Medical Mycology Case Reports 46 (2024) 100676

Contents lists available at ScienceDirect

Medical Mycology Case Reports

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

First case of fungal peritonitis caused by *Neosartorya hiratsukae* in China

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ARTICLE INFO

Handling Editor: Dr Adilia Warris

ABSTRACT

Fungal peritonitis, an uncommon complication in continuous ambulatory peritoneal dialysis (CAPD), has recently garnered increased attention due to its incidence and potential mortality. To the best of our knowledge, this is the first confirmed case of *Neosartorya hiratsukae* (*N. hiratsukae*) causing CAPD-related peritonitis in a patient with chronic nephrotic syndrome in Guangzhou, China. After prompt removal of the peritoneal catheter and active antifungal therapy, no clinical manifestations of peritonitis were observed. Our report underscores the importance of enhancing clinical awareness regarding *N. hiratsukae* and ensuring timely diagnosis in cases of CAPD-related fungal peritonitis.

1. Introduction

The occurrence of fungal peritonitis in continuous ambulatory peritoneal dialysis (CAPD) historically has high mortality rates but low morbidity [1]. The *Aspergillus* section *Fumigati*, one of the invasive pathogens causing occasional opportunistic infections in humans, contains 33 taxa: 10 strictly anamorphic *Aspergillus* species and 23 teleomorphic *Neosartorya* species [2]. However, the opportunistic pathogen *N. hiratsukae* has only been associated with a limited number of fungal peritonitis cases, leading to insufficient awareness among many clinicians. Moreover, conventional diagnostic methods are time consuming and labor intensive, leading to missed opportunities for timely medical treatment and an escalating mortality rate [3–5]. The number of reported cases of fungal peritonitis caused by *N. hiratsukae* is limited [6]. Therefore, raising awareness among clinical laboratories and clinicians about this uncommon fungus is crucial.

2. Case presentation

A 49-year-old male patient was admitted to the Guangdong Provincial People's Hospital on 30th April 2019 due to nonremission in one local hospital, where cefazolin and ceftazidime were used for his unbearable abdominal pain. The patient was diagnosed with chronic renal syndrome, and catheterization for peritoneal dialysis was performed 5 years ago. Medical history mainly included renal hypertension, chronic nephritis syndrome, chronic kidney disease stage 5, secondary nephrogenic hyperparathyroidism, and hyperphosphatemia.

On day 0, his body temperature was 38.6 °C, his pulse was 106 beats/min, and his blood pressure was 126/84 mmHg. During examination, his abdominal mobility dullness was positive, and the abdomen was tense with tenderness and rebound pain. Moreover, his peritoneal fluid was opaque. The C-reactive protein level increased to 165 mg/L, while peritoneal fluid WBC counts were 5523×10^6/L with more than 85 % of multinucleate cells. The patient was treated with intraperitoneal pentahydrate cefazolin (400 mg, q5d) and ceftriaxone (400 mg, q5d).

On day +2, his abdominal CT scan showed numerous free fluid density shadows in the abdomen and pelvic cavity, thickening peritoneum, and multiple patchy nodular shadows, indicating peritonitis. The peritoneal fluid WBC counts increased to 7725.00×10^6/L with 95 % of multinucleate cells. Given that the patient was not clinically improving, meropenem (500 mg, qid) was empirically added to the treatment regimen. On day +5, his blood and peritoneal fluid bacterial cultures remained negative, but fungal balls were seen in a BACT/ALERT® FA PLUS Culture vial inoculated with peritoneal fluid, but the strain was not identified yet (Fig. 1a). Thus, the treatment regimen was empirically switched to vancomycin (500 mg, q3d), amikacin (200 mg, qd), and voriconazole (200 mg, q12h). On day +7, after conventional macroscopic analyses, anosporogenic filamentous fungi were considered (Fig. 1b). The patient clinical status slightly improved, where the peritoneal fluid WBC decreased to 1849.00×10^6/L.

