

Hematologic Abnormalities in the Small Animal Cancer Patient

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KEYWORDS

- Cancer • Hematology • Anemia • Thrombocytopenia
- Coagulopathy

Hematologic abnormalities are frequently encountered in small animal cancer patients, and may result from the direct effects of tumor growth or from paraneoplastic syndromes. Cancer-related hematologic disorders may be characterized by decreases or increases in the absolute numbers of circulating formed elements of the blood, alterations of hemostasis, or plasma protein dyscrasias. Hematologic abnormalities are more common in human cancer patients with hematopoietic malignancies or disseminated solid tumors than in patients with localized solid tumors.^{1,2} The same situation is likely true in small animal cancer patients,^{3,4} although epidemiologic data describing the prevalence of hematologic abnormalities in subpopulations of animals with specific tumor types are generally lacking. Small animal practitioners should be cognizant of the hematologic abnormalities that characterize neoplastic disorders for several reasons: (1) Hematologic abnormalities may be hallmarks of specific cancer types, and their identification may facilitate timely diagnosis. (2) Hematologic abnormalities may serve as biomarkers of response to cancer therapy or remission status. (3) Hematologic abnormalities may require therapy beyond that which is needed to address the underlying cancer. (4) Some hematologic abnormalities may be of prognostic relevance in patients with certain tumor types. This review will summarize the various hematologic abnormalities encountered in small animal cancer patients.

It should be noted from the outset that cancer therapy is one of the most common causes of hematologic alterations in dogs and cats with cancer. Cytotoxic chemotherapy, radiation therapy, and receptor tyrosine kinase inhibitors may all produce significant derangements of hematologic parameters. The hematologic side effects of cancer therapy have been described elsewhere⁵⁻⁷ and will not be covered in this review.

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Table 1
Frequency of anemia at the time of diagnosis of various small animal tumors

Tumor Type	Frequency of Anemia (%)	References
Lymphoma (canine)	30–43	52,73,217–220
Lymphoma (feline)	43–58	139,221–224
Acute leukemia (canine)	87–98	91,225
Acute leukemia (feline)	100	50,51,164
Chronic lymphocytic leukemia (canine)	75–86	91,140
Multiple myeloma (canine)	68	191
Multiple myeloma (feline)	56–69	215,226
Histiocytic sarcoma (canine)		
Localized	0–46	227–229
Disseminated	53–94	38,230,231
Mast cell tumor (canine)		
Localized	5–9	147,232
Systemic	64–70	54,233
Hemangiosarcoma (canine)	28–72	234–237
Hemangiosarcoma (feline)	35–82	238–240

ABNORMAL DECREASES IN CIRCULATING BLOOD CELL CONCENTRATIONS

Anemia

Anemia is one of the most common hematologic abnormalities encountered in human cancer patients. Approximately 30% to 50% of patients with solid tumors and 40% to 70% of patients with hematopoietic tumors are anemic at the time of initiating cancer therapy.^{8–10} The prevalence of anemia in these patient populations generally increases as cancer treatment progresses due to the myelosuppressive effects of cytotoxic chemotherapy and radiotherapy.^{9–11} The true prevalence of anemia in small animal cancer patients is unknown; however, anemia is frequently identified in dogs and cats with a variety of cancers.¹² Anemia is especially common in patients with hematopoietic tumors and vascular tumors such as hemangiosarcoma. The reported frequencies of anemia associated with several small animal tumors at the time of diagnosis are listed in **Table 1**.

Cancer-related anemia may arise through several mechanisms and is often multifactorial in nature. The pathogenic mechanisms common to all anemias, including blood loss, increased red blood cell destruction (hemolysis), and decreased red blood cell production, may each play a role in cancer-related anemia. Tumoral hemorrhage may occur with a variety of cancers and may be acute or chronic in nature. Acute, severe tumoral hemorrhage is often seen with splenic hemangiosarcoma^{13,14} but may also occur in patients with other malignant and benign splenic tumors,^{12,14,15} hepatocellular carcinoma,¹⁶ adrenal tumors,^{17–19} and thyroid carcinoma.²⁰ Chronic, low-grade hemorrhage is seen with mucosal epithelial tumors, such as those of the gastrointestinal tract, nasal cavity, and urinary bladder.²¹ These tumors are often quite friable and prone to bleed following even minimal trauma. Paraneoplastic syndromes may also contribute to hemorrhage in veterinary cancer patients—gastrointestinal ulceration and hemorrhage secondary to gastric hyperacidity are common in dogs and cats with mast cell tumor and gastrinoma. In such cases, excessive tumoral production of histamine and gastrin, respectively, are responsible for increased gastric acidity.^{22–24}

Hemolytic anemias in cancer patients may be immune-mediated or non-immune-mediated. Immune-mediated hemolytic anemia (IMHA) is initiated by the binding of immunoglobulins, complement, or both to the erythrocyte membrane.^{25,26} Erythrocytes coated with immunoglobulin or complement are subsequently recognized and destroyed by phagocytic cells in the spleen and liver (extravascular hemolysis). Binding of complement to the erythrocyte membrane also may also result in disrupted membrane permeability and intravascular hemolysis. Neoplasia is the most commonly identified underlying cause for IMHA in small animals.²⁵ Hematologic malignancies, such as lymphomas and leukemias, are the tumor types most frequently associated with IMHA in both small animals and humans.^{2,12,25} Feline leukemia virus (FeLV) infection may cause IMHA in feline cancer patients.^{27,28} The pathogenesis of IMHA in FeLV-infected cats is not entirely clear, but may result from cross-reactivity of antiviral antibodies with normal erythrocyte membrane antigens, or from an immune response directed against erythrocyte membrane antigens altered by viral infection of erythroid precursors in the bone marrow.^{27,28} Concurrent infection with hemotropic *Mycoplasma* spp may also precipitate IMHA in FeLV-infected cats.^{29,30}

Non-immune-mediated hemolytic anemias may arise in veterinary cancer patients due to microangiopathy, oxidative damage to erythrocytes, or tumor cell erythrophagocytosis. Microangiopathic hemolytic anemia (MAHA) is caused by pathologic changes, such as endothelial cell injury and fibrin deposition, in the systemic microvasculature.^{12,31} These pathologic alterations cause shearing and destruction of erythrocytes as they attempt to traverse arterioles and capillaries. This type of hemolysis is characterized by increased numbers of fragmented erythrocytes (schistocytes) in the peripheral blood. The most common cause of MAHA in veterinary cancer patients is disseminated intravascular coagulation (DIC).¹² However, MAHA may also result from inherent abnormalities in tumor microvasculature, such as incomplete or absent endothelial coverage, tortuosity, variations in vascular caliber, and turbulent blood flow.^{32,33} These vascular abnormalities are most notable in hemangiosarcoma,³³ but likely occur in many other tumor types.

Oxidative injury to red blood cells may also play a role in some cancer-related hemolytic anemias. Morphologic changes in erythrocytes that are characteristic of oxidative injury include eccentrocytosis and Heinz body formation. Eccentrocytes are erythrocytes in which the cell membrane has partially collapsed, causing hemoglobin to shift to one side of the cell, and a pale, eccentrically shaped clear zone to form on the opposite side. Heinz bodies are aggregates of denatured hemoglobin which accumulate along the internal surface of the erythrocyte cell membrane. Heinz bodies are the most common manifestation of oxidative damage to feline erythrocytes, while both Heinz bodies and eccentrocytes may be identified in canine blood following oxidative injury.³⁴ Eccentrocytes and erythrocytes bearing Heinz bodies may be destroyed by intravascular or extravascular hemolysis. Intravascular hemolysis results from a decrease in the deformability and increased fragility of the erythrocyte membrane, predisposing the cell to lysis within capillaries or vascular sinusoids. Extravascular hemolysis results from clustering of membrane band 3 proteins on the external surface of the cell membrane; these band 3 protein clusters are subsequently recognized and bound by autoantibodies and the cell is phagocytosed.³⁵ The overall importance of oxidative damage to cancer-related anemias in small animals is unknown, and other predisposing causes such as hyperthyroidism, diabetes mellitus, and exposure to oxidative toxins (eg, garlic, onions, acetaminophen) should be excluded in patients whose hemograms suggest oxidative erythrocyte injury. However, in a recent retrospective study of 60 dogs with eccentrocytosis, neoplasia was identified as an underlying cause in nine (15%); five of these nine dogs had T-cell

