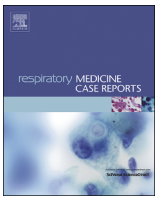
Respiratory Medicine Case Reports 50 (2024) 102068

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr



Case Report

A case of sialadenitis observed as an irAE of atezolizumab: A case report

Kosumi Kumagai [a], Tomohisa Baba [a,*], Takashi Fukushima [a], Erina Tabata [a], Atsuhito Nakazawa [a], Eri Hagiwara [a], Tae Iwasawa [b], Takashi Ogura [a]

[a] Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan
[b] Department of Radiology, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan

ARTICLE INFO

Handling Editor: DR AC Amit Chopra

Keywords:
Immune checkpoint inhibitor
Immune-related adverse events
Atezolizumab
Sialadenitis

ABSTRACT

Various symptoms emerge as immune-related adverse events of immune checkpoint inhibitor (ICI).

A 73-year-old woman, a non-smoker, receiving chemotherapy including atezolizumab for lung adenocarcinoma, presented with fever, bilateral parotid swelling and sicca syndrome after four courses of chemotherapy. Because the lesions were not localized, the diagnosis was ICI-related sialadenitis rather than infectious. Prednisolone improved salivary gland swelling quickly. Six months after the last administration of ICI, there was no obvious progression of lung cancer.

To our knowledge, this is the first case of sialadenitis caused by atezolizumab. ICI-related sialadenitis may be a good prognostic marker for lung cancer.

1. Introduction

Immune-related adverse events (irAEs) caused by immune checkpoint inhibitor (ICI) often involve endocrine glands such as the pituitary, thyroid, and adrenal glands, and exocrine glands other than pancreas are rarely targeted [1]. Sialadenitis has been reported in a few cases with nivolumab, avelumab and pembrolizumab, but not with atezolizumab [2]. We here report a case of initially suspected infection of the salivary glands associated with febrile neutropenia, which was eventually diagnosed as irAEs caused by atezolizumab.

2. Case presentation

A 73-year-old woman with no smoking history had been receiving chemotherapy for 5 years for postoperative recurrence of lung adenocarcinoma with EGFR L858R mutation. Gefitinb and ramucirumab were given as first-line therapy, afatinib as second-line therapy, and osimertinib as third-line therapy. Three months earlier, the patient was started on carboplatin, paclitaxel, bevacizumab, and atezolizumab as fourth-line therapy. Two weeks after administration of four courses of chemotherapy, fever and swelling of the bilateral parotid glands appeared, and the patient was urgently admitted to the hospital the same day. She had a slight fever and swelling/fever in the bilateral parotid and submandibular glands. Dry mouth was noted, but no dryness of the eyes was observed. Blood tests showed a decreased white blood cell count of 1290/μL (neutrophils 520/μL) and an elevated C-reactive protein of 6.47 mg/dL, sug-

* Corresponding author. Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, 6-16-1 Tomioka-higashi, Kanazawa-ku, Yokohama, 236-0051, Japan.
E-mail address: baba.19049@kanagawa-pho.jp (T. Baba).

https://doi.org/10.1016/j.rmcr.2024.102068
Received 12 April 2024; Accepted 31 May 2024
Available online 4 June 2024

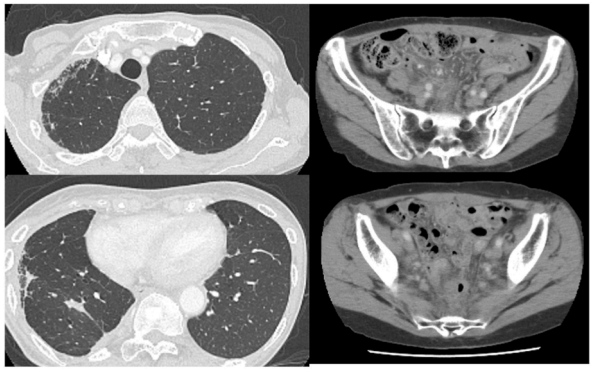


Fig. 1. On chest CT, the right lower lobe had been resected and showed right pleural thickening. Abdominal CT showed enlarged lymph nodes in the region of bilateral iliac arteries and peritoneal dissemination.

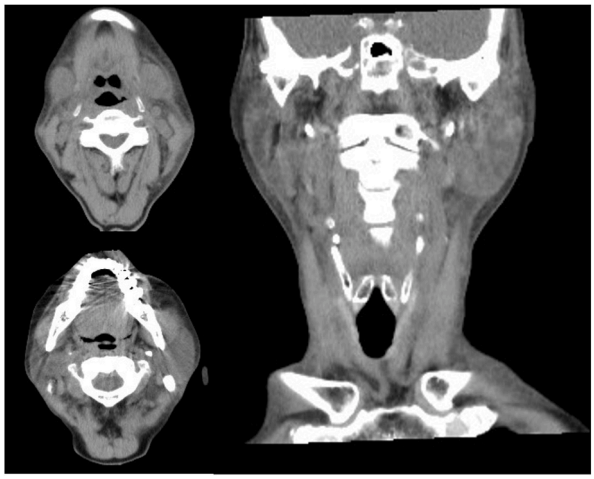


Fig. 2. Non-contrast CT of the neck showed bilateral submandibular and parotid gland swelling.

