Bacterial meningoencephalitis following allogeneic hematopoietic stem cell transplantation: A case report and literature review

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Abstract. Bacterial meningoencephalitis (BME) following allogeneic hematopoietic stem cell transplantation (allo-HSCT) seriously affects the survival of recipients, though it is rarely reported. The present study reported on a 21-year-old man with Ph^+ acute B-lymphocytic leukemia who suddenly had a severe headache, fever and neuropsychiatric disturbances, and quickly became barely conscious at 483 days post-allo-HSCT. *Streptococcus pneumoniae* (*S. pneumoniae*) was found in cerebrospinal fluid (CSF) and blood, and the patient was eventually diagnosed with BME. The patient had received empirical antibacterial treatment with meropenem and vancomycin, as well as anti-inflammatory treatment with dexamethasone, before *S. pneumoniae* was detected in CSF. Headache and fever were quickly relieved. However, due to the delay of antibacterial treatment outside the hospital, the patient presented with severe neurological sequelae in an unconscious state. In conclusion, impaired immune reconstitution post-transplantation increases the risk of BME, a rapidly progressive disease with high disability and mortality rates. This case highlights that recipients presenting with central nervous system symptoms, early identification and diagnosis of BME, as well as empirical antibacterial treatment within 6 h before lumbar puncture, significantly improve the survival of patients.

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Abbreviations: BME, bacterial meningoencephalitis; BM, bacterial meningitis; allo-HSCT, allogeneic hematopoietic stem cell transplantation; CSF, cerebrospinal fluid; CNS, central nervous system; GVHD, graft-vs.-host disease

Key words: allogeneic hematopoietic stem cell transplantation, central nervous system, bacterial meningoencephalitis, cerebrospinal fluid, *Streptococcus pneumoniae*

Introduction

Central nervous system (CNS) infections, particularly bacterial meningitis (BM) and bacterial meningoencephalitis (BME), are serious complications following allogeneic hematopoietic stem cell transplantation (allo-HSCT) that adversely affect recipients' survival (1-3). Patients with CNS complications after allo-HSCT had a significantly shorter median overall survival than those without (5.1 vs. 27.2 months) (4). Although BME and BM share a common pathogenic origin, the brain regions they involve are different (5). These severe intracranial infections have a poor prognosis (6), mainly caused by Gram-negative and Gram-positive bacteria, including *Streptococcus pneumonia (S. pneumoniae*), *Neisseria meningitidis*, *Listeria monocytogenes*, *Klebsiella pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus* (7). BME involves the meninges and cerebrospinal fluid (CSF) (8), and develops through the bloodstream and direct invasion of the CNS after ear and sinusitis infections (9,10). In a randomized study, among subjects who received the tetravalent polysaccharide meningococcal vaccine at 8 or 20 months after allo-HSCT, 76% of those vaccinated at 8 months and 84% of those vaccinated at 20 months achieved protective antibody levels (≥2 μg/ml) against serogroup C one month after vaccination (11). Multiple studies suggest that vaccination is an effective way to prevent CNS infections in recipients after allo-HSCT (11,12).

BM has a reported incidence of 0.0007-0.08%, causing ~318,000 annual fatalities (12,13). It frequently induces severe neurological complications, with a mortality rate of 10-58%, and necessitates costly management that imposes substantial socio-economic burdens (12,14). The present study reported a case of BME in a patient with B-lymphoblastic leukemia following allo-HSCT, supplemented by a literature review, to provide experience for its early diagnosis and precision treatment.

