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Novel SRRM2-Targeted CAR-T cells in a Relapsed and Refractory Multiple Myeloma Patient with Extramedullary Diseases: a case report

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Case Report

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Abstract

Background: Multiple myeloma (MM) is a difficult-to-treat blood cancer, especially in relapsed/refractory cases with extramedullary disease. Chimeric antigen receptor T-cell (CAR-T) therapy targeting B-cell maturation antigen (BCMA) has shown promise but has limitations, such as severe side effects.

Case presentation: This study describes a patient with relapsed/refractory MM and extramedullary disease treated with CAR-T therapy targeting serine/arginine repetitive matrix 2 (SRRM2), a protein highly expressed on MM cells. After treatment, the patient achieved a very good partial response (VGPR) by day 28, with reduced extramedullary lesions. However, the disease returned by day 90. The therapy was safe, causing only mild side effects (grade 1 cytokine release syndrome) and no nerve damage, unlike BCMA-targeted therapies.

Conclusions: The main issue was the therapy's short duration of effect, suggesting a need for better ways to keep CAR-T cells active longer.SRRM2 could be a new target for MM treatment, especially in tough cases, but more research is needed.

1. Introduction

Multiple myeloma (MM) is an incurable hematological malignancy characterized by the clonal proliferation of plasma cells, leading to the accumulation of monoclonal immunoglobulins and end-organ damage. Despite significant advances in treatment options over the past two decades, a substantial proportion of patients eventually develop relapsed or refractory disease that is associated with a dismal prognosis[1].

The introduction of chimeric antigen receptor (CAR) T-cell therapy has revolutionized the management of relapsed/refractory(r/r) B-cell malignancies, including multiple myeloma[2]. CAR-T cell therapy targeting B-cell maturation antigen (BCMA) has shown promise. However, relapses remain a challenge, and developing CAR-T therapies targeting new antigens is essential[3, 4].

Serine/arginine repetitive matrix 2 (SRRM2) locates generally in the nucleus of normal human cells, rich in serine/arginine (RS) repeat sequences, and mainly plays a role in selective splicing of cells. Previous research found SRRM2 can be translocated to the cell membrane for expression due to abnormal metabolism of tumor cells and endoplasmic reticulum stress during tumor occurrence, and may be used as a tumor marker and immunotherapy target[5]. In our previous research, high SRRM2 expression on plasma cells was associated with higher plasma cell infiltration, high-risk mSMART 3.0 risk stratification, cytogenetic abnormalities, more relapses, and fewer autologous stem cell transplant treatments in MM patients[6]. SRRM2 serve as a novel biomarker and immunotherapeutic target for MM patients.

In this report, we describe a 60-year-old patient with relapsed/refractory(r/r) IgD-λ multiple myeloma (MM) who was successfully treated with a genome-edited SRRM2-targeted chimeric antigen receptor T (SRRM2 CAR-T) cell therapy.

2. Case presentation

A 60-year-old male from China with a 11-year history of multiple myeloma (MM) was referred to our hematology department in 2023 due to progressive fatigue and generalized osteodynia. The patient was initially diagnosed with IgD-λ MM in May 2012, confirmed by bone marrow aspiration, immunofixation electrophoresis, and additional diagnostic testing at a local hospital. After the diagnosis, he underwent six cycles of the VTD regimen (bortezomib, thalidomide, dexamethasone) and achieved the first complete remission (CR1), followed by consolidation with autologous hematopoietic stem cell transplantation (auto-HSCT) in 2013 and maintenance therapy with thalidomide.

However, the disease relapsed twice in 2020 and 2021, despite receiving multiple lines of therapy, including carfilzomib (a proteasome inhibitor), pomalidomide (an immunomodulatory drug), and daratumumab (an anti-CD38 monoclonal antibody). Unfortunately, the patient's disease did not respond to subsequent treatments, and progression was documented (Fig. 1A). Due to challenges in accessing newer therapies such as BCMA CAR-T cells, selective inhibitors of nuclear export (SINEs), and T-cell redirecting bispecific antibodies, the patient was referred to our institution seeking eligibility for clinical trial treatment.

