Pulmonary Manifestations of Systemic Lupus Erythematosus: Global and Saudi Arabian Populations

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ABSTRACT

This paper reviews the pulmonary manifestations of systemic lupus erythematosus with particular focus on comparing global and Saudi Arabian populations. Dozens of articles addressing lupus complications in Saudi patients were published in recent years; to our knowledge, this is the first review focusing on pulmonary complications. In this narrative literature review, we conducted a systematic search of MEDLINE and Google Scholar using the words pulmonary complications of systemic lupus in Saudi Arabia. The search covered the period between 2000 and 2019. We found that the rate of pulmonary complications in Saudi lupus patients was consistent with that in global patients; exceptionally higher incidence of acute lupus pneumonitis was reported in Saudi patients. We hope that this study will inform clinicians about the important points regarding pulmonary complications in lupus patients, particularly in the Saudi population.

Keywords

Systemic lupus erythematosus; Pleural disease; Interstitial lung disease; Acute lupus pneumonitis; Diffuse alveolar hemorrhage; Pulmonary hypertension; Thromboembolic disease; Pulmonary infection.


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INTRODUCTION:
Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the development of autoantibodies which attack body organs. It is a recognized worldwide disease with significant mortality and morbidity. The female to male ratio in Saudi Arabia is 9.8:1, which is similar to that for Europeans and higher than that for African Americans[5]. The prevalence of SLE in Asia ranges between 50-70 per 100,000, with higher prevalence in China (70/100,000) [2]. The prevalence in Saudi Arabia is estimated at 19.28/100,000 based on a survey study in the Qassim region only[3]. In the Saudi population, HLA-DRB1*15 haplotypes were found to be associated with SLE, while HLA-DRB1*16 was protective[4].

Pulmonary diseases related to SLE are reported in 30-60% of the cases worldwide, and include lung consolidation, pleural diseases, pulmonary vascular diseases, pulmonary hypertension, pulmonary hemorrhage, atelectasis, shrinking lung syndrome, ground glass opacities, pneumonitis and bronchiolitis obliterans[5]. There is a strong association between high anti double stranded DNA (anti-dsDNA), low complement levels, and pulmonary involvement in lupus patients, but there is no significant difference in mortality among patients with and without pulmonary diseases[6]. In this review, we conducted a systematic search of MEDLINE and Google Scholar using the words pulmonary complications of systemic lupus in Saudi Arabia and we included the relevant literature about the topic (Table 1). We aim to discuss the presentation and differential diagnosis of pulmonary diseases related to SLE, particularly among the Saudi population.

PULMONARY DISEASES
Among Saudi lupus patients with pulmonary involvement, the most common presenting complaints are fever, cough, pleurisy, dyspnea, hemoptysis and palpitations[2].

Pleural Diseases
Pleurisy (defined as chest pain with inspiration and cough) and pleural effusions are the most common pulmonary involvement in SLE. Pleural effusions are usually bilateral and small to moderate in size. However, large effusions were also reported[9]. Alamoudi and Attar[6], studied 184 SLE patients in the western region of Saudi Arabia and found that 61 (33%) had pleural disease. Pleural effusion was identified in 49% of them and this was bilateral in 60% of the cases. This result is similar to rates seen in international studies[6]. In another large prospective study of 113 lupus patients, 63 (56%) had pleural effusion detected by high resolution computed tomography, and some of them presented with massive effusions[9]. Isolated pleural effusion is a nonspecific finding, therefore thoracentesis is recommended. Typically in SLE the effusion is exudative with lymphocytic or neutrophilic predominance, low glucose, low pleural fluid complements and positive antinuclear antibody[6].

