Phenobarbital-Responsive Sialadenosis Associated With an Esophageal Foreign Body in a Dog

A 4-year-old Yorkshire terrier was presented for an esophageal foreign body. After removal of the foreign body, clinical signs of gagging, regurgitation, and vomiting continued unabated for >6 weeks. The dog had enlarged submandibular salivary glands that were histologically normal. Treatment with phenobarbital resulted in a rapid and dramatic resolution of clinical signs. After 3 months, the dog was weaned of phenobarbital and was free of any signs of disease 6 months later. **J Am Anim Hosp Assoc 2010;46:115-120.**

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Introduction

Sialadenosis is a bilateral, uniform, painless, noninflammatory, nonneoplastic enlargement of the salivary glands. In humans, it is often the result of physiological hypertrophy in response to chronic stimulation (as seen in bulimic patients), or it can be secondary to autonomic neuropathies (e.g., alcoholism and type 2 diabetes mellitus). Rarely, no underlying disease can be found.[1]

Sialadenosis is rare in dogs. In a retrospective series of dogs and cats with salivary gland disorders, none of the 160 dogs was diagnosed with sialadenosis.[2] Only a few individual cases and two case series of sialadenosis in dogs have been reported.[3-12] One of these case series describes 19 cases with salivary gland necrosis, 14 of which did not respond to phenobarbital and were associated with an underlying esophageal disease.[3] The other case series describes 13 dogs with phenobarbital-responsive sialadenosis and no apparent underlying disease.[4] Based on these studies, esophageal disease in dogs may be associated with sialadenosis that is nonresponsive to phenobarbital. Most cases of phenobarbital-responsive sialadenosis have not been associated with esophageal disease. In one case report, however, esophageal spasm and narrowing were suspected to be manifestations of phenobarbital-responsive sialadenosis.[5]

Here we report for the first time a case of phenobarbital-responsive sialadenosis associated with an esophageal foreign body. Although no cause and effect were established, the foreign body was not likely the cause of the sialadenosis, but it became lodged as a result of esophageal dysfunction.

Case Report

A 4-year-old, intact female Yorkshire terrier weighing 3.0 kg was referred to the University of Illinois Veterinary Teaching Hospital (VTH) for a 6-week history of intermittent vomiting, regurgitation, gagging, and mild weight loss. The dog was first presented to the referring veterinarian after choking on a piece of gristle. Thoracic radiographs at that time showed an esophageal foreign body that was subsequently pushed into the stomach with an endoscope. A gastric foreign body and mild ulceration in both the esophagus and the stomach were seen on endoscopy. Initial treatment included sucralfate and dexamethasone.

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The dog was presented again to the referring veterinarian 9 days later for frequent, persistent vomiting (sometimes multiple times per hour), regurgitation, and gagging. No abnormalities were seen on thoracic and abdominal radiographs, and a second endoscopy revealed no abnormalities in the esophagus and stomach. Treatment with amoxicillin-clavulanic acid,[a] metoclopramide, and trimeprazine-prednisolone[b] failed, and the dog was presented again 2 weeks later to the referring veterinarian with the same clinical signs. A third endoscopy at that time revealed no abnormalities in the esophagus and stomach. Histopathological examination of endoscopic biopsies from the stomach also did not reveal any abnormality.

Treatment with sucralfate and cimetidine did not result in improvement, and the dog was presented 6 days later with the additional clinical signs of dehydration, inappetence, and lethargy. Blood tests revealed hemoconcentration, leukocytosis, moderate azotemia, high alkaline phosphatase (ALP) activity, and a high lipase concentration. Pancreatitis was suspected based on a high serum canine pancreas-specific lipase[c] (cPLI) (444 µg/L, reference interval 0 to 200 µg/L). An exploratory laparotomy was performed, and no gross abnormalities were found. After 1 day of treatment with intravenous (IV) fluids (i.e., lactated Ringer's solution [LRS]) and antiemetics, the dog was again bright and alert with a normal appetite.

