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Pulmonary Aspergilloma in Immunocompromised Patients: Expanding Treatment Horizons with Voriconazole and Anidulafungin

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ABSTRACT

BACKGROUND. Pulmonary aspergilloma is the most common pulmonary involvement due to *Aspergillus*. It usually develops in a pre-existing cavity in the lung, most often due to tuberculosis. Hemoptysis occurs secondary to local invasion of the blood vessels lining the cavity. Recurrence of which, is an indication to do surgery, lobectomy in particular. Antifungals like amphotecin B given intravenously and itraconazole given orally, have been the traditional management. But with the emergence of newer antifungals, Echinocandins in particular, which functions to inhibit the β-(1,3) p-glucan synthase, an enzyme necessary for the synthesis of an essential component of the cell wall of fungi, one may need not undergo surgery.

The most common antifungal medication for Aspergillus is voriconazole, a second-generation triazole. This case demonstrates the efficient utilization of Voriconazole along with Anidulafungin, which is necessary for the fungal cell wall integrity. For immunocompromised patients with pulmonary aspergilloma, this dual therapy presents a viable substitute for surgical intervention and an efficient treatment approach.

CASE PRESENTATION. We present a case of a 54-year-old married patient, who presented with massive hemoptysis four days before consulting a private physician. She had ten episodes of hemoptysis four hours before admission and was rushed to the hospital. The patient had multiple comorbidities, including diabetes, hypertension, and asthma, contributing to an immunocompromised state. She had a history of anti-tuberculosis treatment in 2000, which was discontinued due to an allergic reaction. During her hospital stay, she experienced febrile episodes, and capillary glucose monitoring was beyond acceptable levels, prompting antibiotic initiation. A chest CT scan revealed pulmonary tuberculosis with cicatricial atelectasis of the lingular segment and infected cavitary formation. A bronchoscopy and biopsy of the cavitary lesion were scheduled.

Surgical intervention, particularly lobectomy, was not pursued due to multiple factors, including the patient's immunocompromised status, her underlying comorbidities, and the response to antifungal therapy.

After eight to 14 fourteen (8-14) hospital days, no episodes of hemoptysis were noted, and the biopsy result revealed fungal colonization consistent with Aspergillus species. The patient was discharged with oral Voriconazole and other maintenance medications. A repeat chest CT scan after five months of antifungal therapy showed regression of the fungus ball.

CONCLUSIONS. In this case, pulmonary aspergilloma in an immunocompromised patient was successfully treated with a combination antifungal therapy utilizing anidulafungin and voriconazole. The favorable clinical response to dual antifungal therapy provides a feasible non-surgical alternative to surgical intervention, which has historically been the preferred option for treating recurrent hemoptysis, particularly in high-risk patients. The fungus ball's regression and the fungal infection's resolution support the growing role of more recent antifungal medications in the treatment of complicated pulmonary infections. This case suggests that echinocandins combined with triazole therapy are a viable less invasive treatment option for pulmonary aspergilloma than surgery.

KEYWORDS: Pulmonary Aspergilloma, Immunocompromised, Voriconazole, Anidulafungin, Fungus Ball, Dual Antifungal Therapy

INTRODUCTION

Aspergillus is a prevalent lung infection that mostly affects middle-aged males. The infection appears systemically in several organs, with the lung being the most prevalent location. The host's immune system plays an important part in the infection, which causes a variety of ailments ranging from mild allergies to invasive disorders. Acute invasive pulmonary aspergillosis (IPA) is usually found in highly immunocompromised individuals, whereas immunocompetent people may not exhibit symptoms. Immunocompetent patients have no symptoms. Other symptoms include acute IPA, subacute IPA, aspergilloma, and an Aspergillus nodule. Chronic Aspergillus infection is categorized into three types: subacute IPA/chronic necrotizing pulmonary aspergillosis (CNPA), chronic cavitary pulmonary aspergillosis (CCPA), and chronic fibrosing pulmonary aspergillosis (CFPA). CCPA is more prevalent in immunocompetent people, whereas CFPA is a late-stage manifestation of CCPA with extensive lung fibrosis due to noncompliance with treatment. [7]