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https://doi.org/10.1016/j.mmcr.2024.100676
Received 31 July 2024; Received in revised form 7 October 2024; Accepted 12 October 2024
Available online 18 October 2024

On day +10, *Aspergillus* was suspected on the basis of microscopic examination with lactophenol cotton blue stain (Fig. 1e), and finally, the agent was identified by comparing the nucleotide sequence of the ITS regions of rDNA with that in the GenBank DNA database. The GenBank accession number for the nucleotide sequence is PQ350418, which revealed a 100.00 % similarity with *N. hiratsukae/A. hiratsukae* (accession number: MW193255.1). Then, the peritoneal catheter was timely removed. Therefore, amphotericin B liposome (5 mg, qd) combined with voriconazole (200 mg, q12h) was added to facilitate anti-infective activities. On day +13, macroscopic and microscopic analyses were performed; under the microscope, Cleistothecia, ascus, and ascospores were seen, and the morphological characteristics were consistent with *Neosartorya* (Fig. 1f, g, and 1h).

On day +15, antifungal susceptibility testing of the strain was performed to determine the minimum inhibitory concentration (MIC) through the use of the approved protocol of the Clinical Laboratory Standard Institute document M-38A. The results were read after 48 h of incubation: amphotericin B 0.25 μg/L, flucytosine 64 μg/L, fluconazole 32 μg/L, itraconazole 16 μg/L, and voriconazole 0.06 μg/L.

During the patient's hospitalization, clinicians removed the peritoneal catheter early and tailored the antifungal therapy based on his response (Fig. 2). Voriconazole tablets (200 mg, q12h) were still used to control the fungal infection after approximately one month post discharge. Then, the patient showed no clinical signs of peritonitis and was in good condition.

3. Discussion

The *Aspergillus* section *Fumigati,* which causes occasional opportunistic infections in humans, comprises 23 teleomorphic *Neosartorya* species in a recent revision [2,7]. These species have been found to be capable of invading the lungs, brain, and other organs, with *N. fischeri* and *N. pseudofischeri* being the primary contributors [8]. To our knowledge, this is also the first reported case of fungal peritonitis caused by this rare *Neosartorya* species in China. So far, only three cases of infection caused by this fungus have been reported in literature (Table 1) [2,9,10]; thus, information about the global distribution of this species is limited. *N. hiratsukae* (sexual stage), the teleomorph of *Aspergillus hiratsukae* (asexual stage), is often misidentified because it cannot be distinguished from the *Aspergillus* section *Fumigati* by conventional morphological macroscopic and microscopic analyses.

The process of *N. hiratsukae* identification was slower than the ideal in this case, primarily due to the following conflicts: (i) Microscopic examination revealed no presence of fungus despite a positive indication from even the BACT/ALERT® FA PLUS Culture vial. This result might be attributed to the little sediment in the bottle, which was not easily observable with naked eye. Additionally, flocculent precipitate might obstruct the needle, making it challenging to obtain the target fungus. Moreover, inadequate fixation during peritoneal dialysis solution staining could contribute to underreporting. These issues can be mitigated by thoroughly mixing the bottle completely before smearing, conducting microscope examinations at low-power magnification, or using a larger syringe for sampling purposes. (ii) False negatives were observed in the BACTEC™ Plus Aerobic/F Culture vial. The filamentous fungi exhibit slower metabolism compared with bacteria, resulting in a flat growth curve that does not meet the positive criteria set by the instrument's algorithm. Therefore, on the basis of our experience with fungal identification in this case study, any precipitate, clot, or floc within peritoneal dialysis culture bottles must be carefully inspected during subculture or prior to disposal.

In this particular case, microscopic examination was conducted, and the utilization of ascospore micromorphology could be considered for identification purposes. The observed characteristics were concordant with *N. hiratsukae.* However, its application was limited due to the lack of availability of a scanning electron microscope in many clinical labs and its inability to differentiate all *Neosartorya species* accurately [7]. Given that the variable MIC values are reported in the literature for *N. hiratsukae*, which mainly show azole-susceptible patterns but also

