Frédéric P. Gaschen, Dr.med.vet, Dr.habil, Diplomate ACVIM (Small Animal Internal Medicine) & ECVIM-CA (Internal Medicine), Louisiana State University

Refractory Gastrointestinal Disease

A 6-year-old neutered male giant schnauzer was presented for a second opinion due to chronic diarrhea, decreased appetite, and weight loss of 6 weeks' duration.

History. The referring veterinarian initiated empiric treatment against intestinal parasites and prescribed a highly digestible diet, which resulted in minor improvement. The dog was also treated with tylosin to rule out antibiotic-responsive diarrhea. However, the clinical signs did not resolve.

Physical Examination. On examination, the dog was lean with a body condition score of 4/9 but otherwise appeared normal. Further discussion with the owners suggested that the diarrhea was mostly of small bowel origin.

Laboratory Results. A workup including complete blood count, serum biochemical profile, and urinalysis was initiated; abnormal laboratory results are listed in the **Table**.

Additional Diagnostics. No abnormalities in intestinal wall layering or thickness were detected on abdominal ultrasound. Inflammatory bowel disease, lymphangiectasia, or alimentary lymphoma were the top differential diagnoses.

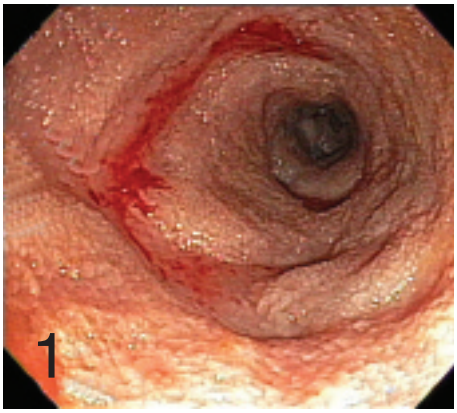
continues

Abnormal Serum Biochemical Profile Results

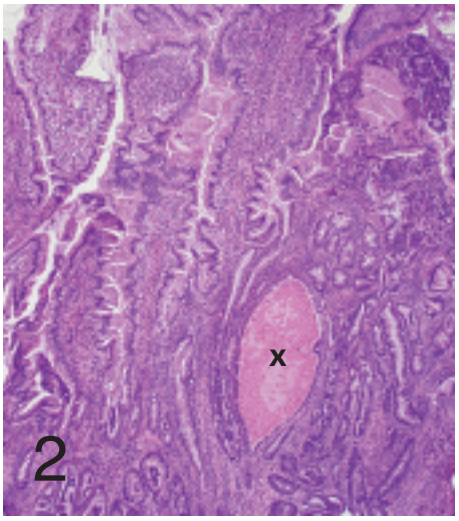
Variable	Result	Reference Interval
Total protein	3.8 g/dL	5.8–7.5 g/dL
Albumin	1.8 g/dL	2.6–4.2 g/dL
Globulin	2 g/dL	2.5–4 g/dL
Calcium	8.9 g/dL	9.4–11.4 g/dL
Cholesterol	95 mg/dL	150–240 mg/dL

Corrected total calcium is within the reference range: The spurious hypocalcemia is due to hypoalbuminemia and unlikely a reflection of low ionized calcium. Hypocholesterolemia is likely a consequence of poor fat absorption and protein loss. Urinalysis and urinary protein-to-creatinine ratio were within the reference range.

IBD = inflammatory bowel disease



Endoscopic view of the descending duodenum. The duodenal villi are distinctly visible. The mucosa is friable and bleeds easily, as evidenced by the focal hemorrhage that was induced while gently pushing the endoscope forward.



Photomicrograph of the duodenal mucosa. A dilated crypt is visible (x). The duodenal villi are infiltrated by an inflammatory cell population consisting mainly of lymphocytes and plasma cells. The findings were moderate to severe inflammatory lymphocytic plasmacytic duodenal infiltration, architectural changes (not shown), and numerous crypt abscesses.

Upper gastrointestinal endoscopy with sampling of gastric and duodenal mucosal tissue was performed (**Figure 1**). The duodenal mucosa appeared to be friable (bleeding easily when touched). Histopathologic evaluation revealed moderate to severe inflammatory lymphocytic plasmacytic duodenal infiltration, architectural changes such as moderate to marked villous stunting, and numerous crypt abscesses (**Figure 2**).

Diagnosis. The diagnosis was determined to be protein-losing enteropathy due to severe inflammatory bowel disease.

