

## CASE REPORT

### The First Case of Extensive Metastatic Pancreatic Mixed Acinar-neuroendocrine Carcinoma (MANEC) in a Cat

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#### ABSTRACT

Mixed acinar-neuroendocrine carcinoma (MANEC) is a rare neoplasm with both exocrine and neuroendocrine differentiation. This report describes a pancreatic MANEC in a 10-year-old male castrated cat presented with alopecia, anorexia, and weight loss. Abdominal ultrasound showed diffuse thickening of the pancreas, omental fat was markedly thickened, heterogeneously hyperechoic, and contained multiple 1–3mm hypoechoic nodules. A round hypoechoic mass (10×11mm) was seen in the splenic mid-body, connecting with the distal left pancreatic lobe. Abdominal CT revealed a soft tissue mass at the distal left pancreatic lobe and an adjacent mass on the medial splenic body. The pancreatic–splenic mass complex showed ill-defined margins, poor enhancement. Despite supportive care, the cat deteriorated and died within 10 days. Postmortem examination showed neoplastic cells with glandular and islet-like morphology. Immunohistochemistry revealed insulin-positive endocrine and Pan-CK-positive exocrine elements, confirming biphasic origin. Metastases were found in the spleen, liver, mesentery, diaphragm, pleura, and heart. This case highlights the diagnostic complexity of feline pancreatic MANEC and underscores the need to consider this tumor in the differential diagnosis of pancreatic masses with mixed histologic features.

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#### INTRODUCTION

Mixed acinar-neuroendocrine carcinoma (MANEC) is a rare tumor composed of both exocrine and neuroendocrine elements within a single neoplasm (Imaoka *et al.*, 2016). This tumor differs from others by involving acinar cells that produce digestive enzymes and neuroendocrine cells that regulate physiological events through hormones secretion. For diagnosis, each component should typically constitute at least 30% of the tumor mass, confirmed through histopathological and immunohistochemical evaluation.

In human medicine, MANEC often behaves aggressively, with high metastatic potential and poor prognosis (Dulskas and Pilvelis, 2020; Grossi *et al.*, 2021). Although the pathogenesis of MANEC remains unclear, it may arise from pluripotent, progenitor cells or from two

concurrent neoplastic processes (Liu *et al.*, 2014; Chen *et al.*, 2015).

To date, metastatic MANEC has not been described as a tumor of veterinary importance. Pancreatic tumors in cats are rare and often diagnosed late. This report describes feline MANEC with metastasis, offering clinical and pathological insights and underscoring the need to recognize this tumor in veterinary oncology.

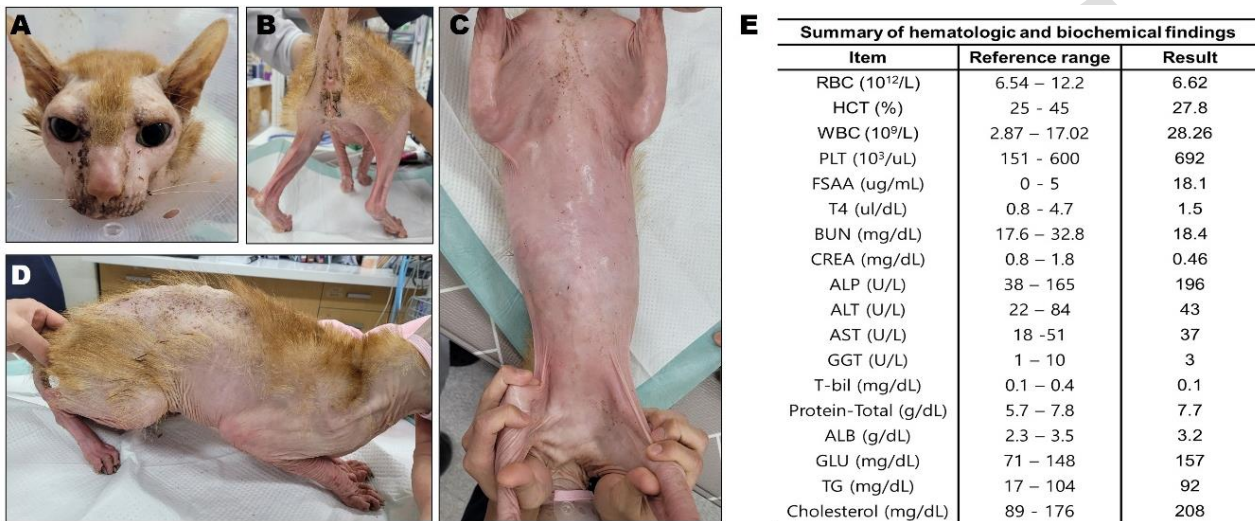
**Case history and physical examination:** A 10-year-old, male castrated Domestic Shorthair cat, weighing 4.35kg, was presented to the Veterinary Medical Teaching Hospital, Kyungpook National University, Daegu, Republic of Korea, on March 28, 2024, with a 3-month history of alopecia, anorexia, and weight loss. The cat had previously been treated with prednisone at a dose of 0.5mg/kg orally twice daily for approximately 3 weeks to

