International Journal of Infectious Diseases 85 (2019) 114–116

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

Case Report

Pulmonary scedosporiosis in a patient with acute hematopoietic failure: Diagnosis aided by next-generation sequencing

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ARTICLE INFO

Article history:
Received 18 April 2019
Received in revised form 15 May 2019
Accepted 25 May 2019
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Scedosporium apiospermum
Pulmonary scedosporiosis
Next-generation sequencing

ABSTRACT

We report the first case of pulmonary scedosporiosis detected by next-generation sequencing (NGS) from bronchoalveolar lavage fluid (BALF) in a 67-year-old male with bronchiectasis and hematopoietic failure. *Scedosporium apiospermum* is a ubiquitous organism present in the environment with intrinsic resistance to many antifungal agents. The patient developed respiratory failure, pulmonary consolidation, and septic shock shortly thereafter, and responded poorly to antifungal therapy. This case highlights the combined application of NGS and traditional fungal culture in the clinical diagnosis of pulmonary invasive fungal disease. NGS is proposed as an important adjunctive diagnostic approach for uncommon pathogens.

Introduction

To date, the genus *Scedosporium* contains 10 recognized species, among which *Scedosporium boydii* and *Scedosporium apiospermum* are the most clinically relevant species causing human infections worldwide (Ramirez-Garcia et al., 2018). *S. apiospermum* is a saprophytic organism that is ubiquitously present in the environment, particularly in soil, polluted water, and sewage (Rougeron et al., 2018). Clinically, the incidence of scedosporiosis caused by *Scedosporium* is relatively rare. Caira et al. reviewed the cases of 8633 patients with acute leukemia over a 15-year period and only five cases of proven scedosporiosis were identified, suggesting an incidence of 0.06% in patients with acute leukemia (Caira et al., 2008). Here we report the first case of pulmonary scedosporiosis diagnosed by combination of next-generation sequencing (NGS) and fungal culture from a bronchoalveolar lavage fluid (BALF) sample in a patient with acute hematopoietic failure.

Case presentation

A 67-year-old male with repeated episodes of bronchiectasis over a 20-year period was initially admitted to the respiratory department in December 2018 due to a cough, bloody phlegm, dyspnea, and fever with a temperature up to 39.4 °C for 1 day. A computed tomography (CT) scan showed severe inflammation in the right lower lobe. Over the past 5 years he had been admitted to the respiratory department three times due to community-acquired pneumonia and had been discharged within 7–9 days after receiving empirical antibacterial treatments, as no specific pathogen was identified from sputum culture. Of note, he underwent a period of moderate leukocytopenia during each hospitalization. This time, his peripheral leukocyte count was decreased to 0.2×10^9/l (Figure 1). Therefore, the patient was transferred to the intensive care unit as an emergency due to severe pneumonia and leukocytopenia.

After admission to the intensive care unit, the patient's respiratory failure deteriorated rapidly despite imipenem and minocycline being administered as empirical therapy. Tracheal intubation was performed on the second day after admission and noradrenaline was shortly also administered due to hypotension (Figure 1). A bedside chest X-ray revealed bilateral disseminated pulmonary infiltrates (Figure 2A). CT re-examination showed worsening of his pulmonary condition and severe exudative inflammation in the bilateral lungs, with consolidation in the right lobe (Figure 2B). Serum virus tests were positive for Epstein–Barr virus DNA, so ribavirin was also administered. Bone marrow aspiration found no malignant pathological cellular change, but severe inhibition of hematopoiesis was observed. His leukocyte count (normal range $4–10 \times 10^9$/l) remained lower than 2×10^9/l, with a minimum level of 0.1×10^9/l; his erythrocyte count and platelet count were also far below the normal range (Figure 1).

