Pleuropulmonary Manifestations in Juvenile Systemic Lupus Erythematosus; A Review and Descriptive Study in 64 Cases

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Abstract

Objective: Juvenile systemic lupus erythematosus (JSLE) is a multisystemic autoimmune disease that can involve multiple organs such as: skin, kidney, musculoskeletal system, brain, and others as well as lung. Pulmonary manifestations may be an initial and/or life-threatening complication of SLE in children. The aim of this report is to describe the first pleuropulmonary manifestation of childhood lupus erythematosus.

Material & Methods: We studied retrospectively 64 children with JSLE, diagnosed as JSLE at the Children's Medical Center Hospital between 1995 and 2005. All met the American College of Rheumatology (formerly American Rheumatism Association, ARA) revised criteria for SLE. They were evaluated for evidence of pleuro-pulmonary involvement.

Findings: During the 10-yr study period, 64 patients were diagnosed as childhood-onset JSLE, who had the disease at or before the age of 16 (3-16 years). Fifty three patients (86%) were females and 9 patients (14%) were males (female: male ratio=6/1). Mean age of this group at the onset of the disease was 10 years (range 3-16). Eighteen cases (28%) had pulmonary involvement. Pulmonary complications include: infectious pneumonia in 38%, pleuritis in 33%, pulmonary vasculitis in 11%, and acute lupus pneumonitis, chronic interstitial pneumonitis and pulmonary embolism (so-called lupus anticoagulant) each one in 5.5%.

Conclusion: The prevalence of pulmonary involvement in patients with JSLE varies according to the method used, but clinically significant pulmonary involvement in our series occurs in approximately 28%. There is few data regarding the treatment for most of the immune mediated pulmonary manifestations of JSLE.

Key Words: Systemic Lupus Erythematosus, Lupus Pneumonitis, Chronic Intestinal Pneumonitis, Pulmonary Hemorrhage, Pneumothorax
**Introduction**

Systemic Lupus Erythematosus (SLE) is a chronic multisystemic disease, resulting from tissue damage caused by complement-fixing immune complex deposition[1]. SLE mainly affects women (10:1 female to male ratio). Juvenile Systemic Lupus Erythematosus (JSLE) is not a common illness in the pediatric population. It is a chronic disorder, which is usually life-long lasting and potentially fatal disease[2]. Although JSLE has been reported in children in the first 2 decades of life, it is rare in children under 5[3]. The peak incidence of childhood SLE occurs around puberty and predominantly involves young women of reproductive age[4]. In 10-20% of JSLE patients, diagnosis is made for the first time in childhood.[4-5] SLE may affect virtually any organ. Predominant manifestations include skin manifestations (malar rash, discoid rash, and photosensitivity), renal involvement, non-deforming arthritis, serositis, hematological disorders, central nervous system involvement and pleuropulmonary manifestations[6].

Pleuropulmonary system is one of the most important systems that can be affected in JSLE[7,8]. Pleuritis is the most common pleuropulmonary manifestation, occurring in 30% of children and may occur with or without pleural effusion[8,9]. Effusion is usually bilateral and little. Clinical presentations include fever, cough, dyspnea and pleuretic chest pain[8,9]. Pleural thickening may occur and is reported in up to 50% of chest radiographs taken in symptomatic patients, but it is unusual in asymptomatic patients[10].

Acute lupus pneumonitis is uncommon but life-threatening, with an estimated incidence of 10% in JSLE. The diagnosis is made by exclusion of infection, acute pulmonary edema, hemorrhage, and infarction. Patients are extremely ill, febrile, tachypneic, and hypoxic. The chest radiograph reveals ill-defined bilateral patchy air space consolidation in the periphery[11,13]. Chronic interstitial pneumonitis (CIP) occurs in 6% of children with JSLE. It is mild and asymptomatic, but rarely severe cases have been reported with abnormalities of pulmonary function tests. Infectious pneumonia, is one of the most common pleuropulmonary manifestations which involves approximately 30% of patients with JSLE. It is more likely that the high infection rate in JSLE is the result of the immune-suppressive agents usage rather than intrinsic immune defects.[14] Many dysfunctions have been described in JSLE, including defects in alveolar macrophage function (such as chemotactic and phagocytotic activity of neutrophils), decline in T-cell number and function, and defect in dendritic-cell, B-cell, and natural killer (NK) cell function. Opportunistic infection may be life-threatening, particularly with immunosuppressive treatment. Bacteria, viruses or fungi are organisms that can cause infection in the lung.[14] Sometimes pneumonitis may occur without infection and is then called non-infectious pneumonitis. Symptoms of childhood pneumonitis are fever, cough, shortness of breath, and chest pain.[15]

