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Hemolysis Associated with Patent Ductus Arteriosus Coil Embolization in a Dog

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A 9-year-old spayed Labrador Retriever was presented for the closure of a patent ductus arteriosus (PDA) by coil embolization. The dog was asymptomatic, but a murmur had been detected 1 year earlier as an incidental finding. Clinical examination, electrocardiography, and thoracic radiography were consistent with a left-to-right shunting PDA without decompensation. The diagnosis was confirmed by 2-dimensional and M-mode echocardiography demonstrating volume overload of the left atrium and left ventricle, and color flow Doppler echocardiography detecting the presence of continuous turbulent retrograde flow in the pulmonary artery. The ductus was visualized, and no other congenital abnormalities were found. A CBC and serum biochemistry profile were obtained (Table 1). Prophylactic sodium cefazolin[a] was administered IV at a dosage of 20 mg/kg. An angiogram was performed under general anesthesia and fluoroscopic guidance by injecting 12 mL of the contrast agent sodium lothalamate[b] into the femoral artery. This procedure confirmed the diagnosis of a PDA and enabled the diameter at the pulmonary artery to be measured (10 mm) by comparison with a 2-cm marker on the pigtail catheter. The ductus was catheterized by a retrograde arterial approach with a 5-fr (1.7-mm) multipurpose catheter.[c] Four embolization coils (MWCE-10-PDA 5, MWCE-8-PDA 5, MWCE-8-PDA-4, and MWCE-5-PDA 5)[d] were positioned in the ductus ampulla. An angiogram performed after the procedure showed only a very small amount of residual flow through the ductus, and no murmur could be detected by the esophageal stethoscope. The femoral artery was ligated (2/0 silk),[e] and the wound was closed in a routine matter. The dog made an uneventful recovery and sodium cefazolin (20 mg/kg) was administered IV 2 more times at 8-hour intervals. A grade 2/6 continuous murmur was audible over the left heart base after recovery (4 hours after anesthesia). Thoracic radiographs documented coil placement (Fig 1).

Eighteen hours after surgery (day 1) dark red-brown urine was noted. Urinalysis showed a specific gravity of 1.050, and Dipstick[f] testing disclosed proteinuria (100 mg/dL) and a positive occult blood reaction, but bilirubin, urobilinogen, glucose, and ketones were absent. After centrifugation, the supernatant remained pigmented. Initially (day 1), no laboratory facilities were available for differentiation of pigmenturia (ie, hemoglobin or myoglobin) but spectrophotometry of a urine sample obtained on day 3 excluded myoglobin as the cause of pigmenturia. Microhematocrit and protein refractometry on day 1 revealed decreased packed cell volume and increased total protein concentration (PCV, 43%; total protein [TP], 7.0 g/dL) compared with preanesthetic measurements (PCV, 49%; TP, 6.3 g/dL). The dog was continued on crystalloid fluids[g] administered IV (initially 3 mL/kg reduced 6 hours later to 1.5 mL/kg) in an attempt to maintain renal perfusion and avoid volume overload. Cefazolin was discontinued and marbofloxacin[h] (55 mg PO q24h for 10 days) was begun. The PCV continued to decrease (35%) but TP stabilized (7.2 g/dL). Hemoglobin also decreased (initially, 17.5 g/dL; 3 days after intervention, 13.7 g/dL) but remained within normal limits (reference range, 12.0–18.0 g/dL) without obvious signs of regeneration (reticulocytes, 0.2%; absolute reticulocyte count, $10.66 \times 10^3/\mu L$ on day 3). Regeneration occurred by day 10 (absolute reticulocyte count, $327.6 \times 10^3/\mu L$; reticulocyte production index, 3.1). The anemia was normocytic (mean corpuscular volume, 65.2 fL) and the mean corpuscular hemoglobin concentration (MCHC) was 39.4%. Schistocytes and marked anisocytosis were observed. The platelet count decreased from 263,000/μL to 188,000/μL (reference range, 200,000–500,000/μL). Hyperbilirubinemia (total bilirubin, 1.9 mg/dL; reference range, 0–0.9 mg/dL) had developed by day 2, accompanied by bilirubinuria on day 3. Blood urea nitrogen, creatinine, and electrolyte (Na^+, Cl^-, K^+) concentrations and all other serum chemistry test results remained within reference ranges throughout hospitalization (Table 1). The dog was discharged 5 days after intervention, but was closely monitored by the referring veterinarian. The urine became macroscopically clear 10 days after the procedure, although a trace of blood was still present on dipstick testing. Myoglobin once again was excluded by spectrophotometry. The urine specific gravity was 1.018, and no red blood cells were seen on microscopic examination of the sediment. The murmur was still present and had not changed in intensity. One month after intervention, the urine was completely clear and the PCV was 45%. A grade 2 continuous murmur over the left heart base persisted.

