



## CASE REPORT

### Idiopathic Phenobarbital-Responsive Sialadenosis in a Maltese Dog: Clinical Findings and Outcomes

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#### ARTICLE HISTORY (13-373)

Received: August 16, 2013  
Revised: October 14, 2013  
Accepted: December 5, 2013

#### Key words:

Dog  
Phenobarbital  
Sialadenosis

#### ABSTRACT

An 11-year-old, castrated male Maltese dog was admitted with history of dyspnea and intermittent vomiting. The dog was presented with facial edema, neck spasms and enlarged mandibular and sublingual salivary glands. Initially, the dog was symptomatically treated with prednisolone, theophylline, doxycycline and clindamycin. Facial edema was mildly alleviated but foamy vomiting continued. The dog was diagnosed as sialadenosis based on results of fine needle aspiration, biopsy and histopathology of salivary glands. The dog was initiated with phenobarbital sodium (1.5 mg/kg PO q12h) and the dog's clinical signs were improved within 24 hours following therapy. Sublingual salivary glands were shrunken 3 months after phenobarbital administration. To the author's knowledge, this case was first reported in a Maltese dog and describes diagnosis and treatment of a dog with sialadenosis for long-term period.

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**To Cite This Article:** Nam YS, MH Kang, SG Kim and HM Park, 2014. Idiopathic phenobarbital-responsive sialadenosis in a Maltese dog: clinical findings and outcomes. *Pak Vet J*, 34(3): 410-413.

#### INTRODUCTION

In the previous reports (Chapman and Malik, 1992; Boydell *et al.*, 2000; Gilor *et al.*, 2010; Dagan, 2011), sialadenosis has been shown as a bilateral, smooth, uniform, painless enlargement of the salivary glands in the absence of inflammation and neoplastic changes. In human literature (Stonehewer *et al.*, 2000), sialadenosis may develop as a result of physiological hypertrophy of salivary glands in response to chronic stimulation, dysfunction of the autonomic nervous system, or certain drugs (e.g. epinephrine-based bronchodilator inhaler). However, the cause in some cases remains unknown.

Sialadenosis is relatively a rare disorder in dogs. Its clinical signs include nausea, vomiting, hypersalivation, lip smacking, dysphagia, throat hypersensitivity on palpation, anorexia and weight loss (Dagan, 2011; Gilor *et al.*, 2010; Schroeder and Berry, 1998).

Until recently, according to several case reviews reported in the veterinary literature (Dagan, 2011; Gilor *et al.*, 2010), it may be that sialadenosis has the possibility of presenting two different forms of the disease. Of them, one is idiopathic with no abnormalities except for enlarged salivary gland. The other form is associated with gastro-esophageal diseases. Another form can be classified into phenobarbital responsive type and non-responsive type. The former case responds rapidly to

treatment with antiepileptic drugs (i.e. phenobarbital, phenytoin, potassium bromide) and the latter generally does not respond. The present case report describes diagnosis and treatment using Phenobarbital in a Maltese dog with sialadenosis.

**History and clinical examination:** An 11-year-old, castrated male Maltese dog weighing 4.4kg was presented for a 1-week history of intermittent vomiting and anorexia. Other clinical signs included dyspnea, bloody and foamy vomiting, cyanotic tongue, and protrusion of third eyelid. To rule out gastric or esophageal foreign body, survey radiographs with barium contrast showed no remarkable abnormalities. Initial symptomatic treatment included cefradine, metoclopramide and cimetidine to rule out infectious etiology and to discontinue vomiting. However, there was no response to therapy.

On physical examination, the dog showed facial edema, protrusion of third eyelid, lip smacking, neck spasms, sensitivity to palpation of the laryngeal area, enlarged mandibular salivary glands (3x3cm) and sublingual salivary glands (Fig. 1).

