

CASE REPORT

A novel bone marrow-sparing treatment for primary erythrocytosis in a cat: Onion powder

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Abstract

Primary erythrocytosis (PE) is a rare myeloproliferative neoplasm in cats resulting in the overproduction of erythrocytes. Current treatment modalities include repeated phlebotomy and chemotherapeutic drugs. These treatments may not be well tolerated by the cat and can present safety and financial challenges to owners. Because of the rarity of PE, prospective studies for new treatment options are difficult to perform. This case report describes the novel use of onion powder in an attempt to produce Heinz body-induced erythrocyte destruction in order to decrease total erythrocyte mass and normalize the hematocrit in a cat with PE. To our knowledge, the use of onion powder in the treatment of PE in cats has never been described before and may have potential as a safe, low-cost, and highly accessible alternative treatment for this rare disease.

KEYWORDS

clinical pathology, feline, oncology, onion, polycythemia vera, primary erythrocytosis

1 | INTRODUCTION

Primary erythrocytosis (PE), also known as polycythemia vera, is a rare myeloproliferative neoplasm that results in the overproduction of erythrocytes.¹ Primary erythrocytosis has been reported in animals, including cats, and is well described in humans, where it is often the result of a clonally acquired mutation in the JAK2 tyrosine kinase, leading to constitutive hyperactivation of hematopoiesis.²⁻⁴ A unique subset of human patients with polycythemia vera (ie, primary polycythemia) has a gain-of-function mutation in exon 12 of the JAK2 gene leading to erythrocytosis only, similar to PE in cats, although the exact underlying cause for PE in cats is still unknown. Primary erythrocytosis is diagnosed based on a persistently increased PCV

(65%-85%) in a euhydrated animal after exclusion of diseases causing hypoxemia or paraneoplastic erythropoietin production.^{5,6} Cats often present with congested mucous membranes and neurological signs, but gastrointestinal signs also have been reported.⁷ Treatment options for animals include repeated phlebotomy and chemotherapeutic agents (eg, hydroxyurea), as well as hirudotherapy (medicinal use of leeches).^{8,9} Although effective, phlebotomy and hirudotherapy may not be tolerated by all patients, and risk of exposure to chemotherapeutic agents may not be acceptable to pet owners, especially those who are pregnant, nursing, or have young children.¹⁰

In this reported case, traditional treatment options were not possible because of the cat's fractious demeanor and the presence of young children in the household. As a result, an alternative treatment for decreasing erythrocyte mass was implemented by using onion powder PO in an attempt to cause low-grade Heinz body-induced hemolysis. The use of onion powder resulted in successful long-term management of the cat's PE with no apparent adverse reactions.

Abbreviations: CK, creatine kinase; G6PD, glucose-6-phosphate dehydrogenase; HCT, hematocrit; HgB, hemoglobin; MCHC, mean cell hemoglobin concentration; MCV, mean cell volume; PE, primary erythrocytosis; RBC, red blood cell; tsp, teaspoon.

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Therefore, onion powder may be considered a useful alternative when traditional treatment options are not feasible. To our knowledge, this case is the first reported use of onion powder as an alternative treatment for PE.

2 | CASE REPORT

A 10-year-old, 5.6-kg, indoor-outdoor spayed female domestic short-hair cat was presented to the William R. Pritchard Veterinary Medical Teaching Hospital at the University of California, Davis for an acute onset of head tremors and inability to walk. Physical examination disclosed dark pink mucous membranes, intermittent tremors of the head and thoracic limbs, and flaccid paresis of the pelvic limbs. The patient had normal temperature (101.2F), heart rate (160 beats per minute), and respiratory rate (30 breaths per minute) and was normally hydrated. Initial diagnostic testing included a CBC, serum biochemistry panel and urinalysis. On the CBC, markedly increased hematocrit (HCT, 73.0%; reference interval [RI], 30-50%), mild-to-moderate microcytosis (mean corpuscular volume [MCV] 38.3 fl; RI, 42-53 fl), rare polychromatophils and moderately decreased platelet count with platelet clumps (68 000/ μ L; RI, 180 000-500 000/ μ L), confirmed by a manual blood smear review, were identified. The only clinically relevant abnormality on the serum biochemistry panel was moderately increased creatine kinase (CK) activity (1177 IU/L; RI, 73-260 IU/L). Urine was collected by cystocentesis and contained blood (8-12 red blood cell [RBC]/high-power field [hpf]; RI, 0-2/hpf) and trace protein (150 mg/dL), thought to be associated with the collection method. The urine-specific gravity was 1.019. Arterial blood gas results were normal. Thoracic radiographs also were normal. Abdominal ultrasound examination identified bilateral irregular margins of the renal cortices and small, multifocal renal cortical cysts.

