

Insulinoma in ferret (*Mustela putorius furo*) – case report

[*Insulinoma em Ferret (Mustela putorius furo) – relato de caso*]

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ABSTRACT

Insulinoma is a tumor of pancreatic beta cells that occurs in ferrets and can lead to symptoms such as hypoglycemia, lethargy, and seizures. Prognosis varies depending on the extent of the tumor and response to treatment. This study describes the follow-up, diagnosis, and therapeutic management of two cases of insulinoma in ferrets. Clinical signs of reported animals varied according to the severity and duration of hypoglycemia. Presumptive diagnosis was based on clinical signs, hematological monitoring (evidenced by hypochromic anemia), biochemical analysis (increased alanine aminotransferase enzyme and hypoglycemia), and imaging exams (hepatomegaly and splenomegaly in one case of this study). Treatment varied according to the intensity of clinical signs, but both cases resulted in death. Regular veterinary follow-up and early detection are important to improve animal quality of life.

Keywords: hypoglycemia, insulin, treatment, tumor, wild animal

RESUMO

O insulinoma é um tumor de células-beta pancreáticas que ocorre em furões e pode levar a sintomas como hipoglicemia, letargia e convulsões. O prognóstico varia dependendo da extensão do tumor e da resposta ao tratamento. Este estudo descreve o acompanhamento, o diagnóstico e o manejo terapêutico de dois casos de insulinoma em furões. Os sinais clínicos dos animais relatados variaram de acordo com a gravidade e a duração da hipoglicemia. O diagnóstico presuntivo baseou-se nos sinais clínicos, no acompanhamento hematológico (evidenciado por anemia hipocrômica), na análise bioquímica (aumento da enzima alanina aminotransferase e hipoglicemia) e nos exames de imagem (hepatomegalia e esplenomegalia em um caso deste estudo). O tratamento variou de acordo com a intensidade dos sinais clínicos, mas ambos os casos resultaram em óbito. O acompanhamento veterinário regular e a detecção precoce são importantes para melhorar a qualidade de vida do animal.

Palavras-chave: hipoglicemia, insulina, tratamento, tumor, animal selvagem

INTRODUCTION

The beta cells in the pancreas are fundamental in regulating blood sugar levels through the production of insulin; diseases that affect these cells, such as type 1 diabetes and insulinoma, can have serious consequences for health (Hess, 2005). In type 1 diabetes, beta cells are destroyed by the immune system, leading to a deficiency of insulin; in insulinoma, beta cells multiply abnormally, producing excess insulin and

causing hypoglycemia (Lurye and Behrend, 2001). The study of these diseases is important for the prevention and treatment of diseases related to blood sugar regulation.

Regarding insulinoma, it is a tumor of the pancreatic beta cells that produce excess insulin, affecting pets such as dogs, cats, and ferrets (Meleo and Peterson, 2014). Ferrets are unconventional pets that are gaining popularity due to their intelligence, playfulness, and curiosity, especially in countries like the United

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States, United Kingdom, and Japan (Lewington, 2007; Perpiñán, 2014). Although they are popular worldwide, their breeding is relatively new in Brazil, and there are no ferret breeds specifically created in the country; generally, ferrets sold in the country are imported, mainly from the United States and Europe (Mota and Marietto-Gonçalves, 2020). Ferrets are active animals that enjoy exploring their surroundings and are social animals that appreciate the company of other ferrets (Lewington, 2007); they require a specific diet and regular veterinary care to maintain their health and well-being, otherwise, they may develop severe and sometimes irreversible endocrine disorders (Perpiñán, 2014).

The most common symptoms of insulinoma in ferrets include weakness, tremors, excessive drooling, and seizures (Perpiñán, 2014). The diagnosis of this disease is made through a combination of physical exams, medical history, and laboratory tests such as blood tests and imaging tests like abdominal ultrasound (Quesenberry and Carpenter, 2011; Perpiñán, 2014). The blood test is used to measure glucose and insulin levels in the blood, while ultrasound is used to detect the presence of tumors in the pancreas (Lurye and Behrend, 2001). An accurate diagnosis is essential to ensure successful treatment and improve the animal's quality of life; it is important to note that ferrets in the wild have a shorter life expectancy, averaging 2 to 3 years, due to risks of predation and disease, but pets have a longer life expectancy, reaching up to 7 or 8 years with proper care (Meleo and Peterson, 2014).

