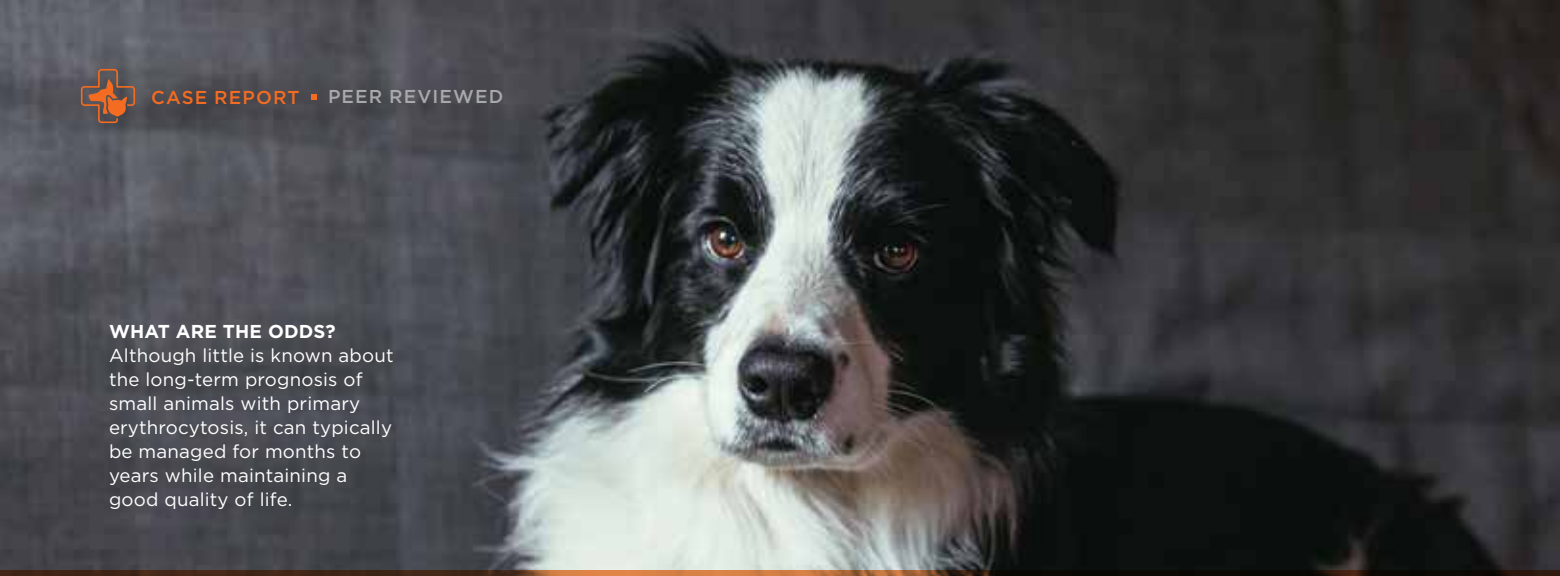

WHAT ARE THE ODDS?
Although little is known about the long-term prognosis of small animals with primary erythrocytosis, it can typically be managed for months to years while maintaining a good quality of life.

CASE REPORT: HEMATOLOGY

Primary Erythrocytosis in a Dog

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Erythrocytosis refers to increased red blood cell (RBC) mass, leading to increased hematocrit. Erythrocytosis can be relative or absolute. Relative erythrocytosis can indicate increased hematocrit resulting from loss of water from the plasma, usually due to severe dehydration, or from splenic contraction. Absolute erythrocytosis is a true increase in RBC mass and can be primary (erythropoietin-independent) or secondary (erythropoietin-stimulated). Absolute erythrocytosis of any etiology causes the blood to become thick, which can lead to signs of hyperviscosity, such as mucosal bleeding, ocular abnormalities, and/or neurologic abnormalities.[1]

Secondary absolute erythrocytosis occurs when increased erythropoietin secretion induces increased RBC production. This system is part of a feedback loop in which, under normal circumstances, decreased oxygen delivery to the kidney mediates increased secretion of erythropoietin, which stimulates RBC production (**FIGURE 1**).[2] Causes of secondary erythrocytosis include conditions that cause whole-body hypoxemia or secretion of erythropoietin out of control of the normal feedback loop. The best-understood hypoxemic

