Case Report

PD-1 Checkpoint Blockade in Patients for Acute Myeloid Leukemia after HSCT Relapse Resulted in Severe GVHD and sHLH

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Treatment with immune checkpoint inhibitors (ICI) such as carrizumab leads to immune-mediated adverse effects including severe acute graft versus host disease (aGVHD) and secondary hemophagocytic syndrome (sHLH). Herein, we present two cases where aGVHD and sHLH developed after ICI administration, which was treated using methylprednisolone (MP). They developed high-grade fever complicated with liver dysfunction and diarrhea 1 day after ICI administration. Treatment with MP does not alleviate symptoms because of steroid resistance. Hyperbilirubinemia, rash with blisters, and watery diarrhea showed severe aGVHD. Hyperferritinemia, hypertriglyceridemia, and cytopenias suggested the diagnosis of HLH and met the criteria for sHLH diagnosis. They were thus administered intravenous high-dose MP, methotrexate (MTX), basiliximab, ruxolitinib, etc, which resolved these symptoms.

1. Introduction

With the progress of treatment, the therapeutic effect of acute myeloid leukemia (AML) has gradually increased from about 10% to about 70% [1], but allogeneic hematopoietic stem cell transplantation (HSCT) is the only treatment option for high-risk AML. AML recurrence after HSCT affects about 30–40% of HSCT recipients, and recurrence is still the primary cause of death in AML patients after HSCT [2]. The prognosis of AML recurrence after HSCT is poor. The 3-year survival rate is about 20–30% [3], and the treatment options are very limited. General management includes immunosuppressant withdrawal, chemotherapy, donor lymphocyte infusion (DLI), chimeric antigen receptor (CAR) T-cell therapy, and second transplantation, which are not very effective. At present, ICI is increasingly applied to solid tumors such as lymphoma, lung cancer, and melanoma, and has achieved encouraging therapeutic effects [4]. Therefore, increasing attention has been paid to the treatment of ICI. Some literature points out that highly expressed cells of programmed death 1 (PD-1) are closely related to leukemia relapse after HSCT [5–7], which provides a therapeutic target for leukemia recurrence after HSCT. However, ICI, including carrizumab, can activate T cells and induce serious autoimmune complications, such as immune-related adverse events (irAE), including aGVHD, secondary hemophagocytic lymphohistiocytosis (sHLH); sHLH is a potentially fatal disease, which can be manifested as fever, rash, cytopenia, coagulation dysfunction, liver dysfunction and hemophagocytic cells in the bone marrow. The occurrence of these two complications can endanger the lives of children.

Here, we report two AML patients who relapsed after HSCT treated with carrizumab, who developed sHLH and severe aGVHD, and were successfully treated with pulse therapy using high-dose MP and other immunosuppressants.

2. Case Report

2.1. Case 1. A 10-year-old girl was diagnosed with AML (M4); chromosome: chromosome:46, XX; negative fusion gene; Lzkf1 negative; full exon sequencing: a frameshift mutation was detected in WTI gene; RNA SEQ detected after
the fusion gene: PRDM16/SKI positive. The patient received induction chemotherapy with daunorubicin, cytarabine, and etoposide (DAE) scheme in June 2020 and achieved a partial response (PR). Then, the patient received consolidation chemotherapy with idarubicin, cytarabine (IA) scheme, and 2 cycles of dicitabine, homoharringtonine, cytarabine, and recombinant human granulocyte colony-stimulating factor (G-CSF) (DEC + CLAG) scheme and achieved a PR. After receiving dicitabine, cladribine, cytarabine, and G-CSF (DEC + CLAG) scheme, the patient achieved a complete response (CR); at this stage, the patient was positive for minimal residual disease (MRD), confirmed through flow cytometry (FCM). The patient underwent allo-HSCT from a HLA-mismatched related donor (5/10), after preconditioning with semustine, CLAG, cyclophosphamide, busulfan (CCNU + CLAG + BuCy), followed by cyclosporine A, mycophenolate mofetil, and short-term methotrexate for prophylaxis of GVHD. The patient achieved CR with MRD negativity (CRMRD-) 1 month after allo-HSCT and no GVHD. In May 2021, 4 months after HSCT, the disease progressed to relapse, and the evaluation of bone marrow (BM) showed that 16.5% of blasts, 84.6% of donor chimeric; and 7.57% of WT1. We performed the HLA-loss test, but no HLA gene loss was detected. So the patient was treated with azacitidine chemotherapy and DLI, but it was still not achieved CR. The second transplantation was performed 5 months after HSCT1. The patient underwent allo-HSCT from a HLA-mismatched unrelated donor (cord blood) (7/10), after preconditioning with total body irradiation (TBI), CLAG, mefenal, followed by cyclosporine A, mycophenolate mofetil, and short-term methotrexate for prophylaxis of GVHD. The patient achieved CR MRD-1 month after allo-HSCT and no GVHD. The patient was treated with azacitidine and interferon for preemptive therapy, but after that, the patient achieved CR MRD, but the copy number of WT1 in the patient increased gradually. Three months after the HSCT2, the patient was treated with azacitidine and camrelizumab (3 mg/kg/d) injection. On that day, the child felt general pain and discomfort, low fever, gradually developed a skin rash, even blisters, diarrhea, dark green watery stool, jaundice, abnormal liver function, 4-degree GVHD, accompanied by repeated fever hyperferrinemia, hypofibrinogenemia, hypertriglyceridemia, cytopenias, and sIL-2R > 2500 pg/ml (Table 1), which was consistent with sHLH. The children were combined with four degrees of GVHD and sHLH and were gradually reduced and treated with methotrexate (MTX) and MP (5 mg/kg/d), and basiliximab. GVHD and sHLH were gradually controlled. The evaluation of bone marrow (BM) showed CR, no hemophagocyte was found, and the copy number of WT1 decreased.