Chronic Interstitial Lung Diseases:
The most common types of interstitial lung disease (ILD) seen in connective tissue diseases include nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organizing pneumonia (OP), lymphocytic interstitial pneumonia, acute interstitial pneumonia (AIP), and rarely desquamative interstitial pneumonia[11]. Systemic lupus erythematosus is usually associated with NSIP, UIP, OP, and AIP. The clue to the diagnosis is the presence of clinical features of lupus and a positive serology[11]. The most common form of ILD associated with lupus is NSIP, which is usually asymptomatic, although some patients may present with insidious onset of dyspnea, exercise intolerance and dry cough. Physical examination reveals fine inspiratory crackles[12]. The presence of antinuclear antibody and anti-dsDNA does not reflect severity of ILD but it is helpful to confirm the diagnosis of lupus. This data was based on a study of 348 mostly Caucasian patients[11]. In contrast, high C-reactive protein and hypocomplementemia reflect the severity of ILD but do not help in the diagnosis[11]. In Saudi patients, two studies support the relation between the severity of ILD and the high anti-dsDNA and hypocomplementemia[6,9]. High-resolution computed tomography of the chest may show diffuse ground glass opacities, diffuse interstitial infiltrates, sepal thickening, traction bronchiectasis, and honeycombing[6]. There are no clear guidelines for ILD screening using high resolution computed tomography in lupus patients[6].

Acute Lupus Pneumonitis
Acute lupus pneumonitis is an uncommon complication of lupus, with a prevalence of 2-8%[14]. In two studies in the Saudi population involving 624 and 184 patients, the incidence of acute lupus pneumonitis was 1.6% and 20% respectively[2,6]. The different study population and the different methods used to define lupus pneumonitis might explain the variation observed between the two studies[1,6]. Alamoudi and Attar[6] used CT chest to define lupus pneumonitis whereas there is no clear information about the definition of lupus pneumonitis in the other study. This possibly explains the higher prevalence of lupus pneumonitis in Alamoudi and Attar[6] study. Patients with lupus pneumonitis usually present with fever, cough, dyspnea, and hemoptysis. Physical examination reveals decreased oxygen saturation and inspiratory crackles. Chest X-ray could reveal diffuse alveolar infiltrations, pleural effusion, and consolidation. High-resolution computed tomography findings include diffuse ground glass opacification and consolidations. The diagnosis of this condition is based on the exclusion of infections, pulmonary edema, and alveolar hemorrhage. Lung biopsy occasionally can be performed and the histopathology reveals diffuse...
TABLE 1.
Summary of included studies done on systemic lupus erythematosus patients in Saudi Arabia