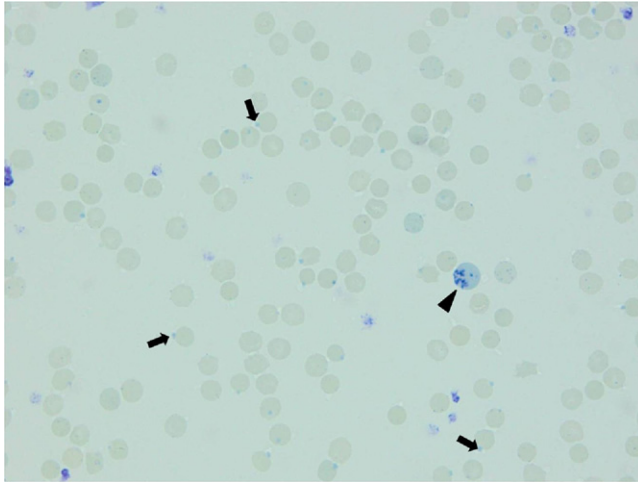


Fig. 1. Peripheral blood smear from a cat with high-grade gastric lymphoma (new methylene blue stain, original magnification $\times 100$). Heinz bodies (*arrows*) are present on the surfaces of many erythrocytes. An aggregate reticulocyte (*arrowhead*) is also visible. The hematocrit was 26% (reference range 30% to 45%). Blood glucose concentration was 88 mg/dL (reference range 75 to 134) and total serum thyroxine concentration was 2.2 $\mu\text{g/dL}$ (reference range 2.4 to 4.6). The cat had no history of exposure to oxidative toxins. Treatment with lomustine, L-asparaginase, and prednisone affected a complete remission of the lymphoma and the cat is alive 3 months later at the time of this report. The anemia resolved with remission of the cancer, although numerous Heinz bodies are persistently noted on blood smear evaluation.

lymphoma.³⁴ In another study of cats with Heinz body anemia, lymphoma was identified as a predisposing cause in 13 of 120 (10.8%) cats, and the association between lymphoma and Heinz body formation was statistically significant.³⁶ Lymphoma in these cats was identified as either gastrointestinal or multicentric in its anatomic distribution. The author has occasionally observed anemia in association with significant Heinz body formation in cats with gastrointestinal lymphoma (**Fig. 1**). An association between lymphoid malignancy and oxidative damage to erythrocytes has also been documented in humans.³⁷

Tumor cell erythrophagocytosis is an uncommon cause of anemia in veterinary cancer patients. This type of anemia is most often identified in dogs with histiocytic sarcoma (**Fig. 2**), particularly of the hemophagocytic subtype.^{38–40} Erythrophagocytosis is believed to be a primary cause for anemia in patients with this cancer, and the anemia is typically markedly regenerative. The mechanism for erythrophagocytosis by this tumor is uncertain, as dogs with hemophagocytic histiocytic sarcoma usually have negative direct antibody (Coomb's) test results.^{38,40} Apart from histiocytic sarcoma, tumoral erythrophagocytosis is rarely observed in veterinary cancers. Erythrophagocytic behavior has been reported in association with canine and feline hepatosplenic lymphoma,^{41,42} canine plasma cell tumors,^{43,44} canine acute megakaryoblastic leukemia,⁴⁵ and feline mast cell tumors.^{46–48} It is noteworthy that not all of the patients in these reports were anemic, and those that were sometimes had other explanations for their anemia, such as bone marrow infiltration by neoplastic cells. Therefore, the importance of erythrophagocytosis as a cause for anemia in patients with tumors other than histiocytic sarcoma is uncertain.

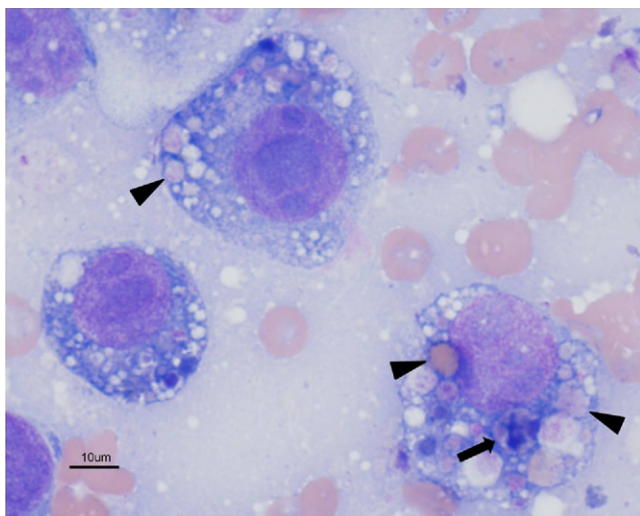


Fig. 2. Fine needle aspirate of a subcutaneous mass from a Golden retriever with disseminated histiocytic sarcoma (Wright's stain, original magnification $\times 100$). The neoplastic histiocytic cells contain numerous phagocytosed erythrocytes (*arrowheads*) in various stages of degradation within phagolysosomes. A phagocytosed neutrophil (*arrow*) is also seen within the neoplastic cell at the bottom right of the image. Erythrophagocytosis is a common cause of anemia in dogs with disseminated histiocytic sarcoma.

Finally, nonregenerative anemias caused by decreased bone marrow production of erythrocytes must be considered. Indeed, hypoproliferative anemias are likely the most common anemias encountered in the veterinary cancer patient, and they may result from direct or indirect effects of cancer upon erythropoiesis. Cancers may directly inhibit bone marrow function by replacement of hematopoietic tissue with neoplastic tissue, a condition referred to as myelophthysis. Myelophthysis occurs with greatest frequency in patients with hematopoietic malignancies which originate in or readily metastasize to the bone marrow, such as acute leukemias,^{49–51} lymphomas,⁵² multiple myeloma,⁵³ mast cell tumor,⁵⁴ and disseminated histiocytic sarcoma.^{38,55} Metastasis of solid tumors to bone marrow is well-documented in humans but is only rarely reported in small animal cancer patients.^{56–58}

Indirect inhibition of bone marrow function may result from nutritional deficits of iron, folate, and vitamin B₁₂ (cobalamin). Such deficiencies are frequently identified in anemic human cancer patients,^{1,59,60} and their recognition is of great clinical importance as they may suggest a medical problem that requires attention (eg, chronic gastrointestinal hemorrhage causing iron deficiency anemia) or an anemia that may be correctable with nutritional supplementation. Nutritional deficiencies are infrequently reported to cause anemia in small animal cancer patients, although decreased serum levels of folate and cobalamin have been reported in cats with lymphomas, particularly lymphomas of the gastrointestinal tract.^{61–63} To date, no studies have thoroughly evaluated whether supplementing these nutrients improves anemia or other clinical, hematologic, or biochemical parameters in these cats. Erythropoiesis may also be indirectly inhibited by myelosuppressive hormones elaborated by a tumor; estrogen produced by Sertoli cell tumors (and rarely interstitial cell tumors or seminomas) of the testis and granulosa cell tumors of the ovary may induce severe bone marrow hypoplasia and aplastic anemia.^{64,65}

Perhaps the most important cause of nonregenerative anemia in cancer patients is the anemia of inflammatory disease (AID), also referred to as anemia of chronic disease. The prevalence of AID in human cancer patients is reportedly as high as 77%,⁶⁶ and some authors assert that it is a nearly universal feature of advanced cancer.⁶⁷ It is likely that AID is similarly prevalent in veterinary cancer patients.¹² AID is typically normocytic and normochromic and occurs in the face of normal bone marrow cellularity. It is characterized by inadequate production of erythropoietin (EPO), decreased response of erythroid progenitor cells in the marrow to EPO, shortened red blood cell survival time in circulation, and perturbations of iron storage and metabolism. The pathophysiology of AID is complex—in cancer patients, this disease is driven by inflammatory cytokines, including tumor necrosis factor (TNF)- α , interferon (IFN)- γ , interleukin (IL)-1 β , IL-6, and IL-10, produced by leukocytes in response to the presence of a tumor.^{8,66,68} A crucial downstream effector of these cytokines is hepcidin, a protein produced by the liver under the influence of IL-6. Hepcidin induces the internalization and lysosomal degradation of ferroportin, a membrane-bound protein whose function is to export iron from macrophages, hepatocytes, and duodenal enterocytes into the peripheral blood.^{66,68} Hepcidin also reduces the expression of the divalent metal transporter-1 (DMT1) protein on the apical surface of duodenal enterocytes, reducing intestinal uptake of dietary iron.⁶⁸ These collaborative actions of hepcidin and inflammatory cytokines facilitate iron sequestration within reticuloendothelial cells and hepatocytes, resulting in hypoferrinemia and decreased availability of iron for erythropoiesis.

