Successful treatment of a dog with phenobarbital-responsive sialadenosis and an oesophageal stricture

Hyung-Kyu Chae¹ | Jeong-Hwa Lee¹ | Min Cheol Choi² | Woo-Jin Song³ | Hwa-Young Youn¹

¹Laboratory of Veterinary Internal Medicine, College of Veterinary Medicine, Seoul National University, Seoul, Republic of Korea
²College of Veterinary Medicine and the Research Institute for Veterinary Science, Seoul National University, Seoul, Republic of Korea
³Department of Veterinary Internal Medicine and Research Institute of Veterinary Medicine, College of Veterinary Medicine, Jeju National University, Jeju, Republic of Korea

Correspondence
Hwa-Young Youn, Laboratory of Veterinary Internal Medicine, College of Veterinary Medicine, Seoul National University, Seoul 08826, Republic of Korea. Email: hyyoun@snu.ac.kr

Woo-Jin Song, Department of Veterinary Internal Medicine and Research Institute of Veterinary Medicine, College of Veterinary Medicine, Jeju National University, Jeju 63243, Republic of Korea. Email: ssong@jejunu.ac.kr

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Abstract
Background: Phenobarbital-responsive sialadenosis (PRS) can cause nausea and vomiting, and is rarely reported in dogs.

Objectives: An 8-year-old neutered, male Pomeranian dog was presented to our teaching hospital with vomiting that began 2 years ago. The clinical signs repeatedly improved and deteriorated despite treatment.

Methods: The only abnormality found on physical examination was salivary gland enlargement, and no specific findings were observed on blood analysis and imaging tests. The results of the fine needle aspirate cytology from the salivary glands revealed possible sialadenosis. Phenobarbital was prescribed, and the patient’s symptoms resolved. However, upon discontinuing drug, the patient’s clinical signs recurred and did not improve even after re-introduction of phenobarbital and the addition of other anticonvulsant drugs. An oesophageal stricture was observed on an oesophagram, and fibrosis was confirmed endoscopically. A balloon dilation was performed to expand the stenosis.

Results: After the first procedure, the patient’s clinical signs initially improved, but relapsed 2 weeks later. A total of three oesophageal dilation procedures were performed using a sequentially larger diameter balloon. After the third procedure, the patient’s clinical signs were managed without recurrence. The cause of recurrent gastrointestinal signs following the initial successful treatment of phenobarbital-responsive sialadenosis was due to oesophageal stricture formation.

Conclusions: This case report demonstrates the successful management of PRS with subsequent oesophageal stricture formation in a dog.

KEYWORDS
Balloon dilation, nausea, oesophageal stricture, phenobarbital-responsive sialadenosis, vomiting

Hyung-Kyu Chae, Jeong-Hwa Lee are contributed equally to this work.

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1 | INTRODUCTION

Phenobarbital-responsive sialadenosis (PRS) is a neurological disorder that causes nausea, vomiting, hypersalivation, dysphagia and inappetence, and is rarely reported in dogs. The pathogenesis of PRS in dogs and cats is unclear, but it has been suggested that PRS may be an unusual form of limbic epilepsy (Stonehewer et al., 2000). Diagnosis of PRS should be based on the distinct response to phenobarbital therapy after excluding other potential extraintestinal and primary gastrointestinal causes (Alcoverro et al., 2014). Initial anticonvulsant therapy reduces clinical signs within 48 hr. However, after tapering the dose of the drugs, a few cases of relapse have been reported (Alcoverro et al., 2014). In such cases, the clinical signs only partially improve, leading to the patient requiring long-term management of symptoms.

Acquired oesophageal stricture is a rare disease in dogs, and usually develops as a consequence of severe oesophagitis (Melendez et al., 1998). It can lead to clinical signs including regurgitation, oesophageal dysphagia, hypersalivation and weight loss (Tams, 2003). Oesophagitis is often a result of mucosal damage due to gastrointestinal reflux, regurgitation or vomiting. Less common causes include chemical or thermal injury, and infection (Willard & Weyrauch, 2000). Although oesophageal complications are relatively infrequent in companion animals, they are more likely to occur after severe irritation of the oesophagus, especially after anaesthesia (Bissett et al., 2009; Wilson & Walshaw, 2004). Oesophageal stricture is also observed in patients with chronic nausea and vomiting (Bissett et al., 2009). Chronic persistence of these symptoms can lead to oesophagitis and fibrous scarring by constant contact with acidic gastric secretions, damaging the oesophageal mucosa. Furthermore, it results in intramural stricture formation when the inflammation extends into the deeper layers (Melendez et al., 1998).

