Tracheobronchial Manifestations of Aspergillus Infections

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Human lungs are constantly exposed to a large number of Aspergillus spores which are present in ambient air. These spores are usually harmless to immunocompetent subjects but can produce a symptomatic disease in patients with impaired antifungal defense. In a small percentage of patients, the trachea and bronchi may be the main or even the sole site of Aspergillus infection. The clinical entities that may develop in tracheobronchial location include saprophytic, allergic and invasive diseases. Although this review is focused on invasive Aspergillus tracheobronchial infections, some aspects of allergic and saprophytic tracheobronchial diseases are also discussed in order to present the whole spectrum of tracheobronchial aspergillosis. To be consistent with clinical practice, an approach basing on specific conditions predisposing to invasive Aspergillus tracheobronchial infections is used to present the differences in the clinical course and prognosis of these infections. Thus, invasive or potentially invasive Aspergillus airway diseases are discussed separately in three groups of patients: (1) lung transplant recipients, (2) highly immunocompromised patients with hematologic malignancies and/or patients undergoing hematopoietic stem cell transplantation, and (3) the remaining, less severely immunocompromised patients or even immunocompetent subjects.

KEYWORDS: Aspergillus, Aspergillus tracheobronchitis, tracheobronchial aspergillosis, pseudomembranous tracheobronchitis, ulcerative tracheobronchitis, obstructing bronchial aspergillosis, invasive Aspergillus pulmonary diseases, fungal tracheobronchitis, allergic bronchopulmonary aspergillosis (ABPA), mucoid impaction

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1. INTRODUCTION

*Aspergillus* forms a genus of ubiquitous, dimorphic molds present in soil, various types of organic debris, water, indoor environment, and many other sites [1, 2]. Airborne *Aspergillus* spores are present virtually everywhere in the atmosphere and are small enough (2-3 µm) to be regularly inhaled into the lower airways [1, 2]. However, due to efficient natural antifungal defense mechanisms (i.e., mucosal barriers, macrophage and neutrophil function) symptomatic pulmonary infections in otherwise healthy subjects are extremely rare. Conversely, the impairment of these mechanisms (local or systemic) significantly increases the risk of airway colonization and progression to various *Aspergillus*-related pulmonary disorders [3–5].

Although more than 250 *Aspergillus* species have been identified, only a minority of them are associated with human diseases [1, 6–8]. *Aspergillus fumigatus* is by far the most common pathogen involved in 50–60% of all *Aspergillus* infections. Three other species which are a relatively common cause of human diseases are: *A. flavus*, *A. niger*, and *A. terreus*. Each of these species may be responsible for 10–15% of invasive human diseases [9–11]. Other species, for example, *A. nidulans* and *A. ustus* are only occasionally identified and constitute less than 2% of isolates in patients with invasive *Aspergillus* infections [9–11]. The predominance of *A. fumigatus* infections in patients with tracheobronchial involvement is even more significant. Karnak et al. reviewed 121 cases reported in the literature, and found that in 76 (63%) patients with diverse *Aspergillus* tracheobronchial infections *A. fumigatus* was identified as the cause of the disease. *A. flavus*, *A. niger*, and *A. nidulans* were cultured in 5 (4.1%), 4 (3.3%), and 2 (1.7%) cases, respectively, while, in 34 (28%), data regarding the species were not available [12].

1.1. Host-Fungus Relationships and Classifications of *Aspergillus*-Related Respiratory Diseases

The wide clinical spectrum of pulmonary aspergillosis reflects the complex relationship between the number and virulence of organisms and the status of the patient’s antifungal defense. As different host-dependent anatomical and immunological factors are the key prerequisite for the development of various clinical entities, the general classification of *Aspergillus*-related lung diseases is based on the type of the host-fungus relationship. This includes saprophytic infections, allergic pulmonary diseases, invasive disease, and toxic reactions [13] (Figure 1). Although this reasonable classification presents a spectrum of *Aspergillus*-related pulmonary diseases in humans, it does not address some aspects of these conditions. For example, it does not reflect the anatomical location of the disease. Thus, the diagram shown in Figure 1 might be further completed by adding subsequent rows in which anatomical location and/or disease subtype would be presented.

Since the anatomical site of the disease plays a crucial role in development of specific signs and symptoms as well as determines the diagnostic and therapeutic strategy, a simple, anatomical classification of *Aspergillus*-related respiratory disease is also used in clinical practice (Table 1).

In all anatomical locations, a spectrum of *Aspergillus*-related disorders involving various host-fungus relationships (saprophytic, allergic, and invasive) may develop. It is important to realize that, on rare occasions, one distinct *Aspergillus*-related entity may change to another; for example, an aspergilloma may progress to semiacute invasive or invasive pulmonary aspergillosis (IPA) [13].

Some of the *Aspergillus*-related respiratory diseases are well defined and common; others are unusual but recognized; still, others are rare and controversial [6]. *Aspergillus*-related upper airway and pulmonary diseases belong to the first group. In a small percentage of patients, the trachea and bronchi may be the main or even the sole site of *Aspergillus* infection. This condition is referred to as lower airway aspergillosis, tracheobronchial aspergillosis, or *Aspergillus* tracheobronchitis.

2. TRACHEOBRONCHIAL ASPERGILLOSION

In 1991, Kramer and coworkers proposed a classification of tracheobronchial aspergillosis. Similarly to upper airway and pulmonary aspergillosis, the authors distinguished saprophytic, allergic, and invasive
FIGURE 1: Classification of the *Aspergillus*-related respiratory diseases based on their pathogenesis, including the status of antifungal defense and the type of host-fungus relationship (upper and middle row, respectively) (based on [13], modified). * In many patients, a true saprophytic nature of the infection is difficult to prove and might be questionable. Note, that in fact, not only vertical (showed with arrows), but also horizontal relationships might exist in the middle and bottom rows (e.g., saprophytic forms can evolve into invasive forms; relationships not shown); EEA: extrinsic allergic alveolitis, ABPA: allergic bronchopulmonary aspergillosis, IPA: invasive pulmonary aspergillosis, ITBA: invasive tracheobronchial aspergillosis.

