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OLGU SUNUMU CASE REPORT

Fatal acute respiratory distress syndrome in children with combined immunodeficiencies

Ağır kombine immün yetmezliği olan çocuklarda fatal akut solunumsal distres sendromu

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ABSTRACT

Acute respiratory distress syndrome (ARDS) is an acute form of severe alveolar-capillary disease that evolves after a direct or indirect lung injury. It is characterized by impaired oxygenation (PaO_2/FiO_2 < 200), bilateral pulmonary densities detectable by radiography and a pulmonary wedge occlusion pressure of less than 18 mmHg. Mortality remains high among children with ARDS, particularly in the presence of serious underlying conditions such as sepsis and multiple organ dysfunction syndrome. Here, we report five children with ARDS who were also diagnosed as either severe or combined immunodeficiency. Surfactant was given to four patients and mechanical ventilation was performed in all children. Although one responded temporarily, all patients died due to ARDS and multiple organ dysfunction syndrome. In conclusion, if pneumonia and ARDS develop in a patient with combined immunodeficiency, it usually ends with multiple organ dysfunction syndrome leading to mortality.

ÖZET

Akut solunumsal distres sendromu (ARDS) doğrudan veya dolaylı olarak ciddi alveoler-kapiller hastalığın ağır tutulumunun akut başlangıçlı formudur. Oksijenizasyonda yetersizlik (PaO_2/FiO_2 < 200), akciğer grafisinde bilateral infiltrasyon ve pulmoner kama basıncının 18 mmHg'dan daha düşük olması gerekmektedir. ARDS'de özellikle altta sepsis ve çoklu organ yetmezliği varsa ölüm hala yüksektir. Burada, ARDS'li ağır ve/veya kombine immünyetmezliği olan beş hasta sunulmuştur. Sürfaktan dört hastaya, mekanik ventilasyon bütün hastalara uygulanmıştır. Bir hasta geçici yanıt vermesine rağmen, bütün hastalar ARDS ve çoklu organ yetmezliği nedeniyle kaybedilmiştir. Sonuç olarak; kombine immünyetmezliği olan bir hastada, eğer pnömoni ve ARDS gelişirse genellikle ölümle sonuçlanan çoklu organ yetmezliği ile sonlanır.

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a form of acute lung injury characterized by impaired oxygenation ($PaO_2/FiO_2 < 200$), bilateral pulmonary densities visible in chest X-ray, and a pulmonary wedge occlusion pressure of less than 18 mmHg[1]. It can develop in all age groups 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 unit (ICU) admissions[1,2]. ARDS may be the result of direct or indirect lung injury. Septicemia is the most common lethal predisposing condition associated with ARDS[1-3].

Defects involving T-cells and B-cells have been described concerning their development, effector functions and their roles in immunoregulation[4]. Severe combined immunodeficiency (SCID) is caused by diverse genetic mutations leading to the absence of all adaptive immune functions and, in some cases, to the lack of natural killer (NK) cells[5,6]. The overall frequency is estimated to be 1 in 75.000-100.000 live births[6]. Affected infants manifest symptoms of pneumonia, diarrhea, otitis, septicemia, and cutaneous infections. Persistent infections due to opportunistic organisms such as *Candida albicans*, *Pneumocystis carinii*, cytomegalovirus (CMV), Epstein-Barr virus and bacillus Calmette-Guérin (BCG) may lead to death. Unless immunologic reconstitution is achieved through hematopoietic stem cell transplantation (HSCT), death usually occurs in the first year of life[5]. Recently, a successful *ex vivo* gene therapy was achieved in 11 out of 15 patients[6-8]. Here, we report a total of five infants with ARDS, accompanied by a T-cell and B-cell (combined) immunodeficiency; three of them with SCID, one with Omenn's syndrome and one with major histocompatibility complex (MHC) class I and II deficiency.

