Sicca/Sjögren Syndrome triggered by PD-1/PD-L1 checkpoint inhibitors

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Data from the International ImmunoCancer Registry (ICIR)

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ABSTRACT

Objective

To analyse the worldwide occurrence of sicca/Sjögren (SjS) syndrome associated with the use of immune checkpoint inhibitors (ICI) in patients with cancer.

Methods

The ImmunoCancer International Registry (ICIR) is a Big Data-Sharing multidisciplinary network composed by 40 specialists in Rheumatology, Internal Medicine, Immunology and Oncology from 18 countries focused on the clinical and basic research of the immune-related adverse events (irAEs) related to cancer immunotherapies. For this study, patients investigating for a clinical suspicion of SjS after being exposed to ICI were included.

Results

We identified 26 patients (11 women and 15 men, with a mean age at diagnosis of 63,57 years). Underlying cancer included lung (n=12), renal (n=7), melanoma (n=4), and other (n=3) neoplasia. Cancer immunotherapies consisted of monotherapy (77%) and combined regimens (23%). In those patients receiving monotherapy, all patients were treated with PD1/PD1-L inhibitors (nivolumab in 9, pembrolizumab in 7 and durvalumab in 4); no cases associated with CTLA-4 inhibitors were identified. The main SjS-related features consisted of dry mouth in 25 (96%) patients, dry eye in 17 (65%), abnormal ocular tests in 10/16 (62%) and abnormal oral diagnostic tests in 12/14 (86%) patients. Minor salivary gland biopsy was carried in 15 patients: histopathological findings consisted of mild chronic sialadenitis in 8 (53%) patients and focal lymphocytic sialadenitis in the remaining 7 (47%); a focus score was measured in 5 of the 6 patients (mean of 1.8, range 1 to 4). Immunological markers included positive ANA in 13/25 (52%), anti-Ro/SS-A in 5/25 (20%), RF in 2/22 (9%), anti-La/SS-B in 2/25 (8%), low C3/C4 levels in 1/17 (6%) and positive cryoglobulins in 1/10 (10%). Classification criteria for SjS were fulfilled by 10 (62%) out of 16 patients in whom the two key classificatory features were carried out. Among the 26 patients, there were only 3 (11%) who presented exclusively sicca syndrome without organ-specific autoimmune manifestations. Therapeutic management included measures directed to treat sicca symptoms and therapies against autoimmune-mediated manifestations (glucocorticoids in 42%, second/third-line therapies in 31%); therapeutic response for systemic features was observed in 8/11 (73%). No patient died due to autoimmune involvement.

Conclusions

Patients with Sjögren syndrome triggered by ICI display a very-specific profile different from that reported in idiopathic primary SjS, including more frequent occurrence in men, a higher mean age, a predominant immunonegative serological profile, and a notable development of organ-specific autoimmune involvement in spite of the poor immunological profile. The close association found between sicca/Sjögren syndrome and primarily PD1 blockade requires further specific investigation.

INTRODUCTION

Immunotherapies are a group of drugs designed to target specific molecules of the immune system. These therapies use different pharmacoimmunological approaches that may include not only the use of specific drugs (monoclonal antibodies, small proteins, fusion proteins) targeting proteins located on the surface of cancer or immune cells, but also the use of other non-specific therapies including cytokines, oncolytic virus therapies, cancer vaccines, or CAR T-cell therapies [1]. Among monoclonal antibodies, immune checkpoint inhibitors (ICIs) target different pathways that harbor immunosuppressive functions used by cancer cells to evade immunosurveillance, and among the ICIs, PD-1/PD-L1 and CTLA-4 inhibitors have showed promising therapeutic outcomes [2].