TABLE 1: Anatomical classification of *Aspergillus*-related respiratory disease.

<table>
<thead>
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<th>Aspergillus-related respiratory diseases</th>
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<tr>
<td>Aspergillus-related upper airway diseases</td>
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<tr>
<td>Tracheobronchial Aspergillus diseases</td>
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<td>Aspergillus-related diseases of lung parenchyma</td>
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forms of *Aspergillus* tracheobronchial involvement. Based on clinical, bronchoscopic, and pathological presentations, they were further subdivided into different clinical entities (Table 2) [14–16].

Recently, Patel et al. reported three patients with different forms of tracheobronchial aspergillosis and presented their own, simplified, classification of *Aspergillus*-related tracheobronchial diseases [17]. Although this classification includes most of the known tracheobronchial manifestations of aspergillosis, it also raises some doubts; for example, pulmonary aspergilloma was classified as tracheobronchial disease, while endobronchial localization of *Aspergillus* fungal ball has not been mentioned [17, 18].

We realize that in view of the variety of different forms of *Aspergillus* tracheobronchial involvement it is difficult to propose a uniform and unequivocal classification involving all entities. A review of 121 cases of *Aspergillus*-related endobronchial diseases reported in the literature, listing 13 different
TABLE 2: Classification of Aspergillus-related tracheobronchial diseases (based on [14–16]).

<table>
<thead>
<tr>
<th>Host-fungus relationship (type of tracheobronchial involvement)</th>
<th>Clinical characteristics of tracheobronchial involvement</th>
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<tr>
<td>Saprophytic</td>
<td>Mucoid impaction</td>
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<td>Obstructing bronchial aspergilosis</td>
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<td>Allergic</td>
<td>Allergic bronchopulmonary aspergilosis (ABPA)</td>
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<td>Bronchocentric granulomatosis</td>
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<td>Invasive tracheobronchial aspergilosis (ITBA)</td>
<td>Ulcerative Aspergillus tracheobronchitis</td>
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<td>Pseudomembranous Aspergillus tracheobronchitis</td>
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bronchoscopic/pathologic descriptions and 17 different diagnoses, clearly demonstrates these difficulties [12]. Nevertheless, we believe that the classification presented by Kramer et al. is still valuable and convincing. Therefore, it will be further used in this paper. However, since, from the original publication in 1991, a large body of papers has been published on different forms of tracheobronchial aspergilosis, new data exceeding the original classification will also be presented.

2.1. Allergic Forms of Tracheobronchial Aspergilosis

2.1.1. Asthma with Hypersensitivity to Aspergillus Antigen and Allergic Bronchopulmonary Aspergilosis (ABPA)

Asthma with hypersensitivity to Aspergillus antigens as well as allergic bronchopulmonary aspergilosis (ABPA) is well-defined entities which can be considered as tracheobronchial manifestations of Aspergillus infections. As both diseases have been extensively discussed in several articles published in the recent years [1, 6, 19, 20], they will only be mentioned in this paper.

Clinical symptoms of asthma developing in patients with type I hypersensitivity to Aspergillus antigens are not different from those found in patients allergic to other molds including Alternaria and Penicillium [6]. Treatment is similar to that recommended for other patients with allergic asthma and includes inhaled steroids and bronchodilators [1, 6].

ABPA usually develops in atopic individuals with extrinsic asthma or patients with cystic fibrosis and affects both, the bronchial compartment and adjacent lung tissue. Its pathogenesis involves Th2-dependent, eosinophilic response to Aspergillus antigens [19]. Chronic inflammation of the airway walls typically results in development of bronchiectasis and recurrent mucous plugging. Five stages of the disease have been recognized with pulmonary fibrosis being its final consequence [1, 20]. Suppression of the immunological response to Aspergillus antigens with systemic corticosteroids is a mainstay of ABPA therapy. It aims at relieving acute symptoms and preventing progressive pulmonary fibrosis [1, 19, 20]. Treatment with new azoles may have some beneficial effect enabling the reduction of corticosteroid doses [1, 19, 21]. Not all authors, however, confirmed the efficacy of antifungal agents [20].

2.1.2. Bronchocentric Granulomatosis

Bronchocentric granulomatosis is an effect of abnormal cell-mediated response to Aspergillus spp. This inflammatory reaction involves the bronch and bronchioles and is characterized by the formation of necrotizing granulomas containing numerous inflammatory cells (mainly eosinophils) [1, 6, 13, 22]. This is often associated with impaction of the airway lumen by a granular basophilic mucin and cellular debris [22]. The Aspergillus hyphae were identified within the granulomas in 40–50% of cases, but typically there
is no tissue or vascular invasion [13]. Two subtypes of bronchocentric granulomatosis are distinguished by some authors [6, 14]. The first is closely related to atopy and asthma. The second subtype may be related to a variety of other diseases, such as rheumatoid arthritis, bronchogenic carcinoma, postradiation pulmonary fibrosis, and Wegener’s granulomatosis [17]. In some cases, bronchocentric granulomatosis may overlap invasive forms of Aspergillus-related pulmonary diseases, namely, semiacute invasive pulmonary aspergillosis (also termed chronic necrotizing aspergillosis) [1]. Corticosteroids are the mainstay of treatment, but they are effective mainly in patients with atopy and asthma.

2.2. Saprophytic Forms of Tracheobronchial Aspergillosis

2.2.1. Mucoid Impaction

Mucoid impaction is defined as intrabronchial retention of the inspissated mucoid secretions. Although it has been found to be a nonspecific finding, inflammatory and allergic reactions to Aspergillus antigens are probably the most common causes of this condition [23, 24]. Intrabronchial obstruction is often associated with an inflammatory reaction in the airway wall. If the affected airway is large or dilated, the secretion may be depicted on a chest radiograph or CT scan as tubular or branching opacities known as the finger-in-glove sign [24]. Although mucoid impaction associated with hypersensitivity to Aspergillus antigens is usually reported in patients with ABPA, it probably can also affect patients with asthma and hypersensitisation to Aspergillus but without ABPA. [25, 26]. Other causes of mucoid impaction have been widely discussed elsewhere [24]. Treatment of mucoid impaction associated with inflammatory response to Aspergillus is not different from that used in patients with ABPA.

