CHEST Special Feature

Pulmonary and Thrombotic Manifestations of Systemic Lupus Erythematosus*

Jeffrey J. Swigris, DO, MS; Aryeh Fischer, MD; Joann Gilles, MD; Richard T. Meehan, MD; and Kevin K. Brown, MD, FCCP

Systemic lupus erythematosus (SLE) is considered the archetypal systemic autoimmune disease. Clinically characterized by multisystem involvement and varied serologic abnormalities, no two patients present or have disease that evolves in exactly the same way. Viewed histologically, SLE is characterized by some combination of inflammation and fibrosis, and the clinical phenotype is dictated by the relative contributions of each and the organs affected. Tissue injury appears to be mediated by characteristic autoantibody production, immune complex formation, and their organ-specific deposition. As expected in a multisystem disease, the entire pulmonary system is vulnerable to injury. Any of its compartments—airways, lung parenchyma, vasculature, pleura, or the respiratory musculature—may be independently or simultaneously affected. This article offers the reader a comprehensive review of the numerous pulmonary and thrombotic manifestations of SLE and suggests approaches to their management.

(CHEST 2008; 133:271–280)

Key words: lung; systemic lupus erythematosus; thrombosis

Abbreviations: aCL = anticardiolipin antibodies; ALP = acute lupus pneumonitis; aPL = antiphospholipid antibodies; APS = antiphospholipid syndrome; β_2GPI = beta-2 glycoprotein I; CAPS = catastrophic antiphospholipid syndrome; DAD = diffuse alveolar damage; DAH = diffuse alveolar hemorrhage; DLCO = diffusion capacity of the lung for carbon monoxide; GGO = ground-glass opacity; HRCT = high-resolution CT; ILD = interstitial lung disease; INR = international normalized ratio; LA = lupus anticoagulant; LIP = lymphoid interstitial pneumonia; NSAID = nonsteroidal antiinflammatory drugs; NSIP = nonspecific interstitial pneumonia; PAH = pulmonary arterial hypertension; PASP = pulmonary artery systolic pressure; SLE = systemic lupus erythematosus; SLS = shrinking lung syndrome; TTE = transthoracic echocardiography

Systemic lupus erythematosus (SLE) most commonly affects women of childbearing age.[1] Studies[1] from the 1960s estimated its prevalence to be between 18.3 and 40 cases per 100,000 for 15- to 44-year-old white women and twice that for 15- to 44-year-old black women. In general, women are afflicted 6 to 10 times more often than men.[2] Hispanics and African Americans present earlier, with more active and aggressive disease than whites.[3] When SLE is diagnosed after age 49 years, there is a lower female/male ratio; less active disease in general, but greater accumulated organ damage; a higher incidence of serositis, pulmonary, and neurologic involvement; and higher mortality.[4] In one study,[5] the 10-year survival rate among all subjects was approximately 90%, with one fourth of deaths due to "active" SLE, thrombotic events, and infection. In another study,[6] active lupus (34%), infection (22%), cardiovascular disease (16%), and cancer (6%) accounted for 144 deaths in 408 subjects with SLE who were monitored over 11 years. SLE-specific deaths usually occur within the first 5 years of symptom onset and are predominantly a result of infectious

*From the Autoimmune Lung Disease Center; National Jewish Medical and Research Center; Denver, CO.
Funding for this work was provided by the Farkas Family Lupus Fund. The authors have no actual or potential conflicts of interest with the information discussed in this article.
Manuscript received January 10, 2007; revision accepted May 14, 2007.

Correspondence to: Jeffrey J. Swigris, DO, MS, Autoimmune Lung Center, National Jewish Medical and Research Center, 1400 Jackson St #G011, Denver, CO 80206; e-mail: swigrisj@njc.org
DOI: 10.1378/chest.07-0079

complications from aggressive immunosuppressive treatment of the manifestations of active disease. Cardiovascular disease and malignancy are the most common etiologies of later mortality.[6]

Pulmonary Involvement

In the 50 years since Sante and Wyatt[7] described a lack of lung involvement "until the terminal stages of the disease," significant advances in our understanding of SLE-related lung involvement have been made. The earliest reports describe a "waxing and waning, migrating bronchopneumonia,"[8] and a diffuse, noninfectious, inflammatory lung disease termed *primary atelectizing pneumonitis*.[9,10] In more recent reports, the frequency and characteristics of lung involvement have depended on the clinical phenotype of the population studied along with the methods of investigation and their sensitivities to identifying disease activity.

Infection

Pneumonia remains a primary concern in patients with SLE, particularly those treated with glucocorticoids or an immunomodulatory agent. In one study[11] of 87 subjects with SLE, over a median 9.4 years of follow-up, 35 subjects had 57 infectious episodes; 16 episodes (28%) were pneumonia. Treatment with IV glucocorticoids and/or an immunomodulatory agent were independent risk factors for infection. In another study,[5] over 10 years of follow-up of an inception cohort of 1,000 subjects with SLE, 360 infections developed, 117 of which (11.7%) were respiratory; bacterial sepsis was the cause of death in 15 of 68 subjects, and there was a pulmonary source in 6 subjects (8.8%).[5] In the authors' experience, infection is the first consideration in all SLE patients, particularly those receiving an immunomodulatory agent, presenting with new/worsening respiratory symptoms or radiologic imaging.

Drug Reactions

There are no systematic studies of pulmonary complications from drugs used to treat manifestations of SLE. For some agents (*eg*, hydroxychloroquine), we could find no reports of drug-induced lung disease. A cellular interstitial pneumonia has been reported to occur with azathioprine or mycophenolate mofetil,[12,13] but we have not observed this complication with either drug. Nonsteroidal antiinflammatory drugs (NSAIDs) are a known cause of chronic eosinophilic pneumonia.[14]

Two types of lung injury due to cyclophosphamide have been described: (1) early onset pneumonitis, developing within the first 6 months of drug exposure, responsive to drug withdrawal and glucocorticoids; and (2) late onset (reported up to 13 years after cyclophosphamide exposure), upper-lobe-predominant fibrosis and bilateral pleural thickening that is poorly responsive to glucocorticoid therapy.[15] Methotrexate-induced lung injury occurs in 2 to 12% of recipients and is unrelated to current or total dose, duration of therapy, or underlying disease.[16,17] Histologic findings are variable and nonspecific, with varying degrees of inflammation and/or fibrosis. Small, ill-defined granulomas may be prominent. Peripheral eosinophilia occurs in up to 40% of patients, and increased tissue eosinophils have been observed.[15,18] Prognosis is favorable with methotrexate discontinuation and glucocorticoids.

