Characteristics and outcomes of autoimmune hemolytic anemia after pediatric allogeneic stem cell transplant

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Abstract

Background: Autoimmune hemolytic anemia (AIHA) after allogeneic hematopoietic stem cell transplant (HSCT) is a rare but complex and serious complication. Detailed descriptions of cases and management strategies are needed due to lack of prospective trials. Objectives: Describe the incidence, clinical characteristics, and management of AIHA after HSCT in a pediatric cohort. Methods: This is a retrospective cohort study of 33 pediatric patients with AIHA after HSCT at an academic tertiary care center from 2003 to 2019. A case-control analysis was performed to compare outcomes. Results: The overall incidence of AIHA after allogeneic HSCT was 3.8% (33/868). AIHA was significantly more common after transplant for non-malignant versus malignant diagnoses (7.0% (26/370) vs. 1.4% (7/498), p<0.0001). AIHA developed at a median of 4.7 months (range: 1.0-29.7) after transplant. Sixteen of 33 patients (48.5%) required new AIHA-directed pharmacologic therapy; 17 (51.5%) were managed on their current immunosuppression and supportive care. Patients managed without additional therapy were significantly older, more likely to have a malignant diagnosis, and tended to develop AIHA at an earlier timepoint after transplant. Patients received a median of 2 red blood cell transfusions within the first two weeks of diagnosis and a median of one AIHA-directed medication (range: 1-4), most commonly corticosteroids and rituximab. Conclusions: AIHA after HSCT is rare but occurs more commonly in patients transplanted for non-malignant diagnoses. While some patients can be managed on current immunosuppression and supportive care, many require AIHA-directed therapy including second-line medications.

INTRODUCTION

Autoimmune cytopenias are a rare but potentially life-threatening complication after hematopoietic stem cell transplant (HSCT). Autoimmune hemolytic anemia (AIHA) is the most common type of post-HSCT immune cytopenia and occurs when antibodies are directed against donor red blood cell antigens. The incidence of AIHA in the pediatric transplant population has been reported between 2.4-6%.[1-3] Given the rarity of post-transplant AIHA, guidelines for monitoring, management, and expected outcomes are not available.

Previously reported risk factors for the development of AIHA include unrelated donor use, conditioning regimens without total body irradiation, peripheral blood and cord blood transplants, non-malignant indication for transplant, and chronic graft-versus-host disease (GVHD).[4-7] Limited evidence suggests that variables within the immunologic landscape, including pre-determined factors such as pre-HSCT serotherapy and T cell depletion as well as post-HSCT factors such as B and T cell recovery, T cell mixed chimerism, and infectious complications, may contribute to the risk of AIHA.[3, 5, 8] The complexity and lack of comprehensive understanding of the pathophysiology of AIHA after HSCT makes treatment challenging, and there are low reported response rates to first line therapy with corticosteroids.[2, 9-11]

We performed a retrospective cohort analysis describing the incidence of post-transplant AIHA in pediatric patients undergoing HSCT at a tertiary care academic institution, characterizing current management strategies, and describing patient outcomes. We also performed a matched case-control analysis to compare outcomes of patients with AIHA to those without AIHA.

METHODS

This retrospective cohort study was approved by the Institutional Review Board at Boston Children's Hospital and included patients undergoing HSCT between January 2003 and June 2019. All patients who underwent allogeneic transplant at Boston Children's Hospital in this time period (n=868) were identified through an HSCT program research database. Patients met inclusion criteria if they had a positive direct antiglobulin test and clinically significant hemolysis, defined by both a decrease in hemoglobin and evidence of at least one additional laboratory feature of hemolysis, including reticulocytosis, low haptoglobin, indirect hyperbilirubinemia, and/or elevated lactate dehydrogenase. The date of AIHA diagnosis was defined as the date on which the patient met these criteria. The study population included patients 0-25 years old who had AIHA following their first transplant. Patients who developed AIHA after a second transplant or who underwent autologous gene therapy were excluded.

Demographic features, clinical characteristics, laboratory data, transplant types, conditioning regimen, GVHD prophylaxis, and treatments were obtained by chart review. Neutrophil engraftment date was defined as the first of three consecutive days of absolute neutrophil count greater than 0.5 x 10^9/L.[12] Acute and chronic GVHD were staged using Center for International Blood & Marrow Transplant Research definitions.[13] Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infections were defined as a detectable blood CMV or EBV polymerase chain reaction (PCR) test on two consecutive tests. Laboratory response to AIHA treatment was defined as a complete response if hemoglobin increased to prior baseline with no evidence of hemolysis by labs while on AIHA treatment, and partial response if hemoglobin increased but evidence of ongoing hemolysis was present while on AIHA treatment.[2, 10, 14] Non-response was defined as any response not meeting complete or partial response. Remission was defined as complete remission if the patient had no evidence of hemolysis while off all treatment for AIHA, partial remission if there was no evidence of hemolysis but patient remained on treatment for AIHA, and not in remission if there was ongoing evidence of hemolysis.

