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PHENOBARBITAL RESPONSIVE SIALADENOSIS IN ROTTWEILER DOG - CASE REPORT ON CLINICAL FINDINGS AND TREATMENTS

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SUMMARY: Sialadenosis is a bilateral, painless, noninflammatory, uniform, and non-neoplastic condition reported in human and animal medicine. It is a rare condition in animal medicine with only a handful of case reports published to date. According to the different case reviews in the veterinary literature, it can be classified under different forms that are associated with enlargement of a salivary gland with gastrointestinal diseases or without any other abnormality and also phenobarbital responsive or non-responsive form. Phenobarbital-responsive sialadenosis associated with an oesophagal foreign body has also been reported in a dog. This communication presents a case report of phenobarbital responsive sialadenosis of a ten-month old male Rottweiler. This dog was presented with the main complaint of acute vomiting together with inappetence, gulping, and progressive weight loss. Imaging studies revealed gastrointestinal inflammation in the stomach with mild ulceration with unclear aetiology. The dog did not show any improvement to symptomatic treatments. Additionally, it developed bilateral enlargement of the submandibular salivary glands which were hard in consistency and evident at the second presentation at 10 days after the first. Treatment with oral phenobarbital brought rapid resolution of clinical signs. Until recently, the pathogenesis of sialadenosis and why it does respond to phenobarbital have not been well understood. Because of the response to phenobarbital treatments, sialadenosis may represent a form of limbic epilepsy or peripheral autonomic dysfunction.

KEYWORDS: sialadenosis, phenobarbital-responsive, limbic epilepsy, autonomic dysfunction

INTRODUCTION

Salivary gland pathology is not very common in dogs and cats (Boland *et al*., 2013). However, the most common salivary gland diseases are salivary gland neoplasm, oedema, sialadenitis, salivary gland infarction, sialolithiasis, and sialadenosis (Boland *et al*., 2013; Perez-Ecija *et al*., 2012; McGill *et al*., 2009).

Sialadenosis is a bilateral, painless, noninflammatory, uniform, and non-neoplastic condition (Dagan, 2011). Other than in the veterinary field there are reported cases in humans well. In humans, this condition occurs due to secretory and metabolic disturbance of acinar parenchyma because of the stimulation, dysfunction of the autonomic nervous system, certain drugs such as bronchodilator inhalers (Stonehewer *et al*., 2000), and is characterized by uniform hypertrophy of functional parenchyma (Sozmen *et al*., 2000). In human medicine, Sialadenosis has been classified under three major groups namely, neurogenic, dystrophic and metabolic. (McGill *et al*., 2009). But the dysfunction of the innervation for salivary glands may be the unifying factor for all cases.

In animals, this condition is most common in laboratory animals and it may be due to some drug applications, hormonal changes, salivary gland resection, or amputation of incisor teeth (Boydell *et al*., 2000).

According to different case reviews in the veterinary literature regarding sialadenosis (Dagan, 2011; Gilor *et al*., 2010), two different forms of sialadenosis have been described. One of them is associated with enlargement of the salivary gland without any other abnormalities and the other form is associated with gastrointestinal diseases. There is another form of classification namely, the phenobarbital responsive form and non-responsive form (Dagan, 2011; Gilor *et al*., 2010).

Phenobarbital-responsive sialadenosis is a rare condition in dogs. This condition is also known as idiopathic sialadenosis due to unclear aetiology. This rare condition in dogs is characterized by sudden onset of retching and bilateral enlargement of salivary glands. Gulping, vomiting, lip smacking, hyporexia or anorexia, and weight loss are other

prominent clinical signs in phenobarbital-responsive sialadenosis (PRS) patients.

There is no precise diagnostic tool for identifying PRS other than excluding other possible disease conditions with similar clinical signs such as hiatal hernia, foreign body, inflammatory bowel disease (IBD), gastritis, abdominal mass, megaoesophagus and Spirocercosis. Diagnosis of PRS is clinically confirmed by the gradual or rapid response to the phenobarbital treatment (Dagan, 2011; Gilor *et al*., 2010).

This report describes a case of acute onset phenobarbital responsive submandibular sialadenosis in a Rottweiler diagnosed by excluding other possibilities.