However, with the increasing use of ICIs the occurrence of a group of side effects referred to as immune-related adverse events (irAEs) is also increasingly recognized. Many of these side effects are driven by the same immunologic mechanisms responsible for the drugs' therapeutic effects, namely the blockade of the inhibitory mechanisms that suppress the immune system and protect body tissues from an autoimmune damage. These irAEs are unique and different than those associated with cytotoxic chemotherapy, radiotherapy, or targeted therapies [3]. Immunotherapy-related irAEs typically have a delayed onset and prolonged duration compared to adverse events from chemotherapy [4]. Clinical features are important in the way of providing evidence that helps to the diagnosis including, in cases where possible, histological confirmation through a biopsy-proven evidence of autoimmune-related damage. Moreover, serological confirmation through of the presence of positive autoantibody testing that should be sought to clarify the nature of the autoimmune process, although the results may be negative in a significant number of patients. Most irAEs consisted of organ-specific autoimmune diseases, and less frequently, systemic and rheumatic diseases [3]. The first case of Sjögren syndrome (SjS) triggered by cancer immunotherapies has been recently reported by Cappelli et al [5], with an increasing number of additional cases reported since then [6].

The objective of this study was to analyse the worldwide scenario of SjS associated with the use of cancer immunotherapies through the development of an international real-life registry of patients with cancer diagnosed with rheumatic and systemic autoimmune diseases using a big data network approach (International Immunocancer Registry Project).

METHODOLOGY

The International ImmunoCancer Registry (ICIR) is a Big Data-Sharing multidisciplinary network composed by 40 specialists in Rheumatology, Internal Medicine, Immunology and Oncology from 18 countries focused on the clinical and basic research of the irAEs related to cancer immunotherapies. The two starting objectives of the Project consisted of:

a) A retrospective study of rheumatic and systemic autoimmune diseases triggered by cancer immunotherapies seen in daily practice by the ICIR members, following a descriptive, non-interventional, data-sharing international network database design. Data were obtained by retrospective evaluation of medical charts by the physician on charge of the patient included into ongoing research projects involving local registries of irAEs (each validated for the corresponding local IRB). For this study, we selected patients presenting with a clinical suspicion of SjS after being exposed to cancer immunotherapies. Exclusion criteria included the concomitant use of standard chemotherapy/radiotherapy or other aetiologies directly related to the development of sicca symptoms.

b) A systematic literature review (SLR) performed until April 15, 2019. We selected biologics from the main groups of cancer immunotherapies, which were crossed with rheumatic and systemic autoimmune diseases using the terms included in the Medical Dictionary for Regulatory Activities terminology (MedDRAVR 15.0). Data were extracted by MRC and AFC. The following information was recorded for each study: first author's name, title, year of publication, study design, underlying cancer, biologic drug and combinations, treatment arms, number of patients available for analysis, number of autoimmune events, grade of toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) defined by the National Cancer Institute, histopathological analysis, immunophenotyping analysis, therapeutic management and outcomes [7]. We selected reported cases fulfilling the same inclusion criteria and exclusion criteria used in the ICIR Registry.

The following variables were collected: age, gender, ethnicity, country of residence, fulfilment of the 2002/2016 criteria items [8,9], antinuclear antibodies (ANA >1/40), rheumatoid factor (RF), C3 and C4 levels, cryoglobulins, and an estimation of systemic damage using the EULAR Sjögren's syndrome disease activity index (ESSDAI). Diagnostic tests for SjS (ocular tests, oral tests and salivary gland biopsy) were evaluated according to the recommendations of the European Community Study Group [10]. Disease diagnosis was defined as the time when the attending physician confirmed sicca syndrome or the fulfilment of the 2002/2016 criteria. Organ-specific autoimmune manifestations (irAEs) concomitant to sicca symptoms and developed after the initiation of cancer immunotherapies were also collected, and were classified in two groups: those who fit into the definitions included in

the ESSDAI index [11], which evaluates 12 domains or organ systems, and those who involved organs not included in the ESSDAI. Descriptive data are presented as mean and range for continuous variables and number and percentage for categorical variables.

RESULTS

We identified in the ICIR Registry a total of 29 patients who were studied for a clinical suspicion of SjS after being treated with cancer immunotherapies. Three patients who received cancer immunotherapies other than ICI (trastuzumab in 2 cases, vemurafenib in 1 case) were excluded for the analysis.