Aspergillus may colonize healthy people, producing allergic bronchopulmonary aspergillosis (ABPA) or Aspergillus sinusitis in atopy patients, and it can also cause invasive aspergillosis in people with weakened immunity. In pre-existing cavities, it might appear as an aspergilloma, also known as a mycetoma or fungal ball. The most prevalent cause of aspergilloma in underdeveloped nations is post-tubercular status, which accounts for more than 95% of cases. Sarcoidosis, asbestosis, cavitary neoplasia, bronchiectasis, lung abscess, and Wegener's granulomatosis are some of the other unusual causes. Aspergilloma has been linked to pulmonary infarction and Invasive Pulmonary Fibrosis (IPF), with only two instances described in the literature. Clinico-radiological and serological confirmation are required for the diagnosis of aspergilloma. The patient may come with hemoptysis or be asymptomatic. [5]

Given that there is sufficient literature on pulmonary aspergilloma, this case provides a rare example of an immunocompromised patient with recurrent massive hemoptysis who was successfully treated with antifungal therapy without the need for surgery. The patient's immunocompromised state was exacerbated by a number of comorbidities, such as diabetes, hypertension, and asthma. Voriconazole and anidulafungin significantly improved clinical outcomes and caused the fungus ball to recede, even though lobectomy is the standard treatment for recurrent hemoptysis. This case broadens therapeutic approaches for pulmonary

aspergilloma by contributing to the increasing body of evidence that medical management is a feasible substitute for surgery in certain high-risk patients.

THE CASE

We present a case of a 54-year-old, female, married, who came in with a chief complaint of massive hemoptysis (500cc).

History of the present illness revealed that four days prior to consulting, the patient experienced a cough, with brownish phlegm. She went to a private physician who prescribed her unrecalled medications which offered slight relief. However, four hours prior to admission, she had ten episodes of hemoptysis, amounting to 500cc in total volume. She was rushed to the hospital and was subsequently admitted.

AT THE EMERGENCY ROOM

She came in stretcher-borne, awake, coherent, and in slight cardiopulmonary distress. There was no recurrence of hemoptysis. Pertinent physical examination findings revealed crackles, on both lung fields, most prominent at the left lung, mid-base with occasional wheezing in the lung area. Laboratories were requested which showed mild anemia with a hemoglobin of 96mg/dl and relative leukocytosis. CXR revealed:

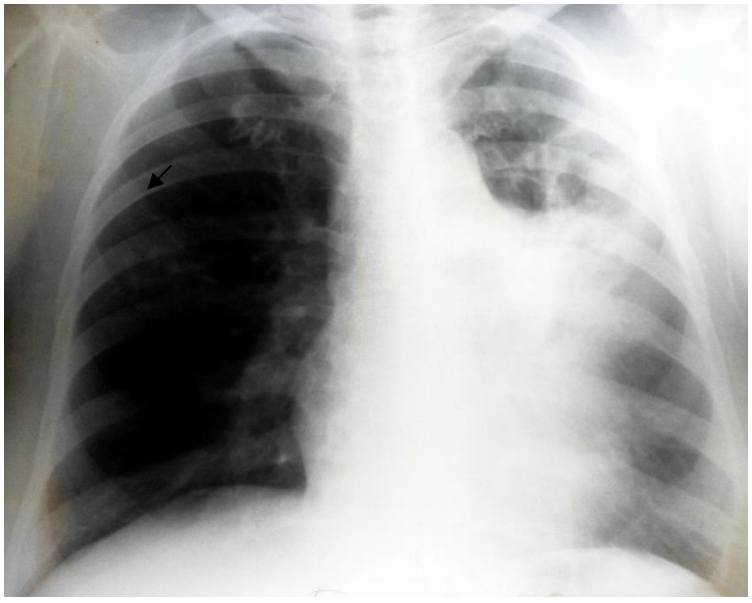

Figure 1. CXR PA view revealed an air-filled cavity at the left upper lung, crescent-shaped, with a fungus ball within.

