PAPER

Juvenile nephropathy in 37 boxer dogs

OBJECTIVES: The purpose of this study was to review and characterise the clinical presentation of young boxer dogs with chronic kidney disease referred to the authors' institutions.

METHODS: Records were collected retrospectively from 37 boxer dogs, less than five years of age, which had presented with azotaemia, inappropriately low urine concentrating ability, and ultrasound or radiographic evidence of abnormal kidneys.

RESULTS: Clinicopathological findings included azotaemia, hyperphosphataemia, anaemia, isosthenuria and proteinuria. Ultrasonographic findings included hyperechoic renal cortices, loss of corticomedullary junction definition, dilated pelves and irregularly shaped small kidneys. Renal histopathological findings included pericapsular and interstitial fibrosis, inflammatory cell infiltration, dilated tubules, sclerotic glomeruli and dystrophic calcification. Survival time of the dogs varied from zero to over five years after diagnosis.

CLINICAL SIGNIFICANCE: This paper documents features of the presentation and progression of juvenile nephropathy in boxer dogs. While juvenile nephropathy has been reported in individual cases of boxer dogs previously, this is the first reported case series.

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INTRODUCTION

Chronic kidney disease is usually considered to be a disease of older dogs, and reduced renal function has been found in more than 20 per cent of dogs over five years old (Leibetseder and Neufeld 1991). The aetiology of renal disease in older dogs is usually unknown (Finco 1995). Renal disease in younger dogs may be congenital (present at birth), inherited (genetically derived), familial (a trait present in a group of related dogs) or acquired. In young animals, renal disease is often thought to be congenital because of the lack of long-term signs; however, development of lesions consistent with an "end-stage kidney" may develop in as little as 60 days (Finco 1995).

Juvenile nephropathies have been described in over 20 dog breeds and many of these have been suspected of being familial or inherited (Maxie 1993). Canine familial renal disease usually presents as renal failure with azotaemia, inability to appropriately concentrate urine and possibly signs of uraemia. The age of onset varies from a few weeks to several years but is often 4 to 18 months of age (Maxie 1993). Hereditary nephritis is characterised by proteinuria, renal haematuria and progressive glomerular disease (Vaden 2004).

Renal dysplasia has been reported in at least 23 breeds of dogs and may or may not have a familial basis (Vaden 2004). Classically, renal dysplasia is characterised histologically as the presence of persistent metanephric ducts surrounded by primitive mesenchyme, fetal or immature glomeruli, fetal or immature tubules, anomalous presence of interstitial fibrous connective tissue, and possibly bone or cartilage in the parenchyma (Picut and Lewis 1987a). Cartilage nodules, found in some dysplastic human kidneys, are rarely if ever present in canine renal dysplasia. Grossly, the kidneys are usually small, misshapen and fibrosed (Maxie 1993).

Juvenile nephropathy with histopathological characteristics of renal dysplasia has been reported in a boxer dog (Peeters and others 2000) and in two boxer dog litter mates (Hoppe and Karlstam 2000). A third boxer puppy in this litter showed similar signs and clinicopathological evidence of renal disease (azotaemia and decreased urine concentrating ability), but necropsy was not performed and histopathology was not available (Hoppe and Karlstam 2000).

Juvenile nephropathies characterised by interstitial fibrosis, infiltration of lymphocytes and plasma cells, and tubular dilatation, without evidence of dysplasia has been reported in dobermann dogs (Chew and others 1983), miniature schnauzer dogs (Morton and others 1990), standard poodles (DiBartola and others 1983) and humans with juvenile nephronophthisis (NPH) (Hildbrandt and others 2001). The standard poodles were related, while familial relationships were either inconsistent or not present in the dobermann

dogs, miniature schnauzers, and in human juvenile NPH (Waldherr and others 1982).

The purpose of this study was to review and characterise the clinical presentation of young boxer dogs with chronic kidney disease referred to the authors' institutions.