The baseline characteristics of the 26 patients treated with ICI are summarized in **Table 1.** There were 11 (42%) women and 15 (58%) men, with a mean age at diagnosis of sicca/SjS of 63,57 years (range 39-79 years, all but one classified as White ethnicity). A previous history of autoimmune diseases was recorded in 4 (15%) cases, and a family history of autoimmune disease in 2 (7%). Underlying cancer included lung (n=12), renal (n=7), melanoma (n=4), and other (n=3) neoplasia. Cancer immunotherapies consisted of monotherapy (77%) and combined regimens (23%). In those patients receiving monotherapy, all patients were treated with PD1/PD1-L inhibitors (nivolumab in 9, pembrolizumab in 7 and durvalumab in 4); no cases associated with CTLA-4 inhibitors were identified. Combined therapies included nivolumab combined with ipilimumab (6 cases) or pergIL10 (1 case). The median interval between onset of ICI treatment and sicca/SjS diagnosis was 6,5 months (range 1 to 28 months).

The main SjS-related features are summarized in **Table 2** and consisted of dry mouth in 25 (96%) patients, dry eye in 17 (65%), abnormal ocular tests in 10/16 (62%) and abnormal oral diagnostic tests in 12/14 (86%) patients. Minor salivary gland biopsy was carried in 15 patients: histopathological findings consisted of mild chronic sialadenitis in 8 (53%) patients and focal lymphocytic sialadenitis (Chisholm-Mason classification $\geq$ 3) in the remaining 7 (47%); a focus score was measured in 5 of the 6 patients (mean of 1.8, range 1 to 4). Immunological markers included positive ANA in 13/25 (52%), anti-Ro/SS-A in 5/25 (20%), RF in 2/22 (9%), anti-La/SS-B in 2/25 (8%), low C3/C4 levels in 1/17 (6%) and positive cryoglobulins in 1/10 (10%). Classification criteria for SjS were fulfilled by 10 (62%) out of 16 patients in whom the two key classificatory features (salivary gland biopsy and Ro autoantibodies) were carried out; 5 (50%) of the 10 patients fulfilled the criteria due to the histopathological findings in the absence of anti-Ro autoantibodies.

Among the 26 patients, there were only 3 (11%) who presented exclusively sicca syndrome without organ-specific autoimmune manifestations. Among those with systemic features, 10 (43%) presented with features included in the ESSDAI classification, 7 (30%) with non-ESSDAI features, and the remaining 6 (27%) presented with both ESSDAI and non-ESSDAI features. The estimated mean total ESSDAI score was 10.26 (ranging between 0 and 48) and 11.68 (ranging between 0 and 56) for clinESSDAI. The involved organs following the ESSDAI classification consisted of features included in the cutaneous (n=10), articular (n=8), glandular (n=5), peripheral nerve system (n=5), constitutional (n=4), muscular (n=4), pulmonary (n=1), renal (n=1) and central nervous system (n=1) domains. Non-

ESSDAI organ-specific autoimmune features included thyroiditis (n=10), enterocolitis (n=5), hepatitis (n=5), vitiligo (n=2), myocarditis (n=1), hypophysitis (n=1), adrenal insufficiency (n=1) and cytokine-release syndrome (n=1).

Therapeutic management included measures directed to treat sicca symptoms and therapies against autoimmune-mediated manifestations. In most patients, sicca symptoms were managed with topical measures, including oral pilocarpine in two cases presenting with severe oral dryness, and topical CyA drops in one case with severe ocular dryness; two patients received systemic corticosteroids. Sicca symptoms persisted in spite of using these therapies. Systemic therapy was used in 11 (42%) patients using first-line therapy with glucocorticoids (including methylprednisolone pulses in 2 cases, plus second-line therapies including hydroxychloroquine (arthritis in 2 cases) or immunosuppressive agents (myositis and hepatitis, respectively), and rescue therapies including intravenous immunoglobulins/plasma exchanges (myositis, cytokine-release syndrome), infliximab (enterocolitis) and tocilizumab (arthritis); therapeutic response for systemic features was observed in 8/11 (73%). No patient died due to autoimmune involvement.

DISCUSSION

Sjögren syndrome (SjS) is a systemic autoimmune disease that mainly affects the exocrine glands. This leads to dryness of the main mucosal surfaces, such as the mouth, eyes, nose, pharynx, larynx and vagina [12]. In the etiopathogenesis of SjS, a specific combination of individual genetic predisposition (intrinsic factors) and environmental agents (extrinsic factors) may be central to the development of the disease [13]. The key SjS symptoms (oral and ocular dryness) have been also linked to a large list of systemic and topical drugs, mainly through their impact on lachrymal and salivary gland secretion [14–16]. Until the arrival of cancer immunotherapies, no association between sicca/Sjögren syndrome and the use of monoclonal antibodies was reported.

