PD-1 inhibitor–associated Sicca syndrome mimicking Sjögren's disease successfully managed without immunotherapy withdrawal

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Abstract

Immune checkpoint inhibitors (ICIs) are increasingly associated with a broad spectrum of immune-related adverse events (irAEs), including rheumatic manifestations. We report a case of ICI-associated sicca syndrome (ICI-S) mimicking Sjögren's disease, with a brief literature review. The patient was a 70-year-old man with BRAF-mutated metastatic melanoma who developed inflammatory arthralgias followed by parotid and submandibular enlargement, severe xerostomia, and xerophthalmia, during pembrolizumab therapy. Treatment was withheld and low-dose glucocorticoids (GC) initiated, with rapid improvement of joint symptoms and gland swelling, although marked xerostomia persisted. The diagnostic work-up revealed elevated inflammatory markers and positive antinuclear antibodies (ANA), with negative anti-SSA/SSB. Salivary gland ultrasound showed grade 3 changes (OMERACT) and PET-CT confirmed bilateral sialadenitis. Minor salivary gland biopsy demonstrated T-cell–predominant lymphocytic infiltrate without CD20+ B cells, supporting an ICI-S rather than primary Sjögren's disease. Pembrolizumab rechallenge triggered a flare of sialadenitis and arthritis, controlled with GC reintroduction plus hydroxychloroquine and supportive measures. This case provides educational insights into the diagnostic differentiation between ICI-S and primary Sjögren's disease, supporting early recognition and appropriate management without compromising oncologic treatment.

Keywords: Mimickers; Arthritis; Rheumatology; Immune-related adverse events; Immunotherapy; Sjogren's syndrome.

Introduction

The expanding indications for immune checkpoint inhibitors (ICI) have reshaped modern oncology but introduced a new spectrum of immune-related adverse events (irAEs) that increasingly intersect with rheumatology practice. ICI enhance antitumor immune responses by blocking inhibitory molecules such as CTLA-4, PD-1, and PD-L1, thereby enhancing T-cell activation. However, their growing use has been accompanied by a rising incidence of irAEs, which can affect virtually any organ system. Rheumatic irAEs are less frequently reported, but clinically significant, encompassing inflammatory arthritis, arthralgia, myositis, and sicca syndrome[1].

They may arise de novo or as a flare of a previously known autoimmune disease[2]. Such presentations may mimic established rheumatic conditions, posing significant diagnostic challenges.

We report a case of sicca syndrome developing after initiation of pembrolizumab, a PD-1 inhibitor, in a patient with metastatic melanoma.

Case report

A 70-year-old male with BRAF-mutated metastatic melanoma of occult primary was started on second line treatment with pembrolizumab (400 mg every 6 weeks), a PD-1 ICI, after disease progression on dabrafenib and trametinib**.** He had multiple cardiovascular risk factors, but no personal or family history of inflammatory rheumatic disease.

After three months of immunotherapy, he developed mild asthenia, anorexia with weight loss and inflammatory arthralgias affecting shoulders, wrists, hands, and knees. Ten months after initiating ICI, he experienced sudden onset of painless swelling of the parotid and submandibular glands, followed by xerostomia, hypogeusia and difficulty swallowing due to dryness, along with a burning sensation on the tongue.

Pembrolizumab was temporarily suspended and the patient was referred for rheumatological evaluation. Low dose prednisolone (PDN) 5 mg/day was initiated, with marked improvement, complete resolution of joint symptoms and reduction of parotid swelling. However severe oral dryness persisted, significantly impairing his quality of life.

On examination, he had a depapillated, erythematous and dry tongue and mild parotid swelling with firm, painless enlargement of the submandibular glands (Figures 1 and 2A).

He also reported xerophthalmia, which was confirmed by a positive Schirmer's test. Although no clinical signs of arthritis were identified, ultrasound revealed tenosynovitis of the right long biceps' tendon, subacromial–deltoid bursitis, and tenosynovitis of multiple flexor and extensor tendons in both wrists, suggesting inflammatory involvement.

The complementary work-up revealed positive antinuclear antibodies (ANA), with an AC-3 centromere pattern (titre 1:640) and an AC-4 fine speckled nuclear pattern (titre 1:160), with negative SS-A and SS-B, rheumatoid factor, and anti-citrullinated protein antibodies. Inflammatory markers were elevated, with a C-reactive protein (CRP) ranging from 2 to 6.7 mg/dL (normal < 0.5 mg/dL) and an erythrocyte sedimentation rate (ESR) of 42 mm/h. Serum angiotensin-converting enzyme, C3, C4, IgG4, and serum protein electrophoresis were within normal limits, and serologies for hepatitis C and HIV were negative.

