—Report on Experiments and Clinical Cases—

The Treatment of Refractory Pneumothorax in Diffuse Panbronchiolitis by Intravenous Administration of Coagulation Factor XIII Concentrate

Akira Murata, Ayumi Kouno, Kazuo Yamamoto,
Hiroko Yoshioka, Kozui Kida and Shoji Kudoh

Department of Pulmonary Medicine, Infection and Oncology, Nippon Medical School

Abstract

This case report presents a patient with advanced diffuse panbronchiolitis accompanied by chronic respiratory failure, marked cachexia, and refractory spontaneous pneumothorax. Because instillation of a pleurodesis agent and thoracoscopy were considered highly risky and invasive, we instead treated the patient with intravenous administration of a coagulation factor XIII concentrate, and the pneumothorax resolved. This case suggests refractory pneumothorax in a restrictive ventilatory disorder can be effectively treated with noninvasive intravenous administration of coagulation factor XIII concentrate.
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Key words: coagulation factor XIII, persistent air leak, intravenous administration, refractory peumothorax

Introduction

Diffuse panbronchiolitis (DPB) was first distinguished from chronic obstructive pulmonary disease in the early1960s and was recorded as a new clinicopathologic entity. This disease is observed mostly among East Asians and is characterized by chronic sinobronchial infection and diffuse bilateral micronodular lesions consisting of inflammatory cells. The current data suggest that the patholosiology of DPB is similar to that of cystic fibrosis and bronchiectasis. End-stage DPB is occasionally complicated by pneumothorax, which makes treatment more difficult.

In cases of prolonged air leakage in which a fistula on the surface of lung dose not close and no bronchial fistula is present, we usually start treatment with long-term tube thoracostomy and instillation of a pleurodesis agent. Thoracoscopy will be considered only when theses treatments are unsuccessful. However surgery itself poses a significant risk for patients whose physical condition and lung function have deteriorated.

Coagulation factor XIII stabilizes fibrin at the final stage of homeostasis, stabilizes fibrinogen, and stops bleeding. It is also an important factor for restoring organization and wound healing[1]. Therefore, a fall in the activity of coagulation factor XIII is an obstacle to the wound healing and is a cause of prolonged air leakage in refractory pneumothorax.

We report on a patient with refractory peumothorax, a poor general condition, and a decreased pulmonary function who we successfully

Correspondence to Akira Murata, Department of Pulmonary Medicine, Infection and Oncology, Nippon Medical School, JPR Ichigaya Building 8F, 4–7–15 Kudan-minami, Chiyoda-ku, Tokyo 102–0074, Japan
E-mail: a-murata@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

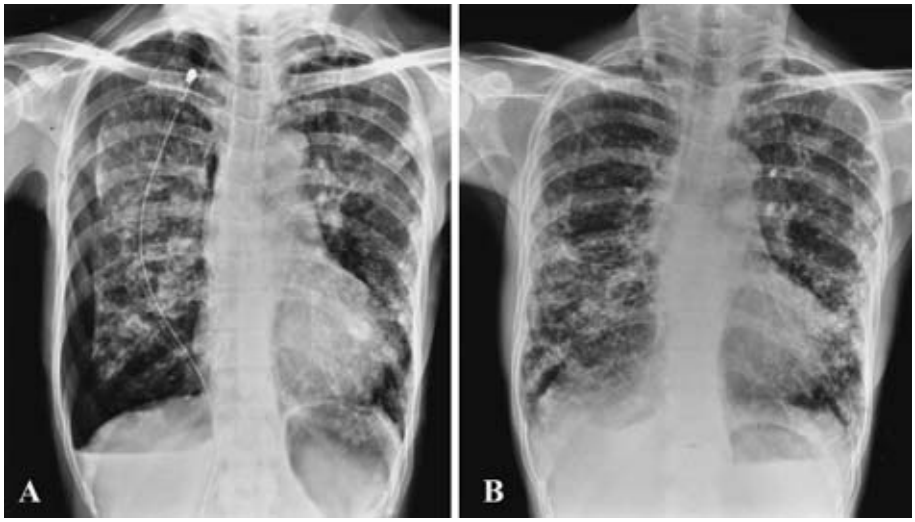

Fig. 1 Plain chest roentgenograms
The left side (A) shows peumothorax with a drainage tube, and the right side (B) shows the re-expanded lung after infusion of factor XIII.

treated with infusion of coagulation factor XIII concentrate.

