Pulmonary Complications of Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease characterized by the production of pathogenic autoantibodies and immune complexes and is responsible for significant morbidity and mortality through a wide range of clinical manifestations which can affect almost any organ. Pulmonary involvement is prevalent and seen in 50 to 70% of SLE patients and may even be the presenting feature in 4 to 5% of patients. By 10 years postdiagnosis, 12% will have accumulated an element of permanent lung damage. Pulmonary complications are broad and include pleural disease, interstitial lung disease (ILD), vasculitis, pulmonary embolism, pulmonary hypertension, large airway disease, shrinking lung syndrome, and infection. Conditions can range mostly from asymptomatic, for example, in mild cases of pleural effusion or obstructive airway disease, to life-threatening disease, for example, in acute lupus pneumonitis or diffuse alveolar hemorrhage. ILD and pulmonary hypertension are both frequently seen in other autoimmune rheumatic diseases such as systemic sclerosis; however, in SLE, they tend to be milder and have a comparatively favorable prognosis. Although collectively pulmonary involvement in SLE is common, the heterogeneity of SLE and rareness of individual complications make clinical trials difficult and treatment is usually based on case series reports and anecdotal experience with various immunosuppressive agents. Some of these immunosuppressive agents such as azathioprine, methotrexate, and cyclophosphamide have also been linked with drug-induced lung injury.

Keywords
- systemic lupus erythematosus
- pulmonary disease
- complications
- interstitial lung disease
- pleural disease

Systemic lupus erythematosus (SLE) is a rare chronic, multisystem autoimmune disorder characterized by the production of nuclear autoantibodies. Virtually, all patients carry antinuclear antibodies (ANAs) (98%), but other common serological abnormalities include anti-dsDNA antibodies (76%), hypocomplementemia (71%), and anti-Ro (SSA) antibodies (35%).[1] There is a vast array of clinical manifestations, which can affect almost any organ, some of which are illustrated by the 2012 Systemic Lupus International Collaborating Clinics classification criteria which are summarized in ►**Box 1**.[2,3] Rheumatological, dermatological, and renal manifestations are common as is pleuropulmonary involvement, with 50 to 70% of SLE patients experiencing pulmonary complications at some point in the disease process. This can range from asymptomatic small pleural effusion to life-threatening pulmonary hemorrhage. Pulmonary involvement can be the presenting feature of the disease in 4 to 5%.[1] By 10 years, following SLE diagnosis, 12% of patients will have permanent lung damage, with increasing age and anti-RNP (ribonucleoprotein) antibodies being associated with earlier damage.[4] While acute pulmonary disease is usually associated with high generalized levels of systemic lupus

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activity, chronic pulmonary disease can progress independently of other organ involvement.[5]

Box 1 SLICC classification criteria (Petri et al, 2012)[2] SLE classification requires at least four criteria to be met including at least one clinical criterion and one immunological criterion

Clinical criteria (in the absence of other known causes)	Immunological criteria
Acute cutaneous lupus	ANA above laboratory reference range
Chronic cutaneous lupus	Anti-dsDNA above laboratory reference range
Oral ulcers	Anti-Sm
Nonscarring alopecia	Antiphospholipid antibody—lupus anticoagulant, false-positive RPR, medium or high titer anticardiolipin, or anti-β2 glycoprotein I
Synovitis of two or more joints	Low complement—C3, C4, or CH50
Serositis—pleural or pericardial inflammation	Direct Coombs' test (in absence of autoimmune hemolytic anemia)
Renal—proteinuria >500 mg per 24 h or red blood cell casts	
Neurologic—seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, and acute confusional state	
Hemolytic anemia	
Leukopenia (<4,000/mm^3) or lymphopenia (<1,000/mm^3)	

Abbreviations: ANA, antinuclear antibody; RPR, rapid plasma reagin; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics.

