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NOTE

Clinical Pathology

A case of feline primary duodenal carcinoid with intestinal hemorrhage

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ABSTRACT. A 15-year-old neutered male Persian cat was presented with recurrent hematemesis and melena. Abdominal ultrasonography and computed tomography revealed a mass in the proximal descending duodenal wall. Endoscopic examination revealed hemorrhage on the luminal side of the mass. Fine-needle aspiration of the mass was performed. Microscopic analysis revealed a cluster of cells with oval nuclei and indistinct cell borders, suggesting a neoplastic disease of neuroendocrine origin. The mass located near the major duodenal papilla was partially resected, and the bleeding was stopped by cauterization. However, the surgical procedures could not control the hemorrhage from the tumor mass, and the cat died of severe anemia. Immunohistopathological analysis revealed that the tumor was a duodenal carcinoid.

KEY WORDS: carcinoid, cat, duodenum, neuroendocrine, ultrasonography

Carcinoids are a group of heterogeneous neoplasms of neuroendocrine origin, also known as neuroendocrine carcinomas [3]. In cats, carcinoids of the liver, extrahepatic bile duct, and pancreas have been reported sporadically [3, 9, 11, 12]. However, carcinoids of duodenal origin in cats have not been reported; thus, the clinical features of these tumors remain unknown. Herein, we describe a case of a feline primary duodenal carcinoid, where the tumor caused recalcitrant intestinal hemorrhage.

A 15-year-old neutered male Persian cat, weighing 2.62 kg, was referred to the Tokyo University of Agriculture and Technology for a detailed evaluation because of chronic vomiting, hematemesis, and melena, with decreased appetite and activity (day 1). The cat had been treated with prokinetic and mucosal protective agents by a private veterinarian, without clinical improvement. At the initial presentation, slight pallor of the mucous membranes was observed on physical examination. Complete blood count (CBC) revealed moderate normocytic normochromic anemia (red blood cells: 491 × $10^4/\mu l$ [reference range: 500–1,000 × $10^4/\mu l$]; hemoglobin: 7.5 g/d*l* [reference range: 8.0–15.0 g/d*l*]; packed cell volume [PCV]: 21.1% [reference range: 24.0–45.0%]), and the biochemical analysis revealed hypoproteinemia (total protein: 5.4 g/d*l* [reference range: 5.7–7.8 g/d*l*]; albumin: 2.0 g/d*l* [reference range: 2.3–3.5 g/d*l*]), hypokalemia (potassium: 3.3 mEq/*l* [reference range: 4.0–4.5 mEq/*l*]), and a mildly elevated fibrinogen level (352 mg/d*l* [reference range: 120–240 mg/d*l*]). Thoracic and abdominal radiographs and echocardiography were unremarkable. Abdominal ultrasonography revealed a mass measuring 11.6 × 16.9 mm around the anterior duodenal flexure to the descending duodenum, as well as a mildly enlarged pancreaticoduodenal lymph node (Fig. 1). The heteroechogenic mass, because of which the normal structure of the duodenal wall was altered, protruded toward the serosa without causing a luminal obstruction. The duodenal mucosa at the level of the mass was thin, and a mucosal defect caving into the mass was noted at the center of the mass. Ultrasound-guided fine-needle aspiration of the mass was performed, and microscopic analysis revealed a cluster of cells with indistinct cell borders. The cells had a moderate amount of eosinophilic cytoplasm, with round to oval nuclei. Scattered naked nuclei were occasionally seen. Mild anisocytosis and anisokaryosis were observed, and mitotic figures were rare. These findings were indicative of a neoplastic disease of neuroendocrine origin.

Because intestinal hemorrhage was suspected to cause anemia, gastrointestinal endoscopy was performed on day 2 to identify

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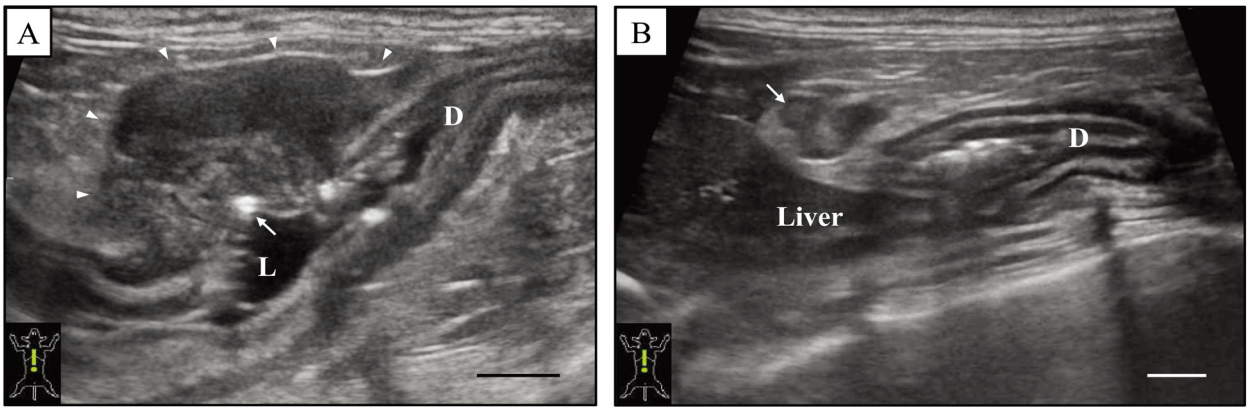

