JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Case Report

A case of pulmonary histoplasmosis treated with voriconazole

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Abstract

Histoplasmosis is an infection caused by the dimorphic fungus *Histoplasma capsulatum.* The lungs are the most common site of infection, especially in patients with immune deficiency. We report a case of 62-year-old male patient presented with cough for 3 months and had been taking immunosuppressive drugs for 10 years after heart transplantation. Chest CT scan showed multiple pulmonary nodules. Lung tissue biopsy specimen culture suggested fungal infection, and *Histoplasma capsulatum* was confirmed by next-generation sequencing (NGS) detection. The patient was diagnosed with pulmonary histoplasmosis. After administration of voriconazole for 46 days, the symptom of cough was markedly relieved and the lesions were partly absorbed. After 13 months of treatment, the lesions completely disappeared, and no significant side-effect of voriconazole was observed. To our knowledge, report of voriconazole as the treatment of histoplasmosis is rare, especially in non-endemic areas. Moreover, this case enriches our experience in the adjustment between immunosuppressive and antifungal agents in treating histoplasmosis.

Key words: Pulmonary histoplasmosis; voriconazole; immunosuppressive drugs.

J Infect Dev Ctries 2022; 16(3):570-574. doi:10.3855/jidc.15297

(Received 09 May 2021 – Accepted 27 September 2021)

Introduction

Histoplasma capsulatum is a soil-based dimorphic fungus that grows in humid and warm areas. It releases fungal spores which can deposit in the alveoli of patients, if inhaled. Traditionally, it is mainly prevalent in the mid-west region of the United States, Latin America, and Central and West Africa [1,2]. In recent years, case reports on histoplasmosis in China have increased, especially in the Yangtze River region [3]. According to the guidelines established by the Infectious Diseases Society of America (IDSA), itraconazole is recommended as the first-line treatment for mild-to-moderate histoplasmosis, and amphotericin B for severe forms [4]. However, due to the variable absorption and poor tolerability of itraconazole, other newer azole agents such as voriconazole have been used in clinical treatment in an attempt to overcome these limitations [5]. Though the clinical efficacy of these new drugs increasingly supports treatment success with *H. capsulatum*, they are limited to small series and case reports to establish new treatment recommendations [6]. Here we report a case of pulmonary histoplasmosis treated with voriconazole effectively, aiming to provide a novel insight and theoretical basis for the treatment of pulmonary histoplasmosis.

Clinical case

Our patient is a 62-year-old male who presented with a three-month history of productive cough. He is an ironmonger from Wenzhou, Zhejiang Province (part of Yangtze River region) without any travel history to endemic countries. He had an orthotopic heart transplant due to dilated cardiomyopathy ten years ago and was on mycophenolate mofetil (0.75 g twice daily), tacrolimus (2 mg twice daily) and methylprednisolone (4 mg twice daily). Besides, his past medical history included high blood pressure, diabetes mellitus, and hyperlipidemia. Medications included valsartan (80 mg daily), bisoprolol (2.5 mg daily), benzenesulfonate amlodipine (2.5 mg daily), rosuvastatin calcium (10 mg daily) and acarbose (50 mg thrice daily). He had smoked one pack of cigarettes per day for 20 years. On

presentation, the patient was afebrile with normal vital signs. Laboratory findings are presented in Table 1. A computed tomography scan (CT) of the chest revealed multiple pulmonary nodules (Figure 1A-C). Percutaneous CT scan guided puncture biopsy of the pulmonary nodule in left upper lobe was performed. Inflammatory cell infiltration and a number of spore-like structures were visible within the cytosol by Hematoxylin and eosin staining (Figure 2A). Immunohistochemistry of the lung biopsy showed positive staining for CD68 (Figure 2B). Periodic acid-Schiff staining (Figure 2C) demonstrated weakly positive staining of fungal elements. Budding yeast cells were strongly positive with Grocott Hexamine-Silver staining (Figure 2D). These results led to the diagnosis of pulmonary fungal infection. After a comprehensive discussion of treatment options with clinical pharmacists, we decided to start on voriconazole (200 mg twice daily, 400 mg twice daily for the first 24 hours) for antifungal therapy. Meanwhile, we adjusted tacrolimus to 50%-70% of the current dose and monitored its concentration at 4-10 ng/mL. A few days later, lung tissue culture revealed growth of fungus, but the specific type of fungus is not yet identified. We sent the isolates from lung tissue culture medium to BGI Diagnosis Co. (Shanghai, China) for next-generation sequencing (NGS) test. Two days later, NGS results indicated *Histoplasma capsulatum*. Taken together, these findings were consistent with the diagnosis of pulmonary histoplasmosis, and antifungal therapy with itraconazole was the first choice as the guideline recommended [4]. However, both animal studies and clinical pharmacological researches demonstrated negative inotropic effect of itraconazole, and data from the US Food and Drug Administration's Adverse Event Reporting System suggested that use of itraconazole is associated with congestive heart failure [7]. Due to the heart transplantation history of the patient, which was considered to be a risk factor of congestive heart failure, and reference of previous observations of effective treatment with voriconazole, the patient was still treated with voriconazole (200 mg twice daily). One month later, his cough was relieved, and chest CT showed smaller lesions (Figure 1D-F). The patient returned to local hospital for follow-ups, after 13 months of

