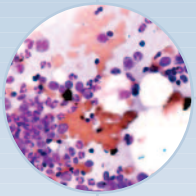

Causes of Canine and Feline Pancytopenia

Shawn Ann Kearns, DVM
Angell Animal Medical Center
Boston, Massachusetts

Patty Ewing, DVM, MS, DACVP (Anatomic and Clinical Pathology)
Genzyme Corporation
Cambridge, Massachusetts

ABSTRACT: Pancytopenia (i.e., a decrease in all circulating hematologic cell lines) can result from peripheral destruction of cells or a primary insult to the bone marrow. Many infectious, immune-mediated, and neoplastic conditions have been associated with pancytopenia in dogs and cats. Bone marrow aspirates and/or core biopsy samples are generally required to fully characterize the marrow disease, especially in cases of decreased hematopoietic cell production. Understanding the mechanisms by which various disorders alter circulating blood or marrow cells may aid in developing a diagnostic and/or treatment plan. The prognosis in pancytopenic patients is variable and depends on the underlying cause.

Pancytopenia (in Greek, "pan" means "all") is defined as decreased circulating numbers of all marrow cell lines: myeloid, erythroid, and megakaryocytic. Clinical signs related to pancytopenia are often nonspecific. Pallor and bleeding tendencies, such as petechiae, are the most common clinical manifestations and are directly related to anemia and thrombocytopenia, respectively. Most clinical signs are referable to the underlying condition. However, certain physical examination findings may help direct the diagnostic course. An accurate and thorough history is essential in determining the cause of pancytopenia (see box on page 123). Physical examination findings, other clinicopathologic abnormalities, and infectious disease testing should help elucidate the cause of pancytopenia.

Depending on an animal's age, normal hemic tissue contains 25% to 75% marrow cells in the unit particles. Marrow cellularity is higher in growing animals because cells are produced to balance normal cell turnover and growth of the cardiovascular system. With age, marrow cellularity decreases because the ratio of the bone marrow space to blood volume increases.[1] Deviations from the normal ratio can assist with distinguishing various marrow diseases because pancytopenia can occur with either increased or decreased hematopoiesis (Figure 1). Diseases resulting in decreased hematopoietic cell production usually require evaluation of bone marrow aspirate or, more often, a bone marrow core biopsy sample to obtain a definitive diagnosis. In most cases related to peripheral destruction or sequestration, a diagnosis may be obtained without a bone marrow sample, especially if there is evidence of erythroid and thrombocyte

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regeneration. This article reviews the etiopathogenesis of canine and feline pancytopenia.

DECREASED HEMATOPOIETIC MARROW CELL PRODUCTION

Causes of decreased hematopoietic marrow cell production include marrow hypoplasia or aplasia, bone marrow necrosis, marrow fibrosis/sclerosis, myelophthisis, and myelodysplastic syndrome (MDS). Many infectious, neoplastic, inflammatory, or immune-mediated diseases can result in decreased cellular production by various mechanisms. Although hematopoietic marrow cells decrease in number, the overall cellularity of the marrow may increase, especially in cases of myelodysplasia, myelophthisis, and marrow necrosis.

Marrow Hypoplasia or Aplasia

Marrow hypoplasia or aplasia is believed to result from one or a combination of the following[1,2]:

- A decrease (i.e., destruction of) or genetic defect in stem cells
- An altered marrow microenvironment, including vascular and stromal components
- Dysregulation of cell production from abnormal humoral mediators or other cellular products

Destruction of stem cells and progenitor cells is a well-established cause of marrow hypoplasia or aplasia and is the proposed or documented mechanism through which many drugs, toxins, and infectious agents exert their marrow-suppressive effect.[2] A marrow sample is considered hypocellular in an adult when at least 75% of the marrow is composed of fat but some hematopoietic cells remain (Figure 2). The term *aplastic* is applied when all marrow hematopoietic cells are markedly reduced or absent. Stromal cells, including adipocytes, reticuloendothelial cells, and macrophages, as well as lymphocytes and plasma cells may still be present in hypoplastic and aplastic marrow despite the decrease in other cell lines.[1,3] Although mast cells are rarely seen in normal marrow, mast cell hyperplasia has been documented in canine cases of aplastic anemia, with proposed mechanisms including localized cellular hyperplasia from intramedullary immunologic reactions, local imbalance or depletion of soluble growth mediators, and the ability of mast cells to proliferate and differentiate in the absence of certain growth factors.[4]

Acute forms of aplastic anemia are frequently associated with destruction of progenitor and/or proliferative cells in bone marrow. This marrow-level destruction results in predictable changes in the peripheral blood. Clinical signs related to leukopenia and thrombocytopenia typically result within 2 weeks of marrow injury because of the life span of neutrophils (i.e., 1 to 4 days) and platelets (i.e., 8 to 10 days). The erythrocyte life span is much longer (i.e., 120 days in dogs; 70 to 80 days in cats); therefore, anemia, when present, is often mild or delayed in onset. If the injurious agent is removed, stem cells will repopulate marrow progenitor cells, and approximately 10 to 14 days after cessation, the cytopenias begin to resolve. Recovery is usually complete within 21 days; however, dysplastic changes can occur in any one or all three cell lines during this recovery phase.

