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Case Report Rapport de cas

Secondary inappropriate polycythemia with splenic hemangiosarcoma in a young adult cat

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Abstract — A 20-month-old castrated male Korean shorthair cat was presented with a 3-week history of intermittent vomiting and anorexia, absolute erythrocytosis, and elevated erythropoietin levels. A diagnosis of splenic hemangiosarcoma was made by histopathology and immunohistochemical identification of factor VIII. Paraneoplastic erythrocytosis caused by a splenic hemangiosarcoma in a cat is described.

Résumé — Polycythémie secondaire inappropriée et hémangiosarcome splénique chez un jeune chat adulte. Un chat commun coréen mâle castré âgé de 20 mois a été présenté avec une anamnèse de 3 semaines de vomissements intermittents et d'anorexie, d'érythrocytose absolue et des taux élevés d'érythropoïétine. Un diagnostic d'hémangiosarcome splénique a été posé par histopathologie et l'identification immunochimique du facteur VIII. L'érythrocytose paranéoplastique causée par un hémangiosarcorme splénique chez un chat est décrite.

(Traduit par Isabelle Vallières)

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Polycythemia is defined as an increase in the red blood cell (RBC) count above the reference interval (RI), and is characterized as either relative or absolute (1). Relative polycythemia, which presents with cases of severe dehydration, cutaneous losses (such as burns), or vascular redistribution, is associated with an elevated hematocrit (HCT) level, but a normal RBC count. Absolute polycythemia is characterized by an increase in RBC count, with causes further described as primary or secondary (1). Primary polycythemia, also known as polycythemia vera, results from neoplastic proliferation of RBCs independent of erythropoietin (EPO) stimulation and has been previously reported in cats (2,3). Secondary absolute polycythemia results from increased EPO concentration and is classified as either appropriate or inappropriate. Appropriate secondary absolute polycythemia occurs as a normal response to systemic hypoxia; the most common causes include congenital cardiac disease, chronic pulmonary parenchymal disease, a high-altitude environment, and severe obesity (1). Secondary inappropriate polycythemia occurs primarily due to the paraneoplastic production of EPO or EPO-like substances (1). Renal associated diseases are the most common cause of secondary inappropriate polycythemia, including solid tumors or diffusely infiltrative neoplasia, polycystic kidney disease, amyloidosis, or pyelonephritis. Other less common causes are related to thyroxine, growth hormone, and cortisol (1,4,5).

Most cases of feline secondary polycythemia are classified as appropriate. Very few cases of feline inappropriate polycythemia have been reported, and those that have were described as being associated with renal tumors (6–8).

In the present report, we describe a case of feline secondary inappropriate polycythemia associated with splenic hemangiosarcoma that resolved following splenectomy.

Case description

A 20-month-old castrated male Korean shorthair cat weighing 5.8 kg was presented with a 3-week history of intermittent vomiting and depression. On physical examination, the patient was mildly dehydrated (5%), and the body condition score was 4/9. Its body temperature was 39.4°C, and no heart murmur was auscultated. Although the capillary refill time was within 2 s, the mucous membrane was slightly hyperemic. Initial diagnostic tests included a complete blood (cell) count (CBC), biochemical analysis, thoracic and abdominal radiography, abdominal ultrasound, and urinalysis. Abnormalities revealed by the CBC were a hematocrit (HCT) of 81% [reference interval (RI): 24% to 45%], RBC count of $14.8 \times 10^6/\mu L$ (RI: 5 to $10 \times 10^6/\mu L$), and hemoglobin (Hb) concentration of 16.8 mmol/L (RI: 14.9 to 28.0 mmol/L). The platelet count was within the RI ($228 \times 10^3/\mu L$; RI: 160 to $700 \times 10^3/\mu L$).

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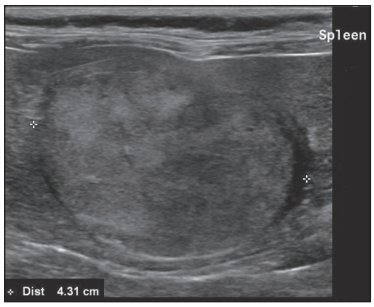

Figure 1. Ultrasound image shows a large heterogeneous mass in the spleen. The mass measured 2.9 × 4.3 cm.

