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Chapter IV

STREPTOCOCCUS EQUI SUBSPECIES *ZOOEPIDEMICUS*: AN EMERGING PATHOGEN OF CATS

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ABSTRACT

Streptococcal disease is a common occurrence in animals. Most streptococcal species are host specific causing sporadic expression of disease in the host. *Streptococcus equi* subspecies *zooepidemicus* (SEZ) is a mucosal commensal in a wide range of animals, most significantly in horses, but is not a recognized commensal of the dog or the cat. Since the early 1980's, there have been increasing reports of SEZ linked to outbreaks of severe fatal respiratory disease in dogs maintained in shelters, research facilities, and kennels. The bacterium has been denoted an emerging pathogen of dogs kept in intensively housed environments. In 2010, a similar clinical presentation was reported in cats maintained in shelters. Similar to intensively housed dogs, sheltered cats exhibited severe fatal pneumonia, but were also reported to contract rhinitis and in some cases meningitis. SEZ is now considered an emerging pathogen of cats. In this chapter we discuss SEZ and expression of disease in the cat.

INTRODUCTION

Streptococcal bacteria are Gram positive, nonmotile, facultatively anaerobic cocci many of which can cause a wide range of pyogenic infections in animals and man [1]. Streptococcal bacteria are associated with sporadic disease in individuals as well as outbreaks of disease in both animals and humans living in intensive housing situations. Numerous classification systems have been developed for streptococci of which hemolytic activity and the Lancefield

serogrouping of cell wall carbohydrates are most commonly utilized [1]. Hemolytic activity is divided into three classes: non-hemolytic, alpha-hemolytic and beta-hemolytic, of which beta-hemolytic strains are considered most pathogenic. The Lancefield method subdivides streptococcal species into 7 groups denoted A,B,C,E,G,L and M [1].

STREPTOCOCCAL DISEASE

Streptococcal disease is uncommon in cats [2]. Beta-hemolytic, Group G streptococcal infection, usually *S. canis*, is the most commonly reported feline streptococcal pathogen. *S. canis* is known to be a commensal of the feline skin, oropharynx, and urogenital tract suggesting that disease expression in cats is likely opportunistic. Two studies of oropharyngeal and rectal commensalism in normal cats revealed 6% and 19% had oropharyngeal carriage and 13% and 30% had rectal carriage of *S. canis* [3, 4] indicating that carriage is not present in the majority of cats and that prevalence of carriage can vary. Two retrospective studies of infectious agents associated with chronic rhinitis and rhinosinusitis in cats and normal control cats failed to recover any beta-hemolytic streptococci [5, 6] suggesting that low prevalence of commensalism may also contribute to low prevalence of feline streptococcal disease.

S. canis is associated sporadically with feline neonatal sepsis, urogenital infections, skin wounds, abscesses [7], pyothorax and pleuritis [2]. Other disease conditions such as arthritis [8], lymphadentitis [9], necrotizing fasciitis [10, 11], rhinosinusitis and meningitis [11] are most often observed in outbreak form in cats maintained in intensively housed conditions such as cat shelters and cat colonies. In two outbreaks with high mortality, suppurative and necrotizing sinusitis and rhinitis also lead to fatal meningitis in many affected cats [11]. It is unknown what virulence factors may be involved with
invasive streptococcal disease, but the recovery of *S. canis* biotype 1 from all affected cats in these two outbreaks suggests that there may be strain specific virulence factors [11].

In 2010, pneumonia, rhinitis and meningitis associated with a beta-hemolytic, group C streptococcal infection, *Streptococcus equi* subspecies *zooepidemicus* (SEZ), was reported in cats housed in Israeli and Canadian shelters for the first time [12, 13]. This followed in the footsteps of increasing numbers of outbreaks of severe fatal respiratory infections with SEZ in dogs maintained in shelters [14, 15, 16], research facilities [17, 18] and kennels [19] indicative of emerging pathogen status of this bacterium for dogs maintained in intensively housed environments.