Oral/ocular dryness are reported as irAE in 98/1832 (5.3%) patients with cancer treated with immunotherapies included in RCTs [17–21] (**Table 3**); the frequency was higher for patients who received combination therapy of checkpoint inhibitors (9.4%) and lower for patients treated with CTLA-4 inhibitors (1.4%). No information about specific SjS evaluations was reported, and all cases but one were classified as CTCAE grade I-II. The ICIR Registry has identified 60 cases of sicca/Sjögren syndrome triggered by ICIs in patients with cancer, 34 from the SLR [5,6,22–32] and the 26 unpublished cases collected among ICIR centers. Among them, the 22 patients (10 from the ICIR Registry and 12 from the SLR) who fulfilled the current classification criteria of SjS had a very specific phenotype, clearly different from that observed in the idiopathic Sjögren syndrome [33] (**Figure 1**):

a) The epidemiological and clinical profile seem to be quite different from primary SjS, with half cases being men (only 5% in primary), a mean age at diagnosis ten years older, a lower frequency of both oral and ocular dryness and a lower frequency of abnormal ocular tests in comparison with the data reported in the “idiopathic” primary SjS [33]. In addition, nearly 20% of cases had a history of previous autoimmune diseases (personal or familial), suggesting a potential predisposing immunogenetic background in some patients.

b) The histopathological profile consisted of the typical focal lymphocytic sialadenitis of the primary form in half the cases biopsied [34]. In primary SjS, the median % of T-cells is around 70% (50% CD4+, 20% CD8+) and of B cells around 22% [35,36]. By immunohistochemistry, Warner et al [6] have recently reported a predominant T-lymphocytic infiltrate, with a slight majority of CD4+ over CD8+ T cells and few CD20+ B cells. This pattern is different from characteristic SjS infiltrates where B cells may represent 20%–62% of all lymphocytes and FS directly correlating with B-cell ratios [37]. The study also reported scattered infiltrating PD-1-positive T cells and epithelial PD-L1 positivity only in the most severely infiltrated cases. Some patients reported by Warner et al [6] were treated with ICI for thymic epithelial neoplasms; the significance of this finding is intriguing but may reflect underlying thymic dysfunction-related autoimmunity, which was exacerbated by an ICI-augmented immune response [38].

c) There was a much lower prevalence of SjS-associated serum autoantibodies (52% ANA, 20% Ro/SS-A, 9% RF, 8% La/SS-B) in comparison with idiopathic primary SjS. The predominant seronegative immunological pattern is similar to that reported for other irAEs related to cancer immunotherapies [31,39–41].
d) These patients required a more intense therapeutic management than primary SjS patients [42]: 20% of patients required specific therapies for severe dryness, 42% of cases required systemic corticosteroids, and 31% second/third line therapies for non-sicca systemic disease.

The etiopathogenesis of immunotherapy-induced SjS/sicca syndrome is unknown. Probably, a specific genetic background that predisposes to their development could play a role. This could also contribute to explain the exacerbations of pre-existing SjS, reported in several patients exposed to cancer immunotherapies. Danlos et al [43] reported one patient who developed a relapse consisting of acute dermatitis and sicca syndrome, Menzies et al [44] reported a relapse in 2 patients with SjS (no further details), and Warner et al [6] reported dry eye or dry mouth prior to ICI treatment in 5 patients. Furthermore, it seems reasonable to hypothesize that patients with pre-treatment positive immunological markers could be more prone to develop autoimmune processes, as has been reported in patients with autoimmune diseases developed after TNF-targeting therapies [45]. From a pathogenic view, two findings should be highlighted from our results: the enhanced risk in patients receiving combined regimens as has been reported for other irAEs [46], and the remarkable association with the use of PD1 blockers (95% of reported cases of triggered SjS were exposed to these immunotherapies). In fact, PD-1 deficiency results in the development of fatal myocarditis in MRL mice due to a massive infiltration of lymphocytes in heart, with additional inflammatory foci being found in the liver, lung, stomach and salivary glands [47]. The close association we found between sicca/SjS and treatment with anti-PD1/PDL1 antibodies may help to better understanding pathophysiology of SjS. Like other systemic autoimmune diseases, SjS is an heterogeneous disease and a better stratification of patients is necessary [48]. A first effort of stratification may be to divide patients between those with a type 1 interferon/BAFF/ B-cell signature from those with a T-cell /NK-cell/type 2 IFN signature. Of note these patients cannot be separated based on the transcriptomic IFN signature since it overlaps between type 1 and type 2 IFN. The pattern of sicca/SjS presented by these patients with cancer treated with ICI suggest that the PD/PDL-1 pathway could play a role in the SjS patients with the T-cell/NK-cell/type 2 IFN signature.

