Acute Respiratory Distress Syndrome (ARDS) Due to Cytomegalovirus Pneumonia in a Case with Severe Combined Immunodeficiency

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Acute respiratory distress syndrome is an acute form of severe alveolar-capillary disease that evolves after a direct or indirect lung injury. It is characterized by impaired oxygenation (PaO₂/FiO₂<200), bilateral pulmonary densities detected by radiography, and a pulmonary wedge occlusion pressure of less than 18 mmHg. Mortality remains high among children with acute respiratory distress syndrome, particularly, with the existence of serious underlying conditions such as sepsis and multi-organ failure. Here, we report a case with acute respiratory distress syndrome due to cytomegalovirus pneumonia, which, was also diagnosed as severe combined immunodeficiency (T-B+NK-SCID). We have demonstrated CMV in peripheral blood and tracheal aspirate specimens. He died despite lung-protective mechanical ventilation and surfactant therapy.


Key Words: ARDS, CMV, SCID

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a form of acute lung injury characterized by impaired oxygenation (PaO₂/FiO₂<200), bilateral pulmonary densities in chest X-ray, and a pulmonary wedge occlusion pressure of less than 18 mmHg. It develops at all ages and has no gender predilection. Although the prevalence of ARDS is unknown in childhood, its range is 0.6 to 7\% of the total intensive care units (ICU) admissions. ARDS may cause direct or indirect lung injury. Causes of direct lung injury include pneumonia, aspiration incidents, and lung contusion. Septicemia is the most common lethal predisposing condition associated with ARDS\textsuperscript{1-3}. Severe Combined Immunodeficiency (SCID) is caused by diverse genetic mutations that lead to the absence of all adaptive immune functions and, in many cases, to the lack of NK cells\textsuperscript{4-6}. The overall frequency is estimated to 1 in 75,000-100,000 live births\textsuperscript{7}. Affected infants manifest symptoms of diarrhea, pneumonia, otitis, septicemia, and cutaneous infections. Persistent infections due to opportunistic organisms such as \textit{Candida albicans}, \textit{Pneumocystis carinii}, varicella, measles, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and bacillus Calmette-Guerin (BCG) may lead to death, making SCID a pediatric emergency. Unless immunologic reconstitution is achieved through bone marrow transplantation (BMT), death usually occurs in the first year of life\textsuperscript{5}. Recently successful ex
vivo gene therapy was achieved in 7 out of 11 patients\textsuperscript{8}. Here, we report a case of ARDS due to CMV in an infant with SCID.

**Case report**

A 9-month-old infant boy has been referred to our hospital with pneumonia and septicemia. He is the second child of healthy, unrelated parents, full termed and normally delivered. Oral monoliasis was noticed starting from 1 to 5 months old. It was followed by recurrent lower respiratory infections from 5 to 9 months old, leading to hospitalizations with pneumonia on three occasions. Physical examination revealed a body temperature of 38.5°C (axillary), palpable peripheral pulses, a blood pressure of 92/58 mmHg, a heart rate of 140/minute, a respiratory rate of 56/minute, suprasternal, intercostal and subcostal retractions, a nasal flaring, bilateral widespread rales, prolonged expirium and ronchi. His liver was enlarged, 9 cm at the midclavicular line, whereas the spleen was not palpable.

Laboratory examination revealed the following findings; 10.1 g/dl of hemoglobin, 3.7x10\textsuperscript{9} l of white blood cell count (WBC) 76% polymorphonuclear leukocyte, 20% lymphocyte and 4% monocyte in the peripheral blood smear with 0.74x10\textsuperscript{9} l absolute lymphocyte count, platelet count of 95x10\textsuperscript{9} l, erythrocyte sedimentation rate of 2 mm/hour, 1.6 mg/dl of CRP. Among coagulation parameters, prothrombin time was 11.8 sec (control 11-14); partial thromboplastin time was 58.8 sec (control 21-35); fibrinogen level 140 mg/dl, and fibrin-degradation products were >2000 ng/ml indicating the presence of severe disseminated intravascular coagulation. Serum activities of alanine transaminase (ALT) 68 U/L (10-31); aspartate transaminase (AST) 495 U/L (10-31) and γ-glutamyl transpeptidase (GGT) 735 U/L were elevated. Urine and renal function tests were normal. Arterial blood gases and cerebrospinal fluid (CSF) analysis were normal. There was bilateral infiltration on his chest X-ray (Figure 1). High levels of peripheral blood (6.1x10\textsuperscript{9} copy/ml) and tracheal aspirate CMV DNA (2.2x10\textsuperscript{7} copy/ml) copies were detected. CMV was accepted as the causing factor for pneumonia and hepatitis. *P. aerugenosa* was identified in the blood and tracheal aspirate specimens. Other viral studies, such as adenovirus, respiratory syncytial virus, influenza, and parainfluenza, were negative in serum and tracheal aspirates. *P. carinii* was negative at the tracheal aspirate smear test. Tracheal aspirate, and CSF mycobacterium tuberculosis PCR’s were negative. Gancyclovir was added to cefepime and amikacin, which had been started two days prior to his admission.

