

[ CASE REPORT ]

## Sjögren's Syndrome as an Immune-related Adverse Event of Nivolumab Treatment for Gastric Cancer

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### Abstract:

Immune checkpoint inhibitors can affect any organ, including the salivary glands. A case of Sjögren's syndrome (SjS) induced by nivolumab for the treatment of gastric cancer is herein presented. Nivolumab treatment caused marked tumor shrinkage, but xerostomia developed after two cycles. It took 3 months after symptom onset to confirm the diagnosis of SjS. Prednisolone and pilocarpine hydrochloride did not relieve the symptoms. SjS is a relatively rare immune-related adverse event that might sometimes be overlooked. Since SjS can severely impair a patient's quality of life, oncologists should not miss any signs of salivary gland hypofunction and cooperate with specialists for SjS.

**Key words:** immune-related adverse event, Sjögren's syndrome, immune checkpoint inhibitors

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### Introduction

Immune checkpoint inhibitors (ICIs) targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA4), programmed death-1 (PD-1) receptor, and its ligand PD-L1 have revolutionized the treatment of various types of tumors. Although ICIs can achieve remarkable responses, their use can also cause unique immune-related adverse effects (irAEs). The notable irAEs are rash, pneumonitis, colitis, and thyroid disorders (1). ICIs can affect not only common organs, but also a variety of other organs, including the salivary glands. A case of nivolumab-induced Sjögren's syndrome (SjS) during the treatment of gastric cancer is herein presented.

### Case Report

A 60-year-old man was referred to our hospital for the treatment of human epidermal growth factor receptor 2 (HER2)-positive advanced gastric adenocarcinoma with a single liver metastasis and multiple lung metastases. He had been treated with 14 courses of capecitabine plus cisplatin with trastuzumab as the first-line chemotherapy and weekly

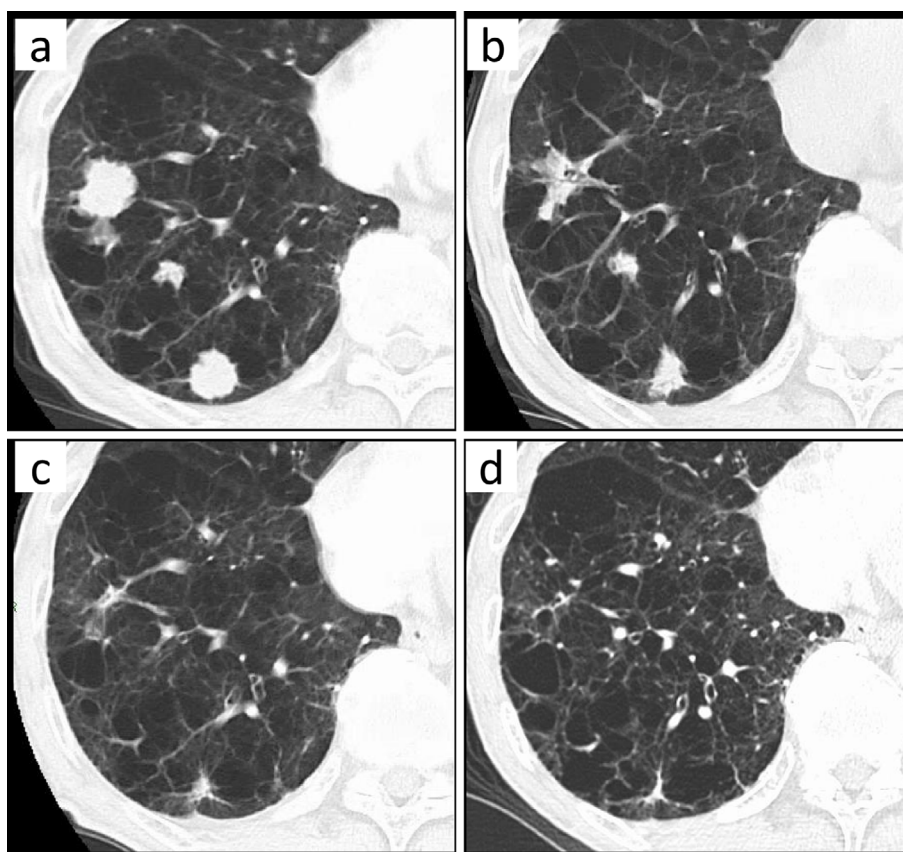
paclitaxel (PTX) as the second-line chemotherapy. After 6 courses of weekly PTX treatment, he had undergone total gastrectomy and radiofrequency ablation (RFA) to treat the liver metastasis, because positron emission tomography-computed tomography (PET-CT) showed the disappearance of the lung metastases. Six months after surgery, CT scans showed left adrenal gland metastasis. He subsequently received irinotecan monotherapy, radiation therapy, and ramucirumab monotherapy, but the adrenal gland metastasis kept increasing in size, and multiple lung metastases also recurred (Fig. 1a).

