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Pulmonary Manifestations of Systemic Lupus Erythematosus

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1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that primarily affects women of childbearing age with 10:1 female to male ratio.(Siegel & Lee, 1973) Any organ can be affected by SLE; pulmonary involvement is usually in the latter course of the disease.(Haupt *et al.*, 1981; Orens *et al.*, 1994; Quadrelli *et al.*, 2009) It is important to note that lung involvement is proportionately more common in men.(Kamen & Strange, 2010) Any part of the pulmonary system can be affected including airways, lung parenchyma, pulmonary vasculature, pleura and diaphragm.(Gross *et al.*, 1972; Haupt *et al.*, 1981; Kamen & Strange, 2010; Orens *et al.*, 1994; Quadrelli *et al.*, 2009; Weinrib *et al.*, 1990) If SLE develops after age 49 years, it has a higher incidence of serositis, pulmonary involvement and mortality.(Boddaert *et al.*, 2004) It is difficult to find out the true prevalence of pulmonary complications of SLE since many cases are due to infections.(Kamen & Strange, 2010) A recent autopsy study of 90 patients diagnosed with SLE, according to the American College of Rheumatology, pleuropulmonary involvement occurred in 98% of the autopsies. (Quadrelli *et al.*, 2009) The most frequent findings were pleuritis (78%), bacterial infections (58%), alveolar hemorrhage (26%), followed by distal airway alterations (21%), opportunistic infections (14%) and pulmonary thromboembolism (8%), both acute and chronic.(Quadrelli *et al.*, 2009) In a larger series, 25% of patients with SLE had clinical and/or radiographic evidence of pulmonary involvement.(Pego-Reigosa *et al.*, 2009)

2. Clinical features

SLE can affect the lungs in many ways. In the next section we will review the pulmonary diseases associated with SLE according to the anatomic involvement.

2.1 Pleural diseases

Pleuritis is the most common pleuropulmonary manifestation of SLE.(Orens *et al.*, 1994) It is the initial manifestation in 5% to 10%.(Winslow *et al.*, 1958) Symptoms of pleuritis are present in 45% to 60% of patients with SLE and may be associated with pleural effusion.(Good *et al.*, 1983; Orens *et al.*, 1994; Pines *et al.*, 1985) Pleural effusion in SLE tends to be bilateral, small to moderate in size; however, large effusions may occur.(Bouros *et al.*, 2008) Typical presentation of pleural involvement is pleuritic chest pain (pain that increases with inspiration), dyspnea, and fever. Physical examination may reveal pleural friction rub

and signs of pleural effusion. Chest X-ray shows blunting of the costophrenic angle. Some patients may have asymptomatic pleural effusion. Other causes of pleural effusion such as parapneumonic effusion, pulmonary embolism, and heart failure need to be ruled out. Pleural fluid analysis is needed to rule out other etiologies and to confirm the diagnosis of lupus pleuritis. Pleural fluid is exudative (elevated pleural fluid protein and lactate dehydrogenase levels) when analyzed. Cell counts are elevated with predominance of lymphocytes or neutrophils. Pleural fluid glucose level is low, but not as low as in patients with rheumatoid arthritis. Special tests reveal low pleural complement level and positive anti-nuclear antibody (ANA). These tests are not sensitive enough to rule out lupus pleuritis when tests are negative. (Hunder *et al.*, 1972; Small *et al.*, 1982) Pleural fluid ANA titer $\geq 1:160$ and pleural fluid / serum ANA ratio of ≥ 1 strongly support the diagnosis. (Good *et al.*, 1983) The finding of lupus erythematosus cells in pleural fluid confirms the diagnosis; however this test is rarely performed. (Kamen & Strange, 2010) Pleural biopsy is rarely needed, if done it will show a peculiar immunofluorescent pattern characterized by staining of nuclei with anti-IgG, anti-IgM and anti-C3. (Pertschuk *et al.*, 1977) Patients with pleural disease usually respond to nonsteroidal anti-inflammatory drugs (NSAIDs). Low doses of oral glucocorticoids hasten the resolution. Small asymptomatic effusions usually resolve without treatment. (Winslow *et al.*, 1958) NSAIDs are sufficient for mild cases; for severe cases or for patients on steroids, giving higher doses of steroid is required. (Orens *et al.*, 1994; Wiedemann & Matthay, 1989) In refractory pleural effusions tetracycline or talc pleurodesis can be an alternative option. (Gilleece *et al.*, 1988; Kaine, 1985; McKnight *et al.*, 1991)

2.2 Parenchymal lung disease

2.2.1 Acute lupus pneumonitis

Acute lupus pneumonitis (ALP) is an uncommon but well recognized complication of SLE. There is some controversy over the definition ALP. (Swigris *et al.*, 2008) In two recent series, the prevalence of ALP in patients with SLE was 2% to 8%. (Kim *et al.*, 2000; Mochizuki *et al.*, 1999) It is difficult to estimate the exact prevalence given the significant clinical and radiological overlap between ALP, bacterial pneumonia and alveolar hemorrhage. ALP tends to affect younger patients and those with recent diagnosis of SLE. In 50% of patients with SLE who develop ALP, the pulmonary complication is the initial presentation of lupus. (Matthay *et al.*, 1975) Clinical presentation includes abrupt onset of fever, cough, dyspnea, pleuritic chest pain and occasionally hemoptysis. (Matthay *et al.*, 1975) Physical examination usually reveals signs of hypoxia and bibasilar crackles. Radiographic findings include bilateral alveolar infiltrates with predominance in lower lung fields (figure 1). Pleural effusion occurs in half of the cases. (Matthay *et al.*, 1975) Rarely the initial chest radiograph may be normal or may show pulmonary nodules. (Susanto & Peters, 1997) CT scan of the chest may show diffuse ground glass opacities and areas of consolidation. (Swigris *et al.*, 2008) A fulminant form of ALP may occur during pregnancy. (Comer *et al.*, 1996) The clinical and radiographic features are not specific. Other causes of alveolar infiltrates like infectious pneumonia, alveolar hemorrhage, pulmonary edema, and organizing pneumonia should be considered. It is important to rule out infectious complications. Many of these patients are on systemic steroids and other immunosuppressive medications and are at increased risk of opportunistic infections. Early bronchoscopy and bronchoalveolar lavage (BAL) with or without transbronchial biopsy is mandatory in most cases. BAL should be sent for cell count and differential, bacterial, fungal

