Polycythemia vera and glomerulonephritis in a dog

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An eight-year-old, 17 kg spayed female Shetland-type dog was examined because of episodic hypersalivation, excessive panting, shaking, and restlessness. Polyuria and polydipsia were also reported by the owner. Physical abnormalities were limited to hyperemic mucous membranes. Abnormal hematological findings are listed in Table 1 (week 0). The packed cell volume (PCV) was monitored weekly, and by the third week it reached 0.88 L/L. Phlebotomy (350 mL) and fluid replacement (1 L of 0.9% NaCl) reduced the PCV to 0.75 L/L. Two weeks later, the PCV was 0.80 L/L and fluid therapy alone was administered. The PCV remained stable at 0.75 L/L during the following two weeks.

The dog was referred to the Veterinary Teaching Hospital (VTH) of the Ontario Veterinary College for evaluation of polycythemia. Abnormal physical findings were limited to hyperemic skin and mucous membranes. The dog was well hydrated, and no cardiovascular or pulmonary abnormalities were detected. A fundoscopic examination revealed no abnormalities. Abnormal hematological, biochemical, and urinalysis findings are presented in Table 1 (week 8). A bacteriological culture of urine was negative, and thoracic and abdominal radiographs revealed no abnormalities. Hepatic and renal ultrasonographic abnormalities were limited to a loss of clarity of the corticomedullary junction of the right kidney. A bone marrow aspiration and core biopsy from the ilium had mild hypercellularity with hyperplastic but synchronous erythroid, myeloid, and megakaryocyte lines, and a myeloid to erythroid ratio of 1:1. Arterial blood gas abnormalities were limited to a low PO_2 (68.6 torr; reference range: 88–118 torr). Arterial blood pressures were normal as measured using an oscillometric technique (Dynamap, Critikon Canada Inc., Markham, Ontario) at the dorsal pedal artery with the dog in lateral recumbency.

A serum sample was sent to an external laboratory for determinaton of erythropoietin level. Phlebotomy was performed and 350 mL of blood (20 mL/kg) were replaced with 1 L of 0.9% NaCl. The postphlebotomy PCV was 0.59 L/L, total plasma protein was 35 g/L, and the arterial PO_2 was normal (102 torr).

No gross abnormalities were found at exploratory laparotomy. Needle cortical biopsies (Tru-cut biopsy needle, Baxter Canlab, Mississauga, Ontario) were taken from both kidneys. Severe chronic segmental glomerulonephritis was diagnosed on routine histopathology. Subsequent immunocytochemical examination using the direct immunoperoxidase method to detect deposition of immunoglobulin G (heavy and light chains) demonstrated extensive tubular immunoglobulin deposition and some staining of glomeruli. However, this was assessed to be mainly serum-associated, and the pattern observed was not suggestive of immune-mediated glomerulonephritis.

At the time of discharge, the PCV was 0.52 L/L and the total plasma protein was 44 g/L. A low protein diet (Prescription Diet Canine k/d, Hill's Pet Products, Topeka, Kansas, USA) and acetylsalicylic acid (ASA; 20 mg twice daily) were prescribed.

The serum erythropoietin level was reported to be less than 4.4 mIU/mL (undetectable) six weeks later, indicating that the polycythemia was primary (polycythemia vera). The abnormal hematological, biochemical, and urinalysis parameters found at that time are presented in Table 1 (week 14). Phlebotomy (350 mL) and fluid replacement (1 L of 0.9% NaCl) reduced the PCV to 0.45 L/L, and the serum total protein to 40 g/L. Oral hydroxyurea therapy (Hydrea, Squibb Canada, Montreal, Quebec) was begun at a loading dose of 30 mg/kg/day for seven days, followed by 15 mg/kg/day for maintenance. The results of evaluation at weeks 15, 16, 17 and 19 are presented in Table 1. No side-effects of hydroxyurea were reported and the dog was clinically normal.

The clinical signs and consequences of polycythemia are related to blood hyperviscosity, which results in hemodynamic changes and decreased tissue perfusion and delivery of oxygen

Polycythemia is a term that refers to a syndrome characterized by an increase in the red blood cell (RBC) count, hemoglobin concentration, and PCV. Depending upon the pathogenesis, the disorder may be classified as relative (hemoconcentration), or absolute, which is characterized by an increase in the total RBC mass. Absolute polycythemia is differentiated into either polycythemia vera (primary polycythemia) or absolute secondary polycythemia. Absolute secondary polycythemia results from excessive secretion of erythropoietin. When erythropoietin is secreted in response to systemic hypoxia, the polycythemia represents an appropriate physiological compensatory mechanism. Physiologically inappropriate secondary polycythemia is associated with increased production of erythropoietin in the absence of systemic hypoxia, and is usually a paraneoplastic event.

