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Combination Therapy of Prednisolone and Toceranib Phosphate in a Dog with Malignant Metastatic Insulinoma

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Abstract : A 14-year-old intact female Yorkshire terrier was presented with a 2-month history of shivering, intermittent pelvic limb weakness and collapse. Biochemical abnormalities revealed inappropriately increased serum insulin concentration with persistent hypoglycemia. Abdominal ultrasound revealed multiple various sized nodules in liver and fine-needle aspirates of the nodule showed typical neuroendocrine cells with high cellularity. Computed tomography (CT) revealed well-defined hyperattenuating mass in the right pancreatic lobe with homogenous enhancement. CT findings were consistent with a pancreatic tumor with malignant metastasis. Treatment was initiated with low-dose prednisolone and toceranib phosphate. The dog was maintained stable with no more progression of clinical signs and it is worth to try toceranib phosphate in a dog with metastatic insulinoma for improving the quality of life.

Key words **:** Canine, hypoglycemia, malignant insulinoma, toceranib phosphate.

Introduction

Insulinomas are pancreatic beta-cell tumors characterized by the presence of episodic clinical signs due to the excessive secretion of insulin (1). These tumors are uncommon, but the most common islet cell tumors of endocrine pancreas in dogs (6). The predominant clinical signs are related to hypoglycemia including weakness, ataxia, collapse, disorientation, extreme fatigue after exercise and seizures. Contrary to predominantly benign in human insulinomas, insulinomas in dogs are often malignant (> 95%) and it is likely to have already been metastasized in 40-50% of cases at the time of diagnosis (3,6). Diagnosis can be clinically challenging due to the nonspecific and unremarkable clinical signs associated with hypoglycemia. Intermittent clinical signs due to the episodic release of insulin make diagnosis difficult and affected dogs usually adapted to chronic hypoglycemic state (1). Documented hypoglycemia concurrent with inappropriately increased insulin concentrations strongly suggest insulinoma (10). Further diagnostic tests such as imaging methods, mass FNA, exploratory celiotomy can be helpful to confirm the pancreatic mass and establish presence of metastatic regions (8). Clinical symptoms as well as comprehensive interpretation of diagnostic test results are important to diagnose insulinomas (10).

In the present case, we describe diagnostic features of malignant insulinoma in a dog and medical therapy with toceranib phosphate. This is the first case of treatment approach using tyrosine kinase inhibitor as a medical therapy of malignant insulinoma in a dog.

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Case

A 14-year-old, intact female Yorkshire terrier dog was referred with a history of shivering, intermittent collapsing episodes and behavioral changes during the previous two months. The clinical signs of shivering and collapsing episodes were frequent in the morning of the fasting state and extreme fatigue was presented after exercise. On physical examination, the dog showed abdominal pain and borborygmus, but otherwise normal with no neurological deficits. Initial bloodwork revealed marked fasting hypoglycemia (8 hr fasting, 27 mg/dl; reference interval (RI) 74-143 mg/dl). Other abnormalities included hypocholesterolemia (94 mg/dl; RI 110-320 mg/dl) and slightly elevated ALT (103 U/L; RI 10-100 U/L) and GGT (11 U/L; RI 0-7 U/L). Complete blood cell count, urinalysis, thoracic and abdominal radiographic findings were unremarkable. Insulin concentration during hypoglycemic episodes revealed high (59.3 uIU/mL; RI 5.2-41.5 uIU/mL, IDEXX laboratories). The insulin:glucose ratio (IGR) and amended insulin:glucose ratio (AIGR) were 219.6 U/mol and 5930 U/moL, respectively (IGR of > 13.5 and AIGR of > 30 is consistent with insulinoma) (10). Based on the laboratory results, insulinoma was strongly suspected and other extra-pancreatic tumor such as hepatocellular carcinoma was considered.