Chronic aplastic anemia generally results from hematopoietic stem cell injury. In these cases, the resulting anemia, thrombocytopenia, and leukopenia are often moderate to severe. Marrow repopulation is unpredictable in these cases and often takes weeks to months, if it occurs at all.[2]

Estrogen

Exogenous or endogenous estrogen exposure has been implicated in dogs with mild to severe myelosuppression.[5–13] Cats appear relatively resistant to the effects of estrogen on bone marrow. Although dose and frequency of exposure are important factors in the development of bone marrow suppression, there also appear to be variations in individual susceptibility unrelated to age, sex, breed, nutritional plane, route of administration, or type

Essential Historical Information in Patients with Pancytopenia

- Were **therapeutic drugs** administered within 4 weeks of the presentation?
- Could the patient have been exposed to **human medications**?
- Has the patient **traveled** to other regions of the United States or other countries?
- What is the patient's **vaccination history**?
- Has the patient been exposed to **other animals**? In what way?
- Has the patient had **previous health problems**?
- Has the patient been exposed to **chemicals** (e.g., benzene) or **radiation**? (This is rare in the clinical setting.)
- For male dogs, **were both testicles descended** at neutering?

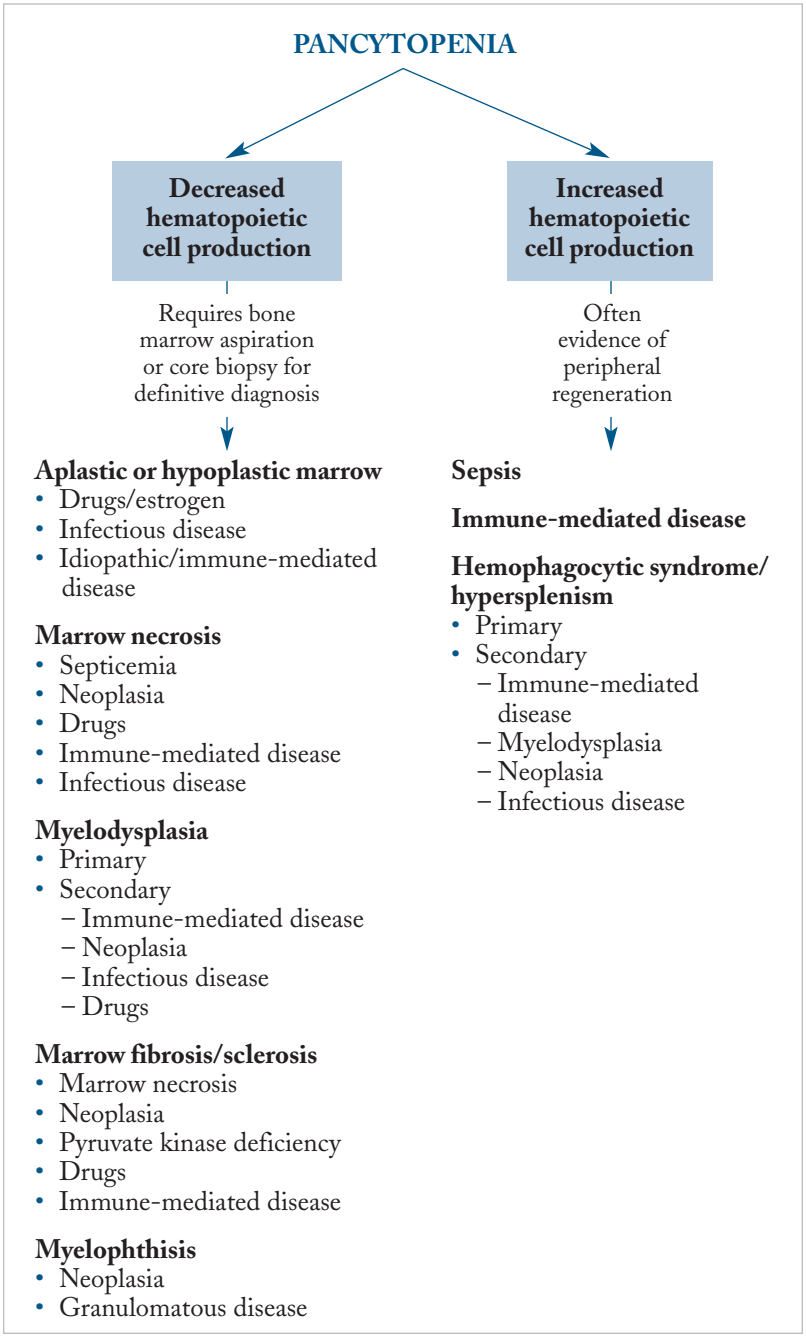

Figure 1. Summary of diseases resulting from decreased or increased hematopoietic cell production.

