LUNG INVOLVEMENT IN SLE

INTRODUCTION

SLE (Systemic lupus erythematosus) is a multisystem autoimmune disorder which has a waxing and waning course. The clinical manifestations of SLE are variable. They include erythematous photosensitive malar rash, oral ulcers, non-erosive polyarthritis/ polyarthralgias, polyserositis, immune-mediated cytopenias, renal, neurologic, pulmonary and cardiac abnormalities, depending on the organs involved. The diagnosis of SLE is not only difficult, but can often pose challenges due to the insidious onset of non-specific constitutional symptoms like low grade fever, fatigue and malaise. SLE commonly affects females of the reproductive age-group with a female: male ratio being 9:1. However, lung involvement in SLE can be seen more commonly in males. SLE can affect any organ at any stage, during the course of the disease, but the lungs are relatively involved late. However sometimes, lung involvement can be the presenting feature of SLE in the form of pleuritis, pleural effusion, lupus pneumonitis or interstitial lung disease (ILD).

The pattern of lung involvement in SLE is listed in Table 1.

Since the initial non-specific features of low grade fever, fatiguability, malaise, reduced appetite are common in SLE and TB; most of the Indian patients of SLE with pleural effusion are invariably initially wrongly labelled as tuberculous pleural effusion and started on antituberculous treatment. When there is no improvement or response to therapy, only then other diagnoses are considered. Finding the true prevalence of lung involvement may be difficult due to the higher rate of respiratory tract infections.

<table>
<thead>
<tr>
<th>Table 1: Lung involvement in SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural Diseases</td>
</tr>
<tr>
<td>Pleuritis</td>
</tr>
<tr>
<td>Pleural Effusion</td>
</tr>
<tr>
<td>Parenchymal lung disease</td>
</tr>
<tr>
<td>Acute lupus pneumonitis</td>
</tr>
<tr>
<td>Chronic lupus pneumonitis (Chronic Interstitial lung disease)</td>
</tr>
<tr>
<td>Shrinking lung syndrome (SLS)</td>
</tr>
<tr>
<td>Diffuse alveolar hemorrhage (DAH)</td>
</tr>
<tr>
<td>Adult respiratory distress syndrome (ARDS) or Acute lung injury (ALI)</td>
</tr>
<tr>
<td>Pulmonary Vascular Disease</td>
</tr>
<tr>
<td>Pulmonary Hypertension (PH)</td>
</tr>
<tr>
<td>Pulmonary thromboembolism</td>
</tr>
<tr>
<td>Acute reversible hypoxemia</td>
</tr>
<tr>
<td>Airway Disease</td>
</tr>
<tr>
<td>Pulmonary Infections</td>
</tr>
<tr>
<td>Drug induced lung disease</td>
</tr>
</tbody>
</table>
**Epidemiology and Risk Factors**

In a person who is genetically susceptible to develop SLE, multiple environmental factors such as air pollution, smoking, exposure to toxins and gases and infections can act as triggers to develop the clinical features of SLE. Tissue chimerism also plays an important role in producing lung disease in SLE.1

**Clinical Features, Investigations and Treatment of Individual Lung Problems Seen in SLE**

1. Pleural Involvement

Serositis is one of the diagnostic ACR (American College of Rheumatology) criteria for SLE. Amongst all the connective tissue disorders, pleural involvement is most commonly seen in SLE. Approximately 30-50% of patients with SLE develop symptomatic pleural inflammation in the form of pleurisy 2 manifesting as sharp prickling type of chest pain aggravated on deep breathing or can present with shortness of breath (pleural effusion). Pleuritis can be the initial manifestation of SLE in 5-10% of patients. 3 Pleural effusion is usually bilateral, may be asymptomatic and picked up incidentally on ultrasonography of thorax. The pleural fluid is exudative in nature consisting of neutrophils or lymphocytes, low glucose and low complement levels. The effusions may heal spontaneously without any residual damage or cause pleural thickening leading to chronic breathlessness.

