Proceedings of the 35th World Small Animal Veterinary Congress
WSAVA 2010

Geneva, Switzerland - 2010

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PROTEIN-LOSING ENTEROPATHIES (PLE)
Karin Allenspach, Dr.med.vet. FVH Dipl ECVIM-CA PhD FHEA
London, UK

INTRODUCTION
Protein losing enteropathies (PLE) are a syndrome of many different diseases which cause loss of protein through the gastrointestinal mucosa. Typical clinical signs can be seen when the albumin drops below 20g/l (2 g/dl), at which point loss of oncotic pressure leads to formation of ascites, thoracic effusion and peripheral oedema. Causes for PLE can be diverse and include inflammatory changes of the mucosa, ulcerations, erosions, neoplasia and lymphangiectasia.

DIAGNOSIS
Clinical signs associated with PLE are those of chronic small intestinal diarrhoea which can be accompanied by weight loss and vomiting. It is possible that the diarrhoea is not very obvious to the owners and that the presenting complaint is ascites alone. Other clinical signs that have been described in cases with PLE are PU/PD and thromboembolism.

It is important to perform a thorough workup for these dogs. In case of hypoalbuminaemia, it is essential to exclude other causes of hypalbuminaemia, such as protein losing nephropathy (PLN) or liver failure. If indicated, a urinary protein:creatinine ratio will help decide whether there is significant loss of proteins through the kidneys (normal values less than 1.0). This test should only be performed when there is no noticeable urine sediment, as this could falsely increase the protein:creatinine ratio in the urine. In addition, bile acid stimulation tests could be performed in order to rule out liver failure in suspected cases. Typically, PLE will cause panhypoproteinaemia, as both, albumin and globulin will be lost through the GI mucosa. Severe panhypoproteinaemia should therefore always prompt the clinician to the possibility of PLE.

BREED PREDISPOSITIONS
Yorkshire Terriers have been found to have a 10-times higher incidence of PLE as compared to other breeds. Most Yorkies show some degree of lymphangiectasia in their mucosal biopsies, however, lymphoplasmacellular infiltration of varied severity has also frequently been described. In addition, ionized hypocalcaemia and hypomagnesaemia have been described to occur with PLE in this breed.1 Soft-Coated Wheaten Terriers have been described to develop a familial form of PLE and/or PLN. Ten to 15% of all SCWT in the USA have been described to be affected2. The age range is about 4-6 years in these cases and the disease progression is fast and usually fatal. Some dogs with very mild signs and without evident protein loss can be treated with hypoallergenic diets and it has been proposed that this could prolong survival.

Shar Peis are another breed where PLE has been frequently diagnosed. As amyloidosis is a familial disease in this breed as well, it is important to differentiate protein loss through the GI tract from protein loss through the kidneys in these cases. PLE has a far less aggressive progression than amyloidosis in the Shar Pei and is in most cases treatable with immunosuppressive drugs. Basenjis have been described to develop a so called immuno-proliferative inflammatory bowel disease (IBD). This syndrome was originally described to be similar to the disease occurring in human beings, however, hypergammaglobulinaemia does not seem to be as commonly seen as in people with the disease.3,4

INFLAMMATORY BOWEL DISEASE (IBD) AS CAUSEOF IBD
IBD is a common cause of PLE and is usually accompanied by severe infiltration with lymphocytes/plasmacytes and/or eosinophils. These cases need to be treated aggressively with immunosuppressive drugs. The usual protocols for prednisolone usage recommend dosages of 1-2 mg/kg.
BID for approximately 2-4 weeks, followed by a slow tapering period over weeks to months. However, a number of dogs treated with immune suppressive doses of corticosteroids will show either no response at all to the drug or will relapse after weeks to months of treatment.

Cyclosporin A (cyA) has been shown to be effective in steroid refractory attacks of human IBD. The cellular infiltrate in canine chronic idiopathic enteropathies mainly consists of lymphocytes and plasma cells in the lamina propria. The anti-inflammatory effect of cyA in IBD is thought to be due to its action on T-cells that infiltrate the mucosa. CyA binds intracellularly to calmodulin, which reduces the release of calcium from the endoplasmic reticulum, thereby inhibiting further down-stream signalling and, finally, inhibiting the expression of IL-2. Since IL-2 is necessary for the survival of T cells for longer than 24-48 hours, it is hypothesized that cyA decreases the number of infiltrating T-cells in the mucosa of the dogs, thereby reducing the amount of pro-inflammatory cytokines and, finally, the clinical signs of the disease. We performed a pilot study to evaluate the pharmacokinetics and clinical efficacy of cyA in dogs with severe steroid-refractory clinical IBD. A total of 14 dogs were included into the clinical efficacy study, 5 of them showing signs of severe PLE. All of these dogs had been treated with 2mg/kg per day of prednisolone p.o. for a period ranging from a minimum of 6 weeks with only minimal clinical effect before being tapered off. After the first endoscopic examination, all dogs received treatment with cyA 5mg/kg p.o. once daily for a total of 10 weeks and clinical activity scores were assessed every second week after starting treatment during the entire study period. Four out of 5 dogs with PLE responded very well to cyclosporine treatment and could even be weaned off completely after 10 weeks of treatment. Cyclosporine could therefore be life-saving in such patients and should be considered as an early treatment option.

Side effects attributed to cyA during the study transiently occurred over the first two weeks of treatment. Reported side effects were vomiting and partial anorexia in 4/14 dogs, gingival ulceration in one dog and alopecia followed by hypertrichosis in one dog.

If vomiting occurs 1-2 hours each time after pilling with cyA, there is a possibility that the serum peak levels are too high in that individual dog. Serum peak levels should then be measured within 1-2 hours after pilling. If levels above 750ng/ml occur, it is advisable to reduce the dose of cyclosporine to 2.5mg/kg po for the first 2 weeks of treatment.

THROMBOEMBOLISM AS A COMPLICATION IN PLE
Thromboembolism has been most frequently described in SCWT with familial PLE and/or PLN, but anecdotal evidence suggests it also happens in other breeds affected with PLE. We recently performed a prospective study in 15 dogs with PLE at the Royal Veterinary College in London, where we investigated the coagulation status of dogs with severe PLE. Thromboelastography (TEG) was used to measure all aspects of clotting at the time of diagnosis. All dogs were found to be severely hypercoagulable as measured by TEG. In addition, in 9 out of 15 cases, it was possible to repeat a TEG measurement 10-14 days after starting immunosuppressive treatment. All 9 dogs remained hypercoagulable even though their clinical activity of disease and albumin serum concentrations had significantly improved. Antithrombin III measurements were not correlated with the albumin levels, which suggests that pathogenetic factors other than loss of Antithrombin III may play a role in the hypercoagulability of dogs with PLE. It is important to realize the potential for thromboembolic complications in these cases and care should be taken with the use of steroids which could increase this risk even further.

References