Thirsty eyes: a look at dry eyes in autoimmune/inflammatory syndrome induced by adjuvants

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Abstract

Objective

Many patients with autoimmune/inflammatory syndrome induced by adjuvants due to breast implants (ASIA-BII) complain of dry eyes, which may be due to impaired tear production or increased tear evaporation. The clinical differences between ASIA-BII patients with dry eyes, compared to other rheumatic diseases (e.g. Sjögren's Disease (SjD)) are largely unknown. We aimed to better classify dry eye disease (DED) by determining if their symptoms stemmed from impaired tear production. We also explored whether common biomarkers present in SjD patients were detected in DED patients with ASIA-BII.

Methods

We utilised a cross-sectional design to enroll 78 consecutive patients with ASIA-BII, SjD (n=16), and healthy controls (HC) (n=17) from a single centre in our study. We assessed each participant using a Schirmer's test and the SjD Screening Questionnaire (SSSQ).

Results

73.1% of ASIA-BII patients had impaired tear production (Schirmer test <15mm), with severe impairment of tear production (Schirmer's test <5mm) in 47.4%. Severely impaired tear production was similar in prevalence to the SjD patients (p=0.68). ASIA-BII and SjD patients had similar SSSQ scores and rates of abnormal SSSQ scores. Differences were, however, observed in the frequency of positive antinuclear antibodies, anti-Sjögren Syndrome-A (anti-SSA) and anti-Sjögren Syndrome-B (anti-SSB) antibodies between the two groups. When ASIA-BII patients with severely impaired tear production were compared to ASIA-BII patients with normal tear production, a reduction of circulating naive helper T cells (0.014) was observed suggesting a potential role for immune dysregulation in potentiating tear production in ASIA-BII patients.

Conclusion

ASIA-BII patients suffer from dry eyes due to impaired tear production. The SSSQ was unable to differentiate SjD patients from ASIA-BII patients, however, biomarkers such as autoantibodies differ between SjD and ASIA-BII patients. Further investigations are required to further characterise ASIA-BII patients with dry eyes.

Key words

dry eye disease, sicca syndrome, Sjogren's disease, breast implants, autoimmune diseases

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Introduction

Silicone breast implants (SBI) are some of the most commonly inserted prostheses in female patients. They are inserted either because of cosmetic reasons or for breast reconstruction after a mastectomy. Complications related to silicone breast implants are categorised as early post-surgical ones, but some complications may ensue much later (1, 2). The most common, yet poorly understood, complication related to silicone breast implant insertion is a form of autoimmune/inflammatory syndrome induced by adjuvants (ASIA) or so-called 'breast implant illness (BII)' (2). Criteria for ASIA-BII are well described (2-8) and include severe fatigue similar to myalgia encephalomyelitis/chronic fatigue syndrome (ME/CFS) with associated diffuse joint and muscle pain that is similar to that described in patients with fibromyalgia (FM). Other frequently occurring symptoms are brain fog, pyrexia, and non-specific sensory and/or autonomic symptoms (*e.g.* paresthesia and dry eye disease (DED)) (5, 6, 8). Although the etiology of ASIA-BII is often debated (9-11), it is clear that there is a link between the development of ASIA-BII and patient symptoms, particularly in relation to pain which often improves following explantation (8, 12).

Among the non-specific symptoms described in ASIA-BII, DED is frequent (up to 75% of patients) but is poorly understood. The prevalence of DED is 5–34% worldwide (13). DED is associated with reduced quality of life and increased mental health disease burdens (14). In addition to individual patient challenges related to DED, its toll on the overall economy is substantial with an estimated toll of over $540 million dollars per year (15). DED is a huge area of unmet needs. DED occurs more frequently in patients with various rheumatic diseases (16) – suggesting that inflammatory triggers may be mechanistically linked precipitating DED. Based on its pathogenesis, DED can be divided into two clinical subgroups: a) patients with decreased tear secretion or Aqueous Deficient Dry Eye (ADDE), b) patients with increased tear evaporation or Evaporative Dry Eye (13, 16). Both subtypes produce similar clinical symptoms but have different risk factors. Evaporative dry eyes are commonly caused by non-inflammatory aetiologies (*e.g.* thyroid eye disease, facial nerve palsy) and stem from excessive evaporation from the tear film in the presence of normal secretory functions (16). In contrast, ADDE results from reduced lacrimal secretion due to inflammatory aetiologies and is broadly categorised into either Sjögren's Disease (SjD) or non-Sjögren's Disease-associated DED (16). While the mechanisms of SjD-associated DED are better understood (17), distinguishing between both forms is clinically difficult – particularly as histological biopsies are infrequently obtained (18), there is a paucity of biomarkers that can distinguish them, and validated patient-reported outcomes related to SjD-DED have not been explored in non-SjD-related DED causes.

