



Atezolizumab Induced Sicca Syndrome: A Case Report

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: <https://doi.org/10.9734/ijmpcr/2025/v18i2414>

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://pr.sdiarticle5.com/review-history/132692>

Case Report

Received: 15/01/2025

Accepted: 17/03/2025

Published: 20/03/2025

ABSTRACT

Immune checkpoint inhibitors have made a drastic improvement in the management of cancer though it is not completely free from adverse outcomes, which may be due to the dysregulated immune system. These negative outcomes following treatment with checkpoint inhibitors are collectively known as immune related adverse events. Though there are many case reports of sicca syndrome induced by immune checkpoint inhibitors, Atezolizumab was free from this adverse outcome. In our patient care setting we observed sicca syndrome in one elderly patient during treatment with Atezolizumab. It was managed with corticosteroids; pilocarpine eye drops and other standard care of treatment.

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Keywords: Atezolizumab; immune checkpoint inhibitors; immune related adverse events; sicca syndrome.

1. INTRODUCTION

"Immune checkpoint inhibitors have transformed the prognosis of several advanced malignancies, establishing new standard of care in both adjuvant and metastatic settings. It is unfortunate that their higher potency and wide use are being limited by rare but often life-threatening adverse effects that is different from the existing range of adverse effects of chemotherapy" (Juřica et al., 2022). "The use of immune checkpoint inhibitors causes wide range of immune side effects, known as immune-related adverse events (irAEs), which may affect any organ. The immunological mechanisms beyond irAEs haven't been fully illustrated" (Ghosn et al., 2018). Although immune checkpoint inhibitors' use continues to increase, consequences of these therapies as a result of inducing autoimmunity or through other mechanisms are only beginning to be understood. The data from literature (Khan & Gerber, 2020) showed an incidence of irAE occurs up to 60% for immune checkpoint inhibitors and 10–30% for more severe grades (G 3-4). These adverse effects do not appear to be dose-dependent (Juřica et al., 2022)

Atezolizumab is a monoclonal antibody targeting programmed death ligand 1 (PD-L1 antigen). It selectively targets PD-L1 to prevent interaction with receptors PD-1 & B7-1, thus reversing T-cell suppression. The most common adverse reactions ($\geq 20\%$) with Atezolizumab in combination with Bevacizumab in patients with Hepatocellular carcinoma (HCC) were hypertension, fatigue and proteinuria (Finn et al., 2020).

Sicca syndrome is a systemic disease characterised by lymphocytic infiltration mainly in exocrine glands - salivary and lacrimal glands. Dry eyes and xerostomia are the most common glandular symptoms of sicca syndrome. Sicca syndrome has not been observed as an adverse effect of Atezolizumab so far even though it has been reported as an adverse effect of other immune checkpoint inhibitors such as Nivolumab or Ipilimumab (Warner et al., 2019). Immune checkpoint inhibitors induced sicca syndrome is likely underdiagnosed, even though it has a significant impact on the quality of life (Bitoun et al., 2024).

In the general population, sicca syndrome considerably reduces the quality of life. Here we report a rare case involving an elderly man who developed sicca syndrome as an adverse event of immunotherapy with Atezolizumab for HCC.

2. CASE PRESENTATION

A 54-year-old man was diagnosed with Hepatocellular carcinoma with portal vein thrombosis in 2020. The patient underwent laparotomy and the tumor was found to be inoperable and therefore, he was started on Lenvatinib. The standard treatment option for unresectable hepatocellular carcinoma is either treatment with lenvatinib or sorafenib, taking into consideration the potential side effects of sorafenib as well as patient's financial constraints, the patient was started initially on lenvatinib and not on sorafenib but as the disease showed progression he had to be started on other treatment options. With progression of the disease evidenced by rising alpha feto protein (AFP) values, he was started on chemotherapy with liposomal Doxorubicin. As a result, the AFP values decreased from 7100 to 250. After 12 courses of chemotherapy the AFP value became relatively constant. In view of this, the patient had undergone TACE (Trans arterial chemo embolization) procedure twice after which he was treated with Cabozantinib. It had to be discontinued as the patient developed cerebrovascular accident. The patient subsequently underwent SBRT (Stereotactic body radiation therapy) to liver. He was later started on immunotherapy using combination of Atezolizumab and Bevacizumab as AFP values continued to rise.

He experienced diminished vision after few days of 1st course of immunotherapy. The patient presented with complaints of mild dryness of eyes which was initially treated in an outside hospital with artificial tear eye drops. He also experienced dryness of lips as well as reduced salivary secretion. After the 5th course, patient experienced more prominent symptoms including absence of sweat secretions along with weight loss. The patient also had complaints about blurred vision even though he was on treatment with eye drops hence, Schirmer's test was

carried out and wetness of the eye was found to be 0 % as there was no wetness observed in the strip (0 mm). The wet area length of 0-5 mm indicates extremely dry eyes whereas, longer than 15mm indicates normal tear production. He was also diagnosed with left side parotitis. Ultrasound scan revealed Left side parotid gland showing heterogenous echotexture.