Pleural Disease

SLE and rheumatoid arthritis are the most common autoimmune rheumatic diseases to involve the pleura.[6] Recurrent pleuritic pain occurs in 45% of SLE patients while not usually life-threatening can be a significant contributor to morbidity. Pleural effusions can be detected in 30%.[7] Acute pleurisy can present with chest pain, dyspnea, fever, cough, and a friction rub on examination.[8] Pleural effusions in SLE can be due to primary autoimmune pleuritis, but it may be difficult to distinguish this from other causes including pulmonary embolism (PE), parapneumonic effusion, viral infections, tuberculosis, renal, cardiac disease, or drug therapy.[6,9]

In lupus pleuritis, pleural effusions are usually small and are bilateral in 50% of patients.[10] Biochemical analysis of the fluid reveals they are exudative in nature.[9] They are difficult to tell apart from other causes of exudative effusion as other fluid characteristics are variable; the appearance of the fluid can range from clear to serosanguinous; the leucocyte content of the fluid can range from counts of 230 to 15,000 cells/μL with polymorphonuclear cells making up anywhere between 10 and 100% of these.[9] Low glucose or pH of the fluid can occur but would be unusual.[9] Although studies have previously demonstrated a high pleural fluid ANA titer in lupus pleuritis, this also reflects the serum titer and is therefore not a helpful test to be performed routinely.[6,9,11]

Drug-induced lupus often has pleural involvement, with procainamide-induced lupus being a particular example.[8,12]

Management of pleural involvement involves excluding other possible causes. In drug-induced lupus, the offending drug should be withdrawn. In mild cases of pleurisy, short-term nonsteroidal anti-inflammatory drugs may be sufficient to control symptoms. More severe cases may require systemic corticosteroids, which will usually rapidly clear a lupus pleural effusion. Azathioprine, methotrexate, mycophenolate, cyclophosphamide, intravenous immunoglobulin, and ciclosporin have all been used in more severe and refractory cases.[8] In rare cases of chronic symptomatic pleural effusion refractory to drug therapy, pleurodesis or pleurectomy has been used.[8,13]

Parenchymal Involvement

Interstitial Lung Disease

Interstitial lung disease (ILD) is a common occurrence in many autoimmune rheumatic diseases. SLE is the exception, where it is an unusual finding affecting only 1 to 15% of patients.[14] Even then it is rarely severe and clinical progression is usually slow and stabilizes over time.[3,15] Two-thirds of SLE patients will demonstrate asymptomatic abnormalities in pulmonary function tests (most commonly a reduction in carbon monoxide diffusing lung capacity) and one-third of unselected SLE patients shows changes consistent with ILD on high-resolution computed tomography (CT) chest.[16,17] Moderate or severe ILD was seen in only 4 out of 120 SLE necropsy specimens.[18] It is most commonly seen in patients with long-standing SLE (>10 years) and patients who were older at the time of initial presentation (>50 years old).[19] Patients with scleroderma-like features are at an increased risk of ILD development as demonstrated by the association of sclerodactyly, abnormal nailfold capillaries, anti-RNP antibodies, and Raynaud's phenomenon with ILD development in SLE.[14,20] Clinical and serological measures are not particularly helpful in distinguishing the nature or severity of ILD. High levels of C-reactive protein, hypocomplementemia, and presence of cryoglobulins or lupus erythematosus cells in the serum have all also associated with ILD.[14] Anti-SS-A (Ro) antibodies were found in 81% of patients with chronic interstitial pneumonitis in one study,[21] but other studies have found no correlation with anti-SS-A (Ro), anti-SS-B (La), or anti-Sm, and the development of ILD.[17] Organizing pneumonia, nonspecific

interstitial pneumonia, and lymphoid interstitial pneumonia patterns have all been described.[22]

Acute Lupus Pneumonitis

Within the spectrum of SLE-ILD is acute lupus pneumonitis which is characterized by fever, cough, dyspnea, pleuritic chest pain, and hypoxemia. It occurs in 1 to 4% of patients.[3] This historically has a high mortality of up to 50% in the acute setting and can be difficult to distinguish from severe infection and acute respiratory distress syndrome.[23] For those who survive the acute episode, 50 to 100% will progress to chronic interstitial pneumonitis.[24] Acute lupus pneumonitis can occur as the initial presentation of SLE, making diagnosis particularly challenging.[25]

Chest radiographs show unilateral or bilateral infiltrates, and histology will show alveolar wall damage, inflammatory cell infiltration, edema, hemorrhage, and hyaline membranes. Once infection has been ruled out, then immunosuppression should be considered. Important differentials to consider are pneumonia, tuberculosis, pulmonary hemorrhage, and systemic vasculitis.