Pathologic, Physiologic, and Radiologic Findings

In early autopsy series[19,20] of patients with SLE, an infectious "bronchopneumonia" (Fig 1) was the most common finding. Diffuse "interstitial pneumonitis," "interstitial thickening," "alveolar hemorrhage," "organizing pneumonia," and "diffuse alveolar damage" (DAD) were also observed. Pleural effusions and acute pleuritis were seen frequently. In the most recent autopsy series,[21] after excluding abnormalities not believed to be "directly related" to SLE, in 120 subjects 18% had significant lung pathology, including 22 with pleuritis, 11 with cellular interstitial pneumonia, and 5 cases of mixed inflammatory/fibrotic interstitial disease.

Pulmonary physiologic abnormalities are common. In one study,[22] lung function was entirely normal in only 33% of 70 nonsmoking SLE subjects compared with 83% of 70 age-matched non-SLE control subjects, The most common defect is a low diffusion

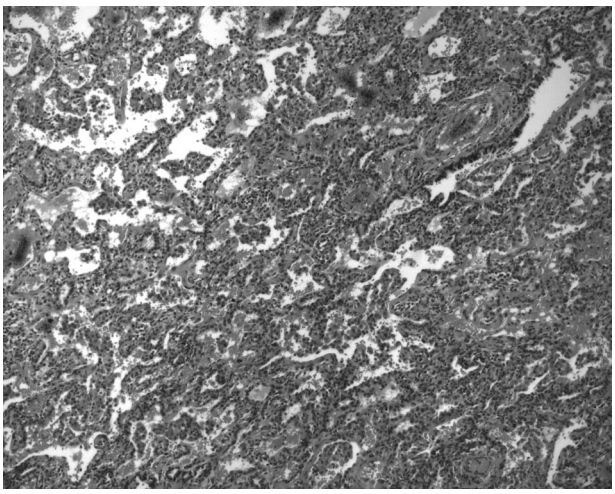

Figure 1. Surgical lung biopsy specimen showing acute pneumonia in which neutrophilic exudates fill airspaces (hematoxylin-eosin, original × 4).

capacity of the lung for carbon monoxide (DLCO) with or without a concomitant restrictive ventilatory defect.[22,23] One third or more of SLE subjects will have isolated diffusion impairment.[23] Airflow limitation, usually subclinical, is identified in a minority of patients.[22,24,25] Longitudinal changes in physiology have been examined. In 25 subjects with baseline mild restriction and reduced DLCO, after a mean 56 months, no significant changes in total lung capacity or DLCO were documented, whereas declines in FEV_1/FVC and forced expiratory flow at mid-lung volume were noted.[26] Interestingly, these changes appeared to be driven predominantly by the nonsmokers in the cohort.

Exercise impairment is also frequent in patients with SLE. Female subjects with SLE exercise for a shorter duration and with lower values for peak oxygen uptake than sedentary, non-SLE, female control subjects matched for age, body mass index, and waist/hip ratio.[27] Some of these abnormalities may be explained by abnormal hemodynamics: compared with healthy control subjects, higher baseline pulmonary artery systolic pressure (PASP) [30 mm Hg vs 25 mm Hg, $p < 0.05$] and peak exercise PASP (52 mm Hg vs 44 mm Hg, $p = 0.055$) as assessed by transthoracic echocardiography (TTE), as well as higher peak exercise systemic diastolic pressures (*ie*, exercise-related diastolic hypertension) have been observed in unselected SLE patients.[28]

High-resolution CT (HRCT) scan results are commonly abnormal. Radiographic features of interstitial lung disease (ILD) are present in at least a third of asymptomatic subjects,[29,30] and airway abnormalities are seen in one fifth.[29,30] The most common HRCT pattern is a combination of ground-glass opacity (GGO) and reticular opacities (Fig 2).[29,30] Other common abnormal features include interlobular and intralobular lines, parenchymal bands, centrilobular nodularity, and focal consolidation. These changes predominate in the mid- and lower-lung zones.[31] One fifth of patients have mediastinal lymphadenopathy accompanying parenchymal opacities.[30]

Involvement by Anatomic Compartment: Pleura

Pleural disease is believed to be the most common clinically relevant pulmonary manifestation of SLE. Up to 35% of SLE subjects will present with pleuritis[32,33]: symptoms of pleurisy with or without pleural effusion. When present, effusions are usually bilateral and small to moderate in size; however, extremely large effusions can occur. At autopsy, effusions are present in up to two thirds of subjects.[19] While NSAIDs may be used for milder cases, we have found that 2 weeks of oral glucocorticoids are helpful when NSAIDs are ineffective or when symptoms are more severe. In cases of recurrent pleuritic involvement, use of a maintenance immunomodulatory agent, including a glucocorticoid-sparing agent such as azathioprine, methotrexate, leuflonominde, or mycophenolate mofetil, may be required.

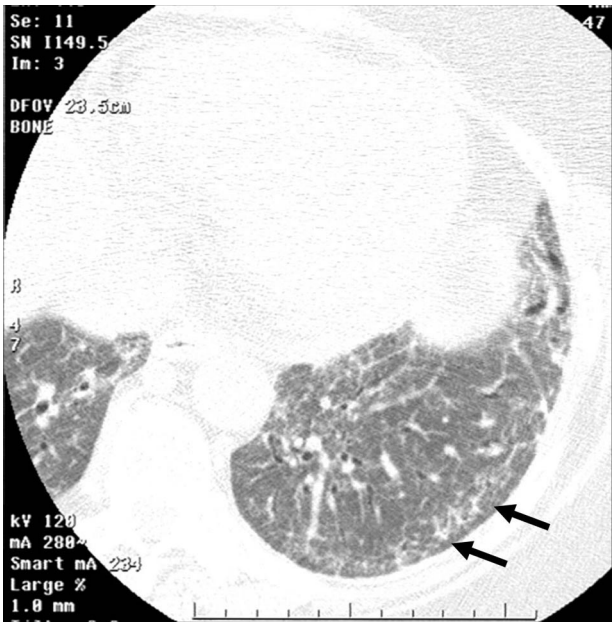

FIGURE 2. Image from a HRCT scan from a patient with SLE-related ILD. This image of the lower lobes shows predominant abnormalities of diffuse GGO and peripherally based reticular opacities. Note the subpleural sparing (arrows) that is sometimes seen in scans from patients with an NSIP pattern of lung injury.

