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Chapter

Perspective Chapter: Pulmonary System and Sjogren’s Syndrome

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Abstract

Sjogren’s syndrome (SS) is a connective tissue disease targeting the exocrine glands with subsequent sicca symptoms mainly in eyes and mouth. Respiratory symptoms may be the most frequent extraglandular manifestation following fatigue and pain. Mucosal dysfunction may affect the upper and lower airways, being the small airways more frequently involved. Parenchymal disease carries most of the morbidity and mortality. Nonspecific interstitial pneumonia (NSIP) is the most common radiographic feature, whereas the fibrotic NSIP type is the most reported finding in biopsies. Pulmonary lymphoma may arise from bronchial-associated lymphoid tissue lesions, and although rare, it is prevalent in SS. Chronic hypertrophic bronchial wall changes may ascribe to the various cystic lesions. Under their presence, possible lymphocytic interstitial pneumonia, amyloidosis, and lymphoma should be explored. Pulmonary arterial hypertension may present as frequently as in lupus, especially in Asian populations. Advanced knowledge in the pathogenesis has helped in understanding the various presentations within the respiratory system, contrasting with the scarce therapeutic options to treat both the airway and parenchymal disease. Anti-fibrotic parenchymal lung therapy offers promising outcomes. The pulmonary involvement in SS may associate with a decline in quality of life and reduced life expectancy. Subsequently, clinicians should know these facts for a timely intervention.

Keywords: Sjogren’s syndrome, interstitial lung disease, airway disease, lymphoma, cystic lung disease

1. Introduction

Sjogren’s syndrome (SS) is a chronic, progressive, and systemic autoimmune disease, with exocrine (mainly salivary and lacrimal) glands as the main target organs, leading to the development of sicca symptoms [1, 2]. They are the main clinical feature of the disease. Fatigue, diffuse pain, cognitive dysfunction, and arthralgias follow, constituting common findings [3, 4]. A subset of patients may express disease in extraglandular organs/systems, reflecting the systemic nature of the disease [5–7]. This pattern is more prevalent in the pediatric population [8]. Articular, peripheral neurological and pulmonary manifestations are described often [5], followed by other disease features: hematologic, gastrointestinal, renal, cutaneous, and endocrine [5, 9]. A subset of patients may progress to develop lymphoproliferative diseases, mainly stemming from mucosal-associated
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lymphoid tissue but also presenting as other types of non-Hodgkin (mainly B-cell) lymphomas [10]. Pulmonary manifestations are reported with various frequencies, depending on the criteria and methodology used to define them averaging an estimate of 9–24% in most of the studies [9, 11, 12]. Sjogren's syndrome when presenting alone is labeled as primary SS (pSS), while if it associates with another autoimmune (and mainly connective tissue) disease [13].

2. Epidemiology of Sjogren's syndrome

The disease affects more women than men in a proportion of 9:1 [14, 15] and peaks in the fourth to sixth decade of life [16]. The pooled incidence ratio for primary SS (pSS) is 6.92 per 100,000 person-years, and has a prevalence ranging from 0.05% to 0.23% [15, 17–19]. It is considered the second (if not first) most common connective tissue disorder, with an estimate of 1–3% of the population being affected [20].

3. Pathogenesis

3.1 Histopathology

The cellular [21] and humoral [22] components participate actively in the gland dysfunction and eventual destruction. Invasion of mononuclear cellular infiltrate, mainly composed of lymphocytes, tends to localize around the salivary ducts, vessels, and adjacent to the intact mucous acini [23]. This infiltrate tends to aggregate forming clusters, and if they count ≥50 cells, they are named as focal lymphocytic sialadenitis (FLS) (Figure 1). Quantifying the number of FLS within 4 mm² and dividing it by the area of normal glandular tissue will give an outcome. If this result is ≥1, it is reported as a focus score [24]. Focus scoring constitutes the main histopathological definition of SS [23, 25] and may range from 1 to 12. Higher values are obviated as they will be difficult to interpret due to the confluency of lymphocytic aggregates. Presence of a focus score helps the expert to define SS and to differentiate it from other inflammatory sialadenitides, including nonspecific chronic sialadenitis, sclerosing chronic sialadenitis, and others (Figure 1) [23].

3.2 Serology

Specific serology in SS associates with characteristic disease phenotypes and helps defining the disease [26]. The most characteristic and specific antibody is anti-SSA/Ro [27], and it is included in the 2016 classification criteria of SS [28]. Other serology, although less specific or not so prevalent, associates with SS as well, but is excluded from the currently accepted European-American classification criteria for Sjogren's syndrome. For instance, in a large multicenter cohort study of 10,500 patients, serology at the time of diagnosis of SS showed the following frequencies in decreasing order: antinuclear antibody (ANA) (79.3%), anti-SSA/Ro (73.2%), rheumatoid factor (48.6%), and anti-SSB/La antibodies (45.1%) [26]. Despite this distribution, anti-SSA/Ro and anti-SSB/La antibodies have been specifically identified to participate in SS's pathogenesis. They are also present in other connective tissue diseases (CTDs), lowering their specificity [29]. Cryoglobulins and low complements, mainly low C4, may reveal disease activity and define prognosis [27, 30, 31]. Their presence is additionally predictive of lymphoma [32]. Presence of circulating autoantibodies in patients with SS prior to the diagnosis
suggests that the immune activation has been previously triggered by an unknown antigen, and it may take months or years to progress onto a phenotypical expression [33]. A two-hit hypothesis, in this scenario, may possibly be the most likely explanation for this phenomenon. Sensitization and priming of the immune system by a prior insult (first hit) may define and determine the fate of the upcoming a programmed immune response following the exposure of a second stressor (second

Figure 1.
a (10×), b (20×): H&E section of this excisional biopsy of minor salivary gland tissue reveals periductular lymphoplasmacytic infiltrate. Multiple foci of periductular nodular lymphoplasmacytic infiltrates are identified. The number of mononuclear cell infiltrate per nodular focus is estimated to be greater than 50 lymphocytes per 4 mm² of tissue examined, and each lobule examined contains at least one focus of inflammation. Thus, the focus score for the above biopsy was estimated to be ≥1. Therefore, this picture of chronic sialadenitis with a focus score ≥1 in the right clinical context is consistent with Sjögren's syndrome.
hit). During this second insult the immune tolerance seems to be breached, with which the sequence of autoimmune events activate the disease [34, 35]. Presence of other circulating antibodies reported in SS may be the result of the polygenic nature of the disease and possibly due to different antigens activating the immune system, and hitting specific targets [26, 36–39]. Novel autoantibodies linked with sicca eyes reveal our still limited knowledge in SS’s pathogenesis [40, 41].

4. Symptoms and disease definition

Symptoms associated with dry mucosae in the eyes and mouth (sicca) are complains the clinicians should explore to consider the disease [42, 43]. To define the dry eyes and mouth, several techniques objectively measure their quantity [2, 44]. In addition, recommendations on to elaborate questions regarding sicca symptoms, fatigue, arthralgia, Raynaud’s, and other remarkable features common in SS, are detailed in the new consensus guidelines for the evaluation and management of pulmonary disease in Sjogren’s syndrome [45]. Sicca symptoms constitute the core finding in SS and have always been included in any classification criteria. The composite of sicca eyes, mouth, positive serology (anti-SSA/Ro antibodies) and abnormal findings in the histopathology (a focus score of ≥1), constitute the current four pivotal components to fulfill the SS classification criteria [28]. Along the last five or more decades, the classification criteria have been modified more than 15 times [46–49]. These changes reveal the difficulties met on agreements to define the disease, and mainly due to variability in the cohorts used, the protean disease manifestations, variability in the serology on different populations, and the need for more than one expert (specialist) to define each one of the criteria components. In addition, the continuous changes in the classification criteria mirror the difficulties to understand the intricate and still poorly understood immunopathogenesis [12, 50].