Diagnostic imaging methods were conducted to identify a pancreatic or extra-pancreatic tumor. On abdominal sonography, multiple various sized nodules with cavitary target lesion (relatively hypoechoic central zone) were identified in the hepatic parenchyma. Pancreatic parenchyma had generally increased echogenicity compared to surrounding mesenteric fat and irregular in margination (Fig 1). There were no prominent tumor lesions in pancreatic parenchyma. Insulin-like growth factor 1 result was within normal range (3 nmol/

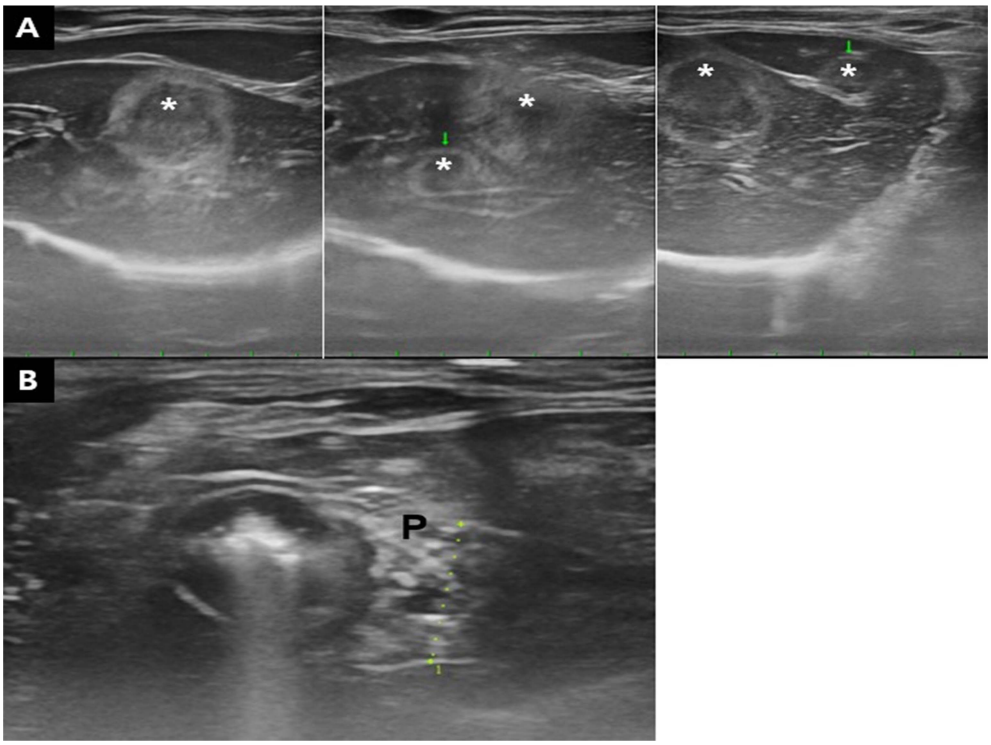

Fig 1. Abdominal ultrasonography of the dog with metastatic insulinoma. (A) Multiple various sized hepatic nodules (asterisk) with hyperechoic periphery and hypoechoic center in the hepatic parenchyma. (B) Hyperechoic changes of pancreas (P) made it difficult to distinguish from surrounding mesenteric fat. No obvious mass lesion is identified in the pancreatic parenchyma.

