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CORRESPONDENCE

Pure red cell aplasia and minimal residual disease conversion associated with immune reconstitution in a patient with high-risk multiple myeloma

Dear Editor,

Multiple myeloma (MM) is characterized by the excessive production of monoclonal immunoglobin. As a lot of novel agents were approved during the last two decades, deeper responses and longer survival have been achieved in MM patients, such as minimal residual disease (MRD) measured via flow cytometry (FCM).[1] The development of oligoclonal bands (OB) and immunoglobin isotype (Ig) switch predicted favorable outcomes after high-dose therapy followed by autologous stem cell transplantation (ASCT) in newly diagnosed MM (NDMM) patients.[2] However, even if the appearance of OB is linked to a better response, MRD negativity requires further discussion.

Pure red cell aplasia (PRCA) is a rare hematological disorder characterized by erythroid hypoplasia and maturation arrest in the bone marrow. There are several pathogenic factors associated with acquired PRCA, including allogeneic hematopoietic stem cell transplantation (allo-HSCT), B19 parvovirus infection, autoimmune disorders, and others.[3–5] Several case reports have described PRCA in the scenario of MM.[3,6,7] However, the mechanism of PRCA in MM patients is still unknown. Here, we reported a case who presented OB after ASCT and developed PRCA during maintenance. MRD tested by FCM was negative during the updated follow-up.

In August 2019, a 56-year-old man was newly diagnosed as MM in our department with λ type; Durie Salmon (DS) stage IIIB, international staging system (ISS) III, and revised-ISS (R-ISS) III. Laboratory examinations at baseline revealed a white blood cell (WBC) count of 6.47×10^9/L, hemoglobin of 96 g/L, platelet count of 197×10^9/L, lactate dehydrogenase (LDH) 144 U/L , β2-microglobulin (β2-MG) 12.1 mg/L, albumin 44 g/L, calcium 2.07 mmol/L, creatine 272 μmol/L, estimated glomerular filtration rate (eGFR) 34.46 mL/min/1.73 m^2, serum M protein 4.91 g/L, serum free light chain (sFLC) λ 14,200.0 mg/L, and 24 h urine light chain λ 63,250 mg. The proportion of abnormal plasma cells in the bone marrow cytology was 27.5%. Fluorescent in situ hybridization (FISH) analysis demonstrated the presence of 1q21 amplification (58%), immunoglobulin heavy chain (IGH) deletion (55%), *Myc* rearrangement (15%), and 17p deletion (10%) in CD138 sorted cells. Furthermore, multiple osteolytic bone lesions were detected in the thoracic vertebra and lumbar vertebra by magnetic resonance imaging (MRI).

The patient was treated with a front-line BCd regimen (Bortezomib 1.3 mg/m^2, hypodermic injection, Days 1, 8, 15, 22; cyclophosphamide 300 mg/m^2, oral intake, Days 1, 8, 15; dexamethasone 40 mg, oral intake, Days 1, 8, 15, 22) for seven cycles. Complete response (CR) was achieved after two cycles and sustained after ASCT with conditioning high-dose melphalan (200 mg/m^2) in June 2020. Total CD34+ cells were 4.40×10^6/kg. At 3 months post-ASCT, the emergence of OB was first described by immunofixation electrophoresis (IFE), which was different from the initial Ig pattern at diagnosis. Serum M protein quantity was 1 g/L, and sFLC λ was 157 mg/L, 24-h urine light chain $\lambda < 5.00$ mg/dL. MRD evaluated using a Euro-flow panel of bone marrow nucleated cells illustrated that malignant plasma cells accounted for 0.0022%. Maintenance therapy with lenalidomide 25 mg every other day (qod) was initiated in September 2020 but was discontinued after a month due to grade 4 pancytopenia. Considering the patient's high-risk cytogenetic status, ixazomib was administrated at an initial dosage of 3 mg once a week for 3 weeks per month. However, ixazomib was ceased in March 2021 due to refractory anemia, and severe thrombocytopenia. Stanozolol was not effective. At that time, OB was not detectable, serum M protein turned negative and sFLC was normal, indicating that a stringent CR was achieved. The evolution of OB was displayed in Figure 1. However, despite receiving two transfusions of cryopreserved hematopoietic stem cells as supportive care (CD34+ cells were 1.39×10^6 and 2.79×10^6/kg, respectively), the patient remained dependent on blood

