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**Case Report Title**

Incidental diagnosis of a spindle cell type gastrointestinal stromal tumor in a dog with ethylene glycol intoxication

**Running header title**

Spindle gastrointestinal stromal tumor in a dog

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**ABSTRACT**

A 6-year-old castrated male American Pit Bull Terrier dog was presented for evaluation of acute onset of tonic-clonic seizures, anorexia, and vomiting. On physical examination, neurologic signs, such as generalized proprioceptive ataxia, salivation, circling to the right, and absent patellar reflexes bilaterally, were noted. A complete blood cell count revealed mild hemoconcentration and an inflammatory leukogram, while a chemistry panel showed severe azotemia, marked hypochloremia, and a severe titrational metabolic acidosis, suggesting a possible ethylene glycol intoxication. However, an irregularly round, small mass was identified in the large intestine on abdominal ultrasound. Additionally, bilateral hyperechoic renal cortices with medullary rim sign were suggestive of acute nephritis or tubular necrosis. The cytologic evaluation of a fine-needle aspiration biopsy of the abdominal mass revealed a large population of mesenchymal cells, suggesting the presence of neoplasia. Due to the worsening of symptoms, the dog was humanely euthanized. Necropsy confirmed ethylene glycol intoxication, and the incidental finding of a neoplastic intestinal mass was diagnosed as spindle cell sarcoma. Immunohistochemical staining showed strong, diffuse positivity for CD117, smooth muscle actin, and S-100, indicating the final diagnosis of a spindle cell type gastrointestinal stromal tumor (GIST). This report briefly discusses the classifications of nonlymphoid, nonangiogenic intestinal mesenchymal tumors (NIMTs), characteristics of GISTs, and the importance of the immunohistochemical classification of mesenchymal tumors of the gastrointestinal tract.

**Keywords:** canine, CD117, cytology, GIST, immunohistochemistry, neoplasia, NIMT

## 1. CASE PRESENTATION

A 6-year-old castrated male American Pit Bull Terrier dog weighing 36.8 kg was presented to Purdue University Veterinary Teaching Hospital (PUVTH) emergency service to evaluate an acute onset of tonic-clonic seizures; five episodes occurred in approximately five hours previous to presentation. The owner reported that the dog appeared uncoordinated and running into objects for four days, had not eaten for two days, and vomited water and a greenish material two days before presentation. The owner speculated the possibility of ivermectin or bromethalin intoxication (the dog ate horse manure after the horses were dewormed, and rat baits were present around the house, respectively).

On physical examination, the dog was panting, tachycardic (144 bpm), and with dull mentation. Mild to moderate generalized proprioceptive ataxia, salivation, circling to the right, and absent patellar reflex bilaterally were noted. Shortly after being admitted, the patient had two other episodes of tonic-clonic seizures medically managed. The complete blood cell count (Advia 2120, Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA) revealed a mild erythrocytosis (hematocrit 58.1%, reference interval [RI] 37 – 55; hemoglobin 20.7 g/dL, RI 12 – 18) and leukocytosis characterized by mild neutrophilia and moderate monocytosis (white blood cell count 17900/µL, RI 6000 – 17000; neutrophils 13000/µL, RI 3000 – 12,000; monocytes 2510/µL, RI 150 – 1350; and lymphocytes 1400/uL, RI 1000 - 5000). The chemistry panel (Vitros 5,1 FS Chemistry System, Ortho-Clinical Diagnostics, Raritan, NJ, USA) showed severe azotemia (urea nitrogen 97 mg/dL, RI 7 – 32; creatinine 10.6 mg/dL, RI 0.5 – 1.5), marked hypocalcemia (7.2 mg/dL, RI 9.7 – 12.3; ionized calcium was 0.73 mmol/L, RI 1.12 – 1.40), marked hypochloremia (corrected chloride 93 mmol/L, RI 105 – 117), and a markedly high anion gap (39.7 mmol/L, RI 9 – 18). Additionally, ALT (134 IU/L, RI 3 – 69), amylase (3021 IU/L, RI 378 – 1033), and lipase (1905 IU/L, RI 104 – 1753) had increased activities. Other parameters, such as phosphorus (7.8 mg/dL, RI 2.2 – 7.9), sodium (144 mmol/L, RI 138 – 148), total $CO_2$ (14 mmol/L, RI 9 – 18), serum total protein (6.7 g/dL, RI 4.8 – 6.9), and albumin (3.9 g/dL, RI 2.3 – 3.9), were within reference intervals.