Initial Treatment. The dog was discharged, and treatment was initiated with prednisone at an immunosuppressive dose (2 mg/kg PO Q 12 H for 4 days, then Q 24 H), metronidazole (15 mg/kg PO Q 12 H), and a novel protein diet. A follow-up visit 2 weeks later showed no improvement.

ASK YOURSELF...

Which of the following steps should be taken next? (More than 1 choice can be selected.)

A. Question the owners about their compliance with prescribed diet and medication.

B. Continue with the same treatment for another 2 weeks.

C. Rule out bacterial intestinal infection (eg, campylobacteriosis).

D. Perform an adrenocorticotropic hormone stimulation test.

E. Consider adding additional immunosuppressive drugs to the treatment.

Correct Answers:

A. Question the owners about their compliance with prescribed diet and medication.

C. Rule out bacterial intestinal infection (eg, campylobacteriosis).

E. Consider adding additional immunosuppressive drugs to the treatment.

Not surprisingly, owner compliance is essential to treatment success. Additionally, enteric bacterial infections can complicate chronic enteropathies in dogs, and a fecal sample should be submitted for culture and sensitivity. If no intercurrent disease is identified, adding other immunosuppressives, such as cyclosporine A or azathioprine, may be indicated. Atypical hypoadrenocorticism (Addison's disease) may cause chronic, intermittent gastrointestinal signs but would have responded to prednisone therapy.

Assessment. IBD is diagnosed by a lack of response to diet change (to a novel protein or hydrolyzed peptide–based diet) or antimicrobials (such as metronidazole) and by evidence of inflammatory infiltration of the gastrointestinal mucosa. Cases refractory to steroid treatment are not uncommon and have been reported to occur in 16% to 55% of dogs with IBD.

Before attributing clinical signs to refractory disease, however, consideration should be given to other possible causes, including insufficient owner compliance, concurrent diseases (eg, concurrent parasite infestation or campylobacteriosis), and misdiagnosis (eg, exocrine pancreatic insufficiency, or alimentary lymphoma).

Consequently, the recommended approach for dogs with refractory IBD includes a discussion with the owners; reevaluation and possible recheck of test results obtained; fecal parasitology studies (nematodes and protozoa); fecal culture and sensitivity for enteropathogens; and measurement of serum cobalamin (vitamin B12), folate, and trypsin-like immunoreactivity.

Further treatment. If all tests confirm that refractory IBD is the most likely diagnosis, the treatment protocol should be modified to include additional immunosuppressive drugs.

Cyclosporine A is mainly an inhibitor of cell-mediated immunity with helper T lymphocytes as a primary target. The recommended dose is 5 mg/kg PO Q 24 H. The drug is relatively expensive and can cause such side effects as vomiting, anorexia, epiphora, gingival hyperplasia, and hirsutism.

Azathioprine is an inhibitor of purine metabolism that prevents proliferation of immune cells. It is given at 2 mg/kg Q 24 H for 14 days, then 2 mg/kg Q 48 H, and is then decreased to 1 mg/kg Q 48 H. Time to peak therapeutic effects may be several weeks. Side effects include bone marrow suppression, acute pancreatitis, and hepatotoxicity.

Cobalamin is essential for processes occurring in intermediary cell metabolism. In a recent study, hypoalbuminemia (< 2 g/dL) and hypocobalaminemia (< 200 ng/L) were both shown to be associated with a negative outcome in dogs with chronic enteropathies. Hypocobalaminemia reflects involvement of the distal small intestine; it can be due to a congenital defect in giant schnauzers. However, in dogs with IBD it reflects involvement of the distal small intestine in the inflammatory process. Parenteral *vitamin B12* supplementation is indicated in hypocobalaminemic dogs (for a 32-kg dog: 6 weekly SC doses of 1200 mcg with a follow-up measure-

continues

Tx at a Glance

Initial Treatment

- **Prednisone**: 2 mg/kg PO Q 12 H for 4 days, then Q 24 H
- **Metronidazole**: 15 mg/kg PO Q 12 H
- **Novel protein diet**

Further Treatment

- **Cyclosporine A**: 5 mg/kg PO Q 24 H
- **Azathioprine**: 2 mg/kg PO Q 24 H for 14 days, then 2 mg/kg Q 48 H, then 1 mg/kg Q 48 H
- **Vitamin B12**: 6 weekly doses of 1200 mcg/dog (parenteral injection)

TAKE-HOME MESSAGES

- In dogs with severe chronic protein-losing enteropathy and no evidence of blood loss, differential diagnoses include lymphangiectasia, severe IBD, and alimentary lymphoma.
- Some dogs with IBD may have disease that is refractory to prednisone treatment. If owner compliance is good, treatment failure should prompt the clinician to reevaluate the diagnosis and rule out concurrent diseases.
- Once the diagnosis of IBD is confirmed, cyclosporine A or azathioprine may be added to the treatment regimen.
- Severe hypoalbuminemia and hypocobalaminemia are negative prognostic factors in dogs with chronic enteropathies. Once documented, hypocobalaminemia should be treated with parenteral injections of vitamin B12.

