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CASE REPORT

A Rare Case of Lymphoma with Invasive Pulmonary Aspergillosis Developing Azole Resistance

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ABSTRACT

This study reports a rare case of azole-resistant invasive pulmonary aspergillosis (IPA) in a patient with diffuse large B-cell lymphoma and to underscore the clinical relevance of emerging azole resistance in hematologic malignancies. Clinical, microbiological, and radiological findings were reviewed in a patient who developed IPA. Antifungal susceptibility testing was performed, and the clinical response was evaluated after modification of antifungal therapy. Despite antifungal treatment with voriconazole, azole resistance was detected. Switching back to amphotericin B resulted in marked clinical and radiological improvement, supporting the diagnosis of azole-resistant IPA. Azole resistance, though uncommon, is an increasingly important therapeutic concern in immunocompromised hosts. Early recognition and timely initiation of alternative agents such as amphotericin B may improve outcomes.

Keywords: Aspergillosis. Voriconazole. Azole Resistance. Invasive Pulmonary Aspergillosis. Hematologic Malignancy.

Azol Direnci Gelişen İnvaziv Pulmoner Aspergilloz'lu Nadir Bir Lenfoma Olgusu

ÖZET

Diffüz büyük B-hücreli lenfoma tanılı bir hastada gelişen nadir bir azol-dirençli invaziv pulmoner aspergilloz (İPA) olgusunu sunmayı ve hematolojik malignitelerde ortaya çıkan azol direncinin klinik önemini vurgulamayı amaçladık. İPA gelişen bir hastada klinik, mikrobiyolojik ve radyolojik bulgular geriye dönük olarak değerlendirildi. Antifungal duyarlılık testleri yapıldı ve antifungal tedavide yapılan değişiklik sonrasında klinik yanıt incelendi. Antifungal ajan olarak verilen vorikonazole rağmen azol direnci saptandı. Tedavinin amfoterisin B'ye değiştirilmesi ile belirgin klinik ve radyolojik düzelme gözlendi. Bu bulgular azol-dirençli İPA tanısı ile uyumluydu. Azol direnci nadir görülmekle birlikte, immünsüprese hastalarda giderek daha önemli bir terapötik sorun haline gelmektedir. Direncin erken tanınması ve amfoterisin B gibi alternatif antifungal ajanların zamanında başlanması, klinik sonuçların iyileştirilmesinde kritik rol oynayabilir.

Anahtar Kelimeler: Aspergilloz. Vorikonazol. Azol Direnci. İnvaziv Pulmoner Aspergilloz. Hematolojik Malignite.

Invasive aspergillosis is one of the most common invasive fungal infections caused by Aspergillus species and can lead to significant morbidity, particularly in immunosuppressed individuals. Azole antifungals are used as the primary therapeutic option in the management of Aspergillus infections. However, the increasing incidence of azole resistance in recent years has complicated treatment management and contributed to higher mortality rates[1,2].

Azole resistance is most commonly observed in *A. fumigatus* and represents a major cause of treatment failure. The development of resistance is typically associated with mutations in the *Cyp51A* gene, which frequently result in high-level resistance to one or more azole agents[3,4]. Resistance may arise either from prolonged azole exposure or from environmental use of azole-based agricultural fungicides[5,6].

Although azole resistance in *A. fumigatus* isolates is not highly prevalent in Türkiye, it was first demonstrated in our institution[7,8].

In this case report, we present a patient with diffuse large B-cell lymphoma (DLBCL) who developed IPA, in whom azole resistance and subsequent clinical refractoriness were identified following voriconazole therapy.

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Case Presentation

A 46-year-old female patient presented with complaints of dyspnea and cough. Her medical history revealed propylthiouracil use for hyperthyroidism and a diagnosis of diffuse large B-cell lymphoma (DLBCL), which had been in remission for nine months. On physical examination, diminished breath sounds were noted in the right lung, accompanied by bilateral basal crackles and pretibial edema. Based on imaging and laboratory findings, disease relapse and concomitant pneumonia were identified (Figure 1). The patient was initiated on R-DHAP (Rituximab, Dexamethasone, Cisplatin, Cytarabine) chemotherapy along with piperacillin–tazobactam.

On day 12 of follow-up, the patient developed a fever. Given the clinical context of febrile neutropenia, antimicrobial therapy was switched to meropenem and levofloxacin. As no clinical response was achieved, and because persistent fever and elevated acute phase reactants were noted on day 14 of R-DHAP chemotherapy, empirical amphotericin B was initiated.

Subsequently, serum galactomannan positivity was detected on day 14 of chemotherapy, and *A. terreus* was first isolated from the sputum culture on day 17. Considering the possibility of amphotericin B resistance, amphotericin B was discontinued on the third day of therapy, and voriconazole was initiated.

