CASE STUDY

Acute respiratory distress syndrome due to methicillin-resistant Staphylococcus aureus sepsis in hyper-IgE syndrome

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Acute respiratory distress syndrome (ARDS) is characterized by marked respiratory distress, tachypnoea, refractory arterial hypoxaemia, and diffuse alveolar and interstitial infiltrates on chest radiographic film in the absence of cardiac failure [8]. It is a common and highly lethal complication of sepsis [9]. Although chemotactic activity of neutrophils was impaired in this patient, neutrophils accumulated in the lungs as assessed by bronchoalveolar lavage fluid (BALF) counts.

Hyperimmunoglobulin E syndrome (HIES) is an immunodeficiency disorder characterized by recurrent severe staphylococcal infections, associated with an elevated serum concentration of immunoglobulin E (IgE) [1, 2]. Although the immunological abnormalities of HIES are still unclear, several immunological aberrations have been reported, including high titres of IgE antibodies to staphylococcal antigens [3, 4], a deficiency of suppressor T-cells [5, 6], and chemotactic defects of neutrophils [7].

Acute respiratory distress syndrome (ARDS) is characterized by marked respiratory distress, tachypnoea, refractory arterial hypoxaemia, and diffuse alveolar and interstitial infiltrates on chest radiographic film in the absence of cardiac failure [8]. It is a common and highly lethal complication of sepsis. Several lines of evidence support the concept that neutrophils play a central role in the development of ARDS. The activated neutrophils release some mediators, such as oxygen radicals and proteases, leading to microvascular damage and to an increase in pulmonary permeability [9].

We encountered a case of ARDS with HIES. This patient, with a chemotactic defect of neutrophils, developed ARDS. We treated the patient with antibiotics active against methicillin-resistant Staphylococcus aureus (MRSA), oxygen supplement and recombinant human granulocyte colony-stimulating factor (rhG-CSF), resulting in a remarkable recovery. We speculated that rhG-CSF might contribute to the improvement of sepsis by modulating the functions of neutrophils.

Case report

A 34 year old woman was admitted to hospital with a history of cough, slight fever and dyspnoea for several days. She had been diagnosed as having HIES because of a history of recurrent pneumonia, pulmonary abscess predominantly caused by Staphylococcus aureus, chronic eczematoid dermatitis and marked elevation of serum IgE since she was 13 yrs of age. She had been receiving interferon-γ (IFN-γ) therapy once a week (80 µg·week-1) for 2 yrs. Her clinical symptoms had improved during this treatment. She had last received IFN-γ therapy 7 days previously.

At admission, she had cyanosis and tachypnoea, with a respiratory rate of 36 breaths·min-1. Heart rate was 100 beats·min-1, blood pressure 114/68 mmHg, and body temperature 37.0°C. Auscultation of the heart sounds revealed no abnormalities. Examination of the lungs disclosed diffuse bilateral crackles. The patient had no signs of jugular venous distension, hepatojugular reflux or peripheral oedema. Petechiae appeared on the lower limbs. Arterial blood gas tensions with 5 L·min-1 oxygen administration were: pH 7.41; arterial oxygen tension (P_a:o_2) 9.8 kPa (69 mmHg) and arterial carbon dioxide tension (P_a:CO_2) 6.0 kPa (40 mmHg). Laboratory data on admission showed the following values: haemoglobin 10.8 g·dL-1; haematocrit 31.4%; and white blood cell (WBC) count 7,880 cells·mm-3, with 87% neutrophils, 3% eosinophils, 2% monocytes and 8% lymphocytes. Serum concentration of immunoglobulin G (IgG) was 2,227 mg·dL-1; immunoglobulin A (IgA) and immunoglobulin M (IgM) were normal. Serum IgE concentration was strikingly elevated to 19,798 IU·mL-1. C-reactive protein (CRP) was 31 mg·dL-1, and antinuclear antibody was negative. Coagulation tests were consistent with disseminated intravascular coagulation (DIC) syndrome: thrombocyte count 68,000 platelets·mm-3; fibrinogen 186 mg·dL-1; fibrinogen degradation product 1,895 µg·mL-1; erythrocyte sedimentation rate 10 mm·h-1. Bacteriology of sputum and arterial blood cultures yielded MRSA.
Chest radiographic films showed pneumatocele in the right upper lung fields and bilateral diffuse alveolar and interstitial infiltrates (fig. 1). Right heart catheterization revealed a pulmonary capillary wedge pressure of 12 mmHg, mean pulmonary artery pressure of 25 mmHg and cardiac output of 8.26 L·min⁻¹. Cytological examination of bronchoalveolar lavage fluid (BALF) revealed a total cell count of 2.1×10⁵ cells·mL⁻¹, with the following distribution: macrophages 25%, lymphocyte 10%, neutrophils 55%, and eosinophils 12%. Neutrophil chemotactic activity toward N-formyl-methionyl-leucyl-phenylalanine (FMLP) was reduced to 70% compared with normal control [10], but production of superoxide anion was not impaired.

With the diagnosis of ARDS and DIC secondary to sepsis, antibiotics (minocycin, cefotiam, sulphamethoxazole and vancomycin), and gabexate mesilate as protease inhibitor, antithrombin-III and high dose methylprednisolone (1 g·day⁻¹) for 3 days were administered within a few hours of admission. The patient was given 100% oxygen, 10 L·min⁻¹, via a tight-fitting face-mask. However, on the second hospital day respiratory failure progressed, arterial blood gas analysis showed: pH 7.35; PaO₂ 7.9 kPa (59 mmHg), and PaCO₂ 7.2 kPa (54 mmHg).

