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Differences between radioactive iodine-induced sialadenitis and chronic obstructive parotitis

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Abstract. The purpose of this study was to clarify the differences in the diagnosis and treatment outcomes between radioactive iodine-induced sialadenitis (RAIS) and chronic obstructive parotitis (COP). The study cohort comprised 47 consecutive patients diagnosed with RAIS and 50 patients with COP. All patients were treated by interventional endoscopy. Clinical, sialography, and endoscopy characteristics and treatment outcomes were compared between the two groups. Compared with the COP group, the RAIS group included more females (male:female ratio 1:8.4 vs 1:2.1; $P = 0.011$) and had a younger onset age (42 vs 50 years; $P = 0.001$) and shorter disease duration prior to hospital visit (5.4 vs 34.8 months; $P < 0.001$). In the RAIS group, sialography revealed obliteration of the main duct (20.4% vs 0%; $P < 0.001$), non-visualization of the main gland (23.7% vs 0%; $P < 0.001$), and incomplete contrast filling of the main gland (19.4% vs 6.4%; $P = 0.008$), which were scarcely observed in the COP group. Endoscopy revealed a higher percentage of duct atresia in RAIS compared to COP (20.4% vs 0%; $P < 0.001$). During follow-up, a higher percentage of RAIS patients had duct atresia and gland atrophy (49.5% vs 1.1%, $P < 0.001$). Compared with COP, RAIS more commonly involves younger females and has a shorter disease duration. Atresia of the main duct and atrophy of the gland parenchyma occur more often despite the use of interventional endoscopy.

Key words: parotitis; sialography; iodine radioisotopes; sialadenitis; therapy.

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Radioactive iodine (RAI) therapy has become the main type of adjuvant therapy for differentiated thyroid cancer, aimed at the ablation of residual thyroid tissue after total thyroidectomy. However, iodine 131 (^{131}I) can cause glandular damage and consequent salivary dysfunction, named radioactive iodine-induced sialadenitis (RAIS)[1,2]. Clinically, RAIS manifests as swelling and pain in the affected parotid gland, as well as xerostomia, which seriously affects patient quality of life[3].

Chronic obstructive parotitis (COP) is characterized by repeated swelling of the affected gland after a meal or upon salivary stimulation. The cause is still unclear and might include scar stricture, developmental anomalies, allergy, and autoimmune factors[4].

COP and RAIS share similar symptoms and imaging findings. However, the path-

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ogenesis of these two diseases, as well as the principles and outcomes of clinical treatment, can differ. Few studies have focused on the differentiation of these two entities. The aim of this study was to investigate the clinical, radiographic, and sialendoscopic features of RAIS and COP, as well as their responses to treatment.

Materials and methods

The study protocol was approved by the review board of Peking University School and Hospital of Stomatology (PKUSSIRB-201840185). All participants provided written informed consent.

Study cohort

Forty-seven consecutive patients with RAIS diagnosed between November 2012 and May 2020 at Peking University School and Hospital of Stomatology were included retrospectively. The bilateral glands were affected in 46 patients (97.9%) and the right gland was involved in the other patient. The diagnostic criteria for RAIS were (1) history of ^{131}I treatment; (2) no history of COP before ^{131}I treatment; (3) swelling and painful symptoms in the salivary glands after ^{131}I uptake; (4) exclusion of salivary gland stones or space-occupying lesions.

Fifty patients with idiopathic COP diagnosed at Peking University School and Hospital of Stomatology during the same period formed the control group. The bilateral glands were affected in 44 patients (88%) and unilateral glands were involved in the remaining six patients (12%). The main diagnostic criteria for COP were recurrent salivary gland swelling and discomfort of unknown cause. For all of the included COP patients, clinical signs, serum tests, and ultrasonography were acquired to exclude benign hypertrophy of the parotid glands, chronic recurrent parotitis, Sjögren's syndrome, or tumoural lesions.

Statistical estimation confirmed that the sample size would satisfy the requirements of hypothesis testing.

