SIALADENOSIS IN A DOG

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ABSTRACT

An 18 months old miniature Pincher cross was presented with a history of acute vomiting, gulping, inappetence, weight loss, sensitivity to palpation of the laryngeal area and neck spasms. Blood work and imaging studies revealed gastro-intestinal inflammation and ulceration but no underlying cause. The dog did not improve with aggressive medical treatment. Additionally, it developed bilateral enlargement of the submandibular salivary glands, which appeared normal in cytological exam. Treatment with oral phenobarbital brought rapid resolution of clinical signs. This is the first reported case of phenobarbital-responsive sialadenosis in a dog in Israel.

Keywords: sialadenosis, necrotizing sialometaplasia, dog, submandibular, salivary glands, phenobarbital.

INTRODUCTION

Sialadenosis is a rare disease in dogs and cats with only a handful of case reports published thus far (1,2,3,4,5,6,7,8,9). In some reports the disease is termed necrotizing sialometaplasia. It is characterized by bilateral, smooth, uniform enlargement of salivary glands without evidence of inflammation or neoplasia. Clinical signs include retching or gulping, vomiting, ptyalism, lip smacking, snorting, sensitivity to gentle external palpation of the throat, mild depression, inappetence and weight loss. The submandibular salivary glands are most commonly affected but the parotid or zygomatic glands may be affected as well. In the latter case, clinical signs may include exophthalmus.

Reviewing the cases reported in the veterinary literature raises the possibility that two different forms of the disease exist; or rather they may represent two distinct entities. One form is associated with an underlying esophageal disease and cytology or histopathology of the affected salivary gland reveals necrosis and metaplasia. The other form is idiopathic with no abnormalities except for possible mild hypertrophy diagnosed on cytology or histopathology, and unlike the former variety, responds rapidly to treatment with phenobarbital.

The pathogenesis of sialadenosis and the rationale why it responds to anticonvulsant therapy are unknown. In people, sialadenosis is recognized in about 6% of diseases of the salivary glands. It may develop (1,3) as a result of physiologic hypertrophy in response to chronic stimulation (as in patients with compulsive eating disorders like bulimia), autoimmune neuropathies (e.g. diabetes mellitus, alcoholism), or certain drugs (one report of an excessive use of an epinephrine-based bronchodilator inhaler(10). In some cases the cause remains unknown. It has been proposed that in humans a primary abnormality of the sympathetic innervation to the salivary gland maybe the cause.

This is the first published case report of sialadenosis in a dog in Israel. In this case no underlying disease was identified and the dog had complete resolution of clinical signs after treatment with phenobarbital, which indicates that it may belong to the second form of sialadenosis.

CLINICAL REPORT

An 18 month old, 6.4 kg, intact male Miniature Pincher-cross was presented with a 3 days history of vomiting, gagging and reduced appetite. The dog had no significant medical problems in the past and it was up to date on vaccines and parasites control, including tri-monthly prophylactic doramectin injections against spirocercosis (*Spirocerca lupi*). The dog's diet was solely made of home made chicken without bones. The owners reported that the dog was otherwise in a good mood, normal energy level and had normal bowel movements. They also reported that he occasionally picks up scraps or garbage outside, but they were unaware of any such recent incident.

On physical examination the dog showed sensitivity to palpation of the laryngeal area and responded with gagging and spasms of the neck after only mild touch. On the other hand, it demonstrated no dysphagia when offered canned food and had no observed problems in prehension or swallowing. Rectal temperature was slightly elevated at 39.60°C but it was also very nervous and excited and ambient temperature was high. No other abnormalities were detected in the rest of the physical examination. The dog was sedated with a combination of medetomidine (Domitor, Pfizer, NY, NY, USA, 0.01mg/kg IM) and butorphanol (Torbugesic, Fort Dodge Animal Health, Fort Dodge, Iowa, USA, 0.1mg/kg IM) to allow for a full laryngeal examination, however no abnormalities were identified. A complete blood count (CBC) and chemistry profile showed mild hemoconcentration and mild hyperglobulinemia (Table 1). Radiographs of the chest and abdomen revealed only mild subjective thickening of the gastric wall and small intestines. A presumptive diagnosis of gastro-intestinal inflammation with secondary laryngitis or esophagitis was made. The dog was treated at the clinic with lactated ringer's solution (40ml/kg SQ), cimetidine (Tagamet, GSK, Brentford, UK - 5mg/kg SQ) and amoxicillin-clavulanic acid (Synulox, Pfizer, Sandwich, UK - 9mg/kg SQ). It was then sent home to continue treatment with amoxicillin-clavulanic acid (Synulox, Pfizer, Sandwich, UK - 20.5mg/kg PO q12h), famotidine (Gastro 10, Unipharm,