Case report

A 21-year-old male presented with gingival and nasal bleeding in May 2019 at an external hospital and was

eventually diagnosed with Ph-positive B-cell acute lymphoblastic leukemia at The 940th Hospital of Joint Logistics Support Force in Lanzhou, China. The patient received five chemotherapy regimens and was in complete remission. The patient underwent allo-HSCT from a human leukocyte antigen (HLA)-mismatched sibling (6/10 HLA match) (Table SI). Acute graft-vs.-host disease GVHD prophylaxis included cyclosporin A (1.25 mg/kg 1/12 h), mycophenolate mofetil (0.5 g 1/12 h) and a short course of methotrexate (15 mg/m^2 +1d, 10 mg/m^2 +3d, +6d, +11d) (Fig. 1A). On day 182 after allo-HSCT, the patient developed grade II chronic GVHD of the skin, which responded well to prednisone at 1 mg/kg/d. The dosage was gradually tapered after two weeks of therapy. Owing to recurrent acute pulmonary infections following allo-HSCT (15), the patient did not receive any pneumococcal vaccine or other vaccines.

On post-transplantation day 483, the patient had a sudden, bilateral frontotemporal throbbing headache without any apparent cause. The following day, the patient developed delirium. Neuroimaging revealed mild cerebral edema and diffuse paranasal sinusitis, while a concurrent chest CT showed pneumonia. After ineffective antimicrobial therapy, the patient was transferred to the 940th Hospital of Joint Logistics Support Force on day 485. Neurological examination revealed preserved consciousness, appropriate responsiveness, meningeal irritation signs and bilateral lower limb pathological reflexes. Serum procalcitonin was elevated to 16.39 ng/ml (reference range, 0.00-0.07 ng/ml). CSF analysis showed a white blood cell count of 158x10^6/l (reference range, 0-5x10^6/l) with 82% neutrophils (reference range, ≤1%) and 18% lymphocytes (reference range, 60-80%), chlorine 122.3 mmol/l (reference range, 120-130 mmol/l), glucose 0.07 mmol/l (reference range, 2.5-4.5 mmol/l) and CSF protein 8,157.0 mg/l (reference range, 80-320 mg/l). Both CSF and blood cultures were positive for *S. pneumoniae*. Cranial MRI demonstrated bilateral cerebral and cerebellar leptomeningeal enhancement, ventriculomegaly with intraventricular purulent collections and periventricular edema (Fig. 2A-D). Based on these neuroimaging and laboratory findings, BME was initially suspected. Empiric antimicrobial therapy was initiated promptly with meropenem (1 g q8h) and vancomycin (0.5 g q6h) prior to the availability of CSF and blood culture results. Adjunctive treatments included mannitol for intracranial pressure control and dexamethasone for anti-inflammatory action (Fig. 1B). Subsequently, antimicrobial therapy was adjusted to ceftriaxone (3 g q24h) based on drug susceptibility testing while continuing vancomycin. However, the patient's condition deteriorated with recurrent fever on day 489, culminating in acute unresponsiveness at 23:00 on day 491, manifesting as upward gaze deviation, generalized tonic-clonic seizures and trismus. Neurological examination revealed nuchal rigidity, bilateral lower limb pathological reflexes, withdrawal to pain, symmetrical tendon reflexes and normoactive muscle tone. A repeat lumbar puncture showed marked CSF leukocytosis (3,750x10^6/l, 75% neutrophils), with chloride 109.5 mmol/l, glucose 2.24 mmol/l, protein 2,830.0 mg/l and an opening pressure of 260 mmH_2O (reference range, 80-180 mmH_2O). Subsequent cranial MRI confirmed bilateral meningoencephalitis involving the left fronto-parietal and right temporo-parietal regions (Fig. 2E-H). Given meropenem superior blood-brain barrier penetration compared with ceftriaxone and the observed treatment response (16), the antimicrobial regimen was switched to meropenem, with continued vancomycin and adjunctive dexamethasone on post-transplant day 492. Following this adjustment, the patient's body temperature normalized. The patient remained comatose with intact pain withdrawal reflexes and spontaneous limb movements, but without verbal responses.

The patient subsequently underwent neurological rehabilitation. The patient continued oral antiepileptic medication with levetiracetam tablets 0.25 g/12 h and oral targeted therapy with dasatinib tablets 50 mg/d. A follow-up cranial MRI on post-transplantation day 1,199 revealed bilateral fronto-temporo-parietal-occipital atrophy with encephalomalacia and gliosis (Fig. 2I-L). By day 1,443, the patient exhibited severe neurological sequelae, including a flat affect and significant cognitive impairment. In January 2025, the patient remained hemodynamically stable and in a minimally conscious state, with blunted affect, severe cognitive impairment and no spontaneous speech, but responded to painful stimuli.