He was treated with nivolumab as the fifth-line chemotherapy. After four cycles of nivolumab, CT showed a marked shrinkage of the lung metastases (Fig. 1b) and no change in the size of the adrenal gland metastasis. At the end of two cycles of nivolumab, xerostomia occurred. His tongue was dry and developed many fissures (Fig. 2). Since he was not taking any drugs with anticholinergic side effects and showed no findings of diabetes mellitus, his xerostomia seemed to have been caused by dehydration, and adequate daily fluid intake was thus recommended at that time. He did not have any ocular dryness symptoms and other systematic manifestations. Since the xerostomia persisted for 3

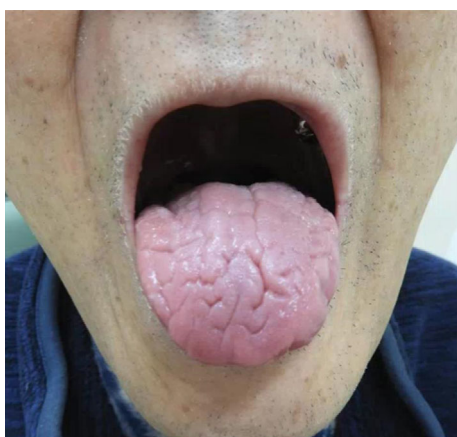
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**Figure 1.** Computed tomography (a) before treatment with nivolumab, (b) after 7 cycles of nivolumab treatment, (c) after 15 cycles of nivolumab treatment, and (d) 1 year after the cessation of nivolumab treatment.



**Figure 2.** Oral cavity. The patient shows significant papillary atrophy with erythema and fissuring of the dorsum of the tongue. A fissured tongue is a benign condition characterized by deep grooves (fissures) in the dorsum of the tongue. Dry mouth may cause fissured tongue.

months without any improvement, salivary function tests were performed and resulted in the definitive diagnosis of SjS. The diagnosis was based on the Japanese Ministry of Health criteria for the diagnosis of SjS (Table 1) (2). We made the definite diagnosis of SjS according to the following three positive results: i) decreased salivary secretion by

