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Sicca Syndrome Induced by Immune Checkpoint Inhibitor Therapy: Optimal Management Still Pending

We read with great interest the recent work by Warner et al. [1], who reported 20 patients developing sicca syndrome (SS) associated with immune checkpoint inhibitor (ICI) therapy. They characterized clinicopathologic features of SS in patients treated with ICIs. We also evaluated 15 patients with metastatic cancer who developed SS under ICIs (anti-programmed cell death protein 1/programmed death-ligand 1, anti-cytotoxic T-lymphocyte-associated protein 4 or ICI under development, either in monotherapy or in combination; Table 1). Accessory salivary gland biopsy was performed in all cases (Fig. 1), suggesting an absence of correlation between SS clinical grade induced by ICIs and histologic classification. Like Warner et al., our ancillary immunostaining analysis suggested that ICI-related SS is mediated by an immunologic mechanism through the triggering of cytotoxic CD4+/CD8+ T-cell activation (Fig. 2A–2C).

However, we reported one patient with grade 3 xerostomia (Fig. 3) and no history of pre-existing autoimmune disease who developed Sjögren's syndrome under ICI therapy according to American College of Rheumatology/European League Against Rheumatism criteria [2].

We have some concern that systemic corticosteroids and/or discontinuation of immunotherapy may represent the first-line therapy for grade 2–3 SS, as suggested by Warner et al. Although most of their patients treated with oral corticosteroids seemed to ameliorate (8/10), objective improvement in whole unstimulated saliva flow remained of mild benefit. Moreover, ICIs were held simultaneously in eight of the improved patients, so the impact of oral corticosteroids alone is difficult to assess. Furthermore, the only patient treated with oral corticosteroids without holding ICI (patient 4) did not ameliorate. Also, SS improved without oral corticosteroids in two patients (patients 17 and 18) in whom ICIs were stopped as a result of completed protocol. We observed a slight to moderate progressive improvement after discontinuation of ICIs in eight of our patients (because of either tumor progression or other severe immune-related adverse events [irAEs]). Two of our patients were significantly relieved by a short course of prednisolone (1 mg/kg/day) prescribed for grade 3 transaminitis.

As SS is immune related, we can speculate that oral corticosteroids may benefit patients with ICI-induced SS. However, proposing oral corticosteroids for grade 2–3 SS seems premature (Table 2) [6–10]. In our series, basic oral care [5] without oral corticosteroids led to a mild improvement in almost half of our patients.

Neither interruption nor discontinuation of ICIs due to oral symptoms was required in any of our cases. Holding ICIs in patients who develop SS, a non-life-threatening adverse event, should be a case-by-case multidisciplinary issue, because ICIs may potentially impact tumor response and/or overall survival. Prospective randomized studies with objective measures are required to assess the impact of high-dose oral corticosteroids (0.5–1 mg/kg/day) on the management of this irAE, in order to define the optimal dose and duration of the treatment.

In the meantime, we would propose a new algorithm adapted from the one by Warner et al. and according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0:

GRADE 1: Basic oral care. Maintain ICI therapy and reassess within 2 weeks.

GRADE 2: Reinforce grade 1 management. Discuss introduction of pilocarpine/anetholtrithione. Maintain ICI therapy and reassess within 2 weeks.

INTOLERABLE GRADE 2: Consider grade 3 management.

GRADE 3: Refer to Grade 2 management. Multidisciplinary decision to introduce oral corticosteroids (0.5–1 mg/kg/day)

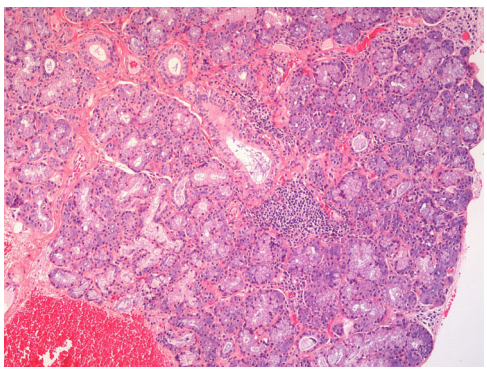

Figure 1. Lymphohistiocytic infiltrate surrounding salivary glands (hematoxylin and eosin staining, original magnification ×10).

