Medical Mycology Case Reports 6 (2014) 25–28

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

Aspergillus tracheobronchitis, bronchopleural fistula and empyema after lobectomy for aspergilloma

Peter Rummens *, Marie Bruyneel, Michele Lungarella, Vincent Ninane

Department of Pneumology, Centre Hospitalier Universitaire Saint-Pierre, Rue Haute 322, B-1000 Brussels, Belgium

ARTICLE INFO

Article history:
Received 29 May 2014
Received in revised form
31 July 2014
Accepted 31 July 2014

Keywords:
Aspergillus fumigatus
Pseudomembranous tracheobronchitis
Empyema
Lobectomy complication

ABSTRACT

Aspergillus tracheobronchitis and Aspergillus empyema are two rare manifestations of Aspergillus infection. This case report presents a patient with chronic obstructive pulmonary disease who developed a pseudomembranous Aspergillus tracheobronchitis, bronchopleural fistula and empyema 16 months after lobectomy for an aspergilloma. Bronchoscopy proved to be important for assessment of severity. Combined systemic anti-fungal treatment (voriconazole) and open window thoracostomy were used to successfully treat the patient.

1. Introduction

Aspergillus infection, and especially invasive pulmonary aspergillosis, is associated with high morbidity and mortality [1].

Aspergillus tracheobronchitis (ATB) is thought to be a rare manifestation, occurring in less than 7% of patients with an Aspergillus infection [2], and primarily affecting lung and other solid organ (e.g. heart or kidney) transplant recipients [3], patients with malignancies (primarily of hematological and pulmonary origin), and immune deficiencies like AIDS [4]. ATB can also be found in patients with chronic obstructive pulmonary disease (COPD) [5], with post-tuberculosis tracheal or bronchial stenosis [2,6], at the level of a bronchial stump after lobectomy [7], or in association with hepatic disease (e.g. cirrhosis) [2], septic shock and ARDS [8], or diabetes mellitus [9,10]. Risk factors for developing ATB include steroid and broad-spectrum antibiotic use, neutropenia, and alcoholism [11].

A review of 121 cases by Karnak et al. showed that *Aspergillus fumigatus* was identified in 63% of Aspergillus tracheobronchial infections. *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus nidulans* were cultured in 4.1%, 3.3%, and 1.7%, respectively, whereas in 28% of the cases data regarding the species were not available [12]. Diagnosis of ATB may be delayed because of its insidious onset, non-specific signs and symptoms, and scarcity of radiographic abnormalities [13]. Therefore bronchoscopic evaluation should be performed in patients with high risk profile and respiratory symptoms (e.g. dyspnea, hemoptysis, persistent cough, fever, wheezing or stridor), especially when sputum cultures show growth of Aspergillus species in these high-risk patients.

2. Case

A 67-year-old man underwent a right upper lobectomy and systemic treatment (voriconazole) for lung aspergilloma complicated by an invasive aspergillosis. Sixteen months after lobectomy the patient complained of a chronic cough and weight loss. A bronchopleural fistula from the right main stem bronchus to the pleural cavity was seen on a computed tomography (CT) scan (day 0).

Bronchoscopy showed an inflammatory mucosa of the trachea and bronchial tree with patchy white pseudomembranes (Fig. 1, left panel) (day 4). These white pseudomembranes were very adhesive to the mucosa and showed signs of superficial bleeding when aspiration was performed. The orifice of the bronchopleural fistula was visualized in the right main stem bronchus. Pseudomembranes covered the mucosa of the fistula and the bronchus intermedius (Fig. 1, right panel). When entering the fistula opening, a cavity filled with pus and walls covered with green-gray debris and white crystals appeared. Bronchial aspirates of the trachea and pleural cavity were sent for microbiological examination. *Escherichia coli* was found in the samples of the pleural cavity and treated by Amoxicilline-Clavulanic acid (day 5). Although the cultures for *A. fumigatus* came back negative, invasive aspergillosis was the most likely diagnosis because of the highly suspect appearance of the lesions, and an elevated Aspergillus antigen

