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Case Report

Non-functional neuroendocrine tumor with multisystemic metastasis in a cat

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Abstract

An eight-year-old castrated female feline was referred for necropsy with a history of apathy, inappetence, abdominal distension, hypersensitivity to abdominal palpation, and evidence of abdominal neoplasms on ultrasound. Macroscopically, multifocal to coalescent, yellowish-white, firm and infiltrative nodules were observed on the surface of the parietal peritonium and in abdominal and thoracic organs. Microscopic characteristics of the neoplasm suggested a neuroendocrine origin, but did not allow a definitive diagnosis and determination of the origin. Immunohistochemistry revealed that neoplastic cells expressed vimentin, CD56, neuron specific enolase, and PGP 9.5 and were negative for biogenic amines and hormonal peptides. Based on anatomopathological and immunohistochemical findings, diagnosis of metastatic non-functional neuroendocrine tumor was confirmed.

Key words: neuroendocrine neoplasm, cat, immunohistochemistry.

Intro

Neuroendocrine neoplasms (NENs) originate in neuroendocrine system that are present in different regions of the body, such as endocrine glands, respiratory tract (10), gastroenteropancreatic tract (13), and urogenital tract (15), among others (8, 18, 19).

Neuroendocrine cells express neuronal markers, but also present an endocrine phenotype with capacity to synthesize, store, and secrete biogenic amines, as catecholamines and histamines; hormonal peptides, as glucagon, gastrin, somatostatin, chromogranins, and pancreatic polypeptide; and tachykinins, as neuropeptide K (2, 10). Thus, NEN is functional when there is an increased synthesis and secretion of these substances in blood associated with a clinical hormonal syndrome directly related to products of neoplastic secretion (7). When NEN is non-functional, clinical signs are due to primary tumor location or metastases, size of the tumor, and infiltration in adjacent organs (6).

The World Health Organization and the European Neuroendocrine Tumor Society proposed two histological classifications for human NEN: low grade - G1 (well-differentiated neoplastic cells); intermediate grade - G2 (moderately differentiated cells), and high grade - G3 (poorly differentiated cells) and staging. However, histological classification may be insufficient to identify the site of origin, mainly in metastatic cases, and hormonal production, requiring a complementary immunohistochemical evaluation.

In humans, NEN has already been described in most organs; however, the primary sites most frequently affected are lungs and gastrointestinal tract (1). In felines, neuroendocrine neoplasms of the skin (19), digestive tract organs as esophagus (18), stomach (5), intestine (16), liver (3, 11, 20), and pancreas (12), as well as aortic body (8, 17) among others (4, 9) have already been described. However, multisystemic metastatic spread is rare (8,12)

The purpose of this report is to describe anatomopathological and immunohistochemical findings of a non-functional neuroendocrine tumor with multisystemic metastasis in a cat.

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Case report

An eight-year-old mixed-breed cat, 2.5 kg, was evaluated at the Veterinary Hospital of the Universidade Federal do Piauí, presented with a history of prolonged apathy and loss of appetite. On physical examination, the animal was intensely apathetic, with reduced level of consciousness (semi-comatose state), 8% dehydration, cachexia; rectal temperature of 38.6oC, heart rate of 187 beats/min, and respiratory rate of 21 breaths/min; moderate abdominal distension with hypersensitivity to abdominal palpation. Further tests as blood count, serum biochemistry, and abdominal ultrasound were performed.

The blood count, performed in an automated SDH®-3 VET system, showed leukocytosis (total leukocytes: 40,800 cells / µL, VR: 5,500-19,500 cells / µL) with neutrophilia (segmented: 38,760 cells / µL, VR: 2,500-12,500 cells / µL). Biochemical analyses of the serum, performed in an automated Chem Well®-T system, revealed high levels of alkaline phosphatase (109 U / L, VR: 25-93 U / L) and gammaglutamyltransferase (17 U / L, VR: 1.3-5.1 U / L) and decrease in serum albumin (1.1 g / dL, VR: 2.1-3.3 g / dL). These values were maintained after five days of hospitalization. Abdominal ultrasound showed free fluid in the cavity and nodules in the liver and mesogastric region, suggestive of neoplasia. Cytological examination of the abdominal fluid revealed a large number of atypical cells and neutrophils. Animal died on the sixth day of hospitalization due to worsening clinical condition and was referred to necropsy.

