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CASE REPORT

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Probable paraneoplastic leukocytosis in a dog with a gastrointestinal stromal tumor

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Abstract

A 9-year-old female spayed Boston Terrier presented for diagnostic investigation of lethargy, poor appetite, weight loss, and a marked leukocytosis. Significant muscle wasting and a palpable abdominal mass were present on physical examination. Abdominal imaging revealed the mass to be of small intestinal origin; consequently, an intestinal resection and anastomosis were performed without complication. The histopathologic diagnosis was a gastrointestinal stromal tumor, verified by immunohistochemical positivity to CD117 (KIT). Two weeks after discharge, the leukocytosis had resolved. Though the exact molecular mediator of the severe leukocytosis was undetermined, resolution following tumor removal suggests a paraneoplastic cause. To the authors' knowledge, this is the first reported case of probable paraneoplastic leukocytosis secondary to a gastrointestinal stromal tumor in the dog. Gastrointestinal tract imaging should be performed when this uncommon hematologic abnormality is present.

KEYWORDS
CD117 (KIT), dog, gastrointestinal tract, immunohistochemistry, neutrophilia

1 | CASE PRESENTATION

A 9-year-old female spayed Boston Terrier presented to the referring veterinarian for poor appetite, lethargy, and weight loss of a 4-week duration. A complete blood count performed prior to referral (day 1 in Table 1) revealed a moderate macrocytic hypochromic anemia (25%, RI: 36%-60%), thrombocytosis, and severe leukocytosis (81 700/µL, RI: 4000-15 500/µL) characterized by a segmented and band neutrophilia, monocytosis, and basophilia. Treatment with prednisone (0.65 mg/kg, PO, q 12 hours), amoxicillin (32 mg/kg, PO, q 12 hours), and ciprofloxacin (32 mg/kg, PO, q 24 hours) was initiated; however, despite 4 weeks of treatment, clinical signs did not improve. Therefore, the dog was referred to the Virginia-Maryland College of Veterinary Medicine (VMCVM) for further evaluation.

At the time of referral, the dog had pale mucous membranes, a grade III/VI left-sided systolic heart murmur, diffuse muscle wasting, and a palpable abdominal mass. From referring veterinarian evaluation to referral, the dog had lost 20% of its body weight. A marked normocytic, hypochromic anemia (15.3%, RI: 37.3%-61.7%) with mild regeneration (reticulocytes 98 100/µL, RI: <60 000/µL), a mildly decreased reticulocyte hemoglobin concentration, mild thrombocytosis, and a progressive leukocytosis (182 540/µL, RI: 5050-16 760/µL) were present on complete blood count (Day 27 in Table 1; Figure 1). Serum biochemistry revealed a mildly elevated alkaline phosphatase (208 U/L, RI: 8-70 U/L) without hyperbilirubinemia presumed secondary to prednisone administration and hypoalbuminemia (2.0 g/dL, RI: 2.8-3.7 g/dL) compatible with a negative acute phase response and possibly blood loss. Abnormalities on

TABLE 1 Serial complete blood count data from a Boston Terrier with a gastrointestinal stromal tumor and probable paraneoplastic leukocytosis