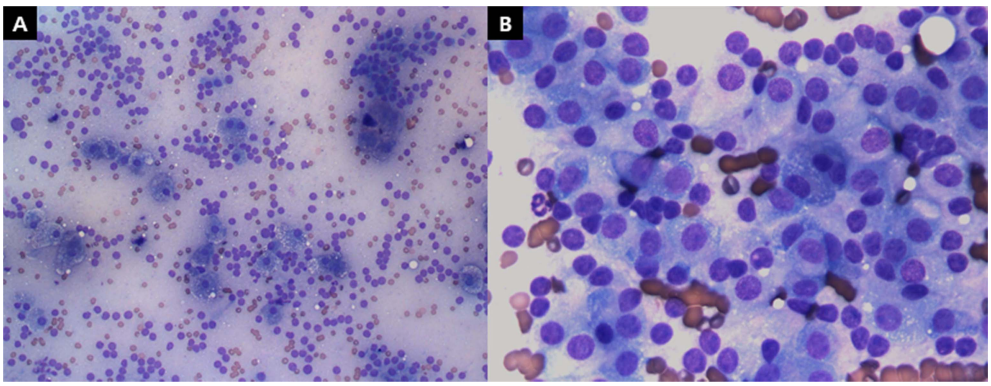

Fig 2. Cytologic features of ultrasound-guided fine-needle aspirates of a hepatic nodule. (A) The samples contained two types of cell clusters. Hepatocytes with foamy cytoplasmic vacuolation and cytoplasmic rarefaction is consistent with hydropic degeneration. Large number of free nuclei embedded in pale basophilic cytoplasm is readily seen in a low-power view. These cells are connected as loose clusters, but cytoplasmic borders are poorly distinct. Round to oval naked nuclei morphology is often appeared in neuroendocrine tumors (Diff-Quik stain, × 200 objective). (B) Cytologic appearance of moderate anisocytosis, anisokaryosis and prominent nucleoli represents the features of malignant tumor (Diff-Quik stain, × 630 objective).

L; RI 4-95 nmol/L).

Ultrasound-guided fine-needle aspirates of the oval-shaped hepatic nodule were performed. Samples are highly cellular and have cell clusters of hepatocytes and typical neuroendocrine cells (Fig 2). Most of hepatocytes had foamy cytoplasmic vacuolation and cytoplasmic rarefaction which is consistent with hydropic degeneration. The typical neuroendocrine cells characterized by free nuclei (round to oval) embedded in a pale basophilic cytoplasm with indistinct cytoplasmic borders. The cells also displayed moderate anisocytosis, anisokaryosis and had prominent nucleoli which indicates malignant feature. The cytologic findings are most consistent with metastatic pancreatic neuroendocrine tumors and other extra-pancreatic tumors such as hepatocellular carcinoma or hepatoma, hemangiosarcoma, and carcinoma were ruled out. Based on these results, pancreatic beta-cell neoplasia with metastasis to liver was mostly suspected.

Triple-phase computed tomography (CT) scanning (Siemens Medical Systems, Erlangen, Germany) was performed to identify primary tumor lesion and determine the degree of

