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Case Report

Clinicopathological and immunohistochemical features of insulinoma in an adult mixed breed dog

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Abstract
Canine insulinoma is a common non-specific neoplasm with high metastasizing ability. Its epidemiology, diagnosis, and treatment are well described. However, its long-term prognosis is considered poor. We report a rare case of insulinoma in a small-size, mixed-breed adult dog, which presented with a circling walk, seizures, weakness, depressed mental state, and hypoglycemia. Glucose continuous rate infusion, diazepam, and phenobarbital were initiated to stabilize the glycemia and control the convulsion. Blood tests, fine needle aspiration cytology, ultrasound and radiological tests, and histology and immunohistochemical analysis confirmed the diagnosis of insulinoma, emphasizing the relevance of considering it as a differential diagnosis for small canine breeds and younger animals. Further, dogs can be regarded as an experimental animal model for human insulinoma research as they share characteristics.

Keywords: insulinoma, canine, hypoglycemia, metastasis, pancreas.

Introduction

Insulinoma is considered the most frequent neuroendocrine pancreatic tumor in dogs and humans, resulting in hypoglycemia-related symptoms and insulin hypersecretion (3). Canine insulinoma is known as a non-specific clinical sign disease (10). The endocrine pancreatic beta cells in adenocarcinoma are functional and may produce insulin in some cases. Glucose homeostasis is affected when there is hyperinsulinism; consequently, hypoglycemia occurs, resulting in signs of neuroglucopenia (6). The most reported symptoms of insulinoma are weakness, seizures, mental state and behavioral changes, and unconsciousness. The forebrain is the most affected neurological site (3).

More than 95% of insulinomas in dogs are malignant with high metastasizing ability, unlike human insulinomas, which are usually benign (2). The clinical diagnosis may be demonstrated with simultaneous hypoglycemia and serial blood insulin level occurrence. Histopathological analysis confirms the final diagnosis. There are various therapeutic protocols, and surgery is considered the most viable treatment option with longer survival expectations (10). Disease control is difficult due to recurrent hypoglycemia, metastasis, or continuous tumor growth, and poor long-term prognosis (2). Thus, studies on canine insulinoma are relevant because clinicians and pathologists must be aware of the tumor's biological behavior, therapeutics, and diagnosis to improve canine life expectations. In addition, this neoplasm could be considered an experimental animal model for human

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insulinoma since it shares histopathological characteristics with its benign form (3).

Case description

A 5-year-old sterilized female canine of undetermined breed weighing 13 kg was referred to the Veterinary Hospital at the Faculty of Veterinary Medicine and Animal Sciences at São Paulo State University, Botucatu campus, presenting with circling walk, seizures, weakness, depressed mental state, and hypoglycemia.

Glucose continuous rate infusion, diazepam, and phenobarbital were initiated to stabilize the glycemia and control the convulsion. Blood analysis revealed a leucogram with lymphopenia and eosinopenia due to the convulsions, increased gamma-glutamyl transferase, hyperalbuminemia, and hypouricemia because of dehydration. Ultrasound and radiographic images revealed the pancreas with preserved contours and no signs of neoformations. The patient did not present clinical improvement during the hospitalization; thus, the owners opted for euthanasia and necropsy.

Necropsy showed a whitish lobulated nodule measuring 1.6 × 1.5 × 1.0 cm in the pancreatic body (Fig. 1). Fine needle aspiration cytology revealed abundant cells arranged individually or in low cohesion groups, with an ovoid eccentric nucleus, occasionally with free nuclei aspect, homogeneous chromatin with a single evident nucleolus, moderate basophilic cytoplasm showing mild anisokaryosis and anisocytosis, compatible with neuroendocrine tumor (Fig. 2A). Histopathology demonstrated a focal encapsulated neoplasm with cells arranged in lobules surrounded by thin connective tissue septae. The neoplastic cells showed oval nuclei, with one evident nucleolus, moderate to lightly eosinophilic cytoplasm. Mild pleomorphism and binucleated cells were present. No mitotic figures were seen. The peripancreatic lymph node and the liver were free of neoplasia, corresponding to an insulinoma stage I case (Fig. 2B). Immunohistochemistry revealed positive neoplasm cells to insulin, chromogranin, and synaptophysin, confirming the diagnosis of a pancreatic neuroendocrine tumor (Fig. 3).

Discussion

Many reports of dogs present classical secondary neurological signs such as seizures, disorientation, weakness, and abnormal mental and consciousness states due to hypoglycemia from insulinoma. Furthermore, the animals diagnosed with insulinoma were generally middle-aged to old dogs with a median age of 9 years. Middle to large-sized breeds, such as German Shepherds, Irish Setters, Boxers, Golden Retrievers, and Terrier breeds, were more commonly reported to have insulinoma (1). However, in rare cases, it is described in younger and smaller breeds (8). Herein, we present a case of insulinoma involving a small, mixed breed, 5-year-old dog diagnosed with insulinoma during post-mortem examination.

