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Original Article

Cardiopulmonary involvement in pediatric systemic lupus erythematosus: a twenty-year retrospective analysis

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Background and Purpose: Cardiovascular and pulmonary involvement is frequent among patients with systemic lupus erythematosus (SLE). It is important that the frequency and characteristics of pulmonary and cardiovascular involvement in childhood-onset SLE are understood. Thus, we conducted a retrospective analysis of childhood-onset SLE at a tertiary medical center in Taipei.

Methods: Children with SLE diagnosed at the National Taiwan University Hospital between 1985 and 2004 were evaluated by chart review. Records included the age at diagnosis, gender, family history, presenting manifestations with American Rheumatism Association criteria and initial laboratory data, other associated complications and duration of follow-up.

Results: A total of 157 cases were included. The male-to-female ratio was 18:82, with the mean age at diagnosis 12.2 years. Overall, pulmonary and cardiovascular involvements were recorded in 89 patients (56.7%) and 75 patients (47.8%), respectively. Among the more frequent lung disorders were pneumonia treated under hospitalization (in 36.9% of patients), increased pulmonary interstitial marking or infiltration (35.0%), and pleuritis (33.1%). The more common cardiovascular manifestations included cardiomegaly (in 33.8%), pericarditis (28.7%) and arrhythmia/conduction anomaly (12.7%).

Conclusions: The frequencies of pulmonary and cardiovascular complications were high. Blood creatinine >1 mg/dL, hematuria and anemia with hemoglobin <12 g/dL obtained at diagnosis of SLE were associated with cardiovascular complications during the disease course, while anti-double stranded DNA at diagnosis was associated with pulmonary complications.

Key words: Heart diseases; Lung diseases; Lupus erythematosus, systemic; Risk factors

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by excessive autoantibody production against 'self' antigens and immunocomplex formation, resulting in frequent widespread inflammatory damage to target multiple organ systems. It may affect any organ and produce a broad spectrum of clinical manifestations.

Cardiopulmonary involvement is common among SLE patients [1]. Pulmonary or pleural involvement was estimated to occur in as many as 60% of patients [2], with even higher rates in autopsy reports (50-83%) [3]. The reported pulmonary manifestations include pleuritis with or without pleural effusion, lupus pneumonitis, pneumonia, pulmonary hemorrhage, pulmonary hypertension, pulmonary infarction, interstitial lung disease, restrictive changes, and decreased diffusion capacity for carbon monoxide. The cardiac complications include pericarditis, valvular diseases with Libman-Sacks vegetation, myocarditis, cardiomyopathies, coronary artery diseases and conduction abnormalities. Pleuritis is the most common pulmonary manifestation, while pericarditis is the most common cardiovascular manifestation of SLE (12-48%). Impairment may occur at any level of the lungs and heart, and the manifestations have been varied [2-6].

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The purpose of this study was to evaluate the frequency and characteristics of cardiopulmonary involvement in childhood-onset SLE in a medical center during the past 20 years.

Methods

Children with SLE diagnosed at the National Taiwan University Hospital (NTUH) between 1985 and 2004 were retrospectively evaluated by chart review. All of these patients fulfilled 4 or more of the American Rheumatism Association (ARA) 1982 revised diagnostic criteria for SLE for patients under 18 years of age. They were all followed-up at our medical center until loss of follow-up, death, or the end of the study period (December 2004). This cohort also included patients referred from other hospitals, but excluded those with incomplete medical records. Records included the age at diagnosis, gender, family history, presenting manifestations with ARA criteria and initial laboratory data, other associated complications and duration of follow-up.

Records of laboratory abnormalities at diagnosis included anemia (hemoglobin [Hb] <12 g/dL), hemolytic anemia with reticulocytosis, leucopenia <4000/mm^3, lymphopenia <1500/mm^3, thrombocytopenia <100,000/mm^3, proteinuria (>0.5 g/day or >3+) or cellular cast in urinalysis, positive antinuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA), anti-ribonucleoprotein antibody (anti-RNP), anti-Smith antibody (anti-Sm), anti-Ro (SSA), anti-La, anti-scl-70, lupus erythematosus cells, false-positive serologic test for syphilis, positive rheumatoid factor, low complement C3 (<80 mg/dL) and C4 (<20 mg/dL), and elevated erythrocyte sedimentation rate (1 h >20 mm/2 h >40 mm). Abnormal image findings were based on reports of chest X-ray, chest and abdominal ultrasonography, echocardiography and chest computed tomography. Electrocardiography anomalies were also recorded.