Salivary gland ultrasound confirmed marked parenchymal heterogeneity with poorly defined borders and multiple sialectasis, consistent with grade 3 on the OMERACT scoring system. A follow-up PET-CT demonstrated bilateral increased ^{18}F-FDG uptake in the parotid and submandibular glands, consistent with sialadenitis (Figure 3A).

Oral GC were gradually tapered over a three-week period and hydroxychloroquine (400 mg/day) initiated. Artificial tears, pilocarpine, a saliva substitute, and measures to ensure adequate oral hygiene were introduced for the management of sicca symptoms. Xerophthalmia resolved, while xerostomia showed only mild improvement.

Pembrolizumab was restarted after a minor salivary gland biopsy which demonstrated periductal lymphocytic infiltration predominantly composed of CD3+ T cells, including both CD4+ and CD8+ subsets, with absence of CD20+ B cells. The focus score was 0.22 foci/4 mm², with no evidence of germinal centre formation or significant acinar destruction or fibrosis.

Three weeks after pembrolizumab was restarted, there was recurrence of painless parotid and submandibular enlargement and wrist arthritis, requiring reintroduction of PDN 7.5 mg/day. Arthritis resolved rapidly, while submandibular enlargement and xerostomia improved more gradually, with complete resolution after seven months of treatment (Figure 2B). A subsequent PET-CT performed eight months after treatment demonstrated a marked reduction in ^{18}F-FDG uptake in the salivary glands, consistent with clinical improvement (Figure 3B).

The chronological sequence of clinical events is summarised in Table I.

The patient is currently receiving pembrolizumab 200 mg every three weeks, with maintenance therapy including PDN 5 mg on alternate days and hydroxychloroquine. To date, two years after initiating pembrolizumab, the patient remains in complete oncologic remission for the last year. No additional irAEs were identified during follow-up, namely neurological, cardiac, or pulmonary toxicities. Discontinuation of pembrolizumab is currently under consideration.

Discussion

The reported prevalence of ICI-associated sicca syndrome (ICI-S) varies across published cohorts, ranging from 2% to 11%[3]. The vast majority of reported cases have occurred in individuals treated with PD-1 inhibitors, accounting for approximately 95% of those described[4]. In comparison, ICI-induced inflammatory arthritis develops in approximately 5–7% of patients and is similarly most often reported in association with PD-1 blockade[5, 6].

The mechanisms underlying ICI-S remain uncertain. A potential role for individual genetic susceptibility has been suggested and may partly account for reports of flares of pre-existing Sjögren's disease in patients exposed to ICI[4].

A comprehensive diagnostic assessment is essential to document objective exocrine gland inflammation, including clinical evaluation, laboratory testing, imaging, and biopsy.

In our case, although primary Sjögren's disease was the leading differential diagnosis, several clinical and pathological features favoured the distinct ICI-S. The patient did not fulfil the 2016 ACR/EULAR classification criteria for primary Sjögren's disease, meeting only one criterion (positive Schirmer's test). Anti-SSA antibodies were negative, and minor salivary gland biopsy lacked the histopathological features typically required for classification.

Although a high-titre centromere-pattern ANA was detected, the patient had no Raynaud's phenomenon, skin thickening, telangiectasia, interstitial lung disease, or other features of systemic sclerosis. The ANA positivity was therefore interpreted as part of ICI–induced autoimmunity, rather than raising suspicion of systemic sclerosis–associated sicca.

Notably, the patient was not taking any medications typically associated with xerostomia, including anticholinergic agents, had no history of head-and-neck radiotherapy, and his diabetes was well controlled, making a drug or treatment-induced sicca syndrome unlikely.

In ICI-S, a male predominance has been reported, with a mean age at diagnosis approximately ten years higher than in primary Sjögren's disease[4]. Unlike our patient, approximately 20% of described cases have a personal or family history of autoimmune disease[4].

An abrupt and severe onset has been described, often occurring within the first few months of therapy in published small case series[2]. Xerostomia is typically the most reported feature, whereas xerophthalmia tends to be less prominent[4]. These findings differ from the sicca syndrome typically seen in older individuals or in patients with Sjögren's disease. In our patient, the degree of oral dryness met criteria for grade 2 xerostomia, as it clearly interfered with oral intake. Mild (grade 1) disease is generally limited to bothersome dryness without functional

impairment, whereas severe (grade 3) xerostomia is characterised by marked disability, sometimes necessitating tube feeding or parenteral nutritional support[3].