MATERIALS AND METHODS

Records were retrospectively collected from boxer dogs that had presented with polyuria and azotaemia between January 2000 and May 2006 to the Hospital for Small Animals, University of Edinburgh (group 1), University of Glasgow (group 2), University of Bristol (group 3), Davies Veterinary Specialists (group 4) and Royal Veterinary College (group 5). Inclusion criteria were initial referral presentation at less then five years of age, increased serum urea and/or creatinine, an inappropriately low urine concentrating ability (urine specific gravity equal to or less than 1·025 as determined by refractometer), and ultrasound or radiographic evidence of abnormal kidneys.

Kidneys were considered small on radiographs if less than 2·5 times the length of the second lumbar vertebrae (Dibartola 2005). Renal size was judged subjectively at ultrasound (Nyland and others 2002) but was generally considered small if less than 6 cm in length (Green 1996). Thirty-seven dogs met the inclusion criteria.

Where available, data collected from the dogs' records included presence or absence of incontinence in the history (available in 36 dogs), packed cell volume (PCV) (36 dogs), serum phosphorus (35 dogs), urine culture (30 dogs), urine protein to creatinine (UPC) ratio (27 dogs), renal ultrasound results (36 dogs), excretory urogram findings (four dogs), indirect systolic blood pressure measurement (11 dogs), renal histopathology (nine dogs) and long-term outcome (26 dogs).

Dogs were staged according to serum creatinine concentration based on the system of the International Renal Interest Society (IRIS). Also using this staging system, dogs with a UPC ratio of greater than 0·5 were considered proteinuric, those with a UPC of 0·2 to 0·5 as having borderline proteinuria and those with less than 0·2 were considered non-proteinuric (Polzin and others 2005).

Where the data were distributed normally, means were used to describe the central tendency of the data; where it was not distributed normally, median values were used. The linear relationships between time to euthanasia or death *versus* PCV, UPC ratio, and serum creatinine were determined by linear regression using Minitab 1·4. The P values and goodness of fit of the regression were assessed by R^2. Before the regression analysis was carried out, the time to death data required square root transformation to normalise the residuals. A Kaplan-Meier plot of time from diagnosis of renal failure to death or to loss of follow-up was performed. In all cases, a $P<0·05$ was taken to indicate statistical significance.

RESULTS

The median age of the 37 dogs at presentation was two years, with a range of four months to five years. There were 14 neutered female dogs, 15 entire female dogs, three neutered male dogs and five entire male dogs. Nineteen of 36 dogs had a history of incontinence; this information was not available for one dog. The incontinent dogs included 10 neutered females, five entire females, two neutered males and two entire males.

Neither the serum urea nitrogen nor the serum creatinine concentrations were normally distributed. The median serum urea nitrogen for 37 dogs was 22·8 mmol/l (range 7 to 122·5 mmol/l). Median serum creatinine for 36 dogs was 370 µmol/l (range 110 to 1538 µmol/l), and data were not available for one dog. This dog was included as she had a serum urea concentration of 89 mmol/l (reference range 2 to 7 mmol/l), a urine specific gravity of 1·012 and ultrasonographic evidence of chronic renal disease.

Using the classification system of the IRIS (based on serum creatinine), two of the dogs were diagnosed as having stage I, five as stage II, 15 as stage III and 14 as stage IV renal failure (Polzin and others 2005). UPC ratio was available for 27 of the dogs and had a median of 1·74, with a range of 0·09 to 6·6. The UPC was above 0·5 in 25 dogs and above 2·0 in 10 dogs. Using the IRIS system, one stage II dog was non-proteinuric and one stage IV dog was borderline proteinuric. The other 25 dogs were proteinuric.

Indirect systolic blood pressure measurement was performed in 11 of the dogs and data were normally distributed. The mean indirect systolic blood pressure was 155 mmHg (range of 110 to 184 mmHg). Using the IRIS system, of the stage II dogs, one was classified as moderate risk and two were classified as high risk of extrarenal end-organ damage. Of the stage III dogs, one was classified as high risk and one as moderate risk, and of the Stage IV dogs, there were four classified as minimal risk and one classified as moderate risk of extra-renal end organ damage.

Serum phosphorus concentration was normally distributed, and the mean for 33 dogs was 2·80 mmol/l (range 1·21 to 11·4 mmol/l).