Five days after surgery, complete blood count (CBC) and serum biochemical profile results were normal, but the dog was still vomiting, regurgitating, and gagging with the same frequency as in the initial visit for these problems. A fourth endoscopy at that time failed to reveal any abnormalities in the upper gastrointestinal tract. A percutaneous endoscopic gastrostomy (PEG) tube was placed, and the owner was instructed to feed Hill's a/d[d] and administer ondansetron, cisapride, and omeprazole through the feeding tube. A week later (6 weeks after the esophageal foreign body episode) and still with no change in frequency of the vomiting, regurgitation, and retching), the dog was referred to the VTH.

On presentation to the VTH, the dog was quiet, alert, and responsive. Vital signs were normal (temperature 39.0˚C [101.7˚F], heart rate 128 beats per minute, panting). Mucous membranes were pink and moist with a capillary refill time of <2.5 seconds. The dog was estimated to be <5% dehydrated. Body condition score was 3/9. The mandibular salivary glands were mildly enlarged. Fundic examination revealed normal retinas. No other abnormalities were seen on the physical examination.

Initial diagnostic tests revealed a packed cell volume of 36%, total solids of 9.0 g/dL, and a systolic blood pressure of 210 mm Hg (Doppler[e]). The CBC revealed mild normocytic normochromic anemia; a high total white blood cell count with mature neutrophilia and monocytosis; and normal lymphocyte, eosinophil, and platelet counts [Table 1].

Table 1

Complete Blood Count Results

Test*	Day 1	Day 4	Reference Range	Units
WBCs	45.1	39.2	6.00-17.00	k/µL
Neutrophils	36.5	33.3	3.00-11.50	k/µL
Bands	0	0	0.00-0.30	k/µL
Lymphocytes	2.3	3.53	1.00-4.80	k/µL
Monocytes	6.3	2.35	0.20-1.40	k/µL
Eosinophils	0	0	0.10-1.00	k/µL
RBCs	5.02	4.78	5.50-8.50	M/µL
Hemoglobin	11.4	11.0	12.0-18.0	g/dL
Hematocrit	33.6	32.8	35.0-52.0	%
MCV	67.1	68.6	60.0-77.0	fL
MCH	22.8	22.9	20.0-25.0	pg
MCHC	34.0	33.4	32.0-36.0	g/dL
Platelets	476	504	200-900	k/µL

* WBCs=white blood cells; RBCs=red blood cells; MCV=mean corpuscular volume; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration

Abnormal serum biochemical results included a moderate elevation in blood urea nitrogen concentration; a mild increase in the serum concentration of creatinine; borderline hyponatremia and hypochloridemia; severe hypokalemia; and increased ALP activity [Table 2]. The elevation in ALP was primarily due to an increase in the corticosteroid-induced ALP (cALP) fraction, consistent with chronic stress. The concentrations of albumin and globulins were normal. The bicarbonate concentration was slightly decreased, and the anion gap was slightly increased. Venous blood gases were measured a few hours after presentation and showed moderate acidemia (pH 7.225) and a metabolic acidosis with respiratory compensation (HCO_3^- 12.4 mmol/L, PCO_2 29.9 mm Hg). Urine (obtained by cystocentesis) had a specific gravity of 1.018, and proteinuria, bacteriuria, and coarse granular casts were present [Table 3]. A sample of the urine was submitted for bacterial culture. Prothrombin time (PT) and partial thromboplastin time (PTT) were within normal limits (PT 7 seconds, reference interval 6.0 to 10.0 seconds; PTT 11 seconds, reference interval 6 to 16 seconds). Serum D-dimers were mildly increased at 250 to 500 ng/mL (reference interval <250 ng/mL).

Thoracic radiographs were unremarkable except for mild left atrial enlargement. No abnormalities were seen in the esophagus. Abdominal radiographs and ultrasound were also unremarkable except for the presence of radioopaque material that was consistent with barium within the PEG tube, stomach, and small and large intestines.

