SICCA/SJÖGREN'S SYNDROME INDUCED BY CANCER CHECKPOINT INHIBITORS

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OBJECTIVE

To analyze the clinico-serological characteristics, treatment responses, and outcomes of sicca/Sjögren's syndrome (SS) triggered by immune checkpoint inhibitors (ICIs) in cancer patients.

METHODS

A retrospective observational study was conducted from January 2016 to December 2023 at two tertiary university hospitals. Patients investigated for a clinical suspicion of SS following exposure to ICIs were included.

RESULTS

We identified 20 patients (50% men), with a mean age at diagnosis of 60.5±11 years. None had prior autoimmune diseases.

Table 1 summarises their general characteristics, cancer types, and ICI molecules.

Underlying cancers included lung (12 patients), melanoma (2), and other neoplasms (6).

ICI comprised monotherapy (90%) and combined regimens (10%). In monotherapy cases, all were treated with PD-1/PD-L1 inhibitors; no CTLA-4 inhibitor-associated cases were identified. Three patients (15%) received additional oncologic treatments.

The median time from cancer diagnosis to ICI initiation was 9 months (IQR 25th–75th: 2-19 months), and from ICI initiation to SS onset was 153 days (IQR 45-209 days).

The main SS-related features included a relatively abrupt onset of dry mouth in 19 (95%) patients, dry eye in 11 (55%), abnormal ocular tests in 11 (55%), and abnormal oral diagnostic tests in 19 (95%) (see Table 2). Salivary gland scintigraphy, performed in 16 patients, confirmed salivary hypofunction in all cases (mild in 7, moderate in 7, severe in 2). No minor salivary gland biopsy was conducted. Among the 20 patients, 9 (45%) presented exclusively with dry mouth.

Immunological markers showed positive ANA in 8 of 16 patients (50%) at titers from 1/80 to 1/640, anti-La/SS-B in 1 patient (6.25%), and anti-Ro 60/SS-A in 2 patients (12.5%). RF was negative in all tested cases (Table 2).

Based on available serological data, only 2 patients met the AECG criteria for primary Sjögren's syndrome (pSS), 3 met the 2012 SICCA-ACR criteria, and 2 met the 2016 ACR-EULAR criteria.

Fifteen patients (75%) exhibited extraglandular manifestations (Table 2): eight (40%) presented symptoms classified under the ESSDAI criteria and seven (30%) showed non-ESSDAI features. The affected organs according to the ESSDAI classification included symptoms in the skin (n=2), joints (n=6), peripheral nervous system (n=1), and lungs (n=1). In most instances, these manifestations were categorized as independent irAEs (unrelated to SS) rather than as part of the triggered SS (systemic form of the disease).

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After a median follow-up of 23.5 months (IQR 10.2 – 41.2), ICIs had been discontinued in 55% of cases (11/20) due to tumour progression (4 patients), completion of treatment with full ONC RECIST response (3), or adverse effects (4). Three patients (15%) had died from cancer

Specific therapeutic management included measures directed at treating sicca symptoms (pilocarpine in 75% of cases) and therapies against the autoimmune-mediated response (glucocorticoids in 75% and HCQ in 20%).

At the last follow-up, sicca symptoms had completely resolved in 6 patients (30%) without any relapses following the cessation of specific treatments (ICI was withdrawn in four of these cases). Among the remaining 14 patients, 4 were on replacement therapy alone, 5 were using saliva substitutes plus pilocarpine, and 5 were additionally on low-dose prednisone and/or HCQ. In seven of these 14 cases, sicca symptoms persisted despite the discontinuation of ICI.

Table 1. General characteristics, type of cancer and ICI molecules

	N =20
Gender (Women/Men)	10 (50%) / 10 (50%)
Age, yrs (mean ± SD)	60.5 ± 11
Median time from ICI initiation and SS onset, months (IQR 25th–75th)	5 (IQR 1-6)
Type of cancer*	
Lung	12 (60%)
Melanoma	2 (10%)
Renal-Urothelial	1 (5%)
Breast	1 (5%)
Endometrial	1 (5%)
Rectum	1 (5%)
Pancreatic	1 (5%)
Oral squamous cell carcinoma	1 (5%)
Mesothelioma	1 (5%)
Type of Checkpoint inhibitors	
Monotherapy	
Nivolumab	6 (30%)
Pembrolizumab	8 (40%)
Atezolizumab	2 (10%)
Durvalumab	2 (10%)
Combined Therapy	
Nivolumab + Ipilimumab	1 (5%)
Durvalumab + Tremelimumab	1 (5%)
Additional treatments	
Pemetrexed	1 (5%)
Galunisertib	1 (5%)
BO-112	1 (5%)

*One patient presented synchronously with adenocarcinoma of the lung and rectal cancer.

Table 2. Main clinical and laboratory data, and outcome of the study cohort.

Clinical features	
Sicca symptoms	100% (20/20)
Oral and ocular symptoms	50% (10/20)
Only dry mouth	45% (9/20)
Only dry eyes	5% (1/20)
Salivary hypofunction confirmed by salivary gland scintigraphy (performed only in 16 cases; missing data 4)	100% (16/16)
Abnormal ocular tests (including Schirmer ≤ 5 mm/5 min on at least one eye)	55% (11/20)
Parotidomegaly	0% (0/20)
Extraglandular involvement	
Arthritis	30% (6/20)
Hypothyroidism / Hyperthyroidism	45% (9/20)
Cutaneous	30% (6/20)
Hepatitis	10% (2/20)
Pneumonitis	5% (1/20)
Colitis	5% (1/20)
Pancreatitis	5% (1/20)
Esophagitis	5% (1/20)
Adrenal insufficiency	5% (1/20)
Autoantibody Results	
Positive Rheumatoid Factor (missing data = 3)	0% (0/17)
Positive ANA ≥ 1/40 (missing data = 4)	50% (8/16)
ANA ≥1/320 (missing data =4)	19% (3/16)
Positive anti-La/SS-B antibodies (missing data=4)	6.2% (1/16)
Positive anti-Ro 60/SS-A antibodies (missing data = 4)	12.5% (2/16)
Treatment	
Pilocarpine	75% (15/20)
Glucocorticoids	75% (15/20)
Mean initial dose of prednisone, mg/day	15.7 ± 7.5
Hydroxychloroquine	20% (4/20)

* Some patients presented more than 1 non-rheumatic irAE.

CONCLUSION

Patients with ICI-triggered SS exhibit a profile distinct from that reported in idiopathic pSS. We found a significant overlap between some organ-specific irAEs and the clinical domains included in the ESSDAI, making it difficult to classify these organ-specific features either as independent irAEs or as part of the triggered SS.

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