Table 1. Clinical, histological, and immunostaining features of sicca syndrome in patients treated with ICIs

Patient no. (sex/age, yr)	Metastatic cancer	ICI	Time to onset, wk	Clinical grading[a]	Histological[b] ± immunostaining features	Immunological findings	Other irAEs	Management and outcome/tumor response to ICI
1 (M/42)	Renal adenocarcinoma	Anti-PD1	36	2	0 (no lymphocytic infiltrate)	Anti-SSA/SSB: negative	Pruritus Psoriasis Xerophthalmia Myalgia and arthralgia	No specific symptomatic measures Tumor response: ICI continued
2 (M/60)	Melanoma	Anti-PD1 + ICI under development	4	1	0	Anti-SSA/SSB: negative	Psoriasiform eruption Hemorrhagic rectocolitis Acute pancreatitis Xerophthalmia	Symptomatic measures[c] for xerostomia: mild improvement Tumor progression: ICI discontinued
3 (F/61)	Oral squamous cell carcinoma	Anti-PD1 + ICI under development	4	2	1	Anti-SSA/SSB: negative	Myalgia Hypothyroidism Pruritus Dysgeusia	Symptomatic measures[c] for xerostomia: mild improvement Tumor progression: ICI discontinued
4 (F/78)	Melanoma	Anti-PD1 + anti-CTLA-4	8	2	2	Anti-SSA/SSB: negative	Exanthema Vitiligo Hepatic cytolysis Hypothyroidism Xerophthalmia	Symptomatic measures[c] for xerostomia + short course of oral corticotherapy (1 mg/kg/day) for grade 3 hepatic cytolisis: improvement Tumor stability: ICI discontinued because of hepatic cytolysis
5 (M/63)	Oral squamous cell carcinoma	Anti-PD1	8	3	2	Anti-SSA/SSB: negative	Eczematiform reaction Pruritus Dysgeusia	Symptomatic measures[c] for xerostomia: no information about outcomes Follow-up discontinued by patient
6 (F/65)	Endometrial adenocarcinoma	Anti-PD1	28	3	0	Anti-SSA/SSB: negative	Myalgia Xerophthalmia	Symptomatic measures[c] for xerostomia: mild improvement Tumor progression: ICI discontinued
7 (F/71)	Endometrial adenocarcinoma	Anti-PD1	8	2	0	Anti-SSA/SSB: negative	Xerosis Xerophthalmia	Symptomatic measures[c] for xerostomia: mild improvement Tumor progression: ICI discontinued
8 (M/68)	Renal adenocarcinoma	Anti- PD1	12	3	1	Anti-SSA/SSB: negative	Myalgia Palmar desquamation	Symptomatic measures[c] for xerostomia: mild improvement Tumor progression: ICI discontinued

(continued)

Table 1. (continued)

Patient no. (sex/age, yr)	Metastatic cancer	ICI	Time to onset, wk	Clinical grading[a]	Histological[b] ± immunostaining features	Immunological findings	Other irAEs	Management and outcome/tumor response to ICI
9 (F/76)	Melanoma	Anti-PD1	68	2	2 (2/3 T cells CD4+, 1/3 T cells CD8+)	Anti-SSA/SSB: negative	Xerosis Prurigo Xerophthalmia	Symptomatic measures[c] for xerostomia: no improvement Tumor stability: ICI continued
10 (F/47)	Melanoma	Anti-PD1 + anti-CTLA-4	20	1	2	Anti-SSA/SSB: negative	Sarcoidosis-like Hepatitis Nephritis	No specific symptomatic measures Patient died
11 (F/39)	Melanoma	Anti-PD1 + anti-CTLA-4	2	3	3 (2/3 T cells CD4+, 1/3 CD8+)	Anti-SSA/SSB: negative	Myalgia Hepatic cytolysis Erythema nodosum Xerosis Parotid glands swelling	Symptomatic measures[c] for xerostomia + short course of oral corticotherapy (1 mg/kg/day) for grade 3 hepatic cytolysis: improvement Tumor stability: ICI discontinued because of hepatic cytolysis
12 (M/74)	Non-small cell lung carcinoma	Anti-PD1	16	3	2 (2/3 T cells CD4+, 1/3 T cells CD8+)	Anti-SSA/SSB: negative	Xerosis	Symptomatic measures[c] for xerostomia: no information about outcomes Follow-up discontinued by patient
13 (M/62)	Pancreatic adenocarcinoma	Anti-PD1 + ICI under development	28	2	1 (2/3 T cells CD4+, 1/3 T cells CD8+)	Anti-SSA/SSB: negative	Skin rash Arthralgia Dysgeusia	Symptomatic measures[c] for xerostomia: mild improvement Tumor response: ICI continued
14 (M/74)	Melanoma	Anti-PD1 + ICI under development	12	2	1 (2/3 T cells CD4+, 1/3 T cells CD8+)	Anti-SSA/SSB: negative	Pruritus Hypothyroidism	Symptomatic measures[c] for xerostomia: mild improvement Tumor progression: ICI discontinued
15 (M/69)	Oral squamous cell carcinoma	Anti-PD-L1	4	3	4 (2/3 T cells CD4+, 1/3 T cells CD8+)	Positive anti-SSA/SSB Positive rheumatoid factor Cryoglobulinemia	Xerophthalmia Hypothyroidism	Symptomatic measures[c] for xerostomia: mild improvement Tumor stability: ICI continued