Despite voriconazole therapy, the patient's symptoms persisted and serum galactomannan levels remained positive. Consequently, bronchoscopy was performed. Viral pathogens—including influenza A, human coronavirus 43, cytomegalovirus, adenovirus, and human metapneumovirus—were identified by real-time PCR (BIOFIRE® Respiratory 2.1 [RP 2.1] Panel, bioMérieux, Nürtingen, Germany). In addition, *A. fumigatus* was isolated from BAL specimens, and BAL galactomannan positivity was confirmed (optical density indices of 6.2 and 9.2, respectively).

Five colonies of the isolated *A. fumigatus* were tested for antifungal resistance using agar screening plates[9]. Resistance to itraconazole, voriconazole, and posaconazole was detected. Accordingly, antifungal susceptibility testing was performed using the microdilution method, following the Clinical and Laboratory Standards Institute (CLSI) M38 guidelines[10]. The minimum inhibitory concentration (MIC; µg/ml) values were determined as 4, 4, and 2 µg/ml for itraconazole, voriconazole, and posaconazole, respectively. It was hypothesized that prolonged azole exposure may have led to the selection of a resistant strain.

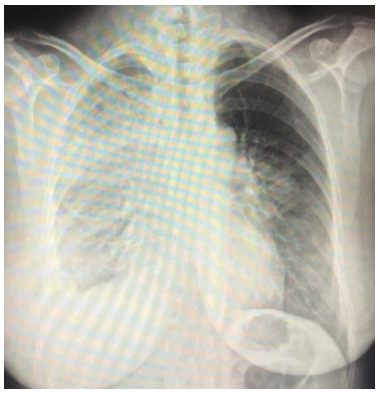
Following the detection of azole-resistant *A. fumigatus* in BAL samples, antifungal treatment was switched back to amphotericin B. After this adjustment, significant clinical improvement was observed. The patient's laboratory parameters during follow-up are summarized in Table I, chest imaging findings after voriconazole and amphotericin B therapy are demonstrated in Figures 2 and 3, respectively, and the temporal changes in galactomannan levels during follow-up are illustrated in Figure 4.

Written informed consent was obtained from the patient.

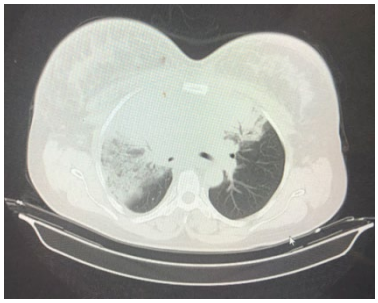
Table I. Major Laboratory Parameters of the Patient During Follow-up

	At diagnosis	Before antifungal therapy	End of antifungal therapy (end of voriconazole therapy)	End of antifungal therapy (end of amphotericin B administered after azole resistance)
WBC	1980 10^9/L	740 10^9/L	3440 10^9/L	4100 10^9/L
NEU	1210 10^9/L	210 10^9/L	3160 10^9/L	3800 10^9/L
HGB	7.3 g/dL	10 g/dL	9.1 g/dL	8.9 g/dL
PLT	139000 10^9/L	51400 10^9/L	176000 10^9/L	96500 10^9/L
CRP	103 mg/L	250 mg/L	55 mg/L	11 mg/L
Erythrocyte Sedimentation Rate (ESR)	46 mm/h	89 mm/h	4 mm/h	83 mm/h
Procalcitonin	0.57 µgr/L	0.03 µgr/L	0.10 µgr/L	0.17 µgr/L
Galactomannan	Negative	Three times positive (Median: 5.741)	Positive fourteen times (Median: 4.496)	Negative
Urea	52 mg/dL	50 mg/dL	78 mg/dL	104 mg/dL
Creatinine	1.1 mg/dL	0.86 mg/dL	0.87 mg/dL	1.35 mg/dL
ALT	24 U/L	36 U/L	20 U/L	106 U/L
AST	25 U/L	22 U/L	59 U/L	102 U/L
pH	7.46	7.45	7.44	7.20
HCO3	22 mEq/L	26 mEq/L	34 mEq/L	13.3 mEq/L
CO2	31 mmHg	37 mmHg	50 mmHg	30 mmHg
LDH	459 U/L	258 U/L	522 U/L	418 U/L

Abbreviations: WBC, White Blood Cell; NEU, Neutrophil; HGB, Hemoglobin; PLT, Platelet; CRP, C-Reactive Protein; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; LDH, Lactate Dehydrogenase.



a. Chest X-ray

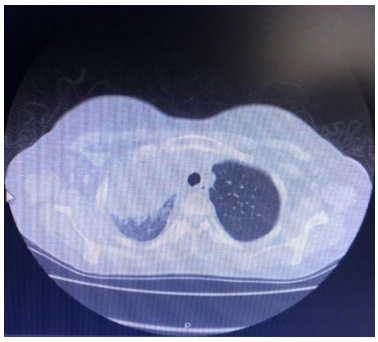


b. Thoracic CT

Figure 1:
Consolidation and ground-glass opacities in the right upper lobe at the time of diagnosis on chest X-ray and thoracic CT.



