Clinical and histological features of patients with primary Sjögren's syndrome and autoimmune thyroiditis: a national multicentre cross-sectional study

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Abstract

Objective

Primary Sjögren's syndrome (pSS) is frequently associated with autoimmune thyroiditis (AT). The aim of this study was to evaluate the prevalence of AT in a national cohort of pSS and to describe the clinical and histological phenotype of patients with pSS and associated AT.

Methods

In this multicentre cross-sectional study, data from 2546 pSS were collected and the presence of AT was reported. In a subgroup, the histology of minor salivary glands was evaluated. Differences between pSS with and without AT were evaluated.

Results

A concomitant pSS and AT was detected in 19.6% of cases. Patients with pSS and AT displayed a lower prevalence of lymphoma, male sex and disease-modifying anti-rheumatic drugs (DMARDs) use and a higher prevalence of fibromyalgia, coeliac disease and hypergammaglobulinaemia. Multivariable analysis confirmed a higher prevalence of fibromyalgia and coeliac disease and lower use of DMARDs. In a subgroup of patients (n=232), a significantly higher focus score and number of foci was detected in pSS without AT (n=169) as compared to pSS with AT (n=54).

Conclusion

This is the largest study evaluating the coexistence of pSS and AT. We confirm a high association between pSS and AT and describe the presence of a different phenotype characterized by a higher rate of celiac disease and fibromyalgia. Although not significant, the lower prevalence of both lymphoma and intake of DMARDs, along with a significantly lower focus score and number of foci, possibly suggest a more favourable outcome in concomitant pSS and AT which further deserve future investigations.

Key words

Sjögren's syndrome, autoimmune thyroiditis, prevalence, clinical, histology, fibromyalgia, coeliac disease, DMARDs

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Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune inflammatory disease affecting salivary and lacrimal glands and characterised by a progressive loss of secretory function and development of xerostomia and xerophthalmia (1). Around 15% of pSS patients present with a severe disease course exemplified by the occurrence of extra-glandular manifestations (2) and, in rare cases, a significant higher risk to develop B-cell non-Hodgkin's lymphoma (NHL) (3-4).

Autoimmune thyroiditis (AT) is one of the most frequent organ-specific autoimmune diseases with an estimated prevalence in the general population around 10% (5). In AT, the occurrence of xerostomia (6) and/or xerophthalmia (7) is particularly remarkable with a risk of true overlap with pSS even ten times higher compared to the general population (8). Accordingly, detection of AT in patients with pSS is extremely common being reported between 10 to 30% of cases (9). AT is characterised by the development of anti-thyroperoxidase (TPO) and anti-thyroglobulin (TG) antibodies and, similarly to pSS salivary glands' histology, by the presence of thyroid lymphocytes' infiltrates. Interestingly, similarly to pSS, patients with AT display an increased risk of developing NHL, specifically MALT lymphoma of thyroid gland (10).

Previous studies on relatively small case series pointed out a milder clinical phenotype in patients with concomitant pSS and AT (11). However, clinical data related to overlapping patients are still controversial and it remains unclear whether a concomitant diagnosis of pSS and AT could increase the risk of lymphoproliferative complications. Additionally, although histology of pSS minor salivary glands is key to provide information on disease activity and prognosis (12-13), no histological data are currently available on patients with pSS and associated AT.

Aim of this study is to describe in a national multicentre pSS cohort the prevalence and phenotype of patients with concomitant AT and to investigate in a subgroup of patients the main histological features of patients with and without concomitant AT. This work, representing the largest cross-sectional study exploring the clinical picture of patients with associated pSS and AT, provides the first evidence of both a different clinical phenotype and a different histology in overlapping patients and corroborates previous indications on a better disease prognosis.

Materials and methods

Study design and patients' recruitment

To pursue the objective of the study, a cross sectional design was chosen. The study was conducted on a multicentre national Italian cohort of patients affected by pSS fulfilling the AECG criteria (14). This study was conducted within the Harmonicss project (Horizon2020) and rheumatologic centres participating in the study belonged to the Italian Working Group on SS (GRISS: Gruppo di Ricerca Italiano sulla Sindrome di Sjögren). Permission to conduct the study was obtained from the Sapienza University of Rome ethics committee (protocol no. 4688).

