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CASE REPORT

Management of CMV Pneumonia, DAH, and BOS Following HSCT in a Child with β-Thalassemia: A Case Report

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Abstract: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a curative treatment for thalassemia major but carries a high risk of post-transplant complications. We report a pediatric case with β-thalassemia major who developed steroid-refractory grade III acute graft-versus-host disease (aGVHD) after HLA-9/10 mismatched unrelated donor allo-HSCT. This was followed by cytomegalovirus (CMV) reactivation that progressed to severe CMV pneumonia complicated by diffuse alveolar hemorrhage (DAH). Notably, after failure of first-line antiviral therapy, a combination of ganciclovir and letermovir was employed, resulting in complete virologic clearance and marked respiratory improvement. During follow-up, bronchiolitis obliterans syndrome (BOS) was diagnosed on day +154. The patient received repeated infusions of umbilical cord-derived mesenchymal stromal cells (UC-MSCs), initially for refractory intestinal aGVHD and later in conjunction with the FAM regimen (fluticasone, azithromycin, montelukast) for BOS, ultimately achieving full clinical recovery. This case highlights two key management insights: (1) the ganciclovir–letermovir combination can be effective in pediatric refractory CMV pneumonia, and (2) sequential UC-MSC administration may contribute to controlling both acute GVHD and late pulmonary complications. Finally, multidisciplinary collaboration and individualized strategies are essential in managing such complex post-transplant pulmonary syndromes in children.

Keywords: pulmonary complications, HSCT, cytomegalovirus pneumonia, DAH, BOS

Introduction

β-thalassemia major is a severe inherited anemia requiring lifelong transfusions, which inevitably lead to iron overload and multi-organ damage.[1] Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is currently the only curative treatment for β-thalassemia major.[2] However, transplant-related complications remain critical challenges.[3–5] Pulmonary complications, particularly those associated with cytomegalovirus (CMV) infection, represent a leading cause of non-relapse mortality after pediatric allo-HSCT.[6]

CMV pneumonia in children carries a high risk of progression to respiratory failure and can be complicated by conditions such as diffuse alveolar hemorrhage (DAH).[7,8] The management of refractory CMV pneumonia in the pediatric HSCT setting remains particularly challenging, due to limited evidence on optimal antiviral combinations, the potential role of cellular therapies, and strategies to mitigate subsequent chronic pulmonary sequelae such as bronchiolitis obliterans syndrome (BOS).[9,10] Current guidelines are primarily based on evidence from adult studies, and data regarding the sequential or combined use of agents such as letermovir and ganciclovir in pediatric populations remain limited.[11,12]

We present a pediatric β-thalassemia major patient who underwent a 9/10 HLA-mismatched unrelated donor allo-HSCT, subsequently developing steroid-refractory acute GVHD followed by severe CMV pneumonia complicated by DAH and later BOS. This report highlights the successful use of ganciclovir combined with letermovir for refractory CMV pneumonia, along with the sequential application of umbilical cord-derived mesenchymal stromal cells

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(UC-MSCs) for both acute GVHD and BOS. Our aim is to contribute to the limited evidence on integrated management strategies for severe, sequential pulmonary complications following HSCT and to highlight the critical role of timely, multifaceted intervention in improving outcomes.

Case Report

A 7-year-8-month-old female (height 109 cm, weight 21 kg) was admitted for anemia persisting since infancy. At 2 months of age, she presented with severe anemia (hemoglobin 50 g/L), lethargy, poor appetite, and pallor. Laboratory evaluation showed hemoglobin F 26% (reference 2–22%), with normal red cell indices and reticulocyte count. Serum iron was elevated at 34.46 μmol/L (reference 10–30), total iron-binding capacity 38.46 μmol/L (reference 30–70), iron saturation 89.6% (reference 20–30%), and serum haptoglobin low at 0.22 g/L (reference 0.3–2.1). Beta-thalassemia gene testing identified compound heterozygous mutations (CD41-42 and CD17). Alpha-thalassemia testing was normal, as were coagulation studies, Coombs test, HAM test, and G6PD gene analysis. Bone marrow cytology was consistent with hemolytic anemia. A diagnosis of β-thalassemia major was established after excluding other anemias.