There remains some controversy surrounding the existence of acute lupus pneumonitis, given that radiographical and histological findings are nonspecific. A large necropsy case series found that most histological findings in suspected cases could be explained through another pathology such as infection, aspiration, cardiac dysfunction, or uremia.[18]

Vascular Involvement

Vasculitis associated with SLE is thought to occur by one of two mechanisms. The first suggested pathogenesis is of immune complex deposition in blood vessel walls leading to complement activation and infiltration of neutrophils.[26] Alternatively, intravascular activation of complement causing neutrophil and platelet activation and sludging within the vessels may lead to an occlusive vasculopathy.[27] SLE with or without antiphospholipid syndrome can produce a small vessel vasculitis in the lungs leading to diffuse alveolar hemorrhage (DAH). Vasculitis may also play a role in the development of pulmonary artery (PA) hypertension.

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) can be difficult to identify until it is relatively advanced, and the frequency of PAH in SLE varies from 0.5 to 17.5%.[28] Typically, it occurs in women under the age of 40 years, with an SLE disease duration of more than 5 years.[14] Serositis, Raynaud's phenomenon, anticardiolipin, and anti-U1 ribonucleoprotein antibodies have all been linked to an increased risk of developing PAH.[29]

Pathogenesis is multifactorial with pulmonary vasculitis, thrombosis, and PA vasoconstriction all potentially contributing.[3] PAH is diagnosed if the mean PA pressure is more than 25 mm Hg with a pulmonary wedge pressure of $<$15 mm Hg.[30] It can be classified as primary or secondary.

PAH usually first presents with dyspnea during exercise, and in SLE, 60% also had Raynaud's syndrome at presentation.[31] Physical examination may reveal a loud pulmonary component of the second heart sound (P2), systolic murmur, and hepatomegaly (indicative of right heart failure). Electrocardiogram may show right axis deviation and right ventricular hypertrophy, and chest radiograph may show cardiomegaly. Echocardiography can estimate the PA pressure but is subject to significant operator error. Pulmonary function testing may show reduced gas transfer values and 6-minute walk distances may be useful prognostically. Right heart catheterization to measure mean PA pressure and PA wedge pressure is the definitive test for PAH.

Historically, connective tissue disease-related PAH had a poor prognosis. However, the availability of advanced therapies of prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors has improved outcomes, with a recent registry study showing a 3-year survival rate of SLE-PAH of 89.4%.[32] Outcomes are more favorable compared with systemic sclerosis–associated PAH which has a 3-year survival of only 47%.[33] In SLE, it is generally recommended to give immunosuppression as well as specific PAH therapy to give optimal long-term outcome.[34]

Diffuse Alveolar Hemorrhage

Diffuse alveolar hemorrhage (DAH) is a rare but potentially catastrophic complication of collagen vascular disorders. The reported frequency in SLE cohorts ranges from 1 to 5.4%.[35] It tends to occur early in the disease course, and for up to one-third of patients, it is the presenting feature of SLE.[14] It is seen mostly in patients with active disease indicated by high SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) scores.[35] Active renal disease particularly increases the risk of DAH, with renal involvement being seen in 60 to 93% of patients at the time of DAH diagnosis.[5,36]

Patients present with abrupt onset dyspnea over hours to days with investigations revealing tachycardia, fall in hemoglobin, and bilateral diffuse infiltrates on chest radiograph. Fever ($>$38°C) and dyspnea are present in the majority of patients, whereas hemoptysis is only observed in 30% patients.[37] Infection, catastrophic antiphospholipid syndrome, and overlap with other primary vasculitides are important differentials to consider.

Classical imaging findings are nonspecific diffuse bilateral alveolar infiltrates, although unilateral, lobar infiltrates have been reported.[35] Evaluation of carbon dioxide transfer factor can assist in the diagnosis of early pulmonary hemorrhage. An increase of 30% above baseline or a measured value over 130% of the predicted value would suggest pulmonary hemorrhage.[38] Studies where lung biopsy specimens have been obtained have shown that histopathological findings are also nonspecific, with most cases displaying bland hemorrhage without associated interstitial inflammation, although capillaritis and neutrophilic infiltration of the alveolar septate and alveolar wall destruction has also been described.[39,40] Although lung biopsy may aid the diagnosis, these patients are frequently critically unwell and the procedure carries significant risk of morbidity. It is therefore not generally recommended except in selected cases.[5,41]

The best treatment for DAH is uncertain as there have been no studies in this area. Anecdotal and case report evidence suggests that the mainstay of treatment is high-dose corticosteroids