Thromboembolism, so-called lupus anticoagulant, has been demonstrated in patients with JSLE[16-18], and it is associated with an increased risk of intravascular thrombosis. Acute and chronic pulmonary embolism are well recognized complications of the anticardiolipin antibody existence. Pulmonary hemorrhage is a rare, but potentially catastrophic, complication of JSLE. Clinical features are non-specific but diffuse alveolar infiltrates, hypoxemia, dyspnea and anemia are characteristic. Pulmonary vasculitis occurs in 7% of children with JSLE[19], and primary pulmonary vascular disease is uncommon in these patients. Although the pathogenesis of pulmonary hypertension remains obscure, multiple factors may play a role; including pulmonary vasculitis, thrombosis, and pulmonary artery vasoconstriction.

Pneumothorax, opportunistic pulmonary infections, and drug toxicity from immunosuppressive therapy have been reported in patients with JSLE[18].

Pulmonary involvement is relatively frequent in adult patients rather than children; the group which pulmonary defects
are rarely reported for them. However, pulmonary manifestations may be an initial and/or life-threatening complication of JSLE in children[16].

Various laboratory abnormalities have been described in JSLE, most commonly CBC defects (anemia, lymphopenia, and thrombocytopenia), rising ESR and C-reactive protein (CRP) titer, increased BUN and creatinine, abnormal urinalysis, positive F-ANA (more than 1:160), antibodies directed against double-stranded DNA (ds-DNA), positive Anti- phospholipide antibodies (APL-ab), nuclear ribonucleoprotein, Smith (Sm) antigen, anti Ro/SS-A, and La/SS-B[17,18].

Also, chest X-ray examination, thoracic computed tomography (CT) scan, pulmonary fuction test, blood and bronchoalveolar lavage (BAL) sample cultures has been done. These complications require a complete and aggressive approach using appropriate cultures and, if needed, fibroptic bronchoscopy, transbronchial biopsy and even open lung biopsy[20-23].

The aim of this report is to describe the first pleuropulmonary manifestations of childhood SLE.

Material & Methods

We studied retrospectively 64 children with JSLE, diagnosed as JSLE at the Children’s Medical Center Hospital between 1995 and 2005.

We have classified specific pulmonary lesions in this paper, as we aim to emphasize on the descriptive evaluation of pulmonary involvement of our patients with childhood-onset of JSLE. We studied retrospectively 64 consecutive patients with JSLE, either as inpatients or outpatients, who were followed up by the same attending physicians. All patients met the American College of Rheumatology (formerly American Rheumatism Association, ARA) revised criteria for SLE. The patients, who were diagnosed with JSLE at the Children’s Medical Center Hospital between 1995 and 2005, were retrospectively evaluated for evidence of pulmonary involvement. Using a standardized data-sheath, we obtained data regarding the age, sex and presenting complaints of the patients, previous therapies given, clinical and laboratory features, treatment and outcome. Informed consent was obtained from all patients.

Findings

During the 10-year study period, 64 patients were diagnosed with childhood-onset SLE. All the patients had the disease at or before the age of 16 years (3-16 years). Fifty five patients (86%) from the childhood onset group were females and 9 patients (14%) were males (ratio =6:1). Mean age of this group of disease onset was 10 years (range 3-16). Table 1 shows Clinical manifestation of SLE in our patients. Malar rash and musculoskeletal symptom were the most common symptoms. Eighteen (28%) of JSLE patients had pulmonary involvement, and infectious pneumonia and pleuritis were the most common pulmonary involvement in our patients. (table 2)

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>No (%)</th>
</tr>
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<tbody>
<tr>
<td>Malar rash</td>
<td>62 (96%)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>54 (84%)</td>
</tr>
<tr>
<td>Oral ulcer</td>
<td>50 (78%)</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>45 (70%)</td>
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<tr>
<td>Hematologic</td>
<td>40 (62%)</td>
</tr>
<tr>
<td>Renal</td>
<td>35 (54%)</td>
</tr>
<tr>
<td>pulmonary involvement</td>
<td>18 (28%)</td>
</tr>
<tr>
<td>cardiovascular</td>
<td>15 (23%)</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>10 (15%)</td>
</tr>
</tbody>
</table>
Table 1- Pulmonary involvement in 18 patients with SLE