In this study, we hypothesised that DED in ASIA-BII patients was similar to the clinical features of SjD-associated DED. We specifically aimed to better classify DED in these patients by determining if their symptoms stemmed from impaired tear production. We also explored whether common biomarkers present in SjD patients were detected in DED patients with ASIA-BII.

Methods

Patients

Consecutive patients with ASIA-BII and/or SjD were prospectively recruited for this study and were evaluated in the rheumatology department at the University of Alberta in the Kaye Edmonton Clinic. Patients were classified as suffering from ASIA-BII according to previously described criteria (3, 4, 8) (see online Supplementary Table S1), or primary SjD using the 2016 ACR-EULAR classification criteria for SjD (19). Patients were included between January 2019 and July 2024. We used the following exclusion criteria: Age under 18 or over 75 years, use of contact lenses, and/or use of insulin. Inclusion and exclusion criteria were uniformly applied. The study was approved by the University of Alberta Research Ethics Board (Pro00085583, Pro00090050). Written

consent was obtained from all study participants.

Clinical parameters

Clinical parameters collected included age, sex, and body mass index (BMI). Patients' charts were reviewed regarding implant date, explant date (if applicable), breast implant type, and if patients had other (non-breast) implants. Other clinical parameters collected from the peripheral blood included indicators of granuloma activity (*e.g.* angiotensin converting enzyme (ACE)), autoantibodies (antinuclear antibody (ANA), anti-SSA/B autoantibodies, antineutrophil cytoplasmic antibodies (ANCA), Proteinase 3 (PR3)-ANCA, Myeloperoxidase (MPO)-ANCA, rheumatoid factors), and C-reactive protein (CRP). We also collected other parameters including complete blood count with differential (CBC-D), total immunoglobulin levels (immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM), immunoglobulin E (IgE), and IgG subclasses (IgG1, IgG2, IgG3, IgG4)). As patients with SjD and ASIA-BII often harbour abnormalities in their B and T cell subsets, we also collected the frequencies of circulating immune cell subsets via flow cytometry. Natural killers (NK) cells were assessed as they help control local immune response and play a vital immunoregulatory role in initiation and chronicity of inflammatory and autoimmune responses (20). In addition, we assessed CD4 Helper T cells ($CD3^+CD4^+$), CD8 Suppressor/Cytotoxic cells ($CD3^+CD8^+$) and various subgroups of T cells such as, naive T Helper cells ($CD3^+CD4^+CD8^-CD45RA^+CD27^+$), terminally differentiated T Helper cells ($CD3^+CD4^+CD8^-CD45RA^+CD27^-$), central memory T Helper cells ($CD3^+CD4^+CD8^-CD45RA^-CD27^+$), Effector Memory T Helper cells ($CD3CD4^+CD8^-CD45RA^-CD27^-$), naive T Suppressor/Cytotoxic cells ($CD3^+CD8^+CD4^-CD45RA^+CD27^+$), terminally differentiated T Suppressor/Cytotoxic cells ($CD3^+CD8^+CD4^-CD45RA^+CD27^-$), central memory T Suppressor/Cytotoxic cells ($CD4^+CD8^+CD4^-CD45RACD27^+$), effector memory T Suppressor/Cytotoxic cells ($CD3^+CD8^+CD4^-CD45RA^-CD27^-$). T cells are crucial for immune function to maintain health. Differences in groups and subgroups could be critical in understanding the pathogenesis of the dry eyes (21). Lastly, as B cells play a complex role in promoting and regulating immune function and inflammation, we assessed naive B cells ($CD19^+CD27^-IgD^+$), class switched B cells ($CD19^+CD27^+IgD^-$) and non-class switched B Cells ($CD19^+CD27^+IgD^+$) (22).

Table I. Patients' clinical and demographic information.