gesting the possibility of febrile neutropenia. In addition, there was an increase in S-type predominant amylase. All antinuclear antibodies including anti–SS–A and anti–SS–B antibodies were negative and serum IgG4 was within normal range. Tumor marker such as carcinoembryonic antigen and cytokeratin 19 fragment were elevated but not markedly increased compared to preadministration. Chest radiographs showed increased opacity in the right lower lung field and thickening of the right pleura due to a post-right lower lobectomy. Contrast-enhanced CT of the abdomen showed enlarged lymph nodes and peritoneal dissemination in the region of bilateral iliac arteries, but the disease status of the lung cancer was unchanged (stable disease) (Fig. 1). Non-contrast CT of the neck showed bilateral salivary and parotid gland swelling (Fig. 2). Meropenem and filgrastim were started on the day of admission for the treatment of febrile neutropenia. Sialolithiasis, bacterial sialadenitis, IgG4-related diseases, and Sjogren's syndrome were listed as differential diseases. The former two diseases were ruled out because multiple salivary glands were swollen. IgG4 and anti–SS–A and anti–SS–B antibodies were also negative leading to a diagnosis of sialadenitis caused by atezolizumab. On day 2 of hospitalization, prednisolone 25 mg (0.5 mg/kg/day) was started. Over time, serum levels of C-reactive protein and amylase decreased, bilateral salivary gland swelling improved, saliva secretion was normalized (Fig. 3). Six months later, the prednisolone has been tapered down to 2.5 mg/day, but there has been no flare-up of sialadenitis and no evidence of re-growth of the tumor.

3. Discussion

Sialadenitis as an irAE has been reported in 0.03 % of nivolumab [3]. The symptoms are reported to appear a median of about 70 days after ICI administration [2]. Secondary Sjogren's syndrome as an irAE is reported to be more prominent in salivary gland symptoms than in lacrimal gland symptoms [4]. In the present case, there was no ocular dryness, but dry mouth was prominent, and the symptoms appeared approximately 2.5 months after the ICI administration, which is consistent with previous reports.

In salivary gland biopsy specimens, CD20-positive B-cell infiltration is predominant in idiopathic Sjogren's syndrome, while CD3-positive T cells are observed more frequently in ICI-related sialadenitis [2]. Furthermore, in sialadenitis as an irAE, the higher the PD-L1 positivity of salivary gland specimens, the more severe the symptoms have been reported. Although higher PD-L1 expression has been reported to increase the incidence of irAEs, the association between PD-L1 expression and severity of irAEs is not clear [5]. PD-L1 expression in the salivary glands is not known because a salivary gland biopsy was not performed in this case.

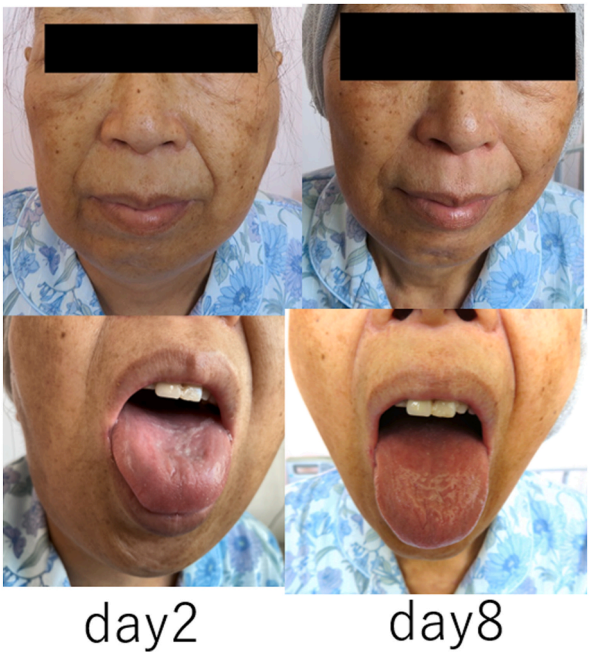


Fig. 3. Swollen salivary glands and dry mouth were noted on the second day of admission, but both symptoms improved by the eighth day.

Nivolumab and avelumab have been reported to cause salivary gland inflammation as an irAE, but to our knowledge, there have been no reported cases with atezolizumab.

ICI treatment may be interrupted in patients with salivary gland inflammation as an irAE, but ICI can be resumed after steroid treatment in some cases. In one report, seven patients were re-treated with ICI, and four of them received prednisolone to prevent worsening of the sicca syndrome, but all patients did not have a relapse of an irAE [2]. Our patient is also scheduled to resume ICI after steroid reduction.

Non-small cell lung cancer patients with irAEs such as endocrine disorders, skin lesion, and gastrointestinal diseases have been reported to have better progression-free survival and overall survival than those without irAEs [6,7], but the number of cases of sialadenitis is small and the association between the development of irAEs and antitumor efficacy is unclear. In this patient, there was no obvious progression of lung cancer even six months after the last administration of ICI, and ICI-related sialadenitis may be a good prognostic marker.

4. Conclusion

This is the first report of sialadenitis as an irAE cased by atezolizumab. ICI-related sialadenitis may be a good prognostic factor for lung cancer.

CRediT authorship contribution statement

Kosumi Kumagai: Writing – original draft. **Tomohisa Baba:** Writing – original draft. **Takashi Fukushima:** Writing – original draft. **Erina Tabata:** Writing – original draft. **Atsuhito Nakazawa:** Writing – original draft. **Eri Hagiwara:** Writing – original draft. **Tae Iwasawa:** Writing – original draft. **Takashi Ogura:** Writing – original draft.

Declaration of competing interest

This study complies with the Declaration of Helsinki. Written informed consent was obtained from the patient in the study.
The authors declare that they have no competing interests.

Acknowledgements

Not applicable.

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