Anemia is a significant problem in clinical oncology. It contributes to fatigue, poor performance status, and diminished quality of life in human cancer patients. Moreover, anemia is frequently associated with poor treatment outcome and shortened survival times. A large meta-analysis showed that the relative risk of death was increased by 65% in anemic patients relative to nonanemic controls with a variety of cancer types.⁶⁹ The reasons for this phenomenon are unclear; one hypothesized mechanism is that anemia produces or exacerbates intratumoral hypoxia.^{8,60} Cancer therapies that induce cytotoxicity through the generation of oxygen free radicals, such as radiation therapy, doxorubicin, and bleomycin, are less effective in the setting of hypoxia.⁷⁰ Hypoxia slows the progression of cancer cells through the cell cycle, further contributing to resistance to chemotherapy and radiotherapy, which are most active against rapidly dividing cells. Hypoxia also prevents the degradation of the HIF-1 α transcription factor protein, allowing for the upregulation of several genes associated with cancer progression, angiogenesis, and metastasis.^{8,60,70}

Although anemia is highly prevalent and of serious concern in human cancer patients, the optimal treatment of cancer-associated anemia has not been defined. Therapeutic options for anemia include iron supplementation, blood transfusion, and erythropoiesis stimulating agents (ESAs). The most commonly used ESAs are the recombinant human erythropoietins epoetin alfa (Epogen; Procrit) and darbepoetin alfa (Aranesp).⁷¹ ESAs reduce transfusion requirements in anemic cancer patients,^{1,2,8} and may also improve quality of life in patients with symptomatic anemia. Parenteral iron supplementation may enhance the bone marrow response to ESAs.¹⁰ ESA use in cancer patients is controversial, and has been associated with thromboembolic events, development of antibodies to the ESA, increased risk of tumor progression, and shortened survival times.^{8,71} ESAs are only labeled for the treatment of chemotherapy-related anemia, and their benefit in the treatment of AID and other cancer-associated anemias is unproven. The American Society of Clinical Oncology and American Society of Hematology recommend that ESAs be given at the lowest dose possible so as to achieve the lowest blood hemoglobin concentration (in many

cases, approximately 10 g/dL) that allows avoidance of transfusion.⁷¹ Further study is required to determine how best to manage anemia in human cancer patients.

The incidence, prevalence, clinical relevance, and optimal therapy of anemia in veterinary cancer patients are largely undefined. Although the frequency of anemia at the time of diagnosis is reported for several tumor types (see **Table 1**), large-scale studies describing the incidence, prevalence, and etiologies of anemia in dogs and cats with all cancer types have not been published. Furthermore, the effect of anemia on treatment outcome or prognosis for dogs and cats with cancer has not been examined across tumor types. Recent studies have identified anemia as an independent negative predictor of survival in dogs treated for lymphoma^{72,73} and cats treated for nasal lymphoma⁷⁴ and soft tissue sarcoma.⁷⁵ Given the significance of anemia in human oncology, more thorough investigation of the epidemiology, pathogenesis, prognostic relevance, and treatment of anemia in canine and feline cancer patients is warranted.

Thrombocytopenia

Thrombocytopenia is frequently noted in veterinary cancer patients. Up to 36% of untreated canine cancer patients present with thrombocytopenia⁷⁶ and 39% of thrombocytopenic cats are diagnosed with underlying neoplasia.⁷⁷ Thrombocytopenia is especially common in dogs and cats with hematopoietic and vascular tumors.^{32,76-78} The reported frequencies of thrombocytopenia associated with several small animal tumors at the time of diagnosis are listed in **Table 2**. The mechanisms underlying cancer-associated thrombocytopenia include decreased platelet production, increased platelet sequestration, increased platelet destruction, and increased platelet consumption or utilization.

Decreased production of platelets by the bone marrow is often associated with myelophthisis from hematologic malignancies such as lymphomas, acute leukemias, multiple myeloma, and disseminated histiocytic sarcoma. Acute megakaryoblastic

Table 2

Frequency of thrombocytopenia at the time of diagnosis of various small animal tumors

Tumor Type	Frequency of Thrombocytopenia (%)	References
Lymphoma (canine)	22–49	52,217,219,220
Lymphoma (feline)	10–18	222,223
Acute leukemia (canine)	46–90	91,225
Acute leukemia (feline)	92–100	51,164
Chronic lymphocytic leukemia (canine)	15–45	91,140
Multiple myeloma (canine)	33	191
Multiple myeloma (feline)	50	226
Histiocytic sarcoma (canine)		
Localized	0–22	227,229
Disseminated	56–88	38,230
Mast cell tumor (canine)		
Localized	9	147
Systemic	20–36	54,233
Hemangiosarcoma (canine)	25–75	33,234–237
Hemangiosarcoma (feline)	25–33	238,239

leukemia, a neoplastic proliferation of platelet precursors in the bone marrow, may be associated with thrombocytosis, but more commonly produces thrombocytopenia, which is often severe.^{45,79,80} Thrombocytopenia resulting from decreased platelet production may also accompany estrogen-secreting testicular or ovarian tumors; the megakaryocytic lineage appears to be particularly susceptible to estrogen-induced aplasia.^{64,65,79}

Thrombocytopenia secondary to increased platelet sequestration is a feature of splenic and hepatic malignancies, particularly those characterized by diffuse organomegaly. Approximately one third of the body's platelets are stored in the spleen, and any pathologic process resulting in splenomegaly will increase splenic blood pooling and enhance platelet sequestration.⁷⁹ Diffuse hepatosplenomegaly and consequent platelet sequestration may be seen in splenic or multicentric lymphomas and feline mast cell tumors.^{79,81} Platelet sequestration may also occur in highly vascularized neoplasms, such as hemangioma and hemangiosarcoma, of the spleen, liver, and other anatomic sites.^{79,81}

Increased platelet destruction may be immune-mediated or non-immune-mediated in nature. Cancer-associated immune-mediated thrombocytopenia (ITP), like IMHA, is most often associated with hematological malignancies in both humans and small animals. Chronic lymphocytic leukemia (CLL) and B-cell non-Hodgkin's lymphoma are cancers commonly associated with ITP in humans.⁶⁷ In dogs, ITP has been identified in association with lymphoma, multiple myeloma, and histiocytic sarcoma.^{4,82,83} Although less frequent, ITP may also occur in patients with solid tumors.⁸⁴ Non-immune-mediated destruction of platelets most frequently occurs secondary to microangiopathy in cancer patients.^{79,81}

Increased consumption or utilization of platelets is the final, and perhaps most significant, mechanism underlying cancer-related thrombocytopenia. Increased utilization of platelets occurs in patients with chronic low-grade hemorrhage, but should not result in thrombocytopenia until the regenerative capacity of the bone marrow has been exhausted.⁷⁹ Significant thrombocytopenia may also accompany acute, severe hemorrhage, such as that which occurs in patients with ruptured splenic tumors. However, thrombocytopenia associated with acute blood loss is self-limiting, and should resolve shortly after hemorrhage ceases.⁸⁵ In most cases, increased platelet consumption likely results from the hypercoagulable state that is extremely common in cancer patients.⁸⁶ Hypercoagulability may result in clinical thromboembolic disease in some patients, but in other cases it may manifest in more subtle ways. For instance, patients with chronic, compensated DIC may present with only mild thrombocytopenia, while lacking other clinical or clinicopathologic evidence of coagulopathy.⁸⁷ Experimental evidence supports the contention that chronic platelet consumption occurs in veterinary cancer patients. Platelet counts and kinetics in circulation were studied in a series of 52 tumor-bearing and 34 normal dogs.⁸⁸ Tumor-bearing dogs had significantly lower platelet counts than normal dogs, although moderate to severe thrombocytopenia was primarily seen in dogs with splenic or bone marrow disease. The mean survival time of circulating radiolabeled platelets in tumor-bearing dogs (3.5 days) was significantly shorter than that of normal control dogs (5.4 days).⁸⁸ Moreover, platelet survival time decreased in proportion to stage of disease—the mean platelet survival time for dogs with metastatic tumors (3.2 days) was significantly shorter than that for dogs with localized tumors (4.4 days).⁸⁸ Slichter and colleagues⁸⁹ report similar reductions in platelet survival in human cancer patients: platelet survival times in 77 patients with untreated malignancies averaged 2 to 4 days, depending upon type and stage of malignancy, while the mean platelet survival time in normal control patients was 9.5 days. Platelet

survival was shortest (approximately 1 day) in patients with terminal cancer who died within two weeks of study enrollment. Interestingly, patients whose tumors showed a measurable response to therapy experienced corresponding increases in platelet survival.⁸⁹ These experimental observations suggest that a low-grade consumptive coagulopathy (ie, compensated DIC) is common, if not ubiquitous, in cancer patients, and the severity of this process is proportional to the stage of the cancer. Chronic, compensated DIC may therefore be the most common cause for thrombocytopenia in veterinary cancer patients.

It should be noted that thrombocytopenia occurs without an obvious underlying etiology in some cancer patients.^{78,88} In a series of 214 thrombocytopenic dogs with cancer, 61% (130 of 214) had no identifiable explanation for their thrombocytopenia.⁷⁸ However, few dogs in this series were tested for antiplatelet antibodies, and thus ITP may have been underdiagnosed. Moreover, accelerated platelet consumption due to a hypercoagulable state was also likely underdiagnosed in this study, since platelet consumption has been historically challenging to diagnose without cumbersome tests such as radiolabeling studies, as described above. The increasing availability of global tests of coagulation, such as thromboelastography, may facilitate the diagnosis of hypercoagulability and help to identify the etiology of unexplained thrombocytopenia in canine and feline cancer patients. Further discussion of the hypercoagulable state and cancer follows later in this review.

