Review

Practical diagnostic tips for the Sjögren Clinic: pearls, myths and mistakes

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ABSTRACT

More than 90 years have passed since Hendrik Sjögren began to consider that behind the dryness that several of his patients presented, there could be a systemic disease potentially linked to abnormal immune responses. For many years, the disease was mostly considered a minor syndrome compared with other systemic autoimmune diseases such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and vasculitis, and advances in its understanding were slow and little recognised. The irruption of new technologies at the end of the 20th century rapidly promoted the development of international projects with a wide impact and diffusion. In the last 20 years, a significant improvement has been achieved in epidemiological determinants, pathogenic mechanisms, diagnostic accuracy, and a standardised therapeutic approach for patients with Sjögren's syndrome (SS). These developments have provided the tools for an early diagnosis and personalised management for most patients. However, a significant number of early myths and ongoing controversies are still making the appropriate management of SS difficult in daily clinical practice. This review provides a selection of pearls, myths, and mistakes that may serve as practical diagnostic tips for the Sjögren Clinic in four specific scenarios: defining the appropriate epidemiological background, enabling the earliest diagnostic suspicion as possible, improving the systemic characterisation of the disease, and designing an optimal follow-up of patients.

Defining the appropriate epidemiological scenario (Table I)

MYTH. Sjögren's syndrome is a rare disease. The frequency of Sjögren's syndrome (SS) varies widely according to the study design and the classification criteria used. A large population-based study carried out in Catalonia has recently estimated that SS may affect 1 in 400 people (1), with an incidence rate of seven new diagnoses per 100,000 person-years (2). Considering that the European Union defines a disease or condition as rare if it affects fewer than 1 in 2,000 people in the general population, SS is far from being a rare disease.

PEARL. For every 100 people newly diagnosed with Sjögren syndrome, 95 will be women. SS has the most unbalanced gender ratio among systemic autoimmune diseases. The disease is diagnosed overwhelmingly in middle-aged women (95%), with a recent Big Data study reporting a female/male ratio of 10:1 (3). Therefore, the closer to the typical epidemiological profile of SS the patient is (women aged 30-60 years), the greater the suspicion of the disease should be.

MISTAKE. The disease is underdiagnosed in men due to the lower severity compared with women. The fact that explains the underdiagnosis of SS in men is that the disease overwhelmingly affects women, not a potential lower degree of clinical severity. In fact, SS is more severe in men, which is not necessarily related to a potential delay in the diagnosis, considering it is an unexpected diagnosis in men. Men are more likely to present serious ocular complications and higher systemic activity at diagnosis including higher mean EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) and clinESSDAI scores, especially in the lymphadenopathy, glandular, pulmo-

Table I. Defining the appropriate epidemiological scenario.

- SS is not a rare disease and affects 1 in 400 people.
- For every 100 people newly diagnosed with SS, 95 are female.
- SS is more severe in men.
- Only 1% of patients are diagnosed in childhood.
- Black/African American patients have a severe systemic phenotype.
- Asian people less frequently report dryness symptoms.
- SS patients may have a familial history of other autoimmune diseases.
- People with jobs related to solvent exposure may have an enhanced risk of SS.
- Smoking and alcohol intake are often avoided by SS patients.

nary, peripheral nervous system (PNS) and central nervous system (CNS) domains (4). This severe systemic expression contrasts strongly with the lower frequency of autoantibodies in comparison with women (5). But the key finding that confirms the greater severity of SS in men is the poor disease outcome, related to a 2-4-fold higher risk of neoplasia or death (6, 7).

PEARL. Consider age at diagnosis a key driver of how the disease is clinically expressed. Although SS occurs at all ages, it is mainly diagnosed between the fourth and sixth decades of life. SS in children is very rare (around 1% of cases have a childhood onset), while in older people, the diagnosis is more frequent (around 10% of patients are aged > 75 years at diagnosis) (8). The wide phenotypic variation in the presentation of primary SS is strongly linked with the age at diagnosis, since the frequency of the main features (glandular, extraglandular and immunological) are modulated by age. There is a progressive increase in the frequency of dry mouth and pulmonary involvement at diagnosis with age (2.2% increase per each 10 years), and a progressive decrease in the frequency of lymphadenopathy, glandular involvement, and the positive rate of anti-Ro/La antibodies and immunological markers (4). Therefore, it is important to know that the phenotype at presentation of Sjögren's will be very different in a 10-year-old child than in an 80-year-old person.

MISTAKE. Sjögren's syndrome does not affect children. Primary SS may have a childhood-onset in around 1% of patients, with a clinical phenotype dominated by sicca features, parotid enlargement, and systemic disease. However, the systemic disease at diagnosis differs from that observed in adult-onset patients, consisting mainly of constitutional, lymphadenopathy, glandular, cutaneous and haematological activity (9). A significant challenge in daily practice is that nearly 80% of cases clinically diagnosed with SS by pediatricians did not meet the adult 2016 ACR/EULAR classification criteria, often because diagnostic testing are not universally performed in children (10).

MYTH. People diagnosed at older ages has a milder systemic expression. In more than 20% of cases, SS is diagnosed in people aged ≥65 years (11). When the disease is diagnosed at older ages, the frequency of dryness symptoms and abnormal diagnostic tests (parotid sialography, ocular tests, minor salivary gland biopsy) is similar to that reported in middle-aged people (12). With respect to systemic disease, the Big Data cohort showed that patients with a diagnosis at >70 years have an enhanced risk of activity in the articular, pulmonary, muscular and peripheral nervous system domains despite a lower frequency of anti-Ro/La autoantibodies and low C3 levels (13).