Involvement by Anatomic Compartment: Parenchyma

ILD: The presentation of ILD in the setting of SLE is consistent with ILD in other settings. Dyspnea, cough, and/or exercise intolerance are common symptoms. Auscultatory crackles and physiologic restriction with a gas exchange abnormality are often present. HRCT defines the presence and pattern of the disease, and abnormalities suggestive of ILD are reported in at least a third of even asymptomatic patients. A variety of diffuse lung disease patterns have been described on surgical lung biopsy. In early series[34,35] of SLE patients, honeycomb lung and lymphocytic interstitial infiltrates with fibrosis accompanied by peribronchial lymphoid hyperplasia were described. Using our current idiopathic interstitial pneumonia pathologic or radiographic classification criteria, the most common patterns observed include cellular (Fig 3), fibrotic, or mixed nonspecific interstitial pneumonia (NSIP)[36] (Fig 4); although organizing pneumonia,[37] and more rarely diffuse amyloidosis,[38] have been reported. Patterns of usual interstitial pneumonia and lymphoid interstitial pneumonia (LIP), par-

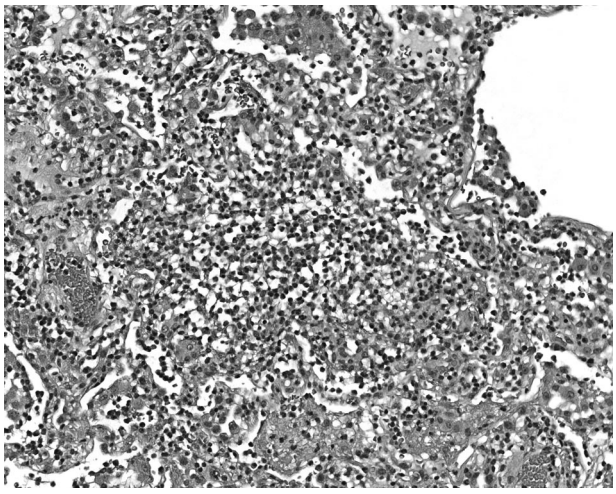

FIGURE 3. Surgical biopsy specimen from a patient with SLE-related ILD. The predominant finding is a lung injury pattern of cellular NSIP, a pattern characterized by homogeneous infiltration of alveolar walls with large numbers of lymphocytes and scattered plasma cells (hematoxylin-eosin, original × 4).

ticularly when secondary Sjögren syndrome is present, are also seen.[36,39]

There are no placebo-controlled trials of therapy for SLE-related ILD; however, in our opinion, response rates are likely dictated by the underlying pathologic pattern. In general, glucocorticoids have been used with modest success. In one small, open-label study,[35] prednisone (60 mg/d for at least 4 weeks) was administered to 14 subjects; pulmonary symptoms resolved entirely in 3 subjects, improved in 6 subjects, were unchanged in 1 subject, and worsened in 4 subjects.[35] Immunomodulatory agents may hold additional promise.[40] In subjects with SLE and clinically significant chronic ILD (*eg*, NSIP, usual interstitial pneumonia, or LIP pattern), our group generally uses an initial combination of oral glucocorticoids and an immunomodulatory agent, with the goal of weaning to low-dose corticosteroids, or an immunomodulatory agent alone. We use cyclophosphamide as initial therapy for the most severe and rapidly progressive disease and transition to an alternative agent (most often mycophenolate mofetil or azathioprine) after 12 to 18 months. For less severe cases, or when cyclophosphamide is not tolerated, we have found mycophenolate mofetil or azathioprine to be useful initial agents. We have also had anecdotal success with rituximab, especially in the setting of LIP or when glucocorticoids cannot be lowered because of antibody-mediated extrathoracic manifestations (*eg*, thrombocytopenia or hemolytic anemia).

Diffuse Alveolar Hemorrhage: One of the better recognized and clinically severe pulmonary manifestations of SLE is diffuse alveolar hemorrhage (DAH). The syndrome of DAH is rare, occurring in only 1 to 5% of patients with SLE.[41,42] The sudden onset of dyspnea, new GGO, and declining hematocrit with or without hemoptysis should raise suspicion of DAH. Hemoptysis or nephritis is observed in > 50% of cases.[41] The diagnosis is confirmed during BAL (generally performed to rule out infection) when an increasingly or persistently bloody return is noted in serial aliquots. Pathologic findings include intraalveolar hemorrhage and hemosiderin-laden alveolar macrophages, with capillaritis (Fig 5) or without

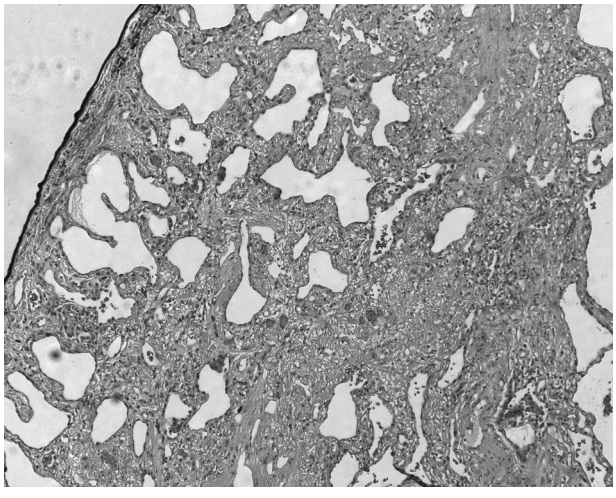

FIGURE 4. Surgical lung biopsy specimen with an injury pattern of fibrotic NSIP, a pattern characterized by diffuse widening of the alveolar and subpleural interstitium predominantly by relatively dense fibrosis (hematoxylin-eosin, original × 2).