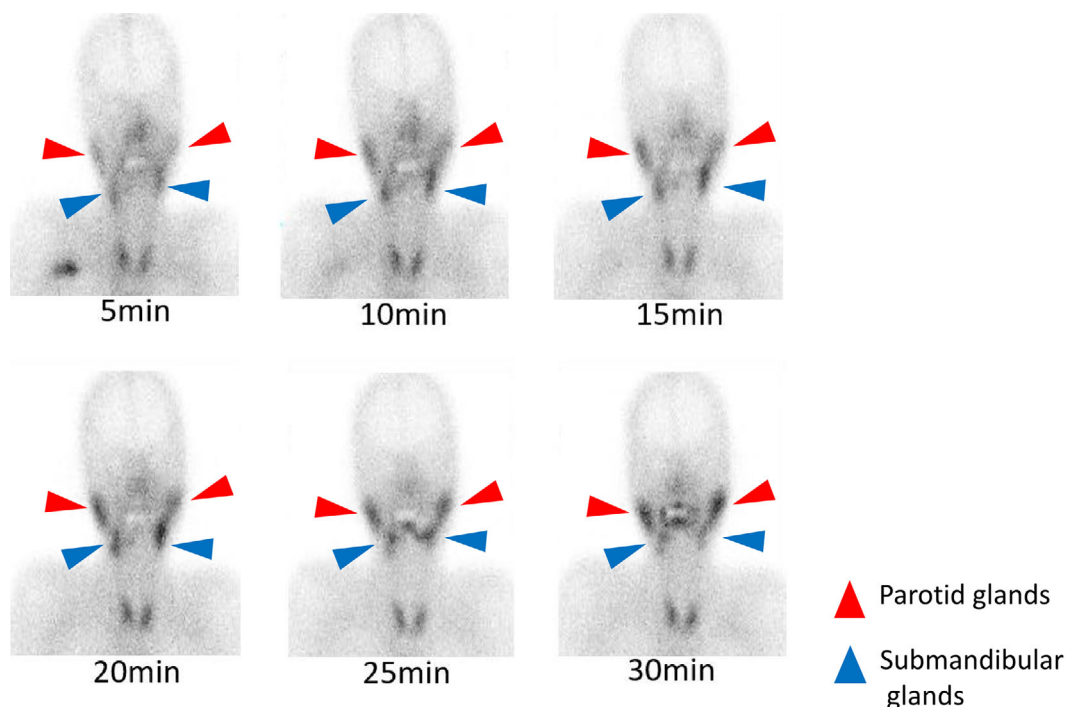
the Saxon test (0.3 g/2 min) and a poor uptake on salivary gland scintigraphy (Fig. 3); ii) decreased tear secretion by Schirmer's test (right was 5 mm/5 min and left was 1 mm/5 min) and the fluorescein staining test; and iii) lymphocyte infiltration to labial salivary glands. A histopathological examination of the labial salivary gland biopsy specimens showed focal lymphocytic sialadenitis composed of both CD20+ B-cells and CD3+ T-cells with predominant T-cells. There was a predominance of CD8+ over CD4+ T cells. PD-1 and PD-L1 were both negative (Fig. 4). Serum SS-A/Ro, SS-B/La antibodies, rheumatoid factor (RF) and antinuclear antibody (ANA) were all negative.

A two-week oral treatment of prednisolone 0.5 mg/kg/day (20 mg/body) and pilocarpine hydrochloride did not improve his subjective symptoms and the salivary flow rates on the Saxon test (0.5 g/2 min). The dose of prednisolone was tapered, and was stopped one month later. A sticky feeling in the mouth and denture instability severely interfered with the patient's dietary intake. Nivolumab was suspended after 21 courses because of persistent SjS and an exacerbation of comorbid chronic obstructive pulmonary disease. One year after the cessation of nivolumab, CT showed that the shrinkage of lung metastases was maintained (Fig. 1c, d), and the adrenal gland metastasis remained unchanged in size. At that time, there was no improvement in both his subjective symptoms and salivary flow rates on the Saxon test (0.1 g/2

**Table 1. The Revised Japanese Ministry of Health Criteria for the Diagnosis of SjS (2).**

Oral examination	Definition: Positive for at least one of (A) or (B): A) Abnormal findings in sialography $\geq$ Stage I (diffuse punctate shadows of less than 1mm) B) <u>Decreased salivary secretion (flow rate <math>\leq</math> 10mL/10min according to the chewing gum test or <math>\leq</math> 2g/2min according to the Saxon test) and decreased salivary function according to salivary gland scintigraphy</u>
Ocular examination	Definition: Positive for at least one of (A) or (B): A) Schirmer's test $\leq$ 5mm/5min and rose bengal test $\geq$ 3 according to the van Bijsterveld score B) Schirmer's test $\leq$ 5mm/5min and <u>positive fluorescein staining test</u>
Histopathology	Definition: Positive for at least one of (A) or (B): A) Focus score $\geq$ 1 (periductal lymphoid cell infiltration $\geq$ 50) in a 4-mm <sup>2</sup> minor salivary gland biopsy B) Focus score $\geq$ 1 (periductal lymphoid cell infiltration $\geq$ 50) in a 4-mm <sup>2</sup> lacrimal gland biopsy
Serological examination	Definition: Positive for at least one of (A) or (B): A) Anti-Ro/SS-A antibody B) Anti-La/SS-B antibody
Diagnostic criteria	Diagnosis of Sjögren's syndrome can be made when the patient meets at least two of the above four criteria

The underlined items were matched for this case.