<table>
<thead>
<tr>
<th>Author/Reference</th>
<th>Year of Publication</th>
<th>Design</th>
<th>No. of Patients</th>
<th>Prevalence of Pleural Diseases</th>
<th>Prevalence of ILD</th>
<th>Prevalence Acute Lupus Pneumonitis</th>
<th>Diffuse Alveolar Hemorrhage</th>
<th>Pulmonary Hypertension</th>
<th>VTE</th>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamdani et al[9]</td>
<td>2017</td>
<td>Prospective cross-sectional study</td>
<td>113</td>
<td>49.6%</td>
<td>NSIP 30 UIP 14% OP 15%</td>
<td>11.5%</td>
<td>14.2%</td>
<td>20.4%</td>
<td>27.4%</td>
<td>12.4%</td>
</tr>
<tr>
<td>Hamdani et al[7]</td>
<td>2015</td>
<td>Cross-sectional study</td>
<td>96</td>
<td>41.8%</td>
<td>NSIP 30 UIP 14% OP 15%</td>
<td>15.5%</td>
<td>8.6%</td>
<td>15.5% Based on ECHO</td>
<td>3.4%</td>
<td>43.1%</td>
</tr>
<tr>
<td>Alamoudi and Attar[6]</td>
<td>2015</td>
<td>Retrospective study</td>
<td>184</td>
<td>58%</td>
<td>NSIP 30 UIP 14% OP 15%</td>
<td>15.5%</td>
<td>8.6%</td>
<td>15.5% Based on ECHO</td>
<td>3.4%</td>
<td>43.1%</td>
</tr>
<tr>
<td>Abid et al.[8]</td>
<td>2013</td>
<td>Retrospective study</td>
<td>46</td>
<td>6.5%</td>
<td>NSIP 30 UIP 14% OP 15%</td>
<td>15.5%</td>
<td>8.6%</td>
<td>15.5% Based on ECHO</td>
<td>3.4%</td>
<td>43.1%</td>
</tr>
<tr>
<td>Al Arfaj et al.  [1]</td>
<td>2009</td>
<td>Retrospective study</td>
<td>624</td>
<td>15.8%</td>
<td>NSIP 30 UIP 14% OP 15%</td>
<td>15.5%</td>
<td>8.6%</td>
<td>15.5% Based on ECHO</td>
<td>3.4%</td>
<td>43.1%</td>
</tr>
<tr>
<td>Heller et al.[22]</td>
<td>2007</td>
<td>Retrospective study</td>
<td>93</td>
<td>19%</td>
<td>NSIP 30 UIP 14% OP 15%</td>
<td>15.5%</td>
<td>8.6%</td>
<td>15.5% Based on ECHO</td>
<td>3.4%</td>
<td>43.1%</td>
</tr>
<tr>
<td>Alzeer et al.</td>
<td>2004</td>
<td>Prospective Cohort study</td>
<td>48</td>
<td>N/A</td>
<td>NSIP 30 UIP 14% OP 15%</td>
<td>15.5%</td>
<td>8.6%</td>
<td>15.5% Based on ECHO</td>
<td>3.4%</td>
<td>43.1%</td>
</tr>
<tr>
<td>Gari et al.[8]</td>
<td>2002</td>
<td>Retrospective study</td>
<td>65</td>
<td>4.6%</td>
<td>NSIP 30 UIP 14% OP 15%</td>
<td>15.5%</td>
<td>8.6%</td>
<td>15.5% Based on ECHO</td>
<td>3.4%</td>
<td>43.1%</td>
</tr>
</tbody>
</table>

ILD: Interstitial lung disease; NSIP: Nonspecific interstitial pneumonia; UIP: Usual interstitial pneumonia; OP: Organizing pneumonia; VTE: Venous thromboembolism; ECHO: Echocardiogram; N/A: Not available.
alveolar damage in most cases\[8\]. Bronchoalveolar lavage is helpful to exclude infectious causes and diffuse alveolar hemorrhage\[9\].

**Diffuse Alveolar Hemorrhage**

Diffuse alveolar hemorrhage is a rare complication of lupus with a prevalence of 2-5.4%, but it can be the initial presentation of the disease. Diffuse alveolar hemorrhage is a serious complication of lupus with a mortality rate of about 50%, usually associated with lupus nephritis\[8\]. In a study conducted in Saudi Arabia involving 624 lupus patients, six died from pulmonary hemorrhage\[11\]. The clinical presentation includes: fever, dyspnea, and hemoptysis. Hemoptysis is only present in 50% of the cases\[8\]. In patients with hemoptysis two features suggest significant disease: a hematocrit drop in the first 12-36 hours and an unexplained increase in the diffusing capacity of carbon monoxide\[16\]. High-resolution computed tomography findings include pulmonary hemorrhage characterized by patchy infiltration and consolidation in 2-5.4% of the cases in international studies, compared to 14.2% in the Saudi population\[8\]. Bronchoscopy and bronchoalveolar lavage will reveal a hemosiderin stained macrophage and help to exclude infectious causes. Surgical lung biopsy is rarely required\[8\].

