Jap. J. vet. Sci. 41, 119~129 (1979)

Canine Interstitial Nephritis with Special Reference to Glomerular Lesions and Filariasis

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(Received for publication September 20, 1978)

Abstract. Interstitial nephritis was observed in 118 of 215 (55%) dogs autopsied during a period from 1974 to 1975. More than 59% of dogs aged 4 years or over were found to have the renal lesions, while only 10% of these less than 1 year of age. Either diffuse or focal infiltration of mononuclear cells with fibrosis was recognized in the interstitium of these cases, some of which have very extensive tubular degeneration and necrosis. In 92 of these cases (78%) having interstitial nephritis there were diffuse or focal glomerular lesions characterized by thickening of the capillary wall, mesangial proliferation, hyalinization, sclerosing and amyloid deposition. Filariasis was the most frequent complication being detected in 67% of dogs with interstitial nephritis. On the other hand, interstitial nephritis was seen in 79 out of 102 (78%) dogs with filaria, while in 39 of 113 (35%) dogs without filaria. No inclusions suggesting canine hepatitis virus infection were seen in all cases examined. Another group of 26 dogs with interstitial nephritis were examined for leptospiral infection, revealing no leptospirae in the kidney tissue and only one antibody positive case.

Interstitial nephritis (IN) is frequently encountered in dogs [16] and cats [12]. Among them canine cases are more common, being attributed to either leptospirosis [14, 29] or infectious hepatitis [27, 28]. On the other hand, IN has been found also in human patients with some acute infection such as diphtheria or scarlet fever [6] as well as autoimmune diseases as systemic lupus erythematosus [3] or Sjögren's syndrome [25]. Furthermore, it is known to be produced after administration of therapeutic agents [6] or renal transplantation [8]. Recently, involvement of immune process has been suggested for pathogenesis of IN and much attention has been paid to having experimental model for human cases [2, 6, 13]. NZB and NZB/NZW F1 hybrid mice have provided a model of autoimmune nephritis [15].

The term "interstitial nephritis" is reserved for cases in which there are prominent tubular and interstitial changes without primary glomerular damages. However, in Aleutian disease of mink [5] and lymphocytic choriomeningitis virus [7] and Coxsackie B4 virus [23] infection in mice, glomerular lesions were reported to be associated with interstitial mononuclear cell infiltration. Also in canine cases with IN, we noticed frequently coexistence of various kinds of glomerular changes.

This paper describes histopathology of canine IN in relation to glomerular lesions and heart filaria (*Dirofilaria immitis*) infection.

Materials and Methods

Two hundreds and fifteen autopsy cases were from either Tokyo University Animal Clinic or some practitioners in Tokyo area during a period

from 1974 to 1975. Most of them were examined immediately after death and tissue samples were fixed in neutral buffered formalin. Paraffin sections were made by a routine procedure and stained with hematoxylin-eosin (HE), periodic acid-Schiff (PAS) and others, if necessary. Another group of 26 IN cases from the same sources were subjected to examination for leptospiral infection. Kidney sections of these cases were stained with HE or PAS and after Levaditi, and sera from 11 of 26 cases were examined for agglutination-lysis antibody to *Leptospira canicola* (*L. canicola*) and *L. icterohemorrhagiae* by Schüffner-Mochtar test [20].

Results

Histopathologically IN was detected in 118 of 215 (55%) cases examined and the severity varied greatly without difference in incidence between breeds or sexes. IN was found in 59% or more of dogs aged 4 years or over, while in only 10% of cases less than 1 year of age (Table 1).

The infiltration of macrophages, lymphocytes and plasma cells appeared either focally or diffusely in the cortical and medullary interstitium (Fig. 3). In most cases, plasma cells were predominant. In the diffuse type, there were tubular changes varying in grades. Some cases with less severe cellular infiltration had considerable swelling, degeneration and necrosis of epithelial cells with interstitial edema. In cases having diffuse fibrosis and cellular infiltration in the interstitium, tubular changes were much more severe and sometimes significant vascular lesions were seen (Fig. 4). Focal infiltration sometimes accompanied by tubular changes was seen in different parts of the organ (Figs. 5 and 6). Even in cases where the infiltration was not so severe, there was tubular involvement.

