Pulmonary Manifestations of Primary Sjögren’s Syndrome

Pralay K. Sarkar1, Nick Patel1, Richard A. Furie2 and Arunabh Talwar1

Departments of Pulmonary Medicine1 and Rheumatology,2 North Shore University Hospital and Long Island Jewish Medical Center, North Shore Long Island Jewish Health System, New York, USA

ABSTRACT

Sjögren’s syndrome (SS) is a complex autoimmune exocrinopathy with multifactorial pathogenesis and multisystem manifestation. It is called primary Sjögren’s syndrome (PSS) when the manifestations are seen without any other co-existent rheumatic diseases. The incidence of respiratory system involvement varies widely in the reported medical literature, partly due to lack of a universal agreement over the diagnostic criteria of the disease and the type of study methods employed. Respiratory system manifestations are protean; upper airway symptoms are very common and so is the complaint of dry cough. The PSS patients may develop interstitial lung diseases (ILDs) such as usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), lymphocytic interstitial pneumonia (LIP), bronchiolitis obliterans and organising pneumonia (BOOP), etc. They may also develop the whole spectrum of lymphoproliferative disorders of the lung ranging from LIP to follicular bronchiolitis, nodular lymphoid hyperplasia and low-grade lymphomas. Therapeutic options include symptomatic and supportive measures and corticosteroids as the mainstay of the treatment for ILDs occurring in these patients. In recent years, rituximab (anti-CD20) has emerged as a promising treatment for this disease, though data from controlled trials are still lacking. Pulmonary involvement may be a source of significant morbidity in these patients, though only rarely, it is the cause of death. [Indian J Chest Dis Allied Sci 2009;51:93-101]

Key words: Primary Sjögren’s syndrome, Non-specific interstitial pneumonia, Lymphoid interstitial pneumonia, Marginal zone B-cell lymphoma, Rituximab.

INTRODUCTION

Sjögren’s syndrome (SS) is an autoimmune exocrinopathy with clinical hallmarks of keratoconjunctivitis sicca and xerostomia. The SS may be classified as primary Sjögren’s syndrome (PSS) or secondary Sjögren’s syndrome (SSS) depending on the co-existence of another rheumatic disease. At least six sets of criteria have been suggested for the diagnosis of SS; however, none are universally accepted and the controversy and disagreement seem to center around whether or not inflammation and auto-immunity should be included in the definition.1 A revised version of the European criteria proposed by the American-European consensus group in 2002 is shown in table 1; a revised rule for classification (table 2) was also proposed by the same group.2

PATHOGENESIS AND PATHOLOGY

Sjögren’s syndrome appear to be a complex autoimmune disease with multifactorial pathogenesis. A genetic predisposition to Sjögren’s syndrome has been suggested on the basis of familial aggregation, animal models and candidate gene association studies.3 Genetic polymorphism of some minor histocompatibility antigens, transforming growth factor-β gene, apolipoprotein E or tumour necrosis factor-α (TNF-α) have been associated with susceptibility, age of onset or some of the systemic involvement of the disease. It has been postulated that in a patient with distinct genetic and hormonal milieu, an environmental trigger factor most likely leads to initial glandular inflammation, disturbed cytokine expression and failed antigen clearance or neoantigen presentation; these in turn, lead to T-cell activation, aberrant B-cell activation with disturbed differentiation, migration and homing, cytokine dysregulation with enhanced proinflammatory cytokines, local and systemic autoimmunity.4 Triantafyllopoulou et al5 recently presented a strong line of evidence implicating A13 and B4 strains of Coxsackie viruses in the induction and maintenance of autoimmunity in PSS. The B-lymphocytes have a pivotal role in the pathogenesis of PSS and B-cell activating factor (BAFF), a member of the TNF superfamily that regulates B-lymphocyte proliferation, maturation and survival has a key role in the B-cell disturbances and malignant complications in PSS.6,7

[Received: June 23, 2008; accepted after revision: September 11, 2008]

Correspondence and reprint requests: Dr Arunabh Talwar, Department of Pulmonary Medicine, North Shore Long Island Jewish Health System, Suite 107, 410 Lakeville Road, New Hyde Park, New York 11040, USA; Phone: 1 516 465 5416; Fax: 1 516 465 5454; E-mail: Arunabht@NSHS.edu and pralay.sarkar@gmail.com
V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following two tests:

Schirmer’s I test, performed without anaesthesia (5mm in 5 minutes)
Rose Bengal score or other ocular dye score (4 according to van Bijsterveld’s scoring system)

IV. Histopathology: In minor salivary gland (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score 1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4mm² of glandular tissue.

