

Hepatic amyloidosis in two Chinese Shar Pei dogs

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- Amyloidosis should be considered as a cause of hepatic disease in Chinese Shar Pei dogs, even without evidence of renal involvement.
- Hepatic disease, along with episodic fever and subcutaneous swelling of the hock region, may be manifestations of familial amyloidosis in these dogs.

An 18-month-old spayed female Chinese Shar Pei (dog 1) was examined because of acute onset of lethargy, anorexia, and irritability. Physical examination abnormalities included lethargy and icterus. When 3 months old, this dog had an episode of fever (40.4 C), moderate signs of bilateral hip pain, anorexia, subcutaneous swelling, and signs of pain involving the lips, face, and neck. Laboratory evaluation at that time revealed marked leukocytosis (53,020 cells/ μ l), neutrophilia (41,886 cells/ μ l), and left shift (5,302 band cells/ μ l). The dog had been treated with amoxicillin, and the fever, anorexia, lethargy, and irritability had resolved within 24 hours.

The dog was treated for the current episode with iv administration of lactated Ringer's solution and cephalothin (22 mg/kg of body weight, q 6 h).^a Examination of the hemogram revealed a left shift (2,415 band cells/ μ l), with toxic changes and without neutrophilia, and a normal WBC count (11,500 cells/ μ l). Results of serum biochemical analysis included high alkaline phosphatase (ALP; 2,157 IU/L; reference, 20 to 160 IU/L) and alanine transaminase (ALT; 89 IU/L; reference, 12 to 88 IU/L) activities, and high total (9.1 mg/dl; reference, 0.1 to 0.6 mg/dl) and conjugated bilirubin (4.2 mg/dl; reference, 0.0 to 0.2 mg/dl) concentrations. Urinalysis (obtained after fluid treatment) revealed specific gravity of 1.016, pH 6.5, trace proteinuria, 3+ bilirubinuria, and positive reaction for urobilinogen. Abdominal radiography revealed moderate hepatomegaly. A coagulation profile (including fibrinogen, fibrin degradation products, platelet count, prothrombin time, and partial thromboplastin time) was within reference range.

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The author thanks Dr. Gene Bailey, Rock Creek Animal Hospital, Fort Lauderdale, Fla; Dr. Sharon Wilson, Associated Regional and University Pathologists Inc, Salt Lake City, Utah; Dr. George Parker, Biotechnics Inc, Sterling Va; and Dr. Stephen DiBartola of Ohio State University, Columbus, Ohio, for technical assistance.

^aKeflin, Eli Lilly & Co, Indianapolis, Ind.

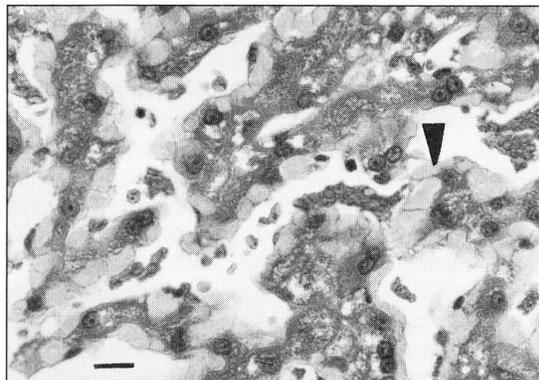


Figure 1—Photomicrograph of section of liver biopsy specimen from dog 1. Notice severe amyloidosis, with a large amount of pale-staining, homogeneous material in the spaces of Disse (arrowhead). H&E stain; bar = 16 μ m.

The dog was medicated with atropine (0.04 mg/kg, sc) and butorphanol^b (0.2 mg/kg, sc), followed by induction of anesthesia with iv administration of diazepam (0.28 mg/kg) and ketamine^c (5.5 mg/kg), endotracheal intubation, and maintenance of anesthesia with isoflurane^d and oxygen. Celiotomy and liver biopsy were performed because a less-invasive, ultrasound-guided needle biopsy technique was not available to the author at that time. Surgical findings included moderate hepatomegaly, with pale, friable lobes and prominent, rounded edges. The dog was discharged from the hospital 3 days after admission, without postsurgical complications, and was afebrile, alert, and eating. Cefadroxil^e (22 mg/kg, po, q 12 h) and a protein-restricted diet^f were prescribed.

