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Case Series

Chronic graft versus host disease: A case series providing diagnostic and therapeutic perspectives

Monika Kumari[1], Kingshuk Chatterjee[1], Arun Achar[1]*, Adityendu Chakraborty[1], Sayoni Ghosh[1], Mahormi Mazumder[1], Sadia Rifat[1]

[1]Dept. of Dermatology, Venereology and Leprosy, Nil Ratan Sircar Medical College and Hospital, Kolkata, West Bengal, India

Abstract

Background: Chronic graft-versus-host disease (cGVHD) is a complex and serious complication that can arise following allogeneic hematopoietic stem cell transplantation (HSCT), leading to significant morbidity. It presents with diverse clinical patterns and can show marked variability depending on the underlying malignancy of the transplant recipient.

This case series aims to provide insight into the clinical characteristics, histopathological findings, and treatment outcomes of patients diagnosed with cGVHD according to the NIH consensus criteria.

Materials and Methods: A retrospective analysis was conducted on five patients with cGVHD who visited from January 2024 to January 2025. Among the patients, two were diagnosed with B-cell acute lymphoblastic leukemia (B-ALL), one patient with large cell lymphoma, another one with acute myeloblastic leukemia presented exhibited lichenoid-type cGVHD, while one patient with B-ALL mixed-type cGVHD. Comprehensive clinical evaluations and histopathological assessments were performed for each patient.

Results: Two patients with B-ALL, one patient with anaplastic large cell lymphoma and another one patient with AML displayed lichenoid-type cGVHD, characterized by symptoms including a pruritic rash and mucosal involvement, confirmed by skin biopsy findings.

One patient with B-ALL demonstrated mixed-type cGVHD, exhibiting features of both lichenoid and vitiligo types.

All patients were started on immunosuppressive drugs, including corticosteroids and additional targeted therapies. By the latest follow-up, three patients showed substantial improvement in their symptoms; however, one patient required continuous modification of their treatment due to persistent cGVHD manifestations. One patient lost to follow up.

Conclusion: This case series illustrates distinct manifestations of cGVHD in patients with different underlying malignancies, underscoring the importance of tailoring treatment strategies. Early recognition and appropriate management are essential for enhancing patient quality of life in those affected by cGVHD.

Keywords: Chronic graft versus host disease, hematopoietic stem cell transplantation, Lichenoid type, NIH consensus criteria.

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1. Introduction

Chronic graft-versus-host disease (cGVHD) is a complex and significant complication that often arises after allogeneic hematopoietic stem cell transplantation (HSCT). It remains the principal cause of late morbidity and mortality in this patient population, significantly affecting their quality of life and long-term survival prospects. cGVHD occurs when donor-derived immune cells, particularly T lymphocytes, recognize the recipient's tissues as foreign and initiate an immune response against them. This pathological response can lead to a wide range of clinical manifestations, impacting several organ systems, including the skin, liver, gastrointestinal tract, and lungs.[1,2]

The pathophysiological mechanisms underlying cGVHD involve a complex interplay between the donor and recipient immune systems, shaped significantly by the degree of human leukocyte antigen(HLA) disparity

*Corresponding author: Arun Achar
Email: arunachar1967@gmail.com

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between donor and recipient. When donor T cells are infused into a recipient, they can recognize the recipient's tissues as foreign, especially if multiple minor and major HLA mismatches exist.[3] Initially, the engagement of recipient antigen-presenting cells (APCs) leads to the activation of donor CD4+ and CD8+ T cells. Upon activation, these T cells proliferate and migrate to target tissues, causing immune-mediated damage through both direct cytotoxic effects and the release of pro-inflammatory cytokines such as TNF-α, IL-2, and IFN-γ.[3,4] These cytokines generate a cascade of inflammatory responses, resulting in tissue damage and fibrosis in affected organs.