The initial descriptions of pulmonary manifestations are detailed in accurate observations almost a century ago, and are described ahead.

5. History

5.1 Sjogren’s syndrome as a systemic illness

The initial description of Sjogren’s syndrome (SS) included the dry eye, and Leber [51] described filamentary keratitis (FK) [51], a finding that years later was linked with the lacrimal gland dysfunction (described by Stock in 1925). Around the same time, descriptions of a combination of dry eyes and mouth, detailed by Hadden [52], was followed by further clinical associations of deforming arthritis, and detailed by several authors in case series [53–55]. In his doctoral thesis in 1933, Henrik Sjogren, a Swedish ophthalmologist, accurately detailed what we know as the syndrome that carries his name. In his treaty, he accurately depicted the disease as we currently know, “ocular changes because of dry eyes and hypofunction of salivary secretion, along with the arthritis and other systemic symptoms deals with a generalized disease and is not purely a coincidence” [56]. Ever since we know the concept of SS and its extent. Dr. Sjogren’s pristine and sharp description made it possible to link all the clinical manifestations within a syndrome. This concept of a systemic illness manifesting in various organs was already familiar facilitating him to launch it as a unique disease. Decades prior, Dr. William Osler described systemic lupus on several patients (in 1895 and 1903) who presented with multorgan involvement, other than the skin [57]. During the postwar era, in the 1950s, several
scientists uncovered thyroid antibodies, and following Dr. Hashimoto’s hypothesis from 1912, in which he sustained the thyroid gland to be the target of specific auto-antibodies. Dr. Jones applied this knowledge in SS. In this case, the salivary/lacrimal glands were the main target rather than the thyroid gland [58]. And indeed, the collaborative group of scientists from the National Institutes of Health in Maryland, USA, were able to identify them [53]. Two other concepts evolved as well: primary SS (pSS), when the disease presented alone; and secondary SS (sSS), when it was associated with other CTDs [13, 59].

5.2 Sjogren’s syndrome and the respiratory system in history

The pulmonary involvement was documented in the 1950s. In a registry of pSS, pulmonary infiltrates were reported in 7/40 cases [60]. In the original case series, Dr. Sjogren early on (in the 1930s and 1940s) described diverse respiratory findings including rhinitis sicca, pharyngitis sicca, and laryngitis sicca, and considered them to be components of the whole dryness spectrum added to keratoconjunctivitis sicca and xerostomia. In the mid-1940s, Dr. Weber extended this concept to other tissues, proposing that the exocrine gland’s dysfunction and destruction might precede sicca manifestations with an inflammatory continuum in the nasal, pharyngeal, and laryngeal mucosa, and other distant organs: the skin, vagina, gastric mucosa (this later with subsequent achlorhydia) [61]. Management was mostly symptomatic. Further progression of several discoveries made it possible to elaborate definitions of lung compromise within SS’s disease spectrum. Baruch and coauthors launched the concept of SS to be classified in two types: (1) those related to major CTD, and (2) sicca complex in the lungs that encompassed the following: chronic bronchitis, subsegmental atelectasis, bronchiectasis, pneumonia, lymphoproliferative pulmonary infiltrates, and chronic interstitial pneumonia, later leading to fibrosis [62]. Bloch published a series of 62 SS cases 37 (60%) who complained of nasal dryness and adherent crusts. One of them had sudden hearing loss linked to otitis, and chronic sinusitis was present in 4 (6%), throat dryness in 28 (45%), hoarseness in 20 (32%), and chronic dry cough in 5 (24%) [49]. In the lower respiratory tract, Bloch and coauthors reported: pleurisy, pleural adhesions, focal and lipoid pneumonia, pulmonary atelectasis, and fibrosis [49].

5.3 Pathology in history

Histopathological findings of most cases revealed submucous gland atrophy and lymphocytic infiltration intermixed with plasma cells at all levels of the respiratory tract [49, 63, 64]. The descriptions of pulmonary disease detailed different scenarios, from asymptomatic to severely ill patients. In this latter group, authors described two cases of acute parenchymal infiltrates in the setting of recurrent bronchitis and pneumonia. These cases presented with pneumonia composed of different cellular types with lymphocytic predominance and nodular lesions without evidence of an underlying infection or malignancy [49]. Brown attributed the cellular clustering to the diminished secretion of mucus, poor bronchial drainage, and secondary infection. Poor cellular immune response was considered [65], but it was also linked secondarily to a phenomenon known as pseudolymphoma [66, 67]. The latter consisted of marked cervical lymphadenopathy, pulmonary infiltrates of lymphocytes without enough atypia or monoclonality to label it as lymphoma [49]. Years later (1972), a full description further reinforced the diversity on pulmonary presentations, ranging from asymptomatic cases to overwhelming lymphoproliferation. Examples within this process were considered, such as pseudolymphoma, Waldenstrom’s macroglobulinemia, reticulum-cell sarcoma within the lymph nodes
and other types [68]. Similar findings were described in lymphoproliferative processes arisen in other autoimmune diseases (e.g., lupus), certain immune deficiency states, and hydantoin and use of other anticonvulsant drugs [68]. Finally, knowledge of SS in the respiratory system was expanded. Cases of amyloid in the lungs in patients with SS were reported in the 1970s [69], and other lower airway manifestations such as bronchiolitis, asthma, bronchiectasis, bronchiolitis obliterans with organizing pneumonia and also parenchymal disease, such as the interstitial pneumonia with potential to lead to diffuse interstitial pulmonary fibrosis, were linked with SS [62, 70, 71].

6. Prevalence and patterns of pulmonary disease in Sjogren’s syndrome

As described in the history, respiratory symptoms exhibit a plethora of manifestations with variable ranges of severity of different areas within the respiratory system. The airways and the lung parenchyma, or an admixture of both, may present alone and combined. Rarely the pleura may show inflammatory changes [72, 73], and pulmonary hypertension, although rare, has been more frequently recognized in East Asian populations [74]. Each one of the compartments may present with a range of different pathologies expanding the disease variety. For instance, in the lung parenchyma, NSIP may prevail [75, 76], but other manifestations have been reported [77].

The prevalence of lung and respiratory manifestations fluctuates from 9 to 24% [9, 11, 12] that include symptoms and abnormal pulmonary function tests or abnormal radiographic findings. Prevalence can go up to [78] 43%-75% [79] if patients are followed prospectively and analyzed based on a composite of multiple studies [80–83]. Symptoms may represent an estimate of an average of 40–66% [84–86], with an increase in sensitivity if radiographic images are included. The involvement of lower airways seem to be the most common respiratory presentation in SS [84, 87, 88]. The cumulative incidence of interstitial lung disease (ILD) at 1 year of pSS diagnosis was found to be of 10%, and went up to 20% after 5 years and 47% at 15 years, a fact that becomes relevant as SS patients age, making an impact on the prevalence [89]. The high prevalence of SS and the respiratory system involvement are a concern for the clinician, alerting her/him to have a full evaluation consisting of obtaining a detailed medical history, at the onset and during the follow-up appointments [45].

