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Pulmonary Oxalosis Caused by *Aspergillus Niger* Infection

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=국문초록=

Aspergillus Niger 감염에 의한 폐옥살산염 1예

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조계중, 주진영, 박경화, 최유덕*, 김규식, 김유일, 김수옥, 임성철, 김영철, 박경옥, 남종희*, 윤 웅**

Aspergillus 종 특히 Aspergillus niger는 폐조직에 칼슘 옥살산 결정(oxalate crystal)을 침착시키면서 폐손상을 초래하는 것으로 보고되고 있다. 저자들은 Aspergillus niger 에 의해 생성된 옥살산염(oxalaic acid)에 의해 환자의 폐손상이 야기되고 그 결과 대량객혈이 발생한 것으로 추정되는 증례를 경험하였기에 보고하는 바이다.

과거에 식도암과 폐결핵으로 치료받은 적이 있는 46세 남자 환자가 고열과 간헐적 객혈, 그리고 흉부 방사선상 공동을 갖는 폐의 이상 음영을 주소로 내원하였다. 입원 후 항생제와 항결핵 치료를 병합하였지만 고열이 지속되었다. 객담 검사상 Aspergillus niger가 반복적으로 배양되어 정맥내 amphotericin B를 주입을 시작하였고, 이후 환자는 간헐적인 객혈은 지속되었으나 열은 소실되었다. 경기관지폐생검으로 얻은 조직에서 균은 동정되지 않았으나, 수많은 칼슘 옥살산 결정과 주위로 급성 염증성 삼출물이 관찰되었다. 환자는 입원 63일째 약 800ml 가량의 대량 객혈이 발생하였고, 기관지 동맥 색전술을 시행하였으나 출혈이 지속되었고 결국 호흡부전으로 사망하였다. **(Tuberculosis and Respiratory Diseases 2003, 55:516-521)**

Key words : Aspergillus niger, Pulmonary Oxalosis, Calcium Oxalate Crystals.

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Introduction

At least 19 species of Aspergillus have been reported to cause disease in humans[1], and the most important determinant of an infection is the immune status of the patient[2]. *Aspergillus niger* is one of the etiologic agents of both an invasive and noninvasive aspergillosis, which is associated with pulmonary oxalosis[3]. Oxalic acid, which can cause pulmonary injury, is a product of *A. niger* fermentation[4,5]. We report a case with a localized pulmonary oxalosis associated with a chronic necrotizing pulmonary infection by *A. niger* in an immune-competent patient, which was complicated by fatal hemoptysis.

Case Report

A 46-year-old man was admitted to our hospital complaining of hemoptysis. He had experienced intermittent fever with chills, coughing, and a yellowish occasionally blood-tinged sputum for two weeks prior to admission. In addition, he had progressive exertional dyspnea (ATS grade III) and left pleuritic chest pain, and a large amount of hemoptysis (about 100 mL/day) was noted on the day prior to admission.

His medical history revealed that he had had an esophagectomy due to esophageal cancer six years previously. He had also been given a diagnosis of pulmonary tuberculosis and had completed an 18-month course of anti-tuberculous therapy with isoniazid (400 mg), rifampin (600 mg), ethambutol (800 mg), and pyrazinamide (1500 mg) 20 months before being admitted. He had a 35-pack-year history of tobacco use, and had no history of immunosuppressive disease or alcohol abuse.

His vital signs were a blood pressure 120/80 mmHg, a pulse rate 98 beats per minute, a body temperature 38.6℃, and a respiration rate 26 breaths per minute. On a physical examination,