We also found a significant overlap between some organ-specific irAEs and the clinical domains included into the score that measures systemic activity in primary SjS (ESSDAI), making difficult to consider these organ-specific features either as independente irAEs (unrelated to SjS) or as forming part of the triggered SjS (systemic form of the disease). This may be even more difficult when the

patient develop ESSDAI features highly characteristic of the disease (parotid enlargement, articular or cutaneous features, autoimmune neuropathies). It is unclear whether the ESSDAI can be used in scoring systemic activity in patients with SjS triggered by ICI, a clinical scenario for which this score was not specifically designed for. Another key message is that nearly 60% of patients in whom a SjS was clinically suspected and that were fully evaluated for the disease (including both immunological and histopathological studies) fulfilled the current classification criteria for SjS. This significant percentage raises two questions: a) whether a history of ICI use should be included as a new exclusion criterion in a future review of SjS criteria, and b) whether the fulfilment or not of the current criteria could modify the therapeutic approach of the triggered SjS, especially of those cases presenting with systemic involvement.

The retrospective design of the study means that our results need to be interpreted cautiously. The level of association between a drug and the induced autoimmune disease cannot be evaluated by a retrospective analysis of individual reported cases and should always be studied according to the estimated total population exposed to this agent. We cannot rule out the possibility that some cases may have a latent SjS, especially in women of middle-age in whom the cancer diagnosis (and the corresponding treatment) was coincidental with the initial development of a SjS, with the frequent medical visits and the enhanced medical follow-up favouring the discovery of an underlying SjS. Indeed, the overwhelming majority of reported cases defined the induced autoimmune disease as newly diagnosed, although in some cases this was not clearly stated. More importantly, a complete study for confirming the fulfilment of the current classification criteria for SjS (salivary biopsy + anti-Ro determination) was carried out in only 36 cases, of whom 61% fulfilled the criteria; in nearly half the confirmed cases, the diagnosis was achieved with salivary biopsy in immunonegative patients.

In spite of these limitations and the scarce quality of the available data, most of the previously reported recommendations for the management of patients with autoimmune diseases triggered by biological agents would seem to remain valid when applied to patients initiating cancer immunotherapy [49]. Before initiating the biological therapy, a careful pre-therapeutic evaluation paying special attention to pre-existing clinical or immunological autoimmune features is recommended. Discontinuation of biological therapy is mandatory in patients with severe involvement of internal organs, while in patients with sicca features, continuation could be considered (always with a closer follow-up). If they are diagnosed timely, most irAEs, except endocrine and some inflammatory arthritis cases, are reversible, requiring the use of immunosuppressive agents only in very limited cases [50]. This does not appear to be the case for sicca/Sjogren syndrome, whose triggered sicca symptoms overwhelmingly became chronic, following the same pattern of the idiopathic form of the disease. Therefore, corticosteroids are not recommended to treat exclusively sicca features as is recommended for primary SjS, and should be carefully used in patients with cancer [51,52]. Corticosteroids and/or

immunosuppressive agents may be required in severe cases to control the induced systemic manifestations of SjS despite the withdrawal of the immunotherapy.

