Type 1 Diabetes Mellitus in a Dorper Ram: A Case Report

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SUMMARY

Diabetes Mellitus (DM) is a rare condition in sheep, characterized by insulin deficiency and consequent hyperglycemia. This report describes a 3-year-old, 57 kg, male Dorper sheep presenting with progressive weight loss, hyporexia, polyuria and jaundice. The diagnosis of DM was confirmed through a glucose tolerance test. Insulin treatment proved challenging in terms of both economic viability and management, leading to the euthanasia of the animal. Necropsy revealed multifocal granulomatous inflammation in the pancreas and the presence of trematode eggs compatible with *Eurytrema* spp. within the pancreatic ducts. Although no direct causal relationship could be established, these findings suggest a potential link between parasitic lesions and pancreatic endocrine dysfunction. This case emphasizes the diagnostic value of the glycemic curve, the complexity of managing DM in production animals, and highlights the importance of further studies on pancreatic parasitoses in small ruminants.

KEY WORDS

Hyperglycemia; Pancreatitis; Glycemic curve; Small ruminants.

INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion and/or action. While it is widely recognized in dogs, cats, and humans, the occurrence of DM in ruminants-particularly sheep-is extremely rare, with only a few documented cases in the veterinary literature (1,2,3). In cattle, some cases have been linked to immune-mediated processes resembling type 1 diabetes in humans, with destruction of pancreatic β-cells (4).

In small ruminants, however, the pathophysiology, clinical presentation, and management of DM remain poorly defined. Diagnosing the disease in these species is challenging due to its rarity and the lack of standardized diagnostic and therapeutic protocols-especially in production animals. The limited clinical and laboratory data available for sheep with DM restrict understanding of disease progression and complicate therapeutic decision-making.

Recently, some studies have hypothesized potential contributing factors to pancreatic disorders in ruminants, including infections by trematodes of the genus *Eurytrema* (5,6).

Pancreatic eurytrematosis is a chronic infection caused by trematodes of the genus *Eurytrema*, traditionally considered to have low clinical significance in small ruminants. However, recent studies suggest that it may have notable productive and sanitary impacts, in addition to a widely overlooked geographic distribution (7).

Although traditionally associated with exocrine pancreatic dysfunction, chronic inflammatory responses caused by *Eurytrema spp.* may also affect endocrine components, such as the islets of Langerhans (21, 22). Nevertheless, the relationship between *Eurytrema* infection and the development of DM in small ruminants remains unclear and warrants further investigation. This report aims to describe a clinical case of type 1 Diabetes Mellitus in a Dorper sheep, including clinical signs, laboratory findings, glucose tolerance testing, and pathological findings.

MATERIALS AND METHODS CASE PRESENTATION

History

A 3-year-old male Dorper sheep weighing 57 kg (125.6 lb) was admitted to the

Large Animal Internal Medicine Service of the Veterinary Teaching Hospital, School of Veterinary Medicine and Animal Science, São Paulo State University (UNESP), Botucatu-SP, Brazil.

The sheep presented with a 3-month history of progressive weight loss, hyporexia, polyuria, jaundice, and a clinical suspicion of haemonchosis.

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Clinical Examination

During the initial physical examination, the sheep was alert, standing, with normal appetite (normorexia), polyuria, and polydipsia. The clinical evaluation revealed small skin wounds, tachycardia (148 beats per minute; reference [bpm]; 90 to 115 bpm), tachypnea (60 breaths per minute; reference: 20 to 30 bpm), normothermia (39.9ºC; reference: 38.5 to 40ºC), pale mucous membranes, capillary refill time (CRT) of 2 seconds, palpable lymph nodes (mandibular, prescapular, and prefemoral) were examined and found to be non-reactive. Gastrointestinal examination showed a normal abdominal contour, normal intensity of abdominal sounds, and no pain on superficial or deep abdominal palpation. Ruminal evaluation revealed reduced motility (0-1 contractions/2 min; reference: 2-4/2 min) with moderate amplitude, normal consistency of ruminal contents, and absence of pain on ruminal palpation. Feces were pasty in consistency, without evidence of blood or mucus. Additionally, the animal exhibited hyperglycemia (414 mg/dL; reference: 60 to 70 mg/dL) and hyperketonemia (HI [high]; reference: < 0.8 mmol/L).

