Chronic renal failure in an English bull terrier with polycystic kidney disease

An entire female English bull terrier, aged five years and one month, was diagnosed with polycystic kidney disease by renal ultrasonography. It had thickening and abnormal motion of the mitral valve on 2D and M mode echocardiography, and left ventricular outflow tract obstruction, characterised by turbulence in the left ventricular outflow tract and elevated aortic blood flow velocity, detected by colour flow and spectral Doppler echocardiography, respectively. Two years later, haematology, serum biochemistry and urinalysis data suggested the presence of compensated renal failure. The dog was euthanased at 10 years and eight months of age, with haematology, serum biochemistry and urinalysis data indicating decompensated chronic renal failure. Postmortem examination confirmed polycystic kidney disease, chronic renal disease, mitral and aortic valvular myxomatous degeneration, and mixed mammary neoplasia. This case demonstrates that bull terriers with polycystic kidney disease may develop associated chronic renal failure.

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Journal of Small Animal Practice (2004) **45**, 563–567

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INTRODUCTION

This report describes a case of chronic renal failure (CRF) in a dog with bull terrier polycystic kidney disease (BTPKD) and demonstrates that terminal uraemia can be associated with BTPKD. Previous descriptions of dogs with BTPKD have included animals aged from seven weeks to over six years, all being apparently asymptomatic for renal failure (Burrows and others 1994, O'Leary and others 1999). However, few were tested for azotaemia and, in contrast to this case, most were young and had abundant normal renal parenchyma.

CASE HISTORY

An entire female English bull terrier was initially examined at five years and one month of age as part of a study into BTPKD (O'Leary 2002). This animal was diagnosed with BTPKD by renal ultrasonography, which demonstrated the presence of fluid-filled cysts in the cortices and medullae of both kidneys (O'Leary and others 1999).

At initial examination, no murmur was detected on cardiac auscultation but an uncharacterised arrhythmia was present. A repeat examination at six years and two months of age revealed the presence of a grade I/VI murmur, loudest in the left thorax. Further characterisation was not possible due to the dog's barrel chest and panting.

The animal was examined echocardiographically on two occasions with an ATL Ultramark 9, and either a 2·25 or 5 mHz phased array transducer (O'Leary and others 2003). Initial examination at five years and one month of age revealed left ventricular outflow tract obstruction (LVOTO) as characterised by an aortic velocity of 4·4 m/second (normal value <2·3 m/second (O'Leary and others 2003) and left ventricular outflow tract turbulence using spectral and colour flow Doppler, respectively (Sisson 1992). A similar examination at six years and two months of age revealed an aortic velocity of 4 m/second and turbulence in the left ventricular outflow tract. Abnormal mitral valve function in respect to the arrhythmia was also present. Systolic blood pressure was 120 mmHg, measured using a Doppler blood pressure monitor (model 811-BTS; Parks Medical Electronics) (O'Leary and others 2003).

Haematology, serum biochemistry and urinalysis were performed routinely by the University of Queensland Clinical Pathology Laboratory on four occasions (Table 1). Blood was stored in EDTA, serum and sodium fluoride tubes at 4°C until measurements were performed. Serum measurements were performed using a COBRAS MIRA analyser (Roche Diagnostic Systems) and reagents made by Roche and Trace Scientific. Haematology profiles were performed on blood collected into EDTA on an ABX MINOS Vet Analyser (Montpellier). Differential white

Table 1. Serial haematological, serum biochemical and urinalysis results from an English bull terrier with bull terrier polycystic kidney disease