The patient was symptomatically managed with Pilocarpine, Polyethylene glycol ophthalmic solution, artificial tear eye drops - Hydroxypropylmethyl cellulose eye drops and Hyaluronic acid eye gel ointment for dryness of eyes. Triamcinolone buccal paste, Chlorhexidine gluconate mouth wash for buccal dryness and Dexamethasone 4mg daily. Dietary modifications were also recommended as to include more fluid/soft liquid-diet. On further follow up after a month, there was an improvement in lacrimal function evidenced by the Schirmer's test with wetness of both eyes improving to wet-area Length of greater than 10 mm in both eyes. Dexamethasone was discontinued as the patient developed hyperglycaemia.

A causality assessment was done and his observed adverse drug reaction (ADR) was categorized as "probable" by both Naranjo and the World Health Organization (WHO) causality assessment scales. The severity was evaluated using Hartwig's Severity Assessment Scale, which classified the reaction as a level 3 moderate.

3. DISCUSSION

Immune checkpoint therapy is associated with autoimmune induced sicca syndrome distinct from Sjögren's syndrome, with abrupt onset which generally develops within the first 3 months of treatment with associated sialadenitis and glandular injury. Sialadenitis has been previously reported with other immune checkpoint inhibitors such as nivolumab (Takahashi et al., 2018). Improvement can be obtained with graded approach depending on severity, including withholding the ICI and initiation of corticosteroids. Deep deficits in salivary flow, however might not go away quickly (Warner et al., 2019). Additionally, Sjogren's syndrome exhibits inflammatory cells infiltrating the internal ducts of the salivary gland lobules and CD 20+ B cells forming a follicular structure and infiltrating the ductal

epithelial structures, while sicca syndrome include CD3+ T-cell infiltration into the salivary glands (Warner et al., 2019). Clinical characteristics include xerostomia, ocular dryness, and reduced salivary secretion in tests are similar to those of Sjogren's syndrome (Segawa et al., 2023).

Atezolizumab, is an immune checkpoint inhibitor that works by binding to the protein PD-L1 which keeps the cancer cells from suppressing the Immune system. Sicca syndrome caused by Immune checkpoint inhibitors was first reported by Cappelli et al. in 2017. In that study conducted in patients receiving ICI, it was observed that Nivolumab and Ipilimumab caused sicca syndrome along with inflammatory arthritis. In a case report by Segawa T et al., a 70-year-old man receiving Ipilimumab and Nivolumab therapy for metastatic renal cell carcinoma was found to have sicca syndrome. After 13 weeks of treatment, he experienced xerostomia and dysgeusia. A salivary gland biopsy revealed the infiltration of lymphocytes and plasma cells into the salivary gland. The ultimate diagnosis was sicca syndrome as an irAE caused by ICI (Segawa et al., 2023).

Sicca syndrome can be symptomatically managed with or without corticosteroids. According to a report by Warner et al., using corticosteroids or stopping ICI nearly completely cured the illness (Warner et al., 2019). In contrast, Brugués et al. reported that there was no need to stop ICI treatment because they discovered that in half of their patients, xerostomia alleviated with basic oral care without the need for corticosteroids (Ortiz Brugués et al., 2020). Segawa T et al reported that sicca syndrome was managed with the use of Pilocarpine hydrochloride (15 mg/day) initiated without corticosteroids, while ICI therapy was continued (Segawa et al., 2023). In this case, grade 2 xerostomia was treated with oral care and Pilocarpine, and it alleviated without the use of corticosteroids or discontinuation of ICI treatment. In our case also, the patient was managed with Pilocarpine and other ophthalmic agents along with corticosteroids which was later on discontinued.

A report by Kumagai K et al., (2024) showed a case of sialadenitis as an irAE of atezolizumab and also that irAEs in Non-small cell lung cancer patients have been reported to have better progression-free survival and overall survival

than those without irAEs, but the reported cases of sialadenitis is small and the association between the development of irAEs and antitumor efficacy is unclear. In this report, it showed that there was no obvious progression of lung cancer even six months after the last administration of ICI, and thus ICI-related sialadenitis could also be a good prognostic marker (Kumagai et al., 2024).

4. CONCLUSION

Though, sicca syndrome is a rare adverse outcome of treatment with Atezolizumab, it can be considered as an immune check point inhibitors class effect likely arising from a dysregulated immune response as the same kind of syndrome occurred with other Immune check point inhibitors. Selecting appropriate management options for Sicca syndrome is also important as different management options though limited, are available.

CONSENT

The authors have obtained written consent from the patient to conduct the study.

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
<https://pr.sdiarticle5.com/review-history/132692>