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Different outcomes of multiple sialadenitis involving the submandibular and zygomatic salivary glands in a Welsh Corgi dog

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Abstract: A ten-year-old indoor, castrated male Cardigan Welsh Corgi (*Canis familiaris*) presented with the chief complaints of chronic vomiting, retching, hypersalivation, and bilateral submandibular masses for two months. The systemic examinations, including serum chemistry, radiography, ultrasonography, and fluoroscopy, were unremarkable. A fine-needle aspiration revealed bilateral submandibular sialadenitis. Broad-spectrum antibiotics with phenobarbital were prescribed to alleviate the ptyalism. Thereafter, the left submandibular glands were normalised, and the right submandibular glands decreased to half their size. Three weeks later, the animal had an emergency visit because of a sudden left exophthalmos. Computed tomography and magnetic resonance imaging revealed enlarged left zygomatic and right mandibular salivary glands. The affected glands were surgically removed; the histopathologic examination confirmed non-septic sialadenitis, and the patient was finally diagnosed with idiopathic sialadenitis. Vomiting continued after the gland removal and the dog required a gradual increase in the phenobarbital dosage and an additional antiepileptic drug (potassium bromide) to manage the symptoms. The patient died eight months later from an unknown cause. This case report of bilateral submandibular sialadenitis concurrent with unilateral zygomatic sialadenitis in a Welsh Corgi dog suggests that when multiple salivary glands are involved, the response to anti-epileptic drugs and the prognosis is poor compared to that involving a single salivary gland.

Keywords: hypersalivation; limbic epilepsy; phenobarbital

Sialadenitis rarely occurs in dogs and cats and its pathophysiology is not yet understood (Spangler and Culbertson 1991). An affected animal has the primary symptoms of retching, vomiting, and hypersalivation. Depending on the gland affected, exophthalmos and orbital problems can arise. The four salivary glands have different susceptibilities, with zygomatic glands being the least affected (Mason et al. 2001).

Sialadenitis has been proposed to be classified as either oesophageal or idiopathic (Dagan 2011). Oesophageal sialadenitis tends to resolve when the

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underlying oesophageal disease is treated. Idiopathic sialadenitis exhibits no evident underlying cause, but shows a dramatic response to anticonvulsants, such as phenobarbital (Schroeder and Berry 1998). Although studies clarifying phenobarbital's relationship with anti-epileptic medications are lacking, some studies used phenobarbital to treat the idiopathic form, which resolved the clinical signs (Gibbon et al. 2004; Dagan 2011; Alcoverro et al. 2014). This gave rise to the theory of limbic epilepsy (Mawby et al. 1991; Stonehewer et al. 2000; Gilor et al. 2010). The vagus nerve, which is anatomically connected to the limbic system, controls the glandular secretion as parasympathetic nerves are stimulated (Breit et al. 2018), and induces vomiting in association with sialorrhea. Our report describes a dog (*Canis familiaris*) with bilateral mandibular sialadenitis and an unusual case of concurrent zygomatic sialadenitis. This animal was managed with phenobarbital therapy and surgical resection for the acute sialadenitis in multiple salivary glands.

Clinical course

MEDICAL HISTORY AND CLINICAL SIGNS

A ten-year-old indoor, castrated male Cardigan Welsh Corgi weighing 10.2 kg presented with the chief complaints of retching, hypersalivation, fever, and chronic vomiting for 2 months. The referring veterinarian prescribed prednisolone (PDS) (1 mg/kg, p.o. q24 h) and omeprazole (2 mg/kg, p.o. q24 h) for 4 days. The clinical signs did not improve, and the animal was referred to our Veterinary Medicine Teaching Hospital.

At presentation, the dog showed mild depression, distressed respiration, reverse sneezing, and retching, which worsened after neck palpation. The physical examination revealed hyperthermia (39.7 °C), tachycardia, and bilateral mandibular masses. The mucous membranes and capillary refill time were normal.

A thorough diagnostic examination was performed including the following: complete blood count with differential counts; serum biochemistry; radiography of the thorax, abdomen, and skull; ultrasonography of the salivary glands and abdomen; fluoroscopy of the pharynx and larynx; and a fine-needle aspiration (FNA) of the bilateral mandibular glands.

