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Progressive renal disease in Soft-coated Wheaten Terriers: possible familial nephropathy

A. S. NASH, D. F. KELLY AND C. J. GASKELL

Department of Veterinary Medicine, University of Glasgow, and Departments of Veterinary Pathology and Veterinary Clinical Science, University of Liverpool

ABSTRACT

Clinical and pathological features are described in seven young Soft-coated Wheaten Terriers with chronic renal disease. The oldest dog was $2\frac{1}{2}$ years; in the other six, ages at death ranged from one to 15 months. Two of the puppies were littermates: one died at 4 weeks, the other at 12 months. Two of the dogs were examined at intervals up to 14 months, during which time there was progressive deterioration in renal function. All seven dogs had abnormal kidneys with cortical narrowing. The histological features were not consistent and included: tubular dilatation and basement membrane thickening; an unusually large proportion of immature glomeruli; persistence of interstitial connective tissue resembling foetal mesenchyme. Inflammatory change was minimal except in two dogs with super-imposed pyelonephritis.

The clinical and laboratory data suggest that these dogs had dysplasia of the kidneys that progressed to chronic renal disease during early life. In three dogs there was a familial relationship.

INTRODUCTION

Chronic renal failure in the dog may result from a number of primary causes, each of which can lead progressively to a reduction in functioning renal mass. In recent years there has developed increasing awareness of renal dysplasias as a cause of chronic renal failure in the young dog. These dysplasias are probably uncommon causes of renal failure in dog populations as a whole, but may be important in particular breeds (Lucke, *et al.*, 1980; Cowgill, 1983; Bovée, 1984). Awareness of possible renal dysplasia in a breed may be hindered by lack of diagnostic precision and by geographical dispersion of related animals so that suspicions about a possibly inherited renal abnormality may exist only at anecdotal level. Such

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suspicions appear to have been present during the past decade about the Soft-coated Wheaten Terrier. This paper summarizes the clinical and pathological observations on seven young dogs of this breed that were investigated for renal disease. The data lend support to earlier suspicions about the existence of an inherited nephropathy in the Soft-coated Wheaten Terrier.

MATERIALS AND METHODS

The ages and sex of these dogs are shown in Table 1. Clinical and laboratory data were abstracted from case records. Complete post mortem examinations were carried out on dogs 3, 5, 6 and 7. For the other three dogs pathological observations are available only for the kidneys. Tissues for histological examinations were fixed in 10 per cent formalin (dogs 1–4) or Zenker-formol (dogs 5–7). Paraffin-embedded sections were cut at 6 microns and routinely stained by the haematoxylin-eosin, periodic acid-Schiff, Weigerts' elastic-Van Gieson, Martius Scarlet Blue and Von Kossa techniques.

RESULTS

Clinical and biochemical findings

All seven dogs had clinical or biochemical evidence of renal disease during the first few months of life (Table 1). Dogs 1 and 3 were poorly grown; the latter weighed only 1·27 kg., by comparison with its littermates' average weight of 10 kg.

TABLE 1. Clinical features of Wheaten Terriers with Renal Disease

Case No.	Age*	Sex	Presenting signs	Polydipsia	Duration	Condition
1	2½ years	♂	Weight loss, anorexia, vomiting	+	2 years	Poor
2	4½ months	♂	Stunted; anorexia; vomiting; low urine specific gravity; raised blood urea	+	NR	NR
3	17 weeks	♀	Anorexia; stunting		6 weeks	Fair
4	6 months	♀	Urinary incontinence	±	4 weeks	NR
5	4½ weeks	♂	Fits, vomiting. Died within 24 hrs.	NR	1 day	Poor
6	12 months	♀	Vomiting, partial anorexia	+	10 months	Poor
7	15 months	♂	Vomiting	+	14 months	Poor

* at death/euthanasia

NR: Not recorded

Dog 1 had a blood urea of 36·6 mmol/l, urine specific gravity of 1·016, and normal values for serum alkaline phosphatase and plasma proteins. The sire of dog 2 was reported to have died from renal failure but no precise details are known (personal communication, Soft-coated Wheaten Terrier Club of Great Britain). Dogs 3, 6 and 7 were investigated over periods ranging up to several months and the observations on these three dogs are recorded below in greater detail.

Dog 3. This puppy grew only slowly and was the smallest of a litter of seven. She was always a reluctant feeder. Initial physical examination at eleven weeks revealed no abnormality other than reduced size. Biochemical investigation revealed slightly elevated blood urea (11·2 mmol/l) and serum alkaline phosphatase (327 iu/l); alanine aminotransferase and plasma proteins were all within normal ranges. This puppy was mildly anaemic (PCV 26, Hb 8·5 g/dl) and had unremarkable white cell values. On re-examination six weeks later similar biochemical and haematological values were obtained: at this time the puppy collapsed and was moribund.

