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PATHOLOGY

Meningoencephalitis secondary to rhinitis caused by *Pythium insidiosum* in sheep

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ABSTRACT: A case of meningoencephalitis caused by *Pythium insidiosum* secondary to rhinitis is reported in a three-year-old crossbred sheep from a herd of 15 animals, raised extensively and with free access to a weir. The animal presented mild dyspnea, blindness, mydriasis, opisthotonos, nystagmus, incoordination, decreased mandibular tone, and spasticity of the pelvic limbs. Macroscopic examination of the nasal cavity showed a blackish-red, irregular, friable mass that bilaterally compromised the nasal septum and the rostral portion of the nasal turbinates. In the brain, there was diffuse thickening of the leptomeninges of the cerebellum and ventral portion of the brainstem characterized by yellowish, granular material associated with vessel hyperemia. On the floor of the fourth ventricle, there was deposition of yellowish, irregular, slightly granular material that protruded towards the obex and displaced the cerebellum dorsolaterally. Microscopically, there were pyogranulomatous, eosinophilic, necrotizing rhinitis and fibrinosuppurative, eosinophilic, necrotizing meningoencephalitis, both associated with thrombosis, vasculitis, and intralesional hyphae. The hyphae were impregnated with silver and presented thin, parallel walls, rarely septate and branched. At immunohistochemistry, the hyphae were immunostained with polyclonal anti-*P. insidiosum* antibody in fragments of the cerebellum and nasal cavity. The findings showed that *P. insidiosum* rhinitis can secondarily affect the nervous system of sheep, causing nonspecific neurological clinical signs.
Key words: hematogenic dissemination, vasculitis, pythiosis, *Pythium insidiosum.*

Meningoencefalite secundária a rinite por *Pythium insidiosum* em um ovino

RESUMO: Relata-se um caso de meningoencefalite por *Pythium insidiosum* secundária a rinite em uma ovelha mestiça, três anos de idade, proveniente de um rebanho de 15 animais, criados extensivamente e com acesso livre a açude. O animal apresentava dispneia leve, cegueira, midríase, opistótono, nistagmo, incoordenação, diminuição do tônus mandibular e espasticidade dos membros pélvicos. O exame macroscópico da cavidade nasal evidenciou uma massa vermelho-escura, irregular, friável, que comprometia bilateralmente o septo nasal e a porção rostral dos cornetos nasais. No encéfalo, havia espessamento difuso das leptomeninges do cerebelo e porção ventral do tronco encefálico caracterizado por material granular amarelado associado à hiperemia dos vasos. No assoalho do quarto ventrículo, havia deposição de material amarelado, irregular, levemente granuloso, que se projetava em direção ao óbex e deslocava o cerebelo dorsolateralmente. Microscopicamente, havia rinite piogranulomatosa, eosinofílica, necrosante e meningoencefalite fibrinossupurativa, eosinofílica, necrosante, ambas associadas à trombose, vasculite e hifas intralesionais. Pela utilização da técnica de GMS as hifas foram impregnadas pela prata e apresentavam paredes finas e paralelas, raramente septadas e ramificadas. Na imuno-histoquímica, houve imunomarcação com o anticorpo policlonal anti-*P. insidiosum* em fragmentos do cerebelo e cavidade nasal. Os achados evidenciaram que rinite por *P. insidiosum* pode afetar secundariamente o sistema nervoso de ovinos, causando sinais clínicos neurológicos inespecíficos.
Palavras-chave: disseminação hematogênica, vasculite, pitiose, *Pythium insidiosum*.

Pythiosis is a chronic pyogranulomatous/granulomatous disease caused by the aquatic oomycete *Pythium insidiosum,* filamentous eukaryotic microorganism aquatic which taxonomically belongs to the Stramenopiles-Alveolata-Rhizaria supergroup (MCCARTHY; FITZPATRICK, 2017; BURKI et al., 2020; YOLANDA & KRAJAEJUN, 2022). The equine species is the most affected by this disease (SANTURIO et al., 2006), followed by dogs, cattle and sheep (YOLANDA & KRAJAEJUN,

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2022). Infection occurs when the animal comes into contact with water contaminated with motile zoospores (SANTURIO et al., 2006; YOLANDA; KRAJAEJUN, 2022) or ingests water contaminated with the infectious form (PESSOA et al., 2012).