HAEMATOLOGY AND CYTOLOGY

The complete blood counts were unremarkable. The serum chemistry profile revealed elevated creatine kinase (CK, 10.58 μkat/l; reference range: 0.17–3.33 μkat/l), aspartate transaminase (AST, 1.23 μkat/l; reference range: 0–0.8 μkat/l), lactate dehydrogenase (LDH, 10.11 μkat/l; reference range: 0.67–6.67 μkat/l), as well as hypophosphatemia (phosphorus, 0.67 mmol/l; reference range: 0.8–2.19 mmol/l). The blood gas analysis revealed hyperlactatemia (lactate, 0.35 mmol/l; reference range: 0.05–0.28 mmol/l), hypokalaemia (potassium, 2.2 mmol/l; reference range: 3.5–5.8 mmol/l), hypochloraemia (chloride, 107 mmol/l; reference range: 109–122 mmol/l), and metabolic alkalosis (pH 7.49; reference range: 7.31–7.41), which were related to the animal's persistent vomiting and dehydration. The D-dimer level (93.09 nmol/l; reference range: 0–16.43 nmol/l) was also elevated. A snap kit (IDEXX Laboratories, Westbrook, ME, USA) was used to measure the canine pancreas-specific lipase (cPL) with the results being within the normal range. The FNA of the bilateral mandibular glands showed non-degenerate neutrophils and lymphocytes. No infectious agents were identified, which is consistent with non-septic sialadenitis. Additional results of the FNA sample corresponding to the aerobic and anaerobic cultures were negative. The thyroid hormone levels and the acetylcholine receptor antibody test results were within a normal range.

DIAGNOSTIC IMAGING AND TREATMENT

The thorax radiograph showed a mild bronchointerstitial pattern on the overall lung field. The abdominal and skull radiographic findings were normal. The ultrasound of the salivary glands showed mandibular bilateral swelling and heterogenous echogenicity without salivary ductal dilation. The abdominal ultrasound examination revealed elevated echogenicity of the pancreatic parenchyma, suggesting chronic pancreatitis. The overall gastrointestinal layer showed reduced overall peristaltic motility in the small intestine, but was otherwise normal. The fluoroscopy showed no unusual laryngopharyngeal movements.

Medications were administered as follows: 1 mg/kg phenobarbital (p.o. q12 h) for hypersialorrhoea,

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5 ml renal potassium supplements for hypokalaemia (p.o. q12 h), 12.5 mg/kg amoxicillin-clavulanic acid for fever, 0.5 mg/kg famotidine (p.o. q12 h), 5 ml sucralfate (p.o. q12 h) for gastrointestinal inflammation, 10 mg/kg ursodeoxycholic acid (p.o. q12 h), and half a tablet of *S*-adenosylmethionine (Zentonil, Vetoquinol, Magny-Vernois, France) (200 mg, p.o. q12 h) for liver protection. We also administered 10 mg/kg clopidogrel (p.o. q24 h) on the first day and reduced the dose to 4 mg/kg (p.o. q24 h) thereafter to treat the elevated D-dimer levels. In a telephone consultation with the owner, improvement in the enlarged mandibular glands and symptoms was reported, as well as a normal appetite and better overall condition.

On day 7, the animal was bright, alert, and responsive, and its weight had increased from 10.3 kg to 10.9 kg. A blood analysis showed improvements in the hypokalaemia (potassium 2.7 mmol/l; reference range: 3.5–5.8 mmol/l) and normalised phosphorus, CK, AST, LDH, lactate, and D-dimer levels. On day 14, the left mandibular gland was palpated and found to be normal, the right mandibular gland had reduced to 50% of its size from the previous examination, and the potassium level had normalised.

On day 21, however, the dog showed sudden signs of left exophthalmos, chemosis, and protrusion of the third eyelid with respiratory distress (Figure 1). The left mandibular gland was still considered to be normal by palpation and the right mandibular gland had not changed in size. The owner reported no trauma. A funduscopic examination revealed a mass behind the left eyeball.

