Fat embolism syndrome (FES), a serious but uncommon disorder, is characterized by the presence of petechial rash, respiratory distress, and mental disturbances with an onset of 24 to 72 hours following a pelvic or long-bone fracture. The incidence of FES increased from 3% in patients who sustained a single long-bone fracture to up to 30% in patients with multiple injuries [1]. Recent studies suggest that an increase in the percentage of fat-containing macrophages in the bronchoalveolar lavage (BAL) fluid may be helpful in the early diagnosis of FES [2–4]. However, little information is available on how this percentage changes in the clinical course of FES. We describe a case of FES and explore the sequential changes in BAL fluid. The BAL fluids from four other patients with acute respiratory distress syndrome (ARDS) but without FES were also analyzed for comparison.

**Case Report**

A 19-year-old man with no history of illness sustained a compound fracture of his right femoral bone in a traffic accident on October 6, 2000. Following the accident, his consciousness remained clear and there was no evidence of chest or brain contusion. Open reduction with internal fixation was performed smoothly at a local hospital on the day following the accident, without the need for blood transfusion. However, chills and high fever developed soon after the operation. Progressive hypoxia, hemoptysis, and mental disturbance were noted on October 8 and he was transferred to our intensive care unit the next day. On examination, he was drowsy and his body temperature was 38.6°C. His blood pressure was 162/97 mmHg and his pulse rate was 102 per minute. He was in severe respiratory distress, with a respira-
tory rate of 32 per minute. The conjunctivae were pale but without hemorrhage. Coarse breathing sounds were heard over both lung fields. The surgical wound was clean. No petechial rash was found on the neck or anterior chest wall. Other physical and neurologic examinations were unremarkable. The hemogram revealed normocytic anemia (hemoglobin 103 g/L), thrombocytopenia (105 x 10^9/L), and normal leukocyte count (5.16 x 10^9/L). Arterial blood gas analysis showed hypoxemia with pH 7.42, PaCO₂ 33.9 mmHg, PaO₂ 63.8 mmHg, and bicarbonate 21.5 mmol/L when breathing through a non-rebreathing mask. The chest roentgenogram revealed diffuse alveolar consolidation and bilateral pleural effusions (Fig. 1). Because of progressive hypoxemia, he was intubated soon after admission. His oxygenation was maintained by pressure-controlled ventilation and a high positive end-expiratory pressure, with intermittent prone positioning.

Laboratory studies showed an aspartate aminotransferase concentration of 171 U/L, an alanine aminotransferase concentration of 48 U/L, and a lactate dehydrogenase (LDH) concentration of 1213 U/L. The prothrombin time was 16.4 seconds (control, 12.4 s) and the activated partial thromboplastin time was 48.6 seconds (control, 37.0 s). The serum lipase concentration was 34 U/L (normal < 190 U/L), the blood triglyceride concentration was 1.41 mmol/L, and the cholesterol concentration was 3.15 mmol/L. Urinalysis revealed proteinuria (100 mg/dL) and microscopic hematuria (10–15 red blood cells per high power field). Analysis of the pleural fluid showed elevated LDH (866 U/L), but the triglyceride concentration was low (0.21 mmol/L). Neither cholesterol nor lipase could be detected in either urine or pleural effusion. Microscopic examination of urine and pleural effusion using Sudan III staining did not reveal any fat droplets. BAL performed on the third hospital day yielded bloody fluid that contained 3.6% lymphocytes, 63.4% neutrophils, and 27% macrophages. Sudan III staining revealed many fat droplets in the cytoplasm of alveolar macrophages (Fig. 3). A thoracoscopic lung biopsy of the right middle lobe was performed on the fourth hospital day and the pathologic examination indicated diffuse alveolar damage with hyaline membrane formation and type II pneumocyte hyperplasia. Numerous fat globules were found in the alveolar capillaries and arterioles (Fig. 4). Extensive extravasation of fat globules to the pulmonary interstitium and alveolar septum was also noted, with diffuse pulmonary hemorrhage in a background of scanty neutrophils. All cultures of specimens were negative for pathogens, including blood, urine, suction sputum, pleural effusion, BAL fluid, and lung tissues.

