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MORPHOLOGICAL FEATURES OF THE CLINICAL COURSE OF INVASIVE PULMONARY ASPERGILLOSIS

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Annotation

Aspergillosis is the collective term used to describe all disease entities caused by any one of ~35 pathogenic and allergenic species of Aspergillus. Only those species that grow at 37°C can cause invasive infection, although some species without this capability can cause allergic syndromes. A. fumigatus is responsible for most cases of invasive aspergillosis, almost all cases of chronic aspergillosis, and most allergic syndromes. A. flavus is more prevalent in some hospitals and causes a higher proportion of cases of sinus and cutaneous infection and keratitis than A. fumigatus. A. niger can cause invasive infection but more commonly colonizes the respiratory tract and causes external otitis.A.terreus causes only invasive disease, usually with a poor prognosis. A. nidulans occasionally causes invasive infection, primarily in patients with chronic granulomatous disease.

Key words: aspergillus, neutropenia, glucocorticoid therapy, pneumonia, COPD, galactomannan, dyspnoe.

Aspergillus has a worldwide distribution, most commonly growing in decomposing plant materials (i.e., compost) and in bedding. This hyaline (nonpigmented), septate, branching mold produces vast numbers of conidia (spores) on stalks above the surface of mycelial growth. Aspergilli are found in indoor and outdoor air, on surfaces, and in water from surface reservoirs. Daily exposures vary from a few to many millions of conidia; the latter high numbers of conidia are encountered in hay barns and other very dusty environments. The required size of the infecting inoculum is uncertain; however, only intense exposures (e.g., during construction work, handling of moldy bark or hay, or composting) are sufficient to cause disease in healthy immunocompetent individuals. Allergic syndromes may be exacerbated by continuous antigenic exposure arising from sinus or airway colonization or from nail infection. High-efficiency particulate air (HEPA) filtration is often protective against infection; thus HEPA filters should be installed and monitored for efficiency in operating rooms and in hospital environments that house very–high-riskpatients.

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The incubation period of invasive aspergillosis after exposure is highly variable, extending in documented cases from 2 to 90 days.Thus community-acquired acquisition of an infecting strain frequently manifests as invasive infection during hospitalization, although nosocomial acquisition is also common. Outbreaks usually are directly related to a contaminated air source in the hospital.

The primary risk factors for invasive aspergillosis are profound neutropenia and glucocorticoid use; risk increases with longer duration of these conditions. Higher doses of glucocorticoids increase the risk of both acquisition of invasive aspergillosis and death from the infection. Neutrophil and/or phagocyte dysfunction is also an important risk factor, as evidenced by aspergillosis in chronic granulomatous disease, advanced HIV infection, and relapsed leukemia. An increasing incidence of invasive aspergillosis in medical intensive care units suggests that, in patients who are not immunocompromised, temporary abrogation of protective responses as a result of glucocorticoid use or a general anti-inflammatory state is a significant risk factor. Many patients have some evidence of prior pulmonary disease—typically, a history of pneumonia or chronic obstructive pulmonary disease. Glucocorticoid use does not appear to predispose to invasive Aspergillus sinusitis but probably increases the risk of dissemination after pulmonary infection.

Invasive pulmonary aspergillosis is a serious infection with pneumonia. It can spread to other parts of the body. This infection occurs most often in people with a weakened immune system. This can be from cancer, AIDS, leukemia, an organ transplant, chemotherapy, or other conditions or medicines that lower the number or function of white blood cells or weaken the immune system. Invasive pulmonary aspergillosis (IPA) is a severe disease, and can be found not only in severely immunocompromised patients, but also in critically ill patients and those with chronic obstructive pulmonary disease (COPD). Chronic necrotising aspergillosis (CNA) is locally invasive and is seen mainly in patients with mild immunodeficiency or with a chronic lung disease. Aspergilloma and allergic bronchopulmonary aspergillosis (ABPA) are noninvasive forms of Aspergillus lung disease. Aspergilloma is a fungus ball that develops in a pre-existing cavity within the lung parenchyma, while ABPA is a hypersensitivity manifestation in the lungs that almost always affects patients with asthma or cystic fibrosis.

Alveolar macrophages are the first line of defence against inhaled Aspergillus conidia. In the lungs, pathogen recognition receptors, such as Toll-like receptors, dectin-1 and mannose-binding lectin, identify specific fungal wall components and produce cytokines that stimulate neutrophil recruitment, the main defence mechanism against Aspergillus hyphae. The major