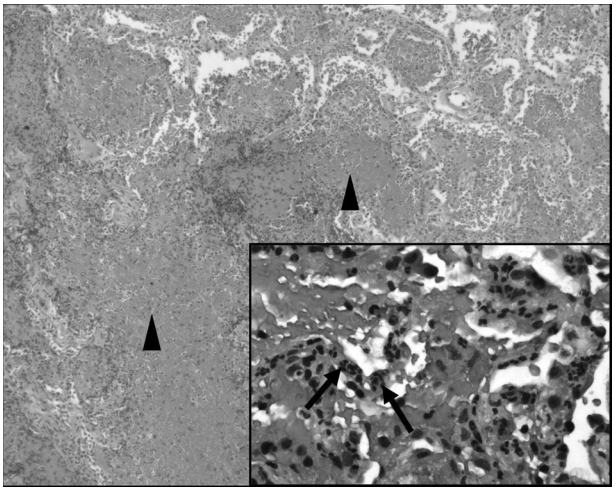

FIGURE 5. Surgical lung biopsy showing DAH with capillaritis. At lower power, there is extensive hemorrgage (arrowheads) [hematoxylin-eosin, original × 2]. Inset: At higher power, there is hemorrhage along with infiltration of alveolar walls with inflammatory cells, predominantly polymorphonuclear leukocytes (arrows) [original × 10].

capillaritis (*ie*, bland hemorrhage).[43] A pattern of DAD, with its hallmark hyaline membranes (and varying degrees of cellular interstitial infiltrates), is occasionally observed.[44] Electron microscopy has infrequently identified electron-dense deposits consisting of various Ig and complement proteins in alveolar septae and within walls of small blood vessels.[44]

Rarely, DAH can be the presenting manifestation of SLE. Respiratory failure may develop, and mechanical ventilation is frequently necessary. Along with supportive intensive care, the authors' therapy generally includes the initiation of high-dose IV corticosteroids (*eg*, 1 g/d of methylprednisolone for 3 days followed by prednisone at 60 mg/d or equivalent) in the hospital. An immunomodulatory agent such as cyclophosphamide at 500 to 1,000 mg/m^2 IV every 4 weeks is almost always added, but if clinical circumstances permit, it is preferred to initiate this after hospital discharge to lower the risk of in-hospital infection or the potential clinical confounding from drug-induced reaction. Plasmapheresis has been employed with success in refractory cases.[41] The prognosis is variable; on average, approximately 50% of patients will die during their hospitalization. Survival depends on the degree of hypoxemia, the presence and severity of coincident extrapulmonary SLE manifestations, and the presence of concomitant lung infection at the time of DAH diagnosis.[43] DAH can recur multiple times in the same patient; factors that drive recurrence are not known.[41]

Acute Lupus Pneumonitis: There is great controversy over the definition and even the existence of acute lupus pneumonitis (ALP). This is because other potential explanations for its clinical presentation (*eg*, infection, uremia) are often present, and because there is extensive overlap between ALP and DAH. For clarity, we use the following guidelines offered in Table 1. ALP has been described as an illness characterized by the abrupt onset of nonspecific symptoms including dyspnea, cough, fever, pleuritic chest pain, and occasionally hemoptysis.[45] Radiographic abnormalities are usually extensive and include diffuse GGO and areas of consolidation. When surgical lung biopsy is performed, the histologic pattern has been described as DAD with or without alveolar hemorrhage and capillaritis.[46,47] In this respect, ALP can be considered a mild case of DAH, and we treat it similarly.

Table 1—*Terms and Definitions for the Common Noninfectious Acute Respiratory Disorders in SLE*

Terms	When To Use Term
DAH	Surgical lung biopsy reveals extensive alveolar hemorrhage (with or without DAD). Capillaritis may or may not be present.
Bland DAH	
DAH with capillaritis	
ALP	Surgical biopsy reveals a DAD pattern without hemorrhage or capillaritis.
Acute interstitial pneumonia-like reaction	

ARDS: ARDS may occur in 5 to 15% of patients with SLE.[48,49] Known inciting factors include infection and the antiphospholipid syndrome (APS). In SLE, there is clinical and pathologic overlap between DAH and ALP; in fact, when there is no readily identifiable cause for ARDS and no evidence of alveolar hemorrhage, ARDS is best defined as a severe form of ALP. Infectious, SLE-related ARDS has been linked to high-dose glucocorticoid intake.[48,49]

Involvement by Anatomic Compartment: Airways

Various studies[29,30] have shown that HRCT reveals bronchial wall thickening and bronchiectasis in approximately 20% of subjects with SLE, but it is infrequently clinically relevant. Obliterative bronchiolitis has rarely been described.[50,51] The authors have observed obliterative bronchiolitis in patients with SLE, particularly those with secondary Sjögren syndrome. In this setting, we have had limited success treating with corticosteroids and an immunomodulatory agent. We consider cyclophosphamide for those with rapidly progressive deterioration. Improvement is uncommon; it is unknown whether any therapy has beneficial effects in these patients.

Involvement by Anatomic Compartment: Pulmonary Vasculature

Pulmonary Arterial Hypertension: The prevalence of pulmonary arterial hypertension (PAH) in patients with SLE is unknown but is lower than that seen in scleroderma.[52] Using TTE, PAH has been identified in approximately 6 to 14% of subjects; of these, approximately one half have no identifiable cause other than the presence of SLE.[53,54] In a small (n = 36) longitudinal study,[55] after 5 years, the prevalence of PAH (as determined by TTE) had increased from 14 to 43%. Raynaud phenomenon occurs in 75% of SLE subjects with PAH, compared with only 20 to 35% without clinically evident PAH.[52,56] Pathologically, fibrocollagenous intimal thickening, medial thickening, alterations in the elastic lamina, and luminal narrowing of muscular arteries are identified. In one study,[57] histologic vasculitis was reported in approximately 50% of cases. Granular deposits of IgG and the complement protein C1q (and to a lesser extent IgM and C3) have been found in vessel walls, suggesting that immune deposits may be involved in the pathogenesis of SLE-related PAH.[58] Aside from

the capillaritis seen in DAH, the authors have rarely, if ever, seen evidence of vasculitis in blood vessels within surgical lung biopsy specimens from patients with SLE; however, one must consider that the overwhelming majority of such specimens come from patients with diffuse parenchymal lung abnormalities and secondary PAH.