With regard to the etiological diagnosis, blood and sputum samples collected for bacterial culture on admission revealed no bacterial growth after 2 days. Therefore, considering the possibility

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https://doi.org/10.1016/j.ijid.2019.05.033

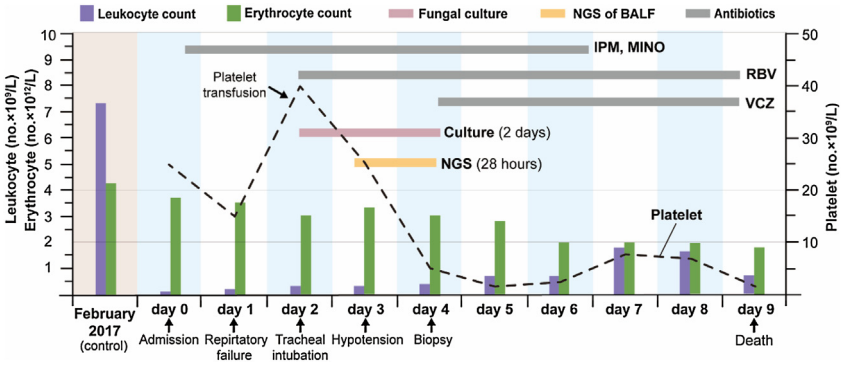

Figure 1. The daily course of the patient in the intensive care unit. Major events are indicated with arrows. The purple bars show the peripheral blood leukocyte counts and the green bars refer to the erythrocyte counts, being compared with the blood cell count tested in February 2017. The dashed line illustrates the change in platelet count. The horizontal pink bar indicates the course and turnaround time (2 days) for clinical fungal culture, while the yellow bar indicates those for next-generation sequencing (28 h). The horizontal thick gray lines show the medications administered: IPM denotes imipenem, MINO minocycline, RBV ribavirin, and VCZ voriconazole.

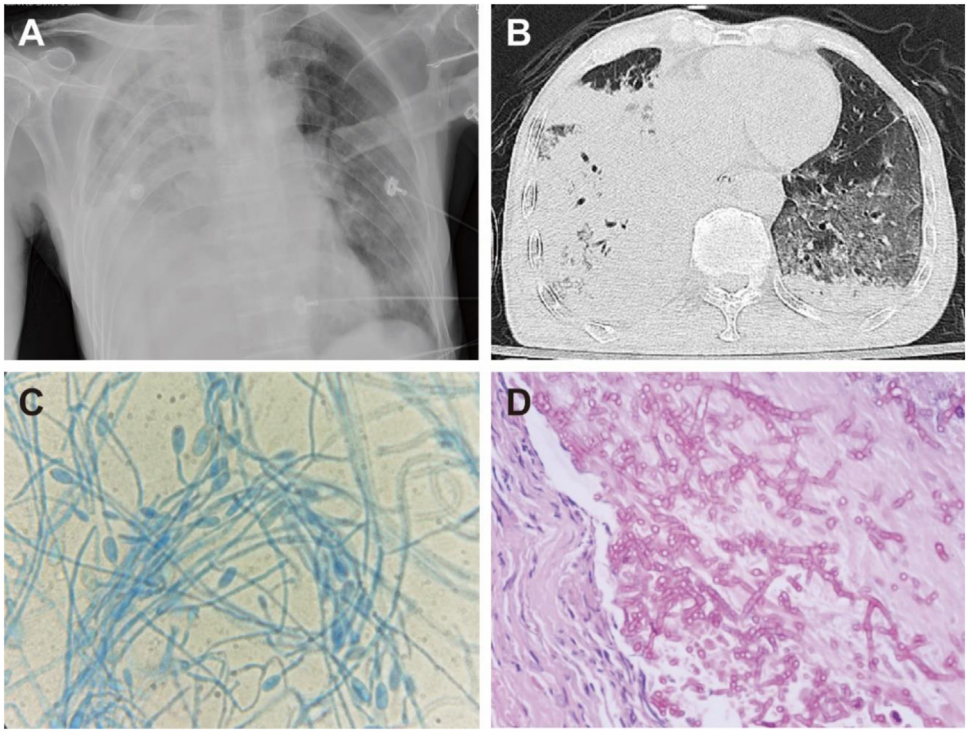

Figure 2. Imaging features of pulmonary scedosporiosis and microscopic features of *Scedosporium apiospermum*. (A) Bedside chest X-ray revealing disseminated high density shadows in the bilateral lungs, particularly in the right lobe. (B) Computed tomography scan showing extensive consolidation in the right lobe. (C) Fungi that grew from bronchoalveolar lavage fluid were stained with lactophenol cotton blue: hyaline filamentous hyphae with oval conidia can be seen. (D) Histopathological biopsy revealed invasive branched septate fungal hyphae in the bronchial tissue; hematoxylin–eosin stain, magnification 200×.

of infection with opportunistic or non-cultivable pathogens, NGS was adopted as an adjunctive diagnostic method (Parize et al., 2017). BALF, the sample for NGS, was obtained by bronchoscopy on the third day after admission. NGS was conducted at the Beijing Genomics Institute. Simultaneously, another portion of BALF and a sputum sample were also sent to the laboratory for traditional culture using Sabouraud agar medium.