Regenerative anemia developed after coil embolization in this dog with a PDA. Total proteins increased despite a decrease in PCV and thus blood loss was excluded as a reason for the regenerative anemia. No blood loss was noticed during or after the operation. The increased TP initially (day 1) was attributed to subclinical dehydration after

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Table 1. Hematology and biochemistry profiles preoperatively (Pre), and 3 days (Day 3), and 10 days (Day 10) after the procedure in a dog with coil embolization of a patent ductus arteriosus.

	Pre	Day 3	Day 10	Reference Range, Units
RBC	7.51	5.33	5.46	5.50–8.50 × 10⁶/μL
PCV	50	35	35	39–55%
Hemoglobin	17.5	13.7	13.8	12.0–18.0 g/dL
MCV	66.0	65.2	64.7	60.0–77.0 fL
MCHC	35.3	39.4	39.0	32.0–36.0%
WBC	5,700	14,100	9,390	6,000–15,000/μL
Neutrophils (segmented)	3,933	12,408	7,980	3,600–12,000/μL
Neutrophils (bands)	0	282	90	0–0/μL
Lymphocytes	570	282	560	700–4,800/μL
Monocytes	285	846	660	0–1,500/μL
Eosinophils	912	282	0	0–1,000/μL
Basophils	0	0	0	0–200/μL
Platelets	263,000	188,000	113,000	200,000–500,000/μL
Normoblasts			520	/μL
Reticulocytes		0.20	6.00	0.00–0.50%
ALT	46	22		15–60 U/L
AP	96	46		20–60 IU/L
Bilirubin		1.9		0–0.9 mg/dL
Calcium	10.6	9.8		9.2–12.0 mg/dL
Cholesterol	228	222		147–271 mg/dL
Creatinine	0.9	1.0	1.045	0–1.116 mg/dL
Glucose	101	99		54–90 mg/dL
Magnesium	0.8	0.8		0.7–1.2 mmol/L
Phosphorus	2.6	4.8		2.8–3.7 mg/dL
T_4	3.1	3.0		1.2–3.7 μg/dL
Total protein	6.3	7.2		5.8–7.3 g/dL
Urea	17	15	18	4–20 mg/dL
Sodium	147	147		144–160 mEq/L
Chloride	114	114		109–122 mEq/L
Potassium	4.6	4.2		3.5–5.8 mEq/L

RBC, red blood cells; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; WBC, white blood cells; ALT, alanine aminotransferase; AP, alkaline phosphatase; T_4, levothyroxine.

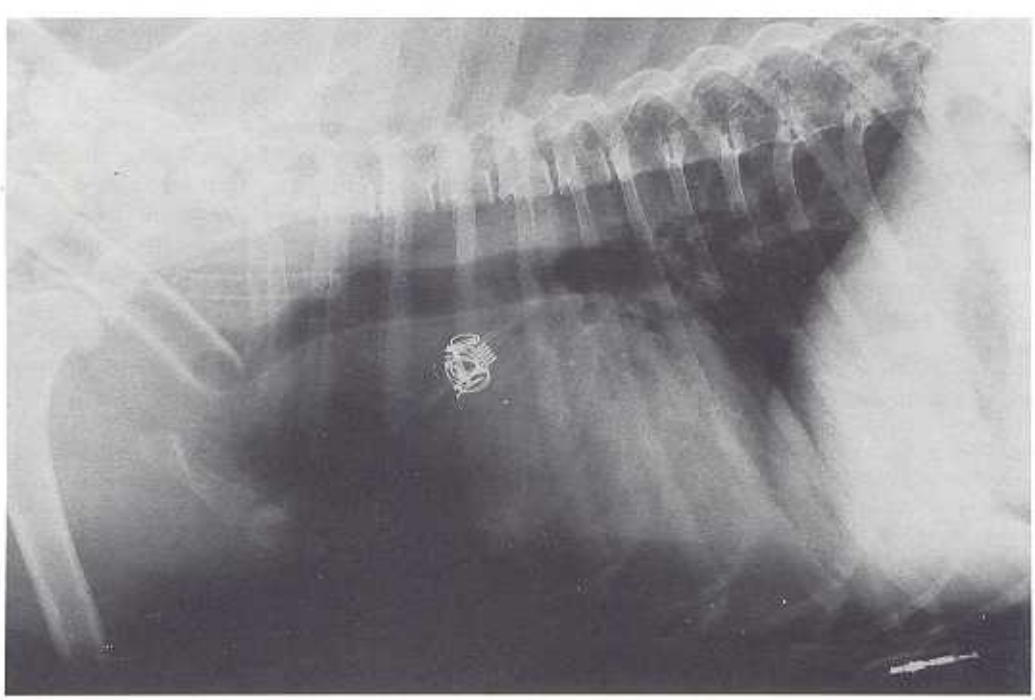

Fig 1. Right lateral thoracic radiograph after coil placement.