The treatment of insulinoma in ferrets involves understanding the animal's stress, as this factor can worsen insulinoma symptoms, so it's important to minimize stress in the animal's daily life (Meleo and Peterson, 2014); administration of medication; a protein-rich diet (Lisart *et al.*, 2018); and in severe cases, surgery (Krause, 2014). Balanced nutrition, a safe environment, and hygiene are essential to maintaining the health of pet ferrets, as well as regular visits to a veterinarian who specializes in exotic animals (Meleo and Peterson, 2014). Specialization in exotic animal clinics is important to ensure quality care for these animals, which have specific health and well-being needs. Exotic animals include a wide variety of species, from reptiles and amphibians to birds and mammals,

such as ferrets. It is essential that professionals who deal with these animals have specialized knowledge and skills to diagnose and treat diseases, as well as provide accurate guidance to owners on proper care for these animals.

Studies that assist in the early detection of insulinoma in ferrets are essential to ensure the success of treatment and improve the animal's quality of life. So, the present work focused on reporting the clinical and laboratory follow-up of two cases of insulinoma in ferrets, carried out at the Veterinary Hospital of Anhanguera University Center in Leme - SP, Brazil.

CASUISTRY

Case 1. An unneutered male ferret (*Mustela putorius furo*), three years and six months old, weighing 1.15kg, with white and gray fur, owned by a private owner, was attended at the Veterinary Hospital of Anhanguera University Center of Leme – SP, Brazil, in January 2010, with a complaint of diarrhea and recurrent abdominal distension for two weeks. During the physical exam, the animal's general condition seemed appropriate, without lymph node enlargement, with healthy fur, responsive nervous and locomotor systems, and alert excitability, but tachycardia (280bpm) and tachypnea (70mpm) were confirmed. The mucous membranes were light pink, the Capillary Refill Time (CRT) was 2 seconds, but there was an increase in abdominal cavity volume, with splenic enlargement and presence of ascites upon palpation. An abdominal radiography in ventrodorsally position was performed, confirming the spleen was heterogeneous - with a two-fold increase in volume compared to its normal size, and well-defined hypoechoic nodules were observed in the liver. The recommended treatment was the application of subcutaneous enrofloxacin 0.15mL for 5-7 days (Flotril®).

After five days the owner returned with the animal, claiming that although the ferret was no longer with diarrhea, it continued to be apathetic, eating less, and the urine was darker. During the anamnesis, the animal had tachypnea (96bpm) and was hypothermic (37.4°C), besides still presenting an increase in the abdominal cavity. An abdominal ultrasound was performed, already under clinical suspicion of hepatomegaly and splenomegaly, and the report was that the

intestine, kidneys, and prostate had normal shape and volume, but the spleen showed an increase with heterogeneous echotexture and the liver was slightly increased ($\pm 25\%$), with irregular borders and presence of fibrosis in the parenchyma. The previous treatment was continued.

The owner returned after a week and reported an improvement in the condition, including increased appetite, normal thirst, and normal bowel movements, but the urine color remained dark and two days later, 30 minutes after administration of enrofloxacin medication, the animal vomited. During the physical examination, the ferret showed normal cardiac, respiratory, and mucosal parameters, but still had an increased volume in the abdominal cavity. A repeat abdominal ultrasound, complete blood count and biochemical analysis were suggested. Hepatomegaly and splenomegaly were observed in the ultrasound, while the complete blood count showed hypochromic macrocytic anemia and the presence of polychromatic red blood cells. In the biochemical analysis, alanine aminotransferase (ALT) and serum protein levels were within normal limits, but the glucose level was at 91 (with the reference values for this species at 94-207mg/dL according to the Veterinary Hospital laboratory). The same treatment continued.

After twenty-one days, the owner returns to the Veterinary Hospital and reports an improvement in the condition but noticed a difference in the color of the feces, which were whiter. A new veterinarian began to follow the case and on physical examination, observed the animal to be more apathetic with slight tremors in the hind legs. The animal had gained weight since the first consultation, 1.34kg, with slight ascites and still with an enlarged spleen throughout the abdominal area. With suspicion of a hemoparasitic disease (babesiosis), a blood smear was performed, and the result was negative. Treatment with doxycycline 20mg, once a day for 3 weeks, was recommended.

