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CASE REPORT

Horses and other equids

Pulmonary cryptococcoma in a Friesian horse in the Netherlands

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Abstract

A 6-year-old female Friesian horse was admitted with pyrexia, dullness, weight loss, watery faeces and mild bilateral mucoid nasal discharge. Radiographic and ultrasonographic examination of the thorax indicated a large mid-thoracic soft tissue mass, and the horse was euthanased because of a poor prognosis. At postmortem examination, it was found that the lung tissue was partly replaced by multiple to coalescing soft tissue lesions with a yellow gelatinous aspect, varying in size up to 15 × 15 × 20 cm. Histologically, the mass showed mild pyogranulomatous inflammation associated with large numbers of globular encapsulated 10–20 μm yeasts with or without narrow-based budding, consistent with multiple coalescing cryptococcomas. Quantitative PCR testing of formalin-fixed paraffin-embedded tissue led to the identification of *Cryptococcus gattii* species complex. To the authors' knowledge, this is the first case reported in the Netherlands of pulmonary cryptococcomas due to *C. gattii* sensu lato in a horse that had never travelled abroad.

KEYWORDS

cryptococcosis, *Cryptococcus gattii*, equine, pathology, pulmonary

BACKGROUND

Fungi of the *Cryptococcus gattii/Cryptococcus neoformans* species complex are opportunistic fungal pathogens of mammals, including people, which can cause disease in both immunosuppressed and healthy hosts.[1] Cryptococcal organisms are yeasts with a characteristic appearance on cytology due to the large polysaccharide capsule.[2] Cryptococcosis has a worldwide distribution, although most cases of equine cryptococcosis occur in Western Australia.[1] Infections caused by members of the *C. gattii* species complex are more likely to produce pulmonary lesions,[3] and are more common in immunocompetent hosts.[1] Horses tend to have lower respiratory tract involvement.[3] This case report describes the clinical presentation, imaging findings, pathological findings and quantitative PCR (qPCR) testing of the first case of a *C. gattii* species complex infection in a horse in the Netherlands, despite no history of travelling abroad.

CASE PRESENTATION

A 6-year-old female Friesian horse was referred to the Utrecht University Veterinary Hospital with a history of pyrexia, partial anorexia, dull demeanour, watery faeces and weight loss of approximately 1 week. In addition, in the 10 days preceding presentation to the hospital, sporadically occurring nasal discharge and cough, mostly occurring at the onset of exercise, had been noted by the owner. Repeated doses of flunixin had been administered in the days before presentation, and the horse had been treated for a suspected colonic sand impaction with paraffin and psyllium before referral. There had been no

TABLE 1 Relevant results of the blood examinations performed at the veterinary hospital.

	Result 1	Result 2	Reference values
Leukocytes (10^9/L)	19.9	17.1	4.7 – 10.0
Neutrophils (10^9/L)	16.9	14.2	2.3 – 6.5
Lymphocytes (10^9/L)	2.4	2.3	1.1 – 5.1
Total protein (serum) (g/L)	80	ND	52 – 79
Albumin (g/L)	28	ND	26 – 37
α1 (g/L)	1	ND	1 – 7
α2 (g/L)	14	ND	3 – 13
β1 (g/L)	10	ND	4 – 16
β2 (g/L)	13	ND	3 – 9
γ (g/L)	14	ND	6 – 19

Note: Result 1 = values from the first blood examination after being admitted to the hospital. Result 2 = values from the second blood examination that was done 3 days later.
Abbreviation: ND, not done.

recent changes in management or other notable events in the horses' history. No other horses on the premises presented any clinical complaints. The horse had been in its current owner's possession for 3 years, and before that had resided at its breeder's premises. Both the breeder and the current owner were based in the Netherlands. The horse had never travelled abroad. The horse had experienced prior episodes of having somewhat loose faeces in the years before presentation, but those had in the past never been accompanied by signs of systemic illness and had not previously required veterinary attention.

On presentation, the mare was quiet but alert and responsive, with a heart rate of 44 beats per minute with a strong, regular pulse, a respiratory rate of 24 breaths per minute with a costo-abdominal breathing pattern and no dyspnoea, and a rectal temperature of 38.6°C. Watery, hyperfrequent borborygmi was noted on auscultation of the abdomen. Some mild bilateral mucoid nasal discharge was present bilaterally. No coughing was noted. No other abnormalities were noted on clinical exam upon presentation.

