Hospital-acquired pneumonia caused by *Kodamaea ohmeri* during extracorporeal membrane oxygenation treatment: A case report and literature review

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Abstract. *Kodamaea ohmeri* (*K. ohmeri*) is an ascosporogenic species of yeast that belongs to the genus *Ascosporogenous* and the family of Saccharomycetaceae. It has recently been found to cause various types of infections, particularly in critically ill immunocompromised patients. The present study describes a case of hospital-acquired pneumonia caused by *K. ohmeri* during veno-arterial extracorporeal membrane oxygenation. The fungal culture turned negative after the administration of caspofungin and amphotericin B. Extracorporeal membrane oxygenation (ECMO) is an adjunctive medical technique that provides temporary cardiopulmonary support for patients. Previous observations have suggested that the immune function of patients will typically decline during the use of ECMO, rendering infection to be one of the main complications of ECMO. *K. ohmeri* is a rare pathogenic fungus, particularly in immunocompromised individuals with vascular catheters, while amphotericin B is the most common antifungal therapy administered to treat *K. ohmeri* infections. It is important to raise awareness of rare fungal infections and actively treat them.

Introduction

Kodamaea ohmeri (*K. ohmeri*), previously known as *Pichia ohmeri* (1), is an ascosporogenic yeast that belongs to the genus *Ascosporogenous* and family of *Saccharomycetaceae*. It is widely used in the fermentation of various food products, such as in the production process of bread (2) and it does

not colonize the human body. It was initially identified as a contaminant of a pleural effusion specimen (3). This fungus has been increasingly reported to be found in critically ill immunocompromised patients, especially in patients who require invasive monitoring and intervention (4). *K. ohmeri* causes both invasive and non-invasive infections, although they are mainly invasive. Amphotericin B, fluconazole, caspofungin, voriconazole, micafungin and itraconazole are currently the most common antifungal therapies administered to treat *K. ohmeri* infection. In the present case, a patient with hospital-acquired pneumonia caused by *K. ohmeri* during veno-arterial (VA) extracorporeal membrane oxygenation (ECMO) was reported. The fungal culture of this patient's bronchoalveolar lavage fluid turned negative after the administration of caspofungin and amphotericin B. A review of the related literature was also performed. The aim of the present case report is to remind clinicians to pay attention to the infection of patients with ECMO, especially infection by rare pathogens.

Case report

A 54-year-old male patient presented to a tertiary care hospital in December 2021 with recurrent chest pain for >1 month and decreased blood pressure for 1 day. An electrocardiogram (ECG) suggested acute inferior myocardial infarction. The patient was treated orally with aspirin (300 mg) + ticagrelor (180 mg) and with heparin (5,000 units) by intravenous injection. The patient also underwent coronary angiography (CAG). Complete stenosis was found in the anterior descending and circumflex branches, whilst 99% of the stenosis was in the right coronary artery. Percutaneous coronary intervention (PCI) was performed for the circumflex branch lesions. Refractory cardiogenic shock occurred after the emergency PCI operation. The patient received VA-ECMO therapy and was transferred to The First Affiliated Hospital of Nanjing Medical University and Jiangsu Province Hospital (Nanjing, China) after consultation with the ECMO team.

After this admission in December 2021, the patient had a continuous high fever reaching a peak of 39.2˚C, where the white blood cell count was 24.74x10⁹/l (normal range, 3.5-9.5x10⁹/l) and procalcitonin level was 3.73 ng/ml (upper