At necropsy, the animal was emaciated, and diffusely, subcutaneous tissue showed a translucent gelatinous material characteristic of edema. The abdominal cavity contained a large amount of translucent fluid with fibrin filaments. There were nodules of various sizes distributed on the surface of parietal and visceral peritoneum (Fig. 1). In the right paraovarian region, there was an

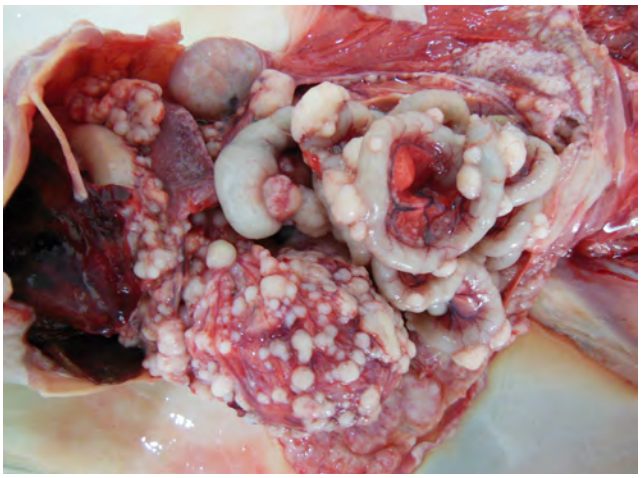

Figure 1. Neuroendocrine tumor in an eight-year-old mixed-breed cat. Coalescent neoplastic nodules of various sizes distributed on parietal and visceral peritoneal surface.

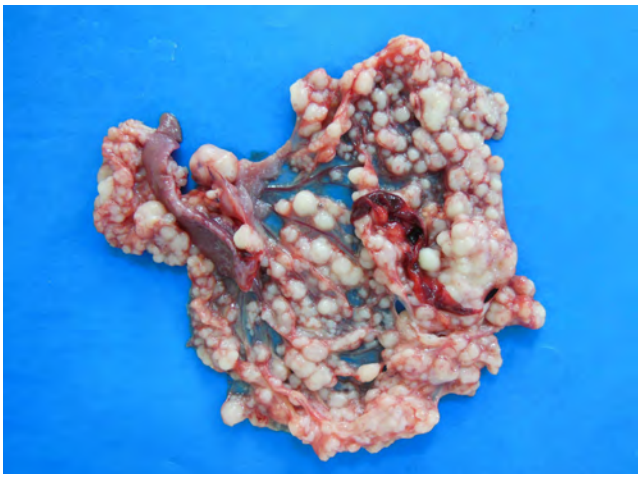

Figure 2. Neuroendocrine tumor in an eight-year-old mixed-breed cat. Coalescent neoplastic nodules of varying sizes in the omentum and spleen.

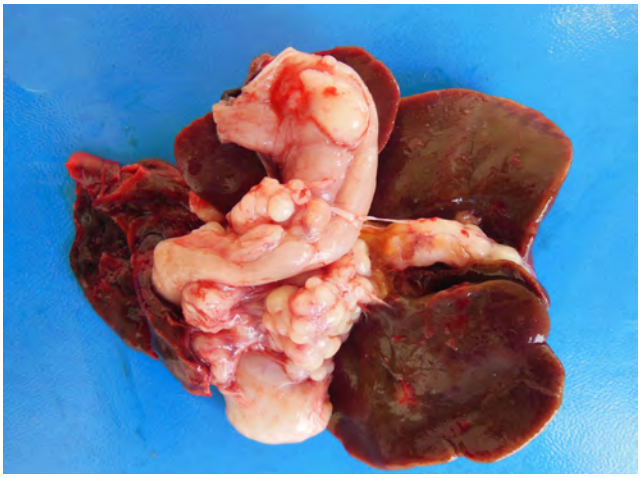

Figure 3. Neuroendocrine tumor in an eight-year-old mixed-breed cat. Coalescent neoplastic nodules of varying sizes in stomach serosa, duodenum, liver, and pancreas.