Variable or analyte	Day 1[a]	RI	Day 27[b]	RI	Day 46[c]	RI	Day 157[b]	RI
White blood cells (/µL)	**81 700**	4000-15 500	**182 540**	5050-16 760	6810	6000-17 000	6390	5050-16 760
Segmented neutrophils (/µL)	**68 628**	2060-10 600	**156 984**	2455-9170	5060	3000-12 000	5290	2455-9170
Band neutrophils (/µL)	**2451**	0-300	**5476**	0	ND	0	0	0
Lymphocytes (/µL)	4085	690-4500	1825	913-3281	1030	1000-4800	**610**	913-3281
Monocytes (/µL)	**4902**	0-840	**16 429**	79-1160	**190**	200-1500	380	79-1160
Eosinophils (/µL)	817	0-1200	1825	0-1900	430	0-800	60	0-1900
Basophils (/µL)	**817**	0-150	0	0	100	0-400	50	0
Platelets ($\times 10^3$/µL)	**687**	170-400	**493**	148-484	**667**	165-500	346	148-484
Red blood cells ($\times 10^6$/µL)	**3.0**	4.8-9.3	**2.3**	5.65-8.87	6.4	5.5-8.5	6.8	5.65-8.87
Hemoglobin (g/dL)	**7.1**	12.1-20.3	**4.7**	13.1-20.5	13.9	12.0-18.0	16.0	13.1-20.5
Hematocrit (%)	**25**	36-60	**15.3**	37.3-61.7	46.5	37.0-55.0	45.1	37.3-61.7
MCV (fL)	**81**	58-79	67.4	61.6-73.5	73	60-77	66.1	61.6-73.5
MCH (pg)	23.5	19-28	**20.7**	21.2-25.9	21.7	19.5-24.5	23.5	21.2-25.9
MCHC (g/dL)	**29**	30-38	**30.7**	32.0-37.9	**29.8**	31-39	35.5	32.0-37.9
Reticulocytes (/µL)	ND	<60 000	**98.1**	<60 000	ND	<60 000	59.3	<60 000
Reticulocyte hemoglobin (pg)	ND	None	**18.6**	None	ND	None	ND	None

Note: Values outside the RIs are bolded.

Abbreviations: ND, not done; None, no RI available.

aHematology performed on an Advia 2120i hematology analyzer (Siemens). Leukocyte counts were confirmed by microscopy.

bHematology was performed on a Sysmex XN-1000 hematology analyzer (Sysmex). Leukocyte counts were confirmed by microscopy.

cHematology was performed on a Vetscan HM5 hematology analyzer (Zoetis). Leukocyte counts were not confirmed by microscopy.

abdominal ultrasonography were an irregular, 6 cm×4 cm circumferential hypoechoic small intestinal mass (suspect jejunal) with loss of wall layering and scant anechoic peritoneal effusion. No intra-abdominal metastatic disease was evident and thoracic radiographs were unremarkable.

Given the severity of the anemia (19%), 90 mL (13 ml/kg) of DEA 1.1-packed red blood cells were administered prior to a humeral bone marrow aspirate on day 28. Cytologic evaluation of the aspirate demonstrated a sample with adequate particles. The particles were hypercellular with a cell to adipose ratio of 90% to 10%, respectively. There was an increased myeloid to erythroid ratio of 8:1. The myeloid lineage cells were increased, with mild left-shifting back to promyelocytes with a notable storage pool and mild toxicity within non-proliferating cells. The erythroid lineage, although decreased, demonstrated no dysplasia or dyscrasia, with infrequent polychromatophils in the background. The megakaryocyte numbers were increased, with five to six for each field at ×10 magnification. Iron stores were significantly decreased. No neoplastic cells or infectious agents were observed (Figure 2). In the context of the day 27 complete blood count, an interpretation of marked myeloid hyperplasia, erythroid hypoplasia, and megakaryocyte hyperplasia was made. The marked myeloid hyperplasia was compatible with increased demand secondary to an inflammatory nidus or paraneoplastic response to a non-hematopoietic neoplasm. The severe anemia was likely multifactorial, with anemia of inflammatory disease considered most probable. In addition, blood loss/iron deficiency from chronic hemorrhage associated with the small intestinal mass was also a possible factor, given the reduced bone marrow iron stores and mild hypochromasia noted in the indices and peripheral blood smear. Furthermore, the decreased reticulocyte hemoglobin value was supportive of iron deficiency anemia since levels <20.9 pg support iron-deficient hematopoiesis with good sensitivity and specificity.[1] However, trends in this value could not be assessed due to subsequent complete blood counts being performed by the referring veterinarian or at a commercial reference laboratory. Interestingly, this patient did not exhibit a microcytosis on any complete blood count, which is a common finding with developed iron deficiency anemia. Finally, the thrombocytosis was presumed a reactive process in association with the marked inflammation, although iron deficiency anemia may also have contributed. A serum ferritin concentration would have been useful in this case but was not performed.