Medical history and examination

For each patient, the treatment history of thyroid cancer and total doses of RAI were recorded in detail. The duration of swelling and/or pain (months) and the presence of xerostomia were also recorded. Clinically, the amount and quality of saliva flow upon massage were assessed.

Among the 47 RAIS patients, severe Wharton's duct stenosis of the bilateral submandibular glands was found in the two patients with obvious xerostomia. In the remaining 45 patients, clinical examination showed abundant excretion from the submandibular gland. Therefore, sialography was conducted mainly in the parotid glands. After intubation of a washing needle (5 G), 1 ml of water-soluble contrast agent (ioversol; Hengrui Medicine, Jiangsu, China) was injected carefully. A lateral view and a 5-minute emptying film were taken. The appearances of the main and branch ducts, as well as contrast filling of the main gland, were analysed. Two experienced oral radiologists analysed each case independently and reached a consensus by discussion.

Sialography findings of the main duct were divided into three types: (1) stenosis of the main duct; (2) stenosis and ectasia of the main duct; (3) occlusion of the main duct. Sialography findings of the main gland were divided into four types: (1) non-visualization of intraglandular main and branch ducts; (2) incomplete contrast filling of the main gland; (3) ectasia of intraglandular main and/or branch ducts; (4) approximately normal.

Sialendoscopy

Endoscopy procedures were performed under local anaesthesia in an outpatient setting. An endoscope (PD-ZS-0084; PolyDiagnost, Hallbergmoos, Germany) with a diameter of 0.90 mm and 1.15 mm and a working length of 9 cm was introduced to explore the main duct of the gland, under continuous irrigation with a solution comprising a mixture of physiological saline (0.9%) and dexamethasone (100 ml: 10 mg). Disorders of the salivary ducts were noted; for example pale mucosa, mucus plugs, ductal debris, polypus, and stenosis. Ductal debris and mucous plugs were removed by gland massage after saline lavage, with or without a grasping wire. If a stenotic lesion was observed, mechanical dilation by the working tip was performed. Finally, intraductal administration of 50 mg prednisolone acetate (25 mg/mL) was undertaken for each gland. After the procedure, maintenance of oral hygiene and regular gland massage were recommended. In addition, intraductal administration of prednisolone (50 mg/gland) was performed once a month for 3 months.

Treatment evaluation

Three months after the procedure, clinical outcomes were assessed by physician assessment. They were scored as 'good' (asymptomatic with good secretion of saliva), 'fair' (occasionally mild symptoms that could be alleviated autonomously with acceptable secretion of saliva), or 'poor' (persistent symptoms, severe xerostomia, duct atresia, or gland atrophy). For patients with a poor outcome, ultrasonography was performed to evaluate the gland function. For a small proportion of patients who could not be revisited directly, the follow-up data were obtained by telephone calls.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). The mean $\pm$ standard deviation or median values were assessed for continuous variables, and comparisons were made by independent *t*-test or Wilcoxon rank test. Categorical variables were expressed as percentages and were compared using the χ^2 test or Fisher's exact test. The relationship between variables was analysed by Pearson correlation test. $P < 0.05$ was considered significant.

Results

Clinical characteristics

The RAIS group comprised five male patients and 42 female patients, and the COP group comprised 16 male patients and 34 female patients. A significant difference in the male to female ratio was noted between the two groups (1:8.4 vs 1:2.1; $P = 0.011$). Additionally, the patients in the RAIS group (age range 26–67 years, median 42 years) were significantly younger than those in the COP group (age range 26–74 years, median 50 years) ($P = 0.001$).

Among the 47 patients with RAIS, 23 received a single RAI treatment with a median dose of 110 mCi (range 35–150 mCi), 21 patients underwent two sessions of treatment with a median dose of 200 mCi (range 125–320 mCi), and the remaining three patients received three sessions of treatment with a median dose of 270 mCi (range 220–320 mCi). Overall, the mean dose was 167.2 mCi.

The time interval between RAI and symptom onset was <3 months in 16 patients (34.0%), 3–6 months in 10 patients (21.3%), 6–12 months in 17 patients (36.2%), and >12 months in the remaining four patients (8.5%). The mean interval was 6.2 months.