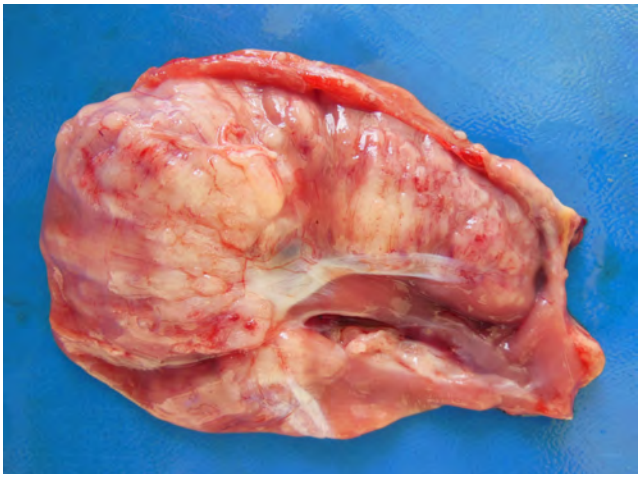

Figure 4. Neuroendocrine tumor in an eight-year-old mixed-breed cat. Diaphragm with areas of thickening and nodules due to neoplastic infiltration.

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approximately 20 cm large yellowish-white, solid, firm nodule with a pedunculated aspect. Intestines and stomach presented numerous multifocal to coalescent nodules, restricted to the serous layer, ranging from a few millimeters to 5 cm in diameter, with the same characteristics as that of the paraovarian nodule. Similar nodules were observed diffusely across omentum (Fig. 2) and pancreas; and multifocal nodules were noted in spleen (Fig. 2), kidneys, urinary bladder and liver (Fig. 3). The parietal peritoneum and the abdominal face of the diaphragm presented thickening areas and multifocal to coalescent, yellowish-white and firm nodules (Fig. 4).

A discrete amount of translucent fluid was also observed in pleural space. In the left caudal lobe of the lung, there were some yellowish-white, solid and firm nodules ranging from 0.5 to 2 cm in diameter. The tracheobronchial lymph nodes were intensely enlarged, yellow, and firm with loss of cortico-medullary distinction.

Fragments of neoplasms and the thoracic and abdominal organs were collected in a 10% formaldehyde buffered solution, processed using routine paraffin embedding technique, and stained with hematoxylin-eosin for histopathological evaluation.

Microscopically, neoplasm had similar characteristics in all committed organs. Intestines and stomach had nodules restricted to serous layer (Fig. 5A). Neoplasia was poorly defined and not encapsulated, formed by cells arranged predominantly in solid pattern, but sometimes organized in cords and lobes limited by a thin conjunctive stroma (Fig. 5B and Fig. 5C). Cytoplasm was eosinophilic, sometimes granular in appearance. Nucleus was round to oval with dense chromatin and moderate nucleus:cytoplasm ratio (Fig. 5D). Discrete anisocytosis, anisokaryosis, and low mitotic index (less than 1 mitosis per field at 40× magnification) were noted. Individual cell necrosis and neoplastic emboli in lymphatic vessels were observed. Neoplasm was supported