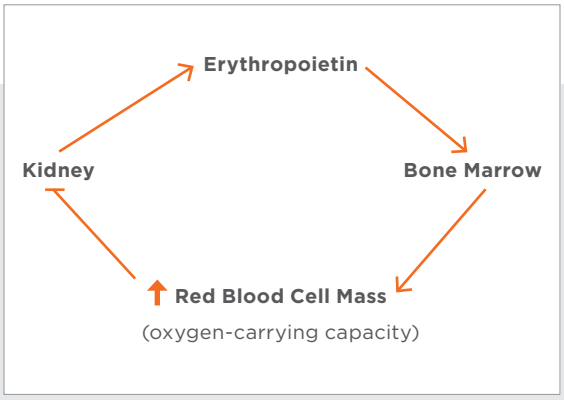

FIGURE 1. Erythropoietin feedback loop. When oxygen delivery to the kidney is decreased, erythropoietin secretion is increased, which stimulates the bone marrow to increase red blood cell (RBC) production. The increased RBC mass increases oxygen delivery to the kidney.

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cause is cardiac disease causing right-to-left shunting.[3,4] On the basis of clinical experience and biological plausibility, chronic pulmonary disease is considered a differential diagnosis; however, support for this assumption is lacking in the veterinary medical literature. Hereditary methemoglobinemia can cause erythrocytosis through decreased oxygen saturation of hemoglobin despite normal oxygen partial pressure.[5] Secretion of erythropoietin out of control of the normal feedback loop can result from paraneoplastic erythropoietin secretion[6-8] or hormonal stimulation of erythropoietin secretion by thyroid and other hormones.[9] Inappropriately elevated erythropoietin has also been reported in a patient with erythrocytosis and necrotizing pyelonephritis.[10]

Primary absolute erythrocytosis is the result of RBC production in the bone marrow, independent of stimulation by the normal hypoxemia–erythropoietin feedback loop. Although this condition is sometimes termed polycythemia vera because of clinical similarities with the human disease of the same name, these conditions are not synonymous because diagnosis of polycythemia vera in humans requires documentation of diagnostic criteria that are not present or not evaluated in dogs. Most notably, although the identification of characteristic bone marrow abnormalities is a major criterion for diagnosis of polycythemia vera in humans,[11] bone marrow biopsy is not useful for the diagnosis of primary erythrocytosis in dogs. This case report describes a case of primary erythrocytosis in a dog, from initial presentation through treatment.

THE CASE

Initial Presentation and Diagnostics

The patient was an 8-year-old intact male border collie presented to his primary care veterinarian for hematemesis. At the time of examination, mild preputial bleeding was noted. A complete blood count (CBC) revealed a markedly elevated hematocrit of 83%. Eight days later, after additional preputial bleeding was noted, a recheck CBC indicated a persistently elevated hematocrit (86%). Jugular phlebotomy removed 500 mL of whole blood, and the patient was referred for further evaluation. Amoxicillin was given in case urinary tract infection was a cause of the preputial bleeding.

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Referral Presentation and Diagnostics

At the time of presentation to our referral hospital, no additional bleeding episodes were reported. Physical examination revealed moderate conjunctival hyperemia but was otherwise unremarkable, with no evidence of dehydration. An additional CBC indicated that the spun packed cell volume (PCV) was elevated at 76%; plasma protein was within reference range at 6.7 g/dL. A moderate reticulocytosis of 393 370/µL was present. RBC indices were mean cell volume (MCV) within reference range at 68.7 fL and mean corpuscular hemoglobin concentration below reference range at 30 g/dL. Other blood abnormalities included moderate leukocytosis (25 240/µL) characterized by moderate neutrophilia (21 706/µL) with a regenerative left shift (1262 bands/µL) and moderate thrombocytopenia (81 000/µL). A serum chemistry panel revealed no abnormalities. On visual inspection, blood subjectively appeared normal red, which was inconsistent with methemoglobinemia.

To rule out causes of secondary erythrocytosis, additional testing was performed. Echocardiography ruled out structural heart defects causing right-to-left shunting. An arterial blood gas sample indicated normoxemia. A computed tomography scan of the abdomen to screen for neoplasia that could cause paraneoplastic erythrocytosis showed focal thickening of the cecum. This finding was considered most likely to be secondary to incomplete filling during the study; however, focal typhlitis or neoplasm could not be definitively ruled out at that time.