The evolution of cGVHD typically follows an early initiating phase, characterized by the activation of donor T cells, which may progress into an extensive chronic phase lasting years. Chronic cGVHD often presents with diverse manifestations affecting skin, liver, and gastrointestinal organs, but may also involve other systems such as the lungs and salivary glands. The organ involvement varies from patient to patient, leading to challenges in diagnosis and treatment.[4,5]

Patients with cGVHD may experience a plethora of debilitating symptoms that can significantly compromise their quality of life. Dermatological manifestations may include lichen planus like lesion, poikiloderma, sclerodermatous changes, skin rashes, and xerosis. Gastrointestinal involvement can manifest as nausea, vomiting, diarrhea, and malnutrition, while liver involvement often results in hepatic dysfunction.[6] However, the most complex aspect of cGVHD arises from its long-term sequelae, which may include the development of secondary cancers, infections, and other long-term complications, increasing the burden on healthcare systems and affecting patients' psychosocial well-being.[7]

In tackling cGVHD, early recognition and intervention play a critical role in improving patient outcomes. The potential to identify biomarkers in peripheral blood or affected tissues could facilitate earlier diagnosis and prognostication.[6,8] Unfortunately, the clinical management of cGVHD often suffers from the absence of standardized scoring systems and lack of universal clinical criteria, which complicates timely diagnosis and intervention.[2,9]

2. Case Presentation

2.1. Case 1

An 8-year-old boy diagnosed with B-cell acute lymphoblastic leukemia (B-ALL), who underwent HSCT. At six months post-transplant, he exhibited symptoms of cGVHD, including lichenoid lesions affecting his nails and mucosa, a generalized rash, and complaints of weakness.(**Figure 1**) A skin biopsy demonstrated a lichenoid tissue reaction pattern characterized by interface dermatitis, with a band-like infiltration of lymphocytes at the dermal-epidermal junction and degeneration of the basal cell layer. The patient was treated with oral steroids and cyclosporine, significant improvement noted in his symptoms and skin lesions.(**Figure 2**a,b)

2.2. Case 2

An 18-year-old female diagnosed with anaplastic large cell lymphoma (ALCL), who developed lichenoid dermatitis four months after HSCT. She presented with pruritic erythematous papules and plaques on her extremities. Histopathological evaluation revealed apoptosis of keratinocytes consistent with a lichenoid tissue reaction. Treatment with oral steroids and topical tacrolimus was initiated, leading to a marked improvement in her skin lesions and overall symptoms. However, she experienced recurrence of his symptoms after six months, for which modification of treatment was done. (**Figure 3a,b**)

2.3. Case 3

A 27-year-old male who underwent HSCT for B-ALL. One year post-transplant, he developed chronic cGVHD characterized by lichenoid skin lesions and painful oral erosions. His skin presented with erythematous papules and plaques, while significant erosion and discomfort were noted in the oral cavity. A biopsy confirmed superficial interface dermatitis, indicative of cGVHD. The patient was managed with oral steroid, cyclosporine and symptomatic treatment for his oral lesions and skin manifestations. (**Figure 4**)

2.4. Case 4

A 22-year-old female who underwent HSCT following treatment for acute myeloid leukemia (AML). Eleven months post-transplant, she developed mixed-type cGVHD, presenting with both lichenoid skin lesions and features of vitiligo affecting his back. She also reported oral involvement characterized by mucosal erosion and discomfort. A skin biopsy revealed features of interface dermatitis with lichenoid tissue reaction, alongside areas of sclerosis. The patient was started on systemic corticosteroids and topical therapy. This patient lost to follow up.(**Figure 5**)

2.5. Case 5

A 10-year-old male patient with a history of B-ALL who underwent HSCT 8 months prior. He presented with a widespread lichenoid eruption affecting his body, mucosa, and nails. A course of steroid therapy resulted in a positive response, with significant improvement in his condition. (**Figure 6,7**)

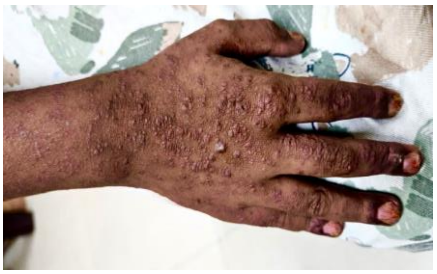

Figure 1: Lichenoid papules over dorsum of hand and longitudinal ridging of nails.