Data collection

Data extraction was performed by dedicated personnel on a designed electronic database gathering the main clinical and laboratory features of pSS patients. Information regarding the presence of a confirmed diagnosis of AT was collected. Regarding the presence of a concomitant AT, personnel collecting the data were asked to state "yes" or "no" according to the following definition: state "yes" in case the patients has both positive anti-thyroid antibodies (anti-TPO and/or anti-TG defined as positive according to the cut off level provided by the laboratory) and the typical thyroid sonographic findings (such as a reduction in thyroid echogenicity) (15). As reported below, to refer to the group of patients where the answer was "no" (without AT) we used the term "isolated pSS". Additional collected clinical data comprised the presence of sicca symptoms, recurrent swelling of major salivary glands, extra glandular involvement, organs' specific involvement, history of NHL and the most associated comorbidities described in pSS such as coeliac dis-

ease, described in 6% (16) to 14% (17) of cases, and fibromyalgia, described in up to 19% of patients (18). The presence of a coeliac disease was indicated when the patient tested positive in serology and had a histology of duodenal biopsy consistent with coeliac disease (shortened villi, crypt hyperplasia, an abnormal cytological appearance of the absorbent surface and an increase in the cells in the lamina propria) (19). The presence of a fibromyalgia was diagnosed according to the ACR 2010 criteria (20). Laboratory data included the presence of autoantibodies [*i.e.* ANA, anti-Ro/SSA, anti-La/SSB, rheumatoid factor (RF)], hypergammaglobulinaemia (gammaglobulins >16 gr/L), monoclonal component, leukopenia (WBC <4000) and hypocomplementaemia (C3 <80 mg/dl, C4 <15 mg/dl). Past or present use of glucocorticoids, hydroxychloroquine and other disease-modifying anti-rheumatic drugs (DMARDs) (including methotrexate, azathioprine, cyclosporine A, mycophenolate and rituximab) was also pointed out.

Minor salivary gland biopsies

To provide histological information regarding patients with isolated pSS and patients with pSS and AT, minor salivary gland biopsies performed for diagnostic purposes in a subgroup of pSS patients attending the SS Clinic at Sapienza University of Rome were retrospectively collected. All biopsies from patients with a confirmed diagnosis of pSS (AECG) (14), consecutively performed for diagnostic purposes between January 2017 and March 2023, were analysed.

Histological evaluation of minor salivary glands

After biopsy collection, consecutive paraffin embedded minor salivary glands sections measuring 3 μm in thickness were cut and stained by Haematoxylin & Eosin (HE) and immunohistochemistry (IHC) for the identification of inflammatory infiltrates, characterisation of T and B lymphocytes [rabbit polyclonal antibody anti-CD3 (DAKO); mouse monoclonal antibody anti-CD20 (DAKO)], detection of germinal centres (GCs) like structures [nodular aggregates with a "dark" and light" zone at HE and positive staining for CD21 (mouse monoclonal antibody anti-CD21 long isoform, DAKO)], detection of lymphoepithelial lesions (LEL) [anti-CD20+ cells (DAKO) infiltrating ductal epithelial cells] and detection of fibrosis (by HE). Samples were analysed at a single cutting level according to the standard of practice. The histological parameters, also described in our previous work (21) included: focus score (FS), number of foci, presence of GCs, presence of LEL and presence of fibrosis. Methods for staining procedure and histological analysis are reported in the supplementary material.