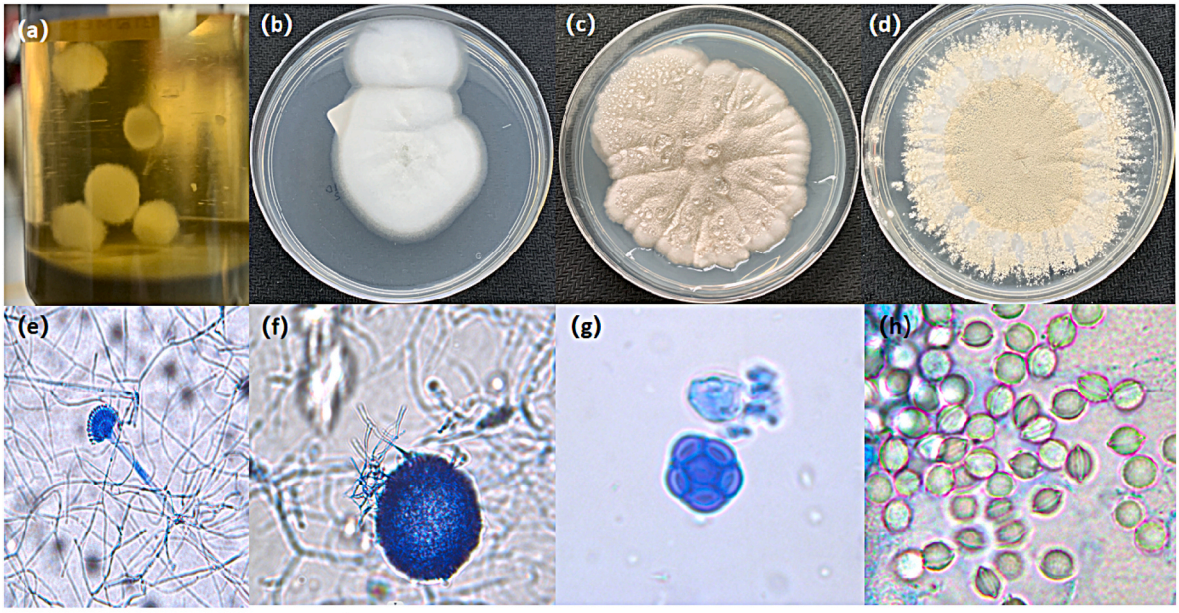

Fig. 1. (a) BACT/ALERT® FA PLUS Culture vial, inoculated with peritoneal fluid, exhibits fungal balls after 5 days of incubation. **(b)** Colony morphology after 2 days of incubation on Potato Dextrose Agar at 28 °C. **(c)** Colony morphology after 5 days of incubation on Potato Dextrose Agar at 28 °C. **(d)** Colony morphology after 10 days incubation on Potato Dextrose Agar at 28 °C. **(e)** Conidial heads are short, columnar, and uniseriate. Conidiophore stipes are smooth walled, and vesicles are usually subglobose to flask shaped (stained with lactophenol cotton blue; original magnification × 400). **(f)** Cleistothecia after 10 days of incubation on Potato Dextrose Agar at 28 °C (stained with lactophenol cotton blue; original magnification × 200). **(g)** Ascus of *N. hiratsukae* after 10 days of incubation on Potato Dextrose Agar at 28 °C (stained with lactophenol cotton blue; original magnification × 1000). **(h)** Ascospore of *N. hiratsukae* after 10 days of incubation on Potato Dextrose Agar at 28 °C (stained with lactophenol cotton blue; original magnification × 1000). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