a. Chest X-ray

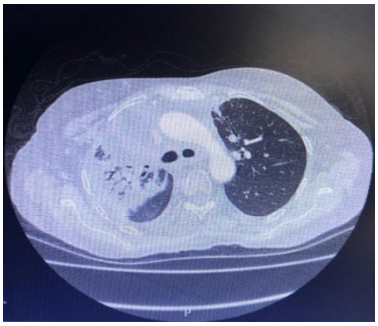


b. Thoracic CT

Figure 2:
Consolidation and ground-glass opacities in the right lung on chest X-ray (posteroanterior view) and thoracic CT after voriconazole therapy.



a. Chest X-ray



b. Thoracic CT

Figure 3:
Consolidation and ground-glass opacities in the right lung on chest X-ray (posteroanterior view) and thoracic CT after amphotericin B therapy.

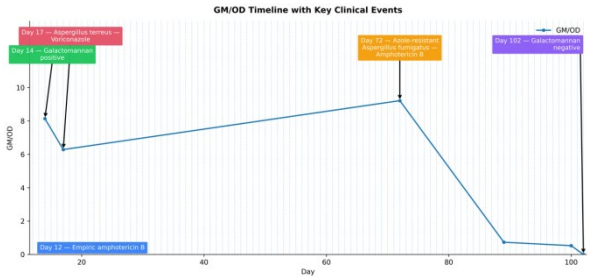


Figure 4:
Temporal changes in galactomannan levels during the follow-up period

Empirical amphotericin B therapy was initiated on day 12. Serum galactomannan positivity was detected on day 14, and *A. terreus* was first isolated from sputum culture on day 17, prompting a switch to voriconazole. On day 72, *A. fumigatus* was isolated from BAL specimens, and BAL galactomannan positivity was confirmed. Voriconazole was subsequently discontinued, and amphotericin B therapy was reinitiated. By day 102, serum galactomannan had become negative, accompanied by marked clinical improvement.

Discussion and Conclusion

Invasive aspergillosis is associated with significant mortality, particularly in patients with a history of hematologic malignancy or immunosuppression[11,12]. Although voriconazole is the first-line agent for the

treatment of IPA, treatment failures due to resistant strains have been increasingly reported in recent years[13,14]. Previous studies from our institution have demonstrated the presence of azole-resistant *A. fumigatus* isolates through in vitro experiments[7,8]. In the present case, infection with azole-resistant *A. fumigatus* developed after prolonged voriconazole therapy, leading to clinical refractoriness and supporting the possibility that azole resistance may contribute to treatment failure.

Although serum levels of azole agents could not be measured in our center, the detection of in vitro resistance in this case and the subsequent clinical response to amphotericin B strongly support azole resistance as a major contributing factor to treatment failure. In addition to immunosuppression, the presence of viral co-infections in our patient further aggravated the course of invasive aspergillosis, consistent with previous reports in the literature[15]. Initially, our patient developed invasive aspergillosis due to *A. terreus*; however, we believe that prolonged voriconazole use led to the selection of azole-resistant *A. fumigatus* colonizing the respiratory tract, resulting in a second episode of invasive aspergillosis.

Studies from our center and the literature have shown that the most important mechanism of resistance involves mutations in the *Cyp51A* gene (such as the TR34/L98H mutation)[16]. In this case, the specific mutations in the resistant isolate were not identified. Nevertheless, our findings emphasize that close monitoring of serum galactomannan, timely collection of BAL samples, and rapid azole resistance screening tests may be life-saving in high-risk patients with hematologic malignancies by facilitating the early switch to alternative antifungal strategies. In this patient, the azole-resistant *A. fumigatus* infection that developed after prolonged voriconazole therapy was successfully controlled following a switch to amphotericin B. Although a definitive causal relationship could not be established, azole resistance is considered one of the most likely contributing factors to treatment failure. The inability to perform molecular resistance testing and therapeutic drug monitoring in this case constitutes a limitation of our study.

Azole resistance is an emerging clinical challenge with increasing significance in the management of invasive aspergillosis. In high-risk patients with hematologic malignancies, azole resistance should always be considered in cases of treatment refractoriness. This case underscores the importance of identifying resistance and highlights the clinical success achieved through therapeutic modification.

Researcher Contribution Statement:
Conceptualization, Study Design: Ş.Y.; Data Analysis, And Drafting Of The Case Report: Ş.Y.; Editing Of The Case Report: T.E., V.Ö. Beyza Supervised The Overall Study, Critically Revised The Case Report, And Contributed To İts İnterpretation: B.E., F.Ö.;
Fundıng Stataement
None.
Conflict of Interest Stataement
The authors declare no conflicts of interest.

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