She has suffered from diabetes for ten years, according to a review of her medical history, and is currently taking 25 units of insulin glargine (Lantus) subcutaneously once daily. Even though her diabetes was reported to be well controlled, persistent hyperglycemia may still exacerbate immune dysfunction and make her more vulnerable to infections. She was also known to have asthma and hypertension, and she was taking long-acting β2 agonists and inhaled steroids, which can further affect the immune response.

She had a history of pulmonary tuberculosis in 2000, for which she was initiated on standard first-line anti-tuberculosis therapy consisting of rifampicin and isoniazid. However, she developed an allergic reaction to rifampicin and isoniazid within the early phase of treatment, leading to premature discontinuation of therapy before completion. The incomplete treatment may have contributed to the

development of residual cavitary lung lesions, predisposing her to secondary infections such as pulmonary aspergilloma.

Her family history was positive for hypertension, diabetes, and bronchial asthma. She was a housewife, nonsmoker, and nonalcoholic beverage drinker. Given her multiple chronic illnesses, prior tuberculosis, and long-term steroid use, the patient was considered immunocompromised, increasing her risk for invasive fungal infections such as pulmonary aspergilloma.

COURSE IN THE WARDS

1st – 6th Hospital Day

The patient required insulin titration due to frequent episodes of fever and capillary glucose levels that were above acceptable limits. Intravenous Amikacin (500 mg once daily) and Cefotaxime (1 g every 8 hours) were used to start antibiotic treatment. The presence of pulmonary tuberculosis sequelae, such as cicatricial atelectasis of the lingular segment and an infected cavitary formation, on a chest computed tomography (CT) scan raised the possibility of a *fungus ball*. Additional findings included thickening of the left major fissure, unenlarged mediastinal lymph nodes, bronchiectatic changes in the left upper lung, intercurrent bilateral pneumonia, and a minimal left-sided pleural effusion. A bronchoscopy and biopsy were planned in order to confirm the diagnosis due to the cavitary lesion's complexity.

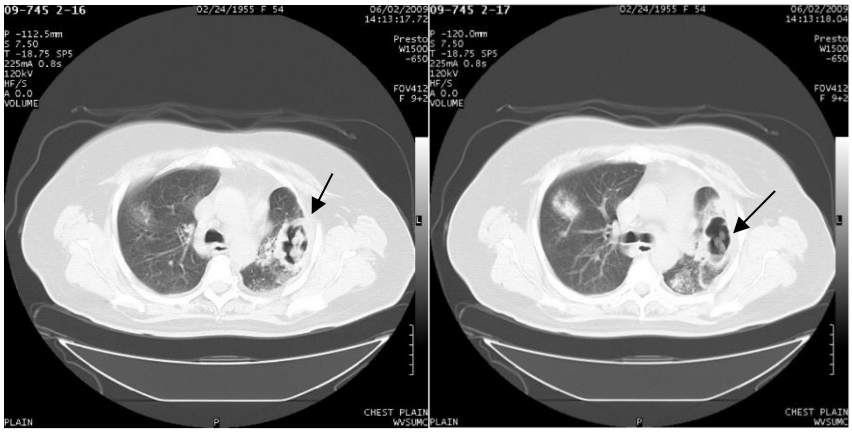

Figure 2. Showed a thick-walled ovoid air-containing lesion with internal lobulated margins, and mobile soft tissue densities - cavity formation with a fungus ball – aspergilloma considered.

7th Hospital Day

The plan was to give Anidulafungin through bronchoscopy at first. But the procedure was made harder by bronchospasm, which caused respiratory failure and required intubation. Because the patient's breathing was getting worse, antifungal instillation was put off. Instead, bronchial washing and a biopsy of the lesion were done. After that, a soluset was used to give Anidulafungin intravenously at a dose of 100 mg IVTT. After the procedure, the patient's oxygen levels got better, and she was taken off the ventilator before being moved to her inpatient room for more monitoring and antifungal treatment.