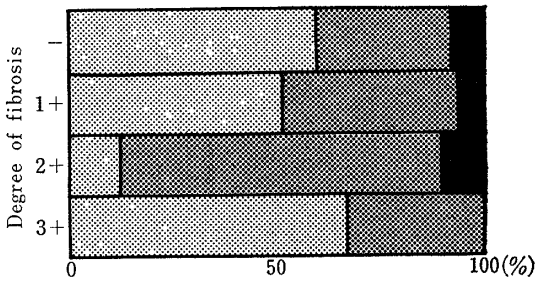
With fibrosis the tubular epithelium was mostly atrophied and degenerated or sometimes hyperplastic and regenerated. Dilatation of the lumen (Fig. 7) and the thickening, distortion or duplication of tubular

Table 1. Age and incidence of IN

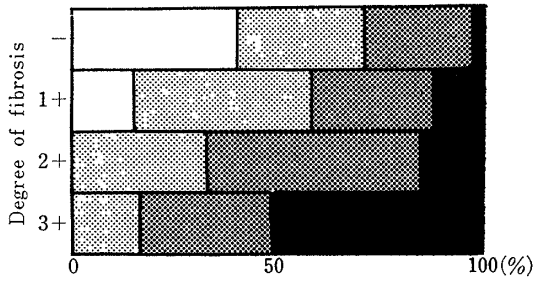
Age in years	No. of cases	
	Autopsied	With IN
<1	29	3 (10%)
1—4	38	18 (47%)
4—7	39	23 (59%)
7—10	31	21 (68%)
10—13	33	25 (76%)
13<	19	12 (63%)
Unknown	26	16 (62%)
Total	215	118 (55%)

Fig. 1. Relationship between the degree of interstitial fibrosis and that of cellular infiltration or glomerular changes in IN cases

a. Relation between cellular infiltraton and fibrosis



b. Relation between glomerular changes and fibrosis



Remarks.
Degree of cellular infiltration and glomerular changes illustrated as follows:
−, 1+, 2+, 3+.

Table 2. Association of glomerular lesions with IN

Glomerular lesions		No. of cases	
Yes	Diffuse	62 (53%)	92 (78%)
	Focal	30 (25%)	
No			26 (22%)
Total			118 (100%)

Table 3. Type of glomerular lesions associated with IN

Type of glomerular lesions		No. of cases	
Diffuse	Membranous	28 (30%)	62 (67%)
	Mesangial-proliferative	12 (13%)	
	Membranoproliferative	9 (10%)	
	Hyalinization or sclerosing	11 (12%)	
	Amyloidosis	2 (2%)	
Focal	Hyalinization or sclerosing Segmental-sclerosing		30 (33%)
Total			92 (100%)

Table 4. Relationship between the degree of glomerular changes and that of interstitial changes

Type and degree of glomerular changes	Interstitial changes: Cellular infiltration	Interstitial changes: Fibrosis	No. of cases
Membranous			
+	+	−	5
	+	+	2
	++	−	2
++	+	−	2
	+	+	2
	++	−	8
	++	+	3
	++	+	2
+++	+	+	1
	++	+	1
Membranoproliferative			
+	++	−	1
++	+	+	2
	+	++	1
	++	−	2
	+++	++	1
+++	++	−	1
	++	+	1
Mesangial-proliferative			
+	+	−	2
	+	+	1
	+	+++	1
	++	−	1
	++	++	1
++	+	−	1
	+	+	1
	++	−	1
	++	++	1
+++	+	+++	2

basement membrane also occurred (Fig. 8). Glomeruli were also atrophic with occasional hyalinization, sclerosis and periglomerular fibrosis. The degree of fibrosis seemed to be parallel with the severity of interstitial cellular infiltration as shown in Fig. 1-a, but some cases had severe fibrosis with slight cellular infiltration.

As shown in Fig. 1-b, also the degree of glomerular changes depended on the severity of interstitial fibrosis in most cases.

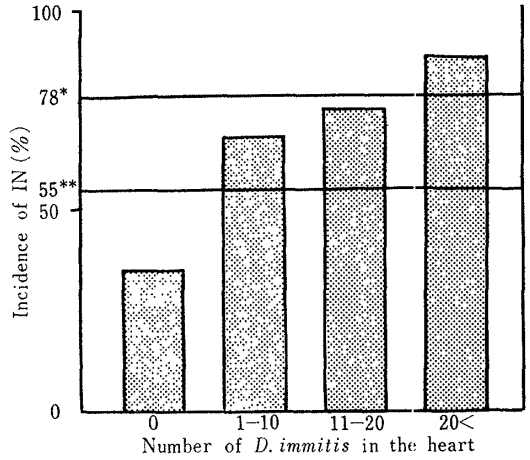
In 92 of 118 (78%) cases with IN, glomerular lesions were detected (Table 2). Histopathologically, they were grouped into seven types as shown in Table 3 and Figs. 9 to 13. In the segmental sclerosing type, mesangial proliferation and sclerosis were seen in some capillary tufts of glomeruli.

