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The emergence of *Aspergillus* species in chronic respiratory disease

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1. ABSTRACT

Chronic lung disease is recognized as an important risk factor for developing pulmonary aspergillosis. The development of specific aspergillus-associated syndromes depends on host immunity and underlying lung disease. In the setting of asthma, hypersensitivity to *Aspergillus* can lead to allergic bronchopulmonary aspergillosis (ABPA) or severe asthma with fungal sensitization (SAFS). Chronic use of systemic or inhaled corticosteroids coupled with recurrent antibiotic use for exacerbations prevalent in chronic obstructive pulmonary disease (COPD) predisposes to chronic pulmonary aspergillosis (CPA). Prior pulmonary tuberculosis is a risk factor for CPA, a syndrome with a wide range of presentations including a simple aspergilloma, chronic cavities, necrosis or fibrosis. Accumulating evidence suggests that the presence of or colonization by *Aspergillus* in the setting of chronic lung disease can worsen clinical course and outcomes even in the absence of overt pulmonary aspergillosis. We propose that understanding the complex interplay between host and fungi may provide key insights into the pathogenesis of *Aspergillus*-associated pulmonary syndromes in the setting of chronic lung disease, and provide novel therapeutic approaches to improve its identification and management.

2. INTRODUCTION

A historical case series published in 1968 surveyed 107 consecutive patients attending hospital with various chronic chest diseases including asthma, bronchiectasis, emphysema, chronic bronchitis, and cavitatory lung disease. It found that precipitins to *Aspergillus* spp. were common, with approximately 10% of patients having confirmed pulmonary aspergillosis (1). Today, over four decades later chronic lung disease is clearly becoming an increasingly important predisposing factor for the development of pulmonary aspergillosis. This is in addition to established risks from malignancies and solid organ transplantation. There clearly is a growing number affected with structural lung disease or dysfunctional immune states. These are associated with either the chronic inflammatory respiratory disease itself or as a consequence of their management conferring higher risks for pulmonary aspergillosis. In fact, *Aspergillus* has now overtaken *Candida* as the chief cause of fungal disease (2).

Here we review the specific pulmonary aspergillosis syndromes occurring in asthma, COPD, bronchiectasis, cystic fibrosis (CF) and pulmonary tuberculosis. We also present evidence of the ability of *Aspergillus* to influence the clinical course and outcomes of patients with chronic respiratory disease. We propose that understanding and recognizing the role of the pulmonary mycobiome is crucial for developing new therapeutic strategies to counter the growing threat of *Aspergillus* in chronic respiratory disease states.

3. *ASPERGILLUS* SPP. AND PULMONARY ASPERGILLOSIS SYNDROMES

Aspergillus species are ubiquitous molds commonly found in soil and decaying organic matter. Also

widely disseminated in the atmosphere as spores, each of us regularly inhales thousands of spores daily that are able to access even the most distal airways owing to their size and durability. There are over 180 species of *Aspergillus* described with *A. fumigatus*, *A. flavus* and *A. niger* representing the most common implicated in human disease.