The cytological analysis, which is quick and efficient, contributed to the diagnosis, revealing typical neuroendocrine tumor cell features such as a group of cells with free oval nuclei, fine homogeneous chromatin, and a prominent nucleolus. In addition, histopathological examination showed polygonal to round pancreatic islet-cell groups with round to oval nuclei and evident nucleoli, binucleation, and eosinophilic cytoplasm surrounded by connective tissue septae. Pleomorphism, anisokaryosis anisocytosis, and mitotic figures were also observed in our case; these characteristics have been previously reported (9). Insulinoma is characterized into three stages based on the neoplasm dispersion. In the present case, no neoplastic cells were detected outside the pancreas, indicating an insulinoma stage I (7).

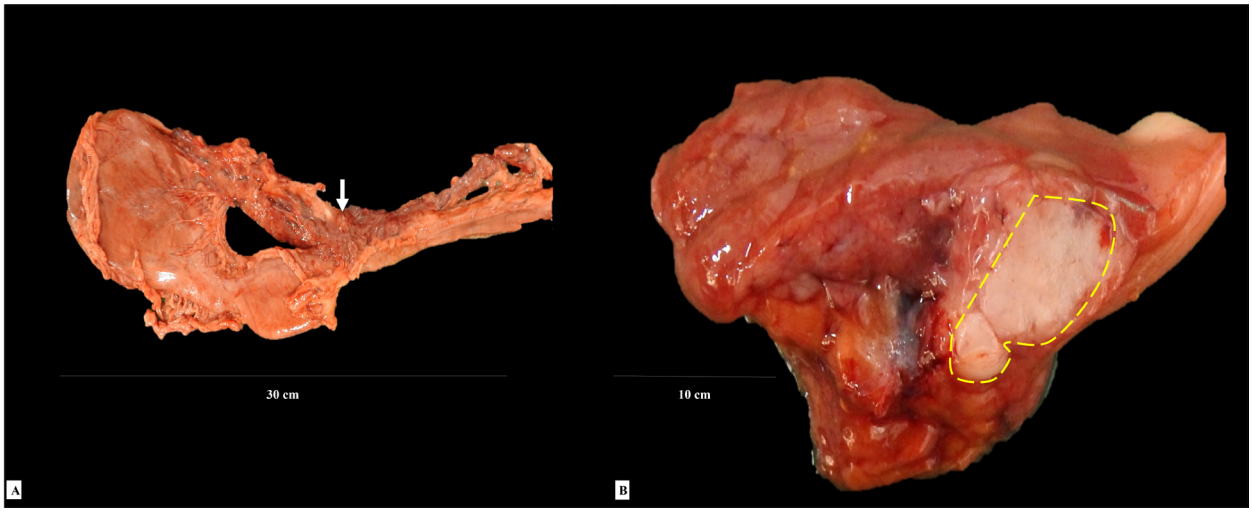

Figure 1. Canine, mixed breed, insulinoma. A- The pancreatic body exhibiting a whitish lobulated nodule (white arrow). B- Insulinoma morphology evident through the longitudinal incision of the whitish lobulated nodule (yellow surrounded area).

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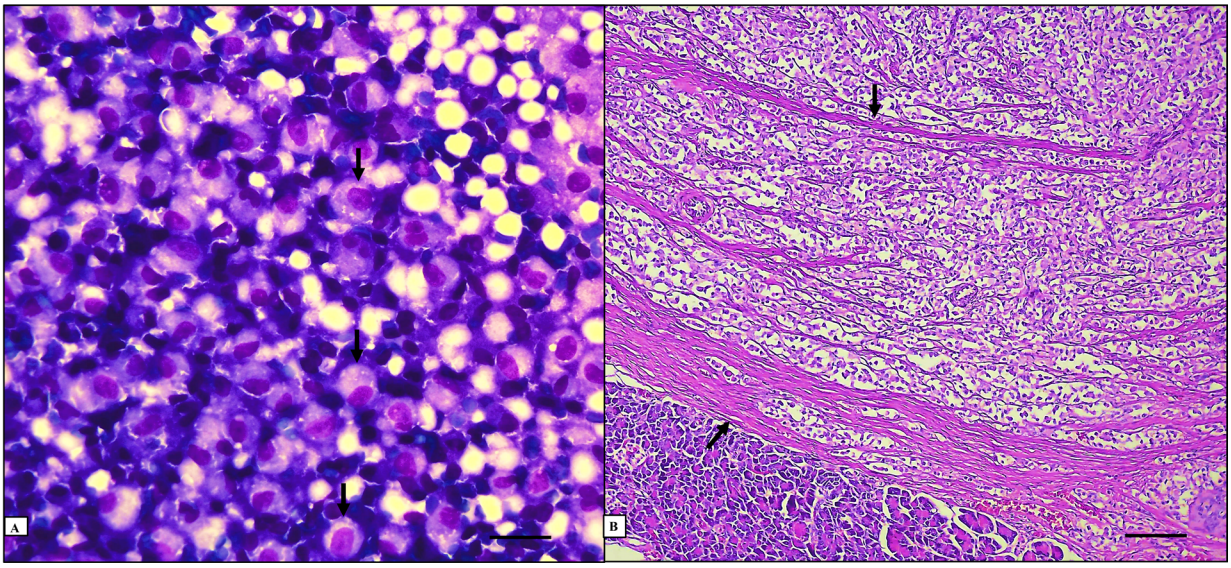

