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Pathogenesis and Pathology of Bovine Pneumonia

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KEYWORDS

- Bronchopneumonia • Fibrinous pneumonia • Pleuropneumonia
- Aspiration pneumonia • Caseonecrotic pneumonia
- Interstitial pneumonia • Embolic pneumonia
- Verminous pneumoniae

Despite availability and use of many bovine respiratory pathogen vaccines and new antimicrobial drugs as well as greater understanding of the pathogenesis of bovine respiratory disease (BRD), pneumonia, ranging from subclinical to fatal, remains a major cause of morbidity, mortality, and economic loss to the beef and dairy cattle industries.^{1,2} When cattle are subjected to stresses, such as weaning, shipment, and commingling with animals from other sources, transmission of various infectious agents and proliferation of endogenous—yet potentially pathogenic—microbes occur often, resulting in damage to the respiratory tract with subsequent upper or lower respiratory disease.³ Most fatal forms of BRD and often the outcome of this stress/infectious agent scenario are severe bacterial (including mycoplasmal) pneumonias. In addition, other forms of severe respiratory disease and pneumonia, such as acute interstitial pneumonia (AIP), exist whose pathogenesis are less well established. Finally, incidental and less frequent causes of bovine pneumonia include embolic, verminous, and aspiration pneumonias.

This article focuses on pathogenesis and pathologic characteristics of selected types of bovine pneumonia with emphasis on gross pathologic changes. Readers are referred to several recent articles and textbooks for more complete histopathologic descriptions.^{3–5} Emphasis is on bacterial and AIP, major causes of losses primarily in feedlot and stocker cattle. Bacterial pneumonia usually occurs within the first 6 to 10 days after stress, such as shipping or commingling, with interstitial pneumonias often occurring 70 or more days later.⁶ Bacterial pneumonia is second to diarrheal disease as a cause of illness and losses in dairy calves. In addition, several

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of the minor pneumonias of cattle are discussed on a lesion recognition and differential diagnosis basis.

BOVINE BACTERIAL PNEUMONIA

The role of bovine respiratory viruses in precipitating severe BRD and bacterial pneumonias has long been known. Bovine herpesvirus-1 (BHV-1) (infectious bovine rhinotracheitis virus); parainfluenza virus-3 (PI-3); and bovine respiratory syncytial virus (BRSV) are recognized as primary respiratory pathogens.^{5,7} During the past 25 years, the roles of other viruses have been speculated on and investigated; several, including bovine rhinoviruses and adenoviruses, have been dismissed as minimal pathogens at best and bovine viral diarrhoea virus (BVDV) has been recognized as a major pathogenic partner in BRD.⁸ A pathogenic role for bovine respiratory coronavirus has been postulated, but if such a role exists, it is still under investigation.⁹ BHV-1, PI-3, BRSV, and BVDV can cause some degree of acute respiratory disease. BHV-1 is well recognized as a cause of severe upper respiratory lesions, ranging from hemorrhage to diphtheritic membranes.⁴ With the exception of certain instances of BRSV, fatality is usually not associated with those infections alone. Instead, their roles are primarily to assist in establishing a respiratory environment that is favorable to colonization and replication by several pathogenic bacteria resulting in pneumonia.^{10–14} This is done through two major mechanisms. The first is by alteration in mucosal surfaces such that adhesion of bacteria to virus-infected cells is enhanced; further colonization occurs more readily in areas of virus-induced mucosal erosion than in intact mucosa.^{15–17} The second is modification of the innate and adaptive immune systems through altered alveolar macrophage function, suppression of lymphocyte proliferation and induced apoptosis, and modified cytokine and other inflammatory mediator release.¹⁷

In an overview of the pathogenesis of pneumonia in feedlot cattle in a 1983 symposium on BRD, Thomson¹⁸ described only *Mannheimia haemolytica* (formerly *Pasteurella haemolytica*) and *Pasteurella multocida* as bacterial pathogens in the BRD complex. Since that time, *Histophilus somni* (formerly *Haemophilus somnus*), *Arcanobacterium pyogenes*, *Mycoplasma bovis*, and, most recently, *Bibersteinia trehalosi* (formerly *Pasteurella trehalosi*) have also been recognized as additional bacterial agents associated with severe bovine bacterial pneumonia (**Table 1**).^{19,20} These bacteria are ubiquitous in the cattle population as normal nasopharyngeal commensals and, after stress or viral infection, can proliferate and be inhaled into the lungs. Each has its own cadre of virulence factors, including biofilm, capsules, adhesins, toxins, and enzymes, that enhance its ability to colonize the lower airway, evade the immune system, resist antimicrobial treatment, cause tissue destruction, and incite an intense inflammatory response.¹⁰

Differences in various virulence factors possessed by each bacterial species are responsible for the relative pathogenicity and lesions indicative of that particular infection (see **Table 1**). *M haemolytica* virulence factors include protein adhesins, capsular polysaccharide, lipopolysaccharide (LPS), iron-binding proteins, secreted enzymes, and a ruminant-specific RTX toxin—leukotoxin (LKT).¹⁴ LPS and LKT are the two factors responsible for most of the destructive lesions of *M haemolytica* infection. Specific adhesins include a glycoprotein, N-acetyl-D-glucosamine, that mediates adherence to tracheal epithelial cells and activates the oxidative burst of bovine neutrophils. Heat-modifiable outer membrane protein A (OmpA) and the surface lipoprotein 1 mediate *M haemolytica* binding to bronchial epithelial cells. In addition, the *M haemolytica* capsule may function as an adhesin in addition to its antiphagocytic

Table 1
Major BRD pathogenic bacteria and their virulence factors

| Bacterium | Capsule | Endotoxin | Exotoxins | Adhesin Proteins | Secreted Enzymes | Other Factors |
|---------------------------------|---------|-----------|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| <i>Mannheimia haemolytica</i> | Yes | LPS | LKT | <ul style="list-style-type: none"> • OmpA • Lipoprotein I • N-acetyl-D-glucosamine • Fibrinogen-binding proteins | <ul style="list-style-type: none"> • Neuraminidase • Sialoglycoprotease | <ul style="list-style-type: none"> • Biofilm |
| <i>Pasteurella multocida</i> | Yes | LPS | <i>P. multocida</i> Toxin—rarely in BRD isolates | <ul style="list-style-type: none"> • OmpA • Type IV fimbriae • FHA | <ul style="list-style-type: none"> • Neuraminidase | <ul style="list-style-type: none"> • Biofilm |
| <i>Histophilus somni</i> | No | LOS | None | | | <ul style="list-style-type: none"> • Biofilm • IgBPs • Histamine |
| <i>Mycoplasma bovis</i> | No | No | Polysaccharide toxin (?) | <ul style="list-style-type: none"> • VSPs | | <ul style="list-style-type: none"> • Biofilm • Hydrogen peroxide |
| <i>Arcanobacterium pyogenes</i> | No | No | Pyolysin | <ul style="list-style-type: none"> • Collagen-binding protein | <ul style="list-style-type: none"> • Proteases • DNAase | <ul style="list-style-type: none"> • Biofilm |
| <i>Bibersteinia trehalosi</i> | Yes | Yes | LKT ± (strain dependent) | <ul style="list-style-type: none"> • Two OmpA • Fibrinogen-binding proteins | <ul style="list-style-type: none"> • Novel protease • Superoxide dismutase | |