and viral culture, cytology and for *Pneumocystis jiroveci* stain. Occasionally a thoracoscopic lung biopsy may be needed. The pathological findings are not specific. The most common findings include diffuse alveolar damage (DAD) with or without alveolar hemorrhage and capillaritis.(Harvey *et al.*, 1954; Keane & Lynch, 2000) Other pathologic features include alveolar wall injury, alveolar edema, hyaline membrane formation, immunoglobulin and complement deposition. There seems to be some association between ALP and anti-Ro/SSa antibodies. One study showed that patients with SLE and pulmonary complications had an 81% positive result for anti-Ro/SSa antibodies, while patients without pulmonary involvement had a 38% positive antibody.(Boulware & Hedgpeth, 1989) A more recent review confirmed this association (Mochizuki *et al.*, 1999) The high frequency of anti-Ro/SSa antibodies raises the possibility of their role in the pathogenesis of ALP.(Cheema & Quismorio, 2000) Prognosis is poor, with mortality reaching up to 50% as reported in an old study.(Matthay *et al.*, 1975) The outcome is worse if ALP occurs postpartum.(Matthay *et al.*, 1975) Eosinophilia or neutrophilia on BAL carries worse prognosis than lymphocytosis.(Witt *et al.*, 1996) Because infectious causes can't be ruled out, empiric broad spectrum antibiotics should be started immediately and continued until infection is excluded. There are no randomized clinical trials for the treatment of ALP, however it is agreed on that the main treatment is systemic corticosteroids (prednisone 1-1.5 mg/kg/day). If no adequate response within 72 hours, treatment should be with intravenous pulse steroids (1g methylprednisolone daily for three days).(Kamen & Strange, 2010) Additional immunosuppressants such as cyclophosphamide should also be considered. In patients refractory to corticosteroids, intravenous immunoglobulin, plasma exchange or rituximab can be of some help with very little evidence (Eiser & Shanies, 1994; Lim *et al.*, 2006; Pego-Reigosa *et al.*, 2009; Winder *et al.*, 1993)

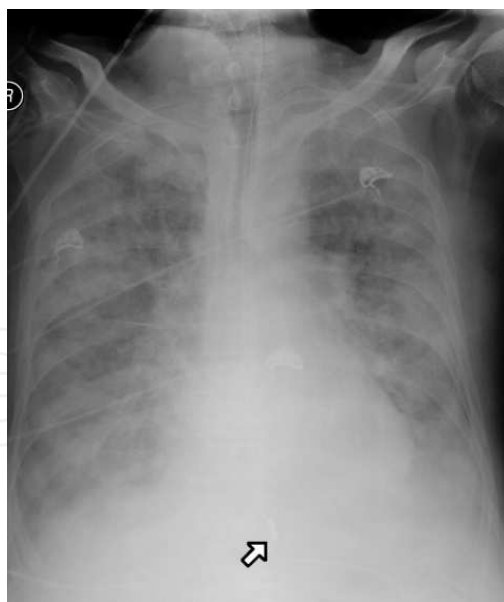


Fig. 1. Chest X-ray showing diffuse alveolar infiltrates in a patient with acute lupus pneumonitis

2.2.2 Diffuse alveolar hemorrhage

Diffuse alveolar hemorrhage (DAH) is a rare complication of SLE. (Badsha *et al.*, 2004; Eagen *et al.*, 1978; Zamora *et al.*, 1997) Its prevalence among SLE patients ranges between

<2% and 5.4 % (Santos-Ocampo *et al.*, 2000; Zamora *et al.*, 1997), and the mortality rate ranges between 50% to 90%. (Erickson *et al.*, 1994; Schwab *et al.*, 1993) Usually it occurs in established disease, especially with lupus nephritis. (Zamora *et al.*, 1997) Other extrapulmonary manifestations occur with variable degree. (Abud-Mendoza *et al.*, 1985; Barile *et al.*, 1997; Koh *et al.*, 1997; Liu *et al.*, 1998; Myers & Katzenstein, 1986; Schwab *et al.*, 1993; Zamora *et al.*, 1997) However it can occasionally be the initial presentation of SLE. (Zamora *et al.*, 1997) Risk factors thought to be contributing to the development of DAH are higher titer of circulating anti-DNA antibody, active extra-pulmonary disease, and established SLE diagnosis. (Orens *et al.*, 1994)

Clinical presentation of patients with DAH is not specific; symptoms include acute shortness of breath, cough, hemoptysis and fever. The absence of hemoptysis doesn't rule out DAH. In fact hemoptysis is only present in 54% of patients. (Santos-Ocampo *et al.*, 2000) Fever is present in more than 80% of patients. (Santos-Ocampo *et al.*, 2000) Signs of respiratory distress and hypoxia are noted upon physical examination. Chest radiograph shows bilateral alveolar infiltrates. Unilateral pulmonary infiltrates is noted in up to 18%. (Santos-Ocampo *et al.*, 2000) CT imaging demonstrates new bilateral ground glass opacities and consolidation. Acute drop in hemoglobin is frequently encountered. In most series anemia was noted >90 of all episodes of DAH. (Abud-Mendoza *et al.*, 1985; Barile *et al.*, 1997; Koh *et al.*, 1997; Liu *et al.*, 1998; Myers & Katzenstein, 1986; Schwab *et al.*, 1993; Zamora *et al.*, 1997) If diffusion capacity for carbon monoxide (DLCO) is measured it will be elevated due to the excess hemoglobin in the alveolar spaces. An increase of DLCO by 30% or a value of >130% predicted suggest DAH in the right clinical setting. (Carette *et al.*, 1984; Dweik *et al.*, 1997; Ewan *et al.*, 1976; Harmon & Leatherman, 1988; Leatherman *et al.*, 1984; Young, 1989) Low complement level is found in more than 70% of all episodes of DAH. (Koh *et al.*, 1997; Liu *et al.*, 1998; Myers & Katzenstein, 1986; Santos-Ocampo *et al.*, 2000; Schwab *et al.*, 1993;) Magnetic resonant imaging (MRI) is another imaging study that can suggest the presence of blood in the alveoli given the paramagnetic effect of iron. (Hsu *et al.*, 1992) BAL is mandatory to rule out infection and help in the diagnosis of DAH. BAL can confirm the diagnosis if bloody return increases with serial aliquots. BAL should be evaluated for the presence of hemosiderin-laden macrophages, their presence indicate alveolar hemorrhage. Transbronchial biopsy (TBBx) may be attempted in stable patients. Unfortunately many of these patients require ventilatory support and may not be able to sustain the complication of TBBx. Thoracoscopic lung biopsy is rarely needed. Two pathological patterns have been described. Bland hemorrhage is more common and occurs in 72% while capillaritis occurs in 14% of the times. Both pathological patterns are associated with intra-alveolar hemorrhage and hemosiderin-laden macrophages. (Myers & Katzenstein, 1986; Schwab *et al.*, 1993b; Zamora *et al.*, 1997) IgG, C3 or immune complexes deposition occurs in 50% of the cases. (Myers & Katzenstein, 1986) There are no randomized control trials addressing treatment options for DAH. Supportive care is highly valued since many of these patients end up in the intensive care unit requiring mechanical ventilation. The most acceptable regimen include pulse intravenous steroids (methylprednisolone 1gm per day for three days) followed by 1mg/kg of oral prednisone plus intravenous cyclophosphamide every four weeks. (Schwab *et al.*, 1993a; Swigris *et al.*, 2008) DAH is one of the few indications where plasmapheresis has been shown to be effective, especially in refractory cases. (Erickson *et al.*, 1994; Santos-Ocampo *et al.*, 2000) Plasmapheresis may improve survival in patients who failed treatment with high dose steroids and cyclophosphamide. (Erickson *et al.*, 1994) More recently rituximab has been used in

refractory cases with promising results.(Pottier *et al.*, 2011) The mean duration of alveolar hemorrhage from onset to radiographic resolution is 7.8 days.(Santos-Ocampo *et al.*, 2000) DAH is known to recur within the same subject. In one study, recurrence occurred in more than 40% of patients.(Santos-Ocampo *et al.*, 2000)

