Jefferson
Thomas Jefferson University
HOME OF SIDNEY KIMMEL MEDICAL COLLEGE

Thomas Jefferson University
Jefferson Digital Commons

Department of Medicine Faculty Papers | Department of Medicine

3-7-2022

Laryngeal blastomycosis with subsequent heart failure from itraconazole therapy.

Daniel Tsang
Thomas Jefferson University

S Haddad
Thomas Jefferson University

Mitchell Sternlieb
Main Line Health

Follow this and additional works at: https://jdc.jefferson.edu/medfp

 Part of the Cardiology Commons

Let us know how access to this document benefits you

Recommended Citation

Tsang, Daniel; Haddad, S; and Sternlieb, Mitchell, "Laryngeal blastomycosis with subsequent heart failure from itraconazole therapy." (2022). *Department of Medicine Faculty Papers.* Paper 346.
https://jdc.jefferson.edu/medfp/346

This Article is brought to you for free and open access by the Jefferson Digital Commons. The Jefferson Digital Commons is a service of Thomas Jefferson University's Center for Teaching and Learning (CTL). The Commons is a showcase for Jefferson books and journals, peer-reviewed scholarly publications, unique historical collections from the University archives, and teaching tools. The Jefferson Digital Commons allows researchers and interested readers anywhere in the world to learn about and keep up to date with Jefferson scholarship. This article has been accepted for inclusion in Department of Medicine Faculty Papers by an authorized administrator of the Jefferson Digital Commons. For more information, please contact: JeffersonDigitalCommons@jefferson.edu.

IDCases 28 (2022) e01463

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcases

Case report

Laryngeal blastomycosis with subsequent heart failure from itraconazole therapy

Daniel Tsang[a,*], Sara Haddad[a], Mitchell Sternlieb[b]

[a] Thomas Jefferson University Hospital, United States
[b] Main Line Health, United States

ARTICLE INFO

Article history:
Received 23 January 2022
Received in revised form 3 March 2022
Accepted 4 March 2022

Keywords:
Blastomycosis
Laryngeal blastomycosis
Itraconazole
Heart failure

ABSTRACT

Blastomycosis is an endemic mycosis in the United States that typically affects the respiratory tract and presents as a pneumonia. Dissemination can occur to any organ system, most commonly involving the skin or bones. Treatment of blastomycosis depends on the severity of disease and consists of itraconazole with liposomal amphotericin B added in during the initial stage in those with more severe disease or those who are pregnant. This case report describes an immunocompetent individual with mild to moderate blastomycosis of the larynx who was started on itraconazole therapy. However, after two months of treatment, he developed new symptomatic heart failure with reduced ejection fraction due to the itraconazole. His therapy was stopped after five months with improvement of his left ventricular ejection fraction days after discontinuation of therapy. He remained without relapse of disease after his abridged therapy duration.

© 2022 Published by Elsevier Ltd.
CC_BY_NC_ND_4.0

Introduction

Blastomyces species are dimorphic fungi primarily found in Midwest, Central, and Southeastern United States as well as along the Great Lakes and St. Lawrence River area. Infection in humans can occur via inhalation of aerosolized conidia during recreational or occupational activities that disrupt the soil. Therefore, disease most commonly presents as pneumonia [1].

Extrapulmonary dissemination occurs in 15–48% of cases and is more likely in those with prolonged duration of pulmonary symptoms and those who are immunosuppressed. Dissemination to almost any organ system can occur. In those with disseminated disease, the skin is the most commonly affected (40–80%), followed by the bone (15–44%), genitourinary system (20–30%), and central nervous system (< 10%) [1]. Dissemination to the larynx is rare and therefore data is limited. However, laryngeal blastomycosis has been described in case reports [2,3].

Treatment should be initiated in all patients with blastomycosis and typically consists of itraconazole for six to twelve months. Initiation of treatment with liposomal amphotericin B is recommended for those with moderate to severe pulmonary blastomycosis, central nervous system involvement, and those who are pregnant [4].

