Case Report

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Pancytopenia Followed by Mucormycosis-Related Cavernous Sinus–Orbital Apex Syndrome After Chimeric Antigen Receptor T-Cell Therapy: A Case Report

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Background: Chimeric antigen receptor T-cell (CAR-T) therapy has revolutionised the treatment of relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL). Still, it can lead to severe immunosuppression and late-onset complications. We report a rare case of mucormycosis-related cavernous sinus orbital apex syndrome (CSOAS) in a patient with r/r DLBCL who developed prolonged pancytopenia after receiving anti-CD19 CAR-T therapy.

Case Presentation: A patient with r/r DLBCL received anti-CD19 CAR-T therapy and subsequently developed prolonged pancytopenia. The patient was initially treated with a combination of amphotericin B and isavuconazole, but amphotericin B was discontinued due to nephrotoxicity before reaching the target dose (30 mg/day). Surgical removal of the lesions and drainage of the sinuses was performed, and the patient continued on isavuconazole. Supportive treatments, including granulocyte colony-stimulating factor and eltrombopag, were administered.

Results: After surgery, the patient's fever and facial oedema resolved, and their vision improved. Blood cell counts normalised (white blood cell 4–11 $\times$ 10^9/L) 1 week later.

Conclusion: This case represents one of the first reports of mucormycosis-associated CSOAS following CAR-T therapy successfully managed despite challenges with antifungal treatment. It underscores the importance of dynamic infection surveillance and multidisciplinary intervention in managing rare and life-threatening post-CAR-T complications.

Keywords: chimeric antigen receptor T-cell therapy; mucormycosis; cavernous sinus–orbital apex syndrome; relapsed/refractory diffuse large B-cell lymphoma

Introduction

Chimeric antigen receptor T-cell (CAR-T) therapy has emerged as a promising treatment for haematologic malignancies, particularly CD19-targeted CAR-T therapy for relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL). The overall response rates reported ranged from 52% to 74% and the 1-year OS was 48%–59% [1]. The specific adverse events of CAR-T therapies are cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which may happen within days after infusion and can be treated with tocilizumab (a humanised interleukin-6 receptor monoclonal antibody) and/or corticosteroids [2]. There are also long-term adverse events, including B-cell aplasia, prolonged CD4 T-cell lymphocytopenia, prolonged neutropenia and thrombocytopenia, which might increase the risks of infections and bleeding [1].

Cytopenia and infections following CAR-T therapy are known complications. A cohort study of infectious complications after CD19-targeted immunotherapy estimates the infection density between day 29 and day 90 to be 0.67 infections for every 100 days at risk. Bacterial infections are the most common, whereas viral and fungal infections have also been found in some patients [2]. Fungal infections include invasive infections of *Candida* spp., *Aspergillus* spp. and *Cryptococcus* spp. [2,3]. Mucormycosis is primarily an opportunistic invasive fungal infection affecting immunocompromised individuals [4]. Common risk factors include poorly controlled diabetes mellitus, solid organ transplantation and haematological malignancies [5]. However, mucormycosis-related cavernous sinus–orbital apex syndrome (CSOAS) has not been previously reported in this setting. Here, we present a unique case of a patient with r/r DLBCL who developed prolonged pancytopenia following anti-CD19 CAR-T therapy and subsequently suffered from mucormycosis-related CSOAS. No-

tably, the patient was successfully managed with surgical debridement and isavuconazole after developing intolerance to amphotericin B.

Materials and Methods

Clinical Data Collection

Patient demographics, clinical history, treatment regimens and outcomes were recorded. Relevant laboratory results, including haematological parameters, were also obtained from patient medical records. Key dates, such as symptom onset and treatment initiation, were documented for each patient.

Blood Examination

Complete blood counts were analysed using an automated haematology analyser (Sysmex XN-3100, Sysmex Corporation, Kobe, Hyogo, Japan). Biochemical parameters were measured using a clinical chemistry analyser (Roche Cobas 8000), including markers of liver and renal function, electrolytes and C-reactive protein.

