

## Case Report

# *Fusarium solani* infection after antimicrobial treatment of a severe bacterial peritonitis: a case report and review of the literature

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## ABSTRACT

Fungal peritonitis is a rare but serious complication of peritoneal dialysis. This infection has been reported to be mostly caused by *Candida* species, and less frequently by a variety of other yeasts and moulds, such as *Aspergillus*, *Penicillium*, and *Fusarium* spp. are commonly isolated from soil, plants and environmental surfaces, and rarely from non-immunosuppressed subjects. In this report, author describe a case of infection caused by *Fusarium solani* in a 59-year-old man undergoing continuous ambulatory peritoneal dialysis. The fungus was recovered from cultures of peritoneal dialysate and the pathogen identification was carried out by mass spectrometry. The patient's outcome was favorable without complications after liposomal amphotericin B treatment along with peritoneal dialysis catheter removal.

**Keywords:** Antifungal treatment, Catheter removal, *Fusarium*, Matrix-assisted laser desorption ionization-time of flight mass spectrometry, Peritonitis

## INTRODUCTION

Peritonitis is one of the most common complication of Peritoneal Dialysis (PD), leading to patient's hospitalization and, in some cases, death.<sup>1</sup> Bacteria, in particular Gram-positive cocci, are the most frequent etiological agents causing peritonitis, while fungi account for 2, and 23.8% of all cases in industrialized and developing countries, respectively.<sup>2</sup> Fungal peritonitis are related to a poor therapeutic outcome and to high mortality and morbidity.<sup>3-6</sup> About 60-90% of fungal peritonitis are due to *Candida* species, in particular *Candida parapsilosis*, while infections due to other yeasts or filamentous moulds have been rarely reported.<sup>3,6,7</sup> Filamentous fungi are widely distributed in nature. Among them, strains of *Aspergillus* genus and *Penicillium* species are the most frequent isolates causing peritonitis in PD patients.<sup>8,9</sup> Other filamentous fungi belonging to the genera *Acremonium*, *Fusarium* and

*Exophiala* are less commonly reported as pathogens in PD patients.<sup>3</sup>

*Fusarium* spp. cause a broad spectrum of human infections that can be divided in single-organ invasion, such as keratitis and onychomycosis, and in disseminated disease, especially in immunocompromised individuals, such as patients undergoing solid organ transplantation, patients with hematological malignancies, and patients with severe burns.<sup>10</sup>

Moreover, *Fusarium* spp. are able to adhere to the surface of foreign bodies, e.g. contact lenses and catheters, to release proteases and collagenases, and to produce mycotoxins that can suppress the immune system.<sup>10</sup> In this case study, author report a case of infection caused by *Fusarium solani* in a 59-year-old man undergoing PD. This infection was likely acquired after antimicrobial treatment for a previous severe bacterial peritonitis.

## CASE REPORT

A 59-year old Caucasian man, undergoing continuous ambulatory peritoneal dialysis since 2015, was admitted in February 2019 to this hospital with abdominal pain, fever, and cloudy peritoneal effluent. His past medical history was significant since he suffered from an end-stage renal disease due to a membranoproliferative glomerulonephritis secondary to hepatitis C diagnosed in 2000 for which he was treated with interferon and ribavirin until 2013. In February 2018 he had a negative culture peritonitis event. The patient was reported to practice moderate physical activity despite peritoneal dialysis.

On February 20, the initial laboratory investigations showed normal complete blood tests (hemoglobin 11.4 g/dl, hematocrit 32.0 %), without leukocytosis or thrombocytopenia (peripheral White Blood Cell (WBC) count 6,100/mm<sup>3</sup>, platelet count 173,000/mm<sup>3</sup>). Systemic inflammation tests were positive: C-reactive protein (CRP) 34.3 mg/L (reference range: 0-5 mg/l) and Procalcitonin (PCT) 8.03 ng/ml (reference range: 0-0.5 ng/ml). The PD effluent was sent for microscopy and culture, and an empiric Intraperitoneal (IP) antimicrobial therapy with cefazolin and ceftazidime was started (1 g/l daily), as suggested by international guidelines.<sup>11</sup> PD effluent cell count revealed an elevated WBC count (4,794/mm<sup>3</sup>). Two days later, cultures yielded growth of *Serratia marcescens*, *Enterococcus faecalis* and *Klebsiella oxytoca*. Grown bacteria were identified using Vitek® Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOF MS) system (bioMérieux). Consequently, a personalized IP vancomycin administration was performed (500 mg/l). On February 25, PD effluent was clear, showing a reduced WBC count of 36/mm<sup>3</sup>, while CRP and PCT were negative. On March 4, the recrudescence of fever and abdominal pain associated with cloudy PD effluent made it necessary to carry out a new culture test on peritoneal discharge liquid. PD fluid analysis showed an increased value of WBC count, 360/mm<sup>3</sup>, and concomitantly, an increased peripheral WBC count of 9,800/mm<sup>3</sup> was observed. CRP was positive (21.92 mg/l).

