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A Case of Aspergillosis Battling Thrombosis: Challenging Diagnosis and Treatment in an Immunocompetent Patient

Tromboz ile Mücadele Eden Aspergillozis Olgusu: İmmünokompetan bir Hastada Zorlu Tanı ve Tedavi Süreci

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Abstract

Invasive pulmonary aspergillosis (IPA) is typically seen in immunocompromised patients, but may also develop in immunocompetent individuals, and is associated with high mortality rates. We report here on the case of a 47-year-old male patiet with a history of asthma who presented with fever, cough and sputum production. He was initially diagnosed with hospital-acquired pneumonia and started on appropriate treatment, however, his symptoms persisted. Further investigations revealed Aspergillus spp., leading to a diagnosis of invasive aspergillosis. Radiological imaging revealed a lesion in the left upper lobe, and the diagnosis was confirmed through transthoracic needle biopsy. The patient was started on intravenous voriconazole, but developed thrombosis in the right cephalic vein. Anticoagulation therapy with enoxaparin was added to the protocol, however, balancing the treatment of thrombosis with the risk of bleeding presented a challenge. This case highlights the challenges that can be encountered in clinical diagnosis and treatment, and shows that aspergillosis should be considered even in immunocompetent patients. It further clarifies the need to find the optimum balance between thrombosis treatment and bleeding risk, as a critical aspect of the treatment process in cases of invasive aspergillosis.

Keywords: *Invasive pulmonary aspergillosis, immunocompetent individual, thrombosis, anticoagulant therapy.*

Öz

İnvaziv pulmoner aspergilloz (İPA), genellikle immünkompromize bireylerde görülen ve yüksek mortalite oranlarıyla ilişkilendirilen bir enfeksiyondur. Ancak nadiren immünkompetan bireylerde de ortaya çıkabilir. Bu olguda, astım öyküsü olan 47 yaşındaki erkek hasta ateş, öksürük ve balgam şikayetleri ile başvurdu. Başlangıçta hastane kaynaklı pnömoni tanısı konularak tedavi başlandı; ancak semptomları devam etti. Yapılan ileri tetkiklerde Aspergillus türleri tespit edilerek invaziv aspergilloz tanısı konuldu. Radyolojik incelemelerde sol üst lobda bir lezyon saptandı ve tanı transtorasik iğne biyopsisi ile doğrulandı. Hastaya intravenöz vorikonazol tedavisi başlandı, ancak sağ sefalik vende tromboz gelişti. Enoksaparin ile antikoagülan tedavi eklendi; ancak tromboz tedavisini kanama riski ile dengelemek önemli bir zorluk oluşturdu. İPA hastalarında tromboza yatkınlık ve tedavi sürecinde karşılaşılan zorluklar, terapötik kararlar alınırken dikkatli olunması gerektiğini vurgulamaktadır. Bu olgu, immünkompetan bireylerde dahi aspergillozun göz önünde bulundurulması gerektiğini göstermekte ve invaziv aspergilloz olgularında tromboz tedavisi ile kanama riski arasındaki dengenin sağlanmasının kritik bir önemi olduğunu ortaya koymaktadır.

Anahtar Kelimeler: *İnvaziv pulmoner aspergilloz, immünkompetan birey, tromboz, antikoagülan tedavi.*

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Invasive pulmonary aspergillosis (IPA) is a severe fungal infection caused by *Aspergillus* species, and is associated with high mortality rates. The main risk factors for IPA include neutropenia, hematopoietic stem cell transplantation (HSCT), solid organ transplantation, prolonged treatment with high-dose corticosteroids, hematological malignancies, cytotoxic therapy, advanced AIDS and chronic granulomatous disease, all of which can significantly impair the immune system (1). While IPA predominantly affects severely immunosuppressed hosts, immunocompetent patients may also be affected (2). The symptoms of IPA are nonspecific and may include antibiotic-resistant fever, cough, sputum production, dyspnea, and mild to severe hemoptysis (3).

The early diagnosis of IPA in severely immunosuppressed patients can be challenging, and high-resolution CT is the preferred imaging modality in cases with a high index of suspicion for invasive disease. Typical chest CT findings include multiple nodules and the halo sign appearing as a ground-glass opacity surrounding a pulmonary nodule, indicating hemorrhage, and typically observed during the early stages of infection (usually within the first week) in neutropenic patients. Another radiological feature is the air-crescent sign, which may be seen in the late stages due to necrosis, and appears as a crescent-shaped density in the primary nodule region (4). Bronchoscopy and bronchoalveolar lavage (BAL) can be useful for detecting *Aspergillus* antigens and ruling out other infections. In selected cases, though less frequently, CT-guided transthoracic biopsies, open lung biopsies, transbronchial biopsies or convex endobronchial ultrasound-guided transbronchial needle aspiration may be performed (5).