Upon admission, physical examination revealed a pale appearance and occasional grimacing due to pain, with significant tenderness noted in the rib area. Laboratory results indicated leukopenia (white blood cell count, WBC, 3.65×10^9/L), anemia (hemoglobin, Hb, 67 g/L), and thrombocytopenia (platelet count, PLT, 20×10^9/L). Immunofixation electrophoresis confirmed the presence of IgD and λ light chains in both serum and urine. The free light chain (FLC) assay showed an elevated λ light chain level (1590 mg/L) and a reduced κ light chain level (446 mg/L), with a κ/λ ratio of 0.28, consistent with active disease. Bone marrow aspiration, analyzed by flow cytometry, revealed 2.5% plasma cells, while morphological examination indicated 5.5% plasma cells (Fig. 1B-C). Histopathological examination of a bone matrix biopsy demonstrated significant infiltration of abnormal plasma cells within the bone trabeculae, accounting for approximately 90% of nucleated cells (Fig. 1D).

Positron emission tomography-computed tomography (PET-CT) revealed multiple heterogeneous bone lesions involving the skull, vertebrae, bilateral clavicles, ribs, pelvis, and limbs, with associated soft tissue masses near the spinal cord and bilateral pleura (Fig. 1E-G). Ultrasound-guided biopsy of a pleural soft tissue mass confirmed the presence of extramedullary plasma cell tumor, with immunohistochemistry showing positive expression of CD38, CD138, MUM1, and Ki-67 staining in more than 60% of cells (Fig. 1H).

Based on the clinical presentation, laboratory findings, and medical history, the patient was diagnosed with relapsed/refractory multiple myeloma (r/r MM) with extramedullary disease (EMD). Given the failure of prior therapies and the novel targeting approach, the patient was enrolled in an investigator-initiated clinical trial registered at the Chinese Clinical Trial Registry (ChiCTR2000040368). The protocol of this research was approved by the Ethics Committee of the Second Affiliated Hospital of Anhui Medical University (NO. YJ-YX2021-139).

Pre-treatment analysis revealed that SRRM2 was widely expressed on malignant plasma cells, with minimal expression on neutrophils, lymphocytes, and monocytes (Fig. 2A). The SRRM2-targeted CAR construct was engineered with an anti-human SRRM2 single-chain variable fragment (scFv), linked to a CD8 hinge and transmembrane domain, as well as intracellular 4-1BB co-stimulatory and CD3ζ activation domains (Fig. 2B). $CD3^+$ T cells were isolated from autologous T cells using magnetic bead and transfected with the anti-SRRM2 CAR.

The patient underwent lymphodepleting chemotherapy of FC with fludarabine (30 mg/m²/day on days − 5 to -3) and cyclophosphamide (500 mg/m²/day on days − 5 and − 3). On Day 0, SRRM2-targeted CAR-T cells (1.06×10^6 cells/kg) were infused (Fig. 2C), with a transfection efficiency of 32.71% (Fig. 2D).

Post-infusion monitoring revealed rapid expansion of CAR-positive cells, which peaked at 23.26% on Day 21, then gradually declined to 17.38% at Day 28 and 7.39% at Day 60 (Fig. 3A-B). Corresponding with CAR-T cell expansion, CT imaging revealed the complete disappearance of the pleural mass (Fig. 3C). A follow-up bone marrow aspiration was performed, and compared to pre-treatment results, flow cytometry, morphology, and bone marrow biopsy all indicated a significant reduction or complete disappearance of abnormal tumor cells by Day 28(Fig. 3D). By Day 21, there was notable relief of osteodynia. The patient's bone pain significantly improved by Day 60 (Fig. 3E).

