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[Case Report]

Neonatal high-permeability pulmonary edema based on serial cytokine profiles and KL-6 in serum : case report

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Abstract

A newborn male with pulmonary edema was delivered at term by elective Caesarian section. Cytokine profiles of 17 cytokines and KL-6 in cord blood and serial serum values were investigated. The cord blood values of all 17 cytokines and KL-6 were within normal limits. Subsequently, IL-6, IL-8, IL-10, IL-13, IL-17, and IFN γ rapidly elevated during the first several hours after birth and dramatically decreased thereafter, whereas KL-6 rose to 611 U/ml on the 3rd day of life and then gradually decreased. These cytokines may induce pulmonary permeability, and KL-6 secreted in lining fluid could result in influx into the bloodstream. This is the first report that we have differentiated neonatal pulmonary edema from TTN by the measurement of serial cytokine profiles and KL-6 in serum.

Key words : pulmonary edema, high permeability, cytokine profiles, KL-6, neonates.

Introduction

Transient tachypnea in newborns (TTN) is characterized by delayed clearance of fetal lung fluid and may also represent transient pulmonary edema resulting from delayed clearance of this fluid. From the pathophysiological viewpoint, TTN is different from pulmonary edema, especially the noncardiogenic type, which occurs when permeability of the microvascular membrane increases. We may have been able to differentiate noncardiogenic pulmonary edema from TTN by serial changes in cytokine profiles and KL-6 in plasma.

Case report

A male infant was born at 38 weeks of gestation by elective Caesarean section because his mother (gravida 2, para 2) had previously undergone Caesarian section. The mother was confirmed that systemic inflammatory diseases such as systemic lupus erythematosus were negative by preoperative examination. His birth weight was 2,224 g (-1.78 SD), and Apgar scores were 8 and 8 at 1 and 5 min-

utes, respectively. His amniotic fluid was normal in volume and not turbid. The placenta was not abnormal macroscopically. He had 2 healthy siblings and no significant family history. He was admitted to the neonatal intensive care unit soon after birth because of persistent central cyanosis while breathing ambient air without other respiratory disturbance at the time. Oxygen supplementation was initially started at an F_IO₂ of 0.35. His peripheral oxygen saturation (SpO₂) fell to 80% after crying and recovered slowly afterwards. Laboratory examination revealed a peripheral white blood cell count of 20,000/ μ L (reference range [RR]: 9,000-30,000), C-reactive protein <0.02 mg/dL (RR: \sim 1.0), plasma immunoglobulin M 8.5 mg/dL (mean \pm SD: 11 \pm 5), total protein 6.7 g/dL (mean \pm SD: 5.45 \pm 0.42), lactate dehydrogenase 432 IU/L (mean \pm SD: 333 \pm 206), pH 7.303 (RR: 7.3-7.4), PaCO₂ 40.8 mmHg (RR: 33-36), PaO₂ 73.3 Torr (RR: 63-87), HCO₃⁻ 19.6 mmol/L (RR: 20-22), and BE -6.0 mmol/L (RR: -8.0 - -2.0) at 1.5 hours after birth. Ultrasonographic examination of brain and heart showed no abnormal signs except for low end-systolic wall stress (ESWS) of 18.7 g/m² (mean \pm SD: 30.2 \pm

8.7)¹. No pathological bacteria were identified from blood, nasal cavity, and external ear. Because his SpO₂ remained between 95% and 97%, the F_IO₂ could gradually be reduced from 35% to 28% at 2 hours after birth. However, because his SpO₂ was sluggish after a long period of crying, the F_IO₂ was increased to 35% of the initial dosage at 3.5 hours after birth. He suddenly became tachypnea (100–120/minute) at 8.5 hours after birth. Chest X-ray showed coarse, fluffy densities appearing throughout

the lungs as alveoli filled with fluid (Fig. 1). He then received nasal directional positive airway pressure for 4 days and oxygen supplementation for 8 days. He was successfully discharged from the hospital on the 15th day of life.

Our investigation was approved by the Musashino Red Cross Hospital ethics committee. The parents of the infant were informed of the study design, and written informed consent was obtained from them.