INVESTIGATIONS

Extensive comprehensive haematology and biochemistry on presentation showed a leukocytosis, with high total protein and increased beta fraction, and low albumin (Table 1).

Initially, the watery faeces, pyrexia and anorexia were attributed to mild colitis, and investigations including abdominal radiography, faecal culture and faecal PCR for equine coronavirus (ECoV) were performed. A moderate amount of sand was noted on abdominal x-ray, faecal culture did not demonstrate pathogens, and the ECoV PCR returned negative.

In the days following admission, the horse continued to be anorexic, presented rapidly progressing dyspnoea, nasal discharge and spontaneous coughing. As a result, a more detailed endoscopic and radiographic evaluation of the respiratory tract was undertaken.

Upon airway endoscopy, abundant quantities of orange-yellow exudate in the trachea were visible, extending into both main bronchi (Figure 1). The proximal airways, including guttural pouches, were unremarkable.

Radiographic examination of the thorax showed a homogeneous, irregularly marginated increase in soft tissue opacity dorsal and caudal to the cardiac silhouette, extending to and partially superimposed to the caudal vena cava and diaphragm. The dimensions of this lesion could not be measured reliably due to the ill-defined margins and border effacement of the cardiac silhouette cranially and the diaphragm caudally (Figure 2).

Ultrasonographic examination from the ventrolateral thoracic wall on both sides showed an ill-defined, heterogeneously hypoechoic increase in soft tissue opacity dorsal and caudal to the heart, both on the left and right side. This space-occupying lesion had a rounded to ovoid shape, with a depth of approximately 13 cm and a length of approximately 12 cm (Figure 3). At this level, on both sides of the thoracic cavity, no aerated lung tissue could be noted. Ill-defined, subjectively enlarged tracheobronchial lymph nodes were noted. Due to limited penetration of the ultrasound beam in large objects, clear images or measurements could not be obtained.

LEARNING POINTS/TAKE-HOME MESSAGES

- Although uncommon, a fungal infection is not to be ruled out with a focal mass in the respiratory tract.
- Cytology of respiratory secretion via tracheal or bronchial sampling or ultrasound-guided fine-needle aspiration biopsy of abnormal tissue might have revealed this uncommon pathogen; *Cryptococcus* spp. have a characteristic appearance.
- Identification of the species of *Cryptococcus* is epidemiologically relevant and requires serotyping or molecular detection.

DIFFERENTIAL DIAGNOSIS

Based on the imaging findings, the mass in the thorax was assumed to be either a neoplastic process (i.e., lymphoma), or an inflammatory or septic process (i.e., equine multinodular pulmonary fibrosis, hydatid disease). A neoplastic process like a lymphoma was considered most likely at this point. An ultrasound-guided fine-needle aspiration biopsy and transtracheal aspirate were considered for further diagnostic evaluation.

OUTCOME AND FOLLOW-UP

Given the rapidly progressing dyspnoea, dull demeanour and ongoing weight loss, combined with the extent of the thoracic imaging abnormalities, which were thought to carry a poor prognosis regardless of nature of the lesion, a decision was reached to euthanase the horse.

Comprehensive postmortem examination was performed at the Utrecht University Veterinary Pathology Diagnostic Centre. Macroscopy showed multiple to coalescing

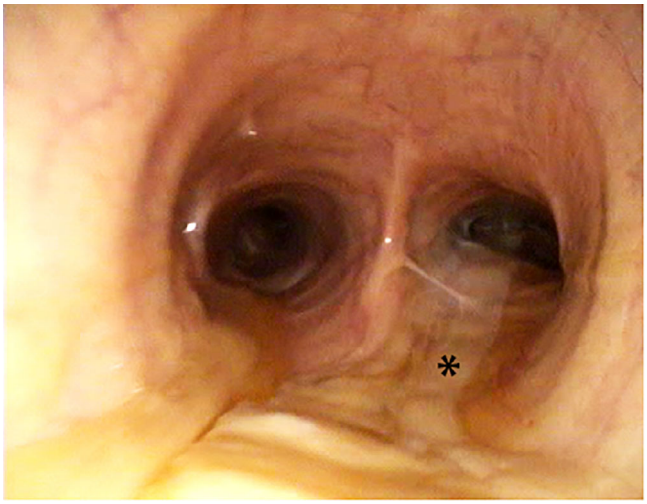

FIGURE 1 Endoscopic view of the main bronchial bifurcation that demonstrates large quantities of exudate (asterisk) apparently originating from both bronchi.

