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Autoimmune Hemolytic Anemia after Allogeneic Stem Cell Transplantation: Single Centre Experience

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Abstract: ***Purpose: Auto immune hemolyticanemia (AIHA) post allogeneic hematopoetic stem cell transplantation (HSCT) is a rare and still poorly understood complication. Detailed work on this complication are needed due to lack of prospective trials. Methods: This is a retrospective cohort study of 7 patients with AIHA after HSCT in a tertiary care Medical College Hospital from 2012 - 2023. Results: The overall incidence of AIHA after allogeneic HSCT was 3.93%. All transplants were performed for non - malignant condition.57.1 % of the patients who developed post transplant AIHA did not have any ABO Incompatibility.42.8% patients who developed post transplant AIHA had concurrent GVHD. All patients responded well to oral corticosteroids. Conclusion: Though a rare complication, post transplant AIHA is seen more commonly in patients undergoing HSCT for non - malignant conditions. Multi centric trials are the need of the day to understand this rare yet morbid post transplant complication.***

Keywords: Autoimmune hemolyticanemia, allogeneic HSCT, ABO incompatibilty, Graft versus Host Disease.

1. Introduction

Auto immune cytopenias after stem cell transplantation are a rare and poorly understood complication and occur due to complex process of lymphodepletion, immunosuppression, immune reconstitution and graft versus host effects during and after successful transplantation.

Autoimmune hemolyticanemia (AIHA) is the most common type of post hematopoetic stem cell transplant immune cytopenia and is due to antibodies directed against donor red blood cell antigen. In the pediatric transplant group the incidence of AIHA has been reported between 2.4 and 6% [1 - 3].

Risk factors reported in earlier studies include unrelated donor graft, conditioning regimens without total body irradiation, peripheral blood and cord blood transplants, graft versus host disease and transplants for non - malignant conditions [4 - 7].

Autoimmune cytopenias in the setting of allogeneic HSCT represent a donor against donor immune reaction. The complexity and lack of comprehensive understanding of the pathophysiology of AIHA after HSCT makes treatment challenging [2].

This is a retrospective cohort analysis describing the incidence of post - transplant AIHA in pediatric patients undergoing HSCT for thalassemia major at a tertiary care Medical College Hospital.

2. Materials and Methods

The retrospective cohort study was approved by the Institutional Ethics committee of Mahatma Gandhi Medical College and Hospital and included patients who underwent HSCT between February 2012 and March 2023 at the bone marrow transplant unit of Mahatma Gandhi Medical college & hospital in this time period (n=178) and were identified through HSCT program database.

Inclusion criteria were a positive direct antiglobin test and clinically significant hemolysis defined both by a decrease in hemoglobin and presence of at least one additional laboratory feature of hemolysis including reticulocytosis, low haptoglobin, indirect hyperbilirubinemia and/or elevatedlactate dehydrogenase. The date AIHA was diagnosed was defined as the date on which the patient met these criteria. The study included patients 1 - 16 years old who had AIHA following their first transplant. Demographic features, clinical characteristics, laboratory data, transplant types, graft versus host disease (GVHD) were obtained using chart review. Acute and chronic GVHD were staged using centre for International Blood & Marrow transplant research definitions [8]. Cytomegalovirus (CMV) and Epstein - Barr virus (EBV) infections were defined as a detectable blood CMV or EBV polymerase chain reaction. Laboratory response to AIHA treatment was defined as complete response if hemoglobin increased to prior baseline with no evidence of hemolysis by laboratory investigations while on AIHA treatment and partial response if hemoglobin increased but evidence of ongoing hemolysis was present [2,

9, 10]. 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 an ongoing evidence of hemolysis. Statistical analysis

3. Results

Over an eleven year period 7 of 178 patients (3.93%) who underwent allogeneic HSCT developed AIHA.

Table 1: Incidence

Number of Transplants	Developed AIHA	Percentage
178	7	3.93

The incidence was 57.1% (4/7) in HLA identical transplants and 42.85% (3/7) in haploidentical transplants.

In patients with AIHA, the median age at the time of transplants 5.5 years (range 4 - 7 years) and median time to development of AIHA after day of transplant was 7.7 months (range - 4 - 12 months). At the time of diagnosis of AIHA all patients had a positive direct antiglobin test. Gender mismatch was seen in 2 patients (28.5%) and of these one each underwent haplo identical and HLA matched allogeneic HSCT respectively.

Of all the patients who developed AIHA, 4 (57.1%) did not have any ABO Rh incompatibility and one each (14.28%) had bidirectional, major and minor ABO incompatibilty.

