

Clinico-Epidemiological Study of Dermatological Complications in Post Allogeneic Bone Marrow Transplant Patients: A Cross-Sectional StudyPrasaneet Dash¹, Ransingh Tanwar², Vinay Kumar³, Saurabh Sarda^{4*}¹Senior Resident, Department of Dermatology, Venerology and Leprosy, GMC Ratlam, Madhya Pradesh²Senior Resident, Department of Dermatology, Venerology and Leprosy, GMC Bhopal, Madhya Pradesh³Assistant Professor, Department of Pediatrics, PCMS & RC, Bhopal, Madhya Pradesh⁴Senior Resident, Department of Dermatology, Venerology and Leprosy, Dr. Ulhas Patil Medical College, Jalgaon, Maharashtra

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Conflict of interest: Nil

Abstract:

Background: Dermatological complications are quite prevalent in post-allogeneic bone marrow transplant patients but are often overlooked. Although several studies have been dedicated to systemic complications in post-allogeneic bone marrow transplant patients, only a few reports have been published on dermatological complications. Furthermore, to the best of our knowledge, no systematic study has been done to classify and compare the prevalence of various dermatological complications in post-allogeneic BMT patients. Thus, we have planned this study to develop a better insight into dermatological complications in post allogeneic BMT patients which will further help in its effective prevention, control and treatment in the future.

Objectives: To study different dermatological complications in post allogeneic bone marrow transplant patients.

Methodology: This study was conducted in the Department of Dermatology, Venereology and Leprosy in collaboration with the Bone Marrow Transplant unit of Maharaja Yeshwantrao Hospital, Indore from October 2020 to September 2021. All patients undergoing allogeneic bone marrow transplantation in the Bone Marrow Transplant unit of MY hospital, Indore were included in the study.

Results: The mean age of patients in the study was 7.82 years. The majority (17/37) of the patients were between 6-10 years of age. The most common indication for allogeneic bone marrow transplantation in the study was Thalassemia major (26/37). Dermatological complications were more frequent in patients belonging to the lower-middle socio-economic class (19/37) and patient who received BMT in the winter months from January to March (6/13). However, the association was not statistically significant. Among non-dermatological complications, the most frequent complication seen was mucositis (16/37) followed by hypertension (13/37) and veno-occlusive disease (5/37).

Conclusion: Post-allogeneic BMT patients experience various dermatological disorders, including side effects of different drugs and common infectious diseases (such as herpes zoster and tinea corporis), with an unusually high frequency. Prompt diagnosis and treatment of these simple skin changes such as erythema multiforme and candidiasis may reduce SJS/TEN and septicemia rates. Also, early intervention in paediatric transplant recipients may prevent several other diseases like skin tumours, common in adults suffering from complications.

Keywords: Dermatological Complications, Bone Marrow Transplant, Post Allogeneic.

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Introduction

Bone marrow transplantation was proposed as a treatment strategy just over 60 years ago. Owing to great advances in the field, it has become an established method for the treatment of many haemato-oncological, immunological and hereditary conditions with the potential of cure. The number of bone marrow transplants performed worldwide reached one million by 2012.[1] According to the Worldwide Network of Blood and Marrow Transplantation, approximately 90,000 first bone marrow transplantation, 53% autologous

and 47% allogeneic are performed globally every year.[2] Bone marrow transplantation (BMT) is a procedure during which a patient receives healthy stem cells (blood-forming cells) to replace their stem cells that are destroyed by treatment with radiation or high doses of chemotherapy.[3] It is done to re-establish haematopoiesis in patients with diseased bone marrow or certain malignancies. In an allogeneic bone marrow transplant, the healthy stem cells are obtained either from the bone marrow of an unrelated donor who is genetically

similar to the patient or from a related donor who is not an identical twin of the patient. It requires that both recipient and donor share some level of identity of class I and class II human leukocyte antigens (HLAs).[4] The recipients of allogeneic BMT are required to go through different types of conditioning regimens before the transplantation.