7. Morbidity, mortality, and prognostic factors in Sjogren’s syndrome and pulmonary compromise

Many of patients with SS and respiratory manifestations, and mainly interstitial lung disease associated with SS (ILD-SS), experience a decline in their quality of life [90, 91]. This seems to be tightly associated with increased morbidity that ultimately will decrease their life expectancy [89]. Mortality risk increases fourfold in a 10-year timeframe [90], making lung involvement one of the most common causes of death [92] and a predictor for mortality [89]. In a meta-analysis of large cohorts of patients with pSS, the overall mortality risk was 1.46-fold higher than that of the general population, and patient profiles with this higher risk revealed to be in the European group, older age, males, presence of ILD, cryoglobulinemia, positive serology (anti-SSB/La), and low complement) [93]. This coincided with another meta-analysis, in which results of mortality risk showed the same, plus additional factors, such as the parotid enlargement, abnormal parotid scintigraphy,
and extraglandular involvement [94]. The hazard ratio (HR) for death in pSS and ILD is between 2.1 and 3.2 [89, 95]. Among patients with pSS and already established ILD, respiratory failure accounted for the most common cause of death, and risk factors for mortality were older patients, with smoking habit, and carriers of severe ILD [96], either based on the number of reticulations on the chest HRCT and lymphoblastic foci in the biopsy [97].

8. Radiographic features in Sjogren’s syndrome and respiratory involvement

The chest X-ray may disclose features of both the airway, parenchymal and pleural involvement, but has a lower sensitivity than the chest HRCT [98]. The high-resolution chest computed tomography (HRCT) represents the most sensitive technique to uncover pulmonary features even in asymptomatic patients, followed by the pulmonary function tests (including plethysmography) [82]. Computed tomography (CT) changes have been reported in 34–50% [98]. In a cohort of 527 patients with pSS, prevalence of ILD was identified in 39.1% (206/527) based on abnormal chest HRCT. In this large cohort, the most common characteristics in the HRCT reported were associated with parenchymal disease in decreasing order: reticular pattern in 92.7%, ground-glass attenuation in 87.4%, and bronchovascular bundle thickening in 82% [99].

9. Pulmonary function testing in SS and respiratory involvement

The pulmonary function tests are of relevant utility since they will describe patterns of either obstructive, restrictive or a combination of both diseases. Prevailing features in pSS are seen in a pattern of obstruction in most patients and is mainly observed in the maximal expiratory flows (MEFs) 25–50% that test the small airway disease [84, 100]. Decreases in DLco have been reported in several studies [99, 101–104], but the significance of such findings is still unclear. Usually, they precede the FVC decline. Correlations of DLco and higher Schurawitzki score on the chest HRCT have been made, representing a prognostic factor for mortality [104]. Disproportionally low DLco in equivalence to the FVC might represent alveolitis in ILD cases, or pulmonary arterial hypertension (PAH), seen in pSS more than thought in the past. The decline in FVC is more prominent once ILD is established [105, 106].

10. Bronchoalveolar lavage in Sjogren’s syndrome and respiratory involvement

Bronchoalveolar lavage in patients with SS may represent an extraordinary tool to define on whether the respiratory system is involved, especially in patients who would present with symptoms and negative changes on PFTs or chest HRCT [100, 107]. Results may disclose prevailing specific CD4(+) T lymphocytes in the cellular differential [108]. Thus, it may improve the sensitivity to detect disturbances in the respiratory system [84], especially for patients with unexplained respiratory symptoms with normal HRCT and PFTs. Furthermore, BAL will reveal an inflammatory pattern on cases with alveolitis, showing the T lymphocyte predominance [108].
Figure 2.  
H&E sections from a right upper lobe of lung wedge resection reveal focal areas of subpleural scar and fibrosis admixed with cystic airway distention (image a). These areas are associated with an adjacent prominent lymphoplasmacytic inflammation with lymphoid follicular hyperplasia (images b and c). The lymphoid expansion is associated with frequent airspace cholesterol clefts, histiocytes, eosinophilic debris, and sparse neutrophils (image A), mostly resembling changes secondary to localized airspace obstruction possibly secondary to the degree of hyperplastic lymphoplasmacytic reaction. Subpleural cysts and lymphoid hyperplasia are seen in Sjogren’s syndrome.
11. Biopsy utility in Sjogren’s syndrome and respiratory involvement

Biopsy is currently limited to specific scenarios to (1) determine a clear etiology of the disease, (2) define fibrotic non-interstitial pneumonia (NSIP) vs. usual interstitial pneumonia (UIP), or admixed patterns (3), and establish underlying malignancy, especially in cases with lymphocytic interstitial pneumonia (LIP). In the biopsy, most of results may disclose a fibrotic NSIP pattern (Figures 2 and 3) [97]. Furthermore, many of the biopsies will reveal presence of small airway inflammatory changes in association with ILD. Amyloidosis will be identified in association with SS and nodular lung disease, and UIP will increase a yield to up to 33% with the biopsy [97, 103, 109, 110].

The significance of SS exhibiting extraglandular manifestations represents a higher inflammatory state. This is remarkably noticed when the respiratory system is affected. Hypergammaglobulinemia reflects this notion [81, 107]. Additionally, positive anti-SSA/Ro and anti-SSA/La antibodies may associate with the respiratory system [78, 111], so were other acknowledged makers: ANA and the rheumatoid factor (RF) [81, 83]; in addition, some authors consider the evidence of serology as a predictor for lung disease in SS conflicting [80].

12. European league against rheumatism and measurers of disease activity in Sjogren’s syndrome

The European League Against Rheumatism (EULAR) task force on SS has created the EULAR-SS Disease Activity Index (ESSDAI) to determine specific organ expression [112, 113]. It is used now as an index to quantify the disease activity in pSS, and applied in randomized control trials [114]. This index includes 12 domains, and representing the target organs and systems affected by the disease (organ systems that are explored are: cutaneous, respiratory, renal, articular, muscular, peripheral nervous system (PNS), central nervous system (CNS), hematological, glandular, constitutional, lymphatic, and immunological). For each domain, the scoring assigns the disease activity in 3–4 levels depending on the severity. Low activity is the ESSDAI of < 5 points; moderate-activity falls between 5 ≤ ESSDAI ≤ 13; and high activity scores the ESSDAI ≥ 14 [115]. A minimal clinically important improvement (MCII) is established as a decrease of at least three points in follow-up visits, when the prior scoring showed moderate activity [115]. The pulmonary domain is divided into four categories, based on the activity level, and range from no activity equivalent to 0, or to symptoms unrelated to pSS, to high activity level or scored as 4 (Table 1). The range between low and high activity levels will define the severity based on symptoms (the magnitude of dyspnea will be determined and scored by using the NYHA stratification) and progression of the respiratory symptoms analyzed with ancillary tests (PFTs) or alternatively with the chest HRCT. Patients who fall in the high-activity group may have a worse outcome.

In a large cohort of 921 pSS patients, the pulmonary domain of ESSDAI scoring at the time of the diagnosis revealed any pulmonary activity in 6.1% of them, 94% of patients had no pulmonary symptoms. At the end of 75 months, 15% had any pulmonary activity, and sixty percent of the cumulated score corresponded to a new activity [5]. The pulmonary activity had the highest mean cumulated score at the last visit along with the renal and muscular domains, revealing the higher incidence as longer the disease progresses in these three domains [5].

Sjogren’s syndrome may selectively affect different compartments within the respiratory system, but it seems it affects almost all and frequently simultaneously.
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Figure 3.
H&E sections from this right upper lobe lung wedge biopsy (image a) reveal a cellular interstitial inflammatory infiltrate predominantly composed of lymphocytes admixed with interstitial fibrosis, which is mostly centrilobular. These constellations of findings are consistent with a cellular interstitial pneumonitis with fibrosis. Sections from the right lower lobe wedge biopsy (images b and c) reveal a more markedly altered lung parenchyma compared with the right upper lobe. There is extensive panlobular collagen fibrosis with multifocal areas demonstrating cystic spaces lined by bronchiolar epithelium and fibrotic walls (honeycomb changes). The findings identified in the lower lobe biopsy are not specific to an interstitial lung process but points toward the differential diagnosis of lesions that can have a nonspecific interstitial pneumonia (NSIP) pattern with temporal heterogeneity and extensive honeycombing, which would include connective tissue disorders such as Sjögren’s syndrome.
They may present in an overlap complicating their identification for the subsequent therapeutic intervention. For a better understanding, however, the following compartments should be studied separately.

