REVIEW

Derleme

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Clinical Types of Pulmonary Aspergillosis: A Clinical Spectrum Review

Pulmoner Aspergillozisin Klinik Tipleri: Bir Klinik Spektrum Derlemesi

ABSTRACT

Aspergillus fungal species are found in nature and are the cause of pulmonary aspergillosis diseases in humans. It is generally seen in four forms clinically and radiologically, these are aspergilloma, chronic pulmonary aspergillosis, invasive pulmonary aspergillosis and allergic bronchopulmonary aspergillosis. However, overlap syndromes in which types of pulmonary aspergillosis are seen together should not be overlooked. Clinical symptoms, radiological imaging, serum antigen and antibody levels, body fluid cultures, rapid skin antigen tests, serum immunoglobulin levels are helpful for diagnosis. Although treatment options are evaluated on a case-by-case basis; antifungal therapy, surgery and corticosteroid agents are the main options. Invasive pulmonary aspergillosis associated with COVID-19 has been observed in association with COVID-19 infection. It should not be missed in patients with COVID-19 due to poor clinical prognosis.

Key Words

Aspergillosis, Thoracic Surgery, COVID-19, Medical Treatment

ÖZ

Aspergillus mantar türleri doğada bulunur ve insanlarda pulmoner aspergilloz hastalıklarının nedenidir. Klinik ve radyolojik olarak genel olarak dört formda görülür; bunlar aspergilloma, kronik pulmoner aspergilloz, invaziv pulmoner aspergillozis ve allerjik bronkopulmoner aspergillozistir. Ancak pulmoner aspergillus türlerinin bir arada görüldüğü örtüşme sendromları da gözden kaçırılmamalıdır. Klinik semptomlar, radyolojik görüntüleme, serum antijen ve antikor düzeyleri, vücut sıvısı kültürleri, hızlı deri antijen testleri, serum immunoglobulin düzeyleri tanıya yardımcıdır. Tedavi seçenekleri vaka bazında değerlendirilse de; antifungal tedavi, cerrahi ve kortikosteroid ajanlar ana seçeneklerdir. COVİD-19 ile ilişkili invaziv pulmoner aspergillozis, COVİD-19 enfeksiyonu ile tanımlanmıştır. Kötü klinik prognoz nedeniyle COVİD-19 hastalarında gözden kaçırılmamalıdır.

Anahtar Sözcükler

Aspergillozis, Göğüs Cerrahisi, COVİD-19, Medikal Tedavi

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INTRODUCTION

Aspergillus, with more than 200 subspecies, is a saprophytic, filamentous fungus that lives in soil, debris, and rotten plants (1, 2). Pathogenic types are Aspergillus fumigatus, Aspergillus flavus, and Aspergillus niger (1, 2). Aspergillus terreus, Aspergillus clavatus, Aspergillus niveus, and Aspergillus nidulans are rare pathogens (1). The route of transmission occurs via inhalation of airborne spores. Aspergillus grows at 37 oC and has small spores (1, 2). Spore inhalation leads to colonization (1, 2). Mucociliary activity does not cause illness in healthy persons (1, 2). Patients suffering from cavitary lung disease may develop aspergilloma (1-3). Patients with modest immunosuppression or chronic lung illness are at risk for developing chronic necrotizing/pulmonary aspergillosis (1-3). Immunocompromised individuals are susceptible to invasive pulmonary aspergillosis (1-6). Patients with a history of asthma are more likely to develop allergic bronchopulmonary aspergillosis (1-3, 5, 7) (Figure 1).

