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Plasma Exchange as an Effective Salvage Treatment for Atypical IEC-HS Complicating CAR-T Therapy in Multiple Myeloma: A Case Report and Literature Review

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AI statement

The authors used Deepseek online version as a language-editing tool to improve grammar, clarity, and readability. The AI tool was not used for data analysis, data generation, image processing, or scientific content creation. All outputs were carefully reviewed and verified by the authors, who take full responsibility for the final content.

Abstract

Relapsed/refractory multiple myeloma (RRMM) poses substantial therapeutic challenges, and chimeric antigen receptor T-cell (CAR-T) therapy has emerged as a promising treatment modality. However, CAR-T therapy is often complicated by life-threatening adverse events, most notably cytokine release syndrome (CRS) and secondary hemophagocytic lymphohistiocytosis(sHLH). However distinguishing atypical Immune Effector Cell associated Hemophagocytic Lymphohistiocytosis-like Syndrome(IEC-HS) from conventional CRS or sHLH remains clinically difficult but is critical for patient survival. Their overlapping clinical manifestations frequently complicate accurate diagnosis and clinical management. Here, we report a patient who developed an extremely elevated interleukin-6 (IL-6) level (1,227,475 pg/mL) during CAR-T therapy and concurrently met all key diagnostic criteria for sHLH, leading to a diagnosis of severe CRS complicated with sHLH, which was atypical IEC-HS. After three courses of tocilizumab treatment proved ineffective, therapeutic plasma exchange (TPE) was performed and successfully alleviated the severe adverse events associated with CAR-T therapy. These findings indicate that TPE represents a viable therapeutic option for the atypical IEC-HS following CAR-T infusion.

We comprehensively explored the diagnosis of CRS combined with sHLH in RRMM patients after CAR-T therapy through the treatment process of individual cases, with a focus on analyzing the therapeutic effect of plasma exchange. This review aims to provide evidence-based guidance and decision support for clinicians to manage these complex and potentially fatal complications, ultimately improving the prognosis of patients with atypical IEC-HS in RRMM after CAR-T therapy.

Keywords

Relapsed/Refractory Multiple Myeloma; Chimeric Antigen Receptor T-Cell Therapy; Cytokine Release Syndrome; Hemophagocytic Lymphohistiocytosis; Therapeutic Plasma Exchange

Introduction

The therapeutic landscape for relapsed/refractory multiple myeloma (RRMM) has undergone a profound transformation with the advent of chimeric antigen receptor T cell (CAR-T) therapy. The introduction of CAR-T cells targeting antigens such as B-cell maturation antigen (BCMA) has revolutionized this paradigm, demonstrating unprecedented response rates and durable remissions in pivotal clinical trials. Products like idecabtagene vicleucel (Ide-Cel) and ciltacabtagene autoleucel (Cilta-Cel) have achieved deep and sustained responses, including minimal residual disease negativity, in heavily pretreated populations. This breakthrough underscores the potential of CAR-T therapy to alter the natural history of RRMM, shifting the treatment goal from disease control toward potential functional cure in a subset of

patients. However, this remarkable efficacy is inextricably linked to significant and sometimes life-threatening toxicities, which pose substantial challenges to safe clinical implementation. The potent activation and expansion of CAR-T cells in vivo trigger a cascade of immune reactions that, while essential for anti-tumor activity, can escalate into uncontrolled systemic inflammation,such as CRS and IEC-HS. This case report aims to provide an overview of the signs and symptoms, diagnosis, and the entire process of plasma exchange therapy for atypical IEC-HS in patients with relapsed and refractory multiple myeloma after CAR-T treatment. The purpose of this case report is to contribute to the timely detection and rational treatment of atypical IEC-HS after CAR-T treatment by elucidating the diagnostic difficulties of atypical IEC-HS and the effectiveness of plasma exchange.

Case presentation

Medical History and Disease Course

A 77-year-old female was admitted in February 2022 due to recurrent cough, fever, and fatigue. She was diagnosed with IgG-κ multiple myeloma (MM) at ISS stage III, based on serological, radiological, and bone marrow examinations. The patient initially received four cycles of standard first-line chemotherapy with the VRd regimen (bortezomib, dexamethasone, and lenalidomide), achieving a complete response (CR). Following relapse, she was switched to the VCD regimen (bortezomib, cyclophosphamide, and dexamethasone) for five cycles, again achieving CR, and subsequently maintained on lenalidomide (Fig. 1A).

In December 2024, the patient was readmitted presenting with dizziness, chest tightness, and fever (peak 38.5°C). Chest computed tomography (CT) revealed pulmonary space-occupying lesions with infection, and nucleic acid testing confirmed an influenza A virus infection. Concurrent laboratory tests indicated biochemical relapse of MM (Fig. 2A). Despite broad-spectrum antimicrobial therapy and a switch to carfilzomib-based treatment (Fig. 1B), a re-evaluation in February 2025 demonstrated refractory disease progression (Fig. 2B, 1C), prompting the decision to proceed with BCMA-directed CAR-T cell therapy.

CAR-T Infusion and Early Management

On February 7, 2025, the patient was admitted for lymphodepleting conditioning with fludarabine and cyclophosphamide (FC) over three days, followed by infusion of BCMA-targeted CAR-T cells (Shenzhen Cell Valley, Shenzhen, China) at a dose of 5×10^6/kg.

At Day +1 post-infusion (+8 hours), the patient developed grade 2 CRS, manifesting as high fever (39.0°C), hypoxemia (SpO_2 92%), and neutropenia. By Day +3, the patient developed hypotension (89/54 mmHg), meeting the criteria for grade 3 CRS. Clinical management included tocilizumab and dexamethasone, broad-spectrum antibacterial and anti-staphylococcal therapy, antifungal prophylaxis, and intravenous

immunoglobulin (IVIG) administration for immune modulation. Blood cultures were performed repeatedly before and during broad-spectrum antibiotic administration, and all results were sterile (no microbial growth detected).

Critical Evolution of Atypical IEC-HS and Salvage Therapy

Despite these interventions, the patient's condition deteriorated rapidly on Day +5. Laboratory findings revealed a hyperinflammatory state: markedly elevated interleukin-6 (IL-6) (1,227,475 pg/mL)and soluble CD25 levels (60319.0u/ml, reference range: 223-710 u/ml), severe pancytopenia, coagulopathy, and hypofibrinogenemia. Ferritin levels exceeded 2000 μg/L (reference range: 10–291 μg/L), with persistent fever exceeding 38°C (Table 1). Based on the HLH-2004 diagnostic criteria (1), sHLH was diagnosed. With the patient rapidly progressed to multiple organ dysfunction syndrome (MODS), involving cardiac, hepatic, and renal function, accompanied by severe coagulopathy and oliguria.

Further evaluation using the IEC-HS criteria (2,3) suggested atypical IEC-HS. Unlike typical cases where IEC-HS emerges during CRS resolution, this patient developed sHLH concurrently with refractory CRS.

Given the critical status, therapeutic plasma exchange (TPE) was urgently initiated as a salvage strategy. Following three consecutive days of TPE (2000 mL per session), IL-6 levels plummeted from 11,227,475 pg/mL to 454.12 pg/mL (Figure 3). Subsequently, the patient’s organ function gradually recovered, laboratory parameters stabilized, and sHLH/IEC-HS achieved remission. Follow-up evaluations at day 28 and 5 months post-treatment confirmed sustained complete remission (Fig. 2C, 2D).

Methodology, Limitations, and Discussion

Serum IL-6 levels were quantified using flow cytometry-based cytometric bead arrays. On Day +5, the IL-6 concentration exceeded the upper limit of detection; therefore, a 1:50 serum dilution was performed, and the final value was extrapolated from the standard curve.Besides, tocilizumab blocks the IL-6 receptor, potentially preventing the clearance of free IL-6 and leading to its accumulation (shedding) in the bloodstream. Therefore, the detected peak likely represents total or free IL-6 rather than bioactive IL-6, which is a plausible explanation for the extraordinarily high levels observed in this patient.

During the emergency TPE intervention, pathogen-inactivated fresh frozen plasma served as the replacement fluid. The procedure utilized citrate-anticoagulated preservation solutions, 18G catheters for vascular access, and a volume of 2000 mL per session. Hypocalcemia was the primary adverse event, managed prophylactically with calcium supplementation.