8th -14th Hospital Day

There were no more episodes of hemoptysis, and hemodynamic stability was maintained. Vital signs stayed normal, and blood sugar levels stayed stable. The patient's condition clearly got better, and they

were getting better over time. The biopsy sample showed that fungi had taken over, and it found a fungus ball that looked like Aspergillus species.

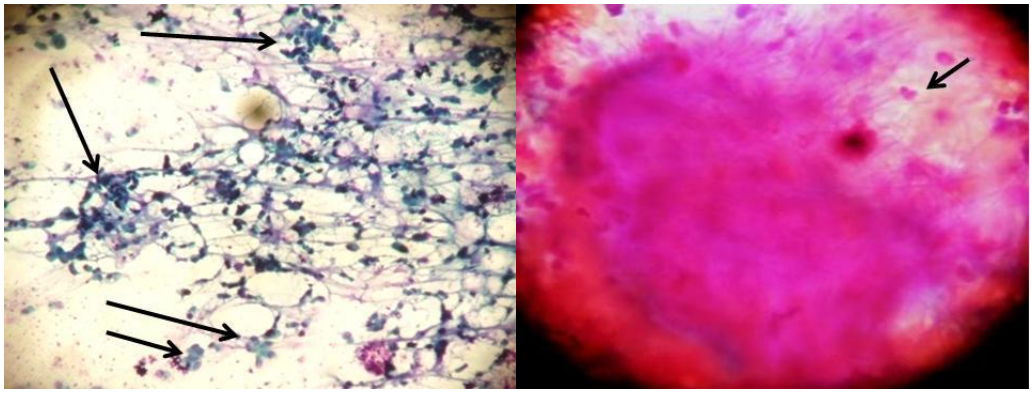

Figure 3. Showed acutely angled, branching, septated, non-pigmented hyphae, with conidia.

The patient was discharged with oral Voriconazole as part of her antifungal regimen, together with other maintenance medications. Following five months of consistent antifungal therapy with good adherence, a repeat chest computed tomography (CT) scan demonstrated significant regression of the *fungus ball*, indicating a favorable therapeutic response.