The total plasma protein level was 67 g/L (RI: 54 to 80 g/L) and the urine specific gravity was 1.040. Abdominal ultrasound revealed a hyperechoic round mass (2.9 × 4.3 cm) within the body of the spleen (Figure 1), but was otherwise unremarkable, as was the size of the kidneys. Before phlebotomy, serum samples were collected and stored at −80°C for measurement of the EPO concentration.

During phlebotomy, 70 mL of blood was removed from the cat's jugular vein q12h over 2 d. The post-phlebotomy Hb concentration was 12.2 mmol/L and the HCT level was 59%. At this time, treatment with hydroxyurea (Hydrine Cap.; Korea United Pharm, Seoul, South Korea), was initiated at an initial dosage of 15 mg/kg body weight (BW), q12h, for 20 d.

After 23 d, a splenectomy was performed (Figure 2); the HCT level was 65.7% immediately prior to surgery. A CBC taken the day after the splenectomy revealed an HCT of 59.8%, RBC count of 11.3 × 10^6/μL, and an Hb concentration of 14.0 mmol/L. The splenic mass was submitted to an IDEXX diagnostic laboratory (Westbrook, Maine, USA) for examination.

Upon histopathological examination, an unencapsulated, infiltrative, loosely cellular splenic neoplasm composed of spindle cells that formed streams, and multiple blood-filled vascular spaces supported by fibrous connective tissue was observed. The nuclei were oval to elongate in shape and exhibited coarsely stippled chromatin and 1 to 2 small distinct nucleoli. Moderate anisocytosis and anisokaryosis were noted, with 4 mitotic figures per 10 high-power fields (× 40, Figure 3). Immunohistochemical analysis for factor VIII was positive and was consistent with a diagnosis of splenic hemangiosarcoma (Figure 4).

Administration of hydroxyurea was discontinued the day before splenectomy and a doxorubicin-based chemotherapy protocol was proposed but was declined by the owner. Instead, a metronomic chemotherapy protocol with toceranib (Palladia; Zoetis, Kalamazoo, Michigan, USA), 15 mg PO, q24h on Monday, Wednesday, and Friday was initiated 10 d after the splenectomy, and at the time of initiation of toceranib the HCT was 55.4%. Approximately 1 mo after the splenectomy, the cat's HCT was 43.6% and the RBC count was 7.9 × 10^6/μL with a normal Hb concentration (9.7 mmol/L). Follow-up evaluations were performed for 3 consecutive months, then once every 3 mo thereafter.

Toceranib was discontinued approximately 4 mo after initiation, at which time the owner reported that the cat was

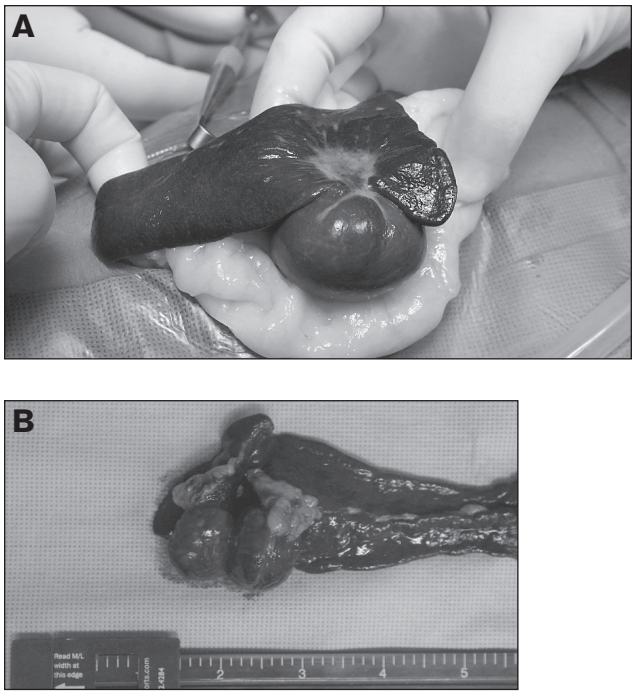

Figure 2. Gross images of the cat's spleen. A – Intraoperative appearance of the spleen. B – Resected spleen.