Table 1. Laboratory test results of the patient.

Parameter	Value	Reference range
RBC ($\times 10^{12}$/L)	3.74	4.3-5.8
Hemoglobin (g/L)	120	130-175
Platelets ($\times 10^{9}$/L)	137	125-350
WBC ($\times 10^{9}$/L)	5.06	3.5-9.5
Total lymphocyte count ($\times 10^{6}$/L)	268	unavailable
Actual CD4 + T-cell count (cells/μL)	320	unavailable
CD4 + T cell subsets (%)	18.3	unavailable
CD4/CD8 T cell ratio	0.7	unavailable
hs-CRP (mg/L)	1.5	0-3
ESR (mm/H)	15	< 20
ALT (U/L)	148	9-50
AST (U/L)	88	15-40
Albumin (g/L)	29.7	35-55
(1-3)-beta-D-glucan (pg/mL)	37.2	< 100.5
Mycobacterium tuberculosis-specific T cells test*	negative	negative
Cryptococcus capsular polysaccharide antigen test**	negative	negative
Tumor biomarkers		
Pro-GRP (pg/mL)	49.5	< 65.7
AFP (ng/mL)	2.3	< 20
CEA (ng/mL)	2.8	< 5
CYFRA21-1 (ng/mL)	4.6	< 3.3
NSE (ng/mL)	10.5	< 16.3
SCCA (ng/mL)	1.4	< 3
Rheumatic related indexes		
Anti-nuclear autoantibodies	negative	negative
Anti-double-stranded DNA antibodies (IU/mL)	< 10	< 100
Anti-neutrophil cytoplasmic antibody	negative	negative
Proteinase 3 (RU/mL)	< 2	< 20
Myeloperoxidase (RU/mL)	< 2	< 20

Diagnosis kit was provided by **Oxford Immunotec Ltd, UK* and ***Immuno-Mycologics, Inc, USA* respectively. RBC: red blood cells; WBC: white blood cells; hs-CRP: high sensitivity C-reactive protein; ESR: erythrocyte sedimentation rate; ALT: alanine-aminotransferase; AST: aspartate-aminotransferase; Pro-GRP: pro-gastrin-releasing-peptide; AFP: alpha-fetoprotein; CEA: carcinoembryonic antigen; CYFRA21-1: cytokeratin 19; NSE: neuron-specific enolase; SCCA: squamous cell carcinoma-associated antigen.

voriconazole treatment, with therapeutic drug levels of both voriconazole and tacrolimus monitored during treatment, his lesions completely disappeared without any significant side-effects.

Discussion

Histoplasmosis can occur as an opportunistic infection in immunosuppressed patients, such as those infected with the human immunodeficiency virus, patients receiving anti-tumor necrosis factor treatment and solid organ transplant recipients [8]. According to the guidelines for the clinical management of patients with histoplasmosis by IDSA, for mild to moderate progressive disseminated histoplasmosis, it can be treated with itraconazole more than one year (200 mg twice daily). Immunocompromised individuals may require itraconazole (200 mg daily) for life-long therapy [4]. However, the newer generations of azole drugs, such as voriconazole, demonstrate in vitro activity against *H. capsulatum*. Besides, in contrast to itraconazole, voriconazole had better tolerance, especially with long term use [9]. It also has in-vitro activity against *Histoplasma capsulatum* with minimum inhibitory concentrations (MICs) and minimum fungicidal concentrations (MFCs) within the achievable range [10,11]. Furthermore, Lv *et al*. have reported that three patients received effective treatment with voriconazole [12]. A retrospective cohort study of Hendrix *et al*. indicated that histoplasmosis treated with voriconazole as initial azole treatment was associated with a higher risk of mortality during the first 42 days when compared to those treated with itraconazole and no significant difference at 180 days [13]. Freifeld *et al*. have demonstrated that voriconazole was active against histoplasmosis, blastomycosis and coccidioidomycosis with 95.8% (22/24) of clinical outcome was favorable (improved or stable) within 2 months of starting treatment and 83.3% (20/24) at the last follow-up [14]. However, the available literatures on *Histoplasma capsulatum* treated with voriconazole are few, and more relevant studies are essential to provide new evidence in order to update the guidelines.