The duration from the onset of clinical symptoms to the first visit to Peking

University School of Stomatology was significantly shorter for the patients with RAIS when compared to the patients with COP ($P < 0.001$). In the RAIS group, the duration was in the order of days or months (mean 5.4 months), while in the COP group the duration was in the order of months or years (mean 34.8 months). Dry mouth was more common in patients with RAIS than in patients with COP (36.2% vs 20%). Glands without obvious salivary secretion after squeezing the parotid glands were more prevalent in RAIS patients than in COP patients (27/93 vs 1/94), indicating that gland function in RAIS was more seriously impaired.

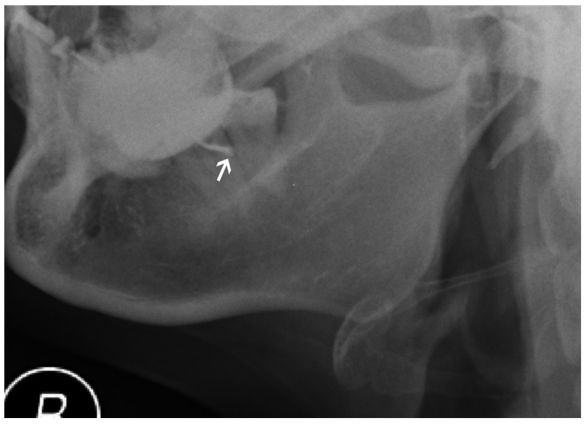

Fig. 1. Sialography of radioactive iodine-induced sialadenitis (RAIS) showing obliteration of the main duct (arrow).

Sialography

Regarding the main duct, the prevalence of main duct obliteration (Fig. 1) was significantly higher in RAIS patients than in COP patients (20.4% vs 0%; $P < 0.001$), while COP was associated more commonly with stenosis and ectasia of the main duct (85.1% vs 61.3%; $P < 0.001$) (Fig. 2). With regard to the main gland, the prominent sialography features in RAIS patients were non-visualization (23.7% vs 0%; $P < 0.001$) (Fig. 3) and incomplete contrast filling (19.4% vs 6.4%; $P = 0.008$) (Fig. 4), which were rarely observed in the COP patients. Furthermore, type 3 (ectasia of the intraglandular main and/or branch ducts) and type 4 (approximately normal) sialograms were significantly more prevalent in COP patients than in RAIS patients (Table 1).

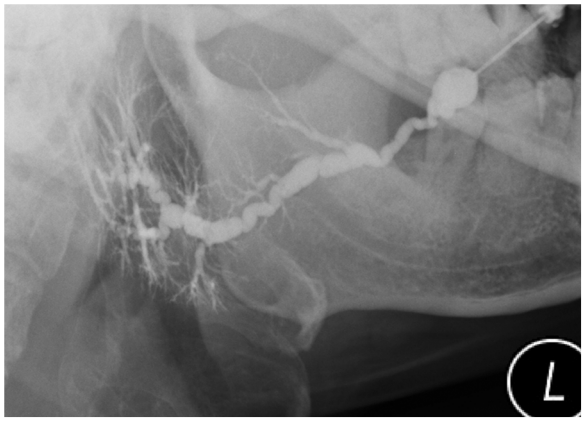

Fig. 2. Sialography of chronic obstructive parotitis (COP) demonstrating a 'sausage'-like appearance of the main duct and ectasia of the intraglandular branches (arrow).

Sialendoscopy

Sialendoscopy was undertaken for all 93 RAIS and 94 COP glands. Endoscopy revealed that RAI-inflicted ducts had bleached ductal walls and lumen stricture in all affected glands; moreover, mucous plugs (11 glands; Fig. 5A) and debris (27 glands) were often detected. Ductal atresia was observed significantly more commonly in RAIS glands (20.4%, 19/93) (Fig. 5B) than in COP glands (0%, 0/94). In 11 of the 19 glands with ductal atresia, the obstructed lumen of the proximal duct was reopened after dilation of the severe stenosis. Also, four RAIS glands (4.3%) showed polypoid proliferation (Fig. 5C), which was scarcely seen in COP patients. By contrast, COP was associated more commonly with stenosis and ectasia of the main duct (Fig. 5D) (Table 1).

