Tumor thrombus formation in two dogs with insulinomas

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Case Description—A 9-year-old sexually intact male Staffordshire Bull Terrier (dog 1) and a 9-year-old neutered male Boxer were evaluated for intermittent neurologic signs including muscle tremors, ataxia, episodic collapse, disorientation, and seizures.

Clinical Findings—Both dogs had low blood glucose and high serum insulin concentrations. Results of abdominal ultrasonography were unremarkable for both dogs. Exploratory laparotomy revealed a mass that extended from the body of the pancreas into the pancreatosplenic vein in each dog.

Treatment and Outcome—Marginal resection of pancreatic masses was performed, and tumor thrombi were removed via venotomy in both dogs. Histologic evaluation indicated the masses were pancreatic islet cell tumors with tumor thrombi. Clinical signs resolved following surgical resection of tumors and tumor thrombi, and the dogs were euglycemic during the follow-up period (17 and 45 months after surgery).

Clinical Relevance—Although gross tumor thrombus formation has been identified in humans with insulinomas, tumor thrombi have not been previously reported for dogs with insulinomas. Surgical removal of tumor thrombi via venotomy seemed to be well tolerated by the dogs. Tumor thrombus formation did not seem to adversely affect prognosis for the 2 dogs of this report. (J Am Vet Med Assoc 2012;241:1065–1069)

A 9-year-old sexually intact male Staffordshire Bull Terrier (dog 1) was evaluated by the primary care veterinarian for a 1-month history of weight gain and a 2-week history of episodic collapse, disorientation, generalized twitching, and transient blindness during exertion, withholding of food, or within a short period after eating. No abnormalities were detected during physical or neurologic examination. Results of blood biochemical analyses were unremarkable, including a blood glucose concentration (4.1 mmol/L) within the reference range (3.3 to 6.8 mmol/L).

Ten days after the first examination (approx 3 weeks after the first episode of collapse), dog 1 was brought by the owner to a veterinary emergency clinic because of status epilepticus. Blood biochemical analyses revealed the dog was hypoglycemic (blood glucose concentration, 1.2 mmol/L; reference range, 3.3 to 6.8 mmol/L) and hypokalemic (blood potassium concentration, 3.2 mmol/L; reference range, 3.4 to 4.9 mmol/L). Administration of compound sodium lactate solution (5 mL/kg/h; 2.3 mL/lb/h), IV) and potassium chloride (0.05 mmol/kg/h [0.023 mmol/lb/h], IV) was started. Glucose (0.22 mg/kg [0.1 mg/lb], IV) was administered to the dog during a 5-minute period. Seizure activity subsided and mentation of the dog became clinically normal. Blood biochemical analyses performed 3 hours after admission of the dog to the emergency clinic revealed persistent hypoglycemia (blood glucose concentration, 2.3 mmol/L). Glucose (125 mg/kg/h [57 mg/lb/h], IV) was administered to the dog via CRI. The dog had another seizure (60-second duration) 6 hours after admission. Blood glucose concentration was not measured at that time. Seizure activity subsided following administration of diazepam (0.66 mg/kg [0.3 mg/lb], IV). Blood glucose concentration (3.2 mmol/L) of the dog was below the reference range 1 hour after that seizure.

Dog 1 was referred to the Melbourne Veterinary Specialist Centre for further assessment. During physical examination, the dog seemed to be disoriented. Blood glucose and insulin analyses revealed hypoglycemia (blood glucose concentration, 1.2 mmol/L) and an inappropriate elevation of serum insulin concentration (87.2 mU/L; reference range, 5.0 to 20.0 mU/L). The left and right lobes of the pancreas were examined via abdominal ultrasonography, but the body of the pancreas could not be imaged because of interference from gas in adjacent portions of the gastrointestinal tract. No mass lesions were identified. Mild, homogenous prostatic enlargement was detected. Results of the remainder of the abdominal ultrasonographic examination were unremarkable. Results of thoracic radiography were unremarkable. Administration of compound sodium lactate solution (5 mL/kg/h, IV) was resumed, and glucose (0.45% sodium chloride and 2.5% glucose solution; 5 mL/kg/h, IV) was administered via CRI.