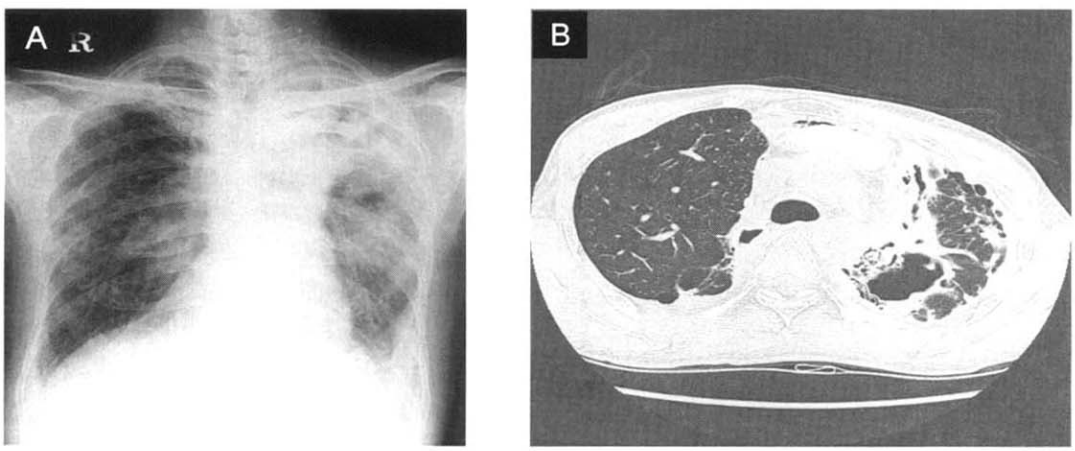

Fig. 1. A) Chest radiograph demonstrates ill-defined consolidations with a 3-cm cavitary lesion in the left upper lobe. **B)** Thin section CT scan shows an irregular cavity, multifocal bronchiectasis and airspace consolidations in the left upper lung zone.

the chest auscultation demonstrated decreased breath sounds over the left upper lung field; the remainder of the examination was within the normal limits. The chest radiograph and thin section CT scan revealed ill-defined consolidations with a 3-cm cavitary lesion in the left upper lobe (Fig. 1).

The laboratory tests on admission showed the following: hemoglobin, 11.5 g/dL; hematocrit, 33.0%; white blood cell count, 15600 /mm^3 with 74.6% segmented neutrophils, 3.3% lymphocytes, 9.9% monocytes, and 2.2% eosinophils; platelet count, 446,000 /mm^3; sodium, 137 mEq/L; potassium, 3.2 mEq/L; chloride, 104 mEq/L; serum urea nitrogen, 8.5 mg/dL; and serum creatinine, 0.8 mg/dL. The arterial blood gas measurements while breathing room air were as follows : PO_2, 86.9 mmHg; PCO_2, 33.1 mmHg; pH, 7.504. The sputum cultures on admission showed no bacterial growth, including mycobacteria, but yielded *A. niger* and *Candida albicans*, which were considered to be contaminants at that time. The blood cultures were sterile.

The patient was given cefpiramide sodium (1 g every 12 h) and amikacin sulfate (750 mg daily) soon after blood and sputum culture specimens were obtained, but the sequential chest radiographs showed a progressive pulmonary infiltration, and he had a sustained fever with continued hemoptysis. Since there was no clinical response to the antibiotic therapy, and the cavitary lesion was suspected of being related to his tuberculosis infection, he began anti-tuberculosis chemotherapy on the 6th hospital day. However, the patient continued to deteriorate and five sequential sputum cultures yielded *A. niger*. With a tentative diagnosis of chronic necrotizing aspergillosis (semiinvasive), intravenous amphotericin B with a dose of 0.25 mg/kg/day was begun on the 11th hospital day. His fever subsided beginning on the 12th hospital day, so the amphotericin B dose was increased to 1 mg/kg/day.

On the 23rd hospital day, the patient's respiratory status deteriorated, and he was intubated orotracheally. A bronchoscopic examination demonstrated generalized inflammatory changes in the mucosa with white exudates in the apicoposterior segment of the left upper lobar bronchus. The pathological specimen obtained by a transbronchial lung biopsy revealed numerous calcium oxalate crystals in the necrotic tissue with infiltrates of mononuclear cells, which suggested chronic necrotizing pneumonia due to an *A. niger* infection. However, no fungal hyphae could be found in the specimens (Fig. 2). The patient was transferred to the ICU (intensive care unit) and given mechanical ventilatory support, while continuing the therapy with the intravenous amphotericin B to a cumulative dosage of 1600 mg. The patient's condition stabilized for approximately two weeks, but on the 35th hospital day, a massive hemoptysis, approximately 200 mL, developed. Subsequently, intermittent hemoptysis continued and his hypoxemia gradually worsened. On the 63rd hospital day, the patient presented with a massive hemoptysis, about 800 mL, and the hypotension systolic blood pressure 80 mmHg, which necessitated a bronchial artery embolization. Nevertheless, the massive hemoptysis continued and the patient died of respiratory failure 64 days after admission.