After identification of the cases, controls were identified in a 2:1 ratio through the HSCT program research database and matched for age, recipient sex, and malignant versus non-malignant diagnosis (Supplemental Table S1).

STATISTICAL ANALYSIS

The data were collected using REDCap.[15] Descriptive statistics reported are count and percentage for categorical variables and median and range for continuous variables. Kruskal-Wallis test and Fisher's exact test are used to identify variables, categorical and continuous respectively, that are associated with treatment group in cases. Wilcoxon rank sum test is used to identify pairwise differences for continuous variables. McNemar and Wilcoxon signed-rank test are used to compare variables, categorical and continuous respectively, in the cases and controls. P-values are two-sided, and p-values <0.05 are considered statistically significant. No adjustments were made for multiple comparisons.

RESULTS

Description of Cases with AIHA

Incidence of AIHA

Over a 16-year period, 33 of 868 patients (3.8%) who underwent allogeneic HSCT developed AIHA (Table 1 and 2). The incidence of AIHA was significantly higher in those transplanted for non-malignant versus malignant conditions (7.0% (26/370) vs. 1.4% (7/498), $p<0.0001$).

Clinical characteristics of patients with AIHA

In patients with AIHA, the median age at time of transplant was 7.4 years (range: 0.1-23.2) and median time to development of AIHA after the day of transplant was 4.7 months (range: 1.0-29.7). At the time of AIHA diagnosis, all patients had a positive direct antiglobulin test, including IgG and C3 (n=16), IgG only (n=11), C3 only (n=4), and two patients in which neither IgG nor C3 was identified. IgM, IgA, and Donath-Landsteiner antibodies were not tested. Fifteen patients (15/33, 45.5%) converted their blood type from recipient to donor prior to the time of AIHA diagnosis, 6 converted after AIHA diagnosis, 8 recipient/donor pairs had identical blood types, and, in 4 patients, time to conversion was unable to be determined. Sixty-nine percent of patients (20/29, unknown = 4) had >28 days between their last packed red blood cell transfusion (pRBC) and onset of AIHA. The median number of days between last pRBC transfusion and development of AIHA was 73.5 days (range: 1-889).

CMV and EBV infections occurred either prior to or concurrently with AIHA diagnosis in a portion of patients with AIHA. CMV infection occurred in 24.2% (8/33) of patients with AIHA; of those with an infection, 62.5% (5/8) had positive blood CMV PCR testing at the time of diagnosis of AIHA. EBV infection occurred in 21.2% (7/33) with AIHA, and, of those with an infection, 100% (7/7) had positive blood EBV PCR testing at the time of AIHA. GVHD was diagnosed in a minority of patients with AIHA; 7 patients (21.2%) had acute GVHD in the first 100 days after transplant (grade range 1-3). Two patients required GVHD treatment with systemic steroid monotherapy and 4 patients required combination therapy with systemic corticosteroids and additional agents. Eight patients (24.2%) had chronic GVHD in the first-year after transplant with 1 patient (12.5%) having limited disease and 7 patients (87.5%) having extensive disease. Seven of these patients required treatment with systemic corticosteroids and additional agents.

Chimerism in patients with AIHA

Twenty-six patients had chimerism checked between 1 month before AIHA diagnosis to 1 year after diagnosis. Most patients (16/26; 61.5%) had >95% total donor chimerism (full chimerism); 15.4% (4/26) had chimerism between 50-94% donor (high mixed chimerism); 11.5% (3/26) had 10-49% donor (low mixed chimerism); and 11.5% (3/26) had <10% donor (no donor). Many patients (25/44, 75.8%) had at least 1 peripheral blood chimerism observation within 30 days of their AIHA diagnosis. Using the observation closest to AIHA diagnosis, 64% (16/25) showed full chimerism, 24% (6/25) showed high mixed chimerism, 8% (2/25) showed low mixed chimerism, and 4% (1/25) showed no donor.