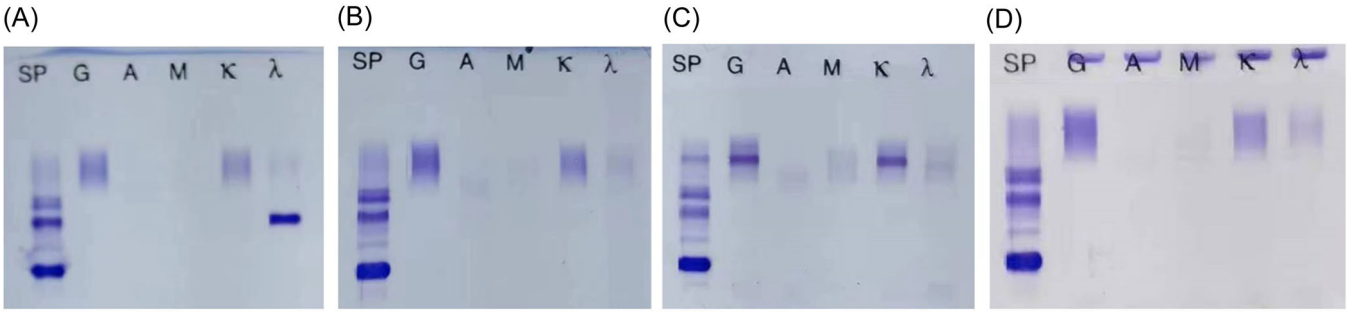

FIGURE 1 The OB evolution figures. (A) λ light chain isotype was present at diagnosis (2019-8). (B) IFE detection was negative before ASCT (2020-4). (C) A new monoclonal component was identified at 3 months after ASCT (2020-9). (D) The OB disappeared at 5 months after maintenance therapy (2021-2). ASCT, autologous stem cell transplantation; IFE, immunofixation electrophoresis; OB, oligoclonal bands.

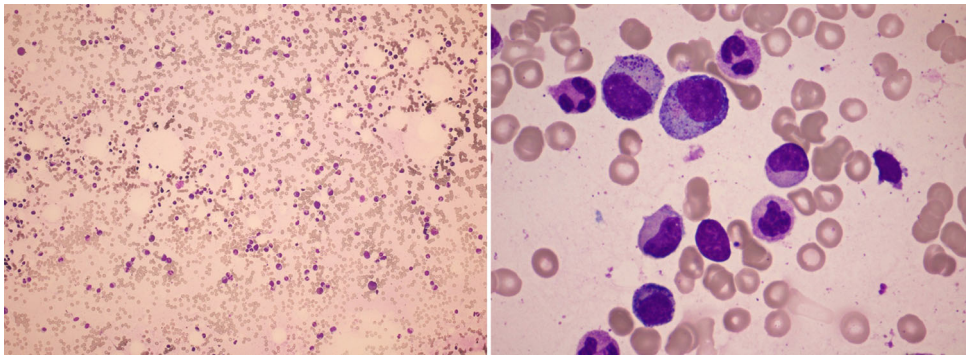

FIGURE 2 A second bone marrow aspiration and biopsy showed pure red cell aplasia in this case.

transfusion. A second bone marrow aspiration and biopsy were performed in September 2021, which showed hypercellularity with a myeloid lineage of 87.5% and only 0.5% erythroid lineage (Figure 2). Thus, PRCA was diagnosed. Parvovirus B19 (PvB19) was negative, and serum vitamin B12 and folic acid were within the reference ranges. Cyclosporine at 150 mg/day was prescribed for PRCA, and the patient's hemoglobin elevated to 126 g/L within 3 months. Antimyeloma therapy was exempted due to concerns about cytopenia. Subsequent Euro-flow marrow MRD was tested in March 2022, which switched to the negativity of malignant plasma cells. Stringent CR and complete recovery of blood cells have been maintained until February 2023. Figure 3 illustrates the treatment and progression of the patient's condition.

Immune reconstitution after transplantation is a predictor of favorable outcomes in patients with NDMM. The presence of OB after ASCT indicates partial recovery of the immune function. Here, we propose a potential association between the presence of OB and conversion to MRD negativity in a patient with high-risk cytogenetic abnormalities. Moreover, concurrent PRCA may be related to immune disturbance and complicated the situation.

OB persisted for 6 months in our case. Flow MRD was positive the first time. Despite the intolerability of maintenance therapy, MRD converted to negativity 21 months after ASCT in this high-risk patient. The PETHEMA/GEM2012MENOS65 trial launched by Paiva et al., revealed that attaining undetectable MRD overcame the adverse impact of high-risk cytogenetics at diagnosis.[8] The positive trend of MRD kinetics may be associated with the presence of OB. According to the 16-year study published by Alejandre from the University of Buenos, OB was observed in 15.5% of patients between 1 and 20 months after ASCT (mean 4.4 months), which persisted for a median of 7.9 months (range 1–36 months). Moreover, the mean overall survival (OS) time in the OB group was statistically longer ($p < 0.05$).[9] In addition, researchers from Princess Margaret Cancer Center identified the development of OB as an independent favorable prognostic factor for OS and PFS by multivariate analysis.[10] However, Fujisawa et al. questioned the positive prognostic impact of OB because they failed to verify improvement in survival, especially in patients with at least very good partial response or CR.[11] Molecular studies suggested that the occurrence of OB posttransplant reflects the recovery of B-cell function rather than active myeloma-related cells.[12]

