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Case Report

Neurotuberculosis in a Holstein-Friesian Calf from the State of Rio Grande do Sul, Brazil

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Abstract
Bovine tuberculosis is a chronic granulomatous disease caused by *Mycobacterium tuberculosis* var *bovis*. Despite control programs, bovine tuberculosis presents a significant challenge worldwide and it remains a concern in Brazil. Neurotuberculosis is a relatively rare form of the disease in which *Mycobacterium* reaches the central nervous system, leading to the formation of multiple small granulomas on the meningeal surface. This study reports a case of neurotuberculosis in an 8-month-old Holstein-Friesian calf from the state of Rio Grande do Sul, southern Brazil. The clinical course was chronic, of nearly five months, and clinical signs were mainly neurological, including ataxia, motor incoordination, stiff neck, muscular tremors, and seizures. These clinical signs resulted from granulomatous lesions affecting the central nervous system. Similar granulomas were also present in the lungs, mediastinal and mesenteric lymph nodes, and adrenal glands. Histologically the granulomas were characterized by caseous necrosis associated to inflammatory infiltration of epithelioid macrophages, Langhans multinucleated giant cells, lymphocytes, and plasma cells, proliferation of fibrous tissue, as well as occasional mineralization. Ziehl-Neelsen staining method yielded acid-alcohol resistant bacilli amidst necrotic debris and in the cytoplasm of Langhans cells. Clinic-pathological findings, *postmortem* and histological examinations, along with Ziehl-Neelsen staining, confirmed the diagnosis of neurotuberculosis in the present case. This report highlights the importance of control measures for tuberculosis, given the debilitating and zoonotic nature of the disease and the lack of effective treatment.

Keywords: bovine, dairy cattle, infectious diseases, central nervous system, tuberculosis.

Introduction

Bovine tuberculosis is a chronic granulomatous disease primarily caused by *Mycobacterium tuberculosis* var *bovis*, that belongs to the *Mycobacterium tuberculosis* complex. Besides cattle, *M. bovis* can affect other species of vertebral, domestic and wild animals, as well as humans (2, 5, 11). These mycobacteria are aerobic, gram-positive, nonmotile, and nonspore-forming pleomorphic coccobacilli, often resistant to Gram staining. However, they can be effectively stained using carbolfuchsin (Ziehl-Neelsen stain) or fluorescent dyes like auramine-rhodamine (12).

While control programs have significantly reduced bovine tuberculosis in developed nations, such as countries in North America and Oceania, its prevalence remains a concern in Brazil, with data scarcity in various regions (2, 5). Notably, within the state of Rio Grande do Sul, Brazil, dairy cattle demonstrate the highest incidence of tuberculosis (5).

The most common route of infection is through the respiratory route, leading to upper and lower airways

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infections. Oral infection is also possible, though it requires a higher bacterial load to induce disease and results in lesions in the intestines and associated lymph nodes (2, 5, 11). Moreover, calves that are fed with milk from cows with tuberculosis or that drink from contaminated water sources can become infected through the digestive route, after which the bacteria spread hematogenously (5). Less common routes of transmission encompass transplacental, percutaneous, and genital routes (2). Occasionally, the pathogen may disseminate the infection by implantation on pleural, peritoneal, pericardial, or meningeal surfaces. Although uncommon, when *M. bovis* reaches the meninges, it can lead to a condition known as neurotuberculosis, characterized by neurological clinical signs, mainly in younger cattle (5, 9, 10, 15). In these cases, the neurological involvement of tuberculosis constitutes a differential diagnosis for other conditions that present with chronic neurological manifestations in cattle. Thus, the aim of this report is to describe the clinic-pathological aspects of a case of neurotuberculosis in a Holstein-Friesian calf from the Rio Grande do Sul state, southern Brazil.

Case description

In November of 2022, the Setor de Patologia Veterinária (SPV) from the Universidade Federal do Rio Grande do Sul (UFRGS) was contacted regarding a calf that had been presenting neurological signs for the past five months. The SPV conducted a visit to the property located in the municipality of Viamão, Rio Grande do Sul, southern Brazil (30° 04' 51" S 51° 01' 22" O). During the visit epidemiological and clinical data were collected, and a necropsy evaluation was performed.