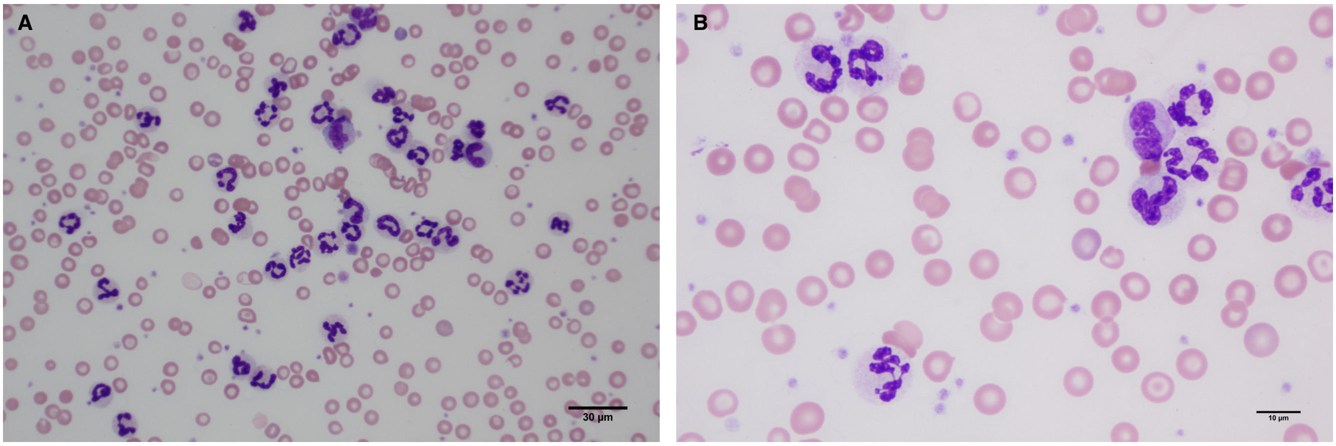

FIGURE 1 Photomicrographs of a blood smear from a Boston Terrier dog with severe leukocytosis and mildly regenerative anemia. A reduced red blood cell mass with slight hypochromasia (noted on indices and slide) and occasional polychromatophils and multiple segmented neutrophils and few hypersegmented forms are shown. There is moderate toxic change characterized by increased cytoplasmic basophilia, Dohle bodies, and vacuolization. Occasional monocytes are shown along with an increased number of platelets. Wright-Giemsa. A, Bar = 30 µm. B, Bar = 10 µm