Statistical analysis

The statistical analyses consisted of four steps. First, medians and interquartile ranges or frequencies and proportions were reported for continuous or categorical variables, respectively. Mann-Whitney and Chi-square tests (univariate analyses) were used to compare the statistical significance of differences in the distribution of continuous or categorical variables between patients with isolated pSS and patients with pSS and AT, respectively. Second, to account for the baseline clinical differences between isolated pSS and patients with pSS and AT, multivariable logistic regression models were used and covariates were selected according to a clinical criterion. Similarly, in the histological analysis multivariable linear and logistic regression models accounting for the main clinical confounders were used. Third, the hypothesis that specific subgroup of patients with pSS and AT might be more likely to experience the specific outcomes found to be different between the two groups, was tested using interaction terms at logistic regression analysis. For interaction tests, we selected the most relevant clinical and laboratory data. All statistical tests were performed using the RStudio graphical interface v. 0.98 for R software environment v. 3.0.2 with the following libraries, packages and scripts: Epi, epiR, tidyverse, Stat2Data, tableone, compareGroups, Resource selection, stats4. All tests were two-sided with a significance level set at $p<0.05$.

Results

In patients with pSS and AT univariate analysis reveals a higher prevalence of fibromyalgia and coeliac disease and a lower prevalence of NHL, male sex and DMARD use

Clinical and laboratory data from 2546 patients affected by pSS referring to 6 different Italian centres were collected. Five hundred and fifty patients out of 2546 (19.6%) had a diagnosis of pSS and associated AT. Median age in isolated pSS and pSS associated with AT was 53 (IQR 42, 62) and 51 (IQR 43, 60) years, respectively (p=0.077). Results from the univariate analysis comparing clinical and laboratory features between patients with pSS with or without AT are reported in Table I and in Supplementary Figure S1. In patients with pSS and AT the prevalence of coeliac disease, fibromyalgia and hypergammaglobulinaemia was significantly higher (Table I). Conversely, the prevalence of NHL, male sex and use of DMARDs (other than hydroxychloroquine) was significantly lower as compared to the isolated form of pSS (Table I).

The most frequently reported NHL in the entire cohort of patients was represented by MALT lymphoma (94.2% of cases, mostly parotid lymphoma followed by gastric and pulmonary lymphoma); none of patients, either in the isolated form of pSS or in the form associated to AT, experienced a thyroid MALT lymphoma.

Multivariable analysis confirms the higher prevalence of coeliac disease and fibromyalgia and the lower use of DMARDs in patients with concomitant pSS and AT

Confounding factors were controlled by performing a multivariable logistic regression analysis adjusted for the following covariates: age, sex, presence of anti-Ro/SSA and anti-La/SSB antibodies and RF. In patients with pSS and associated AT, multivariable analysis confirmed a higher rate of both coeliac disease and fibromyalgia and a lower intake of DMARDs (Table II). Although in the univariate analysis we found a lower rate of NHL in patients with concomitant pSS and AT,

Table I. Univariate analysis accounting for the main clinical and laboratory features of patients with isolated pSS and patients with pSS and AT.

