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Acute necrotising pulmonary vasculitis and pulmonary hypertension in a juvenile dog

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Abstract

A five-month-old female Jack Russell terrier was presented for investigation of acute lethargy, anorexia, coughing, respiratory distress and weakness. Examination findings included cyanosis, a grade 3 of 6 systolic heart murmur and prolonged capillary refill time. Radiography and echocardiography revealed severe pulmonary hypertension, cor pulmonale and right-sided heart failure. Indirect measurement of the systolic pulmonary artery pressure estimated pressures over 100 mmHg. Despite treatment the patient died. Post-mortem examination did not identify a congenital cardiovascular anomaly. Histopathology confirmed acute necrotising pulmonary arteritis and immunohistochemistry failed to identify any immune complex or complement deposition.
**Introduction**

Vasculitis is a pathological process characterised by inflammation and necrosis of blood vessels. Vessels of any type and virtually any organ system may be affected and hence may lead to a multitude of clinical manifestations and syndromes. Acute necrotising vasculitis affecting the pulmonary vasculature exclusively has been rarely reported in dogs. Kolm and others (2004), Gavaghan and others (1998) and Turk and others (1981) each described a single case of acute necrotising pulmonary vasculitis in immature dogs with patent ductus arteriosus (PDA). Turk and others (1984) also described a case of acute necrotising pulmonary vasculitis in a young miniature schnauzer with peritoneopericardial hernia. All these case reports described histopathological evidence of acute necrotising pulmonary vasculitis with circumferential myointimal thickening. Each patient developed severe pulmonary arterial hypertension (PAH), right-sided heart failure and died or was euthanased because of progression of clinical signs. Gavaghan and others (1998) proposed that in circumstances of pulmonary vascular dysfunction, a relatively transient or mild hypoxic, metabolic, inflammatory or flow-related insult may serve as a catalyst for self-perpetuating progressive pulmonary hypertension.

Pulmonary arteritis in human patients with medial hypertrophy and fibrosis is associated with a poor clinical prognosis. A variety of mechanisms have been proposed to cause pulmonary vascular dysfunction in people. Increased endothelin-1, reduced nitric oxide-mediated vasodilation, pulmonary hypoxaemia and imbalances of endothelin-1 receptor subpopulations associated with the increased pulmonary blood flow contribute to impairment of normal physiological vascular responses (Wong and others 1995).
This case report describes severe acute necrotising pulmonary panarteritis that caused terminal PAH in an immature Jack Russell terrier. To the authors’ knowledge, acute necrotising vasculitis affecting the pulmonary vasculature alone has not been described in dogs without concurrent congenital disease.

Case Report

A five-month-old female Jack Russell terrier, weighing 5.8 kg, was presented with acute lethargy, anorexia and coughing of five days’ duration. Over the preceding two months, the patient had presented to the referring veterinarian on several occasions with dysuria and pigmenturia. Urinalysis results included pyuria, proteinuria and bacteriuria consistent with urinary tract infection (UTI). Aerobic urine culture yielded a pure heavy growth of non-haemolytic Escherichia coli sensitive to β-lactams, trimethoprim-sulphonamides, fluoroquinolones, aminoglycosides and tetracyclines. Initially, 20 mg/kg amoxicillin-clavulanate was administered orally twice daily for two weeks and the clinical signs were resolved. When clinical signs recurred within two days of therapy completion, a course of 20 mg/kg cephalexin twice daily was administered for five weeks. The dog was referred five days after completion of antibiotics.

The dog was presented to the emergency service of Murdoch University Veterinary Hospital. Physical examination showed generalised weakness, collapse, cyanosis, tachypnoea, prolonged capillary refill, weak irregular femoral pulses, jugular distension and pulses, hepatomegaly, severe tachycardia (heart rate 250 beats per minute) and a (grade 3 of 6) systolic heart murmur with point of maximal intensity over the right cardiac apex. These
findings were consistent with right-sided heart failure and poor peripheral perfusion.