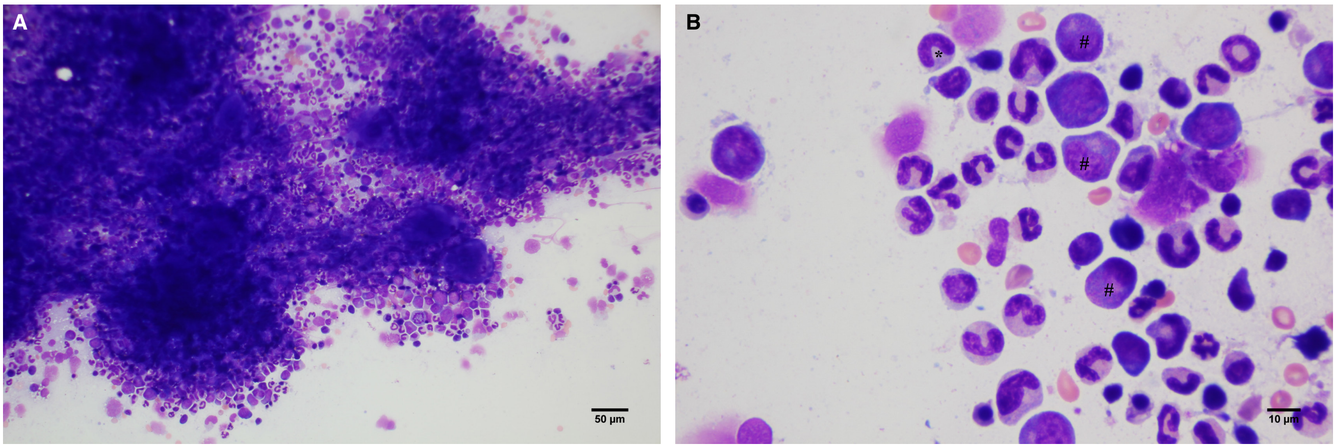

FIGURE 2 Photomicrographs of a bone marrow aspirate from a Boston Terrier dog with severe leukocytosis and mildly regenerative anemia. Wright-Giemsa stain. A, Hypercellular marrow particle with a severely increased M:E ratio (8:1), a blast percentage of 6%, megakaryocytic hyperplasia, and no appreciable iron stores, Bar = 50 µm. B, Mild toxic change in maturing myeloid cells (asterisk, Dohle bodies, and increased cytoplasmic basophilia) and slight left shifting to promyelocytes (pound signs), Bar = 10 µm

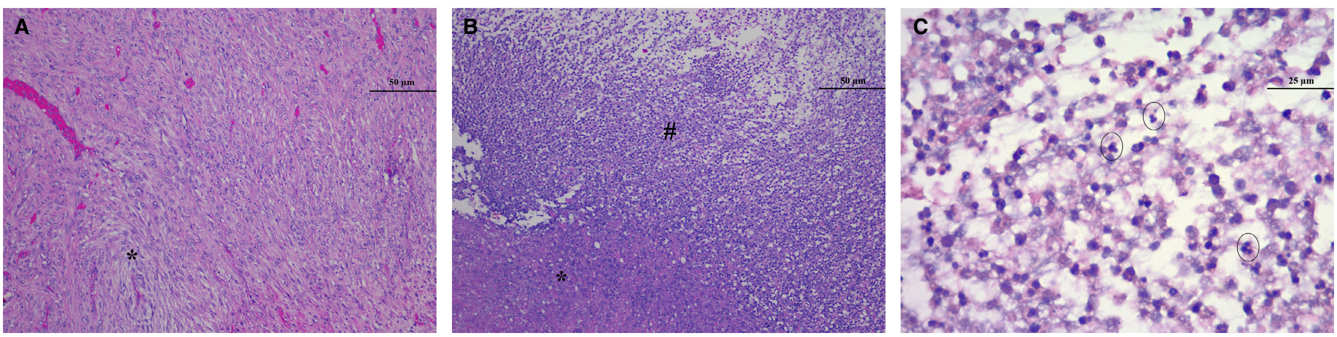

FIGURE 3 Histologic sections of a duodenal mass from a Boston Terrier, H&E stain. A, The mass is composed of spindle cells forming streams and occasional whorls (asterisk) within a moderate amount of collagenous stroma, Bar = 50 µm. B, Extensive necrosis (asterisk) with associated severe neutrophilic inflammation (pound sign) was present in 70% of the examined mass, Bar = 50 µm. C, Degenerate neutrophils (circles) from the inflammatory area in Image B (pound sign) demonstrating shrunken, circular, hyperchromatic nuclei, Bar = 25 µm

Based on suspicion that the small intestinal mass was causing the hematologic abnormalities, the dog underwent an exploratory laparotomy (Day 29). In the duodenum, at the level of the caudal duodenal flexure, was a large mass with extensive adhesions to the surrounding mesentery and omentum. An intestinal resection and anastomosis with 5 cm margins aboral and oral to the mass was performed without complication. Two days after surgery (Day 31), the dog was discharged with a stable packed cell volume (27%).

