

# Fatal Airway Obstruction Caused by Invasive Aspergillosis of the Thyroid Gland

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Invasive aspergillosis is a common form of fungal infection in patients with hematological malignancies. Because *Aspergillus* species have angioinvasive properties, they frequently disseminate from the lung to a variety of organs via hematogenous spread. Extra-pulmonary involvement occurs at an advanced stage of invasive aspergillosis, and represents an ominous sign. However, few reports have been published on extra-pulmonary involvement in cases of aspergillosis. Its clinical features have not been fully clarified. We experienced a patient who developed thyrotoxicosis and fatal airway obstruction caused by invasive aspergillosis of the thyroid. A 26-year-old man was admitted to our hospital for the treatment of non-Hodgkin's lymphoma. During myelosuppression following the chemotherapy, he developed cervical swelling and hyperthyroidism. We suspected lymphoma infiltration to the thyroid, and irradiated it with a total of 26 Gy. However, the cervical lesion enlarged rapidly, and he complained of wheezing and dyspnea. We underwent immediate tracheostomy to secure the airway, but he died. Autopsy findings were striking. Extensive necrosis with diffuse infiltration of *Aspergillus* hyphae was observed in the thyroid gland. Necrotic tissues of the thyroid protruded into the tracheal lumen, causing airway obstruction. This case demonstrated that invasive aspergillosis of the thyroid can lead to medical emergency.

**Keywords:** Invasive aspergillosis; Thyroid; Lymphoma; Thyroiditis; Thyrotoxicosis

## INTRODUCTION

Invasive aspergillosis is a common form of fungal infection in patients undergoing cytotoxic chemotherapy for hematological malignancies. Despite the improvement of its recognition, prophylaxis and treatment, it is still associated with high morbidity and mortality [1]. The survival of these patients depends on early diagnosis and prompt initiation of therapeutic measures [2], but a critical problem is the difficulty in making an early diagnosis of invasive aspergillosis.

The lung is a common portal of entry for *Aspergillus* spores, and invasive pulmonary aspergillosis is the most common form of *Aspergillus* infection in immuno-compromised patients. Because *Aspergillus* species have angioinvasive properties, they frequently disseminate from the primary lesions, usually in the lung, to a variety of organs via hematogenous spread. These organs include the central nervous system, liver, spleen, gut, adrenal glands and skin [3].

Extra-pulmonary involvement occurs at an advanced stage of invasive aspergillosis, and represents an ominous sign in immuno-compromised patients. However, few reports have been published on extra-pulmonary involvement in cases of aspergillosis [3–6], and its clinical features have not been fully clarified. We experienced a patient who developed thyrotoxicosis and fatal airway obstruction caused by invasive aspergillosis of the thyroid gland. A detailed description of his clinical course provides important information on the clinical features of thyroid involvement by invasive aspergillosis.

## CASE

A 26-year-old man was admitted to our hospital in July 1998. He was diagnosed as having stage IV diffuse large B-cell non-Hodgkin lymphoma 8 months before admission. He had received four courses of combination chemotherapy consisting of cyclophosphamide, vincris-

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tine, adriamycin, and prednisolone (CHOP) [7]. To increase the dose intensity of the chemotherapeutic regimen, we added  $150 \text{ mg m}^{-2}$  enocitabine (BH-AC) to the original CHOP regimen. He partially responded to the treatment, and partial remission had persisted until this hospitalization.

On admission, he complained of severe malaise. Physical examination revealed swellings of cervical, axillary, and supraclavicular lymph nodes. Chest X-ray revealed a right pleural effusion and bilateral hilar lymphadenopathy. Lymphoma cells were present in the peripheral blood. Thus, progression of non-Hodgkin's lymphoma was highly suspected. We initiated high-dose cytarabine and mitoxantrone [8] on the 9th hospital day, but to no avail. The lymph nodes enlarged, and the number of peripheral lymphoma cells increased rapidly. On the 34th hospital day, 92% of the peripheral leukocytes were lymphoma cells. The patient received trimethoprim/sulfamethoxazole as prophylaxis for *Pneumocystis carinii* infection. However, no anti-fungal agent was administered as prophylaxis for fungal infection.

The patient developed a high-grade fever on the 41st hospital day, when WBC count was  $1.20 \times 10^9 \text{ l}^{-1}$  with 2% neutrophils. We empirically initiated intravenous administration of cefotaxim and amikacin, but the fever persisted. Chest X-ray showed infiltration in the left lung, and *Aspergillus fumigatus* was cultured from the sputum. He was diagnosed as having invasive pulmonary aspergillosis. We initiated intravenous administration of  $0.5 \text{ mg kg}^{-1}$  amphotericin B, but to no avail. Generalized lymphadenopathy progressed rapidly, and the high-grade fever persisted.

One week after the initiation of amphotericin B, the patient developed palpitations, hoarseness and marked perspiration. He also noticed a painful swelling in the anterior neck. Physical examination revealed enlargement of the thyroid gland. Serum levels of free T3 and free T4 were 15.3 and  $48.3 \text{ pmol l}^{-1}$ , respectively. Serum level of thyroid stimulating hormone was suppressed to  $0.084 \text{ mIU l}^{-1}$ . He was diagnosed as having thyrotoxicosis due to acute thyroiditis. Because his clinical course was rapidly progressive, we suspected that infiltration of lymphoma cells had damaged the thyroid gland, leading to the development of thyrotoxicosis. Thus, we irradiated the thyroid gland with fractionated doses of 2.0 Gy up to a total of 26 Gy. However, the symptoms associated with thyrotoxicosis did not improve even after the completion of local radiotherapy.