These conditioning regimens have two major purposes: to eradicate the malignant disease and to suppress the recipient's immune system to decrease the chance of graft rejection. The marrow, mixed with peripheral blood, is usually harvested from the posterior iliac crests in case of paediatric patients. About 10 to 12 mL marrow/kg of the recipient's body weight is removed with the patient under general or, occasionally, spinal or epidural anaesthesia. In the allogeneic/syngeneic setting, the harvested marrow is heparinized, filtered, and then infused into the recipient. In case of Major ABO incompatibility between the donor and the recipient, red cells or plasma is removed from the bone marrow. Allogeneic BMT is indicated as a treatment option for various hematologic, neoplastic, and congenital disorders such as acute leukaemia, chronic leukaemia, adrenoleukodystrophy, aplastic anaemia, bone marrow failure syndromes, Hodgkin's lymphoma, hemoglobinopathies, inborn errors of metabolism, immune deficiencies, myelodysplastic syndromes, multiple myeloma, neuroblastoma, non-Hodgkin's lymphoma, POEMS syndrome, plasma cell disorders, and primary amyloidosis. [5]

Dermatological complications are quite prevalent in post allogeneic bone marrow transplant patients but are often overlooked. Although several studies have been dedicated to systemic complications in post allogeneic bone marrow transplant patients, only a few reports have been published on dermatological complications. Furthermore, to the best of our knowledge, no systematic study has been done to classify and compare the prevalence of various dermatological complications in post allogeneic BMT patients.[6] Thus, we have planned this study to develop a better insight into dermatological complications in post allogeneic BMT patients which will further help in its effective prevention, control and treatment in the future.

Objectives: To study different dermatological complications in post allogeneic bone marrow transplant patients.

Material and Methods

This hospital-based observational cross-sectional study was conducted after approval from the Institutional review board and ethical committee, MGM Medical College and Maharaja Yeshwantrao Hospital, Indore, Madhya Pradesh from October 2020 to September 2021. Since all the patients were below 18 years of age a written informed consent was obtained from each of the patient's parents/guardians after properly explaining to them about the study procedure in their language. All 37 patients admitted for allogeneic bone marrow transplantation in the Bone Marrow Transplant unit of Maharaja Yeshwantrao Hospital, Indore were recruited in our study. Recruited patients were subject to detailed history taking that included socio-demographic details, age at diagnosis, duration of illness, family history, the indication of transplant, date of transplant, duration of hospital stays and current treatment history.

Medical reports including clinical symptoms on presentation and details of co-morbidities were obtained. Reports of patient's routine investigations such as complete blood count, erythrocyte sedimentation ratio, C-reactive protein, random blood sugar, renal and liver function tests, serum electrolytes, PT/INR, electrocardiogram, chest X-ray and ultrasonography of abdomen were reviewed. Details of preparation done before allogeneic bone marrow transplantation including the type of conditioning regimen, granulocyte colony-stimulating factor (G-CSF) priming, graft versus host disease (GVHD) prophylaxis were noted. Next, the patients underwent a detailed general, physical and dermatological examination. Their body weight and height were measured. They were examined for active skin, hair and nail lesions, their morphology, number, colour and distribution in the body.

After examination, confirmation of diagnosis was made with help of consultants of the Department of Dermatology, Venereology, and Leprosy and appropriate laboratory investigations such as Wood's lamp examination, Gram staining, KOH mount, Patch test, Tzank smear, dermoscopy and skin punch biopsy. Contact details of the patients were recorded and the parents/guardians were instructed to notify the investigator in case any medical attention is required by the patient. All data was compiled using Microsoft Excel software. All the records about the identity of patients were kept confidential. SPSS v28.0 was used for analysis of the data.