The patient remained transfusion-dependent, receiving approximately 400 mL of red cells monthly. By age 4, ferritin had risen to 3000–5000 ng/mL, prompting iron chelation with deferasirox 500 mg daily. At age 7, ferritin reached 6656 ng/mL, with progressive splenomegaly (thickness 3.6 cm, longitudinal diameter 9.7 cm). Pre-transplant virology showed CMV-DNA 6.26×10^2 IU/mL and EBV-DNA 1.42×10^3 IU/mL in urine.

In August 2022 (at the age of 7 years and 8 months), she underwent a 9/10 HLA-matched unrelated-donor allo-HSCT from a 32-year-old male. The conditioning regimen comprised fludarabine (50 mg/m^2, −12d to −10d), busulfan (1 mg/kg q6h, −9d to −6d), cyclophosphamide (50 mg/kg, −5d to −2d), and anti-thymocyte globulin (2.5 mg/kg, −5d to −2d). The graft contained 6.05×10^6/kg CD34$^+$ cells and 15×10^8/kg mononuclear cells. GVHD prophylaxis included CD25 monoclonal antibody (basiliximab, SIMULECT®, 10mg at 01d, +3d); tacrolimus (0.05mg/kg/d starting from −5d, maintain concentration at 8–10ng/L); mycophenolate mofetil (0.25g q12h, starting from −5d); short-range low-dose methotrexate (+1d: 15mg/m^2, +3d, +6d, +11d: 10mg/m^2) (Figure 1). Additionally, 1×10^6/kg umbilical cord-derived mesenchymal stromal cells (UC-MSCs, developed by iCELL Biotechnology) were infused on days –1, +7 and +14. Hematopoietic reconstitution was achieved by day +16. Tacrolimus plus mycophenolate mofetil were continued for the prevention of GVHD. Antimicrobial prophylaxis consisted of acyclovir (against CMV), sulfamethoxazole (against Pneumocystis Jirovecii Pneumonia, PJP), and fluconazole (against fungal).

On day +19, skin rash consistent with grade I aGVHD (stage 2) appeared and responded to methylprednisolone 1 mg/kg/day. By day +24, severe diarrhea developed, indicating steroid-refractory intestinal aGVHD (grade III, stage 3). Second-line therapy was initiated, including continuation of glucocorticoids, four doses of CD25 monoclonal antibody (days +24, +27, +31, +37), three UC-MSC infusions (days +25, +32, +38), ruxolitinib (days +28 to +67), and budesonide (days +27 to +44). With supportive measures, diarrhea resolved by day +57 (Figure 2).

On day +47, cough productive of jelly-like bloody sputum emerged, without fever or dyspnea. Sputum Gram stain showed chain-like Gram-positive cocci; fungal smear, 1,3-β-D-glucan test (G test) and galactomannan test (GM test) were negative. The CMV and EBV DNA was monitored by PCR each 2 weeks after transplant and remained undetectable until 47 days post-transplantation. Serial CMV/EBV monitoring, previously negative, now revealed elevated CMV-DNA in blood (2.19×10^3 IU/mL) and urine (5.21×10^5 IU/mL), and EBV-DNA in blood (2.61×10^3 IU/mL). The sequence number of human cytomegalovirus (HCMV) in nasopharyngeal swabs was 28455, and the pathogen concentration was

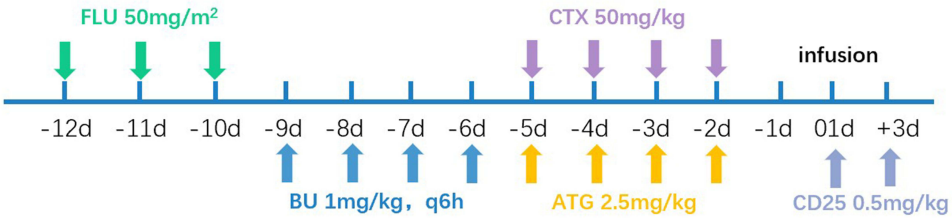

Figure 1 The conditioning regimen. Flu, fludarabine; BU, busulfan; CTX, cyclophosphamide; ATG, anti-thymocyte globulin.