An ill-defined soft tissue mass within the mid-abdomen overlaying the intestines and colon was noted on the abdominal radiographs. The mass was defined as irregularly round on ultrasonographic evaluation,

measuring 4.8 x 2.5 cm, with only a small craniodorsal area that was vascularized. The jejunal lymph nodes were mildly enlarged and diffusely hypoechoic. Moreover, bilateral hyperechoic renal cortices with a medullary rim sign were suggestive of acute nephritis or tubular necrosis. The urinary bladder was empty, with mildly thickened walls, indicating probable anuria.

A fine-needle biopsy of the abdominal mass was performed. The specimen was highly cellular on cytologic evaluation. It consisted of large aggregates and numerous bare nuclei in a purplish background with mild blood contamination and moderate amounts of cell-free lipid (Figure 1). Some of the cells were associated with variable amounts of pink, amorphous, extracellular matrix. Rare intact cells were round to spindle to stellate in shape, with indistinct borders. The cytoplasm was mildly basophilic and occasionally contained a few colorless pinpoint vacuoles. One round to oval to elongated nucleus with a variable chromatin pattern, and one to two occasionally round and prominent nucleoli, were observed (Figure 2). There was no evidence of significant inflammation, and no infectious agents were identified. The cytologic impression was neoplasia, likely of mesenchymal origin, with a minor possibility of neuroendocrine origin based on the presence of bare nuclei.

Based on the worsening depression and anuria despite more than six hours of high-rate fluids (90 mL/kg per day), the owner elected humane euthanasia. Necropsy was performed due to a concern for ethylene glycol intoxication and the incidental finding of a neoplastic intestinal mass.

Necropsy revealed tubular necrosis with the presence of intratubular oxalate crystals, consistent with ethylene glycol toxicity. The abdominal mass was unencapsulated, poorly demarcated, densely cellular, arising from the cecal wall (Figure 3). It was composed of spindle cells arranged in interlacing streams and bundles on fine fibrovascular stroma. The neoplastic cells had indistinct borders, a small amount of eosinophilic fibrillar cytoplasm, and an oval hypochromatic nucleus with variably distinct nucleoli. Anisocytosis and anisokaryosis were overall mild, and focal areas with increased numbers of pleomorphic cells were present. There were 1-3 mitotic figures per 400x high power fields. Multifocal areas of necrosis were present. The morphologic diagnosis was spindle cell sarcoma, with gastrointestinal stromal tumor (GIST) and leiomyosarcoma being the two primary differential diagnoses. Immunohistochemical staining

showed strong, diffuse positivity for CD117, smooth muscle actin (SMA), and S-100, indicating the final diagnosis of GIST (Figure 3 C).

## 2. DISCUSSION

This is a case of an incidental finding of a gastrointestinal stromal tumor (GIST) in an adult dog that presented to PUVTH due to symptoms associated with an acute ethylene glycol intoxication. Ethylene glycol toxicity was not suspected by the owners or during anamnesis. The presence of significant azotemia in association with hypocalcemia and severe titrational metabolic acidosis, indicated by the markedly high anion gap, however, was highly suggestive of ethylene glycol intoxication[1], which was confirmed on histopathologic evaluation of the dog's kidneys. The remaining alterations in the patient's chemistry panel were likely related to vomiting, decreased glomerular filtration rate, and mild hepatocellular injury.

Intestinal tumors in dogs are rare, representing less than 1% of all canine tumors. Although no recent surveys are available, lymphoma, adenocarcinoma, and nonlymphoid mesenchymal tumors appear to be the most frequent gastrointestinal neoplasms in dogs, with the latter occupying either the second[2] or third[3] place in incidence. The most common intestinal sarcomas reported in dogs are leiomyosarcoma (LMS) and GIST.[2, 3] However, advances in immunodiagnostics have changed the classification of these tumors, and literature searches can be misleading. Currently, due to the morphologic overlap between LMS, GIST, and other intestinal wall tumors on histopathology, the most appropriate nomenclature is nonlymphoid and nonangiogenic intestinal mesenchymal tumor (NIMT) until further immunohistochemistry can specifically classify these neoplasms.[2] Indeed, some studies conducted before the use of CD117 as a marker of GIST used the terms GIST and NIMT interchangeably.[4, 5]

The NIMTs are a group of neoplasms of spindle cells arising from any cell in the intestinal walls: smooth myocytes, fibroblasts, adipocytes, neural cells, and interstitial cells of Cajal. Intestinal cells of Cajal are part of the gastrointestinal pacemaker system, present in the myoenteric plexus and the inner and outer tunica muscularis. GISTs are derived from these cells.[2, 6] In dogs, GISTs can occur in any part

of the GI tract, both in the small and large intestines, with a mildly higher incidence in the cecum (Table 1), while LMS more frequently occurs in the small intestines and stomach (Table 2).[6-12]