On the basis of this diagnostic evaluation, underlying neoplasia, hypoxemia, and dehydration were excluded, and a diagnosis of PE was made. Phlebotomy was performed and 70 mL of whole blood was removed from the jugular vein and replaced with an equivalent volume of crystalloid fluids (lactated Ringer's solution) IV. The cat was returned 14 days later for reevaluation and had a PCV of 65% and normalized CK activity (221 IU/L). Phlebotomy was repeated and 60 mL of whole blood was removed and replaced with 30 mL of crystalloid fluids IV. A second reevaluation 3 weeks later determined that the cat continued to have an increased PCV (74%), and a third phlebotomy was performed, removing 80 mL of whole blood. The patient was asymptomatic at both reevaluations.

Because of the time commitment and expense, the owners declined continued treatment by phlebotomy. The owners also declined treatment with hydroxyurea because of young children in the household and the cat's fractious demeanor. As a result, an inexpensive, easily administered, nonhazardous treatment modality was sought. The owners were offered a novel, bone marrow-sparing treatment of onion powder with the goal of decreasing total erythrocyte mass by controlled hemolysis. A dose of 1/8 teaspoon (tsp) per day of store-bought onion powder was prescribed and directed to be mixed with food (43.5 g of canned food).

This dose was chosen based on the smallest quantity measurable at home with easily accessible kitchen utensils. The patient returned 10 days later for its first reevaluation and diagnostic testing after initiation of onion powder treatment and was reported to be asymptomatic at home. On CBC, the HCT had decreased to 55.2% and microcytosis had improved (39.5 fl) with rare Heinz bodies (<1%) observed on blood smear examination. A serum biochemistry panel at this time was normal (CK, 81 IU/L), and the initial increase in CK activity was considered secondary to decreased perfusion caused by hyperviscosity, as reported in other cats with PE.⁷

Over the course of the next 15 months, the cat returned for multiple reevaluations with repeat CBC to monitor HCT, Heinz body formation, and hemoglobin (Hgb) concentration (Table S1) and to titrate the onion powder dose accordingly. The patient was reported to be free of clinical signs at home throughout this time and physical examinations at all subsequent reevaluations did not identify any overt abnormalities with the exception of dark pink mucous membranes. The second reevaluation was 17 days after initiation of onion powder treatment, and the HCT was similar to the first reevaluation HCT (58.8% vs 55.2%) and dose frequency was decreased to every 48 hours at this time to determine if a lower dosing frequency was equally effective. A third reevaluation (27 days after initiation of treatment) indicated a slightly increased HCT (60.4%) compared to previous visits, and the dose frequency was returned to every 24 hours, Monday through Friday, for owner convenience. Fourth and 5th reevaluations (41 days and 5 months after treatment initiation, respectively) showed a largely unchanged HCT, and dose frequency was increased to 6 days per week, Monday through Saturday. At the 6th and final reevaluation, 15 months after initiation of onion powder treatment, the cat's HCT had normalized (HCT, 47.8%; RI, 30-50%) and microcytosis had resolved (MCV, 46 fl; RI, 42-53 fl). The remaining CBC variables were normal, with the exception of a mildly increased mean cell Hgb concentration (MCHC, 36.4 g/dL) and Hgb concentration (17.4 g/dL), and a repeated serum biochemistry panel was normal.