Fungal Cultures

Blood cultures were processed using an automated system (BD BACTEC™ FX, Becton, Dickinson and Company, Sparks, MD, USA). Fungal cultures were performed on Sabouraud dextrose agar (SDA M253-01, ELITE-MEDIA, Shanghai, China) and incubated at 25 °C to support the growth of a wide range of fungal species. Preliminary identification was based on colony morphology.

Lactophenol Cotton Blue Staining

Lactophenol cotton blue (LPCB) staining was used to visualise fungal morphology. Mycelia from 5–7-day-old cultures grown on SDA were gently scraped using a sterile loop, mounted on glass slides and stained with LPCB. The staining reagent consisted of phenol (Thermo Fisher Scientific, Loughborough, Leicestershire, UK, Cat. No. BP241-500, 20 mL), lactic acid (Merck KGaA, Darmstadt, Hesse, Germany, Cat. No. 1.00935.1000, 20 mL), glycerol (Sigma-Aldrich, Merck Pharmaceutical Manufacturing (Jiangsu) Co., Ltd., Wuxi, China, Cat. No. G5516, 40 mL), distilled water (20 mL) and cotton blue (Sigma-Aldrich, Cat. No. B8898, 0.05 g; 1% aniline blue in ethanol diluted 1:20 with distilled water). The solution was filtered through a 0.22-µm membrane (Millipore, Merck Pharmaceutical Manufacturing (Jiangsu) Co., Ltd., Wuxi, China, Cat. No. HAWP02500). Slides were gently heated over a steam bath for 3–5 minutes, cooled and examined under oil immersion at $\times$1000 magnification. Glycerol served to preserve cellular structures, whereas cotton blue stained chitin in fungal hyphae and conidia, enabling genus-level morphological identification.

Polymerase Chain Reaction

Molecular detection of fungal DNA was conducted using polymerase chain reaction (PCR) assays. Using a commercial kit (QIAamp DNA mini Kit, QIAGEN GmbH, Hilden, North Rhine-Westphalia, Germany), DNA was extracted with automated nucleic acid extraction platforms (QIAcube, MagNA Pure 96, QIAGEN GmbH, Cologne, North Rhine-Westphalia, Germany). Polymerase chain reaction amplification was conducted on a real-time thermal cycler (Applied Biosystems 7500 Fast Dx, Applied Biosystems, Waltham, MA, USA) with genus- or species-specific primers targeting conserved regions of *Mucorales* rRNA genes, such as the internal transcribed spacer region or the D1/D2 domain of the 28S rRNA gene. Positive PCR products were further analysed by gel electrophoresis or subjected to Sanger sequencing (ABI 3500 Genetic Analyser, Applied Biosystems, Life Technologies Corporation, Carlsbad, CA, USA) for species-level identification. The primers targeting conserved regions of *Mucorales* rRNA genes were as follows: forward primer (5′-AGGTCTGTGATGCCCTTAG-3′) and reverse primer (5′-CTCCTTGGTCCGTGTTTCA-3′).

Histopathological Examination

Histopathological evaluation of surgical tissue samples was conducted to assess fungal invasion. Specimens were fixed in 10% neutral buffered formalin, processed with an automated tissue processor (Leica TP1020, Leica Biosystems (Shanghai) Co., Ltd., Shanghai, China), embedded in paraffin and sectioned at 4–5 µm using a microtome (Leica RM2235, Leica Biosystems (Shanghai) Co., Ltd., Shanghai, China). Sections were stained with haematoxylin and eosin (H&E), periodic acid–Schiff (PAS) and Grocott's methenamine silver (GMS) stains using standard protocols. For H&E staining, sections were deparaffinised, hydrated and stained with Harris haematoxylin (Sigma-Aldrich, Cat. No. HHS32) for 5 minutes. Slides were differentiated in 1% acid alcohol, blued in tap water, counterstained with eosin (Merck KGaA, Darmstadt, Hesse, Germany, Cat. No. 1.15935) for 1 minute, dehydrated, cleared and mounted. For PAS staining, deparaffinised and hydrated sections were oxidised in 0.5% periodic acid (Sigma-Aldrich, Merck Pharmaceutical Manufacturing (Jiangsu) Co., Ltd., Wuxi, China, Cat. No. P7875) for 10 minutes, treated with Schiff's reagent (Merck KGaA, Darmstadt, Hesse, Germany, Cat. No. 1.09033) for 15 minutes in the dark, rinsed, counterstained with haematoxylin and mounted. For GMS staining, sections were oxidised with 5% chromic acid, rinsed and stained with GMS solution (Sigma-Aldrich, Cat. No. G1282) at 60 °C for 45 minutes until fungal elements appeared golden brown. Slides were then toned with 0.1% gold chloride, fixed in 2% sodium thiosulfate, counterstained with light green and mounted. Microscopic examination was performed using an Olympus BX53 light microscope (Olympus BX53, Olympus Corpo-