Investigation included evaluation of pulse oximetry, systemic blood pressures, haematology, biochemistry, thoracic radiography, electrocardiography (ECG) and echocardiography.

Systemic arterial blood pressures (systolic), measured by indirect Doppler sphygmomanometry, varied between 90 and 110 mmHg and pulse oximetry estimated oxygen-haemoglobin saturation at 60 to 70 per cent on presentation and 80 to 85 per cent with oxygen supplementation.

Thoracic radiographs (Fig 1) showed marked right-sided enlargement of the cardiac silhouette, a pulmonary hypervascular pattern because of dilation of the pulmonary arteries and mild pulmonary hyperinflation.

ECG (Fig 2) findings included supraventricular tachyarrhythmia (sinus tachycardia or supraventricular tachycardia [SVT]), deep S waves in leads I, II and aVF, tall R waves in lead III and right axis deviation of the mean electrical axis in the frontal plane, consistent with right ventricular enlargement or hypertrophy. Vagal manoeuvres did not alter the heart rate or rhythm.

Echocardiography (Fig 3) showed marked dilatation of the right ventricle and atrium, hypertrophy of the right ventricular free wall, marked enlargement of the main pulmonary artery, marked pulmonary regurgitation ($V_{max}=4.0$ m/s) and severe tricuspid insufficiency ($V_{max}=5.05$ m/s). The left atrial, left ventricular and aortic dimensions were markedly reduced, consistent with left-sided volume depletion. The fractional shortening was elevated...
Hepatic vein dilation was noted on abdominal ultrasound. Two-dimensional and Doppler echocardiography including cephalic vein bubble studies did not identify anomalous vasculature or a shunt.

Complete blood count and serum biochemistry results included mild mature neutrophilia (12.8×10⁹/l, reference 3 to 11.5×10⁹/l), monocytosis (1.58×10⁹/l, reference 0.35 to 1.35×10⁹/l), azotaemia (urea 13.1 mmol/l, reference 3.6 to 10 mmol/l), hyperphosphataemia (2.67 mmol/l, reference 0.8 to 2.2 mmol/l), increased creatine kinase (269 U/l) and hypoproteinaemia (52 g/l, reference 56 to 80 g/l) because of hypoglobulinaemia (globulins 23 g/l, reference 28 to 44 g/l).

**Assessment and treatment**

The most prominent clinical problems were pulmonary hypertension, hypoxaemia and right heart failure. These were considered most likely because of an unidentified congenital left-to-right vascular shunt. Treatment included humidified nasal oxygen supplementation (200 ml/kg/minute), anxiolytics (0.05 mg/kg morphine intramuscularly), intravenous 1 mg/kg frusemide and an intravenous bolus of 0.05 mg/kg verapamil followed by constant rate infusion at 2 μg/kg/minute. The heart rate decreased in response to treatment; however, the patient’s clinical condition continued to deteriorate and progressed to respiratory arrest and death within 12 hours of presentation.
Post-mortem examination

A large amount of intraluminal tracheobronchial (stable) froth and abnormal diffuse multifocal coalescing pulmonary congestion were present. Cardiovascular findings included severe right heart dilation, marked right ventricular hypertrophy and an interventricular septal bulge into the left ventricle. The great vessels and other body systems grossly appeared normal.

The most prominent histopathological changes were in the lung (Fig 4) including a diffuse increase in alveolar macrophages accompanied by prominent multi-focal alveolar fibrin exudate, alveolar oedema and lymphatic dilation. Panarteritis with nuclear dust and fibrinoid necrosis affected the small- to medium-sized pulmonary arteries. Abundant alveolar fibrin and widespread fibrinoid necrosis in arteries of various diameters were demonstrated by Martius scarlet blue staining. Hepatic sections exhibited periacinar zonal congestion and mild hepatocellular necrosis. The kidneys, urinary bladder, adrenal glands, thyroid, heart and brain appeared histologically normal. The post-mortem diagnosis of acute necrotising pulmonary panarteritis and acute fibrinous pneumonia supported the clinical findings of pulmonary hypertension and cardiopulmonary failure.