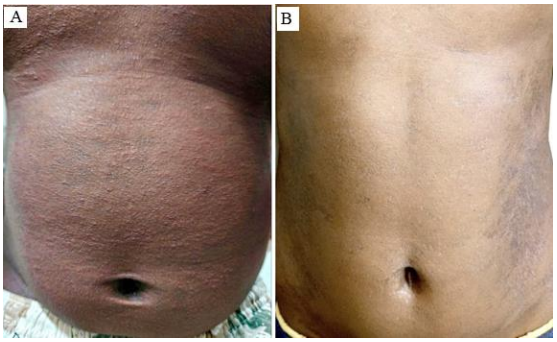

Figure 2: A,B: Illustrating improvement of skin lesion before & after treatment with oral corticosterids and cyclosporine. Patient was followed upto 1-year.(case1)

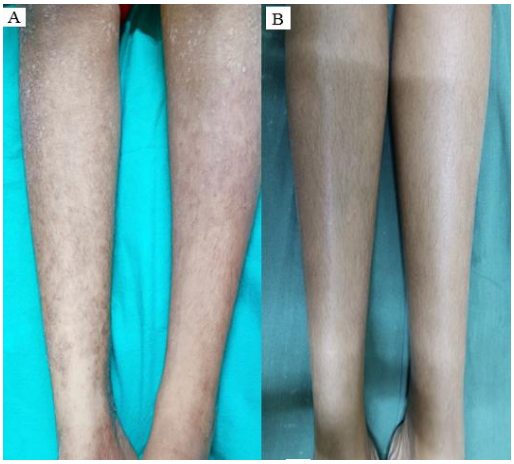

Figure 3: A,B: Showing improvement of skin lesion before and after treatment with oral and topical corticosteroids.(Case 2)

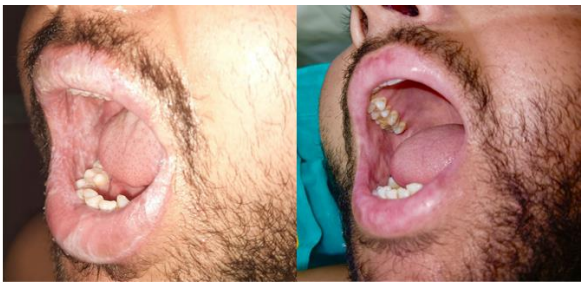

Figure 4: Showing marked healing of oral erosive lesion, treated with topical and systemic steroid for 2 months. (Case 3)

Figure 5: A female patient having mixed type cGVHD - lichenoid & depigmenting type (case 4)

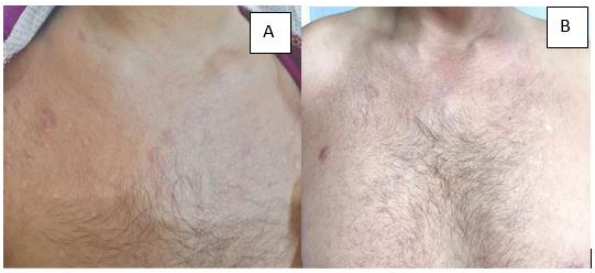

Figure 6: Improvement of skin lesion after treatment with oral steroid for 4 months.(case 5)

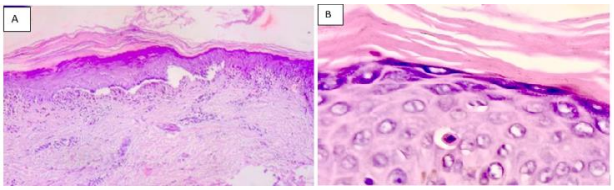

Figure 7: A: showing epidermal acanthosis, vacuolization of basal layer, lichenoid lymphocytic infiltrate in dermis and peri vascular lymphohistiocytic infiltration; **B:** Apoptotic keratinocyte

Table 1:

Case	Age (Years)	Sex	Primary condition	Onset (Days)	Type of skin lesions	Mucosa involvement	Nails involvement	Systemic involvement
1	8	M	B-ALL	180	Lichenoid	Yes	Yes	No
2	18	M	ALCL	120	Lichenoid	No	No	No
3	27	F	B-ALL	365	Lichenoid	Yes	No	No
4	22	F	AML	330	Lichenoid And Vitiligo-Like	Yes	No	No
5	10	M	B-ALL	240	Lichenoid	Yes	Yes	No

Table 2:

Case	BM donor	Skin lesions grade	Hyperkeratosis	Keratinocyte apoptosis	Lymphocytic infiltration	Vacuolar change	Follow up duration	Treatment received	Final outcome
1	Sister	3	Present	Present	Present	Present	1 year	Oral steroid + cyclosporine	Remission
2	Brother	3	Present	Present	Present	Absent	1 year	Oral steroid + topical tacrolimus	Recurrence
3	Sister	2	Present	Absent	Present	Absent	1 year	Oral steroid + cyclosporine	Completely resolved
4	Brother	2	Absent	Present	Present	Present	Patient did not follow up	Oral steroid	
5	Father	1	Absent	Present	Present	Absent	1 year	Oral and topical steroid	Remission