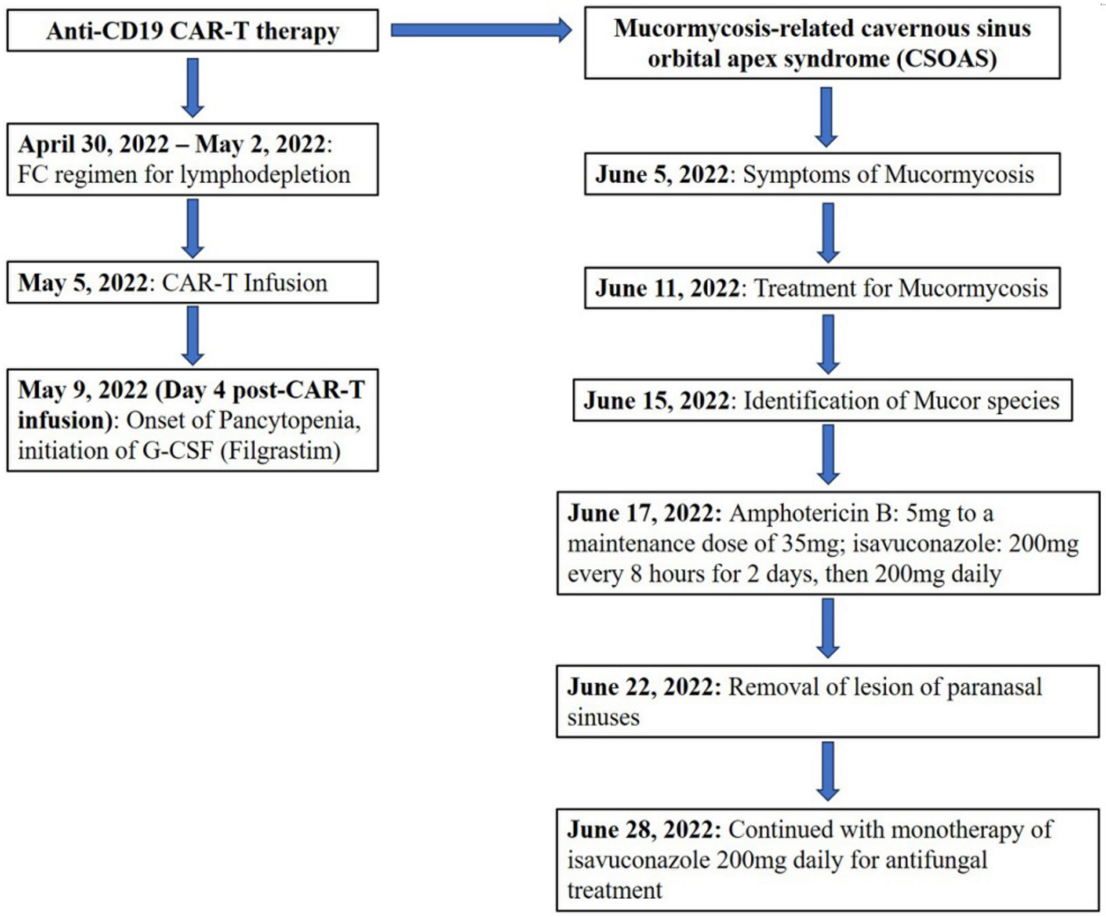

Fig. 1. Timeline of the treatment. CAR-T, Chimeric antigen receptor T-cell; G-CSF, granulocyte colony-stimulating factor. The was created with Microsoft PowerPoint for Microsoft 365 (Microsoft Corporation, Redmond, WA, USA).

ration, Takatsuki, Japan) equipped with a high-resolution digital imaging system to assess fungal morphology, tissue necrosis and angioinvasion.