Non-steroidal anti-inflammatory drugs (NSAID’s) like Indomethacin 25-50 mg tds for 14-28 days or Ibuprofen 600mg tds or any other NSAID’s for 2-4 weeks are the mainstay of treatment of symptomatic pleural inflammation. Occasionally low dose steroids 5-10 mg/day for 4-6 weeks may be required. Recurrent or refractory effusions are treated with high doses of corticosteroids 0.5-1 mg/kg/day orally for 4-6 weeks with tapering of doses every 2 weeks with addition of immunosuppressants like cyclophosphamide, mycophenolate mofetil or azathioprine. Pleurodesis may be required for large and recurrent effusions.

2. Parenchymal lung disease:

A. Acute lupus pneumonitis:

It mimics pneumonia, as the presenting features of fever, dyspnoea, cough and sometimes hemoptysis are commonly seen in both these conditions. Clinical examination reveals bilateral basal crepitations. Arterial blood gas (ABG) analysis and pulse oximetry shows hypoxia. X ray Chest shows bilateral lower zone alveolar pulmonary infiltrates, with or without pleural effusion (Fig. 1).

Although this condition is rare, seen in 1-12% of patients, it is one of the dreadful complication of SLE.4,5 It usually occurs with multiorgan involvement. Sometimes it may be the initial manifestation of SLE and the diagnosis may be difficult unless suspected. Bronchoalveolar lavage (BAL) may be helpful in differentiating infection from lupus pneumonitis. An abnormal interstitial pattern of ground glass appearance or honeycomb appearance is seen on HRCT Thorax.

Acute lupus pneumonitis should be treated with high doses of corticosteroids 1-1.5 mg/kg/day orally for 6 weeks once infection is ruled out. In patients who respond inadequately to oral steroids, pulse methylprednisolone 1 gm/day for 3 days intravenously (IV) with Cyclophosphamide IV followed by oral steroids should be considered. Refractory lupus pneumonitis can be treated with rituximab.6

B. Chronic lupus pneumonitis (Chronic ILD or interstitial pneumonitis):

It is also called fibrotic lupus pneumonitis and is seen in 3-13% of patients of SLE with long standing disease.7,8 The symptoms of chronic lupus pneumonitis are insidious in onset. Gradually progressive exertional dyspnoea, dry cough and recurrent episodes of pleurisy are the characteristic features. Occasionally ILD may appear following an episode of acute lupus pneumonitis. Bibasal Velcro crepitations can be auscultated. X ray Chest may be normal or may show reticulonodular shadows or honeycombing with or without pleural disease. HRCT thorax is useful in determining whether active alveolitis in the form of ground glass appearance is seen (Fig.2) (which needs treatment) or there is presence
Lung Involvement in SLE

of fibrosis (which does not need treatment) (Fig.3). Gallium 67 scan of lungs may be useful in differentiating active from inactive disease. Pulmonary function test (PFT) shows restrictive pattern with reduced lung volumes and reduced diffusing capacity for carbon monoxide (DLCO).

The most common pathologic patterns are nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP) and lymphocytic interstitial pneumonia (LIP). LIP simulates a lymphangitic pulmonary malignancy. But this lesion is associated with active disease and responds well to steroids.

Chronic ILD in SLE is more common than it is seen on plain X rays. A study by Bankier et al identified 38% patients with CT abnormalities who had normal X rays. These findings correlated with the disease duration and decreased single-breath diffusing capacity for carbon monoxide. Asymptomatic patients do not need any therapy. Symptomatic patients respond well to oral steroids. Some patients may need immunosuppressants like cyclophosphamide, azathioprine and mycophenolate mofetil in addition to steroids.

C. Shrinking lung syndrome (SLS):

It is called as shrinking or “vanishing” lung syndrome. It is a condition seen in patients of SLE who have unexplained dyspnoea, small lung volumes with restrictive pattern on PFT in the absence of ILD and bilaterally elevated domes of diaphragm on chest X-rays. These patients present in the late stages of lupus with increasing dyspnoea. The postulated mechanism consists of intercostal muscle weakness or diaphragmatic weakness resulting from an inflammatory myopathy or phrenic neuropathy. Acute and chronic SLS have been described in literature. In a post mortem study done by Rubin et al, the diaphragm in a patient of SLS in late lupus was fibrotic and thinned. Apart from corticosteroids and immunosuppressants, rituximab is also an effective therapy for symptomatic SLS. Theophylline is useful in improving diaphragmatic strength. Residual diaphragmatic weakness may require surgical diaphragmatic pllication.

