Familial Shar-Pei Fever

Jenessa A. Winston, DVM
Shelly L. Vaden, DVM, PhD, DACVIM
North Carolina State University

Profile

Definition

- In familial renal amyloidosis of shar-peis, deposition of amyloid can progressively disrupt normal renal architecture, leading to chronic kidney disease (CKD).
  - Amyloidosis is the extracellular deposition of fibrils formed by polymerization of proteins with a beta-pleated sheet conformation.
  - Reactive amyloidosis secondary to chronic infectious and noninfectious inflammatory disease and neoplasia is the most common form in animals.
  - Renal amyloidosis can result in CKD, proteinuria, and nephrotic syndrome.
- Many shar-peis will have fever and swelling of the tibiotarsal joints (also called *shar-pei fever* or *shar-pei swollen hock syndrome*) before development of renal amyloidosis.
  - The cause of this syndrome in shar-peis is unknown.
- Although this disease is considered genetic, not all shar-peis with the trait will develop renal amyloidosis (see **Genetic Implications**).
- Not all shar-pei fever patients will have renal amyloidosis.

Systems

- Renal dysfunction is the most common; however, other organ systems can be affected by amyloid deposition.

Genetic Implications

- In shar-peis, this is an autosomal recessive trait.

Incidence & Prevalence

- Renal amyloidosis is estimated to occur in 23% of shar-peis in the United States.
  - True prevalence is unknown.

Signalment

Breed Predilection

- Shar-peis are predisposed.
- Familial renal amyloidosis has also been reported in beagles, English foxhounds, collies, Walker foxhounds, and Abyssinian and Siamese cats.

Age & Range

- Age of onset of clinical signs is typically 1–6 years (mean, 4.1 years).

Sex

- More common in female than male dogs (female:male ratio, 2.5:1)

MORE ▶

Amyloid deposition disrupts normal tissue architecture and can cause organ failure.

CKD = chronic kidney disease

Pathophysiology

- Amyloid A protein, formed by the polymerization of the amino acid terminal portion of serum amyloid A (SAA) in response to inflammatory cytokines, is the primary protein involved in reactive amyloidosis.
- Affected shar-peis have increased serum concentrations of interleukin-6, a cytokine that stimulates synthesis of SAA and the release from hepatocytes.
  - Other cytokines (eg, tumor necrosis factor-α, interleukin-1β) are also involved.
  - These cytokines initiate the acute phase response characterized by fever, hepatic production of acute proteins (including SAA), and mobilization of neutrophils.
- Amyloid deposition disrupts normal tissue architecture and can cause organ failure.
  - In shar-peis, amyloid deposition can occur in the kidneys, liver, spleen, pancreas, adrenal glands, thyroid glands, myocardium, prostate, lymph nodes, and GI tract.
    - Most do not show signs of organ dysfunction other than kidney or hepatic disease.
  - Renal amyloidosis in other canine breeds can lead to marked proteinuria.
    - Only 25%–43% of affected shar-peis have proteinuria.[1]
- Nephrotic syndrome—characterized by marked proteinuria, hypoalbuminemia, hypercholesterolemia, and edema—can be present.
- Some affected dogs are at increased risk for thromboembolic disease, in part because of loss of antithrombin through the affected glomerulus.
  - A similar syndrome of fever and synovitis called *familial Mediterranean fever* occurs in humans.

History & Physical Examination

- Intermittent episodes of fever ± joint swelling or pain
  - Episodes often precede amyloidosis, although these episodes may not be detected.
- At initial presentation, intermittent high fever (ie, 103°F–107°F) and joint swelling (eg, tibiotarsal joints) that resolve ± treatment may be present.
  - Affected patients may appear normal if fever and joint swelling are not present.
- Marked CKD may result in oral ulceration, uremic breath, and dehydration.
- Nephrotic syndrome may result in ascites, SC edema, or both.
- Acute onset of respiratory distress, tachypnea, or pelvic limb paresis may indicate thromboembolic disease.
- Jaundice occurs if hepatic amyloidosis is present.
  - Hepatic amyloidosis has been reported in ~11% of cases.[2]

Clinical Signs

- Signs include polydipsia, polyuria, anorexia, vomiting, dehydration, weight loss, weakness, and lethargy.

Dx Diagnosis

Definitive

- Renal biopsy specimen should be obtained from the renal cortex to reduce complications (eg, hemorrhage, infarction).
  - Because amyloid deposits are often limited to the medulla, the diagnosis may be unobtainable on renal biopsy; however, medulla biopsies are not recommended because of risk for complications.
    - Approximately 64% of shar-peis will have glomerular involvement.
- Staining with Congo red (see **Figure 1**)
  - Light microscopy discloses amyloid deposits in various shades of red.
  - Polarizing microscopy discloses amyloid deposits in an apple green birefringence.
  - Amyloid deposition is confirmed by decolorization of Congo-red–stained deposits by potassium permanganate oxidation.
- If intermittent fever and joint swelling precede onset of CKD signs in a shar-pei, renal biopsy is not recommended.
  - Treatment of presumed amyloidosis should be initiated.
- Aspirates from other organs (ie, liver, spleen) can be obtained if positive staining with Congo red is documented.