This patient received immunosuppressive drugs for a long time after heart transplantation, and laboratory findings showed a decrease in cellular immunity, which

Figure 2. A. Hematoxylin and eosin (H & E) staining (400×); **B.** Immunohistochemistry staining of CD68 (400×); **C.** Periodic acid-Schiff staining (400×); **D.** Grocott Hexamine-Silver staining (400×).

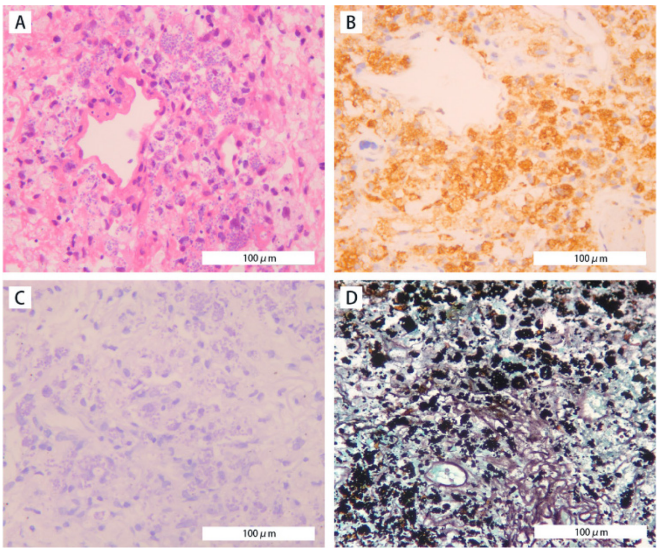
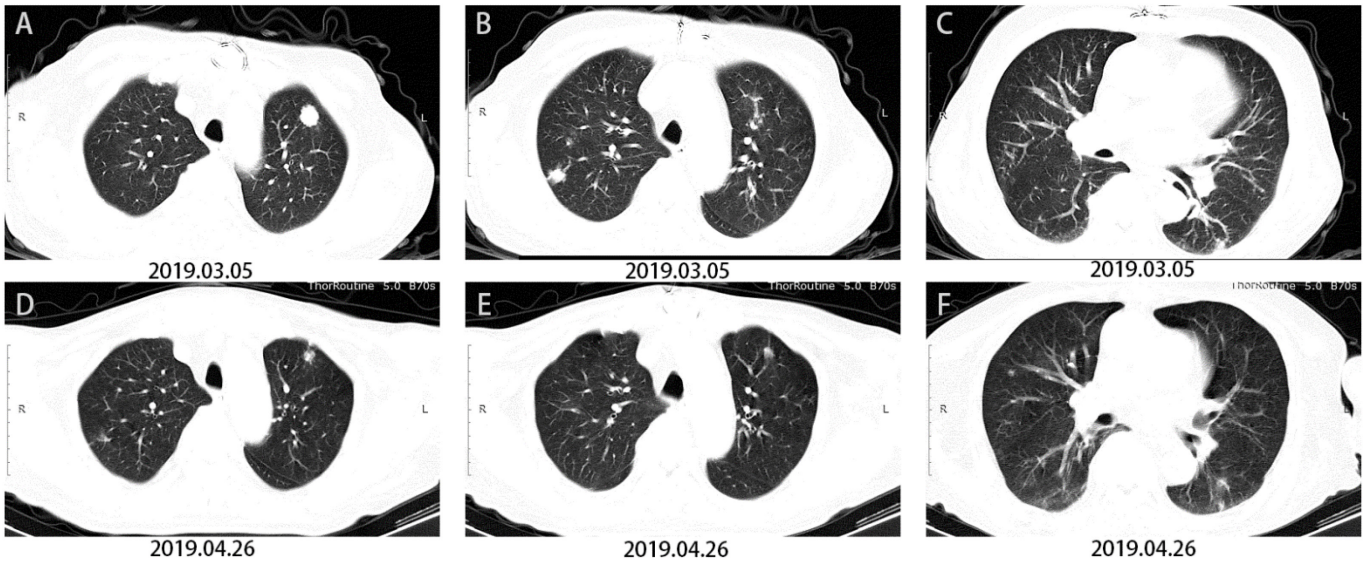


