***Case report***

**ATEZOLIZUMAB INDUCED SICCA SYNDROME: A CASE REPORT**

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.

Keywords:

irAEs – immune related adverse events

ICI – Immune checkpoint inhibitors

PD-L1 – programmed death ligand 1

HCC – hepatocellular carcinoma

AFP – alpha feto protein

**INTRODUCTION**

Immune checkpoint inhibitors have transformed the prognosis of several advanced malignancies, establishing new standard of care in both adjuvant and metastatic settings. 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 [1]. 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.

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 (≥ 20%) with Atezolizumab in combination with Bevacizumab in patients with Hepatocellular carcinoma (HCC) were hypertension, fatigue and proteinuria. (provide citation)

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[2].Here we report a rare case involving an elderly man who developed sicca syndrome as an adverse event of immunotherapy with Atezolizumab for HCC.

**CASE HISTORY** (EXPLAIN – why the standard sorafenib regimen was not used)

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. 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 had complaints of mild dryness of eyes. He also experienced dryness of lips as well as reduced salivary secretion. (Provide staging of the dryness as per Schirmer’s test – it is mandatory if dryness of eyes is being diagnosed) Symptomatic treatment was provided to the patient. After the 5th course, patient experienced absence of sweat secretions along with other symptoms including weight loss. Schirmer’s test was carried out and wetness of the eye was found to be 0 %. (This is not how Schirmer’s test result is classified – please describe the length at which the rim broke) 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 as well as artificial tear eye drops (Lacryl eyedrops) and Aquim eye gel ointment (Hyaluronic acid) for dryness of eyes (mandatory to cite official brand information page if being mentioned). Caziq buccal paste (triamcinolone), Clohex mouth wash (Chlorhexidine gluconate) for buccal dryness and Dexamethasone 4mg daily. Dietary modifications were also recommended as to include more fluid/soft liquid-diet. Dexamethasone was discontinued as the patient developed hyperglycaemia. There was an improvement in lacrimal function evidenced by the Schirmer’s test with wetness of both eyes improving to greater than 10%.

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.

**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. 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. 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. Clinical characteristics include xerostomia, ocular dryness, and reduced salivary secretion in tests are similar to those of sjogren’s syndrome (citation).

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 [3]. 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 [4].

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.[2] 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 [5]. 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 [4]. 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.

**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.

**COMPETING INTERESTS DISCLAIMER**

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

**REFERENCE** (provide 5-10 more citations including those mentioned in the peer-review)

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