	ASIA-BII (n=78)	Healthy controls (n=18)		pSjD (n=17)	
	Count (%)	Count (%)	*p*-value	Count (%)	*p*-value
Sex (F)	78/78 (100)	18/18 (100)	> 0.99	17/17 (100)	> 0.99
Schirmer					
≤15	57/78 (73.1)	11/18 (61)	0.37	14/17 (82.4)	0.37
≤5	37/78 (47.4)	3/18 (16.6)	**0.017**	9/17 (52.9)	0.68
SSSQ ≥7	10/71 (14.0)	0/18 (0)	0.091	4/17 (23.5)	0.34
ANA	27/78 (34.6)	-	-	12/16 (75)	**0.001**
Anti-SSA	0/78 (0)	-	-	10/16 (62.5)	**<0.001**
Anti-SSB	0/78 (0)	-	-	4/16 (25)	**<0.001**
	Median (IQR)	Median (IQR)	*p*-value	Median (IQR)	*p*-value
Age	45 (37;54)	51 (34;60)	0.43	57 (44;60)	0.053
BMI	23.29 (21.1, 28.04)	26.55 (23.14, 31.47)	0.13	29.37 (24.1, 32.5)	**0.002**
Schirmer Total	6 (2;18)	12 (9;30)	**0.003**	5 (0;9)	0.38
SSSQ Total	5 (3;6)	3.5 (3;6)	0.16	4 (4;6)	0.64
IgM	1.24 (0.92;1.59)	-	-	0.75 (0.58;1)	**0.005**
IgA	1.82 (1.42, 2.33)	-	-	1.67 (1.39, 3.29)	0.55
IgG	10.54 (9.25, 11.54)	-	-	11.11 (9.94, 14.1)	0.22
IgG1	5.28 (4.48, 6.18)	-	-	6.76 (4.91, 10.0)	0.064
IgG2	3.37 (2.59, 4.25)	-	-	3.27 (2.08, 4.6)	0.78
IgG3	0.47 (0.33, 0.67)	-	-	0.47 (0.39, 0.74)	0.76
IgG4	0.23 (0.14, 0.46)	-	-	0.12 (0.1, 0.34)	0.051

SSSQ Questionnaire

All patients were evaluated with a validated questionnaire for suspected SjD using the Sjögren's Syndrome Screening Questionnaire (SSSQ) (23). A score ≥7 distinguishes SjD from non-SjD patients (sensitivity=0.64, specificity=0.58) (23).

Schirmer tear test

All patients completed a 5-minute Schirmer tear test (24) which has been previously validated for identifying ADDE in SjD-related DED (sensitivity = 0.42; specificity = 0.76) (25)**.** The reproducibility of the Schirmer is well known, with a moderate to excellent intra-class correlation coefficient but the data is not high quality (26-28). All tests were completed in the same Kaye Edmonton Clinic environment, under similar conditions (temperature, humidity) and in a scent free environment with eyes closed technique. Briefly, test strips are marked from 0-35 mm. Patients are considered to have severe dry eyes if their moisture content is 5 mm or less, while mild dry eyes are defined as a value of 15 mm or less; with normal tear production is defined as 16 mm or more (24, 29).

Statistical analysis

All statistical analyses were completed on STATA 17 (Stata software). Qualitative variables were analysed using Chi Square and continuous variables were analysed through Wilcoxon Rank Sum tests. We used STATA 17 (Stata software) for the sample size calculation. The standard deviation (SD) reported in the literature for the Schirmer test was 3.93 (30). To have a 90% power for a significance level of a=0.05 (type I error associated) with a confidence level of 95% to detect minimal clinical difference of 5mm between study groups (30), the minimum number of participants required in each group was 15.

Results

We included 78 ASIA-BII consecutive patients, with 17 consecutive primary

SjD (pSjD) and 16 HC subjects that were both age and sex-matched to the ASIA-BII patients. Clinical and demographic information for the various patients were comparable and summarised in Table I, with the exception of BMI which was higher in pSjD compared to patients with ASIA-BII (p=0.002).

All ASIA/BII patients fulfilled at least 2 major ASIA criteria (Suppl. Table S1). Patients (n=78) had the following 'typical' clinical manifestations: chronic fatigue: 97%, myalgia/muscle weakness: 92%, arthralgia/arthritis: 97%, dry eyes/dry mouth: 99%, pyrexia: 74%, cognitive impairment/memory loss: 96%, neurological manifestations: 45%. Patients had a median score of 6 (range 4–7) out of these seven 'typical' manifestations. All ASIA-BII patients filled the internationally validated diagnostic criteria for ME/CFS (31) and/or FM (32). Apart from the 'typical' ASIA manifestations, 53% of ASIA/BII patients had Raynaud's phenomenon, whereas 76% had symptoms compatible with irritable bowel syndrome. Furthermore, 10% of ASIA/BII patients had a history of breast cancer. Finally, 41% of ASIA/BII had another autoimmune disorder such as Hashimoto, coeliac disease and/or rheumatoid arthritis. Of these, 44% had an autoimmune thyroid disorder.

Average SSSQ scores were similar in ASIA-BII, pSjD, and HC. A SSSQ score ≥7 was previously demonstrated to be 'diagnostic' for pSjD (23, 33). None of the HC had a SSSQ score ≥7. Importantly, median scores of SSSQ were the same in ASIA-BII patients as in pSjD patients (p=0.166) (Fig. 1B). Moreover, the rate of a positive 'diagnostic' score (SSSQ ≥7) was similar between the two groups (p=0.339) (Table I).