exhibiting mild anorexia. The owner elected to discontinue all therapy at that time. The last evaluation was performed 223 d after splenectomy; the cat's CBC revealed an HCT of 32.9%, an RBC count of 5.81 × 10^6/μL and an Hb concentration of 6.6 mmol/L. The owner reported that the cat was doing well with no apparent clinical signs 20 mo after its first visit.

The cat's pre- and post-splenectomy serum samples were sent to a human clinical pathology laboratory (Samgwang Medical Laboratory, Seoul, Republic of Korea). However, the detection limits for the human assay (chemiluminescence method) were not suitable. Only residual serum sample collected pre-splenectomy was now available. The serum EPO concentration was determined using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Cat Erythropoietin ELISA Kit; MyBioSource, San Diego, California, USA); the pre-splenectomy EPO concentration was 4.17 ng/mL. Because there is no reference interval for this ELISA kit, EPO levels of 7 clinically healthy cats were measured and ranged from 0.06 to 0.67 ng/mL (mean: 0.29, standard deviation: ± 0.20).

Discussion

Secondary erythrocythemia, a rare clinical manifestation in cats, is an EPO-dependent form of polycythemia that is caused by excessive stimulation of RBC production and can be classified as being either physiologically appropriate or inappropriate. Secondary inappropriate erythrocythemia generates an increased EPO level in the absence of systemic hypoxia (1).

Both benign and malignant tumors are the most common causes of secondary inappropriate erythrocytosis; in human medicine, the condition has been reported in association with neoplasms of the kidney, liver, uterus, ovaries, adrenal glands, thymus, and central nervous system (4,9). In veterinary