Complete blood count revealed leukocytosis ( $22.32 \times 10^3$  cells/ $\mu$ L; reference range,  $6-17 \times 10^3$  cells/ $\mu$ L) with stress leukogram and thrombocytosis ( $692 \times 10^3$  cells/ $\mu$ L; reference range,  $200-500 \times 10^3$  cells/ $\mu$ L). Serum biochemical profile revealed increased ALT (90 U/L,

reference range, 19-70 U/L), AST (46 U/L, reference range, 15-43 U/L), ALP (233 U/L, reference range, 15-127 U/L), gamma glutamyl transpeptidase (21.6 U/L, reference range, 0-6 U/L) and hypokalemia (3.0 mmol/L; reference range, 3.8-5.0 mmol/L). There was no remarkable finding in thoracic and abdominal radiographs.

Skull radiograph displayed soft tissue-density on submandibular gland region. Results of fine needle aspiration biopsy from mandibular salivary glands showed no evidence of any inflammatory or neoplastic features (Fig. 2). For alleviation of facial edema and dyspnea, the dog was treated with dexamethasone (1 mg/kg IV, Dexamethasone disodium phosphate. Inj@; Huons, Korea) with oxygen therapy.

During hospitalization, several episodes of hypersalivation, nausea and foamy vomiting in this dog were observed. But facial edema was mildly alleviated. The dog was prescribed with prednisolone (1 mg/kg PO q12h, Solondo@; Yuhan, Korea), theophylline (15mg/kg PO q12h, Theolan-B@; Kunwha pharm, Korea), ranitidine (2 mg/kg PO q12h, Ranitidine hydrochloride@; Nelson, Korea) and sucralfate (1 g/kg PO q12h, Ulcerlmin@; Joongwea, Korea). The dog newly showed clinical sign of hind limb muscle weakness and had lost 20% of his body weight (3.5 kg).

**Differential diagnosis:** To rule out diseases that could cause chronic vomiting such as hiatal hernia, foreign body, inflammatory bowel disease (IBD), gastritis and abdominal mass, the endoscopy was performed. The result showed mildly elongated soft palate, foamy saliva in upper gastro-intestinal tract and no evidence of oropharyngeal foreign bodies, gastro-esophageal obstruction, ulceration and laryngeal paralysis (Fig. 3). Fine needle aspiration of both mandibular salivary glands and sublingual salivary glands revealed no evidence of inflammatory or neoplastic features. There were no remarkable findings of gastric wall in histopathology through endoscopic biopsy sample. The dog was initially treated with antiemetics with ondansetron and metoclopramide but showed no improvement. To rule out the possibility of myasthenia gravis, pyridostigmine, the anticholinesterase inhibitor, was prescribed but turned out to have no response. Also with barium contrast, no megaesophagus was shown and the emptying time was normal.

The dog was diagnosed as sialadenosis on the basis of ruling out diseases causing chronic vomiting by diagnostic approach as endoscopy and radiography with barium contrast. By serologic test results, pancreatitis, hypothyroidism and hypoadrenocorticism were excluded. Also, responsiveness of drugs to antiemetics, immune-suppressive dose of prednisolone was unsuccessful. Normal histological structures of salivary glands supported the diagnosis of sialadenosis.

**Treatment:** The dog was treated with Phenobarbital (1.5 mg/kg PO q12h, Hana phenobarbital@; Hana, Korea) and clinical signs such as vomiting and gagging were responsive within 24 hours contrast to previous therapy. The dog was maintained with phenobarbital sodium for 2 months, with gradual reduction in size of sublingual

salivary glands and improvement of clinical signs. Drug administration failure by owners resulted in relapse of clinical signs within 24 hours. When relapsed, the dog had frequent episodes of vomiting and hypersalivation, followed by treatment of dehydration, pre-renal azotemia and hypokalemia. Due to the frequent recurrence of clinical signs, the client decided to euthanize the dog.