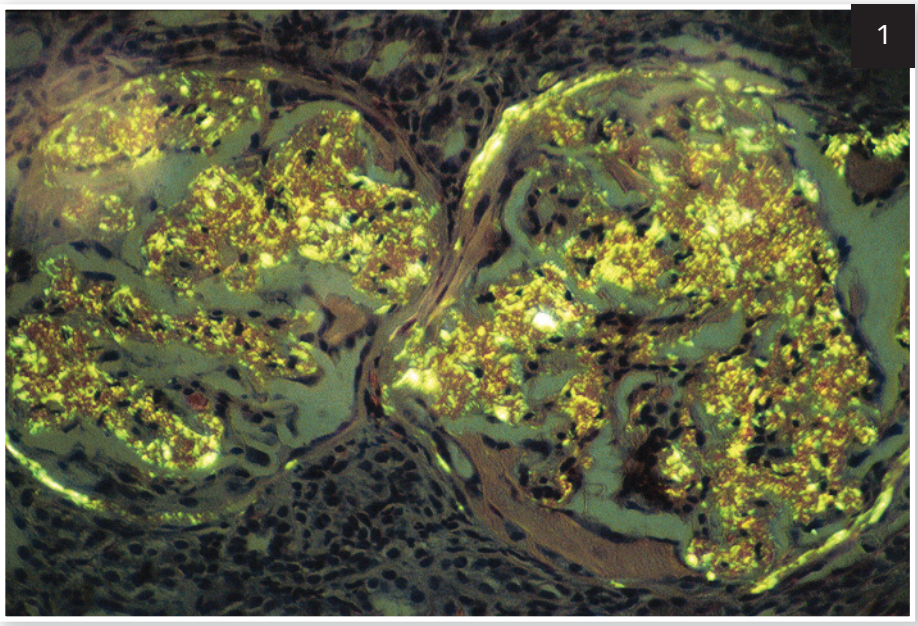
Differentials

- Joint disease
  - Polyarthritis (ie, immune mediated, bacterial, viral, fungal)
  - Lyme disease, especially in endemic areas
  - Ehrlichiosis
  - Vaccine reaction
- Renal amyloidosis
  - Other glomerular diseases

Laboratory Findings

- CBC
  - Nonregenerative, normocytic, normochromic anemia, secondary to CKD
- Serum biochemistry profile
  - If renal amyloidosis is present:
    - Azotemia
    - Hyperphosphatemia
    - Metabolic acidosis
    - Hypoalbuminemia
    - Hypercholesterolemia
    - Hyperglobulinemia
  - If hepatic amyloidosis is present:
    - Increased alkaline phosphatase, alanine transaminase, and aspartate transaminase activities
    - Hyperbilirubinemia

CKD = chronic kidney disease, SAA = serum amyloid A, UP:C = urine protein:creatinine



Renal biopsy specimen stained with Congo red showing typical birefringence of glomerular amyloid deposits. Image courtesy S.P. DiBartola

- Urinalysis
  - Proteinuria is considered the hallmark of glomerular disease but is variable (25%–43%) in shar-pei fever because amyloid deposition occurs mainly in renal medulla.
    - Urine protein:creatinine (UP:C) should be measured if proteinuria is present.
    - UP:C >0.5 is considered abnormal.
  - Isosthenuria
  - Systemic hypertension

Imaging

- Abdominal radiography can show hepatomegaly and relatively normal kidneys.
- Abdominal ultrasonography can show hyperechoic renal cortex, decreased corticomedullary distinction, and a hypoechoic liver with rounded edges.
- Other diagnostics:
  - Assessment of hypercoagulability
    - Coagulation panel
    - Antithrombin or antithrombin III concentrations
    - Thromboelastography
  - Postmortem findings
    - Confirmation of renal (or other) amyloidosis
    - Lugol's iodine can be applied to the cut surface of the kidney, which will yield bluish-black dots within the tissue representing amyloid deposits.
    - Reactive amyloidosis can be confirmed by decolorization of Congo-red–stained amyloid deposits by potassium permanganate oxidation.

