EXTENSIVE ACUTE CUTANEOUS GRAFT VS HOST DISEASE: A RARE CASE REPORT OF SURVIVAL

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Key clinical message:

Graft Vs Host Disease (GVHD), is an immunologically mediated condition seen in allogenic Hematopoietic Stem Cell Transplant (HSCT) recipients. Because of the rarity of the disease, non-specific presentation and lack of clinicopathological correlation, its diagnosis is often delayed and prompt treatment is deferred, with increased mortality.

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Case Report:

BACKGROUND

Graft Vs Host Disease (GVHD) is an immunologically mediated polymorphically presenting condition manifesting with widespread systemic, cutaneous and mucosal involvement.(1) It occurs mostly in allogenic Hematopoietic Stem Cell Transplant (HSCT) recipients, ascribable to cell mediated programmed destruction by cytotoxic T-Lymphocytes.(2) GVHD is etiologically linked to minor mismatch in the Human Leukocyte Antigen (HLA) locus. However, host factor such as age or donor factors such as related vs unrelated, T cell replete vs deplete, or type of conditioning procedure such as reduced intensity radiotherapy or chemotherapy also aid in causation.(3) As around 20,000 allogenic HSCT are performed annually, with 66 Transplants conducted in a single government based tertiary center in Nepal, clinicians need to be vigilant about varied clinical features of GVHD.(4) (5)Multiple organs are involved in GVHD such as Liver, Gastrointestinal tract and Skin, in which the later is almost always involved. Skin involvement can also be varied based on acute or chronic GVHD. In which case, aGVHD presents mostly with maculopapular exanthem with predominant involvement of extremities and trunk and in extreme forms with Toxic Epidermal Necrolysis (TEN) like skin denudation linked with high mortality.(2,6,7)

GVHD, due to its varied presentation is difficult for clinicians to diagnose, which more often than not, leads to fatal consequences.(7) This case report reiterates importance of clinical acumen in preventing non-relapse associated mortality in hematological cancer patients post allogenic HSCT in resource poor settings.(8) Herein, we report a case of aGVHD with extensive skin exfoliation, penile ulcer and survival attributed to good clinical acumen, histopathological correlation and prompt treatment.

OBSERVATION

An 18-year-old male, known case of Acute Myeloid Leukemia (AML), post 58th day of allogenic HSCT (Matched related donor-father, HLA match-5/10), presented with mildly pruritic reddish lesions over bilateral palmoplantar region, with gradual progression of lesion to involve forearm,

legs, trunk, face, scalp and ears over a period of 10 days. (Figure 1: A-D) Initially, multiple pinheads sized, flat, lesion with red color were noted over bilateral palm that became confluent to involve and extend to 95% of Body Surface Area (BSA). Also, a painful solitary ulcer with whitish slough over glans penis was present. (Figure 2: A, B) There was associated swelling of face, lips and limbs. Lesions further progressed over period of 10 days with desquamation of skin colored to brownish scales over the lesion site and extension of penile erosion. (Figure 3 A-D) There was no history of vomiting, diarrhea, abdominal pain or yellowish discoloration of body. On examination, erythematous maculopapular exanthem was noted over generalized body with widespread skin denudation, largest plaque 10 * 5 cm in size irregular shaped over back in the mid-vertebral line of the spine on genital examination irregular erosion of 1 *0.5 cm in diameter was noted over glans penis with whitish thick slough. Laboratory investigations showed pancytopenia, hyponatremia and slightly increased alkaline phosphatase level =167 U/L (Range 30-120) suggestive of mild cholestasis. Biopsy showed vacuolar change of basal layer of cells, hydropic changes, keratinocyte apoptosis and band like lichenoid dermal lymphohistiocytic infiltrates.

Patient was treated with oral methylprednisolone 5 mg (milligram) twice daily tapered over 3 weeks and maintained with Tacrolimus 1 mg twice daily for 6 months, along with cotrimoxazole, Valganciclovir, Ursodeoxycholic acid for cholestasis and sodium chloride tablet for hyponatremia. Topical mometasone furoate ointment was locally applied over erosion of glans penis twice daily for 2 weeks with healing of lesion post treatment. The involved cutaneous and penile erosion healed over three weeks with normal underlying skin devoid of any pigmentation or scarring. (Figure 4) New lesions of aGVHD have not evolved for 6 months till now and patient is under remission for AML.