Discussion

Neurological complications (NCs) following allo-HSCT independently increase the mortality risk (17), with CNS infections being particularly associated with poor prognosis (18). The incidence of BM post-allo-HSCT is 0.07%, representing a 52-fold increase over the general population (1). Although rare, post-transplantation BM results in severe neurological sequelae in 55% of cases and significantly reduces survival (1). The onset of CNS infection is closely linked to the pace of immune reconstitution. Identified risk factors for NCs and CNS infection include older patient age, whole-body irradiation, acute or chronic GVHD, delayed platelet engraftment, neutropenia, impaired T- and B-cell function, central venous catheters and the use of immunosuppressive agents, steroids, chemotherapy or conditioning regimens (4,19-22).

NCs after transplantation are broadly classified as infectious or non-infectious (23). Infectious NCs include viral, bacterial, fungal and parasitic infections (24). Non-infectious NCs include cerebrovascular events (hemorrhagic or ischemic stroke), metabolic encephalopathy, posterior reversible encephalopathy syndrome, seizures, peripheral neuropathies, immune-mediated disorders (e.g., autoimmune encephalitis, Guillain-Barré syndrome, myasthenia gravis) and secondary malignancies (19). Bacterial CNS infections are less common than viral or fungal ones post-transplant (25). A prospective cohort study by Schmidt-Hieber *et al* (23) of 163 recipients with NCs found that 36% had CNS infections, predominantly viral (35%), and bacterial causes accounted for only 9%. The 30-day mortality after neurological symptom onset was 50% (23).

S. pneumoniae, a leading global cause of BM, often asymptomatically colonizes the nasopharyngeal mucosa in healthy carriers. Immunocompromised or malnourished individuals are at increased risk of invasive pneumococcal disease, which can manifest as meningitis, pneumonia or bacteremia (24). Transmission occurs via respiratory droplets (26). In the present case, the patient