Ancillary Tests

Laboratory tests revealed normocytic normochromic anemia (red blood cells 2.86/10 µL, hemoglobin 4.6 g/dL, hematocrit 11%, MCHC 41.8%), hypoproteinemia (5.3 g/dL), elevated gamma-glutamyl transferase (GGT) (56 U/L), and increased creatine kinase (CK) levels (1132.0 U/L). Urinalysis revealed glucosuria and ketonuria. A quantitative fecal examination using the McMaster technique identified 7,500 eggs per gram (EPG) of nematodes belonging to the Strongylida order. Additionally, a sedimentation test (TAMISÉS method) was conducted to screen for fluke infections, with a particular focus on *Eurytrema* spp., but no trematode ova were detected. Although often classified as a neglected parasite in small ruminants, the focus on *Eurytrema* spp. is justified by its growing clinical and productive significance. Recent studies have highlighted its potential impact on pancreatic function, as well as indirect effects related to reduced feed efficiency and compromised overall health of the animals. Therefore, investigating this parasite in sheep and goats contributes not only to filling knowledge gaps but also to supporting strategies for diagnosis, control, and prevention, reinforcing its relevance for the health management of small ruminants.

Therapeutics and Diagnosis

As an initial clinical approach, regular insulin (0.5 IU/kg, SID, SC, for 7 days) was administered to control hyperglycemia, along with monepantel (1 mL/10 kg, SD, PO) for treating parasitism. During the hospitalization period, despite insulin administration, the animal continued to exhibit persistent hyperglycemia and hyperketonemia (Figure 1).

To confirm the diagnosis of Diabetes Mellitus (DM), a comparative glycemic curve was performed between the sick animal and a healthy control sheep. Both animals were fasted for 12 hours, and the patient did not receive insulin on the test day. A 50% glucose solution (0.5 g/kg, IV) was administered over