* Corresponding author. Tel.: +32 25353727; fax: +32 25353362.
E-mail address: peter.rummens@stpierre-bru.be (P. Rummens).

http://dx.doi.org/10.1016/j.mmcr.2014.07.006

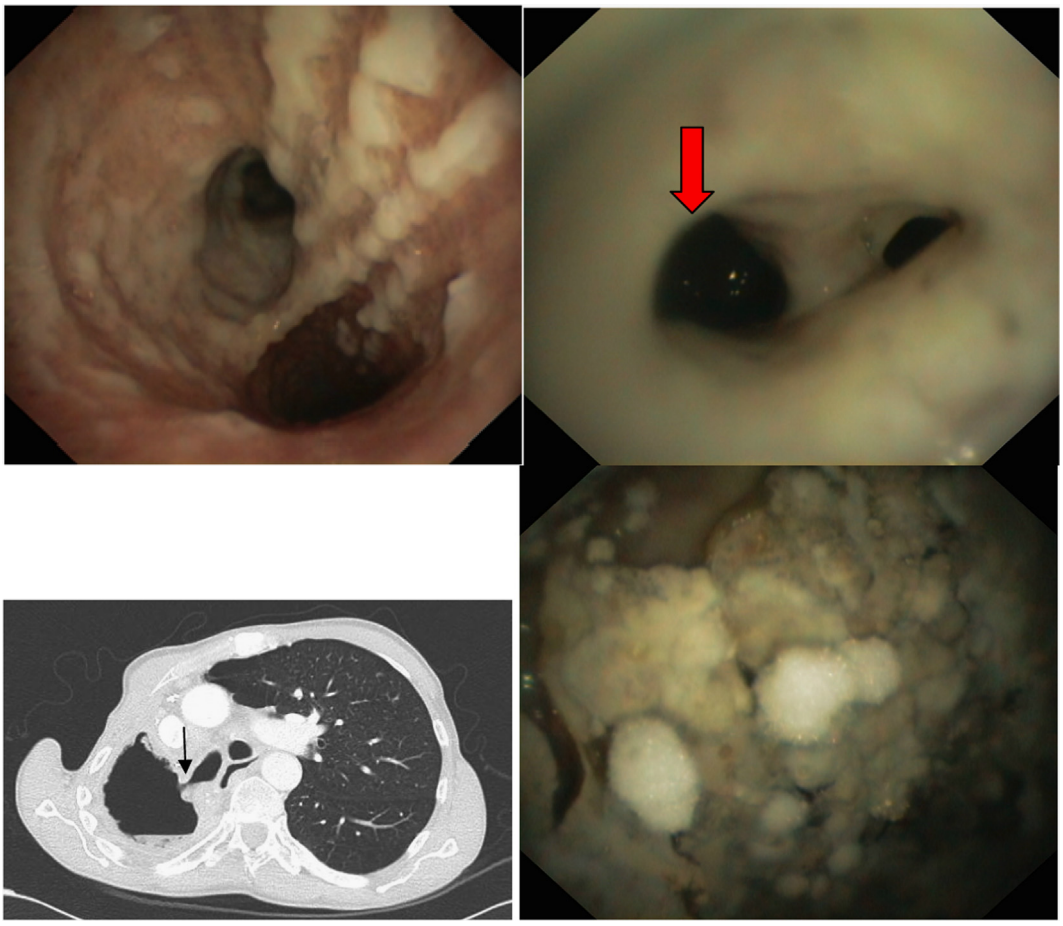

Fig. 1. Left upper panel: Aspergillus tracheobronchitis with white pseudomembranes; Right upper panel: fistula between right main stem bronchus and pleural cavity (red arrow), stenosis of bronchus intermedius due to pseudomembranes. Left lower panel: CT-scan shows bronchopleural fistula (black arrow) and post-lobectomy cavity with air-fluid level and irregular walls. Right lower panel: post-lobectomy cavity with pus and white crystals.

level with optical density (OD) index of 8,14 (reference value: OD index <0.5) (day 0).