Discussion

In human medicine, vasculitides are well described and their classification is based on the pathogenic mechanisms, the anatomical site and histological characteristics of the lesions, together with their clinical manifestations (Schoen and Cotran 1999). Heath and Edwards (1958) originally proposed a histopathological classification of pulmonary vasculopathy describing progressive degrees of pulmonary artery myointimal proliferation, vascular
occlusion, fibrosis, inflammation and necrosis on a graded (I-VI) scale that provided a framework for future study and a guide for prognosis. In contrast, vascular disease in animals is relatively poorly documented, and the underlying aetiology in most cases is unknown (Fox and others 2005). Regardless of the underlying cause, the inflammatory process may become chronic and result in progressive intimal thickening and irreversible fibrosis of the affected vessels.

The signs of vasculitis vary considerably depending on the organ system(s) affected. Reported clinical syndromes in animals involve the skin (Keenan and others 1977, Scott and others 1978, Wilcock and Yager 1986), central nervous system (Kelly and others 1973, Meric and others 1986, Carpenter and others 1988, Scott-Moncrieff and others 1992, Snyder and others 1995, Caswell and Nykamp 2003) and joints (Lewis and Borel 1971). To the authors’ knowledge, there are only five clinical reports of dogs with acute necrotising pulmonary vasculitis in the veterinary literature. Three dogs had PDA (Turk and others 1981, Gavaghan and others 1998, Kolm and others 2004), one dog had a peritoneopericardial diaphragmatic hernia (Turk and others 1984) and another had visceral leishmaniasis (Pumarola and others 1991). Exercise intolerance, dyspnoea and cyanosis with, or without, right heart failure were the most common clinical signs. All dogs had a heart murmur and one dog with a PDA was asymptomatic at initial presentation (Gavaghan and others 1998). Similarly, people with pulmonary vasculitis and PAH may be asymptomatic or have varying degrees of exercise intolerance, fatigue, angina, near-syncope, dyspnoea or right heart failure (Humbert and others 2004).
Pulmonary vasculitis typically results in PAH, its severity being inversely related to the total cross-sectional area of the vascular bed (Goldstein 1985). Chronic pulmonary hypertension leads to a self-perpetuating process of vascular medial hypertrophy and intimal proliferation (Goldstein 1985). Persistent, progressive PAH causes increased right ventricular afterload and wall stress, leading to right ventricular hypertrophy and dilation. The subsequent decrease in cardiac index may result in clinical signs of right-sided heart failure, as was the case in the dog described in this report.

Clinically, a variety of causes of PAH are recognised in human beings and animals. These include increased pulmonary blood flow (left-to-right shunts), dirofilariasis (heartworm disease), pulmonary vascular dysfunction, increased left atrial pressure, chronic obstructive or interstitial pulmonary disease, hypoxaemia, metabolic acidosis and pulmonary thromboembolism (Perry and others 1991, Humbert and others 2004). The diagnostic evaluation of a patient with suspected PAH may include assessment of history, physical examination, haematology, biochemistry, urinalysis, heartworm status, coagulation studies, blood gas analysis, thoracic radiography, ECG, echocardiography, pulmonary perfusion scintigraphy and thoracic computed tomography. Bronchoscopy, bronchoalveolar lavage, cytology and culture may aid diagnosis if primary bronchopulmonary disease is suspected. In this case, heartworm antigen testing was not performed because of the patient's age. Dirofilariasis was therefore considered unlikely and post-mortem examination ruled it out. Unfortunately, urine and blood cultures were not performed. Sepsis or endotoxaemia secondary to ascending UTI, or resulting in UTI, may have the potential to cause vasculitis. However, post-mortem and histological examination of the kidneys did not show any evidence of pyelonephritis or septicaemia. Blood gas analysis may have added further
information regarding the patient’s arterial oxygen tension and acid-base status; yet, none of these measures were likely to have changed the treatment plan or outcome.