Aspergillus spp. cause a wide spectrum of pulmonary disease in the human host, which in turn depends on the state of the underlying host immune system, virulence of the infecting organism and degree of chronic lung disease (3, 4). *Aspergillus* virulence is multifactorial and under polygenetic control. Strategies used by the fungi are multi-faceted and include fungal structure, capacity for growth, adaptation to stressful conditions, the ability to damage host cells and evade immune-recognition, all features that can be exploited as either diagnostic or therapeutic targets (5-9). In individuals with normal immunity and no chronic lung disease, inhaled conidia are usually cleared by anatomical barriers, functional macrophages and neutrophils (7, 10), and as such do not lead to clinically significant sequelae. However, in immunocompetent or mildly immunosuppressed individuals where there is underlying structural lung disease such as cavitation, disease may manifest as a simple aspergilloma or fungal ball sequestered within the cavity. This is usually without evidence of tissue invasion. In patients with ongoing mild immunosuppression for instance from chronic corticosteroid usage; a more indolent focal form of disease known as chronic pulmonary aspergillosis can occur. This can be challenging to identify particularly in the setting of severe and destructive chronic respiratory disease observed in post tuberculosis states or severe bronchiectasis. In severely immunocompromised patients, such as those with hematological cancers or organ/stem cell transplant recipients, *Aspergillus* may cause invasive pulmonary aspergillosis, with germination of the conidia into hyphae that subsequently invade into the lung parenchyma and associated vasculature resulting in systemic spread. This carries very high mortality and remains difficult to diagnose especially in its earliest stage. Paradoxically, immune hypersensitivity to *Aspergillus* can also lead to pathology such as ABPA, which is characterized by uncontrolled airway inflammation and bronchospasm, which if left unrecognized and treated will lead to bronchiectasis and pulmonary fibrosis placing patients at further risk of other *Aspergillus*-associated syndromes.

4. *ASPERGILLUS* SPP. AND CHRONIC RESPIRATORY DISEASE

The manifestations of *Aspergillus*-associated disease differs between the various chronic respiratory disease states however certain forms may be predominant in particular disease. It is however important to note that any patient at any time may exhibit any of the described *Aspergillus*-associated syndromes that is largely dictated by the underlying state of host immunity (Figure 1). Therefore, *Aspergillus*-associated disease exists along a spectrum of structural and functional pulmonary derangements, a single patient therefore can evolve over time from one *Aspergillus*-associated disease to another, or simultaneously exhibit several diseases making the identification of such clinical states particularly in the context of chronic lung disease diagnostically challenging. The host's underlying immune state, while dictating the form of *Aspergillus*-associated disease is often additionally influenced by the specific milieu of immune suppression or hypersensitivity, structural lung or airway changes, and sequelae of treatment for the underlying chronic respiratory disease. Further, in the absence of overt pulmonary aspergillosis, even simple colonization or sensitization to *Aspergillus* can worsen the underlying respiratory disease particularly in terms of pulmonary outcomes such as lung function and exacerbations.

4.1. *Aspergillus* and asthma

Asthma is a chronic inflammatory airways disease with variable airflow obstruction. There is an association between *Aspergillus* and asthma development and, *Aspergillus* can also influence the clinical asthma phenotype. A large case control study conducted in Finland found that exposure to *Aspergillus* and the presence of IgE antibodies to *Aspergillus* increases the risk of adult-onset asthma (11). In addition, *Aspergillus* has been implicated in the development of unique asthma phenotypes (12). One clear example of the link between asthma and *Aspergillus* spp. is ABPA, a recognized phenotype of asthma induced by a type 1 IgE mediated hypersensitivity to *Aspergillus*, most commonly but not exclusive to *A. fumigatus* (13).

Currently, the diagnostic criteria for ABPA includes the presence of asthma, skin prick test sensitivity to *Aspergillus*, total IgE > 416 IU/ml, increased *Aspergillus*-specific IgE or IgG and radiographic infiltrates (14). Additional criteria include peripheral blood eosinophilia, *Aspergillus* serum precipitating antibodies, central bronchiectasis or *Aspergillus*-containing mucous plugs (Figure 2). ABPA tends to present as severe refractory asthma, and its treatment requires prolonged systemic steroids, with potential utility of antifungal agents (15). Itraconazole has been shown in several studies, including randomized control trials, to lead to improvements in disease outcomes including serology (decreased *Aspergillus fumigatus* IgE and IgG levels), improved lung function, reduction in steroid dose and exacerbations (16). Voriconazole and posaconazole have also been demonstrated in retrospective studies to be effective alternate treatments for ABPA (17). Other potential alternative therapeutic approaches have also been examined for instance use of the monoclonal antibody against IgE (Omalizumab) and nebulized