properties. Fibrinogen-binding proteins have been identified.²¹ Neuraminidase and sialoglycoprotease modify cell surfaces and may enhance bacterial adhesion. *M haemolytica* LPS has typical endotoxic and proinflammatory properties, causes vasculitis, and complexes with LKT enhancing LKT receptor production and augmenting LKT activity. LKT induces dose-related changes in bovine leukocytes, ranging from osmotic swelling, membrane pore formation, and necrosis to apoptosis or release of proinflammatory cytokines, oxygen-free radicals, and cellular protease.^{14,22–24} Evidence of biofilm formation with reduced antimicrobial susceptibility has been demonstrated.²⁵

P multocida virulence factors are less numerous than those identified in *M haemolytica*. Several adhesins, a thick polysaccharide capsule, and LPS are the major factors responsible for bacterial colonization, evasion of host defense, tissue destruction, and inflammation.¹³ Adhesins are responsible for bacterial adherence to and colonization of cell surfaces. These include type IV fimbriae, OmpA, neuraminidase, and filamentous hemagglutinin (FHA). In addition, OmpA and various iron-binding proteins, such as hemoglobin-binding protein A and transferrin-binding protein A, bind fibronectin; and other extracellular matrix proteins may aid in invasion. The importance of capsule as a virulence determinant in the pathogenesis of *P multocida* infection is due to its antiphagocytic properties. *P multocida* LPS is a potent stimulator of inflammatory cytokines and a predominant inciter of pulmonary inflammation.¹³ Evidence of biofilm formation with reduced antimicrobial susceptibility has been demonstrated.²⁵

H somni are nonencapsulated, and the virulence factors include lipooligosaccharide (LOS) and various outer membrane proteins, especially transferrin-binding proteins and immunoglobulin-binding proteins (IgBPs).¹² LOS can mediate endothelial cell apoptosis and, through antigenic phase variation, can assist the bacterium to escape the host immune response. LOS is the primary factor responsible for lesion formation by causing thrombosis, inflammation, and tissue destruction. IgBPs assist the bacterium to evade host defenses. They are surface-exposed fibrillar protein networks that bind the Fc domain of bovine IgG2 and are responsible for virulent strains that are resistant to phagocytosis and complement-mediated serum killing.²⁶ *H somni* produces histamine, which in conjunction with anti-major outer membrane protein IgE, may account for early respiratory lesions.^{12,27,28} Recently, biofilm production by *H somni* within the host was documented, which allows the bacterial colonies to evade host defense and resist antimicrobial drugs. FHA proteins may be involved in that process.²⁹

M bovis virulence factors include variable surface proteins (VSPs) that function as adhesins allowing the bacterium to colonize bronchioles. VSPs are responsible for phenotypic variation among *M bovis* strains and, through antigenic phase variations, allow for evasion of host immune responses.^{30,31} A polysaccharide toxin has been described; however, the role or even existence of that toxin remains controversial. *M bovis* strains may produce hydrogen peroxide, which forms oxygen-free radicals and causes host lipid peroxidation. The formation of biofilm has been associated with many *M bovis* strains, and that trait enhances immune and antimicrobial resistance and colonization.³²

A pyogenes produces a collagen-binding protein (Cbpa) that allows it to bind collagen and promotes adhesion to host cells.³³ A cholesterol-dependent cytolysin (pyolysin) that is a pore-forming cytolysin/hemolysin has been characterized.^{34,35} Adhesion may also be mediated by type II fimbriae and by two neuraminidases that cleave sialic acids and expose cell receptors. Several extracellular matrix-binding proteins that bind to collagen or fibronectin and exoenzymes (DNase and proteases)

assist in invasion of tissue and degradation of proteins and nucleic acids. In addition, *A pyogenes* can evade host defenses by invasion of epithelium by intracellular survival in macrophages and by formation of biofilm.³⁶

Virulence factors of *B trehalosi* are not as well understood as those of many of the other BRD bacterial pathogens; however, there are many similarities with *M haemolytica*. Strains are encapsulated, and some strains are positive for LKT whereas others are not.³⁷ It is not clear whether or not strains that are LKT deficient are pathogenic. A novel protease has been demonstrated in *B trehalosi* isolated from bighorn sheep, and high antibodies to it were found in healthy sheep.³⁸ Fibrinogen-binding proteins have been identified.²¹ Adhesion to epithelial surfaces could be mediated by the two OmpA molecules expressed in *B trehalosi*.³⁹

Identification of pathogenic bacteria at necropsy depends on many factors, including type and number of antimicrobial treatments, extent of tissue decomposition, sample collection, holding, and shipping methods, transit time to laboratory, and method of bacterial detection. Traditional culture, immunohistochemistry, in situ hybridization, and polymerase chain reaction (PCR) techniques are available in various laboratories across North America. Technique sensitivity and specificity differ among these tests, and results may vary depending on the test applied. For example, *H somni* was cultured from only 10 of 65 cases of pneumonia, yet the bacterium was demonstrated by immunohistochemistry, in situ hybridization, and PCR in 17, 19, and 29 of the cases, respectively.⁴⁰ In feedlots in particular, there is strong correlation between the time of onset of pneumonia, acuteness of the lesion, and the etiologic agents that can be isolated from that lesion. For example, Booker and colleagues⁴¹ using immunohistochemistry demonstrated that in lungs from cattle dying of peracute to subacute pneumonia, *M haemolytica*, *H somni*, and *M bovis* were demonstrated in approximately more than 80%, less than 20%, and 50% to 60% of the lungs, respectively. In contrast, the incidences of *M haemolytica*, *H somni*, and *M bovis* were approximately 40%, 30%, and 90%, respectively, in chronic pneumonia; lungs were not examined for *P multocida*. Using bacteriologic culture, Fulton and colleagues⁴² demonstrated that when *M haemolytica* was isolated from lungs of cattle dying of pneumonia the mean onset of fatal disease was approximately 19 days in the feedlot. In contrast, when *M haemolytica* was not isolated from the lungs, the mean day at onset was approximately 33 days on feed. The opposite was true for *Mycoplasma* sp isolation, whereas onset of disease was approximately 70 days for positive lungs and 29 days for negative lungs. To complicate matters further, multiple pathogenic bacteria are often isolated from individual cases of bovine pneumonia at necropsy resulting in an inability to identify the primary pathogen or pathogens. In several studies, more than 60% of the lungs from cattle dying of bacterial pneumonia contained more than one potentially pathogenic bacterial species.^{41–43} Therefore, reliance on microbiologic techniques applied to lungs at necropsy, using culture or another means, such as PCR or immunohistochemistry, is likely not providing a clear representation of the role of specific pathogens in initiating the lesion. Finally, the characteristics and type of pneumonic lesion present at necropsy are determined by the inciting causative bacteria and concurrent or predisposing pathogens as well as the effectiveness or ineffectiveness of host defense mechanisms. In addition, lesion characteristics are highly dependent on acuteness or chronicity of the lesion as well as the types, numbers, and length of treatments received.⁵

