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Letter

Long-term adoptive immunotherapy achieves complete response and bone lesion repair in an elderly patient with macrofocal multiple myeloma☆

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Macrofocal multiple myeloma (MFMM) is a distinct entity within multiple myeloma (MM) characterized by the presence of multiple lytic bone lesions, with clonal plasma cells in the bone marrow accounting for <10%.[1,2] The revised 2022 Chinese guidelines for the diagnosis and treatment of MM state: in patients with <10% clonal plasma cells in multi-site bone marrow aspirates, attention should be given to MFMM, characterized by single or multiple bone destructive lesions, often accompanied by involvement of surrounding soft tissues or lymph nodes.[3] Research is limited regarding the long-term use of adoptive immunotherapy for the treatment of MFMM; as such, we report herein the case of an elderly patient diagnosed with MFMM who experienced severe chemotherapy side effects and subsequently underwent adoptive immunotherapy. Remarkably, the patient benefited from 14 years of treatment [Figure 1A].

In April 2007, a 67-year-old man was diagnosed via computed tomography (CT) with expansive lytic destruction and localized swelling of the soft tissue on the outer aspect of the left ninth rib. Positron emission tomography (PET)-CT revealed a localized area of increased fluorodeoxyglucose (FDG) metabolism in the posterior aspect of the left ninth rib with a maximum standardized uptake value of approximately 8.5. CT-guided biopsy of the mass revealed a plasma cell myeloma. The patient did not present with fever, night sweats, or weight loss. Immunoglobulin (Ig)G was 19.8 g/L, Igκ light chain was 4.7 g/L, and the remaining Ig levels were within the normal range. Routine blood tests; renal function tests; lactate dehydrogenase, blood calcium, and serum albumin levels; serum protein electrophoresis; and blood and urine immunofixation electrophoresis showed no abnormalities. Biopsy and aspiration of the posterior-superior iliac spine did not reveal any marrow cells indicative of myeloma. In May 2007, the patient underwent surgical resection of the ninth rib, and a postoperative biopsy revealed a plasmacytoma measuring 4 cm × 3 cm × 1.5 cm. Immunohistochemical staining showed results for κ (+++), λ (focally+), CD38 (++), CD138 (+), CD79α (−), and Ki-67 (+,<25%). The patient was clinically diagnosed with solitary bone plasmacytoma. However, no further treatment plans were proposed. By March 2008, the patient experienced mild tenderness over the left eighth rib. PET-CT revealed a slight increase in uptake, a fracture in the left eighth rib, and increased uptake in the right femoral neck. Compared with the spinal magnetic resonance imaging (MRI) examination in 2007, spinal MRI revealed a clearly round signal with a diameter of approximately 1.0 cm at the T9 vertebra and similar signals with a maximum diameter of 2.1 cm at the L3 and L5 vertebrae. Dynamic postoperative monitoring of humoral immunity revealed an initial decrease in IgG and Ig lambda light chain (LC) levels. Subsequently, there were progressive increases, reaching maximum values of 20.7 g/L and 4.9 g/L, respectively. Additionally, routine blood tests; renal function tests; lactate dehydrogenase, blood calcium, and serum albumin levels; serum protein electrophoresis; and blood and urine immunofixation