Clinical and laboratory features	pSS (n=1996) % (CI)	pSS & AT (n=550) % (CI)	pSS & AT *vs*. pSS OR (CI)	*p*-value
Male	4.9 (4.0, 5.9)	2.36 (1.2, 4.0)	0.48 (0.27, 0.87)	**0.009**
Xerostomia	92.4 (91.1, 93.5)]	93.4 (91.0, 95.3)	1.16 (0.80, 1.70)	0.427
Xerophtalmia	93.2 (92.0, 94.3)	94.3 (92.0, 96.1)	1.20 (0.80, 1.80)	0.365
Salivary glands swelling	28.9 (26.9, 31.0)	31.01 (27.1, 35.1)	1.11 (0.90, 1.37)	0.357
Articular involvement	64.5 (62.3, 66.6)	67.65 (63.5, 71.5)	1.15 (0.94, 1.41)	0.182
Purpura	7.40 (6.2, 8.6)	6.74 (4.7, 9.2)	0.90 (0.62, 1.32)	0.602
Raynaud phenomenon	22.14 (20.3, 24.0)	24.10 (20.5, 27.9)	1.12 (0.89, 1.40)	0.339
Extra glandular manifestations	32.23 (30.1, 34.3)	33.09 (29.1, 37.1)	1.04 (0.85, 1.27)	0.702
Kidney involvement	1.67 (1.0, 2.4)	1.81 (0.8, 3.3)	1.09 (0.52, 2.30)	0.819
Pancreas involvement	0.27 (0.07, 0.7)	0.36 (0.04, 1.3)	1.31 (0.24, 7.15)	0.756
Liver involvement	1.04 (0.5, 1.7)	0.18 (0.004, 1.0)	0.17 (0.02, 1.31)	0.054
Pulmonary involvement	5.56 (4.4, 6.8)	5.63 (3.8, 7.9)	1.01 (0.66, 1.55)	0.952
Dermatologic involvement	5.63 (4.5, 6.9)	5.81 (4.0, 8.1)	1.03 (0.68, 1.58)	0.875
Neurologic involvement	5.91 (4.7, 7.2)	7.06 (5.0, 9.6)	1.21 (0.81, 1.80)	0.352
Haematologic involvement	18.18 (16.1, 20.3)	20.08 (16.9, 25.1)	1.18 (0.89, 1.56)	0.240
Muscular involvement	0.83 (0.4, 1.4)	0.93 (0.3, 2.1)	1.12 (0.39, 3.18)	0.837
Gastrointestinal involvement	2.36 (1.6, 3.2)	1.45 (0.6, 2.8)	0.61 (0.28, 1.32)	0.205
Cardiac involvement	1.32 (0.7, 2.0)	1.09 (0.4, 2.3)	0.82 (0.33, 2.07)	0.677
Lymphoma	4.25 (3.4, 5.2)	2.23 (1.1, 3.8)	0.51 (0.28, 0.95)	**0.030**
Fibromyalgia	24.3 (22.2, 26.4)	31.87 (27.8, 36.1)	1.46 (1.17, 1.81)	**0.0006**
Coeliac disease	2.38 (1.7, 3.1)	4.74 (3.0, 6.9)	2.09 (1.26, 3.45)	**0.004**
Hypocomplementaemia	21.25 (19.3, 23.2)	23.79 (20.1, 27.7)	1.16 (0.91, 1.47)	0.228
Leukopenia	26.94 (24.9, 28.9)	27.18 (23.4, 31.2)	1.01 (0.82, 1.26)	0.911
Hypergammaglobulinaemia	41.87 (39.6, 44.1)	47.61 (43.2, 51.9)	1.26 (1.04, 1.53)	**0.018**
Monoclonal component	7.52 (6.3, 8.7)	6.83 (4.7, 9.5)	0.90 (0.61, 1.34)	0.612
ANA	86.3 (84.4, 88.0)	85.2 (81.9, 88.1)	0.91 (0.69, 1.21)	0.992
Anti-Ro/SSA	67.39 (65.2, 69.4)	69.74 (65.6, 73.5)	1.12 (0.91, 1.37)	0.299
Anti-La/SSB	36.07 (33.9, 38.2)	35.7 (31.6, 40.0)	0.99 (0.81, 1.21)	0.887
RF	46.48 (44.1, 48.8)	48.78 (44.2, 53.2)	1.10 (0.90, 1.34)	0.364
Cryoglobulins	5.31 (4.2, 6.6)	5.82 (3.7, 8.6)	1.12 (0.69, 1.80)	0.695
Glucocorticoids	44.62 (42.3, 46.9)	42.25 (37.8, 46.7)	0.91 (0.74, 1.11)	0.346
Hydroxycloroquine	53.24 (50.9, 55.5)	51.48 (47.0, 55.9)	0.93 (0.77, 1.14)	0.483
Other DMARDs	19.09 (17.3, 20.9)	14.53 (11.6, 17.8)	0.72 (0.55, 0.94)	**0.016**

ANA: anti-nuclear antibodies; Hypergammaglobulinemia: gammaglobulins >16 g/L; Hypocomplementaemia: C3<80 and/or C4<15 mg/dl; Leukopenia: neutrophils <1500 mm^3/lymphocytes <1000 mm^3; RF: rheumatoid factor; SD: standard deviation; NHL: non-Hodgkin lymphoma.

at the adjusted analysis the difference between the two groups did no longer met the conventional levels of statistical significance (Table II). Conversely, no further clinical and laboratory difference between isolated pSS and pSS associated with AT was revealed (data not shown).