(usually starting with pulsed intravenous methylprednisolone), alongside cytotoxic therapy and plasmapheresis in serious nonsteroid responsive cases. Recent abstract data, from the PEXIVAS (Clinical Trial Plasma Exchange In Vasculitis) trial on plasmapheresis in severe vasculitis including patients with pulmonary renal vasculitis, failed to show benefit in improving the end points of death or end-stage renal disease.[42] This trial is unlikely to be replicated in SLE but does call into question the role of plasma exchange in SLE patients with DAH.[42]

Death can occur within hours or days and therefore treatment must be commenced urgently. Survival rates from different case series have been contradictory and varied from 8 to 100%.[43] Poor prognostic markers are renal insufficiency, thrombocytopenia, and requirement for mechanical ventilation.[44] Survivors can develop pulmonary fibrosis and are also at risk of recurrence of DAH.[14,45]

Acute Reversible Hypoxemia Syndrome

In 1991, Abramson et al recognized a pattern of reversible "unexplained" hypoxemia in acutely unwell SLE patients with no evidence of parenchymal involvement on chest radiographs.[46] They noticed this phenomenon in 6 of 22 (27%) patients hospitalized with SLE exacerbations. The term acute reversible hypoxemia (ARH) was coined. The patients had hypoxemia and hypocapnia with an increased alveolar–arterial PO_2 gradient which improved rapidly with corticosteroids.[47] A suggested mechanism behind ARH is that excessive complement activation activates circulating neutrophils and primes endothelial cells to induce leucocyte–endothelial cell adhesions leading to a leuco-occlusive vasculopathy in the pulmonary capillaries.[27]

Venous Thromboembolism

Deep vein thrombosis (DVT) and/or PE is seen in ~9% of SLE patients with the highest risk being in those with active disease.[48] Antiphospholipid antibodies increase the risk of thromboembolic events to 35 to 42%.[49] Chronic pulmonary emboli can lead to the development of pulmonary hypertension. Due to the increased risk of PE, a high index of suspicion must always be held if a patient presents with sudden onset pleuritic chest pain, dyspnea, or hypoxemia. Most cases of PE can be identified though ventilation/perfusion scan or CT pulmonary angiography.[47]

Due to the high future venous thromboembolism (VTE) risk, indefinite anticoagulation with warfarin is recommended in patients with SLE and antiphospholipid antibodies who have had any episodes of DVT or PE.[50] SLE patients who are positive for all three antiphospholipid antibodies, that is, lupus anticoagulant, anticardiolipin antibodies, and β2 glycoprotein 1 antibodies at baseline are at significantly higher risk of future (VTE). The British Society for Rheumatology guidelines for SLE recommend screening all new SLE patients for antiphospholipid antibody markers to help with risk stratification.[51]

Disorders of Respiratory Physiology

Airway Disease

Although abnormalities in pulmonary function tests are detected in up to two-thirds of SLE patients, severe airflow obstruction is rare.[17] A study of 70 life-long nonsmoker SLE patients compared with 70 age-matched controls showed true obstructive pattern of forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio below 0.6 in only 6% of SLE patients, compared with zero cases detected in the control group.[17] Evidence of asymptomatic small airway disease, as defined by the sensitive measure of MEF_{25} <0.6 (maximal expiratory flow at 25% of vital capacity), was more commonly observed and seen in almost one quarter of the SLE cohort.[17] Isolated MEF_{25} reduction can be an early indication of either obstructive or restrictive disease. Another study that did not exclude smokers found the 16% SLE patients showed obstructive disease.[52]

There have been case reports of cryptogenic organizing pneumonia (COP) in SLE, which is an acute inflammatory process of the small bronchi and bronchioles (►**Fig. 1a, b**). Plugs of alveolar debris and strands of fibrin form within the bronchioles causing obstruction which is potentially irreversible.[53] It should be suspected where symptoms such as nonepisodic dyspnea, wheezing, and nonproductive cough