The excised mass was composed of spindle cells arranged in streams and whorls supported by fibrovascular stroma (Figure 3). Neoplastic spindle cells had poorly distinct cytoplasmic borders with moderate amounts of fibrillar, eosinophilic cytoplasm. Nuclei were round and vesiculate with up to three punctate, basophilic nucleoli. Moderate anisocytosis and anisokaryosis were frequently seen. There were eight mitotic figures in 2.37 mm^2 (the mitotic rate is 8). There were poorly discrete foci of necrosis within the neoplastic cell population, characterized by hypereosinophilic cell cytoplasm with nuclear pyknosis, karyorrhexis, and loss of cell architecture. Degenerate inflammatory cells (neutrophils) were mixed within these foci of necrosis, along with fibrin and various amounts of clear to eosinophilic, proteinaceous edema fluid. There was basophilic stippling consistent with mineralization (dystrophic) in areas of necrosis. Aggregates of degenerate neutrophils, fibrin, and necrotic cellular debris were along the serosal aspect. Necrosis and inflammation affected roughly 70% of the examined sections of the mass (Figure 3). A gastrointestinal stromal tumor was the histopathologic diagnosis. Tumor confirmation was achieved with immunohistochemistry (IHC); neoplastic cells stained positive for CD117 (KIT) and vimentin but negative for smooth muscle actin and desmin (Figure 4).[2–4]

Fifteen days following discharge from the VMCVM, a recheck complete blood count at the referring veterinarian revealed resolution of the leukocytosis (6810/µL, RI: 6000-17 000/µL) and anemia (46.5%, RI: 37%-55%, Day 46 in Table 1). Nearly 4 months later, the dog presented to the VMCVM for recheck staging following tumor removal, and multiple enlarged peripheral lymph nodes were incidentally found. Stage IIIa B-cell lymphoma was diagnosed via fine-needle aspirates of the left submandibular and prescapular lymph nodes. A complete blood count performed prior to chemotherapy initiation revealed a normal white (6390/µL, RI: 5050-16 760/µL) and red blood cell (45.1%, RI: 37.3%-61.7%) count (Day 157 in Table 1). The patient is alive at the time of this writing and in remission from lymphoma.

2 | DISCUSSION

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors arising from the wall of the gastrointestinal (GI) tract.[5] In a previous report, the term GIST incorporated all GI mesenchymal tumors, including leiomyomas (LMs) and leiomyosarcomas (LMSs).[6] However, GISTs are now known to represent a distinct GI mesenchymal tumor type that originates from the interstitial cells of Cajal.[2,5] With H&E staining, differentiation between GISTs and LMs/LMSs is difficult, often leading to a misdiagnosis.[4] Consequently, these tumor types require differentiation through IHC.

CD117 (KIT) is a tyrosine kinase receptor encoded by the proto-oncogene c-KIT. Since canine GISTs exhibit mutations in c-KIT exon 11, such tumors will stain positive for CD117.[2–4,7] This is in contrast to LMs and LMSs which stain negative for CD117 as they do not express KIT.[2–4] The tumor in this report was positive for CD117, identifying it as a GIST. Additionally, it was negative for desmin and smooth muscle actin, also IHC characteristics of a GIST.[2,3] Mutations in c-KIT are presumed to play a role in GIST pathophysiology and may represent a therapeutic target for drugs of the tyrosine kinase inhibitor class.

Differentiation of GISTs and LMs/LMSs appears clinically important. A single retrospective study found a prolonged survival time for GISTs (37.4 months) compared with LMSs (7.8 months) in cases surviving the perioperative period.[4] This data, albeit with small case numbers and not statistically significant, suggests the utility of IHC in distinguishing between these tumor types, as it may alter prognosis. Additional studies, however, with larger case numbers are needed to confirm these findings.

Cancer that causes various symptoms not attributable to direct tumor presence or invasion is labeled a paraneoplastic syndrome.[8] In most cases, the symptoms result from tumor secretion of functional peptides and hormones (eg, parathyroid hormone-related peptide and lymphosarcoma) or immune cross-reactivity between tumor and normal host tissues (eg, thymoma and myasthenia gravis).[8] Removal or control of the tumor results in resolution of the symptoms. Conversely, the symptoms return when the tumor recurs.