Exploratory laparotomy was performed the following day. A mass (0.6 × 1.5 cm) was identified in the body of the pancreas adjacent to the common bile duct. Marginal resection of the pancreatic mass was attempted, and the mass was observed to invade the...
cranial pancreaticoduodenal vein. Hemostasis was accomplished with hemostatic clips and electrocautery. A cranial pancreaticoduodenal venotomy was performed following placement of Rummel tourniquets on either side of the tumor thrombus (Figure 1). The venotomy was performed via a stab incision with a No. 11 scalpel blade, and the incision was extended with Potts scissors. The tumor thrombus (0.8 × 2 cm) was exposed, and the thrombus and pancreatic mass were removed. The venotomy site was closed with 5-0 polypropylene suture in a simple continuous pattern. The distal tourniquet was released before placement of the final suture so that air and thrombi could be removed from the vein prior to closure. No other abnormalities were identified during exploratory laparotomy. A liver biopsy was performed with a 6-mm skin biopsy punch; hemostasis was accomplished with a gelatin sponge. A jejunostomy tube was placed to enable enteral feeding if the dog developed signs of pancreatitis after surgery.

Measurement of blood glucose concentration immediately after surgery revealed persistent hypoglycemia (blood glucose concentration, 0.8 mmol/L). Administration of glucose via CRI was resumed. Hypoglycemia resolved within 12 hours after surgery, and blood glucose concentration remained > 3.4 mmol/L during the following 48 hours. No further neurologic signs were observed. Dog 1 was discharged from the clinic 3 days after surgery. The jejunostomy tube was not used for feeding, and it was removed 2 weeks after surgery.

Results of histologic evaluation of the pancreatic mass and tumor thrombus were consistent with islet cell carcinoma. Histologically normal pancreatic architecture was disrupted by a multifocal, nodular, infiltrative neoplastic proliferation of epithelial cells. Neoplastic cells in the tumor thrombus appeared to be similar to those in the pancreatic mass. An average of < 1 mitotic figure/10 hpf (400X magnification) was detected. Surgical margins of < 1 mm were observed. Histologic analysis of the liver biopsy specimen revealed rare scattered lipogranulomas and mild neutrophilic inflammation in the sinusoids. No evidence of metastatic disease was detected in the liver biopsy specimen.

Dog 1 was followed up for 17 months after surgery. The dog did not have recurrence of neurologic signs, and it remained euglycaemic during that period.

A 9-year-old neutered male Boxer (dog 2) was examined by the primary care veterinarian following a single episode of vomiting, muscle twitching, and ataxia. No abnormalities were detected during physical and neurologic examination. Results of blood biochemical analyses performed by personnel in the primary care veterinary clinic were unremarkable except for a low blood glucose concentration (2.4 mmol/L). Results of blood biochemical analyses performed 2 days later were unremarkable, including a blood glucose concentration (3.4 mmol/L) within the reference range. Results of blood biochemical analyses performed 10 days after examination by the primary care veterinarian indicated the dog had a low blood glucose concentration (2.6 mmol/L). At that time, a blood sample was obtained from the dog and submitted to a laboratory for determination of serum insulin and blood glucose concentrations; results indicated the dog was hypoglycemic (blood glucose concentration, 3.2 mmol/L). Serum insulin concentration (123 mU/L) was inappropriately elevated. Frequent feeding of small meals was recommended, and the dog was referred to the Melbourne Veterinary Specialist Centre.

Dog 2 underwent abdominal ultrasonography 3 weeks after examination by the primary care veterinarian; results were unremarkable. The right and left lobes of the pancreas were examined; however, the body of the pancreas was obscured by gas in the gastrointestinal tract. Results of thoracic radiography were unremarkable. The dog had transient signs of disorientation and aggression after radiography. Blood glucose concentration was low (2.8 mmol/L). The dog was fed, and the signs of disorientation and aggression subsided. Exploratory laparotomy was recommended at that time. During the following 2 weeks, the owners fed the dog small, frequent meals, and no further clinical signs of hypoglycemia were observed.

Five weeks after the first episode of hypoglycemia, dog 2 underwent exploratory laparotomy. A 2.1.5-cm mass was identified in the body of the pancreas adjacent to the common bile duct. Marginal resection of the pancreatic mass was performed, and the mass was observed to invade the cranial pancreaticoduodenal vein. Hemorrhage was controlled with electrocautery and hemostatic clips. Rummel tourniquets were placed on the cranial pancreaticoduodenal vein on either side of the mass. A venotomy was performed via the same technique that was performed for dog 1. A tumor thrombus was identified in the lumen of the vein, and the thrombus and pancreatic mass were removed. The venotomy incision was closed with 5-0 polypropylene suture in a simple continuous pattern. The distal tourniquet was released before the final suture was placed so that air and thrombi could be removed from the vein prior to closure. No other abnormalities were detected during exploratory laparotomy. A liver biopsy was performed with a 6-mm skin biopsy punch; hemostasis was accomplished with a gelatin sponge.