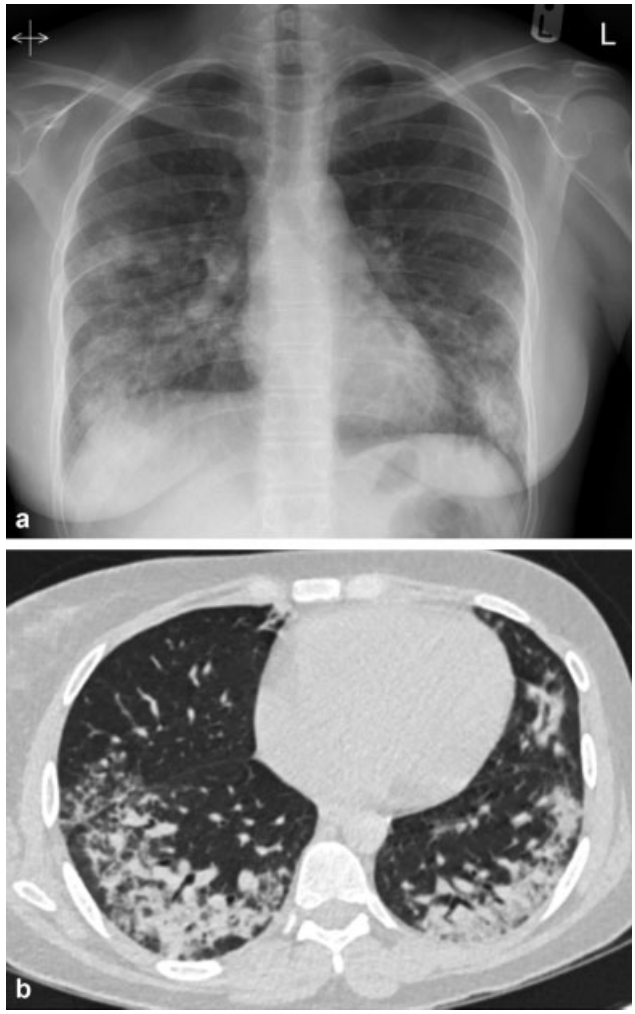

Fig. 1 (a) Chest radiograph of a 25-year-old woman with systemic lupus erythematosus and bilateral mid and lower zone patchy ground-glass/nodular infiltrates. (b) Chest computed tomography showing bronchocentric nodular opacities and associated consolidation suggestive of obliterative bronchiolitis and organizing pneumonia.

are observed in the absence of asthma or chronic bronchitis. A case series of 12 acute lupus pneumonitis cases found evidence of COP in one lung biopsy specimen.[23] It is therefore possible that some cases of presumed acute lupus pneumonitis are actually COP. First-line treatment is corticosteroids with cytotoxic medications reserved for nonresponders or those intolerant of corticosteroid therapy.[53–55]

Shrinking Lung Syndrome

Shrinking lung syndrome (SLS) is a rare complication of SLE affecting less than 1% of SLE patients.[4] It was first described by Hoffbrand and Beck in 1965 and has subsequently been described in very occasional case reports in other autoimmune rheumatic diseases.[56,57] Symptoms include progressive exertional dyspnea and pleuritic chest pain in the context of reducing lung volumes as demonstrated by classical radiographic and pulmonary function test findings. Chest radiography will usually display reduced lung volumes with raised hemidiaphragm. Pleural effusions, pleural thickening, and atelectasis are less common radiographic features.[58] Pulmonary function tests show reduced FEV1 and FVC in a restrictive pattern and a reduced total lung capacity. Carbon monoxide gas transfer capacity may be reduced, but when corrected for alveolar volume (i.e., KCO), it is usually normal.[59] There are no definitive diagnostic criteria and alternative causes of reducing lung volumes should be excluded including pulmonary fibrosis, obesity, diaphragmatic palsy, and central nervous system disorders.[57] SLS is rarely the presenting feature of SLE and onset can vary from 4 months to 24 years postinitial SLE diagnosis.[60] Medical history may reveal pleurisy and less commonly pericarditis or myopathy.[58]

The pathophysiology behind SLS is unclear. Tests for diaphragmatic muscle strength or phrenic nerve function are not performed routinely, but if performed are usually normal. There does appear to be a restriction in chest wall expansion, but the mechanism behind this is unknown.[61] It has been suggested that SLS represents a respiratory muscle myopathy.[60] Phrenic neuropathy, pleural inflammation, adhesions, and pain have all been postulated to play a role in pathogenesis.[62]

Due to the uncertainty of the cause of SLS, the most appropriate treatment options are also unclear. Most reports suggest a good response to high-dose corticosteroids (30–60 mg prednisone daily).[58] Immunosuppressive agents have been used, mainly azathioprine and cyclophosphamide; however there are no trials to provide data on their efficacy and choice is usually guided by other SLE disease characteristics and severity. Theophylline and β-agonist therapies have been reported to improve lung capacity in SLS through improving diaphragmatic strength.[63,64] Unlike pulmonary fibrosis, long-term prognosis is usually good, with the majority of patients improving or stabilizing with treatment.[57,58]