### Case 2

2.2 Case 2. A 2 years old girl was diagnosed with AML (M7); frameshift mutation was detected in the ETV6 gene of myeloid line 67, and CBFA2T3-GLS2 was positive. The patient received induction chemotherapy with daunorubicin, cytarabine, cytarabine, and homoharringtonine (DAH) scheme in March 2021 and achieved a CR with CR MRD+. After receiving HAG, 2 cycle HA, cytarabine, and etoposide (EA) scheme, the patient still achieved a CR with CR MRD; The patient underwent allo-HSCT from a HLA-mismatched unrelated donor (cord blood) (8/10), after preconditioning with CCNU + CLAG + BuCy, followed by cyclosporine A, mycophenolate mofetil, and short-term methotrexate for prophylaxis of GVHD. The patient achieved CR MRD-1 month after allo-HSCT and with 1-degree skin GVHD. In November 2021, 3 months after HSCT, the disease progressed to relapse, and the evaluation of bone marrow (BM) showed that 34% of blasts, 97.6% of donor chimeric; 46.29% of FCM–MRD; and 87.91% of CBFA2T3–GLS2; considering the relapse of AML, and camrelizumab (3 mg/kg/d) targeted antitumor therapy was given. Fever occurred on the same day and then gradually appeared the same 4-degree GVHD symptoms as the first case, such as a rash (including blisters), diarrhea, abnormal liver function, and jaundice. At the same time, the child developed repeated fever, hyperferrinemia, hypertriglyceridemia, cytopenias, sIL-2R > 2500 pg/ml, and

### Table 1: Frequency of acute treatment, emergent GVHD, and laboratory findings: pretreatment, day 14 after the administration of camrelizumab.

<table>
<thead>
<tr>
<th>Stage of aGVHD</th>
<th>Case 1 Pretreatment</th>
<th>Case 1 Day 14</th>
<th>Case 2 Pretreatment</th>
<th>Case 2 Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Stage 0</td>
<td>Stage 4</td>
<td>Stage 1</td>
<td>Stage 4</td>
</tr>
<tr>
<td>Liver</td>
<td>Stage 0</td>
<td>Stage 4</td>
<td>Stage 0</td>
<td>Stage 0</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>146</td>
<td>85</td>
<td>85</td>
<td>77</td>
</tr>
<tr>
<td>Platelet (×10^9/L)</td>
<td>194</td>
<td>61</td>
<td>108</td>
<td>16</td>
</tr>
<tr>
<td>Neutrophil count (×10^9/L)</td>
<td>1.64</td>
<td>1.58</td>
<td>1.64</td>
<td>0.03</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>0.88</td>
<td>4</td>
<td>0.22</td>
<td>4.11</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>6253.6</td>
<td>20920</td>
<td>3796.7</td>
<td>10450</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>2.81</td>
<td>0.71</td>
<td>2.85</td>
<td>4.94</td>
</tr>
<tr>
<td>sIL-2R (U/mL)</td>
<td>1.76</td>
<td>4.94</td>
<td>2.56</td>
<td>5.35</td>
</tr>
<tr>
<td>NK cell activity (&lt;15.11%)</td>
<td>—</td>
<td>12365</td>
<td>—</td>
<td>76806</td>
</tr>
</tbody>
</table>

Acute GVHD stage and responses were scored according to consensus and National Institutes of Health (NIH) criteria, GI = gastrointestinal.
of PD-1 inhibitors can also induce severe GVHD. The evaluation of BM showed that 88% of blast parents gave up treatment.

