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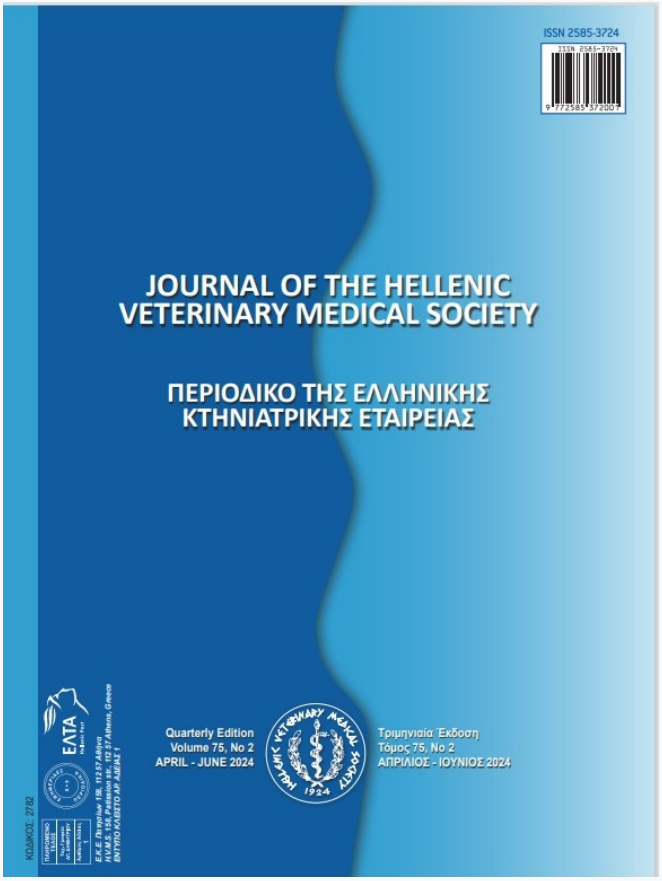

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Research article
Ερευνητικό άρθρο

Gastrointestinal stromal tumor (GIST) in a female Terrier dog

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ABSTRACT: This case report describes two intestinal masses compatible with gastrointestinal stromal tumor (GIST) in a nine-year-old female Terrier dog. The dog presented with complaints of anorexia and vomiting following the ingestion of food. Abdominal ultrasonography revealed two masses in the ventral aspect of the stomach and duodenum. The masses were 6.1×3.7×2.3 cm and 3.2×2×1.7 cm in size, and the cut surfaces of the masses were grayish-white-yellow and had a solid appearance. The greater mass invaded the intestinal serosa and mucosa. Cut surfaces were grayish white - yellow and had a solid appearance. Following routine histopathological processing, masses were sectioned at four µm, stained with Hematoxyline&Eosine (H&E), and immunohistochemically with anti-c-KIT (CD117) antibody. Microscopically, the tumor comprised cells with an oval vesicular nucleus, spindle-shaped eosinophilic cytoplasm, and a prominent nucleolus. Mitotic activity increased significantly (5-6 mitoses at ×400 magnification). Binucleated cells were observed. Large necrotic areas surrounded by inflammatory cells were noticed. The gastrointestinal stromal tumor is a neoplasm originating from intestinal Cajal cells, and the tumor is mainly confused with leiomyoma and leiomyosarcoma; immunohistochemical demonstration of c-KIT is performed for differential diagnosis.

Keywords: c-KIT; gastrointestinal stromal tumor; GIST; dog;