[a]NCI-CTCAE v.5.0.
[b]Chisholm-Mason grade.
[c]Symptomatic measures for xerostomia: hydration, gum, oral hygiene, anetholtrithione/pilocarpine, salivary substitute.
Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; F, female; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; M, male; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PD1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; SSA, anti-Sjögren's-syndrome-related antigen A; SSB, anti-Sjögren's-syndrome-related antigen B.

Table 2. Reported cases of sicca syndrome induced by ICIs [1, 3, 4, 6–10]

Article	No. of sicca syndrome cases/all enrolled patients	Metastatic cancer	ICI	Time to onset, wk	Clinical grading[a]	Accessory salivary glands biopsy	ANA	Anti-SSA/SSB	Other irAEs
Calabrese et al. 2017	5/13	Renal cell carcinoma, melanoma	Anti-PD1 alone or + anti-CTLA-4; anti-PD-L1 alone	2–21.9	Not specified	Not performed	2/5	1/5 anti-SSA	Polymyalgia rheumatica Arthritis Keratoconjunctivitis
Cappelli et al. 2017	4/13 (1/4 with bilateral parotid gland swelling)	NSCLC, melanoma	Anti-PD1 alone; anti-CTLA-4 alone; Combination	8–32	Not specified	Not performed	3/4 1/4 rheumatoid factor	1/4 anti-SSB	Pneumonitis Nephritis Colitis
Teyssonneau et al. 2017	1 case reported (1 Sjögren-like syndrome)	Parotid actinic cell carcinoma	Anti-PD1	33	2	Not performed	Negative	Negative	Skin rash Dry eyes
Le Burel et al. 2018	3/447 (3 Sjogren's syndrome)	Renal cell carcinoma, squamous cell carcinoma of the cervix, melanoma	Anti-PD1 alone or + anti-CTLA-4; anti-PD1 + anti-BRAF+ anti-MEK	8–12	2–3	Performed in 2 cases	3/3	- Anti-SSA positive prior to ICI in 2 cases - Anti-SSA positive in 1 case	Dry eyes Arthralgia Myalgia Paresthesia
Takahashi et al. 2018	1	NSCLC	Anti-PD1	16	Not specified	Performed, severe sialadenitis	Negative	Negative	Colitis
Ghosn et al. 2018	1 (Sjogren's syndrome)	Melanoma	Anti-PD1	32	Not specified	Performed, Chisholm-Mason score 3	Positive	Anti-SSA positive	Neuro-Sjögren's syndrome
Narváez et al. 2018	2/11	NSCLC, pancreatic neuroendocrine cancer	Anti-PD1	15–24	Not specified	Not performed	Positive	Negative	Thyroiditis Hypothyroidism
Warner et al. 2019	20/20	Metastatic melanoma; non-small cell lung carcinoma; metastatic prostate cancer; adenocarcinoma, gastroesophageal junction; metastatic thymic carcinoma; recurrent respiratory papillomatosis	Anti-PD1, alone or + anti-CTLA-4, anti-PD-L1, alone or + TGF-beta	2–29	1 (5) 2 (15)	Focus score 0 (10) FS 1 (4) FS 2 (2)	3/20	2/20	Dermatitis Adrenal insufficiency Thyroiditis Colitis Cardiomyopathy Hypophysitis Encephalitis Rheumatoid arthritis flare Mucositis Elevated CK

[a]NCI-CTCAE v.5.0.