On histologic examination of sections from the liver biopsy specimen, there was moderate congestion of hepatic sinusoids, with a large amount of homogeneous acellular material within the spaces of Disse and moderate atrophy of centilobular hepatic plates (Fig 1). The material within the spaces of Disse stained with Congo red and had bright, apple-green birefringence when viewed with polarized light. Severe hepatic amyloidosis was diagnosed. The Congo red-stained specimen was treated with potassium permanganate and dilute sulfuric acid; Congo red staining was not retained and apple-green birefringence was absent under

^bTorbugesic, Aveco, Fort Dodge, Iowa.

^cKetaset, American Home Propacts, Fort Dodge, Iowa.

^dAErrane, Anaquest, Madison, Wis.

^eCefa-Tabs, American Home Propacts, Fort Dodge, Iowa.

^fHill's K/D, Hill's Pet Products, Topeka, Kan.

polarized light. These findings were consistent with secondary (reactive) AA amyloidosis.^{1,2}

The poor prognosis and several treatment alternatives were discussed with the owners. Sixty days after biopsy, treatment was begun with dimethyl sulfoxide (DMSO; 82 mg/kg as an 18% solution in sterile water, SC, 3 times/wk). One week after treatment was initiated, the dog had another episode of fever (40.2 C), with tachypnea and lameness and moderate swelling in the area of the left tibiotarsal joint. Supportive treatment was initiated with iv administration of fluids and cephalothin. A hemogram was within reference range. Serologic results of testing for Lyme disease, antinuclear antibodies, Coomb's antibodies, and rheumatoid arthritis were negative. Analysis of joint fluid from the left tibiotarsal joint revealed a clear, colorless fluid, with grossly normal-appearing viscosity and without nucleated cells or RBC. Pathogens were not found on bacterial culturing of synovial fluid samples. Urinalysis revealed specific gravity of 1.013, pH 8.0, and no proteinuria. Results of serum biochemical analysis included ALP and ALT activities, 603 and 75 IU/L, respectively, and total bilirubin concentration, 0.2 mg/dl. The dog recovered in 24 hours and was discharged from the hospital. The owners were to administer cefadroxil to the dog.

Five weeks after initiating DMSO treatment, the injections were discontinued because of signs of pain, lethargy, anorexia, and excessive lip licking for 24 to 48 hours after each treatment. The dog did not tolerate oral administration of DMSO. Urinalysis revealed specific gravity of 1.015, pH 6.0, and trace protein.

Five days after DMSO treatment was discontinued, the dog had a 3-day episode of superficial swelling of the left side of the mandible and temporomandibular joint, with signs of pain, lethargy, anorexia, and polyuria. Four days later, the dog was lethargic and inappetent, but the swelling had resolved. Results of serum biochemical analysis included hyperbilirubinemia (total bilirubin concentration, 6.6 mg/dl); high ALP (2,164 IU/L), ALT (202 IU/L), and aspartate transaminase (140 IU/L) activities; and hypercholesterolemia (593 mg/dl). Urinalysis revealed specific gravity of 1.016 and marked bilirubinuria. The dog was treated with cefadroxil and recovered fully.

Six months after biopsy, colchicine^b (0.03 mg/kg, PO, q 24 h) and ascorbic acid (250 mg, PO, q 24 h) were administered. Results of serum biochemical analysis obtained 1 month after initiating this treatment were within reference range, except for ALP activity (479 IU/L) and cholesterol concentration (502 mg/dl). Eight months after biopsy, urinalysis revealed specific gravity of 1.011, pH 8.5, and no proteinuria.

Three months after beginning colchicine treat-

ment, the dog had another febrile episode, with recurrence of muzzle swelling. The dog had 3 or 4 similar episodes over the next 3 months, all of which resolved without treatment within 24 hours.

Six months after initiating colchicine treatment and 12 months after biopsy, the dog was doing well. Repeat serum biochemical analysis indicated stable hepatic and renal function. Urinalysis revealed isosthenuria (specific gravity, 1.011), trace proteinuria, pyuria, and bacteriuria, which were treated with amoxicillin/clavulanic acid.^c Two months later, liver function was further evaluated with measurement of serum bile acids, before (6.5 $\mu\text{mol/L}$; reference, 0.0 to 5.0 $\mu\text{mol/L}$) and 2 hours after feeding (11.5 $\mu\text{mol/L}$; reference, 5.0 to 25.0 $\mu\text{mol/L}$). The next day, the owner reported acute onset of lameness and swelling in the dog's left hock, with lethargy and signs of abdominal discomfort. The dog recovered with aspirin treatment.