Inhaled bacterial pathogens first colonize the bronchoalveolar junction, overcome host defenses, incite inflammation at that site, and spread through contiguous airways or through adjacent components of lung tissue to produce three general types or patterns of pneumonia. These are suppurative bronchopneumonia (also called lobular

bronchopneumonia), fibrinous pneumonia or pleuropneumonia (also called lobar pneumonia or fibrinous bronchopneumonia), and caseonecrotic pneumonia (also called mycoplasmal pneumonia).^{4,44} These various types of bronchopneumonia are classified based on the type of exudation present, initial site of bacterial localization in the airway, influence of various bacterial virulence factors, host resistance, and rapidity and method of spread of the infection within the lung. In addition, specific bronchopneumonia subclassifications are more commonly associated with specific bacteria.

Suppurative Bronchopneumonia (Lobular Bronchopneumonia)

This form of pneumonia is the most common form seen in BRD of young dairy calves and most often associated with *P multocida* infection, although other respiratory bacteria may also produce the lesion.^{3,4,13} Suppurative bronchopneumonia occurs when bronchial colonization of moderately virulent bacteria initiates a suppurative bronchitis with progressive spread along airways resulting in an obviously bronchiole-centered lesion within each lung lobule. The pneumonia is bilateral, cranioventrally distributed, and moderately firm (**Fig. 1**). In acute lesions, affected lobes are fairly uniform in color varying from pink, pink-gray, dark red, red-gray, or gray with minimal to mild interlobular septal edema (**Fig. 2**). Pleuritis is usually not present; however, if present, it consists of small foci of pleural dullness to small clusters of fibrin strands. On cut surface within lobules, there are variable-sized, partially discrete tan to gray foci indicative of a pattern of bronchiolar and peribronchiolar inflammation (**Fig. 3**). Remaining areas of lobules are pink to dark red representing various amounts of inflammation, congestion, and atelectasis. Intrabronchial purulent to mucopurulent exudate may be grossly obvious or in more subtle cases require a gentle squeeze to express exudate.

As bronchopneumonia becomes more chronic, palpation reveals a more lumpy distribution of consolidation with more obvious purulent bronchitis, bronchiectasis, and abscess formation. Inter- and intralobular fibrosis is present. Affected bronchioles may be prominent due to peribronchial fibrosis with dilated, mucoid to purulent, exudate-filled lumens. Shrunken, obscured lumens due to bronchiolitis obliterans become prominent histopathologically, but those changes are not readily grossly recognized. Focal fibrinous to fibrous adhesions may develop between parietal and visceral pleura especially over underlying abscesses. In chronic cases, *A pyogenes* is usually cultured particularly from bronchiectatic airways and abscesses, whereas other parts of the lung may yield multiple bacterial species.

Fibrinous Pneumonia or Fibrinous Pleuropneumonia (Fibrinous Bronchopneumonia, Lobar Pneumonia)

This form of pneumonia is typical of that produced by *M haemolytica* and to a lesser extent *H somni* and is the most common form of acute pneumonia in weaned, stressed beef cattle (shipping fever).^{3,4} Fibrinous pneumonia occurs when there is overwhelming centrifugal spread of the inflammatory process from the primary locus of colonization in the bronchioles via extension from lobules into adjacent lobules within the cranioventral lobes. The rapid intra- and interlobular spread of *M haemolytica* is thought due to the effects of LPS on vascular integrity, severe cytolytic effects of LKT on resident and responding leukocytes, and the tissue destructive effects of released enzymes, oxygen radicals, and inflammatory mediators during that process.^{14,45}

Fibrinous pneumonia is a bilateral, cranioventrally distributed, very firm, minimally compressible lung consolidation (**Fig. 4**). Fibrinous pneumonia is characterized by wide distension of interlobular septa with yellow gelatinous edema or coagulated

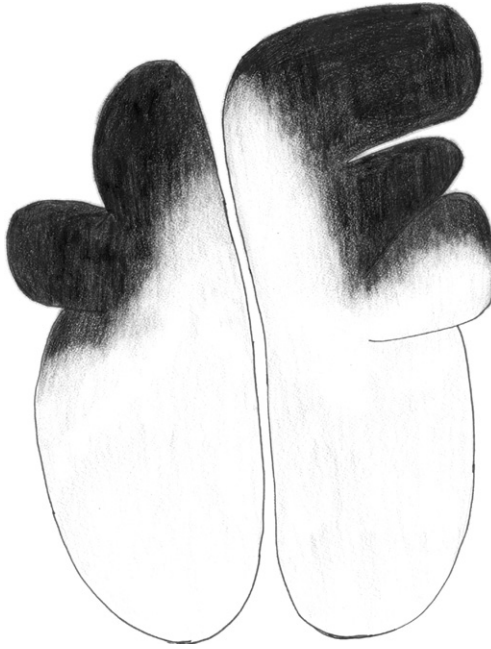


Fig. 1. Bronchopneumonia (suppurative bronchopneumonia, lobular bronchopneumonia).

fibrin. Fibrin thrombi may be visible in distended interlobular lymphatics. Consolidated lobes have a marbled appearance, a descriptive term indicating that each lobule is reasonably uniform in color with a multicolor patchwork or marbled pattern of lobules ranging from pink, pink-tan, dark red, to red-gray (**Fig. 5**). Large, irregular foci of pink-tan coagulation necrosis are frequently within lobules and may involve entire lobules. These necrotic foci are usually outlined by a discrete pale line representing intense accumulations of inflammatory cells and result from intralesional vasculitis and thrombosis that develop. Bronchi contain fibrinous coagulum but not frank pus.