Infection

Patients with SLE have an inherently increased risk of infections. A historical study predating the widespread use of immunosuppression estimated the infection risk for SLE patients to be 40%.[65] Increased susceptibility is multifactorial due to alterations in both the innate and adaptive immune systems. Deficiencies in the complement system are commonly found and will impair the clearance of immune complexes.[66] SLE patients homozygous for mannose-binding lectin variant alleles have a fourfold increased risk of hospitalization with infection.[67] Impaired chemotaxis and phagocytosis of macrophages and polymorphonuclear cells have been demonstrated as deficient T cell–mediated cytotoxicity.[66] Functional asplenia is seen in 5% of SLE patients and leads to an increased risk of pneumococcus and Salmonella sepsis.[68,69] Pneumococcal vaccination should therefore always be considered.

Although immunosuppressive medications are typically associated with increased infection risk, a prospective study by Zonana-Nacach et al of 200 SLE outpatients found that most infections were single, minor, nonlife-threatening and associated with disease activity, but were independent of sociodemographic factors, disease duration, and oral immunosuppression use.[70] However, there was an increased risk with intravenous cyclophosphamide use and prednisone dose. In their cohort, only 6% infections were pulmonary.[70]

The pattern of infectious pneumonia encountered will vary according to local demographics and pathogen prevalence. A Canadian study looking at SLE hospital admissions found that pneumonia due to gram-negative organisms such as *P. aeruginosa*, *H. influenzae*, *S. marcescens*, *K. pneumonia*, and *Legionella* species were most common.[71] In contrast, a Thai study found bacterial pneumonia to be responsible for only 35% of community-acquired pneumonias, with a high incidence of opportunistic lung infections. *Mycobacterium tuberculosis* was responsible for 30% infections, and *Nocardia* species (15%), *Aspergillus* species (12.5%), and *Pneumocystis carinii* (5%) were also notably common.[72] A mean daily dose of prednisolone of $\geq$15 mg per day at the onset of the pneumonia was a risk factor for death.[72]

Lung Cancer

Case series and cohort studies suggest the incidence and mortality of lung cancer in SLE patients is greater than in the general population.[73,74] Most SLE patients (71%) who develop lung cancer are smokers, and this remains a more important risk factor than exposure to immunosuppressant medications.[73] The pattern and histology of lung cancer in SLE patients are similar to that seen in the general population. Pulmonary fibrosis is a known risk factor for lung cancer, although it is not known whether parenchymal lung damage is important in the development of lung cancer in SLE patients.[75]

Drug Toxicity

Several drugs that are commonly used to treat SLE are associated with possible pulmonary toxicity. Drug-induced ILD is the most common form of injury. It is diagnosed if there is a history consistent with the appropriate timing of onset in relation to commencing and ceasing the drug as well as a

Table 1 Examples of drugs commonly used in SLE patients which have been associated with drug-induced lung injury

Drug	Pattern of drug-induced lung injury
Azathioprine	Hypersensitivity pneumonitis or NSIP-UIP
Cyclophosphamide	Diffuse alveolar damage, NSIP or OP
Methotrexate	Hypersensitivity pneumonitis or NSIP-UIP
NSAIDs	Eosinophilic pneumonia

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; SLE, systemic lupus erythematosus; UIP, usual interstitial pneumonia.

radiographic or histopathological pattern consistent with the pattern expected from the particular drug (►**Table 1**), and importantly, only if all other causes have been excluded.[76–78] Failure to identify drug-induced ILD may significantly increase mortality and morbidity.[76] With early withdrawal of the offending agent, prognosis is usually satisfactory.[79]

Conclusion

Pulmonary complications of SLE are common but can range in severity from insignificant to life-threatening. Raising awareness of potential lung involvement will enable it to be identified earlier in the disease course and hopefully minimize the accumulation of damage. Studies in this area are few and far between and therefore a strong evidence base for the treatment of the majority of these complications is lacking and is mostly based on anecdotal or case series evidence. Differentiating infection from inflammation in the lung is a common clinical dilemma and the two pathologies can be superimposed causing additional management difficulties. In these difficult cases, multidisciplinary working alongside respiratory and infection specialists is invaluable.

Conflict of Interest
Dr. D'Cruz reports personal fees from GlaxoSmithKline, during the writing of this review.

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