13. The upper airways

The upper airways seem to be a continuity of the mucosal invasion of inflammatory mononuclear cells, or sialadenitis, affecting the mucosal surfaces in the sinuses, larynx, and ears. The cumulative incidence of chronic rhinosinusitis in pSS has a HR of 2.5 as compared to controls [116].

Dysfunction of salivary glands with the resultant dry mucositis changes the microenvironment in the oral and distant mucosae and thus, promotes a chronic inflammatory state. One good example highlights that pSS patients are at 2.5 times higher risk of developing chronic rhinosinusitis [116]. In addition, the consequent dryness alters or sets off the mucociliary clearance, as seen in the tracheobronchial tree [117]. Furthermore, the histopathology of mucosal surfaces shows infiltrates, similar to what it is seen in the minor salivary glands, where lymphocytic cells surround the mucosal acini configuring the focal lymphocytic sialadenitis [24]. In a study comparing bronchial biopsies of patients with pSS vs. controls, the former showed higher number of infiltrating neutrophils, mast cells, and T lymphocytes. The epithelial damage and structural changes in the subepithelium resembled changes seen in atopic asthma [118]. Moreover, lymphocytic infiltrates are present in BAL of both symptomatic and even asymptomatic patients, representing the continuous and silent inflammatory state along the airways [84, 107, 108, 119].
14. Oral microbiome and Sjogren’s syndrome

Sicca mouth in SS has an impact on the oral microbiome, favoring the growth of a dysbiotic environment that replaces the normal flora compared with controls [120]. It is unclear if this hostile environment predisposes this microbiome shifting, favoring its growth. Also, it is unclear if the dysbiosis may impact on the disease establishment and/or progression. Supporting possible impact on glands by the microbiome, experiments on animal models, revealed an association of dysbiotic oral microbiota with the development of lymphocytic sialadenitis [121]. This hypothesis was evaluated in a recent study that demonstrated the immunomodulatory properties of commensal bacteria (*Haemophilus Parainfluenzae*). This bacterium keeps the regulatory immune homeostasis, explored at the cellular level. In a study of salivary microbiome, patients with pSS had lower amounts of *H. Parainfluenzae*. The analyzed A253 cells, once primed with *H. Parainfluenzae* exposure, induced suppression of CD4 T cell proliferation and induction of PD-L1 expression [122]. Moreover, treatment with low-dose doxycycline normalized the levels of some salivary metabolites associated with the dysbiotic microenvironment in patients with pSS to levels comparable with healthy controls [123]. These findings support the role of the microbiome on pSS pathogenesis and mucosal dysfunction.

15. Dry mucosae in the mouth and upper respiratory airways and SS

Sicca mucosae in SS may impact on dental and periodontal health. It is common to see gum retraction in most of the teeth and specific dental caries at the neck of them. The sicca environment predisposes patients to develop the growth of opportunistic infections, like candida growth. Candida colonization presents in various forms, ranging from asymptomatic, including leukoplakia, and even as burning mouth syndrome [124]. Many patients may lose their teeth and have a significant decrease in their quality of life. This later is in part attributable to the dysphagia and dysphonia, both related with xerostomia [125]. Hoarseness presents in a frequency between 26% and 33% [125, 126]. The laryngeal mucus and vocal folds will harden causing morphological revealing distinctive vessels and/or edema on the exam. In the video-assisted swallowing test abnormal motility will be seen [125]. Gastric reflux may account for this finding predisposing the dysfunctional esophageal motility [127]. The bamboo node represents a chronic inflammatory state of vocal cords reported in SS and other CTDs [126]. Although not fully recognized as a common finding in pSS, hearing dysfunction and loss were reported in 80% of patients (24/30), with severe hearing loss in 10% of them. However, most of the pathology seemed to be linked with vestibulocochlear (cranial) neuropathy [128].

Cough is common in pSS, and especially dry cough is representative of, mainly but not only, airway inflammation. The term xerotrachea defines dry tracheal mucosa with the inflammatory background that extends distally, causing significant morbidity [84]. Again, difficulties in clearance will prolong inflammation and promote further functional and anatomic changes such as atelectasis, bronchiectasis, bronchitis, peribronchial and peribronchiolar scarring and airway narrowing [70, 83, 119, 129–131].

16. Lower airways: epidemiology

Patients with SS have a frequent hyperreactive tracheobronchial response in 42–60% [132, 133], and sustained and extended cough following persistent stimuli
(dust, tobacco, etc.). They will have abnormally bronchial hyperreaction to the methacholine challenge test, but become inert to the adenosine monophosphate, cold, or hyperventilation. Under the chronic inflammatory state, the pulmonary function test will reveal a decline in the different lung volumes [134, 135]. The pathogenic background of bronchial hyperreaction is unclear, making it difficult to interpret and treat [132]. As previously described, the mucosal chronic inflammation will interfere with clearance, perpetuating and aggravating the dysfunctional hyperresponsiveness [117]. The chest HRCT will be of utility to identify lower airway disease. Findings will be: peripheral bronchiectasis in 5-46%, bronchial wall thickening in 68-85%, nodules in 6-29%, and air trapping in 32%. Together with ground-glass attenuation as the representative parenchymal disease, these are the most common features identified with this modality [87, 107, 136].

16.1 Bronchiolitis

Inflammation in bronchioles has predilection for SS and presenting in different types, such as obliterative bronchiolitis, chronic bronchiolitis, lymphocytic bronchiolitis, constrictive bronchiolitis, and panbronchiolitis [11]. However, the most representative type in SS is follicular bronchiolitis. In biopsies, it may associate with interstitial pneumonia (especially NSIP) [97, 109], and in some cases, along LIP, they may form a continuum, the former limited to peribronchiolar area while the latter to the alveolar septa [119, 137]. Frequencies increase from 12% to 24% when radiographic images accompany the pathological interpretation [109]. Follicular bronchiolitis has a bronchovascular distribution, and the hyperplastic lymphoid follicles with reactive germinal centers run along the bronchovascular bundles [117, 138, 139]. The CT scan will define changes of bronchial thickening in 8–22%, and bronchiolar nodules in 6–24% [82, 84, 133, 140]. Many studies have shown a decline in the DLco that is attributable to bronchiolitis, a fact that needs to be fully proven [99]. Symptoms are represented by dry cough, wheezing, dyspnea, and overlapping infection. Treatment for bronchiolitis challenges the clinician since most of the therapies only seem to be partially responsive. Starting with antibiotic therapy aimed at preventing infectious overlap and especially with use of macrolides, given their anti-inflammatory properties, the mainstream therapy remains on inhaler and/or systemic glucocorticoids, if the disease progresses or becomes seriously symptomatic [141, 142]. Applied disease-modifying drug therapies include azathioprine (AZA), mycophenolate mofetil (MMF), and even rituximab [142]. In the presence of comorbid immune deficiencies (i.e., immune globulin deficiencies, mainly IgG), replacement therapy is recommended [143]. Overall, the treatment intensity should correspond the severity of each case. In complex cases combination of therapies might show better outcomes.