Age	5 years 8 months	6 years 5 months	7 years 2 months	10 years 8 months	Reference range
Packed cell volume	0·43	0·42	0·41	0·25	0·37-0·55
Reticulocytes	Not seen	Not seen	Not seen	Occasional polychromatophils	Not seen
White cell count ($\times 10^9$/litre)	15·6	20·30	13·1	33	6-17
Band neutrophils	*	0·2	0	3·6	0-0·3
Neutrophils	*	11·80	7·9	24·4	3-11·5
Lymphocytes	*	5·5	4·5	2	1-4·8
Monocytes	*	1·4	0	3·3	0·15-1·4
Eosinophils	*	1·2	0·8	0	0·1-1·2
Basophils	*	0·2	0	0	0-0·1
Toxic neutrophils	*	Not seen	Not seen	Not seen	Not seen
Sodium (mmol/litre)	148	147	153	137	141-155
Potassium (mmol/litre)	5·12	4·88	5·3	4·7	3·6-5·6
Chloride (mmol/litre)	113	111	113	107	96-122
Bicarbonate (mmol/litre)	19	21	21	22	13-29
Calcium (mmol/litre)	2·58	2·72	2·64	2·54	1·90-2·90
Inorganic phosphorus (mmol/litre)	1·40	1·22	1·35	2·50	1·20-3·90
Calcium/potassium ratio	1·84	2·23	1·96	1·02	1·1-3·5
Anion gap (mmol/litre)	21·12	19·88	24·3	12·7	10-25
Aspartate aminotransferase (U/litre at 37°C)	25	24	32	40	13-40
Alanine aminotransferase (U/litre at 37°C)	22	20	17	30	10-50
Alkaline phosphatase (U/litre at 37°C)	18	8	14	97	20-156
Creatine phosphokinase (U/litre at 37°C)	109	133	198	326	1-170
Gamma glutamyltransferase (U/litre at 37°C)	*	*	6	4	2-20
Amylase (U/litre at 37°C)	902	490	564	1849	1-2000
Lipase (U/litre at 37°C)	87	98	83	1109	0-258
Albumin (g/litre)	28	31	27	23	23-32
Globulin (g/litre)	42	33	47	51	27-44
Urea (mmol/litre)	3·95	6·8	12·8	37·40	4·3-6·4
Creatinine (µmol/litre)	81	81	91	308	20-177
Cholesterol (mmol/litre)	8·69	8·36	16·18	10·72	3·2-6·5
Glucose (mmol/litre)	5·61	5·59	4·2	3·4	3·9-6·1
Urine specific gravity	1·019	1·034	1·031	1·010	1·001-1·065†
Urinalysis					
Red cells	4/µl	1·5/µl	10/µl	Not seen	0-53 (1)‡
White cells	20·5/µl	15·5/µl	140/µl	2426/µl	0-520 (10)‡
Epithelial cells	11/µl	9·5/µl	240/µl	16/µl	0-143 (7)‡
pH	6·6	6·2	5·2	5·2	*
Urine protein:creatinine	0·51	0·24	0·2	6·84	<0·3§
Glucose	Negative	Negative	Negative	Negative	Negative
Casts	Negative	Hyaline	Granular/hyaline	Granular	Negative
Bacteria	Negative	Negative	Negative	Many bacilli	Negative

*Not measured; †Osborne and others (1995); ‡Values are ranges with median values in parentheses, O'Leary and others (1999); §Hood and others (1991), O'Leary and others (1999)

cell counts were obtained by manual counting of air-dried smears stained with Wright's stain and an automated AMES Hema-Tek Slide Stainer (Miles Laboratories). At seven years and two months of age, the dog had mildly elevated fasting urea and a urine specific gravity of 1·031, suggesting early compensated renal insufficiency. At 10 years and eight months of age, non-regenerative anaemia, markedly elevated urea and creatinine, and isothenuria had developed, indicating CRF.

Treatment by the dog's local veterinarian during this time included removal of mammary masses at approximately six years of age and again at nine years and four months. The animal was treated intermittently for years for a chronic skin condition with 5 mg prednisolone (Pred-X tablets; Apex Laboratories) orally every second day. At the age of 10 years and five months, three months prior to euthanasia, the animal was presented for chronic nocturnal coughing and 5 mg benazepril (Fortekor; Novartis) orally once a day was prescribed. The cough stopped and after two to three weeks the dose was decreased to 2·5 mg once a day.