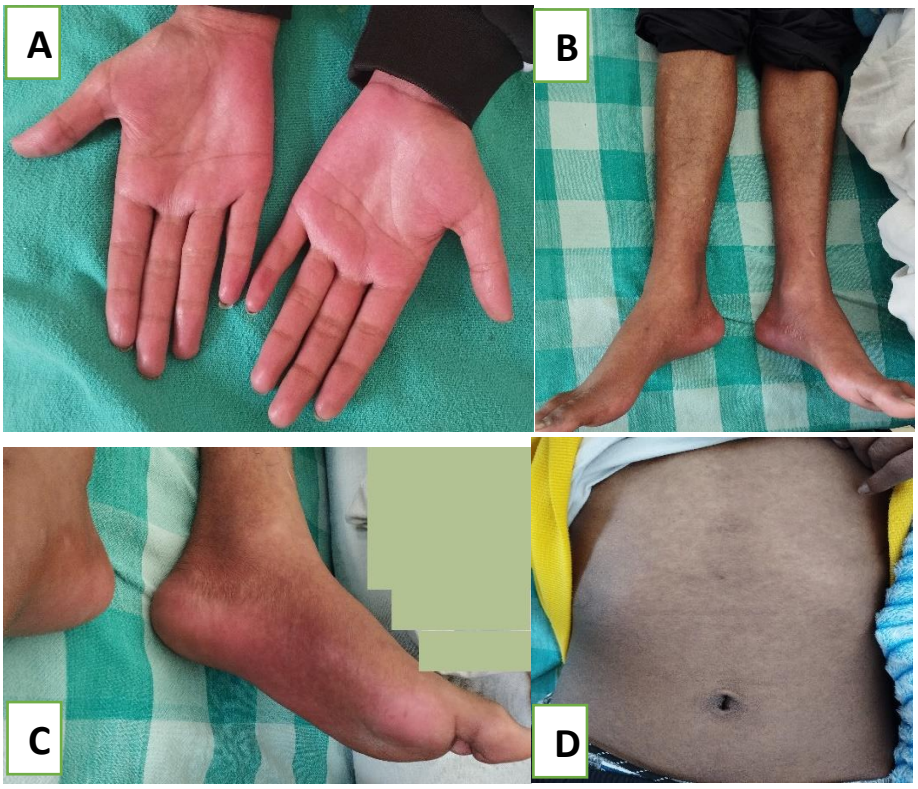

Figure 1 A-D: Erythematous maculopapular exanthem involving Palmoplantar region, extremities and trunk

