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Eosinophilic Esophagitis and Peripheral Eosinophilia from Long-term Posaconazole Treatment for Disseminated Zygomycosis Infection

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Abstract

Introduction: Posaconazole has become a viable option for off-label treatment of Zygomycosis infections. We describe a pediatric patient with B-cell ALL found to have disseminated Zygomycosis infection while undergoing chemotherapy, who developed peripheral eosinophilia to 23.6% and eosinophilic esophagitis after seven weeks of IV posaconazole treatment. Eosinophilia is a rare drug reaction to azole therapy with very little documentation in the literature, and to our knowledge this is the first case reported in a pediatric patient.

Case presentation: A three-year-old previously healthy Hispanic female, recently diagnosed with B-cell ALL undergoing chemotherapy, was found to have disseminated Zygomycosis infection of the skin and maxillary sinus requiring debridement and negative pressure wound therapy. Therapy was initiated with amphotericin B and posaconazole. She developed peripheral eosinophilia to 23.6%, generalized pruritus, and symptomatic eosinophilic esophagitis after seven weeks of treatment with posaconazole. Her symptoms and peripheral eosinophilia resolved shortly after discontinuation of posaconazole therapy, suggesting that the azole therapy was the cause of the eosinophilia.

Conclusion: Posaconazole can be used to treat Zygomycosis infections, usually requiring long-term treatment. However, long term azole therapy can lead to peripheral eosinophilia and symptomatic eosinophilic esophagitis, and patients may benefit from regular monitoring with complete blood counts for these side effects. There are few documented cases of eosinophilia with azole therapy in the literature, and ours is to our knowledge the first reported in a pediatric patient.

Keywords: Eosinophilic esophagitis; Peripheral eosinophilia; Posaconazole; Azole; Zygomycosis

Introduction

Posaconazole is an extended-spectrum triazole antifungal that has become a viable option for off-label use for treatment of Zygomycosis [1]. It is a potent inhibitor of 14α-demethylase which leads to inhibition of ergosterol synthesis in the fungal cell membrane, causing increased cellular permeability, leading to cell death. Additionally, it inhibits the CYP 450 3A4 enzyme which is responsible for drug and toxin metabolism [2]. It is administered as an IV or oral medication, and has greater bioavailability when given with high fat-content meals. It is >98% protein bound (to albumin, primarily), is metabolized by glucuronidation in the liver and undergoes fecal elimination, with a half-life of around 35 hours (range 20-66) [3]. Posaconazole is generally well tolerated, however the most commonly noted side effects include nausea, vomiting, diarrhea, and headache. Less commonly, rash, abdominal pain and elevated liver enzymes have been described [1].

Zygomycetes are fungi found ubiquitously in the soil and organic substrates worldwide. However, Zygomycosis is a rare infection usually seen in immunocompromised patients, [4,5] often manifesting with rhinocerebral, cutaneous, pulmonary or disseminated involvement [6]. Some of the most common species of zygomycetes causing human disease are *Rhizopus*, *Mucor* and *Rhizomucor* [7].

We report a case of an immunocompromised child with disseminated Zygomycosis infection undergoing treatment with posaconzaole who developed eosinophilia and eosinophilic esophagitis following seven weeks of IV treatment. Her eosinophilia and symptoms resolved shortly after discontinuation of posaconazole administration. Eosinophilia is a side effect of the anti-fungal azole class that has only been described thrice in adult patients. However, this is the first report of eosinophilic esophagitis and the first case to be described in a pediatric patient.

Case Report

In May of 2017 the patient, a previously healthy three-year-old Hispanic girl, was diagnosed with B-cell ALL and started on chemotherapy on COG protocol AALL 0932. As part of her chemotherapy, she underwent a lumbar puncture, over which a bandage was placed. At her follow-up visit one week later, she was found to have multiple skin lesions underneath bandages around lumbar puncture site, and a lesion on her right thigh. Primary pathology showed fungal growth suggestive of Mucormycosis, a type of Zygomycosis, and she was started on high dose liposomal amphotericin B at 7.5 mg/kg daily.

Her lesions continued to expand, and she developed left maxillary sinus involvement. Due to further spread of fungal infection despite therapy with amphotericin B, concomitant posaconazole therapy was initiated at a dose of 300 mg IV qday, a standard starting dose [8,9].

Cultures from her thigh and back grew *Rhizopus oryzae*, and sinus

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cultures grew *Mucor circinelloides*, both subspecies of Zygomycetes. Thigh cultures additionally grew *Alternaria sp*, an ascomycete fungi. She required extensive wound debridement of the back and leg lesions for two weeks, as well as two months of negative pressure wound therapy. She also underwent initial sinus debridement, with weekly sinus washouts and amphotericin foam gel placement for one month.

Our patient's posaconazole trough level returned at 4.8 mg/l after two weeks of treatment. The ideal trough levels of posaconazole are debated, however levels of >1.0-1.25 mg/l have been suggested as a goal during treatment of invasive fungal disease [9]. Therefore, her posaconazole dose was decreased to 150 mg IV qday. Subsequently, her trough levels ranged appropriately from 1.1-1.6 mg/l.

Seven weeks after initiation of posaconazole treatment, our patient developed pruritus around her PICC line site. A week later, her pruritus became generalized, and she began complaining of intense vaginal itching. Clotrimazole and hydrocortisone cream 2.5% were trialed without any improvement in symptoms. She additionally developed sore throat, leading to decreased oral intake, so she underwent an esophagogastroduodenoscopy (EGD). There were no signs of mucosal irritation or infections on visual examination, however biopsy results demonstrated eosinophils in the mucosal tissues, consistent with eosinophilic esophagitis.