2.2.3 Chronic interstitial lung disease

Chronic interstitial lung disease (ILD) is a well-recognized pulmonary manifestation of SLE. The prevalence of chronic ILD in symptomatic patients with lupus is 3%.(Haupt *et al.*, 1981; Weinrib *et al.*, 1990) The prevalence increases with an increase in the duration of SLE.(Jacobsen *et al.*, 1998) It may present as a chronic and insidious disease or it may follow the development of ALP (Boulware & Hedgpeth, 1989; Weinrib *et al.*, 1990) Chronic ILD occurs more commonly in men and older patients. Pulmonary fibrosis affects 18% of patients above 50 years compared to 2% of patients under 18 years.(Cheema & Quismorio, 2000) Clinically, patients usually present with gradually progressive shortness of breath. Chronic dry cough can be the initial presentation in some patients. Physical examination may show fine bibasilar inspiratory crackles, however finger clubbing is rare.(Renzoni *et al.*, 1997) Spirometry shows restrictive pattern with proportionate reduction in forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) with normal or increased FEV1/FVC ratio. Lung volumes and DLCO are typically reduced. Early on, the only abnormality in pulmonary function test is an isolated reduction in DLCO. Chest radiographs may be normal at the beginning. As the disease progresses it may show irregular linear opacities and marked interstitial markings. Reduced lung volume is a late finding. High resolution CT (HRCT) of the chest may show diffuse ground glass opacities. Other features include diffuse interstitial infiltrates, septal thickening, honeycombing and traction bronchiectasis (figure2). The pattern of ILD mimics that of idiopathic interstitial pneumonia (IIP). The presence of pleural disease is common in patients with SLE while it is rare in IIP. One study attempted to correlate HRCT findings with clinical and pulmonary function tests (PFTs). There was no correlation between abnormal HRCT, pulmonary symptoms, disease activity and drug therapy.(Fenlon *et al.*, 1996) The PFT findings did not correlate with the presence or the severity of ILD on HRCT.(Fenlon *et al.*, 1996) This lack of correlation was confirmed in another study.(Sant *et al.*, 1997) The rate of abnormal CT findings in asymptomatic patients is high, reaching 30%.(Bankier *et al.*, 1995; Fenlon *et al.*, 1996; Haupt *et al.*, 1981) There is no current recommendation to screen asymptomatic SLE patients with HRCT. Bronchoscopy with BAL is done to rule out infections. Thoracoscopic lung biopsy is needed to identify the underlying pathology. Several histopathological patterns are known to occur. The most common pattern is non-specific interstitial pneumonia (NSIP), cellular, fibrotic or mixed.(Tansey *et al.*, 2004) This pattern is characterized by homogeneous infiltration of alveolar walls with large number of lymphocytes and plasma cells. Organizing pneumonia, which used to be called bronchiolitis obliterans organizing pneumonia (BOOP) has also been reported.(Gammon *et al.*, 1992) Lymphoid interstitial pneumonia (LIP) and usual interstitial pneumonia (UIP) are found more commonly in patients with secondary Sjögren's syndrome or overlap syndrome.(Schattner *et al.*, 2003; Tansey *et al.*, 2004) There are no placebo control trials to guide the treatment of ILD in SLE. Systemic corticosteroids (Prednisone 60mg/d for at least four weeks) improved respiratory symptoms and DLCO in the majority of patients when followed up for a mean of 7.3 years. (Weinrib *et al.*, 1990) In patients who don't respond to corticosteroids, treatment with cyclophosphamide, azathioprine, or mycophenolate should

be considered. Another approach is to start combination therapy; cyclophosphamide and oral glucocorticoids for severe cases and oral steroids with azathioprine for less severe cases.(Swigris *et al.*, 2008) The prognosis of ILD associated with SLE is better than the idiopathic forms.(Renzoni *et al.*, 1997) The course is usually slow and tends to stabilize or improve with time.

2.3 Pulmonary vascular diseases

2.3.1 Thromboembolic disease

Patients with SLE are at increased risk of venous thromboembolism (VTE) with a prevalence of 9%.(Gladman & Urowitz, 1980) It is usually related to disease activity. Patients with antiphospholipid antibodies have an even more increased risk reaching up to 35% to 42%. (Love & Santoro, 1990) Antiphospholipid antibodies (aPL) maybe present in up to two thirds of patients with lupus.(Ruiz-Irastorza *et al.*, 2004; Somers *et al.*, 2002) The two major antibodies that constitute aPL are lupus anticoagulant and anticardiolipin antibodies (IgG or IgM). Criteria of diagnosing antiphospholipid syndrome are discussed elsewhere. In addition to VTE, patients with antiphospholipid syndrome are at increased risk of recurrent abortions, pulmonary hypertension (PH), DAH, acute respiratory distress syndrome (ARDS), and cardiac valvular lesions. (Kamen & Strange, 2010; Swigris *et al.*, 2008) If small-vessel occlusion occurs in three or more organs the condition is known as catastrophic antiphospholipid syndrome (CAPS). (Asherson & Cervera, 1995; Asherson *et al.*, 2001; Cervera *et al.*, 2007; Cervera & Asherson, 2008) Cardiopulmonary involvement is common with this syndrome and it usually results in ARDS (Asherson *et al.*, 2008; Bucciarelli *et al.*, 2006) VTE can occur either acutely (deep vein thrombosis or acute pulmonary embolism) or chronically resulting in chronic thromboembolic pulmonary hypertension (CTEPH). Clinical features and diagnosis of VTE are similar to unprovoked situations. Once VTE develops,