Leukopenia

In the cancer patient, leukopenia is most often characterized by neutropenia.⁴ Myelosuppressive cancer therapy (ie, chemotherapy and radiotherapy) is by far the most common cause of neutropenia in small animal oncology patients.⁴ True cancer-associated neutropenia is less common, and usually is due to myelophthisis caused by hematopoietic malignancies.^{49,51,53,90,91} Neutropenia is common in cats infected with FeLV or cats with late-stage feline immunodeficiency virus (FIV) infection, and in both cases neutropenia is often accompanied by other peripheral cytopenias.^{27,28} Immune-mediated neutropenia may also occur in cancer patients. One report describes four dogs and three cats with untreated solid tumors and neutropenia of unknown origin.⁴ No evidence of myelophthisis was apparent in any animal, and serologic testing for FeLV in all three cats was negative. Remission of the primary tumor resulted in resolution of the neutropenia in all seven animals. This clinical presentation suggests an immune-mediated origin of the neutropenia in these seven animals, although such cases are likely to be rare.

Bicytopenia and Pancytopenia

Bicytopenia is a reduction in the number of cells from two lineages in the blood while pancytopenia is a reduction the number of cells of all lineages. Multilineage cytopenias often result from decreased production of normal cells or increased production of abnormal cells in the bone marrow; thus, bone marrow evaluation is indicated in all cases of bi- or pancytopenia, especially if the cause of the cytopenias is not readily apparent.

Cytopenias in multiple cell lineages often indicate myelophthistic disease in the veterinary cancer patient. Bi- and pancytopenia occur frequently in patients with hematologic cancers, particularly acute leukemias.^{49,51,90,91} Pancytopenia is also reported in dogs with lymphomas, myelodysplastic syndrome (MDS), multiple myeloma, and disseminated histiocytic sarcoma.^{91,92} However, veterinarians treating cancer patients should be aware of etiologies other than myelophthisis for multilineage cytopenias. In a review of 51 pancytopenic dogs, by far the most common

underlying etiology was chemotherapy administration (22 of 51; 43%).⁹² Estrogen-induced bone marrow injury may cause pancytopenia in dogs with Sertoli cell tumors of the testis and granulosa cell tumors of the ovary.^{64,65,92}

ABNORMAL INCREASES IN CIRCULATING BLOOD CELL CONCENTRATIONS

Erythrocytosis

Erythrocytosis is uncommon in veterinary cancer patients. When present, cancer-related erythrocytosis may be due to a primary myeloproliferative disease (ie, polycythemia vera) or may be a paraneoplastic syndrome. Paraneoplastic erythrocytosis is most often reported in dogs and cats with renal tumors.^{93–101} Erythrocytosis associated with renal neoplasia is often attributed to increased serum EPO concentrations, and in some cases,^{94,97} tumoral production of EPO has been documented. However, normal kidney tissue adjacent to a renal tumor may be induced to aberrantly produce EPO as it becomes compressed and hypoxic; this was recently demonstrated using immunohistochemistry in a dog with renal T-cell lymphoma.⁹⁷ Paraneoplastic erythrocytosis has also been reported in dogs with transmissible venereal tumor,¹⁰² nasal fibrosarcoma,¹⁰³ and cecal leiomyosarcoma,¹⁰⁴ with ectopic tumoral production of EPO confirmed in the latter two cases.

Polycythemia vera (PV; also known as primary erythrocytosis) is a rare myeloproliferative disease (MPD) that causes erythrocytosis in dogs and cats.^{105–107} It is characterized by a clonal proliferation of erythroid progenitor cells in the bone marrow, independent of serum EPO concentrations. PV is a diagnosis of exclusion, and distinguishing it from other causes of erythrocytosis is challenging. Patients with PV typically have marked increases in hematocrit (usually >65%), erythrocyte count, and hemoglobin concentration, in the face of normal arterial oxygen saturation.¹⁰⁵ Splenomegaly may also be present, although this is not as common in dogs and cats as it is in humans with PV.¹⁰⁵ Bone marrow is often hypercellular in patients with PV; however, the cellularity may also be normal, and bone marrow evaluation does not reliably differentiate PV from other causes of erythrocytosis. Measurement of serum EPO concentrations is the most reliable method for diagnosing PV in patients with erythrocytosis.^{105,108} EPO concentrations should be low to undetectable in patients with PV, whereas they will be increased in patients with erythrocytosis of nearly all other etiologies.

Because erythrocytosis is uncommonly associated with canine and feline cancers, its identification should prompt a search for other underlying causes. Erythrocytosis may be either relative or absolute. Relative erythrocytosis is caused by a decrease in plasma volume and subsequent hemoconcentration, such as would occur in a dehydrated patient.¹⁰⁸ Transient relative erythrocytosis can also be produced by splenic contraction. Absolute erythrocytosis refers to an increase in a patient's total red blood cell mass. Absolute erythrocytosis may be further characterized as primary or secondary. Primary erythrocytosis is synonymous with polycythemia vera, and has already been discussed. Secondary erythrocytosis is associated with increased production of EPO, which in turn may be appropriate or inappropriate.¹⁰⁸ An appropriate increase in EPO production occurs in response to hypoxemia and is seen in patients that have adapted to high-altitude environments or patients with chronic pulmonary disease, cyanotic heart disease, or hemoglobinopathies. Inappropriate EPO production occurs irrespective of tissue hypoxia, and is associated primarily with renal (and rarely extrarenal) neoplasia, as well as non-neoplastic renal disease.^{108,109}

Thrombocytosis

Although thrombocytosis occurs in up to 60% of human cancer patients,¹¹⁰ it is infrequently documented in association with cancer in the veterinary literature.^{101,111–113} However it is possible that the true incidence of thrombocytosis in veterinary cancer patients is underrecognized or underreported. In one retrospective study of dogs and cats with thrombocytosis, neoplasia was the most commonly diagnosed concurrent disease.¹¹¹

The etiology of thrombocytosis in dogs and cats may be classified as physiologic, reactive, or neoplastic.^{112,114} Physiologic thrombocytosis results from splenic contraction under the influence of epinephrine. Thrombocytosis secondary to splenic contraction is typically transient, lasting only 15 to 30 minutes.¹¹² Physiologic thrombocytosis also occurs in splenectomized patients, since the lack of a spleen eliminates a normal site for sequestration of circulating platelets. Thrombocytosis following splenectomy may be transient or persistent.

Reactive thrombocytosis occurs in response to inflammatory cytokines or hematopoietic growth factors. Cytokines known to stimulate thrombopoiesis include IL-1 α , IL-3, IL-6, and IL-9.¹¹⁴ Thrombopoietin (TPO), produced by the liver and kidney, is the primary thrombopoietic growth factor, although stromal cell-derived factor-1 (SDF-1), stem cell factor, granulocyte-macrophage colony-stimulating factor (GM-CSF), and EPO often act in concert with TPO to stimulate thrombopoiesis.¹¹⁴ Reactive thrombocytosis also occurs in response to iron deficiency and hyperadrenocorticism, although the mechanisms underlying the association between these diseases and thrombocytosis are unclear.¹¹⁴

Both physiologic and reactive thrombocytosis may occur in patients with cancer. Anemic cancer patients with thrombocytosis should be screened for microcytosis and hypochromasia, which may suggest iron deficiency.^{21,115} Thrombocytosis is commonly seen in patients with chronic MPDs, and may result from alterations in the cytokine milieu in the bone marrow microenvironment. Apparent paraneoplastic thrombocytosis has been documented in dogs and cats with a variety of tumors, including lymphomas, malignant melanoma, nasal adenocarcinoma, primary central nervous system tumors, mast cell tumor, mesothelioma, spinal osteosarcoma, primary lung carcinoma, thymoma, intestinal plasma cell tumor, and renal adenocarcinoma.^{101,111–113,115} Thrombocytosis was noted in 18 (46%) of 39 dogs with massive hepatocellular carcinoma in one study.¹¹⁶ It is likely that many of these cases of “paraneoplastic” thrombocytosis are simply examples of reactive thrombocytosis in response to the underlying inflammation induced by a neoplasm, although thrombocytosis due to possible EPO-producing renal tumors was reported in two cats.¹⁰¹

True neoplastic thrombocytosis occurs in essential thrombocythemia (ET), a chronic MPD characterized by persistent thrombocytosis (by definition $\geq 600,000/\mu\text{L}$, and often $>1,000,000/\mu\text{L}$) and clonal proliferation of megakaryocytes in the bone marrow.¹¹⁴ Humans with ET often present with spontaneous hemorrhage or thrombosis, but these clinical signs are uncommon in dogs and cats with the disease.¹¹⁷ Diagnosis of ET is made by excluding other causes of reactive or physiologic thrombocytosis, and by careful assessment of peripheral blood smears and bone marrow cytology and histopathology samples. In particular, acute megakaryoblastic leukemia⁸⁰ and other chronic MPDs,^{118–121} which all may present with thrombocytosis, must be excluded by bone marrow examination. Only a few dogs and cats with ET are reported in the veterinary literature^{122–126}; therefore, more common causes of

thrombocytosis should be given higher consideration in animals presenting with this hematologic abnormality.