An oil-red-O-stained slide of BAL fluid was examined microscopically using the percentage of fat-containing macrophages and the lipid-laden macrophage (LLM) index as previously described [5]. Briefly, macrophages were graded by the amount of lipid in the cytoplasm of each macrophage with a score of 0–4 (0, not opacified; 1, up to 1/4 opacified; 2, 1/4–1/2 opacified; 3, 1/2–3/4 opacified; 4, totally opacified). A total of 100 macrophages was evaluated in each patient; the total score of the index could therefore range from 0–400. The percentage of fat-containing macrophages in our patient was 8.3% and the LLM index was 23. These findings were compared with those in the BAL fluid from four other patients with ARDS but without FES. The underlying diseases leading to ARDS included Wegener’s granulomatosis in one case, pneumo-

Fig. 1. Chest roentgenogram showing diffuse infiltrates and multiple confluent patches of consolidation over both lungs.

Fig. 2. Computerized tomogram showing multiple small patches of peribronchial lesions with several large confluent patches of consolidation (snow-storm pattern).
With supportive care, the general condition of the patient with FES improved gradually and the PaO$_2$ increased to 90 mmHg (under FiO$_2$ 0.4) on the seventh hospital day. Analysis of the follow-up BAL fluid on the eighth hospital day showed a decrease in the percentage of fat-containing macrophages to 4.7% and a decrease in the LLM index to 6. He was extubated smoothly on the ninth hospital day and was discharged from the hospital 1 week later in a stable condition.

Discussion

The diagnosis of FES is usually based on history and clinical manifestations. Our patient developed dyspnea and altered mental status after open reduction and external fixation of a femoral fracture, but did not develop the typical petechial rash of FES. Further, no fat globules could be detected in the urine and blood, and the serum concentrations of lipase and triglyceride were within normal limits. Respiratory distress in patients with traumatic fractures can have different etiologies, such as infection, contusion, transfusion, and aspiration. In addition, neurologic symptoms are often difficult to evaluate in sedated patients, and may be secondary to concomitant cerebral contusion. Furthermore, the characteristic petechial rash may be absent or appear late in the course. Laboratory findings, such as the presence of fat globules in the urine or blood and increased serum concentrations of lipase or triglyceride, have poor sensitivity and specificity for the diagnosis of FES [6].

Several studies have suggested that an increase in the percentage of fat-containing macrophages in BAL fluid might be helpful in the rapid diagnosis of FES [2–4]. The presence of fat globules in the cytoplasm of macrophages, however, has also been described in other pulmonary conditions, including pulmonary aspiration, endogenous lipoid pneumonia, lung cellular hypoxia, and pulmonary infection, especially tuberculosis [7], so its specificity for the diagnosis of FES has been challenged [8, 9].

The LLM index, a quantitative test that grades the amount of oil-red-O-positive material in intra-alveolar macrophages in BAL fluid, was initially described in 1987 for the diagnosis of aspiration in children [5]. However, Knauer-Fischer and Ratjen found that an elevated LLM index could also be found in a variety of pulmonary diseases, including bronchiolitis obliterans, allergic alveolitis, pneumonia during anti-leukemic therapy, cystic fibrosis, and idiopathic pulmonary hemosiderosis [10]. In their study, the mean LLM indexes of these diseases were 178, 150, 125, 115, and
No data on the LLM index in patients with FES have been reported.

Our analysis of the BAL fluid from four ARDS patients without FES showed a wide range in the percentages of fat-containing macrophages and the LLM index, with mean values of 34.2% and 95, respectively. In two of these patients, the percentages of fat-containing macrophages and the LLM index were much higher than that in our patient with FES. This supports the results of Knauer-Fischer and Ratjen that the LLM index has low specificity for the diagnosis of pulmonary disorders. Unexpectedly, both the percentage of fat-containing macrophages and the LLM index in the BAL fluid decreased with improvement in clinical condition on the eighth day of hospitalization. This finding has not been reported previously.

In conclusion, neither the presence nor the percentage of fat-containing macrophages in BAL fluid has been shown to be a reliable indicator for the diagnosis of FES, but the percentage of these cells and the LLM index may be helpful in the follow-up of disease severity. Further studies are indicated for the assessment of these parameters in the early prediction of clinical improvement and prognosis in patients with FES and other pulmonary disorders.

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References