Fig. 1. Sagittal ultrasonography of the duodenal mass. A: Abdominal ultrasonography revealed a mass measuring 11.6 × 16.9 mm in the area of the descending duodenum (arrowheads). The mass, observed as heterogenous echogenicity on the intestinal wall, protruded toward the serosa. The normal five-layer structure of the intestinal wall was altered at the site of the mass. The surface of the mucosa was irregularly delineated and either thin or absent on the mass. A concave mucosal defect was present at the center of the mass (arrow). No sign of luminal obstruction was observed. D: duodenum, L: lumen of the duodenum. Bar=5 mm. B: Mild enlargement of the pancreaticoduodenal lymph node measuring 8.1 × 6.2 mm was observed (arrow). D: duodenum, Bar=5 mm.

any bleeding sites. The examination revealed continuous and copious hemorrhage at a bleeding site in the descending duodenum (Fig. 2A). The bleeding site seemed to correspond to the mucosal defect caving into the mass detected on ultrasonography. No other bleeding sites were detected in the upper digestive tract. Endoscopic biopsy was not performed at this point because of the high risk of duodenal puncture and exacerbation of the underlying hemorrhage.

On the basis of the ultrasonographic and endoscopic findings, intestinal hemorrhage at the bleeding site on the luminal side of the tumor mass was the most plausible cause of the anemia. Hence, surgical excision of the tumor was planned as the first-line treatment. Before the surgery, computed tomography (CT) was performed on day 5 to determine the precise location of the tumor, particularly with respect to its anatomical relationship to the common bile duct or major duodenal papilla, and to detect primary or metastatic neoplastic lesions at sites other than the duodenum. The CT examination revealed a tumor near the major duodenal papilla, with no involvement of the common bile duct (Fig. 2B and 2C). The contrast-enhanced CT findings corroborated the ultrasonographic finding of a concave lesion with a mucosal membrane defect located at the tumor level (Fig. 2D). There were no abnormal CT findings suggesting primary neoplastic disease observed at sites other than the duodenum. Significant lymph node enlargement was observed in the pancreaticoduodenal lymph node alone.

Because of the difficulty arising from the tumor being near the major duodenal papilla, radical excision of the tumor was not performed. Alternatively, cytoreductive surgery and electrocautery to control the intestinal hemorrhage were performed after the CT on day 5. Intraoperative macroscopic observation confirmed the findings on ultrasonography, endoscopy, and CT, that is, the bleeding site was the concave lesion located at the center of an oval ulcer on the luminal side of the tumor mass (Fig. 2E). No macroscopic lesions suggestive of a primary tumor were found in abdominal organs other than the duodenum.

On histopathology, the resected tumor was characterized by cells arranged in nests and cords separated by fine fibrovascular stroma (Fig. 3A and 3B). Individual cells were round to polyhedral with granular eosinophilic cytoplasm. Nuclei were small to moderate in size and contained coarsely clumped chromatin. Mild anisocytosis and anisokaryosis were seen. The mitotic figure counts were 0–1 per high-power field. Invasion of the surrounding tissue, including the underlying muscular layer, was observed. On immunohistochemistry, the tumor was found to be positive for chromogranin A and weakly positive for cytokeratin (Fig. 3C and 3D). Based on the comprehensive results of the immunohistopathological and clinical evaluations, a diagnosis of primary duodenal carcinoid was made.

The cat received the following postoperative treatment: an intravenous injection of carbazochrome sodium sulfonate hydrate (Adona tablets; Nipro ES Pharma Co., Ltd., Osaka, Japan) at a dose of 0.5 mg/kg twice daily; a subcutaneous injection of tranexamic acid (Transamin tablets; Daiichi Sankyo Co., Ltd., Tokyo, Japan) at a dose of 13 mg/kg twice daily; and oral administration of lansoprazole (Takepron OD; Takeda Pharmaceutical Co., Ltd., Tokyo, Japan) at a dose of 0.5 mg/kg once daily and sodium ferrous citrate (Ferromia; Eisai Co., Ltd., Tokyo, Japan) at a dose of 50 mg/head once daily. The clinical signs, including hematemesis and melena, were resolved after the surgical treatment. The anemia was controlled, as evidenced by PCV of 25% on day 13 and 24% on day 21. However, on day 50, the cat's condition suddenly deteriorated with a sharp drop in the PCV to 9.1%. This anemia might have resulted from the duodenal hemorrhage caused by the tumor, as there was no clinical evidence of tumor progression, such as an increase in the size of the tumor mass and pancreaticoduodenal lymph node. Blood transfusion therapy was ineffective, and eventually, the cat died of severe anemia.