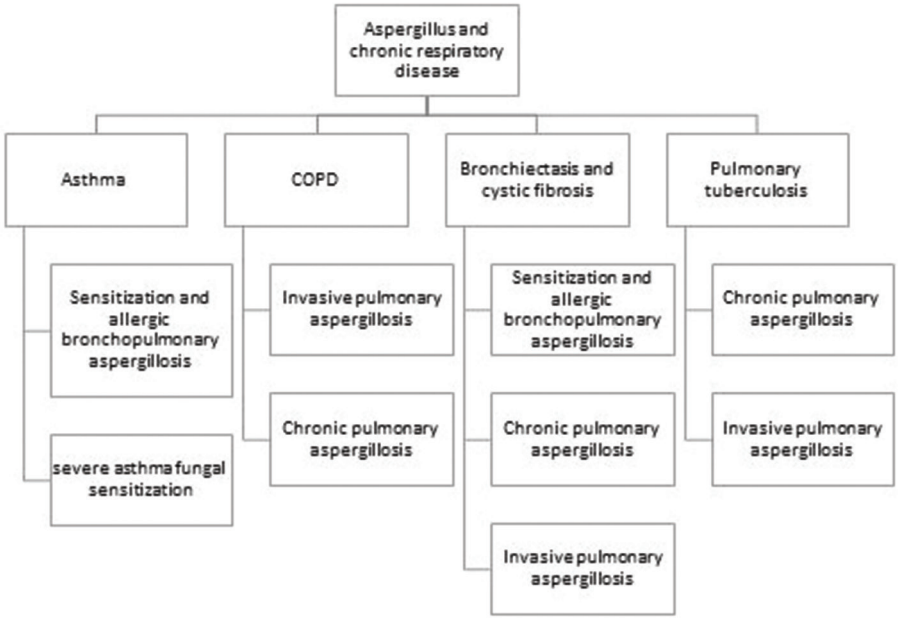

Figure 1. Association between *Aspergillus*-associated disease states in the setting of various chronic pulmonary diseases.

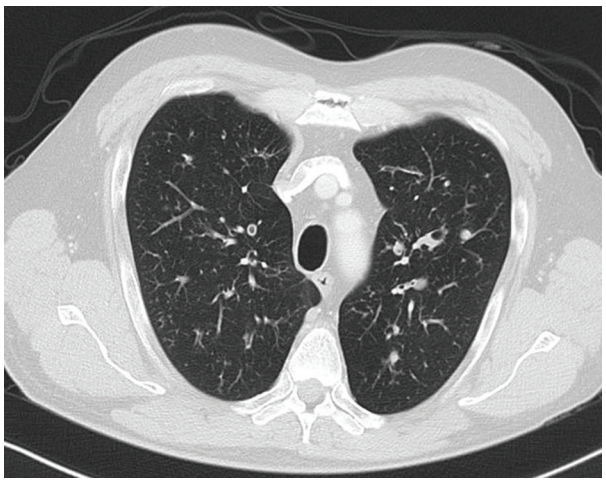

Figure 2. Computed tomography scan of an asthmatic patient with allergic bronchopulmonary aspergillosis (ABPA) showing central bronchiectasis, mucus plugging, bronchial wall thickening and tree-in-bud appearance.

amphotericin B. Both have illustrated efficacy in ABPA in small proof-of-concept studies, but the need for a large, prospective randomized controlled trial to confirm efficacy persists (18, 19). Importantly, treatment of ABPA with long-term prolonged oral corticosteroids places patients at risk of immunosuppression and thus chronic aspergillosis syndromes, a real but unintended side effect of optimal ABPA therapy hence the importance of considering steroid sparing approaches.