Two weeks later, the owner reported that the animal was eating well and had increased the amount of food, but the ferret showed fatigue during interaction with the owner and had very clear urine. The animal was in tachypnea (80 breaths per minute), and an emergency ultrasound confirmed hepatomegaly with irregular borders, mixed echogenicity (not heterogeneous), and evidence of fibrosis in some

areas. The recommended treatment was the administration of a hepatoprotective agent based on silymarin (Legalon®) at a dose of 0.5ml every 8 hours for 1 month.

Unfortunately, 18 days after the last consultation, the owner returned claiming the ferret was totally apathetic, with itching and hair loss in the dorsal region, and experiencing shortness of breath on some occasions during the day. In the physical exam, the animal was heavier, weighing 1.45kg compared to the last consultation, and an abdominal tumor was found near the renal region. Hematological tests were performed, where the same macrocytic hypochromic anemia and presence of polychromatic red blood cells were observed; in the biochemical exam, an elevation in ALT enzyme activity (291U/L) and hypoglycemia (61mg/dL) were found; and in the radiographic exam, displacement of abdominal viscera towards the ventral abdominal wall was observed. An exploratory laparotomy was recommended, but unfortunately, the animal died during the operation.

Case 2. A 3-year-old, unneutered male ferret with white and beige fur was brought to the Veterinary Hospital of Anhanguera University in Leme - SP, Brazil, in April 2012, with a history of several episodes of seizures and weakness in the hind legs. The owner reported that the ferret seemed normal most of the time, but occasionally had tremors, excessive salivation, and seizures. The animal had been treated with anticonvulsants at another clinic, but the episodes persisted and were becoming more frequent. Upon physical examination, the veterinarian noted that the animal was alert and responsive but showed signs of weakness in the hind legs and lack of coordination. The heart rate was accelerated (280 bpm), and the body temperature was normal (38.8°C). Additionally, the ferret was thin (1.05kg) and had a dull and lackluster coat. The veterinarian noted in the evaluation form that he suspected an endocrine or parasitic disease affecting the nervous system, due to the symptoms presented by the patient. A laboratory evaluation was performed, including a complete blood count, blood biochemistry, and hormonal profile. The results showed that the ferret had very low blood glucose levels (40 mg/dL), which confirmed the suspicion of an endocrine disease. Additionally, the biochemical analysis revealed an elevation in ALT enzyme

activity (298U/L), which suggested possible hepatic involvement in the disease. The initial treatment of the patient involved the administration of intravenous glucose to rapidly elevate blood glucose levels and prevent irreversible brain damage. In addition, the use of corticosteroids (1mg dexamethasone sodium phosphate) was prescribed to help control the excessive production of insulin by the pancreas. The owner was also instructed to adjust the animal's diet, including low-carbohydrate and high-protein foods, and provide smaller and more frequent meals to help prevent episodes of hypoglycemia.

Over the next two weeks, the ferret showed gradual improvement in his symptoms, but still had occasional episodes of weakness and tremors. Follow-up exams were performed to monitor his blood glucose and liver function, and the veterinarian also recommended imaging tests to evaluate the size and location of the pancreatic tumor. Unfortunately, in this case, the disease progressed rapidly, and, despite intensive treatment and veterinary care, he did not survive and passed away about two months after the diagnosis.

DISCUSSION

The onset of insulinoma in ferrets usually does not directly affect the feces, however as the disease progresses and hypoglycemia becomes more frequent, there may be changes in the animal's feces (Perpiñán, 2014). Hypoglycemia can lead to symptoms such as lethargy, weakness, and seizures (as observed in case 2) that can affect digestion and elimination; as a result, the animal's feces may become soft or even diarrhea (Krause, 2014; Perpiñán, 2014), as seen in the initial symptoms of case 1. In the initial physical examination, it is important to note that normal values of heart and respiratory rate in ferrets can vary according to age, physical condition, and activity level of the animal; generally, resting heart rate can range from 180 to 250 beats per minute, while resting respiratory rate can range from 33 to 36 breaths per minute (Meleo and Peterson, 2014). Tachycardia is defined as a heart rate above 250 bpm in a ferret, while tachypnea is defined as a respiratory rate above 50 to 60 breaths per minute (Meleo and Peterson, 2014), as observed in the abnormal state of the patient in case 1.