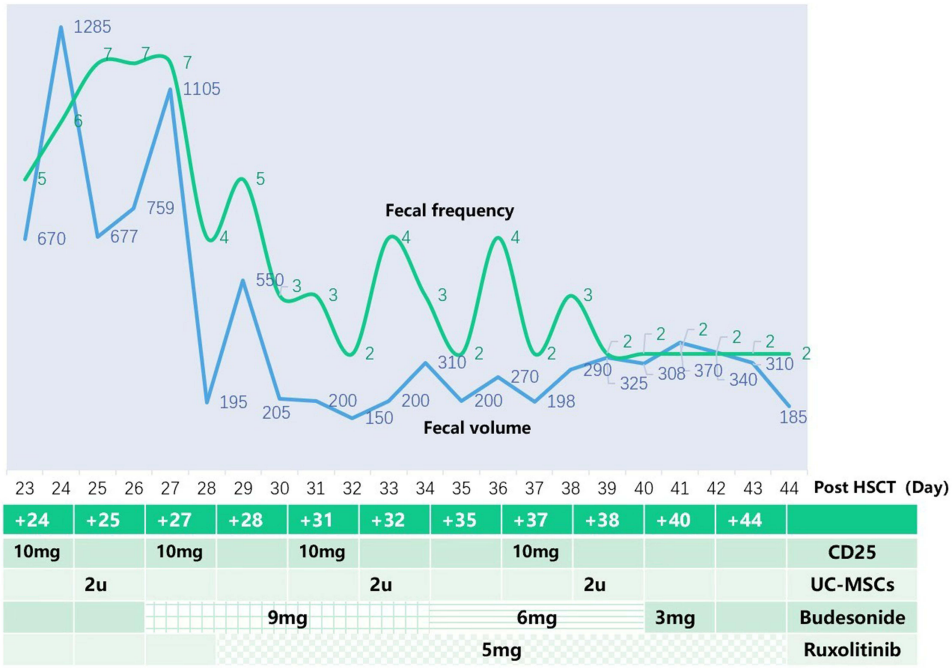

Figure 2 Record of the patient's diarrhea, including fecal frequency and fecal volume. The table in the figure presents the therapeutic drugs administered and their respective durations of treatment.

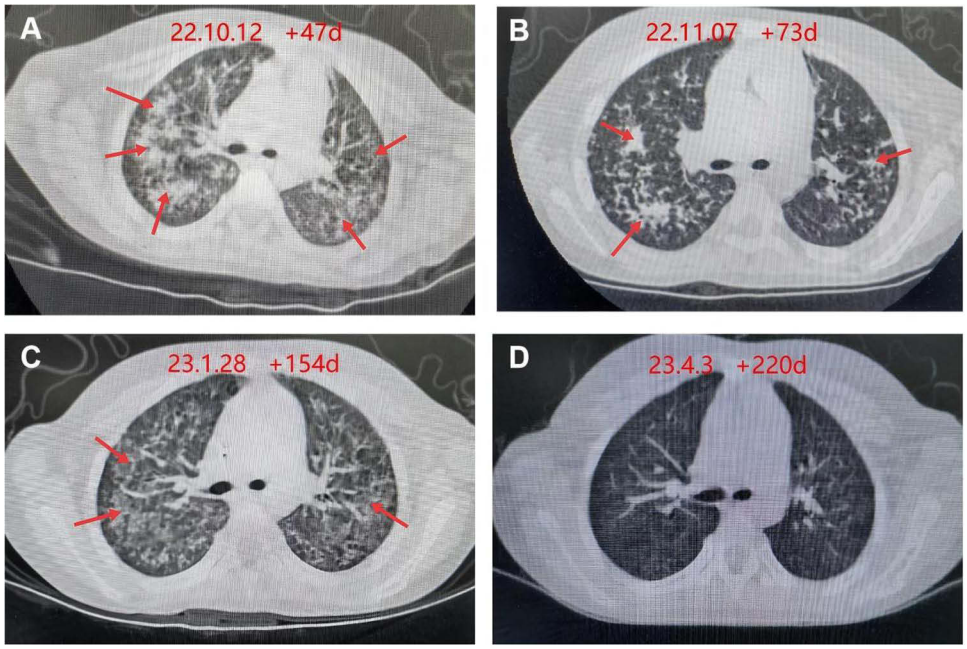

Figure 3 Serial chest CT images illustrating the evolution of pulmonary complications. (**A**) Day +47: Multiple patchy and nodular infiltrates (→) in both lungs, consistent with early CMV pneumonia. (**B**) Day +73: Significant resolution of infiltrates, with residual organizing changes (→) following treatment for diffuse alveolar hemorrhage. (**C**) Day +154: Flocculent opacities and bronchial wall thickening/collapse (→), indicative of bronchiolitis obliterans syndrome (BOS). (**D**) Day +220: Marked improvement in pulmonary parenchyma after combined FAM regimen and UC-MSC therapy.