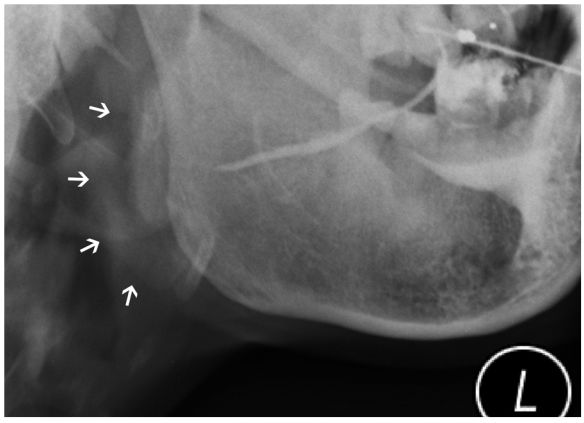

Fig. 3. Sialography of radioactive iodine-induced sialadenitis (RAIS) demonstrating non-visualization of the main gland (arrow).

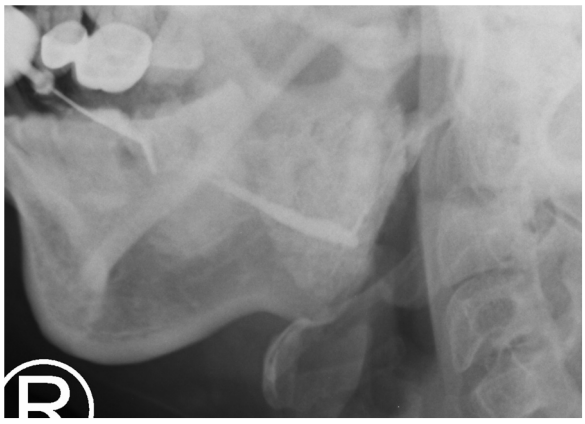

Fig. 4. Sialography of radioactive iodine-induced sialadenitis (RAIS) showing incomplete contrast filling of the main gland (arrow).

Table 1. Comparison of sialography and endoscopy features between the radioactive iodine-induced sialadenitis (RAIS) and chronic obstructive parotitis (COP) groups.

	RAIS	COP	*P*-value
Total number of glands	93	94	–
Sialography features of the main duct			
Stenosis (%)	17 (18.3)	14 (14.9)	0.534
Stenosis and ectasia (%)	57 (61.3)	80 (85.1)	<0.001*
Obliteration (%)	19 (20.4)	0 (0)	<0.001*
Sialography features of the main gland			
Non-visualization (%)	22 (23.7)	0 (0)	<0.001*
Incomplete filling by contrast (%)	18 (19.4)	6 (6.4)	0.008*
Ectasia of intraglandular ducts (%)	37 (39.8)	55 (58.5)	0.010*
Approximately normal (%)	16 (17.2)	33 (35.1)	0.005*
Endoscopy features			
Stenosis of the main duct (%)	74 (79.6)	94 (100)	<0.001* [Au?10]
Ductal atresia (%)	19 (20.4)	0 (0)	

* Significant difference, $P < 0.05$. [Au?11].

Treatment outcomes

The 47 RAIS patients were followed up for a mean period of 12 months (range 3–58 months) and the 50 COP patients were followed up for a mean period of 8.5 months (range 3–55 months). The follow-up data of 43 RAIS and 44 COP patients were obtained via direct clinic visit, while the data of four RAIS and six COP patients were obtained by telephone call.

Among the 93 glands with RAIS, the treatment outcome was evaluated as 'good' in 22 (23.7%), 'fair' in 25 (26.9%), and 'poor' in 46 (49.5%). The poor outcome in 46 glands manifested as atresia of the main duct and gland atrophy during follow-up, but this was asymptomatic or led to very mild discomfort. Among them, 19 glands were occluded at the initial visit to the clinic. In 11 of these 19 glands, the occlusion recurred despite endoscopic reopening of the main duct. In the remaining 27 glands, the main duct was patent at the initial visit to the clinic, but ductal atresia occurred gradually during follow-up. There was no significant correlation between the RAI dose received and the treatment outcomes ($P = 0.523$). The total effective rate (good + fair/total gland number) in the RAIS group was calculated to be 50.5%.