V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:

Unstimulated whole salivary flow (1.5mL in 15 minutes)
Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts
Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer

VI. Autoantibodies: presence in the serum of the following autoantibodies:

Antibodies to Ro (SSA) or La (SSB) antigens, or both

Pathologically characteristic changes in salivary glands in Sjögren’s syndrome include focal periductal mononuclear cell infiltrate composed of T- and B-lymphocytes, a loss of acinar cells and relative preservation of ductal cells. Similar autoimmune inflammation of other mucosal surfaces is also seen. Involvement of extra glandular tissues, like kidneys, biliary tree, is predominated by lymphocytic infiltration. Vasculitis may also develop in some patients. Polyclonal B-lymphocyte activation is a key feature and this B-cell hyperactivity in PSS is reflected by circulating hypergammaglobulinemia as well as by a host of antibodies against both ubiquitous autoantigens (Ro/SS-A, La/SS-B, a-fordin) and organ specific autoantigens (islet cell antigen 69, muscarinic receptor M3).

Table 1. Revised International Classification Criteria for Sjögren’s Syndrome

| I. Ocular symptoms: a positive response to at least one of the following questions: |
| Have you had daily, persistent, troublesome dry eyes for more than three months? |
| Do you have a recurrent sensation of sand or gravel in the eyes? |
| Do you use tear substitute more than three times a day? |
| II. Oral symptoms: a positive response to at least one of the following questions: |
| Have you had a daily feeling of dry mouth for more than three months? |
| Have you had recurrently or persistently swollen salivary glands as an adult? |
| Do you frequently drink liquids to aid in swallowing dry food? |
| III. Ocular signs, that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests: |
| Schirmer’s I test, performed without anaesthesia (5mm in 5 minutes) |
| Rose Bengal score or other ocular dye score (4 according to van Bijsterveld’s scoring system) |
| IV. Histopathology: In minor salivary gland (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score 1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4mm² of glandular tissue. |
| V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests: |
| Unstimulated whole salivary flow (1.5mL in 15 minutes) |
| Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts |
| Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer |
| VI. Autoantibodies: presence in the serum of the following autoantibodies: |
| Antibodies to Ro (SSA) or La (SSB) antigens, or both |

Table 2. Revised Rules for Classification of Sjögren’s Syndrome

| For Primary Sjögren’s Syndrome (PSS) |
| In patients without any potentially associated disease, primary SS may be defined as follows: |
| A. The presence of any four of the six items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive. |
| B. The presence of any three of the four objective criteria items (that is, items III, IV, V, VI). |
| C. The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological survey. |

| For Secondary Sjögren’s Syndrome (SSS) |
| In patients with a potentially associated disease (for instance, another well-defined connective tissue disease), the presence of item I or item II plus any two from among items III, IV, and V may be considered as indicative of secondary SS. |

| Exclusion Criteria |
| Past head and neck radiation treatment |
| Hepatitis C infection |
| Acquired immunodeficiency disease (AIDS) |
| Pre-existing lymphoma |
| Sarcoidosis |
| Graft versus host disease |
| Use of anticholinergic drugs (since a time shorter than 4-fold the half-life of the drug) |

Source: Ref. 2

autoantigens (islet cell antigen 69, muscarinic receptor M3).

PULMONARY INVOLVEMENT IN PRIMARY SJÖGREN’S SYNDROME: EVIDENCE IN THE LITERATURE (TABLE 3)