Differential diagnoses that were considered at this point included various structural and functional motility disorders of the pharynx and esophagus, with secondary complications related to the esophageal foreign body, exploratory

Table 2

Serum Biochemical Results

Test*	Day 1	Day 4	Reference Range	Units
Creatinine	1.8	0.3	0.5-1.6	mg/dL
BUN	90.8	8.6	7-31	mg/dL
Total protein	6.9	6.2	5.4-8.0	g/dL
Albumin	4.1	3.8	2.1-4.3	g/dL
Globulin	2.8	2.4	2.7-4.4	g/dL
Glucose	228	148	65-127	mg/dL
ALP	417	545	12-110	U/L
cALP	280	385	0-40	U/L
ALT	46	84	17-87	U/L
GGT	8	14	1-11	U/L
Total bilirubin	0.2	0.2	0.08-0.5	mg/dL
Cholesterol	309	240	109-315	mg/dL
Triglycerides	56	60	25-145	mg/dL
Calcium	9.2	9.2	7.9-11.5	mg/dL
Phosphorus	3.7	2.9	2.4-6.5	mg/dL
Sodium	141	152	141-161	mmol/L
Potassium	1.7	4.2	3.9-5.7	mmol/L
Chloride	100	110	104-125	mmol/L
Bicarbonate	16.5	25	17-29	mmol/L
Anion Gap	26.2	21.2	8-25	mmol/L

* BUN=blood urea nitrogen; ALP=alkaline phosphatase; cALP=corticosteroid-induced ALP; ALT=alanine aminotransferase; GGT=gamma-glutamyltransferase

Table 3

Urinalysis (Cystocentesis) Results on Presentation to University of Illinois Veterinary Teaching Hospital

Specific gravity	1.018
pH	5.0
Protein	100
Glucose	Negative
Ketones	Negative
Bilirubin	2+
Blood	Moderate
WBCs*	2-4
RBCs†	Rare
Epithelial cells	1-2
Bacteria	Many
Casts	Few coarse granular

* WBCs=white blood cells
† RBCs=red blood cells

laparotomy, and PEG tube placement. Pyelonephritis was suspected based on the acute azotemia with inappropriate urine concentration, the presence of bacteria and casts in the urine, and the inflammatory leukon. Pancreatitis could not be ruled out. The hypertension was suspected to be secondary to pain or stress, but other causes (including endocrine or kidney diseases) were also considered.

The dog was hospitalized, and IV fluids were administered (LRS supplemented with potassium chloride [KCl] at 80 mEq/L). The dog also received buprenorphine (0.01 mg/kg IV *q* 6 hours), sucralfate (50 mg/kg, dissolved in water, via gastric tube *q* 8 hours), famotidine (1 mg/kg IV *q* 24 hours), metoclopramide (0.03 mg/kg IV *q* 6 hours), and ampicillin (22 mg/kg IV *q* 8 hours). On day 2, maropitant[f] (1 mg/kg subcutaneously *q* 24 hours) was added after no change was seen in the frequency of the vomiting. Serum potassium concentrations were monitored frequently, and they gradually normalized. By day 3, the KCl supplementation was decreased to 20 mEq/L of IV fluid. The dog's systolic blood pressure remained elevated throughout this time (ranging from 180 to 230 mm Hg), and enalapril was begun (0.42 mg/kg via gastric tube *q* 12 hours). Although the dog was now bright and alert, she was still gagging almost constantly and had frequent episodes of vomiting and regurgitation (sometimes multiple times per hour).

On day 4, the azotemia and electrolyte imbalances resolved, and the inflammatory leukon was resolving [Tables 1, 2]. Fine-needle aspirates of the enlarged submandibular salivary glands were taken, and cytology revealed no abnormalities. The serum cortisol concentration was measured to rule out atypical hypoadrenocorticism; the concentration was within normal range (cortisol 72.0 nmol/L, reference interval 58 to 144 nmol/L).[6] The next day, the dog was anesthetized, and wedge biopsies were obtained from the submandibular salivary glands. Endoscopy of the esophagus, stomach, and duodenum revealed no abnormalities. Biopsies of the intestinal tract were obtained, and the sucralfate was discontinued. The urine culture grew *Enterococci* (>30,000 colony-forming units per mL) that were sensitive only to trimethoprim-sulfadiazine (TMS). Ampicillin was discontinued, and TMS was initiated (30 mg/kg via gastric tube *q* 12 hours). Systolic blood pressure decreased to 150 mm Hg, and buprenorphine was discontinued.