MISTAKE. Ethnic-related determinants have no role in the phenotype. The presentation of primary SS is also driven by ethnic determinants. First, a two-fold higher prevalence of the disease has been reported in patients with non-European ethnic backgrounds (14). Second, ethnicity influences the age at which the disease is diagnosed, and the disease is diagnosed a mean of seven years earlier in Black/African American (BAA) patients compared with White patients (15), a trend also reported by a French cohort (14). Third, the women:men ratio also varies significantly, with the highest ratio being reported in Asian patients (27:1) and the lowest in BAA patients (7:1) (15). Fourth, the prevalence of sicca symptoms differs significantly, with the lowest frequencies being reported in Asian patients (15), a finding previously related to cultural differences (16), while Hispanic and White patients are more likely to have abnormal results in oral and ocular diagnostic tests (15). And fifth, systemic disease is also driven by ethnic-related determinants, with the highest global ESSDAI scores being reported in BAA, followed by White, Asian and Hispanic patients; BAA patients showed the highest frequency of activity in the lymphadenopathy, articular, PNS, CNS and biological domains, White patients in the glandular, cutaneous and muscular domains, Asian patients in the pulmonary, renal and haematological domains, and Hispanic patients in the constitutional domain (15).

PEARL. Consider geographical determinants when systemic involvement is evaluated. Geolocation is a key influence on how systemic disease is expressed at diagnosis. Global ESSDAI scores are higher in people from the southern countries of each continent, and the distribution of the degree of systemic activity (low, moderate, and high) also showed an organ-by-organ differentiated pattern between northern and southern cohorts. People from northern countries have a lower frequency of ocular involvement and a higher frequency of cryoglobulinaemic-related tests (cryoglobulins and hypocomplementaemia). The highest rates of abnormal diagnostic results are observed in European patients from northern countries, while in America and Asia the highest rates were reported in patients from southern countries. The autoantibody pattern also showed a geographical variation, with the highest frequencies being found in people from European southern countries while, in America and Asia, the highest frequencies were reported in people from northern countries (17).

People working in some jobs may have an enhanced risk of developing the disease. Some retrospective studies have suggested a potential influence of occu-

pational risk factors in the occurrence of SS (18, 19). The risk of SS was significantly associated with a 2 to 4-fold higher rate of cumulative occupational exposure to toluene, white spirit, aromatics, and any type of solvents. Organic solvents are so widely used in the modern world as to be ubiquitous and are employed in paints, pharmaceuticals, degreasants, adhesives, printing inks, pesticides, cosmetics, and household cleaners. Occupations with a high intensity of solvent exposure include dry cleaning, screen printing, rotogravure printing, industrial painting, manufacture of glass, reinforced plastic and tile fixing, among others.

MYTH. Smoking and alcohol intake may enhance the risk of Sjögren syndrome. Almost all studies investigating the potential effect of smoking on the disease have reported an inverse correlation. First, case-control studies including prevalent cases have shown a significantly lower frequency of current smokers amongst SS patients. Second, when pre-diagnostic data are used, current smoking was also associated with a lower risk. And third, smokers have a lower prevalence of focal sialadenitis in comparison with non-smokers. This Sjögren's-related smoking pattern seems to suggest that individuals who develop SS smoke equally as much as the general population during early life but are then more prone to stop (20), since the oral and ocular damage caused by tobacco smoke makes people with SS more likely to discontinue smoking (19). With respect to alcohol intake, patients with SS were less likely to consume alcohol after adjusting for age, sex and education in comparison with the general population (21), suggesting a similar pattern to that observed for smoking (oral discomfort from the intake of alcohol may underlie the lower prevalence in prevalent cases). Alcohol consumption should also be considered in patients already diagnosed with SS who develop parotid swelling during the follow-up, since a recent study (22) has reported that alcohol intake may be associated with an increased risk of parotid swelling. Regardless of the potential "protective" effects of tobacco and alcohol in SS, their negative effects in global health are undeniable and both should be avoided in patients with a suspected disease and in those already diagnosed with SS.

Table II. Tips for an early diagnostic suspicion.

- A history of parotid swelling, subacute cutaneous lupus, hypokalemic paralysis or congenital heart block may be the first sign of SS.
- In children and young people, unexplained well-tolerated fever may be the first sign of the disease.
- SS should be investigated in idiopathic neurological diseases (ataxia, optic neuritis, myelitis, and aseptic meningitis).
- In patients with malignancies presenting with sicca syndrome, check the use of cancer immunotherapies.
- Search for SS in people diagnosed with B-cell malignancies, especially if they are men and have a MALT lymphoma of the salivary glands.
- Test for anti-Ro antibodies in patients presenting with idiopathic scleritis.
- The triad of cytopenia, raised hrocyte sedimentation rate and hypergammaglobulinaemia is a highly-specific biological footprint suggesting SS.
- A positive RF test is more helpful than positive ANA for suspecting an underlying SS.
- Ro autoantibodies may be detected up to 20 years before the diagnosis *in the absence of sicca symptoms*.
- Test for anti-Ro52 antibodies even in the absence of positive ANA or anti-Ro60.
- Test for anti-Ro antibodies in patients with idiopathic immune thrombocytopenia or autoimmune haemolytic anaemia.

MISTAKE. Collecting a family history of autoimmune diseases is useless when the disease is suspected. SS is a non-hereditary polygenic disease and therefore, it is infrequent to see cumulated cases in the same family in daily practice. However, the risk of SS and other autoimmune diseases is increased in relatives of patients with SS (23). The relative risk of developing the disease is increased 19-, 12- and 11-fold in siblings, parents, and offspring of patients with SS, respectively, with an estimated familial transmission (heritability plus shared environmental contribution) of 54%. In addition, first-degree relatives of patients with SS have a 2-6-fold higher relative risk of developing both systemic (systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), vasculitis, and myositis) and organ-specific (type 1 diabetes mellitus, multiple sclerosis) autoimmune diseases.

Tips for an early diagnostic suspicion (Table II)

MISTAKE. Sjögren's syndrome should be considered the major aetiology of sicca symptoms. The list of aetiologies of mucosal dryness is long, including diabetes mellitus, chronic viral infections, dehydration, irradiation of the salivary glands, psychogenic hyposalivation and, especially, the chronic medication use (mainly antihypertensive, antihistamine, and antidepressant agents), especially in older patients. In people evaluated for dry mouth and/or dry eyes, SS is diagnosed in only 5–15% of cases (24, 25), although dryness of the mouth and eyes are reported by more than 90% of SS patients and must be considered the principal features leading to its suspicion, especially when they present in tandem (15), as these symptoms have a positive predictive value of 54–77% (12, 13).