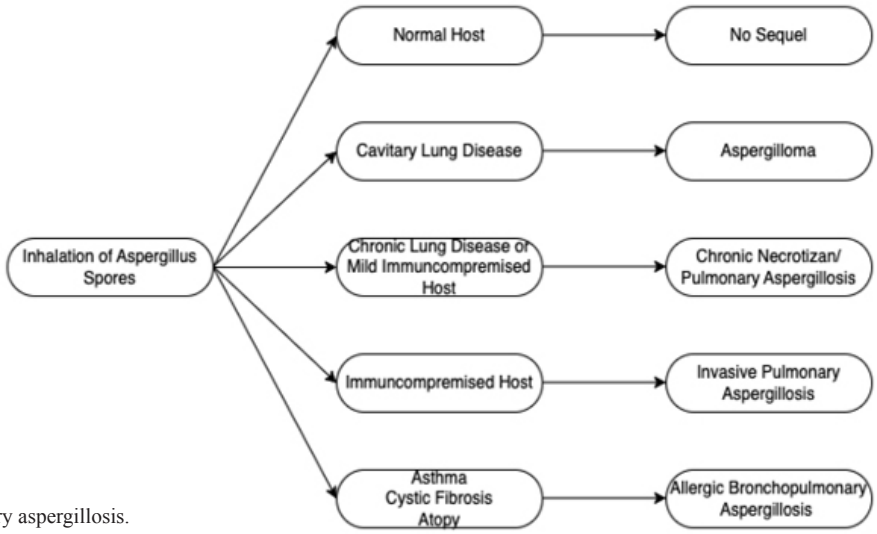

Figure 1. The spectrum of pulmonary aspergillosis.

Aspergilloma

Aspergilloma is the most prevalent disease form of Aspergillus in the lungs (1, 2, 5). Known as a "fungus ball" in Aspergilloma, these masses can include fibrin, mucus, inflammatory cells, and fungal micelles (1, 2, 5, 6). The most common cause of fungus balls is Aspergillus fungus; Zygomycetes and Fumigatus can also form fungus balls (1, 5) (Figure 2).

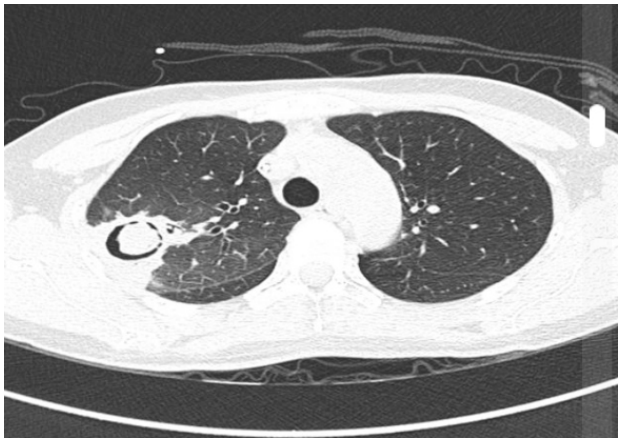

Figure 2. Fungus Ball

The most common predisposing factor in the etiology of aspergilloma is previous tuberculosis (1-3, 5, 6). Sarcoidosis, bronchiectasis, bronchial cyst, bulla, ankylosing spondylitis, and a history of malignancy are other common predisposing factors (1, 2, 5). Surrounding lung parenchyma tissue is preserved in aspergilloma (1, 2, 5). It usually remains stable in size, but in some cases, it may decrease (1, 5, 8). Most of the patients with aspergilloma are asymptomatic (1, 5, 8). Cough, dyspnea, and secondary bacterial infections are milder or less severe symptoms (1, 2, 5). Hemoptysis is a serious symptom of bleeding from bronchial blood vessels (1, 2, 5). Thorax computed tomography and posteroanterior chest radiography are used in radiological diagnostics (1, 2, 5). In radiological differential diagnosis, hematoma, neoplasia, abscess, hydatid cyst, and Wegener's granulomatosis should not be overlooked (1, 5, 8). Although bronchoalveolar lavage and sputum culture are useful in diagnosis, they yield negative results in half of the patients (1, 5, 8). Aspergillus serum IgG positivity is important in the diagnosis; false negatives are rare (1, 2, 5). Inhaled, intracavitary, and endobronchial antifungal treatments are unsuccessful in aspergilloma (1, 2, 5). The success of systemic antifungal therapy is controversial, and minimal inhibitory concentrations are rarely reached in the lung cavity (1, 2). Intravenous use of Amphotericin B also does not show a significant benefit (1, 2, 5). Itraconazole treatment has variable results and is beneficial in selected aspergilloma patients with high tissue penetration (1, 5). Bronchial artery embolization can be used in the control of massive hemoptysis (1, 2, 5). Surgical treatment is recommended in patients with adequate pulmonary reserve (1-3, 5) (Table I). Perioperative mortality and risk of surgical complications are low in