On day 6, an esophagram was performed using fluoroscopy. Oropharyngeal and esophageal motility was normal after administration of liquid barium, although repeated contractions could be seen in the pharynx after swallowing, and the dog was gagging. A large bolus of barium-impregnated soft food and kibble accumulated in the pharynx before pharyngeal contraction was initiated. This was followed by normal esophageal transit, although repeated contractions of the pharynx could again be seen after swallowing of the food.

Sialadenosis was diagnosed on the basis of pharyngeal dysfunction and salivary gland enlargement, normal cytology and histopathology of the salivary gland, and the lack of any structural or histopathological abnormalities in the oropharynx, esophagus, stomach, or duodenum. An acetylcholine-receptor antibody titer was submitted to rule out myasthenia gravis as the cause of pharyngeal dysfunction, and it was normal (0.12 nmol/L, reference interval 0 to 0.6 nmol/L). Treatment with phenobarbital was initiated (1 mg/kg via gastric tube *q* 12 hours), and TMS and enalapril were continued. Famotidine, maropitant, and metoclopramide were discontinued.

Clinical improvement was seen within a few hours of phenobarbital administration. The dog's attitude improved, and the frequency of the gagging, regurgitation, and vomiting decreased. By the next day (day 7), the dog was eating and drinking normally. No more vomiting or gagging episodes were observed, and the regurgitation episodes became infrequent. The dog was sent home on phenobarbital, TMS, and enalapril, and she remained free of any clinical signs of disease for the next 3 months. After 1 month, TMS and enalapril were discontinued. After 3 months, the dog was slowly weaned off phenobarbital. Six months after being released from the hospital, the dog was in good body condition, was healthy, and was not receiving any medications.

Discussion

Phenobarbital-responsive sialadenosis is a rare, idiopathic disease in dogs. It is characterized by a sudden onset of

retching and gulping with bilateral enlargement of salivary glands, most commonly the submandibular glands.[3-5,7-12] Ptyalism, gagging, lip-smacking, weight loss, decreased appetite, and vomiting are also reported. The combination of these clinical signs with enlargement of salivary glands has been reported with an underlying esophageal disease as well as in one case series of 19 dogs with salivary gland necrosis. In these 19 cases, however, only treatment of the underlying disease brought about resolution of clinical signs, while treatment with phenobarbital did not.[3] In truly idiopathic cases, when no disease process can be identified in the salivary glands, pharynx, or esophagus, treatment with phenobarbital typically results in significant improvement within 24 to 36 hours, complete resolution of clinical signs within 1 week, and a decrease in size of the salivary glands within 2 to 4 weeks.[4,5,7] In some cases, salivary gland necrosis has been reported.[3,9-12] This was most likely a secondary process, because surgical removal of the glands did not result in improvement, while treatment with phenobarbital did.[3,9-11]

Idiopathic sialadenosis has been proposed to be a form of limbic epilepsy based on electroencephalographic tracings consistent with seizure activity and the response to antiepileptic drugs (i.e., phenobarbital,[3-5,7-11] phenytoin,[12] potassium bromide[7]). Limbic epilepsy does not seem likely considering that five out of six reported cases that were tested had normal electrodiagnostic results.[3,7,9,12] Also, the response to antiepileptic drugs is seen before a steady-state therapeutic concentration can be reached, with lower doses and shorter durations of treatment than those typically required for idiopathic epilepsy.[4,5,7] However, limbic epilepsy may simply require smaller dosages of antiepileptic drugs for treatment compared to dosages required for idiopathic epilepsy treatment.

