

Pancytopenia in a Cat

Tatiana Rothacker, DVM

University of Missouri

Sarah Guess, DVM, MS

*Columbia River Veterinary Specialists
Vancouver, Washington*

Lisa M. Pohlman, DVM, MS, DACVP

Kansas State University



Case

A 16-month-old neutered male domestic shorthair cat was presented for a 3-day history of poor appetite. The kitten had been found as a stray ≈2 months before presentation; physical examination at that time revealed a BCS of 3/5 and pale pink mucous membranes.

Current CBC showed a hematocrit of 14.89% (reference interval, 24%-45%), WBC concentration of $5.56 \times 10^3/\mu\text{L}$ (reference interval, $5.5\text{-}19.5 \times 10^3/\mu\text{L}$), and platelet concentration of $20 \times 10^3/\mu\text{L}$ (reference interval, $300\text{-}800 \times 10^3/\mu\text{L}$). Treatment with doxycycline (15 mg/kg PO q12h), prednisolone (2.5 mg PO q24h), and fenbendazole (50 mg/kg PO q24h for 3 days) was initiated. The patient's appetite did not improve. After he continued to lose weight over the subsequent 2 weeks, he was referred to a specialty hospital. On presentation, he was quiet, alert, and responsive. BCS was 2/9. Pale pink mucous membranes, increased respiratory rate and effort with increased bronchovesicular sounds,

and clear ocular discharge were noted on physical examination. Rectal temperature was 102°F (39°C).

Diagnostic Results

FeLV antigen and FIV antibody test results were negative. Blood was obtained for serum chemistry profile and repeat CBC (*Table*).

Pancytopenia is suggestive of generalized bone marrow suppression. FIV, FeLV, and/or feline panleukopenia virus infections are top differential diagnoses for pancytopenia in young cats. Additional rule-outs include fungal disease (eg, histoplasmosis). Noninfectious causes of generalized bone marrow suppression in cats can include toxicosis resulting from griseofulvin,¹ chemotherapeutic agents,¹ chloramphenicol,¹ albendazole,¹ immunosuppressive drugs¹ (eg, azathioprine [not generally recommended in cats due to their increased susceptibility to bone marrow suppression], chlorambucil²), and methimazole,¹ although these differential

diagnoses are less likely with the patient's history and physical examination findings. Neoplasia, myelofibrosis, and immune-mediated disease are also possible causes. The patient's respiratory signs could indicate a primary infection or neoplastic process that has disseminated to the bone marrow or a secondary infection associated with immunosuppression.

The patient was admitted to intensive care. He received a blood transfusion and was placed in an oxygen cage. His condition continued to deteriorate, and he died before additional diagnostic testing could be pursued. Bone marrow aspirates were obtained postmortem, and necropsy with histopathologic examination was performed.

Diagnosis

Histoplasmosis

Histoplasmosis was diagnosed based on cytologic findings from the bone marrow aspirate and confirmed via histopathology of the lungs, liver, spleen, lymph nodes, kidney, intestines, and bone marrow.

Histoplasmosis, a systemic fungal disease caused by *Histoplasma capsulatum*, is a dimorphic, soil-borne fungus. The disease is most prevalent in the Midwest and southern regions of the United States and in regions with tropical and subtropical climates throughout the world.³⁻⁶ Infections typically result from inhalation or ingestion of spores from infected soil.³⁻⁷ Development of clinical infection depends on the concentration of fungal inoculum and host immune competence. Infections may be dormant and later reactivated. Disease may remain localized to the respiratory tract or become disseminated.^{3,6,7}

Clinical signs of feline disseminated histoplasmosis are often chronic and nonspecific and may include lethargy, emaciation, tachypnea, dyspnea, coughing, pale mucous membranes, pyrexia, and anorexia.³⁻⁷ Conjunctivitis, cho-

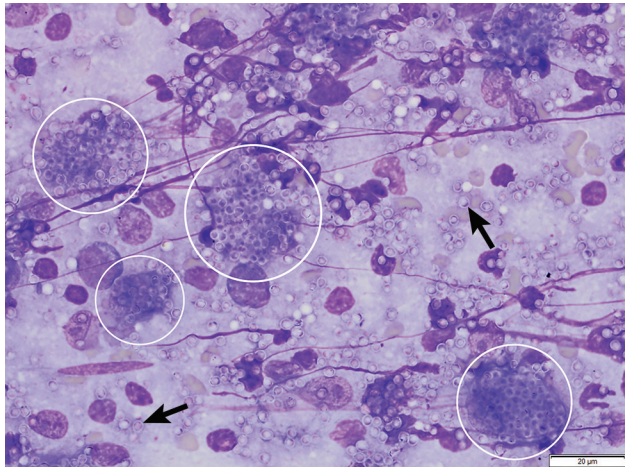
rioretinitis, uveitis, and retinal detachment may manifest with ocular involvement.⁵⁻⁷ Primary GI histoplasmosis is less common in cats than in dogs, and cutaneous forms have been reported infrequently.^{4,7}