Tx Treatment

Medical

- Initial treatments (see **Table**, next page)
  - Supportive care as indicated (eg, NSAIDs) to reduce pain and fever and maintain hydration.
  - Colchicine
    - Colchicine can impair release of SAA from hepatocytes by binding to microtubules, which will prevent secretion; this may also prevent production of amyloid-enhancing factor.
    - Colchicine should be initiated after 2 episodes of fever and joint swelling and after other causes of polyarthritis have been excluded; this can prevent further amyloid deposition.
    - Colchicine will *not* eliminate amyloid that has already been deposited; if azotemia is present, colchicine may not reverse existing organ damage.
    - Therapy is lifelong, independent of persistent fever or swollen joints.
    - Adverse effects of colchicine include vomiting and diarrhea.
    - With long-term administration, bone marrow suppression and hypertension are noted.
- Dimethyl sulfoxide (DMSO)
  - Treatment is controversial; there is no proven clinical benefit to date.

MORE ▶

If intermittent fever and joint swelling precede onset of CKD signs in a shar-pei, renal biopsy is not recommended.

- DMSO does not appear to solubilize amyloid fibrils; any benefit may be related to the antiinflammatory properties of DMSO.
- ❑ Enalapril or benazepril
  - Angiotensin-converting enzyme (ACE) inhibitors for reducing proteinuria
- Low-dose aspirin or clopidogrel
  - ❑ May decrease the frequency of thromboembolic disease
  - ❑ Should be started if serum albumin <2.5 g/dL
  - ❑ Aspirin should not be administered if the patient is receiving other NSAIDs.
- Antihypertensive agents
  - ❑ Additional agents (eg, amlodipine) should be started if persistent hypertension is present (systolic blood pressure >170 mm Hg) after enalapril or benazepril initiation.

Nutritional

- A diet formulated for dogs with renal disease is indicated.
- Ensure adequate caloric intake.
  - ❑ Malnutrition is a major cause of morbidity and mortality in shar-peis with CKD.
- Additional supplementation with omega-3 fatty acids may be beneficial.

Contraindications

- Renal transplantation
  - ❑ Amyloid is likely to deposit in transplanted organs.

Follow-up

Patient Monitoring

- ❑ UP:C, urinalysis, serum albumin concentration, serum creatinine concentration, and body weight should be monitored monthly when adjustments to therapeutic plan are made.
- ❑ If a patient presents with fever only, consider monitoring with urinalysis and measuring serum creatinine concentrations q3mo.
  - Clients can monitor their dog's body temperature to document febrile episodes.

Table **Drugs Commonly Used for Shar-Pei Fever**

Drug	*Dose, Route, & Frequency*	*Indications*	*Notes*
Aspirin (low dose)	0.5 mg/kg PO q24h	■ Antithrombotic agent ■ Used in dogs with serum albumin concentrations <2.5 g/dL	■ Monitor for signs of GI ulceration and bleeding. ■ Monitor renal values.
Colchicine	0.01–0.03 mg/kg PO q24h	■ Antifibrotic agent ■ Used in shar-peis based on efficacy in humans with familial Mediterranean fever	■ May cause vomiting and diarrhea ■ Long-term use can cause bone marrow suppression and/or hypertension. ❑ Serial CBCs are recommended. ■ More studies needed to evaluate effectiveness for shar-pei fever
DMSO	90 mg/kg PO q24h *or* 20–80 mg/kg SC 3 times weekly (diluted 90% solution 1:4 in sterile water)	■ Documented to dissolve some amyloid types in vitro but no evidence that this occurs in vivo ■ Can be used in dogs with amyloidosis	■ Unpleasant odor ■ Can cause nausea and vomiting if given PO ■ Wear gloves while administering. ■ Injections can be painful and cause local irritation.
Enalapril	0.5 mg/kg PO q12–24h	■ Used in dogs with persistent proteinuria as defined by UP:C >1 without or >0.5 with azotemia	■ Can also use benazepril ■ Monitor renal values. ■ Use with caution in azotemic patients.

CKD = chronic kidney disease, DMSO = dimethyl sulfoxide, SAA = serum amyloid A, UP:C = urine protein:creatinine

- Response to therapy
  - 50% reduction of proteinuria (based on UP:C) without increase in serum creatinine
  - Combination of 3–5 pooled urine samples for UP:C evaluation is ideal.
- If systemic hypertension is present, blood pressure should be rechecked q3mo until stable.
  - More frequent monitoring is required if unregulated hypertension is present.
- Once patient is stable, parameters can be monitored q3mo.

In General

Relative Cost

- Shar-pei fever with renal amyloidosis may be costly because of lifelong medications, supportive care, hospitalization, and diagnostic monitoring: $$$$$

Cost Key
$ = up to $100
$$ = $101–$250
$$$ = $251–$500
$$$$ = $501–$1000
$$$$$ = more than $1000

Prognosis

- Poor to guarded
- Optimal treatment is unclear, but early intervention with colchicine therapy may improve prognosis. ■ cb

See **Aids & Resources**, back page, for references & suggested reading.