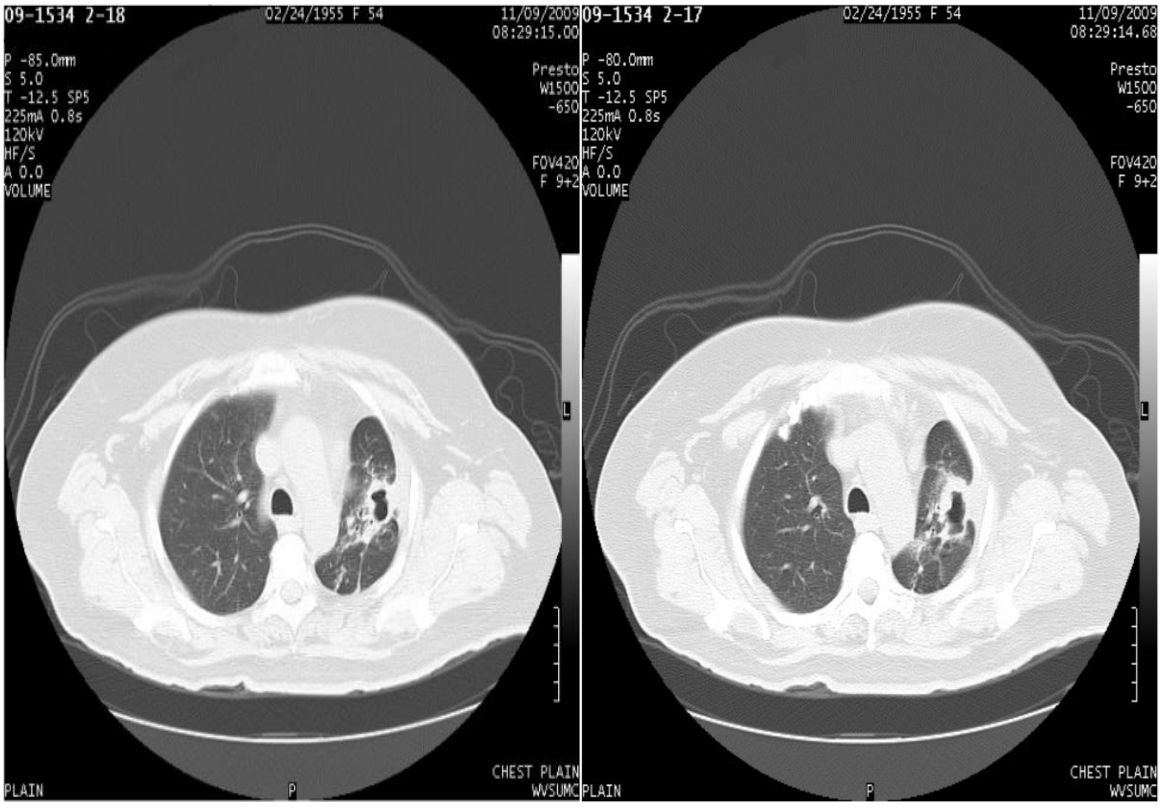

Figure 4. There was a regression of the size of the cavity and resolution of the soft tissue densities within.

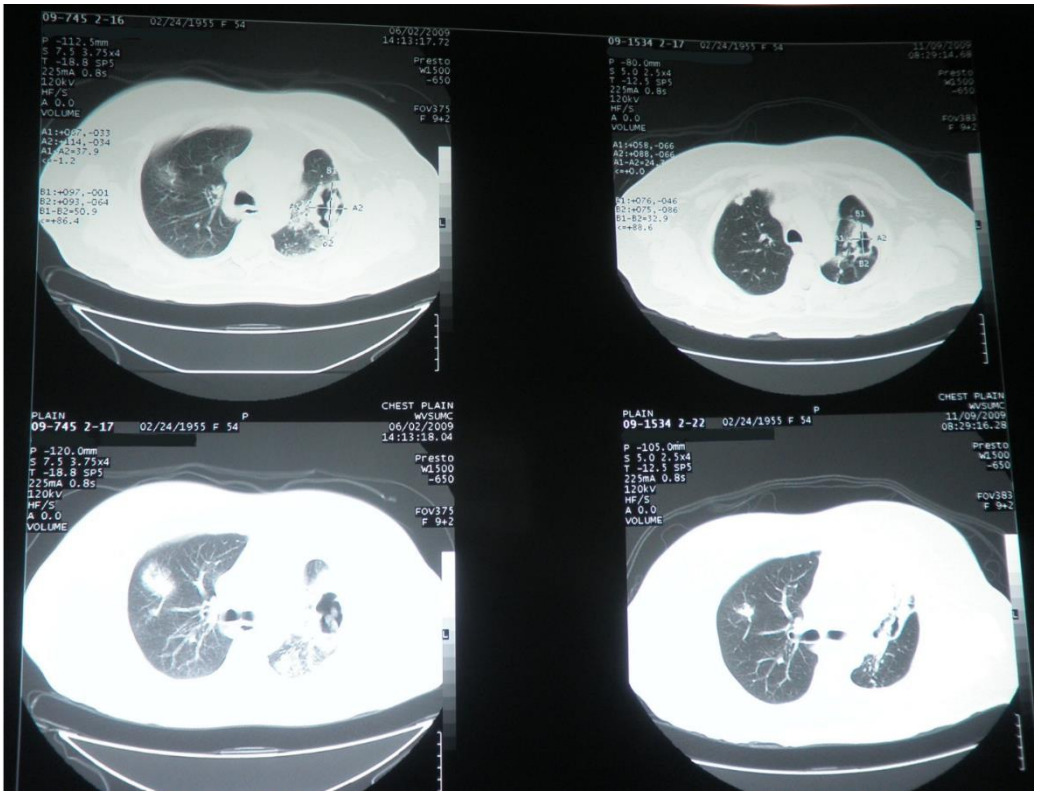

Figure 5. A comparison of chest CT films taken June 2009 at the left vs November 2009 at the right.