The average weight of ferrets varies according to the sex and age of the animal, in general adult males weigh around 1.2 to 2.2kg, while adult females weigh about 0.8 to 1.3kg (Quesenberry and Carpenter, 2004). There are no indications that sex may determine the presence of insulinoma, but according to the literature, male ferrets seem to be affected more commonly than females (Meleo and Peterson, 2014). It is important to remember that, as in other animal species, the ideal weight of the ferret may vary according to its physical constitution and health status (Quesenberry and Carpenter, 2004). Ferrets with insulinoma can both lose and gain weight, with weight loss being more common in advanced cases of the disease, when blood glucose levels are constantly low and the animal cannot properly utilize nutrients from food; on the other hand, obesity can occur in some cases of insulinoma, as increased insulin levels in the blood can lead to fat accumulation in the animal's body (Quesenberry and Carpenter, 2011; Perpiñán, 2014). In addition, some owners may increase the number of high-carbohydrate foods in the animal's diet, thinking that this will help combat hypoglycemia, but this can contribute to weight gain (Lisart et al., 2018). In case 1, it was observed that the animal was already below normal weight and that throughout the treatment (perhaps due to excessive feeding reported by the owner) gained weight, but in the end began to lose weight; while in case 2 there was not enough time to follow weight fluctuations, but the animal was also below the values considered normal for an adult male. The important thing is that any change in the animal's weight should be evaluated by a veterinarian, so that the cause can be identified and treated properly.

The normal temperature of ferrets varies slightly according to the consulted source, but generally ranges between 37.5°C and 40°C (Quesenberry and Carpenter, 2011; Krause, 2014). There is no defined standard for changes in body temperature in animals with insulinoma, as this can vary according to several individual factors (Krause, 2014). In general, insulinoma can lead to a metabolic imbalance in the animal's body, with an impact on several bodily systems, as a result there may be variations in the animal's body temperature, with fever occurring in cases of secondary infections or hypothermia in cases of advanced metabolic decompensation (Perpiñán,

2014; Schoemaker, 2017), which was apparently already occurring in the ferret in case 1. However, it is important to remember that each animal may present different symptoms, so it is essential to regularly monitor the patient's body temperature to check for possible signs of abnormality.

Radiographic and ultrasonographic analysis of a ferret with insulinoma may present some specific alterations (Quesenberry and Carpenter, 2011; Wu *et al.*, 2017). Possible tumors in the pancreas or other abdominal regions can be observed in abdominal radiography (Perpiñán, 2014; Wu *et al.*, 2017). In abdominal ultrasonography, the presence of lesions in the pancreas and/or metastases in other organs can be visualized, as well as the extent and size of these lesions; in the case of insulinoma, hepatic ultrasonography may reveal the presence of nodules in the liver (Meleo and Peterson, 2014; Wu *et al.*, 2017), as in the case 1. Additionally, ultrasonography can be used to monitor tumor progression and the animal's response to treatment.

Hemogram usually does not present significant abnormalities, but in both analyzed cases, the animals had hypochromic anemia (Perpiñán, 2014; Schoemaker, 2017). It is possible for an animal with insulinoma to present hypochromic anemia because it is a tumor that causes hyperinsulinemia, which can lead to hypoglycemia and other metabolic disorders (Meleo and Peterson, 2014; Schoemaker, 2017). When the tumor is in an advanced stage, chronic hypoglycemia can cause damage to red blood cells, leading to hypochromic anemia; in addition, anemia can be secondary to other diseases associated with insulinoma, such as liver or kidney disease (Meleo and Peterson, 2014), as occurred in the end of case 2. According to the literature, the disease can cause other health problems that lead to anemia, such as weight loss, loss of appetite, and chronic inflammatory disease (Lurye and Behrend, 2001; Quesenberry and Carpenter, 2004). Moreover, in severe cases of insulinoma that lead to chronic hypoglycemia, the animal may develop muscle weakness and even fainting, which can lead to injuries and hematomas, resulting in blood loss and anemia (Quesenberry and Carpenter, 2004). In summary, anemia is not a direct consequence of insulinoma, but it may be present in more advanced cases of the disease or because of other related health conditions.