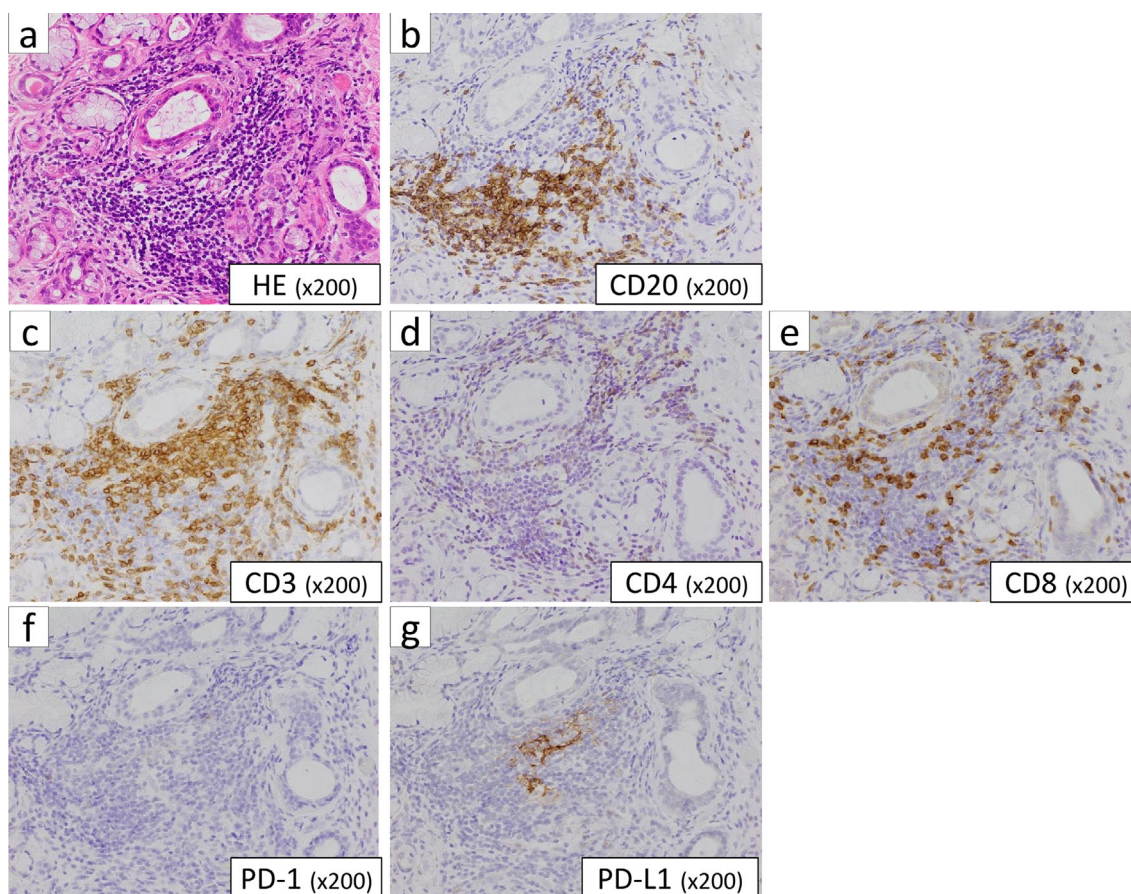
**Figure 3.** Salivary gland scintigraphy shows the normal accumulation of tracer in both the parotid glands and submandibular glands and a decreased secretion velocity in both the parotid glands and submandibular glands after stimulation (taking lemon juice at 20 minutes).

min).

## Discussion

A case of SjS caused by nivolumab as a fifth-line chemotherapy for gastric cancer is herein described. Nivolumab achieved marked tumor shrinkage, but it induced xerostomia at the end of two cycles. The diagnosis of SjS as an irAE was confirmed 3 months after the onset of symptoms. Though prednisolone and pilocarpine hydrochloride were administered, they resulted in little symptomatic improvement.