The definition of pulmonary involvement included persistent cough and/or dyspnea, pleural thickening or effusion, pneumothorax, diffuse interstitial infiltrates or pulmonary alveolitis and fibrosis on radiographs or computed tomography scan, pulmonary hypertension documented by echocardiography, pulmonary hemorrhage, altered lung function test, and infectious lung disorders. Records of pneumonia included only those episodes treated under hospitalization, because the work-ups of image and isolation of infectious organisms were more detailed.

The criteria for cardiovascular involvement included cardiomegaly on image study, pericarditis with or without pericardial effusion, ventricular hypertrophy or dilatation, congestive heart failure, cardiomyopathy, coronary vascular disorders, Libman-Sacks vegetations, and valvular anomalies. Arrhythmia, conduction anomalies, or other abnormal electrocardiography findings were also recorded. Vascular thrombosis was demonstrated by ultrasonography, vascular radiography with contrast media, computed tomographic scan, or ventilation/perfusion scan for pulmonary embolism. Other associated unspecified manifestations, such as hypertension and palpitation, as well as other organ system involvements or complications, were similarly recorded.

The chi-squared test for 2×2 table and two-sided Fisher's exact test were used for statistical analysis.

Results

A total of 157 patients met the entry criteria in the 20-year review period (Table 1). The median age at onset of SLE was 11.8 years, while the average age at diagnosis was 12.2 years (range, 5-17 years). The male-to-female ratio was 28:129 (17.8%:82.2%). There were 32 mortality cases, with a mean age at death of 15.8 years (range, 10-27 years).

The more frequent presenting ARA diagnostic criteria were positive ANA (98.7%), immunologic disorders (80.9%), hematologic disorders (70.7%), malar rash (70.1%), arthritis (59.9%) and renal disorder (50.3%). Serositis with pleuritis (42, 26.7%) was significantly more frequent than pericarditis/pericardial effusion (32, 20.4%) during the disease course (p=0.050), but not at diagnosis (26, 16.6% and 23, 14.6% respectively, p=0.629).

Other frequent presenting manifestations included fever (53.5%), other constitutional symptoms (38.8%), skin rash (35.0%), lymphadenopathy (23.6%), and alopecia (14.6%).

Table 1. Characteristics of childhood-onset systemic lupus erythematosus (SLE) patients (n = 157)

Characteristic	Number (%)
Gender (male:female)	28:129 (17.8:82.2)
Age at onset (years; mean) [range]	11.8 (5-17)
Age at diagnosis (years; mean) [range]	12.2 (5-17)
Family history of SLE	13 (8.3)
Age at death (years; mean) [range]	15.8 (10-27)
Duration of follow-up (years; mean) [range]	5.5 (0.1-20)

Table 2. Pulmonary involvement in childhood-onset systemic lupus erythematosus at diagnosis and during the disease course (n = 157)

Variable	At diagnosis No. (%)	Disease course No. (%)	Overall No. (%)
Involved patients	38 (24.2)	75 (47.8)	89 (56.7)
Infectious pneumonia (inpatients)	6 (3.8)	55 (35.0)	58 (36.9)
Image with increased infiltration/marking	23 (14.6)	41 (26.1)	55 (35.0)
Pleuritis (pleural effusion/thickening)	26 (16.6)	42 (26.7)	52 (33.1)
Lung edema	5 (3.2)	22 (14.0)	24 (15.3)
Lupus pneumonitis	6 (3.8)	19 (12.1)	22 (14.0)
Pulmonary hemorrhage	2 (1.3)	16 (10.2)	16 (10.2)
Lung collapse/atelectasis	1 (0.6)	8 (5.1)	8 (5.1)
Pulmonary hypertension	1 (0.6)	6 (3.8)	7 (4.5)
Interstitial lung disease/fibrocicatricial	1 (0.6)	6 (3.8)	6 (3.8)
Pneumothorax	0 (0.0)	6 (3.8)	6 (3.8)