In summary, immune checkpoint inhibitors should be included in the large list of drugs causing sicca symptoms; 60% of cases fulfil the current classification criteria for primary SjS, and this triggered SjS should be considered a new emerging immunotherapy-triggered form of the disease. These patients display a very-specific profile away from that reported in idiopathic SjS, including an enhanced involvement of men, a higher mean age at diagnosis, a predominant immunonegative serological profile, and a notable development of systemic disease in spite of the poor immunological profile. The close association found between sicca/Sjögren syndrome and cancer immunotherapy, primarily PD1 blockade, requires further specific investigation.

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TABLES

Table 1. Baseline characteristics of 26 patients treated with ICI who developed sicca/SjS included in the ICIR Registry.

Table 2. The main SjS-related features of 26 patients treated with ICI who developed sicca/SjS included in the ICIR Registry.

Table 3. Dryness reported as irAE in patients with cancer treated with ICI included in RCTs [17–21].

Patient	Gender	Age at diagnosis	Previous autoimmune diseases	Underlying cancer	Checkpoint inhibitor	Months	ICI stopped	Specific sicca therapy	Systemic therapy (organ involved)
1	F	61	None	Lung	Nivolumab	10	No	Topical	No
2	F	72	None	Lung	Nivolumab + ipilimumab	7	No	Topical	GC, IFX (colitis)
3	M	39	None	Melanoma	Nivolumab + ipilimumab	1	No	Topical	GC, MMF (CRS)
4	F	52	None	Colon	Nivolumab + ipilimumab	1	No	Topical	GC (hep)
5	F	79	None	Lung	Pembrolizumab	1	No	Topical	GC, ivIG (systemic)
6	F	71	PHEWS	Melanoma	Nivolumab	6	Yes	Topical	GC, TAC (hep)
7	M	64	PM	Lung	Durvalumab	1	Yes	Topical	GC, MMF, IVIG, PeX (musc)
8	M	71	None	Lung	Pembrolizumab	7	Yes	Topical + GC	No
9	M	79	None	Melanoma	Pembrolizumab	28	Yes	Topical + GC	No
10	F	50	None	Lung	Pembrolizumab	5	No	Topical	GC, HCQ (art)
11	M	74	None	Renal	Nivolumab	11,2	No	Topical	GC, TCZ (art)
12	M	77	None	Renal	Nivolumab	5,7	No	Topical + cevimeline	No
13	M	72	None	Lung	Pembrolizumab	2	No	None	No
14	M	70	None	Lung	Nivolumab	18	Yes	Ocular GC/CyA	No
15	F	51	None	Chordoma	Durvalumab	3,7	No	Topical	No
16	M	71	None	Lung	Nivolumab	2	No	Topical	No
17	M	58	None	Lung	Pembrolizumab	6	No	Topical	No
18	M	60	None	Melanoma	Durvalumab	2	No	Topical	GC (art)
19	M	71	Uveitis	Renal	Nivolumab + pegIL10	8,3	No	Topical	GC (iridocyclitis)
20	F	68	None	Lung	Nivolumab	6	Yes	Topical	No
21	M	51	None	Lung	Durvalumab	3	No	Topical	No
22	M	49	None	Renal	Nivolumab + ipilimumab	4,6	No	Topical	No
23	F	56	SpA	Renal	Nivolumab + ipilimumab	2,4	No	None	No