Patients with SLE and PAH may respond to immunomodulatory therapy. In a randomized study[59] of monthly IV cyclophosphamide vs oral enalapril, after 6 months TTE-derived PASP declined in both groups, but the effect was greater in subjects who received IV cyclophosphamide (decrease of 15 mm Hg vs 7 mm Hg, $p = 0.04$). Among subjects with PASP ≥ 35 mm Hg, only IV cyclophosphamide ($n = 11$) dropped PASP a statistically significant degree (from 43 mm Hg to 27 mm Hg, $p = 0.003$). Oral glucocorticoids (usually in combination with an immunomodulatory agent) have also been shown to lower PASP, improve 6-min walk distance, and possibly prolong 5-year survival.[60–62] However, in one of these studies,[61] the presence of ILD, inferred by low FVC values, confounds the results. More recent studies have shown that epoprostenol,[63] bosentan,[64] sitaxsentan,[65] and sildenafil,[66] may also be effective. Our management approach for moderate or more severe PAH is to first confirm and quantify severity by right-heart catheterization. Vascular reactivity to vasodilator challenge is determined during the procedure and treatment decisions are based on the data collected. We do not typically use glucocorticoids and/or an immunomodulatory agent to specifically target PAH in our patients with SLE. However, in patients with mild-to-moderate PAH for whom such a regimen has been prescribed for another indication (*eg*, those with ILD), we will sometimes follow the status of the PAH by TTE after 6 months of therapy and proceed to right-heart catheterization if no benefit is observed.

Other Pulmonary Vascular Abnormalities: Acute reversible hypoxemia, an extremely rare manifestation of SLE, presents clinically as the abrupt onset of hypoxemia with normal radiographic imaging studies.[67] This syndrome is believed to result from endothelial cell and complement-activated neutrophil aggregation within pulmonary capillaries.[68] Hypoxemia rapidly resolves with glucocorticoids.[67] Pulmonary veno-occlusive disease has also been reported in patients with SLE.[69]

Involvement by Anatomic Compartment: Skeletal Muscles

Diaphragm and Other Muscles of Respiration: In 1965, eight subjects with SLE were found to have unexplained dyspnea and elevated diaphragms that moved slowly ("sluggishly"[47] but never paradoxically[70]), a condition known today as *shrinking lung syndrome* (SLS) [Fig 6]. In a study[71] of five SLE subjects with elevated diaphragms on chest radiography, measurement of transdiaphragmatic pressure suggested diaphragmatic weakness (as opposed to parenchymal or pleural abnormalities) was the cause of SLS. Over 4 to 6 years of follow-up, no progression occurred. Findings from electrophysiologic and histopathologic studies of the diaphragms have been variable.[72] At postmortem, the diaphragm in SLS has been described microscopically as diffusely fibrotic and extensively atrophied.[73]

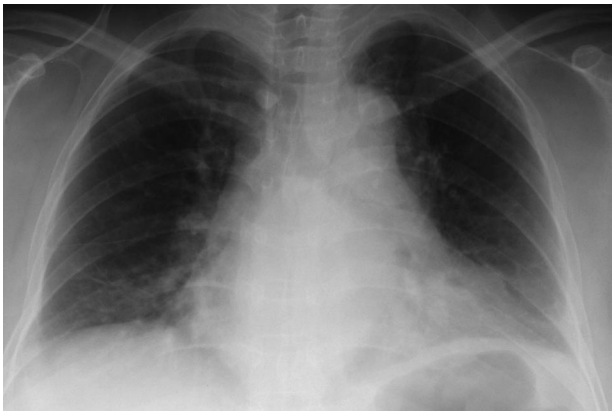

FIGURE 6. Posteroanterior chest radiograph from a patient with SLE and SLS.

Because of the ongoing mystery surrounding its etiology, the therapeutic approach to SLS is empiric. Some investigators, as well as the authors, have anecdotally observed less dyspnea after treatment with glucocorticoids; however, improvements in vital capacity are often minor. With treatment, diaphragmatic motion may not normalize, and it usually occurs only after several weeks of therapy.[70,74,75] Other therapies include high-dose inhaled β-agonists and theophylline.[76,77] The prognosis for patients with the SLS is generally very good.

THROMBOSIS

Antiphospholipid antibodies (aPL), a family of acquired autoantibodies that are associated with vascular thrombosis and pregnancy morbidity, may be present in up to two thirds of patients with SLE.[78,79] The two most well-known and clinically important are the lupus anticoagulant (LA) and anticardiolipin antibodies (aCL). These antibodies bind serum proteins such as prothrombin, various protein/phospholipid complexes, and β_2 glycoprotein I (β_2GPI).[80,81]

APS

The term *antiphospholipid syndrome* refers to the combination of clinically important vascular events

and the presence of LA or aCL, as defined in Table 2.[82] A metaanalysis[83] found that subjects with SLE and aPL were more than six times more likely than subjects with SLE and no aPL to have venous thromboembolism develop; patients with the LA had nearly a three-times-greater risk than patients with aCL. In another study,[78] SLE subjects with LA were five times more likely, and those with aCL were more than two times more likely than those without antibodies to have venous thrombosis develop. Among the aCL, high-titer IgG (and aCL directed against β_2GPI) appear to carry the greatest risk for thrombosis.[84] There are also several nonthrombotic intrathoracic complications associated with the aPL; including PAH, DAH, ARDS, and cardiac valvular lesions.[85] Small-vessel occlusion in three or more organs develops in certain patients with APS, a scenario referred to as *catastrophic APS* (CAPS). CAPS is often associated with physiologic stressors such as infection, neoplasm, and surgery.[86] The cardiopulmonary system is usually involved; respiratory failure is common and often progresses to ARDS.[87]

For patients with aPL, there is controversy over the approach to primary prevention of thrombosis.[80] Consensus dictates that modifiable cardiovascular risk factors be aggressively addressed; however, the role of prophylactic anticoagulant or antiplatelet therapy is still debated. Although the Physician's Health Study did not demonstrate that aspirin at 325 mg/d protects against venous thromboembolism, many physicians, as well as the authors, recommend indefinite aspirin therapy, either low dose (75 to 100 mg/d) or high dose (325 mg/d),[80] because the first clinical manifestation of APS may be a devastating stroke.