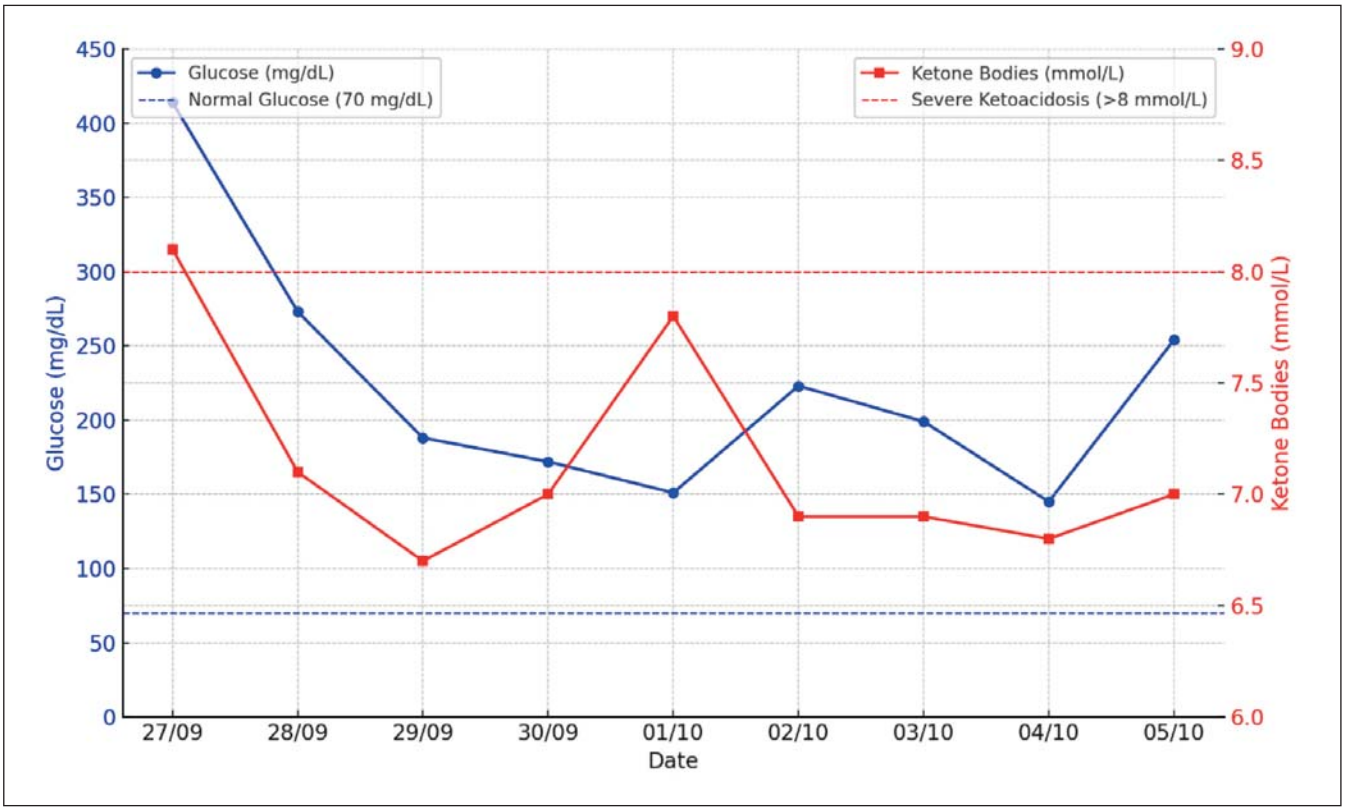

Figure 1 - Monitoring of blood glucose (mg/dL) and ketone bodies (mmol/L) in a Dorper sheep with Diabetes Mellitus. The blue line represents blood glucose levels, with the dashed line indicating the normal glucose reference range (70 mg/dL). The red line indicates ketone body concentrations, with the dashed line showing the threshold for severe ketoacidosis (>8 mmol/L). Insulin therapy was initiated on 28/09, with a progressive response in glucose levels but persistent hyperketonemia. Reference values for glucose in sheep range from 50 to 75 mg/dL, while β-hydroxybutyrate concentrations are considered normal below 0.8 mmol/L. Values between 0.8 and 1.6 mmol/L may indicate subclinical ketosis, and levels above 1.6 mmol/L are suggestive of clinical ketosis or ketoacidosis (21,22).