The voriconazole treatment lasted for a total of eight months. A repeat chest X-ray showed that the pulmonary aspergilloma had completely healed, and the official interpretation said that the chest X-ray was normal.

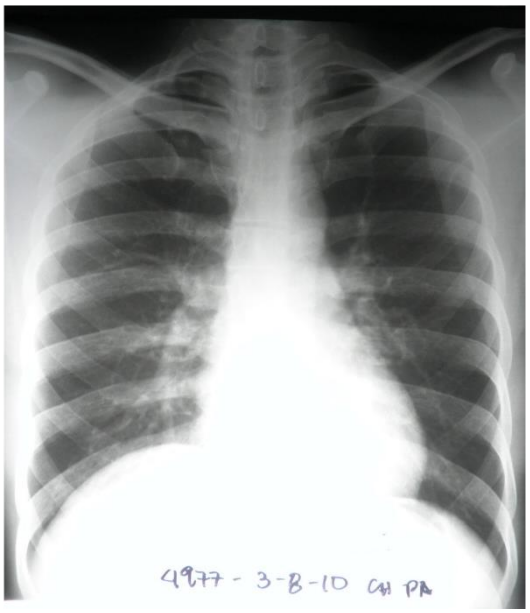

Figure 6. Normal CXR-PA view after 8 months Voriconazole

CASE DISCUSSION

A pulmonary aspergilloma (PA) is a fungus ball made up of Aspergillus hyphae, fibrin, mucus, and cellular debris that grows within the lung cavity. A major risk factor for pulmonary aspergilloma is tuberculosis, which frequently occurs in pre-existing lung cavities. This patient had a history of pulmonary tuberculosis in 2000, which was not fully treated because of an allergic reaction to isoniazid and rifampicin. Chest CT revealed a cavitary lung lesion, which created an ideal environment for fungus colonization and the development of aspergilloma. After therapy for pulmonary TB, lung cavities of 2cm had a 20% probability of developing PA.[1]

This patient experienced significant hemoptysis, the hallmark symptom of pulmonary aspergilloma, with recurrent episodes necessitating immediate medical attention. Patients with chronic or potentially fatal hemoptysis are typically evaluated for surgical intervention, especially lobectomy. However, because of a number of factors, such as her immunocompromised state, diabetes with fluctuating glycemic control, asthma, and hypertension, medical management took precedence over surgery.

Aspergillosis syndromes are diverse and can be fluid if an individual's immune status changes. The immune status determines the form of aspergillosis a patient is at risk of and whether they are likely to get it at all. Sinopulmonary diseases are the most common manifestations of aspergillosis, as Aspergillus species are ubiquitous in the environment and humans inhale Aspergillus spores daily. Aspergillus-related bronchopulmonary syndromes are the major causes of morbidity and mortality due to aspergillosis globally. These include allergic bronchopulmonary aspergillosis (ABPA), a lung disease characterized by worsening asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis; invasive pulmonary aspergillosis (IPA), an acute life-threatening disease mainly seen in patients with severe immunosuppression, such as those on corticosteroids; and chronic pulmonary aspergillosis (CPA), a progressive debilitating parenchymal lung disease in patients with pre-existing lung disease or subtle immune defects. A small group of patients, particularly those with moderate immunosuppression, develop sub-acute invasive aspergillosis (SAIA), a less active invasive disease.[2]

