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Case Report

Diagnosis and Management of Polycythemia Vera in a Ferret (*Mustela putorius furo*)

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A 5-y-old female ferret (*Mustela putorius furo*) was evaluated for diarrhea, anorexia, and lethargy for 1 wk. Only mild dehydration was detected on physical examination. CBC analysis revealed marked erythrocytosis with an unremarkable plasma biochemistry panel; follow-up CBC analyses revealed a consistent primary erythrocytosis. Whole-body radiographs and abdominal ultrasonography were unremarkable except for a small nephrolith in the right kidney and a small cyst in the left kidney. The plasma erythropoietin level was 17.0 mIU/mL and considered normal. In light of the diagnostic work-up and consistent erythrocytosis, a diagnosis of polycythemia vera (primary erythrocytosis) was made. The initial presentation of diarrhea resolved after treatment with oral metronidazole (20 mg/kg PO BID for 7 d). Treatment for the polycythemia consisted of a phlebotomy initially followed by chemotherapy with hydroxyurea (10 mg/kg PO BID). During the subsequent 12 mo, the hydroxyurea dose adjusted according to follow-up CBC results, and finding an optimal dosage regimen proved to be challenging. One year after the initial diagnosis, the ferret presented to an emergency clinic for acute and severe hemorrhagic diarrhea and died shortly thereafter. The postmortem diagnosis was acute venous infarction of the small and large intestine. To our knowledge, this report is the first to describe the diagnosis and long-term management of polycythemia vera in a ferret and the use of hydroxyurea for this purpose.

Abbreviation: PV, polycythemia vera

Case Report

A 5-y-old spayed female ferret (*Mustela putorius furo*) was presented to the Ontario Veterinary College Health Sciences Centre for evaluation of diarrhea, anorexia, and lethargy of 1 wk's duration. Physical examination was unremarkable except for a subjectively enlarged spleen, which was otherwise normal on palpation. No discomfort was elicited on abdominal palpation. The diarrhea was mild. A blood sample was collected from the cranial vena cava and submitted for CBC analysis and plasma biochemistry profile. The ferret was initially treated as an outpatient with metronidazole (20 mg/kg PO BID for 7 d) and sucralfate (75 mg/kg PO BID). A suboptimal sample was obtained for laboratory submission for CBC analysis, but a manual PCV at the time of collection revealed erythrocytosis (PCV, of 89%; reference interval, 47% to 51%).[9] The biochemistry panel was unremarkable.

The next day, the ferret presented for a second CBC analysis, at which time the PCV was 69% and other RBC indices within reference intervals. Clinically, the animal had improved over the previous 24 h, with normal appetite and energy levels and resolution of the diarrhea. Persistent polycythemia in the absence of dehydration was identified. The differential diagnoses included polycythemia vera (primary erythrocytosis), an erythropoietin-producing tumor (most likely of renal origin), and chronic hypoxia associated with cardiac or pulmonary disease.

The ferret was seen for a follow-up examination at 1 wk after the initial presentation and underwent further evaluation of the erythrocytosis. The ferret was sedated with butorphanol (0.4 mg/kg IM) and midazolam (0.2 mg/kg IM). A blood sample was collected from the cranial vena cava for repeat CBC analysis and quantitative erythropoietin assay (NationWide Laboratories, Cambridge, United Kingdom). The CBC revealed a PCV of 55%, with evidence of macrocytosis and hypochromasia with a mildly elevated MCV (56 fL; reference interval, 49.6 to 60.6),[9] normal MCH (18 pg; reference interval, 16.5 to 19.7),[9] mildly decreased MCHC (320 g/dL; reference interval, 325 to 362 g/dL),[9] mildly decreased RBC distribution width (11.9; reference interval, 12% to 16%),[23] and mild thrombocytopenia (53×10^9/L; reference interval, 171 to 1280×10^9/L).[9] Abdominal ultrasonography revealed only a small focus of mineralization (diameter, 2 mm) in the right kidney, a small cyst (diameter, 2 mm) in the left kidney, and splenomegaly. These findings were considered incidental. Ventrodorsal and lateral thoracic radiographs to screen for cardiac and pulmonary lesions were unremarkable. To further assess potential hypoxemia, arterial blood sampling from the ventral tail artery was attempted but was unsuccessful. However, the oxygen saturation measured by pulse oximetry (SpO_2) was normal (100%). Serum erythropoietin levels were 17.0 mIU/mL and were assessed as normal on the basis of extrapolation from the feline reference interval (1.2 to 22.9 mIU/mL).[27] This result ruled out the presence of an erythropoietin-producing tumor. A detailed cardiac work-up was not conducted