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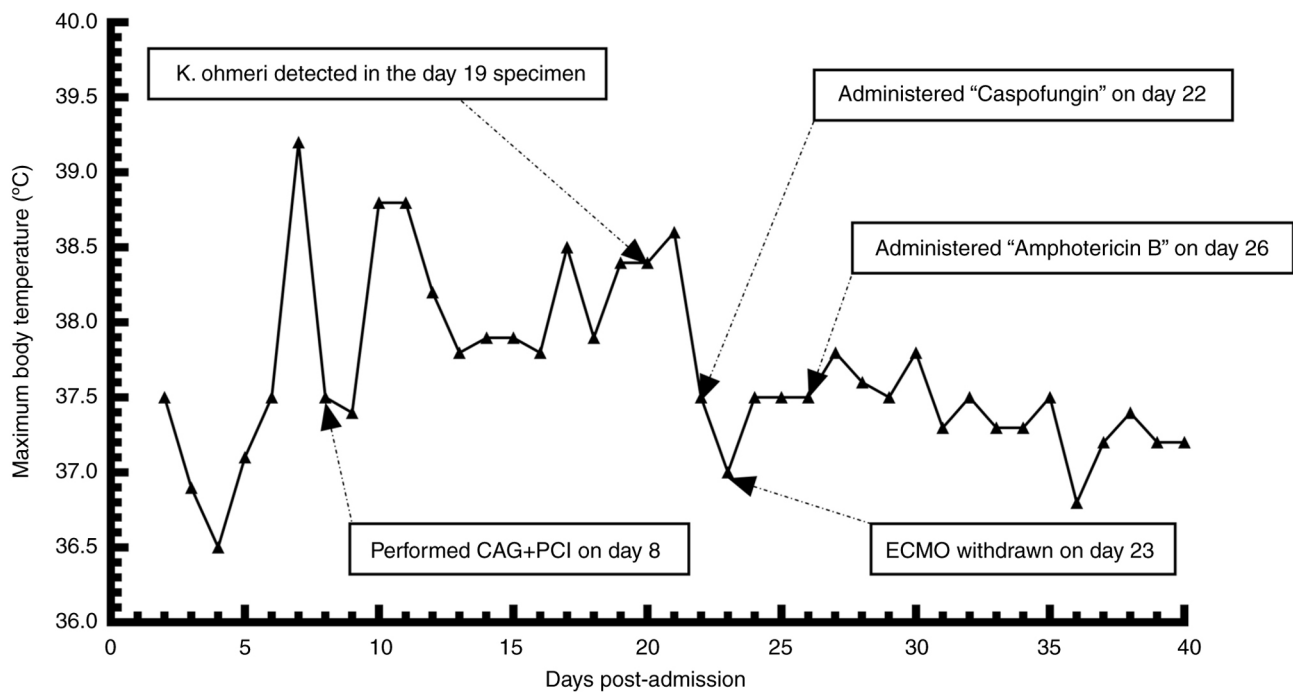E-mail: liwei5477@jsph.org.cn

Figure 1. Maximum daily body temperature of the patient over the course of treatment.

limit, 0.05 ng/ml). Specimens from the blood, lower respiratory tract and catheters were collected for aetiological examination and no positive results were obtained. The empirical antimicrobial protocol used by the hospital was initiated, with imipenem and cilastatin sodium [2 g every 12 h via intravenous drip (IVD)]. Simultaneously, tracheotomy was performed to facilitate airway management and control of pulmonary infection. On day 7, the neutrophil and lymphocyte count were decreased by $12.97x10^9/l$ and $1.05x10^9/l$, while the body temperature was 39.2˚C, which was the highest body temperature after admission. Subsequently, the body temperature was maintained at ~38.0˚C. The daily body temperature of the patient over the course of treatment is presented in Fig. 1. On day 8 of admission, the circulation of the patient was basically stable with the support of ECMO, as the mean arterial pressure (MAP) was between 70 and 80 mmHg. Although the body temperature was 38.8˚C, aetiological tests did not yield any positive results. Considering the severity of the primary disease, cardiologists suggested that the primary disease should be proactively tackled with ECMO support, provided that the patient's circulation is stable. In addition, considering that the time of ECMO bypass is a risk factor for infection-associated complications, active treatment of the primary disease may promote the withdrawal of ECMO and improve the overall prognosis of patients (5,6). Therefore, CAG + PCI was performed as soon as possible on day 8. On day 10, the lymphocyte count decreased to the lowest level observed, which was $0.35x10^9/l$ (normal range, $1.1-3.2x10^9/l$). On day 11, in order to better manage the airway and control pulmonary infection, a tracheotomy was performed on the patient. On day 12, the patient's body temperature dropped significantly, with a peak at 37.9˚C. The white blood cell count dropped to $14.72x10^9/l$ and procalcitonin levels dropped to 0.421 ng/ml. Concurrent multiple plasma 1-3-β-D glucan

measurements and galactomannan tests were performed, all of which were normal. However, despite multiple collections of specimens from the lower respiratory tract, no positive culture results were reported.

