

JUVENILE NEPHROPATHY IN A 2-YEAR-OLD BOXER WITH MYOCARDIAL LESIONS

Juvenile nefropathie bij een 2 jaar oude Boxer met myocardiële letsels

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ABSTRACT

A case of juvenile nephropathy in a two-year-old male Boxer is reported. Clinical aspects, blood analysis, renal pathology and extrarenal changes are described. The renal changes mainly consisted of tubular and glomerular atrophy, tubular swelling, tubular and glomerular hyaline casts, mineralization, glomerular basement membrane thickening and capsular fibrosis. The main extrarenal lesions, which consisted of a necrotizing inflammatory reaction, were localized in the endocardium and myocardium, as well as in the aorta and truncus pulmonalis. Additionally, a septicemia linked to a localized purulent inflammation in the neck was noted.

SAMENVATTING

Een geval van juvenile nefropathie bij een 2 jaar oude Boxer reu wordt beschreven. De klinische aspecten, de bloedanalyse, renale pathologie and extrarenale veranderingen worden vermeld. De renale veranderingen bestonden voornamelijk uit tubulaire en glomerulaire atrofie, tubulaire zwelling, tubulaire and glomerulaire hyaliene afzetting, mineralisatie en glomerulaire verdikking van de basaal membraan en capsulaire fibrose. De voornaamste extrarenale letsels werden teruggevonden in het endocard en myocard evenals in de aorta en truncus pulmonalis en bestonden uit een necrotiserende onstekingsreactie. Bijkomend werd er een septicemie opgemerkt geassocieerd met een gelokaliseerd etterige ontsteking in de nek.

INTRODUCTION

Chronic renal insufficiency is a common finding in dogs. It is usually considered to be a disease of older dogs. However, renal disease associated with chronic renal insufficiency has also been described in immature or young dogs of several breeds, presenting various pathological forms (Picut and Lewis, 1987; De Bosschere *et al.*, 1998; Peeters *et al.*, 2000). The juvenile nephropathies include a variety of morphological disease entities such as agenesis, hypoplasia, dysplasia, primary cystic disease, glomerulopathies, tubulointerstitial nephropathies and tubular transport dysfunction. Whether juvenile nephropathy, which is due to disorganized nephrogenesis, has a familial basis in dogs is questionable, although several pathological entities of this group have been proven to be

'hereditary' or 'familial' (Roels *et al.*, 1997; Peeters *et al.*, 2000). The condition has been shown to be inherited in the Lhasa Apso and Shih Tzu breeds, probably with an autosomal recessive mode of inheritance (Hoppe *et al.*, 1990; O'Brien *et al.*, 1882).

For most of the cases of nephropathy, only advanced clinical signs and end-stage lesions are described. The age of onset of renal failure varies from a few weeks to several years, but in most cases it occurs between four and 18 months (Maxie, 1993).

This manuscript describes a case of juvenile nephropathy in a Boxer with endocardial and myocardial lesions and septicemia. Additionally, a pedigree study was performed in order to find indications for a 'familial' or 'hereditary' basis of this pathology in this breed.

MATERIAL AND METHODS

Case

A male Boxer (pedigree) originated from a litter of two male pups. At the age of 8 months, the dog presented crippling at the end of agility training sessions, which was determined to be due to a deformation of the elbow (see radiographs). At the same time (8 months) the dog manifested incontinence while walking but no treatment was initiated. At the age of 12 months, the animal presented a decrease in appetite and showed more apathy. At the age of 16 months the dog was presented to the veterinarian with a urinary blockade, which was treated with a probe, a special urinary diet and Incurin (Estriol PhEur, Intervet, Boxmeer, The Netherlands). At the age of 23.5 months, the animal was presented with an undetermined conjunctivitis followed by a swelling in the neck (unilateral) and left cheek (mandibular region), which was treated with antibiotics. Nevertheless, the swelling reappeared after a week. The animal also showed pain when abdominal palpation was performed. Due to the continuous decline of the dog's general condition (increasing apathy and emaciation), it was decided to euthanize the animal. Before euthanasia, a blood sample and a punch biopsy of the swelling in the neck were taken in order to do a standard hematological evaluation and to perform cytologic and bacteriologic evaluation of the swelling.

Necropsy

After euthanasia, the animal was brought in for necropsy. Macroscopical lesions were described and samples were taken for further histopathological examination. The pH of the stomach was measured using a qualitative color method (Universal Paper Indicator; UCB).

Histology

For histological examination, samples from the kidneys, lesions in the heart (left atrial wall, truncus pulmonalis and aorta), myocardium, intercostal muscles, prostate, bladder and liver were taken. The tissues were fixed in a 4% phosphate-buffered formaldehyde solution, processed routinely, paraffin-embedded and sectioned at 5 μm . All sections were stained with hematoxylin and eosin, and for the kidneys also Von Gieson and Congo Red staining were applied.