Azole antifungals have numerous drug-drug interactions and side effects. They act as both inhibitors and substrates for CYP3A4. Common side effects include hepatotoxicity, QT prolongation, and gastrointestinal upset. Unique to itraconazole is the possibility of negative inotropic effects – caution should be used in patients with a history of left ventricular dysfunction. This is usually dose dependent and resolves after discontinuation of the drug [5]. This case report describes a patient without a history of heart failure who was started on itraconazole and developed new left ventricular dysfunction, which improved several days after discontinuation of itraconazole.

Case

A 66 year old immunocompetent male presented as a referral to the infectious diseases clinic after he had a laryngeal biopsy suggestive of blastomycosis. He initially presented due to a worsening stridor over the span of two months. He was evaluated by an otolaryngologist and underwent laryngoscopy with microscopic excision of his supraglottic band. No cultures were sent, however, histopathology showed granulomatous inflammation with giant cells. This prompted staining onto Grocott's methenamine silver (GMS) stain which showed broad based budding yeast suggestive of *Blastomyces*. He worked as an electronic engineer and spent most of his life in southern New Jersey and Pennsylvania. During his lifetime,

* Corresponding author.
E-mail addresses: Daniel.Tsang@jefferson.edu (D. Tsang), Sara.Haddad@jefferson.edu (S. Haddad), SternliebM@mlhs.org (M. Sternlieb).

https://doi.org/10.1016/j.idcr.2022.e01463
2214-2509/© 2022 Published by Elsevier Ltd.
CC_BY_NC_ND_4.0

he traveled to California, Texas, Chicago, Maine, and Germany. Over the past year, his travel was more limited and included multiple hikes with his wife in Shenandoah National Park. His neighbor frequently burned vegetative matter.

Vitals and physical exam were unremarkable. Complete metabolic panel and complete blood count were within normal limits. *Blastomyces* antigen quantitative enzyme immunoassay (EIA) of the urine was negative. *Histoplasma* urine antigen and serum serologies were negative. Stains for acid fast bacilli were negative. Computed tomography (CT) of the neck after his excisional biopsy showed no discrete masses. CT of the chest showed multiple sub-centimeter nodules that were new from four years prior.

The presumptive diagnosis of laryngeal blastomycosis was made via histology that showed granulomatous inflammation with giant cells and direct visualization of broad-based budding yeast. Possible sources of exposure included inhalation during his hikes or inhalation of the smoke from his neighbor's burning of vegetation. This likely led to asymptomatic pulmonary disease as evidenced by pulmonary nodules seen on CT which later disseminated to his larynx.

He was initially started on itraconazole 100 mg once daily, but increased to 200 mg once daily after the first month because of subtherapeutic levels (total itraconazole and hydroxy-itraconazole level 0.61 μg/mL). Two months later, he became progressively dyspneic and had unintentionally gained five pounds. Transthoracic echocardiography (TTE) showed a reduction in his ejection fraction from 55% (2 years prior) to 40–45% without evidence of regional wall motion abnormalities. Electrocardiogram showed no ischemic changes and a QTc within normal limits. Total itraconazole and hydroxy-itraconazole level was 2.07 μg/mL. Based on these new findings and the temporal relationship with itraconazole initiation, there was concern for itraconazole induced heart failure. After discussion with his cardiologist, the decision was made to stop the itraconazole after five months of the planned six months of therapy.

After one week off of itraconazole, he lost eight pounds and his dyspnea improved. He had a repeat TTE which showed improvement of his left ventricular ejection fraction to 45–50%. He was monitored off of additional antifungals and had no evidence of relapse or further dissemination.

Discussion

This case describes a patient with laryngeal blastomycosis, which is an uncommon site of dissemination. Due to its rarity, there is limited information on laryngeal blastomycosis. Patients with laryngeal blastomycosis may present with progressive hoarseness, cough, dyspnea, sore throat, or dysphagia. Case reports have described patients being misdiagnosed with laryngeal cancer and subsequently receiving radiotherapy prior to the diagnosis of laryngeal blastomycosis [2,3]. Therefore, laryngeal blastomycosis should be included on the differential of a patient presenting with obstructive upper airway symptoms and risk factors for blastomycosis.

In this case, the patient may have been exposed during one of his hikes in the Shenandoah National Park. An interesting other possible exposure may have been his neighbor burning vegetation. Fungal spores such as *coccidioides* have been shown to be transmitted via smoke from wildfires [6]. However, less is known on whether *Blastomyces* can be transmitted via inhalation of smoke from fires.