Case Report

A 49-year-old Japanese woman with a 6-year history of advanced DPB was treated with erythromycin, 600 mg daily, and had received oxygen therapy over the previous 2 years. She was admitted to our hospital because of hypercapnia (〔O_2 2 L/min., nasal inhalation〕 pH 7.359; $PaCO_2$, 72.9 mmHg; PaO_2, 52.1 mmHg; HCO_3^-, 40.1 mmol/*l*; base excess, 12.0 mEq/*l*; arterial O_2 saturation 〔SaO_2〕, 85.2%) and severe pulmonary dysfunction (vital capacity〔VC〕, 1.07 L; %VC, 41.3%; forced expiratory volume 1 sec 〔FEV_1〕, 0.59 L; FEV_1%, 67.8%; %FEV_1, 85.2%; residual volume/total lung capacity, 57.8%) with marked emaciation (body height, 152 cm; body weight, 32.6 kg; body mass index, 14.1; serum albumin, 3.7 g/d*l*). Sputum culture was positive for *Pseudomonas aeruginosa*.

On the second day of hospitalization (Day 2), the patient complained of right-side chest pain and worsening dyspnea (pH, 7.305; $PaCO_2$, 81.6 mmHg; PaO_2, 47.6 mmHg; HCO_3^- 39.4 mmol/*l*; SaO_2, 78.9%). Chest X-ray films demonstrated a large pneumothorax (**Fig. 1-A**). Air leakage continued despite tube thoracostomy. Instillation of a pleurodesis agent and thoracoscopy were considered highly risky for this patient because of advanced DPB, severe hypoxemia, hypercapnia, and emaciation (**Fig. 2**).

On the 19th hospital day, activity of coagulation factor XIII decreased to 48% (normal, >70%), and coagulation factor XIII concentrate (6 vials/day, Fibrogammin P, Aventispharma Co., Ltd.) was administered intravenously for 5 days, from the 20th to the 24th day. Air leakage resolved on the 25th day, the pneumothorax decreased, and the collapsed lung was re-expanded. However, just after starting rehabilitation, the patient caught a cold and complained of a low-grade fever and persistent cough. Air leakage occurred again on the 37th day. When treatment of the cold began, the symptoms disappeared. The change was confirmed from the blood test result; c-reactive protein level was improved to the normal level. Because the activity of coagulation factor XIII remained low at 56%, coagulation factor XIII concentrate was again given intravenously for 5 days, from the 51st to the 55th day. Air leakage resolved on the 55th day. The drainage tube was clamped on the 63rd day and was removed 2 days later (**Fig. 1-B**). The patient then started rehabilitation because of generalized muscle atrophy during hospitalization. She was discharged on the 79th day. The activity of coagulation factor