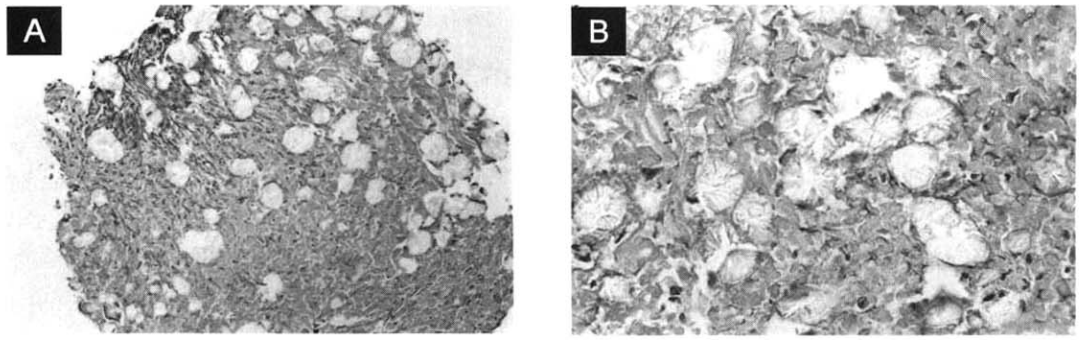

Fig. 2. Numerous calcium oxalate crystals were found in the necrotic tissue with infiltrates of mononuclear cells in the specimen obtained by the transbronchial lung biopsy; H & E stain, ×50 **(A)** and ×200 **(B)**.

Discussion

The Aspergillus species are ubiquitous organisms spread by the aerosolization of their spores. They can cause a spectrum of clinical manifestations, ranging from a benign allergic disease to a life-threatening acute invasive disease[1]. The most common species involved in human lung diseases is *A. fumigatus*, which is followed by *A. flavus* as the second common species. *A. niger* is an infrequent cause of disease in humans[6].

A. niger is associated with pulmonary oxalosis consisting of calcium oxalate crystals, which generate local oxidants that cause cell injury[3]. Wehmer[7] first identified oxalic acid as a fermentation product of Aspergillus species in 1891. In 1958, Oehlert and Düffel[8] observed birefringent calcium oxalate crystals in the pulmonary lesions caused by *A. niger*. The exact mechanism of an oxalosis-associated Aspergillus infection is nunclear. However, it is generally accepted that oxalate is produced via the tricarboxylic acid cycle with the degradation of oxaloacetate, which combines with the patient's serum calcium or the calcium ions in the tissue fluid to form the calcium oxalate crystals[9]. In 1973, Nime and Hytchins[10] described both the local destructive nature of calcium oxalate and the systemic complications of an acute widespread oxalosis. Oxalic acid has been attributed to be the cause of tissue destruction, including blood vessel destruction, because oxalate crystals have been identified under polarized light. Yoshida[11] reported that calcium oxalate crystals produced tissue injury in a rat lung with an experimental *A. niger* infection. He demonstrated deposits of calcium oxalate crystals in the bronchial epithelium before the hyphae of Aspergillus invaded the bronchial wall, and suggested that the crystals might grow in the bronchial epithelium and destroy the cells surrounding them.

In our patient, the pathological specimen obtained by a transbronchial lung biopsy revealed numerous calcium oxalate crystals within the destructive lung lesions, but no fungal elements were identified. Niki *et al.*[12] reported calcium oxalate crystals revealed on the sputum

cytology and transbronchial lung biopsy in *A. niger* pneumonia, and they considered that the findings of crystals in the sputum combined with a positive serological assay for *A. niger* would be useful for an early diagnosis of Aspergillus pneumonia. Anti-fungal therapy was begun early in the hospital course before the pathologic diagnosis was made, but the patient died from exsanguinating hemoptysis. One similar case was reported by Kurrien *et al.*[13], who attributed a case of a fatal pulmonary hemorrhage to the tissue damage and necrosis caused by oxalosis. It is believed that an intra-cavitary Aspergillus infection led to a discharge of the metabolic products into the adjacent lung tissues, including the blood vessels, where these metabolic products caused the lung injury and subsequent fatal hemoptysis.

Abstract

The *Aspergillus* species produces metabolic products that play a significant role in the destructive processes in the lung. We experienced a case of chronic necrotizing pulmonary aspergillosis caused by an *Aspergillus niger* infection, which contained numerous calcium oxalate crystals in the necrotic lung tissue. A 46-year-old man, who had a history of pulmonary tuberculosis, presented with high fever, intermittent hemoptysis and pulmonary infiltrations with a cavity indicated by the chest radiograph. Despite being treated with several antibiotics and anti-tuberculosis regimens, the high fever continued. The sputum cultures yielded A. niger repeatedly, and intravenous amphotericin B was then introduced. The pathological specimen obtained by a transbronchial lung biopsy revealed numerous calcium oxalate crystals in a background of acute inflammatory exudates with no identification of the organism. Intravenous amphotericin B was continued at a total dose of 1600 mg, and at that time he was afebrile, although the intermittent hemoptysis continued. On the 63rd hospital day, a massive hemoptysis (about 800 mL) developed, which could not be controlled despite embolizing the left bronchial artery. He died of respiratory failure the next day. It is believed that the oxalic acid produced by *A. niger* was the main cause of the patient's pulmonary injury and the ensuing massive hemoptysis.

Key words : Aspergillus niger, Pulmonary Oxalosis, Calcium Oxalate Crystals.

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