CASE REPORTS

Case 1

A nine-month-old boy was referred to our hospital with pneumonia and septicemia. He was the second child of healthy, unrelated parents, normally delivered at full term. Oral moniliasis was noticed starting from one to five months, followed by recurrent lower respiratory infections from five to nine months, leading to hospitalizations with pneumonia on three occasions. Physical examination revealed a body temperature of 38.5°C (axillary), blood pressure of 92/58 mmHg, heart rate of 140/minute, respiratory rate of 56/minute, suprasternal, intercostal and subcostal retractions, nasal flaring, bilateral widespread crackles, prolonged expiration and rhonchi. His liver was enlarged, 9 cm at the midclavicular line.

The patient's hemoglobin, white blood cell count, absolute lymphocyte count (ALC), platelet count, erythrocyte sedimentation rate, and C-reactive protein values are given in Table 1. His prothrombin time was 11.8 second (control 11-14); partial thromboplastin time 58.8 second (control 21-35); and fibrinogen level 140 mg/dL and fibrin-degradation products > 2000 ng/mL, indicating the presence of severe disseminated intravascular coagulation. Serum activities of alanine transaminase, aspartate transaminase, and gamma-glutamyl transpeptidase levels are also given in Table 1. Urine and renal function tests were normal. Arterial blood gases and cerebrospinal fluid analyses were normal. There was bilateral infiltration on his chest X-ray

Table 1. Patients' hematological parameters

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5
Hb (g/dL)	10.1	9.7	9.2	8.2	7.2
WBC (x 10^9/L)	3.7	2.8	1.5	99.8	11.2
ALC (x 10^9/L)	0.74	1.4	0.6	62	0.5
Platelet (x 10^9/L)	95	83	122	84	70
CRP (mg/dL)	1.6	0.6	2.3	2.1	1.1
ESR (mm/hour)	2	32	16	32	60
ALT (IU/L)	68	68	40	86	519
AST (IU/L)	495	165	52	320	342
GGT (IU/L)	735	122	79	142	1950

Hb: Hemoglobin, WBC: White blood cell count, ALC: Absolute lymphocyte count, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, ALT: Alanine transaminase, AST: Aspartate transaminase, GGT: Gammaglutamyl transpeptidase.

(Figure 1a). High peripheral blood (6.1 x 10^7 copies/mL) and tracheal aspirate CMV DNA (2.2 x 10^7 copies/mL) copies were detected. CMV was accepted as the causative factor for pneumonia and hepatitis. Ganciclovir was added to cefepime and amikacin, which had been started two days before his admission.

Immunological tests revealed T-B positive NK negative SCID. We could not perform HSCT, as his three-years-old healthy sister proved to be HLA-mismatched. During follow-up, he developed respiratory distress with severe tachypnea, bilateral retractions and crackles. Infiltration of the whole lung area, air bronchograms, and disappearing borders of the heart were observed (Figure 1b). His echocardiogram was normal. He was mechanically ventilated with lung protective synchronized intermittent mandatory ventilation [low peak inspiratory pressure, low FiO_2 (< 0.65)]. His arterial blood gases were pH 7.33, PaO_2 78 mmHg, $PaCO_2$ 42 mmHg, SaO_2 92%, and PaO_2/FiO_2 120 (< 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 a one-day interval. He died of ARDS and multiple organ dysfunction syndrome (MODS) at the 9th day of admission despite lung-protective mechanical ventilation, appropriate administration of antibiotics for CMV infection and surfactant therapy.

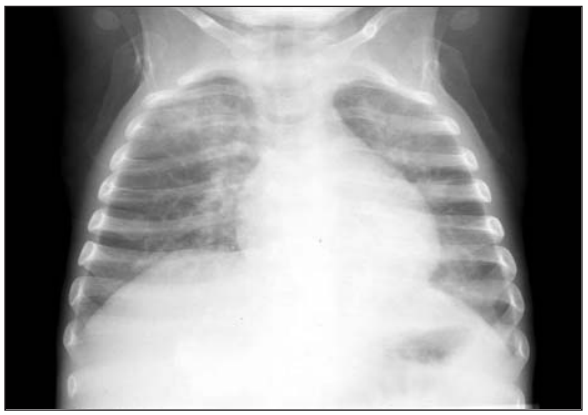

Figure 1a. Bilateral infiltrations due to CMV pneumonia on chest X-ray (Case 1).