Paraneoplastic leukocytosis is a severe neutrophilia accompanied by a left shift (often termed a leukemoid response) caused by tumor cell secretion of a substance that stimulates bone marrow maturation and release of white blood cells.[9] In the dog and cat, tumors causing an established (defined as secretion of a functional peptide or hormone + resolution of the leukocytosis following tumor removal) or probable (defined as resolution of the leukocytosis following tumor removal) paraneoplastic leukocytosis include pulmonary carcinoma (papillary, adenocarcinoma, squamous cell),[10–12] rectal polyp,[13,14] renal carcinoma (tubular, transitional cell),[15–18] mammary carcinoma,[19] and dermal tubular adenocarcinoma.[12] A retrospective study by Weltan et al and a case report describe additional tumors (hemangiosarcoma, lymphoma, mast cell tumor, ovarian carcinoma, mesothelioma, thymoma, Leydig cell tumor,[20] and fibrosarcoma[21]) associated with a moderate to marked leukocytosis, but neither fulfill the previously mentioned established or probable definitions for paraneoplastic leukocytosis. Therefore, no definitive causal relationship can be established for a paraneoplastic leukocytic response to these tumors. To the authors' knowledge, this represents the first reported case of probable paraneoplastic leukocytosis secondary to a GIST in the dog.

One established mechanism for paraneoplastic leukocytosis in humans and companion animals is tumor secretion of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF).[8,12,15,18] Both G-CSF and

