A journey inside the elderly-onset primary Sjögren's syndrome, looking for useful tips for the geriatrician

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Abstract

Primary Sjögren's syndrome (pSS) is a systemic autoimmune rheumatic disease where xerophthalmia, xerostomia and presence of anti-SSA and anti-SSB antibodies are typical features. Its prevalence is higher in over-65 aged population than in other age groups. In the elderly, pSS diagnosis comes up against a whole series of critical points that may favor its misdiagnosis. The aim of our article is to discuss the most relevant of them: the frequent occurrence of a seronegative subset, the presence of systemic features not related to sicca syndrome, the sicca syndrome as iatrogenic manifestation and the possibility of a biopsy false negative of labial salivary glands.

Introduction

Sjögren's syndrome (SS) is an autoimmune disease belonging to the group of 'inflammatory acquired connective tissue diseases'.[1-3] It affects primarily the exocrine glands causing a decrease in their secretions (exocrinopathy), but also common are extraglandular manifestations that can virtually affect all organs and systems. Both glandular and extraglandular manifestations are the result of focal lymphocytic invasion in epithelial tissues causing structural disruption and functional alterations.[4,5] Characteristic autoantibodies named anti-SSA/Ro and anti-SSB/La are detectable in patients with SS, but a seronegative subset of disease is possible.[6-8] SS can be associated with other autoimmune diseases (for example, rheumatoid arthritis or scleroderma): secondary SS; or is not associated with primary SS (pSS).[9]

pSS can occur at all ages, especially during the fourth and fifth decades of life, and has an estimated female-to-male ratio of about 9:1. Elderly-onset primary SS (EOpSS) is conventionally SS appearing after age 65. Its prevalence is approximately 3% in geriatric population. According to published epidemiological studies, the prevalence of pSS in the elderly is 5-8 times higher than in other age groups.[10-12] In the elderly, SS diagnosis comes up against a whole series of critical points.[13,14] The aim of our review article is to discuss the most relevant of them, looking for useful tips in everyday clinical practice.

Clinical features: glandular manifestations

Xerophtalmia and xerostomia are typical features in patients with pSS. In particular, xerophtalmia expresses a decreased production of tear as consequence of lachrymal glands involvement. The patient usually complains of a burning sensation under the eyelids, associated with photosensitivity. Xerostomia (dry mouth) is consequence of decreased production of saliva due to salivary glands involvement. Patients report difficulty in swallowing dry food, a burning sensation in the mouth, and changes in sense of taste. Parotid or major salivary gland enlargement can occur. Decreased production of saliva may in turn favor dental caries or angular cheilitis.[15,16] Both in the criteria proposed by the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) collaborative initiative and by the American European Consensus Group (AECG), reported symptoms of ocular and/or buccal dryness are the first step.[17,18] Vaginal, dermal or tracheal dryness and pancreatic insufficiency may be additional findings related to exocrine glands involvement.

Clinical features: extraglandular manifestations

As already highlighted, pSS is a systemic disease and numerous are the extraglandular manifestations. In Table 1, we list the most common ones. They are commonly divided in two categories: i) periepithelial: are the result of lymphocytic invasion in epithelial tissues; ii) extraepithelial: skin vasculitis, peripheral neuropathy, and glomerulonephritis. The periepithelial extraglandular manifestations mostly affect lungs or liver; appear early and usually have a benign course. On the contrary, the extraepithelial manifestations are associated with increased morbidity and high risk for malignant lymphoproliferative disorders.[19-22]

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Extra glandular manifestations do not serve as classification or diagnostic criteria. Interestingly, some patients may have systemic manifestations unrelated to sicca syndrome, and this possibility is often reported in patients with EOpSS. In particular, in 2019 we conducted a systematic review to explore cognitive impairment (CI) in patients with pSS, with emphasis on diagnostic methods and their relationship with laboratory data and clinical manifestations. According to this review, CI (from the so-called 'Sjo-fog' to dementia) is not rare in patients with EopSS.[23]

Laboratory findings: the diagnostic role of anti-SSA and anti-SSB

A variety of different autoantibodies can be found in patients with pSS because of marked B-lymphocytic cell hyperreactivity.[24,25] A polyclonal hypergammaglobulinemia is also common. However, antibodies against the small ribonucleoproteins SSA/Ro and SSB/La are typical laboratory findings.