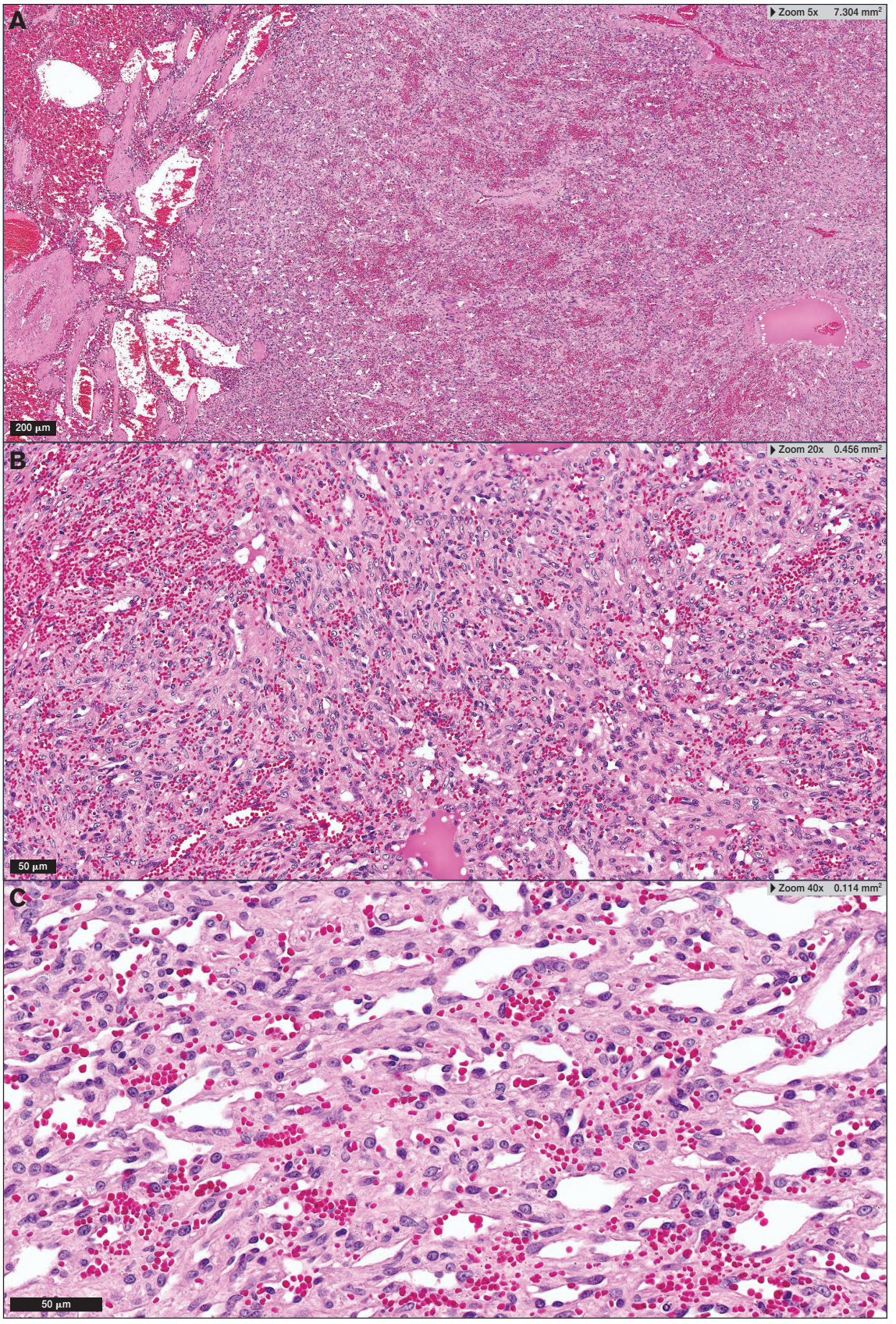

Figure 3. Photomicrographs of the cat's spleen. A – The splenic mass is composed of an infiltrative, unencapsulated, expansile, loosely cellular neoplasm. H&E; ×5 magnification. B – Neoplastic spindloid cells are arranged in streams and multiple blood-filled vascular spaces that are supported by fibrous connective tissue. H&E; ×20 magnification. C – Neoplastic cells have indistinct cell borders and a large amount of eosinophilic fibrillar cytoplasm. Nuclei are oval to elongate and have finely stippled chromatin and small 1 to 2 distinct nucleoli. Moderate anisocytosis and anisokaryosis are seen. H&E; ×40 magnification.