CASE REPORT

A ten-month old, 30kg, intact male Rottweiler was presented with the clinical signs of sudden onset of vomiting just after eating solid foods. But at the time of presentation dog's appetite was unremarkable. The dog was fed with a homemade diet of rice and chicken without bones. The dog had no significant medical problems in the past and his vaccination schedule was up to date. However, proper deworming had not been done during the last three months. The owners reported the dog otherwise was active. The rectal temperature was 103^{o} F and he was very nervous and excited at the presentation. No other abnormalities were detected during the physical examination. The dog was treated with normal saline (IV), cotrimoxazole 10mg/kg (IM), omeprazole 1mg/kg (IV) and promethazine 0.5mg/kg (IV). It was then sent home with the advice to continue treatment orally with cotrimoxazole (10mg/kg) BID, esomeprazole (1mg/kg) SID and promethazine (0.5mg/kg) BID for five days.

Irrespective of the treatment given, the animal continued to show the same signs together with additional clinical signs such as hypersalivation, reduced appetite, and mild bilateral submandibular enlargement. Further, the dog seemed to be lethargic. On the second follow-up, the animal was in poor body condition (body condition score 3 out of 9) and its weight was 25kg. During this visit, owners reported that he occasionally picks up scraps or garbage outside and they suspected a recent incident of a rubber glove being swallowed. Thus, the dog was referred to the Veterinary Teaching Hospital, University of Peradeniya to perform an ultrasonographic examination, radiographic examination, biochemistry panel (creatinine, Blood urea nitrogen [BUN], Alanine Aminotransferase [ALT]) and full blood count (FBC) for rule out possible gastroesophageal disease (megaoesophagus), foreign body obstruction, gastric ulceration, renal impairment, liver impairment and Spirocercosis nodules. The FBC and biochemistry reports did not demonstrate any abnormality and the radiographic examination revealed no evidence of foreign bodies, megaoesophagus or spirocerca nodules except dilated gas-filled stomach and small intestines (Figures 1 and 2). Ultrasonography was performed to further evaluate the foreign bodies and gastric ulcers. But no evidence of foreign body was detected except mild gastric ulceration in the stomach (Figure 3). Empirical therapy for gastritis was started with esomeprazole (1mg/kg per PO q 24 hours) and metoclopramide (0.5mg/kg PO q 12 hours) at Veterinary Teaching Hospital for five days.

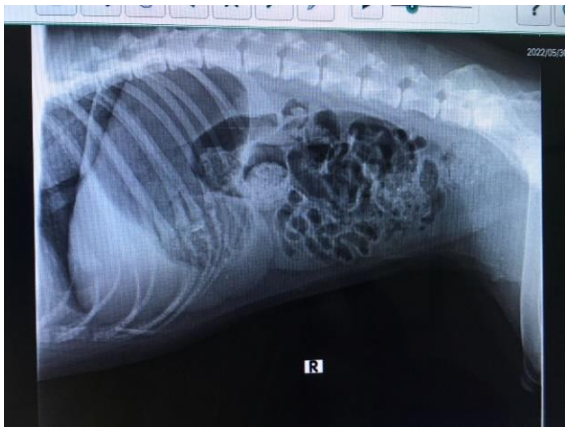

Figure 1: Radiograph of Right lateral abdomen with dilated & gas-filled Stomach and small intestines (no sign of foreign body)

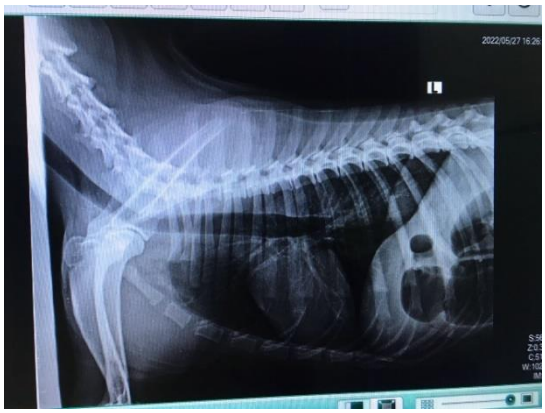

Figure 2: Radiograph of Left lateral abdomen demonstrating normal oesophagus (no features of megaoesophagus)