Visual examination with a laryngoscope confirmed normal movement of the arytenoid cartilages of the larynx, which ruled out laryngoparalysis and laryngopharyngitis. The computed tomography (CT, Canon Aquilion Lightning 160; Canon Medical Systems, Ohtawara, Japan) with a contrast medium (Omnipaque 300, 2.5 ml/kg, i.v.; GE Healthcare, Princeton, NJ, USA) revealed a heterogenous, cystic, enlarged, left zygomatic gland, 22 × 35 × 30 mm [width (W) × length (L) × height (H)] in size (Figure 2). In addition, hypertrophy

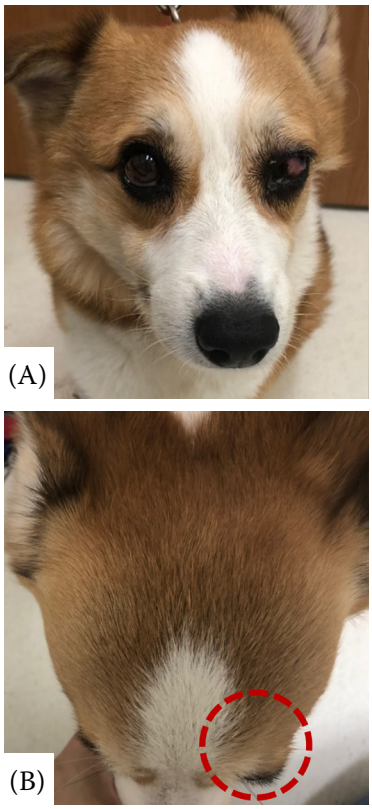

Figure 1. Gross features of the affected dog
(A) The affected dog exhibiting chemosis, protrusion of the third eyelid, and mucous discharge from the left eye. (B) Asymmetry of the orbital line showing the left side exophthalmos (dashed circle)

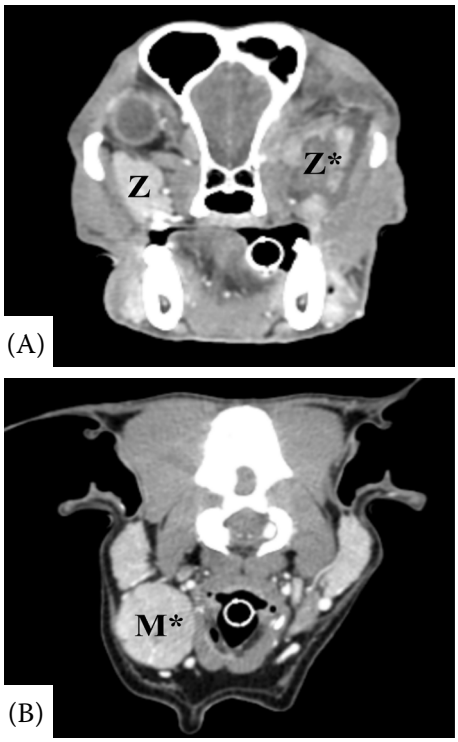

Figure 2. Post-contrast computed tomography (CT) images showing enlarged zygomatic and mandibular gland
(A) Post-contrast CT image at the level of the zygomatic glands. The left zygomatic gland (Z*) is enlarged and heterogeneous compared to the right gland (Z). (B) Post-contrast CT image at the level of the mandibular gland. Note that the contrast-enhanced right mandibular gland (M*) is enlarged

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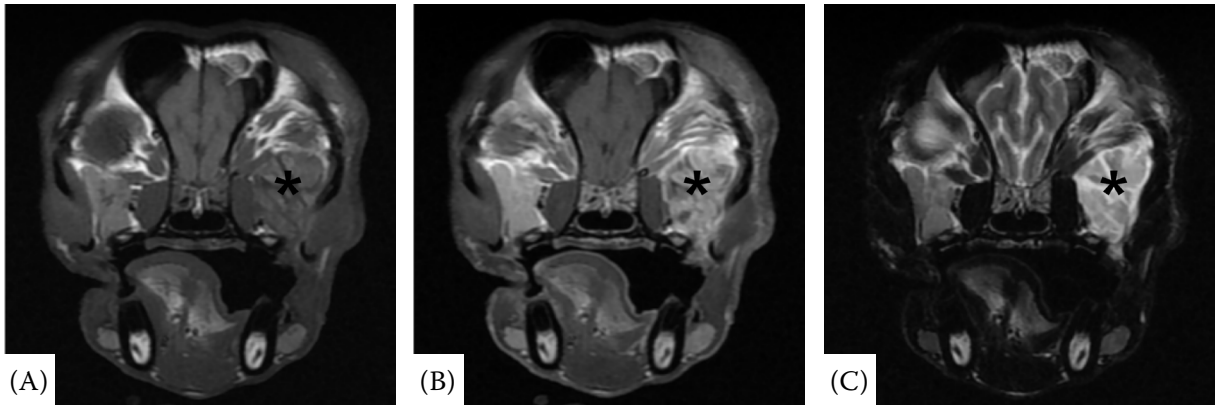