simple pulmonary aspergilloma with thin wall cavitation (3, 8, 9). Complex aspergilloma with thick wall cavitation has a higher risk of surgical complications (3, 8). The surgical technique is frequently thoracotomy; parenchymal adhesion and bleeding are necessary for thoracotomy (4). As the experience of video-assisted thoracic surgery has increased, its application has also increased in aspergilloma patients (4, 10). Postoperative outcomes are better with thoracoscopic surgery (4, 10). The lung resection to be performed is decided according to the location of the aspergilloma (4,10). Fungus ball cavity resection, wedge resection, segmentectomy, and lobectomy can be performed (4, 10).

Chronic Necrotizing/Pulmonary Aspergillosis (CNA/CPA)

In chronic necrotizing/pulmonary aspergillosis (CNA), slow destruction of the lung parenchyma and secondary formation of the fungus ball are present (1, 2, 5, 6). There is no vascular invasion or spread to other organs (1, 2, 5). It is seen in middle-aged or elderly patients with a history of chronic obstructive pulmonary disease (COPD), inactive tuberculosis, lung resection, pneumoconiosis, cystic fibrosis, and sarcoidosis (1, 2, 5). Complaints of slowly progressing cough, sputum, fever, and weight loss are seen for 1-6 months (1, 2, 5). Radiologically, an infiltrative process located in the upper lobe or lower lobe superior segment is observed (1, 5). Pleural thickening indicates an invasive process (1, 2). Diagnosis is made in the sputum or by bronchoscopic percutaneous interventions (1, 2). Aspergillus IgG antibodies and skin reaction tests for Aspergillus are helpful in diagnosis (1, 2, 5). Considering the complications of surgery, systemic antifungal therapy is recommended first (Amphotericin B, Itraconazole, and Voriconazole) (1, 2, 5) (Table I).

Table I. Treatment Recommendations for Pulmonary Aspergillosis.

Disease	Primary Treatment	Other Treatment
Invasive Pulmonary Aspergillosis	Voriconazole	Alternative Therapy: Liposomal amphotericin B Continuation Therapy: Voriconazole or Itraconazole Salvage Therapy: Echinocandin or Posaconazole
Chronic Necrotising/Pulmonary Aspergillosis	Voriconazole	Alternative Therapy: Itraconazole Severe Cases: Intravenous voriconazole or Liposomal amphotericin B Consider Surgical Resection
Aspergilloma	Observation	Bronchial Artery Embolisation Surgical Resection Consider Itraconazole
Allergic Bronchopulmonary Aspergillosis	Corticosteroids	Itraconazole or Voriconazole as Steroid-Sparing Agents

Amphotericin-B is given at doses of 0.5–1 mg/kg/day and liposomal Amphotericin-B at doses of 4-5 mg/kg/day (5, 11). Surgery is appropriate in patients with focal disease, good pulmonary reserve, residual active disease despite antifungal therapy, or young patients (1, 2, 5, 9). Surgery is not the first choice for elderly patients with limited pulmonary reserve (1, 2).

Invasive Pulmonary Aspergillosis(IPA)

Major risk factors for invasive pulmonary aspergillosis(IPA): prolonged neutropenia or neutrophil dysfunction (chronic granulomatous disease), COPD, corticosteroid therapy, transplantation, hematological malignancy, cytotoxic therapy, AIDS (1-3, 5, 6, 12). In cases of respiratory transmission, symptoms are frequently cough, dyspnea, fever, sputum, and hemoptysis (1-3). It can also be transmitted from the skin through the catheter (1, 6). Tracheobronchitis secondary to plaque formation and ulceration is observed in immunodeficiency syndrome (AIDS) and transplant patients, and airway obstruction and atelectasis are observed (1, 3, 13). Sputum culture is positive, and septate and branching hyphae are seen in the lung tissue (1, 2). Positive sputum culture may also colonize the respiratory tract, but it should not be missed in the risky patient group (1, 2, 9). Multiple nodules, the halo sign (low attenuation zone due to hemorrhage surrounding the pulmonary nodule), there is repetition air crescent sign (appearance secondary to necrosis) may be present in thorax computed tomography (1-3, 5). Bronchoalveolar lavage and bronchoscopic biopsies contribute to the diagnosis (1, 2, 5, 13). The detection of galactomannan and beta-D-glucan antigens in body fluids is helpful in diagnosis (5, 7, 13). Surgical biopsy is the gold standard for diagnosis, but surgery is beneficial in patients with massive hemoptysis but not in cases of extensive involvement (1, 3, 12). The chance of treatment increases with high doses of antifungal therapy and correction of the underlying neutropenic clinic (1, 6, 7). Considering the difficulties in the management of the IPA clinic, prophylaxis is important in the risky patient group, and prophylactic treatment is applied in patients with clinical suspicion (1, 2, 5). Triazoles (itraconazole, voriconazole, and posaconazole); echinocandin derivatives (caspofungin, micafungin, and anidulafungin); amphotericin B and lipid formulations in therapy are all mentioned (2, 5, 12) (Table I).