ASIA-BII and pSjD patients had similar Schirmer's tear test results (Fig. 1A). 16/18 (88.8 %) pSjD patients had impaired tear production (Schirmer test ≤15 mm), compared to 11/18 (61%) of the HC (p=0.013), and 57/79 (72.2%) of the ASIA-BII patients (p=0.14) (Table II). 9 (53%) pSjD patients and 37 (47%) ASIA-BII patients had severely impaired tear production (Schirmer test ≤5 mm) (not significantly different (p=0.68) (Table I). Severe impairment

Table II. ASIA-BII patients with normal tear production *vs*. patients with ADDE.

	Normal tear production (n=22) Count (%)	Dry eyes (n=56) Count (%)	*p*-valve
Sex (F)	22/22 (100)	56/56 (100)	> 0.99
Explantation			0.27
Pre-explantation	10/22 (45.5)	18/56 (32.1)	
Post-explantation	12/22 (54.5)	38/56 (67.9)	
Type of implant			0.53
Saline	5/22 (22.7)	11/56 (19.6)	
Silicone	17/22 (77.3)	42/56 (75)	
Both	0/22 (0)	3/56 (5.4)	
Other implant			0.13
No	21/22 (95.5)	46/56 (82.1)	
Yes	1/22 (4.5)	10/56 (17.9)	
SSSQ > 7			0.51
No	16/18 (88.9)	37/45 (82.2)	
Yes	2/18 (11.1)	8/45 (17.8)	
ANA positive	6/22 (27.3)	19/56 (33.9)	0.57
ENA positive	2/22 (9.1)	6/56 (10.7)	0.83
ENA: RNP positive	1/22 (4.5)	3/56 (5.4)	0.88
ENA: SSA positive	0/22 (0)	0/56 (0)	> 0.99
ENA: SSB positive	0/22 (0)	0/56 (0)	> 0.99
ANCA positive	0/22 (0)	6/56 (10.7)	0.11
positive MPO-ANCA	0/22 (0)	2/56 (3.6)	0.37
positive PR3-ANCA	0/22 (0)	0/56 (0)	> 0.99
	Median (IQR)	Median (IQR)	*p*-valve
Age	45.5 (39, 52)	45.5 (39, 54.5)	0.73
BMI	24.56 (21.22, 28.67)	22.975 (22.33, 27.9)	0.45
Implant duration (years)	9.5 (5, 20)	10 (6, 17.5)	0.86
5-minute Schirmer	28 (20, 30)	4 (1, 7)	**<0.001**
SSSQ	5 (4, 6)	5 (3, 6)	0.54
ACE	34.5 (22, 40)	30.5 (22, 38)	0.56
WBC	6.25 (5.4, 7.3)	6.05 (5.05, 7.1)	0.56
RBC	4.37 (4.18, 4.59)	4.57 (4.29, 4.76)	0.17
Hgb	137 (130, 141)	137 (130.5, 145)	0.63
Hct	0.41 (0.39, 0.42)	0.42 (0.4, 0.43)	0.32
MCV	92 (89, 94)	92 (90, 94)	0.64
RDW	12.6 (12.3, 13.2)	12.85 (12.35, 13.55)	0.24
Plts	273 (238, 303)	260 (229.5, 298)	0.63
Neutrophils	3.75 (3, 4.4)	3.6 (2.9, 4.5)	0.79
Lymphocytes	2 (1.5, 2.2)	1.7 (1.5, 2)	0.14
Monocytes	0.4 (0.4, 0.5)	0.4 (0.3, 0.5)	0.92
Eosinophils	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.26
Basophils	0 (0, 0.1)	0 (0, 0.1)	0.49
Neutrophil / Lymphocyte ratio	1.88 (1.32, 2.44)	1.95 (1.54, 2.76)	0.42
CRP	0.6 (0.5, 1.1)	0.65 (0.5, 1.75)	0.73
IgG	9.68 (8.51, 11.13)	10.6 (9.34, 11.56)	0.18
IgA	1.51 (1.15, 2.05)	1.87 (1.45, 2.37)	**0.0498**
IgM	1.235 (1, 1.43)	1.275 (0.9, 1.6)	0.53
IgG1	4.84 (4.47, 5.58)	5.24 (4.52, 6.11)	0.30
IgG2	2.97 (2.33, 3.84)	3.39 (2.6, 4.3)	0.24
IgG3	0.44 (0.31, 0.57)	0.48 (0.35, 0.7)	0.17
IgG4	0.29 (0.17, 0.47)	0.2 (0.14, 0.405)	0.30
IgE	18.5 (8, 39)	12.5 (6, 28)	0.25
Helper T cells (CD4)	0.79 (0.59, 1)	0.73 (0.59, 0.97)	0.52
NK cells	0.23 (0.14, 0.29)	0.23 (0.13, 0.26)	0.55
NK/CD4 ratio	0.257 (0.220, 0.367)	0.263 (0.218, 0.346)	0.77
Naive T helper cells	0.403 (0.267, 0.533)	0.316 (0.196, 0.482)	0.20
Terminal differentiated T Helper cells	0.004 (0.001, 0.013)	0.0095 (0.003, 0.023)	0.064
Central memory T helper cells	0.371 (0.259, 0.447)	0.315 (0.224, 0.389)	0.37
Effector memory T helper cells	0.042 (0.032, 0.066)	0.062 (0.047, 0.101)	0.057
T suppressor / cytotoxic naive cells	0.167 (0.1, 0.197)	0.158 (0.108, 0.207)	0.80
T suppressor / cytotoxic: terminally differentiated	0.035 (0.019, 0.07)	0.076 (0.043, 0.136)	**0.045**
T suppressor / cytotoxic: central memory	0.086 (0.045, 0.143)	0.0635 (0.045, 0.09)	0.40
T suppressor / cytotoxic: effector memory	0.016 (0.011, 0.041)	0.0225 (0.014, 0.057)	0.089
B cell: memory, class switched	0.023 (0.016, 0.026)	0.0195 (0.012, 0.033)	0.88
B cell: naive	0.086 (0.047, 0.125)	0.0945 (0.058, 0.131)	0.37
B cell: memory, non-class switched	0.014 (0.009, 0.017)	0.013 (0.007, 0.021)	0.35

