Clinical Management of Pulmonary Aspergillosis

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Abstract
Pulmonary aspergillosis is deep seated mycosis that occurs as an opportunistic infection, and is known as the disease whose diagnosis and treatment are particularly difficult. Japan's first Guidelines for the Diagnosis and Management of Deep Seated Mycosis were published recently, and it is expected that the guidelines may encourage the standardization of the management of deep seated mycosis. The algorithm of the guidelines is composed of three categories of diagnosis: “Proven infection”, “Clinically documented infection or Probable infection” and “Possible infection”; and 2 categories of therapy: “empiric”, and “targeting” therapy. Treatment using amphotericin B (AMPH-B) is a standard practice even now. However, a more effective voriconazole (VRCZ) has become available and several other combination therapies are being performed. A new treatment standard should be established by collecting more knowledge and clinical experience.

Key words Pulmonary aspergillosis, Guidelines, Immunocompromised host, Amphotericin B, Voriconazole, Combination therapy

Introduction
Recently the number of immunocompromised hosts is increasing because of the application of chemotherapy, organ transplantation and the long-term administration of immunosuppressants. Deep seated mycosis as an opportunistic infection in immunocompromised hosts has become one of the clinically significant disorders. The introduction of azole antifungal drugs and the development of various serum diagnostic methods have resulted in the cure of some types of deep seated mycosis, thereby reducing the share of deep seated mycoses in the total number of pathological autopsy cases every year. However, the frequency of aspergillosis is rather increasing. In particular, invasive pulmonary aspergillosis is a disease whose definitive diagnosis is difficult to establish and often has poor prognosis, with progression to an acute form. Non-invasive pulmonary aspergillosis may often progress to an acute form and lead to poor prognosis. Even aspergilloma as non-invasive aspergillosis after repeating of hemoptysis, and chronic necrotizing pulmonary aspergillosis (CNPA) after following a chronic progression, often become resistant to therapy.

The early diagnosis of, and the establishment of treatment methods for, pulmonary aspergillosis, neither of which are adequate presently, are a pressing need. However, the recent development of several serodiagnostic methods and the release of new antifungal drugs are changing the diagnostic and management strategy for pulmonary aspergillosis. In every case, sufficient understanding of the morbidity of pulmonary aspergillosis is considered to be most important.

In Japan, the first ‘Guidelines for the Diagnosis and Management of Deep Seated Mycosis’ was published in February 2003. This paper discusses recent trends of clinical practice and management of pulmonary aspergillosis, including the Japanese Guidelines.
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Classification

Pulmonary aspergillosis is mostly contracted by a fungus (aspergillus) which enters the body by inhaling conidia and colonizes and grows in the alveolus, bronchiole or existing cavities. Pulmonary aspergillosis presents various morbidities depending on the interaction between the pathogenicity of aspergillus, the immune status of the host (decreased immunity and allergic predisposition), and the pulmonary structure (existing cavitary lesions and cysts). Usually, pulmonary aspergillosis is divided into three categories: invasive pulmonary aspergillosis (IPA); non-invasive pulmonary aspergillosis mainly of fungus ball pulmonary aspergillosis (aspergilloma); and allergic bronchopulmonary aspergillosis (ABPA).

Some researchers advocate that chronic necrotizing pulmonary aspergillosis (CNPA), considered to be clinically positioned between invasive and non-invasive types, is defined as aspergillosis but this has not undergone histopathological examination. Recently a report proposed to categorize chronic pulmonary aspergillosis into various types.