PCV was also normally distributed, and the mean value for the 33 dogs was 36·3 per cent (range 14 to 48·5 per cent). Sixteen of 36 (44 per cent) dogs had a PCV value below the reference range for the laboratory used. As there were five different laboratories used in the study, the results for each centre with their reference ranges are presented in Table 1.

Urine specific gravity values were normally distributed and the mean for the 37 dogs was 1·012 (range 1·005 to 1·022). Urine cultures were negative in 21 of the dogs. Positive urine cultures were obtained in nine dogs: *Escherichia coli* were cultured from the urine of eight dogs, and *Staphylococcus* was cultured from the urine of one dog. Urine cultures were not performed in seven dogs.

Abdominal ultrasonography was performed in 36 dogs, and intravenous urography was performed in four dogs (including the one which had not had ultrasonography). Imaging showed hyperechoic renal cortices in 22 dogs, loss of definition of the corticomedullary junction in 16 dogs, dilated pelves in 18 dogs, an irregular shape of the kidneys in 17 dogs, small renal size in 11 dogs and the presence of cysts in seven dogs. (Most dogs

Table 1. Means for normally distributed data, medians for non-normally distributed data, data ranges and laboratory reference ranges for serum urea, creatinine and phosphorus, and PCV for boxer dogs by contributing veterinary centres

	Group 1, n=10	Group 2, n=2	Group 3, n=14	Group 4, n=6	Group 5, n=5
Urea, mmol/l					
Median	22·1	41·55	21·9	30·0	15
Data range	8·2-122·5	14·8-68·3	7-89	11·7-40·5	9·6-55·4
Reference range	1·7-7·4	2·5-8·5	2·0-7·0	2·8-9·0	3·0-9·1
Creatinine, mol/l					
Median	394·5	398·5	253·0	383	248
Data range	191-1538	178-619	140-1047	234-654	110-569
Reference range	40-132	45-155	70-110	68-104	98-163
Phosphorus, mol/l					
Mean	3·12	3·08	2·71	2·44	2·66
Data range	1·36-11·4	1·69-4·07	1·21-8·62	1·49-3·26	1·24-3·85
Reference range	0·9-2·0	1·29-2·90	0·75-1·25	1·2-2·9	0·8-2·0
PCV, per cent					
Mean	34·52	45·4	37·0	32·2	37·18
Data range	17·1-46·6	45·1-45·7	22·0-48·5	14-47	24·2-45·9
Reference range	39-55	37-55	35-50	37-52	37-55

PCV Packed cell volume, group 1 Hospital for Small Animals, University of Edinburgh, group 2 University of Glasgow, group 3 University of Bristol, group 4 Davies Veterinary Specialists, group 5 Royal Veterinary College

had more than one descriptive comment.) In eight dogs, the kidneys were only described as having poor architecture or simply as being abnormal.

Two of the 19 dogs with urinary incontinence had radiographic evidence of an intrapelvic bladder, and one dog had radiographic evidence of an intrapelvic bladder without incontinence.

Results of renal histopathology, as examined by light microscopy without the use of special stains, were available for nine dogs, either from biopsy (eight dogs) or necropsy (one dog) (Figs 1 and 2). The most consistent finding in the histopathology of the renal biopsies was pericapsular and interstitial fibrosis, which was found in eight of the nine dogs. The ninth dog had two areas of dystrophic calcification, but fibrosis was not noted. Another common finding was the presence of inflammatory cells (lymphocytes and/or plasma cells) found in three dogs. Other findings described included dilated tubules (three dogs) and sclerotic glomeruli (two dogs).

Ten of the dogs were alive at the time of writing; the longest survival times were for two dogs that were still alive five years after initial diagnosis (Fig 3). Four other dogs had lived longer than two years. Sixteen of the dogs had undergone euthanasia or had died; median survival time for these dogs was five months, with a range of zero (had undergone euthanasia at initial presentation) to two years.

Of these 16 non-survival dogs, 10 (62·5 per cent) were anaemic at the time of diagnosis; however, there was no significant relationship between PCV and survival time (P=0·101, R^2=18·4). There was also no significant relationship between UPC ratio and survival time in the 11 dogs for which both data were available (P=0·71, R^2=1·60) or between serum creatinine and survival time in the 16 dogs (P=0·108, R^2=18·7).

