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Chronic Pulmonary Aspergillosis: Current Scenario

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Introduction

Chronic pulmonary aspergillosis (CPA) is a severe fungal infection which is characterized by a slow and progressive destruction of the lung parenchyma and is usually seen in immunocompetent or mildly immunosuppressed patients with underlying respiratory disorders [1-2]. CPA is an important though neglected fungal infection. Diagnosing CPA can be extremely challenging given the fact that the clinical presentation is quite similar to other chronic respiratory illnesses and also due to the unavailability of a single diagnostic test that establishes the diagnosis. CPA is a broad term that encompasses a number of different presentations of varying severity. Also, there is a considerable overlap between the disease forms which adds to the confusion during diagnosis. Antifungal therapy with oral itraconazole is the first line of therapy and is usually recommended for at least 6 months. Since the disease is uncommon, many aspects of it are still unclear and requires further research and attention. This article aims to provide an update on the current developments with regards to CPA.

What is CPA?

Chronic pulmonary aspergillosis (CPA) is a severe fungal infection which is characterized by a slow and progressive destruction of the lung parenchyma in the form of single or multiple cavities, nodules, infiltrates or fibrosis, with or without an aspergilloma and is usually seen in immunocompetent or mildly immunosuppressed patients with underlying respiratory disorders [1]

Subtypes of CPA

CPA is a broad term which encompasses multiple entities. This includes: (1) Aspergilloma (2) Aspergillus Nodule (3) Chronic cavitary pulmonary aspergillosis (4) Chronic fibrosing pulmonary aspergillosis and, (5) Subacute invasive aspergillosis.

Aspergilloma

An aspergilloma is a fungus ball or mycetoma which is composed of Aspergillus hyphae along with cellular debris and mucus. They usually develop in a pre-existing cavity in the lung parenchyma caused due to cavitary diseases such as treated tuberculosis or other necrotizing infection, sarcoidosis, cystic fibrosis and emphysematous bullae. It develops in approximately 15% to 25% of patients with cavitating lung disease resulting from tuberculosis [3]. Aspergilloma are usually classified as simple aspergilloma or complex aspergilloma. If the surrounding lung parenchyma is normal and the cavity containing the aspergilloma is entirely lined by ciliated epithelium, it is termed as simple aspergilloma. On the other hand, if the surrounding lung parenchyma is extensively damaged and is characterized by epithelial distortion and fibrosis, then it is termed as complex aspergilloma.

Aspergillus Nodule

Aspergillus can form single or multiple nodules which may or may not form a cavity. These nodules are usually benign in nature but can sometimes cause symptoms such as cough or exacerbation of existing disease such as asthma [4]. They may mimic tuberculoma, coccidioidomycosis, lung carcinoma and other diagnosis and can only be definitively diagnosed on histology.

Chronic Cavitary Pulmonary Aspergillosis

Chronic cavitary pulmonary aspergillosis (CCPA) is the most common presentation of CPA. It was formerly termed as complex aspergilloma but later on was changed to CCPA because more than 50% of such patients don't have aspergilloma visible radiographically. It has a slowly progressive course that has the ability to last for years. CCPA usually begins as ill-defined regions of consolidation that progress to form clearly defined cavities. There are often multiple cavities of variable sizes. Formation of new cavities and expansion of the existing cavities over time is very common and usually occurs over months in the absence of treatment. Godet et al. in 2014 formulated a criterion to diagnose CCPA which included: constellation of immunosuppression, constitutional symptoms, formation of a single/multiple lung cavitation, a positive serum Aspergillus precipitans test, increased biological inflammatory markers and absence of other pathology that could mimic the aforementioned symptoms [5]. This criterion has been now updated and the current criteria used is the presence of: One large cavity or two or more cavities on chest imaging with or without a fungal ball (aspergilloma) in one or more of the cavities, at least one of the following symptoms for at least 3 months: fever, weight loss, fatigue, cough, sputum production, hemoptysis, or shortness of breath and a positive Aspergillus IgG with or without culture of Aspergillus species from the lungs [6].

Chronic Fibrosing Pulmonary Aspergillosis (CFPA)

CCPA when left untreated can progress to a form of aspergillosis known as chronic fibrosing pulmonary aspergillosis (CFPA). The presence of ongoing inflammation over an extended period of

time leads to extensive fibrosis of the lung parenchyma. CFPA is characterized by the same radiographic findings as CCPA in combination with significant fibrosis. Also, the criteria for the diagnosis of CFPA are similar to those for CCPA. In addition, substantial areas of fibrosis (determined by biopsy or CT scan) in immediate proximity to an area of CCPA are seen.