On Day 3 post-infusion, the patient developed fever (above 38°C) and elevated levels of IL-6, and IL-8, consistent with grade 1 cytokine release syndrome (CRS) (Fig. 3F-H). On Day 28, the patient’s bone pain was nearly resolved, and both serum and urine λ light chain levels had decreased significantly, with a normalization of the λ/κ ratio (Fig. 3I-J). Immunoglobulin levels, hemoglobin, and platelet count also gradually improved (Fig. 3K-L). Due to technical limitations, serum IgD levels could not be accurately measured. According to the International Myeloma Working Group (IMWG) response criteria[7], the patient achieved a Very Good Partial Response (VGPR) with the significantly decreased level of FLC.

At the 90-day follow-up, the patient exhibited complete depletion of CAR-T cells, and tumor relapse was observed, with flow cytometry detecting 32.1% malignant plasma cells in bone marrow. In response, the patient underwent CAR-T antibody immunogenicity testing, which yielded negative results. Consequently, the patient received a second infusion of SRRM2-targeted CAR-T cells (2.33×10^6 cells/kg), leading to a reduction in plasma cells to 5.6%, indicating partial remission (PR). Despite receiving subsequent salvage therapies, the patient's condition deteriorated, and he transitioned to palliative care. Unfortunately, the patient ultimately succumbed to COVID-19 infection. Nonetheless, the patient survived for more than 18 months following the initial SRRM2 CAR-T infusion, highlighting the potential long-term clinical benefits of this innovative targeted therapy, even in cases of limited sustained remission.

3. Discussion

This case represents the first reported clinical application of SRRM2-targeted CAR-T therapy in a patient with relapsed/refractory MM and extramedullary disease. The initial achievement of VGPR, with

significant reductions in both bone marrow and extramedullary lesions, suggests SRRM2 may serve as a novel therapeutic target for MM. The high expression of SRRM2 on malignant plasma cells and its low presence on normal cells likely contribute to its strong specificity and favorable safety profile. The patient experienced only mild CRS, in stark contrast to BCMA-targeted CAR-T therapies, which frequently report severe CRS rates of up to 84% and a notable incidence of neurotoxicity, possibly due to BCMA expression on normal B cells and other tissues[8].

The rapid decline of CAR-T cells after day 28, dropping from a peak of 23.26% to 7.39% by day 60, likely underlies the relapse observed at day 90. This highlights the critical need to enhance the long-term survival of CAR-T cells, potentially through dual-targeting strategies or genetic modifications to optimize T-cell function. Additionally, the patient's extramedullary disease, a known poor prognostic factor in MM, may have contributed to relapse, as EMD often harbors more aggressive clones that could develop resistance to single-target therapies.

Despite the relapse, the patient survived over 18 months following the initial infusion, indicating potential clinical value of SRRM2-targeted CAR-T therapy in high-risk MM patients. Compared to BCMA-targeted approaches, SRRM2 therapy exhibited milder side effects and superior early efficacy, particularly in managing extramedullary disease. Future research should focus on: (1) improving CAR-T cell persistence, such as anti-apoptotic gene modifications; (2) exploring combination therapies, such as pairing with immune checkpoint inhibitors or bispecific antibodies, to address EMD challenges; and (3) conducting larger clinical trials to validate SRRM2's efficacy in MM, especially in patients failing BCMA-targeted treatments.

4. Conclusion

In conclusion, SRRM2-targeted CAR-T therapy offers advantages in safety, specificity, and initial efficacy, particularly for patients with extramedullary disease. Although relapse remains a hurdle, technical refinements and combination strategies could position this approach as a valuable new option for relapsed/refractory MM.

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Anhui Medical University with the approval number: NO. YX2021-139. The trial was prospectively registered on the Chinese Clinical Trial Registry (ChiCTR, http://www.chictr.org.cn) under registration number ChiCTR2000040368 on 28 November 2020. All patients provided written informed consent to participate in the study.

Consent for publication

Written informed consent was obtained from the patient's next of kin for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Data availability

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

Competing interests

The authors declare that they have no competing interests.