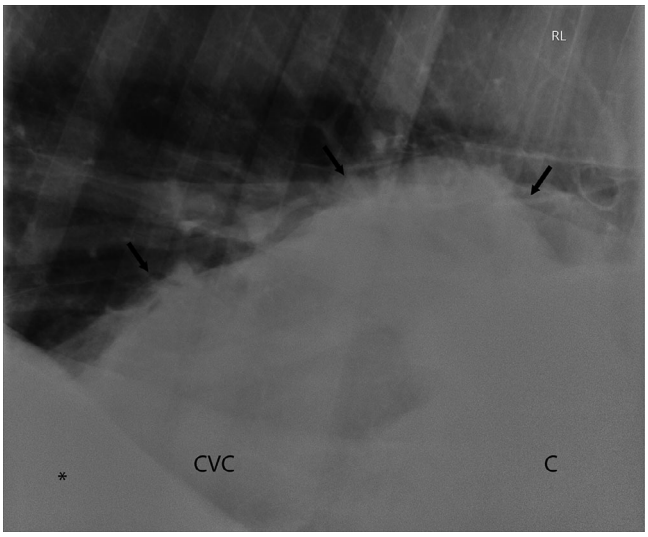

FIGURE 2 Lateral radiographic projection (DS) of the caudodorsal thorax, showing an ill-defined increase in soft tissue opacity (between arrows), superimposed on the cardiac silhouette, caudal vena cava and diaphragm. *Diaphragm; CVC, caudal vena cava; C, cardiac silhouette.

multinodular, yellow gelatinous masses replacing and effacing 70% of the left lung parenchyma, and 30% of the right lung parenchyma, keeping the pleura intact. The masses were primarily centred around the tracheobronchial bifurcation. Cut surface revealed a yellow gelatinous tissue divided by thin bands of fibrous tissue in and around the nodules (Figure 4). The non-affected peripheral lung parenchyma contained mucopurulent exudate within the larger airways. Tracheobronchial lymph nodes were diffusely enlarged. Significant gross lesions were not detected in other organs.

Postmortem cytology of the masses, with Hemacolor Rapid staining, showed foamy macrophages, neutrophils and globular encapsulated yeast cells ranging in size from 10 to 20 μm in diameter.

Representative samples of the lung were fixed in 10% neutral buffered formalin and routinely processed for histological examination.

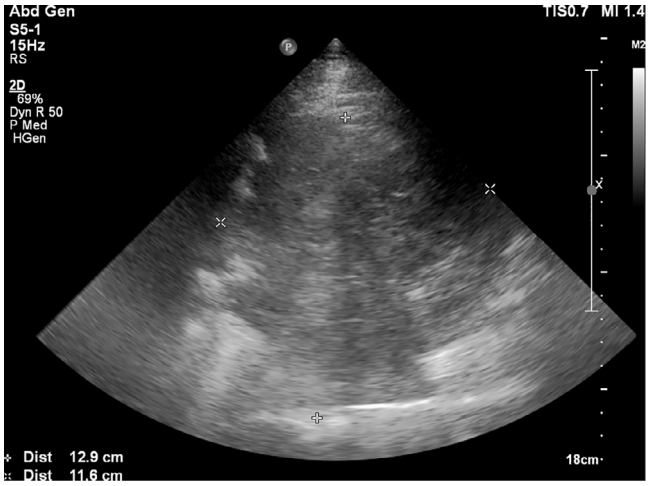

FIGURE 3 Ultrasonographic examination of the thorax showing ill-defined heterogeneous, mass-like lesions (between callipers) caudodorsal to the heart.

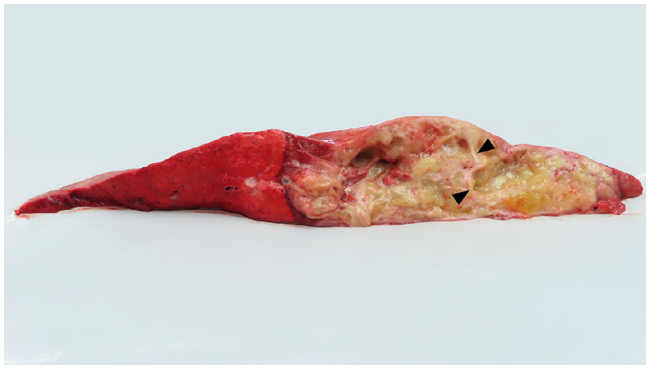

FIGURE 4 Gross image of part of the left lung: Cut surface shows the yellow gelatinous aspect between fibrotic strands (arrowheads) of the multinodular mass. The right lung shows similar changes.