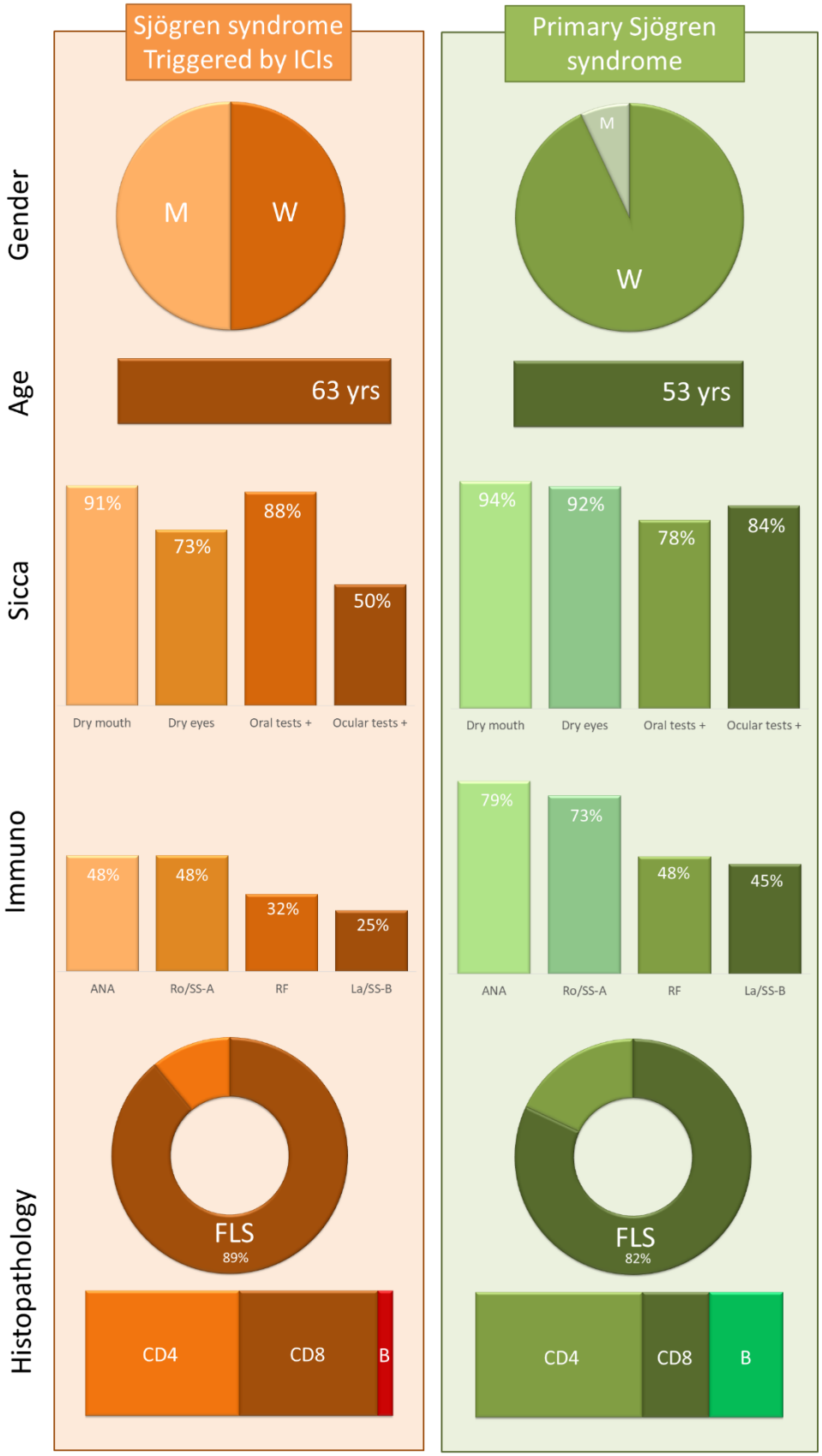
24	F	58	None	Cervix	Nivolumab	2,6	No	None	No
25	M	67	None	Renal	Pembrolizumab	14	No	None	No
26	F	62	None	Renal	Nivolumab	10,5	No	Topical + pilocarpine	GC, HCQ (art)