On day 17 of admission, the fever worsened again, with the highest body temperature reaching 38.5˚C. On day 22, the report from the bacteriological laboratory indicated that 'mycelium 2+' was visible under the microscope in the specimen collected on day 19 from the lower respiratory tract. Meanwhile, the patient's highest body temperature within 1 day was 38.6˚C on day 22, the white blood cell count was $19.83x10^9/l$, the percentage of neutrophils was 77.80% and the G test of blood and specimens from the lower respiratory tract was negative. Considering that the patient was at high risk of fungal infection, caspofungin (50 mg every day via IVD) was empirically administered for antifungal infection. Lower respiratory tract specimens were collected multiple times for aetiological examination. Furthermore, the *in vitro* drug susceptibility test results suggested that it was sensitive to 5-flucytosine, amphotericin B and caspofungin, moderately sensitive to itraconazole, and resistant to fluconazole and voriconazole (Fig. 2). Finally, the organism identification tests reported *K. ohmeri* infection. Antimicrobial susceptibility tests showed that the organism was susceptible to 5-flucytosine and amphotericin B but resistant to fluconazole and voriconazole. Additional specimens from the lower respiratory tract were tested several times later and the results were all suggestive of *K. ohmeri* (++, >10^3 CFU/ml).

On day 23 of admission, when the flow of ECMO was reduced, the MAP was still maintained at ~80 mmHg. Given these haemodynamic improvements and the potential risk of catheter-related bloodstream infection, ECMO weaning was considered and was subsequently withdrawn successfully. Antimicrobial susceptibility testing of the specimens collected
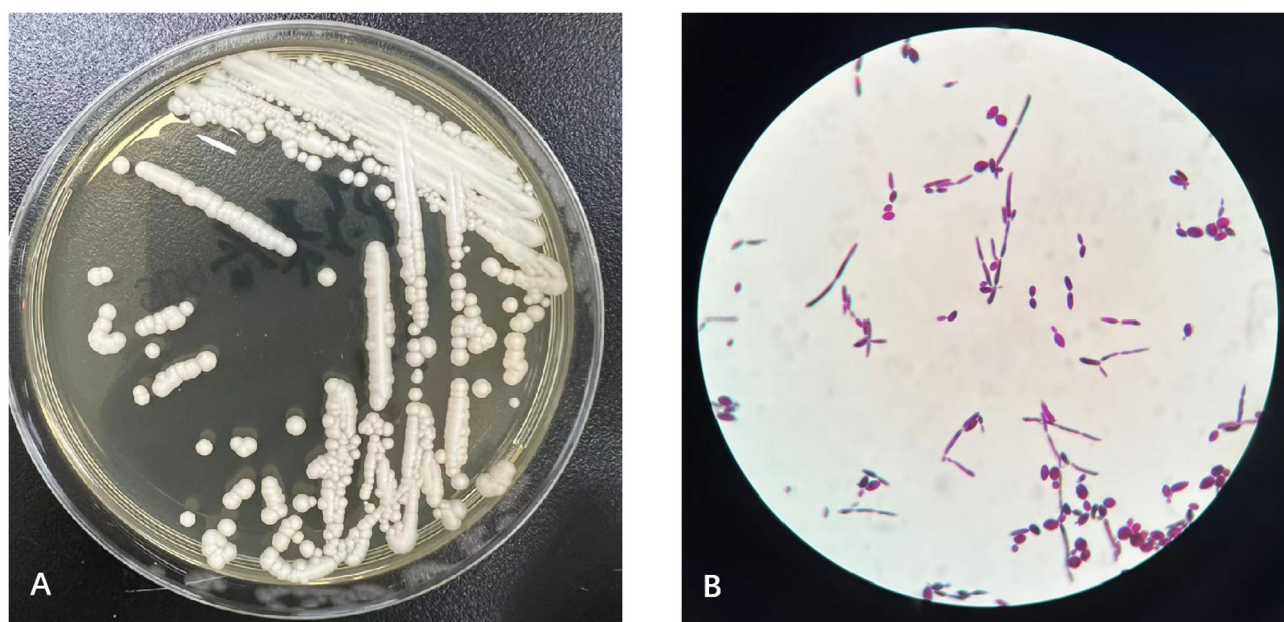
Figure 2. Culture of *K. ohmeri*. (A) Cultivation of *K. ohmeri* for 72 h on a petri dish. (B) Gram staining under the microscope (magnification, x1,000).