Histological examination of the lung parenchyma revealed a thick capsule of mature collagen at the transition between the pre-existent lung tissue and the mass (Figure 5). This surrounded a lake of proteinaceous material that contained many extracellular 8–20 μm circular structures, with a pale amphophilic centre and thin refractile wall, surrounded by a clear, non-staining 5 μm thick capsule (Figure 6). The capsule stained positively in the periodic acid–Schiff (PAS) stain (Figure 7). Fungal structures sometimes showed multiplication through narrow-based budding. Accompanying the agent was mild inflammatory infiltration characterised by numerous macrophages and multinucleated giant cells (foreign body and Langhans type), viable and degenerate neutrophils, and few lymphocytes and plasma cells. Remaining adjacent lung parenchyma was no longer aerated, and instead contained erythrocytes, proteinaceous fluid, and fibrin within alveolar lumina, bronchioles and bronchi. The concentration of exudate in the airways decreased progressively at more distant locations from the mass.

The morphology of the structures and accompanying tissue response were suggestive for a *Cryptococcus* spp. pneumonia, with the formation of a so-called cryptococcoma. DNA extracted from formalin-fixed paraffin-embedded (FFPE; DNeasy Blood & Tissue Kit, Qiagen) tissue sections of the lung were subjected to a pan-*Cryptococcus*-specific

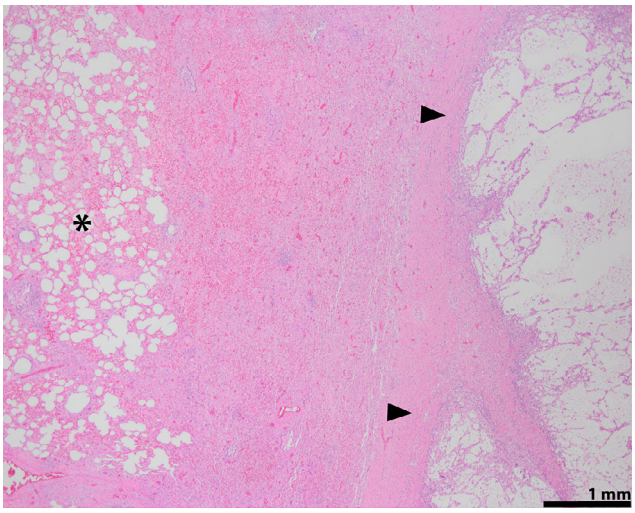

FIGURE 5 Lung histology (original magnification 20×). Unaffected lung (asterisk) borders a zone of collapse centrally, and the focus of cryptococcal proliferation and accompanying inflammation surrounded by fibrous encapsulation (arrowheads). Haematoxylin and eosin. Scale bar: 1 mm.

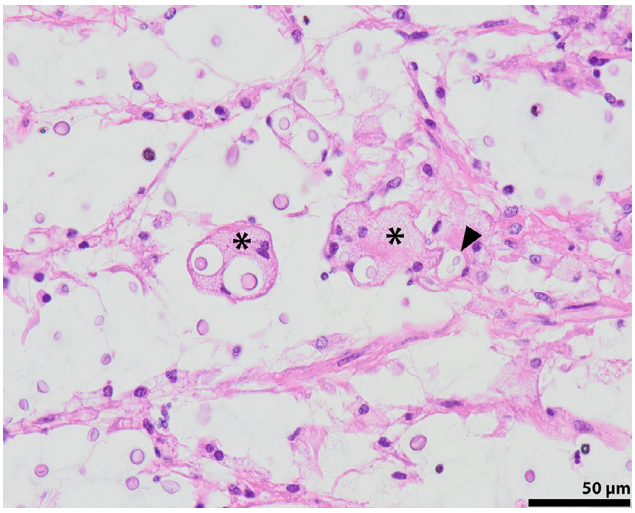

FIGURE 6 Lung histology (original magnification 400×). Numerous circular yeasts, 10–20 μm, with a pale amphophilic centre and thin refractile wall, surrounded by a clear, non-staining 5 μm thick capsule, occasionally exhibiting narrow-based budding (arrowheads). The yeasts are dispersed in a background of light eosinophilic homogeneous material, separated by thin fibrous strands. Additionally, some yeasts are intracytoplasmic within multinucleated giant cells (asterisk). Haematoxylin and eosin. Scale bar: 50 μm.