Abbreviations: ANA, antinuclear antibodies; CK, creatine kinase; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FS, focus score; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; PD1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; SSA, anti-Sjögren's-syndrome-related antigen A; SSB, anti-Sjögren's-syndrome-related antigen B; TGF, transforming growth factor.

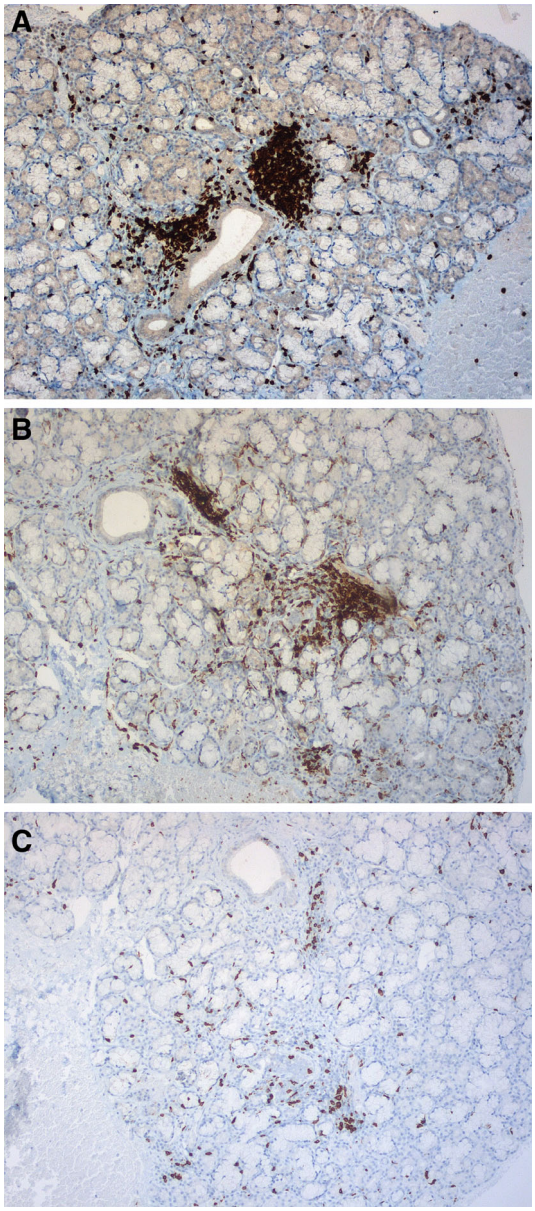

Figure 2. Immunostaining showing CD3-positive T-cell infiltrate (original magnification ×10) (**A**), CD4-positive T-cell infiltrate (original magnification ×10) (**B**) and CD8-positive T-cell infiltrate (original magnification ×10) (**C**).

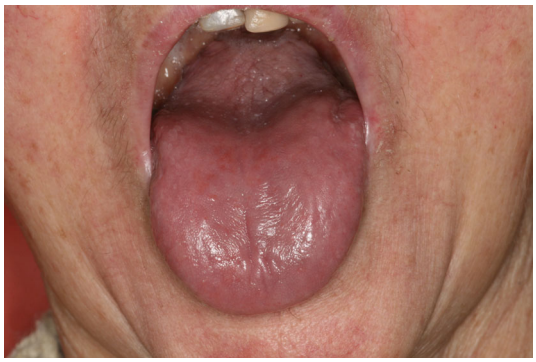

Figure 3. Grade 3 xerostomia induced by anti-programmed death-ligand 1.

for 4 weeks. Maintain ICI therapy and reassess within 2 to 4 weeks.

PERSISTENT GRADE 3: Multidisciplinary decision to interrupt ICI and reassess within 2 to 4 weeks.

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Disclosures

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