ANIMAL MODEL
OF
HUMAN DISEASE

Amyloidosis

Animal Model: Amyloidosis Associated With Canine Cyclic Hematopoiesis in the Gray Collie Dog

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Biologic Features

Cyclic hematopoiesis (CH) in gray collie dogs is characterized by synchronous fluctuations of various blood elements, including cells of both the myeloid and erythroid series.[1,2] It is a genetic disorder which is inherited in an autosomal recessive pattern.

Dogs with CH are periodically predisposed to infectious disease due to their neutropenic episodes, and on autopsy, a large spectrum of lesions is found; the majority of these lesions are inflammatory or degenerative in nature.[3,4]

We have carried out a histopathologic study on 35 dogs with CH from our colony regarding two particularly interesting phenomena of their pathology, namely a deficient development of lymphoid organs and the high incidence of amyloid disease. A direct relationship between splenic changes and the age of the animal was a consistent finding; hypoplasia of the splenic white pulp characterized by an incomplete development and/or absence of splenic follicles was consistently observed in CH dogs less than 2 months old. In CH dogs between 2 and 6 months of age, the splenic white pulp revealed a dramatic depletion of small lymphocytes with a concomitant increase of undifferentiated, pyroninophilic, plasmacytic, and reticuloendothelial cells. Amyloid deposition was detected in the spleen of dogs as young as 4 months, and all CH dogs over 6 months revealed amyloid in the spleen and/or other organs.

Two factors appear relevant to the etiology of CH amyloidosis. First, there are several indications that the lymphoid system of these dogs is affected by a genetic disorder inherent to the CH syndrome. This is

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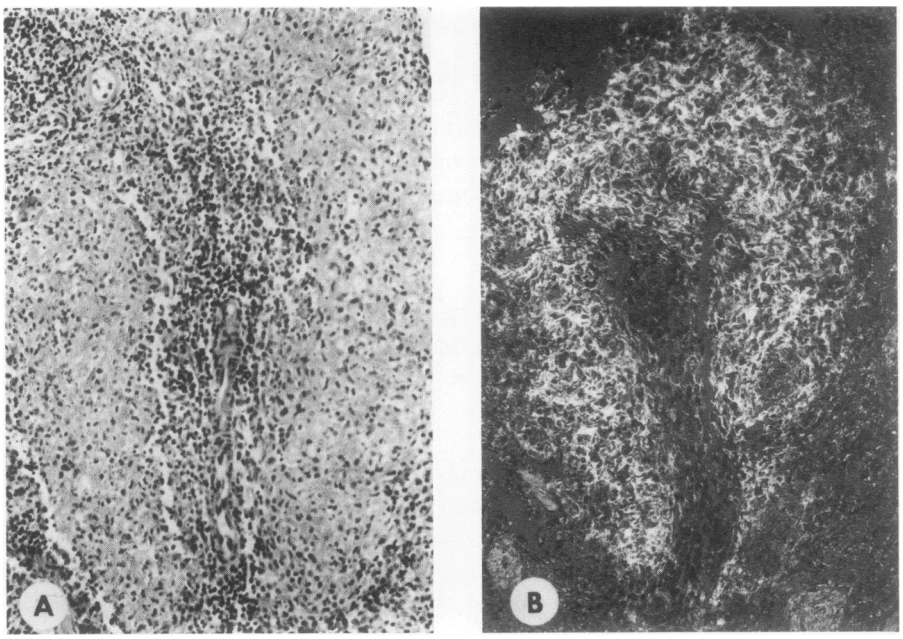

Figure 1A—Splenic follicle replaced by amyloid substance (H&E, × 125). **B**—Fluorescence of amyloid deposits (Thioflavin T; BG 12 exciter filter and OG 4 barrier filter, × 125).

suggested by our findings of lymphoid hypoplasia in CH neonates and the functional abnormalities of the lymphoid compartment reported by other authors.[5] Second, it may be assumed that an increase of antigenic stimulation accompanies the intermittent bouts of acute infectious disease that characterize the CH syndrome. This is in agreement with the present concept that immunologic impairment, in conjunction with various degrees of antigenic exposure, may lead to the development of secondary amyloidosis.[6]

In juvenile and adult CH dogs, splenic amyloid substance was mainly observed in the marginal areas of lymphoid follicles (sago spleen) (Figure 1A and B); while in a few specimens, amyloid deposits acquired a diffuse distribution, involving both white and red pulps (lardaceous spleen). The kidneys displayed the characteristic deposition of the substance in the glomerular tufts (Figure 2A and B) and amyloid was also observed surrounding the renal tubules. In the liver, amyloid deposition varied from a thin layer of this substance in the Disse's and portal spaces to a marked destruction of the hepatic parenchyma. In addition, amyloid substance was found in the pancreas, adrenals, and intestinal submucosa. The pattern of amyloid deposition in CH dog tissues closely mimicked the secondary type in humans. Amyloid substance displayed a positive fluorescent reaction with Thioflavin T,[7] and a slight and inconsistent stain