of disorder treated.[9] Exogenous estrogens are most commonly used in the form of estradiol cypionate for mismating and prostatic hyperplasia. Estrogen has also been used in treating circumanal gland tumors and urinary incontinence. Excess endogenous estrogens in male dogs are most commonly produced by Sertoli's cell tumors.[7,11–14] Male feminization, hyperpigmentation, a history of cryptorchidism, gynecomastia, and symmetric alopecia may be detected in male dogs. The amount of estrogen produced is generally proportional to the tumor size.[14] In females, functional cystic ovaries and granulosa cell tumors have been implicated in clinical cases of hyperestrogenemia.[7,15] The primary complaint in female dogs may be persistent estrus. The exact mechanism of myelotoxicity with estrogen exposure is unknown. Estrogens may interfere with stem cell differentiation, alter iron utilization by erythrocyte precursors, inhibit production of circulating erythrocyte stimulation factors, or stimulate production of a myelopoiesis inhibitory factor.[9,14]

Estrogen exposure initially results in leukocytosis and thrombocytopenia. Normal marrow cellularity is often noted because of myeloid hyperplasia; however, erythropoiesis and thrombopoiesis are decreased. Pancytopenia generally develops 3 to 4 weeks after exposure. Severe chronic aplasia can occur, especially with repeated exogenous injections, and the reversibility of bone marrow damage in these cases is unknown.[2]

Drug-Associated Marrow Suppression

Numerous reports of drug-induced marrow suppression in animals exist; however, many of the agents implicated (see box[2,10,11,15–30] on page 127) are no longer in general use because clinically safer alternatives are now available. In many instances, the mechanism of action of marrow injury is unknown. The reaction may be dose-dependent, idiosyncratic, or associated with hypersensitivity or an immune-mediated reaction. In general, the prognosis for marrow recovery is good with withdrawal of chemotherapeutics because stem cells are spared as a result of their low mitotic rate. The prognosis is variable with other pharmaceutic classes; however, marrow recovery should occur within 1 to 2 weeks after pharmaceutic drug withdrawal in most cases.

Infectious Disease

Infectious causes of aplastic anemia or hypocellular marrow identified in dogs and/or cats include, but are

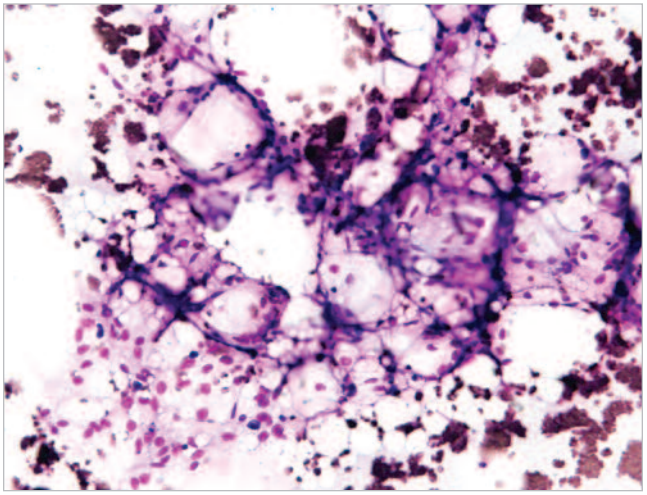

Figure 2. Marrow spicule from a pancytopenic dog. Note that the spicule is almost entirely composed of adipocytes (>90%). Virtually no hematopoietic precursors are present. (Wright's–Giemsa stain, original magnification ×200)

not limited to, parvovirus, FeLV, FIV, *Ehrlichia canis* infection, bacterial septicemia, and endotoxemia.

Parvovirus infection in dogs and cats can cause acute aplastic anemia.[11,31] This is believed to be due to virus proliferation in progenitor and proliferative cells.[2,31,32] Bone marrow alterations can occur in all cell lines. However, the anemia and/or thrombocytopenia may be mild or absent. Changes observed in bone marrow specimens are occasionally indicative of extreme marrow toxicity and reactivity and destruction of normal elements.[31,33] Marrow hypercellularity with granulocytic hyperplasia and myelophthisis has also been reported.[33] Marrow injury secondary to endotoxemia or septicemia often cannot be excluded in many cases, and gastrointestinal blood loss may contribute to, or be the primary cause of, anemia rather than direct bone marrow injury. Vaccination for parvovirus has also reportedly caused refractory anemia and pancytopenia in rare instances.[34] Regardless, hematologic recovery is often rapid if an affected animal survives the acute stage of the disease.

