Case Report

Transbronchial aspergillosis in a patient with diabetes mellitus

Kazuto MIYATA¹, Tatsushi ITO², Kunio YANAGITA²
Hisanaga YAGYU³, Masahiko KURE³, Atsushi ISSHIKI¹

Anesthesiology¹
Tokyo Medical University, Tokyo, Japan
Anesthesia and Intensive Care² and Department of Internal Medicine³
Tokyo Medical University Kasumigaura, Ibaraki, Japan

Abstract

A case of a 57-year-old man with diabetic nephropathy and hypertension developed a fatal transbronchial aspergillosis after admission for surgical treatment of diabetic retinopathy. Soon after the surgery, fever, leukocytosis and radiologically recognized pneumonia occurred. His clinical condition rapidly deteriorated, ending with acute cardiopulmonary arrest. A white-yellowish pseudomembrane in the trachea as well as mucosal necrosis were observed bronchoscopically. Amphotericin B, initially administered intratracheally then intravenously were ineffective, and the patient passed away due to subsequent multiple organ dysfunction.

Invasive pulmonary aspergillosis is known to rapidly deteriorate, sometimes taking an atypical clinical courses which make its diagnosis difficult.

In addition to transplant as well as human immunodeficiency virus patients with decreased immune functions, patients with background diseases such as diabetic mellitus may have latent immunological hypofunction. For this reason, it is necessary to consider anti-infection management against mycosis and others.

Introduction

Aspergillus infections have been reported in recipients of heart¹ and bone marrow transplants². This infection is known to lead to potentially fatal complications in immunocompromised patients. Invasive pulmonary aspergillosis (IPA) is a common form of aspergillus infection in immunosuppressed patients. For patients with IPA infection, early diagnosis and prompt initiation of aggressive antifungal treatment are essential for better prognosis. However, it is often difficult to diagnose this condition at an early stage.

In this paper, we reported a case of a patient with non-insulin dependent diabetes mellitus, who manifested an unexpected transbronchial aspergillosis during admission for treatment of his diabetic retinopathy.

Case Report

A 57-year-old man with non-insulin dependent diabetes mellitus, diabetic nephropathy and hypertension was admitted for surgical treatment of diabetic retinopathy. The perioperative period was uneventful except for difficult control of hyperglycemia. He developed pyrexia and leukocytosis on day 15 postoperatively. Chest X-ray showed an infiltrative shadow and pneumonia was diagnosed. Five days later, decreased consciousness was noted. The patient was immediately intubated and transferred to the intensive care unit.
care unit (ICU). However, he had a cardiopulmonary arrest while being transferred to the ICU. To start cardiopulmonary resuscitation, a bronchoscope was tried, revealing bronchial stenosis by a white-yellowish pseudomembrane. Attempts to wash the trachea met with great difficulty. While injecting saline into the trachea and we did ablation in trachea carefully. During this procedure, trachea mucosa was recognized. Upon admission to the ICU, the leukocyte count and C-reactive protein count (CRP) were above normal. Further tests revealed impaired liver and renal functions (Table 1). Although diabetic nephropathy was recognized before surgery, no hemodialysis was considered necessary. At that point, however, continuous hemodialysis was performed to prevent progressive deterioration of renal dysfunction. Bronchoscopy

| Table 1 |
|-----------------|--------|--------|--------|
| WBC             | 25.9×10³/ul | T-P    | 5.6 g/dl | PT    | 13.1 sec |
| RBC             | 2.94×10⁶/ul | AST    | 43 U/l   | INR   | 1.41     |
| Hematocrit      | 23.8%   | ALT    | 21 U/l   | Fibrinogen | 976 mg/dl |
| Hemoglobin      | 8.4 g/dl | LDH    | 812 U/l  | AT III| 113.6%   |
| Platelet        | 269×10³/ul| CK     | 893 U/l  | FDP   | 14.7 μg/ml |
| T-Bil           | 0.2 mg/dl | BUN    | 106.8 mg/dl |
| Cre             | 6.28 mg/dl | Na     | 141 mEq/l |
| K               | 5.0 mEq/l  | Cl     | 104 mEq/l |
| Ca              | 6.7 mg/dl  | Glu    | 108 mg/dl |
| CRP             | 8.73 mg/dl | Hb Alc | 7.2%    |

Fig. 1 Bronchoscopic findings
Bronchoscopy showed a white-yellowish pseudomembrane and necrotic bronchial mucosa. The upper left photo shows main bronchus. The upper right photo and lower left photo shows right middle and lower bronchus. The lower right photo shows left upper and lower bronchus.
revealed white–yellowish pseudomembrane on the tracheal mucosa and patchy areas of necrotized mucosa (Fig. 1). At the same time, both pleural effusion and infiltrative shadows appeared on the chest CT, although these showed no characteristic features (Fig. 2).