Dog 6. This dog was the littermate of dog 5 whch had died at 4½ weeks of age. Dog 6 was the smallest of the remaining litter of five puppies. At eight weeks this puppy had a blood urea level of 9·2 mmol/l: values in the other littermates were from 2·7 to 5·9 mmol/l.

This puppy was examined at five months when persistent vomiting, polydipsia and variable appetite were recorded by the owner. At this time a pyloric stenosis was detected and treated by pyloromyotomy. Following surgical treatment vomiting stopped and body weight increased. At 8 months the dog was eating less, was thirsty and vomited occasionally. Physical examination revealed a systolic murmur and a palpably hypertensive pulse. Over the following three months the condition of the dog declined into progressive chronic renal failure and euthanasia was carried out at 12 months. The laboratory data obtained from this dog, reflecting deteriorating renal functions, are shown in Table 2.

TABLE 2. Plasma and urine chemistry in a Wheaten Terrier (Dog 6) with progressive renal failure

	Plasma			Urine	
Time from first estimation (weeks)	Urea (mmol/l)	Creatinine (μmol/l)	Phosphate (mmol/l)	Protein (mg %)	Specific gravity
0	9·2	NR	NR	NR	NR
12	33·5	265	2·8	0	1·010
13	21·2	292	NR	0	1·013
14	41·0	265	3·23	NR	NR
15	41·3	NR	2·80	0	1·011
25	33·0	389	1·98	50	1·012
41	55·8	583	4·89	NR	NR
44	59·3	778	5·68	50	1·014

NR: Not recorded

TABLE 3. Plasma and urine chemistry in a Wheaten Terrier (Dog 7) with progressive renal failure

	Plasma			Urine	
Time from first estimation (weeks)	Urea (mmol/l)	Creatinine (μmol/l)	Phosphate (mmol/l)	Protein (mg %)	Specific gravity
0	13·3	NR	NR	0	1·017
3	15·7	NR	2·56	0	1·011
12	31·5	283	2·55	0	1·010
25	37·5	486	3·13	0	1·010
35	41·5	557	3·09	0	1·011
55	47·9	NR	3·22	NR	NR
60*	109·8	583	5·18	20	1·020

* While dehydrated

NR: Not recorded

Dog 7. This puppy was one of two in the subsequent litter to that of dogs 5 and 6, from the same sire and dam. At 3 weeks of age the blood urea was 13·3 mmol/l. At that time the puppy was energetic but thin and thirsty. He was reared and maintained on a low protein, non-meat diet. Re-examination at 6 months revealed a palpably hypertensive pulse and systolic murmur. At 12 months the dog vomited frequently, was anaemic and had uraemic halitosis. Three months later the dog had an episode of uraemic encephalopathy and euthanasia was carried out. Laboratory data are summarized in Table 3.

Renal post mortem findings

In all dogs the kidneys were grossly abnormal with bosselated external surfaces, cortical narrowing and variable intrarenal fibrosis (Fig. 1). Histological features included dilatation of tubules; interstitial fibrosis (Fig. 2); tubular atrophy and basement membrane thickening. Tubules were sometimes lined by atypical epithelium and interstitial connective tissues often had a foetal mesenchymal appearance (Fig. 3). Appearance of glomeruli varied: some were normal, others were sclerotic and some kidneys contained a larger than normal complement of immature foetal-type glomeruli and glomerular blastema (Fig. 4). The gross and microscopic features are summarized in Table 4. A histological observation of note is the relative absence of an inflammatory component in the renal lesions. In most dogs inflammation was usually limited to a few loose interstitial foci of lymphocytes and plasma cells. An exception was dog 3, which also had an active pyelitis, and dog 6 which had an interstitial neutrophilic reaction. Immunofluorescent studies on kidneys from dogs 6 and 7 showed no evidence of IgG in glomeruli, but C3 component of complement was detected on tubule basement membranes. The significance of these immunofluorescent patterns is at present unclear.