Leukocytosis

Leukocytosis attributable to absolute increases in the numbers of any of the leukocyte subsets (granulocytes, lymphocytes, monocytes) in the blood may occur in cancer patients. However, in most cases, leukocytosis in canine and feline cancer patients can be attributed to the etiologies for leukocytosis in any patient⁴; neutrophilic leukocytosis may be attributable to acute or chronic inflammation or tissue necrosis associated with cancer, or may be attributable to stress; lymphocytosis may occur with chronic inflammation or from excitement and epinephrine release; monocytosis may occur with chronic inflammation, tumoral or tissue necrosis, or stress; and eosinophilia or basophilia may be secondary to allergic or parasitic diseases. In general, these pathophysiologic processes should be given primary consideration in any cancer patient with leukocytosis. However, certain types of leukocytosis, which are often paraneoplastic in nature, may be a hallmark of specific malignancies, thereby assisting in timely diagnosis or in assessment of cancer remission status. In other cases, leukocytosis may be of prognostic relevance. These specific examples of cancer-related leukocytosis will be discussed in further detail.

Paraneoplastic neutrophilic leukocytosis is reported in association with adenomatous rectal polyps, renal tumors, pulmonary carcinoma, intestinal T-cell lymphoma, and metastatic fibrosarcoma in dogs,^{115,127-132} and in pulmonary squamous cell carcinoma and dermal tubular adenocarcinoma in cats.^{131,133} Circulating neutrophil counts in these animals were extremely high (range 74,347 to 202,522 cells/ μ L), and the neutrophilia was often accompanied by a left shift, monocytosis, and eosinophilia. Neutrophilic leukocytosis of this magnitude is often referred to as a leukemoid response because it may be challenging to distinguish from chronic myelogenous leukemia (CML). CML is sometimes characterized by a disorderly left shift and the presence of granulocytes having abnormal morphology in the bone marrow. While cytochemical staining may assist in the differentiation of CML from a leukemoid response, in human patients, a distinction between neoplastic versus reactive neutrophilic leukocytosis has not been shown using this procedure.¹³⁴ Leukemoid responses are defined by extreme neutrophilic leukocytosis (neutrophils \geq 50,000 to 100,000 cells/ μ L), usually with a pronounced, but orderly, left shift. They may occur in patients with chronic localized infections (eg, pyometra), *Hepatozoon canis* infection, IMHA, and CD11/CD18 neutrophil protein adhesion deficiency, as well as cancer patients.¹³⁵ Paraneoplastic leukemoid responses are usually attributed to ectopic production of GM-CSF or granulocyte colony-stimulating factor (G-CSF) by a tumor, and tumoral production of these cytokines has been documented in small animal cancer patients.^{131,132} GM-CSF stimulates the proliferation of hematopoietic precursors for the neutrophil, monocyte, and eosinophil lineages,¹³⁶ and this may explain the monocytosis and eosinophilia that can accompany neutrophilic leukocytosis in a leukemoid response. The clinical significance of paraneoplastic leukemoid responses is debatable; some sources claim that they are of little importance, and in many cases a leukemoid response will resolve with appropriate therapy for the underlying cancer. However, two reports^{137,138} show extreme neutrophilic leukocytosis of any etiology to be associated with a high mortality rate. In these two reports, patients with neoplasia were at increased risk of death compared to patients with other diseases.

In addition to neutrophils, increased numbers of lymphocytes, monocytes, eosinophils, and basophils may characterize the leukocytosis seen in cancer patients.

Lymphocytosis occurs primarily in patients with lymphoid malignancies such as lymphomas, acute lymphoblastic leukemia (ALL), and CLL.^{49,50,52,139–142} Indeed, neoplasia is the most common cause of persistent lymphocytosis in dogs and cats.¹⁴³ High-grade lymphomas with circulating lymphocytosis (ie, stage V lymphoma) and ALL are both characterized by large or intermediate size, immature lymphoblasts in circulation, whereas the lymphocytosis in low-grade lymphomas or CLL is characterized by small, mature lymphocytes.¹⁴³ The degree of lymphocytosis in patients with CLL may be considerable (**Fig. 3**), although this disease is often identified incidentally in patients with minimal to no clinical signs. Benign, paraneoplastic lymphocytosis may be observed in dogs and cats with thymomas.^{142,143}

Monocytosis is uncommonly documented in small animal cancer patients, but may occur in patients with MPDs, particularly those of a monocytic lineage.^{144–146} Monocytosis may also be observed in patients with leukemoid responses, as previously noted.

Eosinophilia is also uncommon in veterinary cancer patients and is most often noted in dogs and cats with mast cell tumors^{147–150} and lymphomas,^{116,151–154} particularly T-cell lymphomas. Mast cells produce the eosinophilopoietic cytokine IL-5 as well as eosinophil chemotactic factors,¹⁵⁵ and these likely are responsible for the eosinophilia seen in patients with mast cell tumors. In humans, the production of IL-5 by T-cell lymphomas has been documented,^{116,151,152} and it is hypothesized that this occurs in small animal T-cell lymphomas as well. Paraneoplastic eosinophilia is rare in patients with solid tumors, but has been documented in dogs with oral fibrosarcoma,¹⁵⁶ and mammary carcinoma,¹⁵⁷ and in cats with oral squamous cell carcinoma⁴ and transitional cell carcinoma.¹⁵⁸ Eosinophilic leukemia is a rare chronic MPD characterized by marked peripheral eosinophilia and eosinophil infiltrates in bone marrow and visceral organs.^{159–161} The presence of immature eosinophil precursors in circulation and in tissues helps to distinguish this cancer from benign idiopathic hypereosinophilic syndrome. Eosinophilia, like monocytosis, may be seen in patients with leukemoid responses.

Basophilia is very rarely encountered in veterinary oncology patients. When noted, it usually occurs in dogs and cats with mast cell tumors.^{147,148,150} Basophilia is also occasionally reported in association with chronic MPDs.^{123,124} Rare cases of basophilic leukemia, a chronic MPD characterized by marked basophilia, are reported in dogs and cats.^{120,121,162–164}

Abnormal Cells in Circulation

In addition to perturbations in the circulating numbers of normal blood cells, the hemogram of the veterinary cancer patient may occasionally be characterized by the presence of cells that do not circulate under normal physiologic conditions. This is most apparent, and often striking, in dogs and cats with acute leukemias, MPDs, and MDS.^{49–51,90,119} These diseases are characterized by abnormal proliferation of immature hematopoietic precursor cells in the bone marrow, with subsequent release of these cells into circulation. Other hematopoietic neoplasms affecting the bone marrow, such as lymphoma^{52,141} and, rarely, multiple myeloma⁵³ and histiocytic sarcoma¹⁶⁵ may also present with a leukemic blood profile.

Mast cells may occasionally be seen in the circulation of dogs and cats with mast cell tumors,^{46,48,148} particularly those with visceral or bone marrow metastasis. In health, mast cells are only found in solid organs, and are most numerous in the mucosae of the respiratory and gastrointestinal tracts, where they function as mediators of the innate immune response.¹⁵⁶ The appearance of mast cells in the peripheral blood is always pathologic.¹⁶⁶ However, circulating mastocytosis is not

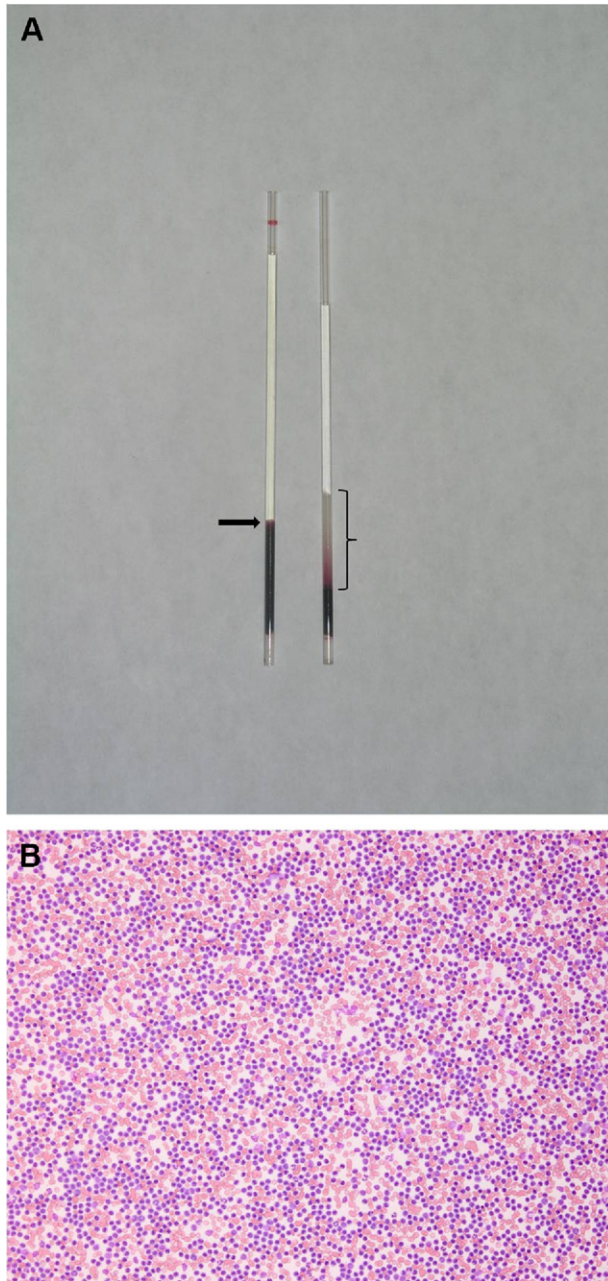


Fig. 3. (A) Spun microhematocrit tubes from a dog with chronic lymphocytic leukemia (*right*) and from a normal dog (*left*). Note the marked discrepancy in the size of the buffy coat of the affected dog (*bracket*) compared to that of the normal dog (*arrow*). (B) Peripheral blood smear from the same dog (Wright's stain, original magnification $\times 20$). The peripheral lymphocyte count was $930,000/\mu\text{L}$. Remarkably, the dog had relatively few clinical signs apart from mild lethargy and inappetance at the time of diagnosis. A partial remission was achieved with chlorambucil and prednisone chemotherapy, but the dog died of acute renal failure 2 months after diagnosis.