In addition to ABPA, *Aspergillus* can have other wide-ranging more subtle effects on the asthma phenotype. For example, some asthma patients have evidence of *Aspergillus* hypersensitivity but do not meet diagnostic criteria for ABPA. They have been described as Severe Asthma with Fungal Sensitization (SAFS) (20). In multiple studies, the prevalence of sensitization to *Aspergillus*, either assessed by skin prick testing or specific IgEs is been estimated to be as high as 28%-45% (21, 22). Sensitivity to *Aspergillus* even in the absence of clinical ABPA is associated with poorer asthma outcomes including severe exacerbations requiring hospitalization (22), intensive care unit admissions (23), lower FEV_1 (24) and fixed airway obstruction (25).

Improvement of asthma in cases of SAFS can be achieved with antifungal usage. The Fungal Asthma Sensitization Trial (FAST) randomized patients with severe asthma to Itraconazole or placebo and demonstrated improvements in symptoms and IgE levels at 32 weeks (26). Other studies have not consistently shown this beneficial effect of antifungals (27), and further trials are necessary to better delineate the role of antifungals in cases of SAFS. Case reports have suggested a possible role for the anti-IgE agent Omalizumab however this requires further and more detailed study (28, 29).

Molecular pathways linking Aspergillus and asthma have recently been further elucidated. *Aspergillus* protease allergens Aspf5 and Aspf13 have been found to be important for the recruitment of inflammatory cells and remodeling of airways in a murine model (30). Recent work in both mouse and human bronchial epithelial cells demonstrate that Aspf13 promotes airway hyperresponsiveness. By infiltrating

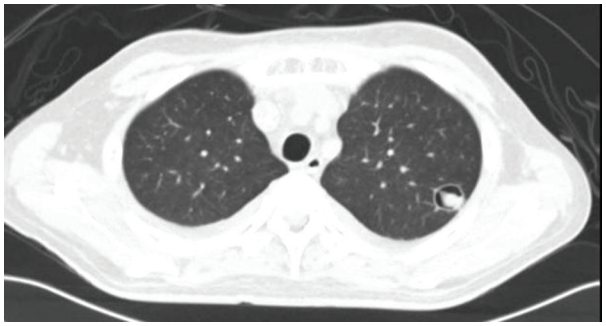

Figure 3. Radiological features suggestive of invasive pulmonary aspergillosis (IPA): An air-crescent sign seen in the left upper lobe of a patient with proven IPA; the sign illustrates a 'crescent of air' noted in instances of parenchymal pulmonary necrosis as seen in IPA.

the bronchial submucosa and disrupting airway smooth muscle cell-extracellular matrix interactions, Aspf13 evokes RhoA-dependent Ca^{2+} sensitivity and subsequent bronchoconstriction (31). This importantly raises the possibility that proteases which degrade airway epithelial integrity could be a future potential therapeutic target for SAFS and ABPA.

4.2. *Aspergillus* and chronic obstructive pulmonary disease (COPD)

COPD is a chronic inflammatory lung disease characterized by progressive irreversible airflow obstruction, usually but not exclusively driven by smoking. *Aspergillus* is commonly recovered from the respiratory specimens of COPD patients, for example, a prospective study looking at patients presenting to hospital with an acute exacerbation of COPD found that the prevalence of *Aspergillus* isolation from sputum was 16.6% on admission and 14.1% at one year follow up. This was also associated with more frequent exacerbations in the preceding year (32). Another multicenter prospective study of patients admitted to the intensive care unit found that COPD and steroids were associated with *Aspergillus* isolation from tracheal aspirates with odds ratios of 2.9 and 4.5 respectively (33). Between 8-15% of COPD patients remarkably show evidence of hypersensitivity to *Aspergillus* (34, 35), which in turn is associated with worse pulmonary function and potentially asthma-COPD overlap syndrome (ACOS) (36).

There is an increasing recognition that *Aspergillus* may not be a mere colonizer of the COPD airway, but in fact possess significant potential to evolve into invasive pulmonary aspergillosis (IPA) (37). This emerging and serious infection in patients with COPD is a particular risk in those receiving high-dose systemic corticosteroids (38, 39) or recurrent courses of antibiotics (40), or even high-dose inhaled corticosteroids (41) all used in the control of airways disease and its course of exacerbations. In an older review of 50 studies of invasive aspergillosis, COPD was found to be the underlying condition in 1.3% of patients (42). Since that review, up to 15.4% of COPD patients who have a positive culture of *Aspergillus* from the lower respiratory tract have been shown to have IPA (43).