2.2.2. Obstructing Bronchial Aspergillosis

Obstructing bronchial aspergillosis was first described by Denning et al. in three patients with AIDS [27]. This was defined as the presence of thick mucous plugs containing Aspergillus hyphae, with little or no airway inflammation and no evidence of invasion or allergic reaction [15, 27]. The disease is characterized by a subacute onset of symptoms, which include cough, hemoptysis, dyspnea, chest pain, and expectoration of fungal casts [14, 27, 28]. Obstructing bronchial aspergillosis was also reported in a heart transplant recipient whose chest radiograph performed on the third postoperative day revealed middle lobe atelectasis. [29]. Multiple, endobronchial casts, containing Aspergillus hyphae were removed during bronchoscopy. Although obstructing bronchial aspergillosis is regarded as a saprophytic form of tracheobronchial aspergillosis, in immunocompromised patients, it can probably progress to invasive tracheobronchitis [27–29].

It should be stressed that saprophytic, obstructing bronchial aspergillosis is an entity distinct from invasive pseudomembranous Aspergillus tracheobronchitis which can also be associated with bronchial obstruction by necrotic pseudomembranes (pseudomembranous, obstructive Aspergillus tracheobronchitis).

2.2.3. Other Saprophytic Forms of Aspergillus Tracheobronchial Involvement

Another saprophytic Aspergillus tracheobronchial infection which had not been included in classification presented by Kramer et al. is saprophytic Aspergillus infection involving bronchial anastomoses. This entity has been described in lung transplant recipients. Devascularization of the bronchial anastomosis in the early posttransplantation period may result in sloughing of epithelial tissue into the airway lumen [30]. This necrotic debris may serve as nourishment for fungal hyphae germinating from airborne spores. The intensive immunosuppression in the early posttransplantation period is an important factor promoting fungal growth. Nunley et al. defined saprophytic fungal infection as positive culture of bronchial washing and presence of fungal organisms in biopsy samples from bronchial anastomosis [30]. In their series, the
incidence of saprophytic fungal infection of bronchial anastomosis was as high as 24.6%, with *Aspergillus* spp. being responsible for two thirds of the cases. The median time from transplantation to diagnosis of saprophytic fungal infection was 35 (range 13–159) days [30]. All patients with anastomotic fungal infection were intensively treated with intravenous and nebulized amphotericin B and oral itraconazole. This intensive treatment and, particularly, the complications which developed in some patients including bronchomalacia, bronchial stenosis and hemorrhage raise some doubt about the truly saprophytic nature of these infections. We suppose, that in some patients fungal infection of bronchial anastomosis which is initially limited to necrotic tissue and defined as saprophytic may easily progress to locally invasive fungal infection. If so, the borderline between saprophytic fungal infection of bronchial anastomosis and local, invasive *Aspergillus* tracheobronchitis in lung or heart and lung transplant recipients might be quite elusive (see further: *Aspergillus* tracheobronchitis in patients after lung transplantation).

*Aspergillus* growth on silk sutures closing a bronchial stump is another example of saprophytic fungal-host relationship. This infection usually develops 6–12 months after lung resection and can spread to mucous plug or debris as well as granulation tissue located in the stump. The removal of the thread solves the problem, and usually no antifungal therapy is necessary [31]. A much longer latency period between lung resection and development of bronchial stump aspergillosis, ranging between 4 and 7 years, was also reported [32, 33]. Noppen et al. found that, albeit bronchoscopic removal of the silk thread seems to be the first choice therapy, treatment with oral itraconazole can also result in resolution of infection [32]. Le Rochais et al. demonstrated that bronchial stump aspergillosis is not specific for silk thread but can also affect patients in whom nylon threads were used [34].

Since invasion of bronchial mucosa was reported in patients with bronchial stump aspergillosis [32], this is yet another example that the line between saprophytic and invasive *Aspergillus* infection may not be well defined, and borderline cases can be expected in clinical practice.

*Aspergillus* can overgrow necrotic debris and mucous plug on the surface of endobronchial tumors. We observed a thick layer of *Aspergillus* hyphae covering an endobronchial carcinoid tumor (data not published). Initially, this caused a diagnostic challenge. A similar situation was reported by others [35].

### 2.3. Invasive Tracheobronchial Aspergillosis (ITBA)

While invasive pulmonary aspergillosis centered on the airways accounts for 14–34% of invasive pulmonary aspergillosis (IPA), invasive tracheobronchial aspergillosis (ITBA) is a relatively rare manifestation of *Aspergillus*-related lung disease [36]. ITBA has been described as an isolated or dominating local manifestation only in a small number of patients (6.9% of patients with intrathoracic aspergillosis in three case series analyzed by Kemper et al.) [37]. In the majority of cases, ITBA is probably associated with IPA, which is the most common form of *Aspergillus* invasion. [38, 39]. Both, IPA and ITBA, predominantly affect severely immunocompromised patients [39]. ITBA has also been reported in patients with various chronic diseases without severe immune suppression (e.g., diabetes) and even in immunocompetent subjects [40–42].

Since the most reliable criterion of invasive fungal airway disease is demonstration of tissue invasion and damage caused by hyphae [15, 43, 44], bronchoscopy with biopsy, microscopy, and culture is the only way to confirm invasive *Aspergillus* tracheobronchial infection in the clinical setting [16].