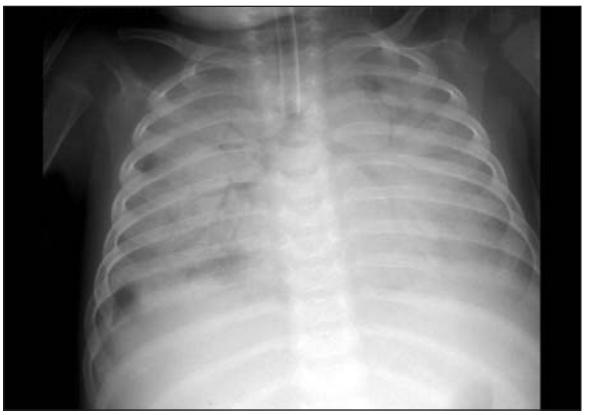

Figure 1b. Bilateral infiltration of the lungs, air bronchograms, and disappeared borders of the heart due to ARDS on chest X-ray (Case 1).

Case 2

A four-month-old girl was admitted to the hospital with recurrent pneumonia and gastroenteritis for the past two months. Her parents were first-degree relatives and her brother died from recurrent infection at the age of nine months. Her physical examination revealed a body weight of 5900 g (10-25%), length of 54 cm (10-25%), body temperature of 37.2°C (axillary), blood pressure of 88/52 mmHg, heart rate of 164/minute, and respiratory rate of 72/minute. She had suprasternal, intercostal and subcostal retractions, and bilateral widespread crackles. Her liver was enlarged, 3 cm at the midclavicular line.

The patient's laboratory findings are given in Table 1. There was bilateral interstitial infiltration on her chest X-ray (Figure 2a). Her arterial blood gases were pH 7.47, PaO_2 72.9 mmHg, $PaCO_2$ 31.3 mmHg, SaO_2 92%, and PaO_2/FiO_2 120 (< 200). She was intubated and mechanically ventilated when admitted to the pediatric ICU (PICU). CMV (416 x 10^7 copies/mL in peripheral blood) was detected as the cause of severe pneumonia and ARDS. Ganciclovir was added to the extended spectrum antibiotics.

Immunological tests revealed MHC class I and II deficiency (Table 2). SCT could not be performed due to the absence of an HLA-identical family donor. On the 5th day of admission, her radiological findings worsened (Figure 2b). Results of blood gases pointed to ARDS (Table 2). Following diagnosis, surfactant was administered intratracheally (130 mg/kg), upon which, oxygenation recovered within the first hour and radiological findings improved in six hours. Despite these improvements, her chest X-ray and blood gas results worsened on the 2nd day of surfactant administration. Upon the addition of a second dose, her blood gases and radiological findings (Figure 2c) improved and mechanical support was decreased.

Peritoneal dialysis was performed because of acute renal failure and anuria developed on the 9th day of admission. She died of nosoco-

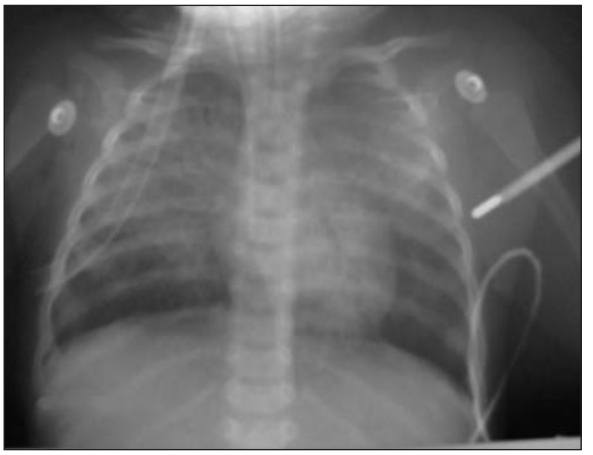

Figure 2b. Bilateral densities, air bronchograms, and concealed lung-heart border in ARDS (Case 2).