Fluorescent Staining

Tissue sections were stained with Calcofluor White M2R (0.1%, Sigma-Aldrich, F3549) to detect fungal cell walls. After deparaffinisation and rehydration, slides were incubated with the dye for 5 minutes in the dark, rinsed with PBS, counterstained with 0.1% potassium permanganate for 1 minute and mounted using Vectashied (VECTASHIELD Mounting Medium H-1000, Vector Laboratories, San Francisco, CA, USA, H-1000). Fungal hyphae displaying bright blue–white fluorescence were visualised under a BX53 fluorescence microscope (Olympus, Japan).

Case Presentation

A 66-year-old man was admitted to Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, on 9 June 2022 with a 3-day history of fever, facial swelling, pain and difficulty opening his right eye. He had been diagnosed with DLBCL in September 2019 with tumour infiltration in the bone marrow and pericardium. The lymphoma was of the activated B-cell subtype and Ann Arbor stage IVB with an IPI score of 5 [6]. The disease progressed after three cycles of standard R-CHOP therapy. The patient received several lines of treatment later, but the disease relapsed rapidly. At the beginning of April 2022, he underwent leukapheresis to obtain peripheral blood mononuclear cells for CAR-T production. On 30 April, he received intravenous fludarabine (30 mg/m^2 body surface area per day) and cyclophosphamide (500 mg/m^2 body surface area per day) on day –5, –4, and –3 before the CAR-T infusion. On 5 May, the patient received a single intravenous infusion of axicabtagene ciloleucel containing 1.5×10^8/L autologous anti-CD19 CAR-T cells [7]. According to the American Society for Transplantation and Cellular Therapy criteria [8], he developed grade 2 CRS on day 4 post-infusion, which was alleviated following treatment with tocilizumab (560 mg) and corticosteroids (15 mg). The patient had transient neutropenia on day 6. The neutrophil (NEUT) cell count returned to normal after treatment with granulocyte colony-stimulating factor (G-CSF) (300 µg) on 3 consecutive days.

The patient declined further inpatient observation and was discharged on day 13, continuing follow-up as an outpatient. He had blood cell count tests every 2 or 3 days as an outpatient, and a substantial decrease in his blood cell counts was found on day 18, with white blood cell (WBC) 2.6 $\times$ 10^9/L (Ref: 3.5–9.5 $\times$ 10^9/L), NEUT 0.3 $\times$ 10^9/L (Ref: 2.0–7.5 $\times$ 10^9/L), haemoglobin (HGB) 86 g/L (Ref: 110–150 g/L) and platelet (PLT) 19 $\times$ 10^9/L (Ref: 100–350 $\times$ 10^9/L). The patient showed no signs of infection. Granulocyte colony-stimulating factor (300 µg, qd) was administered to the patient on 9 May 2022, and he also received blood transfusions intermittently for support. The patient refused to take posaconazole as prophylactic treatment. On 5 June 2022, the patient developed fever, facial swelling and numbness, with right-sided involvement more severe than the left. He was treated with ertapenem (1 g) for 3 days in the emergency room, but his symptoms worsened. Blood cultures were negative for bacterial infections (Fig. 1).

The patient was admitted to Peking Union Medical College Hospital on 9 June 2022 with persistently low blood cell counts, including PLT ranging from 4 to 26 $\times$ 10^9/L, WBC from 1.1 to 1.9 $\times$ 10^9/L, NEUT from 0.11 to 0.23 $\times$ 10^9/L and HGB between 59 and 69 g/L. Bone marrow aspiration revealed hypocellular marrow. Eltrombopag (50 mg qd) and G-CSF (300 µg, qd) were administered on 10 June 2022. Despite these treatments, fever and oedema persisted, and the patient developed headaches and intermittent brownish nasal discharge. A computed tomography (CT) scan of the head showed rhinosinusitis (Fig. 2A). The patient received imipenem (1 g), vancomycin (1 g), voriconazole (0.4 g) and acyclovir (0.5 g) as empiric treatment since 9 June but showed no improvement. On 11 June, the patient reported a sudden loss of vision in the right eye. After a head magnetic resonance imaging scan (Fig. 2B) and optical coherence tomography, the ophthalmologist diagnosed him with CSOAS. On 15 June, the culture of the nasal discharge was positive for *Aspergillus flavus*, *Aspergillus fumigatus* and *Mucorales*. A multidisciplinary team was set up. The patient was diagnosed with mucormycosis-related CSOAS according to previous relevant literature [9]. The empiric treatment was stopped. The trend of blood count recovery during the treatment process is shown in Fig. 3.