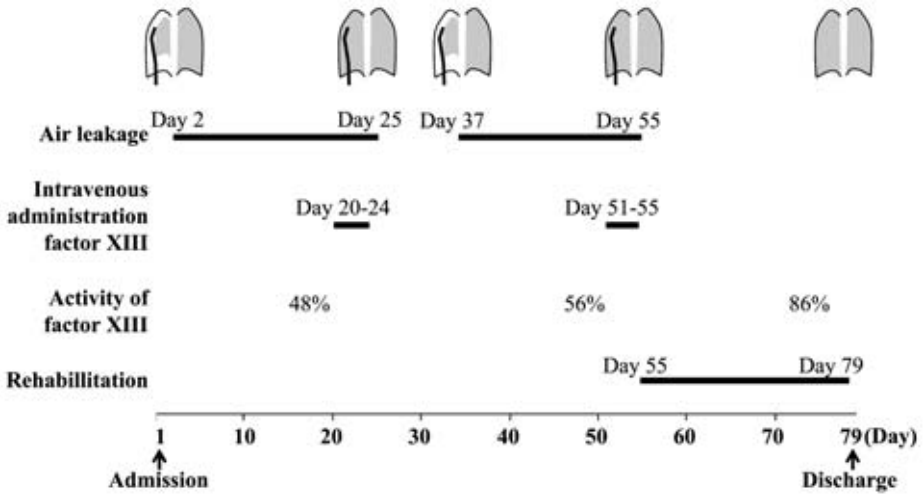

Fig. 2 Clinical course

The pneumothorax occurred on the second day of hospitalization. The coagulation factor XIII concentrate was first administered intravenously from the 20th to the 24th day. Leakage resolved on the 25th day, and the lung expanded. Air leakage occurred again on the 37th day. Because the activity of factor XIII was low at 56%, coagulation factor XIII concentrate was again given intravenously for 5 days, from the 51st to the 55th day. Air leakage resolved on the 55th day. The drainage tube was clamped on the 63rd day and was removed 2 days later. The patient was discharged on the 79th day.

XIII was 83% at the time of discharge.

Discussion

Secondary spontaneous pneumothorax in DPB is rare[2]. However, for patients with advanced DPB, prolonged pneumothorax accompanied by air leakage is occasionally refractory because of severe hypoxemia, malnutrition, frequent bronchiolar infections with resistant strains of bacteria, or a poor general condition. The treatment of pneumothorax associated with DPB, cystic fibrosis, or bronchiectasis is similar to that for pneumothorax associated with chronic obstructive pulmonary disease[3].

The failure of a fistula on the surface of lungs to close causes prolonged air leakage and is affected by many factors: age, sex, condition of the wound, infection, the patient's general condition and nutrition level, and activity of coagulation factor XIII. Of these factors, coagulation factor XIII has the most important role in wound healing, because it is present in the blood and in many kinds of tissue[4].

Coagulation factor XIII activates coagulation factor XIII, interferes with enzymatic function, and enhances binding to fibrin[4]. Therefore, wound healing becomes slower when levels of coagulation factor XIII decrease, for example, in congenital factor XIII deficiency disease, after surgery in severe liver dysfunction, and blood diseases[5-8].

Duckert et al have reported one case of congenital coagulation factor XIII deficiency in which wound healing was delayed[9]. More recent reports indicate that hemorrhagic tendency can be controlled by replacement therapy with a small amount of coagulation factor XIII[10].

However, a large amount of coagulation factor XIII is needed to enhance wound healing[11,12]. Other reports have also recognized the beneficial effects of factor XIII replacement therapy in patients with acute therapy-resistant ulcerative colitis[13] and Crohn's disease fistulas[14].

Therefore, we administered coagulation factor XIII intravenously to a patient with refractory pneumothorax and advanced DPB.

We were able to stop the prolonged air leakage and treat refractory pnemothorax with a coagulation factor XIII concentrate. Therefore, we recommend coagulation intravenous administration of factor XIII concentrate (3～6 vials/day, 5 days) with the

following guidelines.

The indications and contraindications we have presented in this study are new perception. We believe that coagulation factor XIII concentrate is not always effective for every patient with pneumothorax because several factors can delay wound healing. There are also well-established treatments that are tried before coagulation factor XIII concentrate is administered. For example, even though the activity of coagulation factor XIII is less than 70% of the normal value, infection causing severe pneumonia, sepsis, and pyothorax, and severe malnutrition may be responsible for the delay in wound healing. In these cases, the malnutrition and the infection should be treated first. There are other contraindications for treatment with coagulation factor XIII concentrate. Bronchial fistula should be treated before coagulation factor XIII concentrate is administered, because bronchial fistula often causes infection despite treatment with coagulation factor XIII concentrate. Treatment with coagulation factor XIII concentrate should not be the first option before pleurodesis, fibrin infusion into the thorax, or surgery is performed. There is not enough data to show that coagulation factor XIII concentrate should be administered before well-established treatments are attempted.

The present patient required rapid treatment, because *P. aeruginosa* was isolated from the sputum. Infection with *P. aeruginosa* is usually a problem in advanced DPB and increases the risk of pyothorax and sepsis. Gradual weight loss caused by DPB and respiratory failure was another reason to avoid pleurodesis, fibrin infusion into the thorax, or surgery, which are likely to cause further restrictive ventilatory impairment.

After a thorough review of this case, we concluded that infusion of coagulation factor XIII concentrate might be an effective treatment for patients with refractory pneumothorax in addition to aspiration, tube thoracostomy, instillation of a pleurodesis agent and thoracosopy, although its cost-effectiveness must be improved.

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