Basing on the bronchoscopic or pathologic appearance, three different invasive forms of tracheobronchial aspergillosis were described: *Aspergillus* tracheobronchitis, ulcerative *Aspergillus* tracheobronchitis, and pseudomembranous *Aspergillus* tracheobronchitis [14]. Denning and coworkers proposed to apply the term “*Aspergillus* tracheobronchitis” to tracheobronchial disease caused by *Aspergillus* spp., which is characterized by the evidence of bronchial and/or tracheal inflammation and excessive mucus production without invasion of the bronchial mucosa on biopsy [15]. The features of the ulcerative forms include the presence of variable, ulcerative, or plaque-like lesions in the bronchial walls. This form has been most commonly recognized in patients with AIDS and heart-lung or lung transplant recipients [15]. Pseudomembranous form of ITBA is characterized by extensive involvement of the lower airways, with
sloughing of necrotic epithelium which, together with endobronchial mucus, form the pseudomembranes overlying the mucosal surface. This form has usually been found in severely immunocompromised hosts with hematologic malignancies [14, 15, 37, 45]. It is important, however, to be aware that the morphological appearance of airway aspergillosis may easily change and that different forms of Aspergillus-related invasive airway involvement may coexist. Kramer et al. hypothesized that these three forms represent a progressive evolution of the disease ranging from mild bronchitis to widespread pseudomembranous diffuse disease [14]. Many publications seem to confirm this point of view. Thus, it should be stressed that although this classification will be further used to present different aspects of ITBA, it has rather an educational than true clinical value.

A novel classification of isolated ITBA has recently been proposed by Wu et al. According to bronchoscopic findings, the authors recognized four types of invasive airway aspergillosis: type I: superficial infiltration, type II: full-layer involvement, type III: occlusive, and type IV: mixed [46]. Although at first glance this classification significantly differs from that presented by Kramer et al., both classifications have much in common. They both classify several disease stages from relatively mild to severe and more complex forms. As reliability of visual bronchoscopic assessment of the depth of bronchial wall involvement may be questionable, descriptive terms used by Kramer et al. seem more justified [14, 46].

Keeping in mind three different forms of invasive or potentially invasive Aspergillus airway disease, an approach basing on specific conditions predisposing to tracheobronchial infections rather than on the macroscopic and/or pathologic appearance might be of more use for a clinician. This is justified not only by the fact that specific groups of high-risk patients are usually treated by different specialists, but also by the fact that the same form of Aspergillus airway involvement may have a different clinical course and prognosis, highly dependent on a variety of host factors. Therefore, invasive or potentially invasive Aspergillus airway diseases will be further presented in three main groups of patients: (1) lung transplant recipients, (2) highly immunocompromised patients with hematologic malignancies and/or patients undergoing hematopoietic stem cell transplantation, and (3) the remaining, less severely immunocompromised patients, or even immunocompetent subjects.

2.3.1. Aspergillus Tracheobronchitis in Patients after Lung Transplantation

Lung transplant recipients are a unique subset of patients which are particularly susceptible to Aspergillus bronchial invasion. This is a consequence of continuous exposure of the transplanted organ to environmental pathogens and, simultaneously, the use of aggressive immunosuppressive therapy [47, 48]. In a group of 121 patients with endobronchial aspergillosis identified by the literature review, 80 (66%) were lung transplant recipients [12].

In 2000, Nathan et al. reported a relatively high incidence of Aspergillus-related endobronchial abnormalities in lung transplant recipients. These authors found endobronchial involvement in 7 out of 38 patients (18.4%), and, at least in 4 of these patients, bronchial wall invasion was demonstrated [49]. One year later, Mehrad et al. presented the retrospective analysis of the large series of 133 patients and reviewed the literature on Aspergillus infections in lung transplant recipients. The incidence of isolated Aspergillus tracheobronchitis was 5% in the authors’ series and 4% in pooled published data [47]. The incidence of Aspergillus tracheobronchitis was only slightly lower than the incidence of IPA (5% versus 8% and 4% versus 5% in Mehrad et al. and pooled published data, resp.).

Virtually the same results were presented in a Spanish study (6% and 8% of Aspergillus tracheobronchitis and IPA, resp.) [48]. Interestingly, the review of 40 papers, which reported 159 lung transplant recipients who developed Aspergillus infections, showed that tracheobronchitis was the most common form of Aspergillus infection responsible for 37% of cases. IPA, Aspergillus infections of bronchial Anastomosis and disseminated aspergillosis, accounted for 32%, 20%, and 10% of cases, respectively [50].

It seems that, in certain patients, the risk of postoperative ITBA development depends on preoperative airway colonization by Aspergillus. This was shown by Helmi et al. in patients with cystic fibrosis (CF). ITBA developed only in patients with persistent preoperative airway colonization with A. fumigatus
while none of the patients who had not been colonized prior to surgery developed any form of invasive aspergillosis [51]. The authors noted that antifungal prophylaxis did not prevent the development of ITBA, and amphotericin B therapy (with or without endobronchial debridement of necrotic tissue) was required to clear the infection in all patients [51]. A recent study revealed that despite voriconazole prophylaxis, the risk of posttransplant fungal infection in recipients with features of the mold infection in the explanted lung was significantly higher than in patients without mold infection, 43 and 14%, respectively [52]. Results of other studies do not, however, confirm the relationship between pre-transplant Aspergillus airway colonization and the risk of posttransplant colonization and/or Aspergillus infection [53, 54].

The incidence of isolated Aspergillus tracheobronchitis is highest in the first year after transplantation, with virtually all cases diagnosed within the first three-to-six months after transplantation [47, 48, 51]. According to the review by Singh and Husain, the median time from transplantation to diagnosis of Aspergillus tracheobronchitis and/or bronchial anastomotic infection was 2.7 months [50].

All patients with Aspergillus tracheobronchitis seen by Mehrad et al. were asymptomatic, while in other series, the clinical presentation, as well as endoscopic appearance of the isolated tracheobronchitis was variable. One of the reviews showed that none of 13 patients who developed Aspergillus tracheobronchitis and/or bronchial anastomotic infection had fever [50]. Monitoring of the serum Aspergillus galactomannan (GM) level plays no role in the diagnosis of IPA and ITBA in lung transplant recipients. One study showed positive results of the test in only 28.5% of patients with IPA and in none of four patients with ITBA (sensitivity 0%) [55]. Another paper from the same group of authors demonstrated that albeit overall diagnostic sensitivity of GM measurement in BALF was higher (60%), the level of GM in the sole patient with ITBA was below the cut-off value [56], hence, the important role of surveillance bronchoscopy in early diagnosis of isolated Aspergillus tracheobronchitis [47].