Oesophageal strictures are generally diagnosed by oesophagoscopy and barium oesophagram, or fluoroscopy. However, treatment can be difficult and the goal of therapy is to reduce clinical signs, minimize complications, such as aspiration pneumonia, and prevent stenosis recurrence (Ferguson, 2005). As oesophageal surgery is challenging, nonsurgical approaches, such as oesophageal balloon dilation, are acceptable alternatives. This method applies an even radial force to the stenotic area, which is considered to be safe (Glazer & Walters, 2008). However, patients usually require multiple procedures with an average of two to four dilations per patient, with 1–3-week intervals (Leib et al., 2001).

In the case reported here, oesophageal stricture was confirmed in a canine patient with recurrent gastrointestinal symptoms after drug discontinuation. Both PRS and an oesophageal stricture are rare and difficult to diagnose and treat in dogs. These diseases were successfully managed in this patient through phenobarbital treatment and serial oesophageal dilations.

2 | CASE SUMMARY

An 8-year-old neutered, male Pomeranian dog weighing 5 kg was referred to our teaching hospital to identify the cause of chronic vomiting and nausea, which had been ongoing for the last 2 years. The patient vomited with active abdominal retching from once to as many as 10 times a day. Prior to being referred to our teaching hospital, an endoscopic exam performed by the local veterinarian identified no visual abnormalities affecting the oesophagus or stomach. Histopathology of endoscopic gastric biopsies did not support the presence of significant inflammation and no infectious agents were identified. After undergoing an initial endoscopy, the patient’s clinical symptoms persisted despite being prescribed a low-allergy diet (Hill’s Z/D, Hill’s Pet Nutrition Inc.), a short-term course of an antiemetic drug (maropitant 2 mg/kg PO every 24 hr; Cerenia™, Pfizer) and prednisolone (0.5 mg/kg PO every 12 hr, Yuhan Corporation). One week before being referred to our hospital, he had been hospitalized for severe vomiting and had received fluid therapy.

At our teaching hospital, several tests were conducted to determine the cause of chronic vomiting and nausea. Enlargement of both salivary glands was identified on physical examination, with the size of the right and left salivary glands being 1.5 × 2.0 cm² and 1.0 × 1.0 cm², respectively. Cytology of fine needle aspirate samples taken from the salivary glands identified a predominant population of unremarkable epithelial cells with no inflammatory infiltrate, infectious agents or changes suggestive of malignancy. These cytological findings were consistent with a diagnosis of sialadenosis or salivary gland hyperplasia. The results of other tests, including a complete blood count, serum biochemistry (including cobalamin, folate, electrolytes and C-reactive protein assay), urinalysis, thoracic and abdominal radiography and abdominal ultrasonography, were unremarkable. As the examinations conducted at our teaching hospital did not identify any other cause of vomiting, PRS was suspected and treatment with phenobarbital (2.5 mg/kg PO every 12 hr, Hana Pharm Co., Ltd) was initiated. Within 48 hr of commencing phenobarbital treatment, the patient’s clinical symptoms completely resolved, and no further vomiting or nausea occurred in the following month. The patient’s body weight subsequently increased to 5.9 kg. Based on the good drug response to treatment, PRS was diagnosed as the cause of the patient’s clinical signs.

Although the patient’s salivary glands remained enlarged bilaterally (1.0 × 1.0 cm² each), given the improvement in clinical signs, the dosage of phenobarbital was reduced to 1.0 mg/kg. After 3 weeks, the patient experienced no recurrence of vomiting and, thus, phenobarbital therapy was discontinued. However, only 4 days after the cessation of phenobarbital, the patient’s vomiting resumed. Thus, phenobarbital treatment was resumed at the initial dose (2.5 mg/kg PO every 12 hr), but showed minimal clinical benefit, despite increasing the dose based on serum phenobarbital levels. Combination therapy using several other antiseizure medications was therefore tried in addition to phenobarbital, including potassium bromide (20 mg/kg PO every 24 hr, Sigma-Aldrich), zonisamide (10 mg/kg PO every 24 hr, Dong-A Pharmaceutical Co., Ltd) and gabapentin (10 mg/kg PO every 12 hr, Dong-A Pharmaceutical Co., Ltd). The frequency and intensity of dysphagia, nausea and vomiting were reduced, but remained unacceptable and, in addition to active vomiting, the owner reported passive regurgitation of undigested food as...
a new symptom. The patient intermittently required hospitalization to receive fluid therapy and additional symptomatic treatment, and his body weight decreased to 3.37 kg. The owner reported that the dog's regurgitation worsened after eating dried food relative to that after eating wet food.