According to our multivariable analysis, in the entire cohort of pSS patients the probability of NHL was significantly higher in male and in patients with positive RF (Table II). Similarly, in the entire pSS cohort, the probability of coeliac disease was lower in patients with RF while the probability of fibromyalgia was reduced in male and in patients with positive anti-La/SSB antibody; finally, in the entire cohort, the use of DMARDs was significantly higher in male and in patients with positive RF (Table II).

Interaction tests identify subgroups of patients with pSS and AT with different likelihood to experience NHL, coeliac disease, fibromyalgia, and the use of DMARDs

In patients with pSS and associated AT, similarly to patients with isolated pSS, the prevalence of NHL was significantly higher in those with hypocomplementaemia (p=0.050), cryoglobulins (p=0.009) and monoclonal component (p=0.018) (Fig. 1 a-b-c).

In patients with pSS and AT, differently from the isolated form of pSS, the predicted probability of coeliac disease was higher in those with leukopenia (p=0.035) and without anti-La/SSB antibodies (p=0.027) (Fig. 1 d-e); additionally, the predicted probability of coeliac disease significantly decreased over age (p<0.0001) (Fig. 1 f).

Similarly to the isolated form of pSS, in patients with pSS and AT the predicted probability to use DMARDs was higher in patients with hypocomplementaemia (p=0.030) and leukopenia (p=0.002) (Fig. 1 g-h) while the predicted probability of fibromyalgia was higher in patients without anti-La/SSB antibodies (p=0.041) (Fig. 1 i).

Histological analysis of minor salivary glands reveals lower focus score and lower number of foci in patients with associated AT compared to isolated pSS

Two hundred and thirty-two minor salivary glands biopsies were analysed, 169 from patients with isolated pSS and 54 from patients with pSS and AT. Features of patients enrolled for the histological analysis are reported in Supplementary Table S1. No significant differences in laboratory and clini-

Table II. Multivariable models predicting the occurrence of lymphoma, coeliac disease, fibromyalgia and the use of immunosuppressors in patients with isolated pSS compared to patients with pSS and AT.

Multivariable models	Lymphoma (NHL) OR (95%CI)	*p*-value	Celiac disease OR (95%CI)	*p*-value	Fibromyalgia OR (95%CI)	*p*-value	Use of DMARDs OR (95%CI)	*p*-value
Patients								
pSS & AT	0.56 (0.29 – 1.05)	0.070	1.87 (1.02 – 3.22)	**0.022**	1.37 (1.09 – 1.73)	**0.007**	0.69 (0.51 – 0.92)	**0.012**
pSS	ref	-	ref	-	ref	-	ref	-
Age	0.99 (0.97 – 1.00)	0.26	1.00 (0.97 – 1)	0.890	0.99 (0.98 – 1.00)	0.390	1.00 (1.00 – 1.01)	**0.035**
Sex								
Male	3.79 (0.47 – 0.95)	**<0.0001**	2.91 (0.00 – inf)	0.981	0.27 (0.13 - 0.58)	**0.0006**	1.75 (1.11 – 2.77)	0.015
Female	ref	-	ref	-	ref	-	ref	-
Anti-Ro/SSA								
Positive	1.17 (0.62 – 2.22)	0.62	0.99 (0.53 – 1.87)	0.990	1.05 (0.83 – 1.33)	0.660	1.11 (0.84 – 1.46)	0.440
Negative	ref	-	ref	-	ref	-	ref	-
Anti-La/SSB								
Positive	1.49 (0.9 – 2.49)	0.11	1.63 (0.9 – 2.49)	0.110	0.68 (0.53 - 0.87)	**0.002**	1.12 (0.87 – 1.45)	0.350
Negative	ref	-	ref	-	ref	-	ref	-
RF								
Positive	4.17 (2.3 – 7.36)	**<0.0001**	0.39 (2.3 – 7.36)	**0.001**	0.97 (0.78 – 1.2)	0.807	1.39 (1.1 – 1.75)	**0.005**
Negative	ref	-	ref	-	ref	-	ref	-

CI: confidence interval; DMARDs: disease-modifying anti-rheumatic drugs; NHL: non-Hodgkin lymphoma; OR: odds ratio; RF: rheumatoid factor; SD: standard deviation.