Eleven months after initiation of colchicine treatment, the dog continued to do well clinically, despite monthly recurrences of febrile episodes. Repeat urinalysis revealed specific gravity of 1.016, pH 8.0, and normal urinary protein/creatinine ratio (0.04; reference, < 1.5).

In addition to febrile episodes, the dog had 2 cholestatic episodes 15 and 17 months after starting colchicine treatment. Both episodes responded to supportive care. Urine protein/creatinine ratio remained within reference range (0.2) 24 months after initial liver biopsy was performed. The dog was euthanatized 33 months after biopsy, following another severe cholestatic episode. Necropsy was not performed.

A 22-month-old spayed female Chinese Shar Pei (dog 2) was examined because of acute onset of lethargy and anorexia. Pertinent medical history included episodes of lethargy and fever (40.0 C) when the dog was 7 weeks and 9 months old. The dog was febrile (40.2 C), dyspneic, and tachypneic. Lymphadenopathy and splenomegaly were observed. The dog was treated iv with lactated Ringer's solution and cephalothin (22 mg/kg, q 8 h). Evaluation of a hemogram revealed leukocytosis (23,500 cells/ μl), with neutrophilia (19,035 cells/ μl) and mild left shift (705 band cells/ μl). Results of serum biochemical analysis were unremarkable. On urinalysis, specific gravity was 1.051 and pH 8.5; there was 4+ proteinuria, without abnormalities in the sediment.

The next day, dog 2 was clinically improved. Another urinalysis revealed 3+ bilirubinuria and pyuria. Thoracic radiography revealed diffuse peribronchial infiltrates. On repeat serum biochemical analysis, hyperbilirubinemia (total bilirubin concentration, 1.5 mg/dl); increased ALP (519 IU/L), ALT (215 IU/L), and aspartate transaminase (124 IU/L) activities; and high bile acids before (38.7 $\mu\text{mol/L}$) and 2 hours after feeding (153.6 $\mu\text{mol/L}$)

^aDOMOSO, Syntex Animal Health, Palo Alto, Calif.

^bColchicine, Zenith Laboratory, Northvale, NJ.

^cClavamox, Smith Kline Beecham, Exton, Pa.

were found. A hemogram was within reference range. Abdominal radiography revealed hepatomegaly and splenomegaly.

Anesthesia was induced with iv administration of diazepam (0.28 mg/kg) and ketamine (5.5 mg/kg), and was maintained with halothane^l and oxygen. On celiotomy, splenomegaly was found. The liver appeared pale, mottled, and friable, and was biopsied. Histologic examination of the biopsy specimen revealed diffuse moderate vacuolar hepatopathy, multifocal subcapsular telangiectasia, and multifocal portal arteriolar hypertrophy and hyperplasia, with acellular eosinophilic material within the spaces of Disse. Staining characteristics of this material were the same as in dog 1. Hepatic amyloidosis was diagnosed.

Three weeks after surgery, treatment with 0.6 mg of colchicine (0.03 mg/kg, PO, q 24 h) was started. Blood test results were negative for antinuclear antibodies, direct Coomb's antibodies, and lupus erythematosus cells. Another urinalysis revealed specific gravity of 1.051, pH 6.0, trace proteinuria, and bilirubinuria. Urine protein/creatinine ratio was within reference range at 0.04.

Four months after beginning colchicine treatment, dog 2 was evaluated for a febrile episode (40.3 C) and lethargy of 24 hours' duration. Examination of a hemogram revealed leukocytosis (28,400 cells/ μ l), neutrophilia (24,992 cells/ μ l), and mild microcytic normochromic anemia (PCV, 32.5%; mean corpuscular volume and hemoglobin concentration, 54 fl and 32 g/dl, respectively). Serum biochemical results included increased ALP activity (224 IU/L) and bile acids, before (48.5 μ mol/L) and 2 hours after feeding (33.2 μ mol/L). On urinalysis, specific gravity was 1.016, and pH 8.0; there was 1+ proteinuria. The dog responded to iv fluids treatment and cephalothin.