The development of IPA in the context of COPD is multifactorial (44): sub-optimal nutrition leads to infection susceptibility, impairment of ciliary function by chronic tobacco smoke impairs *Aspergillus* clearance from the airway and alterations in microbiological milieu favors *Aspergillus* growth due to use of broad-spectrum antibiotics in recurrent exacerbations. The use of corticosteroids to some extent further promotes the growth of *Aspergillus* and decreases the anti-fungal capabilities of alveolar macrophages, suppresses neutrophil function and Th1 cytokine production. COPD patients with IPA usually present with a non-resolving pneumonia that is refractory to antibiotics in the setting of exacerbated dyspnea. Criteria for diagnosis of IPA in COPD have been proposed (45) which require that proven IPA necessitates histopathological or cytopathological examination illustrating hyphae consistent with *Aspergillus* and evidence of associated tissue damage. A diagnosis of probable or possible IPA can be reached on the basis of a combination of nonspecific computed tomography imaging changes including the halo or air crescent signs (Figure 3), positive cultures from the lower respiratory tract and positive biological markers including serum antibody and/or antigen testing. Extrapolating from a large randomized trial comprising mostly patients with hematological malignancies (46), antifungal therapy in the form of Voriconazole remains first-line in the treatment of IPA. There remains an urgent need for similar therapeutic trials in COPD patients with IPA.

4.3. *Aspergillus* and bronchiectasis

Bronchiectasis is characterized by a permanent irreversible dilatation of the airways, with accompanying inflammation, chronic bacterial infection and destruction of the bronchial walls. In about 10% of patients with "idiopathic" bronchiectasis, ABPA can be identified as the causative factor (47) however *Aspergillus* spp. are now more significantly recognized as a consequence of the disease as destroyed and anatomically abnormal airways place such patients at higher risks of fungal acquisition, colonization and subsequent *Aspergillus*-associated clinical states. Both CF and non-CF bronchiectasis confer risks however detection in CF is more challenging due to the complex microbiological and inflammatory milieu (8). A higher rate of *Aspergillus* hypersensitivity (48) and ABPA (49, 50) are noted among patients with CF. The odds of encountering CF transmembrane conductance regulator mutations (the gene implicated in CF pathogenesis) are higher in ABPA (odds ratio 10.39) when compared to either control or asthmatic patients (51). This suggests that such mutations may potentially be involved in ABPA pathogenesis in combination with environmental exposures or triggers. CF-ABPA is further associated

with poorer clinical outcomes including higher rates of microbial colonization, pneumothorax, hemoptysis, and poorer nutritional status (52). Rates of *Aspergillus* colonization in CF range from 15-50% with up to 10% having ABPA that remains difficult to identify because of overlapping clinical, microbiological, radiological and immunological effects to that seen in a bacterial exacerbation (8). Importantly, no correlation exists between isolation of airway *Aspergillus* and occurrence of CF-ABPA that adds a further level of complexity to differentiate the colonized from diseased state within the CF airway (6, 53). In the context of *Aspergillus* colonization in CF, our group has performed a significant body of work and are now extending this to non-CF settings (7, 53-55). We have shown that the Vitamin D receptor (VDR), a key component of an immune-modulating pathway is down-regulated by gliotoxin, a key immunoevasive fungal virulence factor (9). Treatment with itraconazole decreases bronchoalveolar lavage (BAL) gliotoxin concentrations, restoring VDR expression, diminishing systemic Th2 cytokines IL-5 and IL-13 with concomitant improvement in clinical and radiological patient outcomes (56).