MISTAKE. The disease can be ruled out in the absence of sicca symptoms. SS patients can develop many systemic manifestations that may be the first clinical sign of the disease before the onset of the characteristic features of dryness (24, 26). The list is long and includes general symptoms (some patients, especially children and young people, may present with continuing, well-tolerated fever), skin features (purpura, annular erythema), interstitial lung disease, renal tubular acidosis (hypokalemia, nephrocalcinosis) and neurological involvement (neu-

ropathies, cranial nerve involvement, myelopathy, optic neuritis and aseptic meningitis) (24). In all these patients, detection of Ro/La autoantibodies is a clue to reaching an early diagnosis of SS. Theander *et al*. (27) demonstrated that the frequency of positive autoantibodies was 2-fold higher in patients with early-onset disease compared with those with a late onset. Even in the case of negative results, salivary gland biopsy may show focal sialadenitis, confirming the diagnosis of SS (28).

PEARL. Put SS at the top of the diagnostic list in a patient with a history of parotid swelling. Although there are causes of parotid enlargement other than SS, episodic swelling of the parotid glands in a patient reporting a history of sicca symptoms is a highly specific feature for a diagnosis of SS. Parotid enlargement is reported in 10–20% of patients: it may commence unilaterally, but often becomes bilateral (29).

PEARL. Congenital heart block may be the first sign of an underlying maternal SS. In primary SS, autoimmune congenital heart block could be one of the first "indirect" signs of the disease in women of childbearing-age, in whom the diagnosis is often confirmed several years later (30). Cardiac block in the baby is related to the placental transference of maternal antibodies against Ro and La autoantigens (30, 31). Analysis of maternal autoimmune diseases detailed in nearly 900 mothers showed that more than half were asymptomatic carriers of Ro/La antibodies; in the remaining cases, two thirds had a well-defined systemic autoimmune disease (overwhelmingly SS, SLE or both) (32). A recent large cohort has shown that SS is more frequently diagnosed in comparison with SLE among mothers of children with autoimmune congenital heart block (33).

PEARL. Simple laboratory studies are very helpful in reinforcing the clinical suspicion of the disease. Standard biochemical studies and the haemogram are useful tools in the diagnostic workup of suspected SS. Cytopenia (normocytic anaemia, leukopenia, and/or thrombocytopenia) are reported in one in three patients (mainly neutropenia and lymphopenia). A raised erythrocyte sedimentation rate (often with normal c-reactive protein (CRP) values) and a high percentage of circulating gammaglobulins (hypergammaglobulinaemia) are additional laboratory abnormalities that increase the suspicion of SS. Therefore, the triad of cytopenia, raised erythrocyte sedimentation rate and hypergammaglobulinaemia is a highly-specific biological footprint suggesting SS (29, 34).

MISTAKE. Antinuclear antibodies are central in differentiating the disease from non-autoimmune causes of sicca syndrome. Autoantibodies are the key serological markers of autoimmune diseases and, in patients with SS, may be detected up to 20 years before the disease diagnosis (24, 27). Among them, antinuclear antibodies (ANA) are used to discard autoimmune diseases, especially in primary care and non-specialised settings. Although ANA are the most frequently detected autoantibodies in primary SS (>80%), their specificity is very low due to the high frequency in patients with non-specific symptomatology and even in healthy people (35).

MISTAKE. A negative test for ANA rules out a diagnosis of SS. Anti-Ro antibodies, and not ANA, should be considered the key immunological markers of SS. Nearly 20% of patients fulfilling the current criteria are ANA negative (36). Another immunological misconception is to consider that a negative test for ANA rules out the presence of underlying Ro autoantibodies, since in nearly 10-20% of patients carrying anti-Ro antibodies, ANA may be negative (37). Around 20% of patients with negative tests for anti-Ro/SS-A antibodies may have anti-Ro52 antibodies (37).

PEARL. A positive result in the rheumatoid factor test is more helpful than positive ANA for suspecting an underlying SS. Rheumatoid factor (RF) is present in half the patients with primary SS and has a similar sensitivity to ANA but a greater specificity for SS classification. Several studies have reported that positive RF has been linked with an earlier diagnosis, may predict the development of SS, and is related to systemic and severe disease, including lymphoma (6). Despite this close and evident association with a more active and severe disease phenotype, RF has been excluded in the last two sets of classification criteria. Thus, RF detection in primary SS is clinically useful, especially for the diagnosis of some subsets of patients with SS, such as those with an early diagnosis, systemic/severe manifestations or circulating cryoglobulins.

PEARL. Ro autoantibodies may be detected for up to 20 years before the diagnosis. Anti-Ro/SSA and anti-La/SSB antibodies are strongly associated with the risk of primary SS and are especially linked with an early onset of the disease and a severe disease course. In 2015, Theander et al reported that these autoantibodies can be detected for up to 18-20 years before the diagnosis of primary SS is confirmed, with prediagnostic anti-Ro 60/SSA and anti-Ro 52/SSA antibodies having the highest positive predictive values among all autoantibodies detected (25% and 100%, respectively).

PEARL. SS is the best diagnostic option for patients with sicca syndrome and isolated La autoantibodies. The La autoantigen plays a central role in the etiopathogenesis of SS, as confirmed by several studies published in the last 20 years (38–42). A recent interest in characterizing SS patients carrying isolated La autoantibodies has emerged after the exclusion of this subset of patients from the recently proposed European/American classification criteria (43, 44). In the largest reported cohort of patients with primary SS fulfilling the 2002 AE classification criteria, only 3% carried isolated anti-La/SS-B antibodies. These patients had a systemic SS phenotype that mixed some features characteristic of both immunonegative patients and patients carrying isolated anti-Ro/SS-A antibodies. In clinical trials, where homogenous populations are desirable, such patients could be probably excluded or analysed separately, but in daily

practice, the best clinical diagnosis for this subset of patients remains SS (45).