Dog 2 was doing well 2 years after biopsy, despite monthly to bimonthly febrile episodes. Change in frequency of febrile episodes was not observed when the colchicine dosage was increased to 0.03 mg/kg, every 12 hours, 9 months after biopsy. One episode of cholestasis had developed at that time. Urinalysis 13 and 21 months after biopsy revealed normal protein/creatinine ratios (0.4 and 1.1, respectively).

Recently, DiBartola et al³ reported familial renal amyloidosis in 14 young Chinese Shar Pei dogs. Many of the dogs that develop amyloidosis have had episodic fevers and/or subcutaneous, edematous swelling in the hock region (referred to by breeders as Shar Pei fever and swollen hock syndrome, respectively). The episodic fevers appear to be associated with development of amyloidosis. In a study of 15 Chinese Shar Pei dogs with episodic fevers, 13 dogs had renal amyloidosis.⁴ Mean age at diagnosis of amyloidosis in these dogs was between 4 and 5 years of age.^{3,4} This febrile disorder

also has been associated with high blood interleukin-6 concentrations during afebrile quiescent periods in affected Chinese Shar Pei dogs.⁴

Dogs 1 and 2 had amyloidosis, with clinical signs related to hepatic dysfunction, rather than typical signs of end-stage renal failure. One additional dog evaluated by this author had spontaneous hepatic rupture.⁵ In retrospect, evaluation of renal biopsy specimens would have been informative, and renal involvement was assumed in these dogs. The owners would not allow repeat hepatic or renal biopsies. Although amyloidosis is a systemic disease that affects many organ systems in dogs, it is primarily a renal disease in its clinical signs. The most common cause of death in dogs with amyloidosis is nephrotic syndrome and renal failure.⁶⁻⁸ However, hepatic failure was the primary reason for evaluation in a dog with amyloidosis and widely scattered foci of granulomatous inflammation associated with *Coccidioides immitis*.⁶

Both of the dogs reported here had presumed secondary AA amyloidosis and early onset of periodic, brief febrile episodes, with or without associated joint swelling, cellulitis, dyspnea, or signs of abdominal discomfort. The pedigrees of these 2 dogs included several dogs that were related to Chinese Shar Pei dogs reported previously with familial renal amyloidosis.³

Amyloidosis involves extracellular deposition of insoluble fibrillar proteins in a nonbranching, antiparallel, β -pleated biochemical conformation. In reactive amyloidosis, the precursor protein involves portions of serum amyloid A (SAA), which is an acute-phase protein.⁹ Secondary AA amyloidosis is often associated with chronic infection, inflammation, neoplasia, and immune diseases.¹⁰⁻¹⁶

The staining characteristics associated with the liver specimens in these 2 dogs and with renal biopsy specimens in several cases of renal amyloidosis³ suggested that serum protein AA is the inciting precursor in cases of familial amyloidosis.³ In a Cornell University study,^k renal specimens from 28 Chinese Shar Pei dogs with renal amyloidosis stained with anti-amyloid A antibody. The amount of SAA in affected vs unaffected dogs, and in those that may be silent carriers of the trait, should be ascertained. People with reactive systemic amyloidosis may have SAA concentrations up to 24 times higher than those in control groups.¹⁷ Serum AA concentrations may or may not become a key screening test in Chinese Shar Pei dogs, although SAA concentrations were not found to be predictive for amyloidosis in Abyssinian cats.¹⁸ High concentrations of interleukin-6 have been reported in affected dogs and identification of a genetic marker for the disease and its carriers is in progress.⁴

The early onset of febrile episodes and swollen

^kZeiss C, Zanelli MJ, Suter M. Recurrent fever of unknown origin and renal amyloidosis in Chinese Shar Pei dogs (abstr). *Vet Pathol* 1993;30:460.

^lFluothane, American Home Propacts, Fort Dodge, Iowa.

hock syndrome, and the development of renal AA amyloidosis during early adult life in Chinese Shar Pei dogs are similar to findings in human beings with familial Mediterranean fever. Familial Mediterranean fever is a single-gene, autosomal recessive disorder that is characterized by early onset of recurrent, brief (24 to 48 hours), febrile episodes, including self-limiting bouts of serosal inflammation, arthritis, synovitis, and erysipelas-like erythema, with or without development of systemic AA amyloidosis and nephrotic syndrome. Amyloidosis is observed in 25 to 28% of affected people. Hepatic amyloidosis is rarely the primary clinical sign.^{19,20} In dogs, joint effusions are usually absent in swollen hock syndrome and normal joint fluid is usually found.²¹ Serosal inflammation has not been documented in affected Chinese Shar Pei dogs, but should be investigated.