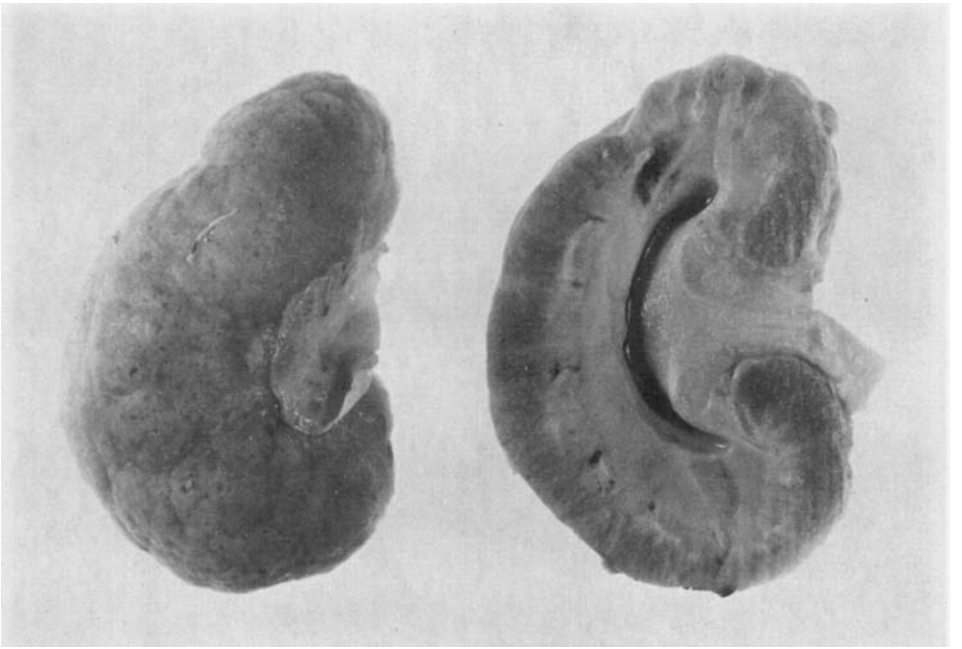

FIG. 1. Dog 4. A 6-months-old female. The kidneys are small (combined weight 36 g.) with irregular surfaces. There is irregular cortical narrowing and slight dilatation of the pelvis. ×1·5.

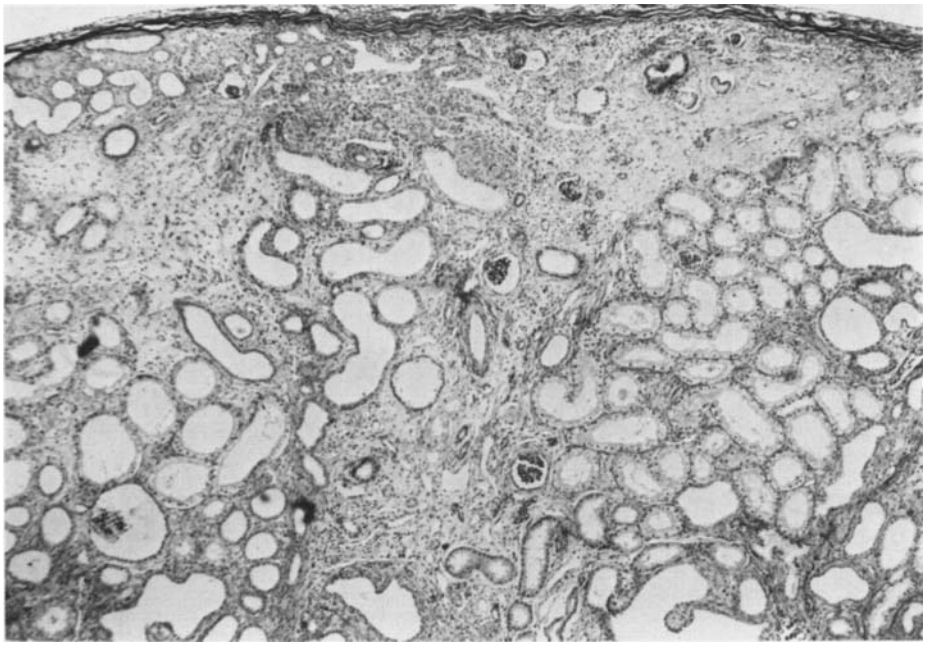

FIG. 2. Dog 2. A 4½-months-old male. Irregular subcapsular radial fibrosis and tubular dilatation. Haematoxylin—van Gieson ×48.