Tel-Aviv, Israel - 0.4mg/kg PO q12h) and a therapeutic diet formulated for gastro-intestinal disease (Royal Canin Intestinal canine dry food, Royal Canin, Aimargues, France).

Table 1: Results of CBC and Chemistry profiles

	Initial presentation	**During hospitalization**	**2 weeks into treatment**	**Reference range**
CBC				
WBC x10^3/µL	11.9	10.8	21.0	6-17
Lymp x10^3/µL	3.5	3.8	9.7‡	1-5
Mid x10^3/µL	0.3	0.4	1.3	0-2
Gran x10^3/µL	8.0	6.5	10	3-12
Lymp%	29.4	35.3	46.1	12-30
Mid%	2.5	4.1	6.3	2-4
Gran%	67.2	60.6	47.6	62-87
RBC x10^6/µL	8.8	8.8	7.3	6-8
Hgb g/dL	18.2	18.2	15.7	12-18
Hct%	55.7	55.1	46.6	37-55
MCV fL	63	63	64	60-77
MCH ρg	20.7	20.7	21.3	20-24
MCHC dL	32.7	33	33.6	31-34g/
RDWc		16.2	16.8	
Plat X10^6/µL	248	237	87*	200-500
Chemistry				
Alb g/dL	3.6	3.1		2-4
ALP U/L	28	37	46	20-150
ALT U/L	76	82	47	10-118
Amyl U/L	409	219		200-1200
TBil mg/dL	0.3	0.4		0-1
BUN mg/dL	17	10	23	7-25
Ca mg/dL	12.4	11.9		9-12
Phos mg/dL	3.2	5		3-7
Creat mg/dL	0.9	0.9	0.8	0-1
Glu mg/dL	135	96	59†	60-110
Na mEq/L	143	143		138-160
K mEq/L	4.2	4.7		4-6
TP g/dL	9.0	7.9	6.8	5-8
Glob g/dL	5.4	4.7		2-5

* Manual platelets count on blood smear is adequate.
† Glucose level is low due to delay in running blood sample.
‡ Lymphocytosis is not confirmed on manual count.

Over the next several days the dog continued to have episodes of neck spasms and vomiting, although according to the owner the frequency and severity of the episodes was somewhat decreased. However, his appetite remained diminished and he seemed less energetic than usual. Repeated physical exam revealed no additional findings. This time the rectal temperature was within the normal range at 38.80°C. The dog received an injection of maropitant (Cerenia, Pfizer, NY, NY, USA - 1.0mg/kg SQ) and the owners were instructed to continue treatment as before with the addition of sucralfate (Ulsanic, Teva, Petah-Tikva, Israel - 82mg/kg PO q8h) and to replace the diet to a different formula (Science Diet i/d canine canned food, Hill's, Topeka, KS, USA). The owners declined an endoscopic examination.