CAR-T cell expansion kinetics appeared normal throughout the clinical course (Table 2). However, due to the critical nature of the event occurring outside routine pharmacokinetic/pharmacodynamic monitoring windows, serial CAR-T copy number

quantification during TPE was not performed, representing a limitation of this case report. Another limitation pertains to the diagnostic criteria for sHLH. According to the HLH-2004 criteria, a diagnosis is established when 5 out of 8 clinical and laboratory parameters are met (1). In this case, data regarding bone marrow aspiration/biopsy and NK cell activity were unavailable. This omission was primarily due to the critical status of the patient during the hyperinflammatory episode, which precluded invasive procedures. Furthermore, the patient had received FC lymphodepleting chemotherapy prior to CAR-T infusion, which is known to suppress NK cell activity. Including such a confounded result would likely have been misleading for the diagnosis of sHLH in this specific case.

In summary, following the onset of grade 2 CRS on Day +1, the patient was managed with tocilizumab, IVIG, and corticosteroids. Despite escalation of care upon progression to grade 3 CRS on Day +3, the patient remained refractory to standard CRS-directed therapy and progressed to MODS. The concomitant extreme elevation of ferritin and soluble CD25 led to the diagnosis of a complex overlap syndrome—refractory CRS merging into sHLH, or atypical IEC-HS. In this context, emergent TPE proved to be a highly effective salvage modality, resulting in rapid cytokine clearance and clinical stabilization.

Discussion

Application and Clinical Manifestations of CAR-T Therapy in Relapsed/Refractory Multiple Myeloma (RRMM)

The clinical landscape for RRMM has been fundamentally reshaped by the advent of B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T-cell (CAR-T) therapies, with idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) representing the vanguard of this therapeutic revolution. These agents have demonstrated efficacy in heavily pretreated patient populations, including those with triple-class and penta-refractory disease(4). The pivotal phase II KarMMa trial for ide-cel reported a best overall response rate (ORR) of 73% and a complete response (CR) or better rate of 33%, outcomes that were subsequently mirrored in real-world settings where 84% of patients achieved an overall response and 42% achieved CR or better, despite 75% of these real-world patients being ineligible for the original clinical trial (5). Similarly, data from the CARTITUDE-1 trial for cilta-cel have shown even more profound responses, with ORRs reaching up to 98% (6) .This capacity to induce rapid and deep remissions, including stringent CR and MRD negativity, is a cornerstone of their clinical value, offering the potential for prolonged treatment-free intervals and improved survival (7). Long-term follow-up data, such as the 5-year results from the LEGEND-2 trial of LCAR-B38M (cilta-cel), underscore the durability of these responses in a subset of patients, with a 5-year progression-free survival (PFS) rate of 21.0% and an overall survival (OS) rate of 49.1%, and curves showing a plateau over time, suggesting the possibility of long-term disease control or even functional cure for some (8) .The efficacy extends to challenging clinical

scenarios, including patients with extramedullary disease (EMD), although responses in EMD can be suboptimal and delayed compared to medullary disease (9). Furthermore, early biomarkers of response are emerging; for instance, achieving serum free light-chain (FLC) suppression by day 28 post-infusion is strongly associated with superior PFS and OS, offering a practical tool for early risk stratification (10). However, the therapeutic triumph is tempered by the reality of relapse, which remains a major impediment to long-term efficacy (11) .Resistance mechanisms are multifaceted, encompassing tumor-intrinsic factors like BCMA antigen loss or downregulation, T-cell exhaustion, and an immunosuppressive tumor microenvironment (12) .Notably, the sequential use of different BCMA-targeted therapies, such as ide-cel followed by cilta-cel upon relapse, has been reported and can yield subsequent responses, highlighting the ongoing evolution of treatment sequencing strategies (13) .The integration of these therapies into earlier lines of treatment is an active area of investigation aimed at improving outcomes further, while real-world evidence continues to confirm their transformative role in the RRMM treatment paradigm (6) .Thus, BCMA-directed CAR-T therapies represent a paradigm shift, delivering deep and often durable remissions for a patient population with limited options, while simultaneously presenting new challenges in managing resistance and optimizing long-term disease control.

Differential Diagnosis of CRS, sHLH and IEC-HS During CAR-T Therapy

The initiation and amplification cascade of Cytokine Release Syndrome (CRS) in the context of chimeric antigen receptor T-cell (CAR-T) therapy for relapsed/refractory multiple myeloma (RRMM) is a complex, multi-step immunopathological process. The core event is the specific engagement of the CAR with its target antigen on the surface of myeloma cells (14). This activation is not merely a binary switch but is critically influenced by the biophysical properties of the CAR-antigen interaction, including affinity, avidity, and antigen density, which collectively shape the functional avidity and subsequent response magnitude of the CAR-T cell (15) .Upon successful synapse formation and signaling, activated CAR-T cells execute their cytotoxic function through the release of perforin and granzymes, leading to target cell lysis. Concomitantly, this activation prompts the CAR-T cells to secrete a burst of primary inflammatory cytokines, most notably interferon-gamma (IFN-γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF) (16,17) .Activated macrophages themselves become prolific producers of a wide array of potent secondary cytokines, including interleukin-6 (IL-6) and interleukin-1 (IL-1) (18) .The dysregulated, excessive production of these primary and secondary cytokines leads to a systemic inflammatory cascade, or “cytokine storm,” characterized by supraphysiological serum levels that drive the clinical manifestations of CRS (19,20) .This cascade can be further exacerbated by factors such as high tumor burden, which provides a large antigenic sink for widespread CAR-T cell activation

and cytokine release. Furthermore, the rapid manufacturing processes used for some CAR-T products, like short-term (st) CAR-T cells, may predispose to a more immediate and severe cytokine release, as demonstrated in preclinical models where stCAR-T cells induced severe adverse events and elevated cytokine levels independent of tumor presence (21) .The resulting systemic inflammation causes widespread endothelial activation, increased vascular permeability, and coagulopathy, culminating in the clinical syndrome of fever, hypotension, capillary leak, and potential multi-organ dysfunction. Understanding this detailed mechanistic cascade from antigen-specific T-cell triggering to myeloid-driven cytokine amplification is fundamental for developing targeted strategies to interrupt the pathway, such as GM-CSF neutralization or IL-6 receptor blockade, thereby mitigating CRS severity while preserving the antitumor efficacy of CAR-T cell therapy (18,22).

Secondary hemophagocytic lymphohistiocytosis (sHLH) is a more extreme hyperinflammatory condition，diagnosis of sHLH presents significant clinical challenges, primarily due to its overlapping features with severe cytokine release syndrome (CRS) and the lack of validated diagnostic criteria specific to this setting. In clinical practice, the diagnosis often relies on adapting established frameworks such as the HLH-2004 criteria or criteria for macrophage activation syndrome (MAS) (23) .However, a critical diagnostic challenge lies in differentiating sHLH from severe CRS, as both conditions share common manifestations like fever, hyperferritinemia, and organ dysfunction (24) .The key distinguishing features that lean towards an HLH diagnosis include persistent high-grade fever, progressive cytopenias, and hepatosplenomegaly (25). From a biomarker perspective, certain patterns are more supportive of HLH. Extremely elevated and sustained levels of interferon-gamma (IFN-γ), along with granzyme B, IL-1RA and IL-10, are hallmarks, differentiating sHLH from CRS (26). Similarly, a marked elevation of soluble interleukin-2 receptor alpha (sCD25) is a strong indicator. Studies attempting to apply traditional HLH diagnostic tools like the HScore or HLH-2004 criteria in the post-CAR-T setting have shown limited utility, as these tools were not designed for this context and many parameters can be elevated in high-grade CRS, leading to poor specificity (27) .For instance, while hyperferritinemia is common to both, levels in sHLH can be extraordinarily high, as illustrated by a case report noting a peak ferritin of 81,540 μg/L (28). The incidence of sHLH is increasingly recognized and may be higher than previously thought, with reported rates varying; one study in pediatric and young adult patients receiving CD19-directed CAR-T therapy found an incidence of 14.8% (29) while another in B-cell maturation antigen (BCMA) CAR-T recipients reported 20.2% (26) .This syndrome is often temporally distinct, typically emerging as CRS is subsiding or after its resolution, although it can also present concurrently with worsening CRS in a syndrome termed CRS with multiorgan dysfunction (30) .Early and accurate differentiation is crucial, and early recognition of CAR-T related complications other than CRS is recommended (31).