specific for mast cell neoplasia, and may occur in patients with acute inflammatory diseases, trauma, regenerative anemia, inflammatory skin disease, and non-mast cell neoplasia.^{167–169} These conditions should be ruled out in a patient with circulating mastocytosis without an apparent mast cell tumor. Moreover, patients with mast cell tumor and circulating mastocytosis should be carefully staged for the presence of visceral or marrow metastasis.

Metarubricytosis, or the presence of nucleated red blood cells (nRBCs) in circulation, is occasionally noted in veterinary cancer patients. Under normal conditions, nRBCs are prevented from entering circulation by the sinusoidal and vascular endothelium of the bone marrow. In highly regenerative anemias, early release of nRBCs may occur in response to accelerated hematopoiesis (appropriate metarubricytosis).¹⁷⁰ Such cases are characterized by marked polychromasia and reticulocytosis. Metarubricytosis in the absence of anemia, or that is disproportionate to the degree of polychromasia/reticulocytosis present, is pathologic (inappropriate metarubricytosis) and is believed to be an indicator of injury to the sinusoidal or vascular endothelium of the bone marrow, allowing premature entrance of nRBCs into the peripheral blood.^{170,171} Inappropriate metarubricytosis may therefore be noted in patients with primary or metastatic bone marrow malignancies, such as leukemias, lymphomas, and other hematopoietic neoplasms.^{51,52,119} If the presence of nRBCs in blood extends to less mature erythroid precursors, including erythroblasts, the possibility of an acute erythroid leukemia should be considered. Metarubricytosis also occurs frequently in patients with hemangiosarcoma,^{14,171,172} although the mechanism behind this is less clear. A regenerative response to tumor-associated hemorrhage is a plausible explanation, although metarubricytosis associated with hemangiosarcoma is often marked (>100 nRBCs/100 white blood cells), and may occur in patients with only mild anemia. Splenic disease may also cause metarubricytosis, as the spleen is responsible for clearing nRBCs inappropriately released into circulation¹⁴; however, metarubricytosis is documented in patients with hemangiosarcoma at extrasplenic locations.^{171,173} Recent findings on the ontogeny of hemangiosarcoma may serve to elucidate the mechanism for metarubricytosis associated with this cancer. Hemangiosarcoma has long been known to express antigens consistent with endothelial cell differentiation (eg, CD31, factor VIII-related antigen).¹⁷⁴ Lamerato-Kozicki and colleagues¹⁷⁵ recently demonstrated that hemangiosarcoma also expresses antigens consistent with early hematopoietic differentiation (eg, CD34, CD45). This suggests the possibility of a bone marrow stem cell niche for this neoplasm, and the proliferation of neoplastic hemangiosarcoma cells in the bone marrow may explain the inappropriate metarubricytosis noted in some patients with this cancer. Gross and microscopic lesions of hemangiosarcoma in the bone marrow are identified at necropsy in some,¹⁷³ but not all,¹⁷¹ affected dogs; however, it is doubtful that complete postmortem examination of the bone marrow occurred in all reported cases. The hematopoietic origin of this cancer is an intriguing hypothesis that merits further investigation.

COAGULOPATHIES IN CANCER PATIENTS

Disorders of coagulation are common in both veterinary and human cancer patients, and both hypocoagulable and hypercoagulable states may occur. In humans, thromboembolic disease associated with hypercoagulability is much more common than bleeding tendencies associated with hypocoagulability.^{110,176} Limited data suggest a similar pattern in dogs and cats with cancer. In a group of 36 dogs with various tumors, 18 (50%) were found to be hypercoagulable (relative to normal control dogs) using tissue factor-activated thromboelastography (TEG).¹⁷⁷ In the same study,

only 6 dogs (17%) were hypocoagulable. However, relatively few large-scale studies detailing the prevalence and types of hemostatic abnormalities in veterinary cancer patients are available. In both small animal and human patients, laboratory evidence of coagulopathy is extremely common, while frank hemorrhage or thromboembolic disease are seen much less frequently. In humans, laboratory evidence of altered hemostasis is present in up to 98% of patients with cancer,¹⁷⁸ although clinically apparent coagulopathies only occur in 15% to 30%.^{110,176,178–180} In a report⁷⁶ describing 100 dogs with untreated tumors, 83% had one or more laboratory abnormalities consistent with altered hemostasis. Dogs with clinical evidence of bleeding were excluded from this report and, in general, dogs and cats with clinically apparent cancer-related coagulopathies are described only in case reports or small case series.^{33,181–187} The pathogenesis and clinical syndromes associated with hypocoagulability and hypercoagulability are described in further detail later. DIC, which may be associated with either hypercoagulability or hypocoagulability, depending on its stage of evolution, shall be considered separately.

Hypocoagulability

Hypocoagulability and associated hemorrhagic diatheses may occur due to decreases in platelet numbers, alterations in platelet function, decreased concentrations or functional alterations of plasma clotting proteins, tumoral production of anticoagulant substances, alterations in plasma viscosity, or combinations of these.¹⁸¹ The etiology and prevalence of cancer-associated thrombocytopenia have already been discussed. Thrombocytopenia associated with decreased platelet function is most commonly seen in association with paraproteinemia in small animal cancer patients. Paraproteinemia occurs in patients with multiple myeloma, Waldenstrom's macroglobulinemia, and lymphomas and leukemias of the B-cell lineage.^{53,181} In these diseases, immunoglobulins or immunoglobulin fragments elaborated by tumor cells coat platelets and decrease their adhesiveness to vascular walls. Immunoglobulin (Ig) A and IgM paraproteinemias are particularly associated with this type of thrombocytopenia.¹⁸¹ Platelet dysfunction may occur in patients with MPDs such as polycythemia vera and essential thrombocythemia.^{110,122} Acquired von Willebrand's disease is an important cause of thrombocytopenia in human cancer patients, particularly those with lymphoid malignancy^{110,181}; however, this disorder has not been documented in veterinary cancer patients.

Numerous qualitative and quantitative alterations in plasma clotting proteins are described in human cancer patients. These include acquired hemophilia A (associated with autoantibodies to factor VIII), isolated clotting factor deficiencies, and production of abnormal or dysfunctional clotting factors.¹¹⁰ Vitamin K deficiency also occurs with some frequency in human cancer patients due to malnutrition, diarrhea, hepatic metastasis or dysfunction, hepatobiliary obstruction, prolonged antibiotic use (which depopulates vitamin K-producing enteric bacteria), and oral anticoagulant therapy.^{110,181} The most common cause of clotting factor dysfunction in veterinary oncology is likely the production of heparin by mast cell tumors.^{181,188} Heparin functions as a cofactor for antithrombin, and the combined activity of these molecules inactivates factor X, preventing the conversion of prothrombin to thrombin.¹⁸⁹ Prolonged bleeding may be encountered following fine needle aspirate, biopsy, or surgical excision of mast cell tumors. Spontaneous hemorrhage may also be observed in some patients (Fig. 4). Only sporadic reports of other clotting factor deficiencies or dysfunction in veterinary cancer patients exist. Prekallikrein deficiency was documented in a dog with renal transitional cell carcinoma¹⁸³ and factor V



Fig. 4. Massive subcutaneous hemorrhage in a golden retriever with a large, recurrent, subcutaneous, high-grade mast cell tumor of the right thoracic wall (not readily apparent in the photograph). The surgical scar corresponding to the site of the original tumor is apparent on the ventral midline. Spontaneous hemorrhage may have resulted from heparin release by the neoplastic mast cells.

deficiency was reported in a dog with nasal adenocarcinoma,¹⁸⁴ although this dog was suspected to have underlying acute DIC.