**Pulmonary Hypertension**

Pulmonary hypertension is defined as a mean pulmonary artery pressure ≥ 25mmHg at rest as assessed by right cardiac catheterization. It is well known that SLE patients can develop PH at any point of time, usually in the first five years of their illness. The prevalence of PH in SLE is between 0.5-43% which is less than the prevalence in systemic sclerosis patients\[17\]. Several studies conducted in Saudi Arabia reported that about 15-20% of Saudi lupus patients have pulmonary hypertension, the diagnosis of which was based on echocardiogram (ECHO)\[8,18\]. SLE is commonly associated with class I pulmonary arterial hypertension, while left heart disease (class II), interstitial lung disease (class III), and chronic thromboembolic disease (class IV) have been reported in a minority of cases\[19\]. Patients with Raynaud’s phenomena and SLE have a 75% risk of developing PH, as compared to a 30% risk in those without Raynaud’s\[20\].

The pathogenesis of pulmonary arterial hypertension in lupus patients involves several factors such as proliferation, remodeling and inflammation of the vessel wall, vasoconstriction, and thrombosis. Endothelial dysfunction leads to an imbalance between vasoconstrictors and vasodilators. These factors lead to tissue injury and inflammation resulting in pulmonary arterial hypertension. Other than pulmonary arterial hypertension, the etiology of PH in SLE includes interstitial lung disease, thromboembolism, and cardiac involvement\[19\]. Clinically, the patient presents with dyspnea, chest pain, fatigue and lower limb swelling. Physical examination findings include a loud second heart sound, high jugular venous pressure, tricuspid and/or pulmonary regurgitation, and lower limb edema\[8\].

There are no guidelines to screen for pulmonary hypertension in asymptomatic lupus patients. The most useful screening method is ECHO to measure the right ventricular systolic pressure and assess for tricuspid regurgitation, which is usually found in 30% of asymptomatic patients\[8\]. Pulmonary function testing adds value to PH screening in lupus patients, as a DLCO <60% with the absence of underlying interstitial lung disease is suggestive of early pulmonary hypertension\[8,19\].

The gold standard modality to diagnose PAH is right cardiac catheterization, with an increase in mean pulmonary artery pressure 25mmHg at rest, pulmonary capillary wedge pressure 15mmHg, and pulmonary vascular resistance 240 dynes/sec/cm\[5\]. There are several predictors of pulmonary hypertension in SLE, including antiphospholipid syndrome, positive lupus anticoagulants, positive anti-smith antibody, black race, anticardiolipin antibody and Raynaud’s phenomena\[19\].

**Thromboembolic Disease**

Worldwide, the incidence of thromboembolic disease in lupus patients is about 9% and 45% in those patients with positive antiphospholipid serology. The incidence of pulmonary embolism among Saudi patients ranges from 2.6%-7%, and is also reported as a cause of early death among those patients\[1,6,22\]. In a study involving 113 Saudi patients, pulmonary embolism was reported in 31 (27.4%) patients and was highly associated with positive anticardiolipin antibodies, lupus anticoagulants and beta-2 glycoprotein\[8\]. Thromboembolic disease can be classified into acute and chronic. The acute presentation is deep venous thrombosis and pulmonary embolism, (PE), while the chronic type is a chronic thromboembolism which eventually leads to pulmonary hypertension\[19\].

**Infectious Complications:**

Infection is a major factor in the mortality and morbidity of lupus patients. In the European lupus cohort, the incidence of infection is about 36% with 30% mortality in the first five years\[21\].

Acute pulmonary infections associated with SLE are indistinguishable from lupus pneumonitis and diffuse alveolar hemorrhage. Early diagnosis depends on proper imaging; isolation of the organisms and sometimes bronchoscopy is required. Systemic lupus erythematosus patients, especially those on immunosuppressive treatment, are susceptible to bacterial, fungal, mycobacterial, and viral infections in decreasing frequency. This variability is related to local epidemics and the type of immunosuppressive treatment\[8\]. The risk factors for infection were demonstrated in a retrospective study of 173 patients with lupus, and include: duration of the disease, low complements, leukopenia, high disease activity, high doses of steroids or other immunosuppressive treatment,
low albumin levels, and high erythrocyte sedimentation rate and C-reactive protein\(^\text{24}\). C-reactive protein and procalcitonin are higher in those with pulmonary bacterial infections compared to those without infections, as demonstrated in a retrospective study of 117 Chinese lupus patients\(^\text{25}\).