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>No (%)</th>
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</thead>
<tbody>
<tr>
<td>Infectious pneumonia</td>
<td>7 (38%)</td>
</tr>
<tr>
<td>Pleuritis</td>
<td>6 (33%)</td>
</tr>
<tr>
<td>Pulmonary vasculitis</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1 (5.5%)</td>
</tr>
<tr>
<td>Acute lupus embolism</td>
<td>1 (5.5%)</td>
</tr>
<tr>
<td>Chronic interstitial pneumonitis</td>
<td>1 (5.5%)</td>
</tr>
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</table>

Discussion

SLE is an autoimmune disease that involves multiple organ systems with various courses and prognoses[1]. It isn’t a common disease in the pediatric population. Although SLE has been reported in children between 5 to 16 years of life, it is rare in children under age of 5 years[2]. The peak incidence of childhood SLE occurs around puberty. In our study, female to male ratio was 6:1, with a mild difference in comparison with the adult onset group[3-5]. The mean age of disease onset in our study was 10 years versus 32 years in the adult onset group. A recent investigation in French children aged 16 years or younger reported an incidence of 0.22 cases/year/100.000 children with 0.36 girls, and 0.08 boys[5,6]. Even though the survival rate among SLE patients has improved during the past few decades[7], there are some host related factors that are associated with death in SLE patients, including the level of disease activity and demonstrable organ damage at presentation[8,9].

Moreover, although pulmonary involvement is relatively frequent in adult patients; it has been rarely reported in children with SLE. However, pulmonary manifestations may be an initial and/or life-threatening complication of SLE in children[9,10]. It has been reported that pleuropulmonary manifestations are seen in approximately 40–50% of patients with JSLE[5-7]. Our retrospective survey for the last 10 yr-data shows 28% patients with JSLE developed pulmonary manifestations and it’s less than other studies’ results in adult groups[8,9].

Pulmonary complications include pleuritis, acute lupus pneumonitis, chronic interstitial pneumonitis, pulmonary embolism, alveolar hemorrhage, pulmonary vasculitis, and atypical pneumonia[11]. However, pleuropulmonary infections and subclinical lung disease are relatively common in childhood-onset SLE[12-14]. In our study infectious pneumonia and pleuritis were the most common pulmonary involvement (71%). Sometimes pneumonia is not resolved with antibiotics, because the etiological agent was not detected. In this group pulmonary findings are resolved with corticosteroids and Azathioprine[26,27]. Because infections are the leading cause of death in patients with JSLE, all pulmonary infiltrates in JSLE should be considered infectious until proven otherwise. So, determining the exact cause requires a complete and aggressive approach using appropriate cultures and, if needed, fibreoptic bronchoscopy, transbronchial biopsy, and open lung biopsy[22-24]. The infectious pulmonary infiltrations are caused by viruses, bacteria, fungi and protozoa[14-16]. Invasive procedures to obtain tissue samples for microbiological and histopathological studies can provide valuable information in lupus lung disorders.

CMV infection was easily detected by non-invasive procedures in our patients, and lung biopsy was not necessary. All of the few reported patients with CMV infection had pneumonia[20]. Our patients with CMV pneumonia were successfully treated with Gancyclovir. Particularly, opportunistic infections such as tuberculosis, aspergillosis, and nocardiosis may only be demonstrated in tissue cultures or histopathological examinations[20,21].

Acute alveolar damage with interstitial edema, hyaline membranes and immune complex deposition in lung tissue has been demonstrated in patients with acute lupus pneumonitis[17,18].
Conclusion

The prevalence of pulmonary involvement in patients with JSLE varied with the method used for diagnosis, but clinically significant pulmonary involvement occurs in approximately 28% of patients. The pleural-pulmonary manifestations of SLE range in severity, from the minor pleuritic pain caused by serositis to life-threatening consequences of pulmonary hemorrhage. There is little data regarding treatment for most of the immune mediated pulmonary manifestations of SLE. Moreover, further investigation is required to find out the pathogenesis of SLE pulmonary complications.

References