The core pathophysiology of sHLH revolves around a profound and dysregulated immune activation, primarily driven by excessive IFN-γ production, leading to a

cascade of hyperinflammation. The initiating event is the persistent and potent stimulation of CAR-T cells and/or residual tumor cells, which results in the sustained activation of CD8+ T cells and macrophages. This activation triggers a massive release of IFN-γ, which plays a key role in the pathophysiology of hemophagocytic lymphohistiocytosis (32). Tissue infiltration by these activated immune cells contributes to end-organ damage and dysfunction. It is important to distinguish the mechanism of secondary, or acquired, HLH from familial HLH. In primary HLH, genetic mutations related to perforin and cytotoxic granule release are associated with disease development, and CD8+ T cell-mediated lymphocytotoxicity is critical for the development of familial HLH (33). In contrast, in CAR-T-related HLH, this perforin/granzyme pathway defect is not the primary driver. The pathogenesis of Secondary hemophagocytic lymphohistiocytosis (sHLH) is considered to differ from that of cytokine release syndrome (24). This concept is supported by biomarker studies showing that sHLH is characterized by a distinct cytokine network, with extreme elevations of IFN-γ, granzyme B, IL-1RA, and IL-10, setting it apart from the cytokine profile of severe CRS (26). The role of myeloid cells, particularly macrophages, is therefore central in the relationship between myeloid cells and CAR-T related toxicity, as well as in targeted combination therapy against myeloid cells (34).

CRS and HLH in the context of CAR-T therapy are best conceptualized as existing on a continuous spectrum of hyperinflammatory responses, where severe CRS may evolve into or overlap with HLH, making early distinction challenging yet critical for therapeutic intervention. The overlapping clinical and laboratory features between CRS and sHLH include high fever and varying degrees of organ dysfunction (24) .This shared pathophysiology contributes to diagnostic ambiguity. However, key differentiating points can guide clinicians.

Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) is one of the hematological toxicities associated with CAR-T, and relevant diagnostic scoring criteria and management strategies have been proposed (35). Regarding the differential diagnosis between sHLH and IEC-HS, the primary distinction lies in their clinical context and timing: IEC-HS is defined by hemophagocytic symptoms arising specifically during immune effector cell therapy, typically emerging during or after CRS resolution. Nevertheless, the therapeutic strategies for both entities remain identical in clinical practice. The presence of definitive hemophagocytosis on bone marrow biopsy, though not always present or required for diagnosis in the CAR-T setting, is a strong indicator. Biomarker profiles offer further discrimination compared to CRS (26) .The cytokine signature is particularly telling; while both involve elevated IFN-γ, the magnitude andpersistence are greater in HLH. A distinct cytokine network with extreme elevations of IFN-γ, granzyme B, IL-1 receptor antagonist, and IL-10 has been shown to differentiate sHLH from severe CRS (26). Temporal patterns also provide clues; IEC-HS often has a delayed onset, occurring after the peak of CRS or even as CRS is resolving, whereas features of HLH that appear concurrently with worsening CRS may indicate CRS

with multiorgan dysfunction (30). Tocilizumab and corticosteroids are mainstays for CRS treatment, and several agents targeting other pathways have been used off-label for sHLH/IEC-HS (36). Failure to promptly identify and treat sHLH/IEC-HS is associated with poor outcomes, including increased non-relapse mortality and reduced overall survival, as evidenced by studies showing that patients developing sHLH had significantly worse survival compared to those without it (29). We observed a complex overlap of severe CRS and sHLH. Given that this presentation diverged from conventional IEC-HS phenotypes (2,3), we classified it as an atypical IEC-HS syndrome.

Conventional Management Strategies for sHLH/IEC-HS in CAR-T Therapy

The management of sHLH/IEC-HS requires a more aggressive and often multi-agent immunomodulatory approach compared to standard CRS therapy, targeting the core pathophysiology of excessive T-cell and macrophage activation. First-line treatment typically involves high-dose corticosteroids for broad immunosuppression (37) .Etoposide-based regimens are sometimes required for the treatment of sHLH, mirroring its use in conventional HLH protocols (38). However, the therapeutic landscape is evolving towards more targeted strategies. Given the pivotal role of IFN-γ in driving HLH pathology, direct blockade of this cytokine has emerged as a promising strategy. Emapalumab, a monoclonal antibody that neutralizes IFN-γ, has shown potential as an effective targeted therapy in case reports of sHLH (39) .Its compassionate use has been reported in patients after corticosteroids, tocilizumab, and anakinra treatment for IEC-HS following CAR-T therapy (40) .Another targeted approach involves inhibiting the downstream signaling of inflammatory cytokines, including IFN-γ. Janus kinase (JAK) inhibitors, such as ruxolitinib, have been used off-label for the management of CAR-T related toxicities (36). Ruxolitinib has been used off-label to control HLH-related inflammation and is under investigation in this setting. Interleukin-1 blockade with anakinra, an IL-1 receptor antagonist, is also employed, targeting the IL-1β-mediated inflammation that contributes to the syndrome (40) .The 2023 American Society for Transplantation and Cellular Therapy (ASTCT) consensus recommendations evaluated therapeutic regimens including corticosteroids, anakinra, ruxolitinib, and emapalumab for IEC-HS (41) .The choice of therapy may be guided by the specific cytokine profile, with emerging evidence suggesting that targeting IL-10, which is markedly elevated in sHLH, could be a worthwhile strategy (26). Ultimately, effective management of rare complications after CAR-T cell therapy hinges on early diagnosis (31).

Significance of Therapeutic Plasma Exchange in the Treatment of sHLH/IEC-HS

Plasmapheresis, or therapeutic plasma exchange (TPE), is an extracorporeal blood purification technique designed to remove pathogenic substances from the plasma. The procedure operates on the principle of separating a patient's plasma from thecellular components of blood, discarding the plasma, and replacing it with a substitution fluid such as fresh frozen plasma, albumin solution, or saline. This separation is achieved through either centrifugation or membrane filtration technology. The primary therapeutic rationale in the context of CAR-T cell therapy-related toxicities like CRS and sHLH/IEC-HS is the non-selective, rapid clearance of circulating macromolecules. This includes inflammatory mediators that drive the hyperinflammatory state, such as cytokines including IL-6, IFN-γ, and GM-CSF (20,42) .The clearance efficiency of TPE for these factors is influenced by several pharmacokinetic parameters, including the molecular weight of the target substance, its volume of distribution, and its half-life. TPE can be used to clear cytokines and may affect the clearance of concurrent medications (43). The procedure's ability to swiftly lower the burden of these pathogenic molecules is considered a key mechanism by which it can interrupt the self-perpetuating cycle of inflammation, thereby mitigating end-organ damage. Evidence from severe COVID-19 supports this concept, demonstrating that plasma exchange can lead to significant reductions in pro-inflammatory cytokines like IL-6, IL-1, and IFN-γ, correlating with clinical improvement (44). This rapid clearance capability positions TPE as a potential rescue modality when the inflammatory cascade becomes refractory to standard pharmacological interventions like tocilizumab and corticosteroids, which target specific pathways but may be insufficient to control a fulminant, multisystem inflammatory response.

The clinical application of plasma exchange in the management of severe, refractory CRS and sHLH/IEC-HS following CAR-T cell therapy is primarily supported by retrospective case series and individual reports, indicating its role as a salvage therapy. These reports consistently describe patients with life-threatening grade 3-4 CRS who did not respond adequately to first-line interventions including anti-IL-6 receptor therapy (tocilizumab) and high-dose corticosteroids (45,46) .In this refractory setting, the initiation of TPE has been associated with observable clinical improvements. Key indicators of response include a rapid reduction in fever and improved oxygenation (46,47). Laboratory corroboration of this clinical response is frequently seen in the significant decline of serum inflammatory cytokine levels after therapeutic plasma exchange (46). Similar clinical and biochemical benefits have been documented in severe inflammatory syndromes analogous to CRS, such as in critical COVID-19, where TPE improved survival and accelerated the resolution of cytokine storm (48,49) .Furthermore, case reports involving other T-cell engaging therapies, like T-cell receptor-engineered T (TCR-T) cell therapy for solid tumors, also highlight the successful use of PE to manage severe CRS, underscoring the broader applicability of this approach for cytokine-driven toxicities (50). Despite these promising signals, the current evidence base remains limited by its retrospective nature, small patient numbers, and the absence of prospective, controlled clinical trials specifically in the CAR-T population. Consequently, the evidence grade is considered

low, and the definitive impact of TPE on long-term survival outcomes for patients with CAR-T-related CRS/sHLH/IEC-HS requires validation through more rigorous, systematic investigation. Its current position in treatment algorithms is therefore that of an adjunctive rescue strategy for the most severe and pharmacologically resistant cases.