We measured serum cytokine levels with the BioPlex protein array system (Bio-Rad, Alameda, CA), as described previously², using the BioPlex human cytokine 17-plex panel. Serum KL-6 was measured by a latex agglutination immunoturbidimetric assay using a commercially available kit (Nanopia KL-6; Eisai).

The serum levels of pro-inflammatory cytokines (interleukin [IL]-1 β , IL-6, IL-17, and tumor necrosis factor- α [TNF- α]), Th 1 cytokines (IL-1, IL-12, and interferon [IFN]- γ), Th 2 cytokines (IL-4, IL-5, IL-10, and IL-13), growth factors (IL-7, granulocyte-colony stimulating factor [G-CSF], and granulocyte-macrophage colony-stimulating factor [GM-CSF]), and chemokines (IL-8, monocyte chemotactic protein [MCP]-1, and macrophage inflammatory protein [MIP]-1 β) were all kept within the range of 2 SD of the controls at birth. The most striking finding of our patient's cytokine profile was the preferentially elevated level of serum pro-inflammatory cytokine IL-6 (765.7 pg/mL) at 1.5 hours after birth. The level of the other pro-inflammatory cytokine, IL-17, was moderately elevated at 2.5 hours after birth. Th 1 cytokine IFN- γ was increased only at 2.5 hours after birth. The levels of Th 2 cytokines IL-10 and IL-13 were also elevated during the initial 2.5 hours after birth. However, except for IL-6 and MIP-1 β , they also declined to within the range of 2 SD of the controls by 68 hours after birth (Fig. 2 (1) to (5), Fig. 3). In particular, two peaks were revealed in the time course of serum IL-6 during the initial 24 hours after birth. Reference control levels were obtained from Takahashi *et al*².

The level of serum KL-6 (RR : 44.3–148.2 U/mL in cord blood³, 50.8–226.3 U/mL in neonates⁴) was not increased at birth but increased markedly to 611 U/mL on the 3rd day of life and decreased gradually thereafter. The levels remained elevated throughout the period of oxygen supplementation (Fig. 2 (6)).

Serial echocardiographic measurements of cardiac function were performed from 3.5 to 120 hours of life (Fig. 4). Left ventricular ejection fraction

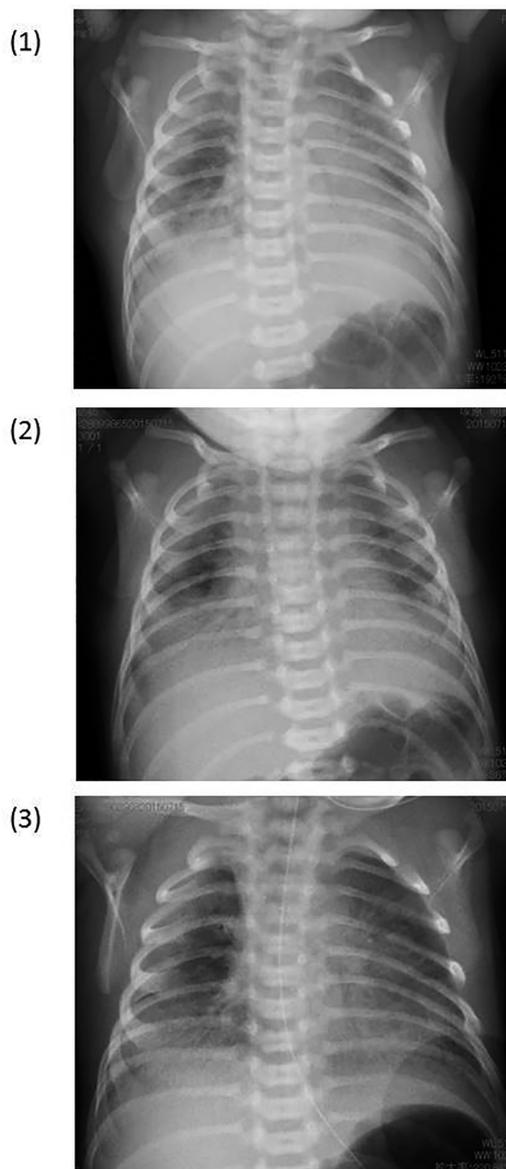


Fig. 1. Supine anteroposterior chest X-ray at 9 hours after birth. (1): 2.5 hours after birth with head box F_IO₂ 0.35; (2): 4.5 hours after birth with head box F_IO₂ 0.3; (3): 9 hours after birth with directional positive airway pressure (DPAP). Coarse and fluffy densities appeared throughout the lungs, especially the mid and lower lung fields, as alveoli filled with fluid over time.