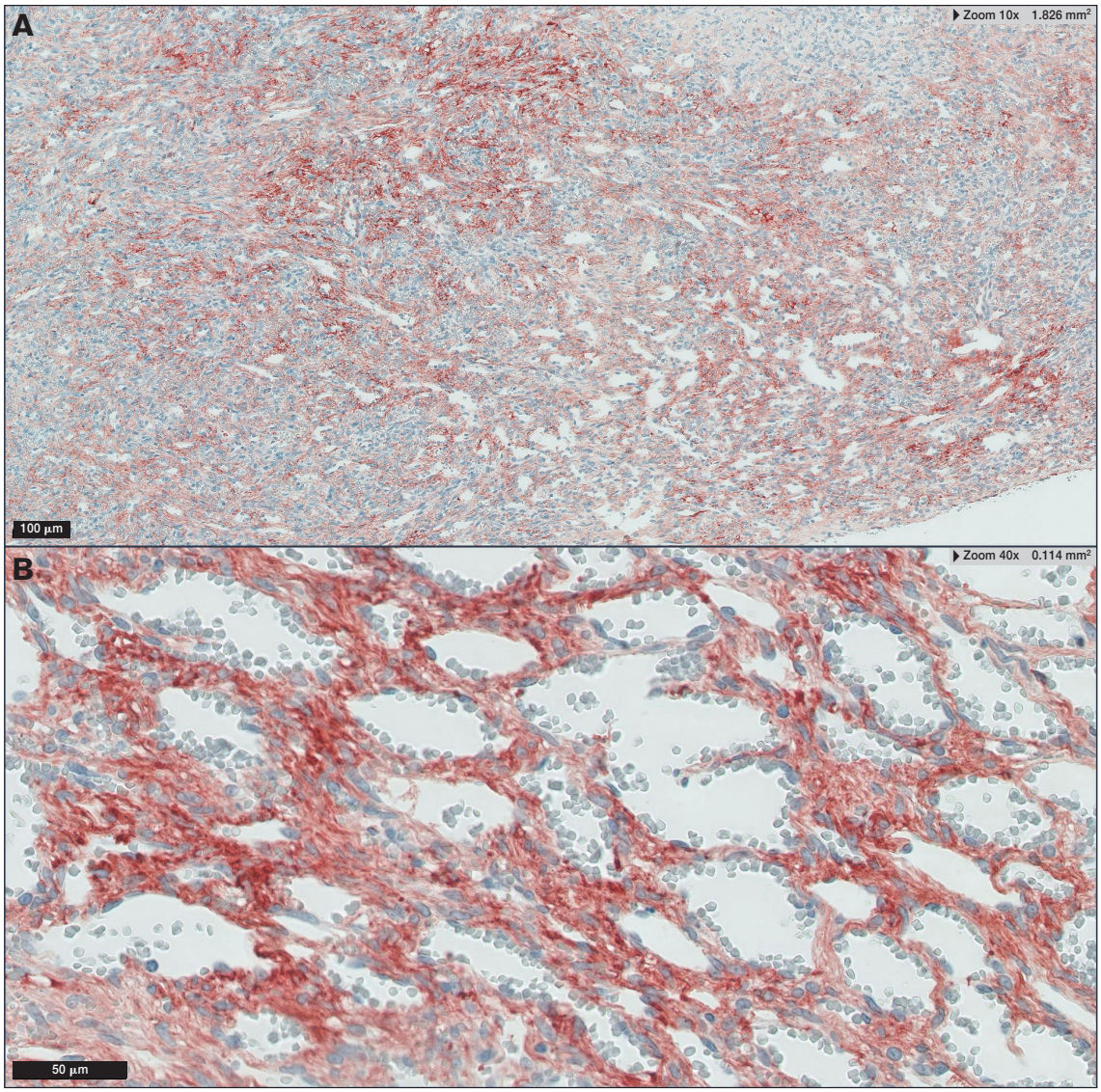

Figure 4. Results of immunohistochemistry. Neoplasm is diffusely positive for endothelial marker (Factor VIII). ×10 (A) and ×40 (B).

medicine, erythrocytosis has been reported to have occurred secondary to renal carcinoma, renal lymphoma, cecal leiomyosarcoma, nasal fibrosarcoma, and schwannoma in dogs (4,10–13), and to tetralogy of Fallot, renal adenocarcinoma, and renal carcinoma in cats (7,8,14).

Most cases of secondary inappropriate erythrocytosis in animals occur in association with tumors affecting the kidney. In fact, all previously reported cases of paraneoplastic secondary inappropriate erythrocytosis in cats were associated with renal neoplasms (8). The kidneys and liver normally contain EPO-secreting cells; however, neoplastic conversion of these cells apparently increases the production of EPO (12,15,16). The spleen may also represent a site of EPO production (15).

Several mechanisms account for the pathogenesis of paraneoplastic erythrocytosis: tumor-induced renal or systemic hypoxia, tumor impairment of EPO catabolism, and production of EPO or other EPO-like substances by tumor cells (17). Secondary erythrocytosis, attributed to ectopic secretion of EPO, is known to be associated with tumors of various tissues. The ectopic production of EPO has been demonstrated in nonrenal lymphoma, mesenchymal tumors, cecal leiomyosarcoma, and 2 cases of pyelonephritis in dogs (4,11,12). These reports documented EPO activity in the tumor using immunohistochemical analysis and real-time polymerase chain reaction (RT-PCR) assay to confirm EPO production by the neoplastic cells. In the present case, a long-term follow-up EPO concentration could not be obtained with ELISA. However, normalization of the cat's hematological parameters post-splenectomy strongly suggests that the erythrocytosis was associated with the well-differentiated splenic hemangiosarcoma.