Pancytopenia may be observed in acute and chronic stages of ehrlichial infection, particularly *E. canis* infection.[4,11,35] In the acute stage, the marrow is often hypercellular because of peripheral cell destruction. Platelet consumption, sequestration, and destruction may all contribute to thrombocytopenia. Erythrocyte destruction and suppression of erythrocyte production may lead to progressive anemia in the acute phase of infection. Chronic infections can lead to aplastic anemia; the mechanism responsible for bone marrow suppression and subsequent hypoplasia of all marrow precursor cells is not understood.[2,35–37] *Ehrlichia* spp infection has also been reported in cats[38–43] and should be considered in a differential list for multiple cytopenias.

FeLV usually causes selective suppression of erythropoiesis and occasionally thrombopoiesis, but infection may also lead to aplastic anemia.[2] Proposed mechanisms of FeLV-induced pancytopenia include[17]:

- Direct cytopathic effects of the virus
- Arrested precursor differentiation
- Myelophthisis/myelosclerosis
- Anemia of inflammatory disease
- Myelofibrosis

Bone marrow findings in cats with FeLV are variable. Hypoplastic marrow is more common in FeLV-infected cats than is aplastic anemia. The bone marrow in FeLV-infected cats can also be hypercellular with erythroid and/or multiple lineage differentiation arrest or disorder.[1,44–46]

Acute aplastic anemia is potentially reversible if the injurious agent is removed. Chronic aplastic anemia resulting from stem cell injury may be irreversible.

FIV has also been documented to cause pancytopenia but usually only in cats with advanced disease or chronic illness.[47,48] Humoral inhibitory substances may be directed at granulocytic or macrophage differentiation in bone marrow.[49] FIV infects megakaryocytes and bone marrow accessory cells, potentially altering the capacity of accessory cells to support normal hematopoiesis of other cell lines.[17]

Chemicals and Radiation Therapy

Chemical injury to stem cells by benzene and related substances has been documented in humans and experimental animals.[3] In clinical practice, chemical exposure is an uncommon cause of pancytopenia. Sufficient doses

Agents Associated with Pancytopenia in Dogs and Cats

NSAIDs
- Phenylbutazone[2,10,16]
- Meclofenamic acid[10]

Chemotherapeutics[2,11,15,17–19]
- Cyclophosphamide
- Cytosine arabinoside
- Doxorubicin
- Vinblastine
- Hydroxyurea
- Cyclohexylchloroethylnitrosurea (CCNU; lomustine)
- 5-Fluorouracil
- Carboplatin
- Azathioprine

Antibiotics
- Sulfadiazine–trimethoprim[2,10,15,20,21]
- Cephalosporins[22]

Anthelmintics
- Albendazole[23]
- Fenbendazole[24]

Others
- Quinidine[10,25]
- Thiacetarsimide[12,25]
- Captopril[26]
- Griseofulvin[17,27–29]
- Methimazole[17]
- Noxema Skin Cream (Procter & Gamble)[30]

Proposed Criteria for a Diagnosis of Idiopathic Aplastic Anemia[51]

- Pancytopenia has been present for >2 wk
- Pancytopenia persists after treatment of endotoxemia and/or sepsis
- No known exposure to aplastic anemia–inducing agents in the 4 wk preceding the development of cytopenias
- Exclusion of chronic renal disease
- No evidence of retained testicles, testicular masses, or persistent estrus
- Negative titers for infectious diseases, including *Ehrlichia*, *Babesia*, *Rickettsia*, and *Leishmania* spp infections
- A bone marrow core biopsy sample revealing replacement of bone marrow with adipose tissue, with hemic tissue occupying only 0% to 25% of the bone marrow space

of total body irradiation induce aplastic anemia in all species.[50]

Idiopathic

In cases in which all infectious, hormonal, and drug-related exposures have been excluded, a diagnosis of idiopathic aplastic anemia can be made. A recent review[51] proposes that a diagnosis of idiopathic aplastic anemia be made only if specific criteria are met (see box on this page). In veterinary medicine, such a diagnosis is rarely supported by complete exclusion of underlying causes.[52] An immune-mediated reaction against hematopoietic precursors has been suggested and is supported in human medicine with evidence of T lymphocyte–mediated stem cell reactions.[53] In vitro studies have shown that overproduction of interferon-γ and tumor necrosis factor–α by T lymphocytes suppresses hematopoietic colony formation and, when secreted into the marrow environment, they inhibit stem cell proliferation by effects on the mitotic cycle and apoptosis.[3,53] Recovery following administration of immunosuppressive drugs further supports an immune-mediated cause, although not all cases respond to treatment.

Idiopathic aplastic anemia has been sporadically documented in dogs.[4,11,34,54] Most reports are of young dogs, and the prognosis is considered poor in many cases.[15] In a retrospective study[17] of causes of feline pancytopenia, three cases of idiopathic aplastic anemia were identified. All three were young cats that died or were euthanized within 1 week of diagnosis.