Over the past few decades, there has been a significant increase in fungal infections worldwide, particularly Aspergillus infections, which can cause a range of health complications. These infections, including acute bronchopulmonary aspergillosis, allergic sinusitis, and IgE-associated asthma, are primarily caused by spore-bearing fungi like Aspergillus fumigatus, A. flavus, and A. terreus. The global burden of Aspergillus-associated infections has been exacerbated by the emergence of drug-resistant strains within Aspergillus species. The lack of early diagnostic indicators for Aspergilli terreus infections poses a significant risk to susceptible individuals. The COVID-19 pandemic has also highlighted fungal infections, with Aspergillosis emerging as a co-infection with mucormycosis.[6]

As early 2018 the optimum antifungal drug for the first therapy of chronic pulmonary aspergillosis remains unknown. Because of economic considerations, itraconazole is frequently the favored medication, followed by the newer triazoles. Nonetheless, they saw equivalent improvements in scores in individuals starting on itraconazole or voriconazole; however, those on voriconazole often had a larger radiological and clinical burden of illness (this is supported by the higher baseline Aspergillus-specific IgG level in patients on voriconazole). Oral itraconazole effectiveness has been found to be relatively varied, with a range of 30-93%, a duration of therapy of 4-12 months, and side effects in 16-33% of patients. The response rate to voriconazole treatment ranges from 13 to 65% after many months of medication, with some side effects occurring in 6-21% of cases. Surprisingly, 13% (n = 19) of the 151 patients using itraconazole discontinued due to microbiological failure (resistance), compared to 5% (n = 2) of the 43

patients taking voriconazole. Voriconazole likely has a greater resistance development threshold. For chronic pulmonary aspergillosis therapy, the first-line agents are oral itraconazole (200 mg twice daily) or voriconazole (150 mg to 200 mg twice daily). The choice between the two is currently based on cost, availability, toxicity, and tolerability; they are thus used interchangeably as first-line agents. Treatment for at least 6 months is sufficient for patients with limited disease; for those with bilateral or extensive disease, 24 months or life-long treatment is required. Voriconazole has been shown to have a response rate of 64% at 3 months and 32% at 6 months, however, it has also been shown to cause side effects.[3]

In this particular case, lobectomy has not been done due to the patient's refusal. Amphotericin B and Itraconazole have not been used due to their possible complications which may push the patient to possible renal failure, the fact that she is a poorly controlled diabetic. Hence, newer antifungals have been used to successfully eradicate the fungus ball. For five days, the patient received a soluset of intravenous anidulafungin at a dose of 100 mg IVTT. By blocking the enzyme β-(1,3)-D-glucan synthase, which is essential for the production of fungal cell walls, this echinocandin compromises the structural integrity of the fungus and stops its growth. Anidulafungin was chosen to improve the early stage of fungal clearance because of its fungistatic activity against *Aspergillus* species, especially when a cavitary fungal colonization is present.

After the intravenous treatment was finished, the patient was switched to oral Voriconazole once daily for six months of maintenance treatment. The patient's clinical stability, lack of additional hemoptysis, and positive reaction to the initial IV treatment were the main factors in the decision to switch to oral therapy. The selection of voriconazole monotherapy was based on its proven effectiveness in treating chronic pulmonary aspergillosis, which has shown notable progress in long-term fungal suppression with better patient outcomes. Frequent follow-up guaranteed treatment compliance while keeping an eye out for possible side effects, such as hepatotoxicity and vision problems frequently linked to long-term triazole use. The patient's vital signs stabilized and their hemoptysis went away after beginning antifungal treatment, suggesting a significant clinical improvement. The biopsy confirmed fungal colonization consistent with Aspergillus species, which further supported the diagnosis.

Several studies have been published regarding the efficacy of Anidulafungin and voriconazole against *Aspergillus spp*. Kirkpatrick et al, compare the efficacy of voriconazole vs anidulafungin alone and in combination in a guinea pig model of invasive pulmonary aspergilloma. They have concluded that voriconazole yielded greater survival than anidulafungin; the combination of both drugs has been superior in reducing tissue burden as evidenced by colony-forming units.[8]

This case emphasizes how combined antifungal therapy may be used to treat pulmonary aspergilloma without surgery, especially in patients who pose a high risk for surgery. The positive reaction to anidulafungin and voriconazole emphasizes the developing function of echinocandins in complicated fungal infections and encourages their use in certain situations where surgery is either refused or not advised.