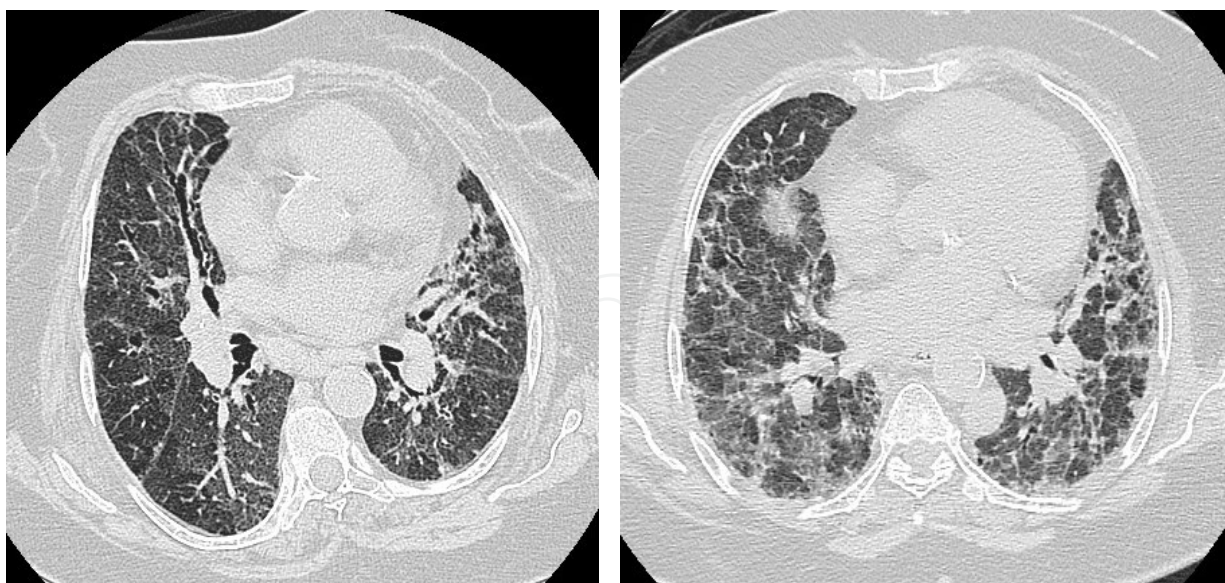


Fig. 2. (Left) HRCT chest showing areas of ground glass opacities and traction bronchiectasis. Surgical lung biopsy confirmed the diagnosis of non-specific interstitial pneumonia (cellular type). (Right) HRCT chest showing interstitial thickening and areas of honeycombing. Fibrotic form of non-specific interstitial pneumonia was evident on lung biopsy

long term anticoagulation with warfarin and a target INR of 2.0 to 3.0 is highly recommended. It used to be recommended to achieve a higher target INR, but in one study, high intensity warfarin (target INR 3.0-4.0) was found not superior to moderate intensity warfarin (target INR 2.0-3.0). Moderate intensity warfarin had lower rate of major bleeding.(Crowther *et al.*, 2003) Recommendation for primary prevention is lacking. Some authors use long term low dose aspirin.(Swigris *et al.*, 2008) Patients with CAPS usually require systemic glucocorticoids, immunosuppressants, plasmapheresis and intravenous immunoglobulin in addition to anticoagulation.(Swigris *et al.*, 2008) Mortality rate can reach up to 50%.(Asherson & Cervera, 1995; Asherson *et al.*, 2001, 2008)

2.3.2 Pulmonary hypertension

Pulmonary Hypertension (PH) is defined as a mean pulmonary artery pressure (PAP) \geq 25mmHg at rest. (McLaughlin *et al.*, 2009) The prevalence of PH in SLE patients varies between 0.5% to 15%. (Asherson & Oakley, 1986; Asherson *et al.*, 1990) In one study, 50 consecutive patients with SLE were carefully tested by transthoracic echocardiogram to look particularly for PH, none was found to have any echocardiographic evidence of PH. In that cohort almost one third were found to have an isolated reduction in DLCO, which could be a marker of early pulmonary vascular involvement.(Hodson *et al.*, 1983; Gari *et al.*, 2009) The prevalence is definitely lower than those with scleroderma. Raynaud's phenomenon occurs in 75% of SLE associated pulmonary arterial hypertension (PAH) compared to only 20% of patients with SLE and no PH.(Matthay *et al.*, 1975) The duration of SLE doesn't correlate with the development of PAH.(Asherson & Oakley, 1986; Asherson & Cervera, 2007) Clinical presentations of SLE associated PAH is similar to idiopathic pulmonary arterial pulmonary hypertension (IPAH). Symptoms include dyspnea, fatigue, chest pain and lower limb swelling. Physical examination includes jugular venous distension with a large v wave, loud pulmonic component with wide splitting of the second heart sound, murmur of tricuspid regurgitation and/or pulmonic insufficiency, and lower limb edema. Physical findings may be minimal in mild PH. In patients with suspected PH, transthoracic echocardiogram is the best initial diagnostic test. Right ventricular systolic pressure (RVSP) which is an approximation of systolic PAP can only be measured if a tricuspid regurgitation (TR) signal is detected. TR signal is only available in 30% of population. Although PH is more common in SLE patients than general population, other causes of PH need to be ruled out. Tests to evaluate for other causes include HIV, hepatitis B and hepatitis C serology, aPL antibodies, HRCT chest to evaluate for interstitial lung disease, ventilation perfusion scan (V/Q) to look for any evidence of chronic pulmonary emboli leading to CTEPH, and polysomnogram if obstructive sleep apnea is suspected. Eventually right heart catheterization is required to confirm the diagnosis of PAH and to rule out PH secondary to left heart disease. The pathogenesis of SLE associated PAH is not clear; the high prevalence of aPL antibodies suggests that thrombosis may play a role. (Prabu *et al.*, 2009) Histopathologic changes are identical to IPAH and include plexiform lesions, intimal fibrosis, and thickening of the media. In addition, complement and immunoglobulin deposits are found in some patients suggesting that immune deposits may be involved in the pathogenesis.(Quismorio *et al.*, 1984) Several aspects need to be considered when it comes to treating SLE associated PAH. All patients should receive long term anticoagulation especially those with aPL antibodies. Oxygen, diuretics and digoxin should be considered in all patients. PH specific therapies used to treat IPAH are also effective in treating SLE associated PAH. Epoprostenol, bosentan, sildenafil, ambrisentan and tadalafil have all been

shown to be effective in treating PAH.(Barst RJ *et al.*,1996; Galie *et al.*, 2005, 2008, 2009; Rubin *et al.*, 2004) PAH specific therapies were found to improve 6-minute walk distance (6MWD) and functional class.

Adding immunosuppressants may provide further improvement. Intravenous cyclophosphamide (monthly for six months) was shown to be effective. It reduced the systolic PAP when measured by transthoracic echocardiogram, and improved 6MWD.(Gonzalez-Lopez *et al.*, 2004; Jais *et al.*, 2008) Oral glucocorticoids in conjunction with immunosuppressants lowered PAP and improved 6MWD.(Tanaka *et al.*, 2002; Sanchez *et al.*, 2006) It is not very clear when to use immunosuppressants in SLE associated PAH. Patients with mild PH may benefit from immunosuppressive therapy while patients with moderate to severe PH need PH specific therapy with or without immunosuppressants.(Swigris *et al.*, 2008) The prognosis of SLE associated PAH is worse than IPAH, with a 5-year survival of only 17% compared to 68% in patients with IPAH.(Chung *et al.*, 2006) Given the rarity of PH in patients with SLE, there is no recommendation to screen asymptomatic patients with echocardiogram. On the other hand, patients with scleroderma should have annual transthoracic echocardiogram to evaluate for the presence of PH.