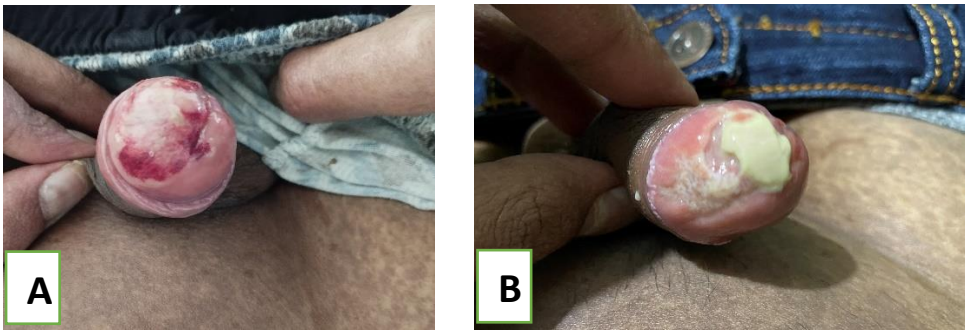

Figure 2: Solitary ulcer with whitish slough over glans penis

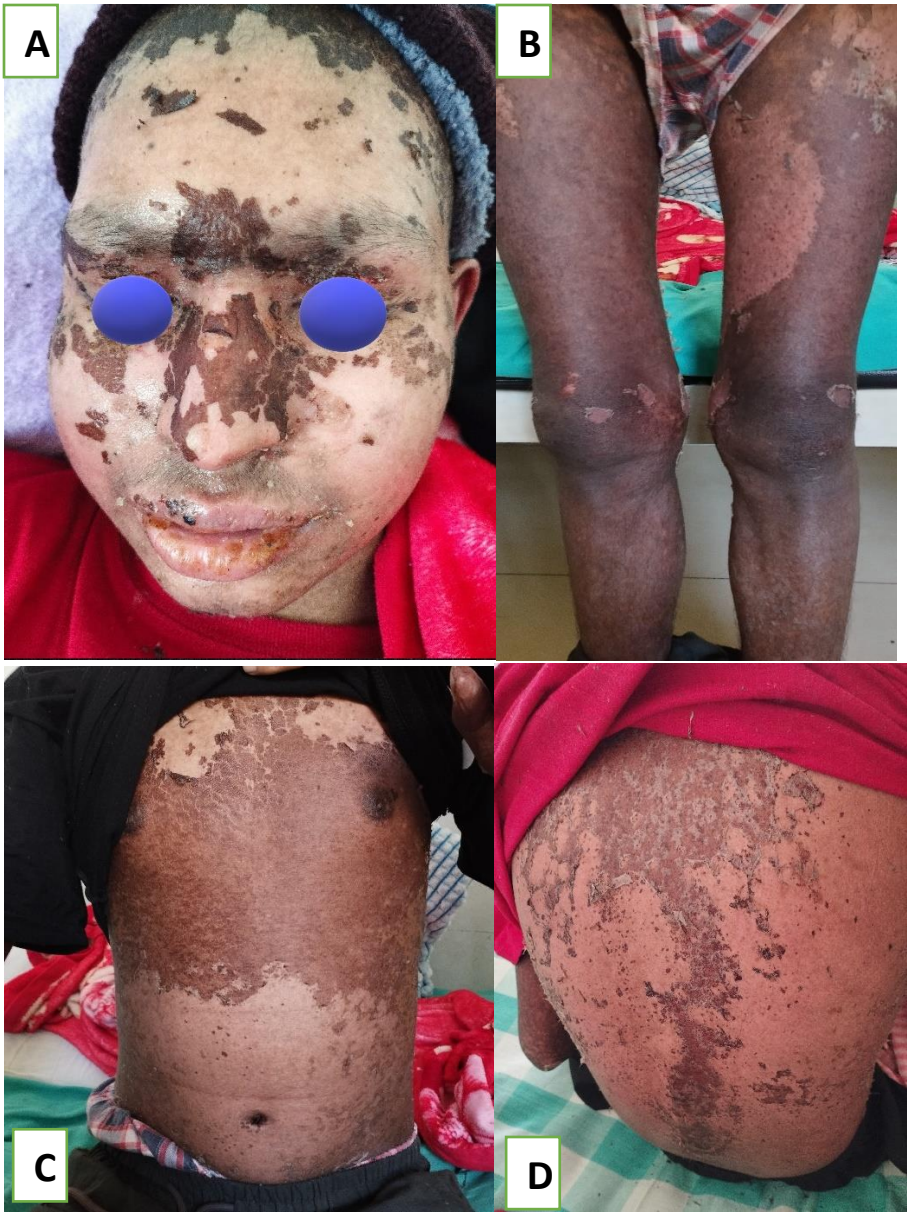

Figure 3 A-D: Post inflammatory desquamation over face, trunk and extremities post 10th day of the disease

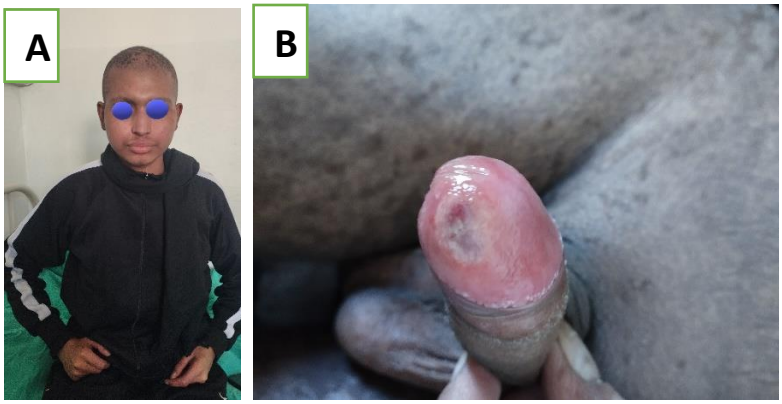

Figure 4 A, B: A-Complete resolution of skin lesion; B-healed penile erosion with post inflammatory mucosal hyperpigmentation