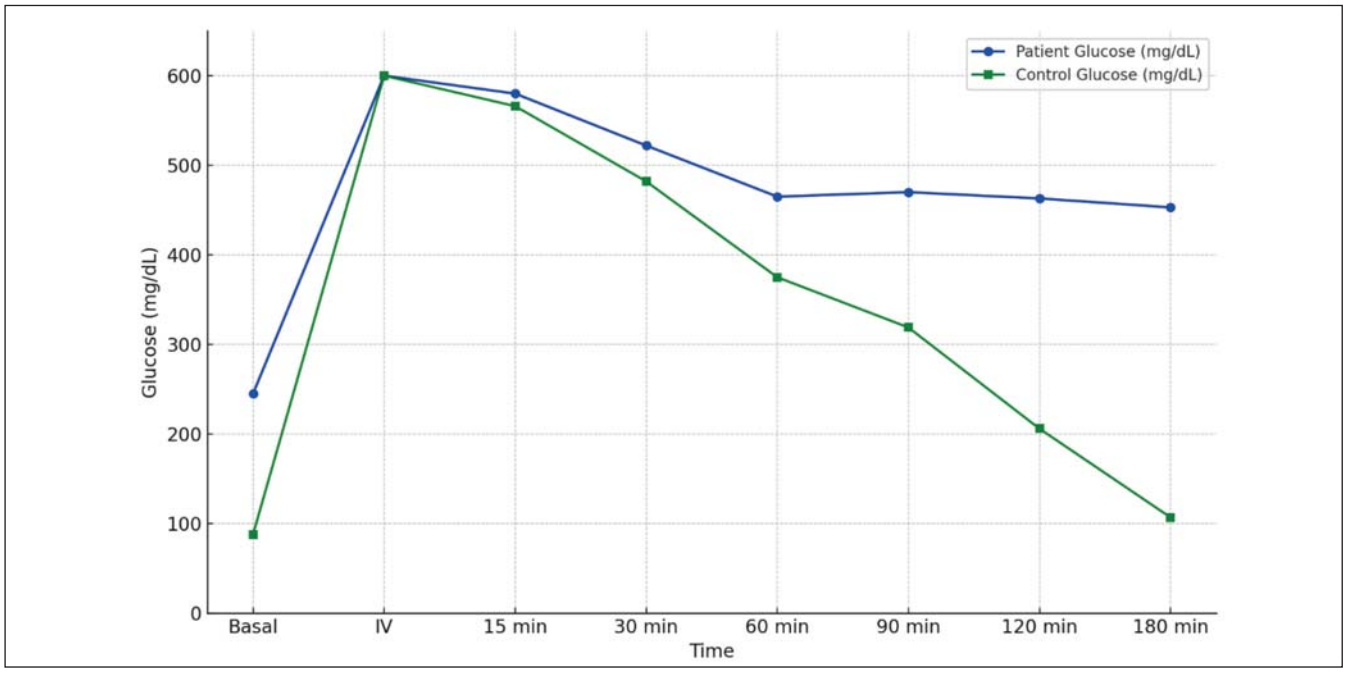

Figure 2 - Comparative Glycemic Curve of a Dorper Sheep with Diabetes Mellitus and a Healthy Control. Glycemic response in a Dorper sheep with Diabetes Mellitus (blue line) compared to a healthy control (green line) following intravenous glucose administration. The graph illustrates the baseline glucose levels (Basal) and subsequent measurements at 15, 30, 60, 90, 120, and 180 minutes post-infusion. The patient exhibited persistent hyperglycemia with minimal reduction over time, indicative of impaired glucose regulation, while the control animal demonstrated a normal glycemic decline to physiological levels.
The glycemic curve showed that the patient maintained persistently high glucose levels, while the control animal exhibited an appropriate physiological response, with a gradual reduction in glucose levels to the species' reference range (50-70 mg/dL). This finding reinforced the diagnosis of Type 1 Diabetes Mellitus, evidenced by the absence of an adequate response to endogenous insulin.

5 minutes, and blood samples were collected at 0, 15, 30, 60, 90, 120, and 180 minutes for glucose and ketone body analysis (Figure 2).

Differential Diagnosis

Faced with the confirmation of a Type 1 Diabetes Mellitus diagnosis and the need for daily insulin administration, the owner was properly informed about the reserved prognosis and the high costs associated with the prolonged management of the condition. Considering the financial impact and the unfavorable prognosis, the owner opted for the humane euthanasia of the animal.

Necropsy and Histopathology and Follow-up

Necropsy revealed a pancreas with a diffuse white surface and firm, multifocal to coalescent, poorly demarcated areas (Figure 3A). The liver was markedly enlarged (hepatomegaly), with a yellowish appearance and a visible lobular pattern (Figure 3B). These findings supported a morphological diagnosis of pancreatic fibrosis and hepatic steatosis.
To confirm these findings, samples of the pancreas and liver were fixed in 10% buffered formalin, embedded in paraffin, sectioned at 4 m, and stained with hematoxylin and eosin (HE), Masson's trichrome stain, or Periodic acid-Schiff (PAS) stain. Additionally, kidney and other endocrine organs (testicle, pineal, pituitary, thyroid, adrenal) were collected and analyzed.
Microscopically, the pancreas showed multifocal, irregular, and poorly delimited areas, mainly in the pancreatic ducts, consisting of amorphous eosinophilic material associated with cellular and nuclear debris (necrosis), along with thick-walled, oval,