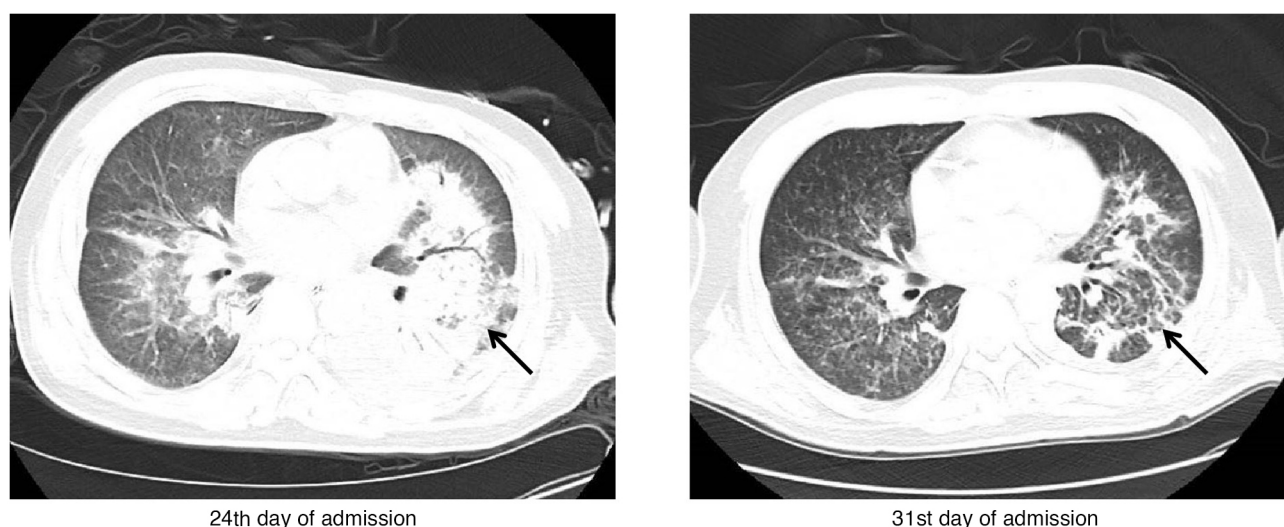| 24th day of admission | 31st day of admission |

Figure 3. Chest CT imaging on days 24 and 31 after admission, with arrows showing the absorption of consolidation shadows and patch shadows.

on day 24 indicated susceptibility to amphotericin B but resistance to caspofungin. Based on this result, amphotericin B (5 mg every day via IVD) was added for antifungal therapy, the dose of which was increased until it reached 40 mg and then maintained. On day 31, the patient underwent chest CT and the lung infection had significantly improved compared with that on day 24, with the absorption of consolidation shadows and patch shadows (Fig. 3). On day 34 of admission, the patient's body temperature dropped significantly, with the highest temperature of 37.3˚C. Therefore, the caspofungin was terminated in combination with the antimicrobial susceptibility testing. On day 40, aetiological examination of the specimen from the lower respiratory tract was negative for *K. ohmeri*. During this period, the patient's blood, urine and stool were tested simultaneously and were negative for *K. ohmeri*. Due to economic reasons, the patient's family gave up treatment and

chose for the patient to be discharged at the end of January, 2022. The total hospital stay was 42 days. The patient died shortly after discharge from the hospital.