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Author contributions

ZW: Writing – review & editing, Writing – original draft, Investigation, Data curation, Resources. ZG: Investigation, Data curation, Resources. FW: Writing – review & editing, Writing – original draft. HW: Investigation, Data curation, Resources. YL: Investigation, Data curation, Resources. ZL: Investigation, Data curation, Resources. LL: Conceptualization, Methodology. CL: Investigation, Data curation, Resources. XL: Investigation, Data curation, Resources. LT: Investigation, Data curation, Resources. KG: Conceptualization, Methodology. JG: Investigation, Data curation, Resources. RZ: Conceptualization, Methodology. ZZ: Conceptualization, Methodology, Funding acquisition. All authors read and approved the final version.

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Figures

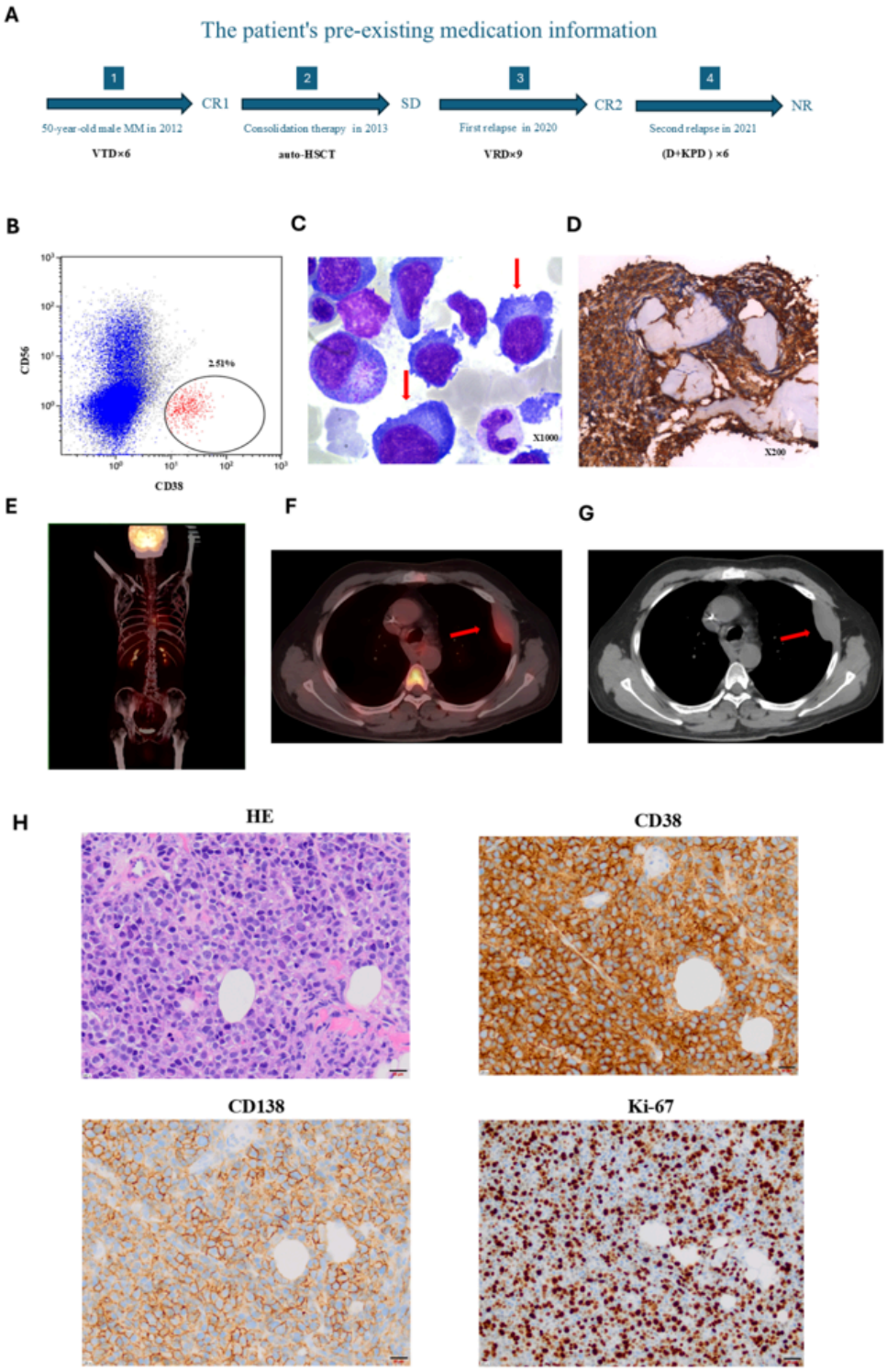


Figure 1

Clinical Features and Diagnostic Data of a Relapsed/Refractory Multiple Myeloma Patient

