Serial Measurements Of Vascular Endothelial Growth Factor (VEGF) In Pulmonary Epithelial Lining Fluid In ARDS Associated With Crow-Fukase (POEMS) Syndrome

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Citation

Abstract
The bronchoscopic microsampling (BMS) probe, which we newly developed, can collect directly and uninvasively the pulmonary epithelial lining fluid (ELF). We present the case of a 44-year-old woman suffered from acute respiratory distress syndrome (ARDS) associated with Crow-Fukase (POEMS) syndrome. We examined the vascular endothelial growth factor (VEGF) concentration in the pulmonary ELF using the BMS procedure and in the blood. Serial collections of samplings were performed at 10 time points from day 0 to day 21 during the period of respiratory failure. During the course, the VEGF concentration in the blood was markedly high (311 pg/ml) on day 0, but variable during the course. Levels of VEGF concentrations in the ELF determined by serial examination were extremely high level (20187.7 pg/ml) at the early stage of ARDS, suggesting that VEGF might be produced in the lung, but these VEGF decreased as the lungs recovered. These findings suggested that BMS procedure was very useful to reveal the information of pulmonary epithelium.

CASE REPORT
A 43-year-old woman was admitted to our hospital in July 1999 because of increasing palpitation and exertional dyspnea. Gloves and stocking type polyneuropathy was also noted, in the distal portion of the lower limbs. Laboratory analyses revealed high levels of the M-protein component of IgG-λ, hypoproteinemia (5.1 g/dl) and a significantly elevated plasma vascular endothelial growth factor (VEGF) level (187.5 pg/ml; normal range < 38.3 pg/ml). The clinical findings and laboratory data indicated a diagnosis of Crow-Fukase syndrome. Steroid pulse therapy and diuretics transiently improved the symptoms of palpitation and dyspnea. However, the polyneuropathy did not improve despite a course of 30 ~60 mg/day of prednisolone, cyclophosphamide (100 mg/day) and melphalan (10 mg/day for 5 days). Severe thrombocytosis (600,000 ~1,050,000 / l) was evident upon admission, and the anti-thrombin drug (argatroban; 20 mg/day) had been prescribed for about one year.

Palpitations and exertional dyspnea re-appeared in August 2000. Because of VEGF production from a suspected extramedullary plasmacytoma, we administered human interferon (IFN-α; 3 million I.U. / day) on August 14. At the 4th day of IFN-α administration, the platelet count rapidly decreased (70,000 / l) and IFN-α was withdrawn. Her respiratory state worsened and she fell into acute respiratory distress syndrome (ARDS). A chest X-ray showed bilateral lower lung infiltration. Pulmonary arterial wedge pressure and the measurement of cardiac output did not show cardiac failure. And the echocardiography and chest X-rays did not indicate cardiogenic pulmonary congestion. Thrombocytopenia was associated with several complications such as renal failure, disseminated intravascular coagulation syndrome, and sub arachnoid hemorrhage. We surmised that IFN-α induced platelet disruption and the release of a large amount of VEGF into the circulation, causing a deteriorated clinical status. Thus, the VEGF concentration in plasma and pulmonary epithelial lining fluid (ELF) were examined for 21-days from the onset of respiratory failure until recovery.

These measurements were obtained using our new method of bronchoscopic microsampling (BMS) [1]. The study was approved by the Ethical Committee for Human Clinical Research, Kyoto Prefectural University of Medicine, and informed consent was obtained from an immediate family
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We measured VEGF concentrations in ELF collected using the BMS probe (OLYMPUS; BC-401C, Tokyo, Japan), consists of a 2.2 mm outer diameter polyethylene sheath and an inner 1.2 mm fiber rod probe attached to a stainless steel guide wire. BMS procedure was described previously [1]. Briefly, BMS probe was inserted into the bronchoscopic channel and advanced gently. After holding the sheath at the sub-segmental bronchus, the inner probe was then advanced slowly into the peripheral airway till the probe itself touched the mucosal surface and was held for 5 to 7 seconds to absorb epithelial lining fluid. The inner probe was then withdrawn into the outer tube and removed together. The wet inner probe was cut at 3 cm distal from its tip and placed in a tube, and stored in a freezer at –80°C until use. The same procedure was performed in triplicate from the subsegmental bronchus of either S4 or S5 at one time point. Before preparing the ELF saline suspension, the frozen probes stored in a freezer at –80°C were weighed. The diluted solution for measurements of the biochemical substances was prepared by adding three frozen probes into 15ml polyethylene tube containing 3ml of saline, and vortexed for 1 minute. The solution was then centrifuged for 15 minutes at 3,000 rpm, and the supernatant collected. The probes were then dried and weighed again to measure the ELF volume recovered by the BMS probes. Concentrations of VEGF in plasma and ELF were determined with the sandwich-type, enzyme-linked immunosorbent assay. Control levels of VEGF in ELF were determined from 8 healthy volunteers.