Another important diagnostic clue lies in the reduced frequency of classical Sjögren's disease autoantibodies, resulting in a predominantly seronegative phenotype that may help differentiate ICI-S from primary Sjögren's disease[4].

Descriptions of salivary gland ultrasound findings in ICI-S remain limited. The available data describe typically mild abnormalities, including parenchymal heterogeneity with hyperechoic bands and hypoechoic areas, which have been reported to persist over time[2]. However, our patient exhibited higher-grade glandular involvement (OMERACT grade 3), suggesting a broader spectrum of imaging severity.

Histologically, both Sjögren's disease and ICI-S exhibit focal lymphocytic sialadenitis. However, the composition of the inflammatory infiltrate differs, being predominantly T-cell–driven in ICI-S and B-cell–dominated in Sjögren's disease. Prior studies have further characterized this infiltrate as composed mainly of CD3+ T cells, with a slight predominance of CD4+ over CD8+ subsets and a relative paucity of CD20+ B cells. Immunohistochemical analyses have additionally demonstrated variable PD-1 expression in infiltrating lymphocytes and PD-L1 positivity in the epithelium in areas of dense inflammation, as well as in some inflammatory cells in the most severe cases of sialadenitis[2]. Together, these features provide important diagnostic clues for distinguishing ICI-S from primary Sjögren's disease.

Regarding therapeutics, a balance must be achieved to provide symptom control while preserving the antitumor activity of ICI[1]. The rationale for the low-dose GC strategy warrants comment. Although our initial GC dose was more conservative than current guidelines—which recommend prednisone 20–40 mg/day for 2–4 weeks in moderate to severe xerostomia and 10–20 mg/day for moderate inflammatory arthritis—the favourable clinical response, the patient's comorbidities and evidence suggesting that low-dose GC do not appear to significantly compromise ICI efficacy supported this individualised approach[1, 3]. However, a flare developed after GC discontinuation, with rapid clinical response following re-introduction, highlighting the potential need for more gradual down-titration in selected ICI-related inflammatory presentations. Hydroxychloroquine was also introduced, consistent with data from case series suggesting it may be an effective first-line option for ICI-associated inflammatory arthritis[8]. Inflammatory markers paralleled clinical evolution, with ESR and CRP declining after treatment reintroduction and ESR normalising alongside symptom improvement[3].

In our case, arthritis resolved rapidly, whereas xerostomia showed a more gradual recovery, requiring supportive measures such as pilocarpine and saliva substitutes, despite immunosuppressive therapy. Prior reports indicate that, although symptoms may improve,

salivary secretion can remain reduced and deficits may be long term, suggesting variable recovery of glandular function[2].

In some cases, permanent discontinuation of ICI is required due to severe irAEs and their impact on quality of life. In this case, symptom improvement after temporary drug withdrawal followed by recurrence upon reintroduction strengthened the causal link and constitutes a pharmacological positive rechallenge. However, irAEs remained manageable, allowing continuation of pembrolizumab until complete oncologic remission was achieved.

This case illustrates the distinctive clinical presentation of ICI-S and the diagnostic challenges it may pose in differentiating it from primary Sjögren's disease and other mimics. Early recognition and tailored immunomodulatory therapy achieved effective symptom control without requiring interruption of cancer therapy.

Overall, no single test reliably distinguishes ICI-S from primary Sjögren's disease. Accurate diagnosis depends on the careful integration of clinical, serological, imaging, and histopathological findings, enabling timely immunomodulatory treatment without compromising oncologic efficacy. Close multidisciplinary collaboration between rheumatology and dermato-oncology proved pivotal in balancing irAEs against immunotherapy interruption, rechallenge, and continuation, enabling individualized management while preserving oncologic outcomes.

Tables and Figures

Table I. Timeline of clinical events following pembrolizumab initiation.