Sub-Acute Invasive Aspergillosis (SAIA)

It is also known as chronic necrotising pulmonary aspergillosis or semi-invasive pulmonary aspergillosis. This form of CPA usually leads to progressive features over the course of 1-3 months usually in people with some degree of immunosuppression. Subacute Invasive Aspergillosis (SAIA) is more common in individuals with immunosuppressive conditions such as diabetes mellitus, alcoholism, malnutrition and prolonged corticosteroid therapy [2].

Epidemiology

Global epidemiological data reveals that approximately 3 million people suffer from CPA [7]. It is estimated that CPA complicates roughly 1.2 million cases of tuberculosis, 4,11,000 cases of ABPA and 72000 cases of sarcoidosis [8-9]. Lowes et al. conducted a study on 387 patients of CPA on predictors of mortality and found out that the survival rate was 86%, 62% and 47% at 1,5 and 10 years respectively [10]. Risk factors associated with high mortality were: Non-tubercular mycobacteria (NTM) infection, Chronic Obstructive Pulmonary Disease (COPD), cavitary disease, pleural involvement, presence of an aspergilloma, low physical activity and low body mass. NTM lung disease is an important predisposing condition for the development of CPA. A study by Jhun et al. reported the follow up results of 566 patients of Non-tubercular mycobacterial lung disease (NTM-LD) who at the time of diagnosis did not have CPA and who received >12 months of treatment for NTM-LD. Around 7.2% developed CPA, within a median duration of 18 months [11]. Sarcoidosis is often complicated by CPA and is associated with high mortality. Uzunhan et al. conducted a retrospective study on CPA complicating sarcoidosis and found out that chronic cavitary pulmonary aspergillosis (CCPA) was the most frequent CPA pattern in the study group [12]. The 5- and 10-year survival rate was 73% and 61% respectively. The Leading International Fungal Education (LIFE) portal has facilitated the estimation of burden of serious fungal infections in various countries for over 5.7 billion people [13]. In India the 5- year prevalence rate of CPA is estimated to be 24 per 100,000 [14]. Similarly, the occurrence of CPA was found out to be about 22% in tuberculous cavities and 2% in healed pulmonary tuberculosis without cavitation in India [14]. A cross sectional study from Nigeria indicates that 8.7 % patients with tuberculosis had CPA [15]. Similarly, a study performed in Uganda, the annual rate of CPA was found out to be 6.5% amongst patients with a prior history of tuberculosis [16]. Overall, in recent times the estimated prevalence of CPA in different regions have increased owing to more precise diagnostic tools and guidelines.

Diagnosis of CPA

Diagnosis of CPA is extremely complex and challenging. Patients usually present with indolent, non-specific symptoms such as fatigue, hemoptysis, weight loss, sweats, cough or dyspnoea. The diagnosis relies on a combination of criteria related to patient characteristics, radiological findings and a direct evidence of Aspergillus infection or an immunological response to Aspergillus spp. i.e., the detection of Aspergillus precipitins (IgG) in serum and/or the isolation of Aspergillus spp. from respiratory samples [17]. It is crucial to rule out alternative diagnosis such as mycobacterial infection either pulmonary TB or NTM, necrotizing lung cancer, pulmonary infarction and rheumatoid nodule before reaching a final conclusion. Additionally, the disease must be present for at least 3 months before the diagnosis is even considered. The diagnostic criteria for CPA of the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), the European Respiratory Society (ERS) and the European Confederation of Medical Mycology (ECCM) include: (1) one or more cavities with or without fungal ball or nodules present on thoracic imaging ≥ 3 months (2) direct evidence of Aspergillus spp., (3) exclusion of alternative diagnosis [2].

Clinical Features and Underlying Risk Factors for CPA

The clinical manifestations of CPA ranges from being asymptomatic as in cases of aspergilloma to severe life-threatening complications in Subacute invasive aspergillosis. Patients with CPA vary in age but are typically middle aged. Patients with CPA usually presents with several month history of weight loss, chronic productive cough, hemoptysis, fatigue, fever and shortness of breath. TB and NTM infection along with COPD are the two most important conditions associated with the development of CPA. Other conditions include pulmonary sarcoidosis, lung cancer and silicosis. Along with this a number of comorbidities such as alcoholism, tobacco abuse, glucocorticoid treatment, diabetes and TNF-α therapy are also associated with its development [18].