Abnormal laboratory findings at diagnosis included anemia with hemoglobin <12 g/dL in 124 patients (79.0%), lymphopenia <1500/mm^3 in 81 (51.6%), leukopenia <4000/mm^3 in 59 (37.6%), hemolytic anemia in 51 (32.5%) and thrombocytopenia <100,000/mm^3 in 38 (24.2%). There were 52 patients (33.1%) with proteinuria >0.5 g/day or >3+, 77 (49.0%) with hematuria and 46 (29.3%) with cellular cast. ANA was positive in 155 patients (98.7%), anti-dsDNA in 111 (74.0%), decreased serum complement C3 in 139 (88.5%) and C4 in 146 (91.2%), SSA in 26 (32.9%), anti-RNP in 25 (31.6%), anti-Sm in 18 (22.8%) and lupus erythematosus cells in 23 (31.1%). Erythrocyte sedimentation rate was elevated in 113 patients (88.3%) and C reactive-protein >1 mg/dL or positive in 32 (25.4%).

The various pulmonary manifestations are summarized in Table 2; Fig. 1 shows radiographic findings of pulmonary involvement. Overall, 89 patients (56.7%) had lung involvement; 38 (24.2%) presented at diagnosis and 75 (47.8%) throughout the disease course. Pneumonia treated under hospitalization was the most common pulmonary manifestation in 58 patients (36.9%). However, the infectious organisms were not identified in most cases. *Pseudomonas aeruginosa* was the most common pathogen in lung infection and sepsis (8 patients), followed by *Mycoplasma*, *Aspergillus* and tuberculosis. There were also cases of *Stenotrophomonas maltophilia*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Candida* spp., *Pneumocystis carinii* and cytomegalovirus. Increased pulmonary interstitial infiltration was the second most common manifestation (55.0, 35.0%), while pleuritis with or without pleural effusion was the commonest presenting manifestation at diagnosis in 26 patients (16.6%), and in 52 (33.1%) overall. Lung edema was also frequent (24 cases, 15.3%). Other manifestations documented included 22 cases with lupus pneumonitis, 16 with pulmonary hemorrhage, 7 with pulmonary hypertension, 6 with interstitial fibrocicatricial change and with 6 pneumothorax. Lung function test was performed in only 6 patients, 3 with restrictive ventilatory defects, 1 with an obstructive ventilatory defect, and 1 with an impairment of diffusion capacity. Dyspnea was the most common nonspecific symptom (61, 38.8%), and pleurisy occurred in 31 patients (19.7%). Endotracheal intubation with ventilatory

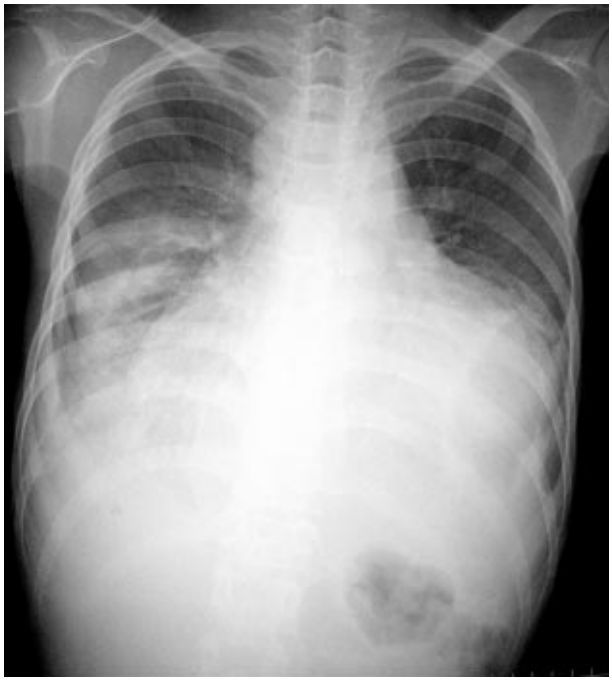

Fig. 1. Chest radiograph of a 20-year-old girl with systemic lupus erythematosus complicated with lung infection, bilateral pleural effusion and thickening, lupus pneumonitis and atelectasis of lower lobes. There is also cardiomegaly with dilatation of chambers and pericardial effusion.