Time from ICI initiation	Clinical events	Management / Outcome
Baseline	Pembrolizumab initiated (400 mg q6w)	
3 months	Inflammatory arthralgias (shoulders, wrists, hands, knees); constitutional symptoms	
10 months	Parotid and submandibular enlargement, xerostomia and xerophthalmia	Pembrolizumab temporarily withheld; PDN 5 mg/day initiated
	Arthralgias improved; salivary swelling reduced; persistent xerostomia	PDN tapered; HCQ initiated; minor salivary gland biopsy performed
11 months		PDN stopped Pembrolizumab rechallenge (200 mg q3w)
11 months 3 weeks	Flare of sialadenitis and wrist arthritis	PDN 7.5mg/day reintroduced
12 months	Arthritis resolved	PDN 5 mg on alternate days
15 months	PET-CT: reduced salivary gland uptake	
19 months	Xerostomia resolved	
24 months	Sustained oncological remission	Pembrolizumab continued

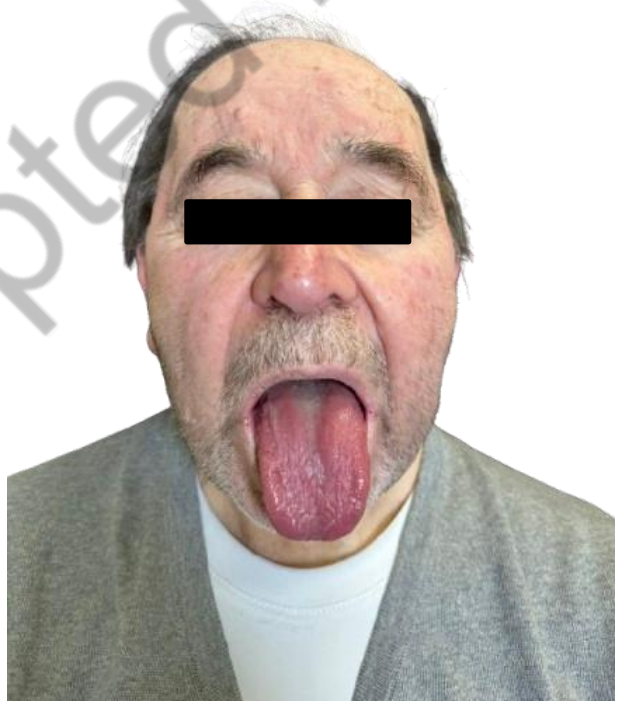

Figure 1: Depapillated, erythematous, and dry tongue in the setting of ICI-associated sicca syndrome.

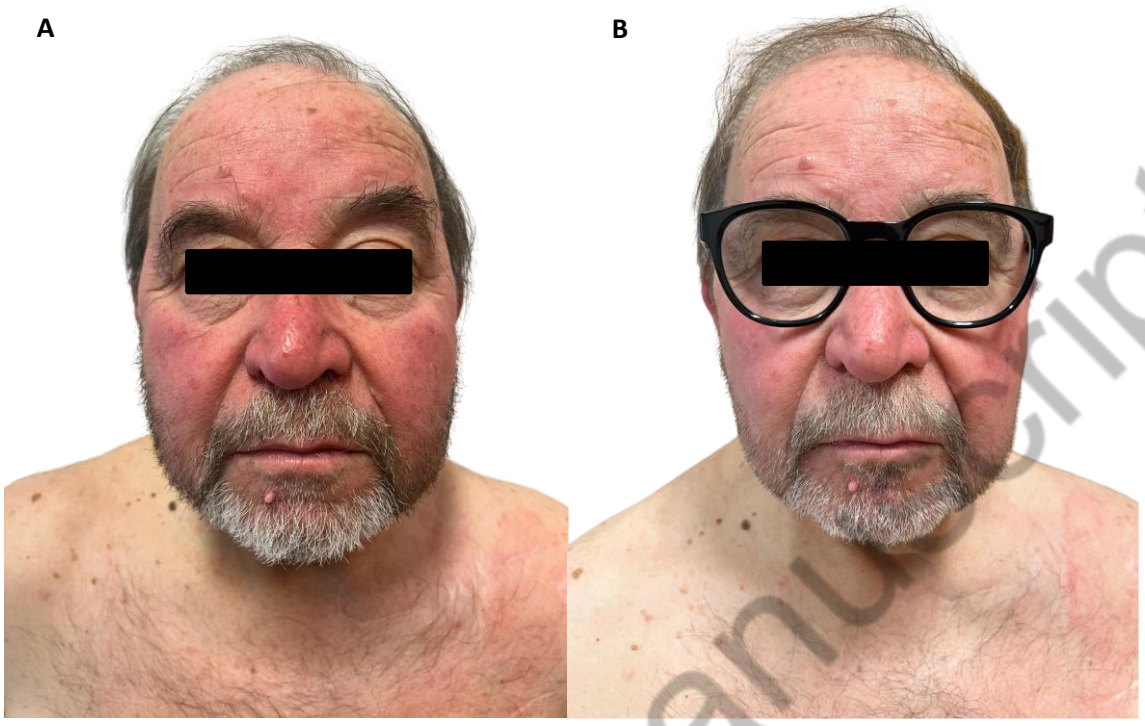

Figure 2: A - Bilateral parotid gland enlargement developing during pembrolizumab treatment; **B -** After four months of treatment with prednisolone and hydroxychloroquine, with complete clinical resolution of the salivary gland enlargement.