D. Diffuse alveolar hemorrhage (DAH):

It is a life-threatening complication of SLE presenting as cough, hemoptysis and dyspnoea which occur acutely. Alveolar hemorrhage is a result of pulmonary vasculitis. It usually occurs in the setting of active lupus nephritis or other organ involvement. The differential diagnoses include ANCA associated vasculitis, Churg Strauss syndrome, anti GBM disease, thrombotic thrombocytopenic purpura (TTP) and other coagulopathies. It may be a marker of DIC in the setting of infection and sepsis. BAL is usually helpful in ruling out infection and BAL can

Fig. 2 : HRCT Thorax suggestive of ground glass appearance in acute lupus pneumonitis

Fig. 3 : HRCT thorax showing bilateral fibrosis suggestive of chronic ILD
demonstrate the presence of persistently bloody fluid with hemosiderin-laden macrophages to confirm DAH. 21 X Ray Chest shows bilateral alveolar infiltrates (Fig. 4) and HRCT Thorax shows bilateral alveolar haemorrhages (Fig. 5). There is a sudden drop in hematocrit and increased DLCO. Lung biopsy in DAH may show capillaritis with immune complex deposition or bland haemorrhages. DAH is treated with high doses of steroids and cyclophosphamide.

Plasmapheresis proves to be beneficial in improving survival in DAH. Despite aggressive and timely therapy, the chances of survival are poor. There are anecdotal case reports which have reported the use of IVIG.

E. Adult respiratory distress syndrome (ARDS):

ARDS is not a specific lung problem of SLE but occurs as a complication of acute lupus pneumonitis, DAH or pulmonary infections. Patients of SLE with ARDS are younger as compared to non-SLE patients and ARDS progresses rapidly in them. The commonest cause of ARDS in SLE is gram negative sepsis in the background of immunosuppression (Fig. 6).

3. Pulmonary vascular disease:

A. Pulmonary hypertension (PH):

The pulmonary arterial pressure > 35 mmHg is considered to be PH. 22 The prevalence of PH in SLE is estimated to be between 0.5-43 per cent. 23 PH can be the initial presenting manifestation of SLE. 24,25 The duration of SLE does not correlate with the development of PH. Dyspnoea, chest pain, dry cough, easy fatigability are the common symptoms. Oedema feet, neck vein distension (raised JVP), loud P2, TR and PR murmurs, hepatomegaly and ascites are the clinical signs demonstrable. It is necessary to closely observe these patients of SLE-PH as they can later on evolve into scleroderma or MCTD. SLE-PH can be diagnosed by prominent pulmonary conus on X ray Chest (Fig. 7). 2 D Echo with Doppler study is necessary to confirm elevated pulmonary arterial pressure and resistance and/or
Lung Involvement in SLE

tricuspid regurgitation. Isolated diffusion defect on PFT may be an early predictor of SLE-PH. Right heart catheterization (RHC) is the confirmatory test to diagnose and quantitate the severity of PH. Exercise during the Echo or RHC increases the diagnostic yield. Ventilation perfusion lung scan should be done. CT pulmonary angiography helps ruling out chronic pulmonary thromboembolism.

Before labelling SLE as the cause of PH, it is necessary to rule out other causes of PH like HIV, antiphospholipid antibody syndrome (APS), obstructive sleep apnoea and COPD. Pulmonary artery vasospasm, pulmonary vasculitis and thrombosis are the mechanisms leading to PH. The high prevalence of Raynaud’s phenomenon and lupus anticoagulant/antiphospholipid antibodies in SLE patients support this theory. Histopathological findings are similar to idiopathic PH like plexiform angiomatous lesions, thickening of muscular wall and intimal fibrosis.