DISCUSSION

Graft Vs Host Disease (GVHD) is an immunologically mediated condition with varied systemic, cutaneous and mucosal clinical features. It occurs mostly in allogenic Hematopoietic Stem Cell Transplant (HSCT) recipients, due to T cell mediated cytotoxicity.(1,2) The cause of this T cell mediated cytotoxicity is largely attributed to minor mismatch in the Human Leukocyte Antigen (HLA) locus.(3) As in our case, HLA match of 5/10, could be attributed to the occurrence of aGHVD. Pathogenically, its occurrence is linked to activation of Antigen Presenting Cell (APC), proliferation of T lymphocytes and cytotoxic destruction of organs such as Liver, Gastrointestinal tract and skin. In addition to this, host factor such as age or donor factors such as related vs unrelated, T cell replete vs depleted, or type of conditioning procedure such as myeloablative radiotherapy or chemotherapy also aid in its causation.(7,9,10) As in our case, GVHD can occur even in Matched Related Donors, despite use of filgrastim in chemo myeloablative conditioning regimen, possibly attributable to minor HLA mismatch.(11) As in our case, aGVHD present as maculopapular exanthem with erythroderma involving almost 95 % BSA and penile ulcer. Usually, extensive erythrodermic patients with systemic involvement have high mortality.(1,6,12) However, on the contrary, our patient with extensive skin denudation, mucosal involvement with cholestatic change survived fatality with no systemic consequences or relapse till date. As in our case, lesions are initially acral followed by involvement of face, scalp, ear and trunk, which can be mildly pruritic. This tell-tale sign of acral initiation and subsequent retrograde progression to involve extremities, trunk and face could be utilized for early diagnosis of the disease.(1,13) Post

inflammatory desquamation with extensive skin denudation and erythroderma is an inevitable sequela in severe forms, linearly correlated to mortality.(13) Also, mucosal involvement presenting as oral aphthous ulcer or penile erosion and slough are a frequent manifestation in aGVHD.(14) Systemic features such as diarrhea, vomiting, abdominal pain and jaundice usually co-occur concurrently with skin manifestation, which was absent in our case.(2,6,7) Laboratory investigations usually show hyperbilirubinemia and transaminitis.(1) In our patient alkaline phosphatase level was slightly increased which depicted feature of cholestasis. Biopsy usually shows keratinocyte apoptosis, vacuolar degeneration of basal layer cells, hydropic changes and band like lichenoid dermal lymphohistiocytic infiltrates as in the histopathological section of our case. (Figure 2)(2) However, diagnosis will often rely on corroboration of clinical corroboration and clinical features, as histopathological mimics of aGVHD are often confounding.(15)

aGVHD is treated with oral or intravenous corticosteroid, in dose of 1 mg/ kg twice daily, in tapering dose, along with prophylactic maintenance with calcineurin inhibitor such as Tacrolimus or cyclosporine. Corticosteroid resistant cases can be alternatively treated with immunosuppressant such as Mycophenolate Mofetil, Tumor Necrosis Factor alpha inhibitors, Janus kinase inhibitor (JAK inhibitor) such as ruxolitinib or commercially available mesenchymal stem cell product.(3,16) Most often the severe sequelae are mitigated with timely diagnosis and treatment. And in about half of the cases control of the disease is fortuitously, achieved. Topical steroid ointment can be applied locally for limited cutaneous or mucosal lesion with healing of lesion post treatment without pigmentary or scarring sequelae as in our case.

GVHD, due to its varied presentation is difficult for clinicians to diagnose, which can lead to unforeseen complications including mortality.(12) This case report reiterates importance of clinical acumen and clinicopathological correlation in preventing non-relapse associated mortality in hematological cancer patients who have underwent allogenic HSCT in resource poor settings.(8) Herein, we report a case of aGVHD with extensive skin exfoliation, penile ulcer and survival attributed to good clinical acumen, histopathological correlation and prompt treatment. This case report iterates the importance of technique in lieu of technology in resource poor tertiary center of low-income countries like Nepal.

Ethical Statement for Clinical Case Reports

Hereby, I Dr Prajwal Pudasaini, MD consciously assure that for the manuscript EXTENSIVE ACUTE CUTANEOUS GRAFT VS HOST DISEASE: A RARE CASE REPORT OF SURVIVAL the following is fulfilled:

1) This material is the authors' own original work, which has not been previously published elsewhere.

2) The paper is not currently being considered for publication elsewhere.

3) The paper reflects the authors' own research and analysis in a truthful and complete manner.

4) The paper properly credits the meaningful contributions of co-authors and co-researchers.

5) The results are appropriately placed in the context of prior and existing research.

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Data availability statement

The data that support the findings of this study are openly available in Clinical Case Reports

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Detailed author's contribution:

PP and SP contributed to the collection of data and the management of the patient. PP and SP wrote the initial draft of manuscript. PP, SP, SA, SG, NT and BT revised and prepared the final version of the manuscript. All authors have read and approved the final manuscript and agree to take full responsibility for the integrity and accuracy of the work.

