PROTEIN-LOSING ENTEROPATHY: THE BEGINNING OF THE END?

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Objectives

- To describe a systematic diagnostic approach to confirm the intestinal protein loss and identify the cause of the problem
- To review the main causes of protein-losing enteropathy (PLE) in dogs
- To provide updated therapeutic options and discuss the prognosis of various forms of PLE

Outline

- Causes of PLE
- Current understanding of pathogenesis
- Clinical features, diagnostic approach
- Treatment considerations
**Diagnostic approach of dogs with CE**

- A simple low cost diagnostic approach can be adopted initially in cases with CE of mild to moderate severity

**EXCEPTIONS:**
- If the disease is severe or
- If protein loss in the intestine is suspected

**Approach to hypoalbuminemia**

- **Hypoalbuminemia**
  - Loss
  - 3rd spacing
  - Lack of production
    - Renal
    - GI
    - Hepatic

**Enteropathies associated with protein loss**

- Severe intestinal parasitism
- GI hemorrhage
- Parvovirus
- IBD
- Intestinal lymphangiectasia
- Alimentary lymphoma
- Intestinal crypt disease
- Systemic fungal diseases
- Chronic intussusception
Heparan hypothesis
Lencer, NEJM 2008

- Heparin sulfate proteins (syndecans, glypicans) play an important role in maintaining integrity of intestinal epithelial layer.
- Mice lacking syndecan-1 cannot maintain a normal epithelial barrier. Exacerbated by TNF-α and IFN-γ, and increase in portal venous pressure.
- Corrected by administration of heparin sulfate analogues.
Clinical features
Presentation may be quite dramatic
- Anorexia, weight loss
- Panhypoproteinemia
- Diarrhea
  (not always present!!!)
- Ascites, hydrothorax, peripheral edema
- Increased risk of thromboses

Intestinal lymphangiectasia
- Etiology & pathogenesis:
  Obstruction of intestinal lacteals
  - Dilation /tear of chyle ducts
  - Emptying of chyle ducts into the intestinal lumen
  Often primary and idiopathic, but secondary dilation may also occur due to IBD or lymphoma
- Breeds:
  Primary: small breed dogs, especially Yorkshire terriers, but also Rottweilers, Lundehunds
  Secondary: any dog with IBD or lymphoma

IZNO - 9 Y.O., F.S. Pug
History
- Diarrhea for 3 weeks (small bowel)
- Lethargy
- Weight loss

Physical exam
- Body weight 12.8 kg
- BCS 2-3/9
- Otherwise NAF
Ariella, 7 y.o. FS Yorkie  
#85717

History:
- 10 days of small bowel diarrhea, otherwise healthy

Physical exam:
- Ascites
- otherwise no abnormal findings

PLE – lab results

- CBC:
  - Variable, lymphopenia may be seen

- Urinalysis:
  - No urinary protein loss

- Chemistry panel:
  - Hypoproteinemia with hypoalbuminemia (often < 15 g/l) and corresponding hypoglobulinemia
  - Hypocalcemia
  - Hypcholesterolemia

Hypovitaminosis D in dogs with IBD and PLE  
(Gow et al., JSAP 2011)

- Lack of Vit. D intake
- Intestinal vit. D loss
- Vit. D possibly involved in abnormal immune response
Hypercoagulability and PLE
(Goodwin et al., JVIM 2011)

- Thromboelastography was performed in 15 dogs with PLE due to severe IBD (14) and lymphoma (1)
- 2 dogs had signs of thromboembolism (1 with acute dyspnea and death, 1 with leg thrombosis)
- 9 dogs were rechecked after 4-24 days of treatment with significantly increased albumin (> 20 g/l) and clinical improvement, however no change in TEG profile
- 10 dogs died within 5 months of diagnosis

Hypercoagulability and IBD in humans – the homocystein hypothesis
(Oussalah et al, Alim Pharm Ther 2012)