Figure 3. Magnetic resonance images showing an enlarged left zygomatic gland (asterisk)
(A) Transverse T1-weighted image showing the enlarged zygomatic gland causing exophthalmos. (B) Transverse T1-weighted post-contrast image with enhanced contrast. (C) Transverse T2-weighted image of the enlarged zygomatic gland showing hyperintensity of the enlarged gland compared to the unaffected gland. The affected zygomatic gland consists of septa inside the gland

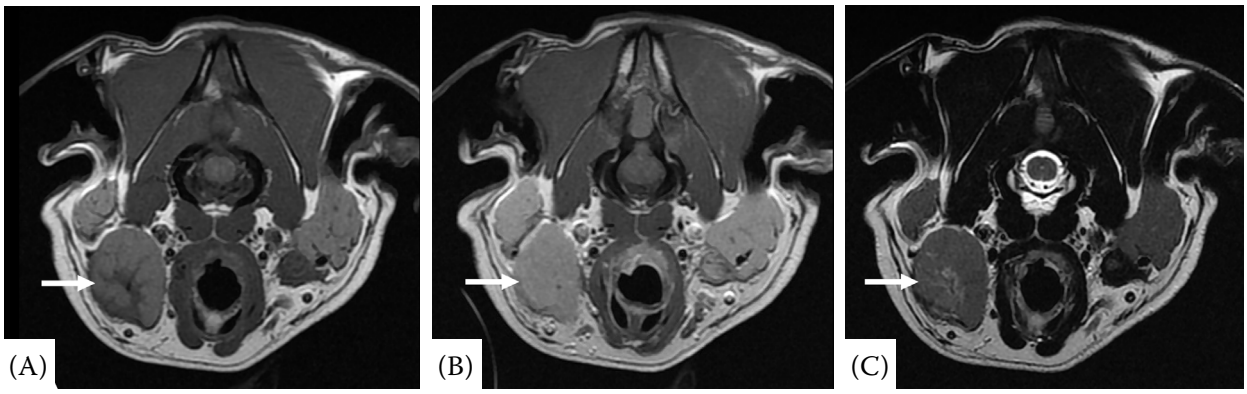

Figure 4. Magnetic resonance images showing an enlarged right mandibular gland (arrow)
(A) Transverse T1-weighted image showing an enlarged salivary gland. (B) Transverse T1-weighted post-contrast image with enhanced contrast. (C) Transverse T2-weighted image of the enlarged salivary gland

of the left mandibular salivary gland [25 (W) × 29 (L) × 31 (H) mm] was visualised. The magnetic resonance imaging (MRI, Signa 1.5 T Excite To 8-channel HD; General Electric, Milwaukee, WI, USA) with a contrast medium (Clariscan, 0.2 ml/kg, i.v.; GE Healthcare, Princeton, NJ, USA) detected a contrast-enhanced left zygomatic gland which consisted of septa inside the gland (Figure 3) and an enlarged right mandibular salivary gland (Figure 4). However, no brain abnormality was confirmed.

Thereafter, both the zygomatic and right mandibular glands were surgically removed. The glands were covered with severely viscous saliva and appeared very friable on visual examination.

Until post-operative day 90 (the final follow-up day), there were no signs of recurrent exophthalmos.

HISTOPATHOLOGY

The histopathologic examination and microscopic evaluation of the excised right mandibular salivary gland showed only small microscopic foci of periductular fibrosis and mild inflammation. This was consistent with mild, chronic pleocellular periductular sialadenitis with reactive fibrosis (Figure 5A). The excised left zygomatic salivary gland included the salivary gland itself and the associated connective tissue. The salivary gland contained extensive neutrophilic inflammation, accompanied by widespread areas of degeneration, necrosis, oedema, haemorrhage, and myxomatous reactive fibroplasia, which was consistent with severe, diffuse, neutrophilic, necrotising sialadenitis with periglandular cellulitis, oedema, and haemorrhage (Figure 5B). The results of the cultures were