Fibrinous pleuropneumonia (fibrinonecrotic pneumonia and pleuropneumonia) is likewise a bilateral, cranioventral, marbled pneumonia in which a fibrinous pleuritis



Fig. 2. Cranioventral, acute, suppurative bronchopneumonia (lobular pneumonia).

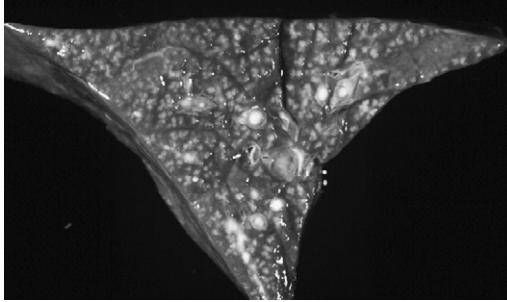


Fig. 3. Acute suppurative bronchopneumonia demonstrating bronchiolar and peribronchiolar pattern of inflammation with pus-filled airways.

of varying intensity is present (**Fig. 6**). The presence of pleuritis is an indication of the aggressiveness of the lung infection such that there is extension of infection and inflammation from alveoli to subpleural connective tissue and onto the visceral pleural surface. In early stages, pleural granularity, dullness, and fine fibrinous strands are present. Later, more intense broad sheets of yellow fibrin may obscure the appearance of the underlying lung. Fibrinous adhesions are likely present between parietal and visceral pleura. Fibrin-rich, yellow fluid within the pleural cavity is highly variable in quantity. In contrast to *M haemolytica*-associated pneumonia, *H somni*-associated fibrinous pneumonia may have accompanying lesions of myocarditis, myocardial infarction, and fibrinous synovitis.

Chronic pneumonic changes similar to those seen in bronchopneumonia occur in cattle that survive acute fibrinous pneumonia or pleuropneumonia.

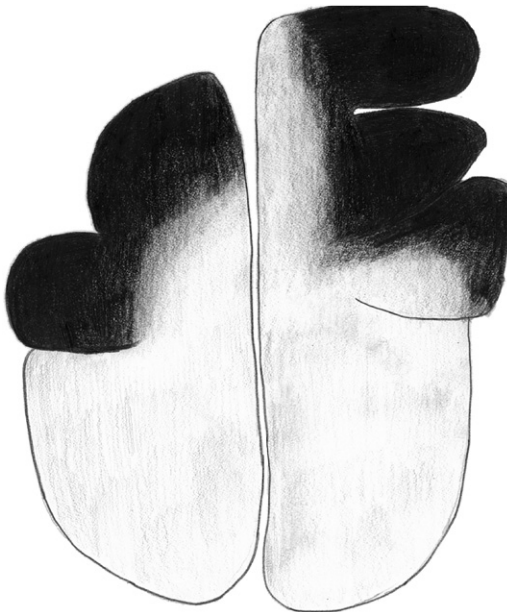


Fig. 4. Fibrinous pneumonia and fibrinous pleuropneumonia (lobar bronchopneumonia).

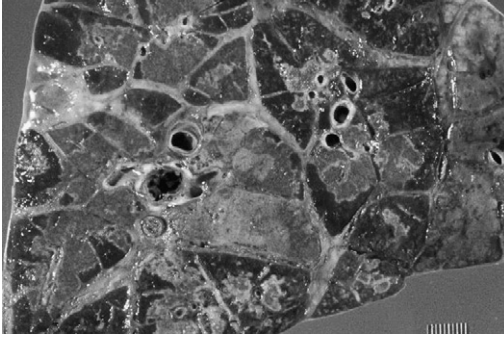


Fig. 5. Fibrinous pneumonia (lobar pneumonia) demonstrating marbled appearance due to pale areas of coagulation necrosis and dark areas of acute pneumonia. Interlobular septa are distended with fibrin-rich exudate.

Caseonecrotic Bronchopneumonia (Mycoplasmal Pneumonia)

In recent years in North America, this type of pneumonia has been recognized as characteristic of chronic *Mycoplasma* infection, especially *M bovis*, which is more virulent than other bovine *Mycoplasma* spp.^{32,46} In many studies of BRD, *Mycoplasma* spp can be demonstrated in more than 70% of pneumonia cases usually in combination with other bacteria. Sole *Mycoplasma* spp isolation occurs in less than 20% of BRD cases.^{41,43}

Mycoplasma spp colonize the ciliated epithelium of the respiratory tract producing a mild mucopurulent bronchitis and bronchiolitis and, through persistent infection, pulmonary lesions may develop.³¹ In mild, subacute cases, the main lesion is large peribronchial lymphocytic cuffs. Systemic spread of *M bovis* may lead to serofibrinous synovitis and otitis media.⁴⁷ Gross examination of the lung at this stage likely reveals no obvious changes or small patchy red to red-gray areas of cranioventral atelectasis.

With *M bovis* infection, however, many calves develop chronic, multifocal, caseous necrosis within the cranial lung lobes (caseonecrotic bronchopneumonia). Although the pathogenesis of this lesion is still under investigation, bacterial antigen is demonstrated surrounding necrotic foci suggestive of a cause and effect relationship.⁴⁸⁻⁵⁰ *M bovis* virulence factors responsible for this lesion are not currently understood. At necropsy, the cranioventral lobes are expanded with firm consolidation, which is often

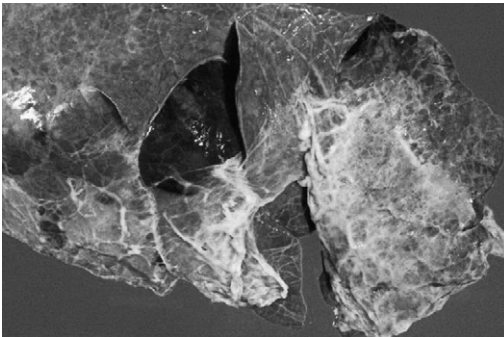


Fig. 6. Fibrinous pleuropneumonia (lobar pneumonia) with extensive fibrinous exudate.