Radiology

Chest X-ray remains the first imaging modality for the suspicion and diagnosis of CPA. CT Thorax helps to provide additional information regarding the characteristics, distribution and extent of the abnormalities. The radiological features of CPA are the result of combination of findings due to underlying lung disorders and changes secondary to Aspergillus infection itself, which reflects the chronic inflammatory and immune response to Aspergillus spp [19]. The most common findings are of one or more cavities, characteristically with an irregular or thick wall, but occasionally can be thin walled, with or without intracavitary material or well-formed aspergilloma [2, 20]. Cavities are more commonly found in the upper lobes and often cause para-cavitary or adjacent pleural fibrosis. Additional features such as areas of consolidation and ground glass opacities may be seen surrounding the cavity. The findings are usually non- specific and can also be seen in various other conditions such as TB, actinomycosis and lung carcinoma. The radiological progression is usually slower and may take several years except in Subacute invasive aspergillosis. In patients of CFPA features of pulmonary fibrosis, traction bronchiectasis, distortion and parenchymal scarring are frequently observed [17].

Microbiology

The mere isolation of Aspergillus fumigatus in sputum is not diagnostic because of the ubiquitous nature of the fungus. However, its presence in bronchoscopic specimen is consistent with infection rather than colonisation [21]. Sensitivity of sputum or bronchoalveolar lavage (BAL) is not very high and remains moderate at best, even when specific fungal media are used. Though, when higher volume of sputum is used, the sensitivity increases proportionally. The sensitivity of BAL in the diagnosis of CPA is usually about 50%, though it can be difficult to distinguish between colonisation and infection [21-22]. A study by Ohba et al. found that 67.4% of the patients had aspergillus spp. colonisation but only 32.6% were diagnosed with CPA [22]. The positivity rates of culture ranges from 56-81% in various studies [17, 23-24]. Molecular detection methods, such as PCR has been found to be more sensitive than culture [25]. A recent study from Japan

evaluated the usefulness of BAL Galactomannan (GM), beta-D-glucan and two PCR assays to diagnose CPA [31]. The positive predictive value (PPV) for BAL GM was found out to be 63.6% and for beta-D-glucan to be 38.9%. While, the PPV for two PCR assays was 57.8% and 74.1%. The negative predictive value (NPV) was >90% for all these tests, hence can be used to rule out CPA [26]. Strong PCR signals detected during antifungal therapy is associated with antifungal resistance [25].

Serology

Serological methods can significantly contribute to the diagnosis of CPA. Initially, Aspergillus precipitans were used but has now been replaced by more sensitive serological assays. The role of Galactomannan antigen testing (in the serum and respiratory secretions) for the diagnosis of CPA is still to be evaluated. A comparison to evaluate the usefulness of testing the GM antigen in the serum and respiratory tract samples for the diagnosis of CPA has been reported in only a few studies. BAL fluid has been found to be more effective than serum testing for GM in the determination of Aspergillus spp. A study by Izumikava et al. found out the sensitivity and specificity of GM assay in BAL to be 77.2% and 77.0% respectively, while in serum was 66.7% and 63.5% respectively [27]. Similarly, in another study by Kono et al. the BAL GM-antigen testing had a sensitivity and specificity of 85.7% and 76.3% respectively [28]. Park et al. conducted a study on patients of aspergilloma and found out the sensitivity of serum and BAL for GM antigen to be 38% and 92% respectively [29]. The GM antigen detection from serum was higher in patients with haemoptysis than those without. Detection of Aspergillus antibodies is a key diagnostic feature of CPA. All patients who are suspected of having chronic or subacute invasive aspergillosis must undergo A. fumigatus IgG antibody or precipitins test. The presence of antibodies against aspergillus helps to differentiate between infected and colonised patients with a positive predictive value of 100% for detecting infection [30]. Majority of patients (85% to 92%) with CPA, including those with simple aspergilloma and Aspergillus nodules, have positive IgG antibodies in the blood [31-32]. Patients with characteristic features of CPA and negative Aspergillus IgG have more immune deficits than those with positive antibody titers [33]. In cases where Aspergillus precipitins is positive isolation of Aspergillus on direct examination or culture is not required for diagnosis of CPA. False positive results are common and can be seen with conditions such as pulmonary actinomycosis. Similarly, false negative results may be seen in patients receiving corticosteroid therapy or due to infection by a species other than A. fumigatus [34]. In cases where the clinical suspicion is high, Aspergillus fumigatus IgE test should be performed especially in asthmatic and cystic fibrosis patients. Very limited data is available on the measurement of A. fumigatus IgA or IgM antibodies and are therefore not recommended. There is almost no relationship between the antibody titres to the extent or severity of the disease, although very high antibody titres have been found in patients of aspergilloma [35]. A sharply rising titre is usually a sign of therapeutic failure or relapse.