Discussion

VA-ECMO can provide life-saving continuous extracorporeal respiration and circulation support for patients suffering from cardiopulmonary failure (5). However, patients with ECMO frequently become immunocompromised due to the critical condition of their primary disease and the unique circuitry characteristics of ECMO.

When Frerou *et al* (7) studied the early immune changes within the first few days of VA-ECMO initiation, they found that VA-ECMO was associated with a significant increase in circulating immature neutrophils and in C5a receptor

expression. In addition, VA-ECMO initiation was found to be followed by lymphocytic dysfunction along with myeloid-derived suppressor cell expansion (5). In another study, Cho *et al* (8) established an ECMO model in rats and found that the overall immune cell proportion changed after ECMO initiation in both the VA and the veno-veno (VV) modes. Specifically, the immunological balance was altered more significantly in the VA mode compared with that in the VV mode, with the proportion of B lymphocytes, helper T lymphocytes and cytotoxic T lymphocytes significantly decreased in the VA modes (8). In the present case, the neutrophil and lymphocyte count were decreased by 12.97×10^9/l and 1.05×10^9/l 7 days after ECMO, which was consistent with the results of the aforementioned previous studies. This suggests that the present case had reduced immune function. Although this phenomenon was not obvious in the VV mode, the overall immune proportion changed in both modes, further confirming that immune function decreased after ECMO initiation.

The unique circuitry characteristics of ECMO can also change the immune function of patients, which is mainly caused by the oxygenator. Previous studies have indicated that oxygenator materials are associated with the dampened activation of neutrophils, characterized by the lower expression of the CD11b adhesion molecule, and neutrophil and superoxide anion release. Variances in how a membrane is configured within the oxygenator may also influence blood flow rates and ultimately cellular and humoral responses. Other ECMO-related factors include ECMO flow rates and the associated non-physiological shear stress exerted. However, current knowledge in this research area remains limited (9).

However, it is becoming increasingly likely that ECMO initiation is associated with early immune changes, which may be responsible for innate and adaptive immune alterations. This in turn may confer an increased risk of infection. Infections are among the most common complications associated with ECMO (10), which may significantly impact the outcomes (11). The infectious risk has been shown to increase with the increase in duration of the ECMO run (10), which represents the most important risk factor for developing infections. Other ECMO-specific factors that can predispose the patient to infections include the severity of the underlying illness, the high risk of bacterial translocation from the gut and ECMO-related immune system impairment (12). In addition, cannula-related infection is frequent in patients who underwent ECMO and is associated with a longer stay in the hospital (13).

In those patients who received ECMO, Gram-negative bacteremia was the most common cause of infection, followed by Gram-positive bacteremia and Candida. Furthermore, *Acinetobacter baumannii* and *Enterococcus faecium* were the most frequently isolated pathogens in VA and VV ECMO, respectively (14).

Kodamaea ohmeri is an ascosporogenic yeast belonging to the genus *Ascosporogenous* and the family of *Saccharomycetaceae*. It is a potent plant pathogen and is used in the food industry for the fermentation of various food products (2). When the first specimen of the fungus was isolated from a pleural effusion, it was initially regarded as a contaminant (3). Since then, reports of cases of infection related to

K. ohmeri have been rare. However, over the past decade, *K. ohmeri* has been increasingly reported to be associated with infections in immunocompromised patients, including those with severe pancreatitis (15), rheumatoid diseases (16), hepatolenticular degeneration (17), severe burns (18), HIV infection (19) and multiple organ dysfunction syndrome (3). A literature search in English databases, such as PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Web of Science (https://www.webofscience.com) revealed no previous report of *K. ohmeri* infection in patients treated with ECMO when using the search terms '*Kodamaea ohmeri*' and 'extracorporeal membrane oxygenation'. Therefore, to the best of our knowledge, the present case was the first report of the infection by this organism in patients who underwent ECMO.