The vast majority of Aspergillus-related tracheobronchial lesions in patients who underwent lung transplantation occurred in the transplanted lung and involved the anastomosis line [47–50]. Aspergillus fumigatus was responsible for almost 90% of all tracheobronchial infections [50]. The bronchoscopic appearance of the airway lesions included pseudomembrane formation, bronchial stenosis in the anastomosis line, ulcerations, and black eschar [47–49]. Severe complications may develop including a nontraumatic disruption of the anterolateral, fibrocartilaginous tracheal wall, as reported by Aerni et al. [57]. The probable pathophysiologic basis for this complication was fungal invasion of the blood vessels resulting in a critical compromise of local blood supply [57].

Prognosis for lung transplant patients with Aspergillus tracheobronchitis is favorable as compared to IPA and disseminated infections. Mortality rate calculated from 40 studies was 23.7% in patients with Aspergillus tracheobronchitis and/or anastomotic infection versus 81.8% and 50% in patients with IPA and disseminated infections, respectively [50]. In the series presented by Sole et al., Aspergillus tracheobronchitis resulted in a 14% mortality rate as compared to 78% in IPA [48]. All six patients treated by Mehrad et al. survived, and pooled data from all series analyzed by these authors showed the mortality rate 18% [47].

The most common therapeutic option for lung transplant recipients with Aspergillus tracheobronchitis was oral itraconazole or intravenous amphotericin B. Some centers used aerosolized amphotericin B as adjunctive treatment. A substantial number of patients required additional local treatment including bronchoscopic debridement, balloon dilatation, laser treatment, and/or stent placement [47–49]. It should be noted, that none of the patients progressed to invasive pneumonia [47].

Prophylactic administration of the antifungal agents has been shown to decrease the incidence of invasive fungal infection after lung transplantation. However, there is no uniformly accepted strategy, and different drugs are used in lung transplant centers throughout the world [58, 59]. They include nebulized amphotericin B, oral voriconazole, or itraconazole, alone or in combinations [59, 60]. Since the use of aerosolized medications may significantly reduce their toxic systemic effects and potential drug interactions, they are an attractive option [61]. This especially regards liposomal and lipid complex forms of amphotericin B which can be administered three times a week or even once a week, respectively [62, 63].
2.3.2. Aspergillus Tracheobronchitis in Immunocompromised Patients with Hematological Malignancies

Although Aspergillus airway infection may complicate the course of different malignant diseases, the highest risk affects severely immunocompromised patients with hematological malignancies. In one of the early reports, 6 out of 9 patients with fungal tracheobronchitis had underlying malignant diseases and in 3 of them different leukemias were diagnosed [64]. In the later review reporting 20 cases of pseudomembranous ITBA, an underlying malignant disease of the hematopoietic system was found in 13 (65%) patients [45]. The proportion of lung versus airway involvement in patients with hematological malignancies is significantly different than that in previously discussed patients undergoing lung transplantation; IPA is responsible for 80–90% of Aspergillus infections, while tracheobronchial aspergillosis is much less common. It is estimated that approximately 10% of patients with invasive aspergillosis may present relevant signs of tracheobronchial invasion, either alone or with pulmonary parenchyma involvement [6].

All the three forms of ITBA listed in the classification by Kramer et al. (Table 2) can probably develop in patients with hematological malignancies. However, a significant predominance of the ulcerative and pseudomembranous forms was found in reports published up to date. If the supposition that the three forms of Aspergillus tracheobronchitis represent a progressive spectrum of fungal invasion is true, the predominance of more invasive forms in patients with severe immunosuppression can be easily understood. This is also consistent with observations that the course of Aspergillus airway infection in these patients is severe, and the prognosis is significantly worse than in patients after lung transplantation.

Some less common forms of invasive airway aspergillosis have also been reported in patients with hematological malignancies. In a severely immunocompromised patient with the graft versus host disease (GvHD) which developed after allogeneic bone marrow transplantation due to low-grade non-Hodgkin lymphoma, Irani et al. found multiple white papular lesions of the tracheal mucosa and plaque-like vascularized changes. Pathological examination of the biopsy specimen confirmed invasion with numerous fungal hyphae consistent with ITBA [39]. Multiple, small, 3 to 5 mm in diameter nodules in both main stem and lobar bronchi were the dominating picture in a patient with ITBA and acute lymphoblastic leukemia (ALL) treated by Sancho et al. [65]. It should also be realized that in many patients with ITBA the endobronchial appearance might not be uniform and include different lesions, even in the context of the same form of Aspergillus tracheobronchitis. For example, ulcerative lesions may be less obvious when covered by fibrin, as compared to uncovered ulcers (Figure 2(a) and 2(b)).
Moreover, features of different forms of *Aspergillus* tracheobronchitis can be found in the same patient. We observed large ulcerative lesions, being the most relevant feature of fungal invasion in both main stem bronchi, coexisting with extensive pseudomembranous bronchitis seen in the peripheral bronchi [66]. The coexistence of different forms of *Aspergillus* tracheobronchitis has also been demonstrated by other authors. Arriero et al. found simultaneous obstructive and pseudomembranous necrotizing tracheobronchitis due to *Aspergillus flavus* in a diabetic patient with ALL [67]. Buchheidt et al. reported a patient with Hodgkin lymphoma and pseudomembranous form of tracheobronchial aspergillosis in whom patchy ulcerations were also found in the trachea and bronchi [68]. Van Assen et al. described “yellowish plaques, ulcerations and pseudomembranes” seen during bronchoscopy in a patient who underwent hematopoietic stem cell transplantation (HSCT) due to acute myeloid leukemia (AML) and who subsequently developed *Aspergillus* tracheobronchitis [69]. It is of note that many of the invasive *Aspergillus* tracheobronchial infections affected patients treated with HSCT who subsequently developed GvHD requiring further, intensive immunosuppressive therapy [39, 69–71].