Figure 1. A. Chest computed tomography scan shows a nodule in left upper lobe; **B.** A nodule in right upper lobe; **C.** The nodule in left lower lobe adheres to the visceral pleura; **D. E. F.** The nodules significantly shrinked after antifungal treatment.



increased his vulnerability to histoplasmosis. Pathological examination and/or culture are the gold standard for the diagnosis of histoplasmosis [15]. However, some pathogens, such as *Penicillium marneffei*, may be confused with histoplasmosis histologically because of their intracellular characteristics and oval shape, and the low positive rate of culture makes diagnosis challenging [16,17]. In addition to histopathology and culture methods, histoplasmosis can be diagnosed by detecting fungal polysaccharide antigen in the blood or urine of the affected patient, with a sensitivity of 90%. Moreover, monitoring the level of antigen may help determine whether a subset of patients is at risk for relapse if azole therapy is discontinued [4]. In contrast, serologic testing has a low diagnostic yield for specific antibodies, especially in immunocompromised patients [18]. However, these methods are not available in China. Due to the lack of antigen and antibody tests, the diagnosis of histoplasmosis in China is difficult, especially pulmonary histoplasmosis [3]. As an important supplement to the diagnostic toolbox, NGS has made accurate and timely diagnoses of some rare and complex infectious diseases. Fungus growth was found in lung tissue culture of our patient, but the strain of fungus was still unclear. We detected *Histoplasma capsulatum* by NGS, and pulmonary histoplasmosis was diagnosed. An online survey study for clinicians managing invasive fungal diseases revealed that 62.7% (183/292) of the respondents had not accepted formal training in medical mycology, of which 38.2% (13/34) were come from China [19]. However, a well-trained professional can identify *Histoplasma capsulatum* in culture, which is the "gold standard" for diagnosis and a cheaper method than sequencing. This situation also usually occurs in the histopathological diagnosis, especially in non-endemic areas. Therefore, it is important to strengthen formal mycological training for laboratory professionals.

After consulting clinical pharmacists, voriconazole was given for antifungal treatment. Considering that the individual variation in absorption and metabolism of voriconazole is obvious, and the interaction between drugs may lead to great fluctuations in the serum concentration of voriconazole, it is necessary to monitor the serum concentration of voriconazole (valley concentration was maintained at 0.5μg/mL ~ 2.0μg/mL) during treatment. Tacrolimus was adjusted to 50%-70% of the current dose, and the concentration of tacrolimus was monitored and maintained at 4ng/mL ~ 10ng/mL. Though itraconazole is the first choice for mild-to-moderate histoplasmosis, it is associated with the risk of congestive heart failure. Considering that the patient has a history of heart transplantation and previous studies which suggested voriconazole was an effective treatment for histoplasmosis, our patient continued the current treatment regimen. The follow-up data showed that the treatment was effective.

Conclusions

In conclusion, we report a rare case of pulmonary histoplasmosis treated with voriconazole, from which we have learned several new facts. Firstly, we must be alert to the possibility of histoplasmosis in immunosuppressed patients. Moreover, it is necessary to be aware of the available tests, like NGS, which can help confirm the diagnosis of histoplasmosis. There remains a crucial need to study and improve diagnostic skills through formal training in medical mycology to identify *Histoplasma capsulatum* in culture and histopathology, which is a cheaper method than sequencing. Besides, voriconazole can be used in the treatment of pulmonary histoplasmosis. In view of the competitive inhibition between antifungal and immunosuppressive drugs, we invited clinical pharmacists to join the management on individual medication plans and blood concentration monitoring for the patient. This case contributes in several ways to our understanding of the diagnosis as well as the treatment of pulmonary histoplasmosis and emphasizes the importance of cooperation among multiple specialties.

Acknowledgements

The patient was asked for agreement for this publication and did not declare any opposition.

Authors' Contributions

Congyi Xie, Yimin Yang and Lin Tong wrote the initial manuscript and conducted the literature review. Xiaodan Wu and Na Zhu contributed to data collection. Zhangzhang Chen, Yuanlin Song and Lin Tong revised the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by Bethune Charitable Foundation (BJ-RW2020017J), and Shanghai Municipal Key Clinical Specialty (shslczdzk02201).

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Conflict of interests: No conflict of interests is declared.