The reported prevalence of pulmonary involvement in SS varies widely in the literature, owing, in part, to a lack of uniform diagnostic criteria. Long-term observational studies evaluating symptomatic pulmonary disease in SS are scant. Coupled with the challenge of distinguish whether existing pulmonary disease stems from SS or a co-existing rheumatic disease, data concerning pulmonary involvement in SS are deficient. In a retrospective study of a community-based cohort of 201 consecutive SS patients from Israel, pulmonary involvement was reported to be present in 15 percent. In a study of 80 Spanish SS patients, pulmonary involvement was more common in those with greater than 10 years of disease. In radiological studies of patients with PSS, pulmonary involvement has been more frequently observed. In an early high resolution computed tomographic (HRCT) study of 30 non-smoking PSS patients, Franquet et al. reported abnormalities in 34% of the patients. It was emphasised that 74% of
this cohort did not have any respiratory symptoms at the time of the radiological studies. The most commonly observed HRCT abnormalities were small airway disease and linear parenchymal opacities. The strength of this study lies in the fact that the study population was recruited from an ambulatory non-smoking population and excluded patients with a history of bronchopulmonary abnormalities unrelated to SS. Subsequently, other radiological studies have shown higher rates of lung involvement in PSS. In a study of 37 PSS patients with normal chest radiographs, Uffmann et al.\(^\text{12}\) reported abnormalities on HRCT in 24 (65%) patients. A retrospective review of HRCT in 24 patients with PSS yielded abnormal scans in 79.2% of patients.\(^\text{13}\)

Correlations between radiological findings and pulmonary function test (PFT) abnormalities have been variable. Uffmann et al.\(^\text{12}\) obtained PFTs in 34 of 37 patients in their study, but observed no correlation between HRCT and PFT results.\(^\text{12}\) In a study of 35 patients who met the European criteria of diagnosis of PSS including positive accessory salivary gland biopsy and had respiratory symptoms, Tauli et al.\(^\text{14}\) described thin-section lung computed tomography (CT) findings and correlated them to an individual’s PFT values. In patients with large and/or small airways disease on CT, obstructive pattern were predominantly found on PFT. A significant correlation was found between scores of air trapping and forced expiratory volume in one second (FEV\(_1\)). Patients with interstitial lung fibrosis and lymphocytic interstitial pneumonitis (LIP) generally had restrictive profile and/or decreased diffusing capacities (DLCO); significant correlation (p<0.01) found between the source of ground-glass attenuation and total lung capacity (TLC) and DLCO.

Sjögren’s syndrome has only rarely been reported from India and from the available literature, it is difficult to ascertain the prevalence of PSS.\(^\text{15,16}\) One possible reason for this rarity may be the lack of awareness of this entity among non-rheumatologists, like dentists, ophthalmologists and internists, who often encounter these patients first, due to the nature of the clinical presentation in this disease.\(^\text{17}\) Lung involvement in Indian patients with PSS has been described in isolated case reports.\(^\text{18}\) Misra et al.\(^\text{17}\) reported a series of 26 PSS patients, diagnosed in the Rheumatology Clinic of a tertiary care hospital over more than 10 years period, out of which 15 patients had definite PSS employing rigorous immunological and histological criteria. None of their patients was reported to have clinical lung disease; however, in the absence of results of PFTs and lung imaging, it is difficult to rule out subclinical pulmonary involvement.

### Upper Airway Manifestation

Symptoms of upper airway involvement are far more common than objective findings in patients with SS. In a retrospective analysis, up to 50% of patients with PSS complained of nasal symptoms, although only 20% had abnormal findings on rhinoscopy.\(^\text{20}\) Epistaxis and sinusitis can occasionally occur as complications. Approximately 60% of patients complained of throat symptoms, although only 20% had abnormal findings on indirect laryngoscopy. Thirty-eight percent of PSS patients had parotid gland symptoms, and 25% had abnormally swollen glands. Parotid gland infection is also a potential complication in these patients.

### Lower Airway Disease

A dry cough of variable intensity may be reported in as many as 50% of patients with SS. As was described in the original report by Henrik Sjögren in 1933, cough is usually attributed to xerotrachea secondary to destruction of bronchial glands by the disease process. However, histological studies often do not support these observations and suggest that the cough may be related to other processes, including lymphocytic infiltration of the bronchial mucosa and submucosa.\(^\text{21}\) About half of the patients with PSS have been shown to have bronchial hyperreactivity (BHR) and intermittent airway narrowing may manifest itself as episodes of cough, dyspnoea and wheezing that might

