Hepatocutaneous Syndrome in a Shiba Inu

Joel D. Ray, DVM, MS

A 13-year-old, 10-kg neutered male Shiba Inu presented for erythema on the plantar and palmar surfaces and pruritus and interdigital crusting of all 4 feet.

HISTORY
The skin disease had a gradual onset of approximately 2 months. Clinical signs included licking and chewing of the feet as well as licking of the perianal area, with subsequent development of erythema, crusts, and hyperkeratotic changes of the footpads. Pruritus was most severe in the feet. The clinical signs were not seasonal.

The owner also noticed tremors that lasted approximately 15 minutes and irregular sleep/wake patterns. The dog had been previously diagnosed with glaucoma, which was managed with 1% prednisolone acetate drops and lanoprost ophthalmic solution. No coughing, sneezing, vomiting, or diarrhea was reported.

Home Care
The dog was the only pet in the house and an indoor/outdoor dog. He was current on immunizations and received monthly heartworm and topical flea and tick preventives. The dog’s diet consisted of a dry kibble supplemented with cooked chicken. Weight loss was not noted; water and food intake was within normal limits.

Previous Treatment
The dog was seen by another veterinarian 2 months previously for inflamed footpads and pododermatitis.

CONSIDER THIS CASE OVERVIEW
This case report describes a 13-year-old Shiba Inu diagnosed with canine hepatocutaneous syndrome (HCS). The initial presenting signs were dull moth-eaten hair coat with erythema, crusts on the feet, and discoloration of pedal hairs. Diagnosis of HCS was made based on abdominal ultrasound and histopathology of skin biopsies. The case was managed with amino acid administration and nutritional and hepatic support. The dog had an excellent dermatologic response for a brief period, but was euthanized several weeks after initial presentation due to a declining quality of life.
Previous topical treatments included:
• Neomycin sulfate
• Isoflupredone acetate and tetracaine hydrochloride (NeoPredef, pfizerah.com)
• Hydrocortisone cream
• Miconazole nitrate 2% and miconazole/chlorhexidine gluconate 2% shampoo (Malaseb shampoo, tevaanimalhealth.com).

All medications had minimal effect. The best results were achieved after initial application of hydrocortisone cream. At presentation, the dog was receiving cephalixin and chlorpheniramine.

**PHYSICAL EXAMINATION**
The dog was extremely pruritic and rubbed his face on the carpet constantly. Additional clinical signs included:
• Motheaten appearance (hair coat)
• Alopecia (ventrum and hindlimbs)
• Erythema, crusts, and hair discoloration (interdigital areas)
• Ulcerations, erythema, and crusts (palmar and plantar surfaces of interdigital areas)
• Hyperkeratosis, ulcerations, and fissures (footpads).

The dog was alert and responsive to stimuli. Body condition score was 3.5/9. The dog was nonvisual and a prosthetic global implant was noted in the right eye (OD). Corneal scarring and a minimal menace response were noted in the left eye (OS).

**DIAGNOSIS**

**Laboratory Analysis**
A CBC, serum biochemical profile, and urinalysis were submitted for in-house testing. The results of the CBC and urinalysis were unremarkable. The cytologist reported the presence of occasional target cells, which can be associated with liver disease.

The serum biochemical profile revealed normal serum albumin, mild hyperglycemia, mild to moderate increase in alanine aminotransferase, marked increase in alkaline phosphatase, and a mild increase in total bilirubin (Table). The sample was also mildly lipemic with slight hemolysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result</th>
<th>Reference Interval</th>
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<tbody>
<tr>
<td>Alanine aminotransferase (mg/dL)</td>
<td>305</td>
<td>10–90</td>
</tr>
<tr>
<td>Alkaline phosphatase (mg/dL)</td>
<td>1263</td>
<td>11–140</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>11</td>
<td>8-24</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>181</td>
<td>75–125</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>1.2</td>
<td>0.2–0.6</td>
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**Dermatologic Tests**
Dermatologic tests included deep skin scrapings, Wood’s lamp evaluation, and tape-preparation cytology stained with Diff Quik and Gram’s stain.

The skin scrape provided no evidence to suggest demodicosis. The cutaneous cytology demonstrated gram-positive cocci with no evidence of yeast. The Wood’s lamp examination was negative, and the dermatophyte culture could not rule out dermatophytosis until complete.

**Diagnostic Imaging**
Radiography and abdominal ultrasound were indicated due to the elevated liver enzymes and bilirubin. The dog was discharged with cephalixin (22 mg/kg PO Q 12 H) and chlorpheniramine (4 mg PO Q 12 H) with instructions to return the following day for the imaging studies. Based on the results of imaging, an adrenocorticotropic hormone (ACTH)-stimulation test and/or skin biopsy of the feet were potential considerations.

**Radiography**
The next morning, the dog was sedated with butorphanol (0.1 mg/kg IM) and radiographs of the abdomen were taken. The radiographs showed irregularity in shape of the ventral margin of the liver and focal caudal displacement of the right aspect of the transverse colon (Figure 1, page 41).

**Ultrasonography**
Ultrasound of the liver showed a severely irregular shape with nodular, coarse parenchyma. Hypoechoic nodules ranging in size from 0.4 cm to 2.2 cm were seen diffusely in all liver lobes, which coalesced to form a reticular, “honeycomb” appearance. A well circumscribed mass (3.3 cm × 3 cm) with a normal hepatic echogenicity was found in the right liver (Figure 2, page 41).