Treatment of CPA

Azoles are the first-line treatment for CPA, but in cases where it is not possible to use this class of drugs, alternative treatment options include polyenes and echinocandins. Treatment aims to eradicate aspergillosis and to provide palliative support to the patient. Treatment is usually not required in cases of simple aspergilloma as spontaneous lysis occurs in 10% of the cases while, clinical and radiological stabilization occurs in 25% [36]. Antifungal therapy is recommended in symptomatic patients, although it is sometimes difficult to differentiate between symptoms associated with CPA and symptoms caused by underlying respiratory disorder. The decision to treat CPA should be based on the patient's phenotype and eligibility for surgical treatment. Antifungal therapy has been associated with improvement of symptoms and radiological findings, although a considerable proportion of patients do not respond to the treatment. The duration is generally recommended to be ≥6months, but should be based on an individual risk to benefit ratio. In a study by Lowes et al 98% of 108 patients received antifungal treatment [10]. Similarly, in a study by Uzunhan et al. antifungal treatment with voriconazole or itraconazole was associated with improved patients condition in the short term along with radiological improvement [12]. In a trial conducted by Agarwal et al, itraconazole was found to be superior over standard supportive therapy [37].

Azoles

Itraconazole has been the most commonly used treatment for CPA and is used as a first-line treatment. Usually 200mg twice daily is administered which may be adjusted according to drug levels if available. In a case series by Denning et al. on 18 immunocompromised patients with CPA initial therapy with itraconazole resulted in improvement or stabilization of the disease in 12 patients (71%) [17]. In a three-centre prospective series involving 29 patients, 44% patients responded to oral itraconazole [38]. In a randomised controlled trial of 31 patients with CCPA, patients who received 400 mg of itraconazole along with supportive therapy daily had a greater likelihood of clinical improvement (35% vs 7%) or stabilization (41% vs 29%) as compared to patients who received only supportive care [37]. In a case series conducted by Sehgal et al. 106 out of 123 patients (84.1%) had a clinical response to itraconazole at 6 months [39]. In cases where patients do not respond or are intolerant to itraconazole alternatives such as voriconazole or Posaconazole should be considered. Voriconazole is structurally different to itraconazole and has an extended spectrum of activity against rarer fungal species. The efficacy of voriconazole has been studied in a single arm prospective study of 22 patients with Chronic cavitary pulmonary aspergillosis (CCPA) and also in 18 patients of Subacute invasive aspergillosis (SAIA). Even though both studies used different outcomes and thus, cannot be directly compared though they showed improvement in approximately one-third of patients [40]. In a multicentre study in Japan, 61% patients responded well to the therapy with only 2 patients stopping therapy [41]. In another study by Al-Shair K et al. the quality of patients treated with voriconazole was improved in 30% at 3 months and in 43% by 12 months [42]. Hepatotoxicity is a major limiting factor for voriconazole administration and hence, regular monitoring with liver function test should be advised in all patients. In a study conducted in Italy, 6 of 21 patients could not tolerate voriconazole, and 9 (42.9%) improved significantly at 12 months [43]. Use of itraconazole and voriconazole is associated with resistance against Aspergillus spp. which in turn has led to evaluation of alternative drugs. Effect of Posaconazole was evaluated in a retrospective study of 67 patients with CCPA who were treated for at least 6 months and also in a study that prospectively assessed the quality of life for a year [42, 44]. Clinical and/or radiological response to or stabilization of disease was observed in 61% of patients at 6 months and 46% of patients over 12 months. The quality of life with Posaconazole was improved in 45% of patients at 3 months and in 60% by 12 months [42]. There is currently not enough data on isavuconazole for the treatment of CPA and needs to be further evaluated.