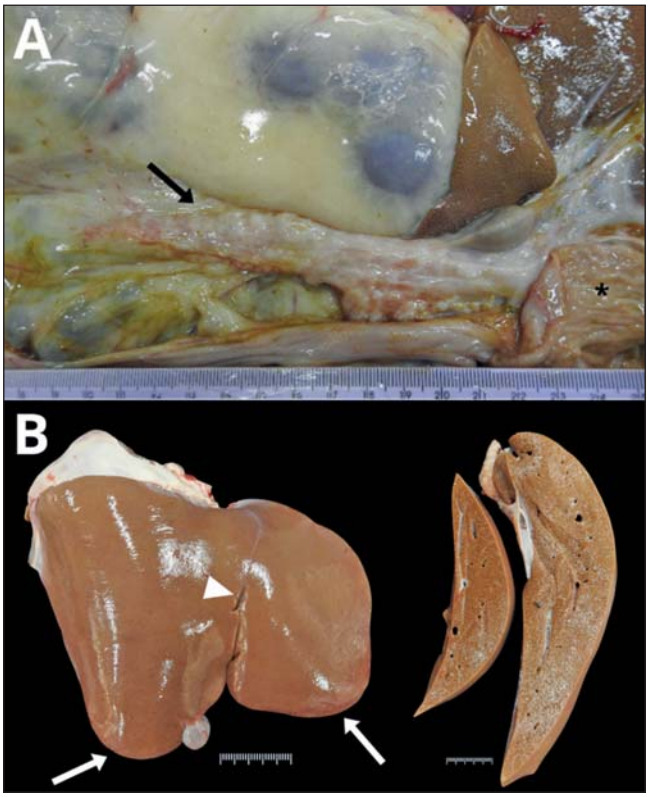

Figure 3 - A - Macroscopic evaluation. The pancreas has a white diffuse surface with firm, multifocal to coalescent, poorly delimited areas (arrow). The initial portion of the duodenum is visible (asterisk). B - Liver. The liver appears greasy with rounded edges (arrow) and small multifocal fissures (arrowhead) with a yellowish surface (left photo). On the cut surface, a well-demarcated lobular pattern is observed (right photo).