manage inflammation, and with felimazole at a dose of 2.5mg orally twice daily for approximately 2 weeks for hyperthyroidism. On physical examination, vital signs (respiration rate, pulse rate and body temperature) were within normal range. The cat was cachectic (BCS 3/9) with facial and whisker pad alopecia (Fig. 1A), hair loss in the perineal and caudal thigh regions (Fig. 1B), shiny, alopecic skin on the ventral abdomen (Fig. 1C), and generalized alopecia, skin thinning, and cachexia (Fig. 1D). Hairs were easily removed when gently grasped, indicating fragility. Laboratory findings showed leukocytosis and elevated feline serum amyloid A, with no other significant abnormalities in hematobiochemical parameters (Fig. 1E).

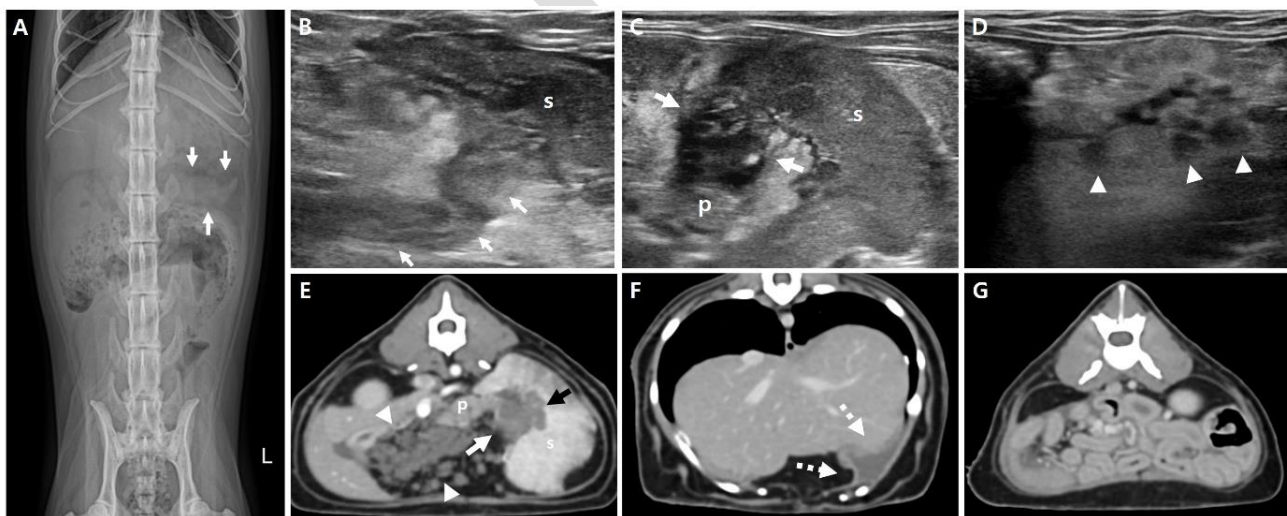
**Clinical examination and diagnosis:** Abdominal radiographs revealed a generalized decrease in serosal

detail, particularly in the left cranial abdomen. A soft tissue structure, suspected to be an enlarged left pancreatic lobe, was observed caudal to the stomach (Fig. 2A). Abdominal ultrasound showed diffuse hypoechoic thickening of the pancreas (Fig. 2B). A round hypoechoic mass (10×11mm) was seen in the splenic mid-body, connecting with the distal left pancreatic lobe (Fig. 2C). Adjacent omental fat was markedly thickened, heterogeneously hyperechoic, and contained multiple 1–3mm hypoechoic nodules (Fig. 2D). Moderate peritoneal effusion with echogenic debris was present. The liver showed mildly increased echogenicity with fine texture and hypoechoic nodules.