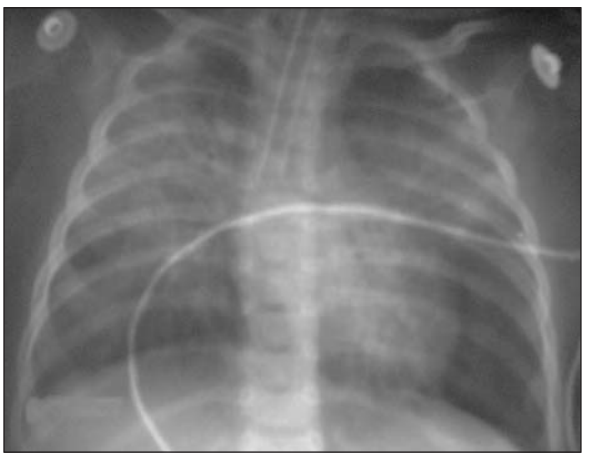

Figure 2a. Bilateral interstitial infiltration on chest X-ray (Case 2).

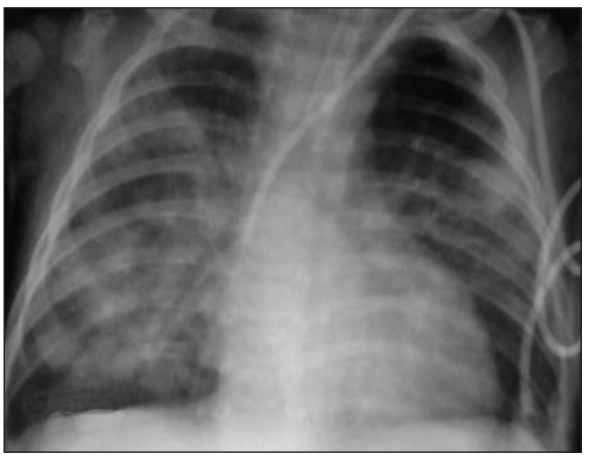

Figure 2c. Improvement on chest X-ray after the second dose of surfactant treatment (Case 2).

Table 2. Patients' immunological data

	Patients					
Immunological data	**1**	**2**	**3**	**4**	**5**	**Normal range (%)**
CD3+(CD16+56-) (%)	**2.2**	57.8	**1.4**	76	**1.7**	51-79
CD3+CD4+ (%)	**1.1**	**13.1**	**1.2**	74	**2.3**	33-55
CD3+CD8+ (%)	**1.1**	35.4	**0.4**	10	**0.7**	11-33
CD19+ (%)	52	30.2	91.2	**1.96**	**2.6**	14-44
CD3-CD16+56 (%)	**3.2**	12.9	6.6	12.2	45.7	5-23
HLADR (%)	95	**0.3**	92.0	45.3	10.5	15-48
HLA ABC (%)	99	**11.9**	99	99	99	99
IgG (mg/dL)	401.0	**35**	**90.7**	**63.6**	77	463-1006
IgA (mg/dL)	68.9	**6.6**	**< 6.6**	**16**	**6.6**	17-69
IgM (mg/dL)	51.8	**4.3**	66	51.4	**30.2**	46-159
Lymphoproliferative response to						
PHA (%)	10	41	11	45	8	65.8 ± 9.2
Anti-CD3 (%)	16	ND	20	42	18	57.5 ± 6.2
Diagnosis	T-B+ NK- SCID	MHC class I and II deficiency	T-B+ NK+ SCID	Omenn's syndrome	T-B- NK+ SCID	

ND: Not determined.

mial infection due to *Klebsiella pneumoniae* and sepsis.