Marrow Necrosis

Myelonecrosis is necrosis of myeloid tissue and medullary stroma in large areas of hematopoietic bone marrow.[55] Causes of marrow necrosis may be due to direct (toxic) damage to hematopoietic cells or secondary to ischemia via injury or disruption of microcirculation.[1] Extensive necrosis can lead to suppressed hematopoiesis and subsequent cytopenias. Bone marrow biopsy may show an absence of normal parenchymal architecture, indistinct cell margins, amorphous eosinophilic background material, and foci of necrotic patches surrounded by normal hematopoietic cells.[1,55] Diseases or processes associated with marrow necrosis include septicemia, disseminated intravascular coagulation, neoplasia, drugs, estrogen, parvovirus, systemic lupus erythematosus, ehrlichiosis, and FeLV infection.[1,56] Pancytopenia is infrequently reported with marrow necrosis but can occur.[57,58] If a patient with myelonecrosis survives, myelofibrosis may develop.

Marrow Fibrosis

Primary or idiopathic myelofibrosis is considered a chronic myeloproliferative disorder of all cell lines. This nonclonal fibroblast proliferation is believed to be due to stimulation by growth factors and fibrogenic cytokines released from abnormal megakaryocytes and/or platelets.[58–61] Alternatively, immunologic abnormalities, including complement activation, have been implicated in the pathogenesis of myelofibrosis.[62] The presence of abnormal megakaryocytes in bone marrow, extramedullary hematopoiesis in the spleen and/or liver, and dysplastic features in all cell lines in idiopathic myelofibrosis helps differentiate it from secondary myelofibrosis.[52,63] Idiopathic myelofibrosis should be differentiated from acute megakaryoblastic leukemia, which can also be associated with prominent marrow fibrosis.

Secondary myelofibrosis usually results from marrow injury, including necrosis, vascular damage, inflammation, neoplasia (with concurrent myelophthisis and neoplasia at extramedullary sites), or myeloproliferative disease. Pyruvate kinase deficiency, primarily documented in basenjis, is associated with subsequent myelofibrosis.[1,64,65] Immune-mediated hemolytic anemia (IMHA), lymphoma, carcinoma, sarcoma, drugs (e.g., phenobarbital, phenytoin, phenylbutazone, colchicine), Zollinger-Ellison syndrome, metastatic adenocarcinoma, and lymphoblastic lymphoma have also been reported in cases of myelofibrosis.[63,66–68] Overproduction of erythropoietin and thrombopoietin in patients with IMHA, immune-mediated thrombocytopenia (IMT), and pyruvate kinase deficiency as well as increased production of cytokines from activated macrophages may contribute to the development of marrow fibrosis.[15,59] Neoplasia has been proposed to cause myelofibrosis by[63]:

- Decreased intramedullary blood flow
- Necrosis secondary to disseminated intravascular coagulation
- Tumor secretion of factors that induce fibroblast proliferation

In cats, myelofibrosis is primarily associated with myelodysplasia or acute myelogenous leukemia (AML).[58,59] FeLV infection is frequently the cause of myelodysplasia with secondary myelofibrosis.[58]

Myelofibrosis should be suspected when repeated attempts at bone marrow aspiration are unsuccessful or if poor-quality aspirates with spindle cells or specimens lacking marrow particles are obtained. A definitive diagnosis can be made only with marrow histopathology showing fibrous tissue containing actively proliferating fibroblasts and an excess of reticulin and/or collagen.[1] Special stains may be required to detect mild myelofibrosis and to differentiate between reticulin and collagen.

Osteosclerosis and Osteopetrosis

Osteosclerosis is thickening of trabecular (i.e., spongy) bone, whereas osteopetrosis is a form of osteosclerosis resulting from decreased bone resorption secondary to decreased numbers and/or abnormal osteoclast function.[1] Space for hematopoiesis decreases with osteosclerosis and, occasionally, hyperostosis (i.e., widening of cortical compact bone from appositioning of osseous tissue at endosteal and/or periosteal surfaces). Mild to severe nonregenerative anemia occurs often, whereas decreases in platelets and leukocytes occur less often.[69–71] A presumptive diagnosis of osteosclerosis or osteopetrosis is based on the presence of combined cytopenias with increased radiographic osseous density; however, the diagnosis can be confirmed only with a bone marrow core biopsy.[72,73] These disorders should be suspected when a marrow sample cannot be obtained because of difficulty advancing the needle through the bone.

Clinical signs related to leukopenia and thrombocytopenia typically develop within 2 weeks after marrow injury because of the life span of neutrophils (i.e., 1 to 4 days) and platelets (i.e., 8 to 10 days).