In the present case, a clinically detectable neoplastic mass was found only on the duodenum. No other lesions suggestive of a primary tumor were detected on diagnostic imaging or direct observation during surgery. These findings suggested that the primary site of this carcinoid was the duodenum. Since the enlarged pancreaticoduodenal lymph node was not sent for histopathological

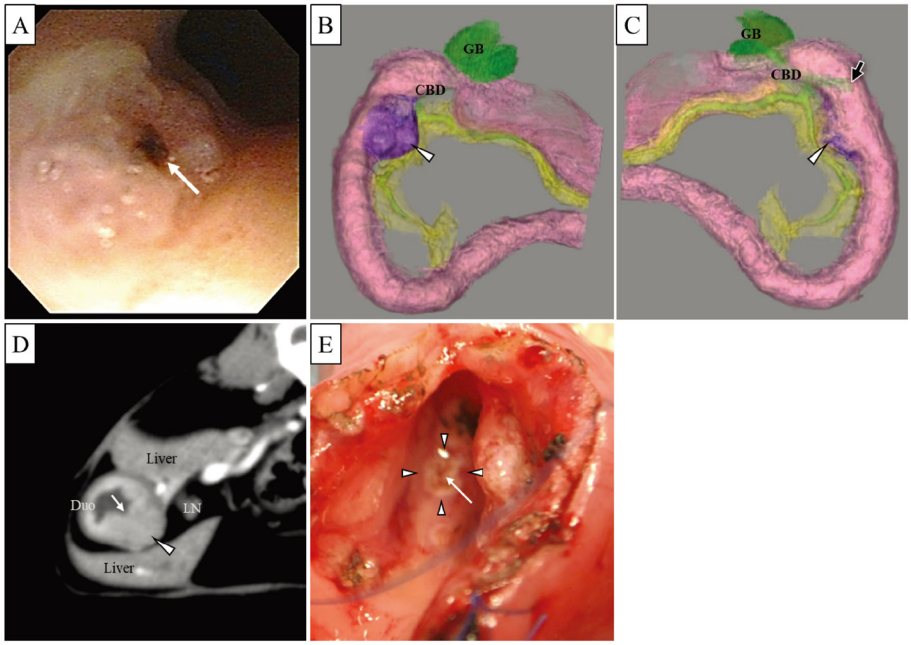

Fig. 2. Endoscopy, computed tomography (CT), and intraoperative macroscopic observation of the duodenal mass. A: Endoscopy revealed a bleeding site in the descending duodenum (arrow). The gelatinous material surrounding the bleeding site might be sucralfate hydrate adhering to the ulcer of the mucosa, around the bleeding site. B (ventral view) and C (dorsal view): Volume rendering CT after administration of contrast media revealed a mass (arrowhead) on the duodenum near the major papilla (arrow) with no involvement of the common bile duct or major papilla. CBD: common bile duct, GB: gall bladder. D: Contrast-enhanced CT revealed a lesion caving into the tumor mass with a mucosal membrane defect (arrow) on the luminal side of the tumor (arrowhead). A swollen pancreaticoduodenal lymph node was noted. LN: pancreaticoduodenal lymph node. E: Macroscopic observation of the duodenal mucosa during surgery confirmed a concave bleeding site (arrow) at the center of an oval ulcer (arrowheads).