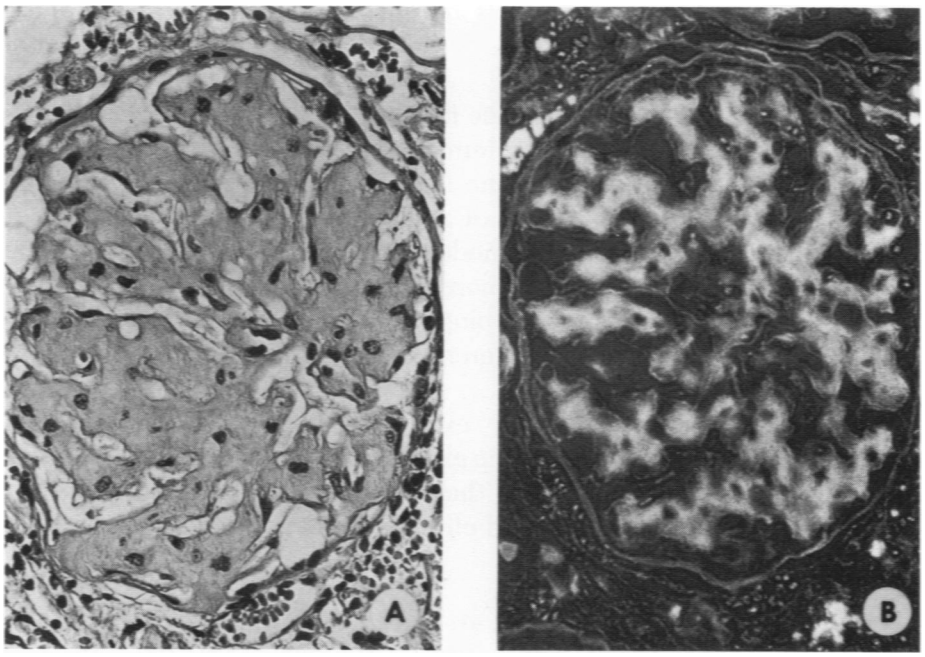

Figure 2A—Renal glomeruli affected with amyloidosis (H&E, × 250). **B**—Fluorescence of renal amyloid substance (Thioflavin T; BG 12 and OG 4 filters, × 250).

with the alkaline Congo red procedure.[8] A positive reaction was also obtained with PAS and the silver reducing method.[9]

Comparison With Human Disease

The spontaneous amyloidosis in CH dogs represents a condition similar to the secondary form observed in humans. As described above, the morphologic characteristics and visceral distribution of secondary amyloidosis in man is essentially replicated by the canine amyloid disease in dogs with cyclic hematopoiesis.

Furthermore, both species seem to share common pathways in the pathogenesis of the disease. Human secondary amyloidosis is routinely associated with both impairment of the immune system, either hereditary or acquired, and antigenic stimulation. Similar factors are presumably involved in CH amyloidosis.

Usefulness of the Model

It must be stressed that while the amyloid disease is spontaneous in CH dogs, it is an induced condition in most animal models. Experimental induction entails the administration of exogenous products, such as sodium caseinate, whose pharmacologic effect may preclude an accurate assessment of the immunologic status of the experimental animal.[10] Al-

though several spontaneous models are now available, these simulate the primary form of human amyloidosis, while CH amyloidosis is a model of the secondary type.

It has also been observed that the fluctuations of serum immunoglobulins that precede and accompany human amyloidosis are likewise seen in CH dogs,[3,4] On the contrary, serum immunoglobulin levels are not consistently altered in various strains of amyloidotic mice.[11]

In comparison to other animal models, such as guinea pigs, rabbits, and mice, the physiology of the dog more closely resembles that of humans; also, in the dog the use of needle biopsies of kidneys, liver, and spleen to develop sequential studies on different stages of this disease in the same animal is possible.

Some disadvantages obviously exist in this model; one such disadvantage is the fact that antigenic exposure is variable, both in duration and magnitude. It is conceivable that monitoring CH dogs in a specific pathogen-free environment would eliminate this problem.

Availability

Dogs with cyclic hematopoiesis are available in limited numbers from our institution. In the past, breeders have been supplied to other investigators in America and Europe.

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