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INTRODUCTION

Gastrointestinal stromal tumor (GIST) is a mesenchymal tumor originating from intestinal cells of Cajal (ICCs), which are intestinal pacemaker cells (LaRock et al., 1997; Meuten, 2002; Girard-Luc et al., 2010; Gillespie et al., 2011). The tumor has been described in humans and dogs, and rarely in cats and horses (Meuten, 2002; Girard-Luc et al., 2010; Elliot et al., 2017) and occurs predominantly in older and female animals (Meuten, 2002; Gillespie et al., 2011; Hayes et al., 2013). The gastrointestinal stromal tumor is commonly located in the large intestine, small intestine, and stomach in dogs (Suwa and Shimoda, 2017) and has the tendency to metastasize (Hanazono et al., 2012; Hayes et al., 2013). The tumor can grow with enlargement and sometimes forms exophytic nodules on the serosal surfaces of visceral organs (Maxie, 2016). Histologically, the tumor is classified into four types: Spindle-shaped, myxoid, fascicular, and epithelioid. Spindle-shaped, myxoid and epithelioid types have been described in dogs (Meuten, 2002; Gamba et al., 2012; Hayes et al., 2013). The tumor is composed of cells that are usually arranged as interlaced fascicules or cells of storiform (curly or matte) with oval nuclei and cells with basophilic cytoplasm in an indefinite border and exhibiting a variable mitotic activity (Gillespie et al., 2011; Maxie, 2016).

CASE HISTORY

A nine-year-old female Terrier dog was referred with a history of anorexia and vomiting. The patient had been operated in a private veterinary clinic with the suspect of foreign body ingestion three months ago. Clinical examinations revealed sensitivity and masses in the abdomen, and ventrodorsal radiography indicated masses with mild opacity. Ultrasonography examination affirmed a hypoechoic mass infiltrating the duodenum. Gastrointestinal system contrast radiography suggested a narrowing of the lumen at the level of the duodenum (Figure 1a-1b). The patient was operated on the mass close to the duodenum, and the other mass, thought to be a mesenteric lymph node, was also removed. The patient was monitored for thoracal and abdominal metastasis for three months, and no pathological findings were observed.

The tumors consisted of two pieces with dimensions of 6.1×3.7×2.3 cm and 3.2×2×1.7 cm (Figure 2a). Histological examination of the tumor revealed that oval to the vesicular structure of the nucleus, spindle-shaped eosinophilic cytoplasm, and prominent nucleoli (Figure 3a). Mitotic activity increased significantly (5-6 mitosis at ×400 magnification), and binucleated cells were observed. There were large necrotic areas surrounded by inflammatory cells. The large mass invaded the intestinal serosa and mucosa, and cut surfaces had white-yellow colour and a solid appearance with medium-hard consistency (Figure 2b). After routine histopathological procedures, the masses were cut with 4 μm thickness and stained

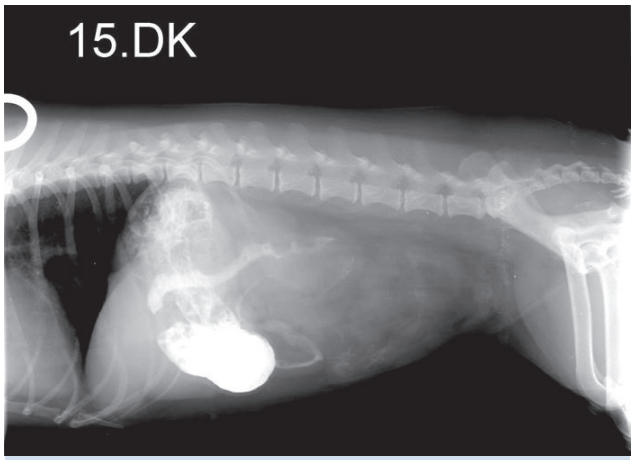

Figure 1a: Decreased transition of contrast medium to duodenum 15 minutes after instillation. Laterolateral view