Inappropriate secondary erythrocytosis caused by tumors or masses is usually treated by surgical removal of the neoplasm after the patient's clinical status has stabilized (18). Although phlebotomy and volume replacement can help with initial reduction of HCT levels, this method requires long-term and repetitive treatment for erythrocytosis, and is seldom a good long-term therapeutic approach (18). If the procedure is

ineffective at maintaining the HCT at an appropriate level, the administration of hydroxyurea can be considered. Hydroxyurea is an alkylating chemotherapeutic agent that suppresses erythrocyte production; it inhibits DNA synthesis without affecting RNA or protein synthesis and may cause reversible bone-marrow depression (19). The starting dose for cats is 10 to 15 mg/kg BW, PO, q12h, and treatment should continue until the target HCT value is reached. Administration of hydroxyurea to treat erythrocytosis appears to increase the median survival time in dogs; however, little information is available regarding its effects in cats. The patient herein exhibited persistent erythrocytosis following phlebotomy and administration of hydroxyurea, but the condition dramatically improved following surgical removal of the splenic mass.

Hemangiosarcoma is a malignant neoplasm of endothelial cells. It is less common in cats, having occurred in approximately 0.5% of cats examined at necropsy in 1 study, and accounting for 2% of all neoplasms evaluated in another (20). Visceral hemangiosarcomas are known to be aggressive and highly metastatic (21), and the spleen is the most common visceral location in cats (22,23). Visceral hemangiosarcomas in cats usually have a poor prognosis; however, a recent report described a cat with a ruptured splenic hemangiosarcoma that survived $>$ 3 y after splenectomy without adjuvant chemotherapy (24). In our case, although loss of contact with the cat's owner prevented long-term follow-up of the cat, the patient was reported to be healthy 20 mo after the splenectomy.

Plasma EPO levels in dogs and cats have been measured using enzyme immunoassays or radioimmunoassays with monoclonal or polyclonal anti-human EPO antibodies in a few studies (25). Serum from the cat herein and sera from 3 clinically healthy cats were sent for EPO measurement using a chemiluminescence immunoassay with monoclonal anti-human EPO antibodies. However, all the results were below the detection level of the assay ($<$ 3.7 mU/mL); these results were confirmed by performing the assay twice. Therefore, we believe that the anti-human EPO antibodies did not cross-react with the feline samples. Although there is a previous report describing measurement of EPO in dogs and cats using monoclonal anti-human EPO antibodies (25), our samples did not appear to exhibit cross-reactivity with anti-human antibodies. Thus, EPO measurement using anti-human antibodies could be unreliable in cats.

This study had several limitations. Tumor immunohistochemical analysis for EPO is considered the most effective method to determine whether EPO was being secreted from tumor tissue itself. Unfortunately, immunohistochemical analysis for EPO was not available at the laboratory to which the cat's sample was submitted. An additional significant limitation was that only the pre-splenectomy EPO concentration was measured; the post-splenectomy EPO concentration would have provided valuable insight into this condition. Furthermore, although we provide the values of EPO concentration for 7 healthy cats measured with the ELISA kit used in our study, a larger number of cats need to be used to validate and set the reference range of the feline EPO concentration with this commercial ELISA kit.

To the best of our knowledge, this the first report to document a case of secondary inappropriate erythrocytosis associated with a splenic hemangiosarcoma in a cat; previously, all feline cases were reported as being secondary to renal neoplasms. Furthermore, while hydroxyurea has been successfully used to treat erythrocytosis in dogs, information on its use in cats is limited. The cat described herein exhibited persistent erythrocytosis despite treatment with hydroxyurea, but its condition dramatically improved following surgical removal of the splenic mass.

