

SHAR-PEI FEVER

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Amyloidosis is a term used to describe a diverse group of diseases that involve the extracellular deposition of fibrils formed by polymerization of proteins with a beta-pleated sheet conformation. Familial occurrence of renal amyloidosis occurs in Chinese shar-peis, with a reported prevalence of 23% in one survey; however, the true prevalence is unknown.

The kidneys in these dogs are not inherently defective; rather, the deposition of amyloid affects the kidneys and eventually leads to chronic renal failure. Many shar-peis have a history of recurrent fever and swelling of the tibiotarsal joints (commonly called *shar-pei fever* or *shar-pei swollen hock syndrome*) before renal amyloidosis develops. The amyloidosis reported in this breed is believed to be a form of reactive amyloidosis because the primary protein involved, amyloid A, is associated with inflammatory disease. Amyloid A protein is formed by the polymerization of the amino acid terminal portion of serum amyloid A protein. Affected shar-peis have increased serum concentrations of interleukin-6, a cytokine that stimulates serum amyloid A protein synthesis and release in the liver. Interleukin 6, along with tumor necrosis factor- α and interleukin-1 β , initiates the acute phase response, characterized by fever, hepatic production of acute phase proteins, and neutrophil mobilization.

Proteinuria with renal amyloidosis can be massive and may lead to the development of nephrotic syndrome (a combination of clinical and laboratory findings including hypoalbuminemia, marked proteinuria, hypercholesterolemia, and third-space fluid accumulation). The loss of both albumin and antithrombin III (AT III) in urine predisposes these animals to the development of thromboembolic disease. This syndrome in Chinese shar-peis is believed to be an autosomal recessive inherited trait. A similar syndrome associated with fever and synovitis, called *familial Mediterranean fever*, is reported in humans.

The age at presentation and clinical signs vary among dogs; however, most shar-peis present with a history of recurrent fever and swollen joints (most commonly the tibiotarsal joint). Aggressively pursuing tests to confirm the diagnosis is important because

treatment is most successful in the early stages of the disease. It is also important to remember that not all shar-peis develop this syndrome, and other causes of fever, synovitis, and renal disease should be ruled out.

DIAGNOSTIC CRITERIA

Historical Information

Gender Predisposition

- Female dogs are more commonly affected than males (male:female ratio, 1:2.5).

Age Predisposition

- The age at onset of clinical signs in affected shar-peis is normally between 1 and 6 years (mean age of onset, 4 years).

Breed Predisposition

- Chinese shar-peis.
- Familial renal amyloidosis is also reported in beagles, English foxhounds, and Abyssinian and Siamese cats.

Owner Observations

- Owners may notice that their dog intermittently has swollen and/or painful joints.
- The most common clinical signs observed include polydipsia and polyuria, anorexia, weakness, lethargy, vomiting, dehydration, and weight loss.
- In dogs that have developed renal failure, owners may note increased thirst and frequency of urination, anorexia, vomiting, and malodorous breath.

Physical Examination Findings

- Dogs usually initially present with intermittent episodes of fever (temperature range, 103°F to 107°F) and swollen joints (most commonly the tibiotarsal joint) that resolve with or without treatment.
- Physical examination may be normal if the dog is not currently experiencing an episode of fever.
- Dogs with advanced renal failure may have

oral ulcerations, dehydration, or pale mucous membranes.

- If renal disease has caused the development of nephrotic syndrome (hypoalbuminemia, hypercholesterolemia, and edema), ascites or edema may be noted.
- In advanced cases, clinical signs of thromboembolic disease—including acute onset of respiratory distress or tachypnea (due to pulmonary thromboembolism)—may be present.

Laboratory Findings \$\$

Initial diagnostics should include a complete blood count with differential, serum chemistry profile, urinalysis, urine culture, and blood pressure measurement. If proteinuria is noted on urinalysis, a urine protein:creatinine ratio should also be obtained. Depending on the stage of the disease process, the following abnormalities may be noted:

- **Proteinuria** is the hallmark of glomerular disease, but its presence is variable in shar-pei fever.
 - In familial renal amyloidosis of shar-peis, the amyloid deposits mainly in the medullary interstitium, where the lesion does not induce significant urine protein loss. As few as 25% to 43% of affected shar-peis have proteinuria.
 - A urine protein:creatinine ratio greater than 0.5 in a urine sample free of hemorrhage or inflammation is abnormal.
 - Microalbuminuria (>2.5 mg/dl) may be detected before an increased urine protein:creatinine ratio develops. In-house urine testing using the E.R.D.-Healthscreen Canine Urine Test (Heska) may be performed; alternatively, a quantitative measurement of microalbuminuria can be obtained from most commercial laboratories.
- **Isosthenuria** (urine specific gravity, 1.008 to 1.012) is also a variable finding in dogs with glomerular disease; it is more common in dogs with renal amyloidosis (occurring in 63% of dogs) and may be an early marker of disease.
- **Hypoalbuminemia** (<2.5 g/dl).
- **Hypercholesterolemia** (>220 mg/dl).
- Animals with nephrotic syndrome (**hypoalbuminemia**, **hypercholesterolemia**, and **edema**) may present with heavy proteinuria.
- If amyloidosis is present in the liver, **high levels of alkaline phosphatase** (>102 IU/L), **alanine transaminase** (>100 IU/L), **aspartate transaminase** (>100 IU/L), and **total bilirubin** (>0.4 mg/dl) may be present.