Table 3. Cardiovascular involvement in childhood-onset systemic lupus erythematosus at diagnosis and during the disease course (n = 157)

Variable	At diagnosis No. (%)	Disease course No. (%)	Overall No. (%)
Involved patients	35 (22.3)	61 (38.8)	75 (47.8)
Cardiomegaly	24 (15.3)	42 (26.7)	53 (33.8)
Pericarditis/pericardial effusion	23 (14.6)	32 (20.4)	45 (28.7)
Arrhythmia/conduction anomaly	7 (4.5)	16 (10.2)	20 (12.7)
Other anomalies on electrocardiography	16 (10.2)	33 (21.0)	39 (24.8)
Valvular anomaly by echocardiography	13 (8.3)	22 (14.0)	31 (19.7)
Ventricular/atrial hypertrophy, interventricular septum thickening	6 (3.8)	14 (8.9)	18 (11.5)
Ventricular/atrial dilatation	4 (2.5)	7 (4.5)	10 (6.4)
Congestive heart failure	3 (1.9)	10 (6.4)	12 (7.6)
Coronary vascular disorder	0 (0.0)	6 (3.8)	6 (3.8)
Heart murmur	8 (5.1)	17 (10.8)	22 (14.0)

support was needed in 37 patients, thoracocentesis in 13, and chest tube placement in 8.

Table 3 lists the cardiovascular manifestations. The overall rate of involvement was 47.8% (75 patients). Thirty five patients were compromised at onset, while in 61 these conditions developed later during the course. Cardiomegaly and pericarditis with or without pericardial effusion were the most common findings (33.8% and 28.7%, respectively). Sinus arrhythmia was the most common type of arrhythmia/conduction anomaly, and included sinus tachycardia or bradycardia. Atrial premature complexes, premature supraventricular complexes, atrioventricular blocks, and right bundle branch blocks were also recorded. However, most patients were asymptomatic or had nonspecific symptoms. Valvular regurgitation was frequently noted on echocardiography, especially tricuspid (n = 27) and mitral (20) regurgitation. Valvular vegetation was documented in only 3 cases by transesophageal echocardiography. Coronary artery anomalies were found in 6 patients, including vascular dilatation, aneurysm, vasculitis and stenosis. Vascular thrombosis occurred in 5 patients, and involved the inferior vena cava (n = 2), lower extremities (large venous, 2), renal vein (1) and internal jugular vein thrombosis (1). Two patients had cardiomyopathy, 1 dilated type and another hypertrophic type. One case of severe aortic aneurysm with dissection was reported. High blood pressure in 69 patients (43.9%) and heart murmur in 22 (14.0%) were the frequently associated nonspecific signs. Fig. 2 is a demonstration of cardiovascular involvement.

Laboratory parameters at diagnosis significantly associated with development of cardiovascular complications during the disease course included increased creatinine >1 mg/dL (p=0.001), hematuria (p=0.009), anemia with Hb <12 g/dL (p=0.018), and blood urea nitogen >22 mg/dL (p=0.018); only anti-dsDNA was associated with pulmonary complications during the disease course (p=0.027).

Non-cardiopulmonary complications are shown in Table 4. These included hematological disorders such as anemia in 119 (75.8%), hemolytic anemia 22 (14.0%), leucopenia 94 (59.9%), and thrombocytopenia in 81 patients (51.6%). Renal involvement occurred in 109 patients (69.4%), with 22 cases of end-stage renal disease that underwent dialysis. Infectious disorders included sepsis (n = 45), urinary tract infections (40), herpes zoster (24), peritonitis (15) and cellulitis (13).