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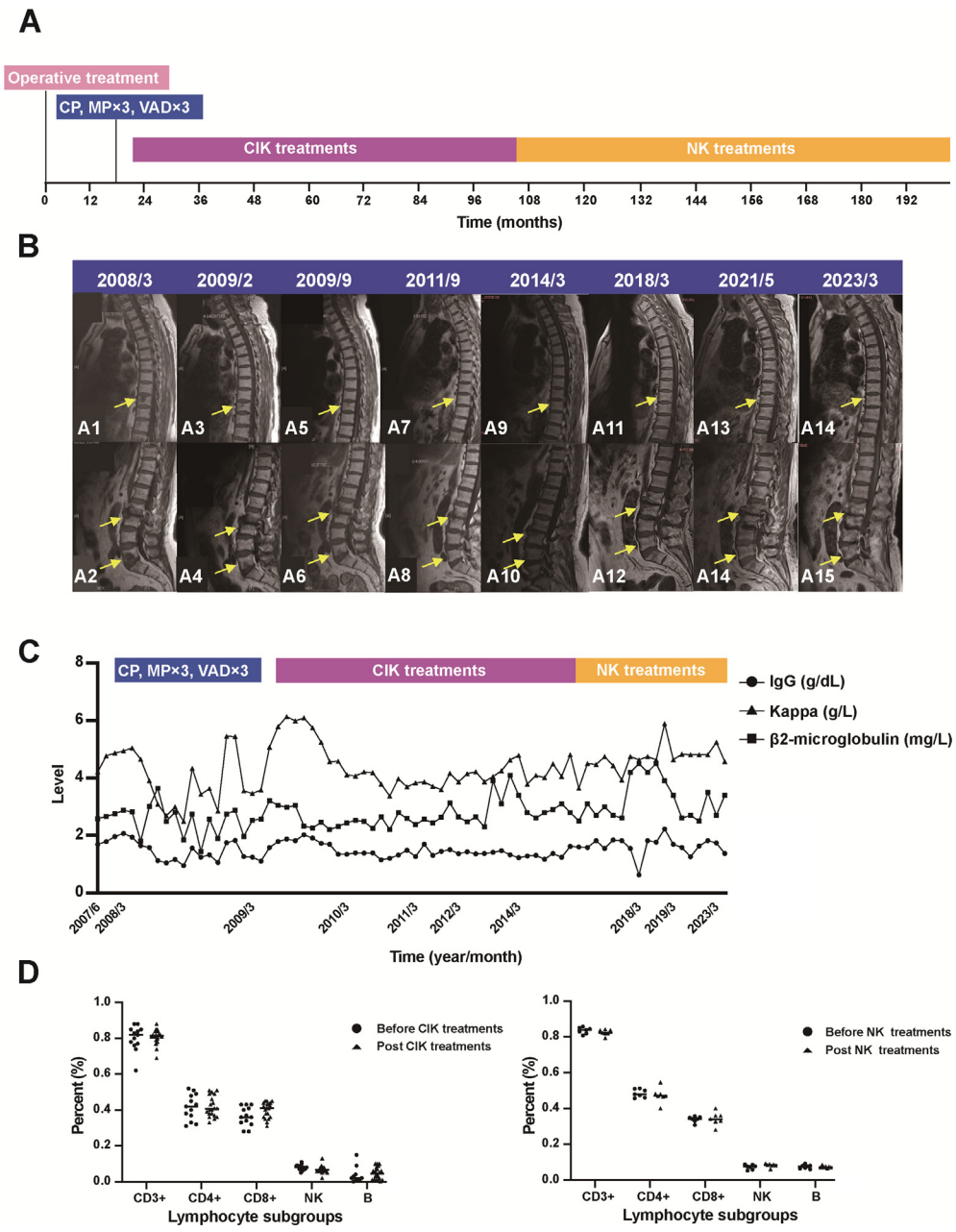

Figure 1. The changes in laboratory parameters and imaging findings during the course of the disease are shown. (A) Treatment timeline. (B) Regular spinal and pelvic magnetic resonance imaging (MRI) examinations showed that, after 10 cycles of CIK cell therapy, the original multiple lytic lesions had gradually diminished, with signs of gradual repair emerging. By the 21st treatment cycle, most of the bone destruction had essentially disappeared, and significant repair had occurred. Importantly, no new lytic lesions appeared throughout the treatment course. T1-weighted magnetic resonance images of the thoracic spine, lumbar spine, and femoral neck were taken at eight different time points corresponding to various stages of the disease: disease progression (March 2008), post-chemotherapy (February 2009), after eight courses of CIK therapy (September 2009), after 21 courses of CIK therapy (September 2011), after 51 courses of CIK therapy (March 2014), after 21 courses of NK therapy (March 2018), after 59 courses of NK therapy (May 2021), and after 81 courses of NK therapy (March 2023). (C) Fluctuation of serum immunoglobulin (Ig)G, β2-microglobulin, and κ chain during the course of the disease. (D) Lymphocyte subset monitoring showed an increasing trend in CD8+ T and B cells after CIK cell therapy ($P > 0.05$) and an elevated trend in NK cells after NK cell therapy ($P > 0.05$). CIK: Cytokine-induced killer; CP: Cyclophosphamide and prednisone; Ig: Immunoglobulin; MP: Melphalan and prednisone; MRI: Magnetic resonance imaging; NK: Natural killer; VAD: Vincristine, doxorubicin liposome, and dexamethasone.