On another follow-up examination 9 days after the initial presentation, the owners reported a mild improvement in appetite. However, the dog continued to have several episodes each day of neck spasms with retching, gulping and vomiting with the addition of ptyalism, lip smacking and reverse sneezing. The owners noted normal bowel movements (albeit decreased) and normal urination. The dog had lost 6% of his body weight (measured at 6.1 kg), had normal rectal temperature (39.20°C), but now had slightly enlarged submandibular salivary glands bilaterally. The dog was hospitalized for observation and treatment with intravenous fluids (LRS), cimetidine (Tagamet, GSK, Brentford, UK - 5mg/kg IV q8h), and metoclopramide (Pramin, Rafa Labs, Jerusalem, Israel - 0.2mg/kg SQ q8h). Sucralfate and amoxicillin-clavulanic acid were continued orally at the previous doses. Later that day the dog was referred to a specialty center for an endoscopic examination, which revealed ulcers and inflammation in the distal esophagus, stomach and duodenum. No underlying cause was identified. The owners decline histopathological examination of biopsies taken from the gastric mucosa and duodenum. Abdominal ultrasound and computed tomography exams were done as well but were unremarkable. Following recovery from sedation for these procedures the dog vomited a large amount of bloody fluid, probably as a result of endoscopy and biopsies.

The dog remained in hospitalization for an additional 9 days (total 21 days since presentation). Differential diagnosis included: esophageal-gastro-intestinal inflammation/infection with ulceration, occult/aberrant spirocercosis, foreign body, atypical hypoadrenocorticism, pancreatitis, inflammatory bowel disease (IDB), neoplasia (e.g. gastrinoma), trauma or injury to the hyoid apparatus and dynamic (intermittent) hiatal hernia. Treatments given during hospitalization included various combinations of antibiotics, anti-emetics and gastrointestinal protectants - sucralfate (Ulsanic, Teva, Petah-Tikva, Israel - 82mg/kg PO q8h), omeprazole (Omepradex, Dexcel, Or Akiva, Israel - 0.9mg/kg PO q24h), cimetidine (Tagamet, GSK, Brentford, UK - 5mg/kg IV q8h), metoclopramide (Pramin, Rafa Labs, Jerusalem, Israel - 0.2mg/kg SQ q8h), ampicillin (Penibrin, Teva, Petah-Tikva, Israel - 20mg/kg IV q8h), trimethoprim/sulfamethoxazole (Resprim, Teva, Petah-Tikva, Israel -13mg/kg PO q12h); intravenous fluids (LRS with added potassium chloride); supportive care; and a onetime injection of dexamethasone sodium phosphate (Dexacort, Teva, Petah-Tikva, Israel - 0.4mg/kg IV) was given to reduce inflammation. However, there was no significant improvement in clinical signs and the dog continued to lose weight, and now weighed 5.5kg. Repeated CBC and chemistry profile was unremarkable (Table 1). Repeated radiographs of the neck area showed mild swelling of the laryngeal soft tissue but the hyoid apparatus appeared normal. The owners declined additional tests such as ACTH stimulation test, serum gastrin level, fluoroscopy and exploratory surgery.

During this time the swelling of the submandibular salivary glands became more prominent and a fine needle aspirate of both glands was obtained. Cytology revealed a normal cellular population for a salivary gland. The absence of pathological changes in cytology together with insufficient response to conventional treatment led to a presumptive diagnosis of sialadenosis. Treatment with phenobarbital (Rekah, Holon, Israel - 2.7mg/kg PO q12h) was initiated and significant improvement was apparent within approximately 24 hours - the dog regained a normal appetite, had no more vomiting and appeared bright and alert. Within 48 hours the neck sensitivity and spasms disappeared and the submandibular salivary glands began to decrease in size. The dog was sent home with instructions to continue phenobarbital at the same dose and to add famotidine (0.4mg/kg PO q12h). All other medications were discontinued.

On a recheck examination 2 weeks after starting treatment with phenobarbital the dog had complete resolution of clinical signs. He regained his original weight, had no more neck spasms, vomiting, inappetence or ptyalism, and the submandibular salivary glands returned to their normal size. To monitor for possible side effects of phenobarbital administration, blood tests were repeated. CBC showed mild lymphocytic leukocytosis (Table 1) and chemistry profile was within normal limits. The dose of phenobarbital was decreased to 1.1mg/kg PO q12h and the owners were instructed to continue medicating for at least 3 months before attempting to taper down the dose.