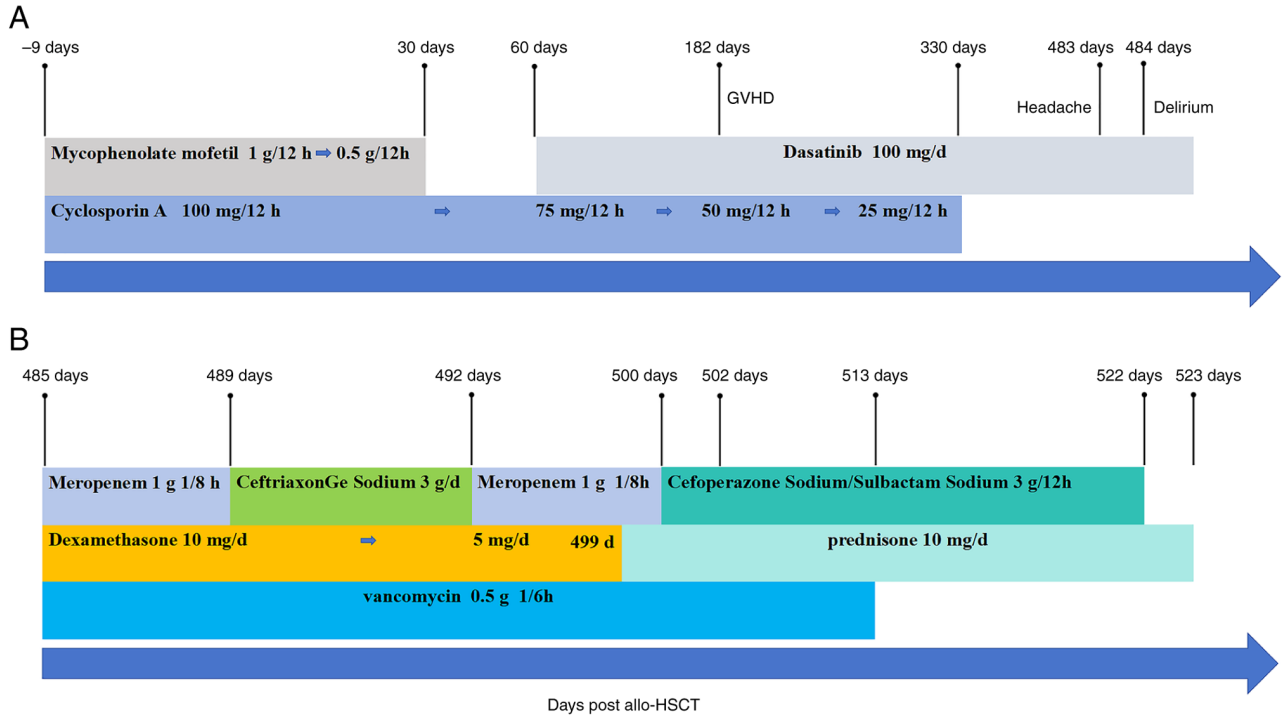

Figure 1. Immunosuppressive and antimicrobial therapy timelines in the patient with BME following allo-HSCT. (A) Immunosuppressive therapy in a patient after allo-HSCT. (B) Antimicrobial therapy in a patient with BME. BME, bacterial meningoencephalitis; allo-HSCT, allogeneic hematopoietic stem cell transplantation; d, days.

was immunocompromised due to post-allo-HSCT immune reconstitution and prolonged tyrosine kinase inhibitor use. This state likely facilitated *S. pneumoniae* colonization of the nasopharyngeal, respiratory and digestive mucosae. Subsequently, *S. pneumoniae* survives by adhering and colonizing, crossing the mucosal epithelial cells and entering the blood vessels (27), penetrating the BBB and ultimately causing meningitis (28,29). Additionally, sinonasal infection may permit direct intracranial invasion (30) and experimental evidence confirms that *S. pneumoniae* can translocate from the nasopharynx to the meninges via the cribriform plate in mice (31).

The primary symptoms of BM include headache, persistent high fever and disturbance of consciousness such as lethargy, psychosis and epilepsy (14). Neuroimaging often reveals cisternal lesions and high-intensity signals. For patients with suspected CNS infection, CT or MRI is routinely performed before lumbar puncture to assess contraindications such as intracranial mass lesions or signs of brain herniation (32). Diagnostic CSF analysis typically shows marked pleocytosis (>1,000x10^6/l leukocytes), hypoglycorrhachia and hypochloridia. While a positive CSF smear or microbial culture remains the diagnostic gold standard (10), metagenomic next-generation sequencing (mNGS) has emerged as a valuable complementary tool (33). Delays in diagnosis and antimicrobial initiation continue to adversely affect outcomes in post-transplant BM (1,34). Therefore, to accelerate pathogen identification, CSF culture protocols should be optimized and mNGS should be employed in selected cases. Differential diagnoses include viral, tuberculous and cryptococcal meningitis, autoimmune encephalitis, pyogenic brain abscess and parasitic CNS infection (35).

In the present study, the patient presented with an acute headache and neuropsychiatric disturbances on day 483 post-transplantation, leading to a confirmed diagnosis of BME by CSF culture. The patient subsequently developed severe neurological sequelae, potentially due to delayed initiation of appropriate antimicrobial therapy prior to admission. Of note, delays of >6 h are known to increase mortality and neurological deficits in BM (36). This case highlights the critical need to administer empiric antimicrobials before CSF culture results are available. Effective regimens must provide broad Gram-positive and Gram-negative coverage with optimal BBB penetration, typically combining a third-generation cephalosporin or meropenem with vancomycin, or linezolid (10,37,38). Notably, meropenem demonstrates superior CNS penetration (up to 39%) compared to cephalosporins (>15%) in severe BM (39). Randomized trials have shown that dexamethasone can suppress inflammatory cytokine release and reduce the mortality and neurological sequelae of BM, excluding *Listeria monocytogenes* infection (40,41). This case therefore highlights the imperative for both prompt and well-targeted antimicrobial therapy in the management of BM.