Because the patient was no longer responding to the antiepileptic drugs and owing to the development of regurgitation, we suspected that the patient's symptoms may no longer be due to PRS alone. We therefore assessed the patient's serum cortisol levels to rule out atypical hypoadrenocorticism and further conducted oesophageal contrast-enhanced fluoroscopy to look for oesophageal disorders. Although cortisol concentration was within the normal range, contrast-enhanced fluoroscopy revealed a narrowed area in the middle of the oesophagus. Moreover, an oesophagram performed after the patient was fed with barium-rich meals (140% barium sulphate, barium powder and canned food) showed delayed swallowing and poor movement in the previously identified narrowed area (Figure 1a). These results were consistent with an oesophageal stricture, which we suspected developed secondary to oesophagitis resulting from chronic nausea and vomiting.

To relieve the stricture, an endoscopic approach and balloon dilation of the stricture site were performed (CRE™ Fixed Wire Esophageal Balloon Dilatation Catheter, Boston Scientific). During the endoscopic approach, stenosis was observed at two sites in the middle and distal oesophagus, and a biopsy was performed to rule out neoplastic changes at the stenotic areas. It was difficult to advance the endoscopic scope passed through the sites of stenosis (EG27-i10, PENTAX Medical) without balloon expansion. During the first procedure, balloon catheters measuring 6 and 8 mm in diameter were held at the sites of stenosis for 40 s to 1 min, and the patient was recovered from anaesthesia after confirming the smooth entry of the endoscopic equipment as a result of applying pressure to the site of stenosis (Figure 1b). Prednisolone was prescribed at a dose of 1 mg/kg PO every 24 hr for 2 weeks to alleviate inflammation.

One week after the first procedure, the patient showed clinical improvements and his body weight increased to 3.8 kg. Although stenosis was improved and smooth movement of the barium meal was observed on oesophagram after the first procedure (Figure 1c), clinical signs of regurgitation and vomiting recurred. Histopathology of the oesophageal biopsies identified no evidence to support malignancy, so repeat balloon dilation was recommended. The second and third procedures (performed 2 and 9 weeks following the first) were done using larger diameter catheters (second: 8 and 10 mm, third: 15 mm), and prednisolone was prescribed at a dose of 1 mg/kg PO every 24 hr for 2 weeks. Following the second and third balloon-dilating procedures, the patient showed significant improvements. With the exception of a short-lived period of acute onset vomiting as a result of foreign body ingestion, to date, the dog has remained symptom free, and his body weight has increased to 5.3 kg (Figure 2a–c). Moreover, when an endoscopy was performed to remove the gastric content...
foreign bodies, although we observed a mild reduction in the oesophageal lumen size, this no longer caused any obstruction to passage of the endoscope.

3 | DISCUSSION

This report describes a case of nausea and vomiting by PRS. PRS is a form of limbic epilepsy and there are no standard tests for its definitive diagnosis in veterinary medicine (Stonehewer et al., 2000). In this case, PRS was diagnosed based on weight gain and recovery from symptoms after phenobarbital administration. However, unlike the initial phenobarbital response, symptoms did not improve after relapse following drug discontinuation. The patient’s body weight was significantly reduced by approximately 40% despite the addition of several doses of phenobarbital based on blood drug concentrations. Other anticonvulsant drugs have been tried based on previous treatment cases (Gilor et al., 2010; Stonehewer et al., 2000), but clinical signs did not improve.

When the dog was reassessed following recurrence of the clinical signs, the owner complained of additional symptoms consistent with regurgitation, especially after feeding dry food. These new manifestations differed from those seen at the initial diagnosis of PRS. Thus, we considered the possibility of other concurrent factors besides PRS and performed additional testing. An oesophageal stricture was suspected on oesophagram under fluoroscopy after feeding the patient barium meals to determine the cause of the refractory and recurrent dysphagia, and this was confirmed by an endoscopic approach.

Oesophageal strictures usually occur secondary to oesophagitis. Common causes of oesophagitis include persistent vomiting, foreign bodies in the oesophagus and gastro-oesophageal reflux that usually occurs during anaesthesia (Adamama-Moraitou et al., 2002). After an oesophageal stricture is diagnosed, improvements in clinical symptoms can be expected only when the reduction in oesophageal diameter is relieved using physical methods such as balloon dilation, application of an indwelling oesophageal feeding tube or stenting (Adamama-Moraitou et al., 2002; Harai et al., 1995; Lam et al., 2013; Tan et al., 2018; Vlasin et al., 2004).