STREPTOCOCCUS EQUI SUBSPECIES ZOOEPIDEMICUS: OVERVIEW

SEZ is a mucosal commensal with a wide host range [20] and occasionally strains can invade host tissue or cross species barriers [21]. The bacterium is the most commonly isolated opportunistic pathogen of horses and is associated with pneumonia, pleuropneumonia, endometritis, arthritis, neonatal septicemia, abortion, mastitis [22] and meningoencephalitis

[23]. Although SEZ is reported to be a commensal in a wide range of animals, it is not a recognized commensal of the dog [4, 24] or the cat [4]. How dogs and cats in shelter environments come to be infected with an equine/farm animal commensal is unclear as no equine or other farm animal exposure could be demonstrated in the reported outbreaks. However, SEZ was isolated from cats with mild respiratory disease during the Israeli shelter outbreak and from oral swabs of dogs housed adjacent to fatally infected dogs in the shelter outbreak reported by Pesavento *et al* in 2008 indicating that once exposure is achieved, SEZ may result in non fatal infection and possibly carrier status in some cats and dogs [12, 15].

Individual pet dogs are rarely affected by fatal SEZ pneumonia [25, 26]. Residence in shelters, research laboratories, and other facilities where close confinement of animals occurs is the major risk factor for development of severe SEZ associated disease in dogs [14, 15]. Why close confinement may predispose to SEZ disease is unclear. Stress arising from transporting animals to new environments, mixing unfamiliar animals from various origins and preexistent viral or bacterial infection may predispose to disease expression in the presence of an asymptomatic carrier [27]. Transportation of horses over long distances can result in severe hemorrhagic to necrotizing bronchopneumonia associated with aerogenous spread of SEZ from the tonsils to the lower respiratory tract [28]. While unaffected horses reveal mixed bacteria in tonsils following transport, pneumonic horses have fewer bacterial species with a much heavier growth of SEZ in their tonsils suggesting that transportation stress may favour tonsillar proliferation and spread of SEZ to the lower respiratory tract in certain individuals [29].

Underlying viral disease can often play a role in expression of bacterial disease. Experimental reproduction of mild non-fatal SEZ pneumonia has been demonstrated in dogs with intranasal installation of SEZ and canine influenza virus whereas intranasal installation of SEZ alone failed to cause significant disease [30]. While influenza infection potentiated mild SEZ disease in the canine study, it did not replicate the severe hemorrhagic pneumonia observed in shelters [30]. This is compatible with observations that co infection with other respiratory pathogens was unrelated to expression of fatal SEZ respiratory disease in dogs in natural outbreaks [14, 15, 17] suggesting that the introduction of either a high challenge or a virulent clone of SEZ into an environment densely populated with susceptible hosts [15] is most likely responsible for the severe disease expression. Unlike intranasal inoculation, experimental intratracheal installation of SEZ in dogs will reproduce severe fatal hemorrhagic pneumonia [17] further suggesting that introduction of a high challenge to the lower respiratory tract likely plays an important role in pathogenesis.

VIRULENCE

Currently there is insufficient data to determine the basis for high virulence of SEZ in dogs [27] and cats. Interestingly, multilocus sequence typing (MLST) found that several isolates of SEZ causing outbreaks of fatal hemorrhagic pneumonia in dogs from geographically remote locations were genetically related. This finding suggests that certain

strains of SEZ are more adept at causing disease in dogs [21]. To date, this type of molecular analysis of feline isolates has not been reported and it remains unknown as to whether particular strains of SEZ are associated with disease in cats.

In general, the virulence of pathogenic streptococci is based on surface structures that either prevent phagocytosis or are involved in adhesion; the best-understood factors are the hyaluronic acid capsule and the antiphagocytic M proteins. Many pathogenic streptococci also have the ability to bind components of the host's plasma, and organisms coated with these components may be able to escape detection of the host's immune system. Specific virulence factors associated with SEZ include capsular hyaluronic acid, streptokinase, proteases, streptolysin S, peptidoglycan, fibronectin binding protein, IgG protein and SzP protein [20].

The cell surface protein, SzP, is an M-like protein and is important in the pathogenesis of infection in equids. The SzP protein binds equine fibrinogen which aids in preventing phagocytosis and limits deposition of C3 on the cell surface [31]. In addition, studies have shown that variation in the SzP protein is a useful measure of diversity among strains of SEZ [32]. However, while SzP is an important virulence factor in equids there does not appear to be a direct relationship between variations in SzP protein and particular disease manifestations in horses [31] nor is SzP phenotype an important determinant of invasiveness or epizootic capabilities [32]. To the best of the authors' knowledge, variations in SzP proteins of SEZ isolates from cats and dogs have not been examined.