In the case reported here, the dog was first presented for an esophageal foreign body. Mild ulceration was seen endoscopically after the foreign body was pushed into the stomach. It is unclear whether the lodging of the foreign body was the initiating cause of or was secondary to esophageal dysfunction. In one case series of 19 dogs, salivary gland necrosis secondary to esophageal disease was associated with chronic and severe conditions (e.g., esophageal granuloma or neoplasia from *Spirocerca lupi*) and was not responsive to phenobarbital administration.[3] In the case reported here, follow-up endoscopic examinations revealed a normal esophagus and stomach while the dog had severe clinical signs. Therefore, it seems unlikely that the foreign body was the initiating cause in this case.

Esophageal dysfunction could have caused the lodging of the foreign body. One case of phenobarbital-responsive sialadenosis with intermittent narrowing of the esophagus due to muscular spasm has been reported.[5] In the case reported here, no structural or functional abnormalities were detected in the esophagus, but intermittent muscular spasm and narrowing could not be ruled out. Most likely the lodging of the foreign body was caused by an esophageal disorder, and this was an unusual manifestation of the phenobarbital-responsive sialadenosis syndrome rather than the cause of it.

This case was challenging because of the rarity of the syndrome and because the dog had multiple concurrent problems. Pyelonephritis, pancreatitis, and local peritonitis (in the PEG tube or surgical sites) could all account for the vomiting, inappetence, inflammatory leukon, and increased cALP. As mentioned previously, pyelonephritis was suspected based on the findings of a urinary tract infection and acute renal insufficiency. A diagnosis of pancreatitis prior to presentation to the VTH was supported by an increased cPLI. No evidence of pancreatitis was seen during exploratory laparotomy at that time, but pancreatic biopsies were not obtained. Importantly, a urinalysis was not performed. Pyelonephritis may have been the cause of the inflammatory leukon and a contributor to the vomiting, but it is unlikely to have caused the increased cPLI. Glucocorticoid administration has been suspected (although not proven) to be a cause of increased cPLI.[13]

The cause of the severe hypokalemia was not determined. Decreased intake, increased loss (gastrointestinal and renal), and transcellular shifts were considered. None of the medications administered prior to the development of hypokalemia were likely responsible. The severe hypokalemia was probably not directly related to the phenobarbital-responsive sialadenosis, because it resolved with symptomatic treatment before treatment with phenobarbital was initiated, and this has not previously been reported in similar cases.[4,5,7,8] Potassium concentration in canine saliva is three to seven times higher than the serum potassium concentration.[14] Ptyalism was not observed in this dog, and increased production and subsequent swallowing of saliva would not have resulted in loss of potassium from the body. Severe loss of potassium secondary to inappropriate use of the PEG tube may have been responsible for the hypokalemia. Concurrent metabolic alkalosis would be expected, but this may have been masked by metabolic acidosis secondary to acute renal failure, hypoperfusion, and lactic acidosis. In this particular case, it seemed that the degree of acute renal failure, hypoperfusion, and lactic acidosis, when considered separately, was not severe enough to explain masking alkalosis; but in combination, they may have been sufficient.

Conclusion

To the best of our knowledge, this is the first report of an esophageal foreign body associated with phenobarbital-responsive sialadenosis. Intermittent esophageal dysfunction may be a component of this disease and may have caused the lodging of the foreign body. The combination of enlarged salivary glands with signs of pharyngeal or esophageal disease should raise the suspicion of phenobarbital-responsive sialadenosis. The diagnosis, however, can only be made after a diagnostic workup to rule out other diseases. The response to treatment in this disorder is rapid, and the prognosis is good. Standard guidelines for treatment with antiseizure medication may not necessarily apply in this disorder. Response to therapy may be seen before steady state is reached, and it may not be necessary to

achieve the level of plasma concentration necessary for control of epileptic seizures.

Footnotes

[a] Clavamox; GlaxoSmithKline, Research Triangle Park, NC 27709
[b] Temaril-P; Pfizer Animal Health, Exton, PA 19341
[c] Spec cPL Test; IDEXX Laboratories, Inc., Westbrook, ME 04092
[d] Hill's A/D; Hill's Pet Nutrition, Inc., Topeka, KS 66603
[e] Parks Medical Electronics, Inc., Aloha, OR 97007
[f] Cerenia; Pfizer Animal Health, Exton, PA 19341

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