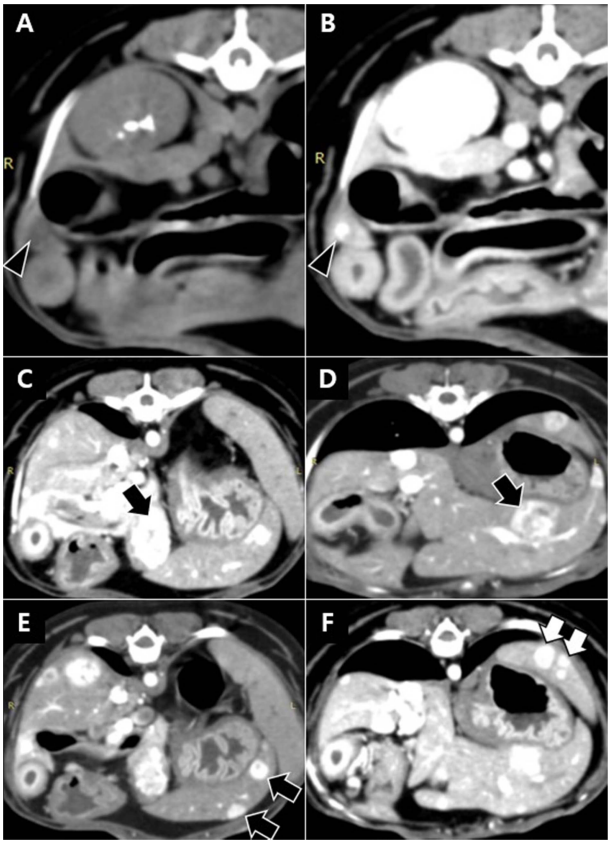

Fig 3. Triple-phase CT images of a dog with metastaic insulinoma. (A) Pre-contrast: the right lobe of pancreas (black arrowhead) is observed adjacent to the descending duodenum. The pancreas is iso-attenuating to liver in this phase. (B) Portal phase: Distinct hyper-attenuating mass (black arrowhead) is well observed. The mass with homogeneous enhancement pattern and well-defined margin with no capsule formation is measured as 3.2 mm × 3.2 mm. (C, D) Two large nodules (black arrows) are observed in the quadrate lobe (C) and left medial lobe (D) of the liver. The margin is irregular with heterogeneous enhancement pattern. (E) Multiple hyper-attenuating nodules (black arrows) are also observed in hepatic parenchyma with various sizes. (F) Similar nodules are also observed in spleen (white arrows).

tumor metastasis. On pre-contrast images, pancreatic mass lesion was not evident. Enhanced CT images were acquired after 40 sec following injection of 15 ml ioversol (320 mg/mL organically bound iodine, Optiray 320, Liebel-Flarsheim company LLC, NC, U.S.A) at a flow rate of 1.4 ml/sec. Portal phase CT images revealed well-defined hyper-attenuating mass in the right pancreatic lobe and measured as 3.2 mm × 3.2 mm. Enhancement pattern was homogenous and there was no capsule formation. Mass lesion became equivocal on later phase (75 sec following injection of contrast medium) and difficult to distinguish from pancreatic parenchyma. There were two irregular, hyperattenuating heterogenous hepatic nodules on the left medial and quadrate lobe. Also, multiple hyperattenuating, distinct hepatic and splenic nodules were detected on portal phase. Enlarged lymph nodes including hepatic, pancreaticoduodenal, colic lymph node were detected and showed rim enhancement (Fig 3). There was no evidence of lung metastasis. The dog was diagnosed as malignant metastatic insulinoma with liver, spleen, regional lymph node metastasis.

Surgical removal was not recommended considering the age and presence of widespread metastasis. Prednisolone (0.25 mg/kg, PO, q12hr; Yuhan, Seoul, Korea) and toceranib phosphate (2.75 mg/kg, PO, EOD; Palladia, Pfizer Animal Health, NJ, U.S.A.) was firstly prescribed with frequent small meals to control hypoglycemia. In addition to dietary modifications, the owner was instructed to avoid strenuous exercise. Clinical signs including shivering and the collapsing episodes (the chief complaint of the dog) were markedly improved over a week. After 1 week, normal blood glucose level (8 hr fasting, 101 mg/dL; RI 74-143 mg/dL) and markedly decreased insulin concentration (24.5 uIU/mL; RI 5.2-41.5 uIU/mL) was identified. The dog remained stable, but sudden death following severe vomiting due to the dietary indiscretion was occurred after 1 month of treatment. Postmortem examination of the dog was not performed due to the owner's refusal.

Discussion

Diagnosis of malignant insulinoma in this case was made by clinical signs as well as laboratory data, imaging diagnosis and cytological findings. Initial diagnosis was made by documented hypoglycemia in the setting of inappropriately elevated serum insulin levels. Although the use of IGR and AIGR to diagnose insulinoma considered controversial because of high number of false-positive results, initial diagnosis can be made through these values (10). In this case, both IGR and AIGR were elevated which suggests insulinoma. Insulinoma was confirmed by further diagnostic examinations. CT and cytological findings identified pancreatic mass and metastatic lesions. Although histopathologic confirmation was not conducted in this case, diagnosis of malignant metastatic insulinoma was confirmed by comprehensive data consistent with previous studies.