For the final three months of the dog's life, the owner reported it to be polydipsic, very thin, but eating, urinating, defecating and exercising reasonably well. No vomiting was noted. Three weeks prior to euthanasia, the dog was given 50 mg/ml nandrolone laurate intramuscularly (0·25 ml Laurabolin; Intervet). One week prior to euthanasia the dog developed vulval swelling and bleeding, and behavioural changes consistent with pro-oestrus. Three days prior to euthanasia, it was noted to be depressed and anorexic and was given subcutaneously 15 mg/ml folic acid and 500 µg/ml hydroxocobalamin acetate (0·5 ml Folic-B12; Troy Laboratories). At the age of 10 years and eight months, the animal was euthanased, due to poor body condition and depression, with 325 mg/ml intravenous pentobarbitone sodium (Lethabarb; Virbac).

At necropsy, the dog was in very poor body condition. Abnormal macroscopic findings included enlarged, firm kidneys measuring approximately $8 \times 5 \times 4$ cm, with a dimpled, irregular surface. The cut surface showed multiple, variously sized cysts up to 2 cm in diameter, usually spherical but sometimes multilocular. Cysts were present in the cortex and medulla, asymmetrically distributed and concentrated at the corticomedullary junction. They contained fluid that was either clear, straw-coloured, blood-tinged or brown. Some contained necrotic debris. The cortex was reduced in thickness and pale.

Other abnormalities included enlarged parathyroid glands and a pale fluid-filled cyst, 0·5 cm in diameter, at the periphery of the right liver lobe. The uterine horns were convoluted, approximately 15 cm long and 2 cm in diameter, with multiple cysts containing clear fluid randomly dis-

tributed on the serosal surface. The cut surface of the uterus revealed numerous endometrial cysts, some of which contained purulent material. The ovaries contained multiple fluid-filled cysts. Multiple masses were present in the cranial mammary glands. These varied in size, with the largest on the left side measuring approximately $8 \times 5 \times 2$ cm and on the right $6 \times 4 \times 2$ cm.

On examination of the heart, the mitral leaflets were mildly thickened, smooth and nodular. The septal cusp was elongated and the mural cusp shortened. The papillary muscles were hypertrophied and dorsally malpositioned, with some pale streaked areas approximately $0{\cdot}15 \times 0{\cdot}5$ cm. The aortic valve leaflets were elongated, ballooned, rigid and severely thickened by fibrous ridges and nodules. Fenestrations were present along the free margins of the aortic and pulmonic leaflets. An area of roughened intima $1 \times 0{\cdot}5$ cm in diameter, presumed to be a jet lesion, was present 1 cm above the junction of the left and dorsal aortic cusps. No asymmetric septal hypertrophy (Liu 1983), subaortic muscular bulging or fixed subaortic stenosis (Sisson 1992) were present. However, some dilation of the proximal aorta was noted. The tricuspid valve had a mildly thickened, smooth, nodular septal cusp.

The dorsal surface of the right caudal lung lobe contained an area of pleural fibrosis. Palpation failed to detect any masses or thickenings in the underlying lung parenchyma.

Histological examination was performed routinely (O'Leary and others 1999), except for the use of sodium-sulphate-alcian Blue staining on cardiac tissue to detect amyloid (Pomerance and others 1976). Histological findings in the kidneys included multiple, variably sized cystic structures lined by a single layer of squamous or low cuboidal epithelium. Some cysts were surrounded by fibrosis. Most cysts appeared empty, but a few contained sloughed epithelial cells, red blood cells, macrophages and neutrophils. Some cysts also contained proteinaceous material with cholesterol clefts. While some apparently normal glomeruli and tubules remained, most normal structures were replaced by extensive interstitial fibrosis, with some areas of oedema, diffuse focal lymphocytic-plasmacytic infiltrate and occasional neutrophilic foci. While glomerular changes were not predominant, some synechiae, periglomerular fibrosis, increased parietal cell numbers and mesangial matrix, tuft collapse and Bowman's capsule dilation were present.