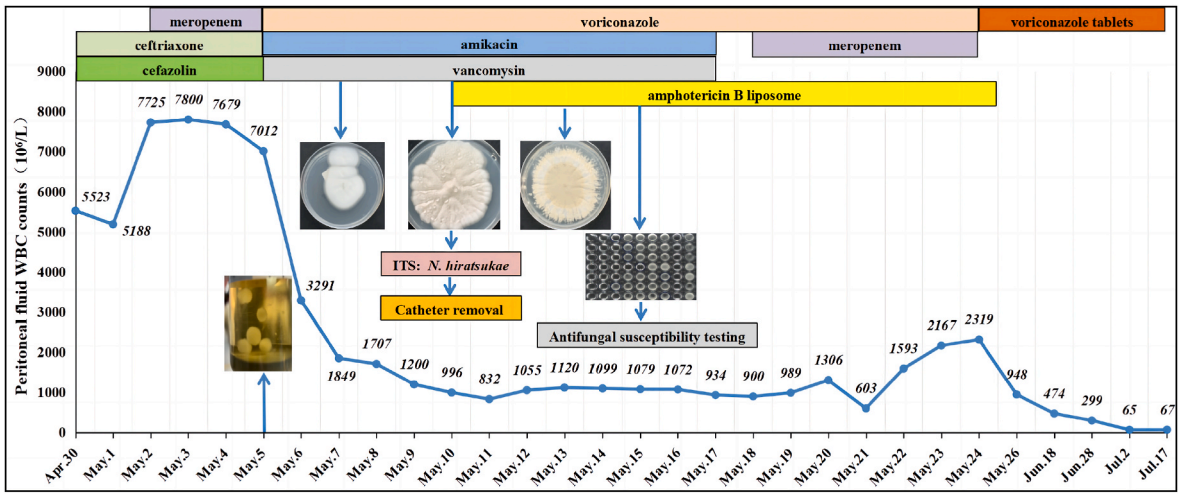

Fig. 2. WBC counts in the peritoneal fluid during the patient's hospitalization.

Table 1
Summary of infections caused by *N. hiratsukae* from 2002 to 2024.

Reference (Year)	Patient origin	Age/ Gender	Clinical specimen	Infection	Antifungal therapy	Outcome
Guarro et al. (2002) [9]	Brazil	75/F	Cerebral fragment	Cerebral Aspergillosis	ITC	Died
Shivaprakash et al. (2009) [10]	India	40/M	Nasal tissue	Allergic fungal rhinosinusitis	Not given	Recovered
Koutroutsos et al. (2010) [2]	Greece	58/M	Peritoneal fluid	CAPD-related fungal peritonitis	AMB + CAS, then switched to VRC	Died
Kaixuan et al. (2024) [Present paper]	China	49/M	Peritoneal fluid	CAPD-related fungal peritonitis	VRC + AMB, then switched to VRC tablets	Recovered

Legend: F, Female; M, Male; CAPD, continuous ambulatory peritoneal dialysis; ITC, itraconazole; AMB, amphotericin B; CAS, caspofungin; VRC, voriconazole.

sporadic high itraconazole MIC values [2,9–11], this species must be differentiated from others in *Aspergillus* section *Fumigati* [12–14]. Rapid and accurate identification of fungi is crucial in terms of therapeutic effectiveness because different species exhibit varying susceptibility patterns to drugs. In our case, the patient was suspected to have initially received antibacterial drugs before peritonitis caused by fungus. Subsequently, treatment was switched to antifungal therapy upon reporting fungal balls to clinicians. Voriconazole and amphotericin B were administered on the basis of the identified species and adjusted in accordance with the patient's response for optimal treatment optimization considering MIC values. Considering the limited number of reported cases involving *N. hiratsukae* and its variable response to antifungal drugs among different species, investigation and documentation of antifungal susceptibilities are essential for therapeutic efficacy.

The importance of this case report cannot be overstated because it presents the first documented instance of CAPD-related peritonitis caused by *N. hiratsukae* in China. This case not only enhances clinical awareness but also contributes valuable geographical distribution information. Furthermore, this case report holds particular importance due to the tendency to discard clinical isolates of *Neosartorya* spp. as mere contaminants, which produce white colonies and do not turn green like *A. fumigatus* colonies.

Therefore, white colonies with microscopic characteristics resembling *Aspergillus fumigatus* and exhibiting a sexual stage are indicative of *Neosartorya*. Consequently, a rapid and accurate method for identifying intractable fungal peritonitis caused by this rare fungus must be developed urgently to enable precise diagnosis and timely treatment to reduce under-reporting of cases and mortality.

CRediT authorship contribution statement

Kaixuan Yuan: Writing – review & editing, Writing – original draft. **Xiaoxiao Wang:** Writing – review & editing. **Yong Ling:** Writing – review & editing. **Ye Long:** Visualization, Data curation. **Zhuoxi Chen:** Visualization, Data curation. **Yunhu Zhao:** Writing – review & editing, Supervision.

4. Ethical form

The human participants involved in this study were in accordance with the Research Ethics Committee of the Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences (KKY2024-578-0). All participants provided oral informed consent. This study did not involve animal-related experiments, and no animal ethical requirements were needed.

Declaration of competing interest

There are none.

Acknowledgments

There are none.

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