PEARL. Test for anti-Ro antibodies in patients with weakness/paralysis related to severe hypokalemia. In patients with SS, renal tubular acidosis (RTA) is diagnosed due to clinical features in two thirds of cases, and due to asymptomatic laboratory findings (renal failure, proteinuria) in the remaining third. In symptomatic patients, hypokalemic weakness/paralysis was the most frequent clinical presentation (including some patients with respiratory failure), followed by renal colic, osteomalacia (some presenting with pathological fractures) and with polyuria/polydipsia (diabetes insipidus) in <5% of cases (46, 47).

PEARL. Test for anti-Ro antibodies in patients presenting with cerebellar ataxia. Recent studies have reported patients presenting with acute or subacute cerebellar ataxia in whom an underlying SS has been identified. In these patients, typical cerebellar ataxia manifests with vermian dysfunction, namely gait ataxia and/or cerebellar speech. In a small series of patients with SS presenting with sensory ataxia, cerebellar signs were found in nearly 40%, most of whom showed cerebellar atrophy on neuroimaging studies (48). Therefore, the diagnostic approach to a patient with cerebellar ataxia of unknown aetiology should rule out an underlying SS, mainly by testing for anti-Ro antibodies and, if necessary, with a salivary gland biopsy (49). A recent study has identified a novel autoantibody against Purkinje cells in a patient with primary autoimmune cerebellar ataxia associated with SS (50).

PEARL. The disease should be investigated in patients with neuromyelitis optica spectrum disorder, especially in those who are AQP4-IgG-positive. Neuromyelitis optica spectrum disorder (NMOSD) is a demyelinating CNS disease consisting of relapsing episodes of optic neuritis and myelitis, in which the diagnosis is supported by the detection of serum autoantibodies against the aquaporin 4 (AQP4) water channel (51). There is a significant overlap between AQP4-positive NMOSD and SS. A quarter of AQP4-IgG-positive patients are also positive for anti-Ro antibodies and 7% for anti-La antibodies, while more than 80% of SS patients presenting with optic neuritis or myelitis are AQP4-IgG positive. In NMOSD patients carrying anti-Ro antibodies, a higher frequency of relapses, disease activity and severe disability has been reported in AQP4-IgG-positive subjects (52, 53).

PEARL. Test for anti-Ro antibodies in patients presenting with idiopathic scleritis. A large study in patients with incident scleritis identified SS as one of the systemic autoimmune diseases most strongly associated with scleritis, with a relative risk of 7, and with only eosinophilic granulomatosis with polyangiitis (EGPA) and Behçet's disease showing a greater degree of association (54). In addition, patients with SS and concomitant scleritis have a greater risk of vision-threatening corneal complications (55).

PEARL. In patients with active cancer presenting with sicca syndrome, check the use of immunotherapies. Patients treated with checkpoint inhibitors may develop a SS-like disease with a very different profile than that reported in idiopathic primary SS, that is characterised by being more frequently reported in men, diagnosed at a higher mean age, and with a predominant immunonegative serological profile (56-58). It has been suggested that these patients could present a different immune-mediated phenotype driven by interferon gamma (IFNγ) that could be classified under the umbrella of interferonopathies, and therefore requiring a different management than idiopathic SS patients (59). Patients treated with kinase inhibitors, another type of cancer immunotherapy may also develop dry eyes/keratitis in around 5% of cases (mainly related to the use of vemurafenib and gefitinib).

Table III. Pearls for an accurate characterisation of systemic SS.

- Age at diagnosis determines which internal organs may be affected by SS.
- SS-related arthritis is characterised by the absence of structural damage.
- Persistent cough may suggest dryness of the respiratory tract, interstitial lung disease or bronchiectasis.
- Non-specific interstitial pneumonia is the most frequent ILD pattern in SS.
- Abdominal X-ray may disclose nephrocalcinosis when renal involvement is suspected.
- In patients with suspected glomerulonephritis, testing for cryoglobulins is mandatory.
- Membranoproliferative glomerulonephritis is the most frequent histopathological subtype of SS-related glomerulopathies.
- Gastrointestinal symptoms are overwhelmingly unrelated to SS.
- Search for IBM in patients with refractory myositis.
- MRI plays a central role in characterising neuro-Sjögren's for inflammatory lesions located in the brain, cerebellum, medulla, or dorsal root ganglia.
- Enlargement or atrophy of the dorsal root ganglion are key imaging signs suggesting ataxic neuronopathy.

Improving the systemic characterisation of Sjögren's syndrome (Table III)

MISTAKE. SS is a mild disease, not a life-threatening disease. A large study of nearly 1600 patients identified severe, potentially life-threatening involvement in 13% of cases (defined as having high activity in at least one ESSDAI domain). One third of these cases corresponded to lymphoma, a quarter to neurological involvement, and the remaining cases consisted of renal and cutaneous involvement, with severe haematological and muscular involvement representing less than 5% of cases. These patients were more frequently male and had a higher frequency of positive cryoglobulin-related markers (rheumatoid factor, hypocomplementaemia and cryoglobulinae-

mia). This subset of patients required intensive therapeutic management, but despite this 1 in 5 patients died.

PEARL. Expect more severe systemic disease in patients with double positivity for Ro and La autoantibodies. Several studies have reported a higher frequency of internal organ involvement in patients carrying both anti-Ro and anti-La antibodies in comparison with those carrying anti-Ro alone (60-62). In the Big Data cohort, analysis of the three Ro/La immunophenotypes in more than 12000 patients (combined Ro and La, isolated anti-La and isolated anti-Ro), showed that a moderate/high ESSDAI activity score was more frequently reported in patients with double positivity (63). In addition, patients with double positivity for anti-Ro60 and anti-Ro52 antibodies have a higher frequency of positive salivary gland biopsy, parotid enlargement, and positive RF, and higher serum IgG and IgA levels in comparison with patients with anti-Ro60 alone (64).