The antemortem diagnosis of pulmonary vasculitis remains a challenge for the clinician as it requires histopathological assessment, and lung biopsy is often not feasible in the living patient. However, if a definitive cause of pulmonary hypertension cannot be made on the basis of the testing described above, a tentative diagnosis of pulmonary vasculitis should be considered. Infectious disease including dirofilariasis, angiostrongylosis, leishmaniasis, ehrlichiosis, Rocky Mountain spotted fever, bartonellosis, borreliosis, sepsis and hepatozoonosis should be ruled out in their respective endemic areas if pulmonary vasculitis is suspected.

Echocardiographic changes accompanying PAH include right ventricular dilation, right ventricular hypertrophy, tricuspid insufficiency, paradoxical septal motion, enlarged pulmonary artery, decreased left ventricular chamber dimension, prolapse of the tricuspid and pulmonic valves and increased left ventricular wall and septal thicknesses (Lombard and Buergelt 1983, Atkins and others 1988, Badertscher and others 1988). In addition, a reduced pulmonary artery acceleration time-to-ejection time ratio may be present in patients with PAH and without tricuspid or pulmonic insufficiency (Schober and Baade 2006). Using the modified Bernoulli equation in this case study, the peak velocity of tricuspid regurgitation ($V_{\text{max}}=5.05 \text{ m/s}$) corresponded to a transtricuspid valve pressure gradient of 102 mmHg. As the patient was in right heart failure, the right atrial pressure was assumed to be at least 8 mmHg. Right ventricular systolic pressure was therefore calculated as the sum of the right atrial pressure and the transtricuspid valve pressure gradient during systole, that is, at least
110 mmHg. In the absence of pulmonic stenosis, this indicated severe pulmonary hypertension. Similarly, using the modified Bernoulli equation, peak velocity of pulmonic regurgitation ($V_{\text{max}}=4.0$ m/s) translated to a pulmonary diastolic pressure of 64 mmHg, which also indicates severe pulmonary hypertension.

The underlying aetiology of the vasculitis in this patient remains unknown. The optimal treatment of PAH ideally involves identification of the underlying cause. If the aetiology cannot be identified and removed before permanent remodelling of the pulmonary vasculature has occurred, the prognosis for recovery is grave. In cases where the underlying cause is unknown or cannot be controlled, the primary aim of therapy is to reduce the pulmonary vascular resistance and right ventricular afterload. In human patients, various drugs are advocated for the treatment of primary pulmonary hypertension and pulmonary hypertension where the underlying causes are either unidentified or untreatable; recommended treatments include oxygen supplementation, anticoagulation, calcium channel blockers, prostacyclin, prostacyclin analogues, endothelin receptor antagonists, phosphodiesterase inhibitors and ultimately lung transplantation (Runo and Loyd 2003, Badesch and others 2004). A number of these strategies have been tried in canine patients.

Nitric oxide is critical in pulmonary vascular homeostasis and is synthesised by nitric oxide synthetase (NOS) from l-arginine. Expression of NOS in PAH is variable, suggesting a multifactorial mechanism and dysfunction of NOS (Giaid and Saleh 1995, Xue and Johns 1995, Tuder and others 1999). Millatt and others (2003) observed increased lung concentrations of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of NOS, with concurrently increased NOS expression in a murine model of chronic hypoxia-induced PAH. They
hypothesised that the increase in ADMA might be related to a dysregulation of
dimethylarginine dimethylaminohydrolase, the enzyme that metabolises ADMA. This
hypothesis is supported by reports of improvement in pulmonary artery pressures and
haemodynamics in human beings with PAH supplemented with l-arginine (McCaffrey and
others 1995, Mehta and others 1995, Nagaya and others 2001). In addition to oxygen,
inhalant NO gas has been advocated as the most effective and specific therapy for primary
PAH in people (Rubin 1997). Gene transfer of NOS has successfully reduced pulmonary
pressures in animal models and is a potential future treatment (Champion and others 2002).