IP vancomycin (500 mg/l) treatment in addition to oral administration of levofloxacin (500 mg/l) and fluconazole (initially 200 mg/l, then 100 mg/l daily) were empirically started for suspected bacterial peritonitis. After five days, PD effluent cultures yielded growth of the filamentous fungus *F. solani* without the presence of other microorganisms. Identification of *F. solani* was carried out by standard methods, which included macroscopic (colony color and pigmentation) and microscopic (shape and size of macro- and microconidia) examinations, and it was confirmed by MALDI-TOF MS analysis with 99.9% confidence. Author used the criteria described in Clinical and Laboratory Standards Institute (CLSI) M61-ED1:2017 for antimicrobial susceptibility cut-off points for *Fusarium spp.*<sup>12</sup> Epsilometer Tests (E-test)

(bioMérieux) were performed to obtain rapid and accurate results for susceptibility and resistance detection. The microorganism resulted resistant to almost all tested antifungals, i.e. fluconazole (Minimum Inhibitory Concentration (MIC) >32 µg/ml), itraconazole (MIC >32 µg/ml), voriconazole (MIC >32 µg/ml), terbinafine (MIC <10 mm), and 5-flucytosine (MIC >32 µg/ml), and sensitive to liposomal amphotericin B (MIC =0.25 µg/ml). Liposomal amphotericin B treatment was started (4 mg/kg daily), while vancomycin treatment was suspended. On March 8, despite normal laboratory tests, PD fluid showed higher value of WBC count (2,167/mm<sup>3</sup>). Therefore, the following day, PD catheter was removed, and the patient was shifted to hemodialysis after central venous catheter insertion. *Staphylococcus haemolyticus* and *Staphylococcus epidermidis* growth was observed on the superficial cuff of the PD catheter. Liposomal amphotericin B treatment was prolonged for ten days. On March 15, CRP value decreased to 3.2 mg/L, and, 4 days later, the test was completely negative (<0.1 mg/L), so the patient was discharged in good health.

## DISCUSSION

*Fusarium spp.* are ubiquitous fungi and are known pathogens for plants, animals and humans. Although they are rarely responsible to cause disease in immunocompetent humans, recently, they emerged as significant opportunistic pathogens often associated with fatal outcome in immunocompromised subjects, in particular those with hematological malignancies.<sup>7,10</sup>

*Fusarium peritonitis* in continuous peritoneal dialysis patients has been rarely reported in the literature.<sup>7,13-14</sup> Important risk factors for *Fusarium* infection are compromised immune system, tissue damages after trauma and presence of foreign bodies.<sup>10</sup> In subjects undergoing continuous ambulatory PD, *Fusarium spp.* can determine either plugging or invasion of the peritoneal catheter, thus leading to fungemia, as previously reported.<sup>7,10,14</sup> Other risk factors associated with fungal peritonitis are previous episodes of bacterial peritonitis, wide-spectrum antibiotic treatments, advanced age, administration of immunosuppressant therapy and hospitalization.<sup>3</sup> In this case, different factors might have contributed to the development of *Fusarium* infection, despite the relative young age and previous good health status of the patient.

These factors include the presence of the PD catheter, a prolonged dialysis period (4 years), recent bacterial peritonitis, and two previous antibiotic treatments. It has been suggested that the use of antibiotics and the declined host defense caused by the peritonitis might favor fungi proliferation.<sup>10,15</sup> Thus, the use of antifungal prophylaxis during antibiotic therapy could be helpful, although the matter is debated, as conflicting results have been reported so far.<sup>6,16-18</sup> In this center, the systematical use of antifungal prophylaxis in case of repeated antibiotic

treatment or invasive procedures in PD patients drastically reduced the incidence of fungal peritonitis.<sup>6</sup> Nonetheless, washing hands, muciporin use, exit-site care, cleansing, adequate trained personnel and management of potential environmental risks, are important measures to reduce risks of both fungal and bacterial peritonitis.<sup>11</sup>

The optimal treatment of *Fusarium* infection remains not established. *Fusarium spp.* are relatively resistant to many antifungal agents, including 5-flucytosine, and the susceptibility to other drugs differs among species.<sup>7,13,14</sup> In this case, *Fusarium solani* strain was resistant to numerous antifungals, including all tested triazoles and the alylamine derivative terbinafine. On the other hand, liposomal amphotericin B treatment, which is considered the drug of choice, was successfully used.<sup>10,13</sup> Nonetheless, this antifungal agent presents some side effects, such as high toxic potential and a low therapeutic index, causing high doses necessary to treat fungal infections.<sup>19</sup>

The International Society for peritoneal dialysis recommends prompt removal of PD catheter in order to treat fungal infections once fungi have been identified by microscopy or culture, as the majority of fungi, including *Fusarium spp.*, have the ability to attach to foreign bodies, thus increasing the risk of mortality.<sup>11,20</sup> In authors experience, catheter removal is recommended in fungal peritonitis and is mandatory to improve patients' survival. In this case, the combination of catheter removal and antifungal therapy resulted in a good outcome for the patient, complying with results previously reported in other works.<sup>3,6,7,14</sup>

## CONCLUSION

In conclusion, this study confirms that peritonitis due to filamentous fungi should be considered during diagnostic procedures, especially when the association of particular patient clinical features and laboratory tests can distinguish a true pathogen from a lab contaminant. Liposomal Amphotericin B is effective as antifungal agent, but the identification of the involved species and the determination of drugs susceptibilities associated with simultaneous removal of peritoneal catheter may improve patient outcomes.

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