A small, hypoechoic nodule in the caudal cortex of the left kidney (6.5 mm × 4.2 mm) produced distal
acoustic enhancement. The pancreas was prominent and moderately hypoechoic with hyperechoic striations and stippling throughout the parenchyma). No abnormalities were noted with regard to the size, shape, or consistency of the adrenal glands.

Preferential consideration was given to possible hepatocutaneous syndrome; neoplasia was less likely.

Further Diagnostics
The owner declined biopsy due to concerns regarding anesthesia but did elect to pursue glucagon and ammonia measurements.

Both ammonia and glucagon levels were within normal limits. Based upon these levels, the liver was eliminating ammonia normally. The possibility of a glucagonoma as the cause of skin disease was less likely. Without a hepatic biopsy, neoplasia could not be ruled out definitively, however, the ultrasound report listed neoplasia as very unlikely. Therefore, the patient was treated for HCS.

TREATMENT
Currently published supportive therapy for HCS is multifaceted and consists of:

- Appropriate antimicrobial therapy
- Supportive therapy of current hepatic disease with S-adenosylmethionine (SAMe), ursodiol, and vitamin E
- Parenteral amino acid supplementation (Note: Monitoring the patient for neurologic signs during amino acid administration is important due to the potential risk for hepatoencephalopathy)

WHAT YOU NEED TO KNOW ABOUT... HEPATOCUTANEOUS SYNDROME
HCS is generally considered a rare disease in the veterinary literature with 1 institution reporting only 0.3% of all nonneoplastic skin biopsy samples having changes consistent with the disease. Although most commonly reported in canines; it has been diagnosed in felines and captive black rhinoceros populations in the United States.

Known by other names, such as superficial necrotic dermatitis (SND), metabolic epidermal necrolysis (MEN), diabetic dermatopathy, and necrolytic migratory erythema (NME), HCS is a progressive dermatologic disorder that typically develops secondary to hepatic dysfunction. The term HCS is given when evidence of hepatic abnormalities are present. MEN, SND, and NME are used to describe the dermatologic component.

Although this syndrome is primarily diagnosed in dogs, its human counterpart is referred to as NME. It is associated primarily with a pancreatic endocrine tumor, whereas in dogs, HCS is associated with glucagonomas in only a minority of cases.
• Oral administration of amino acid solutions and supplementation with raw egg yolks, zinc, and essential fatty acids (not as effective as IV amino acid supplementation)
• Treatment with anti-inflammatory doses of prednisone (considered controversial, but may temporarily improve skin lesions)
• Symptomatic topical therapies for moisturizing skin lesions.

Parenteral amino acid supplementation is the symptomatic treatment of choice for improving skin lesions in animals with chronic liver disease and may prolong survival time by several months. Treatments, which may be repeated every 7 to 10 days as needed, may result in improvement in 1 to 3 weeks. If no improvement is noted by this time, then the prognosis is guarded.

In-Clinic Therapy
The dog received amino acid supplementation, which was performed by administering hydromorphone (0.1 mg/kg) and midazolam (0.1 mg/kg) and placing a central line in the left jugular vein for administration of a 10% crystalline amino acid solution (Aminosyn, abbott.com). This solution is hypertonic and likely to cause thrombophlebitis if administered through a peripheral vein. It was dosed at 150 mLs of Aminosyn, which was added to 250 mLs of 0.9% sodium chloride for a total volume of 400 mLs administered over 10 hours.

At-Home Therapy
A therapeutic plan was outlined with the owner and included:
• A highly digestible, high-quality protein diet with vitamin E and soluble fiber, which absorbs some of the toxins not filtered by the liver (Prescription

Figure 1. (A) Lateral and (B) ventrodorsal radiographs of the abdomen

Figure 2. Ultrasound image of liver gall bladder demonstrating the “honeycomb” appearance (A and B)
Diet l/d, hillspet.com)
- Additional protein supplementation of either 1 boiled egg per day or boiled chicken
- SAMe supplement (Denosyl, nutramaxlabs.com) (225 mg PO Q 24 H)
- Eicosapentaenoic acid supplement (3V Caps, tevaanimalhealth.com) (720 mg PO Q 24 H)
- Zinc supplement (15 mg PO Q 24 H)

The client was advised that the goal of therapy was to aid in resolution of clinical signs (itching, chewing, and licking the feet and perianal region) but that the therapy would not treat the liver disease. The SAMe may slow progression of liver damage but could not address the undiagnosed hepatopathy. The patient was scheduled for a recheck in 1 week.

**FOLLOW-UP & OUTCOME**

**One-Week Recheck**

When the dog was presented 7 days later, the condition of the skin and feet had improved. The client was very pleased that the dog was less pruritic and more playful. The coat was growing and appeared thicker and shinier. The foot pads appeared less hyperkeratotic and devoid of fissures. The prescribed therapy was continued and another recheck scheduled.

**Three-Week Recheck**

The dog returned for evaluation 2 weeks after the first recheck. His attitude had regressed from alert and responsive to depressed. The seborrhea and interdigital crusting had returned and the feet were painful. The owner was concerned about quality of life and was not interested in repeating parenteral amino acid therapy. Humane euthanasia was elected.

Pedal pruritus in a dog may be related to atopy, food allergy, infection, or a wide variety of other dermatologic issues.

A complete and thorough history combined with physical examination will help develop a list of differential diagnoses.

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**ACTH = adrenocorticotropic hormone; HCS = hepatocutaneous syndrome; SAMe = S-adenosylmethionine**

**References**