2.3.3 Acute reversible hypoxia

This is a rare complication of lupus. In one series 27% of hospitalized patients had this condition.(Abramson *et al.*, 1991) It is characterized by an abrupt onset of unexplained hypoxia and hypocapnea. Radiographic chest imaging is normal. Ventilation perfusion (V/Q) scan doesn't show any evidence of thromboembolism. Arterial blood gases demonstrates an increase in Alveolar-arterial (A-a) PO₂ gradient. The pathogenesis of this syndrome is not clear, but it is believed to be due to complement activation leading to leukoaggregation within pulmonary capillaries.(Abramson *et al.*, 1991; Belmont *et al.*, 1994) Plasma C3a level is markedly elevated if measured during the episode.(Abramson *et al.*, 1991) Most cases respond quickly to high dose of systemic corticosteroids.(Abramson *et al.*, 1991; Martinez-Taboada *et al.*, 1995)

2.4 Airway disease

2.4.1 Upper airway involvement

Involvement of the upper airways can occur in up to 30% of patients with SLE. A variety of disorders have been described including laryngeal mucosal inflammation or ulceration, cricoarytenoiditis, vocal cord paralysis, and necrotizing vasculitis.(Langford & Van Waes, 1997; Teitel *et al.*, 1992) Patients present with hoarseness and or dyspnea. Severe upper airway obstruction due to angioedema requiring mechanical ventilation has also been reported.(Thong *et al.*, 2001) Angioedema usually present with lips and mouth swelling, dysphagia, odynophagia and breathing difficulty, it could be due to SLE or medications used in SLE like angiotensin-converting enzyme inhibitors.(Agah *et al.*, 1997) Routine chest imaging with Chest x-ray and chest CT is usually normal in patients with upper airway obstruction. Spirometry may show flattening of the inspiratory or expiratory loop or both depending on the location of the obstruction. Specialized imaging of the upper airways with 3-D reconstruction is important to demonstrate the site of obstruction. Direct visualization with fibro-optic laryngoscopy or bronchoscopy is needed to assess for vocal cord mobility. Generally, corticosteroid therapy will be effective in case of laryngeal mucosal inflammation or ulceration, and vocal cord paralysis.(Smith *et al.*, 1977; Teitel *et al.*, 1992). In those who

don't respond to glucocorticoids, infectious causes should be considered. Typical pathogens are *Haemophilus influenzae* and streptococcus, other rare infections include *Histoplasma*, *coccidioides*, *cryptococcus*, *blastomycosis* and *candida*.(Toomey *et al.*, 1974)

2.4.2 Lower airway involvement

Diseases involving the lower airways in patient with SLE include bronchial wall thickening, bronchiectasias and bronchiolitis obliterans (BO). In a prospective study of 34 subjects with SLE, HRCT chest showed bronchial wall thickening and bronchiectasias in 21% of patients. These changes were predominantly asymptomatic.(Fenlon *et al.*, 1996) Bronchiolar disorders are rare.(Pego-Reigosa *et al.*, 2009) Abnormalities in PFTs have been reported in up to two thirds of patient with SLE.(Andonopoulos *et al.*, 1988) In one study of 57 consecutive lupus patients, mild to moderate airflow obstruction was noted in 16%.(Groen *et al.*, 1992) BO has been rarely reported.(Beylot-Barry *et al.*, 1994; Godeau *et al.*, 1991; Kawahata *et al.*, 2008) The disease is characterized by severe airflow obstruction that's mostly irreversible. Patients usually have progressive dyspnea. PFTs show reduction in FEV1/FVC ratio. If obstruction is severe, gas trapping (elevated residual volume) and hyperinflation (elevated total lung capacity) may be noted. HRCT chest shows mosaic attenuation pattern that gets accentuated in the expiratory images (figure 3). Histopathologic confirmation is rarely required. Disease is usually progressive. Systemic corticosteroids and immunosuppressive therapies have been tried with little success.(Beylot-Barry *et al.*, 1994; Kawahata *et al.*, 2008) More recently anticholinergics were reported to have a favorable outcome.(Kawahata *et al.*, 2008)

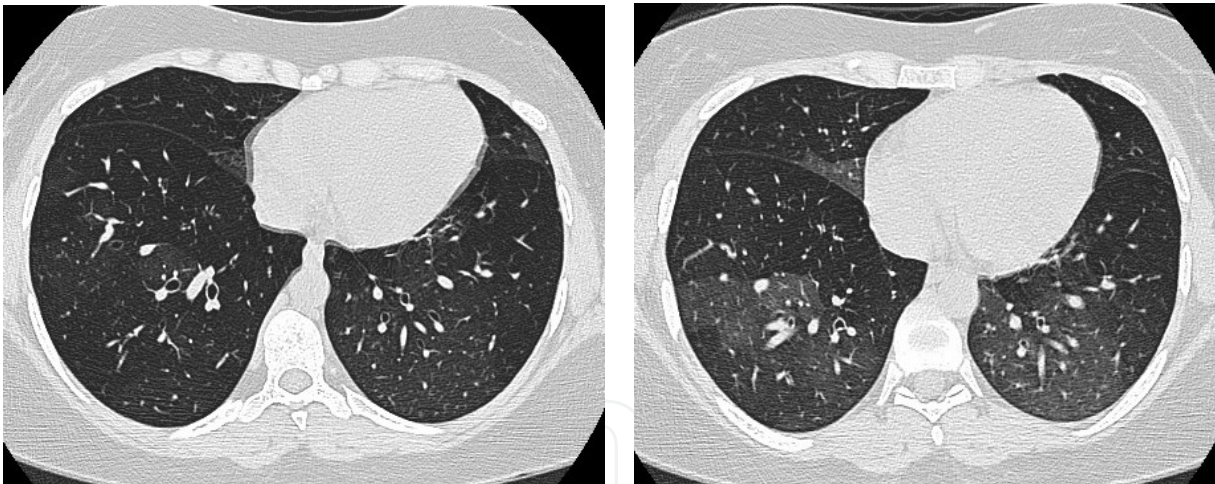


Fig. 3. (Left) Inspiratory HRCT scan of a 35 year old woman with SLE and bronchiolitis obliterans showing mosaic attenuation. (Right) Expiratory HRCT scan in the same subject showing an increase in mosaic pattern indicating small airways disease.