Table 4 shows the degree of membranous, membranoproliferative and mesangial-proliferative glomerular lesions, indicating that the degree of interstitial infiltration and/or fibrosis is not in parallel with the severity of glomerular lesions. In diffuse hyalinization or sclerosing type, glomerular changes were most severe, while interstitial lesions varied in extent and degree. In cases with amyloidosis, interstitial infiltration was seen diffusely in the cortex, while fibrosis rather in the medulla. In focal hyalinization or sclerosing type, glomerular involvement was most frequent in the regions showing inter-

Table 5. Complications

Histopathological change		No. of cases
Inflammatory	Pneumonia	19
	Cystitis	9
	Pancreatitis	6
	Endometritis	6
	Encephalitis	3
	Others	7
Parasitic	Filariasis	78
	Others	3
Tumor	Mammary tumor	6
	Perianal gland tumor	4
	Hepatoma	3
	Lymphosarcoma	3
	Reticulosarcoma	2
	Melanoma	2
	Lung cancer	3
	Others	12
Others		8

Fig. 2. Parasitism of *Dirofilaria immitis* and incidence of IN



Remarks.
* Mean (%) cases with filaria in the heart.
** Mean (%) of cases autopsied.

stitial fibrosis and cellular infiltration. In most cases of segmental sclerosing type, however, interstitial changes were slight being independent of glomerular changes.

As shown in Table 5, most frequent complication with IN cases was filariasis, which was seen in 78 of 118 (66%) cases examined. Extrarenal purulent or nonpurulent inflammatory lesions were observed in 50 (42%) cases, and tumors were detected in 34 (29%) cases. No inclusions suggesting canine hepatitis virus infection were found. Conversely, 79 of 102 (78%) cases with filaria was found to have IN, whereas 39 of 113 (35%) cases without filaria. As shown in Fig. 2, the incidence of IN were 68%, 75% and 88% in mild (1 to 10 worms), moderate (11 to 20 worms) and severe (21 worms or over) heart filariasis, respectively. Some severely infected cases had significant degeneration and necrosis of tubular epithelial cells with hemosiderin deposition (Fig. 14).

From 26 IN cases examined no leptospirae were detected on the Levaditi-stained nephritic kidneys. Antibody to *L. canicola* was detected only in one case at a titer of 1:1,000. In this antibody positive case, there were degeneration and necrosis of tubular epithelium with interstitial edema and mild cell infiltration without glomerular lesion.

Discussion

Nonpurulent IN with or without glomerular lesions was seen in 118 of 215 (55%) dogs autopsied during the recent two years, and the incidence was not greatly different from that described in 1959 by Yamamoto [29] with stray dogs from the same region. There were some correlation between the incidence and ageing but no difference in incidence was observed with breeds and sexes. The grades of interstitial mononuclear infiltration and fibrosis varied greatly between individual cases. This is probably due to either stages of the disease at autopsy or difference in pathogenesis.

Recently, Müller-Peddinghaus et al. [17] reported that 71% of cases with various types of glomerulonephritis had purulent or nonpurulent IN in West Germany. The present studies also revealed that 92 of 118 (78%) IN cases were found to have glomerular changes.

Histopathologically the lesions were very complicated and it seemed difficult to consider that glomerular lesions resulted from only the primary interstitial affection at least in focal segmental sclerosing type as well as some diffuse ones.

Three processes can be considered for the production of glomerular lesions. First, glomerular and interstitial lesions might have occurred independently as mentioned by Müller-Peddinghaus et al. [17]. The second possibility is that the primary glomerular changes might have caused the secondary interstitial inflammation due to either circulatory disturbances or destruction of adjacent tubules. Third, interstitial cellular infiltration and fibrosis may cause disturbance of blood flow to glomeruli and of urinary excretion resulting in the secondary glomerular lesions. Among these, the first one is most probable because the severity of glomerular and interstitial lesions were not always parallel as already described, and there were not some cases where early lesions were detected at the same time in glomeruli and interstitium. Some immunologic reactions to tubular antigen might concern with glomerular lesions as previously mentioned [1, 18, 19, 27].

Since long, leptospirosis [14, 16, 29] and infectious hepatitis [27, 28] have been considered to be related with canine IN. Yamamoto [29] described that about 45% of stray dogs collected from Tokyo region during a period from 1940 to 1942 possessed antibodies against leptospirae and that all of them were shown to have IN. Later in 1974 Ryu et al. [20] observed that the positivity rates of leptospiral antibody in Tokyo and Yokohama regions were much lower. The present study revealed that only one out of 11 IN cases had antibody to *L. canicola* and that no leptospiral organisms were detected from the kidneys of 26 IN cases also from Tokyo region, indicating that there is a still high incidence of canine IN in the same region, not always related with leptospirosis as has been considered before. There were no evidences suggesting that canine infectious hepatitis virus play an etiologic role in IN.