Voriconazole is a broad-spectrum triazole, available in both intravenous (IV) and oral, formulations that has been approved as the first-line treatment for invasive aspergillosis, and is currently among the preferred therapeutic options for patients with IPA. The recommended initial dose is 6 mg/kg IV every 12 hours on day 1, followed by a daily dose of 4 mg/kg IV. After 7 days, treatment can be switched to an oral regimen of 200 mg twice Daily (6,7).

CASE

A 47-year-old male patient with a 10-year history of asthma presented to our hospital with complaints of fever, cough and sputum. His medical history revealed that he had been treated for pneumonia at an external center, where he had spent 18 days in intensive care followed by 12 days in a regular ward, and had been discharged 5 days earlier. The patient was using an inhaler containing 500 micrograms of fluticasone propionate and 50 micrograms of salmeterol, had no chronic diseases other than asthma and had a smoking history of 25 pack-years. A posterior-anterior chest X-ray revealed densities (Figure 1A) and C-reactive protein (CRP) levels were found to be elevated at 116 mg/L (normal value <5 mg/L), prompting hospital admission. Routine biochemistry tests were performed, and Elisa tests were ordered, but no pathology was detected. The close monitoring of vital signs and blood sugar levels was initiated, and a sputum culture was requested.

The patient was referred to the infectious diseases department with a preliminary diagnosis of hospital-acquired pneumonia, and based on their recommendations, Brucella tests were ordered and empiric treatment with piperacillin-tazobactam (3x4.5 g) was initiated. The patient showed no expected clinical or laboratory response, the Brucella tests were negative and the sputum culture revealed normal upper respiratory flora. A respiratory PCR panel was subsequently performed, the empiric treatment was switched to tigecycline (2x100 mg), and the close monitoring of vital signs and CRP levels continued. Despite all efforts, the patient's fever persisted, and the piperacillin-tazobactam therapy was discontinued on the 5th day of hospitalization in favor of imipenem (4x500 mg).

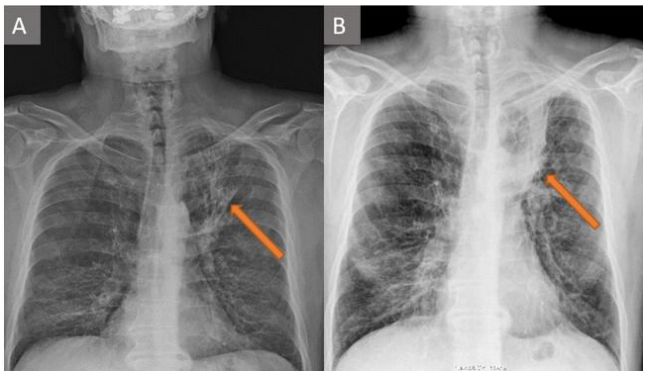

Figure 1: *In the initial chest X-ray, densities can be seen in the upper zone of the left lung and the lower zone of the right lung* ***(A)****. In a follow-up chest X-ray after discharge, a newly developed density can be seen in the upper zone of the left lung* ***(B)***

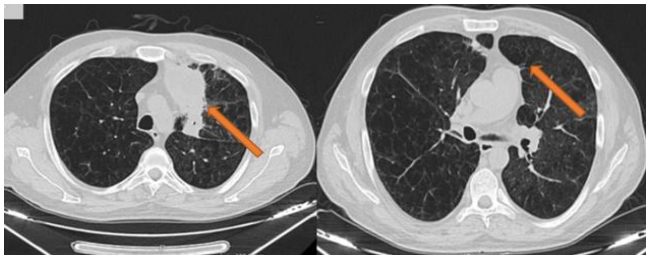

Figure 2: *Parenchymal sections of the chest CT revealing an irregularly contoured area of consolidation measuring 3.5x6.5 cm in the left upper lobe, extending into the paramediastinal area, with a centrally cystic area measuring 4x5.5 cm in the anterior part, and a subsolid nodule measuring approximately 5 mm in diameter in the right upper lobe*

Aspergillus spp. was detected in the fungal culture on the 12th day of hospitalization, but was dismissed as it was thought to be a result of contamination based on the patient's clinical, radiological and laboratory response to antibiotics and immunocompetence, and the absence of any abnormalities in blood glucose levels or vital signs.

During the 15-day hospitalization, the patient's symptoms improved and a decrease in CRP levels (9 mg/L) was noted, and the patient was duly discharged. However, the patient was readmitted 5 days later with similar symptoms, when a density was observed in the left upper lobe on posterior-anterior chest X-ray (Figure 1B), leading to a chest computed tomography (CT) scan (Figure 2). The CT scan revealed a soft tissue appearance in the left upper lobe, prompting a transthoracic fine needle aspiration biopsy to be performed under interventional radiology guidance.