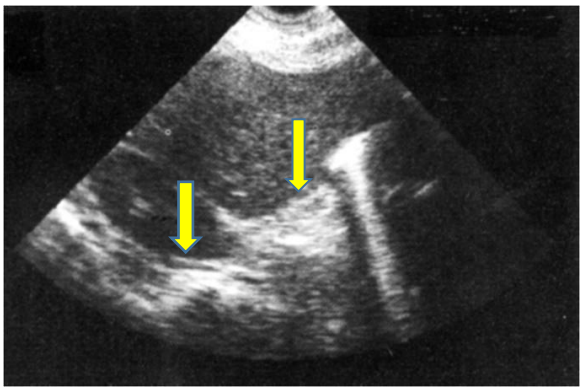

Figure 3: Ultrasonography of stomach ulcers (Indicated by yellow arrows)

Irrespective of the treatment prescribed, the animal continued to show no prognosis with reduced appetite, lethargy, vomiting and enlargement of bilateral submandibular salivary glands. Since radiographic evidence was not sufficient enough to rule out Spirocercosis, one of the differentials, Ivermectin (0.001mg/kg SC) two doses given at ten-day intervals. On the next follow-up in 10 days, the animal's weight was further reduced to 18 kg (body condition score 2 out of 9) (Figure 4) and the animal had no response to ivermectin treatment either. He continued to have hypersalivation and more vomiting episodes when excited.

Figure 4: Animal body condition score 2 out of 9 on the third day of presentation to authors' clinic

Nevertheless, the animal did not show any sign of pain during palpation of submandibular enlargement. It was evident that the bilateral symmetrically enlarged region (length-4cm and width-4cm) had very hard consistency on palpation. The differential diagnosis for the submandibular salivary disease included abscess (fungal and/or bacterial), sialadenitis, hematoma, neoplasia and sialocele (Boland *et al*., 2013; Cannon *et al*., 2011; Hammer *et al*., 2001; McGill *et al*., 2009; Perez-Ecija *et al*., 2012; Wang et al., 2009). Fine needle aspiration was performed under local anaesthesia and a little amount of viscous saliva was aspirated. The microscopic examination of the H&E stained sample confirmed that there were no signs of infection, inflammation, neoplasia or enlargement of acinar cells. A histopathology study should have been done, but the owners refused to perform further tests owing to financial concerns.

A therapeutic trial with phenobarbital (2mg/kg PO q 12 hours) was initiated because of a suspicion of PRS, based on the clinical presentation and exclusion of other conditions related to those clinical signs. Over a phone call made a week later, it was found that the dog had recovered without severe symptoms (e.g., no vomiting, regaining appetite, gaining body weight, and gradually resuming normal activity) except for having hypersalivation after exercise or excitement. Phenobarbital was prescribed for three months, at the rate of 2mg/kg BID and the dog remains healthy up until now.

DISCUSSION

As described previously (Chapman and Malik, 1992; Boydell *et al.*, 2000; Gilor *et al.*, 2010; Dagan, 2011) sialadenosis is a disease that has normal cytological and histopathological features with bilateral enlargement of the salivary gland without evidence of specific aetiologies. The typical clinical signs of the disease include vomiting, nausea, hypersalivation, and enlargement of salivary glands (Gibbon *et al.*, 2004). Because of the unavailability of a precise diagnostic method, the best option is to exclude other possibilities with similar clinical signs to arrive at diagnosis. The rapid response to phenobarbital treatment and relapse of clinical signs after discontinuation of drugs are helpful to come to a definitive diagnosis and management of the idiopathic sialadenosis of dogs (Boydell *et al*., 2000; Dagan, 2011).

When a clinician has to deal with a dog with enlarged salivary glands and chronic vomiting or its variations, a thorough diagnostic approach must be adopted. In the present case, FBC, biochemistry panel (creatinine, BUN, ALT), thoracic radiographs and abdominal ultrasound examination were performed (Table 1). With this diagnostic workup, a clinician can rule out the most important systemic etiologies involved with chronic vomiting (Ettinger et al., 2010). Although it is important to perform endoscopy and histopathology to completely rule out gastro and non-gastrointestinal etiologies, financial constraints caused limitations to proceeding with further investigations.