Supportive Management of AIHA

Patients received a median of two pRBC transfusions (range 0-10) in the first 2 weeks after AIHA diagnosis, with 69.7% of patients requiring at least one transfusion. Twelve patients were already admitted at the time of AIHA diagnosis, 5 patients required a new admission, 3 patients required intensive care unit admission, and 13 patients did not require an admission and were managed on an outpatient basis.

Patients with AIHA treated with AIHA-directed pharmacologic therapy (Fig. 1)

Of the 33 patients with AIHA, only 16 (48.5%) were treated with new AIHA-directed pharmacologic therapy. Patients received a median of one AIHA-directed treatment (range: 1-4). Treatments included: corticosteroids (n=13), rituximab (n=6), intravenous immunoglobulin (n=2), mycophenolate (n=2), erythropoietin (n=2), bortezomib (n=2), cyclosporine (n=1), and plasmapheresis (n=1). Variable treatment responses were seen (Table 2). Six patients required corticosteroids only, 1 patient received rituximab only, 2 patients received an erythropoietin stimulating agent only, and 7 patients received more than one AIHA-directed treatment. First-line pharmacologic treatment was most commonly corticosteroids (n=11). The most common second line treatment was rituximab (n=4).

Corticosteroid only treatment . Of the 6 patients who were treated with corticosteroids only, the median time to development of AIHA after HSCT was 5.9 months (range: 3.7-29.7 months). These patients were a median age of 0.46 years (range: 0.14-3.88 years) at time of transplant. Five of these patients had received bone marrow (BM), and 1 had received peripheral blood stem cells (PBSC). All patients in this group had an immunodeficiency diagnosis, including CD40L deficiency (n=2), severe combined immunodeficiency (n=2),

Wiskott-Aldrich Syndrome (n=1), and NFKB1 deficiency (n=1). Five patients received serotherapy with anti-thymocyte globulin and 5 received myeloablative conditioning. One patient had CMV while 2 had EBV concurrently or prior to the time of AIHA after transplant. At the time of AIHA diagnosis, these patients had a median hemoglobin of 6.4 g/dl (range 4 -10 g/dL). All patients received pRBC transfusions. Five patients (83.3%) had a partial response to corticosteroids at 1 month; one patient had a complete response. One of these patients was diagnosed with EBV 1 week after being diagnosed with AIHA and received rituximab for treatment of EBV. Five patients (83.3%) were in complete remission at last follow up while 1 patient had a partial remission.

Corticosteroids and rituximab treatment . Three patients received corticosteroids followed by rituximab for treatment of AIHA. The median time to AIHA after HSCT in these patients was 6.34 months (range 4.17-6.77 months) and were a median age of 4.98 years (range 1.29-8.04 years) at the time of transplant. Median hemoglobin was 4.8 g/dL (range 4.0-6.9 g/dL). These patients all had non-malignant diagnoses and received matched unrelated donor (MURD) BM transplants with myeloablative conditioning. One month after rituximab, 2 patients had a partial response and 1 patient had a complete response. Six months after AIHA diagnosis, 1 patient was in partial remission and 2 patients were in complete remission; all were in complete remission at last follow up.

Bortezomib treatment . Two patients required third- or fourth-line treatment with bortezomib. One patient developed AIHA at 4.73 months after MURD BM transplant with reduced intensity conditioning including alemtuzumab serotherapy for X-linked lymphoproliferative disease. Hemoglobin at time of diagnosis was 4 g/dL, and the patient received 10 pRBC transfusions in the first two weeks after diagnosis and required ICU care. The patient was started initially on corticosteroids, then rituximab, followed by mycophenolate with non-response and then received bortezomib with a partial response. The patient developed iron overload the year following AIHA diagnosed by T2* MRI. At the time of last follow up, the patient was alive and in complete remission.

The other patient developed AIHA at 3.19 months post-transplant after a matched related BM transplant with myeloablative conditioning for combined immunodeficiency. This patient had a history of AIHA pre-transplant. Hemoglobin at time of AIHA diagnosis was 7.1 g/dL, and the patient received 2 pRBC transfusions in the first two weeks after diagnosis. The patient received plasmapheresis after intravenous immunoglobulin with non-response, corticosteroids with partial response, and then bortezomib with non-response. This patient also had iron overload in the year following AIHA diagnosed by T2* MRI. This patient later developed pure red cell aplasia and graft failure and died after receiving a second transplant.

