Journal of Microbiology, Immunology and Infection 56 (2023) 192—196

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Short Communication

A difficult-to-treat pleuropulmonary histoplasmosis in a patient with rheumatoid arthritis in Taiwan

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Received 14 September 2022; received in revised form 16 November 2022; accepted 6 December 2022
Available online 13 December 2022

KEYWORDS
Histoplasma capsulatum;
Rheumatoid arthritis;
Salvage treatment;
Voriconazole;
Posaconazole;
Non-endemic area

Abstract Amphotericin B and itraconazole are the primary agents for treating histoplasmosis. Newer azoles are alternatives for patients refractory to or intolerant of standard therapy. We report an 83-year-old woman with rheumatoid arthritis complicated with pleuropulmonary histoplasmosis who responded to liposomal amphotericin B, but progressed under voriconazole and posaconazole maintenance therapy.

Introduction

Histoplasmosis is an endemic mycosis widespread in the mid-to southwestern parts of North America.[1] The etiological agent, *Histoplasma capsulatum*, is a dimorphic fungus commonly found in soil contaminated with bird or bat droppings, and humans are infected by inhalation of spores aerosolized by soil disruption. Although histoplasmosis is mainly documented in the U.S., sporadic cases have been reported from many countries including Taiwan in the past decades.[2] In non-endemic areas, the occurrence of histoplasmosis is often related to reactivation of previous focal infection in patients with diminished cellular immunity.[2] While acute pulmonary histoplasmosis is usually self-limited, itraconazole is recommended in mild-to-moderate cases and amphotericin B followed by itraconazole is recommended in severe cases.[3] However, the concerns about oral bioavailability, drug interactions, and tolerability preclude the modern day use of recommended therapy.

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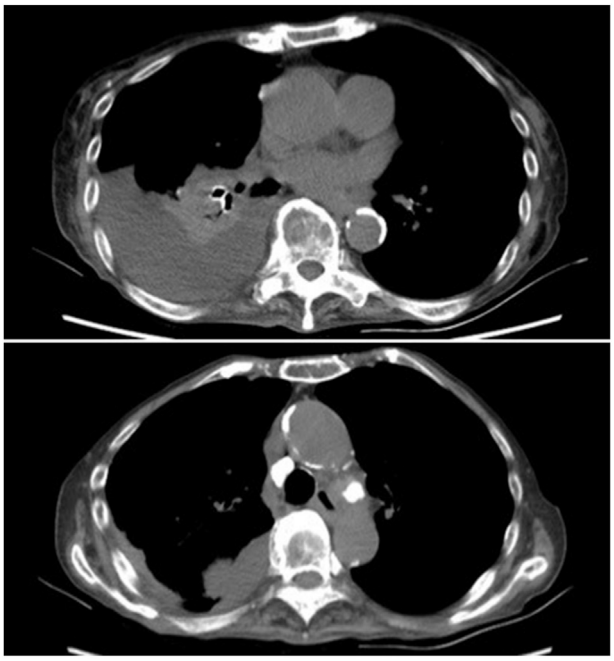
https://doi.org/10.1016/j.jmii.2022.12.005

Therapeutic drug monitoring (TDM) of itraconazole is strongly recommended but is not universally available.[3] The new triazole antifungal agents, including posaconazole and voriconazole, also demonstrate *in vitro* activity against *H. capsulatum*.[4] Given the limited evidence of clinical effectiveness, guidelines recommend newer azoles as second-line alternatives to itraconazole for patients on the basis of disease refractoriness or drug intolerance.[3] We herein report a case of pleuropulmonary histoplasmosis refractory to alternative newer azoles treatment in Taiwan.