anesthesia (urine specific gravity, 1.050) but despite fluid therapy TP remained higher than initially measured. A false increase in TP can occur with hemolysis (because of increased optical density of the plasma), and free hemoglobin may increase TP. Despite the absence of laboratory facilities to detect free hemoglobin, increased MCHC (39.4%) and hemoglobin greater than one third of the hematocrit were compatible with the presence of hemoglobinemia. The absence of spherocytes, lack of autoagglutination, and resolution of anemia without any treatment made immune-mediated hemolytic anemia very unlikely. Unfortunately, a Coombs' test was not performed. Hemoparasites were not observed on microscopic examination of blood smears, and hemoparasites are not endemic in the country in which the animal lives. Other causes of hemolytic anemia (eg, disseminated intravascular coagulation, poisoning, inherited conditions) were unlikely considering the animal's history and the absence of clinical signs. The hypophosphatemia (2.6 mg/dL; reference range, 2.8–3.7 mg/dL) was not severe enough to be responsible for the hemolysis.[1,2] Hemoglobinuria persisted despite changing antibiotics, making a drug reaction less likely. Antibiotic therapy was changed from a cephalosporin to a quinolone because the former have been reported to induce drug-related hemolytic anemia.[3,4] Although completely excluding drug-induced hemolytic anemia is difficult, with extravascular hemolysis only a small amount of hemoglobin is released from the red cells, and hemoglobinemia and hemoglobinuria often are minor. In the dog of this report, the severity of the hemoglobinuria and the presence of schistocytes supported a diagnosis of mechanical intravascular hemolysis.

Transcatheter closure of a PDA with detachable coils has been accepted as an alternative treatment modality for dogs with PDA.[5–7] Transcatheter occlusion of a PDA can be complicated by protrusion of the device causing obstruction of the pulmonary artery or aorta,[8] as well as by embolization of the device into the pulmonary or systemic circulation.[5,9–11] Ductus arteriosus endarteritis,[12] vascular trauma, and femoral artery hemorrhage are other potentially fatal complications. Hemolysis has been reported as an important complication[13] after coil implantation in humans. To our knowledge, this is the 1st report of severe acute hemolysis as a complication of residual shunting after implantation of multiple detachable coils for PDA embolization in the dog. Hemolysis is thought to be due to red cell destruction caused by a high-velocity jet of blood passing through the residual PDA shunt or due to poor positioning of the device. In this case, fluoroscopy and radiography showed correct positioning of the coil, and the hemolysis was more likely due to residual shunting.

Hemolysis depends on mechanical damage of erythrocytes, and is related to the flow dynamics of the residual jet. The flow dynamics are characterized by the velocity of the residual jet (depending on the diameter of the shunt and the pressure difference), the turbulence in the ductus (created by the lumen shape and integrity), and by the presence of single or multiple jets (multiple coils produce multiple jets).[14] A residual shunt was confirmed by color flow Doppler echocardiography 3 days after the operation in this dog, and a continuous murmur (grade 2) still was audible at 3, 10, 30, and 60 days after the procedure. Early residual shunting is a common finding (30%) in humans after coil embolization, and is more common in patients with larger-diameter ductus.[13–15] The percentage of human patients with residual shunting decreases over time.[16] Uzun et al[13] reported that the risk of hemolysis increases with the relative size of the duct as well as with lower body weight, and younger children are at greater risk. The ductus was large in this animal (10 mm) and may have resulted in increased risk of hemolysis. In the dog described here, the hemolysis resolved spontaneously despite persistence of a continuous murmur, and consequently the anemia resolved rapidly. In animal experiments, Rashkind Occluder disks rapidly became endothelialized and were eventually covered with tissue and incorporated into the arterial walls.[17] Endothelization of the device may have occurred in the dog of the present report, thus reducing the potential for traumatic hemolysis while enabling continued ductal flow.

When hemolysis occurs in humans, correction of the anemia by blood transfusion, careful fluid management to avoid dehydration and acidosis, and alkaline diuresis to preserve renal function[18] are recommended. We administered lactated Ringer's solution at a low maintenance rate because sudden pressure changes after PDA occlusion may predispose to volume overload.[19] Urinary output and renal function tests were monitored carefully, and renal failure did not occur. Late acute renal failure has been reported as a consequence of hemoglobinuria and mechanical intravascular hemolysis due to coil implantation in one human patient.[20] The dog of the present report has been stable for 2 months after the operation and was clinically normal at the time of writing. If hemolysis persists, surgical removal of the coil, ligation of the ductus,[21] or positioning of a 2nd device to close the residual shunt[22,23] have been successful in humans. Additional coil implantation was considered in this dog, but hemolysis resolved spontaneously and placement of additional coils was not deemed necessary. With wider adoption of coil embolization in the treatment of PDA in dogs, veterinarians should be aware of the possible complication of coil-induced traumatic hemolysis.

Footnotes

[a] Kefzol, Lilly, Basingstoke, UK
[b] Conray 420, Mallinckrodt, Northampton, UK
[c] Cook, Bjaeverskov, Denmark
[d] MR eye detachable coil, Cook, Bjaeverskov, Denmark
[e] Mersilk, Ethicon, Brussels, Belgium
[f] Dipstick reagent strip, Bayer, Newbury, UK
[g] Isolec, Compound Sodium Lactate, Intravenous fluids, Larne, UK
[h] Marbocyl, Vetoquinol, Oxon, UK

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