Polycythemia vera is a myeloproliferative disorder resulting from clonal proliferation of erythroid precursors that require little or no erythropoietin for differentiation, and does not respond to the normal negative feedback controls of replication. The diagnosis of

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Table 1. Hematological, biochemical, and urinary analytical findings in a dog with polycythemia vera

Week	0	3[a]	8[a]	14[a,b]	15	16	17	19	Reference range
RBC × 10^{12}/L	11.98	—[c]	10.68	8.82	—	—	—	—	5.6-8.5
PCV L/L	0.72	0.88	0.72	0.60	0.46	0.42	0.43	0.42	0.38-0.57
Hb g/L	270	—	239	202	—	—	—	—	132-193
BUN mmol/L	—	—	26.4	31.5	21	38	28	27	2.1-9.7
Cr nmol/L	—	—	233	299	212	327	256	256	55-145
T prot g/L	—	—	53	66	56	58	61	62	50-75
Album g/L	—	—	20	24	23	27	27	23	22-35
U sp gr	—	—	—	1.018	1.013	—	—	—	
U prot g/L	—	—	2	0.4	—	—	—	—	Neg

[a]Phlebotomy with fluid replacement after samples obtained for analysis
[b]Onset of hydroxyurea therapy
[c]Not done
Cr: serum creatinine; T prot: serum total protein; Album: serum albumin; U sp gr: urinary specific gravity; U prot: urine protein

polycythemia vera is made by exclusion of relative erythrocytosis and other causes of secondary polycythemia. A low to undetectable serum erythropoietin level will confirm the diagnosis (1). Although polycythemia vera is a myeloproliferative disorder, the peripheral RBC and the erythroid precursors appear to be morphologically and functionally normal. Mild hyperplasia and a normal myeloid to erythroid ratio are seen when the bone marrow is examined. In dogs, the term "primary erythrocytosis" has been suggested as a more appropriate term because polycythemia implies that leukocytosis and thrombocytosis are also present, as is usually the finding in humans but which rarely occurs in dogs (2). In this dog, the presumptive diagnosis of polycythemia vera was confirmed by the undetectable serum erythropoietin concentration. This also excluded the possibility that the glomerulonephritis could have been the cause of local hypoxia in the renal parenchyma, resulting in secondary inappropriate polycythemia.

The clinical signs and consequences of polycythemia are related to blood hyperviscosity, which results in hemodynamic changes and decreased tissue perfusion and delivery of oxygen. The cerebrum, myocardium, and kidneys, especially the glomerular capillary network, are the organs most susceptible to such injuries. Further, the increased likelihood of thrombosis and hemorrhage associated with hypercoagulability of viscous blood also contributes to tissue damage.

In dogs, renal tumors [carcinoma (3-5), lymphosarcoma (6)] have been associated with secondary inappropriate polycythemia. Benign space-occupying renal lesions (cysts, hydronephrosis) have been suggested as causes of inappropriate polycythemia in dogs, although no cases have been clearly documented. The authors of a case report of a dog with renal cryptococcosis and polycythemia concluded that the polycythemia was secondary to the renal disease (5). However, the serum erythropoietin level was not determined and primary polycythemia could have been a disease unrelated to the renal cryptococcosis.

The majority of cases of glomerulonephritis in dogs are thought to result from immune-mediated injury. Nonimmunological mechanisms, such as hemodynamic and hemostatic abnormalities, have also been identified as causes of glomerular disease (7). In the dog reported herein, histopathological and immunocytochemical examinations of the renal lesions revealed that the glomerulonephritis was extensive, severe, chronic, and unlikely to be of immune-mediated origin.

This case is of interest because the glomerulonephritis appeared to be caused by nonimmunological mechanisms in a dog with polycythemia vera. Other disorders that could potentially explain the glomerular injury were not found in this dog. We speculate that the glomerulonephritis was either unrelated to the polycythemia, or that it may have been a result of hemodynamic or hemostatic abnormalities secondary to polycythemia-associated blood hyperviscosity. The diagnostic algorithm for polycythemia includes searching for renal disease. However, convincing reports of absolute inappropriate secondary polycythemia associated with nonneoplastic renal disease in dogs are lacking. The diagnosis of absolute secondary polycythemia due to renal disease should not be made without the assessment of serum erythropoietin levels.

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