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given the lack of abnormalities on auscultation and the absence of exercise intolerance or coughing, and the cardiac size and silhouette appeared normal on thoracic radiographs. In light of the persistent moderate to severe erythrocytosis, the lack of evidence of hypoxemic disorders or cardiopulmonary disease, normal ultrasound examination, and normal serum erythropoietin level, a diagnosis of polycythemia vera (primary erythrocytosis) was made.

A single phlebotomy was performed removing a volume of 1% of the animal's body weight, and the volume was replaced with an intravenous balanced electrolyte solution. Because of the long distance between the ferret's home and the veterinary hospital, repeated phlebotomies were not performed. The ferret then began chemotherapy with hydroxyurea (10 mg/kg PO BID), and monthly CBC analyses were performed to monitor the effectiveness of treatment and to monitor for evidence of bone-marrow toxicity such as anemia, thrombocytopenia, and leukopenia.[29] The administration of hydroxyurea effectively lowered the PCV and was accompanied by an overall improvement in the energy level of the patient. A summary of treatment and dosage changes over the course of 14 mo correlating with changes in PCV is outlined in Figure 1. It proved difficult to establish a therapeutic dose that maintained the PCV at target levels (less than 60%) without evidence of bone marrow toxicity.

Fourteen months after the initial diagnosis of polycythemia, the ferret presented to a veterinary emergency clinic for severe hemorrhagic diarrhea. Despite aggressive supportive therapy and stabilization, the animal died shortly after admission and transport to our hospital. Gross postmortem examination the following morning revealed that the intestinal tract from the distal duodenum to the distal colon was diffusely dark purple, with an abrupt demarcation between affected and normal tissue. At the time of examination, the intestinal tract was normally positioned, and thrombi were not identified in the major blood vessels. The intestinal lumen was filled with hemorrhagic fluid. The spleen was enlarged, weighing 60 g (reported range in female ferrets, 3.6 to 9.2 g)[9] and constituted 4.5% of the body weight.

Histologic examination of the intestine showed marked transmural hemorrhage. Evaluation of bone marrow revealed erythroid hyperplasia with a cellularity of 50% and a myeloid:erythroid ratio of 1:2, a normal progression of cell maturation, and dilated sinusoids. Extramedullary hematopoiesis was observed in the spleen and liver. Additional lesions included cardiac fibrosis (confirmed with Masson trichrome staining) and acute periacinar hepatocellular vacuolar degeneration and necrosis as well as moderate periacinar fibrosis. Mild membranoproliferative glomerulonephritis was present as an incidental lesion. The cause of death was determined to be generalized venous infarction of the distal duodenum to the distal colon, most consistent with intestinal volvulus.

Discussion

To our knowledge, this report represents the first published case of polycythemia vera in a ferret. The diagnosis was made in light of exclusion of other causes of an elevated PCV, the positive response to treatment, and the evidence of hyperplastic bone marrow on postmortem examination. The prolonged follow-up in this ferret allowed documentation of the dynamic changes of the PCV in association with changes in therapy and the difficulties of adjusting the hydroxyurea dose.

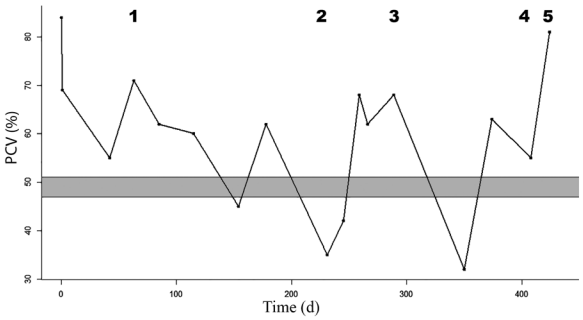

Figure 1. Changes in PCV over time in a ferret (*Mustela putorius furo)* diagnosed with polycythemia vera and treated with hydroxyurea. The gray area denotes a normal PCV for a ferret (47% to 51%).[1] 1, Initiation of treatment with hydroxyurea (10 mg/kg PO BID); 2, dose changed to 10 mg/kg once daily; 3, dose changed 10 mg/kg BID; 4, dose changed to 9 mg/kg PO BID; 5, animal died.