The 2 dogs reported here are unique because they had predominantly hepatic clinical signs. In human beings, severe cholestatic episodes or hepatic failure were caused by AL amyloidosis.²²⁻²⁵ This cholestatic form of the disease was invariably rapidly fatal, with most patients surviving just a few months.²⁴⁻²⁶ These findings did not appear to be comparable with those in Chinese Shar Pei dogs; both dogs had cholestatic episodes and survived > 2 years. The infrequent finding of normal liver enzyme values in both of these Chinese Shar Pei dogs was consistent with similar findings in people with hepatic AL amyloidosis.²⁶

The 2 dogs reported here had little clinical evidence of renal involvement that would have paralleled the amount of amyloid and severe histologic changes in the hepatic parenchyma. Renal involvement was assumed here because of the systemic nature of amyloidosis and evidence of mild renal insufficiency (low urine specific gravities and high-normal serum creatinine concentrations). However, the initial sign of renal amyloid involvement is usually proteinuria. Renal amyloidosis caused the highest protein/creatinine ratios in dogs, with 22 as a median value.²⁷ In both dogs reported here, protein/creatinine ratios were within reference range.

Use of ascorbic acid in treatment of amyloidosis is based on studies concerning casein-induced murine AA amyloidosis.^{28,29} Although some researchers refuted the benefits of ascorbic acid,^{28,30} a significant increase in overall survival/longevity was found in ascorbic acid-treated rats, even though they had extensive amyloid deposits on necropsy.³¹

Dimethyl sulfoxide has long been viewed as a legitimate, albeit controversial, treatment of amyloidosis.³²⁻³⁷ In human medicine, results of DMSO treatment in amyloidosis are inconclusive.^{34,38-41} In a report on the use of DMSO in treatment of renal amyloidosis in a dog,⁴² improvement was apparent in 24-hour urine protein losses. However, a Sertoli cell tumor was removed and interdigital pyoderma was treated in this dog; both conditions could have caused AA amyloidosis. In another study,⁹ a bene-

ficial effect was not noticed when DMSO was administered, at a dosage of up to 300 mg/kg, to dogs with renal AA amyloidosis.

Colchicine is an antimitotic alkaloid that is used in human medicine primarily for the prevention and relief of acute attacks of gouty arthritis. Major adverse effects of the drug include nausea, vomiting, and diarrhea. Chronic use may cause bone marrow suppression and/or hypertension.⁴³ Colchicine has been used to treat severe hepatic fibrosis attributable to chronic hepatitis in a dog. Treatment, at an empirical dosage of 0.03 mg/kg, PO, every 24 hours, resulted in marked clinical, histologic, and biochemical responses.⁴⁴ Studies of murine casein-induced AA amyloidosis^{28,45-48} revealed that colchicine can block formation of AA amyloid if used during the induction phase, but had no benefit if used after AA amyloid was already established. Use of colchicine in the prophylactic treatment of human beings with familial Mediterranean fever and AA amyloidosis reduced the number of febrile episodes and the prevalence of amyloidosis. Colchicine prevented the progression of proteinuria to nephrotic syndrome in such patients, even if the number of febrile episodes were not reduced.^{19,49-52} Even when colchicine was used in young children, major adverse effects were not reported with chronic administration of colchicine for 11 or more years.¹⁹

Both dogs continued to have regular febrile episodes during colchicine treatment. Perhaps the dosages were too low or this syndrome in Chinese Shar Pei dogs is not responsive to colchicine. The author feels that colchicine treatment may have been clinically effective, because both dogs survived > 2 years after biopsy, did not progress to renal failure, and did not have adverse clinical signs between febrile or cholestatic episodes. Determining whether the unique features of hepatic signs in these dogs were attributable to a subset of Chinese Shar Pei familial amyloidosis would require a thorough owner survey, pedigree and genetic analysis, and morbidity/mortality studies. A controlled, double-blind, large-scale study would be required to determine whether colchicine treatment would be protective.

Clinicians who encounter Chinese Shar Pei dogs with unexplained febrile illness or hepatic or renal disease should consider obtaining pedigree information from the owners. The possibility of amyloidosis and the appropriate diagnostic evaluations should be discussed with the client.

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