Treatment consists of calcium channel blockers, oxygen, anticoagulation, vasodilators, selective and non selective endothelial antagonists, phosphodiesterase-5-inhibitors (sildenafil, tadalafil) and prostacyclin derivatives like epoprostenol, iloprost and treprostinil. Treatment of PH in the western world has been revolutionised and differs from India. Due to the availability of prostacyclin derivatives for inhaled therapy and IV infusions which has shown promising results by improvement in dyspnoea and drop in PH with long term use. Epoprostenol is not yet available in India and is very expensive when given as IV infusions for long time (so not cost effective in our set up). Bosentan, an oral non-selective endothelin-1 antagonist has been shown to be effective in PH and is available in India. Again, in resource limited country like ours, high cost of bosentan is a major hurdle for its clinical use. IV Cyclophosphamide 600 mg/m² monthly for 6 months combined with oral steroids 0.5-1 mg/kg/day for 4 weeks (with gradual tapering of steroids) with vasodilators has shown drop in PH. Lung and heart lung transplant are the other options in the West.

B. Pulmonary thromboembolism:

There is a high prevalence of presence of antiphospholipid antibodies IgM and IgG in patients of SLE. This can cause pulmonary embolism, infarction, PH, pulmonary arterial thrombosis and microthrombosis (acute and chronic), intraalveolar haemorrhages and ARDS. With a prior history or episode of a thrombotic event, anticoagulation with heparin and warfarin so as to maintain INR (international normalized ratio) between 2 to 3 is the treatment recommended. Without a prior history of a thrombotic event, aspirin prophylaxis is widely practiced, although evidence to support this is lacking.

C. Acute reversible hypoxemia:

In SLE patients, unexplained hypoxia in the absence of parenchymal lung disease which responds to steroids within 72 hours has been described. Pulmonary leukoaggregation and complement activation with pulmonary capillaries, upregulation of adhesion molecules like E-selectin, VCAM-1 and ICAM-1 have been postulated as the pathophysiological mechanisms for acute reversible hypoxemia.

4. Airway Disease:

Upper airway involvement can be seen in upto 30% of SLE patients. This ranges from laryngeal mucosal inflammation, mucosal ulcerations, cricoarytenoiditis, vocal cord paralysis and vocal cord oedema to life-threatening necrotizing vasculitis with airway obstruction. Hoarseness of voice, dyspnoea and stridor should raise the suspicion of airway disease in SLE. Small airway
dysfunction, bronchial wall thickening and bronchiectasis have also been described. There is a dramatic and sustained response to inhaled and IV steroids.

5. Pulmonary Infections:

Since corticosteroids and immunosuppressants are the mainstay of treatment in taming the wolf (maintaining lupus in remission), majority of patients of SLE will experience some infection during the course of their disease. Serious infections are a major cause of morbidity and mortality in SLE. Immune abnormalities in lupus are due to deficiencies in complement or abnormalities in number and function of cellular components of the immune system. Lymphopenia occurs in 60% SLE patients and thereby it predisposes to infection. Defects in chemotaxis, phagocytic activity and delayed hypersensitivity accounts for susceptibility to infection. Increased disease activity and poor renal function also predispose to infection.

Pulmonary infection in SLE has been reported in a study from Chennai as high as 20 per cent. Pulmonary tuberculosis is the most common infection seen in our country in patients of SLE. Bacterial, viral and fungal pneumonias have also been reported in the setting of immunosuppression. As discussed earlier, it may be difficult to differentiate pulmonary infection from lupus pneumonitis. However, other signs of active lupus like rash, arthralgias, oral ulcers, low complement levels, high urinary proteins and casts may help in differentiating lupus lung from pulmonary infections. Sputum culture is the gold standard to confirm the culprit pathogenic microorganism. Broad spectrum antibiotics covering Gram positive and Gram negative organisms should be started pending culture reports. Antifungals should be considered when fungal infection is strongly suspected clinically.

6. Drug induced lung involvement:

Lung involvement in SLE can also be a part of medications used. Drug induced lupus can cause any of the above described pulmonary manifestations; pleural effusion being the most common of all. Symptoms of drug induced lupus resolve after stopping the culprit drug. In some cases, treatment with small doses of steroids usually causes complete recovery.

CONCLUSION

Lung involvement in SLE is an important cause of morbidity and mortality. Hence, an early diagnosis of lung involvement in SLE is important. There can be challenges in differentiating lupus flare from infections or the two may co-exist. Treatment needs to be tailor-made from patient to patient. Immunosuppression may have to be escalated in lupus flare and reduced to lowest possible doses in the presence of infection. Anticoagulation should be considered in SLE-PH and thromboembolism.

REFERENCES