Erythrocytosis is defined as an increased concentration of RBC in the blood and can be relative (for example, a temporary reduction in plasma volume [hemoconcentration] or a temporary increase in the percentage of total body erythrocytes in circulation) or absolute, where there is a true increase in the body's circulating RBC mass.

The most common form of erythrocytosis encountered in clinical practice is relative erythrocytosis (hemoconcentration); an elevation in PCV as a result of dehydration or splenic contraction due to a sympathetic stimulus in response to excitement, pain, or fear.[13] In the case of dehydration, hemoconcentration is generally accompanied by an increased serum or plasma protein concentration.[4,14] These dynamic and reversible physiologic processes resolve with appropriate fluid therapy or cessation of sympathetic stimulus, as appropriate.

Absolute erythrocytosis can be primary or secondary. Primary erythrocytosis (PV) is a myeloproliferative disorder that occurs as a result of erythroid precursor defects in the bone marrow, leading to an increase in production of cells that are morphologically normal. Secondary erythrocytosis is caused by altered regulation of or excessive production of erythropoietin. Secondary erythrocytosis can occur with exogenous administration of erythropoietin, a renal mass excreting erythropoietin, chronic tissue hypoxia as induced by chronic cardiopulmonary disease, right-to-left cardiovascular shunts, carboxyhemoglobinemia, hyperadrenocorticism, and severe obesity causing hypoxia.[4,6,25,36]

In humans, the vast majority of PV cases result from a mutation in the *JAK2* gene, for which genetic testing is available and recommended.[14] In the veterinary literature, PV has only been described in horses[18] and a subset of dogs,[12] with etiology undetermined despite comprehensive diagnostic work-up.

Diagnosis of primary erythrocytosis in humans is based on the 2008 World Health Organization consensus statement and involves multiple diagnostic tests to rule out secondary disease.[20,35] Stage I consists of routine baseline bloodwork, including CBC analysis and plasma biochemistry panel, chest radiographs, abdominal ultrasonography, and assessment of serum erythropoietin levels and arterial oxygen saturation. Stage II diagnostics in humans include gene analysis, cytogenics, sleep and lung-function testing, and bone marrow aspirates. These measures are irrelevant to veterinary medicine, given that the pathogenesis of disease is better defined in human medicine as a result of primary

genetic etiologies and leukemic transformations.[14] In humans, PV can be caused by chronic myeloid leukemia and can be identified by using leukocyte alkaline phosphatase, a biochemical diagnostic marker.[21] However, this enzyme is absent in dogs and is not reported in ferrets; therefore it was not a valid marker for testing in the current case.[22] Efforts to match the diagnostic features of PV in humans with primary erythrocytosis in companion animals has been unrewarding, because leukemic transformation is relatively infrequent in animals, perhaps suggesting that the disease pathogenesis in companion animals is distinct from that in humans.[30]

The diagnosis of PV in this ferret was based on a persistently high PCV without evidence of an underlying physiologic condition or disease that induced erythrocytosis. Dehydration was not present, according to the clinical examination and consistently normal total solids and plasma biochemistry values. The hematology panel showed no evidence of thrombocytosis or leukocytosis, which occur with PV in humans[7,14,20,34] but have not been identified with PV in dogs.[19] Clinical evaluation did not indicate the presence of cardiopulmonary disease. Arterial oxygen saturation was not assessed due to an inability to obtain an arterial sample, but SpO2 was normal. Normal or low serum erythropoietin concentrations, in relation to previously published values in dogs and cats, supported our exclusion of secondary erythrocytosis.[27,35] Stage II diagnostics were not undertaken in the diagnosis of this patient.