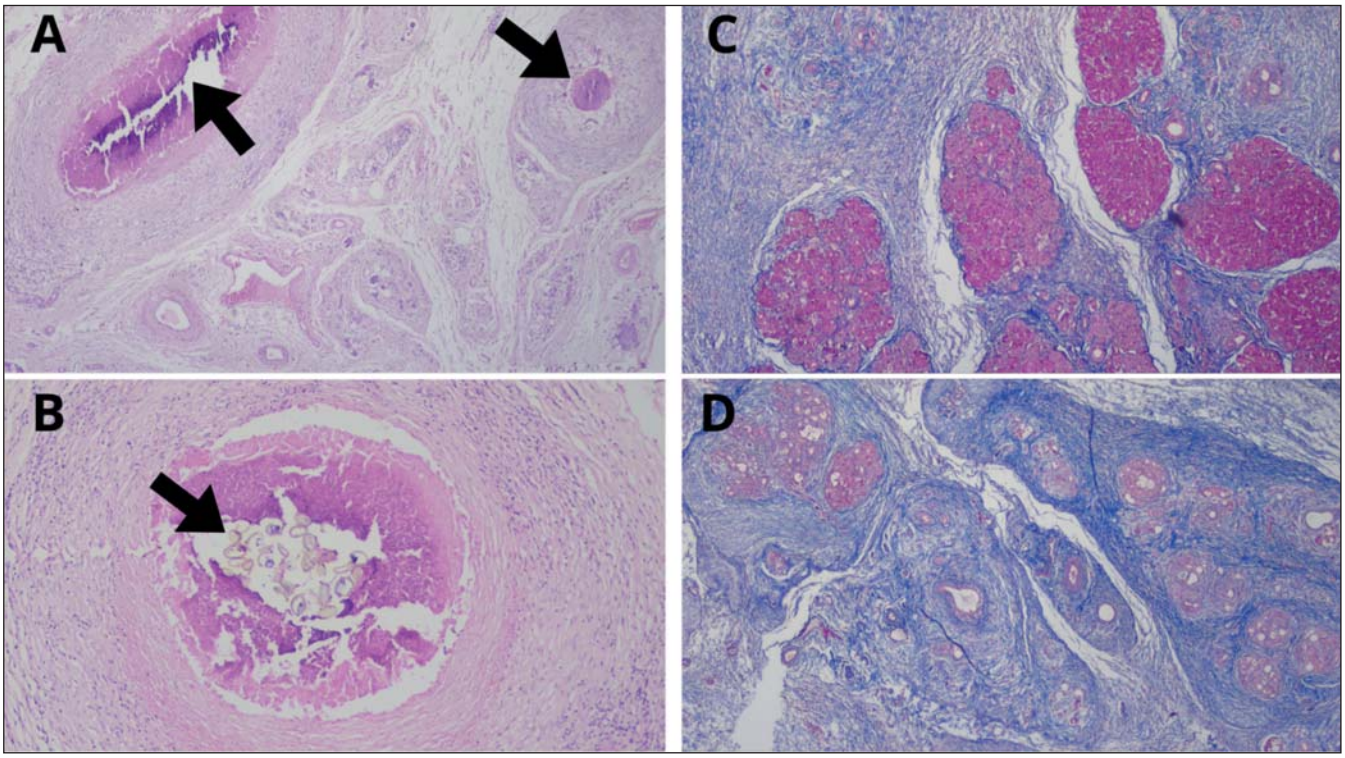

Figure 4 - Microscopy of the pancreas. A. Dilated pancreatic ducts are observed, filled with amorphous amphophilic content (arrow), surrounded by fibrous tissue with multifocal to moderate coalescent lymphohistiocytic inflammatory infiltrate, epithelioid macrophages, and multinucleated giant cells. Retraction of pancreatic tissue is evident, with a decrease/loss of exocrine and endocrine tissue (asterisk). H&E (40X); B. Within the pancreatic ducts, thick-walled, oval, brown-yellowish structures are visible (compatible with parasitic eggs) (arrow). H&E (100X); C and . A significant amount of fibrous tissue (blue) surrounds the pancreatic tissue areas (red) indicating a severe fibrosis. Masson's trichrome Stain (40X).

brown-yellowish structures, occasionally intralessional, compatible with parasitic eggs (Figure 4). These areas were surrounded by discrete fibrous tissue associated with a multifocal to moderate coalescent lymphohistiocytic inflammatory infiltrate, epithelioid macrophages, and multinucleated giant cells (foreign body type). There was an absence of pancreatic parenchyma, which was replaced by marked fibrous tissue, confirmed by Masson's stain. In the few areas with pancreatic parenchyma (exocrine and endocrine), the Langerhans's islets were present in discrete quantities, with most of their cells showing cytoplasmic retraction or large intracytoplasmic vacuoles.

In the liver, hepatocytes of the periportal and mid-zonal zones showed a large intracytoplasmic vacuole that marginalized the nucleus to the periphery, interpreted as fatty degeneration. The kidneys exhibited discrete to moderate, multifocal intracytoplasmic microvacuolation of the tubular epithelium (hydropic degeneration). Additionally, testicular degeneration was observed, with seminiferous tubules displaying azoospermia. No significant microscopic findings were noted in the other organs.

DISCUSSION

This clinical case underscores the importance of thorough evaluation in small ruminants, as nonspecific clinical signs, such as subtle changes in appetite, polyuria, polydipsia, and gastrointestinal disturbances, may indicate conditions of greater clinical and productive significance. Early recognition of these signs, combined with detailed physical examination and careful interpretation of laboratory and ancillary findings, enables more accurate differential diagnoses and guides appropriate therapeutic decisions. Furthermore, this report highlights the need for continuous attention to neglected parasites such as *Eurytrema* spp., which, although often underestimated, can significantly affect animal health and productivity. Thus, this case provides valuable insights for veterinary practice and the development of management and prevention strategies in small ruminant herds.

The sheep exhibited with progressive weight loss, polyuria, jaundice, skin lesions located in the thoracic and abdominal regions, with two on the right side and three on the left side, glucosuria, ketonuria, hyperglycemia, and ketoacidosis, which are characteristic signs of Diabetes Mellitus (DM) (2). According to Clark Z. (2003), there are few reports of DM in ruminants, and no gold standard test has been established for diagnosing this condition.