The cystic structure on the liver was a pseudocyst and was not lined by epithelium. The pseudocyst was present within the capsule of the liver and so had a connective tissue wall. It contained proteinaceous material. In the liver generally, there was mild to moderate portal triad fibrosis, and subcapsular and periportal lymphatic dilation, the latter indicating chronic venous congestion. Many hepatocytes contained granules of yellow pigment, interpreted as ceroid. The same pigment was evident in macrophages in the portal triads.

Histological sections of the heart showed myxomatous degeneration of all four valves. This consisted of endothelial proliferation, replacement of the spongiosa by loose myxomatous connective tissue, and splitting and separation of elastic fibres. The collagen fibres in the fibrosa were also swollen, fragmented and disorganised.

Some intramural coronary arterioles in the left ventricular free wall (particularly the papillary muscles) and interventricular septum showed subintimal and medial fibromuscular hyperplasia and hypertrophy. Intimal deposition of homogeneous, eosinophilic material often protruded into the vessel lumen. This material was determined, by staining with sodium sulphate-alcian Blue, to be mainly amyloid. Fragmentation, duplication and disintegration of the internal elastic membrane were also present. Several foci of coagulative necrosis involving loss of myofibre cross striations, and mononuclear and occasionally neutrophilic infiltrates, were present in the left ventricular free wall. The right ventricular free wall also contained foci of myocardial mineralisation. Sections of the sinoatrial node and bundle of His were apparently normal, although there was some increased interstitial fibrosis in the sinoatrial node, possibly due to the age of the animal (Svanborg 1997).

In the lung, the area grossly identified as fibrosis consisted of interstitial fibrous tissue extending from the pleural surface into the lung parenchyma. No metastatic lesions from the mammary masses were detected. Proteinaceous fluid was evident in some of the alveoli, accompanied by a moderate number of alveolar macrophages, suggesting mild pulmonary oedema.

The mammary masses were identified as benign mixed mammary neoplasia with acini of well differentiated but hyperplastic secretory epithelium, arranged in a papillary pattern and interspersed by a large stromal component consisting of proliferating myoepithelial cells. Necrosis was not evident.

Ovarian cysts were lined with flattened epithelial cells and surrounded by fibrous tissue capsules. However, uterine horn serosal cysts were not lined by epithelium but were formed within connective tissue. Endometrial cysts derived from endometrial glands were lined with cuboidal to columnar epithelium. Some contained proteinaceous fluid and others had large numbers of degenerate neutrophils. No purulent exudate was present in the lumen of the uterine horns.

DISCUSSION

To the authors' knowledge, this is the first reported case of CRF associated with BTPKD and suggests that terminal uraemia can be associated with BTPKD. Support for the occurrence of CRF in BTPKD is also provided by studies on pathologically and clinically similar autosomal dominant polycystic kidney diseases

in humans, Persian cats, rats and genetically engineered mouse models of autosomal dominant polycystic kidney disease. All these polycystic kidney diseases are inherited in an autosomal dominant manner. Affected individuals have renal pathology characterised by cortical and medullary cysts lined by squamous to cuboidal epithelial cells, and interstitial fibrosis and mononuclear inflammatory infiltrates (Cowley and others 1993, Wilson and Kalkenstein 1995, Biller and others 1996, Lu and others 1999). Animals with these polycystic kidney diseases have cysts long before extensive interstitial renal pathology and renal dysfunction develops, and signs of renal failure usually appear in middle to old age (Zeier and others 1992, Cowley and others 1993, Fick and others 1995, Biller and others 1996, Lu and others 1999).

In humans, Persian cats, rats and mice with these autosomal dominant polycystic kidney diseases, renal failure is believed to be principally due to progressive interstitial mononuclear inflammation and fibrosis, matrix accumulation and nephron loss, although glomerular lesions may also contribute (Cowley and others 1993, Wilson and Kalkenstein 1995, Eaton and others 1997, Wu and others 2000). Hence, dogs in previous reports with BTPKD that had abundant normal renal parenchyma may not have had sufficient interstitial renal lesions at the time of renal ultrasound examination for clinical signs of renal dysfunction to be present.