We serially collected samples at ten time points starting from day 0 (onset of ARDS), through days 1,3,5,7, 8,10,14,17 and 21 during artificial respiratory management. The diagnosis of ARDS was identified according to the definitions of the American European Consensus Conference of ARDS/ALI (acute lung injury) [2]. Lung injury score (LIS) was also calculated [3]. The results showed that the VEGF concentration in ELF was 20187.7 pg/ml at day 0, about 6.9-fold higher than that of healthy volunteers (2918.2±371.6 pg/ml of ELF; n=8, mean±S.E). This value gradually decreased (5784.3 pg/ml; day 21) as the lungs recovered from injury. The VEGF concentration in plasma was high (311 pg/ml) on day 0, but subsequent analyses showed that the levels varied from 106 to 777 pg/ml (Table).

During the period from August 20, 2000, through September 10, 2000, the patient treated with artificial respiratory management.

DISCUSSION

Crow-Fukase syndrome is a rare multisystem disorder characterized by polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes that is also known as POEMS syndrome. The pathophysiological role of excess VEGF has been clarified in this syndrome [4]. However, other studies suggest that alveolar constitutive VEGF plays a role in the protection or repair of alveolar cells [5,6]. Thus, we sequentially evaluated levels of VEGF in pulmonary ELF in a patient with Crow-Fukase syndrome who fell into ARDS. Studies indicate that constitutive alveolar VEGF plays a role in the protection or repair of alveolar cells. Lassus et al. [5] found that VEGF levels rapidly increase in the lungs of preterm infants during the first few days after delivery. In addition, VEGF might indicate pulmonary maturity and participate in pulmonary repair after acute lung injury. After cytokine treatment or oxidative stress, the possibility had also showed that cultured lung epithelial cells participate in endothelial repair and angiogenesis through VEGF synthesis [6]. On the other hand, excessive VEGF may be harmful to pulmonary vascular endothelium. Kaner et al. [7] have shown that the over-expression of VEGF in the lung in vivo might increase pulmonary vascular permeability during the early stages of acute lung injury. Thus, VEGF in ELF may be involved in pulmonary repair during ARDS and in increased pulmonary vascular permeability when present in excess, leading to lung edema.

Excessive VEGF in the vasculature induces increasing microvascular hyper-permeability, angiogenesis and
activation of the coagulation pathway \cite{9}, which may lead to multiple organ disorder. The apparent source of VEGF overproduction in Crow-Fukase syndrome has not yet been elucidated, and platelets or myeloma cells have been considered the origin \cite{9,10}. Niimi et al. \cite{10} found that in a patient with pulmonary hypertension and ARDS in Crow-Fukase syndrome, the serum level of VEGF was closely correlated with pulmonary hypertension, whereas those of IL-1β, IL-6 and TNF-α were not. Circulating excessive VEGF may have triggered ARDS in our patient, but the VEGF concentration in plasma during the recovery phase of respiratory failure was not correlated with LIS. On the other hand, VEGF concentrations in ELF were very high at the early phase of ARDS, which might suggest that VEGF is produced in the lung, where it plays an important role in the pathogenesis of lung injury. This finding is too rare until now, particularly in the relation to ARDS. And in this case, the patient had multiple disorders in different organs, therefore it is impossible to relate a real correlation to ARDS. Nevertheless, this is the first report of serial measurements using the BMS that demonstrated very high levels of VEGF in the pulmonary ELF in a patient with Crow-Fukase syndrome. And if there are more cases and a more critical discussion, the study of VEGF and lung diseases will certainly be very interesting by using BMS procedure.

References

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