A clinical explanation of PLE/PLN, their manifestations, recommendations for testing, and a discussion of food hypersensitivity in relation to PLE/PLN with recommendations for dietary management. Allergy (food), Nutrition, PLE, PLN, Diet

PROTEIN-LOSING ENTEROPATHY AND PROTEIN-LOSING NEPHROPATHY OF SOFT COATED WHEATEN TERRIERS
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The Syndrome

In 1990, Drs. Littman and Giger first described protein-losing enteropathy (PLE) and protein-losing nephropathy (PLN) in 19 closely related Soft Coated Wheaten Terriers (SCWT). Unfortunately, the diagnosis has been established in a growing number of dogs. In fact, Dr. Littman has now accumulated data from 222 affected SCWT. Of these dogs, 34% had PLE, 38% had PLN and 27% had both PLE and PLN. The incidence of subclinical PLE or PLN in dogs said to have only PLN or PLE, respectively, has not yet been determined. Ages of affected dogs range from 6 months to 12 years, although most dogs are 4-6 years of age at the time of diagnosis. Females are diagnosed with the disease more commonly than males (Female:Male = 1.5 to 1.7). Affected dogs may exhibit vomiting, diarrhea, weight loss, lethargy, decreased appetite, fluid accumulation (peripheral edema, abdominal effusion), and/or increased water intake and urination. Occasionally, affected dogs will form blood clots within the body (thromboembolic disease) or have hypertension. As many as 23% of the dogs were reported to have skin problems; many of these dogs were diagnosed with allergic skin disease.

The most common clinicopathologic (bloodwork) abnormality in affected SCWTs is a low blood protein (hypoproteinemia). Dogs with PLN usually have only low albumin (hypoalbuminemia). Dogs with PLE can have low albumin (hypoalbuminemia) and low globulin (hypoglobulinemia). Dogs with PLN are losing protein through the kidney and may have increased urine protein:creatinine ratios. Likewise dogs with PLE are losing protein through the intestinal tract and often, particularly in the early stages of the disease have increased fecal alpha1-protease inhibitor (API) concentration. Dogs with advanced PLE that have hypoalbuminemia and hypoglobulinemia may have normal fecal API concentrations. Therefore, finding a normal fecal API and/or a normal urine protein:creatinine ratio should not be interpreted as finding a normal SCWT.

Dogs with PLE may also have low cholesterol (hypocholesterolemia) whereas dogs with PLN may have high cholesterol (hypercholesterolemia). Dogs with PLN may present in kidney failure and have increased phosphorus (hyperphosphatemia) and anemia. Dogs with PLE or PLN may have decreased peripheral blood lymphocyte counts (lymphopenia), and increased (eosinophilia) or decreased (eosinopenia) peripheral eosinophil counts.

Intestinal biopsy of dogs with PLE most commonly reveals lymphangiectasia, inflammatory bowel disease and/or lipogranulomatous lymphangitis. The inflammatory infiltrate can be lymphocyticplasmacytic, eosinophilic or of mixed cellularity. Renal biopsy most commonly shows glomerulonephritis in SCWT with PLN. Glomerulonephritis may be further characterized as membranous or membranoproliferative. Glomerulosclerosis is a common finding in dogs with advanced disease. Immunofluorescent and electron micrographic studies of kidneys from affected dogs have been limited, however, findings are consistent with a secondary glomerular disease resulting form immune-complex induced damage to the glomeruli.

Early Manifestations of PLE/PLN in SCWT

We have a colony of dogs that were borne to affected SCWT. We have 6 purebred SCWT (3 male, 3 female, born 7/94 and 2/95), 8 SCWT x beagle (4 males, 4 females, born 10/96) and 4 inbred SCWT (1 male, 3 females, born 7/97). We have evaluated all dogs in the colony at regular intervals for clinical manifestations of PLE/PLN. All of the 6 purebred SCWT have PLE, 2 definitely have PLN and another 2 may have PLN. All 4 inbred SCWT have PLE. It is too early to comment on the SCWT x beagle dogs, although if the syndrome is found in these dogs it is inherited as a dominant trait.
The earliest abnormal finding in our 6 purebred SCWT was eosinophilia (peripheral eosinophils > 750/ul) occurring in 6/6 dogs at a median age of 6 months. Eosinophilia has persisted beyond 15 months of age in 4/6 dogs. Fecal API concentration increased (> 6 ug/g) in 6/6 dogs at a median age of 8 months; however, increases have been sporadic in 5 dogs persisting in only 1 female dog. Hypoglobulinemia (serum globulin < 2.5 g/dl) developed in 5/6 dogs at a median age of 23.5 months. Hypoalbuminemia (serum albumin < 2.5 g/dl) has occurred in 3 dogs at 19, 19 and 26 months of age. Questionable increases in urine protein:creatine ratios (>0.5) have occurred in 3 dogs at 12, 12, and 15 months of age whereas definitive increases in urine protein:creatine ratios (>1.0) have occurred in only 2 dogs at 20 and 22 months of age. Evaluation of renal biopsy specimens revealed mild glomerular abnormalities in 4 dogs at 12 months of age but definitive changes of glomerulonephritis have been seen in only 1 dog at 24 months of age. The number of intestinal mucosal eosinophils, as determined by morphometric analysis, was increased in intestinal biopsy specimens obtained via gastroduodenoscopy as early as 12 months of age in 6/6 dogs. This finding has been persistent in 5 dogs.