Histologically, the differentiation of leiomyoma, LMS, and GIST must be made to select the most appropriate therapeutic modality; the surgical excision of benign neoplasms tends to be curative, while LMS and GIST could benefit from the combination of resection and chemotherapy.[3] Leiomyomas are discrete, non-encapsulated, non-invasive tumors that are rarely necrotic, where a homogeneous population of densely packed spindle cells with eosinophilic cytoplasm and cigar-shaped nuclei are identified. Fascicles often form a herringbone appearance. Compared with leiomyomas, leiomyosarcomas are frequently invasive and have variable histologic features from well-differentiated, morphologically normal smooth muscle cells to highly pleomorphic spindle to round cells, often having high mitotic counts, evidence of invasion, and necrosis of common areas. The GISTs can be subdivided into four histologic patterns: spindle, epithelioid, myxoid, and fascicular, with only two former ones identified in dogs. Spindle GISTs are most frequent and morphologically indistinct from LMS. In these cases, the tumors should be classified as NIMT, and immunohistochemistry should be recommended.[2]

The cytologic distinction between LMS and GIST is likely not possible. If well-differentiated, those tumors would also be indistinct from leiomyomas and other NIMTs. To our knowledge, there are no descriptions of possible cytologic differences between the spindle and epithelioid GISTs in veterinary medicine, although we could speculate that the latter might display certain epithelial characteristics (eg, polygonal-shaped cells, cohesiveness, acinar-like formation, rosetting, bare nuclei).[13] Given the level of cellular detail observed on cytology, the diagnosis and differentiation between intestinal round cell tumors (eg, lymphoma, mast cell tumors), epithelial, and mesenchymal tumors are frequently possible when the specimen is representative of the lesion. However, determining the cell of origin in carcinomas and sarcomas is commonly not possible, and histopathology and immunodiagnostics remain essential for further characterization.

On immunohistochemistry, canine GISTs are often positive for CD117 and DOG1 (discovered on gastrointestinal tumors protein 1), while these tumors are variably positive for SMA, desmin, CD34,

neuron-specific enolase (NSE), S-100, and PGP 9.5. LMS tumors are negative for CD117, DOG1, and CD34, are consistently positive for SMA and/or desmin, and variably positive for S-100, and PGP 9.5.[7, 9, 11, 12, 14] Cases of GIST confirmed by immunostaining with CD117 have been reported in dogs[6-12, 15], cats[16-18], horses[19, 20], ferrets[21], rats[22], and nonhuman primates.[4, 23]

Canine GISTs often express CD117, the surface receptor tyrosine-protein kinase KIT, encoded by the proto-oncogene *c-KIT*, similarly to hematopoietic stem cells and mast cells.[6, 7] Two primary mutations have been identified in canine GISTs, a single nucleotide polymorphism in exon 9 of *c-KIT* (c.1523A>T, p.Asn508Ile), causing ligand-independent phosphorylation,[24] and variable mutations in exon 11, resulting in deletions, tandem duplications, point mutations, and insertions in the juxtamembrane domain.[7, 10, 25-27]

Clinically, GISTs can present as indolent or malignant in dogs ranging from 1 to 18 years old.[6, 9, 10] Approximately one-fourth of the cases have associated clinical signs, with the remaining being incidental findings[7], as occurred in the case here. A recent study indicated that the median survival time of dogs diagnosed with GIST was 1024 (range 31 – 1456), but approximately one-third of the patients were euthanized due to a sarcoma, and one-third developed metastases. Although all NIMTs could have similar prognoses, the median survival time in dogs with LMSs is approximately half that in dogs with GISTs.[12] Advances in the development of drugs such as toceranib phosphate[28] and imatinib mesylate[24, 26], receptor tyrosine kinase inhibitors, allow for targeted therapy and, possibly, a better prognosis. This example of more specific therapeutic modalities denotes the importance of further classifying NIMTs in CD117-negative (LMS, fibrosarcomas, and others) or CD117-positive tumors (GIST).

We describe an incidental spindle type GIST arising from the cecum wall in a dog after fine-needle aspiration biopsy and cytologic evaluation, later confirmed with histopathology and immunohistochemistry. Although the patient, in this case, did not survive due to the ethylene glycol intoxication, this report describes the pathologic findings and highlights the importance of immunohistochemistry to establish a definitive diagnosis for gastrointestinal mesenchymal tumors. Currently, it is especially valuable since patients could benefit from target-specific chemotherapy, which can improve prognosis and survival. Furthermore, given the high specificity of markers such as CD117

and DOG1 for GIST, these antibodies could potentially be used for immunocytochemistry, allowing a quicker and more reliable diagnosis of GI spindle cell tumors by the combined association of immunostaining and cytomorphology.