On the 67th hospital day, the patient developed wheezing and dyspnea. His respiratory function deteriorated rapidly and the next day he became apneic. Emergency laryngoscopic examination revealed respiratory tract obstruction by the swollen thyroid gland. The patient underwent immediate tracheotomy to secure the airway. His respiratory condition improved transiently, but he finally died of respiratory failure caused by invasive pulmonary aspergillosis on the 82nd hospital day.

Autopsy was permitted. Invasive aspergillosis with multiple abscesses was observed in a variety of organs including the lung, thyroid, trachea, esophagus, pancreas, kidney and internal carotid artery. Extensive necrosis with diffuse infiltration of *Aspergillus* hyphae was observed in the thyroid gland. Growth of *Aspergillus* extended from the thyroid to the mucosal surface of the trachea. Necrotic thyroid tissue protruded into the tracheal lumen, causing airway obstruction. While the thyroid was spared from lymphoma infiltrates, lymphoma cells invaded many organs including lymph nodes, bone marrow, spleen, liver, kidney, pancreas, lung, pleura, salivary gland, tonsil, testis, prostate, pericardium, mediastinum and adipose tissue.

## DISCUSSION

The thyroid is a relatively frequent site of dissemination in invasive aspergillosis [9]. Previous studies showed that involvement of the thyroid gland was identified at autopsy in 9–15% of patients with disseminated aspergillosis [10–12]. Most thyroid lesions of invasive aspergillosis were described as focal abscesses, patchy hemorrhagic lesions due to vascular invasion or diffuse necrotizing thyroiditis [13]. In the case of patients with thyroid aspergillosis, local inflammation and direct tissue destruction caused by invasive aspergillosis of the thyroid can produce leakage of thyroid hormones into the bloodstream, sometimes leading to the development of thyrotoxicosis. However, most of these patients remain asymptomatic throughout their clinical course, and it is usually difficult to establish an antemortem diagnosis of invasive aspergillosis of the thyroid. To our knowledge, there are only few case reports on thyrotoxicosis caused by thyroid involvement by disseminated aspergillosis [14], and this is the first report of airway obstruction caused by thyroid involvement by invasive aspergillosis.

We do not know the exact mechanism through which invasive aspergillosis of the thyroid manifested as thyrotoxicosis and fatal airway obstruction in this patient. Considering that the thyroid is a radiosensitive organ [15], we cannot exclude the possibility that 26 Gy irradiation to the thyroid might have contributed to the destruction of the thyroid. However, post-mortem examination revealed extensive necrosis with diffuse infiltration of *Aspergillus* hyphae in the thyroid. The autopsy findings indicate that invasive aspergillosis was the principal cause of destructive thyroiditis observed in this patient. These findings indicate that invasive aspergillosis can cause acute thyroiditis causing fatal airway obstruction, and that invasive aspergillosis of the thyroid can lead to a medical emergency.

Besides invasive *Aspergillus* infection, a variety of organisms and diseases can involve the thyroid. Berger *et al.* reported 31 cases of fungal thyroiditis, of which 26 cases were due to *Aspergillus* species, three to *Coccidioides immitis*, one to *Candida* and one to

*Allescheria boydii* [16]. Lymphoma cells can also invade the thyroid, sometimes causing thyrotoxicosis [17], and lymphoma involvement of the thyroid is common in the case of patients with refractory lymphoma [17,18]. Considering that invasive aspergillosis and lymphoma require different types of treatment, it is essential to differentiate *Aspergillus* infection of the thyroid from lymphomatous invasion of the organ. However, early diagnosis of thyroid aspergillosis seems to be difficult, as in the case described here. Diagnosis is delayed in most cases of invasive aspergillosis, and the fungal infection is frequently revealed at autopsy [10,19].

Survival of patients with invasive aspergillosis depends on early diagnosis and prompt initiation of therapeutic measures. However, invasive procedures are rarely feasible in patients with hematological malignancies, and a critical problem is the difficulty in making an early diagnosis of invasive aspergillosis. As non-invasive diagnostic procedures, scintigraphy [18,20] and needle biopsy [21] might be useful for the diagnosis of invasive aspergillosis of the thyroid. Bach *et al.* published a case report in which a clinically silent fungal thyroid abscess was identified using Ga-67 citrate scanning [20]. Torres *et al.* reported a patient who was successfully diagnosed as having invasive aspergillosis of the thyroid using fine needle biopsy [21]. These procedures can be performed safely, and are tolerated by most neutropenic patients receiving cytotoxic chemotherapy.

In conclusion, *Aspergillus* infection frequently disseminates to a variety of organs, and extra-pulmonary aspergillosis contributes to the high morbidity and mortality associated with invasive aspergillosis. To improve the prognosis in cases of invasive aspergillosis, it is important to fully recognize the clinical features of extra-pulmonary aspergillosis. We believe that we have clarified some of the clinical features of invasive aspergillosis of the thyroid.

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