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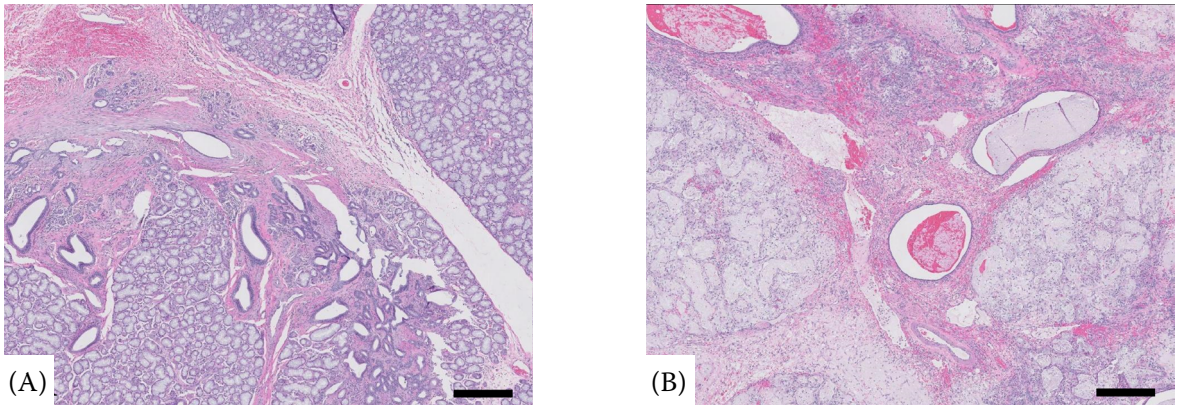

Figure 5. Histological features of the salivary glands in a dog with multiple sialadenitis
(A) The right mandibular salivary gland is largely unremarkable, containing small microscopic foci of periductular fibrosis, and mild inflammation (H&E; scale bar = 200 μm). (B) The left zygomatic salivary gland contains extensive neutrophilic inflammation, accompanied by widespread areas of degeneration, necrosis, oedema, haemorrhage, and myxomatous reactive fibroplasia (H&E; scale bar = 200 μm)

negative. A definite diagnosis of non-septic sialadenitis of the right mandibular and left zygomatic salivary glands was made based on the histopathological examination.

CLINICAL OUTCOME

Hypersalivation recurred after the medication was altered in the surgery department, including phenobarbital cessation. PDS (0.5 mg/kg, p.o. q12 h) was re-administered after post-operative day 12, and carprofen was discontinued. Five days after re-starting PDS, the owner reported worsening sialorrhoea, vomiting, and regurgitation. PDS was stopped and the phenobarbital dosage was gradually increased from 1 mg/kg to 2.5 mg/kg (p.o. q12 h), following which the symptoms resolved. The animal was transferred to the previous local animal hospital for follow-up. However, the gradual recurrence of clinical signs demanded a higher dose of phenobarbital and the addition of another antiepileptic drug (potassium bromide) although the animal had responded robustly to phenobarbital at first. Thereafter, the dosage of phenobarbital was adjusted from 1 mg/kg to 3.5 mg/kg (p.o. q12 h), and potassium bromide was administered at a maintenance dose of 40 mg/kg (p.o. q24 h). Despite continuous medication, there were intermittent recurrences over an eight-month period and the animal finally died at home from an unknown cause. A necropsy was not performed as per the owner's request.

DISCUSSION

In veterinary medicine, sialadenitis is a rare disease with an incidence rate of only 0.28% (Spangler and Culbertson 1991). Sialadenitis can cause gland hypertrophy and a tendency to vomit, retch, regurgitate, gulp, lose appetite, and feel pain on opening the jaws (Spangler and Culbertson 1991; Schroeder and Berry 1998). The mechanism underlying canine sialadenitis is not fully understood, but the presumed causes are infection, trauma, autoimmune disorders (secondary to inflammation surrounding the gland), or chronic vomiting associated with underlying gastrointestinal diseases (Schroeder and Berry 1998; McGill et al. 2009; Martinez et al. 2018). In the present case, the bacterial culture was negative, and the owner of the dog assured us that there was no trauma. Canine Sjögren's syndrome, an autoimmune disease of the gland, causes dry mouth characteristic of lymphocytic infiltration (Nabeta et al. 2019), but the symptomatology was not consistent with our case. The abdominal ultrasound suggested chronic pancreatitis, but the results of the cPL test ruled out this potential diagnosis and clinical signs, such as diarrhoea or abdominal pain, were not detected. Thus, once the gastrointestinal causes had been all excluded, the final diagnosis was of idiopathic sialadenitis.