The most common hematologic abnormality in dogs and cats with histoplasmosis is a normocytic, normochromic, nonregenerative anemia⁴⁻⁷; however, chronically infected cats may demonstrate no hematologic abnormalities.⁷ Leukopenia and/or thrombocytopenia also may be observed when bone marrow is involved, with pancytopenia occurring less commonly in cats than in dogs.⁵ Cytopenias, in these cases, are caused by granulomatous inflammation in the marrow that displaces normal hematopoietic cells (ie, myelophthisis). Hypoalbuminemia is the most common serum

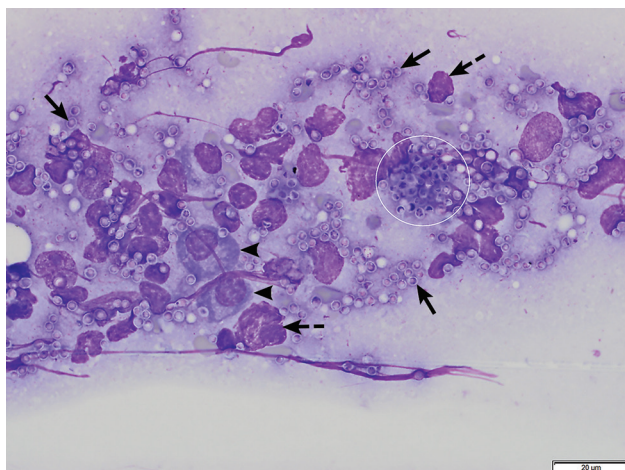
TABLE

DIAGNOSTIC TEST RESULTS

Diagnostic Test	Result	Reference Interval
CBC		
Hematocrit	14%	35%-50%
Platelets	$68 \times 10^3/\mu\text{L}$	$140\text{-}400 \times 10^3/\mu\text{L}$
WBC concentration	$3.2 \times 10^3/\mu\text{L}$	$4.2\text{-}14.1 \times 10^3/\mu\text{L}$
Segmented neutrophils	$1.4 \times 10^3/\mu\text{L}$	$1.9\text{-}8.1 \times 10^3/\mu\text{L}$
Band neutrophils	$0.4 \times 10^3/\mu\text{L}$	$0.0\text{-}0.1 \times 10^3/\mu\text{L}$
SERUM CHEMISTRY PROFILE		
Glucose	153 mg/dL	80-130 mg/dL
Bilirubin	0.6 mg/dL	0.0-0.2 mg/dL
Albumin	2.1 g/dL	3.2-4.5 g/dL
Total calcium	8.5 mg/dL	9.2-12.0 mg/dL



▲ **FIGURE 1** Bone marrow aspirate from a cat with pancytopenia. The numerous yeast organisms seen both extracellularly (**arrows**) and intracellularly within macrophages (**circles**) measure 2 to 4 μm in diameter and have a thin outer halo with eccentrically placed, basophilic, crescent-shaped nuclei. Organisms are consistent with *H capsulatum*. Modified Wright's stain, 1000 \times . Scale bar = 20 microns



▲ **FIGURE 2** Bone marrow aspirate from a cat with pancytopenia. *H capsulatum* yeast structures are seen extracellularly (**arrows**) and intracellularly within a macrophage (**circle**). Plasma cells (**arrowheads**) and nuclear material from lysed cells (**dashed arrows**) are also present. Modified Wright's stain, 1000 \times . Scale bar = 20 microns

chemistry abnormality,^{4,7} and increases in alanine aminotransferase, alkaline phosphatase, and bilirubin may be seen with liver involvement.^{6,7} Hypocalcemia has been reported in cats with histoplasmosis but is likely caused by hypoalbuminemia and a decrease in the protein-bound fraction of calcium.⁴ Mild hyperglycemia in this patient was most likely associated with stress.

Discussion

Diagnostic Testing

A bone marrow biopsy, ideally both an aspirate and a core, is indicated in a patient with pancytopenia of unknown cause. Aspirates enable identification of cell lineages and characterization of morphologic abnormalities within lineages. Core biopsies are required to evaluate overall marrow cellularity and architecture.

