Protein-Losing Enteropathy

Stanley I. Rubin, DVM, MS
Diplomate ACVIM
Clinical Professor
Department of Veterinary Clinical Medicine

Disclosures

- **Consulting, AVL Laboratories, St. Louis, MO**

Isabella

- **Signalment**
  - **7 yo, FS Yorkshire Terrier**
- **History**
  - **Chronic diarrhea (4 wks)**
  - **Acute onset (4 days) of neuro signs**
  - **Circling, head tilt**

Isabella

- **Physical examination**
  - **T 101.1, HR 110, RR 20**
  - **3.3 kg, BCS 4/9**
  - **Leaning, falling to left**
  - **CP deficits left fore and left rear**

Isabella

- **Plan**
  - **Nova**
  - **CBC**
  - **Serum biochemistry**
  - **Urine analysis**
  - **Abdominal U/S**
  - **Chest radiographs**

Isabella

- **Nova**
  - **Ca++ 0.93 mmol/L (1.17-1.37)**
  - **Mg++ 0.36 mmol/L (0.47-0.62)**
  - **BUN 9 mg/dl (9-24.5)**
  - **Creatinine 0.4 mg/dl (0.7-1.19)**

Isabella

- **CBC**
  - **Hct 39.7 (35.0-52.0)**
  - **Platelets 398 (200-900)**
  - **WBC 28.5 (6.0-17.0)**
  - **Segs 22.8 (3.0-11.5)**
  - **Bands 1.14 (0.0-0.3)**
  - **Lymphs 1.43 (1.0-4.8)**
  - **Mono 3.14 (0.2-1.40)**

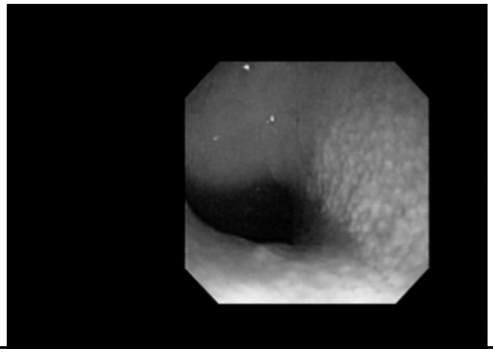
Isabella

	Reference Range	Day 1
Creatinine	0.5-1.5	0.3
BUN	6-30	10
Total protein	5.1-7.0	<3.0
Albumin	2.5-3.8	1.1
Globulin	2.7-4.4	NR
Calcium	7.6-11.4	5.2
Phosphorus	2.7-5.2	2.5
ALP	7-92	15
CALP	0-40	2
ALT	8-65	30
GGT	0-7	1
Total bilirubin	0.1-0.3	0.1
Cholesterol	129-297	74

Isabella

- **Urine analysis**
  - **USG 1.015**
  - **Protein negative**
- **Abdominal U/S**
  - **Thickened SI**
  - **Free fluid**
- **Chest radiographs**
  - **Mild pleural effusion**

Isabella

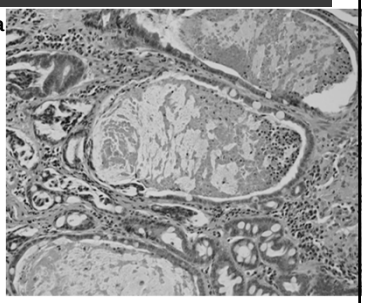


Isabella

Villi and lamina propria are highly cellular

Infiltrated by sheets of plasma cells and lymphocytes with interspersed eosinophils

Crypts are dilated with pools of secretory material and cellular debris



Isabella

- Diagnosis
  - Protein-losing enteropathy
  - Suspected cerebrovascular accident
    - Secondary to hypercoagulability dt PLE

Hypomagnesemia and hypocalcemia associated with protein-losing enteropathy in Yorkshire Terriers: five cases (1992–1998)

Susan E. Kimmel, DVM; Lori S. Waddell, DVM, DACVECC; Kathryn E. Michel, DVM, MS, DACVN

- Yorkshire Terriers were 9X more likely to develop hypomagnesemia & hypocalcemia
- Hypomagnesemia likely dt GI losses
  - Fluid loss with diarrhea
  - Increased GI permeability
  - Decreased absorption

JAVMA, Vol 217, No. 5, September 1, 2000

Hypomagnesemia

- Neuromuscular manifestations
  - Weakness, tremors, tetany
- Metabolic abnormalities
  - Refractory hypokalemia & hypocalcemia

Hypocalcemia

- Associated with panhypoproteinemia
  - Decrease in protein-bound or inactive portion of serum calcium
- Decreased ionized
  - Active fraction of Ca^{++} decreased
- Calcium malabsorption
  - Dt intestinal dz
  - Dt vitamin D deficiency
  - Dt hypomagnesemia – impaired parathyroid function or reduced responsiveness to PTH