PEARL. SS-related arthritis may mimic rheumatoid arthritis but differs due to the absence of structural damage. Arthritis is the inflammation of one or more joints, clinically identified by joint heat, redness, and swelling. The ESSDAI score classifies the severity of arthritis according to the number of joints involved (moderate <5 joints, high >5) (4). Arthritis is reported predominantly as symmetrical polyarthritis overwhelmingly affecting ≤5 joints and predominantly involving the proximal interphalangeal and metacarpophalangeal joints and wrists. Radiologically, SS-related arthritis is overwhelmingly non-erosive (65).

MYTH. Subacute cutaneous lupus is an undeniable sign of SLE, not of primary SS. Subacute cutaneous lupus (SCLE), also known as annular erythema (AE) is an erythematous, photosensitive rash characterised by annular polycyclic lesions with a wide elevated border and central pallor (7). It has been reported in 10% of primary SS patients, and nearly half of the cases included in Asian studies (overwhelmingly Japanese), with positive anti-Ro/La antibodies in more than 90% of patients. AE should be suspected in Ro/La+ patients presenting with photosensitive annular polycyclic lesions: in these patients, both SS and SLE should be investigated (66). In a series from the Mayo Clinic, only 30% of SCLE patients had an underlying systemic autoimmune disease and half had a diagnosis of SS and one third of SLE (67).

MISTAKE. Persistent cough is overwhelmingly linked to sicca involvement. A significant percentage of patients with primary SS may present with persistent cough. The most frequent aetiology in patients with non-productive cough is mucosal dryness of the upper respiratory tract, and the ESSDAI (4) accepts active pulmonary involvement in patients presenting with persistent respiratory symptoms but normal imaging studies. However, do not forget that chronic non-productive cough may also be the first sign of an underlying interstitial lung disease (ILD), especially in patients also presenting with dyspnea. In addition, patients with SS may also present with a persistent productive cough if they have bronchiectasis, which is found in nearly 10% of primary SS patients (68).

PEARL. Interstitial lung disease displays a broad pathological scenario of pulmonary damage in people with SS. A review of biopsy-proven SS-related interstitial lung disease (ILD) included a wide variety of histopathological diagnoses: half the cases were reported as nonspecific interstitial pneumonia (NSIP), followed less frequently by bronchiolitis, usual interstitial pneumonia, lymphocytic interstitial pneumonia and organising pneumonia (46). Enomoto *et al*. (69) reported a ratio of fibrotic:cellular NSIP of 19:3. SS patients suffering from ILD have an increased risk of mortality in comparison with those without (70).

PEARL. Abdominal X-ray may be a useful diagnostic tool when renal involvement is suspected. Renal tubular acidosis (RTA) has been reported in 5–10% of SS patients (15, 46), overwhelmingly classified as distal RTA. Nephrocalcinosis presenting with renal colic is a common clinical expression of distal renal tubular dysfunction in these patients, and nephrocalcinosis is frequently revealed in abdominal X-rays. Type I RTA is diagnosed with the finding of a persistent urine pH of >5.3, even when there is metabolic acidosis induced by NH4+Cl loading (46). The ESSDAI score classifies disease activity in patients with RTA as low or moderate according to the absence or presence of renal failure (glomerular filtration rate (GFR) ≥ or <60ml/min, respectively) (71). Nearly 20% of SS patients with symptomatic RTA present with radiological nephrocalcinosis (46).

PEARL. In patients with suspected glomerulonephritis, testing for cryoglobulins is mandatory. Glomerulonephritis (GN) is an acute or chronic inflammation of the glomeruli, demonstrated by renal biopsy, which often comes to light when routine analyses are abnormal (proteinuria, renal failure). The ESSDAI score classifies disease activity in patients with GN as high with a 24h-proteinuria >1.5 g/d, haematuria, renal failure and proliferative glomerulonephritis/cryoglobulinaemia (71). Glomerulonephritis is a rare systemic SS involvement (<5%) related to cryoglobulinaemia in more than half the cases (46).

MISTAKE. A kidney biopsy is not necessary to confirm renal involvement associated with SS. A review of renal biopsies carried out in 149 SS patients with RTA showed that the diagnosis was confirmed in 94% of cases, and that very few patients present a biopsy-proven tubulointerstitial nephritis without evidence of tubular acidosis (46). These findings suggest that renal biopsy may be avoided when the diagnosis of RTA is solid according to clinical and laboratory findings. However, there are two clinical scenarios in which kidney biopsy is recommended. The first is the suspicion of other concomitant diseases. The second is the suspicion of GN, due to the wide spectrum of histopathological scenarios seen in primary SS. In patients

with biopsy-proven glomerulonephritis, membranoproliferative GN was the most frequent histopathological subtype (closely related to underlying cryoglobulinemia), and other subtypes have been reported less frequently.

PEARL. Glomerulonephritis is linked with poor outcomes. SS-related glomerulonephritis, as compared with tubulointerstitial nephritis, is associated with poor outcomes, including a high risk of lymphoma and poor survival (72). One study showed that 3-year survival was significantly lower in patients with glomerulonephritis compared with those with tubulointerstitial nephritis (66% *vs*. 100%), with no differences in renal survival (73). Since nearly half the cases of GN are related to cryoglobulinaemia, and cryoglobulins are a strong predictor of lymphoma and death in patients with primary SS (74-78), a poorer prognosis of SS patients presenting with GN may be expected.

PEARL. Search for inclusion body myositis in patients presenting with refractory myositis. Myositis is the rarest systemic involvement included in the ESSDAI and occurs in less than 1% of SS patients. In SS patients with confirmed myositis, consider the diagnosis of inclusion body myositis (IBM), especially in patients receiving several lines of treatment with no clinical improvement (79). In fact, patients with IBM were 6-times more likely to have concomitant SS. IBM is associated with increased mortality, with a 10-year survival of 36%, and with pulmonary complications being the leading cause of death (80).