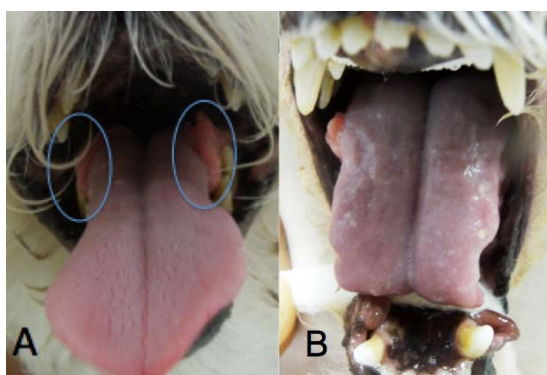
**Postmortem findings:** With the permission of dog's owner, necropsy was performed which showed hypertrophy of bilateral mandibular salivary glands. Histopathological features of enlarged salivary glands showed mild hypertrophy without any other abnormalities (Fig. 4 and 5). These histopathologic examination results supported the diagnosis of idiopathic phenobarbital-responsive sialadenosis.

## DISCUSSION

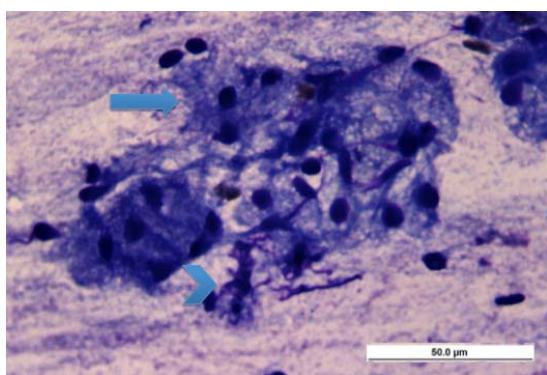
As described earlier (Boydell *et al.*, 2000; Dagan, 2011), sialadenosis is characterized by normal cytology, histopathological features of enlarged salivary glands with no evidence of specific diseases. Definite diagnosis for idiopathic sialadenosis includes typical clinical signs, such as vomiting, nausea, hypersalivation, and enlarged salivary glands, and lack of substantial microscopic lesions and exclusion of other related diseases causing similar clinical signs. Of them, rapid response to phenobarbital treatment within 24 to 36 hours and relapse of clinical signs after discontinuation of drugs are also helpful for the definite diagnosis and management of idiopathic sialadenosis in dogs.

This dog showed consistent clinical signs, such as vomiting, hypersalivation, and enlargement of bilateral salivary glands. Based on exclusion of other etiology resulting in chronic vomiting, no remarkable findings in cytology and rapid responsiveness to phenobarbital lead to the diagnosis of sialadenosis.

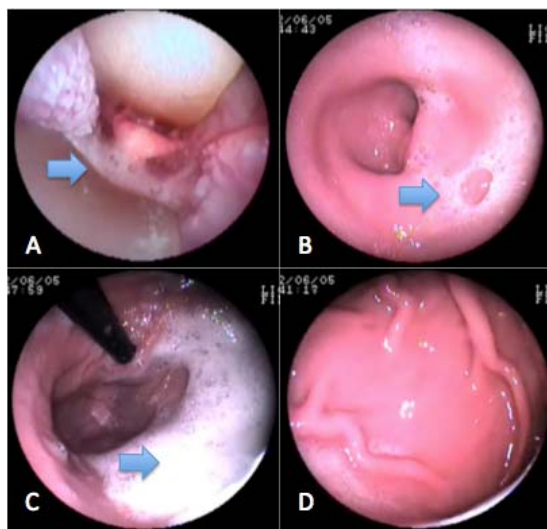
Until recently, the pathogenesis of idiopathic sialadenosis and the reason why it responded to phenobarbital are not well understood. However, the response of idiopathic sialadenosis to anticonvulsants could suggest that it may be a form of epilepsy (Chapman and Malik, 1992; Gilor *et al.*, 2010). Moreover, electroencephalographic tracings performed in several dogs diagnosed this disease are consistent with the seizure activity originating from the limbic system (Gibbon *et al.*, 2004; Stonehewer *et al.*, 2000). In general, the limbic system is associated with emotion, motivation, memory, behavior and various autonomic functions (Brandy, 2010). This system plays an important role in regulating somatic and visceral motor behavior. Signs of limbic epilepsy include vomiting and hypersalivation (Brandy, 2010; Mawby *et al.*, 1991). Also phenobarbital acts via alternative mechanisms that responded to this disease and has local effects on saliva production, gastro-esophageal motility and sedation (Gibbon *et al.*, 2004). Idiopathic sialadenosis responds very rapidly to lower doses (1-2 mg/kg q12h) than control doses of general seizure, and in most cases it can be tapered off after approximately 3 months. Prognosis is good if the dog responds to phenobarbital well and cared properly (Dagan, 2011).