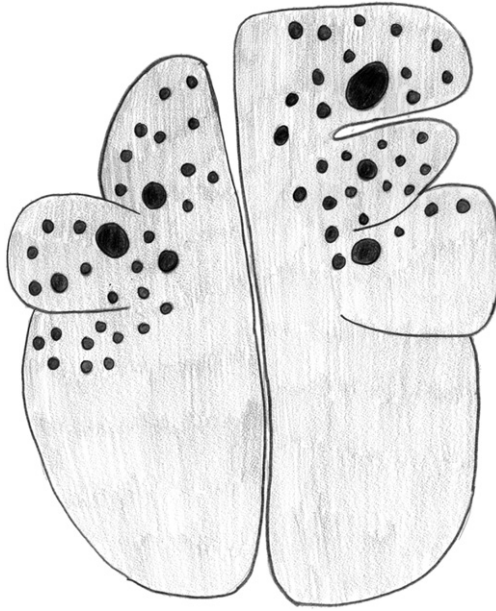


Fig. 7. Caseonecrotic (*Mycoplasma*) pneumonia.

visibly and palpably nodular (**Fig. 7**). Clusters of discrete yellow foci of caseous necrosis are present within lobules, and these foci often range from 1 to 10 mm in diameter (**Fig. 8**). The surrounding lobular tissue is often mottled to uniformly gray to dark red. In more severe lesions, necrotic foci coalesce and can involve an entire lobule. When the lung is squeezed, the necrotic material falls out as a single mass or multiple pieces. Sequestra may be seen. Expressed bronchial exudate may be mucoid to mucopurulent; the character of the exudate is likely determined by the presence or absence of other bacteria. A caseous to caseofibrinous synovitis or otitis may accompany the pneumonia.



Fig. 8. Caseonecrotic bronchopneumonia typical of *M bovis* infection. Small (arrow) to large (asterisk) areas of coalescing foci of necrosis are present. (Courtesy of Dr Jeff Caswell, University of Guelph, Guelph, Ontario, Canada.)

INTERSTITIAL PNEUMONIA

The term, *interstitial pneumonia*, designates a lesion rather than a disease. The lesion may be acquired by delivery of causative factors through pulmonary circulation or by airways. Whatever the route of exposure, primary damage occurs to structures in alveolar septa (ie, alveolar type I pneumocytes or vascular endothelial cells) and to bronchiolar Clara cells. Subsequently, the fibrin-rich plasma exudation phase occurs creating severe edema and intraalveolar hyaline membranes.^{3,5} This exudative phase is followed by type II pneumocyte proliferation, and, with time, alveolar septal fibrosis. Type II pneumocyte hyperplasia can be extensive resulting in alveoli lined by cuboidal epithelium in an acinar or gland-like appearance (sometimes referred to as pulmonary fetalization or adenomatosis).

There are many established causes of interstitial pneumonia, which include, but are not limited to, various chemical compounds, such as 3-methylindole (3MI); viruses, such as BRSV; migrating parasite larvae; immune mechanisms; toxic gases; and perhaps environmental conditions.^{3,51,52} In many instances, however, the causative factor is not known. Interstitial pneumonia occurs in various patterns of lung involvement. The best characterized pathologically is diffuse AIP (**Fig. 9**), whereas less well characterized is secondary interstitial pneumonia, which is distinguished by coexisting, probably preceding, cranioventral bronchopneumonia with extensive interstitial pneumonia in caudal areas of lungs (**Fig. 10**). A third, less well-characterized pattern, involves various areas of lung, predominantly caudal, dorsal with intervening areas of more normal, but prominently pale, overinflated lobules or groups of lobules, forming a so-called checkerboard pattern (**Fig. 11**).⁵¹

Acute interstitial pneumonia

AIP, frequently referred to as acute bovine pulmonary edema and emphysema or, in the United Kingdom, fog fever,⁵ occurs in pastured cattle moved to lush green

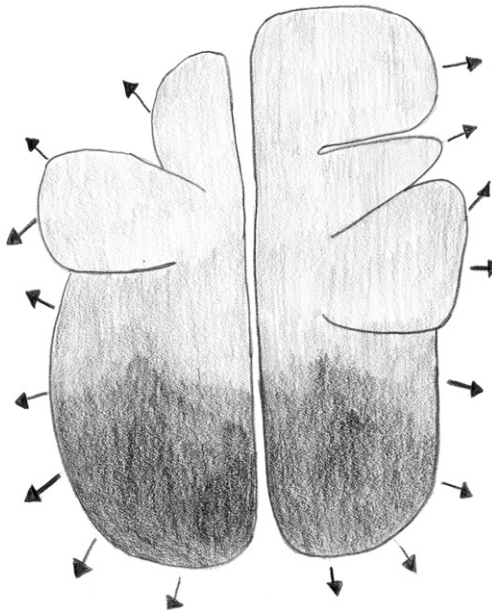


Fig. 9. Acute interstitial pneumonia.

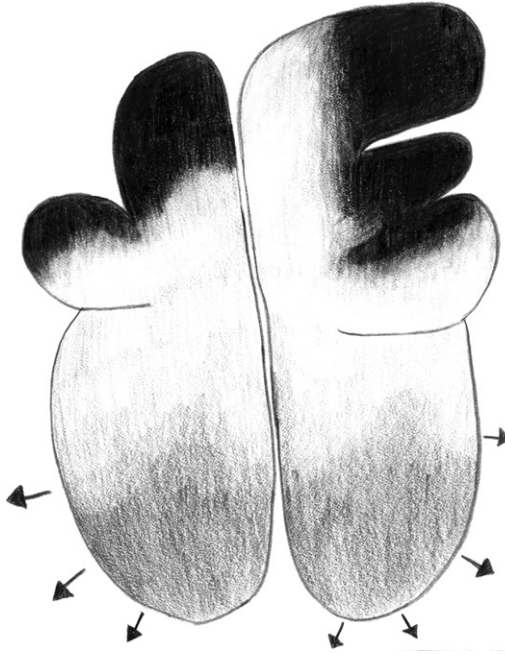


Fig. 10. Secondary interstitial (so-called feedlot interstitial pneumonia).

pastures or by exposure to chemicals, including plant toxins, such as *Perilla* mint ketone and 4-ipomeanol from moldy sweet potatoes.⁵³ Clinical signs usually develop within 2 to 3 weeks of pasture changes or as short as 1 to 2 days after exposure to plant toxins. Classically, movement of cattle to lush green pastures results in excess ingestion of L-tryptophan with conversion to 3MI by rumen flora.^{51,52} Metabolism of



Fig. 11. AIP in a feedlot calf. Overinflated cranioventral lobules interspersed with darker pneumonic lobules (checkerboard). Caudal dorsal lung contains diffuse gray areas of pneumonia. (Courtesy of Dr Amelia Woolums, University of Georgia, Athens, GA.)

3MI in bronchiolar Clara cells and type I pneumocytes results in highly activated intermediates that cause pneumocyte necrosis and exfoliation setting in motion the pathologic processes resulting in interstitial pneumonia. This form of AIP is differentiable from AIP of feedlot cattle (discussed later) by epidemiology, known causative agents, and lesion characteristics.

At necropsy, cattle often have abundant subcutaneous emphysema over the dorsal subcutis, emphysema within the mediastinum, and frothy edema in the trachea. Lungs are diffusely wet, heavy, and fail to collapse. Lobules tend to be individualized (**Fig. 12**). Interlobular septa are distended with edema and gas bubbles. Palpable changes may be subtle to obvious and range from palpably normal to somewhat rubbery in a diffuse distribution. Palpation of single lobules provides critical assessment of lung texture. Parenchyma ranges from pink to tan. Clear, watery, edema fluid readily exudes from the cut surface.