Among the 94 glands with COP, the treatment outcome was evaluated as 'good' in 52 (55.3%), 'fair' in 28 (29.8%), and 'poor' in 14 (14.9%). Of the 14 glands with a poor outcome, one had atresia of the main duct and 13 had persistent symptoms without atresia of the main duct after one or two endoscopic procedures. The total effective rate in the COP group was 85.1%, which was much higher than that in the RAIS group ($P < 0.001$).

Discussion

Thyroid cancer is the most common primary endocrine malignancy and its prevalence has increased worldwide[5]. It has been estimated that the disease afflicted 56,870 Americans in 2017, with females accounting for 75% of cases[5,6]. With the use of RAI therapy, RAIS is garnering the attention of clinicians; the reported prevalence varies from 10% to 67%[1,7–9].

In the present study, the overwhelming majority of RAIS patients were female, and the age at onset of RAIS was, on average, 8 years earlier than the age at onset of COP. These findings could be explained by the much higher prevalence of thyroid cancer in females and the relatively young age of thyroid cancer patients.

Studies have shown that parotid gland dysfunction develops more frequently than submandibular gland dysfunction after RAI ablation[10–12]. In the present study, nearly all patients had mild-to-severe ductal stenosis of the bilateral parotid glands, but only two patients had ductal stenosis of the Wharton's ducts. It is known that serous salivary cells concentrate iodide to a greater extent than mucinous acini. A higher proportion of serous acini in the parotid glands might explain the increased damage to the parotid glands caused by RAI[12].

Lee et al. noted that the development of symptoms related to salivary gland dysfunction was observed most frequently within 6 months after RAI[13]. In the present study, 55.3% of patients developed symptoms within 6 months after RAI. However, the course of COP was often in months or years. Consequently, a history of thyroid cancer and ^{131}I treatment should not be neglected in the investigation of young female patients with an acute onset of obstructive parotitis.

Sialography involves the demonstration of the ductal system of the salivary glands by inflating a radiopaque contrast agent into the system before imaging[14,15]. Although there were several similarities, there were also significant differences in sialography appearances between RAIS and COP. COP was associated more commonly with stenosis and ectasia of the main duct, as well as type 3 and type 4 sialograms of the main gland, indicating that gland function was not seriously impaired but saliva had accumulated in and obstructed the duct system. However, RAIS was often associated with main duct obliteration, as well as type 1 and type 2 sialograms of the main gland, indicating that RAIS involved more serious impairments of the ductal system and gland function.