NCs following allo-HSCT represent life-threatening conditions for recipients (4). Balaguer *et al* (25) analyzed 709 patients with allo-HSCT in a single center, identifying 4 patients with BM. CSF cultures revealed infections caused by *Staphylococcus*, *Mycobacterium tuberculosis*, *S. pneumoniae* and *Nocardia species*. The outcomes included two fatalities and two survivors. Similarly, Oyama *et al* (2) reported 7 BM cases among 1,147 patients undergoing cord blood transplantation, with pathogens including *Enterococcus faecium* (2 patients), *Enterococcus gallinarum* (2 patients), *Staphylococcus hemolyticus* (1 patient), *Streptococcus mitis/oralis* (1 patient)

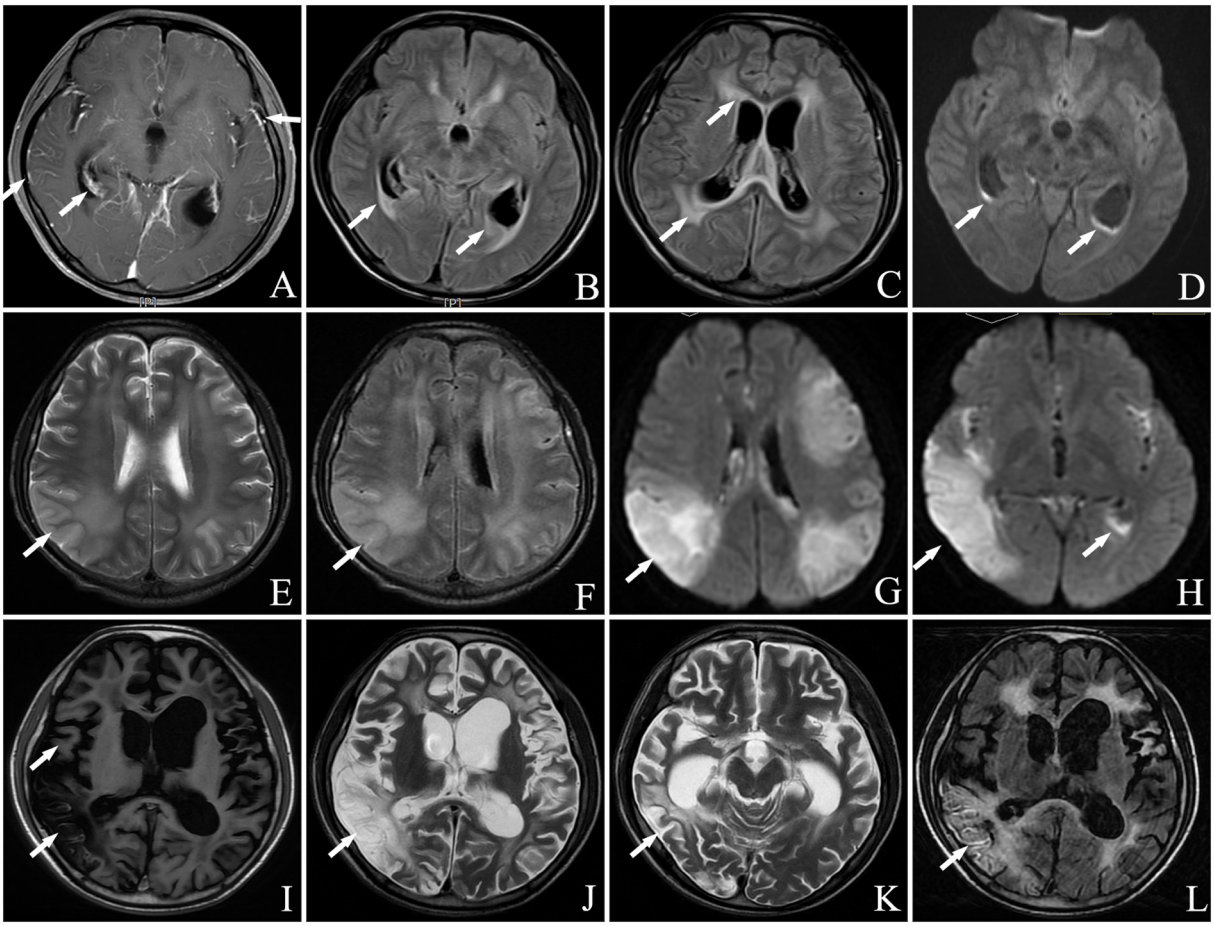

Figure 2. Cranial MRI findings in a patient with bacterial meningoencephalitis pre- and post-treatment following allogeneic hematopoietic stem cell transplantation. (A) Contrast-enhanced cranial MRI at onset revealed abnormal enhancement of the leptomeninges of the bilateral cerebral and cerebellar hemispheres, the tentorium cerebelli and the ependyma. (B) Cranial MRI FLAIR at onset showed a small amount of empyema in the posterior horns of the lateral ventricles and (C) dilation of the supratentorial third ventricle and bilateral lateral ventricles, indicating hydrocephalus. (D) Cranial MRI FLAIR at onset showed periventricular interstitial edema. (E) Cranial MRI T2WI, (F) FLAIR and (G) DWI at the time of clinical deterioration all demonstrated meningoencephalitis involving the bilateral cerebral hemispheres, predominantly in the right temporoparietal region. (H) Cranial MRI DWI at deterioration revealed a small amount of empyema in the posterior horns of the lateral ventricles. (I) Cranial MRI T1WI at two years showed laminar necrosis in parts of the bilateral cerebral cortices. (J) Cranial MRI T2WI at two years demonstrated localized atrophy, encephalomalacia, and gliosis in the bilateral frontal, temporal, parietal, occipital lobes, and (K) laminar necrosis in parts of the bilateral cerebral cortices. (L) Cranial MRI FLAIR at two years showed brain atrophy. MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; T2WI, T2-weighted imaging; DWI, diffusion-weighted imaging.