17. Bronchus-associated lymphoid tissue (BALT)

The chronic antigenic stimulus will drive the follicular bronchiolitis to conform a bronchus-associated lymphoid tissue (BALT), which is a benign inflammatory state of polyclonal lymphoid hyperplasia [144], and dense cluster of lymphocytes with follicular structures. These cells follow an antigen-driven stimulus. Well-defined aggregation within a network will separate B from T cells. The B cell compartment encloses follicular dendritic cells (FDCs), which is related with the vascular structures (venules and lymphatics) [142]. BALT is equivalent to the gastric mucosal-associated lymphoid tissue (MALT). In addition, the perivascular compartments are encased by lymphocytic aggregates, labeled as perivascular.
They may extend to the small airways and run parallel to the vessels. This organized lymphocytic aggregation is known as induced BALT that is a chronic inflammatory state ready to get reactivated after a second insult [145].

18. Chronic obstructive pulmonary disease

Patients with SS have significantly decreased PFTs showing a composite of decreased VC, TLC, FEV1, FEV1/VC, and DLco but high RV. This pattern fulfills criteria for COPD even in nonsmokers, a fact that may be explained by the presence of chronic tracheobronchitis [146].

18.1 Bronchiectasis

Structural damage with dilatation in distal bronchi and bronchioles may associate with dry mucosa, poor clearance, and superimposed infectious processes [147, 148]. In SS, the cylindrical pattern seen on the HRCT seems to be the prevailing finding [149]. Frequencies vary depending on the cohorts, from 7% to 54% [11]. The clinical presentation is frequently seen in women with chronic sinusitis, with age at the time of diagnosis, and comorbid gastroesophageal reflux. Antismooth muscle but uncommon anti-SSA/Ro antibodies were detected in this group. The HRCT will describe cylindrical bronchiectasis localized preferentially in the lower lobes (Figure 4) [11]. A plethora of symptoms may ensue, especially chronic cough, dyspnea, and even recurrent remitting hemoptysis. The concomitant recurrent superimposed infections worsens the prognosis, reported in 10–35% [70, 71, 150]. Multifactorial etiologies play a role, such as gastroesophageal reflux, dysfunction in the tracheobronchial mucociliary clearance, chronic sinusitis, immune suppressor drug therapy, climate, and presence of bronchiectasis [148, 151, 152]. Combination of bronchodilators, secretagogues, chronic antibiotic use as preventative means for flares seem to be the mainstay of therapy [11]. The use of immune suppressor therapy favors higher

![HRCT](https://example.com/image.png)

Figure 4. HRCT. Scattered, ectatic airways more visible in right middle lung and lingula where there is also bronchiectasis and scarring/volume loss. They represent airway-related disease (bronchiectasis).
risks for infections as bronchi may already be chronically colonized with abnormal and pathogenic flora [153].

As described previously, follicular bronchiolitis may be seen in association with parenchymal disease, mainly interstitial pneumonia. The following sections will display the various types of parenchymal disease in SS.

19. Parenchymal lung disease: epidemiology and patterns

Most of the studies report a prevalence of interstitial lung disease associated with primary Sjogren’s syndrome (ILD-pSS) of around 20% [85, 89, 95, 101, 102, 151, 154–158]. Other cohorts report variable frequency, ranging from 3% up to 60% [99, 152]. Furthermore, the EULAR task force reported a prevalence of 49% in 526 group of patients with SS, and based on chest HRCT [9], which appears a real-life frequency. Incident cases range between 8% and 17% [85, 101]. Lymphocytic interstitial pneumonia (LIP) was thought to be the most common ILD type [159], but recent large cohorts reveal the following patterns in decreasing order of frequency, based on the HRCT: NSIP in 41.7%, UIP in 10.7%, OP in 3.9%, and LIP in 3.9% of cases out of a total of 124 patients [99]. Other large cohorts with similar frequencies of the various ILD types include amyloidosis in 11%. Admixed patterns were also present in 82 cases reviewed, with combinations of NISP/OP (43.9%), NSIP/UIP (35.4%), and NSIP/LIP (19.5%). Biopsies confirm NSIP to be the most frequent pathology. Symptoms and findings associated with ILD were found to be dry cough, clubbing, elevated lactate dehydrogenase, and positive anti-SSA/Ro antibodies [99, 103, 160]. Interstitial lung disease associates with older age at the disease onset, longer SS duration, fever, xerostomia, xerophthalmia, and neuropathy [161]. It may be the first presentation in a third to a half of patients [162]. Subsequently, not aware of SS’s features, the disease may run undetected. The contribution of lip biopsy in such cases is crucial for this goal especially in cases with negative serology [163]. Laboratories might help and are important for a full evaluation. Hypergammaglobulinemia, lymphopenia, low C4, and high acute-phase reactants are common findings [160]. The PFTs will disclose a restrictive pattern, and low DLco is frequently reported (even up to 64%) [101, 102, 162]. It is common to see an admixture with an obstructive pattern (25%), as a reflection of the association with lower airway disease [162]. The chest X-ray will be of great utility to determine any possible finding in the lung parenchyma, such as linear and reticular patterns, but it has the limitations in sensitivity to detect fine changes [98, 103, 109]. In the chest HRCT, up to 90% of findings will be disclosed [11]. Frequent findings are bilateral infiltrates in almost 99% of cases and predominance in lower lobes and subpleural spaces. Also, lesions distribute in perihilar areas in 9% [99]. Other common findings are the reticular pattern, ground-glass attenuation (92%), non-septal linear opacities (75%), interlobular septal thickening (55%), cystic formation (30%), reticulation, and fibrosis [109, 164]. Honeycombing and features of UIP are unusual [165] (Figure 4). Cystic lesions may present at different sizes and distributed along and imbibed with the parenchyma. They have thin-walled demarcations and may be a consequence of a valve phenomenon [166]. They are associated with LIP, lymphoma, and even amyloidosis [167].

19.1 Nonspecific interstitial pneumonia

This subtype is the most frequent form of ILD-pSS and presents with variable degrees of symptoms, including cough, dyspnea or, rarely, may run asymptomatic [9]. Alveolitis may correlate with NSIP, and one way to identify it is with the BAL. This later study will disclose lymphocytic cells [108]. Frequencies vary depending
on the cohorts and methodology used. In a series of 33 cases of ILD, the lung biopsy yielded NSIP pattern in 20/33 (61%) with the fibrotic type in 19 (57%) [109]. In a cohort of 263 patients with pSS, 8% were identified with ILD with a third of them having NSIP pattern [85]. In another study, 19.3% had ILD-pSS, and almost half to them had NSIP pattern based on on HRCT [96]. On the chest HRCT, relevant features in this subtype are the ground-glass opacities, mainly in lower lung fields and subpleural predominance. Other findings are reticular abnormalities, traction bronchiectasis, peri-bronchovascular extension, and pulmonary consolidation. Sparing between pleura-parenchyma interface is a hallmark along with tracking of opacities along lower-zone bronchovascular bundles (Figure 5) [168]. The biopsy will reveal preservation of architecture and a composite of inflammatory cells. The distribution characterizes by the lymphocytic expansion of alveolar septa. Fibrosis is also seen and associates with traction bronchiectasis (Figure 3A). Honeycombing is rarely seen. Depending on the cellular/fibrotic predominance, NSIP is subdivided into the cellular or fibrotic types. As said, this later is the most frequent presentation in pSS [97].

The 5-year survival rate was of 83–87.4% [97, 109]. Low PaO2 and presence of microscopic honeycombing were associated with worse survival [109]. In another study, worse survival was associated with PaCo2, extent of reticular abnormality on HRCT, and severity of fibroblastic foci on the biopsy [97]. No differences between the NSIP and UIP patterns in terms of prognosis were identified [97], although this is controversial. The clinical course will vary, but this pattern usually is responsive to the immune modulation.