**Figure 1. Bilateral infiltration due to CMV pneumonia on chest X-ray**

Immunological tests revealed T-B+ NK-SCID (Table 1). We could not perform stem cell transplantation as his 3-year old healthy sister proved to be HLA mismatched. During follow-up, he developed respiratory distress with severe tachypnea, bilateral retractions and wet rales. Infiltration of the whole lung area, air bronchograms, and disappearing borders of heart (Figure 2) were observed on his chest X-ray. His echocardiography was normal. He was mechanically ventilated with lung protective intermittent mandatory ventilation (IMV), (low peak inspiratory pressure, low FO\textsubscript{2} (<0.65). His arterial blood gases were pH 7.33, pO\textsubscript{2} 78
mmHg, pCO2 42 mmHg, SO2 92%, and pO2 / FIO2 120 (<200). These findings supported the ARDS diagnosis. A transient improvement in his oxygenation and radiological findings of the chest were achieved soon after surfactant (60 mg/kg/dose), which was administrated twice, with one-day interval. He died of ARDS at the 9th day of admission despite lung-protective mechanical ventilation, appropriate administration of antibiotics for CMV infection and surfactant therapy.

**Discussion**

The mortality rate of adults with ARDS declined from 60 to 45% during the last 20 years. In contrast, the mortality rate among children with ARDS has remained stable, in part due to an increased numbers of high-risk pediatric patients. The highest mortality rates among patients with ARDS, without pre-existing illnesses, are associated with septicemia, ranging from 46 to 65%. The mortality rate for 121 pediatric bone marrow transplant recipients who required mechanical ventilation is 86%. There have been no advances in the prevention of ARDS. Instead, techniques to preserve lung function while minimizing ventilator-induced lung injury have evolved. Advances in the care of children with ARDS include the use of lung-protective ventilator strategies, permissive hypercapnia, inhaled nitric oxide and surfactant therapy, high frequency ventilation, and extra-corporeal life support.

SCIDs represent a spectrum of illnesses with similar clinical manifestations, which can be subdivided into several categories on the basis of the presence of T, B, NK cells. Nine different molecular defects (γc, Jak3, IL-7Rα, RAG1/RAG2, Artemis, ADA, CD3δ, CD45) are known to cause SCID and engender four distinct immunological phenotypes (Figure 3). Immunological studies in our patient revealed T-B-NK- SCID which can be the result of either γc or Jak3 deficiency.

The natural outcome of SCID is poor. Unless treated by bone marrow transplantation, death occurs in first year of life due to bacterial, viral, fungal and opportunistic infections. Prophylaxis and treatment of infections with intravenous immunoglobulin (IVIG) substitution and cotrimoxazole for P. carinii are required but can at best marginally prolong survival. Other obligatory measures include 25 Gy irradiation of blood products in order to avoid fatal GVHD and avoidance of live vaccines such as BCG.

### Table 1: Patient’s immunological data

<table>
<thead>
<tr>
<th>Immunological parameters</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral blood lymphocyte subsets</td>
<td></td>
</tr>
<tr>
<td>CD3+</td>
<td>2.2%</td>
</tr>
<tr>
<td>CD4+</td>
<td>1.1%</td>
</tr>
<tr>
<td>CD8+</td>
<td>1.1%</td>
</tr>
<tr>
<td>CD19+</td>
<td>52%</td>
</tr>
<tr>
<td>CD16+56+</td>
<td>3.2%</td>
</tr>
<tr>
<td>IgG</td>
<td>401.0 mg/dl (463-1006),</td>
</tr>
<tr>
<td>IgA</td>
<td>68.9 mg/dl (17-69)</td>
</tr>
<tr>
<td>IgM</td>
<td>51.8 mg/dl (46-159)</td>
</tr>
<tr>
<td>Candida skin test</td>
<td>Negative</td>
</tr>
<tr>
<td>PPD*</td>
<td>Negative</td>
</tr>
</tbody>
</table>

* BCG was applied when he was 4-month-old
Early recognition of SCID should be considered a pediatric emergency, because a diagnosis before the onset of opportunistic infections permits life saving bone marrow transplantation. The absolute lymphocyte count is the most useful screening diagnostic test, because lymphopenia is present almost in all patient with SCID from the time of the birth. Although our patient had severe infections requiring hospitalization SCID was not considered before. Finally, our patient died owing to CMV pneumonial, P. aurugenosa sepsis and ARDS.

Cytomegalovirus is member of the Herpesviridae family with a wide distribution. The risk of CMV disease, in its primary or recurrent forms, is increased in immunocompromised individuals such as patients with primary immunodeficiencies, AIDS and bone marrow transplant recipients. Pneumonia, retinitis, central nervous system and gastrointestinal tract involvements are usually severe and progressive. CMV has been the cause of severe pneumonia and hepatitis in our patient who had SCID. High CMV DNA copies detected in the tracheal aspirate and peripheral blood has led to the diagnosis of CMV disease. His pneumonia progressed and ARDS occurred despite gancyclovir treatment.

In conclusion, ARDS is an important issue in pediatric intensive care, due to its high mortality rate, especially, in an immunocompromised patient or in the presence of septicemia. Our patient, who had been diagnosed as SCID- and CMV pneumonia, died of ARDS despite lung-protective mechanical ventilation and surfactant therapy.

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