---

**Table 3. Respiratory manifestations in primary Sjögren’s syndrome**

<table>
<thead>
<tr>
<th>Upper Airways Disease</th>
<th>Lower Airways disease</th>
<th>Lymphoproliferative Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinitis sicca</td>
<td>Xerotrachea-sicca cough</td>
<td>Diffuse lymphoid hyperplasia of the lungs:</td>
</tr>
<tr>
<td>Xerostomia</td>
<td></td>
<td>Follicular bronchiolitis, Lymphoid interstitial pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nodular lymphoid hyperplasia (also known as</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pseudo-lymphoma)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B-cell non-Hodgkin’s lymphoma (commonly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>extranodal marginal zone B-cell lymphomas of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>the bronchus-associated lymphoid tissue)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High-grade malignant B-cell non-Hodgkin’s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lymphoma</td>
</tr>
</tbody>
</table>

**Miscellaneous Pulmonary Manifestations**

- Multiple lung cysts or bullae
- Pulmonary haemorrhage
- Pulmonary amyloidosis
mimic xerotrachea symptoms.22 The BHR has been attributed to the inflammatory infiltrate in the bronchial submucosa with large number of neutrophils, mast cells and lymphocytes and observation of associated increased bronchial epithelial damage and structural change of subepithelium.21 Like many other airway inflammatory diseases, increased amount of nitric oxide has been shown in the exhaled air of PSS patients; the airway epithelial cells or the inflammatory cells in the epithelium may be the source of the increased amount of nitric oxide.24

**Diffuse Parenchymal Lung Diseases**

A wide variety of diffuse proliferative lung diseases have been described in PSS, including the idiopathic interstitial pneumonias and the whole spectrum of pulmonary lymphoproliferative disorders. Since the recognition of non-specific interstitial pneumonitis (NSIP) as a distinct histological category of idiopathic interstitial pneumonias (IIP), two recent histopathological studies25,26 have evaluated the pulmonary pathology of PSS patients presenting with interstitial lung disease (ILD). Ito et al25 retrospectively studied 33 biopsies from multiple centers and found NSIP as the most common histological pattern (20 of 33 cases, 61%). Malignant lymphoma and bronchiolitis were the next most common histological patterns, respectively. In another study25 of 18 patients with PSS and suspected ILD, non-specific interstitial pneumonia (5 patients), organising pneumonia (4 patients), usual interstitial pneumonia (3 patients), and lymphocytic interstitial pneumonia (3 patients) were the four most common histological patterns.

**Non-specific Interstitial Pneumonia (NSIP)**

First proposed by Kitaichi 27 in 1990 as “unclassified interstitial pneumonia”, the definition of NSIP has evolved. It is now recognised as a distinct clinicopathological entity and has been shown to differ from idiopathic pulmonary fibrosis/usual interstitial pneumonia (UIP) with regards to treatment and prognosis.27 In recent histological studies, it has also been recognised as the most common histological pattern in patients with PSS.25,29 Onset of symptoms, which may include breathlessness, cough and fatigue, is insidious. Pulmonary function tests in the majority of cases show a restrictive pattern along with gas transfer abnormalities. The NSIP typically causes bilateral lower zone infiltrates on the chest radiograph. Ground-glass opacity is the predominant finding on HRCT. Irregular reticular or linear opacities may also be observed, but, in general, honey-combing and consolidation are infrequently encountered. Key histological features include mild to moderate chronic interstitial inflammation, type II pneumocyte hyperplasia in areas of inflammation and dense or loose interstitial fibrosis. Lack of any temporal heterogeneity pattern, uniformity of the pathological features and relatively preserved lung architecture as seen with elastic stains, helps to histologically differentiate NSIP from UIP. Ninety-four percent of patients with histological evidence of NSIP had HRCT abnormalities in one study29, however, such a correlation has not been uniformly observed.

**Usual Interstitial Pneumonia**

Early reports found UIP to be a common histological pattern in patients with PSS.25,29 However, more recent reports have challenged the frequency with which UIP complicates PSS perhaps, in part, because of the recent change in the definition and classification of interstitial pneumonias. When occurring in PSS patients symptoms, physical findings, lung imaging, pulmonary function tests and clinical course of UIP are often similar to that in patients with idiopathic pulmonary fibrosis (IPF). The key histological features of the UIP pattern are architectural destruction, fibrosis often with honey-combing scattered fibroelastic foci, patchy distribution, and involvement of the periphery of the acinus or lobule.