Treatment options for insulinomas involve surgical, medical, and multimodal approaches. Surgical resection is recommended for the first treatment choice, but many of cases have malignant features which are mostly surgically incurable (8). The goals of treatment for unresectable metastatic insulinomas focus on improved quality of life, symptom reduction, and prolonged survival (11). Feeding with frequent, small amounts of foods throughout the day and avoiding strenuous exercise help managing the symptoms related to hypoglycemia. Medical treatment therapies preventing hypoglycemic episodes include glucocorticoids, diazoxide, benzothiadiazine, octreotide, and somatostatin analogue (4). Cytotoxic chemotherapy is used in advanced disease with presence of metastasis. An alkylating agent streptozotocin has been used to treat unresectable neuroendocrine tumors (NETs) including insulinomas in humans (4). According to several previous studies using streptozotocin in canine insulinomas, variable response rates and toxicity after administration were commonly reported (7). In human medicine, new therapeutic options for advanced pancreatic NETs have been demonstrated (4). Tyrosine kinase inhibitors (TKIs) are molecular-

targeted agents that have been reported to be effective in pancreatic NETs (3). TKIs interfere the actions of vascular endothelial growth factor receptor and platelet-derived growth factor receptor and result in stopping angiogenesis (11). TKIs have antiangiogenesis activity by blocking this process and used in wide range of solid tumors which require blood supply to survive (5). Despite numerous studies have been conducted in human medicine, it has not been formally studied in veterinary medicine. Toceranib phosphate is multi-targeted receptor TKI used in veterinary practices against several solid tumors as antitumor activities (5).

The dog in this report had widespread metastasis at the time of diagnosis. Toceranib phosphate was applied to control advanced disease and after the treatment of combination therapy of PDS and toceranib phosphate, clinical signs were markedly improved in the beginning of treatment. No more progression or recurrence of clinical symptoms were observed and there were no remarkable side effects of toceranib phosphate. Even though the long-term follow-up was not achieved in this dog, it may effective and well-tolerated treatment option for dogs with insulinoma.

Staging of the tumors is essential to evaluate prognosis or median survival time. Based on the tumor-node-metastasis staging system (4), the tumor was classified as stage IV (any T, any N, M1). Previous study reported that overall median survival time (MST) of stage I, II, III was 785days, 547days, 217days, respectively (9). MST of cases received surgery alone was 785 days, and 196 days for treated with medical therapy alone. Treated with surgical resection followed by medical therapy survived 3.5 years on average (9). In the current case, the exact survival time could not be evaluated because the dog died 1 month after treatment due to the dietary indiscretion.

Because of the subtle onset of the clinical signs and slowly progressive characteristics of the tumor, affected dogs are often symptomatic for several months before presentation. It leads to delayed diagnosis and treatment, and the resultant contribute to poor prognosis. The dog also had clinical symptoms before two months of presentation, turned out to be malignant accompanied by widespread metastasis at the initial diagnosis. In addition to the known common sites of metastatic insulinomas, spleen metastasis was also identified. Spleen metastasis of malignant insulinomas are rarely reported in veterinary practices (1). In metastatic insulinomas, outgrowth of (micro-) metastasis after therapy almost always cause recurrence of hypoglycemia (2). It can be considered as possible causes of sudden death following hypoglycemic seizure. Although the histopathological confirmation of the pancreatic tumor was not available, a thorough examination results are sufficient to establish a diagnosis of insulinoma consistent with the previous diagnostic criteria (8).

Conclusions

In conclusion, this case describes diagnostic features and treatment approaches of metastatic insulinoma in a dog. The use of toceranib phosphate is worthwhile to try in insulinoma dogs with widespread metastasis for improving the quality of life. To our knowledge, this is the first case report suggesting potential benefit of medical management with toceranib phosphate in a dog with malignant metastatic insulinoma.

Acknowledgements

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