Transverse pre-contrast, late arterial (Fig. 2E), venous and delayed phase (Fig. 2F, G) CT images of the cat were taken with bolus-tracking; thoracic CT included only a delayed phase. Apnea was induced via manual



**Fig. 1:** Gross findings of paraneoplastic alopecia in a cat with pancreatic MANEC. (A): Facial and whisker pad alopecia. (B): Hair loss in the perineal and caudal thigh regions. (C): Shiny, alopecic skin on the ventral abdomen. (D): Generalized alopecia, skin thinning, and cachexia. (E): Summary of hematologic and biochemical findings in the cat.



**Fig. 2:** Radiographic (A), ultrasonographic (B-D), and CT (E-G) images of the cat. (A): Ventro-dorsal radiograph showing a soft tissue opacity (arrow) in the left cranial abdomen, caudal to the stomach, suspected to represent an enlargement left pancreas. (B): Ultrasonography revealing a hypoechoic and thickened left pancreatic lobe (arrow). (C): A hypoechoic mass (arrows) in the mid-body of the spleen is connected to the left pancreatic lobe. (D): In the left cranial abdomen, adjacent to the mass and pancreas, hyperechoic fat with multiple small hypoechoic nodules (arrowhead) is observed. (E): Late arterial phase CT image showing a mass in the distal portion of the left pancreatic lobe (white arrow) and another mass on the medial aspect of the spleen (black arrow), both with ill-defined margins. These masses exhibit heterogeneous and relatively poor contrast enhancement compared to the pancreatic and splenic parenchyma. Multiple nodules are observed in the cranial abdominal fat, forming a conglomerated pan-like appearance (arrow heads). (F): Delayed phase CT image showing thickening of the left ventral curv of the diaphragm (dashed arrow) with pleural effusion. (G): Delayed phase CT image showing a small volume of peritoneal effusion. p; pancreas, s; spleen.

hyperventilation. Abdominal CT revealed a soft tissue mass at the distal left pancreatic lobe (10×10×10mm) and an adjacent mass on the medial splenic body (13×11×11mm), both had ill-defined margins (Fig. 2E). These masses were connected, and exhibited heterogeneous and relatively poor contrast enhancement compared to the pancreatic and splenic parenchyma in all phases.

The pancreatic mass exhibited ill-defined rim enhancement. The pancreatic body and right lobe were thickened with homogeneous enhancement. Remaining splenic parenchyma appeared normal. Multiple nodules and fat edema were observed in the omentum surrounding the stomach, liver, pancreas, and spleen (Fig. 2E). Notably, ventral pancreatic body fat and nodules clustered into a pan-like structure. Generalized peritoneal fluid was present. Thoracic CT revealed focal thickening of the ventral left diaphragm and pleural effusion in the caudal thoracic cavity (Fig. 2F). A small volume of peritoneal effusion was also noted (Fig. 2G).

**Diagnosis and differential diagnosis:** The findings described above were consistent with the possibility of a pancreatic neoplasm with splenic involvement and peritoneal-diaphragmatic metastasis, as well as secondary encapsulating peritonitis. The major differential diagnoses considered based on clinical findings, imaging studies, and gross autopsy findings included pancreatic adenocarcinoma, pancreatic neuroendocrine tumor, lymphoma, and carcinoma metastasized from other primary sites. Histopathological examination of the pancreatic mass revealed both acinar and neuroendocrine cell components, and immunohistochemical examination showed results for both insulin-positive endocrine and Pan-CK-positive exocrine elements, leading to a final diagnosis of Mixed Acinar-Neuroendocrine Carcinoma (MANEC).

**Treatment adopted:** The cat received supportive and symptomatic treatment. Oral medications over seven days included gabapentin (15mg/kg TID), amantadine (5mg/kg BID), a fentanyl patch, prednisolone (0.5mg/kg BID), famotidine (1mg/kg BID), mirtazapine (1.88mg/kg SID), and maropitant (1mg/kg SID). Despite therapy, condition of the cat deteriorated and she died 10 days post-diagnosis.

**Postmortem findings:** Postmortem examination was focused on the abdomen due to the suspected pancreatic neoplasia. An irregular, firm, multinodular pancreatic mass was identified, with splenic atrophy and firm adhesions to the pancreas (Fig. 3A). Numerous small, yellow-white nodules were found on the hepatic surface, especially near the gallbladder (Fig. 3B), as well as in the mesentery (Fig. 3C), renal fascia, abdominal wall, and thoracic structures including the pleura and diaphragm.

On histology, the pancreatic tumor exhibited dual differentiation with neuroendocrine and exocrine components. Neuroendocrine cells formed islet-like clusters with a finely granular eosinophilic cytoplasm, mild atypia, and low mitotic activity. The exocrine component showed tubular or acinar structures lined by cuboidal to polygonal cells, with coarse chromatin, prominent nucleoli, moderate pleomorphism, and occasional mitoses,

indicating higher malignancy (Fig. 3D). The transitional zones between the two components were evident.