New methylene blue-stained blood smear preparations were made with each CBC performed at each reevaluation, and used for the quantitation of Heinz bodies. Heinz bodies were reported as a percentage of 1000 erythrocytes and counted by a board-eligible veterinary clinical pathologist. Heinz bodies were noted to be rare (<1%) on every blood smear examination throughout the 15 months (Figure 1). Rare Heinz bodies are considered a normal finding, and healthy cats may have up to 5% of their erythrocytes containing Heinz bodies.¹ Schistocytes and other RBC abnormalities suggestive of hemolysis were not observed on blood smear review.

The increase in the patient's Hgb concentration above the RI could be an artifact of an increased HCT or secondary to mild hemolysis, especially when the HCT was normal (Table S1). Mean cell Hgb concentration was normal to marginally increased throughout treatment, with a mild increase towards the final reevaluation. No discolored urine was reported by the owners, but hemoglobinuria was not definitively excluded because of the cost of testing. Blood coloration was normal throughout treatment, suggesting that clinically detectable methemoglobinemia did not develop with onion powder treatment.

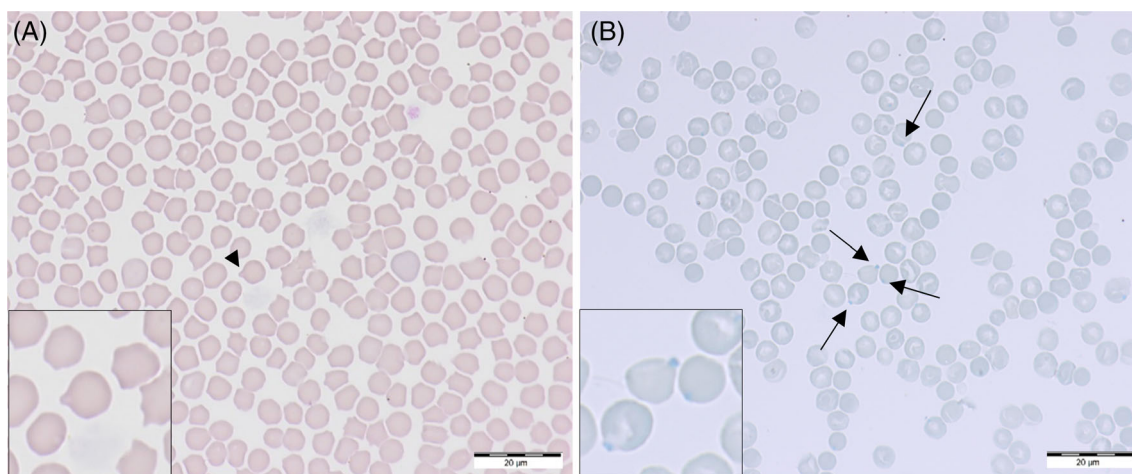


FIGURE 1 Heinz body inclusions in a cat treated with onion powder for primary erythrocytosis. A, Recheck blood smear stained with Wright Giemsa. Heinz bodies are difficult to identify with Romanowsky stains but typically appear as single-rounded projections on the periphery of the erythrocyte (arrowhead, inset). B, The same blood smear stained with new methylene blue to highlight Heinz body inclusions, which appear as round, blue structures (arrows, inset). 100x microscope objective. Scale bar = 20 µm

3 | DISCUSSION

Onions are a known cause of oxidative damage to erythrocytes in domestic species. Oxidative damage occurs because of the presence of aliphatic sulfides in onions, which decrease the production of reduced glutathione in erythrocytes by interfering with the enzyme glucose-6-phosphate dehydrogenase (G6PD). This leaves erythrocyte HgB susceptible to oxidative degeneration and subsequent Heinz body formation.¹¹ Erythrocytes with Heinz body inclusions often are removed or lysed in the spleen and have a decreased lifespan if they persist in circulation. This may lead to hemoglobinemia, hemoglobinuria, or anemia or some combination of these if erythrocyte destruction is uncontrolled or persistent. In addition, oxidative damage to HgB may lead to methemoglobinemia. Cat HgB has increased susceptibility to oxidative damage and Heinz body formation because of the presence of 8 reactive sulfhydryl groups on each globin tetramer.¹² This unique aspect of cat erythrocyte physiology was manipulated in this case to successfully treat PE using onion powder.