PEARL. Electromyographic studies are essential to characterise and guide the treatment of peripheral neuropathy. Peripheral neuropathy is diagnosed in around 10% of patients with SS and has a broad clinical spectrum including axonal neuropathy, ataxic sensory neuronopathy, multineuritis, and demyelinating polyradiculoneuropathies (81, 82). The classification of neuropathy according to the clinical presentation and electrodiagnostic tests is useful not only to characterise the functional outcome, but also to determine the therapeutic response and survival, which is significantly reduced in patients with multineuritis (a neuropathy closely related to underlying vasculitis). However, SS patients may also present small-fibre sensory neuropathy (83, 84) that may have normal nerve conduction studies, because the size of the nerve fibers involved is below the resolution of conventional electrodiagnostic studies, and the diagnosis is confirmed by a skin biopsy showing a decrease in the density of epidermal nerve fibres (85).

PEARL. Neuroimaging may be a useful diagnostic tool for diagnosing ataxic neuronopathy. Sensory ataxia is due to the involvement of the proprioceptive neurological pathways, and ataxic neuropathies are a broad, heterogeneous spectrum of disorders that may affect the dorsal root nerves/ganglia, nerve trunks and distal nerve endings, and are one of the most typical neuropathic involvements associated with SS (86). More than 70% of SS patients with ataxic sensory neuropathies have a long-term, insidious evolution of their symptoms (82). The detection of atrophy of dorsal root ganglia (DRG) with 3-T magnetic resonance neurography has been reported in some studies (87), while others have identified disproportionately enlarged DRGs using 3D isotropic STIR SPACE sequences (88). These findings (enlargement vs atrophy of DRGs) might guide the potential therapeutic response when these patients are treated with immunosuppressive or biological therapies.

MYTH. Central nervous system involvement is a frequent extraglandular manifestation of primary SS. CNS involvement has been considered a frequent extraglandular manifestation due to the large number of studies on this topic published in the late 1980s (89). However, large cohorts of patients (>1000) reported more recently have clearly shown that the frequency of CNS involvement is <1% (5, 90). Some of these patients develop a neurological picture extremely difficult to distinguish from primary CNS diseases, especially autoimmune demyelinating CNS diseases (91). The most probable clinical scenario in SS patients with CNS involvement is coexistence with these demyelinating CNS diseases. A multidisciplinary collaboration with neurologists is essential in these patients.

PEARL. Magnetic resonance imaging plays a central role in characterising CNS demyelinating lesions in people with SS. The diagnosis of multiple sclerosis (MS) is mainly made on a combination of neurological signs and symptoms and radiographic findings demonstrated by magnetic resonance imaging (MRI) T2 lesions, which are central components of the 2017 McDonald Criteria (92). However, it may be difficult to differentiate these lesions from others related to systemic autoimmune diseases. Although neuroimaging studies may disclose white matter lesions in half the patients with primary SS investigated for suspected neurological involvement, these lesions are classified as vascular pathological changes in 80% of patients, with the concomitant presence of cardiovascular risk factors being the key predictive factors (93). For the diagnosis of inflammatory lesions, the detection of perivenular lesions in the brain (the "central vein sign") may improve the specificity of a MS diagnosis. When a threshold of 50% perivenular lesions was applied, the central vein sign discriminated MS from vasculopathies related to systemic diseases with a diagnostic accuracy of 100% (94).

MISTAKE. Gastrointestinal involvement is a systemic manifestation of the disease. Although the frequency of gastrointestinal symptoms reported by SS patients is as high as 95% (95), they are overwhelmingly related to diseases or conditions unrelated to SS. The list is long and includes oesophageal motility dysfunction, chronic atrophic gastritis, lymphocytic colitis, and celiac disease (96), although the most frequently identified disease is irritable bowel syndrome (97).

MYTH. Pancreatitis is a common extraglandular feature of SS. Studies in the 1970s and 1980s found a high fre-

quency of altered pancreatic function in primary SS (>40%), although no data were presented on the clinical significance of these altered tests. These studies led to the consideration of pancreatic involvement as one of the typical extraglandular features of primary SS. However, the frequency of clinical pancreatitis is very low in large series of patients with primary SS (<2%) (5, 98). Some of the early reports of "pancreatitis" occurring in association with "SS" may actually represent cases of IgG4-related systemic disease.

Table IV. Tips for an optimal follow-up of SS.

- Ask about seasonal conditions, air pollution or excess air conditioning in people who have worsening of dry eye complaints.
- People sleeping fewer hours are more likely to have worse dry eye complaints
- Search for Meibomian gland dysfunction in SS with refractory dry eye disease.
- The use of contact lens or dental implants are not contraindicated in SS patients.
- Alcohol intake may favour parotid enlargement in patients already diagnosed with SS
- The Mediterranean diet should be strongly recommended in SS patients.
- Seronegative patients display a dissociated phenotype (poor quality of life and low systemic activity): search for concomitant functional somatic syndromes
- Rule out obstructive sleep apnea in patients with fatigue accompanied by daytime somnolence
- Close cardiovascular monitoring is necessary in SS patients.
- More than 80% of SS patients presenting with white matter lesions have a high-risk cardiovascular profile
- The risk of venous thromboembolism may be increased in seropositive SS
- Expect more severe systemic disease in patients with double positivity autoantibodies (Ro+La, Ro60 + Ro52).
- The systemic features most closely related to poor survival are interstitial lung disease, glomerulonephritis and multineuritis.
- The main prognostic factors enhancing the risk of lymphoma are high systemic activity, cytopenia and cryoglobulin-related immunological markers
- Patients may also develop non-B-cell haematological malignancies, especially those presenting cytopenia and cryoglobulins at the diagnosis of SS
- SS patients have an enhanced risk for thyroid malignancies

Tips for an optimal follow-up of Sjögren's syndrome (Table IV)

PEARL. Seasonal environmental conditions may drive the severity of dry eye complaints. SS patients frequently report significant changes in the intensity of dry eye related to seasonal environmental conditions. An interview carried out in 347 patients found that nearly half reported a high impact of seasonal conditions on dry eye, especially related to the wind, but also to sunshine, heat, and cold weather. Dry eye worsened mainly in summer and winter in European patients, and the seasonal peak of complaints appeared to be mostly related to temperature and humidity (99). In contrast, another study showed that seasonality does not affect patient-reported outcomes on fatigue, pain and global dryness (100).