Figure 1—Intraoperative photograph of a pancreatic tumor in a 9-year-old sexually intact male Staffordshire Bull Terrier undergoing laparotomy for marginal resection of the tumor and an associated tumor thrombus. The pancreatic mass (black arrow) extends into the cranial pancreaticoduodenal vein. Rummel tourniquets are placed on either side of the tumor thrombus (white arrow) in the pancreaticoduodenal vein.
Blood glucose concentration after surgery was within the reference range. Food was offered approximately 12 hours after surgery, but the dog vomited and was anorexic. Postoperative pancreatitis was suspected. Saline (0.9% NaCl) solution (5 mL/kg/h, IV) and metoclopramide (0.07 mg/kg/h [0.03 mg/lb/h], IV) were administered via CRI, prochlorperazine (0.3 mg/kg [0.14 mg/lb], q 8 h) was administered PO, and a bland, low-fat food formulated for dogs was fed (beginning 12 hours after vomiting stopped). The clinical signs attributed to pancreatitis gradually resolved during 6 days after surgery, and the dog was discharged from the clinic 7 days after surgery.

Results of histologic evaluation of the pancreatic mass of dog 2 were consistent with islet cell carcinoma and an associated tumor thrombus. Results indicated the tumor was locally invasive, and 2 mitotic figures/10 hpf's (400X magnification) were observed. Histologic evaluation of the liver biopsy specimen revealed mild hydropic change, but no evidence of metastatic disease was detected.

Results of follow-up physical examination of dog 2 at 10 days after surgery were unremarkable. Results of blood biochemical analyses at that time were unremarkable, except for mild hypokalemia (serum potassium concentration, 3.7 mmol/L; reference range, 3.9 to 5.9 mmol/L), hypochloremia (serum chloride concentration, 98 mmol/L; reference range, 101 to 116 mmol/L), and moderately increased serum alkaline phosphatase activity (925 U/L; reference range, < 141 U/L). Blood glucose concentration (5.1 mmol/L) was within the reference range.

Dog 2 was followed up for 45 months after surgery. No further neurologic signs attributable to hypoglycemia were observed, and the dog remained euglycemic during that period.

Discussion

Functional pancreatic β-cell tumors, including those with a benign histologic appearance, usually have aggressive biological behavior in dogs. Consequently, the term insulinoma includes all insulin-producing tumors in dogs.2 Insulinomas are typically benign in humans.7 Results of other studies10–17 indicate that at least 95% of insulinomas in dogs are malignant and approximately 45% to 51% of insulinomas in dogs metastasize by the time of diagnosis. Other authors4,16 have suggested that such metastases spread primarily via the lymphatic system, but hematogenous spread via the portal vein is also possible. The liver and regional lymph nodes are the most common sites of insulinoma metastasis, but the duodenum, mesentery, omentum, and other distant sites may also be affected.4,5,7 Approximately 16% of dogs with insulinomas have multiple pancreatic lesions, and diffusely infiltrative insulinomas have also been detected.11 Although invasion of insulinomas into blood vessels and lymphatics of dogs has been microscopically detected,2 gross invasion of insulinomas into major blood vessels with tumor thrombus formation in dogs has not been previously reported, to the authors' knowledge.

Splenic thrombosis associated with an insulinoma in a dog has been reported16; that thrombus was identified via ultrasonography, CT, and exploratory laparotomy. On the basis of mild uptake of contrast material in CT images, a tumor thrombus was suspected in that dog. Results of histologic evaluation of the suspected thrombus were not reported; consequently, the thrombus could not be identified as a tumor thrombus (vs a blood clot). In that dog, the splenic vein and the spleen were resected en bloc. The clinical outcome of that dog was not reported.