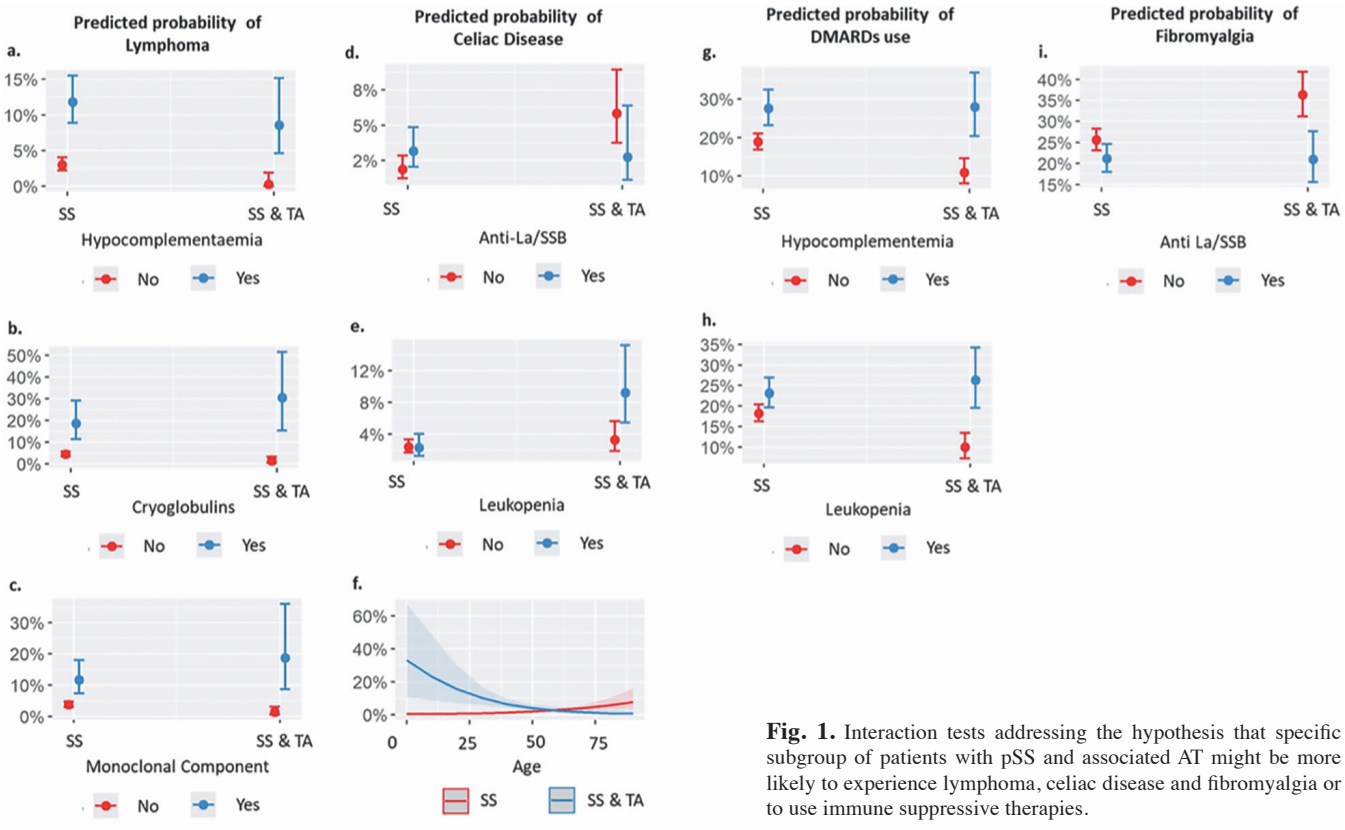

Fig. 1. Interaction tests addressing the hypothesis that specific subgroup of patients with pSS and associated AT might be more likely to experience lymphoma, celiac disease and fibromyalgia or to use immune suppressive therapies.