Interstitial pneumonia in feedlot cattle

This form of interstitial pneumonia is a sporadic cause of death in North American feedlot cattle that usually occurs late within the feeding period.^{6,51,52} Most surveys recognize the lesion in less than 10% of the total feedlot deaths with occasionally larger outbreaks reported.^{6,41,42} Many causes have been investigated, and it is most likely that interstitial pneumonia in feedlot cattle results from one or combinations of several mechanisms. As in AIP of pastured cattle, a role for 3MI has been examined. In the feedlot disease, 3MI has been generally discounted because of the sporadic nature of the disease and lack of association with dietary change. In one feedlot study, however, blood levels of a 3MI metabolite were significantly higher in AIP than in control cattle suggesting a potential pathogenic role for 3MI.⁵⁴ Interstitial pneumonia also was described with some frequency in feedlot heifers fed melengestrol acetate to suppress estrus.⁵⁵ Several studies have investigated the association of BRSV and interstitial pneumonia with conflicting results; however, this may be because attempts to culture or demonstrate viral antigen is done using postmortem-collected specimens, and negative results may not accurately account for the virus' role in pathogenesis.^{51,54,56,57} Lesions of small airway disease, such as bronchiolar necrosis and, more commonly, its healing stage, bronchiolitis obliterans, are frequently found histologically in feedlot cases of interstitial pneumonia.^{4,6,57} It was suggested that feedlot interstitial pneumonia might result from the effects of increased proinflammatory cytokines within lungs due to chronic bronchiolar disease, and endotoxin from gram-negative

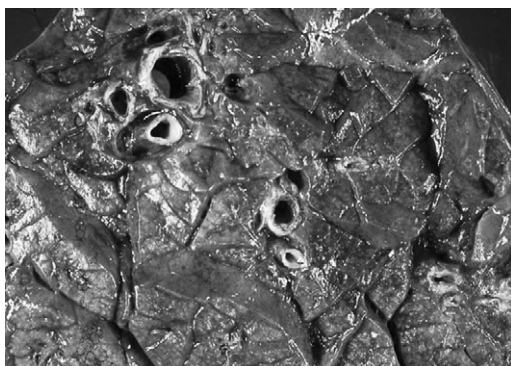


Fig. 12. AIP with lobules clearly separated by interlobular edema. Subtle differences are seen in various lobules. (Courtesy of Dr John King, Cornell University, Ithaca, NY.)

respiratory infections may contribute alveolar and bronchiolar damage leading to interstitial pneumonia.⁵²

Gross patterns of interstitial pneumonia in feedlot cattle include that of acute diffuse distribution but more frequently interstitial pneumonia is in caudal lobes combined with bronchopneumonia cranially (see **Fig. 10**). In addition, interstitial pneumonia may occur in a patchy distribution, with pneumonic lobules separated by prominently pale, bulging, overinflated lobules or groups of lobules (so-called checkerboard pattern) (see **Fig. 11**).^{51,56} Lesions of bronchopneumonia have been reported in 32% to 96% of fatal cases of feedlot AIP. Death due to AIP usually occurs from 21 to 73 days after onset of preceding respiratory illness, such as bronchopneumonia.^{6,57,58}

Gross lesions of feedlot cases of interstitial pneumonia are typical. Bilaterally, lungs fail to collapse and are overinflated and heavy with variable amounts of interlobular edema and emphysema. The lesion may be diffuse, but it is usually more obvious in the caudal dorsal lobes. Cranioventral bronchopneumonia or fibrinous pneumonia is often visible. Palpation of caudal areas reveals a rubbery texture in a diffuse but more commonly a slightly lumpy pattern, wherein rubbery texture is confined to individual lobules separated by palpably normal lobules. Affected lobules range from pale red-gray, pink or tan, to clear fluid exudes or can be expressed from the cut surface unless concurrent suppurative bronchitis or bronchopneumonia is present. The so-called checkerboard pattern of rubbery, perhaps dark lobules interspersed with normal to pale, overinflated lobules may be seen; however, in many cases of interstitial pneumonia, the lesion is not visually obvious but palpably so.

Bronchointerstitial pneumonia

The bronchointerstitial form of interstitial pneumonia is used to describe uncomplicated viral infections of the lung due to BHV-1, PI-3, and BRSV infections.^{4,5,31} Ellis and colleagues⁸ also described pulmonary lesions associated with experimental BVDV type 2 infections as bronchointerstitial pneumonia. Although the lesions of bovine respiratory coronavirus infection are not well documented, and several investigators have failed to reproduce a lung disease with these viruses, experimental infection of calves with a winter dysentery bovine coronavirus resulted in small intestine villous atrophy and bronchointerstitial pneumonia.^{59–61} Bronchointerstitial pneumonia is characterized by bronchiolar epithelial and pneumocytic damage resulting in bronchiolar necrosis, mild inflammatory cell influx, and type II pneumocyte hyperplasia. In the field, bronchointerstitial pneumonia is often complicated with secondary bacterial infection, which obscures and overshadows the primary viral lesion. Therefore, cases of true bronchointerstitial pneumonia are only occasionally recognized. For example, bronchointerstitial pneumonia was recognized in only 3 of 214 (1.4%) pneumonic lungs in a recent feedlot study.⁴²

Gross lesions of bronchointerstitial pneumonia have been documented best in BRSV infections, are cranioventral distributed, and are often subtle ranging from reddened areas of atelectasis to rubbery gray lobules.⁶² If exudate is expressible, it is usually mucoid to mucopurulent. Caudal lobes may be overinflated with emphysematous bullae.

SEVERE ANEMIA

As a differential for diffuse AIP, the gross appearance of lungs from severely anemic cattle must be considered. These lungs fail to collapse and are pale, overinflated, and markedly puffy (**Fig. 13**). A yellowish tint may occur in severe, acute hemolytic

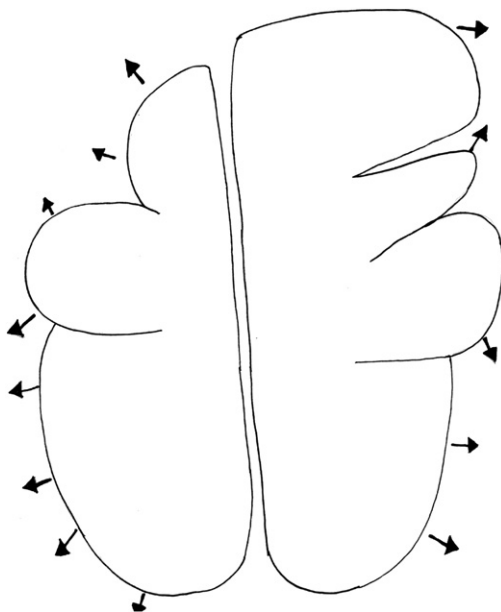


Fig. 13. Severe anemia.

crises and the lungs appear dry on cut surface. In subacute to chronic blood loss, pulmonary edema and pleural effusion may occur.