Unlike *Aspergillus* tracheobronchitis in lung transplant recipients, ITBA in patients with hematological malignancies is usually symptomatic. Dyspnea, inspiratory wheezes, fever, and nonproductive cough belong to the most commonly reported symptoms [66, 68–70]. Airway obstruction may result in atelectasis and severe respiratory failure [72]. It should be emphasized that, in patients with isolated tracheobronchitis, the chest radiograph and CT scan may not reveal pulmonary lesions [36, 67, 69, 70]. Different features and extent of pulmonary involvement, from small parenchymal or peribronchial infiltrations to larger areas of consolidation and nodules, can be seen in patients with simultaneous lung involvement [38, 39, 65, 66]. In some patients, CT scanning, positron emission tomography-CT scanning, and endobronchial ultrasonography (EBUS) can demonstrate bronchial wall involvement with bronchial lumen narrowing [38, 71]. Bronchoscopy plays a crucial role in endobronchial disease assessment and specimen collection for microbiological and pathological evaluations. However, due to *Aspergillus* capability to invade blood vessels, bronchial biopsies may carry the additional risk of bleeding, particularly that many patients have a low platelet count [73]. Fatal hemorrhage was reported when attempts have been undertaken to remove obstructing pseudomembranes [74]. Recently, Casal et al. have shown that EBUS-guided transbronchial needle aspiration biopsy (EBUS-TBNA) can help to obtain adequate tissue specimens in patients in whom the results of endobronchial specimen evaluation were inconclusive [71].

The value of other methods in diagnosing ITBA, including the serum level of circulating GM, is uncertain. The serum concentration of GM was elevated in the patient described by Machida et al. [70] but remained low in a series of 6 serum samples in a patient treated by Van Assen et al. [69]. In the small series of patients with pseudomembranous *Aspergillus* tracheobronchitis reported by Tasci et al., one patient had elevated level of serum *Aspergillus* antigen, while borderline and negative results were found in two other patients, respectively [45]. Low serum *Aspergillus* antigen level in a heart transplant recipient with pseudomembranous *Aspergillus* tracheobronchitis has been recently reported by Ramos et al. [75]. To explain these differences, Van Assen et al. presented two hypotheses. The first assumes that in some patients the fungal invasion is limited to the superficial layer of the airway mucosa and, thus, is not sufficient to cause the spread of *Aspergillus* antigens into the circulating blood. The alternative explanation points out a false negative ELISA reactivity as a cause of low serum GM level [69].

There are some data that BALF, or maybe even bronchial washing, might be a more accurate diagnostic material in patients with ITBA as compared to peripheral blood. In one of our patients, we found a negative result of serum *Aspergillus* GM measurement while the bronchoalveolar lavage fluid (BALF) examination gave a positive result. Also De Rosa et al. showed that BALF GM concentrations in a diabetic patient with pseudomembranous *Aspergillus* tracheobronchitis significantly exceeded GM concentrations in serum [76].

In earlier reports, amphotericin B was invariably used to treat patients with invasive *Aspergillus* tracheobronchitis (Table 3). In the recent years, combined treatment including amphotericin B plus caspofungin or amphotericin B plus voriconazole as well as monotherapy with voriconazole has been the predominant therapeutic options. This is consistent with the latest Infectious Diseases Society of America...
TABLE 3: Characteristics of 19 patients with ITBA and hematological malignancies reported between 1996 and 2010.

<table>
<thead>
<tr>
<th>Author, publication’s year [ref]</th>
<th>Patient’s sex and age (years)</th>
<th>Underlying conditions</th>
<th>WBC ($\times 10^9$/L)</th>
<th>PMN ($\times 10^9$/L)</th>
<th>Classification</th>
<th>Species</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuo et al. 1996 [91]</td>
<td>M, 44</td>
<td>Peripheral T-cell lymphoma, CHTH</td>
<td>0.7</td>
<td>0.3</td>
<td>Ulcerative and plaque-like tracheobronchitis</td>
<td>Aspergillus fumigatus</td>
<td>Amphotericin B followed by itraconazole</td>
<td>Survived</td>
<td>Disseminated aspergillosis, massive hemoptysis</td>
</tr>
<tr>
<td>Sancho et al. 1997 [65]</td>
<td>M, 43</td>
<td>Acute lymphoblastic leukemia, CHTH</td>
<td>3.2</td>
<td>1.6</td>
<td>Multiple white nodules, inflammatory bronchial stenosis</td>
<td>Aspergillus sp.</td>
<td>Amphotericin B</td>
<td>Died</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>Arriero et al. 1998 [67]</td>
<td>F, 64</td>
<td>Acute lymphoblastic leukemia, CHTH, diabetes</td>
<td>7.0</td>
<td>4.7</td>
<td>Pseudomembranous and obstructing tracheobronchitis</td>
<td>Aspergillus flavus</td>
<td>Amphotericin B</td>
<td>Died</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>Machida et al. 1999 [70]</td>
<td>F, 44</td>
<td>Chronic myelogenous leukemia</td>
<td>NA</td>
<td>5.0</td>
<td>Necrotic pseudomembranes</td>
<td>NA</td>
<td>Amphotericin B</td>
<td>Died</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>Ahn et al. 2000 [38]</td>
<td>M, 56</td>
<td>Acute myeloid leukemia, CHTH</td>
<td>0.3</td>
<td>NA</td>
<td>Pseudomembranous tracheobronchitis</td>
<td>Aspergillus sp.</td>
<td>Amphotericin B</td>
<td>Died</td>
<td>Massive hemoptysis</td>
</tr>
<tr>
<td>Tasci et al. 2000 [92]</td>
<td>F, 54</td>
<td>Plasma cell myeloma, CHTH, autologous HSCT</td>
<td>NA</td>
<td>0.1</td>
<td>Multiple white plaques, pseudomembranes, mucous plugs</td>
<td>Aspergillus fumigatus</td>
<td>Amphotericin B</td>
<td>Died</td>
<td>Sepsis, respiratory failure</td>
</tr>
<tr>
<td>Author, publication’s year [ref]</td>
<td>Patient’s sex and age (years)</td>
<td>Underlying conditions</td>
<td>WBC ($\times 10^9$/L)</td>
<td>PMN ($\times 10^9$/L)</td>
<td>Classification</td>
<td>Species</td>
<td>Treatment</td>
<td>Outcome</td>
<td>Cause of death</td>
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<tr>
<td>Routsi et al. 2004 [72]</td>
<td>F, 22</td>
<td>Lymphom, CHTH</td>
<td>0.21</td>
<td>NA</td>
<td>Pseudomembranes, bronchial obstruction</td>
<td>Aspergillus terreus</td>
<td>Liposomal amphotericin B plus voriconazole</td>
<td>Died</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>Tasci et al. 2006 [45]</td>
<td>M, 58</td>
<td>Plasma cell myeloma, CHTH</td>
<td>NA</td>
<td>0.4</td>
<td>Multiple circumscribed lesions, pseudomembranes</td>
<td>Aspergillus fumigatus</td>
<td>Liposomal amphotericin B</td>
<td>Died</td>
<td>Septic shock</td>
</tr>
<tr>
<td>F, 64</td>
<td>Burkitts’ lymphoma, CHTH</td>
<td>Pancytopenia</td>
<td>NA</td>
<td>NA</td>
<td>Pseudomembranes</td>
<td>Aspergillus fumigatus</td>
<td>Amphotericin B plus caspofungin</td>
<td>Died</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>M, 34</td>
<td>Burkitts’ lymphoma, CHTH</td>
<td>NA</td>
<td>NA</td>
<td>Pseudomembranes</td>
<td>Aspergillus fumigatus</td>
<td>Amphotericin B plus caspofungin</td>
<td>Died</td>
<td>Initial improvement in ITBA but lymphoma progression, fatal intracranial bleeding</td>
<td></td>
</tr>
<tr>
<td>Author, publication’s year [ref]</td>
<td>Patient’s sex and age (years)</td>
<td>Underlying conditions</td>
<td>WBC ($\times 10^9$/L)</td>
<td>PMN ($\times 10^9$/L)</td>
<td>Classification</td>
<td>Species</td>
<td>Treatment</td>
<td>Outcome</td>
<td>Cause of death</td>
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</tr>
<tr>
<td>Casal et al. 2009 [71]</td>
<td>M, 65</td>
<td>Chronic lymphocytic leukemia, allogeneic HSCT,</td>
<td>NA</td>
<td>4.0</td>
<td>Bronchial narrowing with necrotic and friable mucosa</td>
<td>NA</td>
<td>Liposomal amphotericin B plus posaconazole</td>
<td>Survived</td>
<td>Respiratory failure, pulmonary embolism</td>
</tr>
<tr>
<td>Krenke et al. 2009 [66]</td>
<td>M, 63</td>
<td>Acute myeloid leukemia, CHTH</td>
<td>0.5</td>
<td>&lt;0.1</td>
<td>Ulcerative lesions and pseudomembranes</td>
<td>Aspergillus sp.</td>
<td>Voriconazole</td>
<td>Died</td>
<td>Respiratory failure, pulmonary embolism</td>
</tr>
</tbody>
</table>