of tear production was, however, significantly less often observed in HC compared to ASIA-BII patients (p=0.017). As anticipated, patients with pSjD more frequently tested positive for autoantibodies including ANA, anti-SSA and anti-SSB than ASIA-BII patients (p=0.001; p<0.001; p<0.001) (Table I). IgM was higher in ASIA-BII compared to pSjD (p=0.002), whereas IgG (Table I) and IgG subclass levels (Table I) were similar between pSjD and ASIA-BII patients.

Dry eyes and disease-related measures in ASIA-BII patients, by tear production level

To further compare ASIA-BII patients with dry eye symptoms, we compared ASIA-BII with one another based on the various levels of tear production. When ASIA-BII patients with normal tear-production (Schirmer's tear test >15 mm) were compared to ASIA-BII patients with ADDE (*i.e.* Schirmer's tear test ≤15 mm), we found that both groups were similar with respect to age, BMI, implant duration, type of breast implant, fatigue and SSSQ scoring (Table II). Also, no differences were observed in the levels of other immunoglobins, CRP, ACE, ANA, ENA, ANCA, CBC-D. Intriguingly, ASIA-BII patients with ADDE had mildly higher IgA levels when compared to normal tear producing ASIA-BII patients, 1.87 *versus* 1.51 g/L (p=0.0498) (Table II). This was associated with a trend towards significance for ADDE patients having reduced effector memory T helper cells compared to patients with normal tear production (p=0.057) (Table II). In addition, patients with ADDE had a significant increase in their suppressor / cytotoxic: terminally differentiated T cells compared to normal tear production patients (p=0.045) (Table II).

To further compare the groups with the most clinical differences, we did an analysis of the 22 ASIA-BII patients with normal tear production (Schirmer's tear test >15 mm) in comparison to the patients suffering from severe ADDE (n=33; Schirmer's tear test ≤5 mm). Again, no differences were found to be significant between the groups in term of age, BMI, implant dura-

Table III. ASIA-BII patients with normal tear production *vs*. severe dry eyes.