ASPIRATION PNEUMONIA

Inhalation of foreign material, in particular liquids, can result in aspiration pneumonia. The characteristics of the resulting pneumonic lesion are dependent on the nature and distribution of the material as well as the extent and type of bacterial contamination.³⁻⁵ Aspiration due to faulty intubation, dysphagia, regurgitation, and infected large particles of necrotic mucosa from upper respiratory lesions can cause aspiration pneumonia. Pail- or bottle-fed calves, intubation and balling gun accidents, traumatic pharyngitis, rumenitis from ingesta of oilfield fluids, and prolonged recumbency have all been implicated in causing aspiration pneumonia. Aspiration of rumen contents is, by far, the most common cause of aspiration pneumonia of cattle. The resulting lesions are often unilateral, necrotizing to gangrenous, and predominantly cranioventral (**Figs. 14** and **15**). Another diagnostically useful feature of distribution exists when the pneumonic lesion is not only unilateral but also caudally situated without cranial lung involvement. Fibrinopurulent to suppurative pleuritis is commonly present and covers the necrotic foci; empyema may result from ruptured foci.⁵⁸ Pneumonic lesions are brown to green and may be hemorrhagic, often forming cystic cavities exuding malodorous brown fluid that may contain ingesta. Putrid odors are especially prevalent in the presence of aspirated rumen anaerobic bacteria. Foreign material may be readily visible within the airways, but terminal aspiration of rumen contents must not be mistaken for a lesion of aspiration pneumonia. If the inciting material is lipid-rich, lipid droplets are visible floating on bronchoalveolar fluids.

The least common form of aspiration pneumonia in cattle is lipid pneumonia, resulting from aspiration of lipid-rich material, such as mineral oil or other oil-based

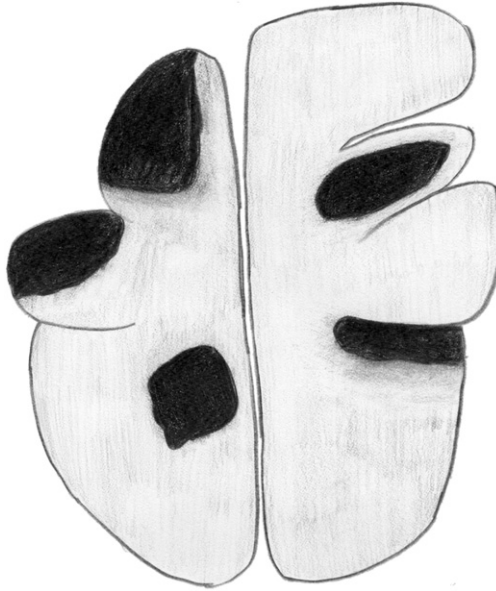


Fig. 14. Aspiration pneumonia.

compounds. Those compounds can stimulate an intense interstitial pneumonia with alveolar exudation of fibrin and leukocytes, type II pneumocyte hyperplasia, and interstitial fibrosis. Uncomplicated lesions may range from diffuse to cranioventral and are wet, rubbery, pale, yellowish, or mottled. Foci of necrosis or suppurative exudation can be present due to bacterial infection.

EMBOLIC PNEUMONIA

Embolic pneumonias consist of multiple, randomly distributed inflammatory foci throughout all lung lobes (**Fig. 16**).³⁻⁵ In contrast, abscesses that develop in chronic suppurative bronchopneumonia and fibrinous pleuropneumonia maintain a cranioventral distribution. Embolic pneumonia is preceded by bacterial infection and suppuration at another location, which in cattle is most commonly liver, but other loci may



Fig. 15. Aspiration pneumonia with severe, multiple, necrotic cavitations.

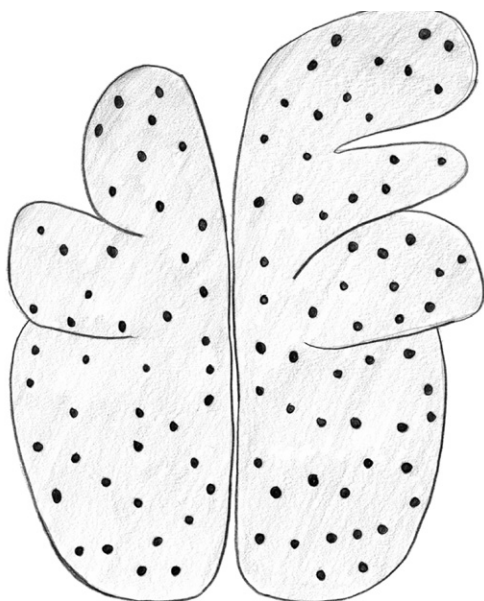


Fig. 16. Embolic pneumonia.

occur, such as traumatic reticulopericarditis, mastitis, endometritis, and jugular thrombophlebitis. Extension of infection into local veins causes thrombophlebitis, pulmonary thromboembolism, and disseminated foci of pulmonary inflammation. Right-side vegetative endocarditis may also be present. Hepatic abscesses, often caused by *Fusobacterium necrophorum*, may erode hepatic veins or caudal vena cava resulting in embolic showering of the lung. The earliest lesions are small foci of acute inflammation and necrosis that may progress to small- to moderate-sized abscesses of liquefactive to caseous necrosis. Lungs are usually edematous and perhaps emphysematous. Infected emboli may erode pulmonary artery branches causing pulmonary hemorrhage and leakage of free blood into major airways. With respiratory movements, redistribution of blood into small airways and alveoli occurs. Hemoptysis may also be present. In those cases, free blood is present in major airways, and on cut surface, aspirated blood is distributed in the lungs as feathery, lacy-appearing, red areas, which are particularly obvious within subpleural lobules (**Fig. 17**). In contrast to aspirated free blood, intrapulmonary hemorrhage associated with trauma, septicemia, or endotoxemia appears as dark red petechia or ecchymoses that are discretely demarcated and might be more randomly distributed than are areas of aspirated blood.

VERMINOUS PNEUMONIA

Dictyocaulus viviparus is the cattle lungworm, and lesions are found in pastured cattle or in feedlots supplied primarily by cattle from Southern states.^{3,5,63} Infection is acquired through ingestion of infective larvae from moist environments. Clinical signs of pneumonia may exist during various phases of infection (prepatent, patent, postpatent, and reinfection). Grossly visible lesions are seen primarily in the patent period.