Bone marrow cytology of this cat (**Figures 1 and 2**) showed no bone marrow particles, rare marrow hematopoietic precursor cells (ie, megakaryocytes, myeloid and erythroid cells), and occasional plasma cells. Macrophages were markedly increased. Numerous round-to-oval yeast bodies measuring 2 to 4 μm in diameter were seen extracellularly and inside macrophages. The organisms had a thin outer halo with an eccentrically placed, basophilic, crescent-shaped nucleus.

Histopathologic examination of lung, spleen, kidney, intestine, bone marrow, and intestinal and tracheobronchial lymph node specimens showed granulomatous inflammation with numerous yeast bodies in the macrophages.

Sporothrix schenckii vs *H capsulatum*

S schenckii is a fungal organism of similar size and appearance to *H capsulatum*. In dogs and cats, histoplasmosis is most commonly diagnosed by identification of the organism in affected tissues or fluid samples.^{4,5,7} *S schenckii* yeast bodies can be round, oval, or

cigar-shaped.⁸ *H capsulatum* yeast bodies can be round or slightly oval but not cigar-shaped. Fungal culture may provide a definitive diagnosis but requires a 2- to 4-week incubation period, and false negatives are possible.⁷ Culture must be performed in specialized laboratories because of biosafety risks. An antigen enzyme immunoassay (EIA) for *H capsulatum* is also available and has been shown to have a sensitivity of 94.4% in urine specimens from cats.⁵ Because this test detects antigen, positive results may indicate active infection, but cross-reactivity with other mycotic organisms (eg, *Blastomyces* spp) can occur.^{5,7,9}

Identification of *S schenckii* during microscopic examination of a cytologic preparation is straightforward when the characteristic oval-to-cigar-shaped yeast forms (~3-9 µm in length and 1-4 µm in width) are seen.⁸ When only the round-shaped yeast forms are present, *S schenckii* is difficult to differentiate from *H capsulatum*,⁸ and other diagnostic techniques are needed.

Treatment & Prognosis

Histoplasmosis is typically treated with itraconazole for 4 to 6 months total or treated until 2 months after resolution of all clinical signs.⁶

Prognosis in patients with pulmonary histoplasmosis without dissemination is good, and signs have been reported to resolve without antifungal therapy, although therapy is strongly recommended.⁷ Disseminated histoplasmosis has a guarded to poor prognosis that depends on the degree of infiltration and organs involved.^{6,7} Bone marrow infiltration and the presence of organisms on peripheral blood smears are signs of a poor prognosis.

Conclusion

H capsulatum is a dimorphic fungus that can cause severe disease in cats. Pancytopenia may be seen with marked bone marrow infiltration. Microscopic identification of *H capsulatum* organisms is often essential for diagnosis,⁶ especially in areas where both *S schenckii* and *H capsulatum* are endemic.⁹ Bird and bat droppings provide an ideal growth medium for *H capsulatum*, so access by cats to chicken coops, birds, and bat roosts should be prevented.^{3,5,7-9} Prognosis is poor to guarded in cats with disseminated disease.⁶

See page 108 for references.

Heartgard® Plus

(ivermectin/pyrantel)

CHEWABLES

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

INDICATIONS: For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) for a month (30 days) after infection and for the treatment and control of ascarids (*Toxocara canis*, *Toxascaris leonina*) and hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*, *Ancylostoma braziliense*).

DOSAGE: HEARTGARD® Plus (ivermectin/pyrantel) should be administered orally at monthly intervals at the recommended minimum dose level of 6 mcg of ivermectin per kilogram (2.72 mcg/lb) and 5 mg of pyrantel (as pamoate salt) per kg (2.27 mg/lb) of body weight. The recommended dosing schedule for prevention of canine heartworm disease and for the treatment and control of ascarids and hookworms is as follows:

Dog Weight	Chewables Per Month	Ivermectin Content	Pyrantel Content	Color Coding On Foil Backing and Carton
Up to 25 lb	1	68 mcg	57 mg	Blue
26 to 50 lb	1	136 mcg	114 mg	Green
51 to 100 lb	1	272 mcg	227 mg	Brown

HEARTGARD Plus is recommended for dogs 6 weeks of age and older.

For dogs over 100 lb use the appropriate combination of these chewables.

ADMINISTRATION: Remove only one chewable at a time from the foil-backed blister card. Return the card with the remaining chewables to its box to protect the product from light. Because most dogs find HEARTGARD Plus palatable, the product can be offered to the dog by hand. Alternatively, it may be added intact to a small amount of dog food. The chewable should be administered in a manner that encourages the dog to chew, rather than to swallow without chewing. Chewables may be broken into pieces and fed to dogs that normally swallow treats whole.

Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes after administration to ensure that part of the dose is not lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

HEARTGARD Plus should be given at monthly intervals during the period of the year when mosquitoes (vectors), potentially carrying infective heartworm larvae, are active. The initial dose must be given within a month (30 days) after the dog's first exposure to mosquitoes. The final dose must be given within a month (30 days) after the dog's last exposure to mosquitoes.

When replacing another heartworm preventive product in a heartworm disease preventive program, the first dose of HEARTGARD Plus must be given within a month (30 days) of the last dose of the former medication.

If the interval between doses exceeds a month (30 days), the efficacy of ivermectin can be reduced. Therefore, for optimal performance, the chewable must be given once a month on or about the same day of the month. If treatment is delayed, whether by a few days or many, immediate treatment with HEARTGARD Plus and resumption of the recommended dosing regimen will minimize the opportunity for the development of adult heartworms.

Monthly treatment with HEARTGARD Plus also provides effective treatment and control of ascarids (*T. canis*, *T. leonina*) and hookworms (*A. caninum*, *U. stenocephala*, *A. braziliense*). Clients should be advised of measures to be taken to prevent reinfection with intestinal parasites.

EFFICACY: HEARTGARD Plus Chewables, given orally using the recommended dose and regimen, are effective against the tissue larval stage of *D. immitis* for a month (30 days) after infection and, as a result, prevent the development of the adult stage. HEARTGARD Plus Chewables are also effective against canine ascarids (*T. canis*, *T. leonina*) and hookworms (*A. caninum*, *U. stenocephala*, *A. braziliense*).

ACCEPTABILITY: In acceptability and field trials, HEARTGARD Plus was shown to be an acceptable oral dosage form that was consumed at first offering by the majority of dogs.

PRECAUTIONS: All dogs should be tested for existing heartworm infection before starting treatment with HEARTGARD Plus which is not effective against adult *D. immitis*. Infected dogs must be treated to remove adult heartworms and microfilariae before initiating a program with HEARTGARD Plus.

While some microfilariae may be killed by the ivermectin in HEARTGARD Plus at the recommended dose level, HEARTGARD Plus is not effective for microfilariae clearance. A mild hypersensitivity-type reaction, presumably due to dead or dying microfilariae and particularly involving a transient diarrhea, has been observed in clinical trials with ivermectin alone after treatment of some dogs that have circulating microfilariae.

Keep this and all drugs out of the reach of children.

In case of ingestion by humans, clients should be advised to contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans.

Store between 68°F - 77°F (20°C - 25°C). Excursions between 59°F - 86°F (15°C - 30°C) are permitted. Protect product from light.

ADVERSE REACTIONS: In clinical field trials with HEARTGARD Plus, vomiting or diarrhea within 24 hours of dosing was rarely observed (1.1% of administered doses). The following adverse reactions have been reported following the use of HEARTGARD: Depression/lethargy, vomiting, anorexia, diarrhea, mydriasis, ataxia, staggering, convulsions and hypersalivation.

SAFETY: HEARTGARD Plus has been shown to be bioequivalent to HEARTGARD, with respect to the bioavailability of ivermectin. The dose regimens of HEARTGARD Plus and HEARTGARD are the same with regard to ivermectin (6 mcg/kg). Studies with ivermectin indicate that certain dogs of the Collie breed are more sensitive to the effects of ivermectin administered at elevated dose levels (more than 16 times the target use level) than dogs of other breeds. At elevated doses, sensitive dogs showed adverse reactions which included mydriasis, depression, ataxia, tremors, drooling, paresis, recumbency, excitability, stupor, coma and death. HEARTGARD demonstrated no signs of toxicity at 10 times the recommended dose (60 mcg/kg) in sensitive Collies. Results of these trials and bioequivalency studies, support the safety of HEARTGARD products in dogs, including Collies, when used as recommended.

HEARTGARD Plus has shown a wide margin of safety at the recommended dose level in dogs, including pregnant or breeding bitches, stud dogs and puppies aged 6 or more weeks. In clinical trials, many commonly used flea collars, dips, shampoos, anthelmintics, antibiotics, vaccines and steroid preparations have been administered with HEARTGARD Plus in a heartworm disease prevention program.

In one trial, where some pups had parvovirus, there was a marginal reduction in efficacy against intestinal nematodes, possibly due to a change in intestinal transit time.

HOW SUPPLIED: HEARTGARD Plus is available in three dosage strengths (See DOSAGE section) for dogs of different weights. Each strength comes in convenient cartons of 6 and 12 chewables.

For customer service, please contact Merial at 1-888-637-4251.



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