Determining the optimal timing for initiating plasma exchange is critical for maximizing its potential benefit while minimizing risks. In the context of CAR-T associated toxicities, TPE can be considered for patients with severe CRS who do not respond to standard therapy including tocilizumab and corticosteroids (45). Early intervention, before the establishment of irreversible multi-organ failure, is suggested to be associated with better outcomes, as observed in studies of COVID-19-related CRS where TPE initiated within the first 12 days of illness was linked to superior survival (48) .A typical TPE protocol for severe inflammatory states involves exchanging 1.0 to 1.5 plasma volumes per session (51) .Sessions may be performed daily or on alternate days, with the treatment course continuing until there is clear evidence of clinical stabilization and improvement in key laboratory parameters. The assessment of efficacy is multifaceted and should integrate clinical, hemodynamic, and laboratory data. After therapeutic plasma exchange, clinical improvement can be observed including resolution of fever and improved oxygenation (46,47) .Laboratory monitoring is essential and should involve the dynamic tracking of inflammatory markers such as C-reactive protein (CRP) and ferritin, as well as key cytokines like IL-6 and IFN-γ to confirm the biochemical effect of plasma clearance (44,46).

The optimization of plasma exchange (PE) within the management of CAR-T cell therapy toxicities, specifically for CRS and sHLH/IEC-HS, necessitates a clear, evidence-based positioning in clinical guidelines and dedicated prospective research to define its role and refine its application. Currently, PE is recognized as an emerging promising treatment for mitigating severe CRS (52) .This involves moving beyond its current often anecdotal or last-resort application to a strategically timed intervention.

These studies should directly compare outcomes in patients with severe CRS/sHLH/IEC-HS managed with standard-of-care (e.g., anti-IL-6 therapy, corticosteroids, supportive care) versus standard care plus early adjunctive PE. The hypothesis is that early PE, by physically removing pathogenic cytokines, autoantibodies, and other inflammatory mediators, could more rapidly abate the hyperinflammatory state, potentially preventing progression to irreversible multi-organ failure and improving survival (52,53) .The design of such trials must carefully consider the technical parameters of PE, as these significantly influence both efficacy and safety. A key area for optimization is the choice of replacement fluid, which directly impacts hemostasis. Studies show that using exclusively albumin-based replacement fluids effectively depletes coagulation factors, particularly fibrinogen, but in low-bleeding-risk patients, this strategy is associated with only rare and mild bleeding events, challenging the routine need for empirical coagulation

testing or plasma supplementation (54) .The effect of fresh frozen plasma replacement on hemostasis is significantly greater than that of other replacement fluids, and thrombin generation and fibrinogen levels are markers that distinguish the effect of different TPE replacement fluids on hemostasis (55) .

By systematically addressingthese questions through rigorous clinical research, the role of PE can evolve from an emergent salvage therapy to a strategically deployed, optimized component of the comprehensive management arsenal for life-threatening CAR-T cell therapy toxicities.

Conclusion

This case report provides an overview of the clinical manifestations, diagnosis, and treatment methods such as plasma exchange for severe CRS with sHLH which an atypical IEC-HS to CAR-T therapy in multiple myeloma, which helps patients turn the crisis into safety. This case study emphasizes the importance of accurate diagnosis when severe CRS and sHLH occur after CAR-T treatment, and the application of plasma exchange therapy is a safe and effective treatment method.The central challenge moving forward is not merely to validate TPE's efficacy, but to strategically position it within a multi-modal treatment algorithm.

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Conflict of interest statement

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.

Credit Author Statement

Songyun Wang: Conceptualization, Data curation, Funding acquisition, Investigation, Validation, Writing – original draft. Zesong Wang: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Visualization, Writing – review & editing. Bian-feng Zhao: Data curation, Writing –original draft. Yuanyuan Jiao: Data curation, Investigation, Writing – original draft. Erqing Yang: Data curation, Investigation, Writing – original draft. Tianjiao Wu: Data curation, Investigation, Writing – original draft. Shuangshuang Chen: Data curation, Writing – original draft.

Haoyang Ma: Data curation, Investigation, Writing – original draft. Jie Li: Data curation,Writing – original draft. Hui-rui Wang: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation,Writing – review & editing.

Consent for Publication

All images and data included in this article were obtained with the patient’s informed consent for publication. All data in this manuscript represent original clinical data.

Ethics Statement

Ethical approval was obtained for this original research per the institutional review board (IRB) guidelines of The Second Affiliated Hospital of Henan University of Science and Technology (Approval No. L2023011, dated November 23, 2023). This study was conducted in accordance with the Declaration of Helsinki. All figures are either original to this work or properly attributed.

References

1. Henter J-I, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatric Blood Cancer* (2007) 48:124-131. doi: 10.1002/pbc.21039

2. Hines MR, Knight TE, McNerney KO, Leick MB, Jain T, Ahmed S, et al. Immune Effector Cell associated Hemophagocytic Lymphohistiocytosis-like Syndrome (IEC-HS). *Transplant Cell Ther.* (2023); S2666-6367(23)01164-8. doi: 10.1016/j.jtct.2023.03.006.

3. Johnson WT, McNerney KO, Frank MJ, Shah NN. How I treat HLH-like toxicities after immune effector cell therapy. *Blood* (2026) 147:2592‑2609. doi: 10.1182/blood.2025032352.

4. Hakan G, Engin K, Elifcan KA, Haluk D, Mehmet T, Suman K, Maxwell K. CAR-t cell therapy in relapsed or refractory multiple myeloma and access in turkey. *Frontiers in medicine* (2024) 11:1413825. doi: 10.3389/fmed.2024.1413825

5. Hansen DK, Sidana S, Peres LC, Leitzinger CC, Shune L, Shrewsbury A, Gonzalez R, Sborov DW, Wagner C, Dima D, et al. Idecabtagene vicleucel for relapsed/refractory multiple myeloma: Real-world experience from the myeloma CAR t consortium. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* (2023) 41:2087–2097. doi: 10.1200/JCO.22.01365

6. Pleitez HG, Saowapa S, Maldonado AO, Kanitthamniyom C, Bernal DO, Tijani L. From trials to practice: A 2025 review of idecabtagene vicleucel and ciltacabtagene autoleucel efficacy across clinical studies and real-world evidence. *European journal of haematology* (2025) 115:533–546. doi: 10.1111/ejh.70025

7. Ding H, Wu Y. CAR-t therapy in relapsed refractory multiple myeloma. *Current medicinal chemistry* (2024) 31:4362–4382. doi: 10.2174/0109298673268932230920063933

8. Xu J, Wang B-Y, Yu S-H, Chen S-J, Yang S-S, Liu R, Chen L-J, Hou J, Chen Z, Zhao W-H, et al. Long-term remission and survival in patients with relapsed or refractory multiple myeloma after treatment with LCAR-B38M CAR t cells: 5-year follow-up of the LEGEND-2 trial. *Journal of hematology & oncology* (2024) 17:23. doi: 10.1186/s13045-024-01530-z

9. Qi Y, Li H, Qi K, Zhu F, Cheng H, Chen W, Yan Z, Li D, Sang W, Fei X, et al. Clinical outcomes and microenvironment profiling in relapsed/refractory multiple myeloma patients with extramedullary disease receiving anti-BCMA CAR t-cell-based therapy. *American journal of hematology* (2024) 99:2286–2295. doi: 10.1002/ajh.27469

