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LETTER TO THE EDITOR

Response to letter regarding "A novel bone marrow-sparing treatment for primary erythrocytosis in a cat: Onion powder"

Dear Editors,

Thank you for the opportunity to address Dr Giger's and Dr Christopher's letter.

We appreciate the excellent literature review provided by Drs Giger and Christopher regarding polycythemia vera (PV), although our case involved a cat diagnosed with primary erythrocytosis (PE), a similar but distinctly different disease that does not share the same features. Their review of the literature reiterated several points discussed in our manuscript, including the difficulty in definitively diagnosing PV or PE in animals. However, Drs Giger and Christopher's critique makes several false claims that clinicopathologic data (eg, total protein, urinalysis) were not reported and that the animal was potentially misdiagnosed with PE after only one phlebotomy. These data are described as unremarkable (ie, normal) or explicitly provided in the manuscript and we reported that three phlebotomies were performed on the animal before a diagnosis of PE was made. It concerns us that the manuscript was not read carefully and that the supplemental information may have been overlooked.

Drs Giger and Christopher argue that not all primary causes of erythrocytosis were completely excluded in this case and that the resolution was likely spontaneous and independent of treatment. Specifically, they suggest that the renal changes observed on ultrasound (small cysts) could have been responsible for secondary erythrocytosis. While we cannot completely exclude this possibility, we find it irrelevant because transient causes were excluded, making onion powder treatment the most likely cause of resolution of the persistent erythrocytosis in this cat. This is supported by the fact the cat's hematocrit (HCT) increased when the onion powder treatment was withdrawn, and decreased again when treatment was reinstated. Moreover, Drs Giger and Christopher remind us that "the reticulocyte count of the cat was never increased, indicating normal rather than increased erythroid production." Interestingly, reticulocytosis was not a consistent feature found in a case series of PE in cats[1] and as such the importance of this feature is debatable.

Drs Giger and Christopher suggest that an HCT of >48% is to be considered abnormal "in any cat" and take issue with the use of >65% HCT as a cutoff in our report. When carefully read, it is plainly stated that we have used the cutoff of >65% HCT in the context of diagnosing PE in accordance with the veterinary oncology literature.[2,3] Moreover, at the institution where this case was seen, the reference interval (RI) is 30% to 50% for HCT in cats, which also makes this claim futile, especially considering that RI represent 95% of a population and normal animals may fall outside these parameters. Additionally, Drs Giger and Christopher discuss at length the low count of Heinz bodies present in this cat's bloodwork. We agree that this was an unexpected finding, and address it in our discussion, including alternative ways onions may interfere with erythropoiesis. We also expected high numbers of Heinz bodies considering that onion powder consisted of approximately 1.2% of the cat's diet. However, claiming with certainty that 1.2% of onion powder would cause "approximately 15% Heinz bodies within 2 weeks" is an overreach in our opinion, as this calculation is based on one small study in a small number of healthy purpose-bred specific pathogen-free cats.[4] It is highly unlikely that the full range of biological responses would be represented by this small cohort of cats with uniform genetic and environmental backgrounds.

We agree with Drs Giger and Christopher that "regular phlebotomies with sedation … every two weeks to two months" can be used to treat PE. However, this treatment modality has limitations that must be considered, including the substantial cost to the owner, which we emphasized was the motivation for alternative treatment in our case. For owners who cannot afford frequent phlebotomy, onion powder treatment might be a reasonable alternative to euthanasia. Additionally, Drs Giger and Christopher suggest that "blaming leeches for causing seizures, as stated in [our] case report, is far-fetched." This is a gross misrepresentation of what is written in our manuscript, and when closely read, it is clear that we discussed and cited what was reported by others as a possible reaction to this therapy.[1] Regardless, Drs Giger and Christopher's claim that phlebotomy is a "desirable" treatment and implication that it is somehow better or safer compared to onion powder, chemotherapeutics like hydroxyurea, leeches, or any other treatment, is not substantiated by evidence and is completely anecdotal.

Lastly, Drs Giger and Christopher conclude that "while onions are an integral part of human diets, they can be toxic to companion animals and livestock and are not a treatment." Yes, we agree that onion powder can be toxic. However, any drug

can be toxic. We would like to take this opportunity to remind the reader of a hallmark principle of medicine and pharmacology: dose determines toxicity. Hydroxyurea and other chemotherapeutic drugs are universally toxic, and they are used despite their potential toxicity, as are hundreds of other drugs used by veterinarians daily. Onions are hardly the first or last plant with toxic potential that has been used medicinally (eg, digitalis, opioids, etc) and if we never used potential "toxins" as drugs, or drugs that had the potential of being "toxic," we would never treat anything.

We are intrigued by the potential use of onion powder as a low-cost, easily accessible treatment of PE in cats, especially as an alternative to euthanasia. We hope that our case report serves as food for thought for clinicians and continues to strike up lively discourse, or better yet, larger studies to determine the safety, efficacy and effectiveness of this and other potential treatments.

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