing a partial role in this digital necrosis, but cases have been seen in summer months as well, and they are not associated with ergotism or fescue toxicity.

Conclusions

To investigate cases of CPPS you need a pathologist who is particularly interested in feedlot pathology and who is not afraid to look at extra histologic sections, especially of lung, ileum and heart. You also need a good postmortem technique and routinely collect tissues that you may not normally submit to the diagnostic laboratory. Multiple pieces of lung, heart, joint exudates/tissues and the ileum are especially important to diagnose CPPS. Proper mycoplasma culturing techniques and IHC for both *M. bovis* and BVDV are obviously important as well. A good IHC laboratory is most essential. We have been very fortunate in Saskatoon to have had a very good IHC service for many years, where virtually all of our important infectious diseases of domestic animals can be diagnosed solely from formalin-fixed tissues.

References

3. Pollock CM, Campbell JR, West KH, Janzen ED: Epidemiological features of the chronic pneumonia-polyarthritis syndrome of calves in a central Saskatchewan feedlot. (submitted)