The farm housed a herd of 14 calves fed with corn silage and trace mineralized salt. One of the calves, an 8-month-old weaned Holstein-Friesian female calf, was displaying clinical signs of ataxia, motor incoordination, stiff neck when standing (Fig. 1A), muscular tremors, and sporadic seizures over the past five months. Despite antibiotic treatment, which initially led to temporary improvement, the clinical signs recurred upon cessation of treatment. The animal was in good body condition and displayed a normal appetite. The farm owners reported that previous calves had shown similar neurological clinical signs, although no definitive diagnosis had been established at the time. Furthermore, months later, adult cows were subjected to the comparative cervical tuberculin test, with several animals testing positive for bovine tuberculin.

At the necropsy of the affected calf, fragments of the main organs (encephalon, spinal cord, heart, lungs, liver, gallbladder, kidneys, urinary bladder, spleen, pancreas, adrenal glands, lymph nodes, forestomaches, abomasum, and intestines) were collected, fixed in 10% formalin, routinely processed, and stained with Hematoxylin and Eosin (HE) and Ziehl-Neelsen for microscopic examination.

The main gross lesions consisted of leptomeningeal thickening, with multifocal to coalescing millimetric nodular structures that were raised, yellowish, and firm. These nodules were more severe and evident at the basilar brain (rhombencephalon and mesencephalon) (Fig. 1B and 1C). Additionally, yellow nodules ranging from 0.1 to 1 cm in diameter and with a gritty texture on the cut surface were observed in the cranial left pulmonary lobe, which was also hypo crepitant, dark red, slightly depressed and firm (atelectasis). Similar nodules were seen in lymph nodes from the mediastinum (Fig. 1D) and mesentery, and a single nodule was present in the right adrenal gland.

Histologically, the lesions in the CNS were characterized by the thickening of the leptomeninges by areas of caseous necrosis with occasional mineralization, which was surrounded by marked inflammatory infiltrates of epithelioid macrophages, Langhans multinucleated giant cells, lymphocytes, and plasma cells, as well by proliferation of fibrous tissue (Figure 2A-C). In some areas, there was also inflammatory infiltration of neutrophils and fibrin deposition. The inflammatory infiltrates, composed of lymphocytes, neutrophils, and macrophages, were also present in the perivascular spaces of the meninges, in the ventricular system, choroid plexus, ependyma, and in the neuropil. In the *pars nervosa* of the hypophysis, in the trigeminal ganglion, and in the meninges of the spinal cord near to the obex, there were multifocal areas of moderate inflammatory infiltration of lymphocytes, plasma cells, and macrophages. Multifocal to coalescent and moderate granulomatous lesions similar to those observed in the nervous system were also seen in the left pulmonary lobe and mediastinal and mesenteric lymph nodes, as well as a focal area in the right adrenal. Additionally, the atelectatic area seen in the macroscopical examination of the left pulmonary lung exhibited multifocal inflammatory infiltration of necrotic neutrophils within bronchi, bronchiole and alveolar spaces (secondary suppurative bronchopneumonia).

In the Ziehl-Neelsen (ZN) stain, a moderate amount of acid-alcohol resistant bacilli was visible amidst the necrotic debris and in the cytoplasm of Langhans multinucleated giant cells in granulomas from the brain (Fig. 2D), lymph nodes, and lungs.

Discussion

The diagnosis of tuberculosis in this case was confirmed through *postmortem* and histological findings, associated with the ZN staining method. Furthermore, the presence of chronic neurological clinical signs along with evident lesions in the CNS established this as a case of neurotuberculosis. Bovine tuberculosis is a granulomatous disease caused by bacteria from the genus *Mycobacterium*, mainly *M. tuberculosis* var *bovis* (5). In the literature, cases of bovine tuberculosis affecting the CNS are scarce and have been documented in a limited number of reports (9, 10, 13, 15).

