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Granulomatous Rhinitis in a Horse due to *Mycobacterium intracellulare* Infection

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Summary

Mycobacterial infections in horses are uncommon, but are caused most frequently by *Mycobacterium bovis* of the *Mycobacterium tuberculosis* complex or *Mycobacterium avium* of the *M. avium* complex. Disease caused by *Mycobacterium intracellulare*, the second most common species within the *M. avium* complex, has not been reported in horses to date. Mycobacteriosis in horses most often presents as enteric, pulmonary, or rarely, systemic disease. Here we report a case of *M. intracellulare* infection in a horse presenting as a granulomatous nasal mass.

Keywords

Mycobacterium avium complex; horse; granulomatous inflammation; nasal mass

Mycobacteria are gram-positive, acid-fast, aerobic bacterial bacilli. Mycobacteria belong to one of two groups: (1) the *Mycobacterium tuberculosis* complex (MTC), or (2) the non-tuberculous mycobacteria, which includes the *Mycobacterium avium* complex (MAC) (van Ingen, 2017). Tuberculosis is caused by the *M. tuberculosis* complex, of which *M. tuberculosis* and *Mycobacterium bovis* (Sano et al., 2014) are members. The MAC is comprised of 12 species (van Ingen et al., 2018), including *Mycobacterium chimaera*, *Mycobacterium intracellulare* and *M. avium*, which possesses four subspecies. The four subspecies of *M. avium* are *M. avium* subsp. *hominissuis*, *M. avium* subsp. *paratuberculosis*, *M. avium* subsp. *avium* and *M. avium* subsp. *silvaticum* (Nishiuchi et al., 2017).

Horses are considered naturally resistant to infections from both the MTC and the MAC (Pavlik et al., 2004). While there have been several reports of granulomatous inflammation

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Conflict of Interest Statement

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due to infection with *M. bovis* (Sarradell et al., 2015; Hlokwe et al., 2016), infections by *M. avium* are considered the most common cause of equine mycobacteriosis (Pavlik et al., 2008; Sano et al., 2014). Within the MAC complex, infections with *M. avium* subsp. *avium* and *M. avium* subsp. *hominissuis* are among the most frequently identified agents (Pavlik et al., 2008). *M. intracellulare* is less commonly isolated from the environment than other members of the MAC (Pavlik et al., 2004) and has not been reported to cause disease in horses. This report describes a unique case of *M. intracellulare* infection that presented as a nasal mass in a horse.

A 22-year-old Quarter horse gelding was presented for evaluation of a 2-month history of unilateral mucopurulent nasal discharge. Rectal temperature, heart rate, respiratory rate, and cardiopulmonary and abdominal auscultation were unremarkable. Other findings included mild stertor, slight left facial enlargement and mild left epiphora. Upper airway endoscopy revealed occlusion of the left nasal passage by a smooth, pink mass with distortion of the nasal meatus and mild yellowing and multifocal scarring of the pharynx and larynx consistent with nasopharyngeal cicatrix syndrome. Radiographs and computed tomography (CT) of the head confirmed an expansile soft tissue mass occupying the entire left rostral and caudal maxillary sinuses, left conchofrontal sinus and left sphenopalatine sinus (Fig. 1). The mass extended from the ethmoid turbinates cranially to the level of the second maxillary molar, effacing the ethmoid turbinates and left dorsal and ventral conchae, with leftward deviation of the left infraorbital canal and rightward deviation of the nasal septum. The differential diagnosis included an ethmoid haematoma and neoplasia. These differential diagnoses were ruled out by biopsy of the mass which showed granulomatous inflammation and granulation tissue. Due to the extent of the mass, age of the horse and concurrent chronic hindlimb lameness, the animal was humanely destroyed.