The pathology report revealed invasive aspergillosis, and the patient was admitted to our service and started on IV voriconazole treatment. Following an evaluation of the patient's immunosuppressive status, the patient, who had no known comorbidities, underwent Elisa and rheumatological marker tests, which yielded no abnormalities. During hospitalization, the patient developed edema and numbness in the right forearm and Doppler ultrasonography was performed, revealing a non-compressible segment of the right cephalic vein in the proximal-middle forearm (~10 cm) with an appearance consistent with a hyperechoic thrombus in the lumen. The thrombus, the patient was duly started on subcutaneous enoxaparin sodium 2x1 for treatment. There was no history of any interventional procedure that could have contributed to thrombosis

Despite the IV voriconazole treatment, the patient's CRP levels and clinical condition did not improve significantly during inpatient follow-up, prompting a consultation with the infectious diseases department, and IV moxifloxacin (500 mg 2x1) was added to the treatment regimen. After a 24-day hospital stay, the patient's general condition improved and they were discharged with oral voriconazole and enoxaparin sodium. The patient was followed up by the cardiovascular surgery department for 3 months following the development of the thrombosis, and the thrombosis resolved after 3 months of treatment, after which the enoxaparin therapy was discontinued. Following 75 days of treatment, a thoracic CT scan revealed a regression of the lesions, and further improvement was observed on a 6-month follow-up thoracic CT (Figure 3).

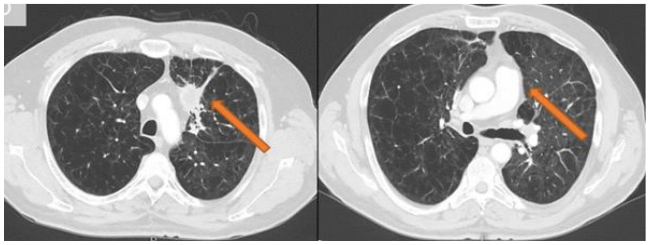

Figure 3: *Chest CT at 6-month follow-up in which the former nodular lesion in the right upper lobe is no longer visible and significant regression can be seen in the lesion in the left upper lobe*

DISCUSSION

IPA is a severe fungal infection with high morbidity and mortality, and predominantly affects the immunocompromised. *Aspergillus* species typically enter the body through the lungs but may disseminate to other organs.

The main risk factors for IPA include neutropenia, solid organ transplantation, hematologic malignancies, cytotoxic therapies and advanced-stage AIDS. The risk of developing IPA with systemic corticosteroid is supported by a number of case reports in the literature, even in immunocompetent patients (8,9). Furthermore, there is a growing body of studies reporting IPA in immunocompetent patients with severe chronic obstructive pulmonary disease (COPD), often associated with prolonged corticosteroid use (10). The use of inhaled corticosteroids (ICS) for the treatment of chronic lung diseases has been suggested in several studies to increase the risk of pneumonia. While this association is more clearly established in patients with COPD (11), there are also studies suggesting a greater risk of pneumonia in asthma patients using ICS when compared to those who do not (12). Although inhaled therapies are thought to increase the risk of pneumonia, there is currently a lack of evidence confirming the causative pathogens. That said, there is no strong evidence that inhaled corticosteroid use predisposes patients to Aspergillus infections, and so the long-term use of inhaled corticosteroids in our patient should be carefully considered as a potential contributing factor.

It has been well-documented that chronic pulmonary diseases predispose airways to colonization by *Aspergillus* species. Under specific conditions, such colonizations can progress to invasive diseases (13). In the presented case, IPA was observed despite the immunocompetent status of the patient, and this, along with the non-specific findings on thoracic CT, led to the initial dismissal of the growth in the sputum culture as a pathogenic cause. Advanced diagnostic measures were thus initiated due to the persistence of symptoms and the need to rule out malignancy. A diagnosis of invasive aspergillosis was finally arrived at based on the results of a transthoracic fine-needle biopsy. Concurring with similar cases reported in the literature, *Aspergillus* spp. was unexpectedly identified as the causative agent of invasive infection in our immunocompetent patient. This highlights the importance of maintaining a high index of suspicion for IPA, even in patients without classic immunosuppressive risk factors, and particularly when clinical and radiologic findings remain unresolved.

The findings of the present study underscore the diagnostic challenges associated with IPA. In patients with chronic

pulmonary diseases, *Aspergillus* spp. Isolated from lower respiratory tract samples should not be dismissed as mere colonization, as *Aspergillus* spp. should be considered a potential causative pathogen, even in immunocompetent patients. In cases where non-specific treatments fail to yield satisfactory results, evaluating *Aspergillus* spp. as an etiological agent can facilitate the implementation of early and accurate therapeutic strategies. Such an approach may prevent disease progression and circumvent the complications associated with invasive aspergillosis, ultimately improving patient outcomes.