K. ohmeri causes both invasive and non-invasive infections, but mainly invasive infections. Among the invasive infections, fungemia dominated, with fever and chills being the most common clinical features (20). The patient of the present case had intermittent fever after admission and the highest body temperature of 39.2˚C, which was in accordance with the aforementioned statement.

In the majority of cases of *K. ohmeri* infections, the patients were immunosuppressed due to haematological or solid malignancies, post-chemotherapy neutropenia, immunosuppressive treatments, diabetes or chronic renal failure (18,19,21). In the present case, the patient was also immunocompromised due to severe underlying diseases, with a minimum lymphocyte count of 0.35×10^9/l on day 10. However, the lymphocyte subsets were not tested further after the reduction of lymphocytes was identified and no peripheral blood smears were performed after the detection of elevated leukocytes to assist in diagnosis, which is a limitation of the present findings.

In addition to underlying diseases, certain patients with *K. ohmeri* infections had also undergone various invasive procedures during hospitalization, specifically implants (central venous catheter, peripheral catheter, pacemaker, bioprosthetic mitral valve, urethral catheter and implanted organs), while some patients have skin impairment due to cellulitis or burns (16,18). These results all suggest that disruption of the mucocutaneous barrier is an important risk factor for *K. ohmeri* infection. For patients who underwent ECMO, the long-term use of arterial, venous catheters and various invasive circuits (such as continuous renal replacement therapy), can lead to the destruction of the skin barrier, increasing the risk of infection by *K. ohmeri*.

Furthermore, a prolonged hospital stay, endotracheal intubation and mechanical ventilation were reported as significant risk factors for developing *K. ohmeri* infections (3); the patient in the present case had been hospitalized for 19 days when *K. ohmeri* was found in the culture of the lower respiratory tract specimen. In addition, the ECMO circulation circuits, endotracheal intubation and mechanical ventilation were maintained for 19 days, all of which provided conditions facilitating the invasion of *K. ohmeri*.

The diagnosis of invasive pulmonary aspergillosis includes three levels of probability: 'Proven', 'probable' and 'possible'. 'Possible' means having the presence of risk factors and clinical manifestations (typically found by medical imaging). In the present case, caspofungin was empirically used to treat antifungal infections at the level of 'possible', which also laid

the foundation for effective infection control at the later stages. In terms of 'probable', in addition to meeting the requirements of 'possible', an aetiological examination is also needed. The lower respiratory tract specimens from this patient were submitted for culture numerous times, where the results were all suggestive of *K. ohmeri* infection, which met the criteria of the 'probable' level. To reach the level of 'proven', it is also necessary to perform lung histopathology to verify that the lung tissue, pleural effusion or blood samples have fungal growth (22). Considering that the basic disease of the patient was serious and the clinical indexes such as body temperature were improved after the use of antifungal drugs, further operations such as lung biopsy and pleural effusion puncture and drainage would not be considered. Thus, the patient of the present study did not meet the criteria for 'proven', which was a limitation of this report.

Amphotericin B is currently the most common antifungal therapy administered to fight against *K. ohmeri* infection, followed by fluconazole, caspofungin, voriconazole, micafungin and itraconazole (20). According to the broth microdilution method, fluconazole was found to be the highest minimum inhibitory concentration required to inhibit the growth of 90% of *K. ohmeri* (8 μg/ml), followed by micafungin, caspofungin and amphotericin B (1 μg/ml) (23,24). Clinically, a combination of two of the aforementioned drugs is typically used to prevent the occurrence of bacterial resistance (20).

On day 22 after admission, combined with the bacteriological results of the patient's lower respiratory tract specimens and considering that the patient was in a high-risk group for fungal infections, caspofungin (50 mg every day via IVD) was empirically added to the antifungal treatment. Subsequently, a fungal species identification prompt for *K. ohmeri* was received. Furthermore, the *in vitro* drug susceptibility test results suggested that it was sensitive to 5-flucytosine, amphotericin B and caspofungin. Following that, the lower respiratory tract specimens were tested several times, all of which suggested *K. ohmeri* (++, >10^3 CFU/ml). Antimicrobial susceptibility testing of the specimens collected on day 24 showed that the organism was susceptible to amphotericin B but resistant to caspofungin. Therefore, according to results from this antimicrobial susceptibility testing, amphotericin B (5 mg via IVD) was added to the antifungal treatment regimen. The dose of amphotericin B was increased by 5 mg daily until it reached 40 mg, following which this was maintained.