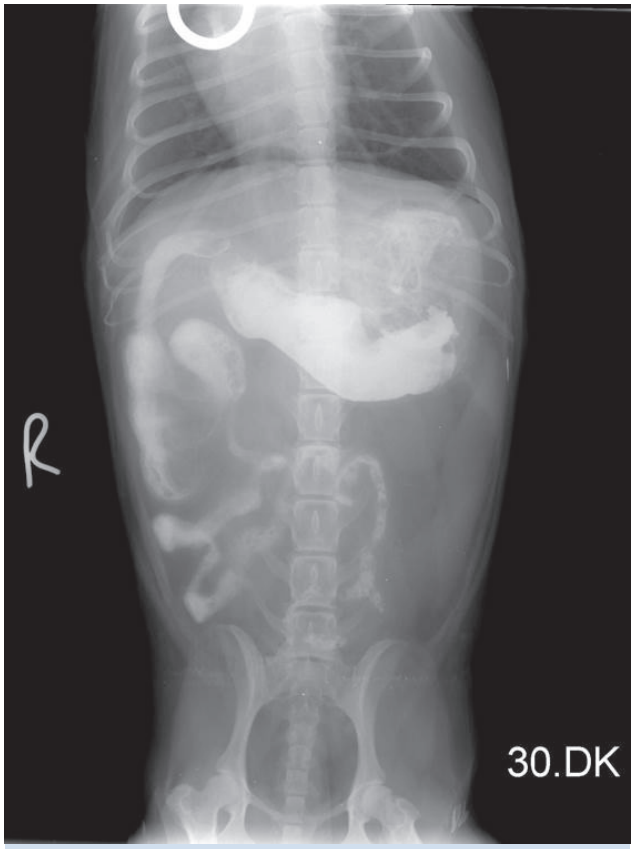

Figure 1b: Decreased transition of contrast medium to duodenum to duodenum after 30 minutes. Ventrodorsal view

immunohistochemically with vimentin and c-KIT antibody (vimentin, anti-mouse sc-6260, Santa-Cruz, USA; CD117, anti-rabbit RB-9038-R1, Freemont, CA). Four μm sections were cut from 4% paraformaldehyde-fixed, paraffin-embedded tissues onto positively charged slides. After deparaffinization in xylene, slides were rehydrated through graded alcohol and rinsed in distilled water. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide in methanol. Samples were boiled in citrate buffer (pH 6.0) in a microwave for 10 min x 600 watts for antigen retrieval. After protein blocking, slides were incubated with the primary antibodies and later with a horseradish peroxidase polymer using 3, 3'-diaminobenzidine tetrahydrochloride (DAB) kit protocol (Ultra Large Volume, Thermo Fisher, United Kingdom). Slides were counterstained with Mayer's hematoxylin and examined under a light microscope. The tumoral cells had intracytoplasmic positivity with vimentin and c-KIT antibodies (Figure 3b-3c).

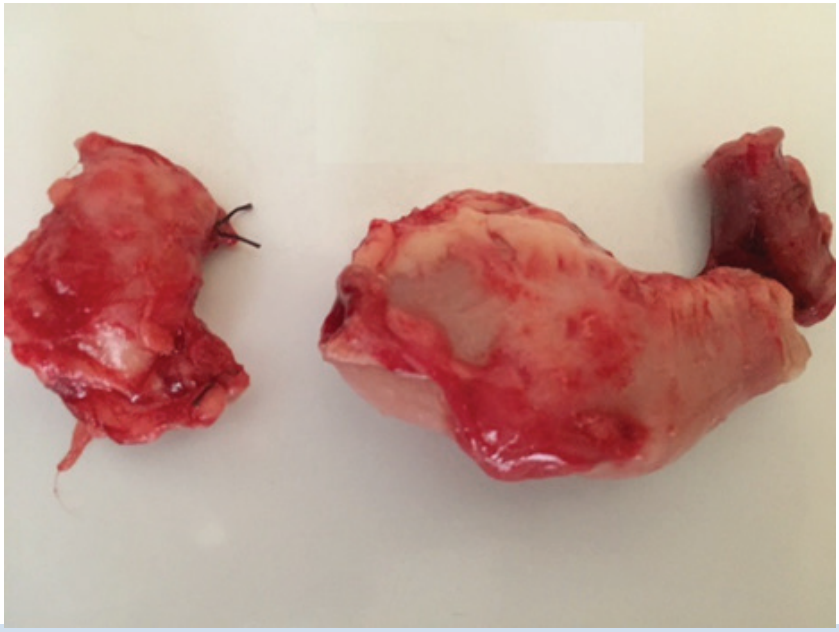

Figure 2a: Two tumoral masses from small intestine (duodenum).