It was interesting to note that all diagnostic workup of this case, FBC and biochemistry panels were unremarkable (Tables 1 and 2). Radiographs did not reveal evidence of foreign body obstruction, megaesophagus and spirocerca nodules except gas-filled dilated stomach and intestines (Figures 1 and 2). Ultrasonography was performed to further evaluate the foreign bodies and gastric ulcers. But no evidence of foreign body was detected except mild gastric ulceration in the stomach. (Figure 3). Results of the fine needle aspirates of the enlargement of the submandibular region revealed viscous clear fluid compatible with saliva and no evidence of infection, inflammation and neoplastic features. On the basis of ruling out diseases causing chronic vomiting by diagnostic approach, the results of fine needle aspiration of the submandibular salivary gland (normal cytological features) and rapid response to phenobarbital lead to the presumption of the disease condition of the dog as sialadenosis.

Test	Aim of the test	Results
FBC	Identify infection	Unremarkable
BUN	Identify kidney/liver impairment	Within normal range
ALT	Identify liver impairment	Within normal range
Creatinine	Identify kidney impairment	Within normal range
Thoracic radiographs	Identify megaesophagus & Spirocerca nodules	Unremarkable
Abdominal radiographs	Identify foreign body obstruction	Gas-filled dilated intestines
Abdominal ultrasound scanning	Identify foreign body obstruction & gastric ulcers	ulcers in the stomach
Salivary gland cytology	Identify salivary gland infection, inflammation & neoplasia	Unremarkable

Table 1: Diagnostic Tests & Results

	Results	Normal Range
WBC	14.86×10^3/µl	5-21
Lym%	15%	6-36
Mon%	8.3%	1-27
N/Gr%	72%	49-92
Eos%	0.0%	<21
Bas%	0.4%	
RBC	5.99×10^6/ µl	3.4-7.6
MCV	57.2 fl	52-76
Hct	34.3%	25-47
MCH	20.5 pg	18-29
MCHC	35.8 g/dl	34-42
Hgb	12.3 g/dl	9-19
PLT	326×10^3/µl	200-500
MPV	7.6 fl	5-12
PDW	9.9	6-10

Table 2: Full Blood Count Report

It was reported that treatment with phenobarbital typically resulted in significant improvement within the first 72 hours, complete resolution of clinical signs within 1 week, and a decrease in the size of the salivary glands within 2-4 weeks (Gilor *et al*., 2010). In this case, clinical improvement began five days following the initiation of phenobarbital therapy. Phenobarbital was used in our case based on previous reports of phenobarbital-responsive sialadenitis and sialadenosis in dogs (Boydell *et al*., 2000; McGill *et al*., 2009; Schroeder and Berry, 1998). The initial dosage of the phenobarbital, in this case, was 2mg/kg PO q 12 hours. Compared with idiopathic epilepsy, PRS requires low doses and shorter durations of treatment (Gibbon *et al*., 2004).

Until recently, the pathogenesis of sialadenosis and why it responds to phenobarbital have not been well understood. Some researchers using electroencephalographic tracings have identified that seizure activity originates from the limbic system in several dogs with sialadenosis. (Gibbon *et al*., 2004; Stonehewer *et al*., 2000). The limbic system is generally associated with emotion, behaviour, memory, motivation and various autonomic functions (Brandy, 2010). Regulating visceral and somatic motor behaviours is done by this system. The main signs of limbic epilepsy include vomiting and hypersalivation (Brandy, 2010; Mawby *et al*., 1991). Phenobarbital is the drug of choice for this disease and the response of idiopathic sialadenosis to this drug could suggest that it may be a form of epilepsy (Chapman and Malik, 1992; Gilor *et al*., 2010). However, there is no evidence in the literature that phenobarbital directly affects oesophagal motility and saliva production. This drug does inhibit small intestinal motility and might, conceivably, have local rather than central effects on this disorder (Gibbon et al., 2004). The maintenance dose rate for phenobarbital is (1-2mg/kg) and it could be tapered after three months. We may expect a satisfactory prognosis if the animal responds to phenobarbital treatment. However, there are some reports where the response to phenobarbital treatment became partial after three months of treatment. Moreover, it must be

taken into account that some digestive abnormalities, such as hiatus hernia, can appear secondarily to chronic vomiting due to PRS in this case (Parnell, 2008).

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