more than 1.0×10^5. Chest CT demonstrated bilateral patchy and nodular opacities (Figure 3A). Two days later, acute hemoptysis and progressive dyspnea developed, with oxygen saturation falling to 75%. Arterial blood gas indicated type II respiratory failure (pH 7.341, PCO_2 59 mmHg, PO_2 64 mmHg). Hemoglobin dropped from 100 g/L to 80 g/L within 48 h; platelets decreased to 48×10^9/L. Chest X-ray showed extensive bilateral infiltrates with right pleural

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effusion. Given hemodynamic instability and severe thrombocytopenia, bronchoalveolar lavage was deferred. A multidisciplinary diagnosis of CMV pneumonia complicated by diffuse alveolar hemorrhage (DAH) was made based on high CMV load, acute hemoptysis, rapid hemoglobin decline, and consistent imaging.

Immediate non-invasive ventilation was instituted. Hemostatic measures included transfusion of red cells, fresh-frozen plasma, platelets, and administration of pituitrin, carbazochrome, etamsylate, and recombinant factor VIIa. Glucocorticoids were continued. Following two weeks of anti-CMV therapy with acyclovir in combination with sodium phosphonoformate, the patient's CMV viral load remained unchanged, leading to a diagnosis of refractory CMV infection. After multidisciplinary team (MDT) discussion, the treatment regimen was modified to ganciclovir combined with letermovir. Empirical antimicrobial coverage was broadened to meropenem, teicoplanin, voriconazole, and micafungin, while trimethoprim-sulfamethoxazole was maintained for PJP prophylaxis.

Clinical improvement ensued: by day +56, cough and hemoptysis subsided, oxygen requirements decreased, and saturation remained 99–100%. Non-invasive ventilation was discontinued on day +59. Blood CMV-DNA cleared by day +67. Follow-up CT on day +73 showed resolving infiltrates with residual organizing changes (Figure 3B). The patient was discharged on day +75.

Follow-up visits were conducted at an external specialized outpatient clinic for transplantation, with continuous monitoring of lung CT scans and pulmonary function. Bronchiolitis obliterans syndrome (BOS) was detected on day +154, with CT showing flocculent opacities and bronchial wall thickening/collapse (Figure 3C) and pulmonary function tests revealing FEV_1 45.2% predicted and FEV_1/FVC 45.84%.

Chest CT on day 154 indicated flocculent blurred shadows, thickening and collapse of the bronchiolar wall (Figure 3C). Pulmonary function test revealed an FEV1 of 45.2% of the predicted value, with an FEV1/FVC ratio of 45.84%. Treatment included the FAM regimen (fluticasone, azithromycin, montelukast), imatinib, and weekly infusions of UC-MSCs (1×10^6/kg, 4-week courses). By day +220, chest CT demonstrated marked improvement (Figure 3D). Immunosuppression was gradually tapered, and the patient returned to school 21 months post-transplant.

Discussion

What this Case Adds to Existing Evidence

This case provides a real-world illustration of an integrated approach to life-threatening pulmonary complications after pediatric HSCT. It contributes to the sparse pediatric literature in two key aspects: (1) the combined use of ganciclovir and letermovir for refractory CMV pneumonia after first-line antiviral failure, and (2) the sequential administration of UC-MSCs within a multimodal strategy for steroid-refractory acute GVHD and subsequent BOS. While letermovir prophylaxis is established in adults, evidence for its *therapeutic* combination with ganciclovir in active pediatric CMV disease remains limited.[13] Similarly, reports on repeated MSC administration across distinct phases of pulmonary complications (acute DAH and chronic BOS) are scarce.[14,15]

Limitations

DAH was diagnosed clinically without bronchoalveolar lavage (BAL) due to severe thrombocytopenia and hemodynamic instability. Although bronchoalveolar lavage (BAL) is the diagnostic gold standard, the diagnosis was supported by acute hemoptysis, a rapid hemoglobin drop, diffuse alveolar infiltrates on imaging, and exclusion of common alternatives.[16] This pragmatic approach is often necessary in critically ill children when invasive procedures are high-risk. Nevertheless, the lack of BAL confirmation underscores the need to interpret findings within clinical constraints. Additionally, the delayed escalation from fluconazole to broader antifungal coverage after aGVHD onset may have contributed to pulmonary infection progression, highlighting the need for regular fungal/viral monitoring and timely prophylaxis adjustment during intense immunosuppression.