Figure 2. Canine, mixed breed, insulinoma. A- Cytology of the nodule with abundant cells arranged in low cohesion groups (black arrows), with an ovoid eccentric nucleus, occasionally with free nuclei aspect, homogeneous chromatin, with a single evident nucleolus, moderate basophilic cytoplasm, showing mild anisokaryosis and anisocytosis. Giemsa, bar = 40 µm. B- Focal encapsulated neoplasm with cells arranged in lobules surrounded by thin connective tissue septae (black arrows). HE, bar = 100 µm.

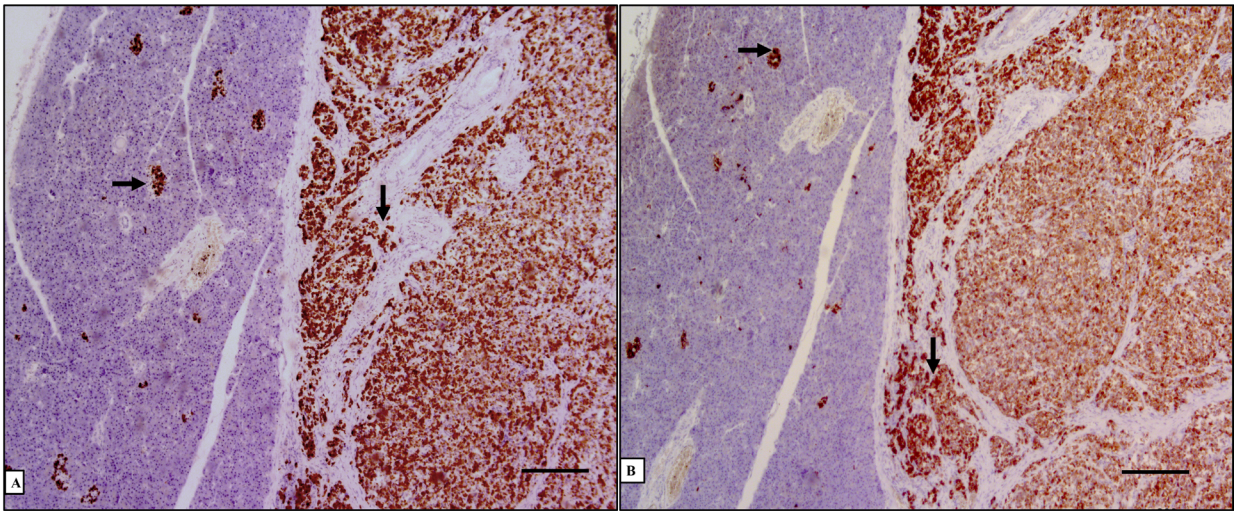

Figure 3. Canine, mixed breed, insulinoma. A- Immunohistochemistry revealed a positive label for insulin (black arrows). Bar = 100 µm. B- Positive immunostaining for chromogranin in neoplastic insulinoma cells (black arrows). Bar = 100 µm.

This report highlights some diagnostic complexities encountered, including the measurement of insulin levels and the utilization of computerized tomography scans, both crucial for accurate diagnosis in living patients. These exams were not performed because of the owner's economic limitations. However, reporting this canine insulinoma case contributes to clinicians and pathologists as elucidative examples of the tumor's clinicopathological and immunohistochemical features. Consequently, we consider the significance of canine insulinoma studies, given the persistent challenges in disease management attributed to recurrent hypoglycemia, metastasis, and continuous tumor growth, leading to discouraging long-term prognosis.

Conflict of Interest

The authors declare no competing interests.

Acknowledgments

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