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Related Allogeneic Hematopoietic Stem Cell Transplantation For Very Severe Aplastic Anemia With Active Pulmonary Fungal Infection: Case Report

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1.Abstract:

1.1. Background:
Heavy aplastic anemia and very heavy aplastic anemia (SAA and vSAA) is a potentially deadly disease due to bone marrow failure, Immunosuppressive therapy (IST) and allogeneic hematopoietic stem cell transplantation (allo-HSCT) are the main treatments [1,2]. Infection is the main cause of death in AA patients [3], and it is also a risk factor affecting the outcome of allo-HSCT Adequate anti-infection treatment is extrahematopoietic stem cell transplantation important for allo-HSCT. During severe periods of active infection, patients develop further fatal neutropenia, transfusion dependence, and persistent fever after broad-spectrum potent anti-infective therapy, and urgent allo-HSCT is needed for faster peripheral blood imaging recovery and infection control. Given that HLA-matched sibling donors (MSDs) and unrelated donors (URDs) are difficult to obtain in the short term, related haploid compatible donors (HID-HSCT) [1] and umbilical cord blood transplantation (UCBT) can be used when IST treatment fails, especially in emergency situations where no MSDS or URDs are available. Patients who undergo umbilical cord blood transplantation UCBT have to face the challenges of delayed engraftment, risk of graft failure, increased transplant-related mortality (TRM) and infection [3], so the relative HID-HSCT is preferred. Related allo-HSCT , including MSD and relative HID-HSCT, promote rapid recovery of neutrophils and are highly effective in controlling infection. Therefore, the related allo-HSCT may be a potentially effective treatment for patients with vSAA combined with active pulmonary fungal infection.

1.2. Case presentation:
In this report, two young patients diagnosed with “vSAA” after 1 month with active pulmonary fungal infection were treated with related allo-HSCT, the peripheral blood images gradually returned to normal, and the lesions of pulmonary infection gradually improved and absorbed.

1.3. Conclusions:
Patients diagnosed vSAA with active pulmonary fungal infection are expected to be cured by the relative allo-HSCT and may achieve long-term disease-free survival.

2. Key worlds:
Related allo-HSCT; vSAA; Active pulmonary fungal infection

3. Case report:

Two patients who were hospitalized in the Hematology Department of the Western Theater Command General Hospital in September 2019 and January 2023 were included (TABLE1). The inclusion criteria are as follows:[1] Having acquired denovo VSAA at age of 14-40 years, as defined by the International Aplastic Anemia Study Group[5], excluding patients with Fanconi anemia, myelodysplastic syndrome,or other congenital bone marrow failures; [2] Related sibling donors; [3] ECOG score ≤3 [4] no decompensated organ disease. [5] Experience refractory pulmonary fungal infections; Invasive Fungal Infection (IFI) is defined as that requires clinical intervention, with highly suggestive imaging features and no objective conditions for microbiological examination`.

Table 1: Patient-, disease-, and transplantation-related characteristics

	Patient 01	**Patient 02**
Gender/Age (y)	Male/29	Female/17
Disease status	vSAA	vSAA
Months from diagnosis to HSCT	1	1
Donor-patient relation	cousin	
Sister		
HLA-matched locus	9/12	12/12
Invasive fungal infections		
(location/type)	Pulmonary/ Aspergillus	

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Figure.1	Pulmonary/ Aspergillus	
Figure. 2		
Status of pulmonary infections at HSCT	Stable	Stable
ECOG at HSCT	3	3
Day 01		
(reinfusion donor peripheral blood stem cells)		
September 27,2019		
January 18, 2023		
MNC count, ×108/kg	7.97	10.8
CD34+ count, ×106/kg	8.9	8
02 Day 02(reinfusion cord blood stem cells	Yes	No
Date of recovery of neutrophil/ platelet	11/13	
Figure.3	15/69	
Figure. 4		
Acute GVHD	No	II
Chronic GVHD	No	No
Viral reactivation	No	CMV viremia at +1 mo
Recovery of pulmonary infections at 1 mo post-HSCT	Improvement	Improvement
Median follow-up (mo)	46	6

Both patients were diagnosed with vSAA according to the guidelines [3]. The patient had neutropenia with recurrent fever, and chest CT showed progressive enlargement of the lesion of right lung infection after strong antibacterial combined with antifungal treatment (Figure.1-2). Due to severe thrombocytopenia, broncho fiber-based perfusion was contraindicated, and etiological evidence of the lesion of lung infection could not be obtained.