Attribution of Therapeutic Success

The patient's recovery likely resulted from a synergistic combination of interventions rather than any single therapy. While UC-MSCs were administered during both the acute GVHD/DAH phase and the BOS phase, their specific contribution is difficult to isolate amid concurrent high-dose steroids, ruxolitinib, targeted antivirals, broad-spectrum antimicrobials, and the FAM regimen. Therefore, the observed clinical and imaging improvement should be interpreted as the outcome of a coordinated, multimodal strategy.

Clinical Context and Therapeutic Choices

Letermovir is a first non-nucleoside inhibitor targeting the CMV DNA terminase complex (UL56, UL89, and UL51) that blocks viral DNA packaging. Approved for CMV prophylaxis in CMV-seropositive adult allo-HSCT recipients, it offers advantages against ganciclovir-resistant strains (eg, UL97 mutations) with minimal myelosuppression. At that time, our anti-CMV treatment for this case was effective. Unfortunately, CMV resistance testing was not performed in this case. The diagnosis of refractory CMV infection was based on the persistence of high viral load and lack of clinical response to initial therapy with acyclovir and sodium phosphonoformate. The testing of CMV resistance, when available, would have provided valuable guidance and further individualized the treatment strategy. The use of acyclovir instead of letermovir for CMV prophylaxis was because, at that time (2023), letermovir had only recently been approved in China (2022) for CMV prevention in adults following allo-HSCT, with no pediatric indication yet and its cost still high. Therefore, acyclovir was used for pediatric CMV prophylaxis in this patient. The pediatric indication for letermovir in CMV prophylaxis has recently been approved in China, and letermovir is now routinely used for CMV prevention in both adult and pediatric patients.

Administering UC-MSCs at 45 and 100 days post-transplantation has been proven to be able to prevent cGVHD and reduce occurrence of severe aGVHD,[17,18] which is included in the Chinese Expert Consensus on Chronic Graft-Versus-Host Disease.[19] The application of UC-MSCs may be beneficial for complex pediatric-associated lung injury, which requires confirmation through large-sample clinical studies.

Conclusions

This case highlights the multifactorial nature of severe pulmonary complications after pediatric HSCT, where CMV-triggered DAH was compounded by potential co-infections, steroid-refractory aGVHD, and subsequent BOS. It underscores the clinical potential of combined antiviral therapy (ganciclovir-letermovir) for refractory CMV pneumonia and the utility of sequential UC-MSC administration within a multimodal strategy. Moreover, the progression to BOS reinforces the critical need for systematic long-term pulmonary surveillance to enable early intervention. Ultimately, managing such complex syndromes requires a timely, integrated approach that simultaneously addresses both infectious and immune-mediated pathways.

Data Sharing Statement

Data are available from the corresponding author upon reasonable request. Our case report strictly adheres to the reporting guidelines required by the journal.

Ethics and Informed Consent

The patient's legal guardian has fully understood the research content and provided written informed consent, authorizing the publication of the patient's case details and associated images in this case report. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Army Medical University (2021-study-075-01).

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This article adheres to the CARE reporting guidelines for case reports.

Author Contributions

Li Li; Conceptualization, Methodology, Formal Analysis, Investigation, Writing – Original Draft. Ting Chen; Data Curation, Validation, Visualization, Writing – Review & Editing. Peiyan Kong; Formal Analysis, Investigation, Writing – Original Draft, Writing – Review & Editing. Yimei Feng; Conceptualization, Methodology, Formal Analysis, Investigation, Writing – Review & Editing. Xi Zhang; Writing – Original Draft, Formal Analysis, Formal Analysis, Writing – Review & Editing. All authors took part in drafting, revising or critically reviewing the article for this author using the CRediT taxonomy terms. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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