![Figure 5](image.png)

*Figure 5.* Parenchyma with reticulation, ground-glass attenuation, and traction bronchiectasis in the lower lobes, middle lobe, and lingula. This process is peribronchial in distribution and extends into peripheral portions of the lung parenchyma. Portions of the subpleural lung parenchyma in these regions are spared. There is no honeycombing. Bilateral pleural effusions larger in right than left lower lobes. Findings are consistent with nonspecific interstitial pneumonia.
19.2 Usual interstitial pneumonia

This subtype is infrequent in SS, but prevalence varies between 10% and 17% [9, 99, 102]. Main differences between UIP and NSIP patterns are based on the HRCT features and interpretation. Intralobular reticulation, honeycombing, traction bronchiectasis, cystic lesions, and temporal heterogeneity may prevail as patterns. The hallmark for UIP is the honeycombing appearance (Figures 2A, 3B and C and 6) [168]. Although rare, UIP needs to be recognized as treatment usually is unresponsive to the therapy [103].

19.3 Lymphocytic interstitial pneumonia

Main histopathologic feature is the polymorphous lymphoid infiltrate involving diffusely the alveolar septa of lymphocytes (T and B cells), plasma cells, and histiocytes [169]. Plasma cells show a polyclonal pattern [170]. As described, lesions may present with follicular bronchiolitis along the bronchovascular structures [171], and occasionally will present with foci of BALT hyperplasia (Figure 5) [144]. Also amyloid deposits may overlap [159]. Lymphocytic Interstitial pneumonia (LIP) is a benign lymphoproliferative disease. Frequencies range between 3% and 15% [9, 99]. Cough, dyspnea, and inspiratory crackles are common. The CT studies will disclose a diffuse ground-glass opacity and consolidation as the most common features. Thin-walled cysts can be present, along with combination of thickened bronchovascular bundles and nodularity in association with follicular bronchiolitis [168]. Frequently, the biopsy is necessary to differentiate from lymphoma. In the

Figure 6.
There is extensive subpleural reticulation, honeycombing, and traction bronchiectasis/bronchiolectasis that predominate in the posterior basal lower lobes. There is no normal lung parenchyma between the fibrotic lung and the adjacent pleural surfaces. There are scattered foci of mild mosaicism indicative of air trapping. Findings are consistent with usual interstitial pneumonia.
presence of germinal centers (GC), this differential has a more relevant importance since both LIP and lymphoma can portray this distinction (Figure 2B and C). B-cell lymphoma arising from BALT lesions presents with monomorphous B-cell infiltrates with invasion of lymphatics, vessel walls, pleura, and subsequent destruction of alveolar architecture. Monoclonal plasma cells, Immunohistochemistry and gene rearrangements will help define this differential from LIP [172–174]. Differential from NSIP relies on the more intense lymphocyte density seen in LIP [173]. Early and aggressive pharmacologic approach with high-dose glucocorticoids, followed by immune modulators/suppressors, seems to halt the disease progression [11].

19.4 Organizing pneumonia

It is an unusual presentation more common in rheumatoid arthritis, with a frequency of 3.9–11% [9, 75, 160]. Symptoms reveal severe dyspnea, cough, and oxygen dependency. A restrictive pattern will prevail, but a mixed combination is seen. HRCT features consist of diffuse or multifocal patchy bilateral ground-glass opacities and/or consolidation without extensive reticulation or honeycombing [175, 176]. Other features are the reversed halo opacity and bronchial wall thickening [177, 178]. Histopathology will reveal plugs of granulation tissue within small airways (Masson bodies) and chronic inflammatory cell infiltration in alveolar walls [179, 180]. Case reports document the favorable response to glucocorticoids [180, 181], but others may be fatal [182]. Differences of OP with cryptogenic OP are the more frequency in women, positive serology, and relapse presentations. Mortality is linked with progressive dyspnea [183].

Figure 7.
Multiple thin-walled cysts noted on CT imaging-central predominance. Surrounding lung appears otherwise grossly unremarkable.
20. Cystic lung disease

Cystic lesions may have different dimensions ranging from 0.5 cm to 7 cm, in internal structure within cysts, and frequently associate with ground-glass opacities and nodules [167]. They typically tend to localize in lower lobes, but distribution may be diffuse. Underlying amyloidosis, LIP and lymphomas should be explored [167, 184]. Thin-walled cysts can also occur in the absence of other parenchymal lesions (Figure 7). Frequently, they have peribronchovascular distribution [167].

20.1 Lymphoma

Sjogren’s syndrome has a higher risk for lymphoma as compared with other CTDs, with a standardized incidence ratio of 37.5, 95%,CI 20.7–67.6 [185]. An estimate of 5% of all SS patients may develop lymphoma with the low-grade extranodal marginal zone B-cell lymphoma (MZL) type being the most relevant histological type [186]. Chronic inflammation adjacent to epithelial cells may predispose to the generation of mucosal-associated lymphocyte tissue (MALT) hyperplasia and in the lungs labeled as bronchial-associated lymphocyte tissue, BALT [144]. The ongoing, relentless, and uncontrolled antigenic stimulus may promote activation of pro-oncogenic genes within lymph nodes or in extranodal lymphocytic aggregates (such as in the lungs), particularly under presence of germinal centers, driving them to endure a monoclonal transformation [187, 188]. MALT lymphomas surge from the marginal zone of B-cells that are localized surrounding the mantle zone and germinal centers, with the denomination of non-Hodgkin’s lymphoma, arising from the extranodal marginal zone B-cell. Other types of B-cell lymphomas are present as well. Frequency of pulmonary lymphomas is of 1%–2% [189], and predictors are difficult to define due to the scarcity of cases. Symptoms reveal a dry, chronic cough, and slowly progressive dyspnea or may run undetected [190]. Few patients may have constitutional symptoms (B-symptoms, lymphadenopathy, fever, weight loss, sweats, malaise, etc.) [191]. Findings on the chest HRCT are bronchial wall thickening and bronchiectasis, preferably in lower lobes. Lung parenchyma surrounding the abnormal airways may associate with confluent alveolar opacifications or ground-glass changes. Nodular densities are common [191]. The biopsies will disclose lymphoepithelial lesions involving the bronchial and bronchiolar epithelium, positive CD20 stain, clonal kappa/lambda distribution, Ki-67 proliferation, and abnormal gene rearrangement. Prominent plasma cell proliferation was observed on flow cytometry [191]. Therapy is based on use of alkylating agents and a combination of chemotherapy drugs. Rituximab seems to be the current standard of care as most of plasma cells express CD20 marker [191]. Most of the combination therapies set lymphoma in remission.

21. Amyloidosis in pulmonary Sjogren’s syndrome

This is a disorder caused by fibrillary plasma protein deposits on different tissues [192]. Rare cases of amyloidosis in SS are present, mainly in the skin and lungs, and very unusual, systemic amyloidosis. Other sites are reported including the tracheobronchial walls, kidneys, lacrimal glands, tongue, and mammary glands. When it affects the lungs or the tracheobronchial wall, symptoms may ensue, such as cough, dyspnea, pleuritic pain, and hemoptysis [193–203]. Amyloid composition in SS is usually of AL type (lambda or kappa) light chains, or less commonly, AA amyloid type [192]. Women are more frequently affected [195]. Radiographic images will reveal nodules, either calcified or not, and of different heterogeneity. They associate
with cystic lesions. Histopathology will reveal infiltration of lymphocytes, plasma cells and amyloid deposits. Amorphous eosinophilic material and Congo red staining will reveal apple-green birefringence. MALT lymphoma should be explored as both associate frequently. Lymphocytic interstitial pneumonia is also frequently present with related cystic formation. The epithelium of cystic lesions may contain amyloid deposits [167]. Symptomatic therapy and glucocorticoids may be of help [192].