CHTH: antineoplastic chemotherapy, HSCT: hematopoietic stem cell transplantation, GvHD: graft versus host disease, $\rightarrow$ change of the treatment regimen.
guidelines which recommend voriconazole for primary treatment of invasive *Aspergillus* tracheobronchitis [77]. Alternative treatments include liposomal or lipid complex form of amphotericin B, caspofungin, micafungin, posaconazole, and itraconazole [77]. Due to poor penetration of antifungal agents into the fungal masses, bronchoscopic removal of pseudomembranes and mycelial masses seems a reasonable component of treatment, but this might be associated with significant risk of severe bleeding [74].

The prognosis in severely immunocompromised patients with hematological malignances and ITBA is significantly worse than in lung transplant recipients. None of the three patients with hematological malignances reported by Tasci et al. survived [45]. Searching through the papers published in the last 15 years, we found 17 reports presenting the outcome in 19 patients with ITBA and hematological malignances. The data from these papers are summarized in Table 3. The mortality rate related to *Aspergillus* infection was as high as 72.2% (only four patients survived). Buchheidt et al., who successfully treated one patient with Hodgkin disease and pseudomembranous *Aspergillus* tracheobronchitis, stress that the key factors which warrant a favorable outcome are an early diagnosis involving bronchoscopy with culture and pathology as well as an adequate antifungal therapy [68]. Although 12 out of 19 patients with isolated *Aspergillus* tracheobronchitis complicating various malignant and nonmalignant diseases reported by Wu et al. survived, the only patient with underlying hematological malignancy (non-Hodgkin lymphoma) died of cerebral dissemination of aspergillosis [46].

Thus, we believe that the prognosis in patients with ITBA depends more on the underlying condition than on the form of *Aspergillus* airway involvement which, to a large extent, is a consequence of the immune status of the infected host. This seems to be confirmed by the comparison of prognosis in lung transplant recipients and patients with hematological malignances (see above). Assuming that the diagnosis of diverse forms of ITBA is based on the macroscopic appearance of endobronchial lesions, we cannot share the opinion of Tasci et al., that the term “ulcerative *Aspergillus* tracheobronchitis” should be reserved for patients with limited involvement of the tracheobronchial tree and that this entity is invariably associated with favorable prognosis [45]. In patients, reported by Van Assen et al. and by Krenke et al., ulcerative lesions were the important features of airway involvement and both patients died because of invasive fungal infection [66, 69]. Hence, there are probably at least two different subforms of ulcerative tracheobronchitis significantly differing in prognosis: one seen around the suture line in lung transplant recipients (reported to have a relatively favorable outcome) and the second which affects severely immunocompromised patients (e.g., HSCT recipients, patients with hematologic malignancies treated with highly cytotoxic regimens) and frequently coexists with the pseudomembranous form of tracheobronchitis. The prognosis in the second group of patients is poor and similar to that in pseudomembranous *Aspergillus* tracheobronchitis. Severe bleeding and respiratory failure are common complications responsible for a high mortality rate in these forms of airway invasive aspergillosis [38, 65, 69].