electrophoresis revealed no abnormalities. Bone marrow biopsy revealed 2% plasma cells without abnormal morphology. After consultation and evaluation by multiple expert hematologists, the patient was diagnosed with postoperative disease progression. The clinical diagnosis was multiple solitary plasmacytomas of the bone (bone MSPs), also known as MFMM (revised according to the guidelines). To control disease progression, treatment was administered according to the protocol for MM. From March 2008 to August 2009, the patient underwent chemotherapy, which consisted of one cycle of the cyclophosphamide and prednisone (CP) regimen, three cycles of the melphalan and prednisone (MP) regimen, and three cycles of the vincristine, doxorubicin liposome, and dexamethasone (VAD) regimen. Lenalidomide was administered between August 2008 and August 2009. A year after therapy, the patient developed grade II drug-related toxicities, which manifested as recurrent oral and conjunctival inflammation, frequent upper respiratory tract infections, and uncontrolled hypertension. Partial response (PR) was achieved. The patient reported a decline in quality of life. Given the risk of mortality, the patient declined allogeneic stem cell transplantation. Starting in March 2009, he received monthly autologous cytokine-induced killer (CIK) cell immunotherapy, and from March 2009 to May 2016, he underwent 86 cycles.

Regular spinal and pelvic MRI examinations showed that, after 10 cycles of CIK cell therapy, the original multiple lytic lesions gradually diminished, with emerging signs of gradual repair. By the 21st treatment cycle, most of the bone destruction had essentially disappeared, and significant repair had occurred [Figure 1B]. Importantly, no new lytic lesions were observed during treatment. After six cycles of CIK cell therapy, the patient's Ig levels returned to normal, and the previous chemotherapy-related side effects subsided [Figure 1C]. Since then, the patient has remained infection-free. In June 2016, owing to adjustments in the hospital's tumor laboratory projects, he was transitioned to monthly autologous natural killer (NK) cell immunotherapy; between June 2016 and July 2023, the patient received 85 cycles. In subsequent follow-ups, he reported controlled blood pressure, increased energy levels, and an enhanced ability to engage in daily activities. At 83 years of age, the patient had

undergone consistent autologous adoptive immunotherapy for >14 years. Improvement was also observed in lymphocyte subsets [Figure 1D].

The steps of CIK cell therapy were as follows: before each treatment, 50 mL of venous blood was collected from the patient on an empty stomach. CIK cells were generated through the cultivation of steady-state isolated products with a cultivation period of 16–19 days; the specific procedures have been described previously.[4] Prior to infusion, CIK cells were required to meet the following criteria: leukemia cell proportion <0.01%, CD3-positive cell proportion >75%, and cell viability confirmed by trypan blue staining, with viability >95%. After the completion of cultivation, CIK cell infusion was performed over a 2-day period in each treatment cycle. The steps of NK cell therapy were as follows: before each treatment, 60 mL of venous blood was collected from the patient on an empty stomach. NK cells were generated through the cultivation of steady-state isolated products over a cultivation period of 14 days. The determination of antitumor cell activity involved flow cytometry to detect cellular granule enzymes and perforin expression. The cell infusion quantity was 5×10^9.

We observed that the application of CIK and NK cell therapies restored bone damage caused by giant lesion-type MM. Therefore, we conducted a literature search to determine why CIK and NK cells promoted bone repair. Previous studies demonstrated that bone fracture healing is controlled by the immune system. During the bone-healing process, immune cells infiltrate the hematoma and release cytokines that participate in the repair of bone fractures. CIK cells, due to their characteristic inclusion of both T lymphocytes and NK cells, can simultaneously utilize these two immune mechanisms. Könnecke et al.[5] found that bone fracture healing was regulated by T cells, which are observed at the injury site during both the early and late phases of the healing process. Nam et al.[6] reported that Rag1−/− mice lacking T and B cells exhibited impaired bone fracture healing compared to wild-type mice. These findings revealed that the absence of T cells in Rag1−/− mice leads to delayed maturation of osteoblasts and reduced bone formation.[7] Additionally, the pro-inflammatory cytokine interleukin-17, produced by T helper 17 cell (Th17) lymphocytes, has been shown to be a crucial mediator of osteogenesis during the bone fracture healing process.[6] However, there have been no relevant reports on the role of NK cells in bone healing. Therefore, we suppose that CIK and NK cell therapies participate in the bone repair process through immune regulation; however, the specific mechanisms require experimental verification.