2.5 Muscular involvement

Shrinking lung syndrome (SLS) is a rare manifestation of SLE. 77 patients with SLS have been reported in the literature, with a prevalence of 0.6% to 0.9%.(Pego-Reigosa *et al.*, 2009; Toya & Tzelepis, 2009) It was first described in patients with lupus who presented with unexplained dyspnea, decreased lung volumes and elevation of the diaphragm on radiographic imaging and restriction on pulmonary function tests in the absence of any parenchymal disease.(Hoffbrand & Beck, 1965; Karim *et al.*, 2002; Warrington *et al.*, 2000) It

can rarely be the presenting feature of SLE.(Stevens *et al.*, 1990) The pathogenesis is still unclear with conflicting results. One hypothesis is myositis of the diaphragm or phrenic neuropathy.(Hardy *et al.*, 2001; Rubin & Urowitz, 1983;) In one study, patients with elevated diaphragms had an abnormal transdiaphragmatic pressure, indicating diaphragmatic weakness.(Gibson *et al.*, 1977) However normal muscle strength of the diaphragm in patients with SLS has been reported.(Hawkins *et al.*, 2001; Laroche *et al.*, 1989) Clinically, patients present with dyspnea that is particularly worse when supine. Pleuritic chest pain is present in 65% of patients.(Toya & Tzelepis, 2009) Physical examination reveals diminished breath sounds at the lung bases with or without basilar crackles. Chest radiographs and CT show elevation of both diaphragms with basal linear atelectasis and without any evidence of parenchymal lung disease (figure 4). PFT's show restriction with preserved DLCO corrected for alveolar volume (DL/VA). Assessment of respiratory muscles show reduced maximal inspiratory pressure (MIP) and stable maximal expiratory pressure (MEP). Diaphragmatic weakness can be established by measuring the transdiaphragmatic pressure or by doing electromyography of the diaphragms. Autopsy findings include diffuse fibrosis and atrophy of the diaphragms. (Rubin & Urowitz, 1983) There are no randomized clinical trials for the treatment of SLS. Several agents have been tried with variable effects. Oral glucocorticoids with or without immunosuppressive medications have been shown effective. (Soubrier *et al.*, 1995; Walz-Leblanc *et al.*, 1992) Other treatment options for SLS include theophylline, azathioprine, methotrexate, cyclophosphamide and rituximab.(Benham *et al.*, 2010; Karim *et al.*, 2002; Soubrier *et al.*, 1995; Toya & Tzelepis, 2009; Van Veen *et al.*, 1993; Walz-Leblanc *et al.*, 1992) Disease usually stabilizes or improves with treatment with good overall prognosis.(Martens *et al.*, 1983) Respiratory failure rarely occurs.(Ernest & Leung, 2010)



Fig. 4. Chest X-ray showing gross elevation of both diaphragms in a patient with SLE and shrinking lung syndrome

2.6 Associated lung disorders

2.6.1 Adult respiratory distress syndrome (ARDS)

The prevalence of ARDS is 4% to 15% in patients with lupus.(Andonopoulos, 1991; Kim *et al.*, 1999) If it develops the mortality rate can reach up to 70%.(Kim *et al.*, 1999) ARDS

related mortality contributes to 30% of all Lupus deaths. The most frequent cause of ARDS is sepsis; other causes include ALP, DAH, and CAPS. In lupus patients, ARDS tend to occur at a younger age and is more progressive than ARDS in non-SLE patients. (Andonopoulos, 1991; Kim *et al.*, 1999; Pego-Reigosa *et al.*, 2009) It is important to identify the underlying cause. Treatment of ARDS is supportive.

2.6.2 Infectious complications

SLE can impair the immune system at multiple levels. (Orens *et al.*, 1994; Rudd *et al.*, 1981) The clinical significance of this is unknown since the risk of infection in the absence of immunosuppression is negligible. Most patients with infectious complications are on immunosuppressive drugs. Infections account for 30% to 50% of all deaths of SLE. (Bernatsky *et al.*, 2006; Zandman-Goddard & Shoenfeld, 2005;) Bacterial pathogens account for 75% of all infections, mycobacteria 12%, fungal infections 7%, and viruses 5%. (Kinder *et al.*, 2007) Opportunistic infections such as *Pneumocystis jiroveci*, *Nocardia*, *Aspergillus* and Cytomegalovirus have been reported. (Fessler, 2002; Petri, 1998; Zandman-Goddard & Shoenfeld, 2005) Clinical picture is indistinguishable from non-infectious complications such as ALP and DAH, hence aggressive diagnostic approach is recommended with chest imaging, bronchoscopy and BAL. Empiric broad-spectrum antibiotics should be started awaiting identification of an organism. Once a pathogen is isolated treatment should be tailored accordingly. Risk of infection can be reduced by influenza and pneumococcal vaccination. (O'Neill & Isenberg, 2006) Since many patients with SLE require systemic glucocorticoids and immunosuppressants at some point, screening for latent Tuberculosis (TB) is important, especially in high prevalence areas. This can be done via skin testing or interferon gamma release assay (IGRA). For those taking glucocorticoids, induration of 5mm or greater is considered a positive tuberculin skin test. If latent TB is identified treatment is recommended with a nine month course of Isoniazid. The role of *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis is less clear. It is suggested for those who are on heavy immunosuppression. (Li *et al.*, 2006)

2.6.3 Lung cancer

Studies have shown an increased risk of lung cancer in patients with SLE. (Bernatsky *et al.*, 2006; Pego-Reigosa *et al.*, 2009) Histological pattern is similar to that in general population, adenocarcinoma being most common. However there is tendency for uncommon thoracic malignancies such as carcinoids and bronchoalveolar carcinoma. (Bin *et al.*, 2007; Pego-Reigosa *et al.*, 2009)

2.7 Drug reactions

In this section we will cover two aspects of drugs and SLE. First we will briefly discuss drugs that can cause SLE and the associated pulmonary manifestations. After that we will elaborate on pulmonary drug toxicity associated with commonly used medications to treat SLE.

Pulmonary manifestations of drug induced lupus are similar to idiopathic SLE. (Cush & Goldings, 1985; Yung & Richardson, 1994) Most commonly it presents with pleurisy and pleural effusion. (Wiedemann & Matthay, 1989) Common drugs include Procainamide and hydralazine. Newer biologic agents such as etanercept have been reported to cause drug induced lupus. (Abunasser *et al.*, 2008)

Common drugs used to treat lupus and are known to cause pulmonary complications include Methotrexate and Cyclophosphamide.

Pulmonary complications related to methotrexate are rare, estimated less than 1%. (Lateef *et al.*, 2005) Methotrexate can cause acute, subacute or chronic lung toxicity. It is usually not dose dependent but rather idiosyncratic. (Imokawa *et al.*, 2000; Ohosone *et al.*, 1997) Subacute pneumonitis is most common and presents with fever, cough and dyspnea. Crackles are usually noted on physical examination. It usually presents within the first year of starting the drug. If left unrecognized it can progress into pulmonary fibrosis in up to 10%. Radiologic findings are not specific. Ground glass opacities and diffuse interstitial infiltrates are frequently noted on HRCT. BAL is needed to rule out infections. Histologic findings include varying degree of inflammation and fibrosis. Ill-defined granulomas, and increased tissue eosinophils have been observed. (Malik *et al.*, 1996; Sostman *et al.*, 1976) Once diagnosis is made methotrexate needs to be stopped and systemic steroids should be started. Prognosis is usually favorable.