RESULTS

Laboratory findings

The hematological examination was rather limited, without any control of the renal parameters. The parameters which were abnormal were an increased sedimentation rate (35mm/h)(normal < 20), decreased hematocrit (33%) (normal 36-54) and erythrocytes ($4.06 \times 10^6/\mu\text{l}$) (normal 5.0-8.5) and an increased level of leucocytes ($44.77 \times 10^2/\mu\text{l}$) (normal 4.5-16.0) mainly due to an increase in neutrophils ($36.43 \times 10^3/\mu\text{l}$) (normal 1.8-7.0) and monocytes ($2.66 \times 10^3/\mu\text{l}$) (normal 0.4-1.0). The microbiological and cytological examination of the swelling in the neck revealed no bacteria, but only epithelial cells (probably of salivary gland origin) interlaced with leucocytes.

Necropsy

At necropsy, the animal showed prominent dehydration and cachexia. The swelling in the neck was visible as a localized elevation of the skin surface, which when opened was found to be a localized purulent non-encapsulated process between the left muscles of the cranial third of the *M. longus capitis*. There was no swelling at the level of the cheek. The heart (both the ventricular and the atrial sections) was dilated (bilaterally). There were yellowish plaques (irregular pattern) on the endocardial site of the left atrium (Fig. 1) and above the aortic valves. Calcification lesions were noted above the valves of the truncus pulmonalis. The stomach contained only mucus interlaced with small digested blood fragments and had a pH of 6. The prostate was enlarged, with two pronounced lobes on the dorsal side. The wall at the exit of the bladder had several reddish points. The kidneys were reduced in size, with the right being much smaller than the left. The capsules were difficult to remove and the renal surfaces were distinctly lobulated (Fig. 2). They had a rubbery cut surface and the cortices were unevenly narrow and pale. The lungs were congested and showed alveolar emphysema.

Histopathology

The left atrial wall showed the subendocardial and superficial myocardial diffuse dense presence of inflammatory cells (neutrophilic granulocytes, lymphocytes and plasma cells) with degeneration and necrosis of the muscle tissue involved. A similar inflammatory reaction was noticed in the aorta wall. The

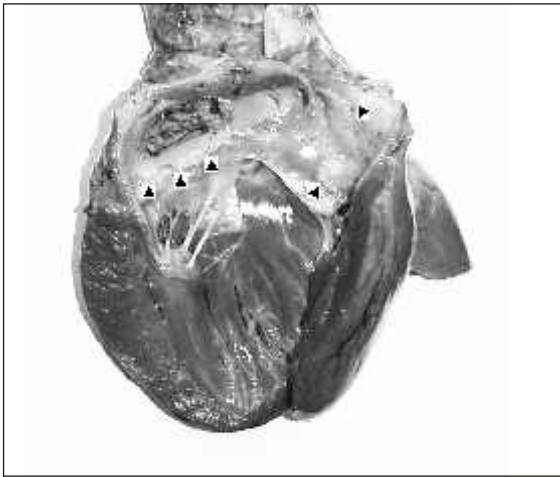


Figure 1. Macroscopical aspect of the endocardial surface (left heart): yellowish decoloration and thickening of the endocardium of the left atrium (arrows).



Figure 2. Macroscopical aspect of left (A) and right (B) kidney: prominent irregular surface and shrinkage.

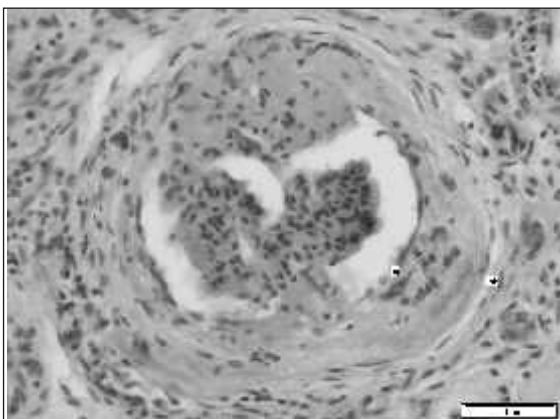


Figure 3. Microscopical image of a glomerulus: basement membrane thickening and capsular sclerosis (arrows) (Hematoxylin Eosin (H.E.)).

truncus pulmonalis showed prominent calcification sites in the tunica media.

The kidneys presented bilateral segmental interstitial cortical and medullar fibrosis with decreased numbers and atrophy of tubuli and glomeruli. The remaining tubuli showed focal cloudy swelling and intraluminal deposition of hyaline casts (cylinders and globules). Focal mineralization was also noted in the proximal convoluted tubules and glomeruli. Additionally, several glomeruli presented basement membrane thickening (Von Gieson positive) and capsular sclerosis (Fig. 3). Other glomeruli were atrophic, and intraluminal casts of proteinaceous material were present in Bowman's space. There was focal interstitial mononuclear inflammatory cell infiltrate (lymphocytes and plasma cells) in both cortex and medulla. Primitive tubular and glomerular structures, resembling those seen in the nephrogenic zone of the fetal kidney, were present in the fibrous areas. Calcification of the basement membranes of Bowman's capsule and cortical tubules was also observed. Congo red staining revealed no amyloid deposition.