The first treatment option is amphotericin-B (1–1.5 mg/kg/day) (5, 7). In cases of side effects, the liposomal Amphotericin-B option is considered (3 mg/kg/day) (5, 7). Voriconazole treatment is 6 mg/kg intravenously twice on the first day, and continuation treatment is 4 mg/kg/day (5, 7). 200 mg taken orally twice a day is administered after seven days (5, 7). In addition to antifungal therapy, immunomodulatory therapy (such as granulocyte colony stimulating factor G-CSF, granulocyte-macrophage colony stimulating factor GM-CSF, and interferon-C) is given to reduce the degree of immunosuppression (5, 7). The place of surgery for immunosuppressed patients is controversial

(3, 5). In the presence of hemoptysis, in the presence of radiological persistence of IPA spaces, and in the presence of bone invasion, surgery is indicated in the vicinity of the pulmonary vessels (3, 5, 9).

Allergic Bronchopulmonary Aspergillosis (ABPA)

Hypersensitivity to Aspergillus antigens causes allergic bronchopulmonary aspergillosis (ABPA) (1, 2, 5). A crucial role is played by IgE-mediated type 1 hypersensitivity, IgG-mediated type 3 hypersensitivity reactions, and aberrant T-lymphocyte responses (1, 2, 5). Patients with cystic fibrosis or asthma have it (5, 7). Patients who have experienced atopy in the past are more likely to experience ABPA (5). When there is a clinical suspicion, radiographic and serological information are used to make the diagnosis (1, 2, 5). Serum IgE levels are high; fast skin test responsiveness is evident; sputum culture positivity is not required for diagnosis (5, 7). Clinically, asthma, episodic wheezing, brown sputum, pleuritic chest pain, and fever are seen (5, 7). Band-like, rounded distal-sided opacities (gloved finger appearance) radiating from the hilum, tram lines due to bronchial inflammation, and ring signs are seen (1, 2, 5, 7) (Figure 3).