Acquired PRCA in MM has occasionally been reported with a potential correlation to antimyeloma therapy, such as lenalidomide.[3] Other differential diagnoses include autoimmune diseases such as

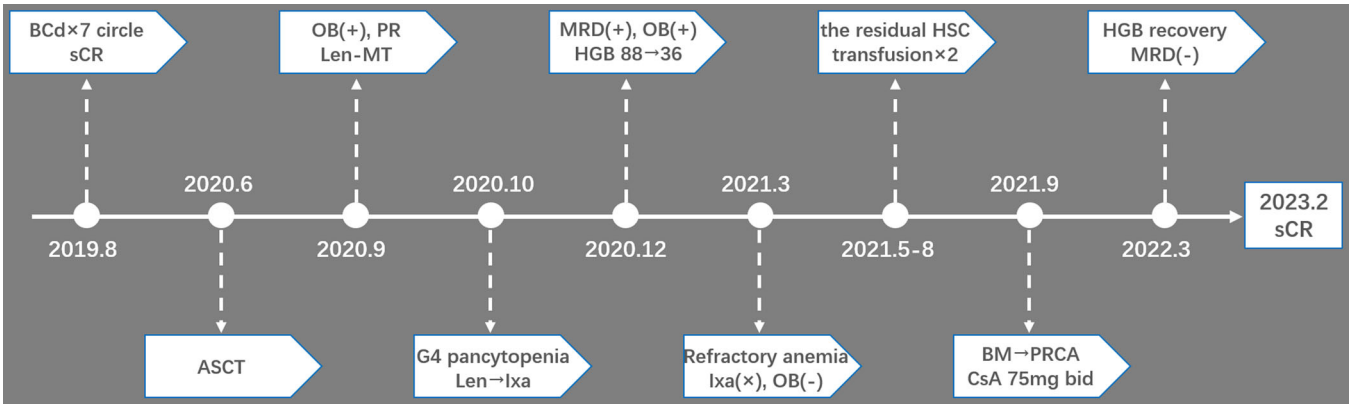

FIGURE 3 An illustration of the time course of the events (HDT, maintenance therapy, MRD f-u, PRCA, cyclosporine, etc.). ASCT, autologous stem cell transplantation; BM, bone marrow aspiration; HDT, high-dose therapy; HGB, hemoglobin; HSC, hematopoietic stem cells; MRD, minimal residual disease; OB, oligoclonal bands; PRCA, pure red cell aplasia; sCR, stringent complete response.

systemic lupus erythematosus, lymphoproliferative disorders such as large granular lymphocyte leukemia, infections, especially PvB19, or drugs. In this case, pancytopenia was first considered as a treatment-related event and recovered after the withdrawal of maintenance therapy. However, the subsequent occurrence of PRCA after stem cell supply was attributed to autoimmune disturbance. Notably, a study has suggested that patients with PvB19-related PRCA have slower immune reconstitution after human leukocyte antigen-haploidentical peripheral blood stem cell transplantation.[13] Another case described immune reconstitution syndrome associated with B19-induced PRCA during highly active antiretroviral therapy.[14] Furthermore, Ye Rebecca's retrospective analysis of 177 patients with MM who underwent ASCT revealed that clonal isotype switch (CIS) was found in 39 (22%) of the cases.[15] Patients with CIS had a lower percentage of CD8+ T cells and a higher CD4/CD8 ratio compared to those who did not exhibit CIS. CIS may play a crucial role in the immune reconstitution process after transplantation and may also have antimyeloma properties. Based on this, we hypothesized that there was a correlation between PRCA occurrence and cellular immunity in this case. Regrettably, the patient's T cell subset was not monitored.

To sum up, we reported the conversion of flow MRD to negativity in a high-risk MM patient in spite of transient maintenance therapy. Therefore, there may be a potential mechanism linking OB, PRCA, and MRD kinetics that could predict immune reconstitution. Further studies in a large cohort are needed to prove these findings.

AUTHOR CONTRIBUTIONS

Xianghong Jin wrote the manuscript. Xianyong Jiang collected pathological images. Wei Wang collected clinical data. Shuangjiao Liu made the figure. Bing Han analyzed the pathological data. Jianhua Han provided the figures of oligoclonal bands and analyzed the results. Junling Zhuang critically revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

Professor Junling Zhuang is a member of the Chronic Diseases and Translational Medicine editorial board and is not involved in the peer review process of this article. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data that support the findings of this study are available from the corresponding author, Junling Zhuang, upon reasonable request.

ETHICS STATEMENT

Written informed consent was obtained from the individual for the report of any potentially identifiable data or images involved in this article.

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