	Normal tear production (n=22) Count (%)	Severe dry eyes (n=37) Count (%)	p-valve
Sex (F)	22/22 (100)	37/37 (100)	> 0.99
Explantation			0.43
Pre-explantation	10/22 (45.5)	13/37 (35.1)	
Post-explantation	12/22 (54.5)	24/37 (64.9)	
Type of implant			0.38
Saline	5/22 (22.7)	7/37 (18.9)	
Silicone	17/22 (77.3)	27/37 (73)	
Both	0/22 (0)	3/37 (8.1)	
Other Implant			0.12
No	21/22 (95.5)	30/37 (81.1)	
Yes	1/22 (4.5)	7/37 (18.9)	
SSSQ >7			0.42
No	16/18 (88.9)	24/30 (80)	
Yes	2/18 (11.1)	6/30 (20)	
ANA positive	6/22 (27.3)	13/37 (35.1)	0.53
ENA positive	2/22 (9.1)	5/37 (13.5)	0.61
ENA: RNP positive	1/22 (4.5)	2/37 (5.4)	0.88
ENA: SSA positive	0/22 (0)	0/37 (0)	> 0.99
ENA: SSB positive	0/22 (0)	0/37 (0)	> 0.99
ANCA positive	0/22 (0)	3/37 (8.1)	0.17
positive MPO-ANCA	0/22 (0)	2/37 (5.4)	0.27
positive PR3-ANCA	0/22 (0)	0/37 (0)	> 0.99
	Median (IQR)	Median (IQR)	p-valve
Age	45.5 (39, 52)	45 (37, 52)	0.97
BMI	24.56 (21.22, 28.67)	23.51 (21.44, 28.04)	0.65
Implant duration (years)	9.5 (5, 20)	10 (6, 17)	0.75
5 - minute Schirmer	28 (20, 30)	2 (0, 4)	**<0.001**
SSSQ	5 (4, 6)	4.5 (3, 6)	0.61
ACE	34.5 (22, 40)	27 (21, 37)	0.28
WBC	6.25 (5.4, 7.3)	6 (4.9, 7.1)	0.59
RBC	4.37 (4.18, 4.59)	4.58 (4.42, 4.76)	0.093
Hgb	137 (130, 141)	138 (132, 145)	0.36
Hct	0.41 (0.39, 0.42)	0.42 (0.41, 0.44)	0.097
MCV	92 (89, 94)	92 (90, 94)	0.93
RDW	12.6 (12.3, 13.2)	12.9 (12.4, 13.5)	0.22
Plts	273 (238, 303)	260 (230, 289)	0.56
Neutrophils	3.75 (3, 4.4)	3.8 (2.9, 4.4)	> 0.99
Lymphocytes	2 (1.5, 2.2)	1.7 (1.4, 1.9)	0.078
Monocytes	0.4 (0.4, 0.5)	0.4 (0.3, 0.5)	0.94
Eosinophils	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.67
Basophils	0 (0, 0.1)	0 (0, 0.1)	0.25
Neutrophil / Lymphocyte ratio	1.88 (1.32, 2.44)	2.24 (1.83, 2.75)	0.19
CRP	0.6 (0.5, 1.1)	0.6 (0.5, 1.6)	0.79
IgG	9.68 (8.51, 11.13)	10.4 (8.86, 12.02)	0.28
IgA	1.51 (1.15, 2.05)	1.87 (1.45, 2.26)	0.067
IgM	1.235 (1, 1.43)	1.24 (0.92, 1.6)	0.66
IgG1	4.84 (4.47, 5.58)	5.28 (4.58, 6.66)	0.29
IgG2	2.97 (2.33, 3.84)	3.33 (2.6, 4.14)	0.44
IgG3	0.44 (0.31, 0.57)	0.5 (0.37, 0.73)	0.10
IgG4	0.29 (0.17, 0.47)	0.19 (0.12, 0.36)	0.19
IgE	18.5 (8, 39)	10 (6, 28)	0.15
Helper T cells (CD4)	0.79 (0.59, 1)	0.605 (0.51, 0.9)	0.15
NK cells	0.23 (0.14, 0.29)	0.195 (0.13, 0.26)	0.28
NK/CD4 ratio	0.257 (0.220, 0.367)	0.259 (0.197, 0.351)	0.81
Naive T Helper cells	0.403 (0.267, 0.533)	0.235 (0.168, 0.359)	**0.014**
Terminal differentiated T helper cells	0.004 (0.001, 0.013)	0.007 (0.002, 0.031)	0.22
Central memory T helper cells	0.371 (0.259, 0.447)	0.289 (0.193, 0.388)	0.21
Effector memory T helper cells	0.042 (0.032, 0.066)	0.0565 (0.041, 0.101)	0.23
T suppressor / cytotoxic naive cells	0.167 (0.1, 0.197)	0.124 (0.095, 0.184)	0.26
T suppressor / cytotoxic: terminally differentiated	0.035 (0.019, 0.07)	0.0765 (0.029, 0.136)	0.14
T suppressor / cytotoxic: central memory	0.086 (0.045, 0.143)	0.051 (0.038, 0.09)	0.34
T suppressor / cytotoxic: effector memory	0.016 (0.011, 0.041)	0.02 (0.014, 0.057)	0.12
B cell: memory, class switched	0.023 (0.016, 0.026)	0.021 (0.008, 0.052)	0.81
B cell: naive	0.086 (0.047, 0.125)	0.098 (0.055, 0.139)	0.44
B cell: memory, non-class switched	0.014 (0.009, 0.017)	0.0085 (0.005, 0.021)	0.16

tion, frequency of explantation, type of implant used, frequency of other non-breast implants, and severity of fatigue or SSSQ scoring (p>0.05) (Table III). As before, no differences were detected in the levels of immunoglobins, ACE, ANA, ENA, ANCA, CBC-D, CRP. However, a significant reduction in naive T helper cells was found when comparing ASIA-BII patients with severe ADDE with ASIA-BII patients with normal tear production (p=0.014) (Fig. 2) (Table III).