Discussion

This study evaluated the frequency and characteristics of lung and cardiovascular involvement in a cohort of

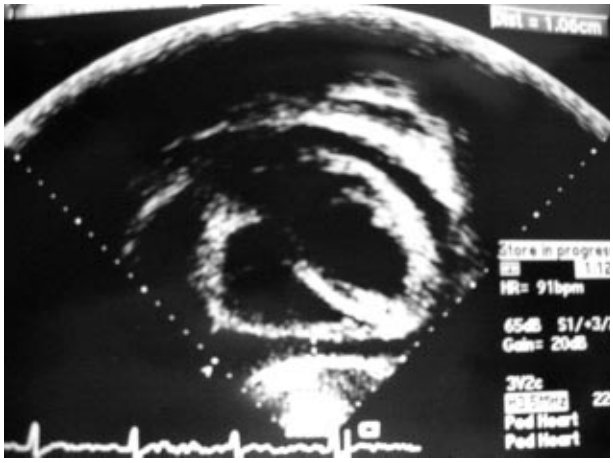

Fig. 2. Echocardiogram showing pericardial effusion around the heart with dilated left atrium and ventricle in a 22-year-old female with systemic lupus erythematosus.

Table 4. Complications not involving the cardiopulmonary system during the course of childhood-onset systemic lupus erythematosus (n =157)

Complication	Number (%)
Hematological	
Anemia	119 (75.8)
Hemolytic anemia	22 (14.0)
Leukopenia	94 (59.9)
Thrombocytopenia	81 (51.6)
Renal disorders	109 (69.4)
Neurologic manifestations	58 (36.9)
Sepsis	45 (28.7)
Ocular manifestations	29 (18.5)
Skeletal manifestations	27 (17.2)
Gastrointestinal bleeding	22 (14.0)

childhood-onset SLE from a single tertiary medical center during the past 20 years. Damage to multiple organ systems is a feature of SLE and any organ may be involved. Damage to the lungs and heart may occur at any level, including the parenchyma, vasculature, endothelium, muscular layer and serosa, endocardium and conduction system [1,2,6]. Respiratory and cardiovascular diseases in patients with SLE may be due to the direct involvement of the organ, or indirectly as a secondary consequence of damage in another organ system, like pleural or pericardial effusion secondary to renal disorders, and hypertension that may cause further heart damage [6,7].

Cardiovascular and pulmonary manifestations were reported in 40-60% of SLE patients. The rate varies greatly among different studies, which was attributed to the presence of clinically non-evident complications. Thus, the frequency had been much more higher in autopsy studies [1,2,6-8]. Serositis with pleuritis and pericarditis with or without effusion are the most common pulmonary and cardiovascular manifestations of SLE, with reported frequencies of 12%-50% for pleuritis, 25% for symptomatic pericarditis, and 40% for asymptomatic pericardial effusions by echocardiography. One study that combined autopsy series reported pericardial involvement in 62%, and pleuritis and pleural fibrosis in up to 50-83% [1,2,9]. Our results demonstrated significant overall rates of pulmonary (56.7%) and cardiovascular (47.8%) involvement in childhood-onset SLE.

Pleuritis occurred in 52 of our cases (33.1%), but was not the most common pulmonary manifestation. Pneumonia treated under hospitalization was the leading pulmonary disorder, occurring in 58 patients (36.9%). Increased susceptibility to pulmonary infection in patients with SLE may be due to several factors, such as intrinsic immunologic abnormalities, depressed alveolar macrophage activity, decreased natural killer cell activity, and immunosuppressive therapy, underlying parenchymal disease, respiratory tract edema, atelectasis and muscle weakness that decrease the clearance of secretions.

Bronchopneumonia was reported as the cause of death in 15% of patients [2]. Either common microbes or opportunistic organisms are responsible. Pyogenic bronchopneumonia was reported in 76% of autopsy series [2]. Opportunistic agents include *Aspergillus*, *Cryptococcus*, *P. carinii*, cytomegalovirus, *S. aureus*, *Mycobacterium*, and *Nocardia*. In our series, the infectious organism was not identified in most cases. *P. aeruginosa* accounted for the most common severe lung infections (8) and sepsis, while alpha-hemolytic *Streptococcus* were frequently positive in sputum cultures. Pulmonary infection is the most frequent cause of parenchymal infiltrates in patients with SLE [6,9]. Acute pneumonitis resulting from alveolar capillary damage injury, in which infection was ruled out, has varied between 1% and 12%. The clinical and radiographic features of acute pneumonitis may be indistinguishable from other causes of pulmonary infiltrates, such as pulmonary infection, embolism or hemorrhage [2,7,9,10].