On retrospective review of complete blood counts obtained during her treatment, it was noted that she had rising levels of peripheral eosinophilia. Her eosinophil level upon admission was 0%, and had risen to 6.3% after about six weeks of posaconazole treatment. On the day of her first pruritic symptoms her eosinophilia level was 12.5%; her maximum level was 23.6% on the day of her EGD.

At this time, posaconazole was stopped with concern for a drug reaction, and was replaced with micafungin 75 mg IV qday for ongoing dual treatment with amphotericin B. Her pruritic symptoms subsided within a week of posaconazole discontinuation. Her peripheral eosinophil level decreased to 15.3% at the time of symptom resolution, and eventually to 2.3% a month later at the time of discharge from the hospital.

She underwent split thickness skin grafting for her back and thigh lesions two weeks after stopping posaconazle, and a week later, micafugin was stopped due to continued clinical improvement. She was discharged on daily amphotericin B IV therapy in the oncology clinic, with close follow-up by infectious disease and oncology specialists.

Discussion

We present a pediatric patient with B-cell ALL and disseminated Zygomycosis infection who developed eosinophilic esophagitis and peripheral eosinophilia after seven weeks of IV posaconazole treatment. We are aware of only three previous case reports of eosinophilic response to azole therapy, and no previous case reports in a pediatric patient.

One case reported peripheral eosinophilia of 10.6% after 11 days of IV voriconazole for the treatment of Aspergillus lung infection following bone-marrow transplant, with decrease of peripheral eosinophilia to 5.7% within two days of stopping azole therapy [10]. The next case reported peripheral eosinophilia to 49%, as well as eosinophilic colitis, following five years of treatment with voriconazole for chronic pulmonary aspergillosis (CPA), and complete resolution of peripheral eosinophilia to 0% 18 days after stopping therapy [11]. This was the first reported case of azole-induced eosinophilic colitis. This same case reported recurrent peripheral eosinophilia to 15% following treatment with posaconazole for a CPA exacerbation after 15 months of treatment. The third case reported eosinophilia to 10.6% following 11 days of voriconazole treatment in patient with type II diabetes mellitus, diabetic nephropathy and end-stage renal disease found to have *Rhizopus* infection around his peritoneal dialysis catheter, which resolved two days after cessation of voriconazole therapy [12].

Our patient is the first pediatric patient to be described with an eosinophilic reaction to azole therapy. The duration of therapy prior to eosinophilia was intermediate to the previously published cases, around seven weeks. Like the second case report, gastrointestinal evidence of eosinophilia was found on esophageal biopsy. Ours is the first report of azole-induced eosinophilic esophagitis.

This report adds to the body of evidence formed by the three previous case reports that monitoring of eosinophil levels should be considered in patients receiving long-term azole therapy for fungal infections, and that clinicians should monitor for pruritus and gastrointestinal symptoms in these patients in order to recognize this adverse effect and tailor therapy appropriately.

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Conflicts of Interest

There are no conflicts of interest for any of the authors.

References

1. Schiller DS, Fung HB (2007) Posaconazole: an extended-spectrum triazole antifungal agent. Clin Ther 29: 1862-1886.
2. Moore JN, Healy JR, Kraft WK (2015) Pharmacologic and clinical evaluation of posaconazole. Expert Rev Clin Pharmacol 8: 321-334.
3. Chang M, Chagan L (2008) Posaconazole (Noxafil), an Extended-Spectrum Oral Triazole Antifungal Agent. Pharmacy and Therapeutics 33: 391-426.
4. Greenberg RN, Mullane K, van Burik JA, Raad I, Abzug MJ, et al. (2006) Posaconazole as salvage therapy for zygomycosis. Antimicrob Agents Chemother 50: 126-133.
5. van Burik JA, Hare RS, Solomon HF, Corrado ML, Kontoyiannis DP (2006) Posaconazole is effective as salvage therapy in zygomycosis: a retrospective summary of 91 cases. Clin Infect Dis 43: e61-65.
6. Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, et al. (2012) Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis 54: S23-34.
7. Alvarez E, Sutton DA, Cano J, Fothergill AW, Stchigel A, et al. (2009) Spectrum of Zygomycete Species Identified in Clinically Significant Specimens in the United States. J Clin Microbiol 47: 1650-1656.
8. U.S. Department of Health and Human Services (2018) Noxafil (posaconazole) prescribing information. Food and Drug Administration, United States.
9. Dekkers BGJ, Bakker M, van der Elst KCM, Sturkenboom MGG, Veringa A, et al. (2016) Therapeutic Drug Monitoring of Posaconazole: an Update. Curr Fungal Infect Rep 10: 51-61.
10. Vishnubhotla P, Ibrahim RB, Abidi MH (2004) Fever and eosinophilia associated with voriconazole. Ann Pharmacother 38: 900-91.
11. Grzegorczyk B, Murata Y (2014) Peripheral eosinophilia and eosinophilic colitis during long-term azole therapy for pulmonary aspergillosis. JMM Case Rep 1: e004135.
12. Alharbi M, Jhinger RK, Wuerz T, Walkty A (2017) Marked peripheral eosinophilia due to prolonged administration of posaconazole. JMM Case Rep 4: e005100.