In Brazil, sheep are frequently infected with *P. insidiosum*, with cases described in the Northeast (TABOSA et al., 2004; RIET-CORREA et al., 2008; PORTELA et al., 2010; CARRERA et al., 2013), Midwest (SANTURIO et al., 2008; UBIALI et al., 2013; MUSTAFA et al., 2015) and South (BERNARDO et al., 2015) regions of the country. The most common clinical forms reported in sheep include the nasal (SANTURIO et al., 2008; PORTELA et al., 2010; BERNARDO et al., 2015; MUSTAFA et al., 2015; CARMO et al., 2021), cutaneous (TABOSA et al., 2004; RIET-CORREA et al., 2008; YOLANDA & KRAJAEJUN, 2022) and digestive (PESSOA et al., 2012; YOLANDA & KRAJAEJUN, 2022).

Cases of meningoencephalitis associated with rhinopharyngeal rhinitis have been reported in sheep as a consequence of infection by *Conidiobolus* sp., and involvement of the nervous system usually occurs by direct extension of the nasal cavity lesions (PORTELA et al., 2010; UBIALI et al., 2013; MUSTAFA et al., 2015). Previously, a case of meningoencephalitis caused by *P. insidiosum* in sheep was described (MORI et al., 2017), but without lesions in other tissues, which made it difficult to identify the route of entry of the agent into the central nervous system (CNS). Therefore, clinical and pathological characterization of pythiosis with brain involvement is necessary to understand the pathogenesis of infection and the spread of *P. insidiosum* in animals. In this context, this study aimed to describe the clinical and anatomopathological aspects of nasal pythiosis with brain involvement in a sheep.

We report the case of a three-year-old crossbred sheep that presented with unbalance, falls and head tilt to the left side for one day. The animal was dewormed, not vaccinated, raised extensively in a herd of 15 animals, with access to a weir. On physical examination, it presented regular body score, dyspnea, blindness, mydriasis, opisthotonos, nystagmus, incoordination, decreased mandibular tone, and spasticity of the pelvic limbs. In view of the clinical signs, polioencephalomalacia was suspected, and a therapeutic protocol was instituted with dexamethasone (intravenous injection to dose of 0.1 mg/kg, SID) and vitamin B1 (intramuscular injection to dose of 10 mg/kg, TID). The next day, the sheep died and was sent for necropsy. Organ fragments were collected, fixed in 10% buffered formaldehyde, processed routinely for histopathology, and stained with hematoxylin and eosin (HE).

Histological sections of the lesions in the nasal cavity and cerebellum were submitted to Grocott methenamine silver nitrate (GMS) and periodic acid-Schiff (PAS) staining. Immunohistochemistry (IHC) was performed according to the protocol of (GABRIEL et al., 2008) modified by (MARTINS et al., 2012) using the primary (non-commercial) polyclonal anti-*P insidiosum* antibody followed by streptavidin-biotin-alkaline phosphatase with Liquid Permanent Red (LPR) chromogen. Histological sections of a confirmed case of equine pythiosis were used as a positive control, and the same sections with replacement of the primary antibody with phosphate-buffered saline (PBS) and polysorbate 20 were used as negative control.

Macroscopic examination showed lesions restricted to the nasal cavity and the brain. After a sagittal cut of the head, a blackish-red, irregular, friable mass measuring approximately 7x5.5 cm that bilaterally compromised the nasal septum and rostral portion of the nasal turbinates was observed in the nasal cavity (Figure 1).

Upon opening of the cranial box, there was diffuse thickening of the leptomeninges of the cerebellum and ventral region of the brainstem characterized by granular, yellowish material associated with vessel hyperemia (Figure 2). On the floor of the fourth ventricle, there was a deposition of yellowish, irregular, slightly granular material that protruded toward the obex and displaced the cerebellum dorsolaterally.