3. Discussion

A total of five patients (three males, two females) diagnosed with cGVHD following HSCT were included in this study. Similarly Arvind et al.[10] also had 5 patients of GVHD in their series. The mean age at presentation was 17.0 +/- 8(range: 8–27 years) in this study. However, in a previous study, GVHD patients had a mean age of 24.8 +/- 9.7 (14-43 years).[11]

In our study all patient had a prior diagnosis of hematologic malignancies, including B-cell acute lymphoblastic leukemia (B-ALL) (three cases), acute myeloid leukemia (AML) (one case), and anaplastic large cell lymphoma (ALCL) (one case). Quite similarly a prior study had 5 patients of ALL, 8 patients of AML and 1 patient of CML developing GVHD.[12] However a prior study had 5 patients of chronic granulocytic leukemia And 1 patient of AML, ALL and aplastic anaemia each, in their series.[11]

The onset of cGVHD manifestations ranged from 4 to 12 months post-HSCT in our study. However, onset of lesions of cGVHD varied between 117 days to 507 days following BMT, in a prior study. [11] In another study time interval from transplantation to the appearance of skin lesions was 4.9 ± 3.95 months.[13]

In our study all five patients exhibited lichenoid skin lesions, with four cases (80%) involving both skin and mucosa. Similarly another study also found majority of its patients having lichenoid skin lesions.[13] However, earlier one study found maculopapular (37.8%), lichenoid (37.8%), or sclerodermoid (13.5%) lesions in GVHD patterns.[14]

Another study found classical presentation with generalised exanthem and perifollicular erythema was the most common manifestation (84.6%).[12] Three patients (60%) had painful oral lesions, including erosions and mucosal discomfort. However a prior study detected mucocutaneous lesions in 37.5% cases.[11] 80% prevalence of oral lesions has been reported in cGVHD in other studies.[15]

Nail involvement was noted in two of our patients (40%). However, in a study Shreberk-Hassidim et al.found nail changes in 15% patients.[13]

Skin biopsy findings in our study were hyperkeratosis (60%), interface dermatitis with a lichenoid tissue reaction (100%), with keratinocyte apoptosis (80%), vacuolar changes (40%) and lymphocytic infiltration (100%) at the dermal-epidermal junction. Similarly Kim et al also found lichenoid histopathological features in majority cases (53%) and dyskeratosis (82.1%) and vacuolar changes (10.7%) were other findings.[16] Another study also demonstrated vacuolar interface dermatitis and dermal melanophages on biopsy.[13]

Our patients were treated with oral corticosteroids, cyclosporine, topical corticosteroids and topical tacrolimus. Similar treatment was also given by Shreberk-Hassidim et al.[13] and T Ruutu et al. in their respective studies.[17] However methotrexate, azathioprine, mycophenolate mofetil, extracorporeal photophoresis were also used in some of their patients.

Follow up duration was 1 year for 4 of our patients. However a previous study had longer duration of follow up.[11] Following treatment, skin lesions completely resolved in 1 patient, 2 were in remission, 1 had full recurrence after tapering of medication dose and 1 patient got lost to follow-up. There was no reported case of mortality among our patients. Similarly high rate of survival (85%) was also seen in a prior study.[13]

However in study of Kim et al.[16] out of the 86 patients, 44 showed complete resolution, and 38 died during follow-up.

4. Limitations

Small Sample Size and lack of long term follow up are limitations of this study.

5. Future Aspects

This case series can help identify various presentations and understanding diagnostic approach. It may provide insights into treatment response and personalized therapy approaches. Long-term impact assessment can guide future management strategies. The findings can also serve as a foundation for larger multicentric studies.

6. Conclusion

In conclusion, this case series outlines the diverse clinical manifestations of cGVHD in patient's post-HSCT, highlighting the importance of early recognition and tailored treatment strategies. All patients demonstrated improvement with steroid therapy except for Case 4 who lost to follow up. However, Case 2 exemplifies the chronic nature of cGVHD, underlining the necessity for ongoing management and follow-up, particularly in cases prone to recurrence.

7. Source of Funding

None.

8. Conflict of Interest

None.

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