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Description	

*Short Communication*

**Sjogren's syndrome and ranula development**

**Running title:** Sjogren's syndrome and ranula development

**Key words:** Sjögren syndrome, ranula, magnetic resonance imaging, adult

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## **Introduction**

Ranulas are rare mucocoeles that tend to recur, and thus far, the debate has been focused on their treatment. Ranulas are caused due to extravasation of saliva from damage to or obstruction of the salivary glands or their ducts (usually the sublingual or surrounding minor salivary glands). Little is known about the cause of such an obstruction or damage. Ranulas have been reported as a complication in children with Sjögren's syndrome (SS) (Means, Aldape, & King, 2017). Additionally, we observed three cases of patients with ranulas who were also diagnosed with SS. Periductal lymphocytic infiltration is a characteristic finding from lip biopsies performed during the early stages of SS (Cawson, Langdon, & Eveson, 2000). The extravasation of saliva from the damaged ducts may be a process of mucus accumulation. An exhaustive literature search was conducted to determine the relationship between ranula and SS in adults.

## **Cases**

The 3 cases had been referred to us for further examination of swelling in the sublingual area. Magnetic resonance imaging (MRI) not only revealed ranulas (Figure 1) but also

findings corresponding to chronic sialadenitis accompanied with an autoimmune disease (SS). The diagnosis of SS was performed alongside treatment of the ranula. Patient characteristics and examination data are shown in Table 1. Finally, patients were diagnosed with SS. Extra-glandular involvement was ruled out by the Division of Internal Medicine and Rheumatology. Cases 1 and 2 were surgically treated. The pathological findings of the salivary glands included ruptures in some ducts with lymphocytic aggregation (Figure 2). The sublingual ranula in case 3 disintegrated and did not recur, and a follow-up examination was requested.

### **Literature Review**

A thorough search of the literature was performed and completed on January 10, 2019 (PROSPERO: registration number, CRD42019121190). Medline (via PubMed), Scopus was the primary database. The database was searched for research pertaining to SS and MRI findings of the submandibular and sublingual gland regions (#1) and reports of ranulas in patients with SS (#2). No studies pertaining to SS and MRI findings of the submandibular and sublingual gland regions were found (#1). However, 3 cases in 2

case reports (Pineiro, et al., 2017; Katayama, Yamazaki, & Nishioka, 1993) of mucocele of the floor of the mouth with concomitant SS were found (#2).

## **Discussion**

All of the cases presented with undiagnosed SS at the initial examination. MRIs were performed to determine the extent of the lesions and complications of neoplastic lesions, and the findings led to the diagnosis of SS according to the Revised Japanese Ministry of Health criteria for the diagnosis of SS: Japan (1999) (Fujibayashi et al., 2004). All 3 cases were diagnosed at the same facility. Furthermore, this finding led to the question of whether there are other such cases, and thus, a systematic review of the literature was performed. However, there were no reports with MRI findings of the submandibular or sublingual glands in patients with SS pertaining to the retention of saliva. However, 2 case reports of 3 cases of ranula similar to our cases were found (Pineiro et al., 2017; Katayama et al., 1993).

A report of 580 ranula cases, (Zhao, Jia, Chen, & Zhang, 2004) suggested that the underlying cause was injury or surgery in approximately 3% of the cases. In many

cases, ranula occurs without an apparent cause. The minor salivary glands were excised in cases 1 and 2. Histopathologically, some ducts showed rupture with aggregation of lymphocytes. The inferred mechanism is that extravasation of saliva from ruptured ducts leads to retention of saliva and thus, formation of a ranula. In their report on 2 adult cases, Katayama et al. (1993) presented a discussion that was similar to ours.

Patients with SS experience reduced salivation and constriction of the ducts.

Additionally, we hypothesized that constriction of ducts close to the opening leads to extravasation of saliva that is more significant at the rupture site. This process is believed to occur in the early stages of SS. In advanced SS, acinar atrophy and loss are observed; acinar cells also exhibit rupture due to lymphocyte aggregation, producing even further decrease in saliva levels (Cawson et al., 2000; Bayetto et al., 2010). In such cases, there is insufficient saliva to form a ranula.