Histopathological examination of the nasal cavity revealed pyogranulomatous, eosinophilic, necrotizing rhinitis associated with vasculitis and thrombosis, characterized by thickening of the lamina propria and marked, diffuse inflammatory infiltrate located mainly around blood vessels and often distending the vascular wall, as well as by eosinophils and fewer neutrophils, macrophages, and multinucleated giant cells associated with multifocal areas of necrosis and negative images of hyphae in longitudinal and transverse sections, sometimes surrounded by amorphous, granular, hypereosinophilic material similar to the Splendore-Hoeppli phenomenon. There was marked congestion and fibrin thrombi occluding the vascular lumen, sometimes associated with hyphae. The nasal mucosa was diffusely ulcerated.

In the cerebellum, brainstem, and parietal cortex there was fibrinosuppurative, eosinophilic meningoencephalitis associated with vasculitis and

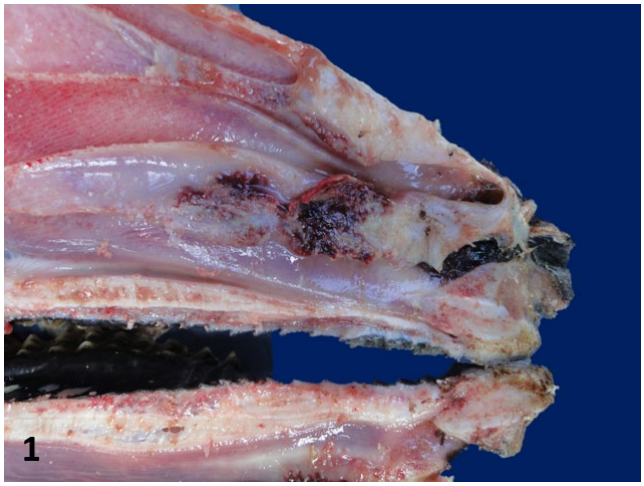

Figure 1 - Nasal cavity. A blackish, irregular, friable mass in the nasal septum and rostral portion of the nasal turbinates.

thrombosis (Figure 3), characterized by multifocal and coalescent areas of marked thickening of the leptomeninges, with inflammatory infiltrate located mainly around the blood vessels, and distending the vascular wall, consisting of eosinophils and fewer neutrophils and macrophages associated with fibrin and negative images of hyphae amid a reaction similar to the Splendore-Hoeppli phenomenon and in the lumen of blood vessels.

There was marked congestion and fibrin thrombi obstructing the lumen of most blood vessels. In the adjacent gray and white matter, a similar

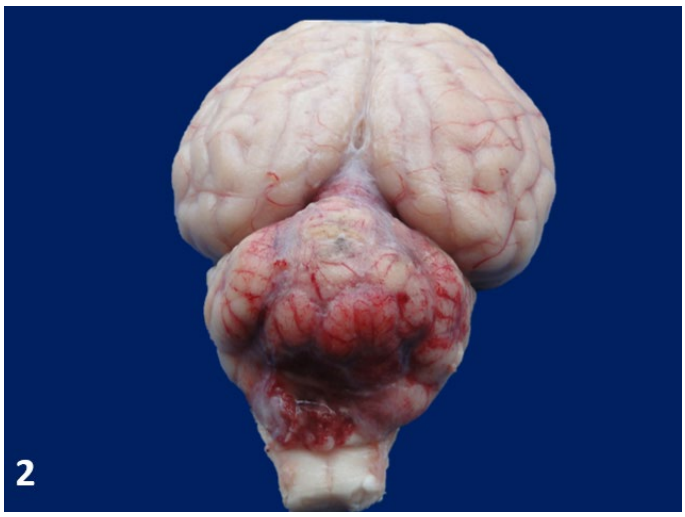

Figure 2 - Brain. Thickening of the leptomeninges of the cerebellum characterized by granular and yellowish material associated with hyperemia of blood vessels.