3. Discussion

At present, chemotherapy, DLI, cell therapy, et al. are still unsatisfactory for patients with AML relapse after HSCT. PD-1 pathway can be used as a checkpoint to limit T-cell-mediated immune response. Blocking the PD-1 receptor on T cells can lead to the activation and proliferation of T cells, and induce an effective antitumor effect of immunotherapy [8]. In recent years, it has achieved certain therapeutic effects for patients with AML relapse after transplantation. Blocking PD-1 after HSCT can enhance the graft versus leukemia (GVL) effect, but at the same time, the activation and proliferation of T cells may lead to fatal aGVHD [9, 10]. Bradley et al. reported that the application of PD-1 inhibitors can also induce severe aGVHD [11]. In this GVHD state, T cells are activated and promote the activation of secondary macrophages, IL-6, IL-1, and IFN-γ, It is reported that PD-1 inhibitors may cause sHLH, mainly in lymphoma, lung cancer, and other solid tumors [12, 13]. However, PD-1 leads to fewer reports of post-transplant HLH. At present, the overall mortality of post-transplant sHLH is high, which can reach 80% [14]. If large doses of glucocorticoids cannot be rapidly alleviated, immune activation will continue, leading to further progress of sHLH and aGVHD, which will endanger life.

After the application of PD-1, the incidence rate of irAE is high. Both aGVHD and sHLH are irAE, but rarely occur at the same time. High fever, rash, diarrhea, and liver dysfunction were initially considered as aGVHD until there were cytopenia, decreased natural killer (NK) cell activity, hepatosplenomegaly, and coagulation dysfunction, especially hyperferrinemia (serum ferritin >10000 μg/ml), which has important clinical significance for the diagnosis of sHLH [15]. Will realize the occurrence of sHLH. For patients with these two complications at the same time, the treatment is often difficult. Single-use of glucocorticoids is considered effective for irAE [16, 17]. However, patients with aGVHD and sHLH may have glucocorticoid resistance, and other immunosuppressants such as basiliximab, MTX, and ruxolitinib need to be used to control the deterioration of irAE. Because of the high mortality rate of sHLH after transplantation, it is essential for early diagnosis and treatment of sHLH. For patients who have had aGVHD, if they have abnormal blood coagulation function, hyperferrinemia, splenomegaly, and other manifestations, they should be alert to the occurrence of sHLH.

Because the relapse of AML after HSCT is always a difficult point, the chemotherapy effect is poor and the overall survival rate is low. The treatment of PD-1 inhibitors provides us with the possibility of treatment. In order to avoid the high incidence rate of aGVHD and sHLH, we may adopt the following methods: (1) whether to use ICI can be determined according to the values of PD-1, PD-L1, and PD-L2. Some studies point out that the proportion of PD-1 or PD-L1 is relatively high, which has a good therapeutic effect [18, 19]; (2) by reducing the therapeutic dose of ICI, the current conventional dose is 3 mg/kg, and the proportion of severe aGVHD or sHLH is relatively high, so the dose can be further reduced. Matthew et al. tried to reduce the dose to 1 mg/kg or even 0.5 mg/kg [20]. If children with irAE I or II can choose to receive ICI treatment again, or even increase the dose if it is level III or IV, it should be avoided; (3) at the same time as ICI treatment, we used glucocorticoid, cyclosporine, and other drugs to prevent aGVHD to reduce the incidence rate of aGVHD or sHLH. Once aGVHD occurs, we should be alert to sHLH. If sHLH occurs, the HLH-94 regimen seems to achieve a better therapeutic effect.

4. Conclusion

In conclusion, these 2 cases represent a particularly early and aggressive form of sHLH with PD-1 inhibitor therapy and report severe aGVHD caused by recurrent PD-1 after HSCT. With the continuous exploration of new PD-1 inhibitors in children with post-transplantation relapsed AML, it should be considered that the incidence rate of sHLH and aGVHD as possible severe irAE is increasing, and the methods and strategies for ICI treatment of post-transplantation relapsed AML can be improved, to achieve the best treatment effect and minimize toxic and side effects.

Data Availability

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethical Approval

This retrospective study was approved by our institutional board and by our ethical committee (Approval No: 2022025) and has been performed in accordance with the ethical standards of the Declaration of Helsinki.

Consent

Written informed consent was obtained from the patient’s relatives for the publication of this case report and any accompanying images.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

SH and PX were involved in the identification, selection, and management of the patient and manuscript review. ZD was involved in the management of the patient and manuscript drafting. SC and MZ were involved in the selection and management of the patient and manuscript review. LC, LL, and LK were involved in manuscript editing. All authors have read and approved the final manuscript.
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