cal parameters were detected between the two groups except for a lower prevalence of RF in patients with pSS and AT (9.2% *vs*. 33.1%, *p*=0.006). The univariate analysis did show significantly lower levels of focus score in patients with pSS and associated AT (1.8±1.5 *vs*. 2.6±1.8, *p*=0.005) along with significant lower number of foci (6.1±4.6 *vs*. 4±3.9, *p*=0.009). No difference in the presence of GCs [93/169 (59.2%) *vs*. 23/54 (47.9%), *p*=0.166],

LEL [32/169 (18.9%) *vs*. 9/54 (16.6%), *p*=0.871) and fibrosis [29/169 (17.1%) *vs*. 7/54(12.9%), *p*=0.465], was detected between isolated pSS and pSS with AT. Because of the difference in the prevalence of RF between the two groups, we also performed multivariable logistic regression analyses accounting for this potential confounder. Even adjusted for the RF, the difference in the focus score was still significant (OR=0.73, *p*=003) as well as the difference in the number of foci (OR=0.90, *p*=0.050); the absence of a significant difference in the prevalence of GCs (OR=0.71, *p*=0.373), LEL (OR=1.12, *p*=0.787) and fibrosis (OR=0.67, *p*=0.404) was confirmed. Three out of 232 (1.2%) patients developed a parotid MALT lymphoma, all of them belonged to the isolated pSS group (Suppl. Table S1).

Discussion

This is the largest cross-sectional study investigating the prevalence and phenotype of pSS patients with concomitant AT. In this national pSS cohort, the prevalence of AT (about 20%) was higher compared to the general population and in line with previous studies (8). Compared to the isolated form, in patients with pSS and AT a different clinical phenotype characterised by higher prevalence of coeliac disease and fibromyalgia was observed. Specifically, in patients with concomitant AT the probability to develop a coeliac disease decreases over age and seems associated with the presence of both leukopenia and positive anti-La/SSB antibodies. Conversely, the probability of developing fibromyalgia seems higher in those without anti-La/SSB antibodies.

As both pSS and AT are characterised by increased risk of MALT lymphoma in salivary gland and thyroid tissue, respectively (3, 22-24), in this study we looked in detail at the prevalence of lymphoproliferative disorders. Despite the similar association with MALT lymphoma, patients with concomitant pSS and AT did not show higher risk of lymphoproliferative complications. Specifically, even with a fifty percent reduction in NHL in patients with concomitant pSS and AT, the multivariable analysis did not confirm a significant lower prevalence. However, both the tendency towards a lower prevalence of NHL and the lower intake of DMARDs might support a trend towards a milder clinical phenotype in pSS patients with an overlapping AT compared to the isolated form of pSS (25). Of note, the histological analysis performed on a large subgroup of patients, revealed the presence of a lower focus score and a lower number of foci in patients with associated AT, thus highlighting the presence of a less aggressive inflammation at tissue level which is in line with the potential milder clinical phenotype. Accordingly, although the number of patients developing MALT lymphoma in the histological cohort was too low to lead to any conclusion, it is remarkable that all three patients developing such a complication belonged to the isolated pSS group.

The strength of this study is represented by the unique sample size which makes this work the largest cohort investigating the association between two of the most common autoimmune conditions worldwide. Hence, this study provides a reliable and accurate picture of the association between pSS and AT and give crucial insights on the pathogenesis and prognosis of both diseases.

Although the observed prevalence of AT was relatively high, a major limitation of this study might be represented by its retrospective nature which allowed us to identify only established diagnosis of AT. Indeed, the presence of anti-TPO and anti-TG is highly reported in pSS (9) and AT can occur with a subclinical course in almost 10–15% of cases (26). Thus, an underestimation of AT diagnoses cannot be excluded. Similarly to AT, a potential underestimation of patients with fibromyalgia and coeliac disease may also have occurred due to the retrospective nature of the study. Another limit is also represented by the lack of a histological analysis for the entire cohort of patients. However, a homogeneous and extended histological analysis, accounting for the same histological parameters and executed by the same observers, could only be performed at a single centre level.