Case 3

Case 3 was a five-month-old girl born to unrelated parents. She had been admitted to the hospital suffering from recurrent pneumonia and persistent moniliasis since she was three months old. Her two sisters died of pneumonia, at three and seven months, respectively. Physical examination revealed a body temperature of 37.8°C (axillary), respiratory rate of 72/minute, intercostal and subcostal retractions, and bilateral widespread crackles.

The patient's laboratory values are given in Table 1. ARDS was diagnosed following blood gases and chest X-ray findings. No pathogen was detected in blood, urine and tracheal aspirate cultures. Blood and tracheal aspirates were negative for CMV and other viruses. Immunological tests revealed T-B positive NK positive SCID (Table 3). SCT could not be performed because of her parents' refusal. She was treated with wide spectrum antibacterial, antiviral and antifungal agents and also received intravenous immunoglobulin (IVIG). She was intubated and mechanically ventilated due to severe pneumonia upon admission to the PICU. There were transient improvements following surfactant administration (120 mg/kg/dose, two times with a two-day interval). She died on the 6th day of admission due to severe ARDS and MODS.

Case 4

Case 4, a five-month-old boy, the first child of consanguineous parents, admitted to the hospital with generalized erythroderma, persistent moniliasis and recurrent pneumonia. Physical examination revealed widespread erythroderma with ichthyosiform lesions, alopecia, generalized lymphadenopathy, hepatosplenomegaly, and pretibial edema.

The patient's laboratory levels are given in Table 1. His biochemical parameters were protein of 3.4 g/dL, albumin of 2.3 g/dL, urea of 78

Table 3. Patients' blood gases and ventilation parameters during ARDS diagnosis

	Case 1	Case 2	Case 3	Case 4	Case 5
PaO_2	78	43.1	60.4	56.3	82
FiO_2	0.7	1.0	1.0	1.0	1.0
PaO_2/FiO_2	120	43	60	56	82
Rate	40	32	35	42	35
IT	0.8	1.2	1.2	0.8	1.1
PIP	37	35	38	34	36
PEEP	10	12	12	10	12

IT: Inspiratory time, PIP: Peak inspiratory pressure, PEEP: Positive end-expiratory pressure, ARDS: Acute respiratory distress syndrome.

mg/dL, creatinine of 1.3 mg/dL, sodium of 158 mg/dL, and potassium of 5.2 mg/dL. Upon the diagnosis of Omenn's syndrome, he was admitted to the PICU, and fluid, albumin, meropenem, acyclovir, liposomal amphotericin B, and IVIG were started. Blood urea nitrogen (BUN) and creatinine levels progressively increased and anuria developed. Peritoneal dialysis was performed on the 7^{th} day of admission. Mechanical ventilation was started because of respiratory failure due to progressive pneumonia. At the 10^{th} day of admission, stem cell (5 x 10^6/kg) transplantation from his HLA-identical mother was performed without conditioning. ARDS developed on the first post-transplant day and he died on the 4^{th} day due to ARDS and MODS.

Case 5

A four-month-old boy, the second child of healthy, unrelated parents, admitted to the hospital with complaints of recurrent pulmonary infections, diarrhea and moniliasis (Table 1). Laboratory evaluation revealed T-B negative NK positive SCID (Table 4). CMV antigenemia (20.6 x 10^7 copies/mL) was detected and he received ganciclovir treatment for three weeks. Because of persistent CMV antigenemia, ganciclovir was changed to foscarnet. During this treatment, CMV load in peripheral blood increased and ganciclovir was added. CMV pneumonia and retinitis developed while he was receiving a combined regimen. He was admitted to the PICU because of severe pneumonia and respiratory failure.

Laboratory data are given in Table 1. Serum sodium was low and urine sodium was high due to the renal consequences of systemic CMV infection. He was intubated and mechanically ventilated in the PICU. At first, bilateral interstitial infiltration was detected on his chest X-ray (Figure 3a), and normocarbia and hypoxia were identified (Table 3). On the 10^{th} day of PICU follow-up, widespread infiltration and severe hypoxemia developed in spite of high mechanical ventilation support. His chest X-ray and blood gases were consistent with ARDS (Figure 3b). Tracheal aspirate and blood cultures were negative for bacteria. In spite of high positive end-expiratory pressure (PEEP) and recruitment maneuvers, ARDS did not improve. On the 15^{th} day of mechanical ventilation, he died of CMV infection and ARDS.