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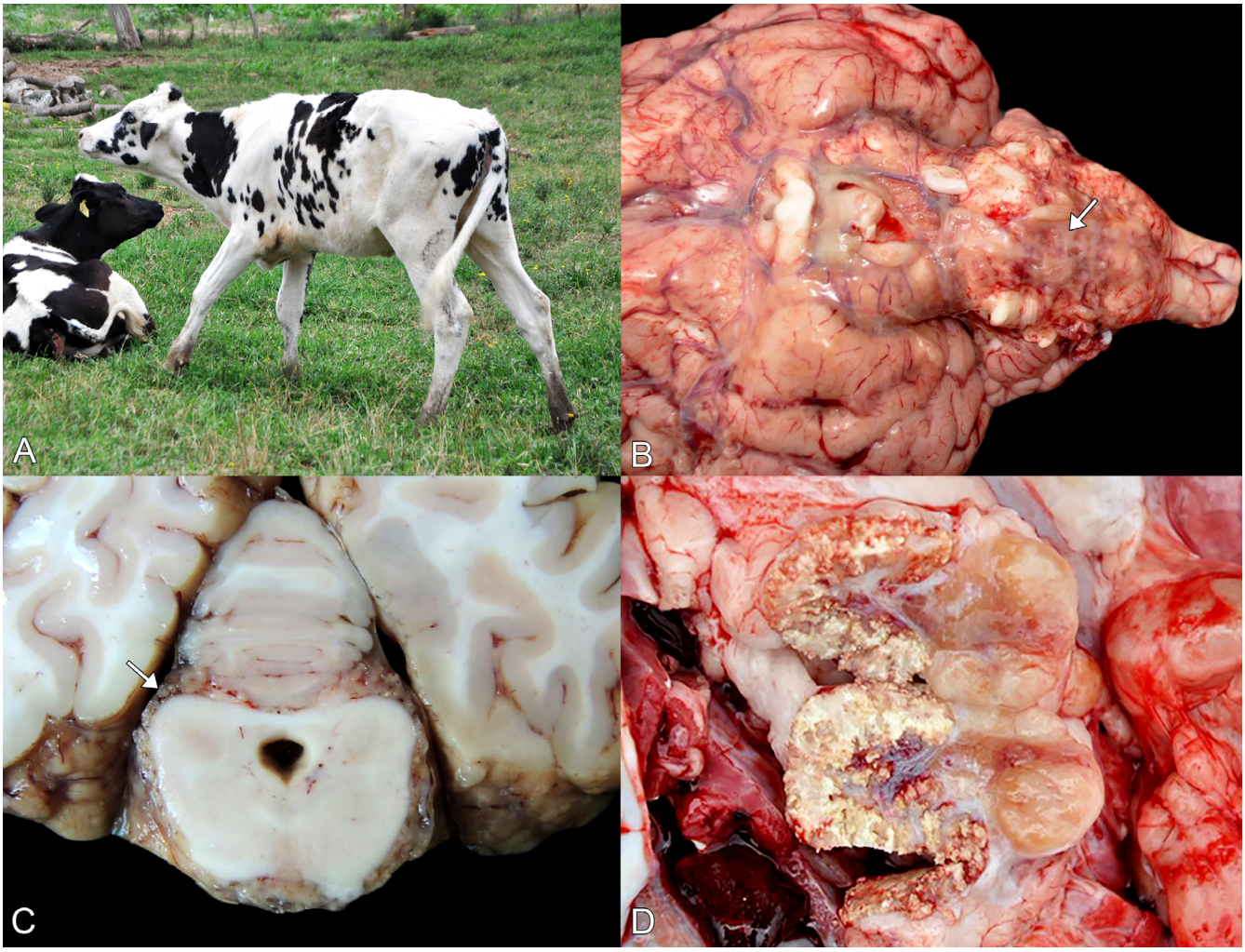

Figure 1. Clinical and macroscopical findings of a case of neurotuberculosis in a Holstein-Friesian calf. A- The affected calf is showing ataxia and stiff neck when standing. B- Marked and multifocal thickening of the meninges in the basilar region of the brain (arrow). C- Transverse cut-section of the brain at the level of the occipital lobes, revealing multifocal to coalescent millimetric nodules (arrow) in the meninges, mainly in the basal region of the brain. D- Cut section of the tracheobronchial lymph node presenting a focal yellow nodule, of up to 2 cm in diameter. When cutting, this nodule exhibited a gritty texture.

Neurotuberculosis is more commonly observed in younger cattle, typically up to two years old (9, 10, 15). This aligns with our case, where the affected animal was 8 months old. However, this disease presentation had also been described in older cattle, up to nine years old (15).

The clinical course in this report was chronic, leading to the euthanasia of the calf due to poor prognosis. Clinical signs were similar to those reported in other studies with neurotuberculosis in cattle (9, 15), and were characterized by ataxia, motor incoordination, stiff neck when standing, muscular tremors, and sporadic seizures over the past five months. This neurological clinical presentation is a consequence of the dissemination of granulomatous lesions throughout the brain. In humans with tuberculosis with neurological involvement, the clinical signs have been reported to persist over three months until the diagnosis (3). In other studies, in cattle, the clinical course was reported to last up to 30 days before the decision of euthanasia because of the poor prognosis (9, 13). However, in the present case, the clinical course lasted longer, up to five months, because it took the farm owners longer to seek veterinary support.