A: Schematic of the patient's treatment history. Diagnosed with MM in 2012, the patient achieved complete response (CR1) after 6 cycles of VTD (bortezomib, thalidomide, dexamethasone) regimen chemotherapy and underwent auto-HSCT in 2013, followed by thalidomide maintenance. The first

relapse happened in 2020 and treated with 9 cycles of VRD (bortezomib, lenalidomide, dexamethasone) regimen chemotherapy, achieving CR2 with lenalidomide maintenance. The disease relapsed again in 2021, and received 6 cycles of D+KPD (daratumumab, carfilzomib, pomalidomide, dexamethasone) regimen chemotherapy resulted in no response (NR).

B: Flow cytometry analysis showing 2.5% plasma cells in the bone marrow.

C: Bone marrow aspirate morphology showing an increased number of plasma cells (arrows), with 5.5% plasma cells observed under microscopic examination.

D: Immunohistochemistry of bone matrix biopsy showing significant plasma cell infiltration in the bone trabeculae. Approximately 90% of the nucleated cells in the bone matrix were abnormal plasma cells.

E: Positron emission tomography-computed tomography (PET-CT) showing multiple heterogeneous bone lesions involving the skull, vertebrae, clavicles, ribs, pelvis, and limbs. Soft tissue masses near the spinal cord and bilateral pleura are also visible.

F-G: PET-CT scans showing heterogeneous lesions in the rib and chest area, with highlighted soft tissue masses surrounding the spinal cord (red arrows), confirming the presence of extramedullary disease.

H: Ultrasound-guided biopsy of pleural soft tissue mass showing extramedullary plasma cell disease. Immunohistochemical staining reveals positive expression of CD38, CD138, and Ki-67 (more than 60% of cells) in the tumor cells, confirming plasma cell neoplasm.