At necropsy examination, red-tinged mucopurulent nasal discharge exuded from the left nostril. On sagittal sectioning of the head, a $16 \times 8 \times 4$ cm, firm, tan to yellow, expansile mass with foci of suppurative exudate filled the mid to caudal left nasal cavity and the left rostral maxillary, left caudal maxillary and sphenopalatine sinuses (Fig. 2). The mucosa of the nasal conchae was thickened and red with multifocal erosions and ulceration. The rostral left nasal cavity and left frontal sinus were filled with suppurative exudate. Mild scarring was apparent in the pharyngeal and laryngeal mucosa. All other organs were grossly unremarkable.

Histologically, the mass was comprised of numerous epithelioid macrophages, multinucleated giant cells and fewer lymphocytes and plasma cells, with multifocal areas of necrosis and degenerate neutrophils (Fig. 3). Faintly-stained bacterial bacilli were visible within macrophages and multinucleated giant cells with haematoxylin and eosin (HE) staining and numerous acid-fast bacilli were evident with Fite's acid-fast stain (Fig. 4). Gram and Gomori's methenamine silver stains were unremarkable. Other histological findings included mild, multifocal, acute, random, necrotizing hepatitis and a cholesterol granuloma within the cerebrum. The spleen, lung, spinal cord, kidney, heart, salivary gland, oesophagus, small intestine and large intestine were unremarkable. Aerobic culture of the nasal exudate yielded a 2+ growth of *Streptococcus equi* subsp. *zooepidemicus* and *Streptococcus dysgalactiae*, which were presumed to be contaminants or secondary invaders.

Acid-fast organisms were not recovered by routine aerobic culture. Anaerobic culture was not attempted. A formalin-fixed sample of the mass was embedded in paraffin wax and submitted to the Washington Animal Disease Diagnostic Laboratory for molecular testing. DNA extracted from the embedded sample was used as a template, and universal *Mycobacterium* spp. primers were used to amplify a portion of the 16S–23S ribosomal internal transcribed spacer region by polymerase chain reaction (PCR). Bidirectional sequencing of the PCR amplicon was compared with previously reported sequences using a BLAST search and matched *Mycobacterium avium intracellulare* with 98% sequence identity in GenBank (GenBank accession number KR856205).

Horses are relatively resistant to infection with mycobacteria (Pavlik et al., 2004; Sarradell et al., 2015). Mycobacterial infections in horses are caused by members of the MTC, particularly *M. bovis* (Sarradell et al., 2015; Hlokwe et al., 2016), or by members of the MAC, particularly *M. avium* subsp. *avium* (Pavlik et al., 2008; Ryhner et al., 2009). Other MAC subspecies reported to infect horses include *M. avium* subsp. *sylvaticum* (Chiers et al., 2012) and *M. avium* subsp. *hominissuis* (Kriz et al., 2010; Mönki et al., 2016). Horses have a strong innate resistance to mycobacterial infections by the MTC (Mair, 1996), and this resistance presumably extends to the MAC as well. The horse in this case was apparently immunocompetent. Although the clinical history included chronic hindlimb lameness, review of the medical records did not reveal evidence of immunosuppressive drug therapy or of other infections that might lead to immunosuppression. Given the age of the horse, brief consideration was given to pituitary pars intermedia dysfunction causing subclinical immunosuppression, but the pituitary gland was radiographically and grossly unremarkable.

The bacteria comprising the MAC commonly infect people, and although they are traditionally considered as opportunistic pathogens of immunocompromised individuals, the incidence of mycobacteriosis in immunocompetent individuals is increasing worldwide (Diel et al., 2018). The disease in man most frequently manifests as pulmonary disease or disseminated infections, and less frequently as localized dermatitis, cervical lymphadenitis, pericarditis, soft tissue abscesses, osteomyelitis or encephalitis (Acharya et al., 2018; van Ingen et al., 2018). Additionally, *M. intracellulare* infection in man has been reported in association with tenosynovitis (Saraya et al., 2018) and keratitis (Ko et al., 2017).

