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Review

Recent advances in chronic pulmonary aspergillosis

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ABSTRACT

Chronic pulmonary aspergillosis (CPA) is a slowly progressing pulmonary syndrome caused by *Aspergillus* spp. Specific knowledge regarding the disease entity, diagnosis method, and management is needed. This review focuses on the recent advances in our understanding of CPA. A new clinical disease entity of chronic progressive pulmonary aspergillosis consisting of chronic necrotizing pulmonary aspergillosis and chronic cavitary pulmonary aspergillosis is proposed. Although newer antifungals are not available, evidence describing the treatment of CPA is accumulating. Longer administration of azoles is required for a better prognosis, but there is a risk of inducing azole resistance. Therapeutic drug monitoring and patient education are required. Establishing a drug-susceptibility test that can be performed in the general laboratory and the referral center are also important. Although the number of publications regarding CPA is growing, there are still many unanswered questions. Additional evidence and translational research regarding diagnosis, management, and drug resistance are urgently needed to improve the outcome of CPA.

Contents

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1. Introduction

Chronic pulmonary aspergillosis (CPA) is defined as a slowly progressing pulmonary syndrome caused by *Aspergillus* species that has recently been recognized as a significant global health burden [1]. The disease entity of CPA is sometimes vague, particularly in the absence of typical clinical features and course due to the complexity of background pulmonary diseases, such as post-tuberculosis infection, bronchiectasis, chronic obstructive pulmonary disease (COPD), previously treated lung cancer, pneumothorax, and coinfection with non-tuberculosis mycobacterium or other bacteria [1]. Recently, we investigated all types of CPA cases diagnosed by histopathological examination, including chronic necrotizing pulmonary aspergillosis (CNPA), chronic cavitary pulmonary aspergillosis (CCPA), and aspergilloma (mainly: simple aspergilloma, SA), to clarify and confirm the differences in the pathogenesis and clinical features of each type [2,3].

Two randomized controlled trials (RCTs) on the intravenous antifungal treatment of CPA were published in 2010 and 2013 [4,5]. Although there are no RCTs on oral antifungals, several studies have recently been published, mainly from Japan [6–10].

Additionally, azole-resistant *Aspergillus* spp. is becoming a major clinical threat that will certainly influence the morbidity and mortality of CPA patients who require long-term antifungal administration. Recent studies have demonstrated that the long-term use of azoles is linked to the acquisition of resistance [11].

This review focuses on the recent advances in our understanding of CPA, including the disease entity, epidemiology, management, and drug resistance.

2. Disease entity

The chronic forms of pulmonary aspergillosis were originally established as CNPA by Binder in the early 1980s [12] and as semi-invasive aspergillosis by Gefter [13]. Both are characterized as slowly progressing inflammatory pulmonary syndrome caused by *Aspergillus* spp.

In the last decade, a new nomenclature and definitions of the chronic forms of aspergillosis have been proposed [14–16], and the latest guidelines from the Infectious Diseases Society of America (IDSA) have indicated three major subtypes of chronic forms of pulmonary aspergillosis, namely CNPA (categorized in an invasive form of aspergillosis), CCPA, and aspergilloma (SA) [17].

Several distinctions can be made between CNPA and CCPA. CNPA is characterized by a disease course lasting 1–3 months, whereas disease lasting more than 3 months is defined as CCPA [18], although this difference is arbitrary. Additionally, CCPA patients present a genetic predisposition for defects in innate immunity, such as mannose-binding lectin and surfactant protein A [19–21]. Toll-like receptors (TLRs) play critical roles in innate immunity, and Carvalho et al. reported that polymorphism (Asp299Gly) of the TLR-4 gene is significantly associated with CCPA (odds ratio, 3.46; $P=0.003$) [21,22]. Among CCPA cases, extensive pulmonary fibrosis occurs in the affected lesion, and these cases are referred to as chronic fibrosing pulmonary aspergillosis (CFPA) [16]. Hope et al. indicated that apparent distinct entities do not exist for this syndrome, and these forms usually overlap [15]; therefore, previous articles describing CNPA included these chronic forms of aspergillosis.

We recently investigated the pathogenesis of CPA using cases with histopathological evidence to clarify the differences in the pathogenesis and clinical features of CPA particularly, CNPA and CCPA. In one case series, we presented four cases of proven CNPA diagnosed based on the histological demonstration of tissue invasion by the fungus, and we presented its clinical features. These four patients were male, the mean age was 62 years (range, 51–75 years), and their underlying conditions were COPD ($n=3$), sequelae of pulmonary tuberculosis ($n=2$), and diabetes mellitus ($n=1$). *Aspergillus* precipitation tests were positive for three patients. The initial radiographic findings were infiltrates or nodular lesions, which slowly progressed and cavitated before the appearance of aspergilloma [2]. Additionally, in another study, there were 7, 5, 8, and 7 cases of proven CNPA, probable CNPA, CCPA, and SA, respectively, in Nagasaki University Hospital between 1964 and September 2010. The radiograph of proven and probable CNPA initially showed infiltrates or nodules that progressed to form cavities with or without aspergilloma, whereas the radiograph of CCPA revealed pre-existed cavities and pericavitary infiltrates with or without aspergilloma [2]. The patients with proven and probable CNPA exhibited not only respiratory symptoms but also systemic symptoms and malnutrition. *A. fumigatus* was the most frequently isolated *Aspergillus* species ($n=14$); however, *A. niger* was the predominant isolated species in proven CNPA cases ($n=4$). Our data indicate that cases with chronic infiltration, progressive cavitation, and subsequent aspergilloma formation should be diagnosed as CNPA, and cases with pre-existed cavities showing peri-cavitary infiltrates with or without aspergilloma would indicate CCPA. However, it may be difficult to distinguish between the two subtypes if a series of adequate radiography films is not available. Taken together, we proposed the new term "chronic progressive pulmonary aspergillosis (CPPA)" for the clinical syndrome that includes both CNPA and CCPA [3], and this may reduce the confusion of the physicians seeing CPA patients (Fig. 1).

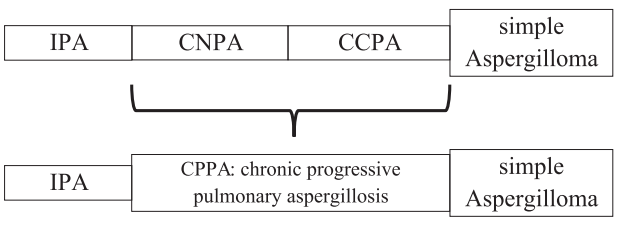

Fig. 1 – The new clinical disease entity of chronic progressive pulmonary aspergillosis. New nomenclature, "chronic progressive pulmonary aspergillosis (CPPA)" for the clinical syndrome including both CNPA and CCPA is proposed. It is difficult to distinguish between these two entities based on the clinical course and characteristics and radiological findings.