Because of the poor nutritional status of the patient due to COPD and extent of the infected cavity, an open window thoracostomy was performed (day 10). The pleural cavity was cleaned and green-grey substance and white crystals were removed. Biopsies taken from the walls of the pleural cavity and fistula were sent for microbiological examination and cultures came back positive for *A. fumigatus*. Voriconazole 250 mg b.i.d. was started (day 4) and antiseptic packages in the pleural cavity were changed regularly. The voriconazole level was 4.7 mg/l at day 8. Trachea, fistula orifice and bronchial tree had almost normal mucosa when bronchoscopy was performed after surgery (day 31), and the Aspergillus antigen level had a lower OD index of 0.83 (day 33). Voriconazole was stopped after 7.5 months of treatment (day 232). Although a therapeutic level at day 150 (3,5 mg/l), dose modification had to be made to 300 mg b.i.d. (day 172) because of subtherapeutic drug level (<0.2 mg/l). Antigen levels had been normal during the last 3 months of the treatment (OD index 0.44; 0.34; 0.24; 0.011 at day 140; 172; 213; and 235 respectively).

3. Discussion

Postlobectomy or postpneumonectomy empyema is a known and feared surgical complication. In this case *A. fumigatus* was found as one of the causative agents of empyema formation. A pseudomembranous ATB and bronchial stump aspergillosis were thought to be the primary event, leading to a fistula, followed by a pleural cavity infection. In this hypothesis the patient was re-exposed to an environmental source of Aspergillus after being successfully treated for an aspergilloma. A second hypothesis suggests an existing Aspergillus colonization of the pleural cavity, in other words an unsuccessfully treated aspergilloma 16 months before. This could have led to a bronchopleural fistula and colonization of the trachea.

In 1970, Young et al. [7] reviewed 98 cases of histologically documented invasive aspergillosis, of which eight had ATB. In five patients, the infection seemed to be limited to the tracheobronchial tree, without signs of parenchymal involvement. However, invasive forms of Aspergillus tracheobronchitis had not been fully described until 1991 by Kramer et al. [3].

Kramer et al. proposed a classification of ATB in three entities: invasive, saprophytic and allergic ATB. In their patients they observed three morphologic subtypes of invasive ATB: tracheobronchitis, ulcerative tracheobronchitis, and pseudomembranous tracheobronchitis.

An impairment of the local natural antifungal defense mechanisms that significantly increases the risk of airway colonization was suggested [3,9]. The hypothesis that local factors play a role in the development of ATB, was also seen in other studies. Wu et al. included nineteen patients with ATB in a retrospective analysis, and observed that malignancy was the most common underlying disease (73.7%). Tracheobronchial tuberculosis and traumatic tracheostenosis were seen in two (10.5%) and one (5.3%) patient, respectively [6]. Noticeably, seven patients (36.8%) had underlying

airway constriction. Wu et al. concluded that airway structures and mucociliary clearance are impaired and hypoxemia is usually present in these patients, which will attenuate the defense functions of airways and lead to opportunistic infections. A relatively normal systemic immune status will prevent the spread of infection and contribute to the localization of the disease [6]. According to the bronchoscopic findings, Wu et al. proposed four types of isolated invasive ATB: superficial infiltration type (type I); full-layer involvement type (type II); occlusion type (type III); and mixed type (type IV) [6].

The present observation corresponds better to the pseudomembranous ATB as defined by Kramer et al. [3] or the type I from Wu et al. [6]. Although our patient had none of the causes of airway stenosis mentioned by Wu et al., he had altered airway structures and mucociliary clearance due to COPD and a bronchial stump after lobectomy. A review of 31 cases of bronchial stump aspergillosis after lobectomy or pneumectomy was done by Tokuishi et al. [14]. Two cases of bronchial stump aspergillosis were found after stapled closure, the other cases were infections of suture threads. Suture material probably initiates a local immune response and may lead to necrosis and airway obstruction. Silk threads are more prone to develop surinfection with Aspergillus species, compared to nylon monofilament threads. Only one case report was found which describes synthetic thread infection. Although bronchial stump aspergillosis due to thread infection is described in patients, even up to 7 years after lobectomy, in our patient it seems less likely to be a cause of Aspergillus colonization [7,14]. First of all a polydioxanone synthetic thread was used for closure after lobectomy, and secondly bronchoscopy performed at the time of the ATB, bronchopleural fistula and empyema, has not visualized any loose threads at the bronchial stump.