qPCR[4] and an in-house *C. gattii* species complex qPCR, which yielded a positive signal. The qPCR was positive for *Cryptococcus* species (Ct values 30.4 and 30), specifically *C. gattii* species complex (Ct values 25.3 and 24.9). Subsequent multi-locus sequence typing designed for short-fragmented FFPE-DNA was applied, as previously described,[5] to determine the species. Unfortunately, the DNA concentrations were too low to obtain MLST fragments, and thus it was not possible to sub-speciate further within the *C. gattii* species complex.[6]

DISCUSSION

In order for cryptococcal infections to result in disease, a few criteria should be met: a virulent cryptococcal strain; an appropriate infective dose; and a susceptible host immune status; the relative importance of each criterium is often not understood in individual cases.[1] Among the over 70 species belonging to the *Cryptococcus* genus, only two primary species complexes evolved the mechanisms leading them to be currently recognised as human and animal pathogens: *C. neoformans* complex and *C. gattii* complex.[6,7] These two distinct primary species complexes have multiple varieties, and vary in ecological distribution and pathogenicity.[8] *C. neoformans* species complex includes the species *C. neoformans* (formerly *C. neoformans* var. grubii) and *C. deneoformans* (formerly *C. neoformans* var. neoformans). The *C. gattii* species complex has been divided into five sibling species, including *C. gattii*, *C. deuterogattii*, *C. bacillisporus*, *C. tetragattii* and *C. decagattii*.[6] The *C. gattii* species complex continues to expand as a new-found, but non-pathogenic, cryptococcal species has recently been discovered.[9]

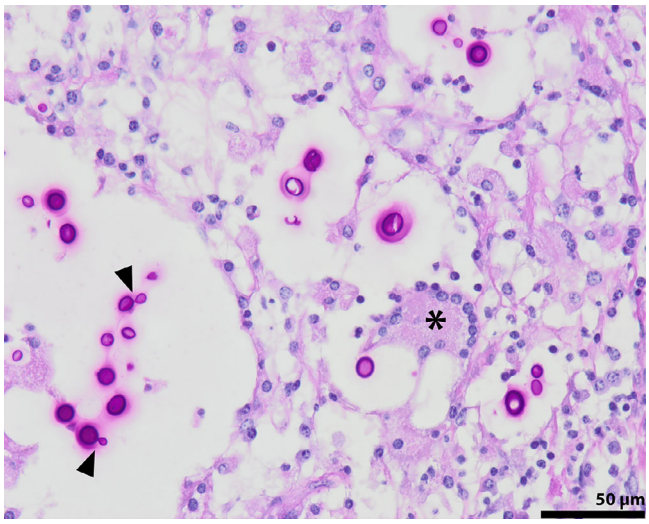

FIGURE 7 Lung histology (original magnification 400×). Periodic acid–Schiff (PAS) staining reveals the yeasts are PAS-positive. The yeasts exhibit multiplication through narrow-based budding (arrowheads). A Langhans-type multinucleated giant cell without intracytoplasmic yeasts is also observed (asterisk). PAS staining. Scale bar: 50 μm.

C. gattii sensu lato is a basidiomycetous yeast, endemic in many tropical and sub-tropical regions, and associated with outbreaks in people and many other mammals.[10] *C. gattii* is abundant in decaying material within hollows of multiple tree varieties.[11] It is frequently linked to various species of eucalyptus trees, as well as to temperate trees like firs and oaks.[12] *C. neoformans* achieves prolific mating and completes its life cycle on pigeon guano, whereas *C. gattii*, thriving on pigeon guano, refrains from sexual reproduction in this setting, suggesting pigeon guano as a fundamental yet unrealised niche for *C. gattii*.[13] Although originally restricted to Australia, Southeast Asia and other tropical regions, during the last two decades, the *C. gattii* species complex is increasingly reported from temperate climate regions, and the geographical distribution includes Mediterranean Europe, the Indian subcontinent and many South American countries.[10,14,15] There are reports of apparent autochthonous *C. gattii sensu stricto* and *Cryptococcus deuterogattii* cases from the Netherlands[16,17] and that environmental isolates have been found in the Dutch environment.[18] This suggests that the pathogen may have a broader global distribution than

previously considered, and is likely endemic to the temperate climate of northern Europe as well.