and *Rothia mucilaginosa* (1 patient). The mortality rate in the present study was 71.4%, with only 28.6% survival. In a similar clinical presentation, Friedman *et al* (42) described a patient with acute myeloid leukemia who developed persistent fever, headache and altered mental status after allo-HSCT. Concurrent endophthalmitis and BME caused by *Enterococcus gallinarum* were confirmed via blood and CSF cultures. Despite receiving antimicrobial therapy with ampicillin and daptomycin, the patient developed persistent fever followed by cerebral hemorrhage, resulting in a poor outcome. Analysis identified 16 cases of post-transplant BM, though detailed clinical data were available for only five patients (Table I), indicating a poor prognosis rate of 61.1% (2,25,42-48). Current guidelines recommend either the 23-valent or 13-valent pneumococcal polysaccharide vaccine for streptococcal meningitis prophylaxis in post-transplant patients (49,50). Transplant recipients should strictly avoid contact with individuals with respiratory infections and maintain rigorous hygiene practices. The management of immune reconstitution post-transplant involves two main strategies: Gradually reducing immunosuppressants like cyclosporine under medical supervision, and using agents or therapies, including IL-2, keratinocyte growth factor, recombinant human growth hormone and adoptive lymphocyte therapy, which are in routine clinical use. By contrast, IL-7, IL-15 and mesenchymal stem cells are still considered exploratory rather than first-line conventional therapies (51). The diagnosis of BM and BME remains challenging due to variable clinical presentations. The classic triad of fever, neck stiffness and altered mental status is present in only 36-58% of patients (14,52). Diagnostic difficulty is further compounded by the possibility of normal neuroimaging findings in certain BM cases, as well as the low sensitivity of CSF culture, often leading to delayed diagnosis (53). In recent years, molecular diagnostic techniques including CSF PCR and mNGS have shown improved pathogen detection sensitivity compared to conventional methods. Major challenges in the management of BM include delays in initiating antimicrobial therapy and inappropriate antibiotic selection (54). A limitation of this study is the lack of analysis regarding surgical interventions for complicated BM.