10. Richardson T, Tharmaseelan H, Kobbe G, Baermann B-N, Holderried TAW, Schmitz F, Crysandt M, Gödel P, Wolfensberger N, Schütte D, et al. Early free light-chain suppression as a prognostic marker in relapsed and refractory myeloma patients treated with BCMA-directed CAR-t cells. *EJHaem* (2025) 6:e70139. doi: 10.1002/jha2.70139

11. Tedder B, Bhutani M. Resistance mechanisms to BCMA targeting bispecific antibodies and CAR t-cell therapies in multiple myeloma. *Cells* (2025) 14: doi: 10.3390/cells14141077

12. Yue T, Sun Y, Dai Y, Jin F. Mechanisms for resistance to BCMA-targeted immunotherapies in multiple myeloma. *Blood reviews* (2025) 70:101256. doi: 10.1016/j.blre.2025.101256

13. Mobascher P, Engelhardt M, Wäsch R. Successful sequential application of CAR t-cell-therapies in relapsed refractory multiple myeloma. *Annals of hematology* (2025) 104:2055–2058. doi: 10.1007/s00277-025-06340-y

14. Hanssens H, Meeus F, Vlaeminck YD, Lecocq Q, Puttemans J, Debie P, Groof TWMD, Goyvaerts C, Veirman KD, Breckpot K, et al. Scrutiny of chimeric antigen receptor activation by the extracellular domain: Experience with single domain antibodies targeting multiple myeloma cells highlights the need for case-by-case optimization. *Frontiers in immunology* (2024) 15:1389018. doi: 10.3389/fimmu.2024.1389018

15. Greenman R, Pizem Y, Haus-Cohen M, Goor A, Horev G, Denkberg G, Sinik K, Elbaz Y, Bronner V, Levin AG, et al. Shaping functional avidity of CAR t cells: Affinity, avidity, and antigen density that regulate response. *Molecular cancer therapeutics* (2021) 20:872–884. doi: 10.1158/1535-7163.MCT-19-1109

16. Guo C, Dong E, Lai Q, Zhou S, Zhang G, Wu M, Yue X, Tao Y, Peng Y, Ali J, et al. Effective antitumor activity of 5T4-specific CAR-t cells against ovarian cancer

cells in vitro and xenotransplanted tumors in vivo. *MedComm* (2020) 1:338–350. doi: 10.1002/mco2.34

17. Wang H, Feng S, Zhu Y, Zhang Y, Zhou Z, Nian Z, Lu X, Peng P, Wu S, Zhou L. The tandem CD33-CLL1 CAR-t as an approach to treat acute myeloid leukemia. *Blood transfusion = Trasfusione del sangue* (2025) 23:338–347. doi: 10.2450/BloodTransfus.786

18. Hao Z, Li R, Meng L, Han Z, Hong Z. Macrophage, the potential key mediator in CAR-t related CRS. *Experimental hematology & oncology* (2020) 9:15. doi: 10.1186/s40164-020-00171-5

19. McBride DA, Kerr MD, Dorn NC, Ogbonna DA, Santos EC, Shah NJ. Triggers, timescales, and treatments for cytokine-mediated tissue damage. *European medical journal Innovations* (2021) 5:52–62. doi: 10.33590/emjinnov/20-00203

20. Zanza C, Romenskaya T, Manetti AC, Franceschi F, Russa RL, Bertozzi G, Maiese A, Savioli G, Volonnino G, Longhitano Y. Cytokine storm in COVID-19: Immunopathogenesis and therapy. *Medicina (Kaunas, Lithuania)* (2022) 58: doi: 10.3390/medicina58020144

21. Jamali A, Ho N, Braun A, Adabi E, Thalheimer FB, Buchholz CJ. Early induction of cytokine release syndrome by rapidly generated CAR t cells in preclinical models. *EMBO molecular medicine* (2024) 16:784–804. doi: 10.1038/s44321-024-00055-9

22. Gabriel K, Heinzerling L, Baumgarten L von, Subklewe M, Kobold S. The role of cytokines in cytokine release syndrome (CRS) after CAR t cell therapy. *Biochimica et biophysica acta Molecular cell research* (2026) 1873:120115. doi: 10.1016/j.bbamcr.2026.120115

23. Sandler RD, Tattersall RS, Schoemans H, Greco R, Badoglio M, Labopin M, Alexander T, Kirgizov K, Rovira M, Saif M, et al. Diagnosis and management of secondary HLH/MAS following HSCT and CAR-t cell therapy in adults; a review of the literature and a survey of practice within EBMT centres on behalf of the autoimmune diseases working party (ADWP) and transplant complications working party (TCWP). *Frontiers in immunology* (2020) 11:524. doi: 10.3389/fimmu.2020.00524

24. Hu J, Feng C, He L, Wang Y. Chimeric antigen receptor t cell immunotherapy-associated hemophagocytic lymphohistiocytosis: Pathogenesis, clinical manifestation, diagnosis and management compared with cytokine release syndrome (review). *Molecular medicine reports* (2025) 32: doi: 10.3892/mmr.2025.13578

25. Soy M, Atagündüz P, Atagündüz I, Sucak GT. Hemophagocytic lymphohistiocytosis: A review inspired by the COVID-19 pandemic. *Rheumatology international* (2021) 41:7–18. doi: 10.1007/s00296-020-04636-y

585 26. Zu C, Wu S, Zhang M, Wei G, Xu H, Cui J, Chang AH, Huang H, Hu Y. A
586 distinct cytokine network distinguishes chimeric antigen receptor t cell
587 (CAR-t)-associated hemophagocytic lymphohistiocytosis-like toxicity (sHLH) from
588 severe cytokine release syndrome following CAR-t therapy. *Cytotherapy* (2023)
589 25:1167–1175. doi: 10.1016/j.jcyt.2023.06.008

590 27. Kim DW, Bukhari A, Lutfi F, Zafforoni F, Merechi F, Ali MKM, Gottlieb D, Lee
591 ST, Kocoglu MH, Hardy NM, et al. Low utility of the h-score and HLH-2004 criteria
592 to identify patients with secondary hemophagocytic lymphohistiocytosis after CAR-t
593 cell therapy for relapsed/refractory diffuse large b-cell lymphoma. *Leukemia &*
594 *lymphoma* (2022) 63:1339–1347. doi: 10.1080/10428194.2021.2024817

595 28. Hoyt R, Ye Z, Dasgupta A. Very unusual extremely high ferritin with cytokine
596 release syndrome in a patient with hematological malignancy after experimental
597 chimeric antigen receptor (CAR)-t-cell therapy. *Clinica chimica acta; international*
598 *journal of clinical chemistry* (2024) 559:119704. doi: 10.1016/j.cca.2024.119704

599 29. Hines MR, Keenan C, Alfaro GM, Cheng C, Zhou Y, Sharma A, Hurley C,
600 Nichols KE, Gottschalk S, Triplett BM, et al. Hemophagocytic
601 lymphohistiocytosis-like toxicity (sHLH) after CD19-specific CAR t-cell therapy.
602 *British journal of haematology* (2021) 194:701–707. doi: 10.1111/bjh.17662

603 30. Johnson WT, McNerney KO, Frank MJ, Shah NN. How i treat HLH-like
604 toxicities following immune effector cell therapy. *Blood* (2026) doi:
605 10.1182/blood.2025032352

606 31. Ortí G, Dachy G, Graham CE, Peric Z, Alarcon A, Bufalo FD, Doglio M, Henter
607 J-I, Roddie C, Stewart O, et al. Less frequent complications following CAR t-cell
608 therapies: Hemophagocytic lymphohistiocytosis, graft-versus-host disease, thrombotic
609 microangiopathy, coagulation disorders and secondary malignancies: Best practice
610 recommendations from the EBMT practice harmonization and guidelines committee.
611 *Bone marrow transplantation* (2025) 60:751–758. doi: 10.1038/s41409-025-02567-5

612 32. Merli P, Quintarelli C, Strocchio L, Locatelli F. The role of interferon-gamma and
613 its signaling pathway in pediatric hematological disorders. *Pediatric blood & cancer*
614 (2021) 68:e28900. doi: 10.1002/pbc.28900

615 33. Sekine T, Galgano D, Casoni GP, Meeths M, Cron RQ, Bryceson YT. CD8 + t
616 cell biology in cytokine storm syndromes. *Advances in experimental medicine and*
617 *biology* (2024) 1448:129–144. doi: 10.1007/978-3-031-59815-9_10