Macroscopic and microscopic findings in our case of neurotuberculosis were consistent with previous reports (9, 10, 13, 15) and were characterized by multiple small granulomas in the meninges of the brain and cerebellum, mainly in the basilar region. In humans, neurological involvement of tuberculosis can be seen as tuberculous meningitis, brain and spinal tuberculomas, and vertebral infection with spinal cord compression (3). Our case was characterized by the thickening of the meninges by multiple granulomas, which resembled the tuberculous meningitis, also the more common presentation in reports of bovine neurotuberculosis. Meanwhile, the tuberculoma form is usually seen with a lower frequency (9, 15).

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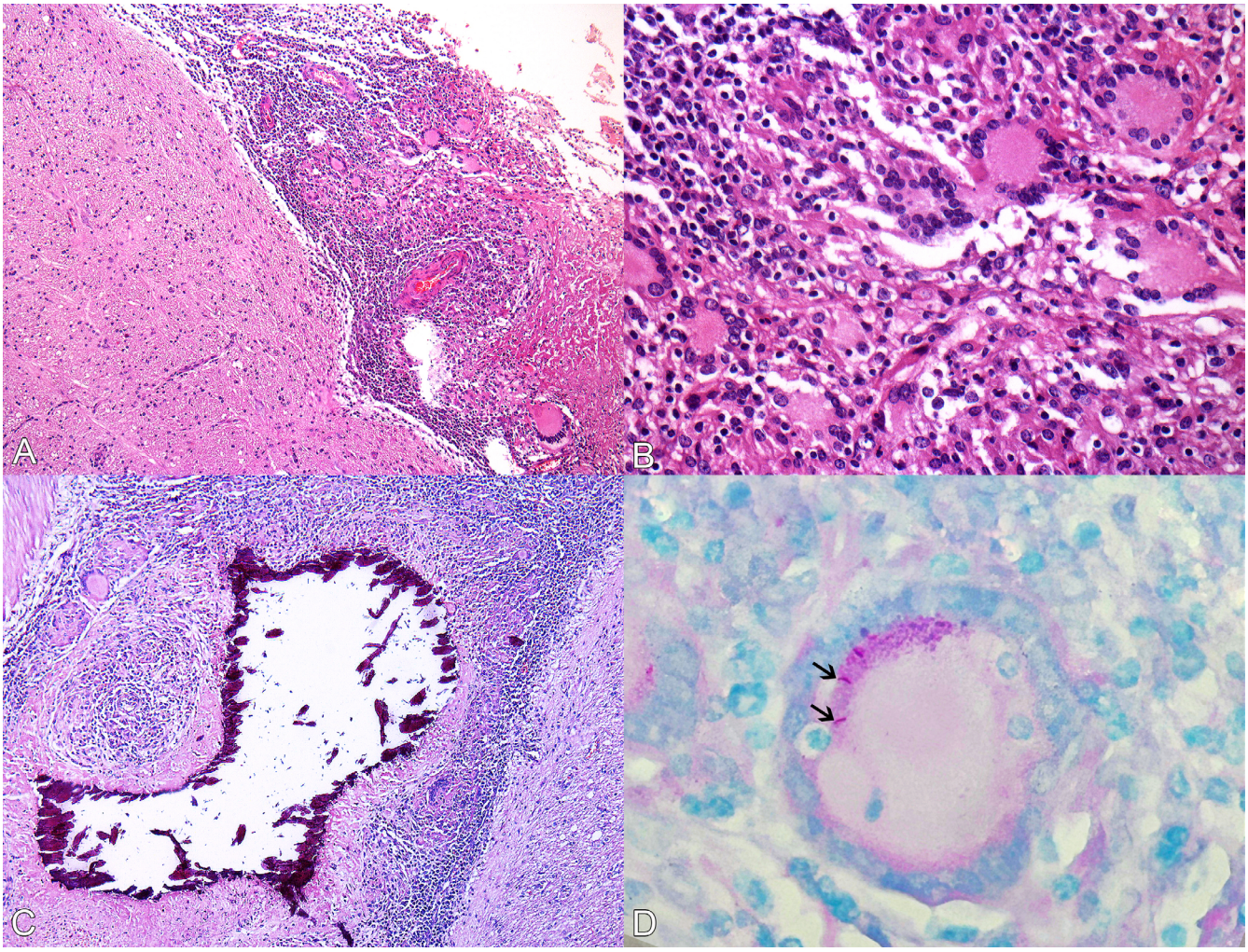