Plasma erythropoietin was measured at <1 mU/µL (reference range provided by laboratory 1.9 to 22.9 mU/mL). Although 1 study documented overlap between erythropoietin values in dogs with primary

erythrocytosis and unaffected dogs,[12] this finding ruled out paraneoplastic erythropoietin secretion. It also provided additional support for primary erythrocytosis by supporting the assumption that the elevated hematocrit was mediating decreased erythropoietin production in the kidney, leading to an undetectable plasma erythropoietin level. In humans, a subnormal level of serum erythropoietin is a minor criterion for a diagnosis of polycythemia vera.[11]

Treatment

After 500 mL of blood was removed by jugular phlebotomy, 800 mL of lactated Ringer's solution was administered through a cephalic catheter. The PCV after phlebotomy was 65%. Two weeks later, the patient's PCV had increased to 75% and another 500 mL of blood was removed from the jugular vein. PCV after the second phlebotomy was 55%. After the target PCV was attained, hydroxyurea treatment was initiated because the patient was reactive to handling and required heavy sedation to be safely restrained for phlebotomy. Hydroxyurea was initially dosed at about 40 mg/kg PO q24h. CBCs were monitored biweekly to ensure that the medication would maintain a PCV below 55% without causing dangerous myelosuppression. The dosage was gradually tapered to a final dosage of about 40 mg/kg PO q48h. Attempts to further taper this dose resulted in recurrence of elevated PCV. No myelosuppression was noted, and the patient's PCV remained in the high-normal range. At this point, the interval between CBCs was extended. No recurrence of hematemesis or preputial bleeding was reported.

Eleven months after initiation of hydroxyurea treatment, onycholysis and skin pigmentation changes of the ventrum developed. Because these dermatologic changes were suspected to be adverse effects of hydroxyurea, treatment was discontinued, after which the changes resolved completely.

Six months after discontinuation of hydroxyurea, the patient's PCV again increased to 65%. Alternative treatment options were discussed, including placement of a venous access port to facilitate phlebotomy or treatment with medicinal leeches. Ultimately, the client declined these treatment options on the basis of cost and impracticality, respectively. After careful client counseling, the decision was made to perform phlebotomy to decrease PCV to 55% and to restart hydroxyurea at 1000 mg PO q48h with the goal of lengthening the interval between (but not eliminating) phlebotomies.

Five months after the previous phlebotomy, the patient was presented for the final referral visit. PCV was 66%, and the dermatologic changes had not recurred. A phlebotomy was performed. Because the current frequency of phlebotomies was reasonable when balanced with the ability to avoid recurrence of dermatologic toxicity, it was decided to not attempt to increase the dose of hydroxyurea. The patient was doing well at this visit, after which he returned to his primary care veterinarian for monitoring.

DISCUSSION

The goal of treatment for erythrocytosis is to maintain a PCV of 55% or lower to eliminate or minimize signs of hyperviscosity. The cornerstone of treatment for absolute erythrocytosis in patients for which the underlying cause cannot be identified or resolved in both human[12] and veterinary medicine is phlebotomy. The typical volume removed is 15 to 20 mL/kg.[13] In some patients, intermittent phlebotomy is the only treatment necessary to achieve control of PCV and clinical signs.[4,14] Placement of a vascular access port[15] can facilitate phlebotomy in patients for which frequent hospital visits and restraint are not unduly stressful. Hirudotherapy, the use of medicinal leeches to control erythrocytosis, in a cat has been described.[16] Each leech is expected to remove approximately 10 mL of blood, and bleeding continues for 24 hours after removal of the leech. Because of the small volume of blood each leech removes, this approach may be most practical for cats or small dogs.

In human patients with polycythemia vera, the chemotherapeutic drug hydroxyurea is administered in addition to phlebotomy to patients with intermediate to high risk for thrombotic or bleeding complications.[17] In dogs, hydroxyurea is used to control RBC mass in patients with absolute erythrocytosis (primary or secondary) for which the cause of the erythrocytosis cannot be resolved and for which the required interval between phlebotomies is unacceptably short. For some patients, the disease may be controlled with hydroxyurea alone,[3,13] whereas some may require concurrent intermittent phlebotomies to maintain a PCV within the target range.[18] Various dosing regimens have been reported, including 40 to 50 mg/kg q48h with titration based on monitoring[3] or a loading dose of 30 mg/kg q24h for 7 days followed by a

maintenance dose of 15 mg/kg q24h.[13] Hydroxyurea is usually well tolerated. Reported adverse effects in dogs include myelosuppression,[19] gastrointestinal upset,[13] dermatologic reactions,[18] and onychomadesis (toenail loss).[20,21] It is not known whether dogs with primary erythrocytosis and those with secondary erythrocytosis (i.e., patients with cardiac defects) would benefit from different dosing schemes.