- Homocystein metabolism intimately associated with folate and cobalamin
- Increased homocystein levels have been associated with venous thrombosis (in patients with enzymatic deficiency)
- Patients with IBD have higher plasma homocystein levels
- High homocystein levels can be normalized with folate and vit. B12 supplementation

PLE and Cobalamin

- Cobalamin (vitamin B12) may be lost / poorly absorbed in dogs with chronic enteropathies.
- Plays an important role in the intermediary metabolism, and its deficiency may be responsible for a vicious circle of complications
- Supplementing cobalamin after documenting deficiency in these dogs may optimize the recovery process
- Dosage: approximately 400 mcg/10 kg body weight weekly for 6 weeks, then once every 2 weeks for another 6 weeks, then once a month
IZNO - Bloodwork

- Stress leukocytosis, otherwise WNL
- Albumin 14 g/l (26-42)
- Globulin 15 g/l (25-40)
- Cholesterol 80 mg/dl (150-240)
- Total calcium 7.8 mg/dl (9.4-11.4)
- Cobalamin 210 ng/L (251-908)
- Folate 12.8 ug/L (7.7-24.4)

Ultrasonography

- Check for:
  - Wall thickness
  - Wall layering
  - Layer echogenicity
  - Mobility
  - Peri-intestinal echogenicity
  - Presence of free fluid
  - Regional lymphadenopathy
  - Focal, multifocal, diffuse distribution of disease

- Lecoindre (Schw. Arch Thk 2010): striations present in 12/21 cases of lymphangiectasia in diff. breeds. Very specific
- Gaschen L (VRUS 2008): mucosal striations sensitive (75%) and very specific (96%) for PLE
5% human albumin infusion
(Vigano et al., JVECC, 2010)

- Constant rate iv infusion of 5% human albumin @ 2 ml/kg/hr (max. daily volume 20 ml/kg/day)
- Largely innocuous in a series of 418 dogs and 170 cats (no anaphylactic reactions observed)
- Very interesting in cases of PLE with severe hypoalbuminemia in preparation for anesthesia and GI endoscopy.

“Ariella

Izno
**Problem**

Biopsies do not allow to make a diagnosis

Insufficient quality, inadequate collection technique processing or transport

Lesions localized to other area (jejenum/ileum) but not in the duodenum.

Anorexic dogs or excessive pre-anesthetic fasting period

Dilated lacteals can rupture easily at the time of biopsy collection

The dog does not have lymphangiectasia

**Explanation**

No lacteals in biopsy specimen

Lesions localized to other area (jejenum/ileum) but not in the duodenum.

Abdominal ultrasound can be useful to identify affected segments. Consider ileoscopy.

Offer a meal with high fat content on the evening before endoscopy

Use sharp biopsy forceps

Differential diagnoses: IBD, cryptitis, alimentary lymphoma

**Solution**

Consider referring to experienced endoscopist. Contact histopathology lab.

No dilated lacteals seen histologically?
Crypt disease in dogs

- Willard et al., 2000: 6 dogs with PLE and dilated or abscessed crypts w/o addl. Lesions. 4 were treated and 2 responded well to dietary and immune-suppressive treatment.
- Willard et al., 2003: 2 cases with PLE and crypt ectasia. 1 survived with dietary and immune-suppressive treatment.
- Lecoindre et al., 2010: 44% of 34 dogs with PLE had crypt dilation.
- Craven et al., ACVIM 2009: no association with bacteria in Yorkshire Terriers.