Myelodysplastic Syndrome

MDS is a group of clonal hematologic disorders originating from a mutational event in hematopoietic stem cells, thus conferring a growth advantage. Such hematopathies are considered preneoplastic or neoplastic and can be lethal, even without progression to AML, because of severe cytopenias from the marrow's inability

to produce mature blood cells.[59] The clonal expansion and apoptotic response observed in MDS arises from interaction between the malignant clone and the microenvironment.[74,75] Multiple defects in growth and differentiation of marrow cells, induction of apoptosis from inflammatory cytokines, and uncontrolled production of myelomonocytic precursors contribute to cytopenias.[59,74,76] Although one cell line may be more severely affected, defects within multipotential stem cells lead to ineffective proliferation of one or more cell lines and result in peripheral cytopenias of the affected population(s). Anemia is present in almost all cases, whereas alterations in peripheral neutrophils and platelet counts are variable.[59] The marrow is typically normo- to hypercellular. Marrow samples occasionally have patchy hypercellularity or decreased cell counts.

MDSs are classified based on characteristics identified by quantitative and morphologic evaluation of blood and bone marrow.[59] The French, American, and British guidelines for MDS classification in humans have been adapted for animals. The Animal Leukemia Study Group of the American Society for Veterinary Clinical Pathology recently established uniform and specific cytomorphologic criteria for characterizing MDS.[77] Increased cellularity, increased blast cells (<30%), and dysplastic features of one or more cell lines define MDS.[11,59] The three main types of MDS in small animals are currently subclassified as MDS with refractory cytopenia, erythroid predominance, or excessive blasts (MDS-EB).[77,78] Many factors are used for prognosis; in general, high marrow blast cell counts and multiple severe cytopenias are predictors of short survival and likely progression to AML.[59,79–81] MDS-EB more commonly presents with pancytopenias compared with other MDS groups.[46,77]

MDS leading to pancytopenia has been identified in dogs and cats.[11,46,79,80,82–84] All three subclassifications of MDS have been identified in cats.[51,80] About 80% of cats with MDS are FeLV positive and have macrocytic anemia.[59,81,84] This anemia may be due to FeLV-induced erythroid hypoplasia or primary FeLV-induced mutational events in hematopoietic stem cells.[46,85] In cats, survival is generally of short duration with all types of MDS.[80]

MDS can be a primary disease (as already defined) or can occur secondary to a concurrent disease, nutritional deficiency (e.g., iron, folate), lead toxicosis, or, most commonly, malignancy or drug administration.[79,86–88] Lymphoma, myelofibrosis, IMT, IMHA, multiple myeloma, and certain drugs have been associated with MDS in dogs.[22,77,89–91] MDS has also been reported in dogs with hepatic disease and following exposure to gamma radiation.[1,92,93] Concurrent diseases identified in cats include lymphoma, stomatitis, toxoplasmosis, FIP, granulomatous meningoencephalitis, bite wounds, and *Aleurostrongylus* spp infection.[84] MDS secondary to chemotherapy treatment may be due to a mutational stem cell event or direct cytotoxic effects.[51] Nearly 20% of human cases are secondary to treatment with chemotherapy agents, particularly alkylating agents, and exposure to radiation or chemicals.[59] Bone marrow evaluation in cases of secondary MDS usually reveals fewer than 5% myeloblasts. The pathogenesis of secondary MDS is poorly understood; however, some cases are potentially reversible with treatment of the inciting cause.[51]

Ehrlichial infections should be considered in the differential diagnosis for cats and dogs with multiple cytopenias.

Myelophthisis

Myelophthisis features infiltration of the bone marrow by neoplastic cells, inflammatory cells, or fibrous connective tissue resulting in loss of hematopoietic space and decreased hematopoiesis. Certain neoplastic or granulomatous conditions can show patchy or multifocal distribution in the marrow, making diagnosis difficult.[72]

Granulomatous Bone Marrow Disease

Histoplasmosis, which is caused by *Histoplasma capsulatum*, is a systemic mycotic disease with preferential involvement of the reticuloendothelial system.[94,95] Although uncommon, pancytopenia secondary to histoplasmosis has been reported in cats and dogs.[94,96] Proposed mechanisms of pancytopenia include displacement of myeloid/erythroid elements by granulomatous reaction to *Histoplasma* organisms, anemia of chronic infection, and toxic effects of the organisms.[94,96] Pancytopenia has also been reported in association with granulomatous disease of visceral leishmaniasis.[97]