Other Diagnostic Findings

- To make a definitive diagnosis, it is necessary to obtain a **renal biopsy** of both the cortex and the

medulla. Normally, renal biopsies obtain samples of only the cortex, but because of the deposition of amyloid in the medulla, it is necessary to obtain a sample from this region. \$\$\$-\$\$\$\$

- Collecting a biopsy sample from the medulla increases the risk of hemorrhage, infarction, and fibrosis.
 - The sample should be stained with Congo red. With conventional light microscopy, amyloid deposits take on various shades of red; when evaluated with polarizing microscopy, they are apple green.
 - Reactive amyloidosis (the form of amyloidosis responsible for shar-pei fever) can be confirmed by decolorization of the Congo red-stained amyloid deposits by potassium permanganate oxidation.
 - Because of the high risk associated with collecting a biopsy sample from the renal medulla, it may be more prudent to obtain samples from other organs commonly affected with amyloidosis in this syndrome—including the liver and spleen—to make a diagnosis.
 - A renal biopsy may not be necessary in the presence of classic findings of recurrent fever and joint swelling or if end-stage renal disease is already present.
- **Abdominal radiography:** Kidneys are usually normal in size and shape. Hepatomegaly may be noted if amyloidosis is present in the liver. \$\$
 - **Abdominal ultrasonography:** Kidneys should be normal in size. Increased echogenicity of the cortex or loss of corticomedullary distinction may be noted. \$\$
 - **AT III** can be measured in many university and commercial laboratories. AT III levels are a good predictor of the potential for thrombi formation. Values between 60% and 75% are associated with an increased risk of thrombosis; values less than 60% are often associated with irreversible organ damage. \$

Summary of Diagnostic Criteria

- Clinical diagnosis is based on the presence of isosthenuria and a history of recurrent fevers and swollen tibiotarsal joints in shar-peis with or without proteinuria and azotemia and with the exclusion of other diseases.
- A renal biopsy stained with Congo red is the only method to obtain a definitive diagnosis.

Diagnostic Differentials

- Lyme disease (in endemic areas).
- Polyarthritis: Immune mediated, viral, bacterial, or fungal.

- Glomerulonephritis.
- Pyelonephritis.
- Trauma.
- Vaccine reactions (Lyme vaccine).
- Systemic lupus erythematosus.
- Polyarteritis nodosa.
- Ehrlichiosis.

TREATMENT RECOMMENDATIONS

Initial Treatment

- Supportive therapy should be provided as indicated to reduce pain and/or fever and maintain hydration.
- **NSAIDs to reduce fever and control pain:** If a temperature exceeds 107°F, there is a significant risk for permanent organ damage and the initiation of disseminated intravascular coagulation. In the shar-pei fever syndrome, fevers often resolve without therapy. The safety of NSAIDs in animals with compromised renal function or hepatic function is unclear at this time. These agents should be used for pain management and/or fever reduction only in well-hydrated, nonazotemic animals with normal liver values. *Use of these agents should be reserved strictly for situations in which the fever is considered life threatening.*
 - Meloxicam: 0.2 mg/kg PO, IV, or SC once on the first day of treatment and 0.1 mg/kg PO once daily thereafter. \$
 - Ketoprofen: 2 mg/kg IV once. \$
- **Colchicine to inhibit amyloid production:** Ideally, this drug should be administered in the predeposition phase, which in shar-peis is presumably characterized by recurrent fevers and swollen hocks; colchicine therapy is not indicated once a patient becomes azotemic. Colchicine impairs the release of serum amyloid A from hepatocytes by binding to microtubules and preventing secretion; it may also prevent the production of amyloid-enhancing factor. Colchicine therapy should be initiated after the first episode of swollen hocks. Early diagnosis and treatment offer the best chance to slow the progression to renal failure.
 - 0.01–0.03 mg/kg PO q24h. \$
 - The primary side effect is gastrointestinal upset.
 - Therapy is lifelong, and owners should continue administration regardless of whether lameness or fever persists.

Alternative/Optional Treatments/Therapy

- **Dimethyl sulfoxide (DMSO):** 90 mg/kg PO or SC three times/week (if administered SC, DMSO

should be diluted 1:4 with sterile saline to reduce the pain associated with injection). DMSO has an unpleasant odor, which may lead to poor owner compliance, and it may contribute to clinical signs of nausea and anorexia. There is controversy as to whether DMSO is beneficial. If given during the rapid deposition phase, DMSO decreases serum amyloid A concentrations and resolves tissue deposits; however, current belief is that it does not solubilize amyloid fibrils. The beneficial effect may be due to the antiinflammatory properties of DMSO. \$

- **Dipyrrone:**

- 25–100 mg/kg IV, IM, SC, or PO q8–24h. \$
- Although dipyrrone has historically been used as an antipyretic, administration of this drug is extremely controversial, and its use is not recommended because of the potential for severe side effects. Dipyrrone has been associated with bone-marrow toxicity, severe agranulocytic anemia, dose-independent teratogenicity, induction of the microsomal enzyme system, and a tendency to increase bleeding times by suppressing the formation of prothrombin.
- Dipyrrone should not be used concurrently with NSAIDs or steroids.