The glycemic curve proved to be an essential tool in this case, providing crucial insights into the animal's glucose metabolism and insulin response. The comparative glycemic curve performed between the diabetic sheep and a healthy control sheep demonstrated a persistently high blood glucose level in the patient, contrasting with the gradual reduction observed in the control animal. This response confirmed the suspicion of Type 1 Diabetes Mellitus, highlighting the absence of adequate endogenous insulin response and reinforcing the diagnostic accuracy of this method. The use of the glycemic curve as a diagnostic tool was particularly relevant in this case, offering a clear, objective measure of the metabolic dysfunction associated with Type 1 Diabetes Mellitus and demonstrating its practical applicability in large animal clinical settings.

In ruminants, glucose is predominantly (approximately 60%) derived from the conversion of propionic acid in the liver, resulting from ruminal fermentation (8). Diets that increase the proportion of propionic acid can thus enhance hepatic glucose production, influencing glycemic metabolism. In systemic hypoinsulinemia, there is a tendency for increased plasma concentrations of cortisol, non-esterified fatty acids, and ketone bodies, contributing to diabetic ketoacidosis (9).

Although insulin therapy is widely used successfully in most animal species, it is not without risks. In sheep, insulin administration may lead to complications such as hypoglycemic seizures, cataracts, recurrent infections, and diabetic ketoacidosis, especially if glycemic control is not stringent (10). The management of Type 1 Diabetes Mellitus requires daily care, including insulin administration, constant blood glucose monitoring, and diet and physical activity adjustments. In the context of livestock production, this complex and costly routine becomes impractical, both due to management logistics and the negative economic impact (11).

Economic viability is a determining factor in therapeutic decisions for production animals. Maintaining a diabetic sheep in the herd not only generates additional costs but also reduces the animal's productive potential. Furthermore, the need for technical knowledge regarding proper insulin storage, correct administration, and monitoring of metabolic variables presents challenges that often exceed the producer's technical capacity (12). Such limitations increase the risk of long-term complications and compromise animal welfare.

Given the reserved prognosis, high costs, and management difficulties, keeping the animal in the herd would not be a practical decision. Additionally, the hereditary risk of Type 1 Diabetes Mellitus could negatively impact the entire herd. On the other hand, the absence of appropriate treatment would lead to severe complications, depriving the animal of welfare. Therefore, humane euthanasia was considered the most ethical and coherent approach, prioritizing welfare and avoiding prolonged suffering of the sheep.

The necropsy findings reinforced the relationship between Diabetes Mellitus and the systemic alterations observed. The hydropic degeneration, evidenced in the liver, reflects a pathological process where there is excessive intracellular water accumulation. This phenomenon occurs due to sodium-potassium pump dysfunction, resulting in sodium and water retention in the cells, leading to cellular edema (13). The intracellular water accumulation is a consequence of osmotic gradient imbalances and absorption and elimination mechanisms of electrolytes, often culminating in cell death (14). A plausible hypothesis for the pathogenesis of the hepatic lesions observed in this case involves metabolic disturbances associated with type 1 Diabetes Mellitus, such as ketotic alterations, lipotoxicity, and glycogen accumulation in hepatocytes. Additionally, although no trematode eggs were detected, potential parasitic involvement, such as *Eurytrema* spp., could contribute to histopathological changes and functional impairment. Considering these mechanisms strengthens the discussion and highlights the need for further studies to elucidate the underlying processes.

In this case, morphological changes were observed in both the exocrine and endocrine pancreas, associated with a multifocal granulomatous inflammatory process. Within some pancreatic ducts, thick-walled, oval, yellowish-brown operculated structures compatible with trematode eggs were identified. Although these findings resemble those described in granulomatous pancreatitis induced by *Eurytrema* spp. eggs (15), the absence of adult parasites and specific diagnostic confirmation limits the etiological interpretation, making it impossible to establish a definitive causal relationship. While most reports associate *Eurytrema* infection with exocrine pancreatic alterations, there are records of islet loss and chronic inflammation in animals with severe infection by *Eurytrema coelomaticum*, which may suggest a potential role in the pathogenesis of endocrine disorders, as proposed by Sousa & Castro (2022).