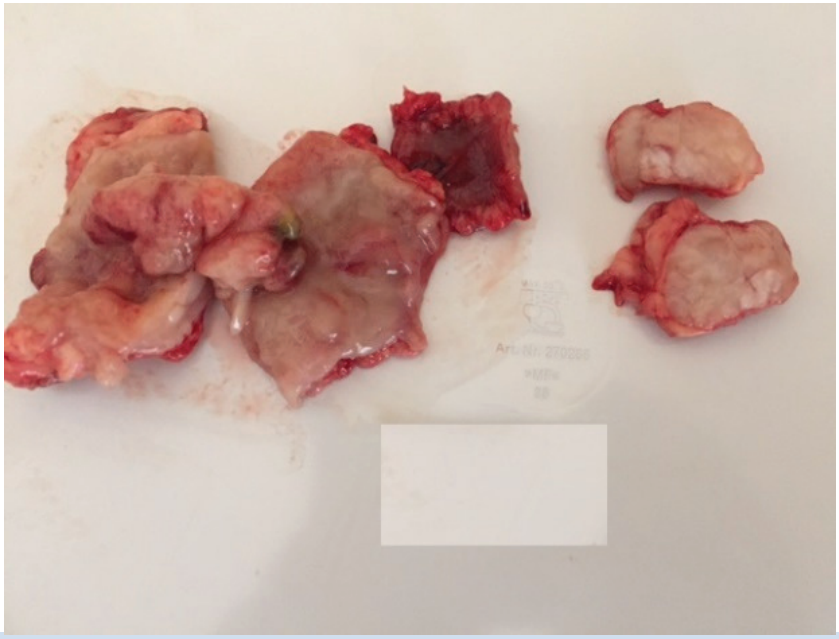

Figure 2b: Cross section of tumoral masses.

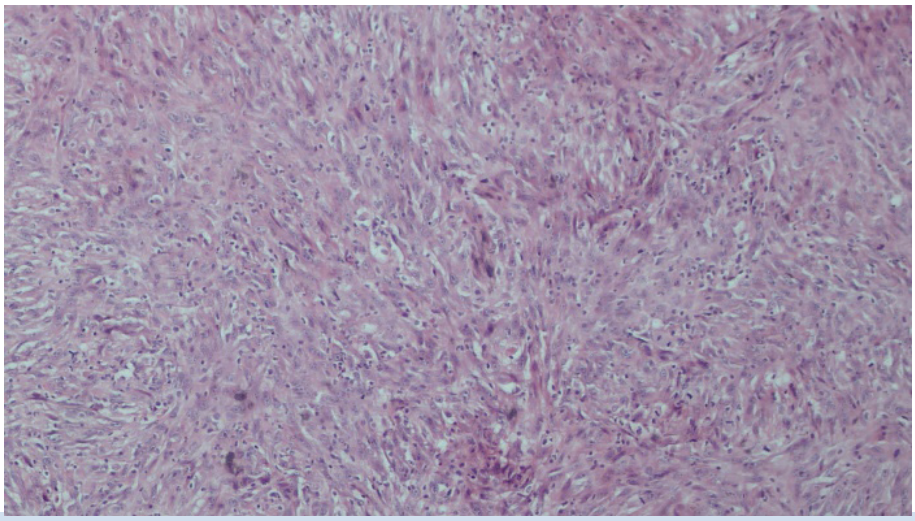

Figure 3a: Spindle shaped tumor cells. H&E, ×4 original magnification.