Observation and results:

Table 1: Demographic Details of Post-Allogeneic BMT Patients (N=37)

| S No | Demographic Details | Frequency N (%) | |
|------|--|-----------------|-----------|
| 1 | Age (Mean \pm SD: 7.82 \pm 4.15 Years) | 1 – 5 Years | 12 (32.4) |
| | | 6 – 10 Years | 17 (45.9) |
| | | 11 – 15 Years | 6 (16.2) |
| | | > 15 Years | 2 (5.4) |
| 2 | Gender | Male | 24 (64.9) |
| | | Female | 13 (35.1) |
| 3 | Socio-Economic Status (According To Modified Kuppaswamy Scale) | Upper | 2 (5.4) |
| | | Upper Middle | 7 (18.9) |
| | | Lower Middle | 19 (51.4) |
| | | Upper Lower | 9 (24.3) |
| | | Lower | 0 (0) |
| 4 | Locality | Rural | 25 (67.6) |
| | | Urban | 12 (32.4) |

Above table no. 1 shows the during the study period, a total of 37 post-allogeneic bone marrow transplant patients were selected as participants. The age of the patients ranged from 2 years to 17 years. The mean age of the study population is 7.82 years with a standard deviation of ± 4.15 . The majority of patients belonged to the 6-10 years age group (n=17) followed by 1-5 years age group

(n=12). There was an increased male preponderance (n=24) with male: female ratio of 1.8:1. Socio-economic status of patients was assessed using modified Kuppaswamy scale. The majority of the patients belonged to the lower middle class (n=19) followed by upper lower class (n=9) and upper middle class (n=7). A bulk of the patients came from rural area (n=25).

Table 2: Indications for Allogeneic Bone Marrow Transplantation and Their Frequency

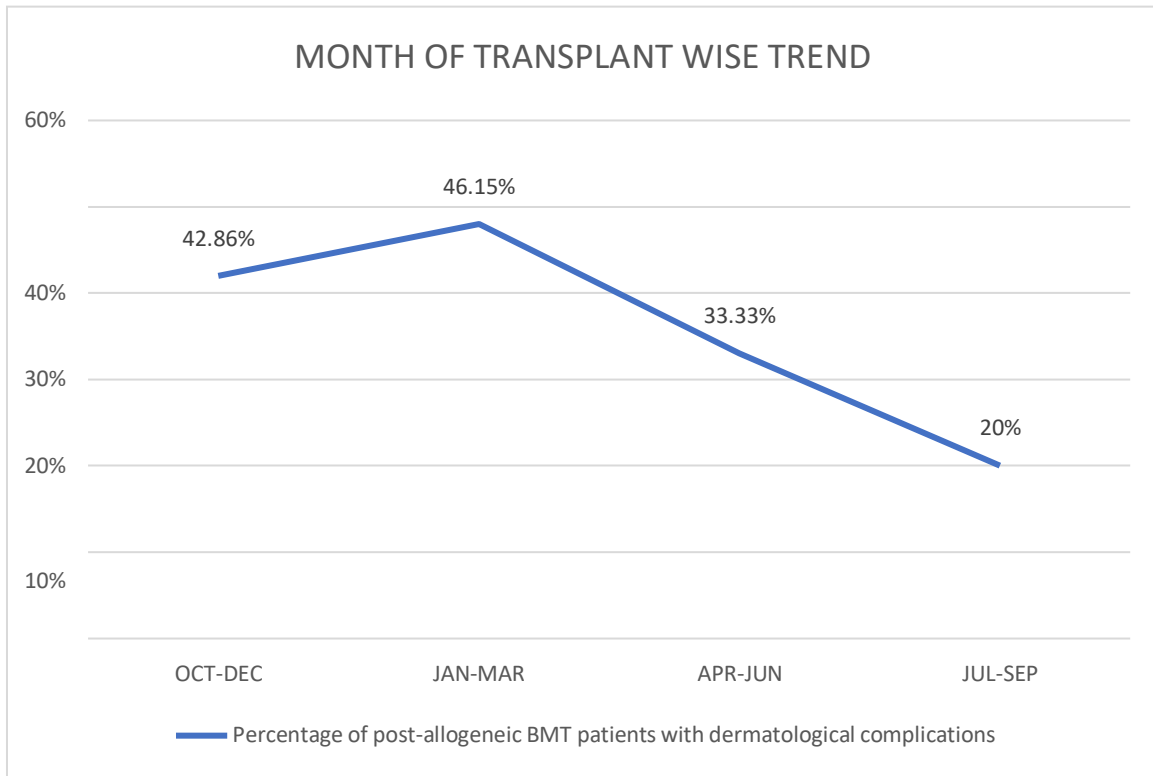
| S No | Indication for Allogeneic Bone Marrow Transplantation | Frequency |
|------|---|-----------|
| 1 | Thalassemia major | 26 |
| 2 | Sickle cell anaemia | 5 |
| 3 | Aplastic anaemia | 4 |
| 4 | Myelodysplastic syndrome | 1 |
| 5 | Chronic myeloid leukaemia | 1 |