Table I. Clinical characteristics and outcomes after allogeneic hematopoietic stem cell transplantation recipients were diagnosed with BM and BME.

Item	Current report	Friedman *et al*, 2021 (42)	Robin *et al*, 2010 (43)	Wiesmayr *et al*, 2005 (44)	Bryce *et al*, 2021 (45)	Yang *et al*, 2021 (46)
Sex	M	F	M	F	F	F
Age, years	21	61	10	35	42	52
Transplantation modality	Haplo-HSCT	Haplo-HSCT	UCBT	MSD-HSCT	MSD-HSCT	MSD-HSCT
GVHD prevention	Cyclosporin A, mycophenolate mofetil, short-term methotrexate	Tacrolimus, mycophenolate mofetil, cyclophosphamide	Cyclosporin A, corticosteroids	Cyclosporin A	Not available	Not available
Presence of GVHD	Chronic GVHD, grade 2, mild	Not available	Not available	Acute GVHD, grade 1-2, mild	Not available	Not available
Onset time of BM, days post-transplantation	483	14	113	120	98	4
MRI/CT result	Bilateral cerebral/cerebellar leptomeningeal enhancement	Obstructive hydrocephalus, transependymal edema	Not available	Occlusive hydrocephalus	Hydrocephalus	Diffuse leptomeningeal enhancement with microabscesses scattered in the brain
CSF findings (reference range)	Chlorine 122.3 mmol/l (120-130 mmol/l), glucose 0.07 mmol/l (2.5-4.5 mmol/l), protein 8,157.0 mg/l (80-320 mg/l)	Glucose 24 mg/dl [CSF-to-serum glucose ratio 0.185 (ref:~0.6)], protein 298 mg/dl (ref: 0-35 mg/dl)	Glucose 4.3 mmol/l (serum glucose, 4.8 mmol/l), protein 0.21 g/l	A low glucose level, high protein and massive leukocytosis of >1,500 cells/μl	Glucose 0.6 mmol/l, protein 2.16 g/l	Glucose 71 mg/dl (ref: 45-60 mg/dl), protein 44.2 mg/dl (ref: 20-40 mg/dl)
Bacterial species	*Streptococcus pneumoniae*	*Enterococcus gallinarum*	*Lactobacillus rhamnosus*	*Listeria monocytogenes*	*Staphylococcus haemolyticus*	*Mycobacterium tuberculosis*
Treatments	Meropenem, vancomycin, dexamethasone	Daptomycin, piperacillin-tazobactam and ampicillin	Clindamycin, amoxicillin	Ampicillin	Vancomycin, daptomycin, linezolid	Isoniazid, linezolid, moxifloxacin, ethambutol, amikacin
Neurologic outcomes	Severe cognitive dysfunction	Died	Favorable	Discrete residual paresis of the right arm and leg	Favorable	Died

Haplo-HSCT, haploidentical hematopoietic stem cell transplantation; MSD-HSCT, matched sibling donor hematopoietic stem cell transplantation; UCBT, unrelated cord blood transplantation; M, male; F, female; CSF, cerebrospinal fluid; GVHD, graft vs. host disease; BME, bacterial meningoencephalitis.

In summary, clinicians should maintain high suspicion for BM in post-transplant patients presenting with fever and neurological symptoms. It is crucial to perform lumbar puncture with CSF culture immediately and to initiate empirical antimicrobial therapy within 6 h to improve patient survival.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YS, TW, YH and XZ conceived and designed the study. JC, HL, RS, XM and QF analyzed and interpreted the data. YS and TW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of anonymized data and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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