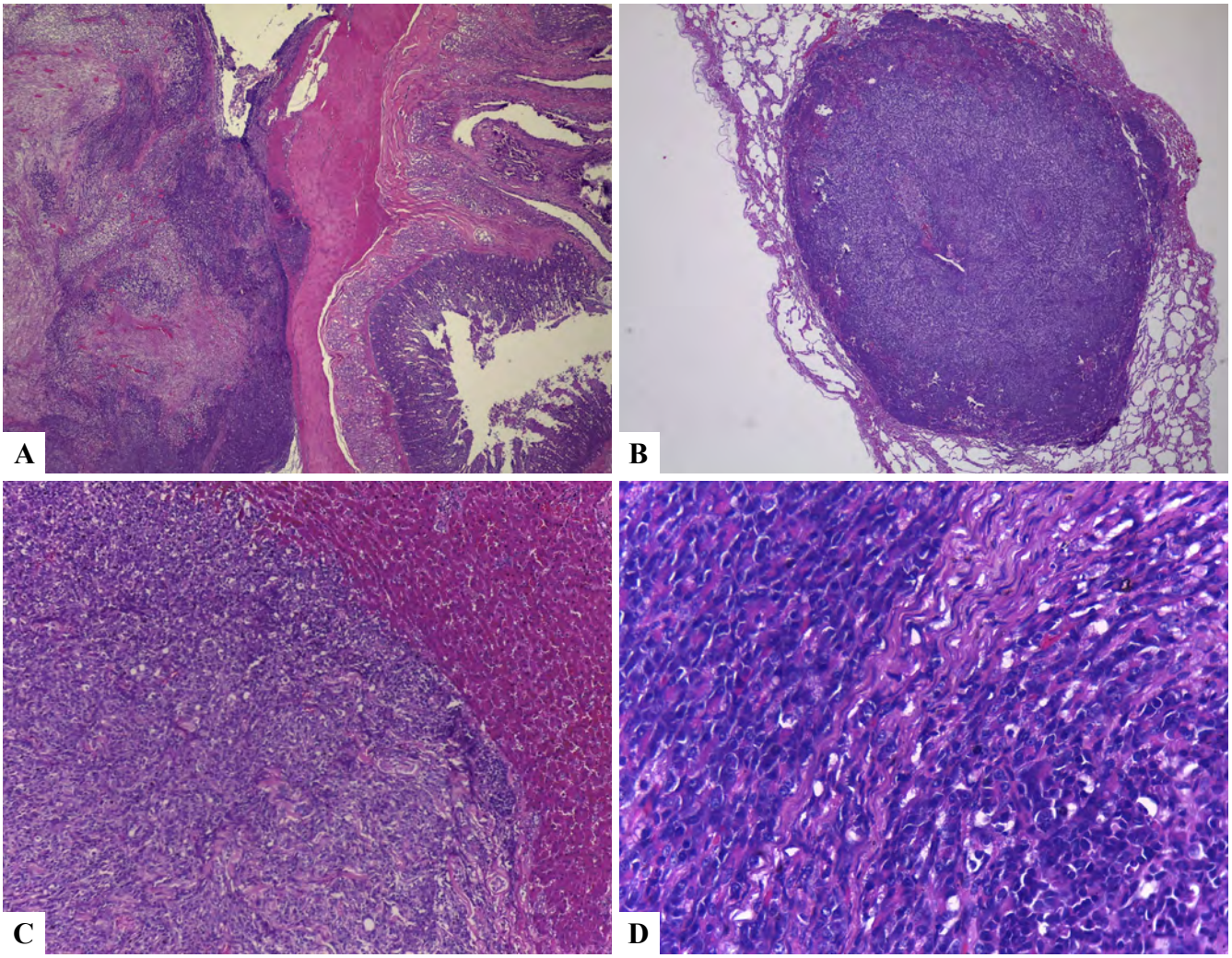

Figure 5. Neuroendocrine tumor in an eight-year-old mixed-breed cat. **A.** Non-encapsulated neoplastic nodule restricted to intestinal serosa. Hematoxylin-eosin, 10×. **B.** Lungs with non-encapsulated neoplasia, with cells arranged predominantly in a solid pattern. Hematoxylin-eosin, 6.25×. **C.** Liver with non-encapsulated neoplasia, with cells arranged predominantly in a solid pattern. Hematoxylin-eosin, 25×. **D.** Neoplastic cells with eosinophilic cytoplasm, round to oval nucleus with dense chromatin and moderate nucleus:cytoplasm ratio. Hematoxylin-eosin, 50×.