PEARL. Worse air quality is linked to worse dry eye complaints. Several environmental factors related to the quality of air (pollution, use of central heating or air conditioning) have a significant impact on the integrity of the ocular surface. Some studies have reported that abnormalities of the ocular surface and eye irritation are related to air pollution (101-103).

PEARL. Ask about hours of sleep per day and sleep quality. One study reported that people sleeping fewer hours are more likely to suffer from dry eye disease (DED), and that each additional hour of sleep reduces the probability of DED by 0.8 times (103), while other studies found no association between DED and hours of sleep (104, 105). Murube (106) hypothesised that rapid eye movement during sleep serves to increase tear secretion and humidify and lubricate the ocular surface.

MYTH. Dental implants perform worse in people with SS. Patients with SS show a greater risk of developing cavities and early tooth loss because of an imbalance in salivary quality and flow. Hyposalivation, xerostomia and changes in saliva quality may compromise the teeth, but also bone integration or maintenance of peri-implant health. A systematic review concluded that dental implant therapy in SS patients seems to present high implant survival rates, low marginal bone loss and few biological complications (accepting as a limitation the small amount of studies and their observational design), and that all studies observed an increase in the quality of life of SS patients who were rehabilitated through dental implants (107). In a recent survey study, SS patients with implants reported that peri-implant health was reasonably good with minor marginal bone loss and a peri-implantitis prevalence of 14%, comparable with healthy controls, with overall high patient satisfaction and a rate of implant survival of 97% after a mean follow-up of 4 years (108).

MYTH. The use of contact lens should be contraindicated. Although earlier studies reported that DED is more prevalent in contact lens wearers, more recent studies are questioning this association (103), perhaps due to the advances in materials and the increased use of daily disposables. In fact, contact lenses are recommended as a treatment for dry eye with the goal of promoting corneal healing, protecting the ocular surface from the lids and environment, reducing desiccation, and lessening ocular discomfort (109).

PEARL. Search for Meibomian gland dysfunction in patients with refractory dry eye symptoms. Patients with refractory/severe ocular dryness require a more intensive ophthalmological follow-up, searching for coexisting ocular problems that could explain the lack of response to the standard therapeutic

approach for keratoconjunctivitis sicca. Infections should always be investigated, together with Meibomian gland (MG) dysfunction. SS patients have a significant frequency of Meibomian gland orifice metaplasia, an increased number of occluded Meibomian gland orifices, and a reduced quality of Meibomian gland secretions (110), while there is a strong correlation between SS duration and MG atrophy, even after adjusting by age (111).

PEARL. Seronegative patients display a dissociated phenotype (poor quality of life and low systemic activity). In the recent 2002/2016 sets of criteria, seronegative patients must be biopsy-proven with negative Ro/La (2002 criteria) (112) or negative Ro (2016 criteria) (43) antibodies. The clinical phenotype is characterised by a higher frequency of fatigue and pain, a milder immunological profile, a lower frequency of systemic involvement, a lower level of B-cell expansion and a lower risk of lymphoma, with no significant differences in glandular involvement (36, 61, 63, 113-118).

PEARL. Search for functional somatic syndromes in seronegative patients. Seronegative patients present with a phenotype that fits into a spectrum of disease which tends more towards functional somatic syndromes such as chronic fatigue syndrome (CFS) and fibromyalgia (FM). The frequency of the overlap of FM in SS patients ranges from 15 to 35% (61, 119-123) and their coexistence has been statistically associated with depression (122, 124), fatigue (119, 125, 126), widespread pain (61, 126) and a 10-fold greater risk of work disability (127). In patients with ocular dryness, chronic pain syndromes are common and are associated with increased severity of ocular dryness even though objective ocular surface signs are no worse (128).

PEARL. Fatigue accompanied by daytime somnolence requires investigation of sleep disturbances. Fatigue is a key symptom of SS. When fatigue is with excessive daytime somnolence, patients should be screened for comorbid sleep disorders. Some studies have reported greater daytime somnolence related to subjective sleep disturbances, more night awakenings and pre-existing obstructive sleep apnea in SS patients (129, 130). Polysomnography studies are recommended to search for abnormal results in snoring and witnessed apnea, rapid eye movement (REM) %, snoring index, and maximum apnea and maximum hypopnea duration (131).

MYTH. Differences between primary and secondary SS have major clinical relevance. In the last 50 years, the scientific literature has used the term "secondary" for patients with SS also diagnosed with another systemic autoimmune disease and "primary" for those without. However, this terminology is overwhelmingly used in patients with concomitant RA, SSc or SLE, and not in those with other systemic (sarcoidosis, vasculitis, antiphospholipid syndrome) or organ-specific (autoimmune thyroiditis, primary biliary cholangitis, autoimmune hepatitis) autoimmune diseases. The distinction between primary and associated SS only reflects a clinical situation of coexistence or overlap, a phenomenon frequently found in patients with autoimmune diseases. For the practical management of patients, it makes no sense to separate between "primary" and "secondary" patients since the key target should be the same, the management of SS in both groups (132).

PEARL. The Mediterranean diet should be strongly recommended. The influence of a well-balanced diet on health is undeniable and should be a key message for SS patients. Conditions related to unbalanced diets such as poor diet quality, vitamin A or D deficiency, eating disorders or a vegan diet have clearly been associated with DED, including a specifically worse role for ultra-processed food (103). Specifically, in SS, adherence to the Mediterranean diet was associated with a lower likelihood of having the disease after adjusting for potential confounders (133), including benefits in various clinical domains, especially linked to fish consumption (134).

PEARL. Close cardiovascular monitoring is necessary. Cardiovascular risk factors should be evaluated in patients with primary SS, with the aim of controlling both traditional and SS-related modifiable risk factors (135). Some case-control studies have identified an increased risk of cardiovascular events (cerebrovascular events and myocardial infarction) (136, 137), especially in seropositive patients who had a higher risk of cerebral infarction, especially ≥10 years after the diagnosis of SS (136). EULAR recommendations include the use of generic cardiovascular prediction tools due to a lack of validated rheumatic disease-specific tools (138), reinforcing the need for developing specific tools for monitoring cardiovascular risk factors in people with SS (139).