Three of the 16 non-survival dogs (18 per cent) were males or neutered males, similar to the percentage (21·6 per cent) of males in the study. One dog which underwent euthanasia two years after diagnosis had evidence of worsening renal disease but had undergone euthanasia for another disorder, and a second dog also underwent euthanasia 16 months after diagnosis for a non-renal disorder. Median

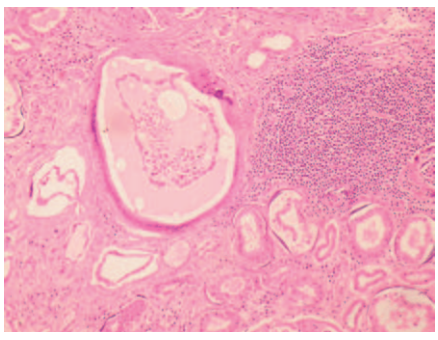

FIG 1. Renal cortex with a distended glomerular remnant, irregular tubular size, thickening and mineralisation of the glomerular and tubular basement membranes, and marked interstitial fibrosis with mononuclear cell infiltration (BA160.04a × 10). H&E. ×100

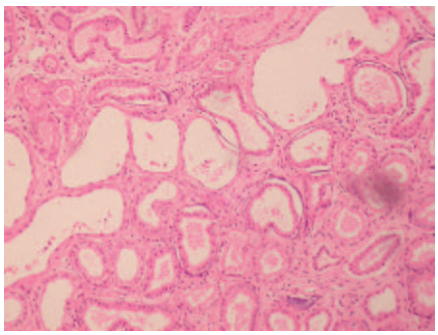

FIG 2. Renal cortex with marked variation in tubular size, thickening and mineralisation of tubular basement membranes, protein and cell debris within their lumina and interstitial fibrosis (BA160.04c × 10). H&E ×100

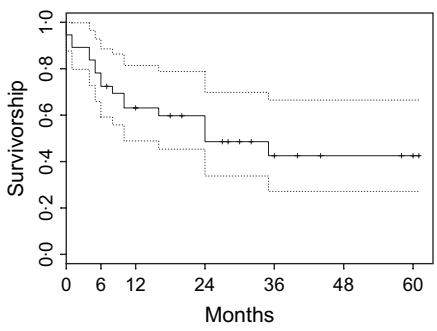

FIG 3. Kaplan-Meier plot of time (months) from time of diagnosis of renal failure in juvenile boxer dogs to death or to loss of follow-up

survival with these two cases omitted was 4·5 months. Eleven of the dogs were lost to follow-up.

DISCUSSION

In this study, 37 boxer dogs aged five years or less with decreased urine concentrating ability, polyuria, azotaemia, and ultrasonographic and/or radiographic evidence of renal disease are presented. Both sexes were represented, although there were more females than males.

Over half of the dogs had urinary incontinence, with the highest incidence in the neutered female dogs. This is likely to be a combination of urethral sphincter mechanism incompetence, which is the most common cause of urinary incontinence in neutered female dogs (Holt 1990), and the increased volume of urine produced secondary to the kidney disease. Boxer dogs have been noted previously to be overrepresented among dogs presenting with sphincter mechanism incompetence (Blendinger and others 1995).

Twenty-five of the dogs had clinical proteinuria with a UPC greater than 0·5, and in 10 dogs, it was greater than 2·0. The 10 dogs with the higher UPC values may have a pathological glomerular renal proteinuria, whereas the other 15 were more likely to have a pathological interstitial renal proteinuria, although early glomerular proteinuria may have been possible (Lees and others 2005). Six of the dogs with documented clinical proteinuria had positive urinary tract infections, but there was no apparent association between the severity of the proteinuria and the presence of a urinary tract infection. The method of urine collection was not stipulated in this retrospective study, so it is possible that the urine protein was affected by extraurinary postrenal factors (Lees and others 2005).