Mycobacterial infections localized to the nasal passages are extremely rare in man. Most reported cases are due to the MTC (Masterson et al., 2011; Malik et al., 2016), but there are reports of the MAC causing a nasal polyp or pseudotumor (Ilyas et al., 2011; Xu et al., 2016). Environmental contamination, especially of tap water, is the primary source of infection, either by ingestion or inhalation (Faria et al., 2015; Balavoine et al., 2019). MAC mycobacteria are able to survive in the environment and are found in soil, water, tropical vegetation and animals (Pavlik et al., 2004).

Transmission of mycobacteria in horses primarily occurs via ingestion or rarely respiration (Pavlik et al., 2008). Enteric infection is associated typically with granulomatous enteritis and colitis (Sarradell et al., 2015; Mönki et al., 2016). Less frequent manifestations include pneumonia (Ryhner et al., 2009), abortion (Cline et al., 1991; Hélie and Higgins, 1996) and systemic infections (Cline et al., 1991; Sano et al., 2014). Enteric infections are thought to be facilitated by ulceration related to parasitism (Pavlik et al., 2004). In the present case,

enteric lesions were absent. It is possible that a nasal mucosal erosion may have permitted a localized infection. The scarring evident in the pharynx and larynx were suggestive of mild nasopharyngeal cicatrix syndrome, an idiopathic condition reported in Texas horses. This condition is associated with scarring of the nasopharynx, epiglottic deformation, bilateral arytenoid chondropathy, thickening of the vocal cords and scarring of the salpingopharyngeal openings (Norman et al., 2013). While severe changes of the syndrome were not evident in this case, it is tempting to speculate that the mild changes may have been a predisposing factor for the nasal infection.

Although infections with *M. intracellulare* have not been reported in the horse, the paucity of reports may reflect diagnostic challenges in speciating members of the MAC. Members of this group cannot be differentiated reliably by culture or biochemical tests. In several early reports, identification of acid-fast bacilli within granulomatous lesions and culture were sufficient for diagnosis of mycobacteriosis, and additional diagnostics were either not pursued or were unsuccessful (Cline et al., 1991; Hélie and Higgins, 1996).

Recognition of mycobacterial infections is challenging due to the diversity of clinical presentations. Weight loss, diarrhoea, pyrexia, ventral oedema, lethargy and inappetence are reported in association with enteric infection of horses (Mönki et al., 2016). In a report of granulomatous guttural pouch eustachitis, pneumonia and lymphadenitis secondary to the MAC, clinical signs included weight loss, bilateral mucoid nasal discharge and poor racing performance (Sills et al., 1990). Clinical signs in a case of pulmonary mycobacteriosis secondary to *M. avium* subsp. *avium* consisted only of inappetence and pyrexia (Pavlik et al., 2008). In the current case, the clinical signs were limited to unilateral mucopurulent nasal discharge until the disease was quite advanced.

In conclusion, we present a novel case of *M. intracellulare* infection presenting as a nasal mass in a horse. Members of the MAC should be considered as differentials for equine nasal masses and granulomatous rhinitis.

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Fig. 1. Radiograph, dorsoventral view of the skull. The left paranasal sinus is occluded by an expansile mass (*) with destruction of the ethmoid turbinates, effacement of the left dorsal and ventral conchae, and rightward deviation of the nasal septum.

Fig. 2.

Left sagittal section of the head. A firm, tan to yellow mass occludes the mid to caudal left nasal cavity and the left rostral and caudal maxillary and sphenopalatine sinuses. Suppurative exudate surrounds the mass, and the sinonasal mucosa is thickened and eroded.

Fig. 3.
The mass is composed of numerous epithelioid macrophages, multinucleated giant cells and fewer lymphocytes and plasma cells. HE. Bar, 50 μ m.

Fig. 4. Numerous red acid-fast bacilli are within macrophages and giant cells. Fite's stain. Bar, 20 μ m.