Metastases were found in the spleen (Fig. 3E), liver (Fig. 3F), mesentery (Fig. 3G), peritoneum, and renal fascia, but the renal parenchyma was spared. The spleen was nearly effaced by tumor cells (Fig. 3E), and the hepatic architecture was markedly disrupted (Fig. 3F). The neoplastic infiltration extended to the pleura (Fig. 3G), diaphragm (Fig. 3H), and heart (Fig. 3I). The tumor composition in the metastases varied by site, with some showed mixed populations and others had predominantly exocrine cells.

Immunohistochemistry revealed strong insulin positivity in the neuroendocrine component (Fig. 3J), absence of insulin positivity in exocrine areas (Fig. 3K), and diffuse Pan-CK expression in all tumor cells (Fig. 3L). Dual insulin and Pan-CK positivity was noted in the spleen (Fig. 3M). The liver metastases showed only Pan-CK expression, confirming exocrine predominance (Fig. 3N). Dual-marker expression in the mesentery further supported a metastatic mixed differentiation (Fig. 3O).

The clinical, imaging, and pathological findings confirmed pancreatic MANEC with paraneoplastic alopecia. The tumor showed dual differentiation and widespread metastasis, including splenic invasion and dissemination to abdominal and thoracic organs.

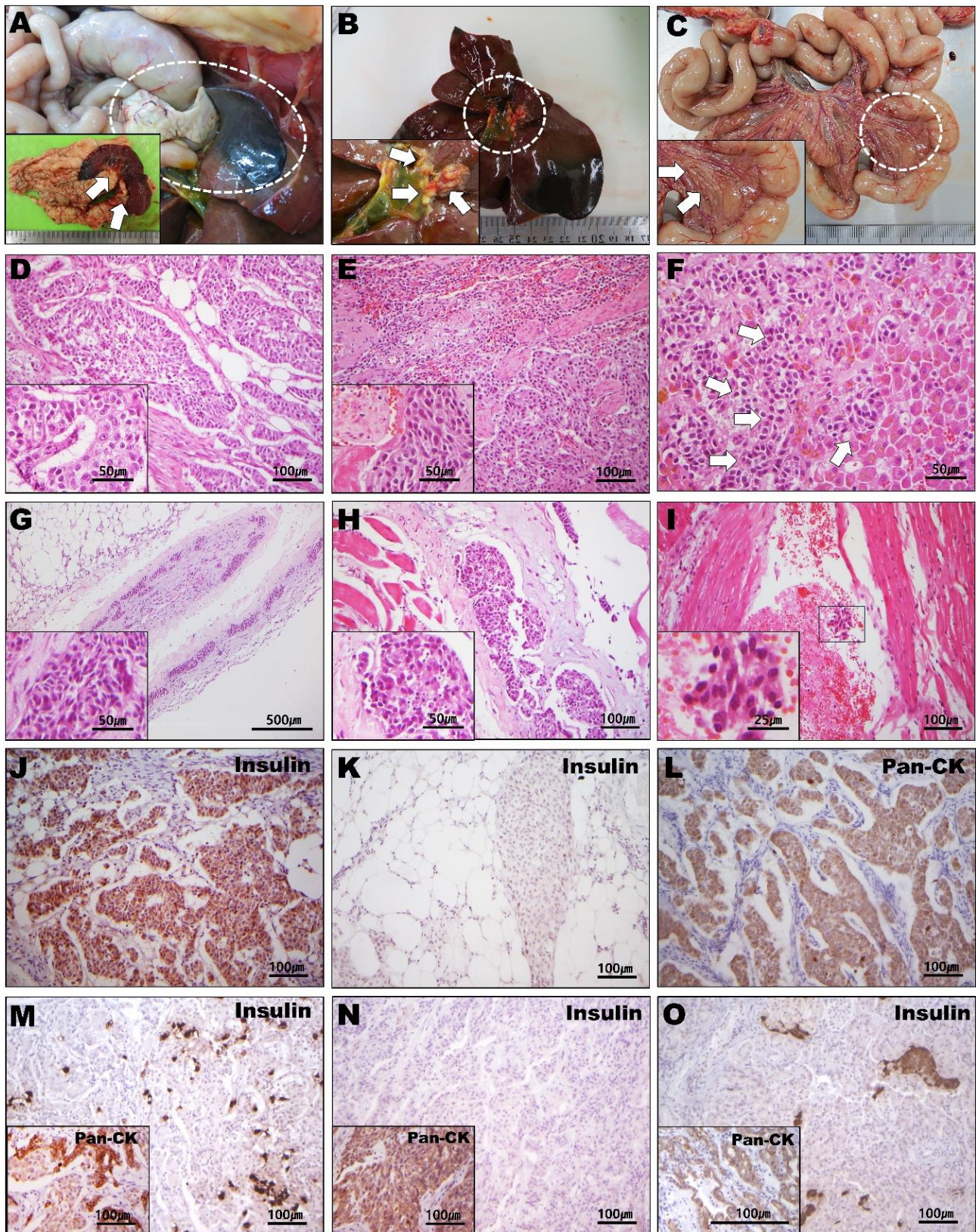
## DISCUSSION

This case describes a rare instance of MANEC in a cat, contributing valuable insight into a neoplasm scarcely reported in veterinary medicine. The MANEC is defined by concurrent exocrine and neuroendocrine differentiation, posing notable challenges in both diagnosis and treatment (Brathwaite *et al.*, 2016).

In the case under study, feline paraneoplastic alopecia was characterized by nonpruritic, symmetrical hair loss affecting the ventral abdomen and limbs, with shiny skin and easily pluckable hair. In this case, alopecia was observed in conjunction with MANEC, suggesting a broader tumor spectrum associated with this dermatologic syndrome. Though not previously linked to MANEC, exocrine component of the tumor may mimic the metabolic behavior of pancreatic adenocarcinomas. Hypoaminoacidemia, hyperglucagonemia, and zinc imbalance have been proposed as contributing mechanisms (Grandt *et al.*, 2015) and similar disruptions may originate from the adenocarcinomatous elements of MANEC.

Histopathological and immunohistochemical analysis confirmed dual differentiation: acinar-like structures representing exocrine features and islet-like clusters indicating neuroendocrine characteristics. Insulin positivity supported the neuroendocrine identity, while Pan-CK reactivity confirmed epithelial (exocrine) origin. The differential diagnoses included acinar cell carcinoma, ductal adenocarcinoma, and insulinoma (Rosol and Meuten, 2020). Acinar and ductal tumors were ruled out due to a lack of insulin expression, and neuroendocrine tumors were excluded based on the presence of dual-marker expression in metastases, confirming a mixed tumor phenotype. These findings highlight MANEC's complexity and need for thorough pathological investigations.