Further work by our group and others has focused on identifying the presence of the filamentous fungi in the respiratory tract of CF patients suspected of *Aspergillus*-associated pathology. We have assessed fungal culture and conidial qPCR however such approaches are either poorly sensitive, expensive and take a significant time period to perform (56). Consequently, a clear need for a more definitive bedside approach to *Aspergillus* diagnostics and the identification of its varied clinical states in bronchiectasis, both CF and non-CF are required. We have successfully explored the use of the basophil surface marker CD203c in determining both the sensitized and ABPA clinical states in CF and have also investigated the potential role of human chitinase enzymes as markers for airway fungal colonization (57-59). We have additionally studied the role of gliotoxin, a potent immune-evasive mycotoxin in *Aspergillus*-associated disease. Immunosuppressive roles of gliotoxin include the inhibition of phagocytosis, T-cell proliferation, mast cell activation and cytotoxicity. Additionally, it inhibits superoxide production and reduces epithelial ciliary movement leading to dysfunction. We are currently assessing its precise role for both diagnostic and therapeutic value in the context of both CF and non-CF bronchiectasis (7-9).

In addition to ABPA, *Aspergillus* may influence and modify the clinical course of bronchiectasis in other ways, for example our group has illustrated that radiology in CF patients colonized with *Aspergillus* spp. appears worse when compared to a non-colonized group (55). In the context of non-CF bronchiectasis, one study has demonstrated that patients isolating *Aspergillus* from their sputum have significantly more daily and purulent sputum (60). Most data however examining *Aspergillus* in the context of bronchiectasis originates from the CF population. *A. fumigatus* is commonly found in sputum collected from non-ABPA CF patients (61), particularly older patients treated with chronic inhaled antibiotics (62). *Aspergillus* spp. have also been linked to respiratory exacerbations and poorer lung function in non-ABPA CF populations (63, 64). While in general, it is now accepted that airway *Aspergillus* is associated with more advanced radiographic disease and worse lung function parameters, recent work has shown (65) no independent effect of *Aspergillus* on lung function over a five year period (66).

Because of the complexities linked to *Aspergillus*-associated disease in the setting of bronchiectasis including CF, novel immunologic classifications have been proposed to better stratify patients. Such classifications are based on serologic, RT-PCR, and galactomannan data. Four groups of patients have been proposed: non-diseased, ABPA, *Aspergillus*-sensitized and *Aspergillus*-bronchitis (67). The recognition of sub-groups of *Aspergillus*-associated disease in the setting of bronchiectasis facilitates improved phenotyping and more directed therapy at patients who most need it. What remains uncertain however are the benefits of treating asymptomatic *Aspergillus* colonization in the absence of ABPA. There is emerging evidence for vitamin D usage in reducing Th2 cytokine responses in CF-ABPA however the benefits of use of anti-fungals such as itraconazole remain unclear (68, 69). A pilot prospective randomized trial of oral itraconazole in the treatment of *A. fumigatus* airway infection, (defined as at least 2 positive sputum cultures in the preceding 12 months) in CF was negative, with no difference in outcomes of lung function, exacerbation rates, and quality of life (70). This was in contrast to observational work performed by our group where clinical and radiological benefits were noted (56). Importantly, the work by Aaron *et al* (70) was significantly limited by lack of power, sub-therapeutic levels of oral itraconazole achieved in more than half of the patients assessed and failed to assess any endpoint beyond FEV_1. As a consequence, the precise role for *Aspergillus* spp. in the context of bronchiectasis particularly in modulating its clinical course and progression requires further and more detailed study beyond measures such as FEV_1 alone.