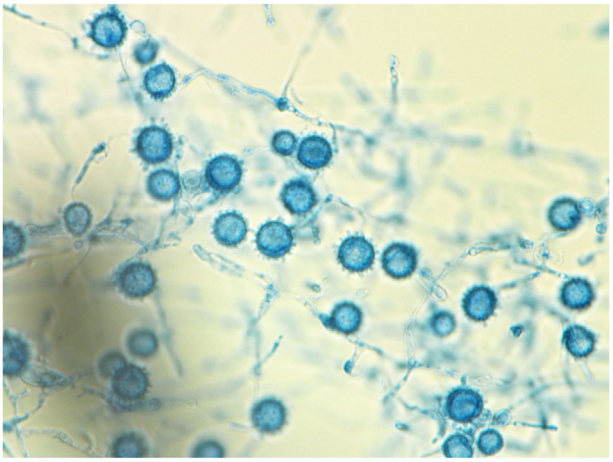
Case presentation

An 83-year-old woman with rheumatoid arthritis and subclinical hyperthyroidism presented to our hospital with progressive dyspnea for one week. She was a housewife with a remote travel history to Thailand, the United States, and European countries. She had received prednisolone (5 mg per day), methotrexate (5 mg every other day), and hydroxychloroquine (200 mg twice per day) for painful and swollen joints, and the medication was discontinued due to an improvement 2 months ago. On examination, the temperature was 37.8 °C, the heart rate 122 beats per minute, the respiratory rate 30 breaths per minute, the blood pressure 118/72 mmHg, and the oxygen saturation 96% while the patient was breathing ambient air. Physical examination showed pale conjunctivae and coarse crackles over her right lung, without joint deformity or swelling. Laboratory testing revealed a leukocyte count of 8930 cells/μL with 2% band and 85% segmented neutrophils, a hemoglobin level of 10 g/dL, a blood urea nitrogen level of 13.8 mg/dL, a serum creatinine level of 0.8 mg/dL, a C-reactive protein level of 4.44 mg/dL, a rheumatoid factor level of 80.3 IU/mL (reference value, <15 IU/mL) with positive anti-cyclic citrullinated peptide antibody, and a free T4 level of 1.06 ng/dL (reference value, 0.70—1.48) with thyroid stimulating hormone level of 0.0195 μIU/mL (reference value, 0.35—4.94). A chest radiograph and computed tomography (CT) demonstrated right lower lobe consolidation with atelectasis, right pleural effusion, and calcified mediastinal lymph nodes (Fig. 1a). The fluorodeoxyglucose-positron emission tomography/CT (FDG-PET/CT) for diagnostic work-up of fever of unknown origin demonstrated intense uptake in right lung, right pleura, and generalized lymphadenopathy. A pleural fluid analysis revealed lymphocyte-predominant exudates with a glucose level of 124 mg/dL.

The cultures of specimens obtained from pleural effusion, lung tissue, mediastinal lymph node, and bronchial washings revealed *H. capsulatum* (Fig. 1b). A diagnosis of pleuropulmonary histoplasmosis with lymph node involvement was made. Considering the uncertainty over the effective bioavailability of itraconazole capsule and lack of itraconazole TDM in our hospital, voriconazole was administered at a dose of 100 mg twice per day, achieving a voriconazole trough concentration of 5.01 μg/mL (targeted concentration, 2—5 μg/mL) after 7 days of therapy. The fever subsided one week after voriconazole treatment. However, the chest radiograph revealed progressive pleural effusion during the following 5 months. Besides, the serum galactomannan (GM) antigen index value failed to decline and was 0.42 at baseline and 0.41 at 5 months after voriconazole treatment.The GM antigen has been used as a surrogate biomarker for assessment of antifungal response on the ground of the cross-reactivity between GM antigen and histoplasmosis. Although the baseline GM antigen index value was within normal limits for invasive pulmonary aspergillosis in this patient, it was still used for monitoring treatment response because *Histoplasma* antigen and serological testing were not available in Taiwan. A failure to decline in GM antigen index may indicate non-response to treatment.[5]



a)



b)

Figure 1. Imaging and microscopic appearance. a, Computed tomography demonstrated right lower lobe consolidation with atelectasis, right pleural effusion, and calcified mediastinal lymph nodes. b, Microscopic appearance of *H. capsulatum*, with lactophenol cotton blue (LPCB) test, magnification × 400.

Due to the suboptimal response to voriconazole, an induction therapy with 2-week liposomal amphotericin B (AmBisome, 3 mg/kg/day) followed by maintenance therapy with oral posaconazole tablet (300 mg/day) was administered, with attainment of a posaconazole trough concentration of 4.3 μg/mL (targeted concentration, >1 μg/mL) after 7 days of therapy. However, a massive pleural effusion developed 2 weeks after oral posaconazole treatment and serum GM index values increased from 0.41 to 0.52. Another 4 weeks of induction therapy with liposomal amphotericin B was administered, followed by oral itraconazole capsule (200 mg twice per day). The following chest radiograph showed resolving pleural effusion with a subsequent decline in serum GM index levels (0.11). The patient died of natural causes at home 3 months later under continuous itraconazole treatment (one year after diagnosis).

Discussion

The present report highlights the need for vigilance for histoplasmosis among immunocompromised patients in non-endemic areas. A recent viewpoint pinpoints the limitation of current diagnostics.[6] A proven diagnosis can be achieved by culture or histopathological findings. However, the blood culture has low sensitivity and the fungus takes weeks to grow. Besides, microscopy and histopathological findings require considerable expertise and the diagnosis missed. Furthermore, in areas where histoplasmosis is not endemic,

Table 1 Characteristics of the alternative therapy studies.

References	Study design	Study population	Classification of histoplasmosis	Treatment	Outcome
Freifeld et al.[8]	Retrospective review	9 patients (5 solid organ transplantation, 2 autoimmune diseases, 1 renal failure, 1 none)	7 disseminated 2 pulmonary	Voriconazole (7 switched from itraconazole, 1 switched from amphotericin B, 1 initial therapy)	3 improved 6 stable[a]
Hendrix et al.[9]	Retrospective cohort	194 patients (41% immunocompetent, 25% HIV infection, 15% malignancy, 11% transplantation)	55% disseminated	175 Itraconazole (78 switched from amphotericin B, 97 initial therapy) 19 Voriconazole (11 switched from amphotericin B, 8 initial therapy)	• 180-day mortality: voriconazole 31.6% vs. itraconazole 23.4% • Early mortality (0—42 days): voriconazole vs. itraconazole (aHR, 4.3; 95% CI, 1.3—13.9) • Late mortality (43—180 days): voriconazole vs. itraconazole (aHR, 0; 95% CI, 0 to >99)
Restrepo et al.[10]	Case series	6 patients (3 HIV infection, 2 steroid use, 1 none)	5 disseminated 1 pulmonary	Posaconazole[b] (3 switch[b]d from amphotericin B, 2 switched from itraconazole, 1 switched from itraconazole/voriconazole)	2 complete success 4 partial success
Thompson et al.[11]	Open-label non-randomized trial	7 patients	4 disseminated 3 pulmonary	Isavuconazole (initial therapy)	1 complete success 3 partial success 1 stable disease 2 progression