Cyclophosphamide lung toxicity is also idiosyncratic. It can present as early onset or late onset pneumonitis. (Malik *et al.*, 1996) Early onset disease appears within the first six months of starting treatment. It presents with non-productive cough, fever and dyspnea. (Pego-Reigosa *et al.*, 2009) CT chest shows bilateral upper lobe predominant ground glass opacities. PFT shows reduction in lung volumes and DLCO. BAL is needed to rule out infections. Discontinuing the drug along with systemic glucocorticoids usually improve symptoms and lung function. Late onset pneumonitis usually occurs after several years of exposure to cyclophosphamide. It is a slowly progressive disease. It presents with progressive dyspnea and dry cough. Chest imaging shows interstitial fibrosis affecting the upper lobes. This condition usually does not respond to steroids. Lung transplantation is an option in appropriate candidates.

3. Assessment of patients with dyspnea

3.1 Assessment of patients with chronic dyspnea

The work up of patients with SLE and chronic dyspnea can be lengthy (Figure 5). Chronic dyspnea can be due to a variety of conditions such as interstitial lung disease related to SLE or drugs used to treat lupus, pleural disease, pulmonary hypertension, systolic heart failure, upper airway disease, obliterative bronchiolitis, shrinking lung syndrome or chronic infections. Certain clues on history can be helpful; for example dyspnea increasing in the supine position suggests diaphragmatic involvement due to SLS, dyspnea and hoarseness suggest upper airway involvement, Dyspnea with pleuritic chest pain suggests pleuritis related to SLE. All patients require CXR, HRCT chest and full PFT. If chest imaging is normal with or without isolated reduction in DLCO, then transthoracic echocardiogram should be done to assess for the presence of PH. If PH is detected, patients should not be labeled to have SLE associated PAH until other causes have been ruled out. So hepatitis B and C serology, HIV testing, and V/Q scan should be done. All patients should have right heart catheterization to confirm the presence of PH and to rule out left heart disease. If SLE-PAH is diagnosed PH specific therapies should be started. If chest imaging shows elevation of the diaphragms, especially in the presence of normal DLCO adjusted for alveolar volume, shrinking lung syndrome should be suspected. Electromyography or transdiaphragmatic pressure measurement should be obtained. Either of these two tests may show evidence of diaphragmatic weakness. If confirmed, trial of systemic steroids is advised. The presence of

pleural effusion on CXR or CT chest suggests pleural disease associated with SLE. The pleural fluid should be analyzed to rule out other causes. In situations where chest imaging is normal but there is flattening of the inspiratory loop, expiratory loop or both, upper airway obstruction needs to be ruled out. Special imaging of the upper airways is recommended. If interstitial changes are the predominant features on chest imaging, interstitial lung diseases related to lupus or drugs are the main differential. Bronchoscopy with BAL should be done to rule out chronic infections. Thoracoscopic lung biopsy is helpful to identify the pathological pattern of involvement.

3.2 Assessment of patients with acute dyspnea

Several conditions can predispose patients to episodes of acute dyspnea. Pulmonary infections, ALP, DAH, PE, and acute reversible hypoxia are the major culprits. Assessment starts with clinical evaluation. (Figure 6) is a proposed algorithm for work up of patients with SLE presenting with acute dyspnea. Most conditions are indistinguishable on clinical bases. The presence of hemoptysis should raise the suspicion of DAH or PE. After clinical evaluation and stabilization of the patient it is important to get a CXR. If CXR is normal then it is more likely that dyspnea is due to either acute reversible hypoxia or PE. V/Q scan will differentiate between the two. V/Q scan will be normal in the former and it will show mismatched perfusion defects in the latter. If CXR shows pleural effusion or wedge shaped

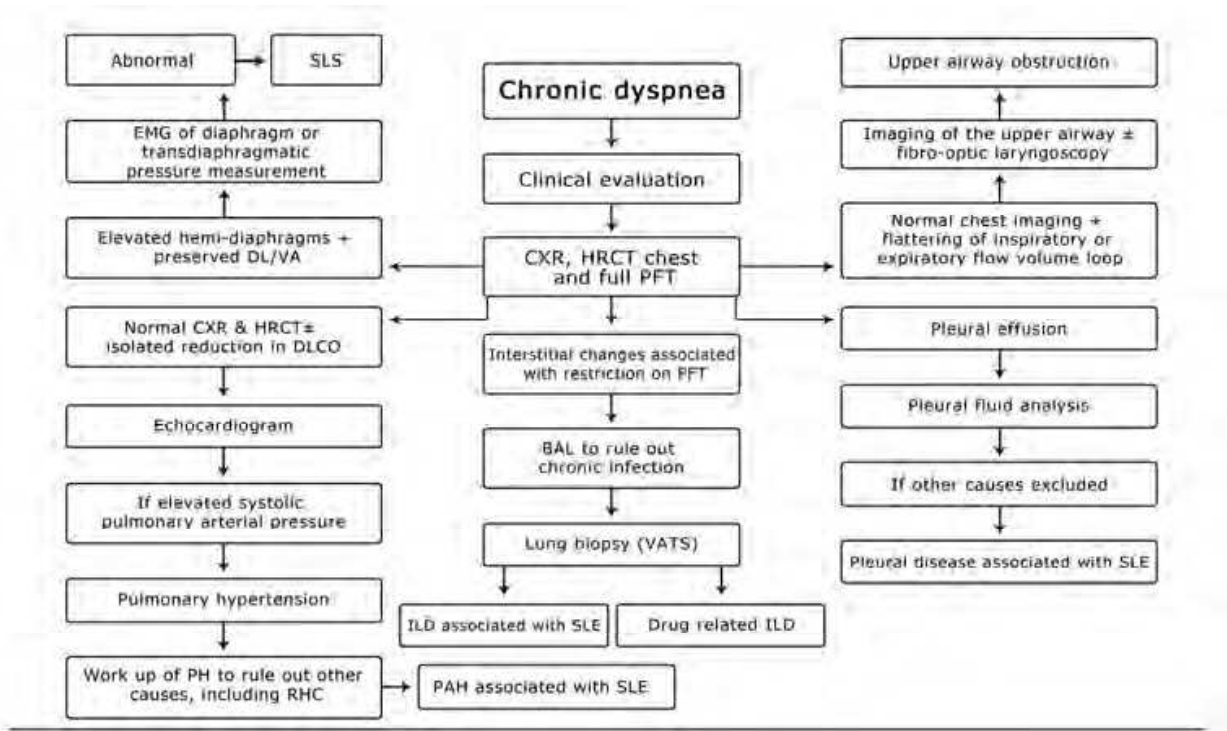


Fig. 5. Work-up of patients with SLE presenting with chronic dyspnea. bronchoalveolar lavage (BAL); chest x-ray (CXR); diffusion capacity for carbon monoxide (DLCO); diffusion capacity for carbon monoxide adjusted for alveolar volume (DL/VA); high resolution computed tomography (HRCT); interstitial lung disease (ILD); pulmonary arterial hypertension (PAH); pulmonary function test (PFT); pulmonary hypertension (PH); right heart catheterization (RHC); shrinking lung syndrome (SLS); systemic lupus erythematosus (SLE); video-assisted thoracoscopic surgery (VATS).