Table 2 shows that, we found thalassemia major (n=26) as the most frequent indication for allogeneic bone marrow transplantation.

Table 3: Dermatological Complications and Their Frequency in Post Allogeneic Bone Marrow Transplant Patients

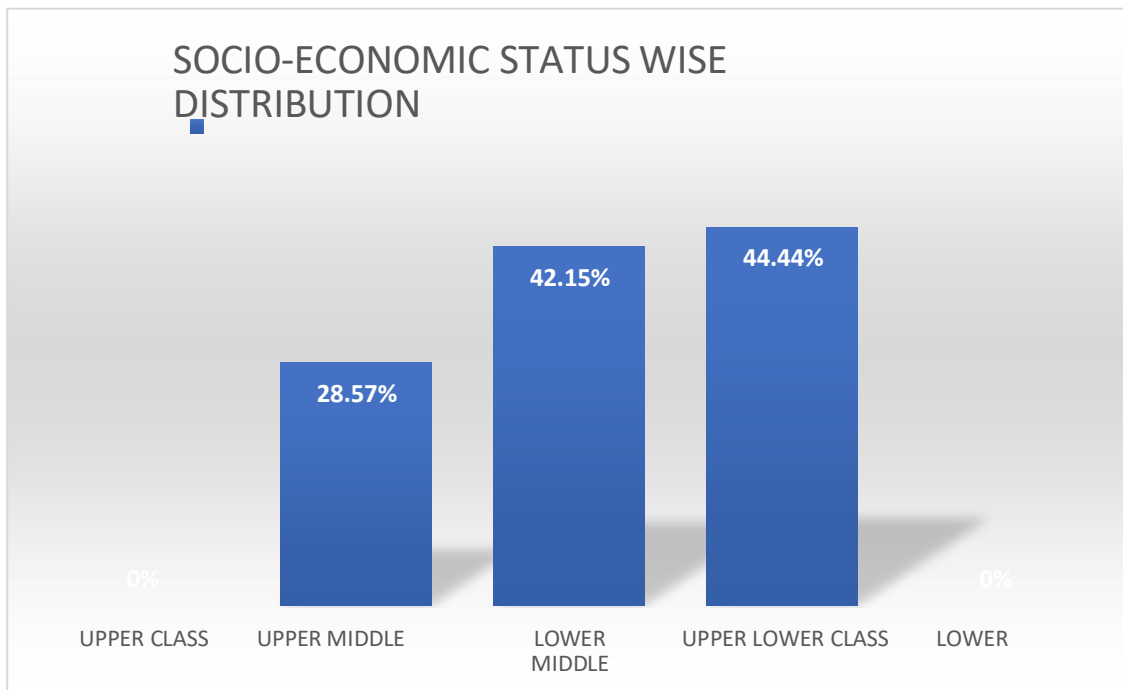
| S No | Dermatological Complications | | Frequency | |
|------|------------------------------|---|----------------------------|---|
| 1 | Drug Induced | A | Morbilloform Drug Reaction | 6 |
| | | B | Erythema Multiforme | |
| | | C | Hypertrichosis | |
| | | D | Urticaria | |
| | | E | Acneiform Eruptions | |
| 2 | Graft Versus Host Disease | A | Acute GVHD | 2 |
| | | B | Chronic GVHD | |
| 3 | Infective Diseases | A | Fungal | 8 |
| | | B | Bacterial | |
| | | C | Viral | |
| 4 | Non-Specific | A | Telogen Effluvium | 4 |
| | | B | Erythema Nodosum | |
| | | C | Atopic Dermatitis | |