[a] One patient switched back to itraconazole when the *H.* antigenuria failed to decline.
[b] Dose of posaconazole was 800 mg/day.
Abbreviation: aHR, adjusted hazard ratio; CI, confidence interval.

serological, antigen-based, and molecular methods for diagnosing histoplasmosis are not universally available. Among them, antigen detection in serum and urine is the most useful method of diagnosing histoplasmosis because it provides early diagnosis before culture and antibody production, tracks treatment responses, and detects relapse.[3] In the absence of antigen detection, diagnosis of histoplasmosis is typically delayed and the case-fatality is high.[6] Sporadic cases of histoplasmosis have been reported in Taiwan, and the lack of antigen detection and serological testing for histoplasmosis may result in an underestimated prevalence in Taiwan. We note a recent report of an indigenous case of disseminated histoplasmosis recurring 3 months after discontinuation of antifungal treatment which included 2-week amphotericin B followed by 12-month itraconazole.[2] In addition to the lack of awareness of this rare disease, poor availability and accessibility of laboratory diagnostics of histoplasmosis contribute to underdiagnosis. In non-endemic areas with limited availability of testing for *Histoplasma* infection, the cross-reactivity between *Histoplasma* and *Aspergillus* GM antigen has been observed. Previous studies have reported the utility of the widely available *Aspergillus* GM antigen as an adjunctive test for the diagnosis and assessment of treatment response in patients with histoplasmosis.[5,7]

Regarding antifungal therapy, amphotericin B has been the antifungal agent of choice for induction therapy of moderate to severe disseminated histoplasmosis, with the sequential use of itraconazole as maintenance therapy.[1,3] The clinical usefulness of the standard regimen is limited due to toxicity, erratic absorption, potential drug interactions, and poor tolerability. However, the effectiveness of alternative treatments, newer triazole antifungals, have not been convincingly shown in studies with small number of patients and low quality of study design (summarized in Table 1).[8—11] Three single-arm studies demonstrated that most patients benefited from receiving voriconazole, posaconazole, and isavuconazole as initial or salvage therapy.[8,10,11] Only one retrospective study compared mortality rates between patients receiving voriconazole (n = 19) and itraconazole (n = 175).[9] In the retrospective study with balanced baseline characteristics between patients receiving either azoles, the 180-day mortality rates were similar in the voriconazole group (31.6%) and itraconazole group (23.4%). However, there was a statistically significant association of voriconazole with an increase in early mortality (0 to 42 days; adjusted hazards ratio [aHR], 4.3; 95% confidence interval [CI], 1.3-13.9). The mortality later in the course of therapy (43—180 days) was similar between the 2 treatment groups as so few deaths occurred during this period. Given the limited evidence on their effectiveness, newer azoles are not recommended as first-line agents for patients with moderate or severe histoplasmosis.[3] Further investigations are warranted to elucidate the role of newer azoles in the treatment of histoplasmosis.

The *in vitro* antifungal susceptibility testing of the *Histoplasma* blood isolate collected from this patient was not performed as there are no standard testing methods for this dimorphic fungus.[12,13] In addition, no consensus exists regarding testing of the pathogenic yeast form, which occurs in blood and tissues and requires 6—8 weeks for conversion, or the saprotrophic mold form presenting in the environment. Notwithstanding the fact that the host immune status plays a vital role in patient recovery, susceptibility testing of dimorphic fungi yields basic information pertaining to its resistance and estimation of clinical response of the therapeutic agent. In summary, we present an HIV-uninfected case of histoplasmosis who had received the alternative treatment of voriconazole and posaconazole in an non-endemic area. Despite optimal trough concentrations of voriconazole and posaconazole, the disease progressed. Later, the clinical condition improved after repeated treatment with liposomal amphotericin B followed by itraconazole. The findings imply that voriconazole and posaconazole may not be as effective as amphotericin B and itraconazole in the absence of *in vitro* susceptibility testing. Therefore, antigen detection for monitoring treatment response and TDM of itraconazole should be established in Taiwan to optimize the treatment for histoplasmosis.

In conclusion, histoplasmosis has been recently recognized as an important public health problem globally. The barrier to prompt diagnosis and treatment optimization in non-endemic areas should be identified and solved to improve management of histoplasmosis, especially among non-HIV infected immunocompromised populations.

Declaration of competing interest

All authors declare no conflict of interest.

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