The biochemical analysis of blood is an important tool to assist in the diagnosis and monitoring of insulinoma treatment in ferrets (Quesenberry and Carpenter, 2011; Meleo and Peterson, 2014). The blood biochemical test can show hypoglycemia (low blood glucose concentration), increased levels of insulin, ALT, and cholesterol, as well as a decrease in total protein and albumin levels; in advanced cases, there may also be an increase in lactate levels and a decrease in potassium levels (Meleo and Peterson, 2014; Schoemaker, 2017). In case 1, initial normalization of the patterns mentioned above was observed, except for glucose, which was below reference values, but during the case follow-up, a high level of ALT and continuous hypoglycemia were observed, just like in case 2. It is important to note that the diagnosis of insulinoma in ferrets is not based solely on imaging and laboratory tests but rather on a combination of clinical signs, imaging, and laboratory tests.

Regarding the medications used, case 2 is noteworthy for the use of corticosteroids, as this medication may be indicated in some cases of insulinoma in ferrets to help control the excessive production of insulin by the pancreas (Schoemaker, 2017). The most used corticosteroid is prednisolone, but the recommended dosage may vary depending on the severity of the disease and the individual animal's response to treatment (Hess, 2005). In general, the recommended initial dose is 0.5 to 1.0mg/kg administered orally once a day (Schoemaker, 2017). This dose may be adjusted up or down based on the animal's response to treatment, as well as the results of blood tests that monitor glucose and other metabolic parameters and it is important to remember that the use of corticosteroids in ferrets should be carefully monitored by a veterinarian.

The use of hepatic protectors may be recommended in cases of insulinoma in ferrets, as occurred at the end of case 1, especially because the tumor can often cause damage to the liver (Schoemaker, 2017). Some examples of hepatic protectors that may be used include S-adenosylmethionine (SAMe), ursodeoxycholic acid, and silymarin (Meleo and Peterson, 2014; Schoemaker, 2017).

Treatment of insulinoma in ferrets may involve the use of medications to control the excessive production of insulin by the pancreas, some of the most common medications include prednisone, diazoxide, and octreotide (Meleo and Peterson, 2014; Perpiñán, 2014; Schoemaker, 2017). Prednisone is a steroid that helps control hypoglycemia, while diazoxide and octreotide work by inhibiting insulin secretion by the pancreas (Perpiñán, 2014). The use of these medications should be guided and monitored by a veterinarian and may be adjusted according to the animal's response and laboratory test results. Additionally, in more severe cases, surgery may be necessary to remove pancreatic tumors that are causing the excessive production of insulin (Schoemaker, 2017; Wu *et al.*, 2017), which could have helped the patient in case 1.

Finally, it is commented that diet is an important aspect in the management of ferrets with insulinoma (Perpiñán, 2014). The diet should be high in protein and fat, with low levels of carbohydrates and sugars, as these can increase insulin production by the pancreas (Quesenberry and Carpenter, 2004; Linsart *et al.*, 2018). It is recommended that owners opt for a natural diet, including prey and raw meats (Quesenberry and Carpenter, 2004). Another suggestion is to offer several small meals throughout the day, rather than one or two large meals, to help prevent hypoglycemia (Perpiñán, 2014). The owner should work together with the veterinarian to develop an appropriate nutritional plan for the animal with insulinoma.

CONCLUSION

Although there are no studies revealing the prevalence of the disease in ferrets in Brazil, it is observed in the literature that the mortality rate is high and that medical and/or surgical intervention should be as quick as possible from the diagnosis of the disease. The cases seen illustrate the importance of early detection of the disease and the search for appropriate treatment. Unfortunately, despite the efforts and dedication of the owners, the rapid progression of insulinoma limited treatment options and resulted in death for the animals. It is important that ferret owners be attentive to signs of illness and take their animals for regular veterinary evaluation.

Given the characteristic clinical picture, even if anemia is present and the blood concentration of the enzyme alanine aminotransferase is not high at the time of hypoglycemia diagnosis, the possibility of insulinoma should not be ruled out, and radiographic, ultrasonographic, and, if possible, histopathological examination should be performed.

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