Patient	Dry mouth/oral tests results	Dry eye/ocular tests results	Minor salivary gland biopsy (focus score)	Autoantibodies (ANA/RF/Ro/La)	Complement levels/cryoglobulins	SjS criteria	ESSDAI (clinESSDAI)	Sytemic features	Other irAEs
1	Yes/abnormal	Yes/abnormal	NA	Neg/neg/neg/neg	NA/NA	NA	9 (10)	Cut. Musc	Col
2	Yes/abnormal	Yes/normal	MCS	Neg/neg/neg/neg	Normal/negative	No	8 (9)	Cut, pulm	Col, thyr
3	Yes/na	Yes/na	MCS	Neg/neg/neg/neg	Normal/NA	No	0 (0)	None	CRS, hep
4	Yes/abnormal	Yes/abnormal	NA	Pos/NA/neg/neg	Normal/NA	NA	3 (3)	Cut	Hep
5	Yes/abnormal	Yes/normal	MCS	Pos/neg/pos/neg	Normal/negative	Yes	48 (56)	Const, gland, art, renal, musc, PNS, CNS	Hep
6	Yes/na	Yes/na	NA	Pos/neg/neg/neg	Normal/NA	NA	0 (0)	None	Hep, col
7	No/normal	Yes/abnormal	MCS	Pos/neg/neg/neg	NA/NA	No	18 (21)	Musc	Myoc, col, thyr
8	Yes/abnormal	No/normal	MCS	Pos/neg/neg/neg	Normal/negative	No	0 (0)	None	None
9	Yes/abnormal	No/normal	FLS (1.8)	Neg/neg/neg/neg	Normal/NA	Yes	5 (5)	Const, gland	None
10	Yes/abnormal	Yes/abnormal	FLS (2)	Pos/neg/neg/neg	Normal/negative	Yes	9 (12)	Art, cut	None
11	Yes/na	Yes/na	NA	Neg/neg/neg/neg	NA/NA	NA	4 (6)	Art	None
12	Yes/na	No/na	NA	Neg/neg/neg/neg	Normal/NA	NA	2 (3)	Art	None
13	Yes/abnormal	Yes/abnormal	MCS	Pos/neg/neg/neg	NA/negative	No	23 (26)	Const, cut, musc, PNS	None
14	Yes/abnormal	Yes/abnormal	MCS	Pos/neg/neg/neg	Normal/negative	No	3 (3)	Cut	None
15	Yes/na	No/na	NA	Neg/neg/neg/neg	NA/NA	NA	0 (0)	None	None
16	Yes/abnormal	Yes/na	NA	Pos/neg/neg/neg	Normal/NA	NA	0 (0)	None	None
17	Yes/na	No/normal	NA	NA/NA/NA/NA	NA/NA	NA	5 (5)	PNS	None
18	Yes/na	No/normal	NA	Pos/neg/pos/neg	Low/pos	Yes	28 (30)	Art, cut, pulm, PNS	Pneum, vitil
19	Yes/na	No/na	FLS (1)	neg/NA/neg/neg	NA/NA	Yes	0 (0)	None	Thyr, iridocyclitis

20	Yes/abnormal	Yes/abnormal	FLS (1)	Pos/neg/neg/neg	Normal/negative	Yes	3 (3)	Cut	Thyr
21	Yes/abnormal	No/abnormal	FLS (4)	Pos/neg/pos/pos	Normal/NA	Yes	3 (3)	Cut	Thyr
22	Yes/na	No/na	NA	Neg/neg/neg/neg	NA/NA	NA	0 (0)	None	Thyr, adren
23	Yes/na	Yes/normal	FLS (nd)	Pos/pos/pos/pos	Normal/NA	Yes	5 (6)	Gland, art	Thyr, col
24	Yes/na	Yes/abnormal	MCS	Neg/neg/pos/neg	Normal/NA	Yes	4 (5)	Gland, art	Thyr, hep, vitil
25	Yes/normal	Yes/abnormal	FLS (1)	neg/NA/neg/neg	NA/negative	Yes	11 (11)	Const, cut, PNS	Thyr, hypoph
26	Yes/na	Yes/na	NA	Neg/pos/neg/neg	Normal/negative	NA	4 (5)	Gland, art	Thyr, pneum

Authors (year)	Checkpoint inhibitor	Combination therapy	Type of study	Population studied	Sicca cases	%
Hodi et al (2018)	Ipilimumab		Phase III	311	7	2,25
Robert et al (2015)	Ipilimumab		Phase III	256	1	0,39
Hodi et al (2018)	Nivolumab	Ipilimumab	Phase III	313	19	6,07
Hodi et al (2018)	Nivolumab		Phase III	313	13	4,15
Motzer et al (2015)	Nivolumab		Phase II	167	11	6,59
Giaccone G et al (2018)	Pembrolizumab		Phase II	40	2	5,00
Long et al (2017)	Pembrolizumab	ipilimumab	Phase I	154	25	16,23
Robert et al (2015)	Pembrolizumab		Phase III	278	20	7,19
TOTAL				**1832**	**98**	**5,35**

Figure 1. Phenotype of 22 cases of SjS triggered by ICIs that fulfilled the current classification criteria for SjS in comparison with patients with primary SjS (reference 37)



ANNEX 1

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