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**Table 1.** Anatomic distribution of gastrointestinal stromal tumors (GISTs) in dogs diagnosed based on positive immunostaining for CD117 in selected peer-reviewed publications. The lesions can be distributed in gastric (2.6%), combined small intestine (46.1%), ileocecocolic junction (2.6%), combined large intestine (46.1%), and other locations (2.6%).

| | Stomach | Duodenum | Jejunum | SI | ICCJ | Cecum | Colon | LI | Other | GIST |
|---|---|---|---|---|---|---|---|---|---|---|
| **Bettini et al 2003** | - | 2 | - | - | 1 | 1 | - | - | 1[a] | 5 |
| **Frost et al 2003** | 2 | 1 | 2 | - | - | 4 | 2 | - | - | 11[b] |
| **Russell et al 2007** | 2 | 4 | 4 | - | - | 16 | 2 | - | - | 28 |
| **Gillespie et al. 2011** | - | - | - | 8 | - | - | - | 18 | 1[c] | 27 |
| **Hayes et al 2013** | - | 2 | 2 | 8 | 1 | 5 | - | - | - | 18 |
| **Dailey et al 2015** | - | 2 | 7 | 12 | 2 | 7 | 2 | | 1[d] | 33 |
| **del Alcazar et al.** | - | - | - | 17 | - | 11 | 3 | - | 1[e] | 32 |
| **Total** | 4 | 11 | 15 | 45 | 4 | 44 | 9 | 18 | 4 | 154 |

Abbreviations: ICCJ, ileocecocolic junction; LI, large intestine; SI, small intestine
[a]Tumor site was stated as "intestine". [b]Despite 21 tumors were classified as "GIST" only 11 were positive for CD117. [c]Tumor site was stated as "abdominal mass". [d]Tumor site was stated as "omentum". [e]One tumor was located in the rectum.

**Table 2.** Anatomic distribution of leiomyosarcomas (LMS) in dogs diagnosed based on negative CD117 immunostaining and positive smooth muscle actin and/or desmin immunostaining in a few selected peer-reviewed publications. The lesions are distributed into gastric (23.5%), combined small intestine (67.6%), combined large intestine (5.9%), and other locations (2.9%).

| | Stomach | Duodenum | Jejunum | Ileum | SI | Cecum | Colon | Other | LMS |
|---|---|---|---|---|---|---|---|---|---|
| **Bettini et al 2003** | - | - | 1 | - | - | - | 1 | - | 2 |
| **Frost et al 2003** | - | - | - | - | - | 1 | 1 | - | 2 |
| **Russell et al 2007** | 3 | - | 5 | 1 | - | - | 1 | - | 10 |
| **Gillespie et al. 2011** | 7 | - | - | - | 6 | - | - | - | 13 |
| **Hayes et al 2013** | - | - | 9 | 1 | 1 | - | - | 1[a] | 12 |
| **Dailey et al 2015** | - | 3 | 4 | - | 8 | - | - | - | 15 |
| **del Alcazar et al 2021** | 6 | - | - | - | 7 | - | - | 1[b] | 14 |
| **Total** | 16 | 3 | 19 | 2 | 22 | 1 | 3 | 2 | 68 |

Abbreviation: SI, small intestine
[a]Tumor site was stated as "unknown". [b]One tumor was located in the rectum.

**Figure 1.** The cytologic specimen of the abdominal mass aspirate is highly cellular, consisting of several spindle cells, mostly lysed, in a mildly hemodiluted proteinaceous background. Modified Wright stain, bar = 100 µm.

**Figure 2.** (**A**) A small aggregate of neoplastic, spindle-shaped mesenchymal cells observed in a smear of the abdominal mass from a dog. Modified Wright stain, bar = 50 µm. (**B**) The cells had basophilic cytoplasm with occasional vacuolation. A few stellate cells at higher magnification. Modified Wright stain, bar = 10 µm. (**C**) The neoplastic cells were occasionally round. Anisocytosis, anisokaryosis, and nuclear pleomorphism are present. Modified Wright stain, bar = 10 µm.

**Figure 3.** Histologic sections of the abdominal mass from a dog showing the **(A)** densely arranged interlacing streams and bundles of neoplastic cells containing eosinophilic cytoplasm. H&E, bar = 100 µm. **(B)** The neoplastic cells display increased nuclear pleomorphism in multiple focal areas. H&E, bar = 50 µm. **(C)** Immunohistochemical staining with CD117 shows strong, diffuse, intracytoplasmic positivity. 3,3'-Diaminobenzidine (DAB) chromogen counterstained with hematoxylin, bar = 50 µm.