In PV, bone marrow histology reveals an overall increase in cellularity, yielding loose megakaryocyte clusters with concurrent pleomorphism. Examination of bone marrow in PV-affected dogs and cats cannot diagnose or differentiate primary or secondary erythrocytosis, because both conditions are characterized by erythroid hyperplasia. Additional factors contributing to our decision against a bone marrow biopsy in this ferret included the invasive nature of sample collection and low probability of obtaining additional useful information; cytogenic abnormalities are detected in less than 20% of cases with PV at diagnosis and are rarely useful to discriminate between the different causes of erythrocytosis.[25,33]

In animals with erythrocytosis, serum erythropoietin determination assists in the differentiation of primary and secondary polycythemia.[12] Erythropoietin, a glycoprotein hormone produced only by the kidney, is the principal regulator of RBC production and acts specifically on erythroid precursors.[2,38] Production of this hormone is normally controlled by a feedback mechanism, whereby tissue hypoxia stimulates its release and a high level of oxygenation inhibits its release.[11] Erythropoietin is measured by radioimmunoassay, which has been described and validated for use in horses, cats, and dogs.[2,18] To date, baseline erythropoietin levels have not been established for ferrets, so we based our conclusions on canine and feline reference intervals.[2,27] We expected that the erythropoietin assay would be accurate in ferrets, given appropriate quantification in this single sample and the high protein sequence homology between ferret and cat erythropoietin (higher than 96% protein sequence identity, BLAST protein sequence alignment, February 2016).

Persistent erythrocytosis, whether primary or secondary, is associated with increased blood viscosity and risk of thrombosis.[14] Clinical consequences include hypertension, increases in pulmonary vascular resistance, episodic bleeding diatheses (epistaxis), decreases in cardiac output, reduction in tissue oxygenation, and central neurologic disturbances such as blindness, ataxia, and seizures due to impaired microcirculation and arterial thrombosis of the brain.[10,11,13,18,25] Systemic oxygen transport begins to decline at a PCV greater than 60%. With a PCV of 70%, the blood viscosity is 2.5-fold higher than normal and will result in hypercoagulability.[10,11] Therefore, the main goal of treatment for polycythemia vera is to reduce the PCV to within reference intervals, thereby alleviating clinical signs and preventing thrombotic and hemorrhagic complications.[30]

Methods of management of polycythemia vera include one or both of the following strategies: the removal of blood volume by phlebotomy or leeching and the destruction of erythropoietic cells with radioactive phosphorus or chemotherapeutic agents such as busulfan, hydroxyurea, and doxorubicin.[8,15,18,19,21,26,28] Therapeutic phlebotomy provides immediate relief of hyperviscosity syndrome but requires frequent repetition. The main disadvantages of repeated phlebotomy are hypovolemia (which can be managed by fluid replacement), iron deficiency, and an increased risk of thrombosis.[11] This risk is a result of increased viscosity associated with reduced malleability of microcytic, hypochromatic iron-deficient RBC.[11,21] We offered therapeutic phlebotomy as a treatment option to the ferret's owner but considered it impractical because it would require frequent sedation to facilitate high-volume venipuncture, and the owner was unable to return repeatedly to the hospital.

Cytoreductive therapy using hydroxyurea has been described for the management of primary erythrocytosis in humans and animals.[12,18,25,34] Hydroxyurea works by inhibiting DNA synthesis through inactivation of RNA diphosphate reductase, provoking cell death in S phase.[11,29] Adverse effects such as anorexia, vomiting, bone-marrow suppression, alopecia, and dysuria can be quickly reversed through discontinuation of the drug.[3,29] Cats treated with hydroxyurea have been reported to develop methemoglobinemia and hemolytic anemia with Heinz bodies, especially at high doses.[37] With the potential to cause significant myelotoxicity, careful dose adjustment to achieve the desired effect necessitates frequent and conscientious patient monitoring.[5,25] The potential leukemogenicity of this agent is a matter of debate, because acute myeloid leukemia is seen frequently in association with chronic PV in humans.[14] Frequent hematologic assessment allows for the detection of iatrogenic leukopenia, thrombocytopenia, or anemia.[22] Monitoring should be performed every 7 to 14 d until the PCV has normalized and then every 1 to 3 mo thereafter.[30] If adverse effects are encountered, hydroxyurea should be discontinued until the blood count returns to normal and then resumed at a lower maintenance dosage or dosage frequency.[28,30] The use of other agents, including chlorambucil and busulfan in conjunction with low-dose aspirin and tyrosine kinase inhibitors, has been described in the human literature but not in veterinary medicine.[14,20,38]