Although other causes cannot be ruled out, we suspect that oesophageal stenosis likely occurred as a sequela of persistent vomiting. After confirming the presence of an oesophageal stricture, balloon dilation was used to increase the diameter of the stenotic lumen and relieve the impairment to passage of ingesta. Improvement of the clinical signs was noted following the first dilation procedure and improved oesophageal transit was confirmed on a barium contrast study; however, symptoms then recurred. The patient’s clinical signs finally improved following repeat balloon dilation procedures. In these procedures, the balloon diameter was gradually increased to reduce the risk of oesophageal perforation.

In view of the recovery to a normal body weight and improvements in clinical signs after correcting the oesophageal stricture, the cause of the patient’s recurrent symptoms was considered to be related to oesophageal stricture formation. In this case, it is thought that successful treatment could be achieved by improving the narrowing of the oesophagus in a specific area. However, as the pathologic mechanism of PRS is unclear, the possibility that the patient recovered due to other factors cannot be excluded. Abnormal oesophageal motility with an increased risk of oesophageal spasm and oesophageal foreign bodies is reported in dogs with PRS (Gibbon et al., 2004; Gilor et al., 2010). This abnormal oesophageal motility may have contributed to the diminishing efficacy of phenobarbital re-dosing in our case. Despite this possibility, improvement in the patient’s clinical signs, following symptom recurrence, is likely related to the identification and improvement of oesophageal stenosis rather than correction of any oesophageal movement disorder caused by PRS. Further studies on the clear mechanisms and relationship between PRS and oesophageal movement deterioration are needed in patients with refractory PRS.

Dogs with suspected PRS generally respond well to phenobarbital, but some patients may be euthanized due to a suboptimal response to treatment (Boydell et al., 2000). Management of PRS is challenging when the patient’s response to phenobarbital is inadequate. Furthermore, in veterinary medicine, the treatment of PRS has not been clearly defined in patients who experience relapses or have a poor drug response. This case report describes the successful management of a dog with PRS and an oesophageal stricture. In this case, the response to several combinations of phenobarbital and other anticonvulsants was poor. As a result of finding other concomitant problems other than PRS, oesophageal stricture was further diagnosed based on the clinical signs of reflux in dogs, and it was expected to worsen the clinical signs. Following balloon dilation to relieve the oesophageal stricture, the patient’s clinical signs resolved. This case highlights the importance of evaluating the oesophageal structure and function to break the cycle of chronic and recurrent vomiting due to PRS or other causes. Our case can further be used as

FIGURE 2 Changes in the patient’s weight during treatment. Severe weight loss was observed when symptoms recurred after phenobarbital discontinuation. After performing three balloon dilation procedures, the patient’s body weight increased and their clinical symptoms showed improvements (the order of the procedure is indicated in the figure as #1, #2, #3).
a reference for treating patients with a cycle of oesophageal stenosis following chronic vomiting.

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CONFLICT OF INTEREST
The authors report no conflict of interest.

AUTHOR CONTRIBUTION
Hyung-Kyu Chae: Conceptualization; Data curation; Investigation; Project administration; Writing-original draft. Jeong-Hwa Lee: Data curation; Investigation; Writing-review & editing. Min Cheol Choi: Investigation; Supervision; Writing-review & editing. Min Cheol Choi: Conceptualization; Data curation; Investigation; Writing-review & editing. Min Cheol Choi: Conceptualization; Data curation; Investigation; Writing-review & editing. Min Cheol Choi: Conceptualization; Data curation; Investigation; Writing-review & editing. Min Cheol Choi: Conceptualization; Data curation; Investigation; Writing-review & editing.

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ORCID
Hyung-Kyu Chae https://orcid.org/0000-0002-6876-9460
Woo-Jin Song https://orcid.org/0000-0002-9195-551X
Hwa-Young Youn https://orcid.org/0000-0002-0283-1348