In above table, 14 (37.84%) out of 37 post allogeneic bone marrow transplant patients developed dermatological complications in this study. Out of the 14 patients, 8 were male and 6 were female. The most frequent complication was infectious diseases followed by drug induced reactions.



Graph 1: Showing Month of Transplant Wise Trend of Post-Allogeneic BMT Patients with Dermatological Complications

In graph 1 it was observed that a majority of patients with dermatological complications underwent transplantation between October to March.



Graph 2: Showing Socio-Economic Status Wise Distribution of Post-Allogeneic BMT Patients with Dermatological Complications

In Graph 2, percentage of patients with dermatological complications was highest in upper lower class and least in upper class. There were no patients from lower class in this study.

Table 4: Comparison between Post-Allogeneic BMT Patients with and Without Dermatological Complications on the Basis of GCSF Priming Status

| GCSF Priming | Dermatological Complications | | No. of Transplants |
|--------------|------------------------------|--------|--------------------|
| | Present | Absent | |
| Done | 0 | 5 | 5 |
| Not Done | 14 | 18 | 32 |

In above table, none of the 5 patients who were GCSF primed, develop any dermatological complication. The chi-square statistic is 3.519. The p-value is 0.061. The result is not significant at $p < 0.05$.

Table 5: Comparison between Post-Allogeneic BMT Patients with and without Dermatological Complications on the Basis of GVHD Prophylaxis

| GVHD Prophylaxis | Dermatological Complications | | No. of Transplants |
|------------------|------------------------------|--------|--------------------|
| | Present | Absent | |
| CSP Only | 1 | 1 | 2 |
| CSP + MTX | 11 | 21 | 32 |
| CSP + MMF | 1 | 1 | 2 |
| CSP + MTX + MMF | 1 | 0 | 1 |

In above table, the majority of patients with dermatological complications (11/14) as well as patients without dermatological complications (21/23) received cyclosporine and methotrexate for GVHD prophylaxis. The chi-square statistic is 2.058. The p-value is 0.561. The result is not significant at $p < 0.05$.

Table 6: Non-Dermatological Complications in Post Allogeneic BMT Patients and their Frequency

| S No | Non-Dermatological Complications | Number of Recipients |
|------|--|----------------------|
| 1 | Mucositis | 16 |
| 2 | Hypertension | 13 |
| 3 | Veno-Occlusive Disease | 5 |
| 4 | Posterior Reversible Encephalopathy Syndrome | 1 |

In this study, we found mucositis and hypertension as the most frequent non- dermatological complications after allogeneic bone marrow transplantation.

Discussion

All the patients in our study belonged to the paediatric age group age ranging from 2 years to 17 years. The average age of the study population was 7.82 years with a standard deviation of ± 4.15 . Out of the 37 patients in the study, 24 patients were male and 13 patients were female. During an 11-year study period, Hierlmeier et al [7] noted that out of 126 paediatric patients that underwent allogeneic BMT, 75 were male and 51 were female. They also reported that the average age of post-allogeneic BMT patients in their study was 9.39 years with a standard deviation of ± 6.826 which was higher than our findings. To decrease the burden of these disorders, we have a dedicated Thalassemia unit in our hospital. Probably due to the above reasons, we found thalassemia major ($n=26$) and sickle cell anaemia ($n=5$) as the most frequent indications for allogeneic bone marrow transplantation in our study. This finding is consistent with a similar study conducted by Zaidman et al [8] where they observed that out of 38 patients suffering from hemoglobinopathy and treated by bone marrow transplantation in their centre, 34 had thalassemia major and 4 had sickle cell anaemia.