Although 80% to 90% of insulinomas in humans are benign, insulinomas can invade the splenic and pancreaticoduodenal veins in humans.3,9 The effect of tumor thrombus on the survival time of humans with an insulinoma is unknown.9 The effect of other types of tumor thrombus on survival time of humans seems to depend on the type of primary tumor and the extent of tumor invasion. Tumor thrombi associated with hepatocellular carcinomas in humans and adrenal tumors in dogs are associated with reduced survival time,10,11 whereas tumor thrombi associated with adrenal tumors in humans are not associated with reduced survival time.19 Renal carcinoma tumor thrombi only have an adverse effect on survival time of humans if the thrombus extends beyond the renal artery into the vena cava.13 Renal carcinoma with vena caval thrombosis has been reported for only 1 dog14; consequently, no conclusions regarding survival time of dogs with renal carcinoma thrombosis can be made.

The median duration of euglycemia and median survival time of dogs that undergo surgical resection of insulinomas with no evidence of metastatic disease (World Health Organization stage I) ranges from 12 to 16.5 months and 12.7 to 26 months, respectively.3,5,7,13,16 Recommendations of the World Health Organization indicate regional lymph node biopsy specimens should routinely be evaluated for accurate staging of tumors.4,17 Although lymph node involvement in dogs with insulinomas reduces the duration of euglycemia following surgery, it does not seem to have an adverse effect on survival time.8 Because grossly abnormal regional lymph nodes were not identified in the 2 dogs of the present report and histologic evaluation of such lymph node specimens was not likely to aid determination of prognosis, lymph node biopsies were not performed for these dogs.

Dogs with insulinomas that have distant metastases, including hepatic metastases, have a short duration of euglycemia after a diagnosis is made (< 1 month) and have a short median survival time (6 to 7.2 months).4,16 In both dogs of the present report, no evidence of distant metastatic disease was identified via ultrasonography, exploratory laparotomy, or histologic evaluation of liver biopsy specimens. Because lymph node biopsy specimens were not obtained, differentiation could not be made between World Health Organization stages I and II disease in these 2 dogs.

The location of a primary insulinoma in the pancreas of a dog does not seem to affect prognosis but may affect the choice of method used for tumor resection.17 Although results of another study including 35 dogs with insulinomas indicated partial pancreatectomy results in a longer median survival time (17.9 months) versus marginal resection of such tumors (median sur-
vival time, 11.5 months), only 4 dogs in that study had insulinomas that involved the body of the pancreas. The surgical techniques (marginal resection vs partial pancreatectomy) used for excision of tumors in the body of the pancreas were not indicated in that report. However, those authors2 reported that the location and size of a tumor were used to determine the surgical method used for excision. Recommendations regarding size of surgical margins for insulinomas have not been standardized by investigators of other studies 2,16 in which survival times of dogs following removal of insulinomas via partial pancreatectomy were determined. Although partial pancreatectomy is recommended for removal of tumors in the lobes of the pancreas, wide resection is rarely feasible for tumors located in the body of the pancreas because of the close proximity of vital blood vessels and the pancreatic duct.2,18 Some authors18 have suggested that resection of insulinomas in the body of the pancreas should not be attempted.

The blood supply to the left lobe of the pancreas is via the splenic and hepatic arteries. The terminal branch of the hepatic artery is the cranial pancreaticoduodenal artery, which enters the body of the pancreas and anastomoses with the caudal pancreaticoduodenal artery in the right lobe of the pancreas.19,20 These arteries supply the body and right lobe of the pancreas and the duodenum. Because a large portion of the pancreatic and duodenal blood supply is shared, preservation of the cranial and caudal pancreaticoduodenal blood vessels during surgery is recommended.20,21

In the 2 dogs of the present report, the pancreatic masses were removed via marginal resection because they were closely associated with the pancreatic ducts (which drain the left and right lobes of the pancreas), the cranial pancreaticoduodenal artery, and the common bile duct. Resection of these structures may lead to exocrine pancreatic insufficiency, devitalization of the duodenum, and a need for reconstructive surgery (eg, intestinal anastomosis and cholecystojejunostomy).21 Because of the high risk of morbidity and death associated with partial pancreatectomy, marginal resection of pancreatic masses was performed in these dogs.

Although en bloc resection of tumor thrombi and associated blood vessel could have been performed in the dogs of the present report, resection of the cranial pancreaticoduodenal vein was not attempted because of concerns that this would compromise viability of the duodenum and the remaining portions of the pancreas. Although collateral circulation may have developed following tumor thrombus formation, this was difficult to assess intraoperatively. Tumor thrombi were removed successfully via venotomy in both dogs, without compromising blood supply to the surrounding tissues. Although thrombosis after venotomy was a potential risk, patency of the blood vessels was not monitored after surgery.