Cases of ICI-induced sicca syndrome were first reported in four (0.5%) of 700 patients treated with nivolumab and/or ipilimumab (3). There have been nine case reports or case series of sicca syndrome caused by any ICI class in various types of cancer, which are summarized in Table 2 (3-11). They were mainly treated with corticosteroids, resulting in an improvement of symptoms in 74% (57/77) of them with various antitumor effects. In detail, Burel et al. reported that the prevalence of SjS was 0.3% with anti-PD-1/anti-PD-L1 agents alone and 2.5% with a combination of anti-PD-1 and anti-CTLA4 agents (6). Since xerostomia could occur in various settings, such as dehydration, hyperglycemia, or as



**Figure 4.** The histopathological examination of the labial salivary gland biopsy specimens. (a) Hematoxylin and Eosin staining shows focal lymphocytic sialadenitis. (b) (c) Immunohistochemistry demonstrates the infiltration of both CD20+B-cells and CD3+T-cells. (d) (e) There is a predominance of CD8+cells over CD4+T cells. (f) (g) PD-1 is negative, and PD-L1 is also considered negative, with faint staining in the extracellular part.

side effects of anticholinergic drugs, ICI-induced sicca syndrome/SjS can sometimes easily be overlooked, and its prevalence may thus be underestimated.

Ramos-Casals et al. identified 26 cases of sicca syndrome/SjS triggered by ICIs in patients with cancer in the data from the International ImmunoCancer Registry (ICIR) (9). Among them, the cases that conformed to the criteria of SjS-induced ICIs had a very specific clinical profile, different from that observed in idiopathic SjS, with half of the cases being men, a lower frequency of positive SS-A/B antibodies, an older age, and a lower frequency of ocular dryness, compared to idiopathic primary SjS. Warner et al. reported 20 patients with new or worsening xerostomia on ICI treatment (10). The histopathological features of labial salivary gland biopsy consisted of mild chronic sialadenitis or focal lymphocytic sialadenitis, with infiltrating cells being predominantly T-lymphocytes and few B cells. This pattern was different from the characteristic idiopathic primary SjS in which B cells account for 20-62% of all infiltrating lymphocytes (12). Though the mechanism of sicca syndrome/SjS caused by immunotherapy has not yet been elucidated, the results of these previous studies suggest that an impairment of the PD-1/PD-L1 pathway caused by ICIs triggers

the activation of T-lymphocytes, leading to infiltration of the salivary gland epithelium. In the present case, it was speculated that ICI induced SjS based on negative results of serum SS-A/Ro, SS-B/La antibodies and absence of other laboratory abnormalities suggesting primary SjS, although a histological examination of labial salivary gland showed a certain amount of B-cell infiltration in all lymphocytes, which was inconsistent with the previous report.

For the management of irAEs, corticosteroids are used according to current practical treatment algorithms (1). Ramos-Casals et al. reported that, in most cases, sicca symptoms were managed with topical measures including pilocarpine and cyclosporine A drops, but which failed to relieve the symptoms in our case (9). Warner et al. reported that subjective improvement in symptoms was achieved in the majority of cases by ICI cessation with or without corticosteroid administration (10); however, few patients regained normal salivary flow rates.

In the present case, prednisolone 20 mg per day and pilocarpine hydrochloride were administered, which did not improve either the subjective symptoms or the salivary flow rates. The poor response to the drugs may have been caused by the continuous administration of nivolumab for 3 months