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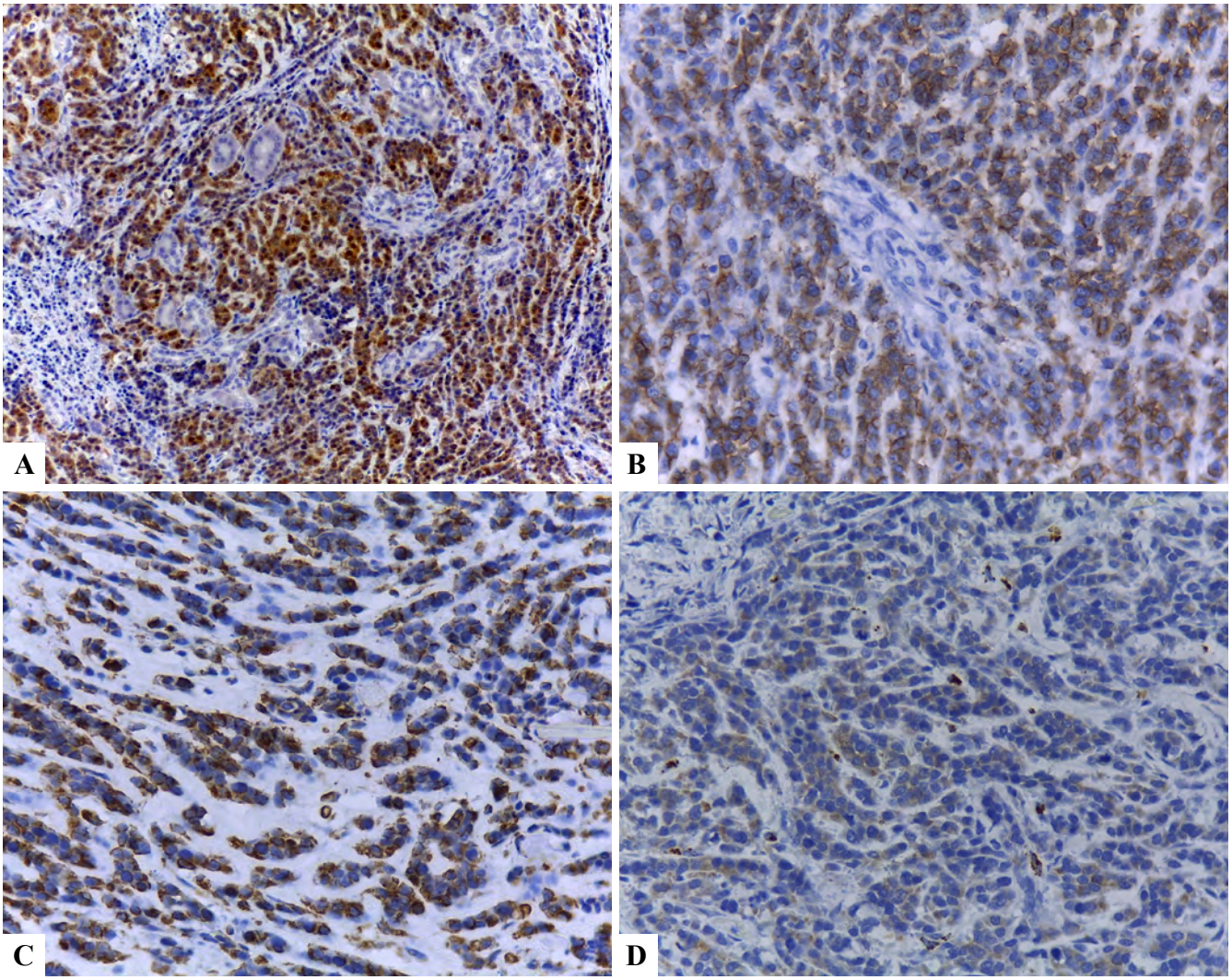

Figure 6. Neuroendocrine tumor in an eight-year-old mixed-breed cat. Neoplastic cells with diffuse and intense cytoplasmic positivity for the antibodies PGP 9.5 (**A**), CD56 (**B**), neuron specific enolase (**C**) and vimentin (**D**). Immunohistochemistry; 3,3-diaminobenzidine tetrachloride (DAB) for all sections and counterstained with Mayer's hematoxylin, 50×.

by a discrete fibrovascular stroma. Multifocal areas of neoplastic tissue necrosis were detected.