Conventional treatment methods for RAIS and COP include conservative ther-

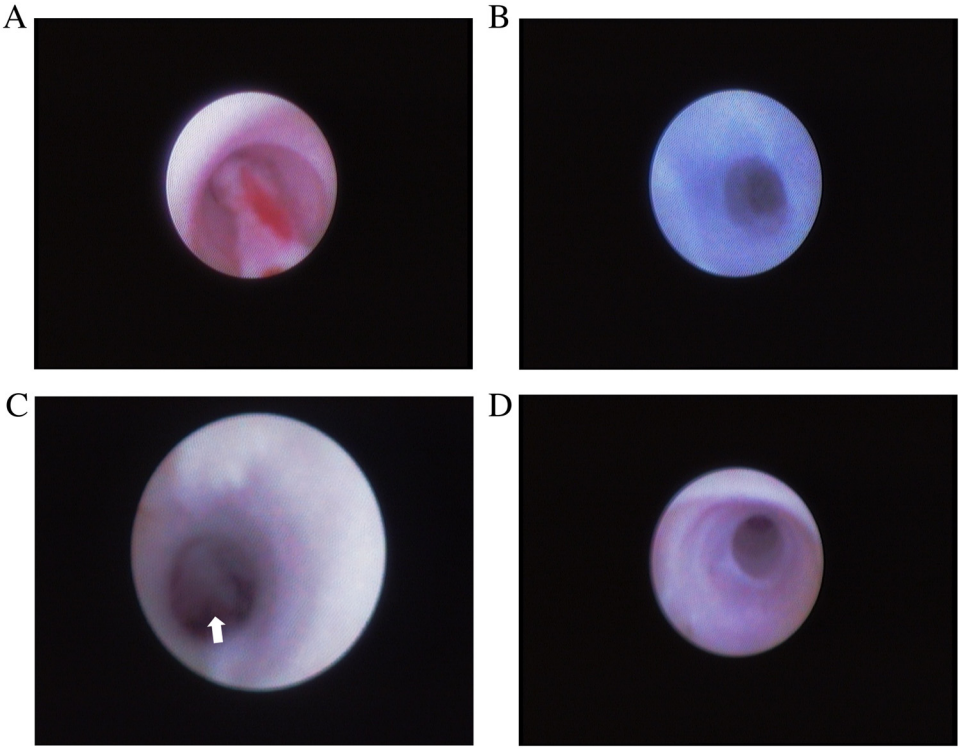

Fig. 5. Endoscopy views of radioactive iodine-induced sialadenitis (RAIS) and chronic obstructive parotitis (COP). (A) RAIS demonstrated a bleached ductal wall and mucus plug (arrow). (B) RAIS showed duct atresia. (C) RAIS demonstrated severe breakage of the ductal wall and polypoid proliferation (arrow). (D) COP (the same case demonstrated in Fig. 2) showed intermittent stenosis (arrow) and ectasia of the lumen.

apies, such as external massage, hydration, corticosteroids, sialagogues, chewing gum, and cholinergic medications[16]. These comprehensive methods are helpful for minimizing the retention time of ^{131}I in the ductal system, and should not be neglected at an early stage[15].

Recently, sialendoscopy has been proposed for the diagnosis and treatment of refractory salivary gland symptoms[9,16]. In the present study, duct system damage in RAIS patients was complicated and serious, which is consistent with the results in other reports[16,17]. The pathological basis may be related to sodium–iodine symporters expressed mainly in the epithelium of the salivary gland ducts, which can take in iodide from blood and cause radiation damage to the ductal system[18]. According to Nahlieli and Nazarian, the symptoms of acute sialadenitis may be relieved by endoscopic dilation, although it might not provide healing of the avascular changes in the mucosal lining[14]. Bhayani et al. reported that endoscopy could lead to a durable improvement in symptoms in the management of RAIS and xerostomia refractory to conservative therapy[1]. Wu et al. stated that the functional gland could recover owing to the renewal ability of ductal cells, provided that the stenosis was unblocked in a timely manner[15]. In the present study, approximately half of the affected glands gained different extents of improvement of symptoms and gland function. This observation could be attributed to the removal of mucus plugs, dilation of strictures, and corticosteroid irrigation at the end of the procedure. However, poor outcomes occurred in the remaining half of patients. In refractory RAIS, endoscopy might fail to restore the function of injured salivary glands even after the mechanical dilation of stenotic ducts, considering that the effect of ^{131}I is dependent upon the dose and time[14].

Limitations of the study are its retrospective design and the lack of a validated objective evaluation of gland function. Moreover, a prospective study with a randomized control trial is required to evaluate the treatment effects of gland massage, sialagogues, and endoscopy at an earlier stage following RAI treatment.

Compared with COP, RAIS is more likely to occur in young female patients, has a shorter duration prior to presentation to the hospital, and is more frequently bilateral. Atresia of the main duct and atrophy of the gland parenchyma are seen more commonly in RAIS than in COP. Interventional endoscopy may relieve the clinical symptoms, but might fail to restore function in the injured gland. Comprehensive therapy at an early stage might be helpful for RAIS.

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Competing interests

All authors have declared that no conflicts of interest exist.

Ethical approval

Ethical approval was obtained from the Peking University School and Hospital of Stomatology Biomedical Institutional Review Board (PKUSSIRB-201840185).

Patient consent

Not required.

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