The prognosis for primary erythrocytosis in dogs is poorly characterized. Survival for 1 year was reported for a dog that underwent phlebotomy alone,[14] and survival for 18 months was reported for a dog that underwent phlebotomy and received hydroxyurea.[18] Other case reports document control of clinical signs of up to 33 months after treatment with phlebotomy followed by hydroxyurea.[1]

This report underscores multiple factors relevant to the general practitioner. It is typically the primary care veterinarian who documents persistent erythrocytosis, so an understanding of possible explanations for this finding is critical. **FIGURE 2** provides a simplified flow chart to assist with decision-making when dealing with patients with persistently elevated hematocrit. When relative erythrocytosis has been ruled out, patients should be referred to a specialty hospital for further diagnostics because underlying causes of secondary erythrocytosis may be resolvable, and if not resolvable, an underlying cause such as a cardiac defect may change the treatment plan and prognosis. If primary erythrocytosis is confirmed, however, monitoring and treatment require no specialized equipment and can therefore be managed by a general practitioner with an understanding of the disease. The occurrence of dermatologic adverse effects resulting from hydroxyurea treatment highlights the need to determine an individualized treatment plan, which requires knowledge of the treatment options available.

When clients are weighing the costs and benefits of treatment, they look to their primary care veterinarian for an understanding of prognosis. General practitioners should discuss that although little is known about the long-term prognosis, the disease can typically be managed for months to years while maintaining a good quality of life. TVP

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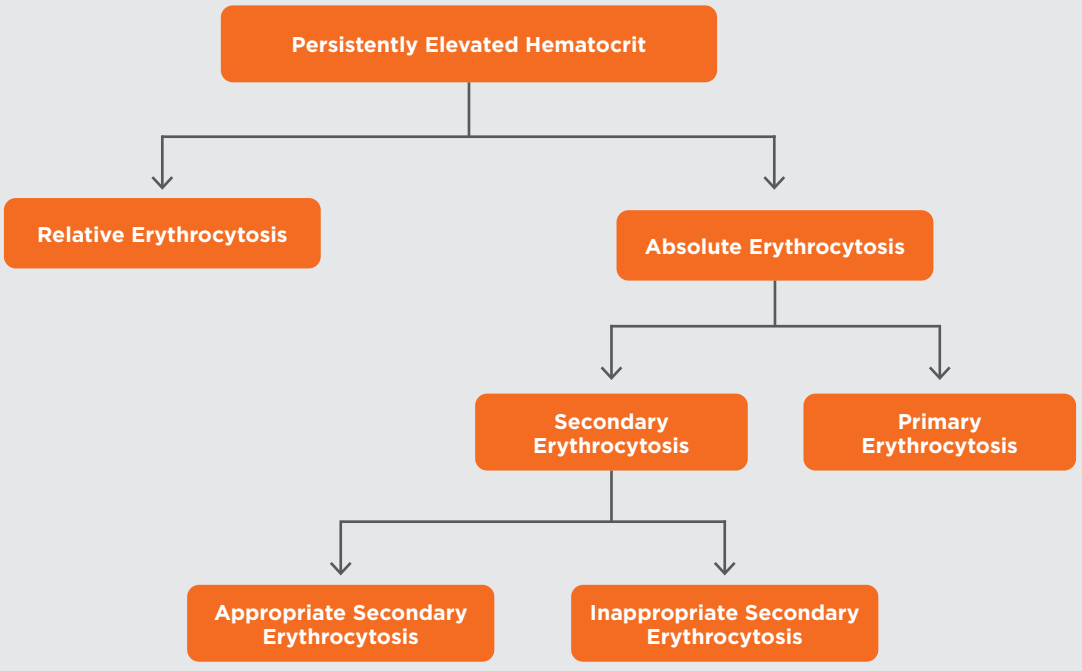

FIGURE 2. Simplified flow chart for diagnosis of persistently elevated hematocrit.

Miratаz®
(mirtazapine transdermal ointment)

For topical application in cats only. Not for oral or ophthalmic use.

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

Before using this product, please consult the product insert, a summary of which follows:

INDICATION: Miratаz is indicated for the management of weight loss in cats.