References:

1. Rodrigues KS, Oliveira-Ribeiro C, Silvia De Abreu •, Gomes F, Knobler • Robert. Cutaneous Graft-Versus-Host Disease: Diagnosis and Treatment. Am J Clin Dermatol [Internet]. 2017 [cited 2023 May 10];19. Available from: https://doi.org/10.1007/s40257-017-0306-9

2. Daniel Villarreal Villarreal C, Cesar Salas Alanis J, Carlos Jaime Pérez J, Ocampo Candiani J, Gonzalez JE. review Cutaneous graft-versus-host disease after hematopoietic stem cell transplant-a review * "Dr. [cited 2023 May 10]; Available from: http://dx.doi.org/10.1590/abd1806-4841.20164180

3. Choi SW, Levine JE, Ferrara JLM. Pathogenesis and Management of Graft versus Host Disease.

4. Passweg JR, Baldomero H, Grzegorz •, Basak W, Chabannon • Christian, Corbacioglu S, et al. The EBMT activity survey report 2017: a focus on allogeneic HCT for nonmalignant indications and on the use of non-HCT cell therapies Nicolaus Kröger 15 • for the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant [Internet]. 2019 [cited 2023 May 10];54:1575–85. Available from: https://doi.org/10.1038/s41409-019-0465-9

5. Poudyal BS, Tuladhar S, Neupane S, Sapkota S, Pandit S, Shrestha PR, et al. Hematopoietic Stem Cell Transplantation in Nepal: International Partnership, Implementation Steps, and Clinical Outcomes. Transplant Cell Ther. 2022 May 1;28(5):268–75.

6. Cho A, Paulitschke V, Just U, Knobler R. Cutaneous manifestations of acute and chronic graft-versus-host disease. Giornale Italiano di Dermatologia e Venereologia [Internet]. 2020 [cited 2023 May 10];155(1):76–87. Available from: https://www.minervamedica.it/en/journals/Ital-J-Dermatol-Venereol/article.php?cod=R23Y2020N01A0076

7. Dermatologic Manifestations of Graft Versus Host Disease: Introduction, Clinical Overview, Pathophysiology [Internet]. [cited 2023 May 10]. Available from: https://emedicine.medscape.com/article/1050580-overview

8. Hematopoietic Stem Cell Transplantation in Nepal: international partnership, implementation steps and clinical outcomes. - Physician's Weekly [Internet]. [cited 2023 May 10]. Available from: https://www.physiciansweekly.com/hematopoietic-stem-cell-transplantation-in-nepal-international-partnership-implementation-steps-and-clinical-outcomes/

9. Im A, Rashidi A, Wang T, Hemmer M, MacMillan ML, Pidala J, et al. Risk Factors for Graft-versus-Host Disease in Haploidentical Hematopoietic Cell Transplantation Using Post-Transplant Cyclophosphamide. Biology of Blood and Marrow Transplantation. 2020 Aug 1;26(8):1459–68.

10. Ferrara. Mouse models of graft-versus-host disease. Stembook. 2009;

11. Kanda J. Effect of HLA mismatch on acute graft-versus-host disease. International Journal of Hematology 2013 98:3 [Internet]. 2013 Jul 28 [cited 2023 May 10];98(3):300–8. Available from: https://link.springer.com/article/10.1007/s12185-013-1405-x

12. Holtan SG, Yu J, Choe HK, Paranagama D, Tang J, Naim A, et al. Disease progression, treatments, hospitalization, and clinical outcomes in acute GVHD: a multicenter chart review. Bone Marrow Transplant [Internet]. 2022 Oct 1 [cited 2023 May 10];57(10):1581–5. Available from: https://www.oncologynurseadvisor.com/home/cancer-types/hematologic-cancers/graft-host-disease-gvhd-diagnosis-disease-progression-treatment-risk/

13. Holtan SG, Yu J, Choe HK, Paranagama D, Tang J, Naim A, et al. ARTICLE OPEN Disease progression, treatments, hospitalization, and clinical outcomes in acute GVHD: a multicenter chart review. [cited 2023 May 10]; Available from: https://doi.org/10.1038/s41409-022-01764-w

14. Ion D, Stevenson K, Woo S Bin, Ho VT, Soiffer R, Antin JH, et al. Characterization of Oral Involvement in Acute Graft-versus-Host Disease. Biology of Blood and Marrow Transplantation. 2014 Nov 1;20(11):1717–21.

15. Fischer A, Jakubowski AA, Lacouture ME, Hollmann TJ, Drucker AM, Maloy M, et al. Histopathologic features of cutaneous acute graft-versus-host disease in T-cell-depleted peripheral blood stem cell transplant recipients HHS Public Access. Am J Dermatopathol. 2015;37(7):523–9.

16. Murata M, Teshima T. Treatment of Steroid-Refractory Acute Graft-Versus-Host Disease Using Commercial Mesenchymal Stem Cell Products. Front Immunol. 2021 Aug 19;12:3277.