### 2.3.3. *Aspergillus* Tracheobronchitis in AIDS Patients

An overall incidence of *Aspergillus* infections in HIV-infected subjects ranges between 0 and 12% [16, 28, 78]. Invasive aspergillosis usually affects patients with advanced AIDS. Neutropenia, an impaired neutrophil and monocyte-derived macrophage function, and/or corticosteroid therapy are important factors contributing to disease development [16, 79, 80].

The majority of the reports on tracheobronchial aspergillosis in this patients group come from the 80`s and the 90`s of the XX century [27, 37, 79, 81]. In the review of 342 patients with AIDS and pulmonary aspergillosis, Myelonakis et al. identified 23 (7%) cases in which infection mainly involved large airways [82]. ITBA was diagnosed in 3 out of 93 AIDS patients (3.2%) with definite IPA [82]. Besides obstructing *Aspergillus* tracheobronchitis representing saprophytic *Aspergillus* airways involvement, different invasive forms of tracheobronchial aspergillosis have been reported. They include ulcerative or plaque-like and pseudomembranous (necrotizing) *Aspergillus* tracheobronchitis [37, 79]. Some of the reported cases are difficult to classify due to incomplete bronchoscopic and pathologic data [81].
Patients with AIDS and ITBA are usually symptomatic, with cough, dyspnea, and fever being the most commonly reported symptoms [37, 79, 81]. Physical examination may reveal wheezes. In a series of four patients reported by Kemper et al., chest radiograph was abnormal in two patients showing patchy multinodular or interstitial infiltrates [37]. Similarly, bilateral alveolar infiltrates were revealed in patient treated by Conte et al., while, in a patient reported by Pervez et al., the chest radiograph was normal [79, 81]. Contrary to variable and nonspecific results of radiographic examination, bronchoscopy with pathology and culture of bronchial specimens plays a key role in diagnosis [37, 83]. The endobronchial appearance of invasive aspergillosis may include erythematous or edematous mucosa, ulcers, white or grayish lesions forming plaques, or pseudomembranes or linings covering bronchial mucosa, causing even airway occlusion [37, 79, 81, 83].

Due to limiter number of reports, the assessment of the prognosis and optimal therapeutic strategy is not easy. Three of the four patients seen by Kemper et al. were treated with intravenous amphotericin B followed by oral itraconazole, and one patient received itraconazole followed by intravenous amphotericin B. One patient was lost to follow up and one patient died of disseminated aspergillosis shortly after the diagnosis. In two other patients, initial clinical response was noted but both patients died between 6 and 12 months after disease onset. The true role of the Aspergillus infection in the fatal outcome of these two patient is equivocal [37]. An initial response has also been noted in a patient treated with oral itraconazole, flucytosine, and nebulized amphotericin B [81].

2.3.4. *Aspergillus* Tracheobronchitis in Other Groups of Patients

Invasive tracheobronchial aspergillosis has also been reported in other groups of patients. Several cases of *Aspergillus* tracheobronchitis in immunocompetent and previously healthy subjects were reported [42, 46, 84–86]. However, in the majority of other publications, different underlying conditions in patients who developed ITBA were diagnosed. They include various malignant diseases, and for example, thymoma, breast, lung, esophageal and renal carcinomas and chronic diseases, for example, diabetes mellitus, chronic obstructive pulmonary disease, solid organ transplantation other than lung, and posttuberculous tracheal stenosis [40, 41, 46, 75, 76, 87–89].

In this heterogeneous group of patients, the spectrum of ITBA-related symptoms can be very wide and range from chronic dry cough and decreased appetite to high fever, severe respiratory distress, and rapid development of respiratory and multiorgan failure [85, 86, 90].

Bronchoscopic appearance did not significantly differ from that found in other patients groups although the extent of endobronchial changes might be limited [84, 88]. Pseudomembranous form of ITBA was reported in the majority of patients. [40, 41, 75, 84, 85, 87, 88]. Serum GM concentration was measured in a patient who had undergone heart transplantation complicated by pseudomembranous *Aspergillus* tracheobronchitis, but the level was low and, hence, not diagnostically useful [75]. On the other hand, strongly positive results of *Aspergillus* antigen testing in serum were observed in an immunocompetent patient in whom both tracheobronchial and pulmonary invasive *Aspergillus* diseases were diagnosed [90].

Intravenous itraconazole with or without nebulized amphotericin B and bronchoscopic debridement was most commonly applied initial therapy in patients treated by Wu et al. [46]. Alternatively, some patients received liposomal amphotericin B, nebulized amphotericin B, or voriconazole [46]. The mean treatment duration was 25 (range 8 to 47) days. In the several case reports, different treatment modalities were relatively equally distributed and included amphotericin B, voriconazole or itraconazole [40, 75, 85–88].

The prognosis seems to be largely dependent on the underlying disease. In the series presented by Wu et al., all five patients who had no or had nonmalignant underlying diseases survived. Conversely, 6/13 (46%) of patients with a malignant underlying disease died [46]. In four of them, the cause of death was directly related to *Aspergillus* infection. A relatively good prognosis in patients with ITBA and nonmalignant underlying disease was also found in other publications. Only one of the five reported patients died (mortality rate 20%) [40, 41, 75, 87]. Considering patients with *Aspergillus* tracheobronchitis and no underlying diseases, two of the three patients survived, but one, a 44-year-old man treated by Oh et al., died due to refractory septic shock and hypoxemia [84–86].
3. SUMMARY

Although tracheobronchial Aspergillus infections are relatively rare, they include a wide spectrum of different entities. Host-fungus relationship plays a key role in the development of these diseases. Thus, conditions affecting host organism and predisposing to tracheobronchial infections are critical in predicting the form, clinical course of the disease, and prognosis. The most serious, invasive tracheobronchial diseases affect patients with profound impairment of the antifungal defense, namely, patients with hematologic malignancies and/or patients undergoing hematopoietic stem cell transplantation. The prognosis in these subjects is generally poor, with mortality rate up to 70%. Key factors which may warrant a favorable outcome are an early diagnosis in adequate antifungal therapy. Bronchoscopy plays the most important role in endobronchial disease assessment and enables specimen collection for microbiological and pathological evaluation.

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REFERENCES


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