Isabella

- Plan
  - Prednisone
  - Chlorambucil
  - Aspirin
  - Calcium carbonate (Tums®)
  - Calcitriol
  - Low fat GI diet

Isabella – Day 30

	Reference Range	Day 1	Day 30
Creatinine	0.5-1.5	0.3	0.5
BUN	6-30	10	16
Total protein	5.1-7.0	<3.0	4.4
Albumin	2.5-3.8	1.1	2.7
Globulin	2.7-4.4	ND	1.7
Calcium	7.6-11.4	5.2	9.3
Phosphorus	2.7-5.2	2.5	5.2
ALP	7-92	15	27
CALP	0-40	2	ND
ALT	8-65	30	76
GGT	0-7	1	4
Total bilirubin	0.1-0.3	0.1	0.1
Cholesterol	129-297	74	105

Smokey

- **Signalment**
  - **9 year old, F, mixed breed dog**
- **History**
  - **Anorexia, lethargy, weight loss**
  - **1 wk duration**
  - **Took to family veterinarian**
    - **Chemistry revealed panhypoproteinemia**

Smokey

- **Physical examination**
  - **Vital signs – NAF**
  - **5.0 kg, BCS 5/9**
  - **Distended abdomen with ascites**

Smokey

- **Plan**
  - **CBC**
  - **Serum biochemistry**
  - **Urine analysis**
  - **Abdominal ultrasound**

Smokey - Results

- **Hct 50.2%**
- **Platelets 339 x 10^3/ul**
- **WBC 15.3 x 10^3/ul**
  - **Segs 13.46 x 10^3/ul**
  - **Bands 0.31 x 10^3/ul**
  - **Lymph 0.61 x 10^3/ul**
  - **Monocytes 0.46 x 10^3/ul**
  - **Eosinophils 0.15 x 10^3/ul**

Smokey - Results

- **Urine analysis**
  - **USG 1.016**
  - **pH 6.5**
  - **Protein negative**
  - **Glucose, ketones, bilirubin – negative**
  - **Microscopic - NAF**

Smokey - Ultrasound

Duodenum wall thickness 4.9mm with mildly hyperechoic mucosa, jejunum wall thickness 3.5mm with mildly hyperechoic mucosa.

The abdomen is filled with a large amount of anechoic free fluid. Mesentery is diffusely hyperechoic.

Smokey

	Reference Range	Day 1
Creatinine	0.5-1.5	0.4
BUN	6-30	15
Total protein	5.1-7.0	<3.0
Albumin	2.5-3.8	1.1
Globulin	2.7-4.4	nd
Calcium	7.6-11.4	5.10
Phosphorus	2.7-5.2	3.1
ALP	7-92	27
CALP	0-40	4
ALT	8-65	28
GGT	0-7	15
Total bilirubin	0.1-0.3	0.2
Cholesterol	129-297	84

Hypoalbuminemia - Ddx

- **Liver disease**
- **Inflammatory disease**
- **Loss**
  - **Protein-losing nephropathy**
  - **Protein-losing enteropathy**

Smokey

- **Interpretation?**

Smokey

- **Plan**
  - **Recommend endoscopy & biopsy**
  - **Prednisone**
  - **Cyclosporine**
  - **Royal Canin Gastrointestinal LF**

Smokey – Recheck Day 50

- **Owner reports doing well**
- **Physical examination unremarkable**
- **Receiving**
  - **Prednisone 5 mg q 24h/Cyclosporine 25 mg q 24 h**
  - **Royal Canine LF diet**

Smokey – Recheck Day 50

	Reference Range	Day 1	Day 50
Creatinine	0.5-1.5	0.4	0.5
BUN	6-30	15	14
Total protein	5.1-7.0	<3.0	4.1
Albumin	2.5-3.8	1.1	2.2
Globulin	2.7-4.4	nd	1.9
Calcium	7.6-11.4	5.10	9.1
Phosphorus	2.7-5.2	3.1	3.5
ALP	7-92	27	474
CALP	0-40	4	373
ALT	8-65	28	135
GGT	0-7	15	4
Total bilirubin	0.1-0.3	0.2	0.1
Cholesterol	129-297	84	165

Smokey – Recheck Day 50

- **Recommended – increase cyclosporine to 25 mg q 12 h**
- **Discussed – changing to chlorambucil**
- **Recheck – 2 – 4 weeks**

Canine PLE - Classification

- **Lymphangiectasia/crypt disease**
- **IBD – lymphoplasmacytic, eosinophilic, granulomatous**
- **Breed-associated**
  - **Eg. Basenjis, soft-coated wheaten terriers, Norwegian lundehunds**
- **Miscellaneous**
  - **Infectious**
    - **Histoplasmosis, parvovirus**
    - **Severe hookworms**
    - **Giardia**
  - **Lymphoma**