Hemorrhagic diathesis may also be a consequence of increased blood viscosity. Significant increases in viscosity alter the rheologic properties of blood, leading to sludging in the microvasculature. This in turn causes overdistention and rupture of capillaries, resulting in hemorrhage.^{181,190} Hyperviscosity may also result in hemorrhage by preventing the conversion of fibrinogen to fibrin.¹⁸¹ Hyperviscosity is most commonly seen in patients with extreme increases in plasma protein concentrations secondary to immunoglobulin-producing tumors.^{53,190} Although dysproteinemias are the most often cited cause of hyperviscosity in veterinary cancer patients, it should be recognized that pathologic increases in the absolute numbers of any of the formed elements of the blood may also produce hyperviscosity and subsequent hemorrhage.¹⁹⁰ The hematocrit makes the greatest contribution to blood viscosity, and viscosity rises logarithmically with increases in hematocrit.¹⁹⁰ It is therefore understandable that extreme increases in hematocrit, as may be seen in paraneoplastic erythrocytosis and polycythemia vera,¹⁰⁶ are associated with microvascular hemorrhage. Due to the relative infrequency of leukocytes in the blood relative to erythrocytes, leukocytosis rarely results in hyperviscosity. However, extreme leukocytosis ($>100,000$ cells/ μL), which may occur in patients with leukemias and leukemoid reactions, is associated with hyperviscosity in humans.¹⁹⁰

Hypercoagulability

The association between malignancy and thrombosis has been recognized for nearly 150 years, since Armand Trousseau described a syndrome of migratory venous thromboembolism in patients with gastric carcinoma.¹⁷⁹ Thromboembolic disease is the second-leading cause of death in human cancer patients.¹⁷⁹ The incidence of clinically apparent venous thromboembolism in humans with cancer is 15%,^{180,192}

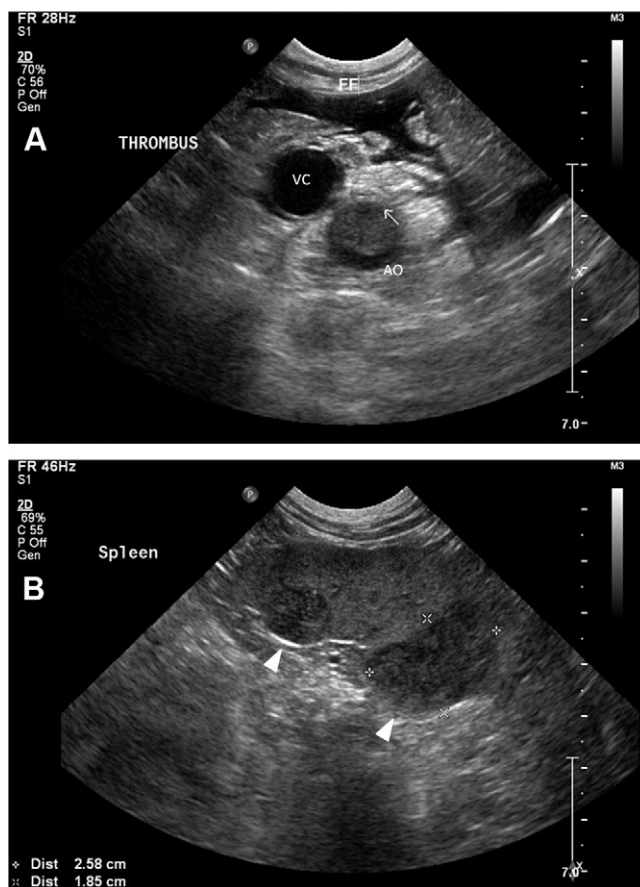


Fig. 5. Ultrasonographic images from a Labrador retriever presented for acute collapse and paraplegia. (A) Transverse images of the caudal abdomen show a large thrombus (*white arrow*) nearly completely occluding the lumen of the aorta (AO). The caudal vena cava (VC) is seen to the left of the aorta. A small amount of free fluid (FF) is seen at the top of the image. Fluid analysis was consistent with a modified transudate, which likely developed as a result of increased arterial hydrostatic pressure. (B) Multiple heteroechoic splenic masses (*arrowheads*) were also identified ultrasonographically. At necropsy a 4-cm thrombus was identified in the caudal abdominal aorta and extending into the external iliac arteries. The splenic masses were confirmed as hemangiosarcoma, and metastases were identified in the lungs, right atrium, and left kidney. Coagulopathies are extremely common in dogs with hemangiosarcoma, and up to 50% present with evidence of DIC.

and thrombosis is detectable in approximately one-half of cancer patients at autopsy.¹⁷⁶ The clinical manifestations of thromboembolic disease in human cancer patients include deep venous thrombosis (DVT), pulmonary thromboembolism (PE), migratory superficial thrombophlebitis (Trousseau's syndrome), nonbacterial thrombotic endocarditis, and DIC. Arterial thromboembolism also occurs in cancer patients (**Fig. 5**) but is less common than venous thrombosis. The incidence of thromboembolic disease in veterinary cancer patients is unknown; however, underlying neoplasia was identified in 3 (27%) of 11 dogs with portal vein thrombosis,¹⁹³ 43 (54%) of 80

dogs with splenic vein thrombosis,¹⁹⁴ and 14 (30%) of 47 dogs with PE¹⁹⁵ in three separate reports. Cancer therefore appears to be a major cause of thromboembolic disease in small animals, and it is reasonable to believe that thromboembolic disease may contribute significantly to morbidity and mortality in small animal cancer patients.

The pathogenesis of thromboembolism in cancer is complex and multifactorial, but may be generally conceptualized in the context of Virchow's classic triad of pathologic conditions necessary for thrombus formation: (1) hemodynamic stasis or perturbations in blood flow, (2) vascular injury or dysfunction, and (3) hypercoagulability of the blood.^{192,196} A major cause for hemodynamic derangement in cancer patients is the morphologic abnormality of tumor vasculature previously described.^{32,33} Blood flow may be further perturbed by hyperviscosity or by tumoral invasion or compression of normal blood vessels. Vascular injury is most obviously manifested by direct tumoral invasion into vessels, but tumors may also mediate functional rather than structural vascular alterations. Inflammatory cytokines, such as IL-1 and TNF- α , elaborated by a tumor or by the host immune response to a tumor, cause endothelial cells to lose their natural antithrombotic properties, and become prothrombotic.¹⁹² These cytokines upregulate endothelial cell production of von Willebrand's factor, platelet-activating factors, and tissue factor, while downregulating the expression of thrombomodulin and the activation of protein C, thus favoring platelet adherence and fibrin deposition. Hypercoagulability in cancer patients occurs through structural and functional alterations in the cellular and soluble protein constituents of the blood. As previously discussed, platelet turnover is accelerated in cancer patients,⁸⁸ and this likely results in part from increased rates of platelet activation and aggregation.^{86,192} Cancer cells and cancer cell extracts have been shown to cause direct platelet activation *in vitro*, and plasma concentrations of platelet activation biomarkers, such as P-selectin and β -thromboglobulin, are increased in cancer patients.¹⁹² Cancer cells may also activate the coagulation cascade through the production of tissue factor or cancer procoagulant, a unique cancer-associated protein that directly activates factor X.¹⁷⁶

Evidence of hypercoagulability in veterinary cancer patients is sparse. Shortening of the prothrombin time (PT) or activated partial thromboplastin time (aPTT), which may imply a hypercoagulable state, were documented in 43% of dogs with mammary carcinoma¹⁹⁷ and 14% of dogs with a variety of malignancies.⁷⁶ *In vitro* platelet aggregometry was used to assess platelet function in dogs with lymphoma¹⁹⁸ as well as dogs with various cancers.¹⁹⁹ In both studies, platelet aggregation in response to agonists (collagen, adenosine diphosphate, or platelet-activating factor) was significantly greater in dogs with neoplasia than in healthy control dogs. TEG, which provides a global functional assessment of the cellular and plasma protein components of hemostasis, may be a more sensitive method for detection of hypercoagulability than other currently available tests. Fifty percent (18 of 36) of dogs with untreated neoplasia were shown to be hypercoagulable using TEG.¹⁷⁷ TEG also documented hypercoagulability in a similar proportion (9 of 16; 56%) of dogs with untreated lymphoma.²⁰⁰ The latter two studies suggest that hypercoagulability may be quite common in small animal cancer patients, although the clinical implications of this are unknown.