Contrary to our hypothesis, however, there have been very few reports of ranulas with SS. Reasons for this lack of reports might be that it is an early-stage pathology, and sublingual ranulas naturally resolve after disintegration, as seen in case 3. A ranula that has formed in the early stages of SS may not recur from the lack of saliva following

disintegration. Submandibular ranulas are less likely to resolve naturally because they are at a site with less stimulation. We believe that patients with SS may also have small submandibular ranulas that do not grow. However, no report including MRI findings of ranulas in the submandibular or sublingual glands were found. MRI is preferred over computed tomography given the high soft tissue contrast resolution. We hope that more reports of MRI findings of the submandibular gland/sublingual gland area of patients with early SS will become available in the near future.

Therefore, should the 3 cases in this study be considered very rare? There may also be many unreported cases. Many cases of SS are believed to “impact daily living”. Early detection and early treatment are pertinent for better outcomes, including curbing the progressive symptoms (Means et al., 2017; Beckman et al., 2017). It can be still disputable to consider whether ranulas may be an early detectable sign of SS. It could be useful to investigate whether patients presenting with ranula are also affected by SS and, conversely, investigate patients with SS longitudinally to see whether they develop ranula.

## **Conflicts of interest and Source of Funding**

There are no conflicts of interest to declare. No funding was acquired for this study.

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## Figure legends

Fig 1: Magnetic resonance images of the oral cavity of the three cases: The arrows show ranulas evidenced by the hyper signal intensity of the T2-weighted images (a, b: case 1, c, d: case 2, e, f: case 3).