Pulmonary hemorrhage is a rare but potentially catastrophic complication, with mortality rates of 50-90% [2,9-11]. Pulmonary hemorrhage in our patients was not rare (16, 10.2%), and 11 died (mortality rate, 68.7%). Six of our patients (3.8%) had chronic interstitial pneumonitis and fibrocicatricial change, similar to those previously reported [9]. Pulmonary arterial hypertension was confirmed by echocardiography in 7 patients (4.5%), for most of whom this was not clinically relevant.

The reduction in diffusion capacity is the most common pulmonary function abnormality in asymptomatic SLE patients. It was reported in 31-94% of cases, while restrictive change was reported in 10-49% [3,5,12]. Lung function test reports were found in only 6 cases of our series; 3 had restrictive ventilatory defect, 1 obstructive ventilatory defect and 1 impairment of diffusion capacity. The most common pulmonary symptoms are dyspnea and poor exercise tolerance (between 40.0% and 57.0%) and chest pain (35%) [6,9]. Our study found 61 (38.8%) with dyspnea and 31 (19.7%) with pleurisy.

Among the 75 patients (47.8%) with cardiovascular involvement in our study, in 35 (22.3%) this occurred at presentation. According to other studies, cardiac involvement was reported in 10% on presentation,

and between 35% and 50% during the disease course [8,13]. Clinically symptomatic pericarditis occurred in 25% of SLE patients and asymptomatic pericarditis was even more common, with 40% reported by echocardiography in unselected patients and diagnosed histologically in as many as 50-62% of autopsies [6, 14]. In our study, the most common cardiac manifestation was cardiomegaly proved by imaging studies in 53 (33.8%), many with nonspecific symptoms, followed by pericarditis with or without effusion in 45 (28.7%), arrhythmia and conduction anomaly in 20 (12.7%), and other electrocardiography anomalies.

Many SLE patients had abnormal valves, but most were not clinically significant. Libman-Sacks endocarditis was commonly reported by others, ranging from less than 10% by transthoracic echocardiography to 30% by transesophageal echocardiography, and 15-60% at autopsy [1,6]. Unlike other studies, valvular vegetation was rare in our series, with only 1 case of Libman-Sacks vegetation over mitral valve. One case had vegetation over the pulmonary valve, and another over the aortic valve but infective endocarditis was suspected. However, valvular regurgitation by echocardiography was the most common valvular disorder in our patients. Congestive heart failure was documented in 7.6%, similar to those reported by others that varied from less than 5% to 10% and were mostly secondary to a combination of factors such as ischemic heart disease, hypertension, renal failure and toxicity from medications [13,14].

Atherosclerosis is the most common cause of coronary artery disease in patients with SLE. Female adults with SLE aged between 35 to 44 years are 50 times more likely to present with myocardial infarction than those without SLE [14,15]. Of our patients, 6 had coronary artery anomaly, mostly with vasculitis documented by echocardiography; 3 cases were associated with coronary artery dilatation or aneurysm.

We expected that the frequency of lung and cardiovascular involvement in our patients would be higher than what was found. The limitations included "clinically not evident disorders" in SLE patients, the refusal of families to allow autopsy, incomplete medical records, and irregular follow-up of some patients. More frequent image studies and lung function testing might help the evaluation and early diagnosis of cardiopulmonary impairment. In this regard, prospective studies should be performed in the future.

In summary, retrospective analysis of pediatric SLE patients at NTUH revealed high frequencies of pulmonary (56.7%) and cardiovascular complications (47.8%). The more frequent lung involvements were pneumonia that required hospitalization, increased interstitial infiltration and pleuritis, while the more common heart complications were cardiomegaly and pericarditis. Blood creatinine >1 mg/dL, hematuria and anemia with Hb <12 g/dL obtained at SLE diagnosis were associated with development of cardiovascular complications during disease course, while anti-dsDNA at diagnosis was associated with development of pulmonary complications. Physicians should be aware of frequent subclinical involvement in SLE patients.

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