22. Pulmonary arterial hypertension, PAH

This is a rare condition in SS; however, the epidemiology reveals new data. Studies in East Asian ethnic group demonstrated a high frequency, such as systemic lupus erythematosus, in nearly half of a large group of 129 patients with confirmed PAH [204]. Women of ages between 30 and 40 are the most affected group [205]. Serology might be of great utility, as well as the biopsy of minor salivary glands. Prognosis at 1, 3, and 5 years is 80.2%, 74.8%, and 67.4%, respectively [206], being the anti-SSB/La antibodies poor predictors [207]. Of course, anti-phospholipid antibody syndrome always should be ruled out among other hypercoagulable risk factors to cause PAH [208].

23. Treatment of Sjogren syndrome and its pulmonary manifestations

23.1 Brief history

Therapy initially relied on symptom management, based on cholinergic pharmacologic drugs (e.g., Pilocarpine), mucolytics, but also radiation therapy (mostly targeting the parotid glands) [61]. The pivotal management, however, and since the 1950s, was based on glucocorticoids [209, 210]. Introduction of hydroxychloroquine in SS was not until the late 1980s and 1990s, and immune modulators have been extensively tried in case reports and case series [211, 212]. In 1998, Schnabel introduced IV cyclophosphamide for pulmonary disease and reported in cases of pseudolymphoma and associated lymphoma with pulmonary compromise [213–215]. Other immune modulators have been used, mainly on cases with advanced disease. Among the therapy, azathioprine [79, 216] and mycophenolate mofetil [217, 218] have been reported. Biologic therapy, such as rituximab, a humanized monoclonal antibody targeting mature B-cells (CD20+), was tried in case series and reports with promising results [219], in reparatory cases [220] and also associated with lymphoproliferative diseases [221–223], in special cases, such as in shrinking lung syndrome associated with SS [224]. Off-the-label cases reported other biologicals, such as tocilizumab [225] and abatacept [226].

24. The overall approach

Pulmonary complications of SS primarily comprise airway mucosal dryness (Xerotrachea), a range of interstitial lung diseases (ILDs), non-Hodgkin lymphomas, pleural effusion and/or thickening, and very rarely it can also cause pulmonary hypertension and/or thromboembolic phenomenon [12, 227].

We will layout an overview of symptomatic treatment of SS and sicca symptoms before discussing treatment of SS-associated pulmonary pathologies. Sicca symptoms are a common feature in most patients with SS, and its treatment can lead to dramatic symptomatic improvement in patients’ health and understanding of the
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Disease. Basic measures for prevention of dry eyes and dry mouth should be advised in all patients [228]. These include maintenance of good oral hygiene [229], avoidance of coffee, alcohol, and sugar-filled liquids [230]. Use of artificial tears and avoidance of medications with anticholinergic properties should be stressed, especially drugs used for urinary incontinence such as oxybutynin [231]. Furthermore, this strategy can be compounded with addition of muscarinic agonists such as cevimeline and pilocarpine. These medications are collectively called sialagogues and have been shown to increase salivary flow and improvement in xerostomia in several randomized trials [232–234].

There have been investigative developments in oral electrostimulators, which induce salivary production and flow [235, 236]. However, their usage is vastly limited due to lack of larger trials, greater efficacy of medications, and cumbersome device management.

Dry eyes (Xerophthalmia) can often be the main feature of SS presentation and is usually the most frustrating symptom faced by most patients. Daily use of artificial tears and nightly use of oral lubricant are highly advised. In patients who still complain of dry and itchy eyes after these measures, topical cyclosporine and/or lifitegrast can be utilized [237]. Topical cyclosporine emulsions can be used with daily use of artificial tears, its efficacy is shown to increase with more frequent daily applications [238–240].

Managing nasal dryness is an important consideration as nasal congestion can lead to mouth breathing and worsening of xerostomia. Nasal dryness can be effectively managed with intermittent nasal saline sprays and room humidifiers. Laryngopharyngeal reflux (LPR) is a known manifestation of SS affecting aerodigestive tract. This should be treated with anti-GERD therapy to mitigate the erosive effects of gastric acid on laryngeal structures [241].

25. Treatment of interstitial lung disease

Management of most SS-related ILDs is based on empiric treatment options as no randomized controlled trials (RCTs) have yet been performed. It is also important to understand that treatment of SS-ILD is based on longitudinal worsening in HRCT/PFT results and overall symptomatic nature of the disease. Asymptomatic patients with mild ILD based on HRCT/PFT may not need a lung biopsy for confirmation of exact ILD type and may be monitored with HRCT/PFT every 6–12 months to assess disease progression. NSIP is often the most common histopathology found with SS-ILD, with UIP being second most common. LIP is rarely observed, but it is classically associated with SS-ILD [85].

Patients with symptomatic SS-related NSIP need treatment and are usually started on prednisone 1 mg/kg up to a total of 60 mg per day [75]. Patients should be assessed in 4–6 weeks with a PFT and symptom evaluation. If improvement is observed, low-dose prednisone is usually continued for at least 6 months with subsequent PFT/HRCT and symptom evaluations. Specific details on caution to use glucocorticoids overall are highlighted on the recently published consensus guidelines for the evaluation and management of pulmonary disease in Sjogren’s syndrome [45].

Immunosuppressive regimen with azathioprine (AZA) or mycophenolate mofetil (MMF) should be considered for patients as a glucocorticoid sparing therapy to prevent developing side effects to it. Both AZA and MMF have been shown to stabilize FVC decline in patients with CTD-ILDs (these cohorts had patients with SS-ILD as well) [79, 242]. In a recently published retrospective study, patients with pSS-ILD (19 cases) had a modest FVC% and DLco% slope improvement over time with use of both AZA and more favorably MMF, revealing the efficacy of both
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immune modulators on this condition [243]. In the same study, utility of rituximab was controversial.

Rituximab is left as an emerging option for patients who have refractory lung disease after use of above mentioned strategies. The benefit to target CD20 receptors in mature B-cell lineage has the advantage to blockade any antibody-mediated autoimmune disease. Its usage has been demonstrated in few case reports and case series in SS [244, 245]; however, there is still need of larger controlled trials to formally evaluate its efficacy. Experiences on rituximab in systemic sclerosis and ILD (SSc-ILD) added to the conventional treatment (methotrexate, AZA, or MMF), showed improvement in FVC after 2 years of use [246], and it may not only be a drug as a rescue strategy over MMF [247], but also possibly a line of standard of care therapy in the future when used upfront of other immune modulators (MMF) [248].

Cyclophosphamide has been used in few cases of SS-related ILD. Experiences from cyclophosphamide use in patients with SSc-ILD show efficacy to prevent FCV decline [249, 250]; however, their usage is markedly limited due to toxic effects and loss of efficacy once the drug is stopped [250]. Substitutes for cyclophosphamide after the induction phase were proposed. During the maintenance phase, azathioprine [251] and MMF [252] have been shown to preserve FVC. In the later study, comparing MMF vs. cyclophosphamide during the induction phase, MMF showed similar results in efficacy but lower toxic drug effects, encouraging providers to consider MMF as the drug of choice [252].

Other conventional drugs, including cyclosporine, have shown to prevent the progression of ILD in SS, but owing to their systemic side effects, their use is limited [110].