4.4. *Aspergillus* and pulmonary tuberculosis

Association between *Aspergillus* and pulmonary tuberculosis (PTB) has been recognized for several decades. In a British series from the 1960s, 25% of all patients with residual cavities >2.5.cm after PTB treatment had detectable *Aspergillus* precipitins in blood and both precipitins and radiological features of an aspergilloma were detected in 14% and 22% respectively at 1 and 4 years (71). In a more recent study of PTB patients in Iran, using direct microscopic examination of

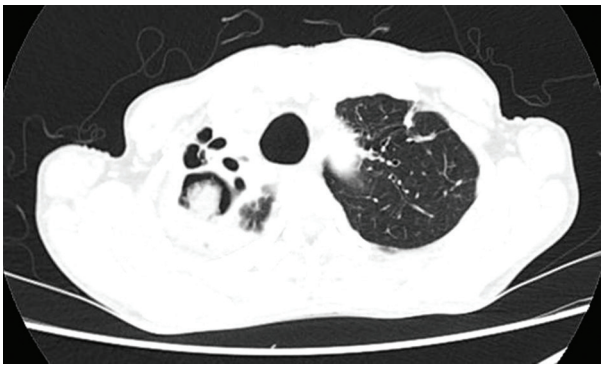

Figure 4. Radiology illustrating chronic pulmonary aspergillosis (CPA) with an aspergilloma - multiple thick walled and coalescent cavities in the right upper lobe in a patient with previous pulmonary tuberculosis. There is a soft tissue density in the largest cavity representing an aspergilloma.

sputum, fungal culture and radiographic examination, 2.4.% of patients met criteria for an aspergilloma and 11.3.% of patients for chronic cavitatory pulmonary aspergillosis (72). Prior PTB remains the strongest risk factor for CPA (73). It is estimated that at least 1.2 million people around the world have CPA as a sequel to PTB (74). In fact, many cases of TB-related CPA are undiagnosed, as CPA regularly masquerades as smear-negative TB with an absence of pyrexia (75).

CPA occurs along a disease spectrum. A simple aspergilloma is a fungal ball occurring in a single pulmonary cavity that remains stable over a period of time (Figure 4). In contrast, chronic cavitatory pulmonary aspergillosis begins as ill-defined regions of consolidation progressing to form clearly defined cavities which may or may not contain aspergillomas. The cavities may expand or coalesce over time without treatment. Chronic fibrosing pulmonary aspergillosis is the same as chronic cavitary pulmonary aspergillosis but with the presence of significant fibrosis. Chronic necrotizing pulmonary aspergillosis is characterized by focal lung invasion and destruction. Presenting signs and symptoms of CPA related to PTB either past or inter-current is usually several months of weight loss, chronic productive cough, hemoptysis, fatigue and/or shortness of breath (76). The cardinal diagnostic test is a positive anti-*Aspergillus* IgG antibody. Radiological findings include cavitatory pulmonary lesions with evidence of paracavitatory infiltrates and adjacent pleural thickening with or without an associated aspergilloma. Sputum or bronchoalveolar lavage culture specimens may or may not grow *Aspergillus* species and many instances of CPA illustrate negative cultures. Galactomannan antigen (a fungal cell wall component) may be raised in bronchoalveolar lavage fluid or serum but suffers from poor sensitivity. Alternative diagnoses such as active tuberculosis, other mycoses, neoplasms, abscess or granulomatosis with polyangiitis should also be aggressively excluded prior to making a diagnosis of CPA. Treatment depends on specific disease manifestations. For a simple asymptomatic aspergilloma which is stable over time, no therapy is required unless ongoing hemoptysis is reported. Antifungal therapy is of limited benefit in this context (77). Surgical resection is offered to prevent or treat potentially life-threatening hemoptysis and is curative (78). In contrast, most patients with chronic cavitatory, chronic necrotizing and chronic fibrosing pulmonary aspergillosis require antifungal therapy (79-81). The American Thoracic Society recommends either voriconazole or itraconazole for mild to moderate disease, and intravenous voriconazole or amphotericin B in more severe disease (82).