Mycobacterial infections are common in lupus patients and the incidence is variable based on the country local epidemics and the type of immunosuppressive treatment. In India the risk of mycobacterial infection is 60-fold higher in lupus patients compared to the normal population, while in China it is about 15-fold higher. In Saudi Arabia the incidence of tuberculosis (TB) is about 8% based on a study of 117 lupus patients\(^\text{6}\). There are no clear guidelines for TB screening in lupus patients but results from several retrospective studies showed a significant number of active and latent TB cases, especially in endemic countries\(^\text{26,27}\).

Screening for latent TB in Lupus patients can be done using either the tuberculin skin test or interferon gamma release assays. The tuberculin skin test is reader dependent and it can be falsely negative in lupus patients due to immunity dysregulation or previous bacillus Calmette–Güérin vaccine. However, QuantiFERON (QIAGEN N.V., Viento, Netherlands) gamma levels are more accurate in this group of patients\(^\text{27}\). Belimumab (Benlysta) (GlaxoSmithKline plc., Brentford, London, United Kingdom) is a targeted, human monoclonal antibody that binds to soluble B lymphocyte stimulator (BLyS). It is approved for the treatment of lupus patients, and the initiation of this medication does not require TB screening\(^\text{28}\). There are no clear data on the use of prophylactic antibiotics such as sulfamethoxazole / trimethoprim in lupus patients to prevent serious infections such as pneumocystis, and further studies are required to assess efficacy\(^\text{29}\).

**CONCLUSION**

Systemic lupus erythematosus is an autoimmune disease associated with pulmonary complications in 30%–60% of the patients. Exudative pleural effusion is the most common complication. Rates of interstitial lung disease in Saudi lupus patients are similar to those seen in other international studies. Nonspecific interstitial pneumonia is the most common type and it correlates with disease activity. The incidence of acute lupus pneumonitis is higher among Saudis compared to international patients (20% and 8%, respectively). There are no studies on the prevalence or incidence of pulmonary hemorrhage among Saudi lupus patients. The incidence of pulmonary hypertension among Saudi lupus patients is consistent with rates in international studies, and group 1 PAH is the most common subtype. However, the incidence of pulmonary thromboembolic diseases in Saudi patients is lower compared to international studies. The studies conducted in Saudi Arabia among SLE patients are limited to the experience of a few centers and may not reflect the actual country-wide patient numbers and disease complications.

A national and multiple center collaboration is needed to study this group of patients.

**Conflict of Interest**

The authors have no conflict of interest.

**Disclosure**

The authors did not receive any type of commercial support either in the form of compensation or finances for this study. The authors have no financial interest in any of the products devices, or drugs mentioned in this article.

**Ethical Approval**

Obtained.

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مضاعفات مرض الذئبة الحمراء على الجهاز التنفسي: دراسة تتضمن مقارنة مرضى المملكة العربية السعودية بمرضى دول أخرى

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المتخصّص.

يعتبر مرض الذئبة الحمراء أحد الأمراض الروماتيزمية الناتجة عن نشاط مفرط في الجهاز المناعي، والذي يؤثر بدوره على أعضاء الجسم، ومنها على سبيل المثال لا الحصر: القلب والكلى والجلد والجهاز التنفسي، وتهتف هذه الدراسة إلى توضيح النتائج المتعلقة بمضاعفات مرض الذئبة الحمراء على الرئتين والجهاز التنفسي، من خلال إجراء استقصاء للمقالات العلمية المنشورة في هذا المجال، كما تتضمن هذه الورقة قراءة مستقبلا لمضاعفات هذا المرض على الجهاز التنفسي وخصوصا مرضى المملكة العربية السعودية، ومقارنتهم بدول أخرى.