Onion powder has been implicated in Heinz body-induced hemolytic anemia in cats that have eaten baby food containing onion powder.¹³ When 2.5% onion powder was added to the diet of purpose-bred cats, their HCT decreased and reticulocytes increased, suggesting regenerative anemia secondary to hemolysis. In the case reported here, 1/8 tsp (0.5 g) of onion powder was given once daily, mixed into 43.5 g of canned food, and resulting in 1.2% onion powder in the diet. However, the cat also had free access to dry kibble and the actual percentage of onion powder consumed in the diet may have been lower. Regardless, the dose and frequency used in this cat did not produce adverse effects (eg, methemoglobinemia, anemia, additional clinical signs), and treatment was well tolerated. Hypothetically, an increased dose or frequency possibly could have been used to achieve normalization of the HCT sooner.

Despite the use of a toxin known to cause Heinz body-induced hemolysis in domestic cats, overt hemolysis was not definitively

documented in this case. Rather, some diagnostic variables were supportive of mild hemolysis as the underlying cause. The patient's increased HgB concentration, even after normalization of the HCT, and increased MCHC in the absence of artifactual causes (eg, lipemia, excessive Heinz body formation) are supportive of hemolysis. The absence of excessive Heinz body formation in the presence of onion powder treatment might be the result of the low dosage used, allowing for splenic pitting function to match the rate of formation of Heinz bodies. In addition, because erythroid precursors are dependent on G6PD for erythropoiesis,¹⁴ onion powder might also decrease erythropoiesis. However, prospective studies are needed to substantiate this hypothesis. Although the exact mechanism that led to a decrease in RBC was not established here, both the decrease in HCT after initiation of treatment and the increase in HCT after decreasing treatment frequency suggest that the onion powder had a role in decreasing the HCT.

Traditional treatment options for PE are not always tolerated by patients and may have substantial adverse effects. Hydroxyurea is a drug commonly used to treat PE in domestic animals and disrupts DNA replication by preventing ribonucleotide reductase from converting ribonucleotides into deoxyribonucleotides.¹⁵ In a recent multicenter case series of cats with PE, most cats (10/18) were maintained with hydroxyurea, but adverse effects were reported in more than half of the cats, including methemoglobinemia, erythrocytic oxidative damage and myelosuppression.⁷ In addition, the same study reported that hirudotherapy caused pain and triggered seizures in 1 patient, and did not adequately decrease the HCT of another patient. Phlebotomy has been a mainstay in the treatment of PE because it rapidly curtails clinical signs, but repeated phlebotomy can have potential adverse effects including thrombosis, thrombocytosis, and iron deficiency.¹⁶ Moreover, repeated phlebotomy may be costly to owners, especially if sedation or anesthesia is required for patient comfort and compliance.

4 | CONCLUSION

In this reported case, onion powder was used successfully without adverse effects as a treatment for PE in a cat. New treatments for PV and primary polycythemia in humans focus on JAK2 inhibitors, which have unknown effectiveness in cats with PE because the underlying cause has yet to be identified. Traditional treatments are not feasible in all cats, and onion powder may be an effective alternative for these cases with careful monitoring.

ACKNOWLEDGMENT

DM Vasilatis was supported by T32 OD011147 during preparation of this manuscript. The authors acknowledge the laboratory personnel at the University of California, Davis, Veterinary Medical Teaching Hospital in Davis, California, where the laboratory work was exclusively performed.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.


INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by University of California, Davis IACUC.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Vasilatis DM, McGill JE, Gilor C. A novel bone marrow-sparing treatment for primary erythrocytosis in a cat: Onion powder. *J Vet Intern Med*. 2021; 35(4):1977-1980. <https://doi.org/10.1111/jvim.16194>