PEARL. The risk of venous thromboembolism may be increased in seropositive patients. Several studies have identified an increased risk of venous thromboembolism in SS patients, with a global hazard ratio (HR) of 3.1 in seropositive patients especially during the first 5 years after the diagnosis of SS (HR of nearly 5) (136). Another study reported similar figures for an increased risk of pulmonary embolism (PE), deep vein thrombosis (DVT), and venous thromboembolism (VTE) (140). A third study estimated that the risks of DVT and PE in patients with SS were 1.83-fold and 3.29-fold greater, respectively (141). The mechanisms linked to the increased risk of venous thrombosis are unknown, since most studies were adjusted by the main confounders unrelated to SS (age, sex, hospitalisation…). A potential coexistence of antiphospholipid syndrome (APS) might be evaluated in these patients, since antiphospholipid antibodies are detected in 16% of SS patients, although only 25% of positive cases had APS (in all cases linked to La positivity) (142, 143). Another study identified LA as an important marker for APS in SS, particularly associated with stroke in young patients (144).

MISTAKE. Monoclonal gammopathy is overwhelmingly related to an underlying haematological malignancy. Circulating monoclonal immunoglobulins

or/and free monoclonal light chains are detected in 7-16% of SS patients (145, 146). In patients with primary SS, detection of serum monoclonal immunoglobulins may indicate cryoglobulinaemia, especially when serum immunoelectrophoresis detects an IgM kappa monoclonal spike, strongly suggesting type II mixed cryoglobulinaemia (147). Less than 10% of patients with circulating monoclonal immunoglobulins presented haematologic neoplasia, and a change in the monoclonal component was detected in previous immunoelectrophoresis determinations before the development of haematologic neoplasia in some of these patients (147). Although most patients did not have underlying neoplasia, monoclonal gammopathy is a key marker related to an increased risk of haematological neoplasia and these patients should be closely monitored (148).

MYTH. An abrupt decline in serum immunoglobulin levels heralds the appearance of lymphoma. In 1964, Talal and Bunim reported five cases of reticulum cell sarcoma (histiocytic lymphoma, a very rare and aggressive lymphoma), of whom two had hypergammaglobulinaemia, two hypogammaglobulinaemia, and one showed a sharp decrease in serum gammaglobulins coincidental with malignancy (149). This finding led the authors to consider that an abrupt decline in hypergammaglobulinaemia was a key prognostic marker for lymphoma in SS (150). Around 20% of patients with diffuse large B-cell lymphoma (DLBCL) had hypogammaglobulinaemia at diagnosis, and this finding is associated with an aggressive evolution and high mortality (151). In SS patients, current data supported by large, prospective studies suggest that lymphoma is associated more closely with ongoing immunological abnormalities than with their disappearance (148). The main prognostic factors identified at SS diagnosis enhancing the risk of lymphoma included higher systemic activity, cytopenia and cryoglobulin-related immunological markers (152).

PEARL. Every lymphoma subtype has specific prognostic factors related to SS. More than 90% of haematological malignancies in SS patients are mature B-cell malignancies, mainly extranodal marginal zone lymphoma (MZL) of mucosa-associated lymphoid tissue (MALT lymphoma) in half the cases, followed by DLBCL (16%), nodal MZL (7%), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL, 4%) and follicular lymphoma (FL, 4%) (153). The main types of haematological malignancies associated with SS have different prognostic factors. Therefore, a higher risk of B-cell MALT lymphomas is observed in patients presenting with cryoglobulins and low C3 levels at the diagnosis of SS, while for B-cell non-MALT lymphomas, the prognostic factors were anemia, monoclonal gammopathy, cryoglobulins and low C4 levels, and for non-B-cell haematological cancers, prognostic factors included anaemia, neutropenia, thrombocytopenia and cryoglobulins (40). These differentiated high-risk profiles, which are present at the diagnosis of SS, may help identify which patients may be at high risk of a specific subtype of haematological cancer at the diagnosis of SS (153, 154).

MYTH. A previous diagnosis of lymphoma rules out a diagnosis of primary SS. It is not uncommon in daily practice for a diagnosis of lymphoma to be the first clue to discovering underlying or undiagnosed SS. The hematologist may be the first physician to ask these patients about a previous history of sicca symptoms which, in most cases, date back a long time. However, pre-existing lymphoma has been traditionally considered an exclusion criterion for classification as primary SS, an erroneous concept that has recently been corrected by the 2016 American College of Rheumatology/European League Against Rheumatism classification criteria. A recent study (97) has examined whether there are differences in lymphoma characteristics depending on whether it was diagnosed before or after confirming SS. Patients first diagnosed with lymphoma were more frequently male, and had a higher frequency of enlarged lymph nodes, MALT lymphoma and salivary gland lymphoma. Another recent study has shown that 10% of primary SS patients have a hematological malignancy diagnosed ≥1 year before the SS diagnosis (153, 155).

MYTH. There is a significantly differentiated risk of lymphoma in patients with primary disease and those with associated SS. Several studies have suggested a potential differentiated risk of lymphoma in patients with primary and associated SS. Of all studies analysing the risk between primary and associated SS, only one reported an enhanced risk in patients with associated disease (156), with most studies reporting a similar or lower frequency of lymphoma in patients with associated SS, although there are no well-designed prospective studies confirming these findings (148).

PEARL. People with SS should be specifically screened for some solid malignancies. Patients with primary SS should be followed closely for an enhanced risk of some types of solid malignancies. Several studies have reported an enhanced risk of thyroid, lip/oral cavity and stomach cancers in primary SS patients (154, 157-159). The highest risk was for thyroid cancer, in which some risk factors (predominantly female involvement, low frequency of smoking, association with autoimmune thyroiditis) are clearly shared with primary SS (154). The finding of a higher risk for cancers of the oral cavity and stomach in women with primary SS is also interesting, since the oral cavity is overwhelmingly involved in primary SS and the stomach is the most-frequent extraglandular site of lymphoma development in primary SS (154).

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