618 34. DeFranco G, Siegler EL, Kenderian SS. The conflicting role of myeloid cells in
619 CAR-t cell therapy. *Cancer research* (2026) doi: 10.1158/0008-5472.CAN-25-4817

620 35. Rejeski K, Subklewe M, Locke FL. Recognizing, defining, and managing CAR-t
621 hematologic toxicities. *Hematology American Society of Hematology Education*
622 *Program* (2023) 2023:198–208. doi: 10.1182/hematology.2023000472

623 36. Walton ZE, Frigault MJ, Maus MV. Current and emerging pharmacotherapies for
624 cytokine release syndrome, neurotoxicity, and hemophagocytic
625 lymphohistiocytosis-like syndrome due to CAR t cell therapy. *Expert opinion on*
626 *pharmacotherapy* (2024) 25:263–279. doi: 10.1080/14656566.2024.2340738

627 37. Eichenauer DA, Rosée PL. [Treatment of hemophagocytic lymphohistiocytosis in
628 patients in the intensive care unit]. *Innere Medizin (Heidelberg, Germany)* (2023)
629 64:955–960. doi: 10.1007/s00108-023-01584-0

630 38. Holloway A, Ahmed S, Manson JJ. Does your unwell patient have
631 haemophagocytic lymphohistiocytosis? *British journal of hospital medicine (London,*
632 *England : 2005)* (2024) 85:1–12. doi: 10.12968/hmed.2023.0394

633 39. Donzelli L, Zullino V, Torelli GF, Propris MSD, Piazzolla M, Ruberto F, Martelli
634 M, Rocco AD. Managing treatment-emergent immune effector cell-associated
635 hemophagocytic lymphohistiocytosis-like syndrome following CAR-t cell therapy:
636 Acase-based review of the use of emapalumab. *Hematological oncology* (2026)
637 44:e70157. doi: 10.1002/hon.70157

638 40. Liang EC, Sidana S. Managing side effects: Guidance for use of immunotherapies
639 in multiple myeloma. *Hematology American Society of Hematology Education*
640 *Program* (2023) 2023:348–356. doi: 10.1182/hematology.2023000435

641 41. Zhang Y, Yang J, Xin H, Ai K, Yang M, Li Y, He Y. Chimeric antigen receptor
642 t-cell therapies related to immune effector cell-associated hemophagocytic
643 lymphohistiocytosis-like syndrome: Diagnosis, high-risk factors, and management.
644 *Chinese medical journal* (2026) doi: 10.1097/CM9.0000000000004066

645 42. Dharra R, Sharma AK, Datta S. Emerging aspects of cytokine storm in
646 COVID-19: The role of proinflammatory cytokines and therapeutic prospects.
647 *Cytokine* (2023) 169:156287. doi: 10.1016/j.cyto.2023.156287

648 43. Shokouhi S, Barati S, Kazeminia N, Jamali F, Roshan B, Sahraei Z. Evaluating
649 the elimination status of medications used for COVID-19 during hemoperfusion and
650 therapeutic plasma exchange: A review. *International immunopharmacology* (2021)
651 97:107707. doi: 10.1016/j.intimp.2021.107707

652 44. Hassaniazad M, Vahedi MS, Samimagham HR, Gharibzadeh A, Beyranvand S,
653 Abbasi H, Nikpoor AR. Improvement of clinical outcome, laboratory findings and
654 inflammatory cytokines levels using plasmapheresis therapy in severe COVID-19
655 cases. *Respiratory medicine* (2021) 189:106669. doi: 10.1016/j.rmed.2021.106669

656 45. Zhang J, Xie D, Tang M, Gong Q, Huang X, Li J, Xu S, Luo N, Sun H, Tan F.
657 Utilizing plasma exchange for severe cytokine release syndrome after CAR-t cell
658 therapy: Clinical experience and literature insights. *Frontiers in immunology* (2025)
659 16:1597512. doi: 10.3389/fimmu.2025.1597512

660 46. Pu Y, Zhao Y, Qi Y, Liu Y, Zhang M, Xiao X, Lyu H, Meng J, Zhu H, Xu K, et
661 al. Multi-centers experience using therapeutic plasma exchange for
662 corticosteroid/tocilizumab-refractory cytokine release syndrome following CAR-t
663 therapy. *International immunopharmacology* (2024) 130:111761. doi:
664 10.1016/j.intimp.2024.111761

665 47. Gluck WL, Callahan SP, Brevetta RA, Stenbit AE, Smith WM, Martin JC, Blenda
666 AV, Arce S, Edenfield WJ. Efficacy of therapeutic plasma exchange in the treatment
667 of penn class 3 and 4 cytokine release syndrome complicating COVID-19.
668 *Respiratory medicine* (2020) 175:106188. doi: 10.1016/j.rmed.2020.106188

669 48. Kamran SM, Mirza Z-E-H, Naseem A, Liaqat J, Fazal I, Alamgir W, Saeed F,
670 Saleem S, Nisar S, Yousaf MA, et al. Therapeutic plasma exchange for coronavirus
671 disease-2019 triggered cytokine release syndrome; a retrospective propensity matched
672 control study. *PloS one* (2021) 16:e0244853. doi: 10.1371/journal.pone.0244853

673 49. Fonseca-González G, Alamilla-Sánchez M, García-Macas V, Herrera-Acevedo J,
674 Villalobos-Brito M, Tapia-Rangel E, Maldonado-Tapia D, López-Mendoza M,
675 Cano-Cervantes JH, Orozco-Vázquez J, et al. Impact of plasmapheresis on severe
676 COVID-19. *Scientific reports* (2023) 13:163. doi: 10.1038/s41598-022-25930-8

677 50. Zheng X, Zhang S, Wu H, Xia J, Zheng K, Wang Y, Qin Y. Plasma exchange as
678 an effective treatment for cytokine release syndrome following t cell
679 receptor-engineered t cell immunotherapy: A case report. *Oncology letters* (2024)
680 28:607. doi: 10.3892/ol.2024.14740

681 51. Patidar GK, Land KJ, Vrielink H, Rahimi-Levene N, Dann EJ, Al-Humaidan H,
682 Spitalnik SL, Dhiman Y, So-Osman C, Hindawi SI. Understanding the role of
683 therapeutic plasma exchange in COVID-19: Preliminary guidance and practices. *Vox*
684 *sanguinis* (2021) 116:798–807. doi: 10.1111/vox.13067

685 52. Synnott D, O'Reilly D, Freitas DD, Naidoo J. **Cytokine release syndrome in**
686 **solid tumors**. *Cancer* (2025) 131:e70069. doi: 10.1002/cncr.70069

687 53. Carcillo JA, Shakoory B. Cytokine storm and sepsis-induced multiple organ
688 dysfunction syndrome. *Advances in experimental medicine and biology* (2024)
689 1448:441–457. doi: 10.1007/978-3-031-59815-9_30

690 54. Raval JS, Griggs JR, Romero AEM, Reyes C, Mertens S, Ornelas C, Marinaro L,
691 Rollins-Raval MA. Multiple consecutive daily therapeutic plasma exchange using
692 exclusively albumin replacement fluid in low bleeding risk patients is associated with
693 only rare and mild bleeds. *Transfusion* (2026) doi: 10.1111/trf.70159

694 55. Kohli R, Allen E, Platton S, Griffin J, Manson L, MacCallum P, Green L. Effect
695 on haemostasis of different replacement fluids during therapeutic plasma exchange-a
696 comparative multicentre observational study. *Journal of clinical apheresis* (2022)
697 37:534–543. doi: 10.1002/jca.22008

Figure 1.