From the third hospital day, we administered rhG-CSF, 75 µg·day⁻¹ intravenously, for 3 days. After administration of rhG-CSF, peripheral WBC counts were 17,670 cells·mm⁻³ with 96% neutrophils, 3% monocytes and 1% lymphocytes. The patient was placed on mechanical ventilation using an inspiratory oxygen fraction (F₁O₂) of 0.5 and 8 cmH₂O of positive end-expiratory pressure (PEEP). The postintubation arterial blood gas values were: pH 7.47; PaO₂ 10.1 kPa (76 mmHg) and PaCO₂ 4.7 kPa (35 mmHg). From the fourth hospital day, the patient showed a remarkable improvement; and arterial blood gas tensions improved thereafter. Further mechanical ventilation was undertaken with a volume ventilator at F₁O₂ of 0.4 and 10 cmH₂O PEEP for 3 days. On the seventh hospital day, CRP was 3 mg·DL⁻¹ and the patient was weaned from the ventilator. In chest roentgenograms the infiltrate disappeared on the 20th hospital day. Cytological examination of BALF revealed a total cell count of 1.6×10⁵ cells·mL⁻¹, with the following distribution: macrophages 74%, lymphocytes 13%, neutrophils 4%, and eosinophils 10%. The patient was discharged on the 36th hospital day.

Discussion

In 1966, Davis et al. [1] reported the cases of two girls with frequently infected eczematous dermatitis, sinusitis, acute pulmonary infections and recurrent cold abscesses caused by Staphylococcus aureus. They named this combination of symptoms "Job's syndrome". Two more children with high serum IgE concentration and Staphylococcus aureus infections were reported by Buckley et al. [2] in 1972. Until the present time, about 130 cases of HIES have been reported. The clinical manifestations of this syndrome have included severe atopic eczema with onset in early childhood, recurrent pyogenic infections of the skin, characteristically due to Staphylococcus aureus, mucocutaneous candidiasis, and visceral abscesses. Laboratory findings have included exceedingly high serum IgE and low grade blood eosinophilia. During the past two decades, several highly variable immunological aberrations were reported in patients with this disorder, including high titres of IgE antibodies to Staphylococcal antigens [3, 4], deficiency of suppressor T-cells [6], and chemotactic defects of neutrophils [7]. In our case, a diagnosis was made when the patient was 13 yrs of age due to the history of recurrent Staphylococcus aureus infections and high serum IgE concentrations above 20,000 IU·mL⁻¹.

ARDS is a common and highly lethal complication of sepsis. Evidence is accumulating that neutrophils play an important role in the development of ARDS [8, 9]. Various cytokines and adhesion molecules play a role in mediating neutrophil accumulation and activation. The activated neutrophils release mediators, such as eicosanoids, oxygen radicals and proteases, leading to microvascular damage and increased pulmonary permeability in patients with ARDS. Although the neutrophils in our patient showed chemotactic defects, she developed ARDS with accumulation of neutrophils evaluated by the findings in BALF.

Recently, encouraging data were reported on treatment with IFN-γ in patients with atopic dermatitis and elevated IgE levels [11]. Inhibitory production of IFN-γ may explain susceptibility to infections in HIES patients [12–16]. Our patient had been receiving IFN-γ therapy for 2 yrs and her clinical symptoms were improved. However, several lines of evidence suggest the possibility that IFN-γ may play a role in the development of ARDS. Firstly, IFN-γ has often been detected in endotoxin challenged nonhuman primates and has been found to be elevated in the serum of patients with septic shock [17, 18]. Secondly, microorganisms other than animal viruses elicit the appearance of interferons [19]. Finally, IFN-γ results in enhanced monocyte cytotoxicity by inducing tumour necrosis factor, a potent cytokine believed to participate in the development of ARDS [20]. In our case, IFN-γ might, at least partly, play a role in the
development of ARDS in spite of the decrease in chemo-
tactic response of neutrophils.

RhG-CSF, a glycoprotein with a molecular weight of
approximately 19,000, is capable of increasing neutrophil
numbers in the peripheral blood and stimulating neu-
trophil function, including chemoattractant activity of mature
neutrophils in vitro and in vivo [21, 22]. Although rhG-
CSF may exert a potential negative effect on the course
of ARDS by activating neutrophils leading to the re-
lease of some mediators, the application of rhG-CSF was
an effective therapeutic approach for preventing the
fatal outcome of ARDS. Whilst neutrophil depletion
prevents lung injury in a variety of intact animal mod-
els [23], Heyll et al. [24] reported that administration
of rhG-CSF resulted in a successful outcome in a neu-
 tropenic leukaemia patient with ARDS. Kozumi et al.
[25] reported that G-CSF, in spite of the increase in
peripheral neutrophil count, did not aggravate lung
injury induced by endotoxin in a sheep model. We used
rhG-CSF with antibiotics and steroids for the therapy of
infection because the respiratory failure progressed rapi-
dly despite antibiotic therapy. Treatment with rhG-CSF
may induce a therapeutic effect in the patient with HIES
with neutrophil chemoattractant defect.

ARDS is a fatal complication of sepsis in which sur-
vival seems to be associated with early diagnosis and
therapy. This patient had been diagnosed as having HIES,
which was characterized by recurrent staphylococcal
infections; sputum and blood cultures yielded MRSA.
Although early treatment with antibiotics active against
MRSA resulted in the survival of our patient, rhG-CSF
might have contributed to the success of the treatment
of sepsis associated with HIES.

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