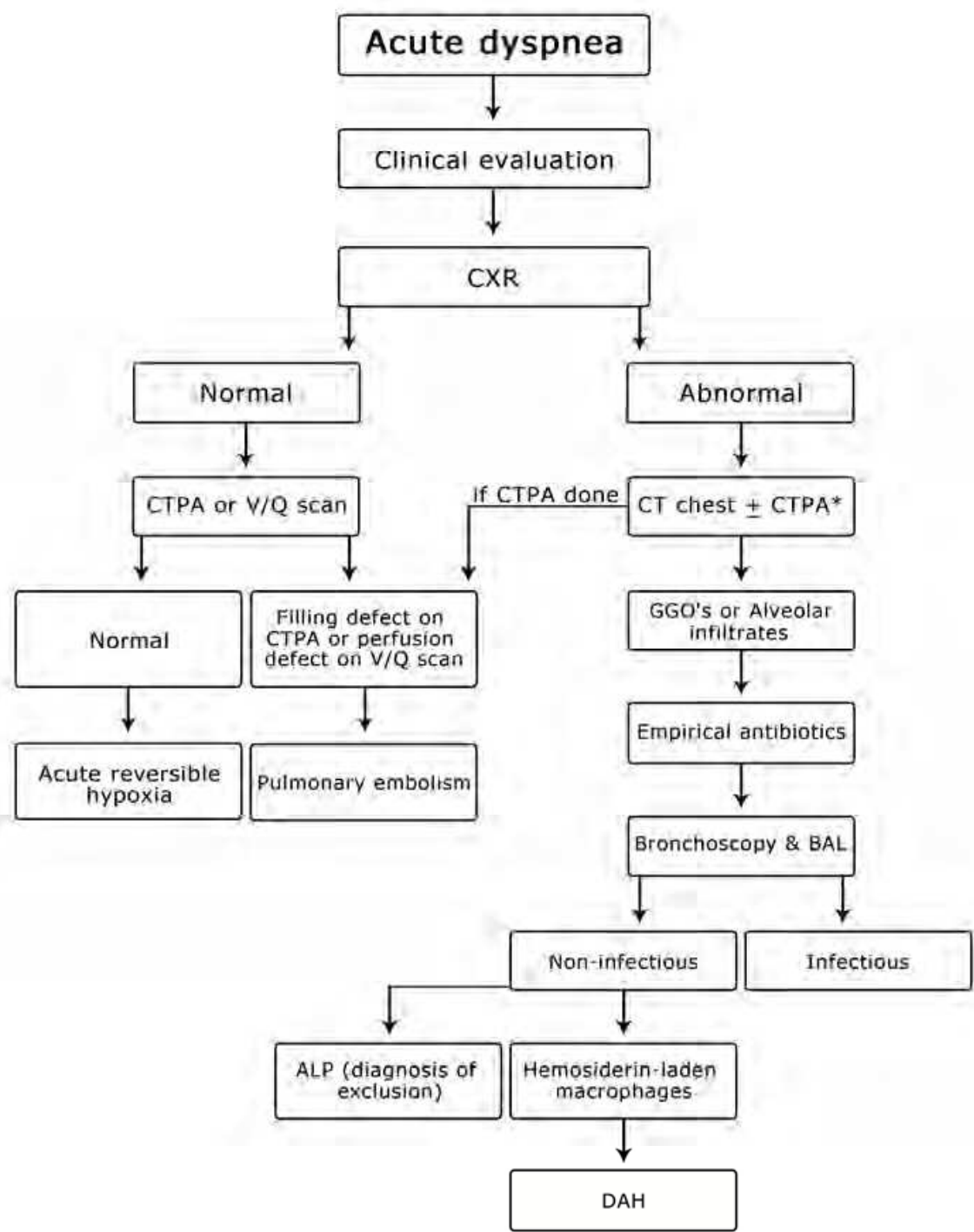


Fig. 6. Work-up of patients with SLE presenting with acute dyspnea. acute lupus pneumonitis (ALP); bronchoalveolar lavage (BAL); chest x-ray (CXR); computed tomography (CT); computed tomography pulmonary angiogram (CTPA); diffuse alveolar hemorrhage (DAH); ground-glass opacities (GGO's); ventilation/perfusion lung scan (V/Q Scan)

* CTPA is done if pulmonary embolism suspected

opacities it is important to get CT pulmonary angiogram to look for evidence of PE. If CXR shows mainly alveolar infiltrates, CT chest should be considered. In these situations bronchoscopy with BAL, with or without TBBX, is highly recommended. The presence of hemosiderin laden macrophages confirms the diagnosis of DAH. If TBBX is performed and it showed features of DAD, then the likely diagnosis is ALP. BAL should be routinely sent for cultures. Empiric antibiotics should be started immediately until the results of cultures are known. It is not unusual to start patients on both broad spectrum antibiotics and systemic corticosteroids while the work up is being actively pursued.

4. Conclusion

SLE can affect many aspects of the pulmonary system. There is significant overlap in the clinical presentation of many SLE associated pulmonary conditions. Aggressive work up is needed early on to identify the underlying etiology.

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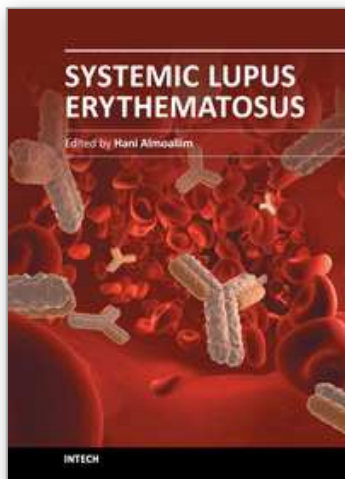
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This book provides a comprehensive overview of the basic and clinical sciences of Systemic Lupus Erythematosus. It is suitable for basic scientists looking for detailed coverage of their areas of interest. It describes how advances in molecular biology have increased our understanding of this disease. It is a valuable clinical resource for practicing clinicians from different disciplines including rheumatologists, rheumatology fellows and residents. This book provides convenient access to information you need about cytokines, genetics, Fas pathway, toll like receptors and atherogenesis in SLE. Animal models have been reviewed as well. How to avoid delay in SLE diagnosis and management, in addition to various clinical manifestations including pregnancy and SLE have all been explained thoroughly in this book.

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