Table 2—*Diagnostic Criteria for APS**

Clinical criteria
Vascular thrombosis
At least one episode of arterial, venous, or small-vessel thrombosis in any tissue or organ confirmed by imaging, Doppler ultrasound, or histopathology
Pregnancy morbidity
At least one unexplained fetal death at or beyond 10 wk, or
At least one premature birth of morphologically normal neonate at or beyond 34 wk due to preeclampsia, eclampsia, or severe placental insufficiency, or
Three or more spontaneous pregnancy losses before 10 wk of gestation
Laboratory criteria
Anticardiolipin antibodies: medium- or high-titer IgG and/or IgM on two occasions at least 12 wk apart
Lupus anticoagulant: on two occasions at least 12 wk apart
Detection of anti-β_2GPI antibodies: high-titer IgM or IgG on two occasions at least 12 wk apart

*Definite APS is confirmed when at least one clinical criterion and at least one laboratory criterion are present.[88]

There is a similar debate over the long-term management of patients with APS. Recurrent thrombosis is common, approaching 70%.[89] Data are conflicting regarding whether high-intensity anticoagulation (international normalized ratio [INR] > 3.0) or lower-intensity anticoagulation (INR, 2.0 to 3.0) are the most effective secondary prevention strategy.[90,91] Still more controversy revolves around how to treat patients with arterial thrombosis: Some experts[92] recommend high-intensity anticoagulation. For patients with arterial thrombosis, particularly those with recurrent events, our practice is to maintain an INR of approximately 3. The treatment of CAPS includes anticoagulation, glucocorticoids with an immunomodulatory agent, and often plasmapharesis and IV Ig. Despite these, the mortality rate from the acute episode approaches 50%.[86]

Conclusion

The respiratory and thrombotic manifestations of SLE are numerous, complex, and present diagnostic and therapeutic challenges for the clinician. Many of these manifestations are more common than previously thought and may contribute greatly to symptoms, including impaired exercise tolerance. Several manifestations are life threatening; the pathogenesis of each is generally uncertain; and definitive therapies are uncommon. In general, we add a glucocorticoid-sparing immunomodulatory agent to an SLE patient's regimen if > 20 mg/d of prednisone is required to control disease activity. More research is necessary to help determine which immunomodulatory agent is best suited to treat respiratory, thrombotic, and myriad other potential manifestations of SLE. Despite current therapeutic limitations, with early recognition and appropriate treatment, the clinical course of SLE patients who have respiratory or thrombotic manifestations can often be positively altered.

References

1 Siegel M, Lee SL. The epidemiology of systemic lupus erythematosus. Semin Arthritis Rheum 1973; 3:1–54
2 Lam G, Petri M. Assessment of systemic lupus erythematosis. Clin Exp Rheumatol 2005; 23:S120–S132
3 Alarcon GS, Friedman AW, Straaton KV, et al. Systemic lupus erythematosus in three ethnic groups: Iii. A comparison of characteristics early in the natural history of the LUMINA cohort; Lupus in Minority Populations: Nature vs Nurture. Lupus 1999; 8:197–209
4 Boddaert J, Huong DL, Amoura Z, et al. Late-onset systemic lupus erythematosus: a personal series of 47 patients and pooled analysis of 714 cases in the literature. Medicine (Baltimore) 2004; 83:348–359
5 Cervera R, Khamashta MA, Font J, et al. Morbidity and

mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine (Baltimore) 2003; 82:299–308
6 Bertoli AM, Alarcon GS, Calvo-Alen J, et al. Systemic lupus erythematosus in a multiethnic US cohort. XXXIII: clinical [corrected] features, course, and outcome in patients with late-onset disease. Arthritis Rheum 2006; 54:1580–1587
7 Sante LR, Wyatt JP. Roentgenological and pathological observations in antigenic pneumonitis, its relationship to the collagen diseases. AJR Am J Roentgenol Radium Ther Nucl Med 1951; 66:527–545
8 Klemperer P, Pollack A, Baehr G. Pathology of disseminated lupus erythematosus. Arch Pathol 1941; 32:569–631
9 Foldes J. Acute systemic erythematosis. Am J Clin Pathol 1946; 16:160–173
10 Rakov H, Taylor J. Acute disseminated lupus erythematosus: without cutaneous manifestations and with heretofore undescribed pulmonary lesions. Arch Intern Med 1942; 70:88–100
11 Noel V, Lortholary O, Casassus P, et al. Risk factors and prognostic influence of infection in a single cohort of 87 adults with systemic lupus erythematosus. Ann Rheum Dis 2001; 60:1141–1144
12 Bedrossian CW, Sussman J, Conklin RH, et al. Azathioprine-associated interstitial pneumonitis. Am J Clin Pathol 1984; 82:148–154
13 Gross DC, Sasaki TM, Buick MK, et al. Acute respiratory failure and pulmonary fibrosis secondary to administration of mycophenolate mofetil. Transplantation 1997; 64:1607–1609
14 Goodwin SD, Glenny RW. Nonsteroidal anti-inflammatory drug-associated pulmonary infiltrates with eosinophilia: review of the literature and Food and Drug Administration adverse drug reaction reports. Arch Intern Med 1992; 152: 1521–1524
15 Malik SW, Myers JL, DeRemee RA, et al. Lung toxicity associated with cyclophosphamide use: two distinct patterns. Am J Respir Crit Care Med 1996; 154:1851–1856
16 Imokawa S, Colby TV, Leslie KO, et al. Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. Eur Respir J 2000; 15:373–381
17 Ohosone Y, Okano Y, Kameda H, et al. Clinical characteristics of patients with rheumatoid arthritis and methotrexate induced pneumonitis. J Rheumatol 1997; 24:2299–2303
18 Sostman HD, Matthay RA, Putman CE, et al. Methotrexate-induced pneumonitis. Medicine (Baltimore) 1976; 55:371–388
19 Purnell DC, Baggenstoss AH, Olsen AM. Pulmonary lesions in disseminated lupus erythematosus. Ann Intern Med 1955; 42:619–628
20 Gross M, Esterly JR, Earle RH. Pulmonary alterations in systemic lupus erythematosus. Am Rev Respir Dis 1972; 105:572–577
21 Haupt HM, Moore GW, Hutchins GM. The lung in systemic lupus erythematosus: analysis of the pathologic changes in 120 patients. Am J Med 1981; 71:791–798
22 Andonopoulos AP, Constantopoulos SH, Galanopoulou V, et al. Pulmonary function of nonsmoking patients with systemic lupus erythematosis. Chest 1988; 94:312–315
23 Traynor AE, Corbridge TC, Eagan AE, et al. Prevalence and reversibility of pulmonary dysfunction in refractory systemic lupus: improvement correlates with disease remission following hematopoietic stem cell transplantation. Chest 2005; 127:1680–1689
24 Gold WM, Jennings DB. Pulmonary function in patients with systemic lupus erythematosus. Am Rev Respir Dis 1966; 93:556–567
25 Groen H, Ter Borg EJ, Postma DS, et al. Pulmonary function in systemic lupus erythematosis is related to distinct clinical, serologic, and nailfold capillary patterns. Am J Med 1992; 93:619–627
26 Eichacker PQ, Pinsker K, Epstein A, et al. Serial pulmonary function testing in patients with systemic lupus erythematosus. Chest 1988; 94:129–132
27 Tench C, Bentley D, Vleck V, et al. Aerobic fitness, fatigue, and physical disability in systemic lupus erythematosus. J Rheumatol 2002; 29:474–481
28 Winslow TM, Ossipov M, Redberg RF, et al. Exercise capacity and hemodynamics in systemic lupus erythematosus: a Doppler echocardiographic exercise study. Am Heart J 1993; 126:410–414
29 Bankier AA, Kiener HP, Wiesmayr MN, et al. Discrete lung involvement in systemic lupus erythematosus: CT assessment. Radiology 1995; 196:835–840
30 Fenlon HM, Doran M, Sant SM, et al. High-resolution chest CT in systemic lupus erythematosus. AJR Am J Roentgenol 1996; 166:301–307
31 Ooi GC, Ngan H, Peh WC, et al. Systemic lupus erythematosus patients with respiratory symptoms: the value of HRCT. Clin Radiol 1997; 52:775–781
32 Swaak AJ, van den Brink HG, Smeenk RJ, et al. Systemic lupus erythematosus: clinical features in patients with a disease duration of over 10 years, first evaluation. Rheumatology (Oxford) 1999; 38:953–958
33 Jacobsen S, Petersen J, Ullman S, et al. A multicentre study of 513 Danish patients with systemic lupus erythematosus: i. Disease manifestations and analyses of clinical subsets. Clin Rheumatol 1998; 17:468–477
34 Eisenberg H, Dubois EL, Sherwin RP, et al. Diffuse interstitial lung disease in systemic lupus erythematosus. Ann Intern Med 1973; 79:37–45
35 Weinrib L, Sharma OP, Quismorio FP Jr. A long-term study of interstitial lung disease in systemic lupus erythematosus. Semin Arthritis Rheum 1990; 20:48–56
36 Tansey D, Wells AU, Colby TV, et al. Variations in histological patterns of interstitial pneumonia between connective tissue disorders and their relationship to prognosis. Histopathology 2004; 44:585–596
37 Gammon RB, Bridges TA, al-Nezir H, et al. Bronchiolitis obliterans organizing pneumonia associated with systemic lupus erythematosus. Chest 1992; 102:1171–1174
38 Marenco JL, Sanchez-Burson J, Ruiz Campos J, et al. Pulmonary amyloidosis and unusual lung involvement in SLE. Clin Rheumatol 1994; 13:525–527
39 Schattner A, Aviel-Ronen S, Mark EJ. Accelerated usual interstitial pneumonitis, anti-DNA antibodies and hypocomplementemia. J Intern Med 2003; 254:193–196
40 Swigris JJ, Olson AL, Fischer A, et al. Mycophenolate mofetil is safe, well tolerated, and preserves lung function in patients with connective tissue disease-related interstitial lung disease. Chest 2006; 130:30–36
41 Santos-Ocampo AS, Mandell BF, Fessler BJ. Alveolar hemorrhage in systemic lupus erythematosus: presentation and management. Chest 2000; 118:1083–1090
42 Barile LA, Jara LJ, Medina-Rodriguez F, et al. Pulmonary hemorrhage in systemic lupus erythematosus. Lupus 1997; 6:445–448
43 Zamora MR, Warner ML, Tuder R, et al. Diffuse alveolar hemorrhage and systemic lupus erythematosus: clinical presentation, histology, survival, and outcome. Medicine (Baltimore) 1997; 76:192–202
44 Eagen JW, Memoli VA, Roberts JL, et al. Pulmonary hemorrhage in systemic lupus erythematosus. Medicine (Baltimore) 1978; 57:545–560
45 Boulware DW, Hedgpeth MT. Lupus pneumonitis and anti-SSA(Ro) antibodies. J Rheumatol 1989; 16:479–481