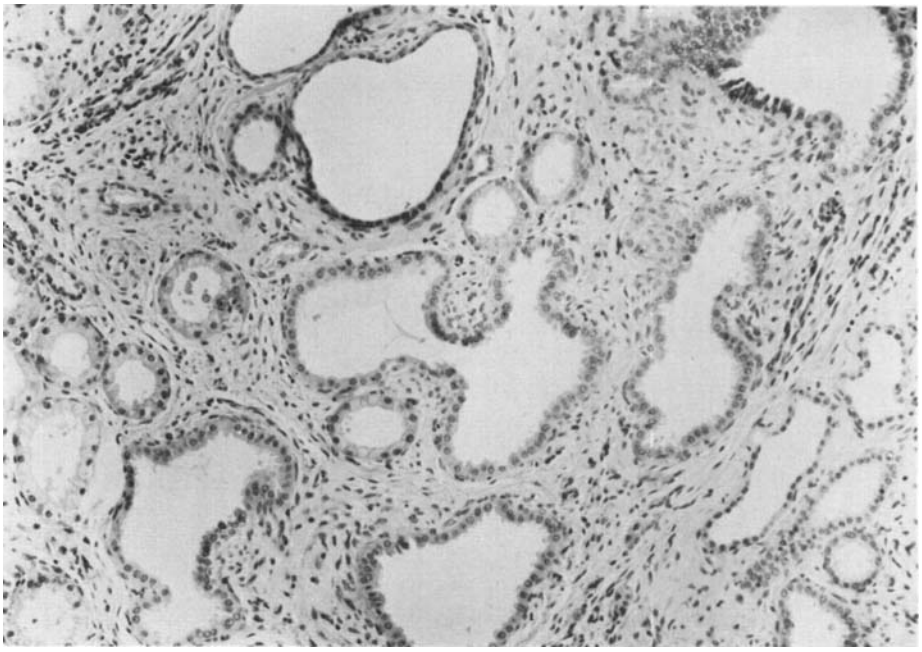

FIG. 3. Dog 2. Dilated tubules are lined by atypical epithelium and separated by excess interstitial mesenchymal connective tissue. Haematoxylin—Eosin (HE) ×120.

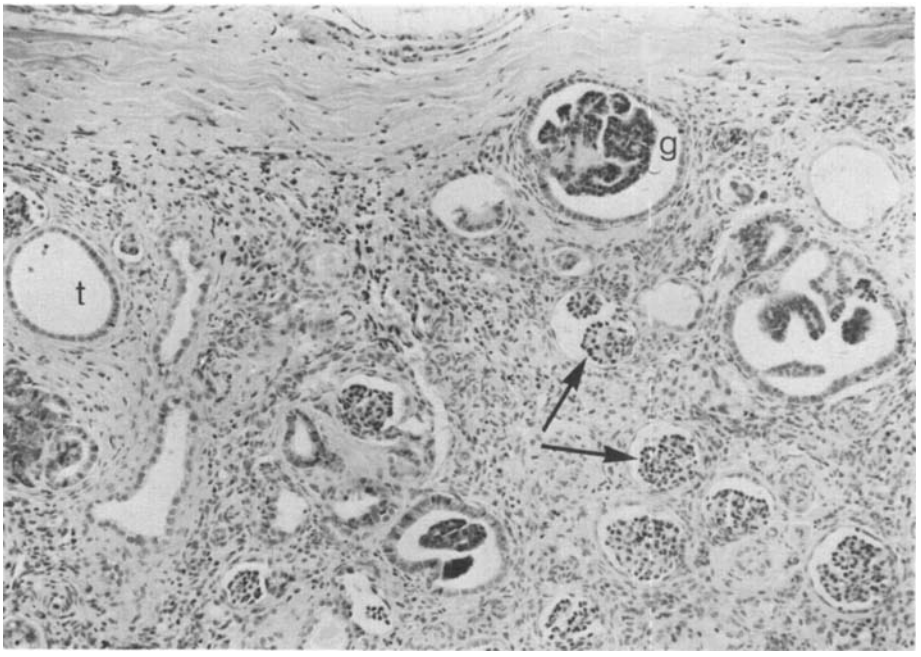

FIG. 4. Dog 2. Subcapsular cortex contains dilated tubules (t), abnormal interstitial connective tissue, glomerular blastema (g) and crowded foetal glomeruli (arrows). HE ×120.