Figure. 1:

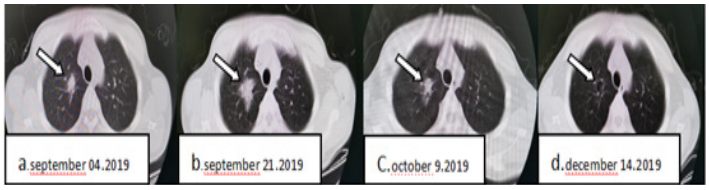

Figure 1 a. The chest CT of patient 01 showed a little inflammation and fibrous lesions in the right lung. b. A larger right pulmonary lesion was shown before relative HID-HSCT . c. The lesion showed smaller on day +11. d. Disappearance of nodule and foci lesions on day +77 .

Figure. 2:

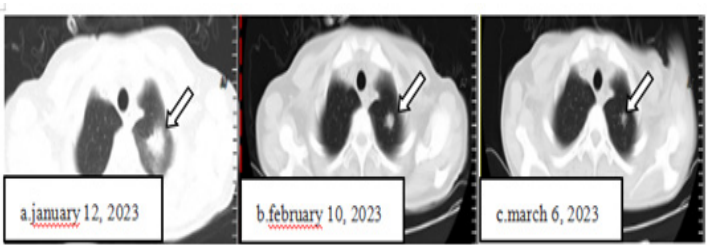

Figure 2 a. The chest CT of patient 02 showed a big inflammation and fibrous lesions in the left lung. b. A smaller lesion was shown on day +23. c. The lesion was getting smaller, almost disappearance on day +47.

Patients generally continue to deteriorate, with fatal neutropenia, transfusion dependence, and persistent fever. In order to achieve faster neutrophilic recovery [7], both patients underwent emergency kin peripheral blood stem cell transplantation (PBSCT) more than 1 month after their first diagnosis of vasa with active pulmonary fungal infection. With the full informed consent of the patients and their families, the related allogeneic hematopoietic stem cell transplantation was pretreated with the following protocols: fludarabine/cyclophosphamide/rabbit anti-human thymocyte immunoglobulin (ATG), prevention of graft -versus-host disease (GVHD) regimen: cyclosporine A + mycophe- no late motif ate tablets methotrexate. Cyclosporine A (3mg/kg/ day) was gradually reduced at 3 months and stopped at 12 months after transplantation. Oral mycophenolate motif ate tablets (20 mg/kg/ day) for 1 month. Methotrexate was injected at a dose of 15mg/m2 on day +1 (1 day after stem cell infusion) and 10mg/m2 on day +3, day +6, and day +11. Antimicrobial and antifungal therapy was continued during transplantation. Peripheral blood stem cells were transfused on day 01, and the peripheral blood image changes were as follows (Figure.3-4). After neutrophil implantation, the patient's temperature gradually returned to normal, and the peripheral blood T cell chimerism was all found to be complete chimerism. Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) screening was performed weekly until day 100, and then once a month. Monthly review of chest CT indicated gradual absorption of the lesion until 6 months after transplantation, and then every 3 months thereafter.

Figure 3:

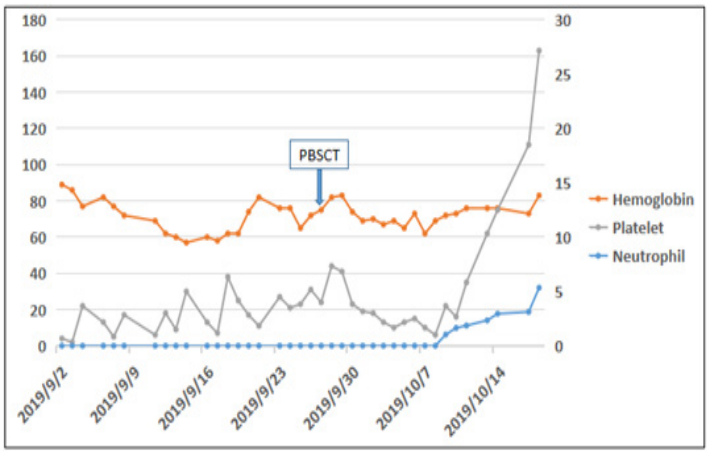

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Figure.3 Hematological parameters of the patient 01 during treatment with relative HID-HSCT.