46 Keane MP, Lynch JP III. Pleuropulmonary manifestations of systemic lupus erythematosus. Thorax 2000; 55:159–166
47 Harvey AM, Shulman LE, Tumulty PA, et al. Systemic lupus erythematosus: review of the literature and clinical analysis of 138 cases. Medicine (Baltimore) 1954; 33:291–437
48 Andonopoulos AP. Adult respiratory distress syndrome: an unrecognized premortem event in systemic lupus erythematosus. Br J Rheumatol 1991; 30:346–348
49 Kim WU, Kim SI, Yoo WH, et al. Adult respiratory distress syndrome in systemic lupus erythematosus: causes and prognostic factors: a single center, retrospective study. Lupus 1999; 8:552–557
50 Kallenbach J, Zwi S, Goldman HI. Airways obstruction in a case of disseminated lupus erythematosus. Thorax 1978; 33:814–815
51 Weber F, Prior C, Kowald E, et al. Cyclophosphamide therapy is effective for bronchiolitis obliterans occurring as a late manifestation of lupus erythematosus. Br J Dermatol 2000; 143:453–455
52 Shen JY, Chen SL, Wu YX, et al. Pulmonary hypertension in systemic lupus erythematosus. Rheumatol Int 1999; 18:147–151
53 Pan TL, Thumboo J, Boey ML. Primary and secondary pulmonary hypertension in systemic lupus erythematosus. Lupus 2000; 9:338–342
54 Simonson JS, Schiller NB, Petri M, et al. Pulmonary hypertension in systemic lupus erythematosus. J Rheumatol 1989; 16:918–925
55 Winslow TM, Ossipov MA, Fazio GP, et al. Five-year follow-up study of the prevalence and progression of pulmonary hypertension in systemic lupus erythematosus. Am Heart J 1995; 129:510–515
56 Matthay RA, Schwarz MI, Petty TL, et al. Pulmonary manifestations of systemic lupus erythematosus: review of twelve cases of acute lupus pneumonitis. Medicine (Baltimore) 1975; 54:397–409
57 Fayemi AO. Pulmonary vascular disease in systemic lupus erythematosus. Am J Clin Pathol 1976; 65:284–290
58 Quismorio FP Jr, Sharma O, Koss M, et al. Immunopathologic and clinical studies in pulmonary hypertension associated with systemic lupus erythematosus. Semin Arthritis Rheum 1984; 13:349–359
59 Gonzalez-Lopez L, Cardona-Munoz EG, Celis A, et al. Therapy with intermittent pulse cyclophosphamide for pulmonary hypertension associated with systemic lupus erythematosus. Lupus 2004; 13:105–112
60 Li EK, Tam LS. Pulmonary hypertension in systemic lupus erythematosus: clinical association and survival in 18 patients. J Rheumatol 1999; 26:1923–1929
61 Tanaka E, Harigai M, Tanaka M, et al. Pulmonary hypertension in systemic lupus erythematosus: evaluation of clinical characteristics and response to immunosuppressive treatment. J Rheumatol 2002; 29:282–287
62 Sanchez O, Sitbon O, Jais X, et al. Immunosuppressive therapy in connective tissue diseases-associated pulmonary arterial hypertension. Chest 2006; 130:182–189
63 Robbins IM, Gaine SP, Schilz R, et al. Epoprostenol for treatment of pulmonary hypertension in patients with systemic lupus erythematosus. Chest 2000; 117:14–18
64 Cozzi F, Montisci R, Marotta H, et al. Bosentan therapy of pulmonary arterial hypertension in connective tissue diseases. Eur J Clin Invest 2006; 36(suppl 3):49–53
65 Barst RJ, Langleben D, Frost A, et al. Sitaxsentan therapy for pulmonary arterial hypertension. Am J Respir Crit Care Med 2004; 169:441–447
66 Wilkins MR, Paul GA, Strange JW, et al. Sildenafil Versus Endothelin Receptor Antagonist for Pulmonary Hypertension (SERAPH) study. Am J Respir Crit Care Med 2005; 171: 1292–1297
67 Abramson SB, Dobro J, Eberle MA, et al. Acute reversible hypoxemia in systemic lupus erythematosus. Ann Intern Med 1991; 114:941–947
68 Belmont H, Buyon J, Giorno R, et al. Up-regulation of endothelial cell adhesion molecules characterizes disease activity in systemic lupus erythematosis: the Schwartzman phenomenon revisited. Arthritis Rheum 1994; 37:376–383
69 Kishida Y, Kanai Y, Kuramochi S, et al. Pulmonary venoocclusive disease in a patient with systemic lupus erythematosus. J Rheumatol 1993; 20:2161–2162
70 Hoffbrand BI, Beck ER. "Unexplained" dyspnoea and shrinking lungs in systemic lupus erythematosus. BMJ 1965; 1:1273–1277
71 Gibson CJ, Edmonds JP, Hughes GR. Diaphragm function and lung involvement in systemic lupus erythematosus. Am J Med 1977; 63:926–932
72 Thompson PJ, Dhillon DP, Ledingham J, et al. Shrinking lungs, diaphragmatic dysfunction, and systemic lupus erythematosus. Am Rev Respir Dis 1985; 132:926–928
73 Rubin LA, Urowitz MB. Shrinking lung syndrome in SLE–a clinical pathologic study. J Rheumatol 1983; 10:973–976
74 Warrington KJ, Moder KG, Brutinel WM. The shrinking lungs syndrome in systemic lupus erythematosus. Mayo Clin Proc 2000; 75:467–472
75 Walz-Leblanc BA, Urowitz MB, Gladman DD, et al. The "shrinking lungs syndrome" in systemic lupus erythematosus: improvement with corticosteroid therapy. J Rheumatol 1992; 19:1970–1972
76 Munoz-Rodriguez FJ, Font J, Badia JR, et al. Shrinking lungs syndrome in systemic lupus erythematosus: improvement with inhaled β-agonist therapy. Lupus 1997; 6:412–414
77 Van Veen S, Peeters AJ, Sterk PJ, et al. The "shrinking lung syndrome" in SLE, treatment with theophylline. Clin Rheumatol 1993; 12:462–465
78 Somers E, Magder LS, Petri M. Antiphospholipid antibodies and incidence of venous thrombosis in a cohort of patients with systemic lupus erythematosus. J Rheumatol 2002; 29: 2531–2536
79 Ruiz-Irastorza G, Egurbide MV, Ugalde J, et al. High impact of antiphospholipid syndrome on irreversible organ damage and survival of patients with systemic lupus erythematosus. Arch Intern Med 2004; 164:77–82
80 Bertolaccini ML, Khamashta MA. Laboratory diagnosis and management challenges in the antiphospholipid syndrome. Lupus 2006; 15:172–178
81 McNeil HP, Chesterman CN, Krilis SA. Anticardiolipin antibodies and lupus anticoagulants comprise separate antibody subgroups with different phospholipid binding characteristics. Br J Haematol 1989; 73:506–513
82 Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 1999; 42:1309–1311
83 Wahl DG, Guillemin F, de Maistre E, et al. Risk for venous thrombosis related to antiphospholipid antibodies in systemic lupus erythematosus: a meta-analysis. Lupus 1997; 6:467–473
84 Amengual O, Atsumi T, Khamashta MA, et al. Specificity of ELISA for antibody to β 2-glycoprotein I in patients with antiphospholipid syndrome. Br J Rheumatol 1996; 35:1239–1243
85 Asherson RA, Cervera R, Shepshelovich D, et al. Nonthrombotic manifestations of the antiphospholipid syndrome: away from thrombosis? J Rheumatol 2006; 33:1038–1044
86 Asherson RA, Cervera R, Piette JC, et al. Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. Medicine (Baltimore) 2001; 80:355–377
87 Bucciarelli S, Espinosa G, Asherson RA, et al. The acute respiratory distress syndrome in catastrophic antiphospho-

lipid syndrome: analysis of a series of 47 patients. Ann Rheum Dis 2006; 65:81–86
88 Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006; 4:295–306
89 Khamashta MA, Cuadrado MJ, Mujic F, et al. The management of thrombosis in the antiphospholipid-antibody syndrome. N Engl J Med 1995; 332:993–997
90 Crowther MA, Ginsberg JS, Julian J, et al. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. N Engl J Med 2003; 349:1133–1138
91 Finazzi G, Marchioli R, Brancaccio V, et al. A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). J Thromb Haemost 2005; 3:848–853
92 Ortel TL. Thrombosis and the antiphospholipid syndrome. Hematology (Am Soc Hematol Educ Program) 2005:462–468