As mentioned before invasive aspergillosis has a high mortality. In the search for a good indicator for systemic spread of Aspergillus species the value of the serum level of circulating Aspergillus antigen level or galactomannan remains uncertain. The patient in this case report had elevated serum concentration of Aspergillus antigen; however a review of the literature by Krenke et al. showed series of serum samples with low levels of Aspergillus and series with elevated levels [9]. To explain these differences, Van Assen et al. presented two hypotheses [9,17]. The first assumes that in some patients the fungal invasion is limited to the superficial layer of the airway mucosa and, is not sufficient to cause the spread of Aspergillus antigens into the circulating blood. A second hypothesis could be that the low serum Aspergillus antigen level is a consequence of a false negative ELISA reactivity.

In the series from Wu et al. oral or intravenous antifungal agents were administered, mostly combined with intermittent bronchoscopic interventions, including electrocauterization, cryotherapy, mechanical debridement and intraluminal antifungal instillation with amphotericin B. Two patients were only treated with local interventions. However mechanical debridement seems to be a reasonable solution, it may be warranted in some cases of pseudomembranous aspergillus tracheobronchitis with necrosis. Removing the pseudomembranes by bronchoscopic procedures may be useful because of the poor penetration of antifungal agents into the abnormal pseudomembranous tissues; however it may cause bleeding because of the angioinvasive nature of Aspergillus [2]. Putnam et al. reported a case of ATB localized to the right main stem bronchus and invading the right pulmonary artery in which the patient had a fatal hemorrhage after bronchoscopic intervention [15]. Because of the bleeding risk Casal et al. described the first case of invasive ATB in which the diagnosis was facilitated by the use of endobronchial ultrasound guided trans-bronchial needle aspiration (EBUS-TBNA) [16]. They suggested that EBUS-TBNA may be a useful tool to evaluate the degree of invasion and the involvement of vascular structures in patients prior to bronchoscopic manipulation of the affected areas in an effort to avoid potentially fatal hemorrhage.

In our patient voriconazole was given for primary treatment of invasive ATB according to the latest Infectious Diseases Society of America guidelines [18]. No local bronchoscopic interventions were required at the level of the trachea and right main stem bronchus. As an additional, local treatment, antiseptic packages were stuffed in the thoracostomy cavity.

Alternative treatments could have been liposomal or lipid complex form of Amphotericin B, caspofungin, micafungin, posaconazole, and itraconazole [18].

More advanced immunosuppression, mechanical ventilation delay in performing bronchoscopy, severe hemoptysis, and persistent positive culture of respiratory secretions after initiation of treatment seem to be related to an adverse prognosis [13].

In conclusion, we presented a rare case of invasive *A. fumigatus* infection in a COPD patient after a lobectomy for an Aspergilloma. Although radiological imaging showed a bronchopleural fistula and a fluid filled cavity, bronchoscopy was the most important examination for evaluation of the extent of the fungal infection.

Although in this case the Aspergillus antigen level in the blood was elevated, the exact role in the diagnosis of aspergillus tracheobronchitis is still uncertain.

Combined systemic anti-fungal treatment (voriconazole) and open window thoracostomy were used to treat the patient. This therapeutic approach is based on case reports and current surgical management of bacterial empyema. Open window thoracostomy proved to be a good and safe procedure in this high-risk patient, and systemic voriconazole seemed to be sufficient to eradicate the tracheobronchial pseudomembranes. However further research is needed to determine the role of local therapeutic bronchoscopic interventions in the treatment of ATB.