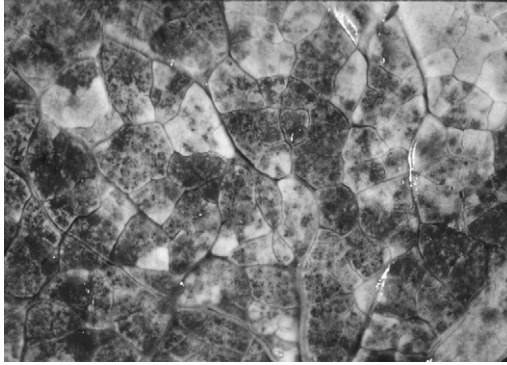


Fig. 17. Aspirated (inhaled) blood distributed as feathery, lacy-appearing dark areas throughout lobules.

During the prepatent period as larvae migrate and develop within the lung, small foci of interstitial pneumonia and eosinophilic bronchiolitis develop, which may appear grossly as small multifocal areas of lobular atelectasis and pulmonary edema. In the patent period, adult worms develop in bronchi and induce eosinophilic to mucopurulent bronchitis, resulting in atelectasis, emphysema and a verminous pneumonia.^{3,4,64} Gross examination of patent infections reveals bilateral lesions first in the caudal lung lobes consisting of caudal-dorsal, wedge-shaped areas of moderate firmness (**Fig. 18**) and in severe infections throughout the lungs. Lesions vary from red and atelectatic to consolidated and gray or pale and overinflated. Emphysema due to forced expiration and bronchiolar lesions may be seen in severe cases. When severe, prominent

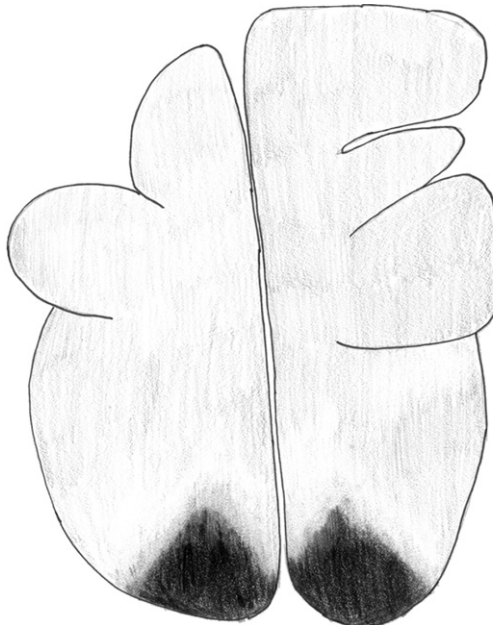


Fig. 18. Verminous (parasitic) bronchitis and pneumonia (*Dictyocaulus viviparus*).

emphysema may cause the prosector to miss the verminous lesions and incorrectly interpret the case as an AIP. Bronchi need to be carefully followed into the caudal-dorsal lobe, wherein distal bronchi contain cloudy to frothy mucus and slender adult white nematodes 4 to 8 cm long.

TUBERCULOUS PNEUMONIA

Bovine tuberculosis is a reportable disease, and current control programs in North America have limited the prevalence of disease. Endemic and sporadic tuberculosis in some wild and farm-reared cervids throughout the United States and occasional diagnoses in cattle, particularly in the northern Midwestern states and along the southern US border, are reminders that vigilance is still needed to accurately recognize and diagnose the disease.⁶⁵⁻⁷⁰

In cattle, *M bovis* causes caseous granulomas in the lungs and occasionally in other organs.⁷¹ Regional lymph nodes, especially retropharyngeal and bronchial, particular targets of *M bovis* infection, are usually involved and help distinguish tuberculosis from other purulent to caseous pneumonias (Fig. 19). The classical lesion of tuberculosis is the tubercle. Tubercles are usually circumscribed, often encapsulated, 1- to 40-mm granulomatous foci containing white to pale yellow caseous necrosis with or without foci of mineralization.⁴ Liquefaction may develop in some older lesions.⁶⁸ At necropsy, lesions may not be obvious even in an animal that reacted positively on a tuberculin skin test. Careful examination of lymph nodes, in particular retropharyngeal, bronchial, and mediastinal, may demonstrate granulomatous inflammation and tubercle formation. Lung lesions are present in approximately 10% to 20% of the cases. In rare generalized cases, small disseminated caseous to caseocalcareous tubercles are present throughout the lungs. More commonly, solitary or clusters of tubercles are present, particularly in the caudal lung lobe. Liquefaction may occur in large

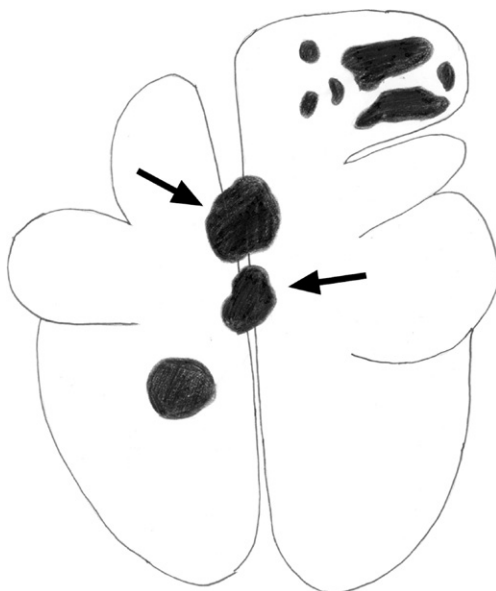


Fig. 19. Tuberculous pneumonia with enlarged regional lymph nodes (arrows).

lesions and could be misinterpreted as an abscess due to *A pyogenes*. Tuberculous lymphadenitis and pneumonia must be differentiated from mycotic lymphadenitis and granulomatous pneumonia, which is sometimes seen in slaughtered cattle.⁷² Mycotic pneumonia is relatively rare in cattle but can occur due to *Coccidioides immitis*, *Aspergillus* spp, *H capsulatum*, and other opportunistic fungi.⁷³

SUMMARY

Pneumonia is a major cause of death and economic losses to the cattle industry. Recognizing the patterns of pneumonic lesions and understanding the pathogenesis of the various types of pneumonia are important for correct diagnosis and interpretation of the lesions. Bacterial pneumonias consist of bronchopneumonia and fibrinous pneumonia and pleuropneumonia as well as caseonecrotic, aspiration, and tuberculous pneumonias. Two major patterns of interstitial pneumonia are recognized in cattle, and verminous pneumonia is associated with *Dictyocaulus viviparus* infection.

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