In particular, according to diagnostic criteria proposed in 2016 by ACR/EULAR collaborative initiative, diagnostic importance has been only accepted for SSA/Ro autoantibodies, whereas presence of anti-SSB/La (without positive serology for anti-SSA/Ro), antinuclear antibodies (ANA) and rheumatoid factor (RF) are no longer diagnostically significant.[17] It is worth highlighting that anti-SSA/Ro are not pathognomonic. Indeed, they may be also present in other disorders including autoimmune liver diseases, active hepatitis C infection, coeliac disease; or in different autoimmune rheumatic diseases such as cardiac neonatal lupus erythematosus and polymyositis. Therefore, their presence must always be linked to clinical or histopathological findings.

The relationship between SS and active hepatitis C virus (HCV) infection deserves to be discussed. Active hepatitis C is one of the exclusion criteria for diagnosis of pSS, because it may cause for itself xerostomia, xeropthalmia and/or presence of anti SSA ed anti SSB.[26,27] Therefore, active HCV - confirmed using PCR- must be carefully excluded. Furthermore, the availability of effective drugs for HCV eradication proposes the necessity to reconsider pSS diagnosis once the absence of serum HCV RNA has been obtained.

Histopathological features: labial salivary gland biopsy

A focal lymphocytic sialadenitis (FLS) with a focus score (FS) >1 is another, rele-

Table 1. Primary Sjögren's syndrome: organ and system-specific symptoms.

Eye DES, keratoconjunctivitis sicca, corneal erosions, filamentary keratitis, corneal ulcers, decreased vision, eye infections, cicatrizing conjunctivitis
Salivary glands Mouth dryness, burning of the tongue, increased dental caries, trouble swallowing, difficulty speaking, and enlarged parotid glands (periodontitis)
Joints Arthralgia and arthritis
Skin Annular erythema, palpable purpura (vasculitis, and cryoglobulinemia), xerosis
Hematologic Leucopenia, neutropenia, thrombocytopenia, anemia, cryoglobulinemia, monoclonal proteins, MGUS, and mucosa-associated lymphoid tissue lymphoma
Muscle Myalgia and myositis
Ears, nose, and throat Otitis media, nosebleeds, crusting damage, poor sense of smell, impeded swallowing, hearing loss
Bronchi and lung Recurrent bronchitis, bronchioles, bronchial hyper-reactivity, dry cough, interstitial lung disease (NSIP, LIP, UIP, and OP), pleurisy and pleural effusion
Peripheral nervous system Sensory and combined sensory-motor neuropathy, mononeuropathy with cranial nerve involvement, mononeuropathy, multiple mononeuropathy (mononeuritis multiplex) and demyelinating syndromes, including Smith-Magenis-like syndrome and autonomic neuropathies, restless leg syndrome
Central nervous system Focal lesions, changes with pyramidal symptoms, encephalopathy, changes typical for aseptic meningitis, transverse myelitis, optic neuropathy, and demyelinating symptoms (Smith-Magenis-like syndrome), cognitive impairment (from brain fog to frank dementia)
Kidney Interstitial nephritis with distal renal tubular acidosis, glomerulonephritis with coexisting cryoglobulinemia, and urolithiasis
Gastrointestinal tract Gastro-esophageal reflux, gastritis, primary biliary cirrhosis,* autoimmune hepatitis,* and cholelithiasis
Cardiovascular system Vasculitis (leukocytoclastic vasculitis), purpura, livedo reticularis, Raynaud's phenomenon, pericarditis, carditis, pleuritis, and pulmonary arterial hypertension
Other Autoimmune thyroiditis*

Modified from Manzo, 2020.14 DES, dry eye syndrome; LIP, lymphocytic interstitial pneumonia; MGUS, monoclonal gammopathy of undetermined significance; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; UIP, usual interstitial pneumonia. *Approximately 10% of patient with autoimmune thyroiditis share a primary Sjögren's syndrome.

Table 2. American European Consensus Group (AECGG) proposed criteria.