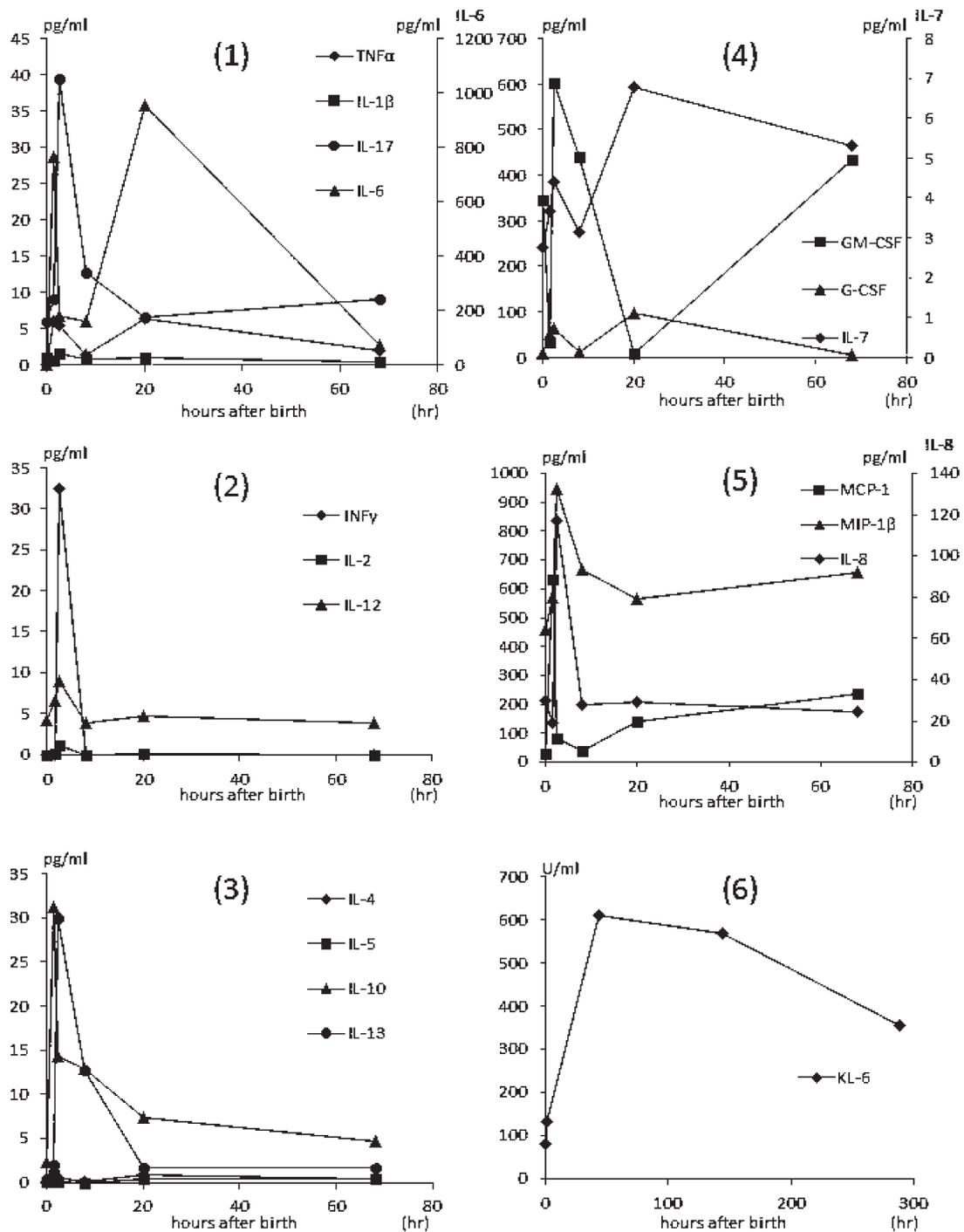


Fig. 2. Time course of the plasma levels of the cytokine profiles and KL-6. (1): Pro-inflammatory cytokines; (2): Th1 cytokines; (3): Th2 cytokines; (4): growth factors, and (5): chemokines. Among the cytokine profiles, serum IL-6, IL-8, IL-10, IL-13, IL-17, and IFN γ levels were remarkably elevated shortly after birth, but they declined rapidly, and all were within normal range by 2 days of life. The level of serum KL-6 (lower right panel) had increased markedly to 611 U/mL at 44 hours after birth and then decreased gradually thereafter.

and rate-corrected mean velocity of circumferential fiber shortening remained at normal values. The mean blood pressure values measured by oscillometric method were greater than those expected for his gestational age (38 weeks). Although the time

course pattern of ESWS was almost the same as that previously reported⁵⁾, the value at 3.5 hours of life was significantly low. The infant could generally be managed well without cardiac support such as dopamine (Fig. 5).