IBD = inflammatory bowel disease

ment of serum cobalamin; dosing frequency can be subsequently reduced to twice or once monthly).

Outcome. No fecal parasites or enteropathogenic microorganisms were identified. Serum trypsin-like immunoreactivity level was within the reference interval, but the dog was hypocobalaminemic (150 ng/L; reference interval, 251–908).

Vitamin B12 supplementation was initiated at 1200 mcg SC weekly. The prednisone dosage was progressively reduced; cyclosporine was started at 5 mg/kg Q 24 H and was well tolerated. However, the clinical signs improved only marginally.

After 2 weeks, azathioprine (2 mg/kg Q 24 H) was added to the treatment regimen but did not result in significant improvement. A few weeks later, the dog developed intractable vomiting, and a jejunal intussusception was diagnosed by abdominal ultrasound. Euthanasia was performed at the owners' request, and necropsy confirmed the earlier biopsy findings.

See Aids & Resources, back page, for references, contacts, and appendices.

our authors
AUGUST 2009

Laura J. Armbrust, DVM, Diplomate ACVR, is an associate professor of radiology at Kansas State University College of Veterinary Medicine. She has authored numerous publications, book chapters, and proceedings, and has presented at state and national continuing education programs. Dr. Armbrust has clinical and research interests in all types of diagnostic imaging.

Deirdre Chiaramonte, DVM, Diplomate ACVIM, is a staff internist at The Animal Medical Center in New York City, a private not-for-profit veterinary hospital that cares for more than 65,000 patients every year. She is also the medical liaison for the Rehabilitation and Fitness Center at AMC. Dr. Chiaramonte received her DVM from Tufts University and completed her postgraduate studies at AMC.

Jill R. Foreman, MBA, CVPM, is a certified veterinary practice manager with 18 years of experience in the veterinary profession. Ms. Foreman received a BA in biology from Evergreen State College, Olympia, Washington, and an MBA from West Virginia University. After many years of active practice management, she is employed as a practice consultant with AAHA, serving states in the mid Atlantic region.

Frédéric P. Gaschen, Dr.med.vet, Dr.habil, Diplomate ACVIM (Small Animal Internal Medicine) & ECVIM-CA (Internal Medicine), is professor and chief of the companion animal medicine service at Louisiana State University. His present research interests include chronic enteropathies of dogs and cats as well as disorders of gastrointestinal motility. Dr. Gaschen is a founding member of the European College of Veterinary Internal Medicine and has lectured many times at the NAVC Conference, most recently in 2007 and 2008. He received his veterinary degree from University of Bern (Switzerland), and taught at this university for 13 years prior to his current position.

Doug Mader, DVM, MS, Diplomate ABVP (Canine & Feline Practice), is the coowner of Marathon Veterinary Hospital, a referral practice in the Florida Keys. He is also the consulting veterinarian for the Marathon Sea Turtle Hospital, Monroe County Sheriff's Zoo, Key West Aquarium, Key West Butterfly Conservancy, and Theater of the Sea. Dr. Mader is president-elect of the NAVC and a fellow in the Royal Society of Medicine. In addition to being an internationally acclaimed lecturer, he is the author/editor of *Reptile Medicine and Surgery* (Elsevier). Dr. Mader received his DVM from University of California–Davis.

Elke Rudloff, DVM, Diplomate ACVECC, is a clinical instructor and director of education at the Animal Emergency Center, Glendale, Wisconsin. She also serves as a scientific program chair and is president-elect of the Veterinary Emergency and Critical Care Society. Dr. Rudloff has a special interest in fluid resuscitation and pain management in critically ill patients. She is an internationally recognized educator in the field of veterinary emergency and critical care and has participated as an instructor at the NAVC Conference, Postgraduate Institute, and regional symposia. Dr. Rudloff is a recipient of the Zaslow Award for service in the field of veterinary emergency and critical care. She received her DVM from Purdue University and completed her residency training at the Animal Emergency Center.

Joseph Wakshlag, DVM, MS, PhD, Diplomate ACVN, is currently the clinical nutritionist at Cornell University Hospital for Animals. His research interests include the influence of nutrition in cancer cell biology and metabolism in sporting dogs. Dr. Wakshlag obtained his DVM and PhD from Cornell University.