Tocilizumab, an IL-6 receptor inhibitor, has been tested in patients with SSc-ILD. Results are promising, especially in those individuals with active disease (alveolitis, high Rodnan skin score, high acute-phase reactants, and early stages of the disease) [253]. The decrease in the FVC slope at 24 and 48 weeks comparing with the placebo group that did worse contrasted the positive findings not described on the primary goal as was the prevention of further cutaneous fibrosis. The following trials of this drug confirmed the efficacy to preserve FVC [254], prompting for its FDA approval for SSc-ILD in early 2021. The utility in SS-ILD has not been systemically explored; yet the evidence reveals good outcomes in SS patients presenting with arthritis [255]. It seems tocilizumab to be a promising therapy for active inflammatory lung disease in SS. As an example, in a case report of refractory organizing pneumonia associated with SS, the use of tocilizumab showed to be very effective [225]. Contrasting with IL-6 blockers, TNF-alpha blocker therapy did not seem to be effective in SS overall [256, 257].

Abatacept is another biological therapy. It encompasses the fusion of a cytotoxic T-lymphocyte-associated protein 4 to the FC portion of an IgG1, with high binding affinity to the CD80 and CD86 receptors of the antigen-presenting cell (APC). This way it blocks costimulatory interaction of CD80/CD86 receptors with the T cell receptor (CD28) necessary for T cell activation and proliferation [258]. Approved for rheumatoid arthritis, the experience reveals stabilization of RA-ILD based on HRCT and FVC prospective evaluations [259–265]. Most of the impact was seen in carriers of the NSIP subtype [263], a finding that follows UIP in frequency in RA. Despite the subtype, the overall evidence reveals benefits of abatacept in this disease [261, 264, 266]. The impact of methotrexate on patients on abatacept seemed not to cause any worse pulmonary function deterioration; however, methotrexate’s use in ILD raises questions on safety. The same may be considered with other medication class, such as the TNF-alpha blockers with frequent reports of worse ILD in the setting of CTDs [267]. In SS, the efficacy of abatacept has shown in salivary gland inflammatory
findings and extraglandular manifestations [268]. A case report revealed improvement in pneumonitis while combining abatacept and tacrolimus [226], suggesting that synergy among both drugs potentiates efficacy on ILD settings.

Belimumab, a specific monoclonal antibody targeting the B-cell activating factor (BlyS), restores circulating B cell numbers, composition, and activity in patients with SS [269]. The BELISS open-label trial of 30 patients with pSS revealed a decline in ESSDAI at 28 weeks, with main improvement in fatigue, but not in sicca symptoms [270]. However, this study did not mention effects on the respiratory system. Main changes in extraglandular manifestations are expected to be observed when its application is sequentially combined with rituximab therapy [271]. Current data regarding the impact of such therapy on the respiratory system are awaited.

Even the backbone in the pathogenesis of SS has a cytokine signature orchestrated by interferon I and II [272, 273], trials on SS of anti-interferon therapies are missing. As compared with lupus trials with this type of treatment modality [274], results of several trials in SS are still pending.

26. Future treatment perspectives for SS-ILD

Two promising antifibrotic drugs, pirfenidone and nintedanib, initially indicated and approved for idiopathic pulmonary fibrosis (IPF), with clear benefits in retarding the annual FVC decline and stabilization, have been recently explored in non-IPF pulmonary fibrotic progressive phenotype. This latter group encompasses different diseases that include sarcoidosis, interstitial pneumonitis, idiopathic NSIP, and unclassifiable idiopathic interstitial pneumonia [275]. Considering this group to share similar pathogenic pathways as in IPF, in that the pulmonary function declines in time along with ominous outcomes, the application of these drugs in this group is reasonable.

Nintedanib, an indoline derivative, has tyrosine kinase inhibitory activity and initially tested as an anticancer drug [276], blocks different profibrotic pathways: fibroblast growth factor receptors, vascular endothelial growth factor receptors, platelet-derived growth factors, and other tyrosine kinases, cytokines and chemokines (CCL18) [277]. With properties to reduce the proliferation and migration of lung fibrocytes and few adverse effects, it has been an effective drug in IPF. Likewise, pirfenidone, a small molecule, a pyridine derivative, inhibits PDGF, transforming growth factor β1 (TGFβ1) [278, 279] and promotes the balance between profibrotic and antifibrotic metalloproteinases [280], in addition to inhibiting proinflammatory cytokines [281].

In the INBUILD trial, 633 patients who had non-IPF progressive fibrosing ILD and that included CTD-ILD patients (i.e., RA patients 89/633, 13%) [282] were tested either with nintedanib or conventional therapy (placebo). Annual FVC showed decreased slope decline in the nintedanib group across all etiologies, including the CTD-ILD group, and without differences even in the UIP-like subgroup [283]. Patients with CTD-ILD group stopped their immune suppressor drugs prior to enrolling in the trial, to avoid confounders [282]. These findings were the ground to establish evidence for nintedanib efficacy in non-IPF progressive fibrosing ILDs independently of the diagnosis, enabling the FDA approval for its use. Even most of the experience falls into patients with SSc-ILD and RA-ILD, based on this evidence, SS-ILD may benefit from nintedanib as well. It is worth to mention the phase III SENSICS trial on 576 patients with SSc-ILD testing nintedanib vs. placebo. Results showed a lower annual rate of decline in FVC (primary endpoint) with nintedanib than with placebo, but with more gastrointestinal adverse events in the nintedanib group [284]. Safety on the use of pirfenidone in SSC-ILD showed similar adverse
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Events as in the placebo group, and moreover, combination of pirfenidone and MMF showed adequate tolerability and safety (LOTUSS trial) [285]. Further ongoing trials will reveal more information regarding safety and efficacy. Similarly, data are pending for RA-ILD and on pirfenidone (TRAIL-1, on phase II trial).

An anecdotal report on SS-ILD with UIP subtype showed promising experience in FVC preservation [286] as single evidence of the experience in SS patients. In this case series, pirfenidone was the applied drug to treat ILD. Again, further studies will reveal much more information on these promising drugs [287].

Until more trials show documented efficacy of the abovementioned regimens, treatment for SS-ILD will be subjected to individual clinical scenarios and physician preferences.

27. Conclusions

Extraglandular expression of SS may encompass many organs, with the respiratory system as one of the most frequently affected systems, carrying significant morbidity. With the lower airways being the most common manifestations in SS, the upper airways may associate with multiple presentations, including sinusitis. The airway disease should be acknowledged to be part of the syndrome, particularly when patients have poor response to therapy and behave differently to bronchial asthma. Airway disease treatment may challenge conventional strategies offered. Although less frequent, ILD may carry most of the main problems. Mortality associates with severe parenchymal disease, shortening life expectations in vulnerable groups (older age, smokers, males, and longer disease duration). Many other parenchymal manifestations are associated with SS such as LIP, amyloidosis, cystic lesions, lymphoma, and pulmonary hypertension and should be contemplated in the differentials. Clinicians should follow up patients with SS keeping in mind that the manifestations of the respiratory system may present at any point in time. Conventional therapies are available with variable results such as mycophenolate mofetil, azathioprine, cyclophosphamide, cyclosporine, and biological therapy. Among the latter, IL-6 inhibitors, costimulatory receptor antagonists, B-cell antagonist therapy, and other cytokine blocker therapy, including interferon blockers, seem to offer promising and safe profiles for the treatment of SS-ILD. New promising antifibrotic therapy (e.g., nintedanib and pirfenidone) will probably change the outcome panorama in SS-ILD. Combination of therapies seems to be an excellent modality to treat difficult cases.
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