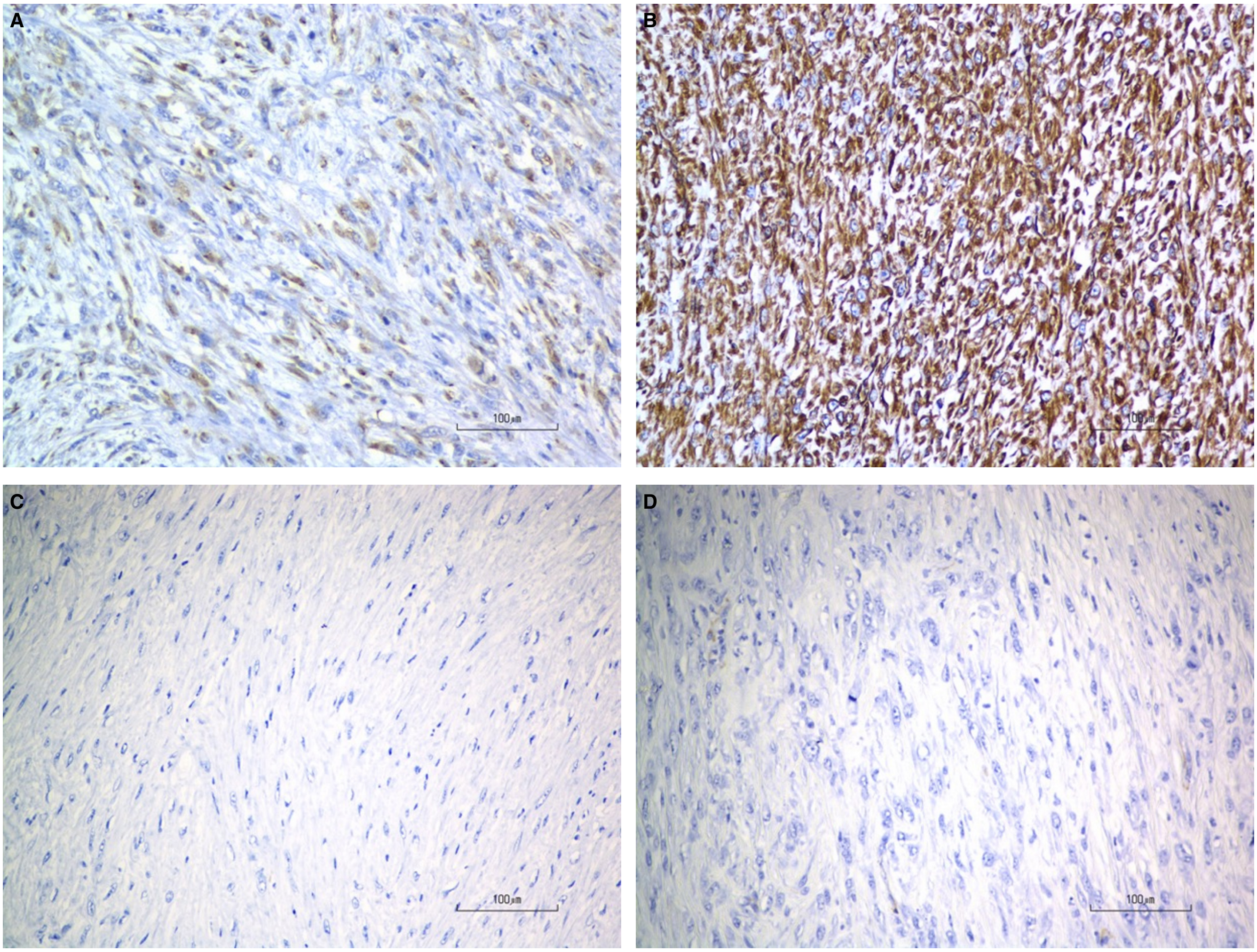

FIGURE 4 Photomicrographs of immunohistochemical staining in histologic sections from a duodenal mass in a Boston Terrier, bars = 100 μm. A, CD117 (KIT) positive. B, Vimentin positive. C, Desmin negative. D, Smooth muscle Actin negative. Findings are consistent with a gastrointestinal stromal tumor (GIST)

GM-CSF are cytokines produced by fibroblasts, endothelial cells, monocytes, and T-lymphocytes in hematopoietic organs (bone marrow, lymph node, spleen) and that can stimulate granulocyte colony-forming unit proliferation, differentiation, and neutrophil release from the bone marrow.[22] An alternative mechanism for paraneoplastic leukocytosis is interleukin (IL)-1, IL-3, and IL-6 secretion by tumor cells, resulting in bone marrow stimulation and release of neutrophils into circulation.[23] In this particular case, the functional peptide or hormone secreted by the tumor was undetermined. Inflammatory IL released by the inflammatory cells found in association with necrosis and its unique microenvironment within the tumor is also plausible but seems less likely given the severity of the leukocytosis.

GISTs in people are linked to numerous paraneoplastic syndromes, including hypercalcemia,[24] nephrotic syndrome,[25,26] acquired hemophilia,[27] pemphigus,[28] hypoglycemia,[29] and consumptive hypothyroidism.[30] Conversely, canine GISTs have been described in association with only a few paraneoplastic syndromes, specifically hypoglycemia[31,32] and hypertrophic osteopathy.[33] With the addition of this case report, GISTs should be added to the differential diagnosis list for a dog with severe leukocytosis. Abdominal imaging in search of this tumor should be performed in cases with this hematologic abnormality.

Prior to surgery, the leukocytosis was severe, persistent, and progressive, as shown by the serial complete blood counts in Table 1. Abnormalities present on the complete blood count on Days 1 and 27 were verified by a clinical pathologist (BT, KZ); thus, the elevated neutrophil and monocyte cell counts were correct. Two complete blood counts following tumor removal revealed normal leukograms, supporting the probable paraneoplastic nature of the leukemoid response.

This is the first reported canine case of a GIST causing probable paraneoplastic leukocytosis. It suggests that a GIST should be added to the neoplastic differentials for a leukemoid response, prompting abdominal imaging as part of the diagnostic workup. Additionally, IHC should be performed on mesenchymal gastrointestinal tumors postoperatively to differentiate GISTs from smooth muscle neoplasms, as this may affect patient prognosis.

DISCLOSURE

The authors have indicated that they have no affiliations or financial involvement with any organization or entity with a financial interest in, or in financial competition with, the subject matter or materials discussed in this article.

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