Microscopic features suggested a neuroendocrine nature of the neoplasm. In order to reach a definitive diagnosis and identify the primary tumor site, histological sections were evaluated based on immunohistochemical panel. The list of antibodies used is summarized in Table 1.

Neoplastic cells showed diffuse and intense cytoplasmic positivity for vimentin, CD56, neuron-specific enolase, and PGP 9.5 (Fig. 6). Cells showed negative staining for CK Pan antibodies, insulin, glucagon, gastrin, synaptophysin, chromogranin, hepatocyte-specific antigen, GFAP, pancreatic polypeptide, somatostatin, and Olig2.

Discussion

The present report describes a case of non-functional neuroendocrine tumor with multisystemic metastatic spread in a domestic cat. Based on histopathological and immunohistochemical results, it was impossible to determine the primary site because multisystemic metastases were observed. However, the histomorphology in correlation with the positive immunostaining for NSE, PGP 9.5 and CD56 were consistent with the diagnosis of neuroendocrine tumor.

Negativity of neoplastic cells for the main biogenic amines and hormonal peptides without clinical symptoms of hormonal syndrome, which is the secretion of large amounts of these substances in the blood, allowed us to define tumoral non-functionality. Thus, clinical signs, such as lack of appetite, apathy, cachexia, abdominal distension, and pain, were due to physical presence of the tumor and multisystemic metastases.

Multisystemic metastatic dissemination is not commonly reported in cases of neuroendocrine neoplasms and is a striking feature in the present report. The low mitotic

Table 1. Immunohistochemistry markers employed in this case.

Antibodies		clone
Vimentin	Intermediate filamento of mesenchymal cells	v9
CK Pan	Intermediate filamento of ephitelial cells	AE1AE3
Insulin	Group of pancreatic islet tumors	K36aC10
Glucagon	Group of pancreatic islet tumors	polyclonal
Gastrin	Neuroendocrine tumors and gastrinomas	polyclonal
Synaptophysin	Neuroendocrine cell marker	SY38
Chromogranin	Neuroendocrine cell marker	polyclonal
Hepatocyte specific antigen	Hepatocyte specific antigen	OCH1E5
NES	Neuron enolase specifies	BBS/NC/VI-H14
GFAP	Glial fibrillary acid protein	polyclonal
Olig2	Glioblastomas and oligodendrogliomas marker	polyclonal
PGP 9.5	(protein gene product 9.5), marker of neuronal and neuroendocrine differentiation	polyclonal
Pancreatic polypetide	Group of pancreatic and bile duct tumors	polyclonal
Somatostatin	Group of pancreatic islet cell tumors and other neuroendocrine tumors	polyclonal

index may be related to the slow growth of the neoplasia. Because it is a non-functional tumor the clinical symptoms were due to metastases.

Metastatic dissemination in several organs, including lymph nodes as well as peritoneum, resulted in a reduction of lymphatic drainage in addition to external compression of blood and lymph vessels, causing pleural and abdominal effusion, aggravated by the hypoalbuminemia.

Based on macroscopic presentation three important differential diagnoses were considered, namely mesothelioma, epithelioid malignant peripheral nerve sheath tumor, and metastatic digestive tract carcinoma. Mesothelioma is a neoplasm of mesothelial cells that are found in the serosa of abdominal and thoracic organs. However, it is a neoplasm that can metastasize to the parenchyma of the organs (14). Mesothelioma was ruled out due to histological pattern and the immunohistochemestry positivity for neuroendocrine markers.

CD56 is a neural cell adhesion molecule expressed in many normal and neoplastic cells, including malignant peripheral nerve sheath tumor. But, peripheral nerve sheath tumor was ruled out due to histological pattern, negativity for GFAP and positivity for neuroendocrine markers.

Metastatic carcinoma in the gastrointestinal tract was also ruled out, because neoplastic cells were negative for cytokeratin without mucosal involvement.

Based on anatomopathological findings, a diagnosis of non-functional neuroendocrine tumor with multisystemic metastatic spread was made.

Conflict of interest

The authors declared that they had no conflicts of interest with respect to their authorship or publication of this article.

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