Subjective findings: i) ocular symptoms complained by the patients ii) oral symptoms complained by the patients
Objective findings: i) Schirmer's test <5 mm/5 min at least one eye or Rosa Bengal score according to the van Bijsterveld score (1 point) ii) objective evidence of salivary gland involvement* (1 point) iii) labial salivary gland biopsy with a FS >1 (3 points) iv) presence in the serum of antibodies to SSA/Ro and SSB/La antigens (3 points)
Diagnosis is possible when the total score is 4

Positive result of at least one the following tests: i) unstimulated salivary flow <1.5 mL in 15 min; ii) diffuse sialectasis (punctuate, cavitary, or destructive pattern) without evidence of obstruction in the major ducts, in parotid sialography; iii) delayed uptake or reduced concentrations and/or delayed excretion of trace in salivary scintigraphy.

vant diagnostic criterion. FS means no less than 50 mononuclear cells in a peri-ductal or peri-vascular localization/4 mm^2 of the glandular section. Given the heterogeneous distribution of the inflammatory infiltrate, analysis of four to seven labial salivary gland (LSG) is suggested to obtain an evaluable sized sample.[28,29] According to the protocol proposed by the Sjögren's International Clinical Collaborative Alliance (SICCA), foci must be adjacent to normal acini.[30]

In Table 2, we list the 2016 ACR/EULAR (or AECG) criteria. LSG biopsy is mandatory if anti-SSA and anti-SSB are lacking (seronegative pSS), whereas it is not if other proposed criteria are present. Indeed, pSS diagnosis is possible when total score is >4 points that is presence of anti-SSA (3 points) plus objective evidence of lachrymal (1 point) or salivary gland involvement (1 point). More recently, some researchers discussed the possibility that a cut-off of 5 points (instead of 4) can raise the specificity of the criteria from 89 to 98%. AECG criteria (as others in published literature) have been validated on adult population and should therefore be applied with caution in the elderly patient.[13,14,31]

Salivary glands ultrasonography: a perspective for the future?

Salivary gland ultrasound (SGU) is a promising and non-invasive technique for assessing the salivary glands. SGU proved sensitive as sialography and salivary gland scintigraphy, but more specific in the assessment of the salivary glands in patients with pSS.[32] Accordingly, some researchers have proposed inclusion of SGU in the classification criteria for pSS in addition to or instead of sialography and salivary gland scintigraphy.[33,34] To date, SGU is not included in the most recently published classification criteria.

Recently, pathological SGU findings proved associated with extraglandular involvement, a higher risk of lymphoma, and autoantibody positivity. These associations could help to select a more severe subset of patients with pSS.[35,36] On the other hand, age-related artifacts can be a confusing factor. Future studies will help to clarify the diagnostic, classification or prognostic rule of SGU in the management of patients with EOpSS.

EOpSS and the geriatrician: what is useful to know in clinical practice?

Sicca syndrome may follow several drugs (Table 3), many of which are commonly used (often in association) in the elderly patient[37-39] These drugs should be withdrawn and replaced whenever possible. In particular, anticholinergics are the most effective favoring drugs, and salivary and lachrymal secretions should always be assessed after a sufficient time of their withdrawal.

In addition, eye drops for glaucoma, or previous (last 5 years) corneal surgery must be considered when ocular symptoms are assessed. On the other hand, the possibility that sicca syndrome may be an iatrogenic manifestation cannot exclude that our patient suffers from EOpSS. In particular, when many suggestive extraglandular features are also present, detection of anti-SSA ed anti-SSB should always be considered.

Sicca syndrome is a common feature in elderly persons, and its prevalence may reach up to 30% in persons aged >65.[40,41] Indeed, older age may associate with a reduction of tear and/or saliva production. This reduction may affect the results of Schirmer's test and/or the assessment of unstimulated saliva flow rate.[42] For instance, in two population-based survey of health elderly people, the prevalence of an abnormal Schirmer's test ranged from 12 to 58%.[42,43] Consequently, ocular staining score (OSS) should be preferred as a confirmation test for subjective referred xeropthalmia in elderly patients. OSS uses fluorescein dye for the cornea and lissamine green dye for the conjunctiva. A summation of the fluorescein score for the cornea and the lissamine green scores for the nasal and temporal bulbar conjunctiva yields the total OSS for each eye . The original cutoff level of the OSS was three or more;[44] however, a cutoff level of five or more in either eye has been adopted for the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification (Figure 1).