Sildenafil, vardenafil and tadalafil are selective type V phosphodiesterase inhibitors that
augment the action of endogenous NO in vitro. Sildenafil reduces pulmonary pressures and
improves symptoms in people with PAH (Ghofrani and others 2002, Wilkens and others
2001). Encouraging results for the use of sildenafil in dogs with PAH have recently emerged;
however, controlled clinical trials are lacking (Bach and others 2006).

It was thought that verapamil, a calcium channel antagonist, might be beneficial by
controlling the SVT and improving pulmonary haemodynamics. Differentiation of sinus
tachycardia from SVT was not achieved with a vagal manoeuvre or precordial thump. The
tachycardia in the described patient may have been appropriate for the degree of heart failure.
Therefore, administering verapamil and reducing the heart rate without treating the
underlying PAH possibly contributed to this patient’s negative outcome. Similarly, frusemide
diuresis may have contributed to this patient’s already compromised left ventricular preload
and systemic hypotension.
References


Figure 1. Lateral (A) and dorsoventral (B) thoracic radiographs. Marked right atrial and ventricular enlargement (large arrows), with dorsal tracheal displacement (small arrows) and dilated pulmonary arteries (arrow heads)
Figure 2. Six-lead electrocardiogram, 50 mm/s, 1 mV=10 mm. A rapid supraventricular rhythm is present with deep S waves in leads I, II, II and aVF, tall R wave in lead III and a right axis deviation.
Figure 3. Two-dimensional, M-mode and Doppler echocardiogram. (A) Right four-chamber view. Severe dilatation of the right atrium (RA) and right ventricle (RV) are present. The left atrium (LA) and left ventricle (LV) are markedly reduced in size. Paradoxical septal motion is depicted by the leftward deviation of interventricular septum bulging into the left ventricle. (B) Two-dimensional and M-mode echocardiogram, right parasternal short axis view. Note the marked right ventricular (RV) dilatation outlined by the right ventricular free wall (RVFW) and interventricular septum (IVS). The left ventricle diameter is markedly reduced and paradoxical IVS motion is evidenced by the leftward deviation during diastole. LVFW left ventricular free wall. (C) Two-dimensional echocardiogram, right parasternal short axis of the heart base. Marked dilatation of the main pulmonary artery (MPA), left pulmonary artery (LPA) and right pulmonary artery (RPA) is present. Ao, aorta; RVOT, right ventricular outflow tract; LA, left atrium; PV, pulmonary valve. (D) Two-dimensional and spectral continuous wave Doppler interrogation of the tricuspid valve from the left caudal parasternal location. Turbulence is present in the right atrium (RA) because of marked tricuspid regurgitation. The transtricuspid jet peak velocity is 5.05 m/s. This represents a transtricuspid pressure gradient of 102 mmHg, indicative of severe pulmonary hypertension.
Figure 4. Histopathology of the lung (A) and pulmonary vasculature (B and C). (A) 400× magnification of the lung (Martius scarlet blue stain) depicts abundant alveolar fibrin exudate (stained red). Collagen stains blue and erythrocytes appear yellow-green in colour. (B) ×400 magnification (H&E) cross-section containing a medium-sized pulmonary artery. Widespread nuclear debris throughout the arterial wall with moderate mixed inflammatory cellular infiltrate in the surrounding elastic laminae connective tissue. (C) ×400 magnification of a small pulmonary artery (Martius scarlet blue). Fibrinoid necrosis exhibited by circumferential red stain in the arterial wall with prominent perivascular inflammation.