**Fig. 3:** Gross, histopathologic and immunohistochemical features of metastatic MANEC. Irregular, firm multi-nodular (arrows) pancreatic mass (A). Multiple nodules (arrows) on the liver (B), and mesentery (C). Mixed acinar and solid neoplastic patterns (arrows) in the pancreas (D). Metastases in spleen (E), liver (F) and mesentery (G). Tumor infiltration of diaphragm (H) and heart (I). Insulin-positive neuroendocrine (J) and insulin-negative exocrine components of the pancreas (K). Pan-CK expression in all tumor cells in the pancreas (L). Dual differentiation confirmed in the spleen (M). Liver metastases of only exocrine origin (N). Dual differentiation confirmed in the mesentery again (O).

Although insulin-positive neuroendocrine cells were identified, normoglycemia (157mg/dL) suggested a non-functional neuroendocrine component, a finding consistent with the majority (60–90%) of human pancreatic

neuroendocrine tumors that do not secrete biologically active hormone levels (Dulskas and Pilvelis, 2020; Wu *et al.*, 2022). In addition, tumor-mediated destruction of pancreatic parenchyma and the metabolic burden of



extensive metastases may have suppressed any potential hormonal effect. Since immunopositivity alone does not confirm hormonal activity (Zhuge *et al.*, 2020), definitive assessment would require serum insulin testing, which was not performed in this cat under study.

**Conclusions:** This report emphasizes the necessity of integrating clinical findings with histopathological and immunohistochemical data to achieve an accurate diagnosis. The absence of clinical signs of hormonal dysfunction does not preclude neuroendocrine differentiation, especially in biphasic tumors like MANEC. Overall, this case enhances the current understanding of feline pancreatic MANEC and advocates for a thorough, multimodal diagnostic strategy when assessing complex pancreatic neoplasms.

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**Authors' contribution:** JK designed and supervised the study. All authors contributed to the diagnosis and had direct contact with the cat. SM performed the histopathological diagnosis. SK interpreted radiography, ultrasound and CT images. SM, TU, JH, WJ and JK performed the necropsy. J, JY, YI were the primary clinicians. SM, SK and YI contributed to writing the manuscript, while all authors reviewed and approved the final version.

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