REFERENCES
Adamama-Moraitou, K. K., Rallis, T. S., Prassinos, N. N., & Galatos, A. D. (2002). Benign esophageal stricture in the dog and cat: A retrospective study of 20 cases. Canadian Journal of Veterinary Research, 66(1), 55.
Alcoverro, E., Tabar, M. D., Lloret, A., Roura, X., Pastor, J., & Planellas, M. (2014). Phenobarbital-responsive sialadenosis in dogs: Case series. Topics in Companion Animal Medicine, 29(4), 109–112. https://doi.org/10.1053/j.tcam.2015.01.003
Bissett, S. A., Davis, J., Subler, K., & Degernes, L. A. (2009). Risk factors and outcome of bougienage for treatment of benign esophageal strictures in dogs and cats: 28 cases (1995–2004). Journal of the American Veterinary Medical Association, 235(7), 844–850. https://doi.org/10.2460/javma.235.7.844
Boyell, P., Pike, R., Crossley, D., & Whitbread, T. (2000). Sialadenosis in dogs. Journal of the American Veterinary Medical Association, 216(6), 872–874. https://doi.org/10.2460/javma.2000.216.872
Ferguson, D. (2005). Evaluation and management of benign esophageal strictures. Diseases of the Esophagus, 18(6), 359–364. https://doi.org/10.1111/j.1442-2050.2005.00516.x
Gibbon, K. J., Trepanier, L. A., & Delaney, F. A. (2004). Phenobarbital-responsive ptyalism, dysphagia, and apparent esophageal spasm in a German shepherd puppy. Journal of the American Veterinary Medical Association, 40(3), 230–237.
Gilor, C., Gilor, S., & Graves, T. K. (2010). Phenobarbital-responsive sialadenosis associated with an esophageal foreign body in a dog. Journal of the American Veterinary Medical Association, 46(2), 115–120.
Glazer, A., & Walters, P. (2008). Esophagitis and esophageal strictures. Compendium, 30, 281–292.
Harai, B. H., Johnson, S. E., & Sherding, R. G. (1995). Endoscopically guided balloon dilatation of benign esophageal strictures in 6 cats and 7 dogs. Journal of Veterinary Internal Medicine, 9(5), 332–335. https://doi.org/10.1111/j.1939-1676.1995.tb01093.x
Lam, N., Weisse, C., Berent, A., Kaee, J., Murphy, S., Radlinsky, M., Richter, K., Dunn, K., & Gingerich, K. (2013). Esophageal stenting for treatment of refractory benign esophageal strictures in dogs. Journal of Veterinary Internal Medicine, 27(5), 1064–1070. https://doi.org/10.1111/jvim.12132
Leib, M. S., Dinneb, H., Ward, D. L., Reimer, M. E., Towell, T. L., & Monroe, W. E. (2001). Endoscopic balloon dilation of benign esophageal strictures in dogs and cats. Journal of Veterinary Internal Medicine, 15(6), 547–552. https://doi.org/10.1111/j.1939-1676.2001.tb01589.x
Melendez, L. D., Twedt, D. C., Weyrauch, E. A., & Willard, M. D. (1998). Conservative therapy using balloon dilation for intramural, inflammatory esophageal strictures in dogs and cats: A retrospective study of 23 cases (1987–1997). The European Journal of Comparative Gastroenterology, 3(1), 31–36.
Stonehewer, J., Mackin, A. J., Tasker, S., Simpson, J. W., & Mayhew, I. G. (2000). Idiopathic phenobarbital-responsive hypersialosis in the dog: An unusual form of limbic epilepsy? Journal of Small Animal Practice, 41(9), 416–421. https://doi.org/10.1111/j.1748-5827.2000.tb03236.x
Tams, T. R. (2003). Disease of the esophagus. In T. R. Tams (Ed.), Handbook of Small Animal Gastroenterology, 2nd ed. (pp. 151–155). W.B. Saunders.
Tan, D. K., Weisse, C., Berent, A., & Lamb, K. E. (2018). Prospective evaluation of an indwelling esophageal balloon dilation feeding tube for treatment of benign esophageal strictures in dogs and cats. Journal of Veterinary Internal Medicine, 32(2), 693–700. https://doi.org/10.1111/jvim.15071
Vlasin, M., Hursnik, R., Fichtel, T., & Raussevová, L. (2004). Acquired esophageal stricture in the dog: A case report. Veterinarni Medicina, 49(4), 143–147. https://doi.org/10.17221/5688-VETMED
Willard, M. D., & Weyrauch, E. A. (2000). Esophagitis. In J. D. Bonagura (Ed.), Kirk’s current veterinary therapy XIII. Small animal practice (pp. 607–610). Philadelphia, PA: WB Saunders.
Wilson, D. V., & Walshaw, R. (2004). Postanesthetic esophageal dysfunction in 13 dogs. Journal of the American Animal Hospital Association, 40(6), 455–460. https://doi.org/10.5326/0400455

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