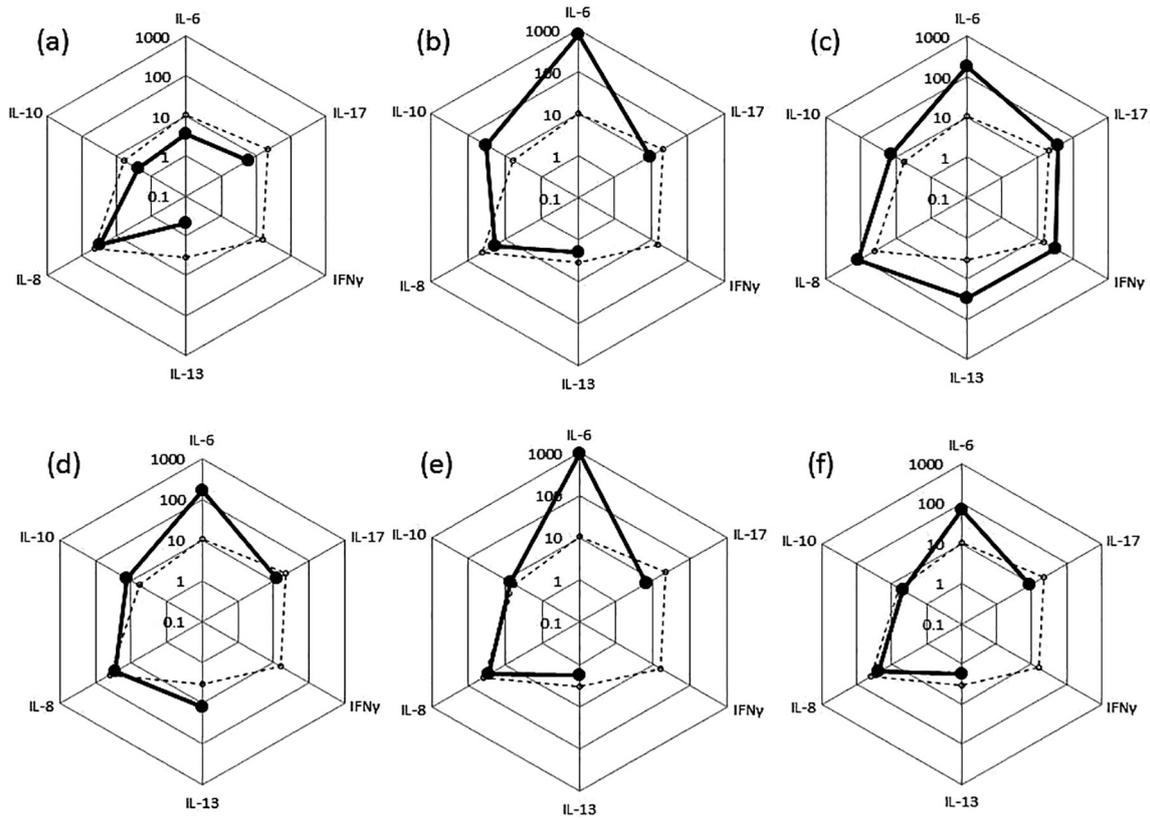


Fig. 3. Cytokine profiles of 6 of 17 cytokines remarkably elevated shortly after birth. (a) Cord blood, (b) 1.5 hours after birth, (c) 2.5 hours after birth, (d) 8 hours after birth, (e) 20 hours after birth, and (f) 68 hours after birth. The solid line indicates the patient and the dotted line indicates the control (mean+2 SD). Because the value of IFN γ of 0.1 pg/mL was less than that of all other values at 2.5-hours after birth, it was plotted on a logarithmic graph for the negative point. IL, interleukin ; IFN, interferon.

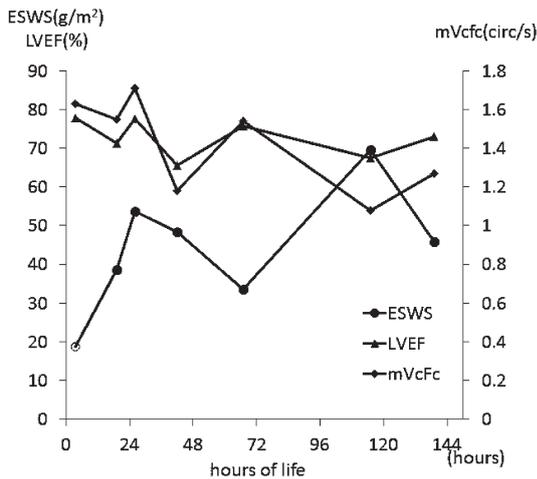


Fig. 4. Serial changes in LVEF, ESWS, and mVcfc. Over the time course following birth, LVEF and mVcfc were always within normal range. Values of ESWS, except for that at 3.5 hours after birth (○), which was particularly low, were all within normal range. ESWS, end-systolic wall stress ; LVEF, left ventricular ejection fraction ; mVcfc, mean fiber shortening velocity.

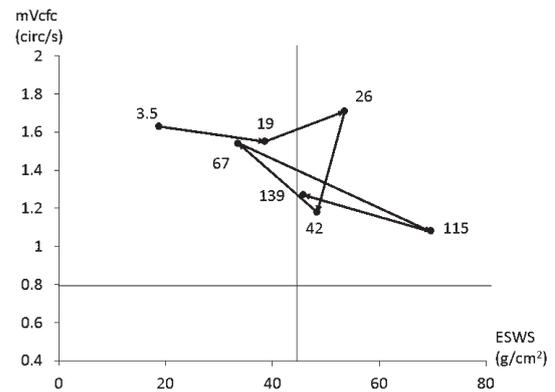


Fig. 5. Stress-velocity relationship (mVcfc-ESWS relationship). The numbers shown to the side of the ● indicate hours after birth. Over the time course, the relationship was always within the normal range. We speculate that there was no left ventricular pump dysfunction due to excessive afterload, but somehow, the pulmonary venous pressure increased, which may lead to pulmonary edema. ESWS, end-systolic wall stress ; mVcfc, mean fiber shortening velocity.

Discussion

TTN is among the most common causes of respiratory distress in the neonatal period. Symptoms of respiratory distress result from the failure to adequately absorb fetal lung fluid and typically start within the first several hours after birth⁶. Delivery by Caesarean section (particularly without preceding labor and the corresponding increase in the level of epinephrine) may not efficiently ensure the modification of lung epithelia from a secreting to a resorptive phenotype.

Pulmonary edema is the abnormal accumulation of water and solute in the interstitial and alveolar spaces of the lung⁷ and occurs only when the rate of fluid filtration exceeds that of lymphatic removal. There are three mechanisms by which this can occur: intravascular hydrostatic pressure increases, permeability of the vascular bed increases, or lymphatic drainage decreases. In the 2nd mechanism, patients may develop pulmonary edema despite having relatively normal vascular pressures. High-permeability pulmonary edema usually implies either direct or indirect injury to the capillary endothelium of the lung. Indirect injuries usually involve blood-borne mediators, such as leukotrienes, histamine, bradykinin, or some proinflammatory cytokines including IL-1 β , IL-6, IL-8, IL-10, and TNF- α ^{8,9}.