**Table 2. Reported Cases of Sicca / Sjögren's Syndrome Induced by ICIs.**

Reference	No. of cases*	Type of malignancy	n	ICI†	n	Time to onset (weeks)	ANA‡	Anti-SSA and/or SSB§	Treatment	n	Improvement of sicca syndrome	Antitumor effect	n
(3)	4	Melanoma NSCLCII	3 1	Nivolumab Ipilimumab Nivolumab and Ipilimumab	2 1 1	8-32	3/4	1/4	Prednisone Pilocarpine Cevimeline	3 1 2	3/4	PR SD PD	1 2 1
(4)	5	Melanoma Renal cell carcinoma	4 1	Nivolumab and Ipilimumab Nivolumab Atezolizumab	3 1 1	2-22	2/5	1/5	Prednisone	5	5/5	N/A	
(5)	1	Parotid acinic cell carcinoma	1	Pembrolizumab	1	33	0	0	Prednisone Pilocarpine Artificial saliva	1 1 1	1/1	SD	1
(6)	3	Renal cell carcinoma Cervical squamous cell carcinoma Melanoma	1 1 1	Anti-PD-1 Anti-PD-1 and Anti-CTLA-4 Anti-PD-L1, BRAF and MEK inhibitors	1 1 1	8-11	3/3	2/3	Prednisone	1	3/3	PR SD	2 1
(7)	1	NSCLCII	1	Nivolumab	1	16	0	0	Prednisone Pilocarpine	1 1	1/1	N/A	
(8)	2	NSCLCII Pancreatic neuroendocrine cancer	1 1	Nivolumab	2	15, 24	2/2	0	Corticosteroids Pilocarpine	1 2	2/2	N/A	
(9)	26	Lung cancer Renal cancer Melanoma Colon cancer Chordoma Cervical cancer	12 7 4 1 1 1	Nivolumab Pembrolizumab Durvalumab Nivolumab and Ipilimumab Nivolumab and pegIL10	9 7 4 5 1	4-112	13/26	5/26	Corticosteroids Pilocarpine Cevimeline CyA drops	2 2 1 1	23/26	N/A	
(10)	20	Melanoma Respiratory papillomatosis Thymic carcinoma NSCLCII Prostate cancer Gastroesophageal junction Adenocarcinoma	10 4 3 1 1 1	Nivolumab Avelumab Pembrolizumab Nivolumab and Ipilimumab Pembrolizumab and Ipilimumab Anti-PD-L1 and TGF-beta	5 8 3 2 1 1	4-30	3/20	2/20	Prednisone	10	9/20	CR PR SD PD N/A	3 2 8 3 4
(11)	15	Melanoma Oral squamous cell carcinoma Renal cancer Endometrial adenocarcinoma Pancreatic adenocarcinoma NSCLCII	6 3 2 2 1 1	Anti-PD1 Anti-PDL1 Anti-PD-1 and Anti-CTLA-4 Anti-PD-1 and ICI under development	7 1 3 4	2-68	not assessed	1/15	Corticosteroids Symptomatic measures¶	2 13	10/15	PR SD PD N/A	2 4 7 2
Our case	1	Gastric adenocarcinoma	1	Nivolumab	1	4	0	0	Corticosteroids	1	0	PR	1

\* Number of sicca / Sjögren's syndrome cases, † Immune checkpoint inhibitor, ‡ Numerator shows positive cases for antinuclear antibody, § Numerator shows positive cases for anti-SSA and/or SSB, ¶ non-small cell lung carcinoma, ¶¶ Symptomatic measures: hydration, gum, oral hygiene, ametholtrithion/pilocarpine, salivary substitute

after the onset of symptoms due to the delay in diagnosis.

Although sicca syndrome/SjS itself is not a fatal irAE, xerostomia can cause dysgeusia, interfere with the oral intake, and significantly reduce a patients' quality of life (13). In addition, long-term salivary gland hypofunction can increase the risk of carious teeth, periodontitis, and denture instability. In the present case, denture instability significantly disturbed the patient's dietary intake. Decreased salivary secretion may imply the early phase of SjS, even if the case does not satisfy the current diagnostic criteria for SjS. It is important for oncologists to cooperate with various specialists including ophthalmologists, otolaryngologists and rheumatologists when the patients show sicca syndrome/SjS.

In the present case, nivolumab had a marked therapeutic effect and maintained tumor shrinkage for one year after its cessation. Some studies have shown that the development of irAEs was associated with the therapeutic outcome of ICI (14, 15). It remains uncertain whether sicca syndrome/SjS can be a positive predictive marker of the therapeutic outcome, though the therapeutic response may have correlated with salivary gland dysfunction in the present case. The salivary gland function is measurable with non-invasive methods such as the Saxon test and the gum test. Additional studies are needed to investigate the relationship between decreased salivary secretion and a good therapeutic outcome.

### Conclusion

A case of SjS caused by nivolumab for gastric cancer was described. Since sicca syndrome/SjS impairs a patients' quality of life, oncologists should be careful not to miss any signs of salivary gland hypofunction and then cooperate with specialists of various fields including ophthalmology, otolaryngology and rheumatology.

**The authors state that they have no Conflict of Interest (COI).**

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