Patients with AIHA who did not require new AIHA-directed pharmacologic treatment

Seventeen patients were managed without modification of their current therapy and received supportive care only for their AIHA. Of these 17 patients, 15 patients (88%) were on immunosuppression at the time of AIHA diagnosis, described further below. Three patients had a history of an immune cytopenia prior to transplant including immune thrombocytopenia (n=1) and AIHA (n=2). These patients were significantly older at the time of transplant (median 10.02 years, range: 0.22-22.71) compared to those treated with corticosteroids-only (median 0.46 years, range: 0.14-3.88) and those treated with more than one AIHA-directed pharmacologic (median 4.98 years, range 0.71-12.91); p=0.009 (Table 3). AIHA occurred at a median of 2.83 months (range: 0.95-12.88) after HSCT in this group in comparison to 5.91 months (range: 3.71-29.73) in the corticosteroid-only treated group and 4.72 months (range 3.19-7.43) in those treated with more than one AIHA-directed treatment. Similar to the corticosteroid-treated group, most (n=15) had a BM donor source, 1 had a peripheral blood source, and 1 had a cord blood source. Most patients in this group had a MURD (n=10). Five patients (29.4%) had malignant disease as compared with only 2 patients (12.5%) in the entire pharmacologic treatment group. Four patients had acute GVHD in the first year after transplant and five patients had chronic GVHD. Five patients (29.4%) had CMV infection and 3 (17.6%) had EBV infection concurrently or prior to AIHA after transplant.

In this group of 17 patients, the median hemoglobin at time of AIHA diagnosis was 7.7 g/dL (range: 5.6-10.8)

compared to 6.4 g/dL (range 4-10) in the corticosteroid-only group and 6.8 g/dL in the group treated with more than one AIHA-directed pharmacologic (p=0.07). Only ten patients (58.8%) in this group received a pRBC transfusion in the first two weeks after AIHA diagnosis compared to 100% in the corticosteroid-only group and 85.7% in the group treated with more than one AIHA-directed pharmacologic (p=0.15). Although 9 of these patients (52.9%) were already admitted at the time of AIHA diagnosis, no patient in this group required a new admission for management of AIHA.

In this group that did not receive new AIHA-directed treatment, 15 patients (88%) were on immunosuppression at the time of AIHA diagnosis. Eight of the 15 patients (53%) were on immunosuppression for prophylaxis of GVHD including cyclosporine, tacrolimus, and mycophenolate; 4 of these patients were also on a corticosteroid taper. Four of the 15 patients were on immunosuppression for treatment of acute GVHD; 2 patients were receiving both cyclosporine and biologics (infliximab and basilixumab) and weaning corticosteroids; 1 patient was receiving cyclosporine and weaning corticosteroids, and 1 patient was on corticosteroids alone. The 3 remaining patients managed with supportive care were on immunosuppressives for other reasons (concern for relapsed leukemia, treatment of nephropathy, and treatment of neutropenia and thrombocytopenia). Two patients were not on immunosuppression.

After one month of observation, 7 patients had a complete response of their AIHA, 7 patients had a partial response, and 1 patient had non-response (unknown, n=2). Longer term follow-up and remission status was more difficult to obtain in this group due to relapsed disease, development of post-transplant lymphoproliferative disease, death due to other causes, need for a second transplant, and patient re-location. It is not evident that AIHA was a contributor to these outcomes.

Outcomes of patients with AIHA

The median time of follow up after AIHA diagnosis was 1.8 years (range 0.02-12.8); median time of follow up after transplant was 2.2 years (range 0.4-13.2 years). There were 9 patients who were deceased at last follow up. No patient deaths were related to complications of AIHA or its treatment. Six months after AIHA diagnosis, of the patients with available data (n=25), 68% (17/25) of patients were in complete remission from AIHA, 20% (5/25) in partial remission, and 12% (3/25) not in remission. One year after AIHA diagnosis, of the patients with available data (n=20), 80% (16/20) were in complete remission from AIHA, 10% (2/20) in partial remission, and 10% (2/20) not in remission.

Cases vs Control Analysis

Of the patients with AIHA, 7 patients had acute GVHD in the first 100 days after transplant, while 14 had acute GVHD in the control group (p>0.99). In the first year after transplant, 8 of the AIHA cases and 13 controls had acute GVHD (p=0.38), and 8 of the AIHA cases and 14 controls had chronic GVHD (p=0.54).

Lymphocyte subsets were checked within 1-month post-AIHA diagnosis in 8 of the AIHA cases; 3 additional cases had lymphocyte subsets checked in the month prior to diagnosis. Lymphocyte subsets were obtained in 25 controls within the first-year post-transplant. Given these small numbers, statistical calculations of comparisons were not performed.