The ultrasound findings of hyperechoic cortices, loss of definition of corticomedullary junction, dilated pelves, irregular shape of the kidneys and small kidney size are non-specific and may be found in many types of renal disease, including chronic pyelonephritis (Green 1996). Urine cultures were positive in nine of the 30 dogs in which urine culture was performed. The urinary tract infections in these dogs may have lead to the nephropathy; however, dogs with abnormal kidneys are also at greater risk for developing pyelonephritis (Maxie 1993). Renal cysts, found in seven dogs, may be inherited or may be acquired as result of obstruction of renal tubules (Green 1996). Cysts are a common incidental feature of renal dysplasia in humans and may also occur secondarily in dogs as a degenerative change as a result of intrarenal obstruction from interstitial fibrosis (Picut and Lewis 1987a).

Although renal dysplasia has been reported in boxer dogs (Hoppe and Karlstam 2000), the renal histopathology from only one of these nine dogs was consistent with dysplasia. The initial interpretation of this biopsy sample was severe fibrosis with a mild, diffuse lymphocyte and plasma cell infiltrate, and it was reclassified as dysplasia after review. The predominant histopathological finding in most of the dogs was pericapsular and/or interstitial fibrosis, which is non-specific and consistent with chronic disease.

Dysplastic changes may affect the kidney focally or segmentally (Risden and others 1975), so it is possible that dysplastic changes may have been found in other dogs after examination of further samples or with histopathological examination of the entire kidney. Wedge biopsies are recommended for diagnosis of renal dysplasia (Lees 1996), and most of the renal tissue in this study was obtained by needle biopsy. It has also been reported that kidneys affected by dysplasia are better distinguished from chronic renal disease if early lesions are examined (Picut and Lewis 1987b), and most of these dogs presented with chronic signs. In Lhasa apso and shih-tzu dogs with renal dysplasia, the secondary changes due to chronicity include fibrosis, dystrophic mineralisation, non-suppurative interstitial nephritis and retention cysts, with severe interstitial fibrosis seen in advanced cases (Picut and Lewis 1987b).

Neither immunofluorescence nor electron microscopy was performed on any of the renal biopsy samples. Immunofluorescence would have provided information about potential immune-related disorders. Electron microscopy would have provided better characterisation of the pathological changes and is the best means of studying the glomerular basement membrane (Senior 2005).

In humans, juvenile NPH, a progressive tubulointerstitial kidney disease, accounts for 6 to 10 per cent of the end-stage renal disease in European children (Konrad and others 1998). Polydipsia, polyuria and decreased urine concentration are the early signs, with progression to azotaemia, anaemia and end-stage renal disease over several years (Gretz and others 1989). Renal ultrasound findings in juvenile NPH include increased echogenicity with loss of corticomedullary definition (Blowey and others 1996). Renal cysts are sometimes found (Garel and others 1984, Blowey and others 1996). Grossly, the kidneys have a finely granular appearance and are normal to small in size (Waldherr and others 1982). Renal histological findings include tubular atrophy with thickened and multi-layered basement membranes, lymphocytic and histiocytic infiltration, marked interstitial fibrosis, and sometimes cyst formation (Hildbrandt and others 1992, Komatsuda and Wakui 2005). Electron microscopy shows predominant changes in the basement membrane (Waldherr and others 1982). The clinical presentation, ultrasonography and some of the renal histological findings of these boxer dogs were similar in many ways to human juvenile NPH, although the findings are not specific and many juvenile nephropathies may present in a similar fashion.

Survival time was quite variable among the boxer dogs in this study, from dogs that underwent euthanasia at initial presentation to dogs which lived for at least five years after diagnosis. Survival time in the dogs which underwent euthanasia was not related to PCV, UPC or serum creatinine, although the power of the tests may have been affected by the low number of the dogs for which data were available.

Data regarding the total number of boxer dogs less than five years of age seen at each centre was not available, so the prevalence of nephropathy in the breed from these centres could not be determined. As complete retrospective screening of databases for affected boxer dogs was not available at all centres, it is

also possible that there were affected dogs omitted from the study. These dogs were also referred from first opinion practices, and it is highly likely that not all young boxer dogs with renal disease are referred.

In summary, this paper documents features of the presentation and progression of juvenile nephropathy in boxer dogs. Further investigation is required to determine if there is one disease with multiple pathological changes or a number of underlying causes. Additional studies would be needed to determine if there is a familial component to some forms of the disorder.

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