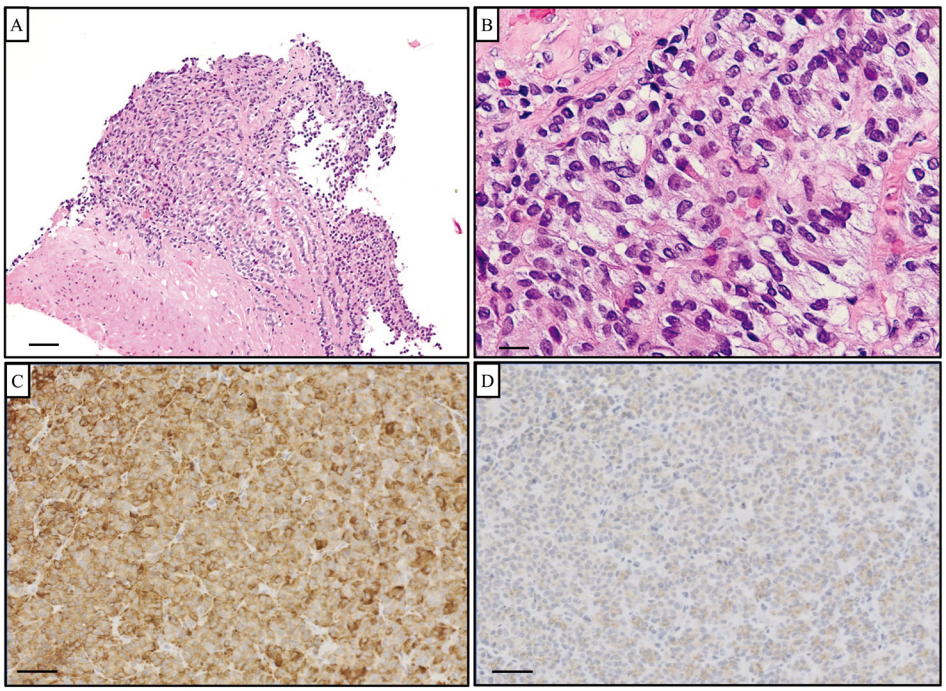

Fig. 3. Histopathological examination and immunohistochemistry of the duodenal mass. A, B: The tumor tissue consisted of cells arranged in nests and cords separated by delicate fibrovascular stroma. The characteristic finding of malignancy, that is, invasion into the surrounding tissue was observed, involving the underlying muscular layer (A, Bar=100 μm). The neoplastic cells were round to polyhedral, with a granular eosinophilic cytoplasm. Nuclei were small to moderate in size and contained coarsely clumped chromatin. Mild anisocytosis and anisokaryosis were seen. Mitotic figure counts were 0–1 per high power field (B, Bar=25 μm). Hematoxylin and eosin stain. C, D: The neoplastic cells were found to be positive for chromogranin A (C) and weakly positive for cytokeratin (D). Immunostaining with hematoxylin counter stain. Bar=50 μm.

examination, the evidence of metastasis was inconclusive.

The first-line treatment of carcinoids is radical surgical excision [10]. Therefore, the anatomical location of the tumor has a great impact on the treatment and prognosis. As a surgical approach in the area near the papilla was difficult and risky, complete resection of the tumor mass was not performed in this cat. In humans, for advanced or unresectable cases, systemic therapy with molecular targeted drugs is generally selected [6]. Recently, an angiogenesis inhibitor has been described as an effective drug for refractory intestinal bleeding associated with tumor-related vascular malformations [7, 8]. Because carcinoids are rich in abnormal blood capillaries [3, 5], and intestinal hemorrhage could be a negative predictor of intestinal carcinoids, angiogenesis inhibitors, such as toceranib, might be an option for the treatment of unresectable carcinoids in veterinary medicine.

Carcinoids are classified as functional and nonfunctional tumors based on the ability to produce bioactive substances. Functional carcinoids often show characteristic clinical signs associated with the substances produced. In cats, some functional carcinoids, including gastrin-, glucagon-, or insulin-producing tumors, have been reported [1, 2, 4, 13, 14]. Functional carcinoids exhibit characteristic clinical signs based on the substances produced, such as Zollinger-Ellison syndrome in gastrin-producing carcinoids, glucagonoma syndrome including necrolytic migratory erythema in glucagon-secreting carcinoids, and hypoglycemic seizure in insulin-producing carcinoids. Zollinger–Ellison syndrome is characterized by recurrent gastrointestinal ulcers secondary to gastric acid hypersecretion due to high serum gastrin concentration and would be suspected if clinical signs such as vomiting, hematemesis, and prolonged diarrhea are present [13, 14]. Although chronic vomiting and hematemesis were the chief symptoms in this case, the endoscopic examination did not reveal any gastric ulcer or bleeding site. Necrolytic migratory erythema associated with glucagonomas and hypoglycemic seizure associated with insulinomas have rarely been reported in cats [1, 4]. In this case, neither skin lesions nor seizures were observed, and the serum glucose concentration was within the normal range, during the entire study period. Considering that the clinical signs and examinations did not indicate hypersecretion of these hormones, the carcinoid was most likely nonfunctional. For definite differentiation between functional and nonfunctional carcinoids, concentrations of bioactive peptides in the serum and immunohistochemistry for the peptides are required.

In conclusion, carcinoids should be included in the differential diagnosis when a mass growing expansively within the intestinal wall is observed. If a putative bleeding site with a mucosal membrane defect is noted on the luminal side of the mass, the risk of severe anemia should be considered regardless of whether it is a functional or nonfunctional carcinoid.

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