Figure 2. Microscopic lesions in the central nervous system in a case of bovine neurotuberculosis. A- The meninge is thickened by marked inflammatory infiltration HE, 100x. B- A closer look from Figure A showing the inflammatory infiltrate mainly composed by epithelioid macrophages, Langhans multinucleated giant cells, and lymphocytes. HE, 400x C- An area of deposition of strongly basophilic and birefringent material (dystrophic mineralization) is also present amidst the necrotic debris (caseous necrosis). HE, 100x. D- Few bacilli (arrow) are noted within a multinucleated Langhan cell. Ziehl-Neelsen stain, 600x.

Inhalation of the bacterium is the most common route of infection (2, 5, 7), and the simultaneous morphological localization of lesions in the CNS, lung, and mediastinal lymph nodes supports this possible route. Other routes of infection in cattle include oral, transplacental, genital, or intramammary (7), which were ruled out based on epidemiological aspects and lesion localization.

The mechanisms of how the bacterium reaches and colonizes the CNS are not well understood. It is suggested that the bacteria may migrate across the blood-brain barrier and the blood-cerebrospinal fluid barrier via infected macrophages and neutrophils in the bloodstream (6) or by invading the brain endothelium, a process mediated by the *PknD* enzyme (1). The animal from this case report also presented with extra-CNS lesions (lungs, adrenal and mediastinal and mesenteric lymph nodes), suggesting that the changes in the CNS likely originated from the hematogenous spread of the agent. The base of the brain is supplied by a complex arterial network (8), which may explain the location of the main lesions in the present case.

The Ziehl-Neelsen staining method serves as an auxiliary tool for identifying acid-alcohol resistant bacilli, such as those from the genus *Mycobacterium*, directly within the granulomatous lesions (5). In the present report, a small number of bacilli were seen in tissue sections from granulomas found in the brain, lung, and lymph nodes stained with ZN. The quantity of bacilli within lesions varies according to the course of the infection. Lesions in the initial stages typically present with a moderate to high number of bacilli within the cytoplasm of macrophages and Langhans cells. In more advanced stages, however, bacilli are mostly found amidst necrosis and occasionally within macrophages and Langhans cells (14).

When considering a differential diagnosis for neurotuberculosis, it is important to take into account other diseases that affect the CNS, such as rabies, cerebral babesiosis, listeriosis, encephalitis caused by Bovine Herpesvirus type 1 and 5 infection, malignant catarrhal fever, botulism, tetanus, polioencephalomalacia, abscesses of the central nervous system, and intoxication by hepatotoxic plants causing hepatic encephalopathy (i.e. *Senecio* spp., *Crotalaria* spp.) (4, 5). However, these conditions present distinct epidemiological and pathological findings. Additionally, the granulomatous changes and the ZN histochemical staining were crucial in establishing the definitive diagnosis of neurotuberculosis in the bovine of this case. The tuberculinization, the most efficient diagnostic test in live cattle (5), was not conducted as the animal showed the atypical neurological presentation of tuberculosis instead of the characteristic signs observed in cattle. However, macroscopic and histological examinations allowed for the diagnosis of tuberculosis in our case, given the highly characteristic nature of the lesions.

Neurotuberculosis is an uncommon manifestation of tuberculosis, sporadically observed in cattle, particularly younger animals, as in the case of the calf from this report. The clinical course is primarily chronic, and the main clinical signs are neurological, such as ataxia, muscular tremors, motor incoordination, and seizures, all stemming from granulomatous lesions affecting the central nervous system. *Postmortem* and histological examinations, supplemented by the ZN staining method, facilitate accurate diagnosis. Given the debilitating nature of the disease and the lack of effective treatment, the primary emphasis should be on implementing measures for tuberculosis control. Furthermore, neurotuberculosis should be considered in the differential diagnosis of neurological diseases with chronic evolution in cattle.

Conflict of Interest

The authors declare no competing interests.

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