In contrast, the present studies strongly suggest that filariasis may be of importance in relation with canine IN. Filariasis and extrarenal inflammatory lesions were associated with 66% and 44% of the present cases of IN, respectively. Monlux [16] described focal mononuclear infiltration in the inner medulla of the kidney in filaria-infected dogs, though such lesions were not always found in our cases. Some severely infected IN cases were shown to have tubular degeneration and necrosis with hemosiderin deposition.

Cassay et al. [4] detected membranous glomerulonephritis in dogs having filaria infection and considered that it might have resulted from deposition of immune complex of the worm antigen and antibodies. Of our IN cases with membranoproliferative or membranous type of glomerular lesions, 89% were shown to be infected with heart filaria. It is probable that glomerular lesions can be produced primarily in immune process to the worm antigen accompanying nonpurulent IN. Tubular changes in some severely infected cases also might be related with heart filariasis.

On the other hand, various kinds of glomerular diseases are known to be attributed to deposition of either circulating immune complex or anti-glomerular basement membrane (GBM) antibodies. Recently, it has been suggested that also tubular and interstitial renal lesions could be mediated by immune reactions [2, 6, 13]. In experimental tubular and interstitial nephritis [21] as well as naturally occurring human

cases [3, 8, 26], some of which accompanied glomerular lesions, the presence of anti-tubular basement membrane (TBM) antibodies and immune complex was evidenced. In chronic cases of canine IN, Krohn et al. [9, 10] showed the presence of immune complex in damaged glomeruli, suggesting that some immune mechanisms might be acting for development of renal lesions also in dogs. In feline cases of contracted kidney, Saegusa et al. [22] detected the deposition of IgG not only in glomeruli but also in TBM. With our present cases, it was unable to make immunopathological studies but further works are attempted to see the role of immune mechanism in triggerring or progress of IN.

The term "IN" has been used commonly for cases where interstitial inflammation and tubular changes are prominent without primary damage in the glomeruli. However, the result of the present study revealed that canine IN cases without any glomerular changes were rather few and that most interstitial lesions were associated with glomerular changes as previously described by Lewis [11] and Müller-Peddinghaus et al. [17]. In advanced cases, it is very difficult to determine which is primary lesions. Takamiya [24] described two types of interstitial nephritis in human being; the primary type which starts from the interstitial vascular system and the secondary type which starts from degenerated or necrotic tubular epithelium. Such conception is very attractive for considering pathogenesis of canine IN.

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要　約

犬の非化膿性間質性腎炎，とくに糸球体病変およびフィラリア症との関連：代田欣二・高橋令治・藤原公策・長谷川篤彦（東京大学農学部家畜病理学教室，家畜内科学教室）——1974～1975 年に剖検された犬 215 例の腎臓を病理組織学的に検索し，118 例 (55%) に非化膿性間質性腎炎を認めた．検出率は 4 歳以上では 59% であったが，1 歳未満では 10% にすぎなかった．病理組織学的には，間質にび慢性あるいは巣状の円形細胞浸潤，線維化がみられ，尿細管の広汎な変性壊死を認める例もみられた．これらの腎炎例中92例 (78%) に基底膜肥厚，メサンギウムの増殖，硝子化，硬化，アミロイド沈着を認めるび慢性あるいは巣状の糸球体病変がみられた．合併症としてはフィラリア症が最も多く，間質性腎炎例の 67% に認められた．フィラリア感染犬 102 例中79例 (78%) に間質性腎炎を認めたのに対し，非感染犬では 113 例中39例 (35%) であった．伝染性肝炎ウイルス感染を示唆する封入体は検索した全例において認められなかった．以上とは別の間質性腎炎例26例についてレプトスピラ感染の検索を行ったが，腎組織標本でレプトスピラ菌体を検出せず，1 例のみが抗体陽性であった．

Explanation of Figures

Figs. 8, 9 and 13 were taken from preparations stained with PAS, and others with HE.

Fig. 3. Diffuse mononuclear cell infiltration in the medulla (×800).

Fig. 4. Deposition of hyaline material in the intima of interlobular artery (×1,600).

Fig. 5. Wedge-shape mononuclear cell infiltration in the cortex (×660).

Fig. 6. Focal infiltration in cortico-medullary area (×360).

Fig. 7. Tubular dilatation and interstitial fibrosis in the medulla (×350).

Fig. 8. Distortion and thickening of tubular basement membrane in the cortex (×700).

Fig. 9. Membranous type of glomerular lesion (×1,630).

Fig. 10. Mesangial-proliferative type of glomerular lesion (×1,500).

Fig. 11. Membranoproliferative type of glomerular lesion (×1,300).

Fig. 12. Hyalinization or sclerosing type of glomerular lesion (×1,560).

Fig. 13. Segmental-sclerosing type of glomerular lesion (×1,440).

Fig. 14. Prominent degeneration of tubular epithelium found in a severely filaria-infected case (×1,470).