Dog 2 had postoperative clinical signs consistent with pancreatitis. This complication was not surprising because results of other studies2,7 indicate that 30% to 43% of dogs that undergo resection of insulinomas have transient postoperative pancreatitis. The moderate postoperative increase in serum alkaline phosphatase activity detected in this dog was likely attributable to pancreatitis. A jejunostomy tube was placed in dog 1 to aid management of potential pancreatitis. In retrospect, it might have been beneficial to place a jejunostomy tube in dog 2.

Young age and high insulin concentration (> 30 mU/L) at the time of diagnosis are associated with reduced survival time of dogs with insulinomas. Although other authors11 have suggested that mitotic index of an insulinoma is inversely correlated with survival time of a dog (as for humans with insulinomas), this theory has not been proven.

Although the 2 dogs of the present report were not young, did not have insulinomas with high mitotic indices, and did not have evidence of distant metastases, both of these dogs had high preoperative serum insulin concentrations and biologically aggressive tumors (as indicated by invasion of blood vessels), and narrow surgical margins were achieved. However, because both of these dogs were euglycemic at 17 and 45 months after diagnosis, tumor thrombus formation did not seem to have an adverse effect on survival time or the period that dogs were free of disease.

One of the dogs of the present report and 16% (4/25) of dogs with insulinomas in another study1 were euglycemic at the time of the initial examination for the problem. Because diagnosis of insulinoma can be delayed by the transient nature of the hypoglycemia, repeated measurement of blood glucose should be performed for dogs with transient neurologic signs. While the portable glucometer used to measure blood glucose concentration of dogs in the present study has been validated for use with canine blood, results of another study22 indicate that 99% of blood glucose concentration values obtained with this glucometer are slightly lower than those determined with laboratory analyzers. Therefore, dogs with blood glucose concentrations at the low end of the reference range (as determined via a laboratory analyzer) may be falsely classified as hypoglycemic (as determined via a portable glucometer).22 Such an error probably did not occur for the 2 dogs of the present report because hypoglycemia was confirmed via analysis of blood samples submitted to laboratories not associated with the clinic. Although a highly elevated circulating insulin concentration in a hypoglycemic dog does not definitively indicate that the dog has an insulinoma, an insulinoma should be strongly suspected when no other explanation (eg, extrapancreatic neoplasia, hepatic insufficiency, administration of exogenous insulin, starvation, or extreme exertion) for those results can be identified.

Presence of gas in the gastrointestinal tract prevented ultrasonographic examination of the body of the pancreas in both dogs of the present report; consequently, the insulinomas and tumor thrombi were not identified before surgery. The sensitivity of transabdominal ultrasonography for detection of insulinomas in dogs is estimated to be between 35% and 78%.3,5,8,23,24 Therefore, our inability to ultrasonographically detect the pancreatic masses in these dogs was not unusual.

Endoscopic ultrasonography, MRI, and contrast CT seem to be more sensitive methods (66% to 100% sensitivity) for identification of pancreatic pathology and vascular invasion of insulinomas in dogs.3,6,23 Unfor-
fortunately, the sensitivity (10% to 50%) and specificity (approx 57%) of these methods are low for identification of dogs with metastatic disease.3,23,25 Somatostatin receptor scintigraphy can be used to identify humans with insulinoma metastases; however, results of studies3,23,25 in which that technique was used to evaluate dogs with insulinomas were disappointing. Although dogs seem to have high-affinity somatostatin receptors, the typically small size of insulinomas and nonspecific scintigraphic uptake in the gall bladders, kidneys, and gastrointestinal tracts of dogs complicates interpretation of somatostatin receptor scintigraphy results.3,23,25

Exploratory laparotomy with surgical biopsy of the pancreas, local lymph nodes, and liver is required to confirm a diagnosis of insulinoma and accurately stage the disease in dogs. Results of another study3 indicate that up to 43% of suspected metastatic lesions identified during exploratory laparotomy of dogs with pancreatic tumors are attributable to a disease unrelated to the primary tumor. That finding supports the recommendation for histologic evaluation of biopsy specimens of suspected metastases. Although surgical excision of an insulinoma is rarely curative for dogs, it results in longer survival times versus medical treatment alone.3,7

Insulinas in dogs may have grossly aggressive biological behavior including invasion of major blood vessels with tumor thrombus formation. However, such biological behavior does not seem to be associated with a poor prognosis for dogs. Surgical removal of tumor thrombi via laparotomy appeared to be well tolerated and effective in the 2 dogs of the present report.

References