Figure.4:

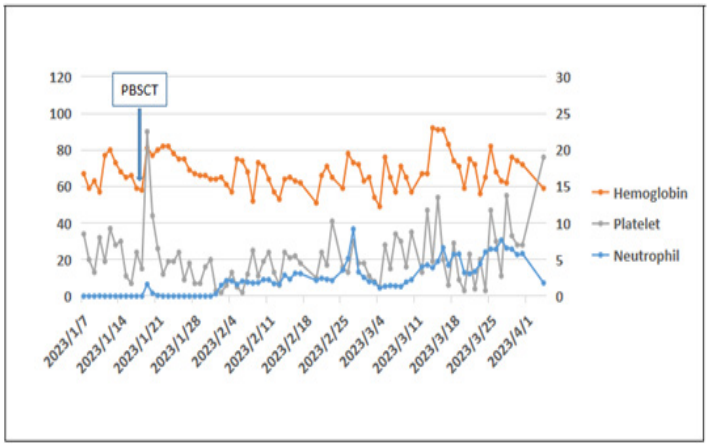

Figure.4: Hematological parameters of the patient 02 during treatment with HLA-matched sibling donors hematopoietic stem cell transplantation (MSD-HSCT).

4. Disscusion:

Long term immunosuppressive therapy based on ATG in SAA/vSAA patients carries the risk of disease recurrence and secondary myelodysplastic syndrome or acute myeloid leukemia, and most hematopoietic recovery typically takes more than 3 months [8]. In contrast, the high cure rate of allo-HSCT provides the best long-term disease-free survival opportunity for SAA patients [9]. MSD-HSCT is the first-line treatment for SAA patients under 40 years of age, and HID-HSCT and UCBT are available as alternative treatment options for SAA patients without MSD or URD. Considering that patients receiving UCBT face challenges such as delayed implantation, risk of transplant failure, increased transplant-related mortality, and spread of infection [4], HID-HSCT is preferred. HID-HSCT is encouraging in terms of survival rate and prevention and treatment of complications, and is comparable to MSD-HSCT, especially in SAA patients under the age of 40 [10]. Wang Q et al [11], retrospectively analyzed the clinical data of SAA patients to evaluate the complications and survival rates of HID-HSCT and MSD-HSCT, and the results showed there were no significant differences in two Median time to transplantation between cohorts, cumulative incidence of acute graft-versus-host disease (aGVHD), chronic graft-versus-host disease cGVHD, and 5-year OS and FFS. Therefore, for SAA/vSAA patients with active infections, peripheral blood stem cell transplantation (PBSCT) can provide faster neutrophil recovery in emergency situations, given the easy availability of related allo-HSCT donors (including MSD and relative HID-HSCT), which is crucial for infection control in patients. In recent years, with the improvement of preconditioning protocols and the development of GVHD prevention and supportive care, the transplantation related mate of allo-HSCT has decreased significantly. Recent reports have shown encouraging results for HID-HSCT, especially in younger patients [12-14]. Given the easy availability of donors, HID-HSCT has been seen as the preferred alternative therapy for patients without MSD or URD. In order to further evaluate the therapeutic effect of HID-HSCT and MRD-HSCT on SAA, a multi-center study led by Li Y et al. [15] pointed out that the overall survival rate of patients receiving HID-HSCT was acceptable, and it was a viable treatment option for patients with SAA. Lan Ping Xu et al. [16] pointed out in a report of a multi-center study that father, mother, siblings, and children are all suitable haploid compatible donors for SAA patients. To the best of our knowledge, the treatment of very severe aplastic anemia with active pulmonary fungal infection by related PBSCT in critical Settings has rarely been reported due to the availability of related donors. In this report, donor screening was performed urgently before transplantation, and PBSCT from cousin to cousin and sister to sister were started in a very short time.