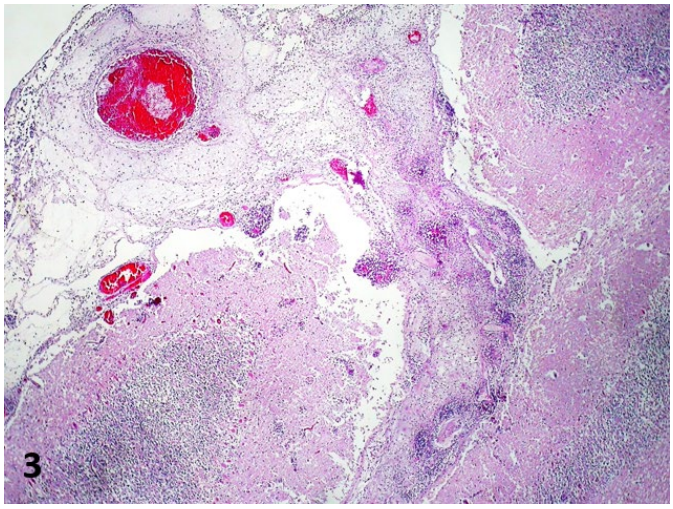

Figure 3 - Cerebellum. Fibrinosuppurative, eosinophilic meningoencephalitis associated with thrombosis and vasculitis. HE. Bar = 100 µm.

inflammatory infiltrate was observed, mainly around the blood vessels, associated with thrombosis and hyphae in the vascular lumen and in the neuropile. The choroid plexus presented mild inflammatory infiltrate consisting predominantly of macrophages, eosinophils, and rare neutrophils and lymphocytes. In the parietal cortex, adjacent to the foci of inflammation, slight neuronal necrosis was observed.

At GMS, the hyphae were heavily impregnated by silver, with thin, parallel walls rarely septate and branched, measuring 4-25µm (Figure 4). The hyphae did not stain in PAS. At IHC, the hyphae were strongly immunostained with polyclonal anti-*P insidiosum* antibody in fragments of the cerebellum and nasal cavity (Figure 4, Inset). The diagnosis of meningoencephalitis secondary to rhinitis caused by *P. insidiosum* was established based on anatomopathological findings and confirmed through IHC.

Generally, animals infected with oomycetes have access to dams (RIET-CORREA et al., 2008), where grazing occurs in swampy areas with low vegetation, most often associated with the large amount of decomposing organic matter, with an ideal temperature for proliferation of the agent (SANTURIO et al., 2006). It is believed that, in this case, access to the reservoir favored the animal's contact with the infective form of *P. insidiosum.*

Meningoencephalitis associated with rhinopharyngeal rhinitis has been frequently described in sheep as a consequence of infection by *Conidiobolus* sp. (RIET-CORREA et al., 2008; PORTELA et al., 2010; MUSTAFA et al., 2015). Involvement of the CNS in conidiobolomycosis occurs by direct extension of proliferative and destructive granulomatous lesions that extend from the middle third of the nasal cavity to the cribriform plaque, olfactory bulb and, more often, to the frontal cortex (RIET-CORREA et al., 2008; PORTELA et al., 2010; UBIALI et al., 2013; MUSTAFA et al., 2015). In the present case, the lesions were located in the rostral portion of the nasal cavity, presenting macroscopic aspects similar to the rhinofacial pythiosis described by other authors (SANTURIO et al., 2008; PORTELA et al., 2010; CARRERA et al., 2013; BERNARDO et al., 2015; MUSTAFA et al., 2015; CARMO et al., 2021). However, the histopathological observation of vasculitis and thrombosis associated with *P. insidiosum* hyphae in the lumen of vessels suggests that the involvement of the CNS occurred through hematogenesis. Moreover, the absence of lesions in the nasal conchae and cribriform plaque, which could possibly facilitate the agent's ascension by direct extension of the lesion in the nasal cavity, reinforces the possibility of the agent having reached the CNS by the hematogenous route.