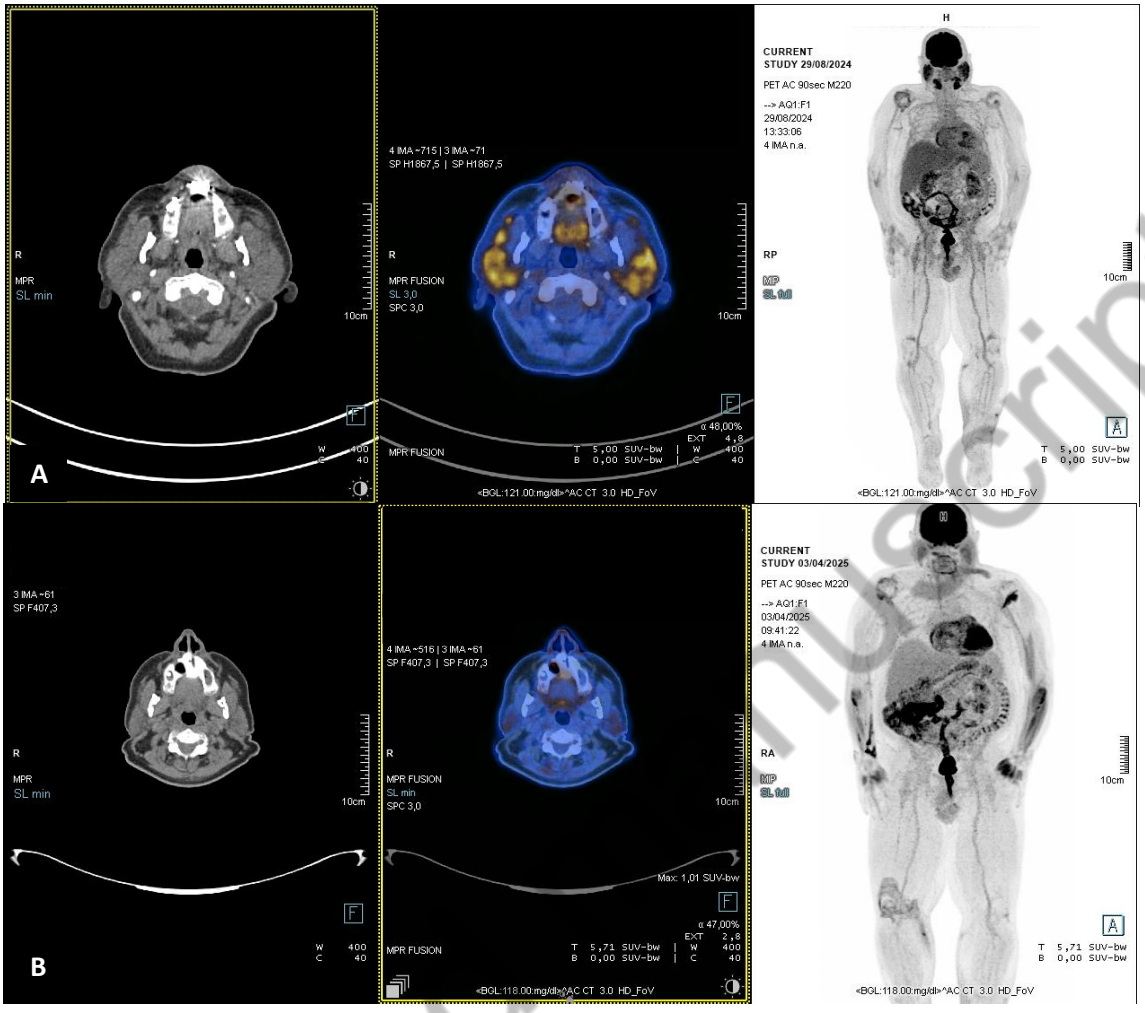

Figure 3: A - Whole-body PET-CT scan demonstrating increased 18F-FDG uptake in the parotid and submandibular glands (upper panel) at the time of diagnosis of immune checkpoint inhibitor-associated sicca symptoms. **B –** Following 8 months of therapy, marked reduction in salivary gland uptake is observed, with no evidence of metastatic lesions (lower panel).

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