**Bronchiolitis Obliterans Organising Pneumonia**

Bronchiolitis obliterans organising pneumonia (BOOP) was described as the second most frequent pathological pattern after NSIP in a recent case series of PSS patients fulfilling the European–American diagnostic classification. As none of the patients in this series received corticosteroids prior to lung biopsy, this might be one reason for the high prevalence of BOOP.25 There are also several case reports of BOOP in PSS, some being complicated by acute respiratory distress syndrome (ARDS) and alveolar haemorrhage.31,32

---

**PULMONARY LYMPHOPROLIFERATIVE DISORDERS**

**Lymphocytic Interstitial Pneumonia**

Lymphocytic interstitial pneumonia (LIP), a component of a spectrum of pulmonary lymphoid proliferative disorders, is the morphological entity that has most consistently been associated with SS. The LIP is an uncommon disease, and SS is the single most common disease entity that has been associated with it. Approximately 0.9% of adults with SS have LIP, and up to 50% of adults with LIP have SS.33-35 The clinical presentation is no different than that observed in patients with diffuse interstitial lung disease; in that most patients have cough, dyspnoea or a combination of both. Weight loss, fever, pleuritic chest pain and arthralgia may also be seen. Basilar rales are the most common physical findings.35 Ground-glass haziness and
Nodular Lymphoid Hyperplasia

Nodular lymphoid hyperplasia, also known as pseudolymphoma, refers to the presence of reactive lymphoid cells in one or more pulmonary nodules or infiltrates. Controversy has surrounded the existence of this condition as some cases of low-grade lymphoid proliferation in lungs have been recognised by others as extra-nodal marginal zone B-cell lymphoma. However, a recent study, using sophisticated immunohistochemical and molecular biology techniques, has confirmed the existence of pulmonary nodular lymphoid hyperplasia. It is infrequently encountered, and the exact relationship with SS is not known. It might be discovered because of an incidental radiological finding in asymptomatic patients, or the patients may be symptomatic with shortness of breath or pleuritic chest pain. The most common radiological finding is a solitary pulmonary nodule or mass. Alternatively, an area of parenchymal consolidation with an air bronchogram may be present. However, multifocal lesions have also been described. In the presence of mediastinal lymphadenopathy or a pleural effusion, a diagnosis of malignant lymphoma should be suspected. Histological evaluation of the lesions reveals numerous reactive germinal centers and a preserved mantle zone.

Pulmonary Lymphomas

Non-Hodgkins lymphoma is an important cause of mortality in patients with SS. In a long-term (greater than 10 years) observational study of patients with PSS, nearly 25% died of malignant lymphomas. Polyclonal B-cell activation, which is seen in the early part of the disease, may transform to a monoclonal B-cell population in some patients. This process may result in mucosa-associated lymphoid tissue (MALT) lymphoma or more uncommonly in high-grade malignant lymphoma. It is a multi-step process in which antigenic stimulation of B-cells and oncogenic events may be important factors. Of those patients who develop lymphoma, nearly half develop it in an extra-nodal site, and the lung is one such extranodal site. In some of these cases, it appears that lymphoma represented a progression from LIP. These primary pulmonary lymphomas are usually low-grade extra-nodal marginal zone B-cell lymphomas (MZCL) of the MALT type.

Clinical presentations of MZCL of the lung are non-specific and may consist of cough, shortness of breath, weight loss, and fatigue; therefore, these symptoms are not helpful in distinguishing lymphoma from other types of lung involvement in patients with SS. Analysis of lung CT scans has revealed the lesions to be randomly distributed with a trend towards a more extensive involvement of the

Centrilobular nodules are almost universally observed on HRCT. Septal thickening, bronchovascular thickening and subpleural nodules, cystic spaces (see Figure) and mediastinal lymphadenopathy are less commonly visualised. The LIP is characterised histologically by a prominent interstitial lymphoid infiltrate that diffusely spreads into alveolar septae. The interstitial infiltrate is rich in lymphocytes with variable numbers of plasma cells. Germinal centers may be seen and scattered multinucleated giant cells or ill-formed granulomas are seen in the lymphoid infiltrates in about half of the cases. The infiltrate is a mixture of B- and T-cells. The B-cells are polyclonal as determined by immunostaining for immunoglobulin light chain. In late stages, LIP can produce advanced interstitial fibrosis and honey-combing. Progression of LIP to pulmonary lymphoma is known but is distinctly rare.