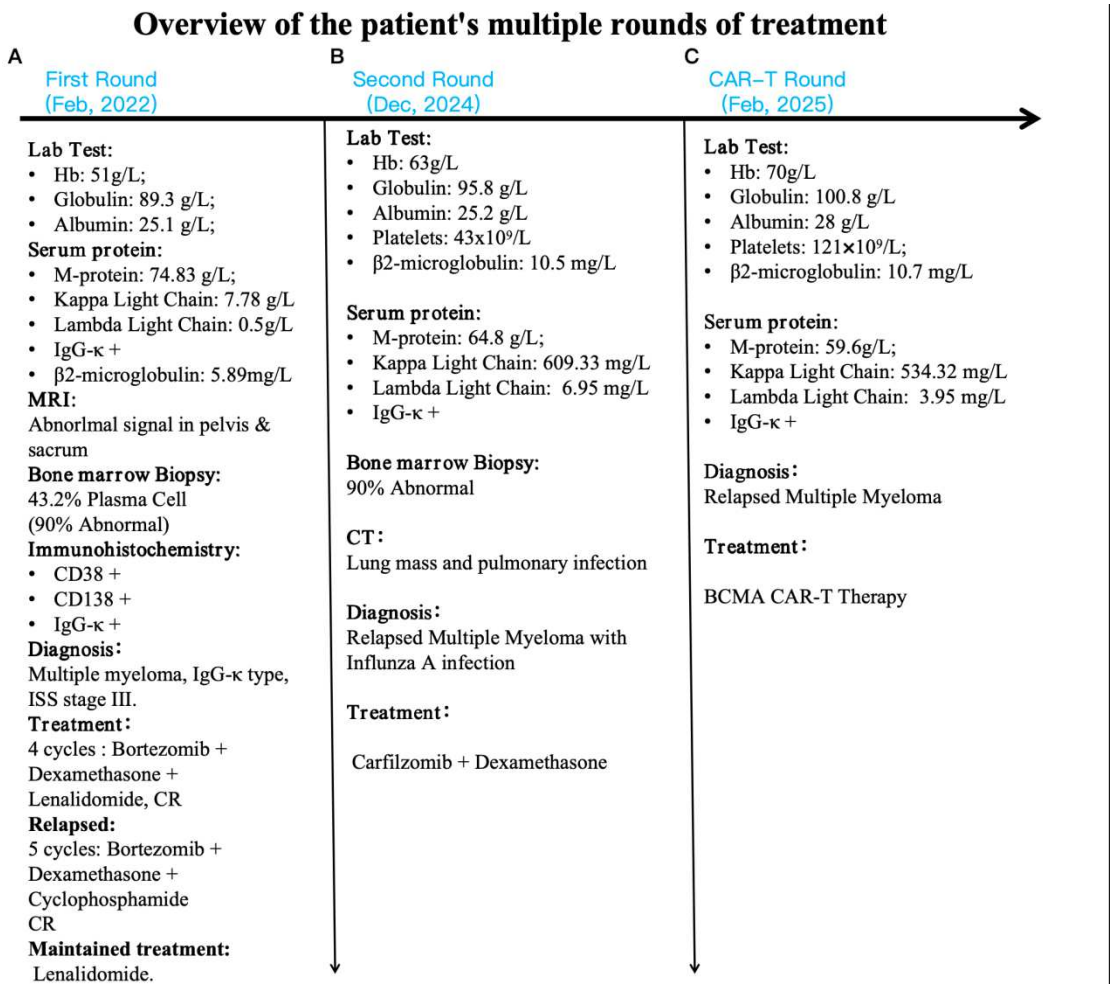


Figure 1. Clinical treatment timeline and disease status of the patient. A: First-line chemotherapy, re-remission after relapse, and maintenance therapy; B: Third relapse and pre-CAR-T therapy treatment; C: BCMA-CAR-T cell infusion and subsequent follow-up period.

Figure 2.

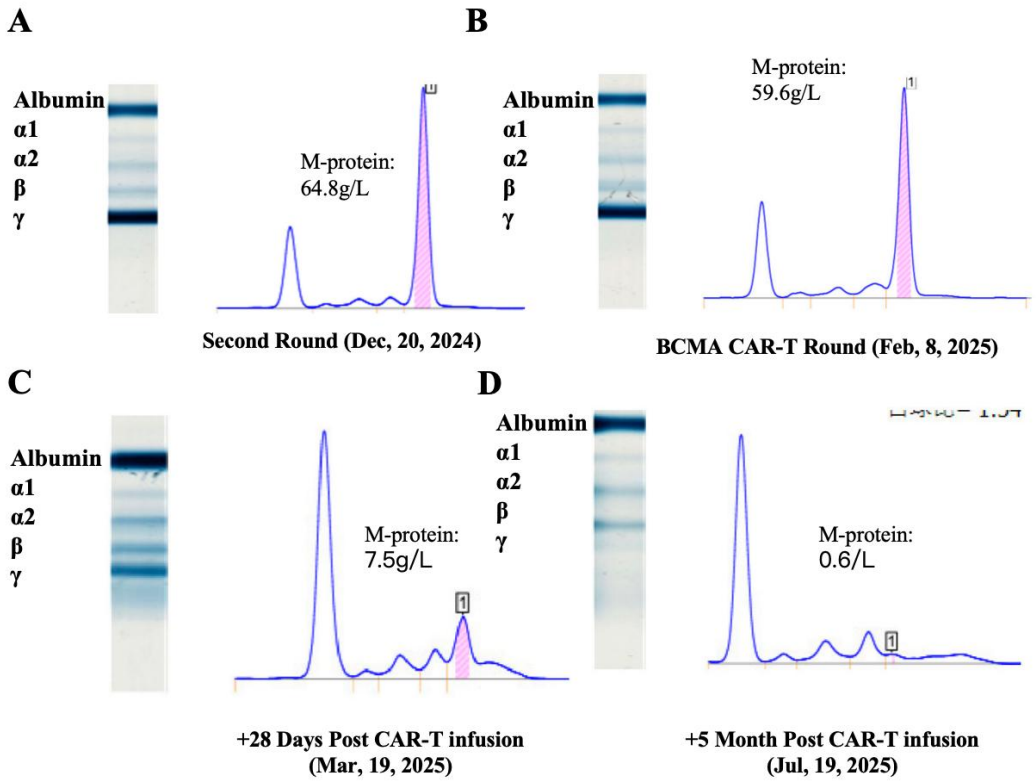


Figure 2. Serum protein electrophoresis results of the patient at multiple time points. A: At the second relapse (M-protein: 64.8g/L); B: At the third relapse (before CAR-T therapy, M-protein: 59.6g/L); C: At 28 days after CAR-T infusion(M-protien: 7.5g/L); D: At 5 months after CAR-T infusion (M-protein: 0.6g/L).

Figure 3.

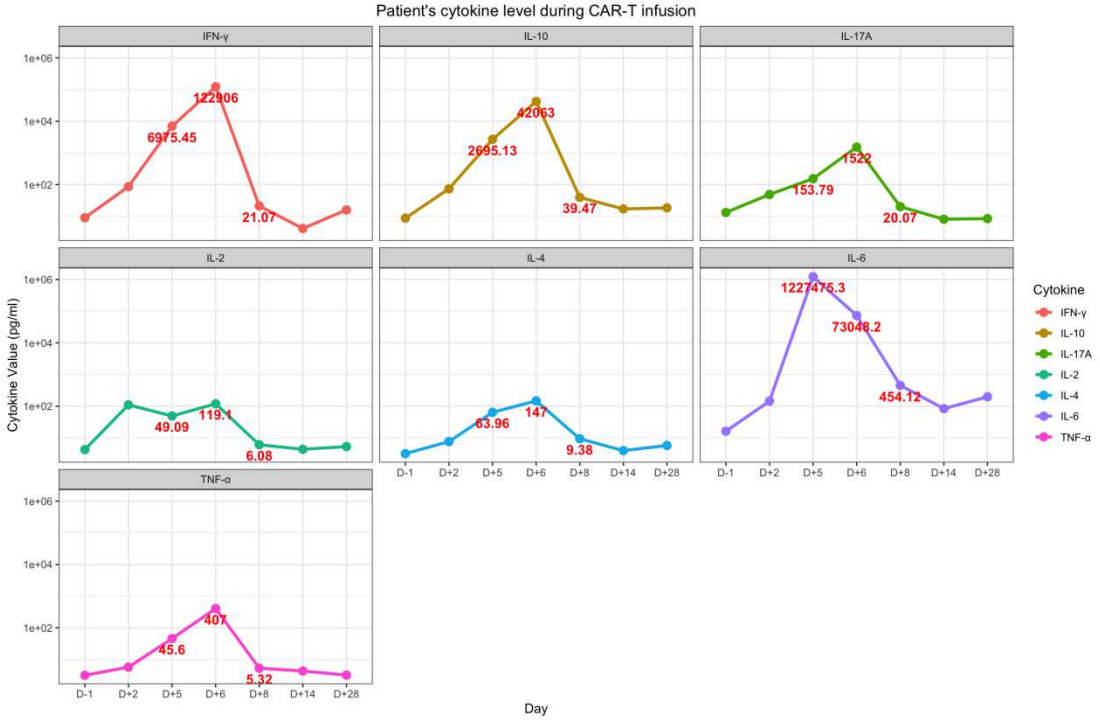


Figure 3. Dynamic changes in serum cytokine levels in the patient during CAR-T therapy. Levels of IFN- γ , IL-10, IL-17A, IL-2, IL-4, IL-6 and TNF- α were detected at D-1, D+2, D+5, D+6, D+8, D+14 and D+28 after CAR-T infusion. The red-labeled values represent the dynamic variation trends of cytokines before and after therapeutic plasma exchange (TPE) treatment.