Gene gain via the horizontal acquisition of mobile genetic elements is a key factor in the emergence of pathogenic strains of streptococci. In humans, the emergence of strains of *S. pyogenes* causing streptococcal toxic shock syndrome (STSS) is associated with the acquisition of genes encoding for superantigens [33]. *S. pyogenes* produces several pyogenic exotoxins which act as superantigens and are associated with increased virulence of this organism. Unlike conventional antigens, superantigens have high immunomodulating capacity [20]. Superantigens activate a large portion of T-lymphocytes leading to exuberant cytokine production and activation of neutrophils and vasoactive factors. These factors act on endothelium to increase permeability, cause vasodilation and promote coagulation [27].

In dogs with SEZ pneumonia, the rapid onset of disease and fast deterioration is similar to STSS in man [27]. Recently three novel superantigens, SzeP, SzeN and SzeF, have been identified from a strain of SEZ isolated from a case of acute fatal hemorrhagic pneumonia in a dog from the UK. This suggests that horizontal transfer of genes encoding for superantigens within the diverse SEZ population could result in the emergence of virulent strains. However, this study was unable to link the presence of superantigen-encoding genes in the broader SEZ population to cases of acute fatal hemorrhagic pneumonia of dogs. Therefore, currently there is insufficient data to determine if superantigens or other bacterial toxins are involved in the pathogenesis of SEZ infections in dogs [27]. To date, the genome of feline SEZ isolates has not been examined for the presence of superantigens, and it is unknown whether these factors may be associated with the emergence and severe disease manifestations of SEZ now being observed in cats.

PNEUMONIA

The majority of feline cases of SEZ disease published to date occurred in one cat shelter with severe pneumonia presenting in outbreak form [12]. Thirty-nine cats in this outbreak exhibited clinical signs characterized by nasal discharge, cough and/or dyspnea prior to death [12]. Necropsy findings described severe acute diffuse suppurative to necrosuppurative bronchopneumonia with intralesional coccoid bacteria similar to that described for dogs and transported horses. SEZ was isolated from all affected lungs, usually in pure culture, but was not isolated from 29 other cats which died without respiratory disease during the outbreak [12]

Infectious pneumonia is uncommon in cats. Retrospective studies examining causes of pneumonia in cats reveal that pneumonia was diagnosed as the cause of death in only 3.5% of cases (110/31,323) over the period 1991 to 2000 and of those cases only 35% (39/110) were infectious [34]. Of the bacterial causes of pneumonia, *S. canis* and *Pasteurella multocida* were isolated most commonly, each representing 29% of the cases [34]. One additional case yielded a non speciable beta-hemolytic streptococcus [34]. In contrast, a second study looking at cats with non-fatal pneumonia over the period 1995 to 2000 found no streptococcal involvement [35]. Recovery of beta-hemolytic streptococci, whether *S. canis* or SEZ, only from fatal bacterial pneumonia in cats suggests that these bacteria have significant virulence.

In the retrospective study of fatal pneumonia in cats, severity of clinical signs correlated closely with severity of pulmonary pathology, but did not correlate significantly with the infectious agents recovered [34]. Fewer than half of the cats with infectious pneumonia presented with clinical signs indicative of respiratory disease (dyspnea, tachypnea, cough and/or nasal discharge) and the other half had no clinical signs whatsoever [34]. This exceedingly variable clinical expression of lower respiratory tract disease is typical of cats and can make detection and diagnosis challenging [36]. In contrast, the shelter outbreak of SEZ disease describes nasal discharge, cough and/or dyspnea prior to death in 100% of cats with pneumonia [12] reflecting
the severity of the pneumonia. Thus when respiratory tract infection is either detected or suspected in cats, inclusion of appropriate antimicrobial therapy aimed at streptococcal disease would be indicated.

RHINITIS AND MENINGITIS

Rhinitis and meningitis have been reported in sporadic cases of SEZ in shelter cats [12, 13]. Although the two cats reported by Britton and Davies had short clinical histories prior to death due to meningitis, the rhinitis in both cats was characterized by increased numbers of plasma cells in the nasal mucosa indicative of chronicity. Myeloid hyperplasia was noted in the bone marrow of both cats indicative of chronic demand for leucocytes, which was concluded to have been associated with the rhinitis as no other chronic source of infection was found in the cats [13]. This suggests that SEZ disease in cats may commence with rhinitis, which if not cleared by appropriate antibiotic treatment, may ultimately spread to the brain and/or the lung.