Intravenous amphotericin B was initiated on 17 June 2022, with a stepwise dose escalation from 5 mg to 10 mg, 15 mg and finally to the target dose of 35 mg/day. On the same day, isavuconazole was administered at 200 mg every 8 hours for 2 consecutive days, then at 200 mg once daily for 2 months. Endoscopic sinus surgery was performed on 22 June 2022 to debride infected tissue and enhance sinus drainage. Bilateral nasal procedures included resection of the uncinate process, ethmoid sinuses and superior turbinates, which showed polypoid changes. The maxillary and sphenoid sinus ostia were widened; both sinuses contained haemorrhagic exudate and viscous secretions. Mucosal surfaces exhibited cobblestone-like oedema, whereas the lamina papyracea remained intact. The CARE Checklist is provided in the **Supplementary Material**.

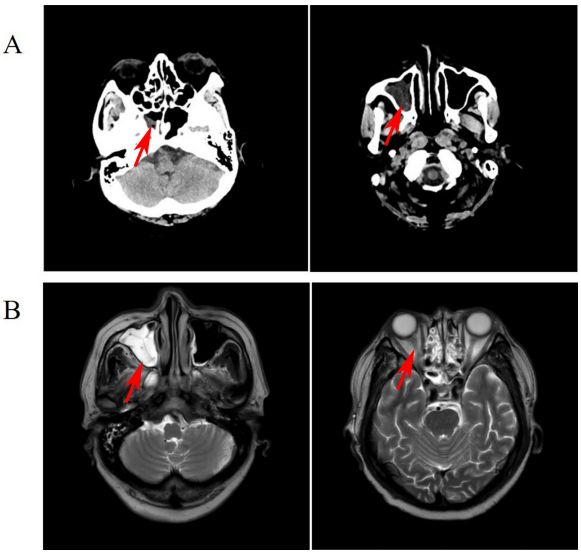

Fig. 2. Imaging findings in the patient. (A) Cranial computed tomography findings show mucosal thickening in the bilateral maxillary and sphenoid sinuses with diffuse mucosal thickening in the bilateral ethmoid sinuses. Fluid density is observed in the right maxillary and sphenoid sinuses. The left arrow indicates fluid accumulation in the right sphenoid sinus, and the right arrow indicates fluid accumulation in the right maxillary sinus. (B) Cranial magnetic resonance imaging shows mucosal thickening in the bilateral frontal, ethmoid, sphenoid and maxillary sinuses, with more prominent thickening in the right maxillary sinus. The left arrow points to mucosal thickening in the right maxillary sinus, and the right arrow points to oedema in the right optic nerve.

The patient's body temperature returned to normal immediately after the surgery. *Mucorales* was found in the specimen from the lesion (Fig. 4), which confirmed the diagnosis of mucormycosis. Antifungal treatment continued. The patient developed a severe headache and kidney injury during amphotericin B treatment at 35 mg/day, with serum creatinine increasing to 160 µmol/L (baseline 67 µmol/L). As a result, amphotericin B was discontinued on 28 June 2022. The patient was subsequently treated with isavuconazole monotherapy at 200 mg daily. His body temperature remained normal. The facial swelling and pain also improved. The visual acuity of his right eye improved from no light perception to counting fingers. Blood cell counts also began to increase from 23 June (day 49 after CAR-T infusion). He was still on eltrombopag (75 mg) and occasionally received G-CSF (300 µg), with WBC 3–6 $\times$ 10^9/L, NEUT 1.5–4 $\times$ 10^9/L, HgB 60–90 g/L and PLT 60–80 $\times$ 10^9/L from 23 to 30 June. He was discharged on 6 July 2022. Results of positron emission tomography/CT indicated considerable remission of the primary disease more than 1 month after receiving CAR-T treatment (Fig. 5A), compared with before treatment (Fig. 5B).