risk factor for IPA is immunodeficiency, which includes neutropenia, HSCT and solid-organ transplantation, prolonged therapy with high-dose corticosteroids, haematological malignancy, cytotoxic therapy, advanced AIDS and chronic granulomatous disease (CGD). The most important risk factor is neutropenia, especially when there is an absolute neutrophil count of <500 cells·mm^{-3}. The risk of IPA correlates strongly with the duration and degree of neutropenia. The risk in neutropenic patients is estimated to increase by 1% per day for the first 3 weeks and then by 4% per day thereafter. HSCT and solid-organ transplantation (especially lung transplantation) are also significant risk factors. Several other factors predispose patients with transplantation to acquire IPA: multiple immune defects including prolonged neutropenia in the pre-engraftment phase of HSCT; the use of multiple anti-rejection or anti-graft versus host disease (GVHD) therapy (such as corticosteroids and cyclosporine); parenteral nutrition; use of multiple antibiotics; and prolonged hospitalisation. There has been a steady increase in the documented cases of IPA following HSCT, where the risk is much higher following allogeneic rather than autologous HSCT (incidences of 2.3–15% and 0.5–4%, respectively). In allogeneic HSCT, the highest risk is in patients with severe GVHD (grade III–IV). The timeline of IPA in these patients follows a bimodal distribution, with a peak in the first month following HSCT, which is associated with neutropenia. The second peak is during the treatment of GVHD (median 78–112 days post-transplantation). Currently, the first peak is less significant because of the routine use of stem cells instead of bone marrow for transplantation, nonmyeloablative regimens, the use of colony-stimulating factors during neutropenia and the widespread use of antifungal agents. The second peak has become more significant, especially with the higher incidence of GVHD associated with unrelated allogeneic transplantation and treatment with intensive immunosuppressive therapy, including corticosteroids, cyclosporine A, anti-TNF agents, and other T-cell depleting strategies.

There are increasing numbers of reports documenting IPA in immunocompetent patients who do not have the classic risk factors. Two at-risk groups stand out: patients with severe COPD and critically ill patients. IPA is an emerging serious infection in patients with COPD. The majority of these patients have advanced COPD and/or are on corticosteroid therapy. Patients with COPD have increased susceptibility to IPA for several reasons, including structural changes in lung architecture, prolonged use of corticosteroid therapy, frequent hospitalisation, broad-spectrum antibiotic treatment, invasive procedures, mucosal lesions and impaired mucociliary clearance, and comorbid illnesses such as diabetes mellitus, alcoholism

and malnutrition. It is also possible that abnormalities or deficiencies in surfactant proteins, alveolar macrophages and Toll-like receptors play a role in the pathogenesis of IPA in some patients with COPD. In addition, it has been documented that chronic lung disease predisposes to colonisation of airways by Aspergillus spp., and it is possible, under certain circumstances, that this colonisation transforms to an invasive disease.

Clinical presentation: In most cases, Aspergillus is introduced to the lower respiratory tract by inhalation of the infectious spores. Less commonly, IPA may start in locations other than the lungs, such as sinuses, the gastrointestinal tract or the skin (via intravenous catheters, prolonged skin contact with adhesive tapes or burns). Symptoms are nonspecific and usually mimic bronchopneumonia: fever unresponsive to antibiotics, cough, sputum production and dyspnoea. Patients may also present with pleuritic chest pain (due to vascular invasion leading to thromboses that cause small pulmonary infarcts) and haemoptysis, which is usually mild, but can be severe. IPA is one of the most common causes of haemoptysis in neutropenic patients, and may be associated with cavitation that occurs with neutrophil recovery. Aspergillus infection may also disseminate haematogenously to other organs, including the brain. This can lead to seizures, ring-enhancing lesions, cerebral infarctions, intracranial haemorrhage, meningitis and epidural abscesses. Other organs such as the skin, kidneys, pleura, heart, oesophagus and liver may be less frequently involved.

The diagnosis of IPA remains challenging. Early diagnosis of IPA in severely immunocompromised patients is difficult, and a high index of suspicion is necessary in patients with risk factors for invasive disease. The gold standard in the diagnosis of IPA is histopathological examination of lung tissue obtained by thoracoscopic or open-lung biopsy. The presence of septate, acute, branching hyphae invading lung tissue along with a culture positive for Aspergillus from the same site is diagnostic of IPA. Histopathological examination also allows for the exclusion of other diagnoses, such as malignancy or nonfungal infectious diseases. The histopathological findings associated with IPA have been shown to differ according to the underlying host. In patients with allogeneic HSCT and GVHD, there is intense inflammation with neutrophilic infiltration, minimal coagulation necrosis and low fungal burden. In neutropenic patients, IPA is characterised by scant inflammation, extensive coagulation necrosis associated with hyphal angio-invasion, and high fungal burden. Dissemination to other organs is equally high in both groups. The most recent advances in the diagnosis of IPA are related to detecting Aspergillus antigens in body fluids, mainly galactomannan and (13)-β-d-glucan (both are cellular wall constituents). Galactomannan is a

polysaccharide released by Aspergillus during growth. Galactomannan detection may allow earlier confirmation of the diagnosis; it may also assist in the assessment of the evolution of infection during treatment if serial serum galactomannan values are obtained. Galactomannan is found in food and may be absorbed by the digestive tract, especially in patients with post-chemotherapy mucositis, resulting in a false-positive reaction. Also, medications such as β-lactam antibiotics (e.g. penicillin/tazobactam) may be associated with a false-positive assay, while antifungal agents with activity against Aspergillus may lead to a false-negative result.

All in all, invasive pulmonary aspergillosis is a serious respiratory disease. The causative agent of this disease is a fungus. The course of the disease creates difficulties for differential diagnosis with other respiratory diseases. In addition, it causes serious complications in patients with concomitant diseases and can even cause death of patients.

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