During the treatment of AA infection, the main concerns of allo-HSCT are mortality and transplant success rates. Aki [17] reported 13 patients with active invasive fungal infections with a mean follow-up of 306 days, and only 4 patients (31%) survived after transplantation. Avivi [18] reported 18 patients with a continuous history of invasive fungal infections, and only 1 of 5 (20%) patients with active infection survived transplantation. For SAA and vSAA with active infections, allo-HSCT results are generally poor due to high infection-related mortality and transplant-related mortality, so it is usually recommended to use broad-spectrum powerful antibacterial and/or antifungal agents before allo-HSCT to completely control the infection. However, many patients with SAA/vSAA infections do not respond well even after treatment with a broad- spectrum of powerful antibacterial. / Antifungal agents. If therapeutic strategies are delayed prior to allo-HSCT until the infection is completely resolved, most patients may never undergo transplantation because they either die from the infection or exhaust financial resources before the infection is resolved [19]. As the Guide [20] described above, our strategy is to perform allo-HSCT as soon as possible and as early as possible, even in the presence of infection, as transplantation offers the best chance of faster neutrophils recovery and infection control. A CIBMTR study by Maziarz et al. [21] showed that although the presence of invasive fungal infection before transplantation was associated with a slightly worse prognosis after HSCT in hematological malignancies, infection before transplantation did not seem to be a contraindication of allo-HSCT. A retrospective study by Xu et al [22] showed that there was no significant difference between the HSCT outcome and the infection control outcome of SAA with uncontrolled infection before transplantation. Some studies have also reported that allo-HSCT has indeed saved a considerable proportion of AA patients with active infection [23-26]. For our patient, infection symptoms persisted, and the patient's general condition continued to worsen despite broad-spectrum antibacterial and antifungal therapy, and emergency treatment with related allo-HSCT was the best treatment option to accelerate neutrophil recovery and infection control.

In short, we report the experience of two young patients with vSAA, both of whom were successfully treated with related allo-HSCT during active pulmonary fungal infections. This suggests that related allo-HSCT may be safe and effective in treating patients with vSAA combined with active

pulmonary fungal infection. However, this report is limited by the small number of patients, and further multi-center, large-scale, and prospective studies are needed to evaluate the safety and efficacy of related allo-HSCT in the treatment of vSAA with active pulmonary fungal infections.

References:

1. Bacigalupo A. How I treat acquired aplastic anemia. Blood. 2017 Mar 16;129(11):1428-1436.
2. Young NS, Longo DL. Aplastic anemia. N Engl J Med. (2018) 379:1643–1656.
3. Maziarz RT, Brazauskas R, Chen M, et al. Pre-existing invasive fungal infection is not a contraindication for allogeneic HSCT for patients with hematologic malignancies: a CIBMTR study. Bone Marrow Transplant. 2017 Feb;52(2):270-278.
4. Zhu X, Tang B, Sun Z. Umbilical cord blood transplantation: Still growing and improving. Stem Cells Transl Med. 2021 Nov;10 Suppl 2(Suppl 2): S62-S74.
5. Camitta BM, Thomas ED, Nathan DG, et al. Severe aplastic anemia: a prospective study of the effect of early marrow transplantation on acute mortality. Blood. 1976; 48:63-70.
6. [6] Killick SB, Bown N, CavenaghJ, et al. Guidelines for the diagnosis and management of adult aplastic anaemia. Br J Haematol 2016; 172:187–207.
7. Bacigalupo A, Socie G, Schrezenmeier H, et al. Bone marrow versus peripheral blood as the stem cell source for sibling transplants in acquired aplastic anemia: survival advantage for bone marrow in all age groups. Haematologica 2012; 97:1142–8.
8. Rosenfeld S, Follmann D, Nunez O, Young NS. Antithymocyte globulin and cyclosporine for severe aplastic anemia: association between hematologic response and long-term outcome. JAMA. 2003; 289:1130-1135.
9. Georges GE, Doney K, Storb R. Severe aplastic anemia: allogeneic bone marrow transplantation as first-line treatment. Blood Adv. 2018 Aug 14;2(15):2020-2028.
10. Huang YR, Xie CQ, Tong JF, Zhang XH, Xu Y, Yuan XG. Successful treatment with matched unrelated donor peripheral blood stem cell transplantation for very severe aplastic anemia in presence of active infections: A case report. Medicine (Baltimore). 2020 Apr;99(14): e19807.
11. Wang Q, Ren H, Liang Zoet al. Comparable Outcomes in Acquired Severe Aplastic Anemia Patients With Haploidentical Donor or Matched Related Donor Transplantation: A Retrospective Single-Center Experience. Front Med (Lausanne). 2022 Jan 24; 8:807527.
12. Zhang YY, Mo WJ, Zuo YY, Zhou M, Zhang XH, Wang Y , et al. Comparable survival outcome between transplantation from haploidentical donor and matched related donor or unrelated donor for severe aplastic anemia patients aged years and older: a retrospective multicenter cohort study. Clin Transplant. (2020) 34: e13810.
13. Xu LP, Jin S, Wang SQ, Ling HX, Hai B, Su J, et al. Upfront haploidentical transplant for acquired severe aplastic anemia: registry-based comparison with matched related transplant. J Hematol Oncol. (2017) 10:25–34.
14. Kim H, Lee JH, Joo YD, Bae SH LEE SM, Jo JC, et al. Comparable allogeneic hematopoietic cell transplantation outcome of a haplo-identical family donor with an alternative donor in adult aplastic anemia. Acta Haematol. (2016) 136:129–39.
15. Li Y, Duan F, Xiao H, et al. Therapeutic Outcomes of Haploidentical Allogeneic Hematopoietic Stem Cell Transplantation in Patients With Severe Aplastic Anemia: A Multicenter Study. Transplantation. 2018 Oct;102(10):1724-1731.
16. Xu LP, Wang SQ, Ma YR, et al. Who is the best haploidentical donor for acquired severe aplastic anemia? Experience from a multicenter study. J Hematol Oncol. 2019;12(1):87.
17. Aki ZS, Sucak GT, Yegin ZA, et al. Hematopoietic stem cell transplantation in patients with active fungal infection: not a contraindication for transplantation. Transplant Proc 2008; 40:1579–85.
18. Avivi I, Oren I, Haddad N, et al. Stem cell transplantation post invasive fungal infection is a feasible task. Am J Hematol 2004; 75:6–11.
19. George B, Mathews V, Viswabandya A, Srivastava A, Chandy M. Fludarabine-based reduced intensity conditioning regimens for allogeneic hematopoietic stem cell transplantation in patients with aplastic anemia and fungal infections. Clinical Transplant. 2009; 23:228-232.
20. Marsh JC, Ball SE, Cavenagh J, et al. Guidelines for the diagnosis and management of aplastic anaemia. Br J Haematol. 2009; 147:43-70.
21. Maziarz RT, Brazauskas R, Chen M, et al. Pre-existing invasive fungal infection is not a contraindication for allogeneic HSCT for patients with hematologic malignancies: a CIBMTR study. Bone Marrow Transplant 2017; 52:270–8.
22. Xu S, Wu L, Zhang Y, et al. Allogeneic hematopoietic stem cell transplantation for the treatment of severe aplastic anemia patients with infection: a single-center retrospective study. Biol Blood Marrow Transplant 2018; 24:2532–9. vvij,
23. Wan L, Yan S, Wang C, et al. Allogeneic peripheral blood stem cell transplantation in the treatment of severe aplastic anemia and severe infection. Chin Med J (Engl) 2003; 116:676–8.
24. George B, Mathews V, Viswabandya A, et al. Fludarabine-based reduced intensity conditioning regimens for allogeneic hematopoietic stem cell transplantation in patients with aplastic anemia and fungal infections. Clin Transplant 2009; 23:228–32.
25. Takahata M, Fukuhara T, Shigematsu A, et al. Successful treatment with allogeneic peripheral blood stem cell transplantation and granulocyte transfusion for severe aplastic anemia with sinusitis. Transpl Infect Dis 2006; 8:44–8.
26. Yue CY, Ding YY, Gao Y, et al. Cotransplantation of haploidentical hematopoietic stem cells and allogeneic bone marrow-derived mesenchymal stromal cells as a first-line treatment in very severe aplastic anemia patients with refractory infections. Eur J Haematol 2018; 100:624–9.