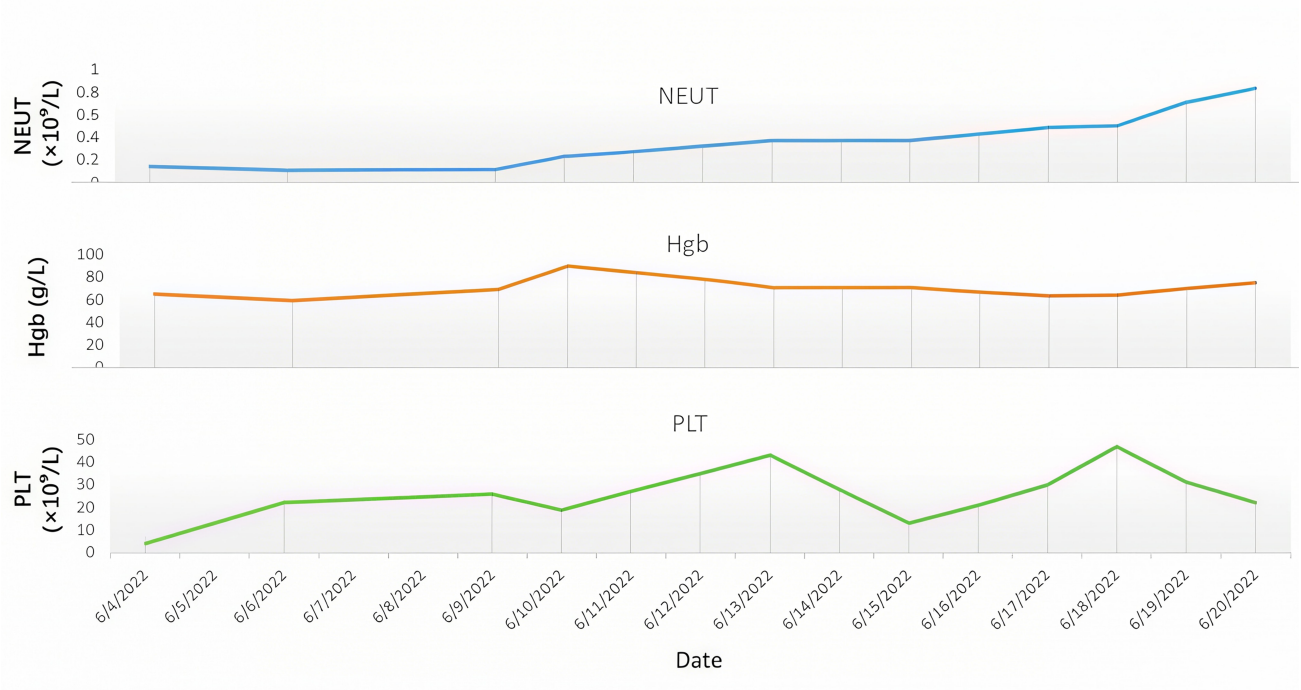

Fig. 3. Trend of blood count recovery, including neutrophilic granulocyte (NEUT), haemoglobin (HGB) and platelet (PLT).