DISCUSSION

Given the morbidity associated with AIHA post-transplant and the absence of management guidelines for this rare complication, detailed review of the clinical characteristics, treatment, and outcomes of cases can be a helpful guide to clinical care. In a tertiary care pediatric transplant center, the incidence of AIHA after HSCT was 3.8%. There was a wide range of severity and treatment for the 33 cases identified. Although 3 required intensive care management, 13 patients were managed in the outpatient setting. In addition, this cohort was divided almost equally between patients who were able to be observed on their current therapy without the addition of new AIHA-directed therapy, while the other half required between 1-4 new AIHA-directed pharmacologic therapies added to their regimen.

The patients in the group that did not require new AIHA-directed therapy (17/33, 51.5%) seemed to have an

overall milder course. Although many of these patients were still admitted at the time of AIHA diagnosis, it is notable that none of the patients in this group required a new admission or an ICU admission for treatment of AIHA. This group had several distinct characteristics compared with those patients who received AIHA-directed therapy: these patients were more often transplanted for malignant disease and were significantly older at the time of transplant. The onset of AIHA also occurred at an earlier timepoint after HSCT, and these patients tended to have a higher hemoglobin at the time of AIHA diagnosis. Notably, most of these patients were on immunosuppressants at the time of AIHA diagnosis, and these therapies may have protected them from development of more severe AIHA. Previously reported factors associated with the development of autoimmune cytopenias post-transplant include unrelated transplants and non-bone marrow cell sources.[4] In this cohort, most patients had bone marrow as the donor cell source and human leukocyte antigen (HLA) matching at 10 out of 10 alleles. Thus, although the incidence of AIHA was similar to previous reports, the milder course in a large number of patients may also correlate with the bone marrow source and HLA-matching in this cohort.

The patients who required new AIHA-directed pharmacologic therapy (16/33, 48.5%) generally experienced more morbidity. In this cohort, the patients who received second-line therapies or combination therapies were more often transplanted for non-malignant diagnoses, most often primary immune deficiencies. Of those who were not admitted at the onset of AIHA, most required a new admission for management of their AIHA. Although 6 patients were treated with corticosteroid monotherapy, many patients in this group received second-line (or higher) treatment. Other reports have shown efficacy with second-line treatment with rituximab, or third-line treatment with agents such as bortezomib and sirolimus or a second transplant. [1, 8, 12, 13] We saw variable responses to therapies in this cohort, although most patients (66.7%) were in either complete or partial remission at 6 months after AIHA diagnosis.

The immune landscape can be difficult to assess in the post-transplant period, and immune testing is not routinely obtained even in the setting of new autoimmune diagnoses. Lymphocyte subsets were only checked in a small number of cases and, therefore, subanalyses could not be completed. Most patients had whole blood chimerism checked within 1 month before or after diagnosis of AIHA and had full or high mixed chimerism. Given the small numbers but high chimerism, it is not clear whether chimerism status correlates with development of AIHA. This highlights the need for prospective studies in which chimerism, immunoglobulins and lymphocyte subsets are routinely collected to determine whether these findings help to identify features associated with the development of AIHA and direct treatment.

Limitations of the study include the small sample size as well as limited observational lab data given the retrospective nature of this study. This was a single center review of a rare post-transplant complication; multi-institutional cohorts would provide more robust data collection and statistical power. This study identified eligible patients through use of direct antiglobulin testing; patients were only included with a positive test. Up to 10% of patients with AIHA have a negative direct antiglobulin test and therefore the incidence is likely an underestimate.[16, 17] In addition, the diagnosis of AIHA is complex in the post-transplant period, at which time, the etiology for anemia can be multifactorial. Long-term follow up of outcomes after AIHA is challenging due to limited data due to patient death from other causes, second transplants, and other causes for anemia over time.

This cohort included 33 patients with AIHA post-HSCT over a sixteen-year time period at a single institution. Overall, the incidence of AIHA was 3.8% and was significantly higher in patients transplanted for non-malignant diagnoses (7%). The clinical course and management were highly variable and different clinical characteristics were noted in patients with a milder AIHA course. Future collaborative multi-institutional studies with prospective data collection would lead to a better understanding of the pathophysiology of this complication and effective directed treatments to limit exposing patients to unnecessary immunosuppressant medications.

CONFLICT of INTEREST STATEMENT

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LEGENDS

Figure 1 AIHA-directed pharmacologic treatment of patients and response at 1 month after treatment

Supplemental Table S1 Case Control Matched Variables

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