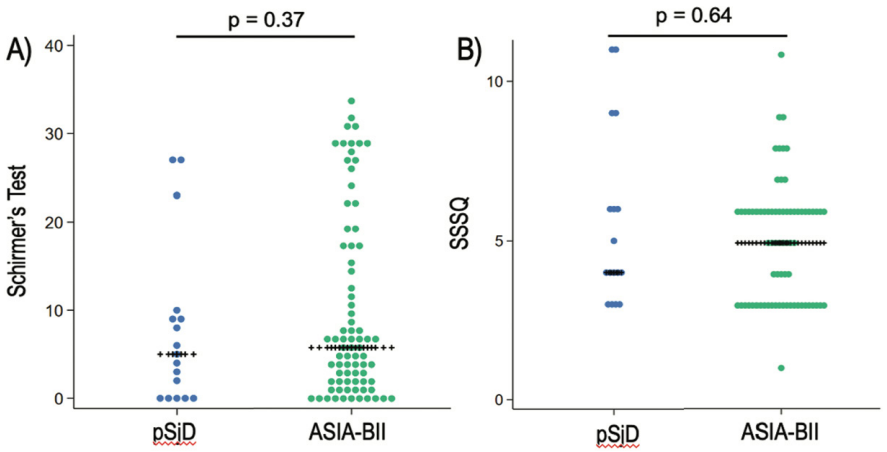

Fig. 1. Schirmer's Test and SSSQ Questionnaire results
A: Schirmer test results between ASIA-BII and primary Sjögren's disease patients.
B: Sjögren's syndrome screening questionnaire (SSSQ): primary Sjögren's disease *vs*. ASIA-BII.
pSjD: primary Sjögren's disease. ASIA-BII: autoimmune/inflammatory syndrome induced by adjuvants due to breast implants.

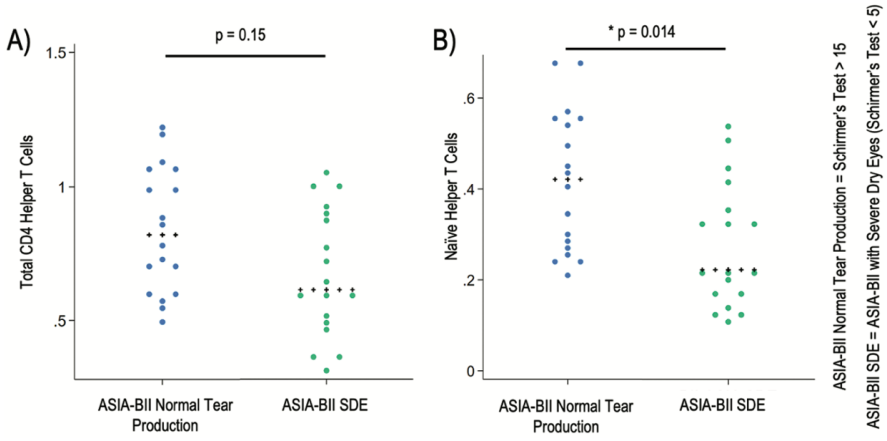

Fig. 2. Peripheral plasma levels of T helper cells in ASIA-BII patients with normal tear production *vs*. severe dry eyes.
A: Comparison of peripheral plasma levels of helper T cells between ASIA-BII patients with severe dry eyes and normal tear production. **B**: Comparison of peripheral plasma levels of naive helper T cells between ASIA-BII patients with severe dry eyes and normal tear production.

Discussion

The existence of ASIA-BII as a 'real' disease is often debated since there are no objective biomarkers that have been validated for this disease (9-11). Importantly, many of the ASIA-BII patients develop symptoms that are frequently observed in other rheumatic diseases, such as severe fatigue, diffuse pain and cognitive dysfunction (34). In this study, we show for the first time that dry eyes in patients with ASIA-BII is largely indistinguishable from patients with pSjD. Specifically, we found similar rates of mild and severely impaired tear production in ASIA-BII patients as in pSjD patients using the Schirmer's test, which is highly clinically used (and validated) for detecting Sjögren's related dry eye disease. Like patients with pSjD, ASIA-BII patients had impaired tear production (Table I, Fig. 1A). Yet, in the absence of histological confirmation or ocular staining data we cannot definitely conclude they are indistinguishable.