Treatment with hydroxyurea lowered the PCV in this ferret and correlated with a noticeable clinical improvement in demeanor and energy levels. The dosage of hydroxyurea was extrapolated from canine and feline sources, and the frequency of reassessment was based on clinician preference and practicality.[29,30] The evaluation frequency for CBC analysis was intended to be monthly but varied depending on owner compliance. A target PCV of 55 was selected but was difficult to maintain because attempts to reduce the dose to minimize adverse effects and to find the lowest effective dose were unsuccessful—minor dose changes resulted in large variations in the PCV. Thrombocytopenia was identified on

one occasion in the presence of a normal PCV, suggesting bone marrow toxicity, which subsequently resolved after dose adjustment. The decision for the target PCV as 55 in this patient was based on extrapolation from recommendations for management of PV in other species[1] but accounting for the higher PCV normally seen in ferrets compared with cats and dogs.[9]

The ferret described here lived for 14 mo from the initial diagnosis of polycythemia and 12 mo from the commencement of treatment with hydroxyurea. Prognosis for resolution of primary erythrocytosis is guarded in dogs,[2] and the median survival time is approximately 18 mo in untreated human patients.[5] The cause of death in this ferret was presumed to be hypovolemic shock, secondary to extensive venous infarction of the intestinal tract. Potential causes of intestinal venous infarction include occlusion of the anterior mesenteric vein by means of a thrombus, mesenteric volvulus, and a reduced blood flow and hypoxia associated with hyperviscosity. No thrombus was identified in the anterior mesenteric vein; however, given the delay between the time of death and postmortem examination, a thrombus might have dissolved. Significant postmortem dissolution of thrombi is known to occur, with only 39% of original clot volume present at 12 h after death.[24] In the current case, 18 h elapsed between the time of death and necropsy examination. In humans with PV, arterial or venous thrombosis is frequently present at the time of diagnosis, and thrombotic complications are a significant cause of mortality.[32] Alternatively, mesenteric volvulus resulting in compression and occlusion of the anterior mesenteric vein might have caused the intestinal infarction but was not present at the time of examination. It is possible that intestinal repositioning occurred prior to postmortem examination.

The necropsy lesions in this ferret's heart and liver can be attributed to previous and recent hypoxia, respectively, as a result of hyperviscosity caused by the episodes of marked erythrocytosis or the acute hypovolemic state. Myocardial fibrosis was mature, indicating that the inciting damage occurred at least 2 mo prior to death.[31] The periacinar hepatocyte degeneration and necrosis were consistent with acute hypoxic damage secondary to hypovolemia caused by gastrointestinal infarction. The mild periacinar hepatic fibrosis is suggestive of previous episodes of hypoxia and hepatocyte loss. Significant postmortem autolytic changes were present in the bone marrow; however, 50% cellularity and a myeloid to erythroid ratio of 1:2, which are indicative of erythroid hyperplasia, were identified and were consistent with the clinical diagnosis of primary erythrocytosis. Our interpretation of the bone marrow histology is extrapolated from other domestic species, because there are no published reference intervals for bone marrow parameters in ferrets. It is worth noting that bone marrow hypercellularity was present despite treatment with hydroxyurea, which reduces hematopoietic activity.[16] Caution should be taken in linking the presence of marked splenomegaly and splenic hematopoiesis with the primary disease process in this ferret, given that as these lesions are recognized to occur incidentally in this species.[17]

This clinical report describes a case of polycythemia vera in a ferret and illustrates the challenges associated with its long-term clinical management. Hydroxyurea shows potential as a medical alternative to phlebotomy to control the disease in this species. However, additional pharmacologic studies and controlled clinical trials are needed to further determine the usefulness of this drug in ferrets.

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