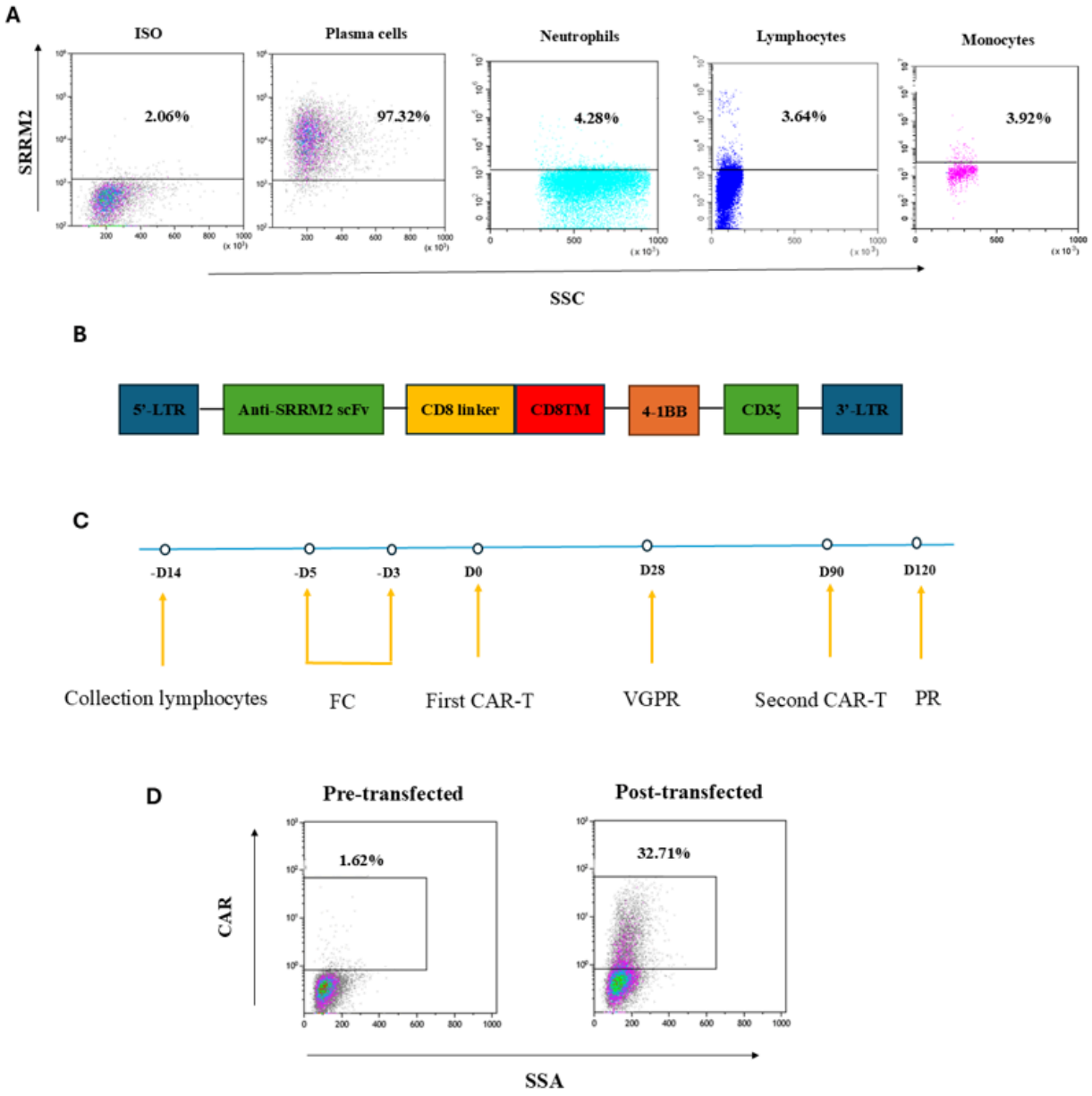


Figure 2

SRRM2-Targeted CAR-T Cell Therapy: Pre-treatment Analysis, CAR Design, and Expansion

A:Flow cytometry analysis before treatment showing SRRM2 expression on various immune cell populations. Malignant plasma cells demonstrate high expression of SRRM2 (97.32%), while neutrophils, lymphocytes, and monocytes exhibit minimal expression (4.28%, 3.64%, and 3.92%, respectively).

B:Schematic representation of the SRRM2-targeted CAR construct.

C:Treatment timeline from lymphocyte collection to infusion of SRRM2-targeted CAR-T cells. Lymphocyte collection was performed on Day -14. The patient then underwent lymphodepleting chemotherapy with fludarabine and cyclophosphamide from Day -5 to Day -3. On Day 0, autologous T

cells, transfected with SRRM2-targeted CAR, were infused. By Day 28, the patient achieved a very good partial response (VGPR). However, relapse occurred by Day 90, prompting a second infusion of SRRM2-targeted CAR-T cells, which resulted in partial remission.

D:Flow cytometry analysis of CAR-T cell expansion. On the left, sorted autologous T cells show 1.62% CAR-positive cells before expansion. On the right, following CAR-T cell expansion, 32.71% of T cells are CAR-positive.