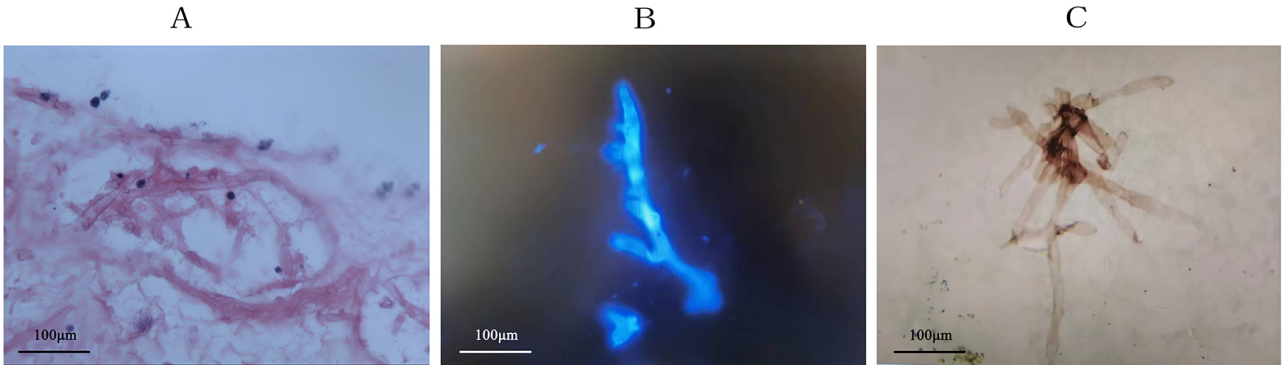

Fig. 4. *Mucorales* found in the specimen obtained during surgery (from the right concha nasalis superior). (A) Haematoxylin and eosin staining of the specimen, with hyphae indicated (magnification ×400). (B) fluorescent staining showing *Mucorales* (magnification ×400). (C) Grocott's methenamine silver staining revealing aseptate, broad-angled hyphae characteristic of *Mucorales* (magnification ×400).

Discussion

Autologous CD19-targeted CAR-T cell therapy greatly improves outcomes in patients with r/r DLBCL; however, adverse events must be recognised and carefully managed. In addition to specific adverse events such as CRS and ICANS, there are latent effects that may impact patients long-term. Reported latent events include late major cytopenia, late hypogammaglobulinaemia, late infections, subsequent malignancies and other immune-related events that occur and/or persist beyond 90 days post infusion of CAR-T cells [10]. The mechanism underlying prolonged cytopenia following CAR-T therapy remains incompletely understood. Although some patients exhibit hypocellular bone marrow after CAR-T infusion, other contributing factors have been proposed. These include lymphodepleting chemotherapy-induced myelo-suppression, immune dysregulation driven by CAR-T cell activation and cytokine-mediated marrow suppression. Recent studies suggest that inflammatory cytokines such as IFN-γ and TNF-α may disrupt haematopoietic stem cell function by altering transcriptional programmes and promoting stem cell exhaustion [11,12]. Additionally, bone marrow dysplasia and fibrosis have been observed from as early as day 6 to as late as day 289 post-infusion [13], and cytopenia persisting for over 20 months has been reported [10], indicating a multifactorial and lasting impairment of haematopoiesis.

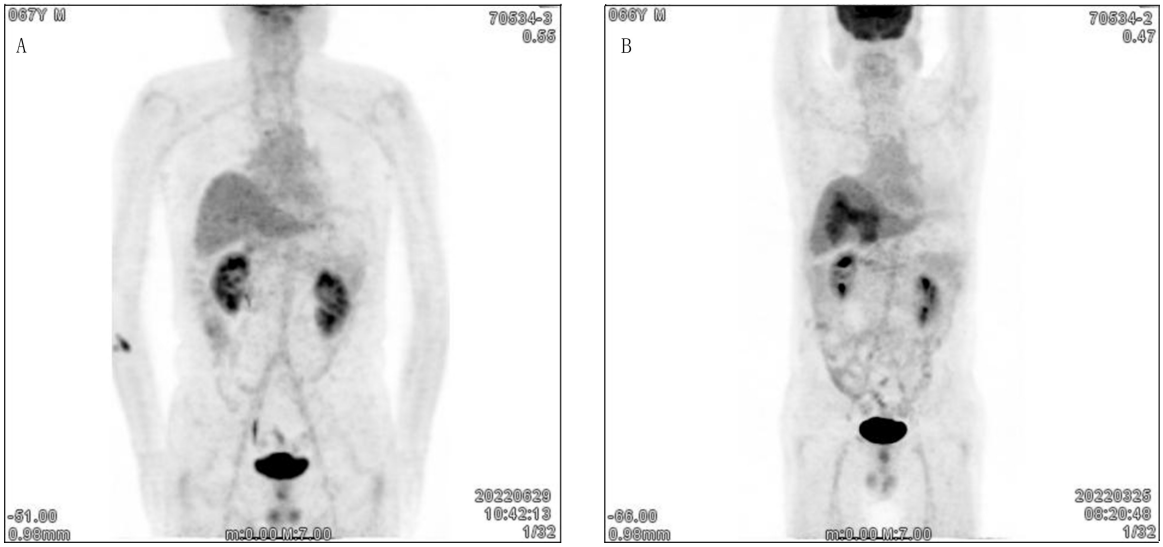

Fig. 5. Positron emission tomography/computed tomography showing CR of the disease ((A) 29 June 2022; (B) 25 March 2022).