Virulence factors that may play a role in the pathogenesis are the presence of polysaccharide capsule, which impairs phagocytosis, activates complement and may suppress T-cell response; the synthesis of melanin, which can modulate the host immunoinflammatory response; the ability to grow in the temperature range of 35°C–40°C[7,19]; and the ability to transform into giant (Titan) cells that enhance dissemination and persistence in the host.[19,20] The route of infection is primarily through inhalation of basidiospores, ingestion of desiccated yeast cells, or rarely through direct cutaneous inoculation. There is no direct transmission between mammals, thus the disease is not considered to be contagious or zoonotic.[3]

Cryptococcal infection triggers a robust host response centred on helper T cells, releasing key cytokines, such as tumour necrosis factor, interferon-γ and interleukin-2, leading to granulomatous inflammation.[12] In humans and small animals, two *C. gattii* members typically affect immunocompetent hosts, while the other three, along with *C. neoformans*, are more common in immunocompromised hosts.[2,21] The underlying pathophysiology is not fully understood.[10] *C. gattii* may employ different methods, inducing distinct innate cytokine responses and pathogen-activated molecular patterns compared to *C. neoformans*.[19] Recent literature suggests a link between biologically inhibitory granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibodies and cryptococcal meningitis caused by *C. gattii* in apparently immunocompetent individuals.[22–24] GM-CSF plays a vital role in controlling innate immune cells, and when neutralised, the development of T-cell-mediated protective immunity against *C. gattii* may be compromised.[23]

The spectrum of responses to the infection varies, encompassing quiescent granulomatous lesions, granulomatous inflammation characterised by intense fungal replication, and at the other extreme, extensive cryptococcal replication with minimal accompanying inflammatory reaction. The latter produces a gelatinous mass lesion containing large numbers of replicating yeasts with very few inflammatory cells.[25] *C. gattii* is much more prone to generating this gelatinous form of cryptococcoma.[26]

Cryptococcosis in horses is infrequently reported. Equine cryptococcosis most commonly manifests as a disease in the respiratory tract as this is the usual portal of entry,[1,3] although localised disease has been reported in the central nervous system,[27] gastrointestinal tract,[28] musculoskeletal system[29] and reproductive tract.[30] After entry into the host through the respiratory tract, the pathogen may colonise and manifest as an acute infection or latent subclinical disease within a small granuloma in the respiratory tract or regional within a lymph node.[31] Dissemination initially occurs within the lung and then spreads to other body systems. Clinical illness presents after a variable incubation period, usually months.[1] Respiratory and central nervous system diseases are the most common clinical manifestations. The incidence of asymptomatic infection is unknown.[32]

Differentiating a cryptococcoma from a neoplastic mass may not be possible based on imaging features alone. The diagnosis of pulmonary cryptococcosis in horses is usually made by the cytological evaluation of respiratory secretions via tracheal wash or bronchoalveolar lavage (BAL). The presence of encapsulated yeasts with narrow-based budding distinguishes *Cryptococcus* spp. from other mycotic infectious agents.[33] In clinical specimens (e.g., pleural fluid, transtracheal aspirates, BAL fluid), the cryptococci can be seen when stained with new methylene blue, Gram stain and Romanovsky-type stains, including Wrights stain. An India ink preparation may demonstrate the capsule.[32] In human patients, the specificity of a cytological examination is excellent, but the sensitivity varies between 30% and 80%.[21] On histology, the prominent capsule can be stained and better visualised with Mayer's mucicarmine, PAS and Alcian blue stains.[21] However, routine histopathology is not adequate in differentiating the different cryptococcal species.[33] Molecular characterisation can be used to identify the species, and help identify the possible source of infection and create epidemiological data.[34]

In summary, this report highlights the importance of considering pulmonary cryptococcal infection in the differential diagnosis for horses with respiratory tract masses, even in the Netherlands where cryptococcosis is a rare fungal disease. It serves as a reminder that travel history abroad should not be the sole criterion for suspecting such infections. Veterinary professionals should remain vigilant and include this possibility in their diagnostic evaluations to ensure timely and accurate treatment for affected horses.

AUTHOR CONTRIBUTIONS

Nadiah van Eijk: Postmortem investigation; conceptualisation; writing—original draft preparation; review and editing. **Rosa Houben**: Clinical investigation; conceptualisation; writing—review and editing; supervision. **Anna Tellegen**: Diagnostic imaging investigation; writing—review and editing. **Ferry Hagen**: Molecular diagnostic investigation; writing—review and editing. **Nynke Ankringa**: Postmortem investigation; writing—review and editing; supervision. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

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ETHICS STATEMENT

Ethical approval was not applicable to this case report.

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