Parvovirusis

Courtesy Dr. N. Wakamatsu, LSU
Crypt lesions (Stroda et al, ACVIM 2012)
- 58 dogs with CE
- 53% have duodenal crypt lesions, 38% have crypt abscesses
- Dogs with crypt abscesses generally older, Yorkshire Terriers overrepresented (OR 19.3)
- No association with severity of inflammatory infiltrate
- Dogs with crypt abscesses often have severe hypoalbuminemia
- Association with higher AUS and endoscopy scores
- Shorter survival

Crypt lesion study - summary
- High prevalence of duodenal crypt lesions in dogs with CE
- No association with severity of inflammatory infiltrate
- High numbers of dogs with PLE and severe hypoalbuminemia
- Association with higher AUS and endoscopy scores
- Shorter survival
PLE – treatment

**Emergency treatment:**
- Reestablish appropriate oncotic pressure
  - Synthetic colloids
  - Plasma transfusion
  - Canine or human albumin transfusion

**Drugs:**
- Prednisone (1-2 mg/kg q12-24h)
- Ciclosporin (5 mg/kg q 24h)

PLE – treatment

**Diet – a major issue!**
- Low fat diet in order to decrease flow through lacteals (associated with fat absorption)
- Hydrolyzed diet in order to decrease possible response to dietary proteins and to facilitate assimilation of nutrients

**Other:** (as needed)
- Cobalamin supplementation sc
- Vitamin D supplementation sc
- Aspirin minidoses po

IZNO - Serum albumin

![Graph showing serum albumin levels over time](image)
The bad side of PLE

- Allenspach et al. (JVIM 2006): of 10 dogs with PLE, none responded to immune-suppressive steroid treatment. 7 responded to cyclosporine. 3 did not and were euthanized
- Craven et al. (JSAP 2005) and Allenspach et al. (JVIM 2007): Hypoalbuminemia < 2 g/dL is a negative prognostic factor, (OR 49, CI 95% 4.7-506.6)
Chlorambucil in canine PLE
(Dandrieux et al., JAVMA 2013)

- Retrospective study with 27 dogs with CE and PLE (serum albumin < 18 g/l)
  - 13 received prednisolone + azathioprine
  - 14 received prednisolone + chlorambucil
- Body weight and serum albumin higher at recheck for pred + chlorambucil group
- Survival positively associated with chlorambucil treatment, and presence of lacteal dilation on histology

Chlorambucil in canine PLE
(Dandrieux et al., ECVIM-CA 2011)

- Week 1:
  - Chlorambucil 4-6mg/m² q24h for 7 d
  - Prednisolone 1mg/kg q24h for 7 d
- Week 2 – 3:
  - Chlorambucil 3mg/m² q24h for 14 d
  - Prednisolone 1mg/kg q24h for 7d, then 0.5mg/kg q24h for 7 d

IZNO – follow up

Albumin

0 0.5 1 1.5 2 2.5
0 7 14 28 42 66 80 94 108 122 139 172

0 7 14 28 42 66 80 94 108 122 139 172
**Recent ACVIM abstracts**

- **Simmerson et al. (2009):**
  - 30 Yorkies with PLE.
  - Histo: 24 lymphatic dilation and 10 crypt abcessation. LP inflammation mild-severe
  - Outcome: 12 pred-responsive, 9 refractory and 2 PTE

- **Craven et al. (2009):**
  - 14 Yorkies with PLE.
  - Histo: all have cystic crypts. FISH: no bacterial association
  - Outcome: 7/12 died or euthanized within 3 mo.

- **Owens et al. (2011):**
  - 68 dogs with PLE, 49 dogs with CE and normal albumin.
  - PLE dogs had decreased serum cobalamin, total and ionized Ca.
  - Survival was shorter for PLE (701 d vs. 3500 d), but not proportional to severity of hypoalbuminemia.

**Dogs with crypt disease - survival**

**Conclusions**

- IL, IBD and alimentary lymphoma are the main causes of PLE.
- Except in a subset of IL dogs, PLE generally represents a therapeutic challenge.
- Dogs with PLE are malnourished, and the dietary approach is of central importance.
- Hypocobalaminemia, hypovitaminosis D, and hypercoagulability are possible complications that may require additional treatment.
- In a number of cases, PLE may indeed be the beginning of the end…