5. THE MYCOBIOME AND TRANSLATING SCIENCE TO TREATMENT

The total lung microbiome is defined as the microbial communities present in the airway and comprises bacterial, fungal and viral organisms. In recent years it has become evident that the microbiome with which each individual is colonized has wide-ranging effects on human phenotype in both health and disease. It has roles in immune-regulation, metabolism and other physiological processes that influence physiological homeostasis. Although most research has mainly focused on bacterial contributions to the human microbiome, fungi remain an important and clearly understudied contributor to airway health and disease. Consequently, the term “mycobiome” has been coined to refer to the fungal component of the described human microbiome (83).

Changes or dysbiosis within the lung micro- or mycobiome composition may potentially provide insight into how *Aspergillus* is able to thrive within chronically-diseased lungs and cause further pulmonary manifestations. One particular view is that the lung mycobiome acts as a reservoir of potential *Aspergillus* (or other fungal) pathogens, which are normally suppressed by the bacterial component of the microbiome (83). Disruption of this microbiome, such as through use of inhaled corticosteroids and antibiotics in COPD for instance in fact may permit the fungal mycobiome to expand subsequently allowing *Aspergillus* to proliferate and cause disease. Recent evidence also suggests that the bacterial component of the microbiome suppresses the mycobiome of the lungs either directly via bacterial-fungal interaction or indirectly by influencing host immune responses (84). An example of this is in CF patients, where there is a known inhibitory relationship exerted by *Pseudomonas aeruginosa* on the growth of *A. fumigatus* mediated by direct contact and the release of small extracellular molecules which reduce the capacity for *Aspergillus* to form hyphae and undergo biofilm development (85). Therefore, mutual interaction between members of the various components of the total lung microbiome may in fact determine flux between asymptomatic fungal colonization and clinical infection.

Conventional culture techniques are limited in their ability to assess the dynamics of the lung microbiome because many organisms are not cultivable by standard culture alone. With the advent of culture-independent techniques employing DNA or RNA sequencing, it is now possible to identify such non-cultivable organisms and therefore assess patterns of coinfection in the context of changing airway microbiome dynamics (86). Additionally, we can correlate the microbiome with different disease states and place them in a phenotypical context. Further study into the mycobiome and the broader microbiome are necessary to help advance our knowledge of the role of *Aspergillus* in chronic lung disease. It may permit novel therapeutic approaches through manipulation of the airway microbiome. Micro- or mycobiome respiratory signatures might in the future importantly serve as biomarkers to predict clinical manifestations of disease to enable early diagnosis, disease phenotyping and/or allow appropriate preventive therapy for pulmonary aspergillosis that is clearly now an important contributor to the chronic respiratory disease state.

6. CONCLUSION

In summary, *Aspergillus* is emerging as a common link across various chronic lung disease states, such as asthma, COPD, bronchiectasis, cystic fibrosis and pulmonary tuberculosis. Different chronic lung diseases have preponderance for different pulmonary aspergillosis syndromes depending on the underlying state of the host immune system. Even in the absence of clinically overt pulmonary aspergillosis, the presence of *Aspergillus* in the airways of patients with chronic lung disease can worsen clinical course and disease outcomes. Understanding lung micro- and mycobiome interaction may provide insights into the pathogenesis of *Aspergillus*-related diseases in the context of chronic lung disease, and provide us novel diagnostic or therapeutic approaches.

7. ACKNOWLEDGEMENT

The authors have no conflicts of interest to declare.

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Abbreviations: ABPA: allergic bronchopulmonary aspergillosis, SAFS: severe asthma with fungal sensitization, CF: cystic fibrosis, COPD: chronic obstructive pulmonary disease, IPA: invasive pulmonary aspergillosis, PTB: pulmonary tuberculosis, TB: tuberculosis, VDR: vitamin D receptor, CPA: chronic pulmonary aspergillosis, DNA: deoxyribonucleic acid, RNA: ribonucleic acid, PCR: polymerase chain reaction

Key Words: Aspergillosis, Asthma, COPD, Bronchiectasis, Cystic Fibrosis, Tuberculosis, Mycobiome, Review

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