Supportive Treatment

- **Diet:** Restriction of dietary protein and dietary phosphorus has extrarenal benefits and is therefore recommended in patients with progressive renal disease. \$
 - Dietary changes should be implemented when serum creatinine concentration exceeds 2.0 mg/dl.
 - It is important to ensure that these dogs maintain adequate caloric intake; malnutrition is a major cause of morbidity and mortality in dogs and cats with chronic renal disease.
 - Diets should not be supplemented with protein because protein aggravates urinary protein losses.
- **Enalapril:** 0.5 mg/kg PO once daily. If no reduction in proteinuria is seen after 2 to 4 weeks, the frequency of administration should be increased to twice daily. Serum creatinine concentration should be monitored, although it is uncommon for dogs to have worsening azotemia. \$
- Supplementation with **omega-3 fatty acids** (eicosapentaenoic acid [EPA], α -linolenic acid, and/or docosahexaenoic acid [DHA]) has been shown to be renoprotective, to mitigate hypertension in dogs with chronic renal failure, and to reduce serum triglyceride and cholesterol concentrations in humans. \$

—When using EPA–DHA omega-3 fatty acids (3V Caps, DVM Pharmaceuticals), the *North American Companion Animal Formulary* recommends the following doses:

- <14 kg: 103 mg EPA and 68 mg DHA (3V Caps for Small & Medium Breeds): One to two caps PO daily.
 - 13–27 kg: 180 mg EPA and 120 mg DHA (3V Caps for Medium & Large Breeds): One to two caps PO daily.
 - >27 kg: 250 mg EPA and 167 mg DHA (3V Caps for Large & Giant Breeds): One to two caps PO daily.
- **Low-dose aspirin therapy** (0.5 mg/kg PO once or twice daily) may decrease the frequency of thromboembolic disease. Because the dose is so small, a compounding pharmacy must compound aspirin powder into a gelatin capsule. AT III loss can be estimated by measuring the serum albumin concentration, and aspirin therapy is indicated when concentrations fall below 2 to 2.5 g/dl. Additionally, dogs with AT III concentrations less than 70% of normal and fibrinogen concentrations greater than 300 mg/dl are candidates for therapy. **\$**
- **Antihypertensive agents:** Additional antihypertensive agents may be needed if hypertension (systolic blood pressure >170 mm Hg) persists after initiation of angiotensin-converting enzyme inhibitor therapy. **\$\$–\$\$\$**
- Amlodipine: 0.1 mg/kg PO twice daily. Dose can be titrated upward weekly (to 0.2–0.4 mg/kg PO twice daily) if indicated; blood pressure should be monitored weekly until normotensive, and then once every 3 to 6 months.

Patient Monitoring

- Urine protein:creatinine ratio, urinalysis, body weight, and serum albumin and serum creatinine concentrations should be evaluated monthly when adjustments in the therapeutic plan are being made. If clinical signs are stable and therapeutic changes are not being made, these values can be monitored every 3 to 6 months. **\$\$**
- If proteinuria is present, assessing trends in the urine protein:creatinine ratio over time is preferred to a single measurement of urine protein.
- If systemic hypertension is present and blood pressure is stable, systemic blood pressure should be measured every 3 to 6 months; more frequent measuring is indicated if hypertension is unregulated.

Milestones/Recovery Time Frames

- If proteinuria is present initially, a reduction in proteinuria of more than 50% as measured by a urine protein:creatinine ratio without an increase in serum creatinine concentration indicates improvement or response to therapy.
- In one study of dogs with amyloidosis, 58% died or were euthanized at the time of diagnosis. In the remaining dogs, survival ranged from 2 to 20 months; survival of a year or longer was reported in only 8.5%. It is important to note that these studies were not restricted to only Chinese shar-peis, and the stage of the disease (whether the animal was azotemic) was not noted.

Treatment Contraindications

Renal transplantation is not currently an option because amyloid deposits are likely to accumulate in the transplanted organ.

PROGNOSIS

There have been no studies on the survival of shar-peis with familial renal amyloidosis receiving colchicine, but long-term survival with lifelong colchicine therapy has been reported anecdotally.

Favorable Criteria

- Early diagnosis and institution of therapy.
- Normal renal values.
- Normal albumin.

Unfavorable Criteria

- Azotemia.
- Severe proteinuria.
- Systemic hypertension.

RECOMMENDED READING

- DiBartola SP: Familial renal disease in dogs and cats, in Ettinger SJ, Feldman EC (eds): *Textbook of Veterinary Internal Medicine*. Philadelphia, Elsevier Saunders, 2005, pp 1819–1824.
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