The absence of craniofacial asymmetry drew attention in this sheep. This clinical aspect has been frequently described in cases of rhinofacial

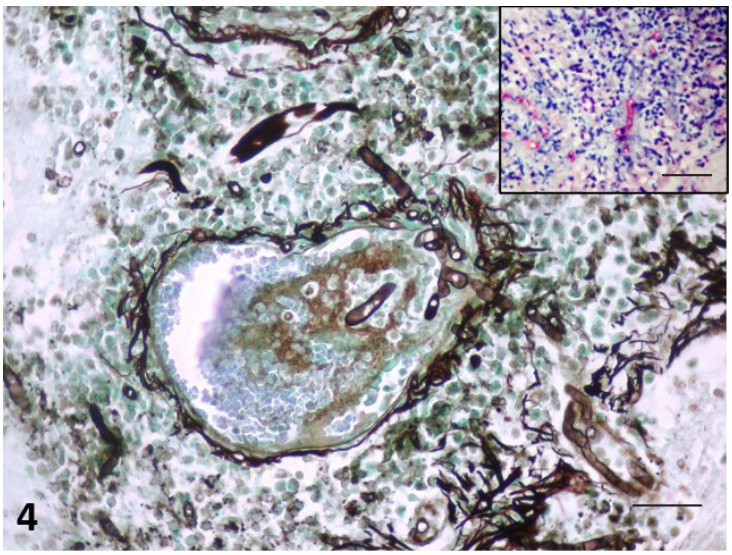

Figure 4 - Cerebellum. Hyphae with strong silver impregnation characterized by thin, parallel walls, rarely septate, in the lumen and wall of a blood vessel. GMS. Bar = 20 µm. Inset: Cerebellum. Hyphae red-immunostained with polyclone anti-*Pythium insidiosum* antibody. IHQ. Alkaline phosphatase. Bar = 20 µm.

pythiosis (SANTURIO et al., 2008; PORTELA et al., 2010; BERNARDO et al., 2015; MUSTAFA et al., 2015), and popularly characterizes the disease as 'bull snout'. It is believed that the impairment of the CNS and the evolution of the neurological clinical condition and, consequently, the death of the animal did not allow the evolution of the nasal cavity lesions and the appearance of craniofacial asymmetry.

Although, polioencephalomalacia was considered a presumptive diagnosis, the animal did not respond to therapeutic treatment with dexamethasone and vitamin B1 and died the following day. The anatomopathological findings in the brain stem and cerebellum associated with *P. insidiosum* were serious and justified the neurological condition.

Considering the macroscopic and microscopic findings observed in this case, which corroborated those described in the literature for a case of *P. insidiosum* meningoencephalitis with the absence of lesions in other organs (MORI et al., 2017), it is proposed that infection by *P. insidiosum* should be included in the list of differential diagnoses of meningoencephalitis associated with rhinitis, or of diseases that affect the CNS of sheep. The main diseases that can also cause injuries in the places identified in this case are rabies (GUEDES et al., 2007; BORGES et al., 2016), nervous form of listeriosis (GUEDES et al., 2007), and bacterial meningitis (GUEDES et al., 2007).

The lesions observed in the nasal cavity must be differentiated mainly from the rhinofacial form of conidiobolomycosis (PORTELA et al., 2010; UBIALI et al., 2013; MUSTAFA et al., 2015) and from infection by the fungus *Cryptococcus* spp. (SILVA et al., 2010; MACÊDO et al., 2020). In the property of the case studied, there were no reports of pythiosis previously in other sheep, but some cases have already been described in the area covered by our diagnostic laboratory.

In conclusion, it is suggested that *P. insidiosum* spreads via the hematogenous route and causes meningoencephalitis in sheep with nasal pythiosis, which may trigger varied and nonspecific neurological symptoms. This feature has not yet been described in the literature. In addition, pythiosis with brain involvement should be included in the differential diagnosis of diseases that affect the central nervous system of sheep.

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DECLARATION OF CONFLIT OF INTEREST

The authors have no conflict of interest to declare.

AUTHORS' CONTRIBUTIONS

All authors contributed equally to the design and writing of this manuscript. All authors critically reviewed the manuscript and approved the final version of the manuscript.

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