ASIA/BII patients not only suffered from dry eye disease but 70 of 78 (90%) our patients also complained of a dry mouth. As in SjD (17), about 10% of our ASIA/BII patients had isolated eye dryness, *i.e*. without oral dryness. In our study, we evaluated our ASIA-BII patients with the SSSQ questionnaire, a tool used to screen for SjD in rheumatology practice. A SSSQ score ≥7 distinguishes SjD patients from non-SjD patients (23). In previous studies, a SSSQ score ≥7 was observed in 42–64% of SjD patients (23, 33). In our study, we found that only 27.7% of SjD patients had a SSSQ score ≥7. In addition, we found that the questionnaire was unable to differentiate SjD from ASIA-BII, as both groups had similar average SSSQ scores and rates of abnormal scores (SSSQ ≥7). We did find, however, that the measurement of ANA, anti-SSA/SSB, and IgM may be helpful in differentiating the patients with ASIA-BII and SjD patients.

The question whether our ASIA-BII patients suffered from undiagnosed SjD cannot be answered by our study. Previously, it was demonstrated that patients with breast implants are at increased risk to develop SjD (35,36). Notably, the majority of our ASIA-BII with severe ADDE were not positive for anti-SSA and/or SSB antibodies suggesting that our patients have non-SjD ADDE. Indeed, others have previously demonstrated that minor labial biopsies in patients with breast implants and SjD-like disease differed from patients with 'idiopathic' SjD (37). Since we did not perform minor labial biopsies in our ASIA-BII patients, we, however, cannot exclude that our patients suffer from so-called seronegative SjD, a form of SjD that accounts for about 9% of the SjD population (38-40). We postulate, however, that it is more likely that our ASIA-BII patients suffer from so-called sicca asthenia polyalgia syndrome (38, 41).

Previous research determined that ASIA-BII patients have humoral immune deficiencies (2, 4, 42). In the

current study, we did not observe differences in IgG and/or its subclasses between ASIA-BII patients with severely impaired tear production *versus* those with normal tear production. The finding, however, that ADDE in ASIA-BII is associated with T cell population changes suggests that ongoing immune activation (2, 6, 8), likely plays a causal role in ASIA-BII and the development of ADDE. Implanted biomaterials have been shown to trigger foreign body reactions resulting in chronic inflammation (5). The chronic inflammation may be driven by the biomaterial enhancing the immune response (5). The decrease in circulating helper T cells as observed in ASIA-BII patients with severely impaired tear production should be further investigated and mechanisms characterised. Moreover, assessment of the tear fluid and ocular structures could be of benefit to ascertain causality. Whether there is a positive relationship between dry eye symptoms and activity of the underlying autoimmune rheumatic disease as has been observed in SjD, systemic lupus erythematosus, and systemic sclerosis (43), remains to be seen.

Limitations

This study had some limitations, one of note is that our evaluation through surveys/questionaries comes with biases such as social desirability bias or responder bias. In addition, a notable limitation is that our evaluation of patients' dry eyes was based on assessment using the Schirmer test. The Schirmer test can be affected by multiple factors, in particular air pollutant, light, wind, temperature and humidity. For this study, the test was done in the same building with controlled temperature, humidity and in a scent free environment. In addition, medications and comorbidities (*e.g.* thyroid disease) can potentially confound the data. We did, however, not observe a more impaired tear production in patients with thyroid disease compared to those without, whereas we also did not observe more severe tear impairment in those patients who used antidepressants or antihistamines. Lastly, our study is limited since we did not perform tear film analysis and/or ocular staining, whereas we also did not obtain minor labial biopsies in our BII-ASIA patients. Those more invasive tests could further expand the notion whether BII-ASIA and SjD are indistinguishable of each other or not.

Conclusion

In conclusion, ASIA-BII patients with breast implants likely suffer from dry eyes due to impaired tear production. Specifically, the SSSQ and the Schirmer test were unable to differentiate whether sicca symptoms were due to development of SjD or not in ASIA-BII patients. Our study highlights the need for biomarkers that can better classify patients with dry eye diseases, and inflammatory conditions. As advised by Marriette (39), to further progress our understanding of ASIA-BII *versus* pSjD, we will be investigating ultrasound imaging of the major salivary glands (44, 45) in ASIA-BII to determine the probability for SjD-like glandular changes.

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