Chronic rhinitis associated with SEZ infection was recently reported in two pet dogs resident on horse farms, one of which also exhibited chronic pneumonia [37, 38]. A third dog on one of the horse farms was positive on oropharyngeal culture for SEZ but exhibited no clinical signs, indicative of the potential for asymptomatic carrier status [37]. Interestingly the asymptomatic dog was colonized by SEZ strain ST173, the same virulent strain isolated from an outbreak of hemorrhagic pneumonia in shelter dogs [39]. All dogs were responsive to antibiotic treatment including the dog with chronic pneumonia [37, 38]. Emergence of sporadic non-fatal disease and asymptomatic carrier status in dogs on horse farms suggests that SEZ infection may indeed initially arise from exposure to horses but that, in addition to the strain of SEZ, other factors play a role in the severity of disease expression.

Streptococcal meningitis is described in both humans and animals and usually occurs as a result of bacteremia and breaching of the blood brain barrier [40]. However, experimental spread of *Streptococcus pneumonia*e from rhinitis along olfactory neurons to the brain has been achieved in mice [41]. In the two outbreaks of *S. canis* meningitis in shelter cats and in one cat with SEZ rhinitis and meningitis, inflammatory damage to the nasal bones and cribriform plate was present and the authors concluded that the meningitis, in the absence of pneumonia, most likely occurred due to olfactory spread of bacteria through the cribriform plate to the brain [11, 13]. Interestingly, lysis of nasal turbinate was also identified in a dog with chronic rhinitis associated with SEZ infection but no meningitis was identified [38]. SEZ meningitis has also been reported in a pet cat with otitis media/interna suggesting another possible route of infection to the brain via the auditory pathway [42].

SEZ is a zoonotic bacterium which most often presents as meningitis in humans. Although there is widespread SEZ carriage in horses and widespread exposure of humans to horses, zoonotic infection in man is uncommon [27]. Of 19 human SEZ cases reviewed in the literature, 14 had meningitis of which 9 were exposed to horses and 5 ate infected unpasteurized milk or cheese [43]. One recent case of upper respiratory infection occurred in a human exposed to a dog with chronic rhinitis and pneumonia subsequent to the dog sneezing in the human's face [39]. Strain ST178 of SEZ was identified in both the dog and the human, distinct from the ST-173 strain identified in outbreaks of shelter dogs, again suggesting that degree of virulence may be strain related [39]. In a retrospective study of strains of SEZ associated with disease from multiple countries, it was found that isolates from 8 outbreaks of acute fatal hemorrhagic pneumonia in British and American dogs were genetically related, but not identical, suggesting that certain subtypes of SEZ may be more virulent for dogs [21]. Five of these canine strains were also recovered from equine disease [21] compatible with a study which found it unlikely that a single virulent strain of SEZ is responsible for equine pneumonia [32]. Interestingly, cats were housed at two of the dog shelters which experienced outbreaks of fatal hemorrhagic SEZ pneumonia [15, 16]. All cats were clinically unaffected in one outbreak [16], while one cat died in the second outbreak carrying a different strain of SEZ to that affecting the dogs [15]. This suggests that different strains of SEZ may be involved in feline expression of the disease or that other factors may precipitate disease in the cat.

CONCLUSION

SEZ is a bacterium which has recently been designated an emerging pathogen of cats causing a disease spectrum characterized by acute severe pneumonia, meningitis, rhinitis and otitis media/interna. The disease is most often reported in shelter cats, but has also rarely been isolated from pet cats [12, 42]. SEZ should be included in differential diagnostic workup of cats with respiratory, neurological or obscure illness with appropriate antibiotic selection for streptococcal pathogens being included in therapeutic regimens. Recent reports suggest that SEZ is associated with chronic rhinitis and otitis media/interna and cats with these conditions might represent the point of introduction into shelters. Thorough physical examination of cats upon introduction to shelters and prompt treatment of rhinitis and/or otitis media/interna with antibiotics effective against streptococcal bacteria may help to prevent outbreaks of acute fatal disease.

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