Intravenous Antifungal Drugs

Antifungal intravenous therapy is generally reserved for patients with progressive disease and those who fail and are intolerant or who have triazole resistance. Some studies have mentioned the use

of I.V agents during induction phase as a strategy to control the infection followed by an oral maintenance therapy with antifungal drugs. Amphotericin B and echinocandins are the exclusive i.v. drugs and can be used as an alternative to triazoles. IV application of amphotericin B has been found to achieve success against CPA in 80% of patients [17]. However, the response was found to be short lived along with significant associated toxicity. Various other studies have found similar evidence [45-46]. Liposomal amphotericin B has an improved safety profile when compared to deoxycholate but there is no evidence of enhanced efficacy [2, 47]. Micafungin has been proposed as an alternative to voriconazole due to its improved safety profile. A study conducted by Kohno et al found out the efficacy of IV administration of micafungin and voriconazole to be 60% and 53.2% respectively [48]. A study on the safety profile of micafungin found out that adverse effects occurred in 15.8% of the patients, most common being abnormal liver function [49]. A response rate of 61% has been observed with micafungin in a meta-analysis of 12-case series evaluating 380 patients [50]. A prospective study of micafungin in 38 patients with CPA suggested the maximum dose to be 150mg once daily [49]. The use of combination of triazole and caspofungin has been reported in a few cases of CPA complicating sarcoidosis [51].

Role of Surgery and Other Interventional Procedures

Surgical resection of aspergilloma is considered as the definitive option for patients with adequate pulmonary reserve [52-53]. Surgery should be considered in all patients with severe hemoptysis. The success of the surgical procedure depends on the ability to fully resect the aspergilloma without spillage of fungal elements into the pleural space. Bronchial artery embolization can be performed prior to surgery in cases of severe hemoptysis and acts as a bridge towards definite elective surgery. Th most important aspect for a surgery to be successful is the appropriate and careful patient selection as many patients are physically debilitated leading to higher rate of death and peri and post-operative complications. Patients who are unable to qualify for surgery, bronchoscopic removal of the aspergilloma should be considered [54]. Common complication of surgery includes persistent air leak, empyema, persistent pleural space, infection, bronchopleural fistula, respiratory failure, massive haemorrhage and death. Video assisted thoracoscopic surgery (VATS) can reduce the number of complications and also the length of hospitalization. In cases where complete resection is not possible antifungal therapy can be administered to prevent aspergillus empyema or to avoid recurrence of disease [53]. Several studies have described the resolution of aspergilloma through the instillation of antifungal agents directly into the pulmonary cavities and thus can be considered as a viable treatment option when systemic use of antifungals in ineffective [55-57].

Role of Drug Resistance Testing in CPA Management

The emergence of antifungal resistance is a major concern for the treatment of CPA. Azole resistance has been increasingly described in recent studies and is associated with poorer outcomes [58]. Prolonged treatment in patients with chronic disease has a major role in the development of antifungal resistance. Azoles are the major concern in development of resistance as they aremost commonly prescribed as the first-line therapy in the management of CPA. Acquired resistance to amphotericin B or echinocandins is uncommon. Th exact prevalence of azole resistance in A. fumigatus is still unknown, but has been reported between 2-54% in various studies [59]. A link between in vitro resistance and clinical failure has been suggested [58]. Thus, it is extremely important to perform a mycological examination of respiratory specimen at every outpatient visit, and in case of a positive culture drug susceptibility testing (DST) should be performed. Although, several mechanisms of resistance have been found, mutations in cyp51A gene coding for Ianosterol 14α-demetylase is the most commonly involved mechanism. Various molecular mechanisms have been developed to detect cyp51A- mediated resistance in A. fumigatus [60-63]. Some of these methods can be directly applied in clinical specimens thus, can be a good alternative when culture is not available. Additionally, positive cultures during antifungal therapy is indicative of azole resistance [64].

Conclusion

CPA includes heterogenous clinical entities complicated by underlying lung diseases such as tuberculosis, NTM, COPD and sarcoidosis. Clinical presentation is non-specific often leading to delayed or missed diagnosis. Surgery should always be considered when feasible especially in a localized disease though is not always possible due to high risk of morbidity and mortality associated with it. Antifungal therapy leads to clinical stability or improvement, though the response rate is still moderate. Oral therapy with triazoles (Itraconazole/voriconazole) is considered as the first line of treatment, though other azoles such as Posaconazole and isavuconazole can be administered in cases which do not respond to initial therapy. Intravenous agents such as amphotericin B or micafungin can be used for shorter duration, but are suboptimal for long term treatment. Current treatment strategies do provide benefit to patients but have many drawbacks. Optimal treatment is yet to be established and needs further research. Azole resistance is a major concern in the management of CPA and is associated with poorer outcomes, thus should be carried out in all cases who are not responding to antifungal therapy.

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