Clinical Feature and Diagnosis

Invasive pulmonary aspergillosis: (IPA)

IPA is a fungus infection (mycosis) with poor prognosis, which occurs in compromised hosts who have undergone chemotherapy and take immunosuppressant, including steroids, for malignant hematopoietic diseases, hematopoietic stem cell transplantation and malignant tumors. It is known that if the patients who have undergone bone marrow transplantation contract IPA, then 90% of them die. IPA occurs at a higher frequency in the patients with neutropenia, particularly with neutrophils of 500/μl or less. Histopathologically, discrete nodular lesions, accompanied by hemorrhage around the lesions, are observed with strong fungal invasion into blood vessels and the lesions in these cases. As radiological findings single or multiple nodules and infiltrations are often observed in plain chest X-rays. Increased density of groundglass opacity around the nodule in the CT, is a characteristic finding in the relatively early stage. It is called the ‘CT-halo sign’ and is a very useful finding for early diagnosis. This is known to histologically correspond to the hemorrhage around the nodular lesion, but it is not specific to IPA. The recover of the leukocyte count to normal in the progress of the disease would suggest that necrotic tissues are absorbed and removed from the periphery of the nodular lesion to fill air in the periphery, which is known as an ‘air-crescent sign’ in the imaging findings. It sometime reveals radiological findings which look like the fungus ball of aspergilloma at a glance (Fig. 1). However, histopathologically, the nodule in the cavity is the pulmonary tissue coagulated and necrotized by fungal invasion and growth. On the other hand, IPA which occurs in those without neutropenia, shows non-specific
infiltration like bronchopneumonia (Fig. 2).\textsuperscript{12} Japanese Guidelines divide diagnostically IPA into the following three categories: “Proven infection”; “Clinically documented infection or Probable infection”; and “Possible infection.”\textsuperscript{3} For the proven infection, the presence of aspergillus hype in infectious lesions must be mycologically and/or histopathologically proven. Transcutaneous and transbronchial lung biopsies, and invasive examinations such as thoracoscopic biopsy with video assisted thoracoscopic surgery (VATS), may be rarely performed and it is difficult to apply them, in view of the systemic conditions of the patients. The Guidelines include the detection of aspergillus from sputum and bronchoalveolar lavage (BAL) specimen as requirements for diagnosing proven infection. However, the aspergillus culture positive rate is low in many patients with IPA, and the number of patients who can undergo bronchoscopic examination is limited. “Clinically documented infection or probable infection” is diagnosed when the case shows typical imaging findings, such as the CT-halo sign or air-crescent sign, and when the galactomannan antigen and β-D glucan in serum or gene diagnosis using the PCR method is positive.\textsuperscript{13–15} This “Clinically documented infection” corresponds to the “Probable infection” used by the European Organization for Research and Treatment of Cancer (EORTC). Many cases diagnosed in routine medical practice are considered to meet these criteria. “Possible infection” is diagnosed when either imaging findings or serum/genetic diagnosis is positive. However, in the field of respiratory medicine, the cases with risk factors and clinical conditions as well as typical imaging findings, are diagnosed as “Clinically documented infection”. In the clinical setting the early detection of clinical symptoms or risk factors, or imaging findings from which IPA is suspected in the patients with a clinical background such as immunosuppression or risk factors, is of critical importance. It should be followed by serum or genetic diagnosis, and then by prompt administration of antifungal drugs with the performance of invasive examination, if possible, in mind.

**Aspergilloma**

Aspergilloma is contracted by the secondary colonize of aspergillus conidia through the airway into existing cavitary lesion, bronchiectasis or cavity lesion produced by old lung tuberculosis, and its proliferation to form fungus balls. Many patients remain asymptomatic, whereas blood sputum, fever, systemic weariness, weight loss, and massive hemoptysis are observed in some patients. According to a report, blood sputum is seen more than once in over 75% of the patients, and 5% of the patients die from mass bleeding.\textsuperscript{16} Chest X-ray showed cavity wall, thickened pleura, round fungal balls in the cavity and air layers surrounding the cavity. These findings are named as “air-crescent sign” or “meniscus sign”. Partially thickened pleura is considered as an initial finding of aspergilloma.\textsuperscript{17} Diagnosis is relatively easy. Proven infection is diagnosed by detecting aspergillus in the culture of sputum and BAL, or proving the presence of aspergillus in the tissue of transcutaneous and transbronchial lung biopsies. Anti aspergillus precipitation antibody, a parameter in a serological test, is positive in about 90–100% of the aspergilloma patients, and is a useful parameter in adjuvant diagnosis.\textsuperscript{18} Aspergilloma demonstrates various radiological findings and clinical progressions depending on the immunosuppression and changes in the existing lung structure, ranging from asymptomatic with little change in radiological findings in the progress of disease, to those with the factors of CNPA and IPA. A recent report defines chronic pulmonary aspergillosis, including CNPA, as consisting of chronic cavitary pulmonary aspergillosis (CCPA), chronic fibrosing pulmonary aspergillosis (CFPA), and simple aspergilloma. The entity of disease will be the subject of future discussion.\textsuperscript{6}