For many years, thrombosis was considered primarily an epiphenomenon associated with cancer but not causally associated with oncogenesis. Recent experimental data suggest that this paradigm requires revision, and that activation of coagulation may be an intrinsic and necessary step in cancer progression. Fibrin deposition around emerging neoplastic foci forms a provisional extracellular matrix, and is hypothesized to be a critical early event in tumor progression.^{176,201} This fibrin matrix

provides a scaffold upon which angiogenesis may proceed, and also serves to recruit and trap macrophages and other leukocytes. Inflammatory cytokines produced by these immune effector cells amplify the activation of coagulation in the tumor microenvironment, driving continued tumor progression in a vicious cycle. Boccaccio and colleagues²⁰¹ provided evidence linking coagulation and early events in oncogenesis using a mouse model in which an activated *MET* oncogene was targeted to the liver. The development of grossly apparent liver tumors in these mice was preceded by a profound thrombohemorrhagic syndrome, suggesting that widespread activation of coagulation is an early event in *MET*-induced oncogenesis. Gene microarray analysis showed that *MET* activation was associated with upregulation of plasminogen activator inhibitor type-1 (PAI-1) and cyclooxygenase 2 (COX-2), two genes associated with inflammation and thrombogenesis. Compellingly, treatment of these mice with inhibitors of PAI-1 (XR5118) or COX-2 (rofecoxib) prolonged survival, prevented the emergence of a coagulopathy, and in some cases elicited tumor regression.²⁰¹ Activation of the coagulation cascade may also facilitate the metastatic process. The formation of fibrin-platelet-tumor cell complexes increases the adherence of circulating cancer cells to the endothelium, thereby enhancing metastatic efficiency.¹⁷⁶ Platelet coating may also serve to protect tumor cells from immunosurveillance. Amirkhosravi and colleagues²⁰² demonstrated the significance of coagulation in the trapping of circulating tumor cells by injecting MC28 fibrosarcoma cells into the tail vein of Lister rats. Subsequent electron microscopy demonstrated that tumor cells were deposited in complexes incorporating platelets and fibrin within the pulmonary capillaries. Anticoagulant therapy significantly abrogated this process.²⁰¹ Thus, a hypercoagulable state may promote cancer at many stages in its evolution. This would suggest a therapeutic role for anticoagulation, not solely for the prevention of cancer-associated thrombosis but also as a means of halting tumor progression. This is an active area of investigation in both animal models and human cancer patients.

Disseminated Intravascular Coagulation

DIC is a syndrome associated with excessive activation of the coagulation cascade, leading to widespread microthrombosis and multiorgan failure.⁸⁷ Although DIC is initially characterized by hypercoagulability and thrombosis (peracute DIC), eventual consumption of platelets and clotting factors leads to uncontrollable hemorrhage in the terminal stages of the disorder (acute DIC). Peracute and acute DIC may be preceded by a smoldering, asymptomatic form of the disorder (chronic DIC). Chronic DIC is common, if not ubiquitous, in patients with advanced or metastatic tumors,^{87,176,192} and is a manifestation of the hypercoagulable state that commonly accompanies cancer.

The diagnosis of DIC is challenging, particularly so for the chronic form. Typically a constellation of clinical and clinicopathologic abnormalities must be present in order to make a confident diagnosis of DIC. Assessment of platelet count, red blood cell morphology (presence of schistocytes), PT, aPTT, plasma concentrations of fibrinogen, fibrin degradation products (FDPs) and D-dimers, as well as antithrombin (AT) activity is necessary to diagnose DIC.⁸⁷ Alterations in these clinicopathologic parameters, combined with characteristic clinical signs, often facilitates the diagnosis of acute or peracute DIC. On the contrary, patients with chronic DIC often have no clinical signs and may show only subtle alterations in laboratory tests of hemostasis, making the accurate diagnosis of this syndrome particularly vexing.^{87,176} Global tests of hemostatic function, such as TEG,²⁰³ may serve to better identify cancer patients with chronic DIC, but still require validation in a clinical setting. The reader is directed

to Chapter 15 of this VCNA edition for a more detailed discussion of the laboratory diagnosis of DIC in dogs and cats.

DIC is diagnosed relatively frequently in small animal cancer patients, and indeed neoplasia is the most common cause of DIC in dogs.²⁰⁴ One report estimated the incidence of DIC in dogs with neoplasia to be approximately 10%.²⁰⁵ DIC is especially common in dogs with hemangiosarcoma, of which up to 50% may present with DIC on initial evaluation.^{33,205} DIC is also associated with mammary gland carcinoma (particularly inflammatory mammary carcinoma)^{205–207} and pulmonary adenocarcinoma²⁰⁵ in dogs. It should be noted that the cited studies were designed primarily to detect the acute form of DIC, and thus the true incidence of DIC in these patients was likely underestimated.

DYSPROTEINEMIAS

Although perturbations in plasma protein concentrations are common in small animal cancer patients, the most diagnostically relevant of these is hyperglobulinemia. The identification hyperglobulinemia, particularly if marked or persistent, should prompt further characterization of the serum protein profile using electrophoresis. Serum protein electrophoresis separates the serum proteins into distinct groups based upon electrical charge and size. In dogs and cats, six protein groups, corresponding to albumin, and globulins of the α_1 , α_2 , β_1 , β_2 , and γ classes are separated using agarose gel electrophoresis.²⁰⁸ The concentrations of serum proteins corresponding to these groups are plotted on an electrophoretogram. Hyperglobulinemia characterized by a broad-based peak in the α , β , or γ regions of the electrophoretogram is indicative of an increased concentration of globulins of multiple classes, and this is typically seen in patients with acute or chronic inflammatory diseases of numerous etiologies. On the contrary, hyperglobulinemia characterized by a tall, narrow peak is consistent with a monoclonal gammopathy, for which the list of possible etiologies is much shorter.²⁰⁹

Monoclonal gammopathies are pathologic increases in the concentrations of serum globulins produced by a single clone of B-lymphocytes or plasma cells. Monoclonal gammopathies may be characterized by increased concentrations of IgG, IgA, or IgM. Although monoclonal gammopathies are often characterized by spikes in the γ region of the electrophoretogram, clinicians should be aware that IgA and IgM may segregate in the β_2 region, and monoclonal gammopathies of these immunoglobulin classes would produce spikes in the β rather than the γ region.²⁰⁸ In both dogs and cats, monoclonal gammopathies most often indicate the presence of a neoplasm of the B-lymphocyte lineage. These include multiple myeloma, solitary plasmacytoma, Waldenström's macroglobulinemia, B-cell lymphomas, and chronic B-cell lymphocytic leukemia.⁵³ Nonlymphoid neoplasms are also rarely associated with monoclonal gammopathy.⁵³ Reported non-neoplastic causes of monoclonal gammopathy in dogs include ehrlichiosis, leishmaniasis, heartworm disease, chronic pyoderma, and plasmacytic gastroenterocolitis.^{53,209,210} Idiopathic monoclonal gammopathy is also reported in the dog.²¹¹ The most common non-neoplastic etiology of monoclonal gammopathy in cats is feline infectious peritonitis, although monoclonal gammopathy has also been reported in cats with ehrlichiosis and anaplasmosis.²¹²

Multiple myeloma is the most common cause of monoclonal gammopathy in the dog,²⁰⁹ and the same is likely true in cats.^{212,213} This disease is classically defined as a systemic neoplastic proliferation of plasma cells in the bone marrow. However, recent evidence suggests that feline multiple myeloma primarily evolves at extramedullary sites such as the skin, oral cavity, and abdominal viscera.²¹⁴ The paraprotein (also referred to as the M-component) produced by the neoplastic cell population may

be a whole immunoglobulin molecule or an immunoglobulin fragment. Fragments consisting of immunoglobulin light chains may pass through the glomerular filtration barrier and be detected in the urine as Bence-Jones proteins.⁵³

Monoclonal gammopathies evoke a spectrum of clinical and clinicopathologic abnormalities. Precipitation of immunoglobulin light chains within nephrons may lead to tubular obstruction and eventual renal failure and azotemia.⁵³ Bleeding diatheses are common in patients with monoclonal gammopathy; hemorrhage may result from immunoglobulin coating of platelets, which interferes with release of platelet factor 3 and platelet aggregation.⁵³ Hemorrhage may also result from distension and rupture of microvessels secondary to plasma hyperviscosity.^{53,191} The microvasculature of the eye and central nervous system appear to be especially prone to this complication. Hyperviscosity also increases cardiac workload, resulting in compensatory myocardial hypertrophy and possible heart failure.^{53,213} Fortunately, in many cases the deleterious physiological consequences of monoclonal gammopathy can be reversed with appropriate treatment of the underlying neoplasm and correction of the associated paraproteinemia. Approximately 90% of dogs¹⁹¹ and 60% of cats²¹⁵ with multiple myeloma will experience remission of their cancer following chemotherapy. B-cell lymphomas and chronic lymphocytic leukemias are also typically chemoresponsive.

SUMMARY

Veterinarians will encounter hematologic abnormalities routinely while treating small animal cancer patients. Some of these abnormalities, such as monoclonal gammopathy, are relatively rare and highly associated with specific neoplasms. Thus, their detection should compel a search for underlying cancer. Other hematologic abnormalities, such as anemia or thrombocytopenia, are very common in cancer patients, and their identification should prompt clinicians to consider the different mechanisms by which they may have arisen and whether further diagnostic tests are needed to fully characterize their etiology. Although cancer-related hematologic abnormalities are frequently described in the veterinary literature, the incidence, prevalence, and clinical significance of these abnormalities are less well-defined. Anemia and coagulopathies are major causes of morbidity and mortality in human cancer patients, and may have a tremendous impact on disease progression and tumor response to antineoplastic therapy. It is plausible that the same is true for veterinary cancer patients, given the pathological and biological similarity between human and small animal tumors.²¹⁶ Future studies should address the epidemiology and clinical significance of these, and perhaps other, hematologic abnormalities in order to determine whether therapeutic intervention to correct them may improve patient outcomes.

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