Recommendations for Clinical Evaluation of ALL SCWT

All SCWT should be monitored for PLE/PLN on a regular basis. We currently recommend evaluating urine protein:creatinine ratios, fecal API concentrations and serum globulin, albumin and creatinine concentrations yearly. PLN should be suspected when the urine protein:creatinine ratio is increased in a urine sample that has not been contaminated by blood or inflammatory debris. PLE should be suspected when the fecal API concentration is increased. However, a normal urine protein:creatinine ratio and/or a normal fecal API concentration does not exclude the possibility that the dog is affected with this syndrome. The need for evaluation of renal or intestinal biopsy specimens needs to be determined on a case by case basis.

Food Hypersensitivity Reactions in SCWT with PLE/PLN

We hypothesize that food hypersensitivity reactions are involved in the pathogenesis of PLE/PLN of SCWT. We derived this hypothesis on the basis of several findings. First, we had one affected SCWT that was asymptomatic over a period of years when fed a gluten-free diet yet developed mild proteinuria and lymphocytic enteritis within several days of adding gluten, a potent food allergen, to the diet. Secondly, SCWT were found to have a high relative risk factor for food allergy dermatitis. Lastly, many owners of affected SCWT report that their dogs were intolerant of dietary changes at an early age, prior to developing clinical signs of PLE or PLN. In many cases, these dogs were fed elimination diets to avoid or reduce clinical signs. Some diets were gluten-free; however, many owners fed diets free of other allergens before clinical improvement was detected. In some cases there was complete resolution of clinical manifestations of PLE/PLN following dietary changes.

Our initial investigation of the association of food hypersensitivities and PLE/PLN involved feeding our original 6 affected SCWT gluten, a potent food allergen found in wheat, for 6 weeks. The dogs were 17-24 months of age at the time of the study and had only mild manifestations of the disease. There was a significant increase in duodenal mucosal lymphocytes/plasma cells and a significant decrease in serum globulin concentration after gluten administration. However, there were no differences in fecal API or serum albumin concentrations or urine protein:creatinine ratios after gluten administration. Although gluten did evoke some changes, the changes were mild.

To further evaluate for the presence of food hypersensitivity reactions in affected dogs, we performed gastropscopic food sensitivity testing (GFST) followed by oral challenge (provocation) in our 6 purebred dogs. At the time of this study, the dogs were 28-39 months of age and still had only mild clinical signs of disease. Extracts of corn, egg, soybean, wheat, chicken, milk and lamb were used for GFST. Five of 6 dogs had definitive positive reactions: milk, 4, 2: wheat, 1; chicken, 1. During oral challenge, dogs were given 7 test meals of chicken, corn, cottage cheese, farina wheat, lamb, tofu and lactose-free milk over a 14-day period. Abnormal clinical signs (pruritus, vomiting, increased fecal softness or increased defecation frequency) were observed during oral challenge study in all 6 dogs: chicken, 5; corn, 5; tofu, 3; cottage cheese, 2; milk, 2; farina wheat, 2; lamb, 2. Serum albumin was significantly decreased after oral challenge but there were no differences in fecal API or serum globulin concentrations or urine protein:creatinine ratios. Although there was a high occurrence of reactions to lamb and milk, none of the dogs have been given lamb or milk prior to the study.
Dietary Management of Affected SCWT

We conclude that food hypersensitivity reactions do occur in SCWT with PLE/PLN and that they are present during the very early stages of the disease. However, it remains unclear as to the exact role of food hypersensitivity reactions in the pathogenesis of this disorder. It should be emphasized that most of our dogs responded to multiple food allergens. Currently we are recommending that affected dogs be fed either hydrolysate or novel protein source (hypoallergenic) diets. It remains to be determined the exact role these diets will have in the management of affected SCWT. There is no role for these diets in unaffected dogs.

References

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