The current treatment recommendations of six to twelve months for disseminated disease are based in large part due to a prospective, open-label, nonrandomized trial of patients with pulmonary or non-CNS extrapulmonary disease. Those patients received itraconazole 200–400 mg orally for a median of six months (range of 3–24 months) and had a 95% cure rate [4]. The Infectious Disease Society of America's (IDSA) recommended treatment for this patient would have been six to twelve months of itraconazole therapy. However, this patient was only able to tolerate five months of therapy due to side effects, but improved and showed no signs of further dissemination or relapse despite the shortened course. Relapse more commonly occurs within six months of discontinuing therapy [4].

Itraconazole can have negative inotropic effects and can rarely (< 2% of patients) lead to heart failure with reduced ejection fraction. In a healthy volunteer study of patients receiving intravenous itraconazole infusions, asymptomatic decreases in left ventricular ejection fraction were observed using SPECT imaging. These changes were transient and resolved within 12 h. In the medication's post market analysis, heart failure was more frequently seen in those receiving a total daily dose of 400 mg [5]. In this case, the highest dose that the patient took was 200 mg once daily. His left ventricular ejection fraction was noted to be decreased after two months of therapy and began to improve after one week off of therapy.

This case demonstrates that reduction in left ventricular ejection fraction can occur, even at lower doses of itraconazole. Careful monitoring of drug levels should be done after any changes in dose or more frequently if there is concern for drug toxicity. This case also provides some reassurance that shorter durations may be considered in those who have medication side effects.

Conclusion

Blastomycosis typically affects the pulmonary system, but can disseminate to other areas including the skin, bones, and less commonly, the larynx. Treatment typically consists of itraconazole for 6–12 months with liposomal amphotericin B added in for severe disease, immunocompromised patients, CNS involvement, and pregnant patients. Azole antifungals have numerous drug interactions and side effects that should be reviewed prior to initiation of therapy. Unique to itraconazole is the rare side effect of heart failure. This is typically dose dependent, but can also occur at lower doses and improves after several days of stopping the medication.

CRediT authorship contribution statement

Daniel Tsang, DO: Writing – original draft, Writing – review & editing. **Sara Haddad, MD:** Writing – original draft, Writing – review & editing. **Mitchell Sternlieb, MD:** Writing – original draft, Writing – review & editing.

Ethical approval

Patient consent unable to be obtained. Identifying information was removed.

Consent

Unable to be obtained.

Sources of funding

No sources of funding.

Conflicts of interest

No conflicts of interest to disclose.

Acknowledgements

Thomas Jefferson University Hospital (United States of America) will be paying for the $720 submission feel.

References

[1] Bennett John E, et al. Chapter 264: blastomycosis. Mandell, Douglas, and Bennett's principles and practice of infectious diseases 2. Amsterdam: Elsevier; 2020.

[2] Ballestas SA, Magliocca KR, Balter L, Hatcher JL. Laryngeal blastomycosis, an unexpected diagnosis: a case report. J Voice 2020;S0892-1997(20):30351–9. https://doi.org/10.1016/j.jvoice.2020.09.015. [Epub ahead of print. PMID: 33032884].

[3] Hanson JM, Spector G, El-Mofty SK. Laryngeal blastomycosis: a commonly missed diagnosis. Report of two cases and review of the literature. Ann Otol Rhinol Laryngol 2000;109(3):281–6. https://doi.org/10.1177/000348940010900309

[4] Chapman SW, Dismukes WE, Proia LA, Bradsher RW, Pappas PG, Threlkeld MG, et al. Clinical practice guidelines for the management of blastomycosis: 2008 update by the infectious diseases society of America. Clin Infect Dis 2008;46(12):1801–12. https://doi.org/10.1086/588300

[5] Drugs.com [Internet]. Itraconazole; c2000–2021; [Updated 22 July 2021; Cited 26 Dec 2021]. Available from ⟨https://www.drugs.com/pro/itraconazole.html⟩.

[6] Kobziar LN, Thompson III GR. Wildfire smoke, a potential infectious agent. Science 2020;370:1408–10.