Furthermore, diseases that may cause a parotid gland enlargement must be excluded: sarcoidosis, human immunodeficiency virus (HIV) infection, Mikulicz disease and iper-IgG4 syndromes, and parotid gland tumors, among these.[45]

Interestingly, age is not a risk factor for presence of anti-SSA/Ro and anti-SSB/La. On the contrary, patients diagnosed with pSS <45 years old tend to have higher anti-SSA and SSB serum levels than patients with EOpSS.[46] Recently, the Big Data

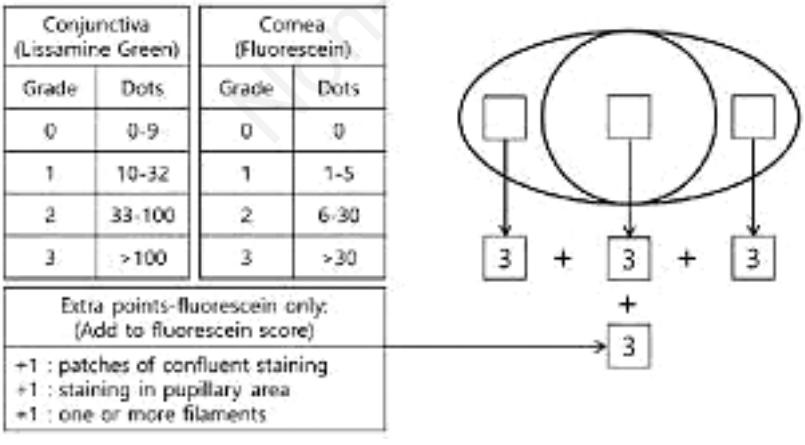

Figure 1. The ocular staining scores. A sequential examination is required. First, fluorescein is instilled in each eye and corneal staining is assessed in a period of less than four minutes using a slit lamp outfitted with a cobalt blue filter. Second, a drop of 1 percent lissamine green dye is instilled in each unanesthetized eye. The number of discrete 'dots' of staining in the cornea and in the nasal and temporal portions of the conjunctiva is counted for each eye and graded. A summation of the fluorescein score for the cornea and the lissamine green scores for the nasal and temporal bulbar conjunctiva yields the total ocular staining score for each eye.

Table 3. Categories of drugs that can induce xerostomia and/or xerophthalmia.

Antihistamines
Decongestants
Antidepressants
Antipsychotics
Some antihypertensive (atenolol, clonidine) and diuretics
Anticholinergics
Anticholinesterases and memantine
Protease inhibitors
Benzodiazepine
Opioids

International Sjögren cohort, a database with more than 10,000 patients, confirmed lower frequency of anti-SSA and anti-SSB in patients with EopSS.[47] Therefore, a seronegative subset of disease is possible in the elderly. When a geriatrician suspects EOpSS but anti-SSA and anti-SSB are not detectable, LSG biopsy is mandatory in order to exclude (or confirm) the first diagnostic suspicion of seronegative EOpSS. According to our literature search, however, LSG biopsy is infrequently performed in elderly patient; in particular, LSG biopsy was not performed in about 50% of published studies on EOpSS.[46,48-50]

In all ages of life, the evaluation of LSG biopsies is not straightforward, and inter-observer variability is often significant.[51,52] In addition, the presence of age-related findings such as acinar atrophy, fibrosis and increased area of fat tissue (possible in healthy older patients) may realize additional confounding scenarios.[53-55] Finally, cigarette smoking is negatively associated with FS >1 in patients with pSS and EOpSS.[56]

Using a grading score such as the Tarpley's grading system that takes destruction of acinar tissue and fibrosis into account can be useful.[57] To date, there is not a full consensus among experts on how to differentiate the Sjögren's typical findings from the aged-related ones.[58]

Conclusions

pSS prevalence is higher in over-65 aged population than in other age groups. The geriatrician should remember the frequent occurrence of a seronegative subset, the presence of systemic features not related to sicca syndrome and the possibility of biopsy false negative in the elderly patient. This may minimize the main diagnostic mistakes.

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