*Aspergillus fumigatus* was identified by sputum culture taken at the time of transfer to the ICU. Invasive aspergillosis was diagnosed by pathologival examination. Accordingly, amphotericin B (5 mg) was administrated via the trachea every other day. This anti-fungal agent could not be administrated intravenously because of the coexisting renal dysfunction. The CRP was persistently elevated and there was no improvement in the general condition was evident. However, blood culture findings were no remarkable even when the CRP elevation was present. Accordingly, treatment with intravenous amphotericin B commenced on the sixth day of ICU admission. The dose of amphotericin B was increased gradually, reading the maximum dose of 0.5 mg/kg. However, the patient failed to respond. A fall in arterial blood pressure was recorded which was considered to represent the development of septic shock caused by systemic fungal infection. Accordingly, the patient was treated with noradrenaline. In addition, the patient also developed leukopenia and multiple organ dysfunction (MOD). He did not respond to various treatments and unfortunately died on day 12 after ICU admission. The numbers of CD4 and CD8 cells were within the normal range. However, there were not only ones as indicators of immunological status. In this case, it was also possible that he might have had immunosuppressed condition in the light of presence of diabetis mellitus which was not well controlled and followed his clinical course. No postmortem examination was performed.

Discussion

Invasive pulmonary aspergillosis (IPA) is a condition associated with poor prognosis. Invasive aspergillosis is recognized in 5 to 8% of cases with IPA. IPA is a relatively common mycosis infection in immunocompromised patients. Four cases of diabetic melitis patients with IPA were reported, of which 3 were non-insulin dependent and 1 was insulin-dependent.

In the present case, although the patient had non-insulin dependent diabetis mellitus, however, control of blood sugar was poor. In other in vitro studies, it was shown that sustaining increased blood sugar level causes decreased leukocyte bactericidal activity and impaired macrophage mobility and phagocytic capacity. These factors, which are all involved in the immune defence against fungal invasion, may predispose to infection. For prophylaxis, insulin therapy should be initiated as soon as possible to strictly control the blood sugar level.

The first clinical symptoms of transbronchial aspergillosis are cough and pyrexia, resembling cold symptoms. The symptoms are often minimal or absent initially, and the chest X-ray and CT findings in this disease are often nonspecific. Aspergillus serology is often negative in patients affected by invasive aspergillosis because of their immunosuppressed state. Therefore, it is often difficult to diagnose this disease at an early stage.

Recent studies have described a new diagnostic
method based on polymerase chain reaction (PCR)—amplification of the aspergillus gene. In the present case, the initial PCR was negative. It is usually considered to be a sensitive test, but can be influenced by some variation of the procedures, which might lead to an equivocal results. This suggests that even in the light of a negative PCR, diagnosis should be continuously done considering in the clinical course.

Three morphologic changes have been recognised in patients with transbronchial aspergillosis; tracheobronchialitis, ulcerative bronchitis and pseudomembranous bronchiolitis. Bronchoscopically, the findings of transbronchial aspergillosis include tracheal obstruction with yellow-white pseudomembrane and ulcer-like lesion. In our patient, we also recognized the above three morphologic changes.

The treatment of the first choice for aspergillosis is amphotericin B. Treatment of invasive aspergillosis is difficult and could be associated with many problems, although intravenous administration of amphotericin B is successful even in patients with renal and cardiac transplant recipients. We initially administered this anti-fungal agent via the trachea to avoid possible adverse effects. The adverse reactions for amphotericin B include fever, vomiting and often fatal nephrotoxicity. We assumed that the adverse effects associated with intravenous injection were more harmful than those with tracheal application. The selection of the tracheal route was based on identification of the organism in sputum cultures and it aimed to produce the highest concentration at the site of infection. The side effects of intravenous administration should be considered seriously, but when wide spread infection is suspected, early intravenous intervention should be considered. Lately some antifungal agents which reportedly have effects similar to amphotericin B but with less side effects have been developed. It is important to consider using these new medications hereafter in cases like the present one.

In conclusion, we described a non-insulin dependent diabetic patient who developed transbronchial aspergillosis. The clinical course was extremely aggressive and was associated with poor outcome. When this disease is suspected, bronchoscopy should be performed as early as possible even if chest X-ray findings is normal, and amphotericin B treatment should be commenced as soon as possible.

References
糖尿病患者に発症した Transbronchial aspergillosis の一例

宮田 和人① 伊藤 樹史② 柳田 国夫③
柳生 久永③ 吳 昌彦③ 一色 淳①

①東京医科大学麻酔学教室
②東京医科大学霞ヶ浦病院 麻酔科・集中治療部
③東京医科大学霞ヶ浦病院 内科

【要旨】侵襲型アスペルギルス症は短期間で急速に状態が悪化することが知られており、通常 immunocompromized host に発症することが多い。今回インスリン治療を受けていない II 型糖尿病患者に侵襲型アスペルギルス症の一つである Transbronchial aspergillosis を発症した 1 例を経験した。症例は 57 歳、男性。既往に II 型糖尿病と糖尿病性腎症があり、加療中であった。肺炎か呼吸不全をきたし ICU に入院した。搬送途中にアスペルギルス症の偽膜による気管挿管チューブ内腔閉塞のために換気不能となり、ICU 入室時には心肺停止状態であった。気管支ファイバースコープ下に洗浄を行い、気道を開放し同時に蘇生術施行したところ心拍は再開した。アノテリシン B の経気管的投与を開始したが、全身状態改善傾向を示さないため全身投与に変更した。しかし真菌による敗血症ショックを呈し死亡した。本症例は早期診断が困難であり、潜在的に免疫機能低下をきたす糖尿病患者に発症するため注意が必要である。

＜キーワード＞II 型糖尿病、Transbronchial aspergillosis、アノテリシン B