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References

1. Nitsche EK. Erythrocytosis in dogs and cats: Diagnosis and management. Comp Cont Educ Pract Vet 2004;14:25–34.
2. Foster ES, Lothrop CD, Jr. Polycythemia vera in a cat with cardiac hypertrophy. J Am Vet Med Assoc 1988;192:1736–1738.
3. Nett CS, Arnold P, Glaus TM. Leeching as initial treatment in a cat with polycythaemia vera. J Small Anim Pract 2001;42:554–556.
4. Kaito K, Otsubo H, Usui N, Kobayashi M. Secondary polycythemia as a paraneoplastic syndrome of testicular seminoma. Ann Hematol 2004; 83:55–57.
5. Tefferi A, Thiele J, Vardiman JW. The 2008 World Health Organization classification system for myeloproliferative neoplasms: Order out of chaos. Cancer 2009;115:3842–3847.
6. Hasler AH, Giger U. Serum erythropoietin values in polycythemic cats. J Am Anim Hosp Assoc 1996;32:294–301.
7. Henry CJ, Turnquist SE, Smith A, et al. Primary renal tumours in cats: 19 cases (1992–1998). J Feline Med Surg 1999;1:165–170.
8. Klainbart S, Segev G, Loeb E, Melamed D, Aroch I. Resolution of renal adenocarcinoma-induced secondary inappropriate polycythaemia after nephrectomy in two cats. J Feline Med Surg 2008;10:264–268.
9. Suzuki M, Takamizawa S, Nomaguchi K, et al. Erythropoietin synthesis by tumour tissues in a patient with uterine myoma and erythrocytosis. Br J Haematol 2001;113:49–51.
10. Couto CG, Boudrieau RJ, Zanjani ED. Tumor-associated erythrocytosis in a dog with nasal fibrosarcoma. J Vet Intern Med 1989;3:183–185.
11. Durno AS, Webb JA, Gauthier MJ, Bienzle D. Polycythemia and inappropriate erythropoietin concentrations in two dogs with renal T-cell lymphoma. J Am Anim Hosp Assoc 2011;47:122–128.
12. Sato K, Hikasa Y, Morita T, Shimada A, Ozaki K, Kagota K. Secondary erythrocytosis associated with high plasma erythropoietin concentrations in a dog with cecal leiomyosarcoma. J Am Vet Med Assoc 2002;220: 486–490, 464.
13. Yamauchi A, Ohta T, Okada T, et al. Secondary erythrocytosis associated with schwannoma in a dog. J Vet Med Sci 2004;66:1605–1608.
14. Kirby D, Gillick A. Polycythemia and tetralogy of Fallot in a cat. Can Vet J 1974;15:114–119.
15. De Franciscis P, De Bella G, Cifaldi S. Spleen as a production site for erythropoietin. Science 1965;150:1831–1833.
16. Hammond D, Winnick S. Paraneoplastic erythrocytosis and ectopic erythropoietins. Ann N Y Acad Sci 1974;230:219–227.
17. Kessler M. Secondary polycythaemia associated with high plasma erythropoietin concentrations in a dog with a necrotising pyelonephritis. J Small Anim Pract 2008;49:363–366.
18. Evans LM, Caylor KB. Polycythemia vera in a cat and management with hydroxyurea. J Am Anim Hosp Assoc 1995;31:434–438.
19. Gray HE, Weigand CM, Cottrill NB, Willis AM, Morgan RV. Polycythemia vera in a dog presenting with uveitis. J Am Anim Hosp Assoc 2003;39:355–360.
20. Patnaik AK, Liu SK. Angiosarcoma in cats. J Small Anim Pract 1977;18:191–198.
21. Johannes CM, Henry CJ, Turnquist SE, et al. Hemangiosarcoma in cats: 53 cases (1992–2002). J Am Vet Med Assoc 2007;231:1851–1856.
22. Scavelli TD, Patnaik AK, Mehlhaff CJ, Hayes AA. Hemangiosarcoma in the cat: Retrospective evaluation of 31 surgical cases. J Am Vet Med Assoc 1985;187:817–819.
23. Engle GC, Brodey RS. A retrospective study of 395 feline neoplasms. J Am Anim Hosp Assoc 1969;5:21–31.
24. Gordon SS, McClaran JK, Bergman PJ, Liu SM. Outcome following splenectomy in cats. J Feline Med Surg 2010;12:256–261.
25. Pechereau D, Martel P, Braun JP. Plasma erythropoietin concentrations in dogs and cats: Reference values and changes with anaemia and/or chronic renal failure. Res Vet Sci 1997;62:185–188.