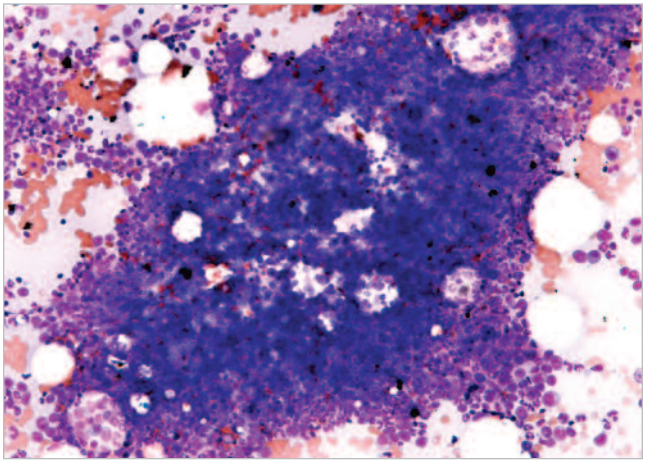

Figure 3. Hypercellular marrow spicule from a dog with neutropenia. Note that the densely cellular spicule is composed of approximately 90% hematopoietic precursors and 10% adipocytes. (Wright's–Giemsa stain, original magnification ×200)

Neoplasia

Malignant histiocytosis (MH) is an aggressive neoplastic condition characterized by pancytopenia and proliferation of atypical macrophages in the liver, spleen, lymph nodes, lungs, and bone marrow or a combination of these sites.[98] MH has been sporadically reported in several breeds of dogs, most notably Bernese mountain dogs.[99–101] Finding greater than 20% macrophages, some of which exhibit criteria of malignancy, in the bone marrow supports a diagnosis of MH.[89,100,102] Pancytopenia may be due to phagocytosis of marrow cells or suppression of hematopoiesis.[100] MH has also been reported in a cat with multiple cytopenias.[103] Pancytopenia has also been reported in association with acute lymphoblastic leukemia, myelogenous leukemia, lymphoma, multiple myeloma, and metastatic disease.[11,17,84,104] The cause of pancytopenia in dogs with malignant disease is uncertain but may be due to rapid proliferation of malignant cells in marrow, thus suppressing normal hematopoiesis.

INCREASED HEMATOPOIETIC BONE MARROW CELL PRODUCTION

In general, peripheral cell destruction of blood cells stimulates bone marrow production of the affected cell lines, leading to hypercellular marrow (Figure 3). Peripheral pancytopenia can result if destruction or sequestration of all cell lines exceeds the capacity of the marrow and/or sites of extramedullary hematopoiesis to replace circulating cells. Compared with decreased marrow cell production, there are fewer causes of peripheral pancytopenia, which are often identified without the need for marrow aspiration or biopsy.

Sepsis

Sepsis is implicated as the primary cause of pancytopenia when hematology results suggest sepsis and more common causes of pancytopenia are not evident.[11,17] Hematologic findings suggestive of septicemia include an inflammatory leukogram with a degenerative left shift and toxic change or neutropenia, mild to moderate anemia, and thrombocytopenia. Septicemia can affect bone marrow in several ways[52]:

- Endotoxin-induced destruction of bone marrow precursors
- Toxic or hypoxic bone marrow necrosis
- Inflammation associated with bacterial infection of the bone marrow
- Inflammatory cytokine-induced suppression of hematopoiesis

Other mechanisms that may contribute to cytopenias included sequestration of neutrophils and platelets in capillary beds, blood loss, red cell fragmentation, and rapid mobilization of neutrophils to the site of infection.[15] If sepsis is directly affecting the marrow, hypocellularity may be noted. Animals may recover with antibiotic treatment and other supportive care.

Immune-Mediated Disease

Pancytopenia has been reported in dogs with IMHA and IMT. Red cells and platelets are the primary targets in these diseases, but neutropenia may be present. The neutropenia is often mild and may be secondary to an acute inflammatory response initiated by the immune-mediated disease, sepsis, or immune-mediated destruction of neutrophils.[11] An association with IMHA and/or IMT in conjunction with a positive Coomb's or antinuclear antibody test may further support an immune-mediated cause. Certain drugs, such as methimazole and anticonvulsants, have been associated with apparent immune-mediated peripheral blood cell destruction, although the exact immunologic and toxic mechanisms underlying these drug reactions are not always clear.[105,106]

Hemophagocytic Syndrome and Hypersplenism

Hemophagocytic syndrome (HPS) is a nonmalignant proliferative disorder of macrophages in the bone mar-

row.[101,107] It can be primary/idiopathic or secondary to other diseases, including IMHA, IMT, MDS, infection (i.e., salmonellosis, parvovirus), and neoplasia (i.e., lymphoma, mast cell tumor, carcinoma, sarcoma).[15,52,102,107,108] Phagocytosis of hematopoietic cells does not appear to be due to a primary immune disorder but rather to inappropriate activation of normal macrophages.[107] The precise pathogenic events that lead to inappropriate reactive histiocytosis have not been characterized. Cytopenias are partly due to cytophagia, but other factors to consider include[107,109]:

- Depression of progenitor cell proliferation due to release of cytokines that inhibit hematopoiesis, such as interferon-γ, tumor necrosis factor–α and interleukin-1
- Inappropriate production of these and other cytokines stimulating phagocytic activity in normal histiocytes
- Acquired, iatrogenic, or congenital immunologic abnormalities

In cases of IMHA, opsonization of erythroid cells as a result of antibody binding may increase phagocytic activity.[110] Bone marrow aspirates in cases of HPS show mild to moderate increases in macrophages and many phagocytized hematopoietic cells.[107,109] Bone marrow may be hypercellular or hypocellular. Erythrocytophagia is commonly observed; however, phagocytosis of platelets and granulocytic cells has also been reported.[102] In one retrospective evaluation of HPS in four dogs and one cat, macrophage percentages in bone marrow varied from 2% to 35% (normal: <3%).[107] Immunosuppression may be valuable in treating underlying immune-mediated disease; however, in reported animal cases, spherocytes and agglutination were not evident and all cases had negative results via Coombs' testing.[107] HPS should be differentiated from systemic histiocytosis, malignant histiocytosis, bone marrow necrosis, granulomatous bone marrow disease, histiocytic lymphoma, and monocytic and myelomonocytic leukemia.[57,102,111] HPS can be difficult to differentiate from MH via cytology in cases in which neoplastic macrophages exhibit minimal cytologic atypia.[98,102] The outcome in HPS depends on the underlying disease implicated.

Hypersplenism is characterized by marked splenomegaly, in which the expanded reticuloendothelial system of the spleen results in blood cell destruction and subsequent cytopenias.[15] This is not a well-established syndrome in dogs, and there is probably some overlap with HPS.[15,112,113] Hypersplenism can develop from several common causes of splenomegaly, including hemolytic anemia, granulomatous inflammation, splenic congestion, and neoplasia.[112,113] The pathogenesis of cytopenias is thought to be due to increased splenic sequestration or phagocytosis of blood cells and expansion of plasma volume. Decreased marrow cellularity may be due to splenic release of humoral and cellular inhibitors of myelopoiesis.[112] Patients with clinical cases present with anemia, thrombocytopenia, and marked splenomegaly with extramedullary hematopoiesis and hyper- or hypocellular marrow.[113] Resolution of cytopenias generally occurs following splenectomy.[112]

CONCLUSION

Identifying and treating patients with pancytopenia should be approached by first excluding the causes of peripheral cell destruction, especially sepsis and immune-mediated disease. If initial diagnostics, including infectious disease testing, do not offer a conclusive diagnosis, bone marrow aspiration and/or core biopsy is indicated. Understanding the etiopathogenesis of marrow-related diseases aids in diagnosing pancytopenic patients and in determining a prognosis for recovery.

Hypercellular marrow may be present despite decreased hematopoietic cell production because of infiltration of neoplastic cells, the presence of inflammatory cells, or an altered microenvironment conferring a growth advantage for other cells lines.

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ARTICLE #2 CE TEST

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1. A bone marrow sample in an adult animal is considered hypoplastic when at least ____% of the marrow is composed of fat.
a. 25
b. 40
c. 60
d. 75

2. Which has not been associated with bone marrow hypoplasia and/or aplasia?
a. borreliosis
b. ehrlichiosis
c. parvovirus
d. FeLV infection

3. FIV can infect _____, which may alter the capacity of accessory cells to support hematopoiesis.
a. erythroid cells
b. myeloid cells
c. megakaryocytes
d. endothelial cells

4. Primary or idiopathic myelofibrosis is believed to be due to stimulation by growth factors and fibrogenic cytokines from abnormal
a. megakaryocytes.
b. myeloid cells.
c. fibroblasts.
d. erythroid cells.

5. Of the MDS subclasses, _____ more commonly occurs with pancytopenia.
a. MDS with erythroid predominance
b. MDS-EB
c. MDS with refractory cytopenia
d. AML

6. Phagocytosis of hematopoietic cells in cases of HPS is due to
a. activation of malignant macrophages.
b. a primary immune disorder.
c. inappropriate activation of normal macrophages.
d. a primary abnormality in the hematopoietic precursor cells.

7. Clinical signs related to leukopenia and thrombocytopenia generally occur within ___ days of bone marrow injury because of the life span of neutrophils and platelets.
a. 5
b. 14
c. 21
d. 30

8. Excess endogenous estrogens in male dogs are most commonly produced by
a. Leydig's cell tumors.
b. Sertoli's cell tumors.
c. granulosa cell tumors.
d. seminomas.

9. An increase in hematopoietic cells in bone marrow aspirate does not occur with
a. hypersplenism.
b. HPS.
c. sepsis.
d. myelofibrosis.

10. Bone marrow hypoplasia or aplasia may result from
a. a decrease or genetic defect in stem cells.
b. an altered marrow microenvironment.
c. dysregulation of bone marrow cell production from abnormal humoral mediators.
d. all of the above