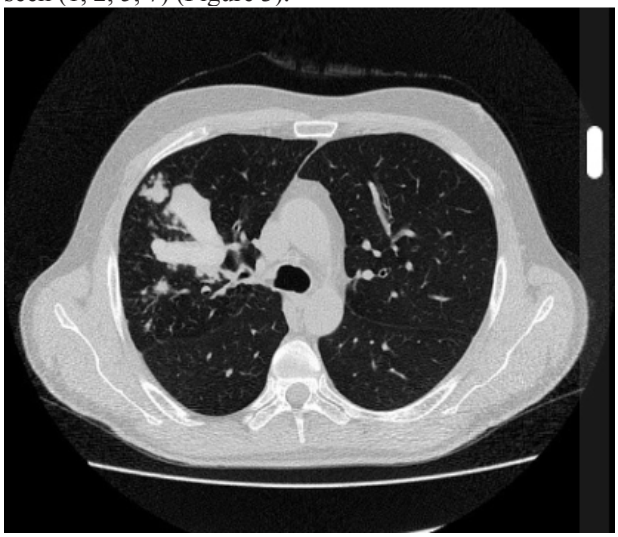

Figure 3. Gloved Finger Appearance

Pulmonary fibrosis and central bronchiectasis develop as the clinic advances (1, 2, 5). ABPA is divided into two groups: those with and without central bronchiectasis (5). In terms of clinical course, it consists of 5 stages (5). Asthma presents in stage 1 (acute stage) with peripheral eosinophilia, high IgE levels, lung infiltrates, and IgG antibodies against A. Fumigatus (5). Stage 2 (remission stage); IgE level decreases compared to Stage 1, but is still higher than normal (5). There is no eosinophilia, and the radiological appearance is normal (5). Stage 3 (flag phase) is the recurrence of Stage 1 in a patient with ABPA (5). Stage 4 (corticosteroid-related stage): It occurs due to the chronic use of high-dose corticosteroids (5). There is a rise in IgE levels, radiographic bronchietasis, clinical aggravation, and asthma worsening (5). Stage 5 (fibrotic stage): bronchiectasis and fibrosis develop, leading to irreversible lung disease (5). Dyspnea, cyanosis, ral, cor pulmonale, and clubbing are seen (5). Serum IgE levels may be high or low (5). The main purpose of treatment is to prevent acute exacerbations (5) (Table I). If treatment is delayed, bronchiectasis and pulmonary fibrosis will occur, and treatment should be initiated in cases of clinical suspicion (5). Treatment includes oral corticosteroids (2 weeks of treatment-oral prednisone 0.5 mg/kg/day, followed by gradual dose reduction) to suppress the immune reaction (1, 2, 5, 7). Hypersensitivity responses and inflammatory responses triggered by A. fumigatus are stopped with corticosteroids (5, 7). Clinical, radiological, and serological improvement is observed (5). In most patients, long-term, low-dose corticosteroid therapy is given to control symptoms and prevent recurrence (5, 7). Itraconazole can be given as an auxiliary agent (5, 7).

Aspergillus syndromes can coexist; this clinical condition is called pulmonary aspergillus overlap syndromes (5) (Figure 4).

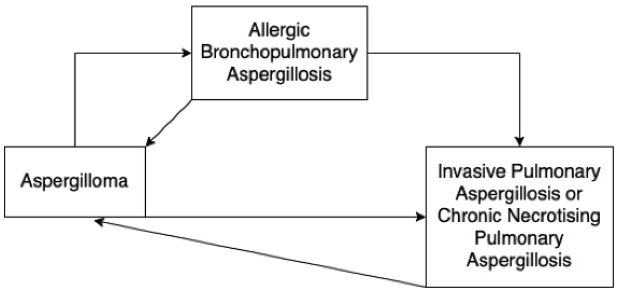

Figure 4. Aspergillus Overlap Syndrome

The risk of Aspergillus overlap syndrome increases in the presence of a high load of Aspergillus fungi, additional viral diseases, genetic predisposition (such as cystic fibrosis transmembrane regulator gene mutation, mannose-binding lectin gene mutation), the presence of serious underlying lung disease, and corticosteroid therapy (5).

In 2019, the SARS-CoV-2 agent was discovered and declared to be a global pandemic agent (14-16). It is known that COVID-19 infection is the cause of coinfection with other respiratory tract disease agents (14-16). Aspergillus spp. It may be a cause of coinfection, especially in severe COVID-19 patients (14-16). The co-infection of COVID-19 and IPA was named COVID-19-associated IPA (14-16). Although there is no risk factor for IPA, COVID-19-associated IPA is seen (14-16). Radiological findings vary according to the stage of IPA, but there is no specific appearance (14, 15) (Figure 5, 5a, 5b, 5c).

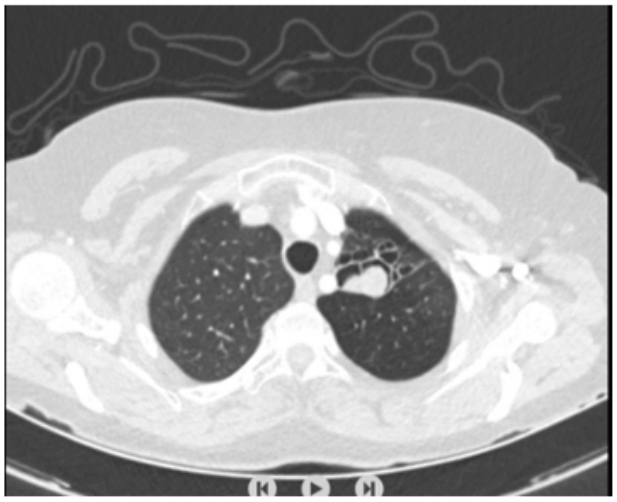

Figure 5. COVID-19-associated IPA. Thorax CT sections of a case of aspergilloma developing in the left lung after COVID-19infection.