During the study period, we examined all the 37 post-allogeneic BMT patients for active skin, hair and/or nail lesions. Among them, 14 (37.83%) patients had dermatological lesions. 8 out of the 14 patients were male and the remaining 6 were female. The diagnosis of the dermatological disorders was confirmed after discussion with the consultants of the Department of Dermatology, Venereology and Leprosy and performing suitable laboratory investigations. Among these 14 patients, 6 patients presented with two different types of dermatological complications at two different instances while the other 8 patients developed a single type of dermatological complication. Infectious skin diseases ($n=8$) were found to be the most frequent type of dermatological complication occurring in 57.14% of all patients. Drug-induced ($n=6$) dermatological disorders followed next occurring in 42.56% of all patients. This finding is in agreement with a study performed by Euvrard et al [9] where infectious disorders were the most frequent skin diseases, occurring in 70% of all paediatric patients after organ transplantation.

Next to infectious diseases, drug induced complications were a major concern in patients who received transplants. In a study done by Manzoni et al, [10] the most frequent type of dermatological complication observed in post BMT paediatric population was drug induced skin disorder. Immunosuppressive medications, especially corticosteroids, methotrexate and

cyclosporine, are primarily responsible for findings such as hypertrichosis, striae, xerosis and acneiform eruptions. These changes can be considered only aesthetic, but they are very relevant to adolescents, intensely interfering with their quality of life. A comparative analysis was performed between post-allogeneic BMT patients with and without dermatological complications. Frequency of dermatological complications was observed to be higher among patients belonging to upper- lower and lower-middle socioeconomic class but the difference was not statistically significant. In a study done by S Fu et al[11], they established association of low SES and inferior overall survival among allogeneic HCT recipients which is not in disagreement with our study. Percentage of patients with dermatological complications was found higher in patients who got transplanted between October to March. Although, the difference was insignificant in this case too. Nina et al[12] showed in a study that the mortality rate in wintertime in the first year after transplantation is significantly greater than if deaths were totally random. Hence, our findings should be replicated at other centres and with larger sample sizes because identifying modifiable pathophysiological factors could have implications relevant for curtailing wintertime mortality. Challenges were faced in the diagnosis of chronic GVHD in a patient. However, the diagnosis was later confirmed by histopathological examination. When it comes to dermatological complications in post allogeneic BMT patients, a lot of conditions can be confirmed by performing a skin punch biopsy. O. Paun et al. [13] found that skin biopsies affected the primary care team's management in a significant percentage of patients to continue to support its use in BMT recipients. Hence, it is recommended to continue the use of skin biopsy when appropriate in patients who have undergone BMT.

Conclusion

Even after the transplant procedure, the recipients of allogeneic BMT are on several immunosuppressive medications for long durations. As a result of which the risk of various complications, including dermatological conditions, increases. Post allogeneic BMT patients experience various dermatological disorders, including side effects of different drugs and common infectious diseases (such as herpes zoster and tinea corporis), with an unusually high frequency. Prompt diagnosis and treatment of these simple skin changes such as erythema multiforme and candidiasis may reduce SJS/TEN and septicemia rates. Also, early intervention in paediatric transplant recipients may prevent several other diseases like skin tumours, common in adults suffering from complications. Preparing patients

and their families for cosmetic manifestations and elaborating strategies to handle those changes can make all the difference regarding the quality of life for post-allogeneic BMT patients. Educating parents and patients about early signs and symptoms of common dermatological complications and simple prevention techniques may lead to the recipients being capable of enjoying the long-term benefits of the transplant procedure. Basic measures, such as regular dermatological assessment after transplantation, may facilitate the reduction of important morbidities such as infections and GVHD.

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