While CRF due to 'old age kidney disease' could not be excluded in the dog in this case, no mineralisation was present in the kidneys, glomerular sclerosis was not prominent and histological evidence of a primary cause for CRF (other than BTPKD) could not be found. Additionally, no histological evidence supporting the presence of bull terrier hereditary nephritis, another inherited renal disease in this breed, was found (Hood and others 1995). Hence, it is likely that the renal lesions and CRF in this dog are associated with the presence of BTPKD.

While it is likely that the terminal illness of the dog in this report was uraemia associated with CRF and BTPKD, it also suffered from benign mammary neoplasia, cystic hyperplastic endometritis and mild congestive heart failure associated with myxomatous mitral degeneration and LVOTO. Hence, these concurrent diseases may have contributed to the dog's final precipitous clinical decline.

The benign mixed mammary tumours present in this dog were unlikely to have contributed greatly to its illness. The tumours were not necrotic and there was no evidence of metastasis on palpation of the lungs, on inspection of the local or thoracic lymph nodes, or the thoracic and abdominal organs. Additionally, these tumours are reported to lack metastatic potential (Knapp and others 2000).

Mild cystic hyperplastic endometritis was also present in this dog, and it is possible that this disorder and the recent onset of pro-oestrus may have partially contributed to its general unwellness. However, it is likely that this was a final blow to an animal in the terminal stages of CRF. This is supported by the lack of clinical signs usually found in dogs with cystic endometrial hyperplasia. Additionally, pyometra was not present in this case and was not likely to have developed until dioestrus. Further, renal lesions characteristic of pyometra, such as membranoproliferative glomerulonephritis due to immune complex deposition (Feldman 2000), were not evident.

At necropsy, this dog had histological evidence of mild pulmonary and hepatic passive congestion. However, as the renal lesions in this animal were not typical of the glomerular basement membrane thickening, increased mesangium or glomerular sclerosis that can occur with moderate to severe congestive heart failure (Cantin and others 1973, Lajoie and others 1994), this is unlikely to have caused the CRF.

The dog in this case also had intramural coronary fibromuscular hyperplasia and amyloidosis, but no evidence of uraemic arteriopathy (Pirie and others 1965). Fibromuscular hyperplasia is common in the hearts of dogs with mitral valve myxomatous degeneration and LVOTO (Buchanan 1977, Lehmkuhl and Bonagura 1993), and this vascular lesion, along with vascular amyloidosis, also becomes more common with advancing age (Jonsson 1972, Buchanan 1977). Interestingly, this case, and all English bull terriers with BTPKD that have been examined for evidence of cardiac disease to date, have also suffered from some form of valvular cardiac disease, often mitral valve endocardiosis or LVOTO (Burrows and others 1994, O'Leary 2002). Additionally, 10 of 11 dogs with BTPKD that were examined postmortem had intramural vascular and myocardial lesions (Burrows and others 1994, O'Leary 2002). Hence, this case report also supports a possible association between BTPKD, cardiac valvular disease and intramural coronary fibromuscular hyperplasia.

Conclusions

This case study demonstrates that dogs with BTPKD may develop CRF associated with interstitial renal fibrosis, interstitial mononuclear inflammatory infiltrate and nephron loss. Dogs with BTPKD should also be examined for evidence of cardiac disease.

Acknowledgements

The authors would like to thank Dr Bruce MacKay for performing renal ultrasonography and echocardiography. Thanks also to Brian Bynon from The University of Queensland School of Veterinary Science clinical pathology laboratory, Chris Cazier from The University of Queensland School of Veterinary Science histopathology laboratory, and Michael Slavin and Gerard Spoelstra from Murdoch Histopathology Laboratory. Thanks also go to Professor Keith Hughes, The University of Queensland, for funding and support. This study was partially funded by the Kibble Bequest and The Queensland Canine Control Council Breeders Fund.

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