Follicular Bronchiolitis

Follicular bronchiolitis (FB) is another pattern of diffuse lymphoid hyperplasia affecting the lung of the patients with SS. The histological difference between FB and LIP is that former is associated with lymphocytic infiltrates that are peribronchial and include coalescent reactive germinal centers adjacent to airways in the absence of clinical or pathologic evidence of chronic obstructive pulmonary disease or bronchiectasis. It is a disease process resulting from hyperplasia of bronchus-associated lymphoid tissue (BALT), which consists of small lymphoid aggregates along the bronchial tree, especially around the division points and respiratory bronchioles. In patients with PSS follicular bronchiolitis usually co-exists with lymphocytic bronchitis, lymphocytic bronchiolitis, or LIP.
lower lobes. Radiological findings can include: confluent alveolar opacification with peribronchial distribution and air bronchograms; peripheral (usually bilateral) alveolar opacification with or without air bronchograms; micronodules and masses; ground-glass opacities; thin wall cystic spaces.

In histopathological specimen, the predominant pattern of growth is interstitial with prominent involvement of peribronchial-peribronchiolar and perivascular interstitium; in some cases, the lymphocytic infiltrate can spill into the alveolar space and alveolar septa. Histological criteria have been proposed for differentiating malignant infiltration from LIP and pseudolymphoma. These include: invasion of bronchial mucosa and erosion of bronchial cartilage, seeding of parietal pleura, involvement of hilar and bronchial mucosa and erosion of bronchial cartilage, LIP and pseudolymphoma. These include: invasion of bronchial mucosa and erosion of bronchial cartilage, seeding of parietal pleura, involvement of hilar and mediastinal lymph nodes; absence of lymphoid germinal centers; and the presence of mitotic figures. However, other criteria have also been proposed, which incorporate the fact that nodal involvement is uncommon even in MZCL. Immunohistochecmical studies show that the majority of lymphocytes are of a B-cell phenotype. Lymphoepithelial lesions, which are epimyoepithelial islands with surrounding halo-like mononcytoid cells, have been thought to be the origin of lymphomas in patients with SS, and in case of salivary glands, the epithelial component of these histological lesions originate from the ductal cells. In the MALT lymphoma of lungs in patients with SS, the existence of a similar epithelial component is proven by a positive staining with cytokeratin antibodies. Monoclonal immunoglobulin light chain can also be demonstrated in these lesions signifying a transition of polyclonal B-cell activation to monoclonal B-cell proliferation during the process of development of lymphoma. The MALT lymphoma can occasionally progress to a high-grade malignant lymphoma.

**Pulmonary Artery Hypertension**

Pulmonary arterial hypertension (PAH) in the absence of any other significant lung disease in PSS patients has been reported in a few cases. There is a paucity of literature regarding pulmonary vascular pathology in this condition given the rarity of PAH, the relative lack of importance that pathology contributes to management and the reported hazards of VATS lung biopsies in patients with pulmonary hypertension. The histopathology of PAH in association with rheumatic diseases is generally indistinguishable from that found in idiopathic PAH. The pathogenic mechanisms involved in PAH associated with PSS remain unclear. The development of PAH may be mediated by prolonged vasospasm and structural vessel remodelling which lead to irreversible and fixed narrowing of pulmonary arterioles and thrombotic obstruction.

**OTHER PULMONARY MANIFESTATIONS**

Several other manifestations have occasionally been reported in PSS. Cases have been described where HRCT has revealed multiple bullae and pathology has revealed thickening of alveolar septae as well as mononuclear cell infiltrates. The authors suggested that the development of bullae might be related to small airway obstruction secondary to follicular bronchiolitis or LIP. Acute pulmonary haemorrhage as part of a pulmonary-renal syndrome related to cryoglobulinemic vasculitis has been described as a rare manifestation in PSS. Pulmonary amyloidosis, with or without pulmonary lymphoproliferative disease, has also been described in patients with PSS.