Eurythrematous disease in small ruminants is considered a neglected disease, yet it has a significant economic impact (16,17). A study categorized the main histopathological patterns of lesions caused by this trematode; however, no morphological changes in the Langerhans's islets or clinical endocrine changes were observed in any of the animals studied. In contrast, Rosa et al. (2021) demonstrated that eurythrematosis can be a possible cause of DM1 in cattle and could serve as a potential experimental study model. Two studies have shown impairment of the islets of Langerhans in cattle with severe eurythrematosis (18,19). Cattle with spontaneous DM showed few numbers of the Langerhans's islets, which sometimes exhibited moderate lymphocytic infiltrate, cellular vacuolization, and fibrosis (20).

The clinicopathological findings observed in this case suggest a possible association between the presence of chronic inflammatory pancreatic lesions and the development of diabetes mellitus. The identification of *Eurytrema* eggs within the pancreatic ducts, along with the granulomatous inflammatory response and the reduction of Langerhans islets, raises the hypothesis that eurytrematosis may be involved in inflammatory or autoimmune mechanisms that could contribute to the onset of Type 1 Diabetes Mellitus in ruminants.

CONCLUSION

In summary, this case highlights the complexity of managing Type 1 Diabetes Mellitus in ruminants, the challenges of insulin treatment, and the importance of considering both clinical aspects and socioeconomic factors in therapeutic decision-making. The multidisciplinary approach employed in this study, integrating clinical management, economic considerations, and ethical treatment, underlines the value of a holistic perspective in veterinary practice. The glycemic curve, as demonstrated, is an invaluable tool for accurate diagnosis, allowing for objective assessment of the metabolic state and supporting informed decisions regarding animal welfare and management strategies. This report highlights the rarity of type 1 Diabetes Mellitus in sheep, emphasizing the importance of considering it as a differential diagnosis in animals presenting compatible clinical signs. The glucose curve proved to be a valuable tool for diagnostic confirmation and for monitoring clinical progression, serving as an essential resource for the objective assessment of metabolic status. Furthermore, this case underscores the complexity of managing this condition in ruminants, particularly in light of the challenges posed by insulin therapy and the practical limitations inherent to field conditions.

Therefore, it is reinforced that the rarity of type 1 DM in sheep requires greater clinical and scientific attention to expand the available knowledge and support the development of more effective diagnostic and treatment protocols. The glucose curve, shown to be decisive in this case, highlights its value as an in-

dispensable tool not only for confirming the disease but also for monitoring its progression and guiding therapeutic decisions. Finally, the difficulties of conducting such cases in field conditions, as widely discussed in this manuscript, emphasize the need for multidisciplinary approaches that integrate detailed clinical evaluation, laboratory testing, and socioeconomic considerations to ensure animal welfare and improve veterinary practice

Author contributions

Paula A. Catharini, **Natália B. Pedroso**, and **Larissa Q. Souza** contributed to the clinical management of the case, including handling the animal, diagnostic processes, and treatment administration. **Fwu Shing Teng** and **Priscila E. Kobayashi** were responsible for performing the necropsy and conducting histopathological analyses. **José Gabriel Lins** contributed specifically to the identification of parasite eggs in the histopathological samples. **Lukas G. Albertino, Rogério M. Amorim, Alexandre S. Borges,** and **José P. Oliveira-Filho** provided clinical insights, suggested treatment interventions, and supported the decision-making process throughout the management of the case. Wanderson A. B. Pereira was the clinician responsible for overseeing the case, provided expert guidance, and wrote and edited the manuscript.

Conflict of interest statement

The authors declare they have no conflicts of interest.

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Ethics statement

In this study, ethical committee approval was not required, as the reported case involved an animal treated as part of the hospital's routine care, and all procedures performed were essential for the proper diagnosis and treatment of the patient. The animal's owner provided written informed consent, authorizing all necessary interventions. We emphasize that all procedures were conducted humanely, following the principles of animal welfare, with the aim of minimizing discomfort and promoting the animal's health and safety throughout the management process.

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