Table 1. CAR-T Serial Monitoring of Biochemistry, Coagulation, and Complete Blood Count. (This table could be Supplementary Table)

Date			20250207	20250215	20250219	20250220	20250221	20250222	20250223	20250224	20250225	20250226	20250227	20250228	20250301	20250302	20250304	20250305	20250307	20250309	20250312	20250315	20250319
					d0 (CAR-T Infusion)	d1	d2	d3	d4	d5	d6	d7	d8	d9	d10	d11	d12	d13	d15	d17	d20	d23	d27
Project	Unit	Range																					
LDH	U/L	120-250	171.7	119	120.1	Undo	101	139.4	166	224	392	1299.9	615.2	602.9	486.9	327.1	212	226.9	140.4	89.5	129.7	129.7	188.5
FCT	ng/ml	<0.052	0.078	Undo	Undo	Undo	0.312	3.25	Undo	3.953	2.864	3.266	2.577	1.54	Undo	0.45	0.309	Undo	Undo	Undo	Undo	Undo	Undo
ESR	mm/h	0-20	117			Undo																	
CRP	mg/L	0-10	0.71	Undo	Undo	Undo	2.44	27.25	12.52	4.91	3.22	2.71	2.1	1.67	Undo	0.9	0.33	Undo	Undo	Undo	Undo	Undo	Undo
ALT	U/L	7-40	11.7	17	11.2	Undo	15	33.2	94	96	49	107.8	80.4	90.4	116.3	139.4	92	93.6	54.9	41.7	40.6	27.1	36.9
AST	U/L	15-35	12.4	14	10.9	Undo	14	17.3	31	35	47	109.3	66.3	67.7	122	89.4	42	38.3	12.9	12.7	14.3	13.1	15.7
GLB	g/L	20-40	87.3	100.8	91.8	Undo	64.4	74.7	67.9	61.1	49.8	42.4	39.7	39.7	38.2	45.2	36.1	40.5	32.7	28.3	33	30.2	30.6
ALB	g/L	40-55	28	28.5	26.8	Undo	35.9	22	20.7	22.5	30.5	30.1	31.8	32.7	32.7	33.9	35.4	37.1	35.6	31.4	37.5	34.9	37.7
DBIL	umol/L	0.4-6.8	2.2	1.3	1.99	Undo	1.9	2.4	5.3	20.8	24.8	37.34	42.11	62.1	74.45	60.27	36	33.02	26.81	18.67	19.56	13.48	11.72
IBIL	umol/L	0-17.39	5.25	3.9	3.44	Undo	4.4	3.49	10.6	21.7	26.3	21.08	24.59	37.36	45.27	13.24	39.1	21.64	19.53	13.46	14.49	12.28	13.63
GGT	U/L	7-45	23	25	21	Undo	35	119	376	568	425	430.6	374.5	581	809.8	880.6	755	723.7	507.4	374.4	306.6	245.1	222.3
BUN	mmol/L	2.5-6.4	6.97	9.3	5.41	Undo	7.25	7.58	8.13	9.89	13.58	22.89	25.61	26.54	23.64	16.28	14.79	12.82	10.59	8.02	7.94	6.03	6.93
CR	umol/L	50-105	57.9	84	79.9	Undo	92	84	85	104	106	132	118.7	106.2	88.4	78.6	55	58.2	64.3	69	61.1	56.9	53
β2MG	mg/L	1-3	6.51	10.7	12.37	Undo	Undo	13.49	13.1	18.9	20.5	21.23	19.52	5.87	11.61	7.54	5.2	Undo	3.92	3.37	2.8	2.72	3.11
PT	s	7.67-10.5	12.3	12.9	Undo	Undo	Undo	Undo	Undo	19.4	17.7	18.1	12.2	11.5	11.3	11.6	11.8	Undo	12	11.9	10.9	11.2	10.4
APTT	s	24.5-37.5	29	32.3	Undo	Undo	Undo	Undo	Undo	44.9	47.3	49	30.1	32.2	32.1	33.9	34.2	Undo	32.2	33.5	29.5	35.9	29.1
Fib	g/L	1.93-4.12	3	2.83	Undo	Undo	Undo	Undo	Undo	0.91	0.89	0.67	1.06	0.94	0.92	0.8	1.02	Undo	1.19	1.01	1.22	1.03	1.34
TT	s	14.5-19.2	18.8	18.1	Undo	Undo	Undo	Undo	Undo	22.4	23.7	30.9	21.2	23.1	22.3	23.9	19.8	Undo	19.4	19.5	18.4	20.2	17.9
DD	ug/L	0-500	350	230	Undo	Undo	Undo	Undo	Undo	6230	8420	24870	50990	34520	12250	7790	4450	Undo	3870	1600	770	570	690
PRO-BNP	pg/ml	0-1800	935.2	210.4	Undo	Undo	Undo	Undo	6706	Undo	Undo	14433	Undo	7827	Undo	Undo	2327	Undo	Undo	Undo	1414	Undo	Undo
Ferrtin	ug/L	10-291	Undo	Undo	Undo	Undo	Undo	Undo	> 2000	Undo	Undo	Undo	Undo	Undo	Undo	Undo	Undo	Undo	Undo	Undo	Undo	Undo	Undo
WBC	1e9/L	3.5-9.5	5	2.79	1.05	0.71	Undo	0.63	0.38	0.15	0.18	0.85	1.83	2.37	1.99	1.07	1.09	0.9	0.94	0.69	1.89	1.25	2.32
NeutH	1e9/L	1.80-6.30	3.91	1.63	0.89	0.68	Undo	0.6	0.29	0.05	0.03	0.06	0.16	0.42	0.54	0.36	0.43	0.46	0.35	0.22	1.26	0.77	1.7
LymphH	1e9/L	1.10-3.20	0.91	0.99	0.09	0.02	Undo	0.03	0.08	0.1	0.15	0.78	1.64	1.92	1.42	0.7	0.64	0.43	0.57	0.46	0.57	0.34	0.33
MonoH	1e9/L	0.10-0.60	0.18	0.14	0	0.02	Undo	0	0	0	0	0.01	0.03	0.03	0.02	0.01	0.02	0.01	0.02	0.01	0.06	0.13	0.26
RBC	1e12/L	4.30-5.80	3	2.68	2.34	2.02	Undo	2.12	2.12	2.4	2.34	2.09	2.47	3.02	2.96	2.71	2.81	2.69	2.39	1.89	2.31	2.32	2.71
Hb	g/L	130-175	93	84	72	63	Undo	67	67	86	74	67	78	95	92	88	88	83	76	59	71	72	86
PLT	1e9/L	125-350	186	121	99	80	Undo	46	31	18	14	13	17	17	15	7	18	19	8	0	22	15	57
soulbe CD25	u/ml	223-710								60319													

Table.2 The patient's CAR-T number post infusion

Date	Post-infusion Day	Copy number (Copies/μg Genomic DNA)	T Cell (10^6/L)	CAR-T Cell (10^6/L)
2025.02.25	D6	170375	91.9	8.4
2025.03.05	D14	356143	194.0	48.6
2025.03.13	D22	113750	354.7	77.6
2025.03.19	D28	64431	367.7	81.2
2025.04.02	D42	40403	415.4	68.4
2025.04.15	D55	5664	1692.6	91.4
2025.05.06	D76	NA	2312.2	0.0