The dog continued to do well until the owners ran out of the medication after about 2 months. Within 24 hours the dog relapsed and started having neck spasms and decreased appetite. The symptoms disappeared again after resuming phenobarbital at 1.1mg/kg PO q12h. At the time of writing this report the dog continues to receive the medication and remains free of all medical problems.

DISCUSSION

Sialadenosis is a rare disease in veterinary medicine. The paucity of published information makes it difficult to draw conclusions regarding pathogenesis, typical clinical course, treatment, prognosis, etc. Yet, after reviewing the literature it seems that most cases apply to one of either two forms of sialadenosis. Moreover, it is not impossible that these two forms actually represent two completely separate conditions. The first form is associated with an underlying esophageal disease while the second is idiopathic. Cytology or histopathology of salivary glands in the first form reveals necrosis and metaplasia, while in the idiopathic form only mild hypertrophy may be seen. The idiopathic form responds quickly only to phenobarbital administration. It should be noted that not all cases can be categorized definitively to only one of

these forms. More research is needed to understand this disease and to classify its different manifestations appropriately.

This report presents the first published case of a dog in Israel diagnosed with sialadenosis. Strangely, most reported cases thus far came from the United Kingdom. A few cases were reported from the US or Japan. It seems that the case reported here presented with the idiopathic form of the disease. Cytology of the affected salivary gland was normal and it responded quickly to treatment with phenobarbital but not to treatment directed at the esophageal and gastro-intestinal inflammation and ulceration. We believe that the esophageal ulceration found in this dog was secondary to chronic vomiting and acid reflux and did not represent an underlying disorder. The reasons are that the ulcers appeared in the distal esophagus (and also in the stomach and duodenum) but not in the proximal or mid-esophagus, and did not have an identifiable original cause (e.g. foreign body (3), spirocerca lupi or megaesophagus (2)). Moreover, the symptoms did not resolve with aggressive medical treatment. Resolution of clinical signs was achieved only after the addition of phenobarbital to the treatment regime. It is reasonable to assume that the abatement of symptoms represents healing of the ulcers as well. At that time the dog was taken off all anti-ulcer and anti-emetic medications except for oral famotidine, which was continued for only several more days, without relapse of clinical signs. However, to complicate matters further, although discomfort and neck spasms following palpation of the laryngeal area was already noted at the first physical examination, enlargement of the submandibular salivary glands was not noted until around 9 days later.

In people, frequency of vomiting is directly proportional to the degree of salivary glands enlargement (13). If the same is true for dogs, then possibly the gland's hypertrophy is not necessarily the primary pathology but rather a consequence of the disease and its symptoms and may appear only later in the course of disease. This conclusion corresponds to the hypothesis that the pathogenesis involves some abnormality in the sympathetic innervation to the gland (11). It is of interest to note that attempts to remove the affected glands surgically did not resolve clinical signs (1,7). This, too, supports the assumption that it is not the physical effect of the glands' enlargement that is the primary pathology.

Criteria for diagnosis of phenobarbital-responsive sialadenosis, i.e. the idiopathic form, have been proposed (1), and include typical patient history and clinical signs (e.g. vomiting, retching, gulping and sensitivity to palpation), bilateral enlargement of salivary glands, lack of microscopic lesions in cytology or histopathology of the glands, and quick response to phenobarbital administration. All these criteria, together with insufficient response to appropriate medical therapy aimed at gastro-intestinal symptoms, were met in this case. Relapse of symptoms after premature discontinuation of medication and repeated remission after resuming treatment add further support to the diagnosis.

Response to treatment with relatively low doses of phenobarbital (1-2mg/kg q12h) is very rapid, i.e. before serum steady-state is reached. This is in contrast to the normal course of treatment required for anti-seizure use of phenobarbital. Prognosis is good and treatment in most cases can be tapered off after approximately 3 months (12). Therefore, standard guidelines for treatment with phenobarbital may not necessarily apply, such as monitoring serum phenobarbital levels or reaching concentrations necessary to control seizures.

Acknowledgements: Special thanks to Drs. Vered Shuv, Zeev Gans and Uri Segal, from Chavat-Daat veterinary specialist referral center, for their help in this case.

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