PLE – Clinical Features

- **Weight loss**
- **Loss of muscle mass**
- **± Diarrhea**
  - **Persistent small bowel diarrhea**
  - **Chronic, relapsing and intermittent**
- **Vomiting**
- **Inappetance**
- **Other signs – dt severe hypoproteinemia**
  - **Edema of limbs or ventrum**
  - **Ascites, chylothorax, pleural effusion**
  - **Gut wall edema**

PLE – Other Complications

- Malabsorption of fat-soluble vitamins
  - A,D, E & K
- Decreased absorption of divalent cations
  - Ca^{++}, Mg^{++}
  - Clinical hypocalcemia, tetany and seizures
- Other protein loss from GI
  - Antithrombin III
  - Increased risk of thromboembolism

PLE – Laboratory Features

- Panhypoproteinemia
- Hypocholesterolemia
- Hypocalcemia
- Hypomagnesemia
- Lymphopenia

PLE – Diagnosis

- Confirm hypoproteinemia
- Rule out other causes of hypoproteinemia
  - Assessment of liver function
  - Urine analysis/UPC
- Fluid analysis
- Abdominal ultrasound
- Folate/cobalamin measurements
- Coagulation assessment

PLE – Therapy

- If possible, ID and correct any underlying cause
- Basic principles of therapy
  - Nutritional support
  - Reverse edema and ascites by increasing oncotic pressure
  - Reducing inflammation associated with leakage of lymph and crypt lesions
  - Addressing or preventing any complications, eg. Thromboembolism
  - Vitamin deficiency
  - Treat hypocalcemia

PLE – Nutritional Support

- Major aspects to address
  - Replacement of proteins lost
  - Provide energy in diet while avoiding fats
- Diet should be
  - Highly digestible
  - 20-25% protein of dm basis, ± novel
  - Less than 10-15% fat, lower in significantly affected dogs
  - Less than 5% insoluble fiber

PLE – Nutritional Support

- Royal Canin Digestive Low Fat
- Hill's Prescription Diets i/d
- Hill's Prescription Diets i/d low fat
- Purina Veterinary Diets EN
- P & G Iams Low Residue
- Royal Canin Hypoallergenic HP
- Hill's Prescription Diet z/d
- Purina Veterinary Diet HA
- Royal Canin Hypoallergenic various
- Hills Prescription Diet d/d duck, salmon

Zoran DL. Protein-losing enteropathies. CVT XV 540-544, 2014

J Vet Intern Med 2014;28:809–817

The Clinical Efficacy of Dietary Fat Restriction in Treatment of Dogs with Intestinal Lymphangiectasia

H. Okanishi, R. Yoshioka, Y. Kagawa, and T. Watari

- **Dietary fat restriction appears to be an effective treatment in intestinal lymphangiectasia in dogs with IL that are unresponsive to prednisolone treatment or have recurrent clinical signs and hypoalbuminemia when dosage of prednisolone is decreased.**

PLE – Nutritional Support

- **Homemade diets**
- **Cobalamin support**
- **Fat-soluble vitamins**
  - **Vitamin D**
  - **Calcium carbonate**

PLE – Oncotic Support

- **Disease so severe that dog requires stabilization before diagnostic evaluation, eg endoscopy**
- **Colloid therapy with Hetastarch®**
- **Plasma not recommended**

PLE – Anti-inflammatory Therapy

- Leakage of lymph and protein into villous spaces surrounding the lacteals causes inflammation and granuloma formation
- Granulomas can cause further lymphatic obstruction and increased lymph leakage
- Aggressive anti-inflammatory therapy
  - Prednisone – Immunosuppressive doses
  - Other drugs
    - Cyclosporine
    - Azathioprine
    - Mycophenolate
    - Chlorambucil

Comparison of a chlorambucil-prednisolone combination with an azathioprine-prednisolone combination for treatment of chronic enteropathy with concurrent protein-losing enteropathy in dogs: 27 cases (2007–2010)

SMALL ANIMAL/EXOTIC/AVIAN

Julien R. S. Dandrieux, Dr med vet, DACVIM; Peter-John M. Noble, BVM&S, PhD; Timothy J. Scase, BVM&S, PhD, DACVP; Peter J. Cripps, BVSc, PhD; Alexander J. German, BVSc, PhD

- 13 Dogs treated with azathioprine-prednisolone
- 14 Dog treated with chlorambucil-prednisolone
- Serum [albumin] was greater in dogs given chlorambucil
- Weight gain was greater in dogs given chlorambucil
- Greater treatment success/duration in dogs given chlorambucil
- Few adverse effects
- Study had a few limitations

PLE – Complications

- Hypercoagulable dt antithrombin deficiency and prone to thromboembolic dz
  - Aspirin 10 mg/kg q24h
  - Clopidogrel 2 – 4 mg/kg q24 h

Questions?

- **References available on request**