DOSAGE AND ADMINISTRATION: Administer topically by applying a 1.5-inch ribbon of ointment (approximately 2 mg/cat) on the inner pinna of the cat's ear once daily for 14 days. Wear disposable gloves when applying Miratаz. Alternate the daily application of Miratаz between the left and right inner pinna of the ears. **See Product Insert for complete dosing and administration information.**

CONTRAINDICATIONS: Miratаz is contraindicated in cats with a known hypersensitivity to mirtazapine or to any of the excipients. Miratаz should not be given in combination, or within 14 days before or after treatment with a monoamine oxidase inhibitor (MAOI) [e.g. selegiline hydrochloride (L-deprenyl), amitraz], as there may be an increased risk of serotonin syndrome.

HUMAN WARNINGS: Not for human use. Keep out of reach of children. **Wear disposable gloves when handling or applying Miratаz to prevent accidental topical exposure.** After application, dispose of used gloves and wash hands with soap and water. After application, care should be taken that people or other animals in the household do not come in contact with the treated cat for 2 hours because mirtazapine can be absorbed transdermally and orally. However, negligible residues are present at the application site and the body of the cat at 2 hours after dosing. In case of accidental skin exposure, wash thoroughly with soap and warm water. In case of accidental eye exposure, flush eyes with water. If skin or eye irritation occurs seek medical attention. In case of accidental ingestion, or if skin or eye irritation occurs, seek medical attention.

PRECAUTIONS: Do not administer orally or to the eye. Use with caution in cats with hepatic disease. Mirtazapine may cause elevated serum liver enzymes (See **Animal Safety** in the product insert). Use with caution in cats with kidney disease. Kidney disease may cause reduced clearance of mirtazapine which may result in higher drug exposure. Upon discontinuation of Miratаz, it is important to monitor the cat's food intake. Food intake may lessen after discontinuation of mirtazapine transdermal ointment. If food intake diminishes dramatically (>75%) for several days, or if the cat stops eating for more than 48 hours, reevaluate the cat. Miratаz has not been evaluated in cats < 2 kg or less than 6 months of age. The safe use of Miratаz has not been evaluated in cats that are intended for breeding, pregnant, or lactating cats.

ADVERSE REACTIONS: In a randomized, double-masked, vehicle-controlled field study to assess the effectiveness and safety of mirtazapine for the management of weight loss in cats, 115 cats treated with Miratаz and 115 cats treated with vehicle control were evaluated for safety. The vehicle control was an ointment containing the same inert ingredients as Miratаz without mirtazapine. The most common adverse reactions included application site reactions, behavioral abnormalities (vocalization and hyperactivity), and vomiting. **See Product Insert for complete Adverse Reaction information.** To report suspected adverse events, for technical assistance or to obtain a copy of the SDS, contact Dechra at 888-933-2472. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at **http://www.fda.gov/reportanimalae**.

EFFECTIVENESS: The effectiveness of Miratаz (mirtazapine transdermal ointment) was demonstrated in a randomized, double-masked, vehicle-controlled, multi-site field study involving client-owned cats of various breeds. Enrolled cats were ≥ 1 year of age and had existing documented medical history of ≥ 5% weight loss deemed clinically significant. The most common pre-existing conditions included renal insufficiency, vomiting, and hyperthyroidism. Some cats had more than one pre-existing condition. Cats were randomized to treatment groups in a 1:1 ratio of Miratаz to vehicle control. A total of 230 cats were enrolled and received either Miratаz (115 cats) or a vehicle control (115 cats) containing the same inert ingredients without mirtazapine. The cats were 2.8-24.6 years of age and weighed 2.1-9.2 kg. The dosage was a 1.5-inch ribbon (approximately 2 mg/cat) mirtazapine or vehicle ointment administered topically to the inner pinna of the cat's ear. A total of 177 cats were determined to be eligible for the effectiveness analysis; 83 cats were in the Miratаz group and 94 cats were in the vehicle control group. The primary effectiveness endpoint was the mean percent change in body weight from Day 1 to the Week 2 Visit. At Week 2, the mean percent increase in body weight from Day 1 was 3.94% in the mirtazapine group and 0.41% in the vehicle control group. The difference between the two groups was significant ($p<0.0001$) based on a two-sample t-test assuming equal variances. A 95% confidence interval on the mean percent change in body weight for the Miratаz group is (2.77, 5.11), demonstrating that the mean percent change is statistically different from and greater than 0.

STORAGE: Store below 25°C (77°F). Multi-use tube. Discard within 30 days of first use.

HOW SUPPLIED: Miratаz is supplied in a 5 gram aluminum tube.

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US Patent 10,603,272

Approved by FDA under NADA # 141-481
NDC 86078-686-01

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