The primary complications of IPA include the endothelial damage, local erosion and deep tissue invasion caused by fungal hyphae through angioinvasion (10). Specifically, galactosaminogalactan secreted by *Aspergillus fumigatus* and *Aspergillus flavus* accumulates on platelet surfaces, triggering platelet activation. This cascade leads to intravascular thrombosis and localized infarcts (10,14). Such pathophysiological mechanisms contribute to disease progression and increased mortality rates. These severe complications of IPA highlight the paramount importance of early diagnosis and aggressive treatment strategies. Timely therapeutic interventions can mitigate the progression of the disease and reduce the associated risks, thereby improving patient survival.

The surface-bound GAG produced by *Aspergillus fumigatus* and *Aspergillus flavus* binds to platelets, triggering their activation and activating the complement system. This process can lead to negative outcomes such as thrombosis, thrombocytopenia and excessive inflammation (10). The complement activation triggered against platelets by GAG plays a significant role in increasing the susceptibility to thrombosis in Aspergillus infections. Although this mechanism is understood, the current guidelines offer no adequate recommendations for the preventive treatment of thrombosis in Aspergillus infections (15). As seen in our case, the clinical outcomes of thrombosis can be observed, and managing potential complications during treatment can be challenging.

Platelets play a dual role in immune response by contributing to normal cell-mediated immunity, while also participating in fungal hyphal elongation and antifungal host defense. Platelets release procoagulant proteins upon stimulation by *Aspergillus*-derived factors, which in turn induce the excessive production of inflammatory mediators. This overproduction leads to tissue damage and thrombosis (10,16,17). In 2023, Vikhe et al. (2) reported a case of IPA complicated by portal vein thrombosis to highlight the challenges posed in patient management and treatment. In the same year, Yun et al. (18) described two pediatric cases of IPA under immunosuppression that developed intracardiac thrombi. Recent case reports underscore that IPA can lead to thrombosis not only in the vascular regions adjacent to the invasive fungal growth, but also in distant vascular areas under systemic effects. In the presented case, the thrombus was detected in the cephalic vein, and while rare, this aligns with previous findings and the suggested systemic thrombotic effects associated with IPA. Such a predisposition to thrombosis reinforces the need for further studies to evaluate the necessity and potential efficacy of antithrombotic prophylaxis strategies in patients diagnosed with IPA.

Lyu et al. (19) carried out a comprehensive cohort study between 2014 and 2020 in a pulmonary intensive care unit during which they analyzed the bleeding incidences and risk factors of patients receiving thromboprophylaxis. Of the 931 patients in the study, 26 were diagnosed with IPA, and 19 of these were identified as being at high risk of major bleeding. The authors reported IPA to be an independent risk factor for major bleeding, and suggested that *Aspergillus* infections could increase bleeding tendencies through vascular damage as a consequence of the infection's impact on vascular integrity, which they attributed to the systemic effects of the circulating infection. They further suggested that *Aspergillus* could contribute to localize bleeding through elastase production and the resulting damage to local tissues. These findings highlight the dual challenge posed by IPA, being the predisposition to thrombotic complications alongside the increased risk of bleeding, and underscore the importance of individualized patient management strategies that balance thromboprophylaxis and bleeding risk in cases with IPA.

The administration of anticoagulant therapy in patients diagnosed with IPA is a complex clinical scenario that requires careful assessment of both the thrombotic risk and bleeding potential. When planning anticoagulant therapy for these patients, it is, therefore, essential to consider not only the risk of thrombosis but also the potential for severe bleeding, to evaluate the clinical situation individually, and to make decisions based on a multidisciplinary approach. Prospective studies are needed to determine optimal management strategies.

CONCLUSION

IPA is a severe infection that can develop even in immunocompetent patients, making early diagnosis and appropriate treatment crucial. *Aspergillus* spp. should not be considered merely as colonizers, but also as potential pathogens, and vascular complications such as thrombosis and bleeding must be carefully managed during treatment. This highlights the importance of a multidisciplinary approach and the need for further studies of this condition.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - N.Y., H.A., E.Ö., E.U.; Planning and Design - N.Y., E.Ö., H.A., E.U.; Supervision - E.U., N.Y., H.A., E.Ö.; Funding - N.Y., H.A., E.Ö.; Materials - N.Y., H.A.; Data Collection and/or Processing - N.Y., H.A., E.Ö.; Analysis and/or Interpretation - N.Y., H.A.; Literature Review - N.Y.; Writing - N.Y., H.A., E.Ö., E.U.; Critical Review - N.Y., E.U.

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