**CNPA, Semi-invasive PA**

The disease type of CNPA is defined as positioned between aspergilloma and invasive pulmonary aspergillosis. It is interpreted as a disease categorized within aspergilloma. But as its clinical symptoms may progress to a severe form, utmost care is necessary. CNPA is often observed in the relatively mild immunocompromised hosts due to subalimentation, diabetes and malignant tumor, or in those with the lung whose immunity is locally reduced due to lung surgery, radiation therapy, chronic obstructive pulmonary disease and pneumoconiosis.\textsuperscript{2} It is reported that approximately 25% of the patients underwent low-dose steroid therapy.\textsuperscript{19} CNPA follows a chronic progress
but often shows a poor prognosis. Chest X-rays demonstrate the thickened pleura and infiltration in the initial stage, to be followed later by cavity lesion. Fungus balls and the air-fluid level may be observed in the cavity. In addition to this, infiltration of consolidation or ground-glass appearance surrounding the area may be also progressed (Fig. 3). Although no detailed histopathological examination has been performed, various findings such as necrotizing granulomatous pneumonia, bronchocentric granulomatosis (BCG), eosinophilic pneumonia and organizing pneumonia have been reported, and there is no histopathological definition for diagnosis.

20 CNPA is diagnosed on the basis of clinical course, consisting of clinical background, symptoms and imaging findings, and the presence of aspergillus in the culture of sputum. In the serum diagnosis aspergillus precipitation antibody shows the highest positive rate, and galactomannan and β-D glucan are also useful in the diagnosis.

**Treatment**

Successful treatment depends on the early administration of a sufficient dose of effective drugs as well as whether or not the recovery from neutropenia or immunocompromised status caused by the administration of immunosuppressive drugs. So far, only four drugs were effective for lung aspergillus, namely AMPH-B, Flucytosine (5-FC), Itraconazole (ITCZ) and Micafungin (MCFG). In addition, the use of VRCZ in Japan has been authorized since July 2005. The treatment methods for pulmonary aspergillus are explained below in accordance with the Japanese Guidelines. IPA cases which were diagnosed as proven and clinically documented infection are subjected to, as a targeted therapy, intravenous drip injection of 1.0–1.5 mg/kg/day of AMPH-B. If this produces an insufficient effect, it is combined with the oral administration of 100–150 mg/kg/day of 5-FC or 200–400 mg/day of ITCZ. Or, the intravenous drip injection of 150–300 mg/day of MCFG is chosen. For the patients who continue chemotherapy, or who are scheduled to undergo bone marrow transplantation, surgical removal of remaining lesion should be considered. The patients with suspected IPA should be subjected to the oral administration of 200–400 mg/day of ITCZ as an empiric therapy, or a drip injection of 0.75–1.5 mg/kg/day of AMPH-B, or 150 mg/day of MCFG will be chosen.