On day 31, the patient underwent chest CT and the lung infection had significantly improved compared to that on day 24. On day 34 after admission, the patient's body temperature had decreased to 37.3˚C. Inflammatory indicators, such as white blood cells and C-reactive protein, were significantly lower compared with day 22, resulting in caspofungin and antimicrobial susceptibility testing being discontinued. On day 40, aetiological examination of the specimen from the lower respiratory tract revealed negativity for *K. ohmeri* and the body temperature was 37.2˚C. However, the maintenance treatment of amphotericin B (40 mg every day) was continued.

Since various implants pose a significant risk factor for *K. ohmeri* infection, removing the catheters is also considered to be a first-line treatment strategy for *K. ohmeri* infection (20). In the present case, after evaluating the recovery of cardiac function, the ECMO-related invasive circuits were removed to optimise antifungal treatment. However, the patient could not be separated from auxiliary ventilation, rendering the necessity of tracheotomy and mechanical ventilation for maintaining the patient's vital signs. Therefore, removing the remaining associated invasive catheters was not considered.

In the ECMO centre of The First Affiliated Hospital of Nanjing Medical University and Jiangsu Province Hospital, another case of fungal infection in an patient who underwent ECMO has also been reported. A young woman with fulminant myocarditis and cardiogenic shock developed endophthalmitis and brain abscess after the improvement of cardiac function, following which the ECMO machine was withdrawn. After sterile sampling and bacterial culture, the infection was confirmed to be *Scedosporium apiospermum*. Despite active treatment with various antifungal drugs, including voriconazole, the patient succumbed to haematogenous disseminated brain abscess, diffuse brain swelling and cerebral haemorrhage (25). This reminded us to pay attention to the infection of those rare pathogens.

In conclusion, ECMO is an adjunctive medical technique that provides temporary cardiopulmonary support for patients. Patient immune function has been documented to decline during the use of ECMO, leading to infection becoming one of the main complications of ECMO. Patients undergoing ECMO, in addition to other critically ill patients requiring invasive monitoring and intervention, are exposed to the same risk factors for infection, particularly those using vascular catheters. Therefore, all patients undergoing ECMO should receive antimicrobial prophylaxis, including antifungal infection and infection surveillance, in addition to undergoing routine testing for pathogens. During the course of treatment, the clinicians should first be attentive to the possibility of pathogen infection and closely monitor the inflammatory indicators and pathogen culture results. Furthermore, timely removal of various invasive lines is an important treatment measure to reduce the risk of hospital-acquired infection. For patients undergoing ECMO, it is necessary to collect body fluid samples several times for pathogenic examination. It is essential to identify the offending pathogen as soon as possible. It is also necessary to combine the most common pathogens of the centre's microbiology and the results of the aetiological examination to objectively analyse and determine whether it is colonization of pathogen, pollution or pathogenic bacteria. Finally, the decisions and changes to therapy plans should be combined with the drug susceptibility results. It is necessary not only to pay attention to the selection of drugs, the doses and timing, but also to consider the combined use of multiple drugs to reduce the occurrence of drug resistance. In this manner, it may be possible to enhance the therapeutic effect and improve the outcome of patients.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

TD, WL and XC searched the literature and conceived the study. ZZ, YZo and DA were involved in obtaining ethical approval, collecting and analyzing clinical data. WL and XC confirm the authenticity of all the raw data. TD wrote the first draft of the manuscript. YZh and WL reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Ethical approval for this study was obtained from the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (approval no. 2020-SR-226).

Patient consent for publication

Written informed consent for the publication of the present case report and any accompanying images was obtained from the patient's spouse.

Competing interests

All authors declare that they have no competing interests.

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