**Fig 1:** Gross appearance of sublingual salivary glands; (A) Before prescribing phenobarbital, sublingual salivary gland (Circle) were enlarged. (B) After prescribing phenobarbital, sublingual salivary glands were shrunken.



**Fig 2:** Cytologic appearance of mandibular salivary glands by fine needle aspiration; Cluster of foamy secretory epithelial cells with small, round nucleoli and abundant cytoplasm distended with clear vacuoles (arrow). Also, diffuse clumps of homogenous pink to violet staining mucin (arrow head) are presented. Diff-Quik stain, Bar = 50 µm.

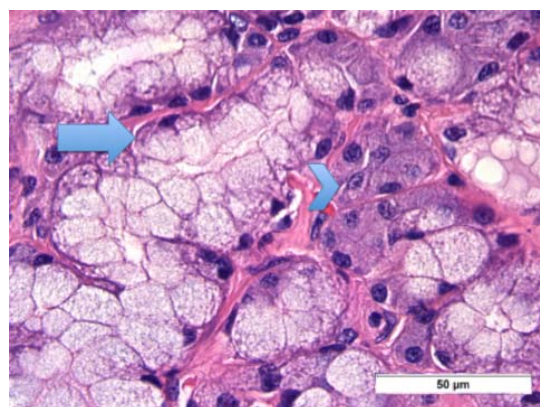


**Fig 3:** Gross appearance of upper gastric-intestinal tract in endoscopy examination; There was no remarkable findings of structural and functional upper gastric-intestinal tract without existing foamy saliva (arrows); (A) Oropharynx. (B) Esophagus. (C) Cardiac region of stomach. (D) Gastric wall.

This case was challenging because of frequent recurrence and no specific clinical signs. When failed to medication, the dog revealed dehydration, secondary pre-



**Fig 4:** Gross appearance of submandibular salivary glands. There was hypertrophy of submandibular salivary glands and ducts.



**Fig 5:** Microscopic appearance of tissue sample from submandibular salivary glands. Salivary gland parenchyma is formed with mucous acinus (arrow) and serous acinus (arrow head). H&E stain, Bar = 50 µm.

renal azotemia and severe hypokalemia due to vomiting and hypersalivation. Hypersalivation could have resulted in hypokalemia in this dog because potassium concentration in canine saliva is three to seven times higher than serum concentration (Gilor *et al.*, 2010). Furthermore, concurrent hind limb muscle weakness might be due to hypokalemia, because potassium is released from muscle cells, causing vasodilation and increased blood flow, and this release of potassium is impaired in state of potassium depletion, resulting in muscle ischemia (Stephen, 2006).

Diagnosis in this case was made, based on ruling out other diseases that could cause chronic vomiting or regurgitation with hypersalivation, absence of pathologic changes in salivary glands and favorable response to the phenobarbital treatment. Management with phenobarbital was effective for improving clinical signs. However, recurrence was frequent and management was complicated.

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