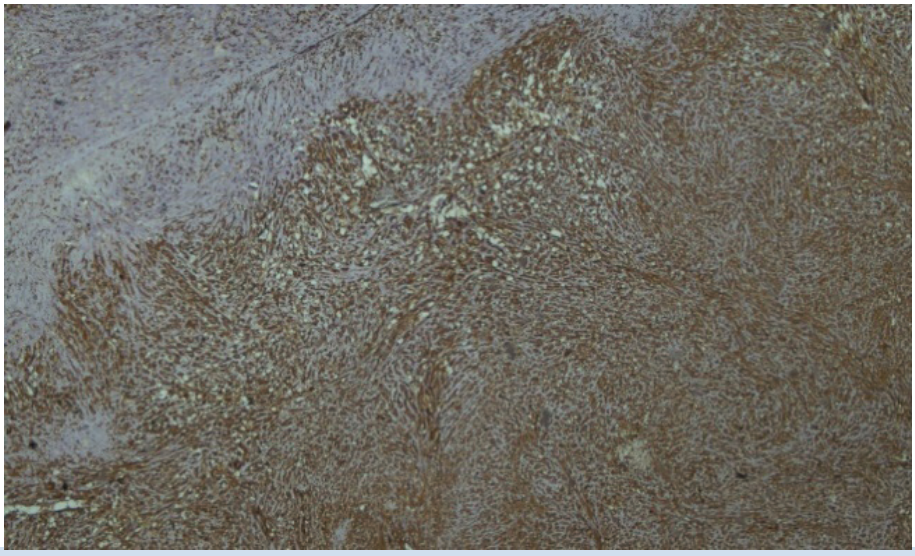

Figure 3b: CD 117(c-KIT) positive tumoral Cajal cells Streptavidin ABC, DAB, ×4 original magnification

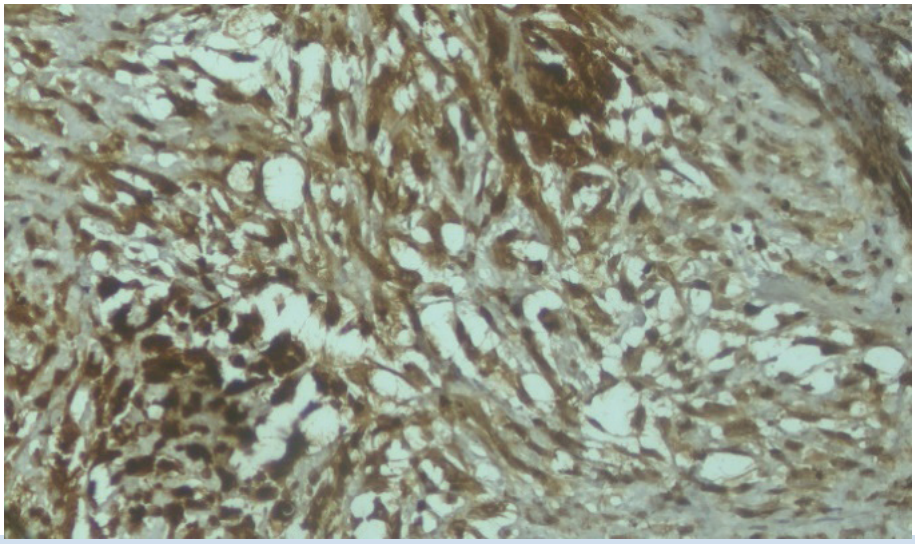

Figure 3c: Vimentin positive tumor cells Streptavidin ABC, DAB, ×10 original magnification.

RESULTS AND DISCUSSION

GISTs are rare mesenchymal tumors of the digestive system in dogs (Girard-Luc et al., 2010). The origin of the tumor is Cajal cells and a network system that coordinates the peristaltic movement of the digestive system (Guzel Cay, 2006; Suwa and Shimoda, 2017). In dogs, GISTs are most found in the large intestine, cecum, colon, and rectum (48-67%), small intestine (29-30%), and stomach (0-19%) (Suwa and Shimoda, 2017). These tumors generally are seen radiographically as masses that are narrowing or obstructing the intestinal lumen (Avci et al., 2012). The vast majority of GISTs arise from the submucosa or muscular layer of the intestine. They can be separated by borders, grow with expansion, and sometimes create exophytic nodules on the serosal surface. The mucosa on the tumor is usually intact but may become ulcerated (Maxie, 2016). It is reported that the transmural spread is more frequent, and the tumor is seen in the mucosa (Meuten, 2002). Invasions of tumor to mucosa, submucosa and serosa have been reported (Bettini et al., 2003). In this case, it was observed that the tumors narrowed the intestinal passage radiographically. At the macroscopical examination, the masses appear solid and invaded in serosa.