It took 28 h for the Beijing Genomics Institute to complete the NGS procedure. The results showed only three reads from *S. apiospermum*. Initially, these three reads were considered more likely to indicate a contaminant. However, considering the patient's poor response to antibacterial drugs, it was decided to administer voriconazole anyway for antifungal therapy, which is the first-line treatment for scedosporiosis in immunocompromised patients (Tortorano et al., 2014). Interestingly, subsequent to NGS, the microbiology laboratory also reported the growth of gray villiform hyphae in both sputum and BALF culture. Microscopic examination revealed hyaline filamentous hyphae with conidia after staining with lactophenol cotton blue (Figure 2C). A piece of mucosa and submucous tissue was obtained for histopathological examination (hematoxylin–eosin stain), in which septate fungal hyphae were seen invading the bronchial tissue (Figure 2D). The colony morphology and microscopic features were fairly classical for *Scedosporium*.

Eventually, the patient was diagnosed with invasive pulmonary scedosporiosis (*S. apiospermum*) and acute hematopoietic failure. Although voriconazole and other supportive treatments were applied as soon as possible, the patient showed a poor response

and he died 9 days after admission due to septic shock and multiple organ dysfunction.

Discussion

Scedosporium species cause infections in both immunocompetent and immunocompromised hosts and produce a variety of clinical manifestations. Notably, *Scedosporium* is one of the major filamentous fungi that colonize the respiratory tract in patients with cystic fibrosis (Rougeron et al., 2018). A recent worldwide case review concluded that the mortality of patients with disseminated infections was 76% (Seidel et al., 2019). In the case presented here, although cystic fibrosis was likely to be excluded, the patient had severe inhibition of hematopoiesis and disseminated lung infections, which seemed to be indicators of a poor prognosis.

The clinical diagnosis of scedosporiosis requires conventional laboratory methods such as culture, direct microscopy, and histopathology (Tortorano et al., 2014). However, the culture-based approach has inevitable limitations, such as relying on the growth of fungal hyphae, which may take several days until the final results. Besides, under microscopy, *Scedosporium* closely resembles *Aspergillus* with dichotomous branches and hyaline septate hyphae (Tortorano et al., 2014), which makes it more difficult to obtain an accurate diagnosis of scedosporiosis. The identification of *S. apiospermum* is critical because *S. apiospermum* has intrinsic resistance to many antifungal agents (Tortorano et al., 2014).

It appears that this is the first case of pulmonary scedosporiosis detected by NGS. NGS is an emerging culture-independent microbiological diagnostic approach (Lefterova et al., 2015), and is relatively effective in cataloging and recognizing pathogens, especially for those uncommon or non-cultivable species (Besser et al., 2018). Therefore, the application of NGS in clinical diagnostics is considered to be promising, not only for its culture-independence, but also the short turnaround time (Fan et al., 2018) and high sensitivity (Jun et al., 2019). In this case, although only three reads were detected, the NGS results coincided with that of traditional culture and also provided a suggestion for specific species classification. Therefore, a combination of NGS and traditional culture may be a better option for fungal diagnosis compared to traditional culture alone. Nevertheless, the lack of classical molecular evidence for precise species identification remains one of the limitations of this case, and further clinical trials are expected to verify the sensitivity and specificity of NGS in the diagnosis of fungal infections.

Ethical approval

The authors declare that ethical approval was not required for this study.

Conflict of interest

We have no conflicts of interest to declare.

Acknowledgements

We thank Zhijiang Xu and Baizhou Li of the Second Affiliated Hospital of Zhejiang University School of Medicine for their help with the selection and description of the images.

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