It has been shown that older patients with MFMM have a poorer prognosis than that of younger patients. This is attributed to a higher resistance to conventional chemotherapy and the more frequent presence of comorbid conditions. Since June 2008, our team has conducted clinical research on adoptive immunotherapy (using CIK and NK cells) for the treatment of hematological malignancies, achieving satisfactory therapeutic outcomes.[8,9] To our knowledge, this is the first report of prolonged use of autologous CIK and NK cell therapy for MFMM with complete response (CR) and bone lesion repair.[10] This case shows that plasma cell tumors, especially MFMM, can be managed with adoptive immunotherapy as a maintenance treatment after achieving a partial response (PR) or CR through chemotherapy, antibody therapy, or targeted therapy. Lymphocyte subset monitoring showed an increasing trend in CD8+ T and B cells after CIK cell therapy ($P > 0.05$) and an elevated trend in NK cells after NK cell therapy ($P > 0.05$). This suggests immunotherapy is beneficial for enhancing the number and function of various immune cells in the body; improvement in various indicators reflecting efficacy may be associated with a shift in the immune status toward a more favorable environment for antitumor immune responses. This approach of long-term and continuous adoptive immunotherapy (including CIK and NK cells) has the potential to achieve long-term remission, disease-free survival, and restoration of bone damage. Future clinical trials of this adoptive immunotherapy (based on CIK and NK cells) are needed and should include more patients with plasma cell tumors to further explore the mechanisms of efficacy.

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Authors contribution

Yang Song, Bo Yang, Ji Wang, and Xuechun Lu were responsible for the study design, data collection, analysis, and interpretation; Lili Cai contributed to the data collection and assisted in the research; Tianyi Liu, Liangliang Wu, and Lu Sun provided guidance for the study and participated in the review process; Xian Xu and Chumeng Gao contributed to the guidance of the study and reviewed and edited the manuscript. The final manuscript was reviewed by all authors prior to submission.

Ethics statement

All procedures involving human participants performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 *Declaration of Helsinki* and its later amendments or comparable ethical standards (approval no. 20110526001). Written informed consent for publication of the case details was obtained from the patient.

Data availability statement

Data used in this study are available from the corresponding author upon request.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15:e538–e548. https://doi.org/10.1016/S1470-2045(14)70442-5.
2. Fan J, Hou J, Du J, et al. Macrofocal multiple myeloma is a particular subgroup of multiple myeloma. *Blood*. 2015;126:1855. https://doi.org/10.1182/blood.V126.23.1855.1855.
3. Chinese Hematology Association, Chinese Society of Hematology. Guidelines for the diagnosis and management of multiple myeloma in China (2022 revision) (in Chinese). *Chin J Intern Med*. 2022;61:480–487. https://doi.org/10.3760/cma.j.cn112138-20220309-00165.
4. Wang Y, Bo J, Dai HR, et al. CIK cells from recurrent or refractory AML patients can be efficiently expanded in vitro and used for reduction of leukemic blasts in vivo. *Exp Hematol*. 2013;41:241–252. https://doi.org/10.1016/j.exphem.2012.10.014.
5. Könnecke I, Serra A, El Khassawna T, et al. T and B cells participate in bone repair by infiltrating the fracture callus in a two-wave fashion. *Bone*. 2014;64:155–165. https://doi.org/10.1016/j.bone.2014.03.052.
6. Nam D, Mau E, Wang Y, et al. T-lymphocytes enable osteoblast maturation via IL-17F during the early phase of fracture repair. *PLoS One*. 2012;7:e40044. https://doi.org/10.1371/journal.pone.0040044.

7. Mombaerts P, Iacomini J, Johnson RS, Herrup K, Tonegawa S, Papaioannou VE. RAG-1-deficient mice have no mature B and T lymphocytes. *Cell*. 1992;68:869–877. https://doi.org/10.1016/0092-8674(92)90030-G.
8. Lu XC, Yang B, Yu RL, et al. Clinical study of autologous cytokine-induced killer cells for the treatment of elderly patients with diffuse large B-cell lymphoma. *Cell Biochem Biophys*. 2012;62:257–265. https://doi.org/10.1007/s12013-011-9273-6.
9. Yang B, Lu XC, Yu RL, et al. Repeated transfusions of autologous cytokine-induced killer cells for treatment of haematological malignancies in elderly patients: a pilot clinical trial. *Hematol Oncol*. 2012;30:115–122. https://doi.org/10.1002/hon.1012.
10. Mortezaee K, Majidpoor J. NK and cells with NK-like activities in cancer immunotherapy-clinical perspectives. *Med Oncol*. 2022;39:131. https://doi.org/10.1007/s12032-022-01735-7.