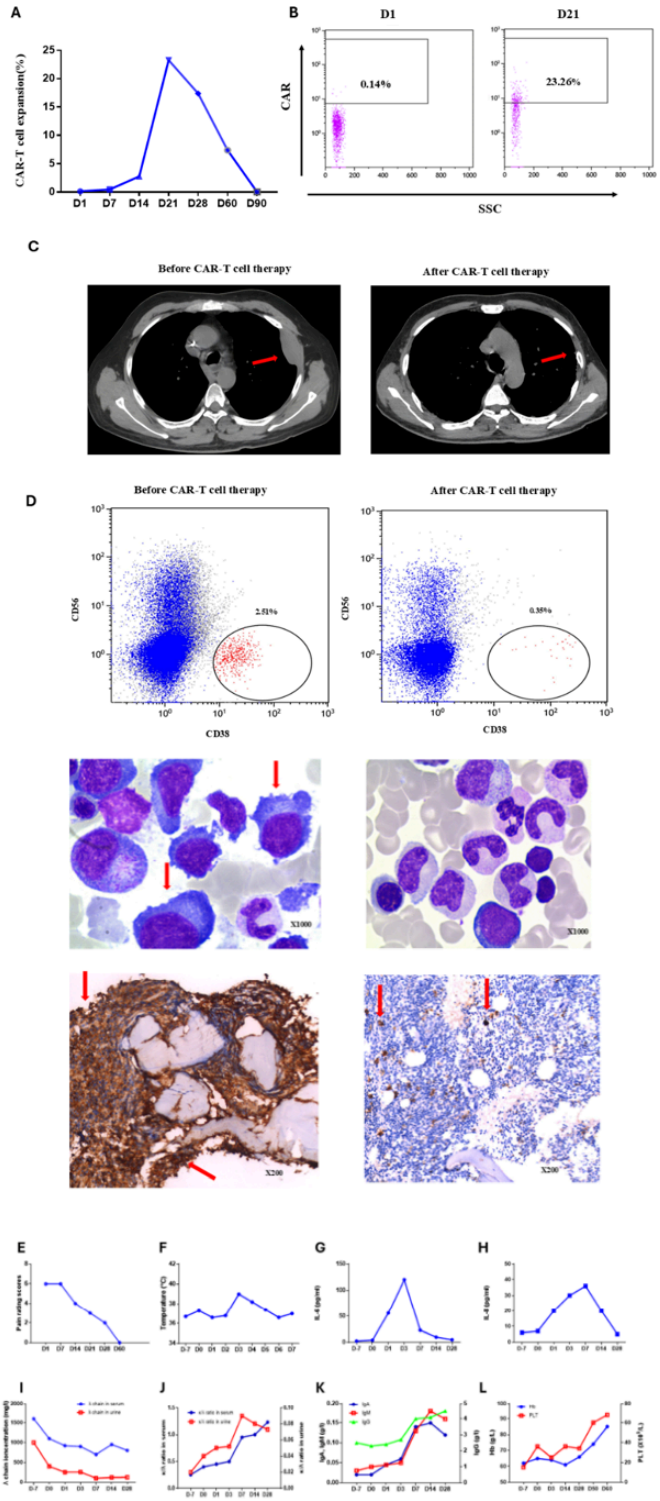


Figure 3

Post-Infusion Monitoring and Clinical Response to SRRM2-Targeted CAR-T Therapy

A:CAR-T cell expansion over time, as measured by flow cytometry. The percentage of CAR-positive cells peaked at 23.26% on Day 21, followed by a gradual decline to 17.38% on Day 28 and 7.39% on Day 60.

B:Flow cytometry analysis showing CAR-positive cells on Day 1 (0.14%) and Day 21 (23.26%).

C:CT imaging of the chest before and after CAR-T cell therapy. On the left, pre-treatment imaging shows a pleural mass (red arrow), which completely disappears after treatment (right).

D:Bone marrow analysis before and after CAR-T cell therapy. Before treatment, flow cytometry and bone marrow biopsy revealed the presence of abnormal tumor cells (arrows in the morphology and immunohistochemistry images). After treatment, a significant reduction or complete disappearance of these tumor cells was observed by Day 28, reflecting the therapeutic effect of the CAR-T cells.

E:Changes in pain levels over time.

F:Temperature trends post-infusion, showing the onset of fever (above 38°C) on Day 3.

G-H: Serum levels of IL-6 and IL-8, showing a sharp rise post-infusion and a return to baseline by Day 28.

I-J: Changes in serum and urine λ light chains and the λ/κ ratio over time. By Day 28, there was a significant reduction in λ light chains, and the λ/κ ratio normalized.

K-L: Immunoglobulin levels (IgA, IgG, IgM), hemoglobin, and platelet count gradually improved over time.