To elucidate the role of cytokines, especially IL-8 and IL-6, in the development of chronic lung disease (CLD) of the neonates, serial and simultaneous measurement of cytokines in the serum and the tracheobronchial aspirate of low birth weight infants were conducted¹⁰. The cord blood IL-6 and IL-8 levels of CLD of the neonates with fetal inflammatory response syndrome (FIRS) were significantly elevated, but those of CLD neonates without FIRS were not significantly different compared with non-CLD neonates with respiratory distress syndrome¹¹. The IL-8 level of the tracheobronchial aspirate in neonates with CLD was higher than that of neonates without CLD on day 10 of age¹⁰. These reports were day-by-day studies and not serial measurement such as our case.

To our best knowledge, there is only one report so far of serial cytokine profiles in newborns¹², but it has a limitation of small sample size. Because it is difficult to draw sequential, daily blood samples in healthy preterm and term infants, infants with mild dyspnea on nasal CPAP were included¹². This means that TTN is included in the subjects of their study. The value of IL-6 was high only in the first

4 hours after birth compared to the period thereafter. No trend over time was found in any of the other cytokine profiles¹².

The serum levels of GM-CSF and G-CSF were widely distributed². Chemokines, especially MCP-1 and MIP-1 β , showed relatively higher serum levels compared to the other cytokines, and the serum level of MIP-1 β was more than 100 pg/mL in 93.8% of the subjects, of which 70.5% were preterm infants, 79.0% had cesarean delivery mode, 16.9% had respiratory distress syndrome².

Therefore, when evaluating the values of each cytokine, it is better to consider the serial change between high and low values rather than to focus on the absolute values of individual measurements. The reason why the serum levels of IL-6 only had two extremely high peaks during the course was unknown. Because this finding has been seen only in this one case, clarification in other patients in future is needed.

Ishizaka *et al.*¹³ reported that alveolar type II cells could produce KL-6 when stimulated by Cytomix, containing IL-1 β , INF- γ , and TNF- α , but cell death was not induced. KL-6, which was released from type II cells in the pulmonary epithelial lining fluid (ELF), could diffuse through the paracellular pathway of lung endothelium and alveolar epithelium into the bloodstream. The level of KL-6 in serum is increased later than that in ELF. In this respect, there may be a limit to recognizing the acute-phase pathological state of the lung by only serum KL-6 levels. In addition to KL-6, surfactant protein D (SP-D) in serum is also produced by type II cells and is expected to be a useful lung disease marker. In the present neonate, serum SP-D was 609 ng/mL (RR: 90-100¹⁴) measured only once, at the peak point of KL-6. The molecular weight of KL-6 is remarkably larger than that of SP-D, so discrepancies in changes of concentration between KL-6 and SP-D by vessel permeability are possible. The result of elevation of both KL-6 and SP-D in serum means that vessel permeability was suspected to be quite high transiently soon after birth.

There was no apparent cause of the hypercytokinemia in this baby born by elective Caesarean section. There are some reports of severe metabolic acidemia possibly having caused abnormal cytokinemia that led to permeability pulmonary edema^{15,16}. However, the metabolic acidemia in the present neonate was mild and not so severe for his age. Furthermore, his mother had no systemic inflammation which might have caused hypercytokinemia. Thus, a diagnosis of TTN in this baby

would seem to be reasonable. However, based on his clinical course and laboratory data, he should be diagnosed as having neonatal high-permeability pulmonary edema induced by transient increase of pro-inflammatory cytokines. We suggest that the high permeability of the pulmonary vessels may reflect a decrease in the ESWS value near birth.

To our knowledge, this is the first case of early neonatal high-permeability pulmonary edema diagnosed by serial laboratory assessment of cytokine profiles and KL-6 in plasma. In newborns diagnosed as having TTN as their respiratory disorder, we surmise that in some of the published reports, the actual diagnosis might really be high-permeability pulmonary edema.

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