DISCUSSION

SCID, Omenn's syndrome and MHC class I and II defects are primary immunodeficiency diseases representing T-cell and B-cell defects as classified by the European Society for Immunodeficiencies (ESID) (Table 3)[9]. SCID is a spectrum of illnesses with similar clinical manifestations, which can be subdivided into several categories on the basis of the presence of T, B and NK cells. Ten different molecular defects (δc, Jak_3, IL-7rα, RAG_1/RAG_2, Artemis, ADA, $CD_3δ$, CD45) are known to cause four distinct immu-

Table 4. General characteristics of SCID, Omenn's syndrome and MHC defects among T-cell and B-cell immunodeficiencies*

Disease	Circulating T-cells	Circulating B-cells	Serum Ig	Associated features	Inheritance
1. T-B+ SCID	Decreased or markedly decreased	Normal or increased	Decreased	Normal or decreased NK cells	XL or AR
2. T-B- SCID	Decreased or markedly decreased	Decreased or markedly decreased	Decreased	Normal or decreased NK cells, defective VDJ recombination, radiation sensitivity	AR
3. Omenn's syndrome	Present, restricted heterogeneity	Normal or decreased	Decreased, increased IgE	Erythroderma, eosinophilia, hepatosplenomegaly	AR
4. MHC class II deficiency	Normal, decreased CD4 numbers	Normal	Normal or decreased		AR
5. MHC class I deficiency (TAP-1/TAP-2 deficiency)	Decreased CD8, normal CD4	Normal	Normal	Vasculitis	AR

* Modified from reference 9.

SCID: Severe combined immunodeficiency, MHC: Major histocompatibility complex, XL: X-linked, AR: Autosomal recessive.

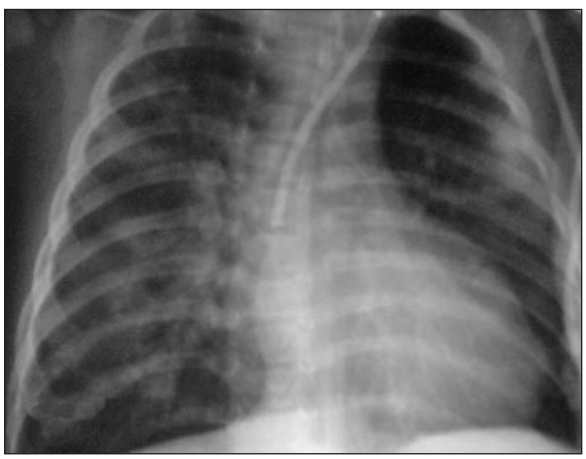

Figure 3a. Bilateral infiltration on chest X-ray.

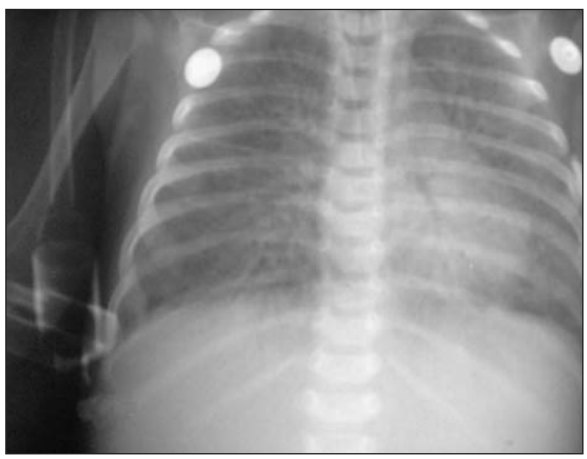

Figure 3b. Bilateral densities and air bronchogram.

nological phenotypes of SCID[10]. Immunological studies in our three SCID patients revealed T-B positive NK negative (case 1), T-B positive NK positive (case 3) and T-B negative NK positive (case 5) phenotypes. If bone marrow transplantation is not performed, death occurs in the first year of life due to bacterial, viral, fungal, and opportunistic infections. Prophylaxis and treatment of infections with IVIG substitution and cotrimoxazole for *P. carinii* are required but can, at best, marginally prolong survival[6,9]. Other obligatory measures include 25Gy irradiation of blood products in order to avoid fatal graft versus host disease and avoidance of live vaccines such as BCG[6,11].