The treatment of aspergilloma, including CNPA, is explained below. Asymptomatic or slowly-grows aspergilloma may be placed under observation without treatment. The patients who show an aggravating trend of symptoms of fever, bloody sputum and hemoptysis require active treatment in which surgical removal is the most reliable method. The patients diagnosed as having proven infection should be subjected to surgery as soon as possible. Those who cannot undergo surgical removal because of advanced age or declined lung functions should be subjected to the following medical treatment: oral administration of 200–400 mg of ITCZ once per day, or intravenous drip of 0.75–1.5 mg/kg/day of AMPH-B, or 150–300 mg/day of MCFG. Inhalation or injection of AMPH-B may be performed, though it is not described in the Guidelines. However, when it is directly administered through the air respiratory tract, safeguards should be taken against the symptoms caused by direct stimulation such as fever, coughing, airway contraction and shock.

The administration of AMPH-B has been the standard therapy for aspergillosis for some time. However, it has often been experienced that renal disfunction and various adverse effects have forced the administration to be discontinued. In Western countries the use of the liposomal preparation of AMPH-B is known to have identical efficacy with, and less adverse effect than, AMPH-B, and ITCZ injections have produced good results. Liposomal preparation of AMPH-B has good transfer into the infected lesions, and
the less adverse effect of AMPH-B has enabled the administration of a sufficient dose of the drug for the patients with poor systemic conditions.\textsuperscript{21} Also VRCZ is the latestazole antifungal which shows a much better outcome in terms of efficacy, survival rate and toxicity than AMPH in IPA, and is thought to be the standard drug of first choice for the treatment.\textsuperscript{22} However, as it causes vision impairment, hepatic disorder and drug interaction in many cases and 23% of Oriental people are poor metabolizers, utmost care should be taken in these cases. In 2002 the clinical use of MCFG, a candin antifungal drug developed in Japan become possible. In the USA caspofungin (CAP), a candin antifungal drug, was approved in 2001. It is an antifungal drug with a new action mechanism to inhibit the synthesis of 1,3-β-D glucan, one of the main components forming the antifungal cell wall. This drug is very safe and has no drug interaction, though it is only in the injection dosage form as yet.\textsuperscript{23} VRCZ has been newly approved after the publication of the Japanese Guidelines, and liposomal AMPH-B and ITCZ injections are scheduled to be approved. Conventionally only AMPH-B has been an effective drug for aspergillosis, whereas there are several options of antifungal drugs with anti-aspergillus activities. It is considered that the choice and optimal use of effective drugs are keys to the success of treatment. However, there is no antifungal drug which may easily cure aspergillosis. Therefore, the combination therapy, the effect of which is improved by the coadministration of an antifungal drug with different action mechanisms, has attracted increasing attention in recent years.\textsuperscript{24} In Western countries combination therapies such as VRCZ + CAP and AMPH + CAP are being tried.\textsuperscript{25} The therapy with the coadministration of AMPH-B + MCFG is being performed.\textsuperscript{26} To establish an evidence base for the combination therapy, it is desirable to collect many cases and perform controlled clinical trials.

**Conclusion**

In the field of fungal infection the treatment of pulmonary aspergillosis has become the most important clinical challenge. There has been great advancement in the prevention of onset and early diagnosis of the disease, and less adverse effects but not yet to a satisfactory level. The publication of the ‘Guidelines on the Diagnosis and Management of Deep Seated Mycosis’ in Japan has improved and standardized the clinical practice for the disease. In every case it is of prime importance to adequately understand the morbidity of pulmonary aspergillosis. Moreover, it is considered that the full understanding of the characteristics of all diagnostic methods, including serological diagnosis, and the most effective usages of them would lead to early accurate diagnosis of the disease. In the treatment, it seems necessary to understand characteristics of each antifungal drug, and to choose the optimal treatment method taking into account any underlying diseases and immune conditions. Also, the effectiveness of the combination therapy is examined in an increasingly number of cases, and the release of several new antifungal drugs is now scheduled. Previously we had to treat the aspergillosis cases with a limited number of drugs, but we are now entering the era when we ourselves should choose the effective and appropriate drugs and the methods of administration, and accumulate experiences in the use of the drugs. A new standard for the management strategy of aspergillosis infection is awaited.

**References**