TABLE 4. Pathological features of the kidneys from Wheaten Terriers with Renal Disease

Case	Gross	Microscopic
1	Normal size, pitted cortical surface, narrow cortices, radial fibrosis	Dilatation of tubules and glomeruli. Tubular atrophy; TBM* thickening, atypical hyperchromatic tubular epithelium. Radial interstitial fibrosis.
2	NR*	Dilatation of tubules. Tubular atrophy; TBM thickening, atypical tubular epithelium. Many foetal glomeruli. Plentiful interstitial mesenchymal tissue.
3	Small; grey-white; capsular adhesion. Narrow pale cortex.	Numerous foetal glomeruli. Radial accumulation of immature interstitial connective tissue. Focal tubular calcification. Active pyelitis.
4	Pale granular surface with subcapsular depressions and radial cortical fibrosis.	Dilatation of tubules and glomeruli. Tubules: atypical epithelium. Many foetal glomeruli. Interstitial accumulation of immature connective tissue. Occasional interstitial lymphocytes and plasma cells.
5	Small; grey-white. Distended renal pelvis and narrowed rim of renal substance. Ureters and urethra patent.	Focal persistence of primitive metanephric connective tissue with many small, poorly developed glomeruli.
6	Small, grey-white; pitted surfaces. Narrowed, irregular cortices; radial fibrosis.	Diffuse interstitial fibrosis with larger focal scars. A few shrunken, poorly developed glomeruli and a few obsolescent glomeruli. Focal interstitial infiltration, predominantly neutrophils. Tubular dilatation and casts.
7	Small, grey-white; pitted surfaces. Narrowed, irregular cortices; radial fibrosis.	Diffuse interstitial fibrosis with larger focal scars. Occasional small infiltrations of plasma cells and lymphocytes. Many cystic and obsolescent glomeruli. Tubular dilatation.

* TBM: Basement membrane of renal tubules
NR: Not recorded

DISCUSSION

All seven animals had clinical evidence of progressive renal disease, for which there was supportive biochemical data in five dogs: no urine or blood samples were obtained from dog 5 which died when $4\frac{1}{2}$ weeks old after an illness lasting only 24 hours and the laboratory data on dog 3 are insufficient to be categorical about the extent of renal disease. The clinical interest in these dogs is in the demonstration of chronic renal disease in early life, with evidence, in some animals, of impaired kidney function dating from the neonatal period. In two dogs (6 and 7), which were

examined at intervals up to 14 months, the biochemical values provided evidence of progressive reduction in functioning renal mass (Tables 2, 3). Proteinuria was absent from these two dogs until a late stage. Their renal concentrating ability was impaired and urine specific gravity remained low throughout the periods of observation.

The pathological findings are interpreted as excluding certain categories of kidney lesion as the cause of the renal failure. None of the dogs had renal lesions compatible with a primary diagnosis of interstitial nephritis, glomerulonephritis, pyelonephritis or amyloidosis. The histological evidence of pyelitis/pyelonephritis in two dogs (3 and 6) is interpreted as being secondary to primary intra-renal fibrosis and obstruction-factors known to predispose the kidney to infection (Kelly, 1984). Partly by exclusion of these entities, and partly by consideration of the range of glomerular, tubular and interstitial abnormalities in these young dogs we conclude that these are dysplastic lesions representing disordered development of the kidney (Fisher & Smith, 1975). The kidney lesions are not morphologically homogeneous so it would not be justifiable, at this stage, to assume that there is only one anatomical form of the renal dysplasia. It is possible that the morphological appearance of the dysplastic kidney may vary with time as progressive abiotrophy of renal tissues occurs: only serial clinical, biochemical and biopsy study of dogs with renal dysfunction will clarify this point. Fuller description of the histopathology of the renal lesions in this breed must, therefore, await more detailed clinicopathological examinations of this kind. Progression of the canine renal lesion with time would be consistent with experience in human hereditary tubulointerstitial nephropathies, in which initially focal tubular atrophy later becomes generalized and is accompanied by interstitial and periglomerular fibrosis, leading to eventual nephronophthisis (Bernstein & Gardner, 1983).

We conclude that renal failure in the dogs reported here results from disordered development of the kidney. Dogs 5, 6 and 7 were born to the same sire and dam in two consecutive litters. This pairing produced four litters in all during a 4 year period and of a total of 18 puppies weaned, nine had died before attaining 3 years of age. Although only three were studied and made available for necropsy, the circumstances leading to the deaths of the other six were in each case suggestive that these dogs could have been in terminal renal failure. Renal disease in this breed has been recognized for some years, but it is unclear if the incidence is unusually high and, in most cases, the cause of the putative renal failure has not been substantiated by pathological examination (personal communications from the Soft-coated Wheaten Terrier Club of Great Britain). Earlier suspicions about 'Wheaten Terrier Nephropathy' were hitherto, therefore, largely anecdotal. The observations reported here lend some support to these suspicions, but underline the need for (a) increased awareness of possibly inherited nephropathy in the breed and (b) critical clinical, biochemical and pathological evaluation of putative renal disease in the young dog in this and other breeds especially when there may be suspicions about a possible familial incidence.

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