CONCLUSION

This case emphasizes the successful management of pulmonary aspergilloma in an immunocompromised patient using a combination of Voriconazole and Anidulafungin, demonstrating a viable non-surgical alternative in high-risk individuals. Traditionally, recurrent hemoptysis in pulmonary aspergilloma often necessitates surgical intervention; however, the favorable therapeutic response in this patient highlights the potential of newer antifungal agents in mitigating the need for invasive procedures. The combination

of a third-generation azole (Voriconazole) and an echinocandin (Anidulafungin) allowed effective fungal clearance by targeting both membrane sterols and cell wall β-glucan synthesis, enhancing efficacy without antagonistic effects.

Moreover, the case adds to the growing evidence supporting combination antifungal therapy, offering a broader spectrum of activity and the potential to optimize drug dosages while reducing the risk of antifungal resistance. The regression of the fungus ball over time, as confirmed by imaging, reinforces the evolving role of antifungal combinations in managing complex fungal infections. This report highlights the importance of individualized treatment strategies and demonstrates the clinical success of dual therapy in cases where surgical intervention is not pursued.

REFERENCES

1. Alemu B. N. (2020). Surgical Outcome of Chronic Pulmonary Aspergilloma: An Experience from Two Tertiary Referral Hospitals in Addis Ababa, Ethiopia. Ethiopian journal of health sciences, 30(4), 521–530. https://doi.org/10.4314/ejhs.v30i4.7
2. Bongomin, F., Asio, L. G., Baluku, J. B., Kwizera, R., & Denning, D. W. (2020). Chronic Pulmonary Aspergillosis: Notes for a Clinician in a Resource-Limited Setting Where There Is No Mycologist. Journal of Fungi, 6(2), 75. https://doi.org/10.3390/jof6020075
3. Bongomin, F., Harris, C., Hayes, G., Kosmidis, C., Denning, D. W. (2018). Twelve-month clinical outcomes of 206 patients with chronic pulmonary aspergillosis. PloS one. 2018; 13(4):e0193732. https://doi.org/10.1371/journal.pone.0193732 PMID: 29634721
4. Kirkpatrick, W. R., McAtee, R. K., Fothergill, A. W., Rinaldi, M. G., & Patterson, T. F. (2000). Efficacy of voriconazole in a guinea pig model of disseminated invasive aspergillosis. Antimicrobial agents and chemotherapy, 44(10), 2865–2868. https://doi.org/10.1128/AAC.44.10.2865-2868.2000
5. Pavirala, S. T., Rao, S. A., Sahu, G., Khurana, A., & Goyal, A. (2022). Aspergilloma in Non-tuberculous Cavities in the Lung: Not to Get Startled. Cureus, 14(8), e27905. https://doi.org/10.7759/cureus.27905
6. Thakur, R., Shishodia, S., Sharma, A., Chauhan, A., Kaur, S., & Shankar, J.. (2024). Accelerating the understanding of Aspergillus terreus: Epidemiology, physiology, immunology and advances. Current Research in Microbial Sciences. 6. 100220. https://doi.org/10.1016/j.crmicr.2024.100220
7. Vangara, A., Gudipati, M., Chan, R., Tuong, V., Bawa, O., & Ganti, S. (2022). Chronic Pulmonary Aspergillosis Infection in Coal Workers Pneumoconiosis With Progressive Massive Fibrosis. Journal of Investigative Medicine High Impact Case Reports. 10. 232470962211271. https://doi.org/10.1177/23247096221127100.
8. Zhang, M., Su, X., Sun, W. K., Chen, F., Xu, X. Y., & Shi, Y. (2014). Efficacy of the combination of voriconazole and caspofungin in experimental pulmonary aspergillosis by different Aspergillus species. Mycopathologia, 177(1-2), 11–18. https://doi.org/10.1007/s11046-013-9719-z