**TREATMENT AND PROGNOSIS**

Primary Sjögren’s syndrome usually runs a slow course but sometimes can progress at faster rates, especially if complicated by extra glandular involvement or the development of lymphoma. Treatment of SS has focused on control of sicca symptoms. Therefore, simple steps to minimise loss and/or to replace moisture are often employed. Sinusitis should be treated with antibiotics and if indicated with surgical drainage. Dry cough due to large airway involvement is treated with normal saline nebulisations; high doses of bromhexine might be tried, although its efficacy is questionable. Corticosteroids and other immunosuppressive agents are not typically used for the more common manifestation of SS given their toxicity and inability to reverse sicca symptoms. However, corticosteroids are the most widely used treatment for follicular bronchiolitis, LIP and BOOP. In patients with UIP and NSIP low-dose corticosteroids and azathioprine are usually recommended. The optimal treatment of extra-nodal MZCL of lung remains unclear in the absence of prospective studies. In localised disease, surgery alone or with chemotherapy can be used. In extensive unilateral or bilateral disease, single or multiple drug chemotherapeutic regimens have been used. Oxaliplatin as monotherapy or fludarabine-containing chemotherapy are promising therapeutic regimens for these patients. The treatment of PAH in patients with PSS or other rheumatic diseases may follow a similar algorithm to that found in idiopathic PAH patients.

In recent years, the development of agents that target cells, molecules and receptors implicated in the aetiopathogenesis of PSS have created opportunities to test these therapies in SS. Some potential future therapies are shown in table 4.

Experience with biological agents in PSS has been gained from open-label studies, Phase I/II studies, or off-label use. Therefore, reports of efficacy of these agents in lung disease associated with PSS have been anecdotal. Optimism regarding the possible efficacy of biologics also
emanates from the experiences in other rheumatic diseases, such as rheumatoid arthritis, systemic lupus erythematosus (SLE) and psoriasis. Of the approved biologic therapies, rituximab (anti-CD20) has emerged as a promising treatment for PSS. Since B-cells are believed to play a role in the pathogenesis of PSS, investigation of the use of a B-cell depleting therapy is warranted. Three recent studies with an open-label design as well as several case reports have shown promising results with rituximab in PSS patients with various extra glandular manifestations. Secor et al. included a couple of patients with refractory pulmonary disease in their series of 18 PSS patients with various systemic manifestations, most of whom received prior immunosuppression without a satisfactory response. One patient with pleural effusion and pulmonary infiltrates responded to rituximab with complete resolution; in the second patient, dyspnea and cough due to LIP disappeared. Both the patients received four infusions of rituximab without any concomitant immunosuppressive therapy. Satisfactory responses were maintained at 17-month follow-up with the first patient and at 12-month follow-up with the second patient. Encouraging response was also seen in treating refractory polyosinovitis, peripheral neuropathy and renal involvement. Majority of the patients tolerated rituximab well without any serious adverse effects. Rituximab has been successfully used in PSS patients with B-cell lymphomas with or without chemotherapy and may emerge as a first therapeutic choice for some PSS patients with indolent B-cell lymphomas. Among the anti-cytokine agents, infliximab was studied in a double-blind, placebo-controlled multi-center trial that included 103 PSS patients. Infliximab was no more effective than placebo in improving joint pain, fatigue and dryness symptoms. It was also not effective in improving the number of swollen and tender joints, basal salivary flow, Schirmer’s test results, focal score in labial salivary gland biopsy and levels of various inflammatory markers and presence of autoantibodies. This study did not report specifically about the efficacy or lack of efficacy of infliximab in pulmonary manifestations of PSS. Results with etanercept in PSS have also been disappointing. Thus, the general opinion is that TNF inhibitors have no role in the treatment of patients with PSS. The T-cell targeted therapies (efalizumab, abatacept, alefacept) might be considered for clinical trials in patients with PSS.

The overall prognosis of PSS patients with or without lung involvement remains favourable. A recent prospective study did not find an increased all-cause mortality in patients with PSS compared with the general population. Lung disease in SS progresses slowly, and death from respiratory failure is distinctly rare. There is a unique subgroup of patients with PSS who over time sustain further lymphocytic organ damage or develop cancer. Presence of hypo-complementemia and/or cryoglobulins at diagnosis has been associated with poorer prognosis and lymphoma development. Treatment typically consists of agents that provide symptomatic relief of sicca symptoms, but in cases with severe organ involvement or lymphoma, corticosteroids, immunosuppressants, chemotherapy, or biologic therapies might be utilised.

### REFERENCES

9. Friedman JA, Miller EB, Green L, Huszar M, Schatter A. A community based cohort of 201 consecutive patients with primary SS...
Pulmonary Manifestations of Primary Sjögren's Syndrome

P.K. Sarkar et al


American Thoracic Society/ European Respiratory Society