The prostate showed several lobuli of hyperplastic epithelia interlaced with a focal mononuclear inflammatory cell population. The reddish points in the bladder wall were found to be nodular sites of mononuclear inflammatory cells. The liver showed diffuse (mainly centrallobular) congestion with the focal intravascular presence of rare neutrophils, which were also interlacing the red blood cells between the hepatocytes.

DISCUSSION

Juvenile nephropathies are characterized by renal failure, mostly in immature or young adult dogs, which cannot be associated with primary renal inflammation (Maxie, 1993). The presence of a subacute, neutrophilic inflammatory reaction in the left atrial wall and aorta, the blood results and the presence of the purulent myositis of the muscles of the neck could have led to the assumption that the animal had a septicemia that could have also affected the kidneys. Nevertheless, given the animal's history, the urinary problems seemed to have been present long before (16 months of age) there was any indication of an inflammatory reaction (only seen at the age of 23.5 months).

Furthermore, the histological changes in both kidneys (mineralization, interstitial fibrosis and glomerular sclerosis) were of a chronic nature (Maxie, 1993) and similar to the cases of juvenile nephropathy

described in the literature. In the Boxer breed, only two cases have been described until now. The first case (Lucke *et al.*, 1980) was an 18-month-old male with polydipsia, stunted bodily condition, good appetite and occasional vomiting. The second was a 7-month-old male with right hindlimb lameness for 2 months, polyuria, polydipsia, progressive muscular wasting, reduced appetite, cachexia and undersized stature (Peeters *et al.*, 2000). The histopathological lesions in the kidneys observed in the present case consisted of a combination of the lesions observed in these two cited cases. The atypical connective tissue changes without cyst formation described in an 18-month-old Boxer (Lucke *et al.*, 1980) were mainly characterized by the presence of segmental wide fibrous bands extending from the capsular surface to the pelvis and alternating with areas of relatively normal parenchyma, occasional foci of lymphocytes and monocytes, tubular atrophy and varying degrees of glomerular tuft sclerosis, dilatation of Bowman's capsule and primitive tubular and glomerular structures. These connective tissue changes were noted to be combined with the types of lesions described in the 7-month-old case (Peeters *et al.*, 2000), including mineralization of the basement membrane of tubules and Bowman's capsules. Unlike the Peeters case, no cystic dilatation of the urinary spaces was observed in the present case.

Additionally, Minkus *et al.* (1994) also reported myocardial alterations in a series of cases of juvenile nephropathy in Bernese mountain dogs. The myocardial lesions were characterized by necrotizing arteritis and foci of myocardial cell necrosis associated with inflammatory infiltrates (neutrophils, lymphocytes and plasma cells). Similar changes were also described in a Weimaraner bitch (Roels *et al.*, 1997). These lesions can be linked to the arteriolar lesions described in uremic animals causing ischemia and dystrophy of myocardial cells (Maxie, 1993; Minkus *et al.*, 1994). In such cases, cardiac murmurs, lameness and pyrexia can occur when the endocarditis involves the valvular tissues, commonly leading to death (Robinson and Maxie, 1993).

Although our hematological data were limited and were taken in the final stage of the disease, we were able to find similar changes as described in other cases of juvenile nephropathy, including anemia. The pronounced increase of leucocytes, mainly consisting of neutrophils, indicates the presence of a septicemia. As chronic renal failure has been proven to induce immunodeficiency, thus explaining the very high frequency of bacterial infections in patients suf-

fering from this pathology (Contin *et al.* 2003; Sharma *et al.* 2000), linkage between a primary juvenile nephropathy and the subsequent septicemia is feasible in our case.

Juvenile nephropathy has been proven to be 'hereditary' or 'familial' in several breeds of dogs. In some breeds, familial juvenile nephropathies have been reported, but inheritance can only be suspected (Nash *et al.*, 1984; Eriksen *et al.*, 1884; Dibartola *et al.*, 1983; Brown *et al.*, 1990; Vilafranca, 1994; Kerlin *et al.*, 1995; Autran de Morais *et al.*, 1996; Schulze *et al.*, 1998). In the two previous cases described in the Boxer, no data on parents and littermates could be obtained. In our case, due to the fact that it concerned a pedigree animal, this information was available but no similar pathology had been noted in the parents, a relative (daughter of the same father) or the other littermate (male). This data suggests that in our case no hereditary or familial factors played a role in the development of the disease and therefore we can only speak of a 'juvenile' and not a 'familial' or 'hereditary' nephropathy.

The renal lesions can mainly be described as atypical connective tissue changes without cyst formation, along with tubular and glomerular mineralization. Additionally, the lesions in the endocardium and myocardium (including the major vessels) are probably the result of the renal failure, whether primary, as described in Bernese mountain dogs (Minkus *et al.*, 1994) and Weimaraners (Roels *et al.*, 1997), or secondary (i.e. chronic renal failure, which results in immunodepression, which in turn results in bacterial infection (septicemia)).

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