However, the spindle cell pattern is mainly seen in dogs. It is composed of spindle cells with a basophilic cytoplasm with spindle or oval nuclei, supported by anaphyous, intense connective tissue stroma and usually arranged as fascicular, loosening to dense, with no capsule (Bettini et al., 2003; Gillespie et al., 2011; Hayes et al., 2013; Maxie, 2016). One study observed that the cell shapes in which the tumoral masses showed solid were spindle-shaped, rounded, and polygonal (Girard-Luc et al., 2010). It has been noted that the cytoplasm varies and shows an eosinophilic structure ranging from light to dark pink. It has been reported that the core structure is in the form of hyperchromatic, long to round, sometimes in blanket or star form, and some areas, multinucleated bizarre giant cells are observed, and in general, pleomorphism (anisocytosis and anisokaryosis) is dominant (LaRock and Ginn, 1997; Bettini et al., 2003; Kumagai et al., 2003; Hayes et al., 2013; Maxie, 2016). Tumoral nuclei are single and unclear (LaRock and Ginn, 1997; Hayes et al., 2013), and the tumor cells are separated by collagen fibers individually. Mitotic figures counted in 10× high-magnification fields showed variable characteristics, and their numbers ranged from 4 to 80 (Bettini et al., 2003; Kumagai et al., 2003; Gillespie et al., 2011; Hayes et al., 2013; Maxie, 2016). Tumors have generally shown coagulation necrosis areas, as well as bleeding and neutrophil leukocytes, including lymphocytes, iron-laden macrophages, and eosinophilic inflammatory infiltrations (Bettini et al., 2003; Kumagai et al., 2003; Hayes et al., 2013; Maxie, 2016). Our study has shown histologically bizarre giant cells, pleomorphism, and increased mitotic figures. These findings were found to be compatible with the results of other studies.

Intestinal tumors include leiomyoma, leiomyosarcoma, GIST, hemangiosarcoma, nerve sheath tumors, fibroma, fibrosarcoma, osteosarcoma, and lipoma. It is recommended that (Maxie, 2016) tumors previously considered leiomyoma and leiomyosarcoma should be reviewed and that immunohistochemistry can be a valuable tool in differentiation (Maxie, 2016). In immunohistochemical staining, Leiomyosarcomas do not express c-KIT but react positively with smooth muscle actin and desmin. Liver, mesenteric lymph node, and omentum metastases are observed in dogs with GIST (Meuten, 2002; Hayes et al., 2013; Hobbs et al., 2015). The average life expectancy for dogs with GIST is reported to be 37 months (Hobbs et al., 2015). Our study suspected fibrosarcoma due to histological staining; however, immunohistochemical staining was needed because the case was located in the intestinal mucosa, and the clinical findings were consistent with the GIST findings. C-KIT positive staining with vimentin due to immunohistochemical staining changed our diagnosis from fibrosarcoma to GIST.

KIT is a tyrosine kinase receptor protein encoded by the c-KIT gene and has an essential role in the proliferation and differentiation of many different types of cells, including interstitial Cajal cells (Meuten, 2002; Hanazono et al., 2013). GISTs are defined by the expression of KIT in neoplastic cells, and this positivity is the gold standard for GIST diagnosis in dogs (Meuten, 2002; Dailey et al., 2015). KIT-positive gastrointestinal tumors have been reported in dogs, horses, Spanish mountain goats, ferrets, primates, and rats (Kumagai et al., 2003; Hayes et al., 2013; Dailey et al., 2015; Suwa and Shimoda, 2017). c-KIT staining is one of the immunohistochemical stainings that must be included in the differential diagnosis of intestinal mucosa tumors.

In conclusion, in this case, macroscopical, histological, and immunohistochemical (c-KIT positive) examinations of the intestinal mass of a nine-year-old female Terrier dog were compatible with GIST. GIST

has been encountered more frequently in dogs in recent years, and this tumor cannot be ignored.

CONFLICT OF INTEREST

None declared.

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