Figure 5a. Cavitary lesion in a patient with aspergilloma.

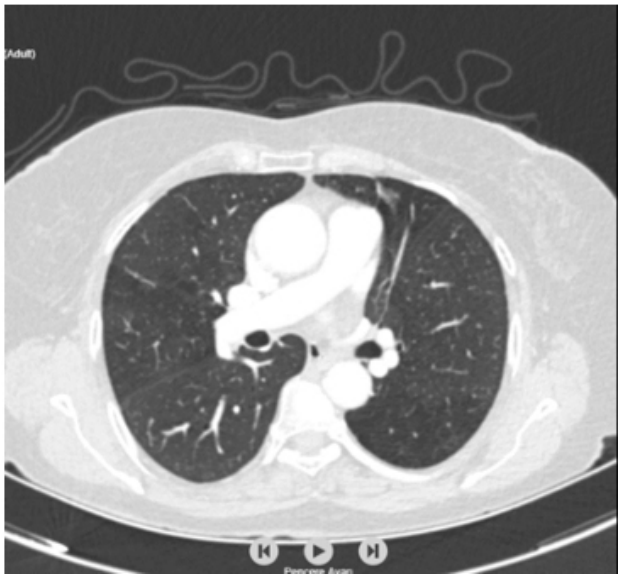

Figure 5b. Ground glass opacity in a patient with COVID-19.

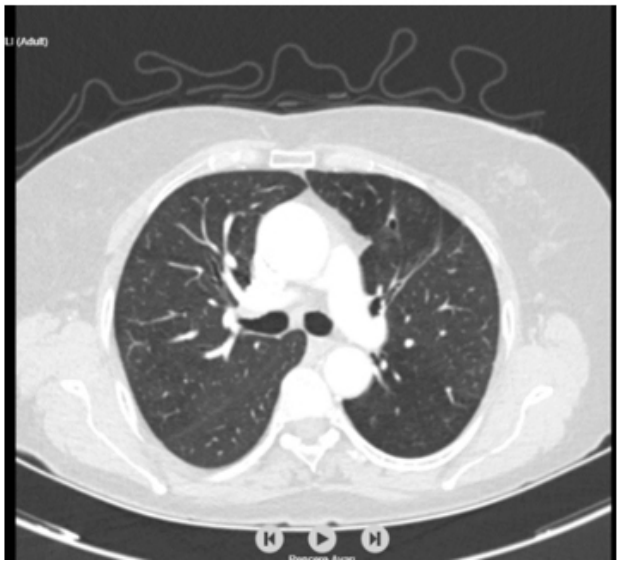

Figure 5c. Ground glass opacity (consecutive CT section).

Sputum culture, bronchoalveolar lavage culture, galactomannan, and beta-D-glucan test positivity are useful for diagnosis (14-16). However, it should not be overlooked that, due to the rapid transmission of the SARS-CoV-2 virus, it is difficult to make current samples (15). The clinical results of COVID-19-associated IPA patients are worse and the mortality is higher, so diagnosis should be made quickly (14, 15). Lopinavir-ritonavir-molnupravir is used for COVID-19, and voriconazole, caspofungin, isavuconazole, and liposomal amphotericin B are used for IPA (14, 15). The most common complication is the need for mechanical ventilation due to acute respiratory distress syndrome (14, 15). Multiple drug interactions should also be considered in the treatment (14, 15).

CONCLUSION

Pulmonary aspergillosis can be seen in different clinics. Treatment modalities vary according to clinical diagnosis. For the treatment of both chronic necrotizing/pulmonary aspergillosis and invasive pulmonary aspergillosis, voriconazole is the primary option. When treating aspergilloma, follow-up and surgery ought to come first. The most advanced medication for treating allergic bronchopulmonary aspergillosis is corticosteroids. Correct diagnosis and treatment are important in prognosis.

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