Primary SS is described in overlap with a variety of autoimmune diseases and the association with AT is the most frequently reported (27). First studies investigating the overlap between pSS and AT date back to the 90s. In these studies, the evidence of both clinical and genetic similarities between pSS and AT raised the hypothesis of a potential disease continuum between the two conditions (13, 27). For instance, from a genetic point of view, the presence of HLA-B8 and HLA-DR3 seem to represent a major predisposing factor (28). Additionally, several shared pathogenic features have been described including the role of "activated" epithelial cells and the presence of similar lymphocytic infiltrates and common immune mediators at tissue level (28). However, despite the existence of such overlapping features, most experts still consider pSS and AT as nosologically different deeming their coexistence as mere cases of polyautoimmunity (27).

Besides confirming a high prevalence of AT, in this study we clearly detected in patients with pSS and AT a significant third association with coeliac disease. The association between coeliac disease and pSS was first described in the 60s and was further confirmed in subsequent studies which reported a prevalence of the overlap between pSS and coeliac disease around 3 to 15% (17). A pathogenic link with the coeliac disease is confirmed not only by the evidence of sicca symptoms in up to 20% of coeliac patients but also by the evidence of a positivity for anti-Ro/SSA and anti-La/SSB antibodies in up to 6.5% of them (29). Interestingly, in patients with pSS and coeliac disease a gluten-free diet does not simply ameliorate intestinal pathology but also improves salivary gland inflammation (30). Although the association that we observed between the three conditions (pSS, AT and coeliac disease) is quite interesting, it is certainly not surprising as the overlap between AT and coeliac disease is the most frequently reported among glandular autoimmune conditions and a common genetic background has also been demonstrated (31).

Finally, in this study we also demonstrate a significant association between

pSS, AT and fibromyalgia. A high prevalence of fibromyalgia in AT has been already reported in about 30–40% of patients (32), and it is interesting to note how patients with thyroid disfunction experience similarities with fibromyalgia in musculoskeletal symptoms. Our finding does not seem isolated as also in patients with rheumatoid arthritis and AT the prevalence of fibromyalgia is particularly high with an estimated odds ratio of 3.4 (33). However, the potential pathogenic link between fibromyalgia and AT is still unknown.

In conclusion, this is the largest cross-sectional study describing the association between pSS and AT. Due to the retrospective nature and cross-sectional setting, its results have to be taken carefully and no relationship of causality can be affirmed. As expected, AT turned out to be a quite common comorbidity in patients with pSS, even higher compared to the general population, and its presence seems to depict a different clinical phenotype characterised by a higher rate of coeliac disease and fibromyalgia. Although the prevalence of NHL was lower in patients with associated AT, multivariable analysis did not confirm a significant lower risk of lymphoma in overlapping patients. However, a tendency towards a lower prevalence of lymphoma and a lower intake of DMARDs was observed which possibly suggests a more favourable outcome deserving future investigations. This hypothesis is in line with the histological analysis which revealed in patients with pSS and associated AT a significant difference in terms of severity of inflammation as detected by a lower focus score and lower number of foci. As the association between histology and peripheral markers has already been described also by our group (22), according to this finding it would be very interesting to look for additional features (such as cytokines, chemokines and cells immunophenotyping) to find potential pathogenic differences between the two subgroups that might support the hypothesis of a different disease course.

Taken together, these findings are likely to have an impact on patient management. As pSS may have a heterogeneous course, the identification of clinical and histological features which might be associated with a more favourable outcome is a relevant tool. All the characteristics that we looked at are easily accessible in clinical practice and could make the difference not only on patient follow up but also on treatment choice. The knowledge of characteristics that are more associated one to another would stimulate the clinicians to find comorbidities that are not always evident at a routine examination where symptoms may not even be reported by the patients.

The relevance of this study is therefore represented by the provided insights on associated comorbidities and histological features of patients with concomitant pSS and AT which we hope will be useful in ameliorating patient stratification and global management.

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