Conflict of interest

There are no conflicts of interest.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

References

[1] Segal BH. Aspergillosis. N Engl J Med 2009;360:1870–84.
[2] Pornsuriyasak P, Murgu S, Colt H. Pseudomembranous aspergillus tracheobronchitis superimposed on post-tuberculosis tracheal stenosis. Respirology 2009;14:144–7.
[3] Kramer MR, Denning DW, Marshall SE, Ross DJ, Berry G, Lewiston NJ, et al. Ulcerative tracheobronchitis after lung transplantation. A new form of invasive aspergillosis. Am Rev Respir Dis 1991;144:552–6.
[4] Kemper CA, Hostetler JS, Follansbee SE, Ruane P, Covington D, Leong SS, et al. Ulcerative and plaque-like tracheobronchitis due to infection with Aspergillus in patients with AIDS. Clin Infect Dis 1993;17(3):344–52.
[5] He H, Ding L, Li F, Zhan Q. Clinical features of invasive bronchial-pulmonary aspergillosis in critically ill patients with chronic obstructive respiratory disease: a prospective study. Crit Care 2011;15:R5.
[6] Wu N, Huang Y, Li Q, Bai C, Huang HD, Yao XP. Isolated invasive Aspergillus tracheobronchitis: a clinical study of 19 cases. Clin Microbiol Infect 2010;16:689–95.
[7] Young RC, Bennett JE, Vogel CL, Carbone PP, Devita VT. Aspergillosis: the spectrum or the disease in 98 patients. Medicine 1970;49(2):147–73.
[8] Gomez F, Tarin V, Cuadrado M, Vecilla F, Blanquer D, Costa-Bauza A, et al. Tracheal oxalosis associated with *Aspergillus niger* tracheobronchitis. Eur Respir J 2013;41:995–7.
[9] Krenke R, Grabczak EM. Tracheobronchial manifestations of Aspergillus infections. SciWorld J 2011;11:2310–29.
[10] Chang S, Kuo HT, Lin FJ, Tzen CY, Sheu CY. Pseudomembranous tracheobronchitis caused by Aspergillus in immunocompromised patients. Scand J Infect Dis 2005;37:937–42.
[11] Hines DW, Haber MH, Yaremko L, Britton C, McLawhon RW, Harris AA. Pseudomembranous tracheobronchitis caused by Aspergillus. Am Rev Respir Dis 1991;143(6):1408–11.

[12] Karnak D, Avery RK, Gildea TR, Sahoo D, Mehta AC. Endobronchial fungal disease: an underrecognized entity. Respiration 2006;74(1):88–104.
[13] Ramos A, Segovia J, Gomez-Bueno M, Salas C, Lazaro MT, Sanchez I, et al. Pseudomembranous Aspergillus tracheobronchitis in a heart transplant recipient. Transpl Infect Dis 2010;12:60–3.
[14] Tokuishi K, Yamashita S, Hashimoto T, Moroga T, Miyawaki M, Chujo Masao, et al. Bronchial stump aspergillosis after stapled lobectomy for lung cancer. Ann Thorac Surg 2012;94:1324–6.
[15] Putnam J, Dignani M, Mehra R, Anaissie E, Morice R, Libshitz H. Acute airway obstruction and necrotizing tracheobronchitis from invasive mycosis. Chest 1994;106:1265–7.
[16] Casal RF, Adachi R, Jimenez CA, Sarkiss M, Morice RC, Eapen GA. Diagnosis of invasive aspergillus tracheobronchitis facilitated by endobronchial ultrasound-guided transbronchial needle aspiration: a case report. J Med Case Rep 2009;3:9290.
[17] Van Assen S, Bootsma GP, Verweij PE, Donnelly JP, Raemakers JMM. Aspergillus tracheobronchitis after allogeneic bone marrow transplantation. Bone Marrow Transplant 2000;26(10):1131–2.
[18] Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2008;46(3):327–60.