There are several previous reports of idiopathic sialadenitis (Dagan 2011; Alcoverro et al. 2014; Martinez et al. 2018). Most of the patients were thoroughly examined and the potential underlying

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causes were excluded before being diagnosed with idiopathic sialadenitis. The reports also indicated that most patients responded well to anticonvulsant drugs, namely phenobarbital (Stonehewer et al. 2000; Gilor et al. 2010; Martinez et al. 2018). In addition, early use of phenobarbital may result in the fast resolution of an animal's symptoms and may even possibly prevent or delay seizure events (Martinez et al. 2018). Another study showed that a relatively low dose of phenobarbital is needed, in contrast to the higher doses used to treat epileptic symptoms, and these low doses may have an effect even before the effective concentration level in serum is reached (Dagan 2011). Interestingly, the sialadenitis was confined to a single salivary gland in those patients that responded well to phenobarbital treatment. On the other hand, the case presented here involved multiple salivary glands, including mandibular and zygomatic glands. A few reports of idiopathic sialadenitis with involving multiple salivary glands are available in the literature (McGill et al. 2009; Nam et al. 2014). In those studies, the involved salivary glands were the mandibular and sublingual in one case, and the mandibular and zygomatic in another one. Both cases responded well to the initial phenobarbital treatment, but were later euthanised due to recurrent clinical signs. This is consistent with our patient, as the rate of retching and vomiting reduced dramatically in response to the initial phenobarbital prescription. However, the recurrent clinical symptoms required a gradual increase in the phenobarbital dosage and the use of an additional antiepileptic drug (potassium bromide) to manage the symptoms, where the patient nevertheless died 11 months after starting the treatment. Thus, we suggest that if idiopathic sialadenitis involving multiple salivary glands is present, both the response to antiepileptic drugs and the prognosis may be poor compared to those from patients in which a single salivary gland is involved.

The aetiology of phenobarbital-responsive sialadenitis is unknown, but the quick response to anticonvulsants suggests a certain connection with limbic epilepsy (Gilor et al. 2010). Limbic epilepsy is a type of seizure activity originating from the limbic system. It affects the somatic and visceral motor function, and emesis could, therefore, be among the potential symptoms (Mawby et al. 1991). In a previous report, an electroencephalography (EEG) revealed that some animals with limbic epilepsy showed brain activity similar to those with classical psychomotor seizures (Stonehewer et al. 2000). In the present case, the MRI of the patient revealed no structural abnormalities in the brain. Thus, an EEG is considered the only modality that could partly detect idiopathic sialadenitis. However, at the time of treatment, an EEG was not available at our hospital, therefore, we were unable to further investigate the theory of limbic epilepsy. In addition, the patient showed continuous clinical signs, even after the surgical removal of the affected glands. This supports the idea that clinical signs, such as salivation and retching, may be the result of the disease rather than the cause (Dagan 2011; Kalayanakoul et al. 2019).

Prednisolone was also prescribed during the treatment, but the clinical signs worsened and the drug was dropped from the medication schedule 5 days after being introduced. This is consistent with previous studies in which none of the patients were responsive to PDS (McGill et al. 2009; Alcoverro et al. 2014). Thus, PDS might not be helpful in the treatment of idiopathic sialadenitis.

The case we report here presented an enlarged zygomatic gland causing lagophthalmos, protrusion of the third eyelid, exophthalmos, and conjunctivitis, which is usually observed in retro-ocular diseases (Mason et al. 2001). As there are many other causes for exophthalmos, including haematoma, abscess, neoplasia, and sialocele, zygomatic sialadenitis must be considered as a potential differential diagnosis (Martinez et al. 2018). An FNA should be performed with extreme caution when the nature of the mass is being verified, as the possibility of additional ocular damage in the presence of exophthalmos is high. A CT was preferred in this case and proved to be very effective at identifying the abnormality (Boland et al. 2013).

This report describes a case of bilateral submandibular sialadenitis concurrent with unilateral zygomatic sialadenitis observed in a Welsh Corgi dog. It describes the exclusion of the possible causes for the observed symptoms, while outlining how multiple therapies achieved different outcomes in the individual salivary glands. Veterinarians should be aware that multiple sialadenitis can simultaneously occur in dogs, even when the animal is responsive to therapy for previously occurring sialadenitis, suggesting a poor prognosis compared to patients with the involvement of a single salivary gland.

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Conflict of interest

The authors declare no conflict of interest.

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