Presence of concurrent GVHD as a possible risk factor for developing AIHA post transplant was seen in 3 (42.85%) patients. All the patients who developed AIHA post transplant showed >90% donor DNA chimerism.

All the patients required at least one PRBC transfusion in the first two weeks of AIHA diagnosis.

Only one patient required ICU admission while the rest were treated on outpatient basis.

Table 2: Clinical Characteristics

S. No.	Clinical Characteristics	Number	Percentage %
1	Gender Mismatch		
	Yes	2	28.5
	No	5	71.5
2	Type of Transplant		
	HLA Identical	4	57.1
	HAPLO Identical	3	42.8
3	GVHD	3	42.85
4	Bidirectional ABO - Incompatibility	1	14.28
	Major ABO Incompatibilty	1	14.28
	Minor ABO Incompatibility	1	14.28
	NO ABO Incompatibility	4	57.1
5	Chimerism >90% Donor DNA	7	100
6	ICU Admission	1	14.25

All the patients received cyclosporin and oral steroids for treatment. After one month of observation 4 patients (57.1%) had complete response of their AIHA, 2 patients (28.5%) had partial response and 1 patient (14.25%) had no response.

Table 3: Response to Treatment qfter 4 Weeks

Type of Response	Number	Percentage
Complete Response	4	57.1
Partial Response	2	28.5
No Response	1	14.25

Long term follow up showed complete response in 6patients (85.7%) and partial response in 1 patient (14.25%). These children are on regular follow up with > 90% donor DNA chimerism and are transfusion free.

4. Discussion

Auto immune cytopenias (AIC) are the most common autoimmune manifestations following allogeneic HSCT in pediatric and adult recipients [11, 12]. Though AIC are rare in post allogeneic HSCT with an estimated incidence of 3% in adults [13 - 21] and nearly 5% in children [12, 21], they sometimes can be seen more frequently in certain allogeneic HSCT settings. Several case series that showed higher than average AIC incidence of 20 - 35% [22 - 24] involved children transplanted for non - malignant indications following intense lymphodepletion. The incidence in our study was 3.93% which is similar to studies by Hillier K [25] who reported an incidence of 3.8% and Zar Ni Soe [26] who reported it as 3.1%.

There was no significant association of post - transplant AIHA with gender mismatched donor transplant which was similar to the study by ZarNi [26].

All of our patients were on immunosuppression at the time of diagnosis of AIHA and probably were protected from developing severe AIHA. Previously reported studies associated unrelated transplants and non bone marrow source as a causative factor [4]. In our study all the patients had bone marrow as the donor cells source and a 10 out of 10 human leukocyte antigen match which may be the reason for a milder course despite a similar incidence to previously reported studies.

Risk factors for the development of AIC in children undergoing HSCT include non - malignant primary diagnosis, use of unrelated donor, lack of total body irradiation in the conditioning regimen, chronic GVHD and the use of peripheral or umbilical cord blood stem cell source [12].

In our study presence of concurrent GVHD was seen in 42.8% cases.

Zar Ni [26] also reported a significantly higher risk of AIHA in patients receiving ABO mismatched stem cell transplant compared with ABO matched. But in our study 4/7 (57.1%) patients who developed AIHA did not have any ABO Rh incompatibility.

Post allogeneic HSCT AIHA is most commonly treated with intravenous immunoglobulins or steroids, rituximab monotherapy and a variety of other approaches including immunosuppression with azathioprine, cyclosporine, 6 mercaptopurine, mycophenolatemofetil and second stem cell transplant [12]. All our children responded to a combination therapy of cyclosporin and oral steroids.

5. Conclusion

Identification of risk factors for developing AIHA in children undergoing allogeneic HSCT and diagnostic characterization are an important tool to understand the biological mechanisms behind development of these complex conditions.

Limitations of the study include the small sample size as well as the limited observational data given the retrospective nature of the study. This was a single centre review of a rare post transplant complication and multi centre cohorts may provide better data collection and statistical power. This would probably help in better understanding of the pathophysiology of this complication and effective directed treatments to limit exposing patients to prolonged immunosuppressants.

Declarations and Statements:
Competing Interests: None
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Nikita Yadav made substantial contributions to interpretation of data, revised it critically for important intellectual content and approved the version to be published.

Shweta Sharma made substantial contributions to interpretation of data, revised it critically for important intellectual content and approved the version to be published.

RachnaNarain approved the version to be published.

PriyaMarwah made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved and drafted the work