As early diagnosis before the onset of opportunistic infections permits lifesaving bone marrow transplantation, early recognition of SCID

should be considered as a pediatric emergency. Lymphopenia is present in almost all patients with SCID from birth onwards; therefore, ALC is the most useful screening test in diagnosis[5]. Although our patients had several severe infections requiring hospitalization, SCID was not considered in the early diagnosis, therefore leading to death due to CMV infection, sepsis, ARDS and MODS.

The mortality rate in adults with ARDS has declined from 60 to 45% during the last 20 years[1]. In contrast, the mortality rate among children with ARDS remained stable, in part due to increased numbers of high-risk pediatric patients. The highest mortality rates among patients with ARDS, without pre-existing illnesses, are associated with septicemia, with a range of 46 to 65%[1]. The mortality rate for 121 pediatric bone marrow transplant recipients who required mechanical ventilation was reported as 86%[12]. 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 extracorporeal life support[13-15]. However, despite lung protective strategies, high PEEP and surfactant treatments, all of our patients died.

In ARDS, the lungs have been shown to have decreased quantities of phosphatidylglycholines, dipalmitoyl phosphatidylcholines and phosphatidylglycerol, as well as decreased levels of SP-A, SP-B and SP-C. Surfactant function is inhibited by leaked plasma proteins and inflammatory mediators[16,17]. Studies on adults with ARDS have shown that natural surfactant improved gas exchange and increased oxygenation, which in turn reduced the intrapulmonary shunt and the resulting mortality. Surfactant has been used in pediatric patients as case studies. Perez-Benavides et al. used surfactant in seven children with severe ARDS and noticed a rapid improvement in their pulmonary dynamic compliance[18]. They did not have an appropriate control group but referred to past data for comparison. They could not find a statistically significant difference in the mortality rate. In a prospective, randomized controlled study of 42 children treated with surfactant for ARDS, Willson et al. showed a rapid improvement in oxygenation, reduced duration of mechanical ventilation and an earlier discharge from the PICU with similar mortality rates[19]. We used surfactant treatment in four of the five patients with ARDS. Surfactant was performed six times in four patients and doses ranged between 70-130 mg/kg/dose. Transient radiological and oxygenation improvements were seen in cases 1, 3 and 4, but radiological deterioration and hypoxemia occurred in all patients on the second day. In case 2, ARDS improved with surfactant, lung-protective mechanical ventilation, and recruitment maneuvers, but she died due to nosocomial infection with *K. pneumoniae*. We did not apply surfactant to case 5 because of progressive uncontrolled systemic CMV infection.

CMV was the cause of severe pneumonia and hepatitis in patients 1, 2 and 5 who had SCID. High CMV DNA copies detected in the tracheal aspirate and peripheral blood in cases 1 and 2 led to the diagnosis of CMV disease. Furthermore, CMV compromised the kidneys in patient 5. CMV infections could not be controlled with ganciclovir (cases 1, 2, 5) and foscarnet (case 5) treatment. CMV is a 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 and acquired immunodeficiency syndrome and bone marrow transplant recipients. Pneumonia, retinitis, central nervous system and gastrointestinal tract involvements are usually severe and progressive[20].

In conclusion, ARDS is an important issue in pediatric intensive care, due to its high mortality rate, especially in immunocompromised pa-

tients or in the presence of septicemia. Our patients, who had been diagnosed with SCID and ARDS, died of ARDS despite lung-protective mechanical ventilation and surfactant therapy.

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