Mucormycosis is an opportunistic invasive fungal disease, and patients undergoing treatment for haematological malignancies are at high risk. Treatment recommended by current guidelines includes antifungal therapy, surgical debridement and correction of underlying predisposing conditions. Amphotericin B and posaconazole show in vitro activity against *Mucorales*, but the nephrotoxicity of amphotericin B limits its clinical use, whereas posaconazole has not yet been approved by the Food and Drug Administration for the treatment of mucormycosis. In clinical practice, posaconazole is often used as a first-line treatment, with a recommended dose of 300 mg daily in the form of delayed-release tablets. Monitoring of blood drug concentrations is required to ensure a target trough concentration of >0.7 µg/mL. Another alternative is isavuconazole, administered at 200 mg daily, which does not require blood concentration monitoring. The patient's refusal of posaconazole prophylaxis may have contributed to the development of invasive mucormycosis. Non-adherence to antifungal prophylaxis is a known risk factor for breakthrough fungal infections, particularly in immunocompromised populations. In the context of CAR-T therapy, where prolonged cytopenia and immune suppression are common, adherence to prophylactic regimens is critical. Enhancing patient education, providing clear explanations of infection risks and involving patients in shared decision-making may help improve adherence and reduce infection-related complications.

Isavuconazole is a second-generation triazole antifungal agent approved for the treatment of invasive mucormycosis. The VITAL study, a single-arm, open-label trial supplemented by a case-control analysis [14], assessed its efficacy and safety. Among 37 patients with mucormycosis, including those receiving isavuconazole as primary therapy, for refractory disease or due to amphotericin B intolerance, the 42-day crude mortality rate was 33%, comparable with 39% in matched patients treated with amphotericin B. However, the study's small sample size and lack of randomisation limit definitive conclusions. Compared with amphotericin B, isavuconazole has a more favourable safety profile, particularly regarding nephrotoxicity, but it is not considered superior in efficacy. In our case, amphotericin B was discontinued due to nephrotoxicity and severe headache, and isavuconazole was administered after surgical debridement. The patient showed clinical improvement and tolerated the drug well. Although this outcome is encouraging, it should be interpreted cautiously. For patients intolerant to amphotericin B, isavuconazole remains a viable alternative, particularly when used in combination with timely surgical management. Further studies comparing antifungal agents in this setting are needed to inform optimal treatment strategies.

This case report has several limitations. As a single case, its findings may not be generalisable to all patients receiving CAR-T therapy. Additionally, due to limited follow-up, long-term haematologic recovery and infection outcomes remain uncertain. Diagnostic challenges, particularly in early recognition of mucormycosis and CSOAS, also limited timely intervention. Future research should focus on larger cohorts and standardised approaches to early detection and management of rare complications after CAR-T treatment.

Conclusion

In this case, the patient's development of mucormycosis-related CSOAS post-CAR-T therapy highlights the complexity of managing severe infections in immunocompromised individuals. The difficulty in diagnosing and treating mucormycosis, especially when compounded by adverse reactions to conventional antifungals, underscores the importance of early detection,

regular antifungal prophylaxis and careful management of immune suppression. This case also emphasises the need for personalised therapeutic strategies, such as considering alternative antifungals such as isavuconazole in patients intolerant to traditional treatments. Future research should focus on optimising antifungal strategies, assessing long-term outcomes and further evaluating the safety and efficacy of newer antifungal agents in similar patient populations.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

Conceptualization of the paper: WZ and DZ; Data Curation, Formal Analysis, Investigation, and Visualization of the paper: ZW and CL. All authors were involved in the drafting or critical revision of the manuscript. All authors have read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and waived ethical approval with the approval of the Peking Union Medical College Hospital Research Ethics Committee, and written informed consent was obtained from the participant. All methods were carried out in accordance with relevant guidelines and regulations.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202537200.177.

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