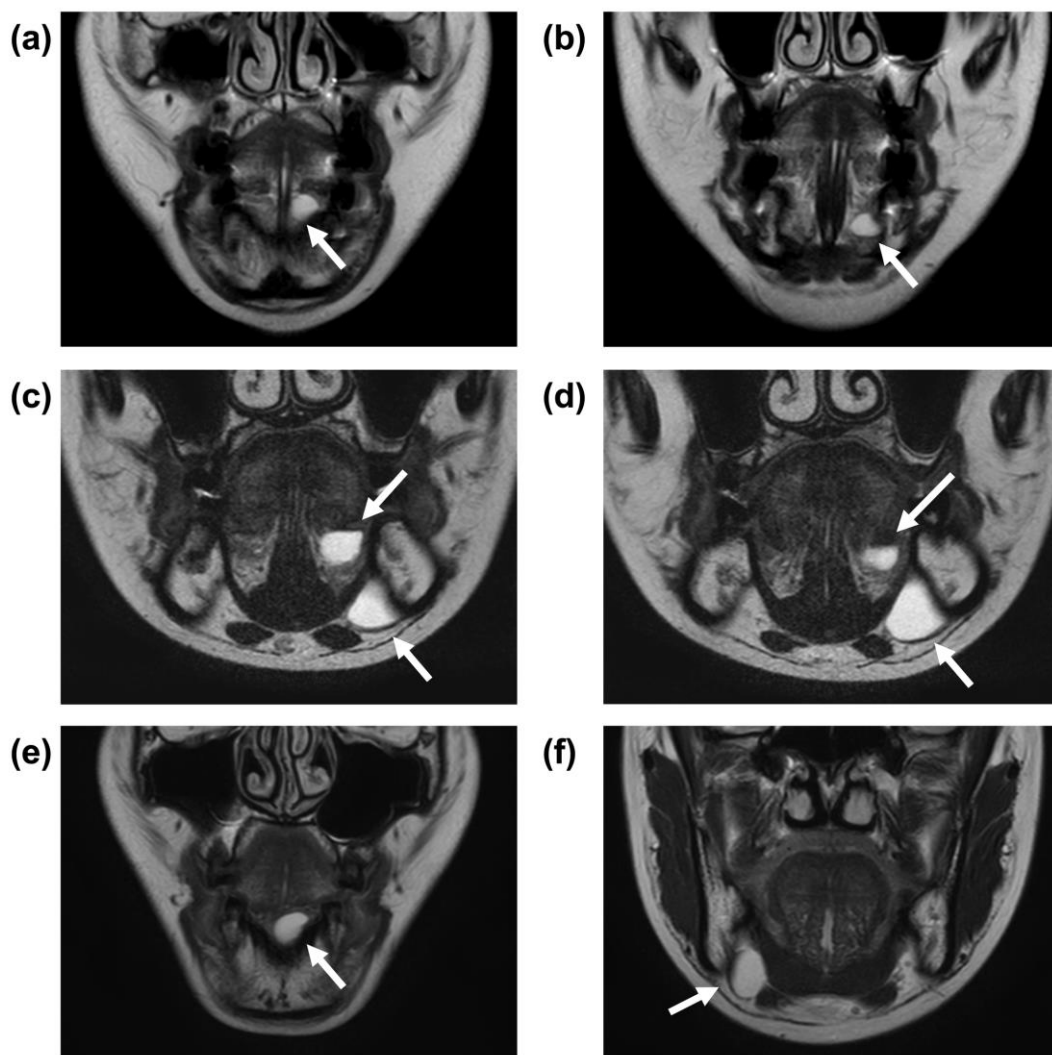
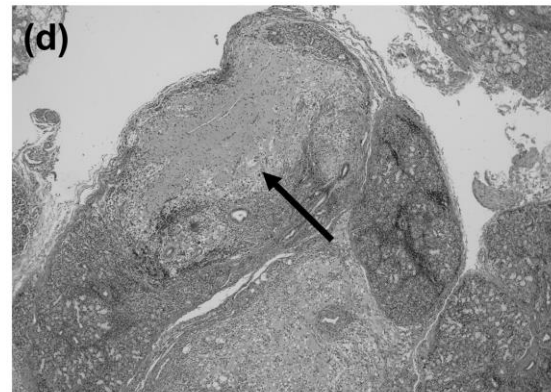
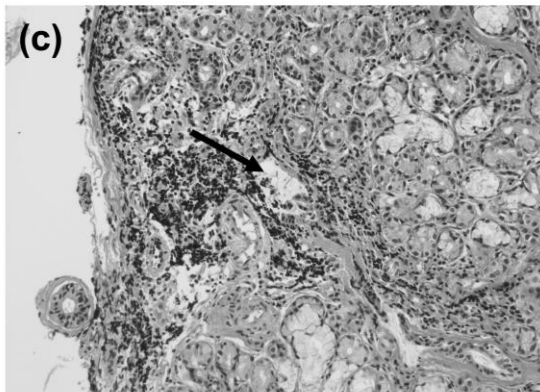
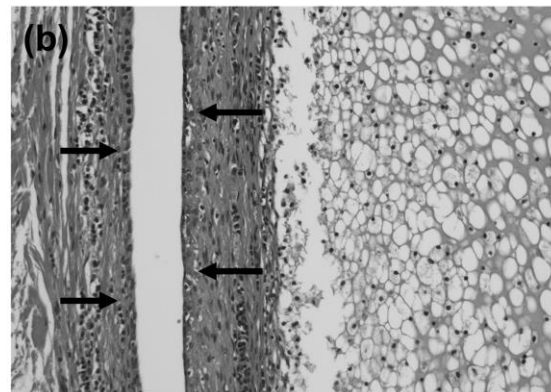
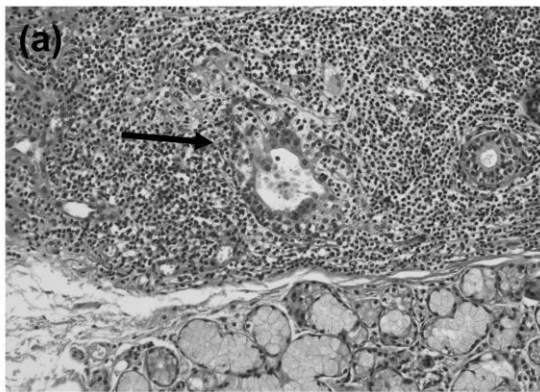


Fig 2: Histopathological findings of the resected samples: (a: case 1) Destruction of the ductal epithelium is shown (arrow). (b: case 1) Atrophy of the ductal epithelium adjacent to the cyst was observed (arrows). (c: case 2) Destruction of the ductal epithelium is shown (arrow). (d: case2) Extravasation of mucous was seen in the stroma of the salivary grand (arrow).



**Table 1 Characteristics and examination data of three cases**

	Age	Gender	Gum test (/ 10 min)	Salivary gland scintigraphy (Tc-99m)	Anti-SS-A antibody Anti-SS-B antibody	Pathological examination of the sublingual gland (Greenspan classification)
Case 1	66	Woman	5 mL	Functional decline	>1,200 U/mL >1,000 U/mL	Grade 4
Case 2	30	Woman	12 mL	Functional decline	>1,200 U/mL 127U/mL	Grade 4
Case 3	26	Woman	3 mL	Functional decline	>1,200 U/mL 4.4U/mL	-

\* Their schirmer's test and a fluorescent staining test did not meet the diagnostic criteria , respectively.