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Original Article

Case series of cutaneous graft-versus-host disease (GVHD) in patients receiving haematopoietic stem cell transplantation in a tertiary Malaysian hospital

馬來西亞一所第三級醫院接受造血幹細胞移植病人發生皮膚移植物抗宿主病的病例系列

SS Yong, WH Han, RKJ Choong, NAA Faheem, YF Toh, PC Bee, Z Kwan

Introduction: Acute and chronic graft-versus-host disease (GVHD) are multisystem disorders which are complications of haematopoietic stem cell transplant (HSCT). It is important to consider other differential diagnoses that may have similar clinical and histopathologic features as GVHD. ***Method:*** A retrospective analysis was conducted on adult patients from a single centre who developed GVHD after HSCT between January 2014 and June 2018. ***Results:*** Fourteen patients were included where 13 had acute GVHD and 1 had chronic GVHD. The median age was 35.0 years (IQR 26 to 44 years) while median onset of cutaneous symptoms for acute GVHD was 70 days (IQR 17.0 - 96.5 days). All cases had histopathological confirmation. For acute GVHD (n=13), classical presentation with generalised exanthem and perifollicular erythema is the commonest (84.6%, n=11), where 61.5% and 38.5% of patients had stage 2 and 3 extent of skin involvement, respectively (n=8, n=5). 76.9% (n=10) of patients with acute GVHD had other organs involvement, such as liver, eyes, and gut. Lerner's grade 2 was the most common histological grade for patients with acute GVHD (53.8%, n=7) followed by grade 1 (38.5%, n=5). One patient with chronic GVHD had lichen planus-like presentation. All patients had received various antibiotics within two months prior to onset. None of the skin biopsies showed significant eosinophilic infiltrates. ***Conclusion:*** Cutaneous manifestations of GVHD are among the earliest presenting complaints among patients who have undergone HSCT. Half of these patients only had skin GVHD without any other organs involvement. Hence, biopsy is important to confirm the diagnosis of GVHD along with clinical correlation.

Division of Dermatology, Department of Medicine, Faculty of Medicine, University Malaya, Malaysia
SS Yong, MRCP(Ireland), Adv M Derm(UKM)
WH Han, MBChB(Edinburgh), MRCP(Ire)
RKJ Choong, MBBS(London), MRCP(UK)
NAA Faheem, MRCP(UK), Adv M Derm(UKM)
Z Kwan, Adv M Derm(UKM), FRCP(UK)

Department of Pathology, Faculty of Medicine, University Malaya, Malaysia
YF Toh, MD(USM), MPath(UM)

Division of Haematology, Department of Medicine, Faculty of Medicine, University Malaya, Malaysia
PC Bee, MD, MMed(UM)

Correspondence to: Dr. WH Han

Division of Dermatology, Department of Medicine, Faculty of Medicine, University Malaya, Malaysia

簡介：急性和慢性移植物抗宿主病是一種多系統疾病，是造血幹細胞移植的併發症之一。重要的是要考慮可能與此病具有相似臨床和組織病理學特徵的其他鑑別診斷。**方法：**對 2014 年 1 月至 2018 年 6 月期間單一中心造血幹細胞移植後發生移植物抗宿主病的成年患者進行回顧性分析。**結果：**共納入 14 位患者，其中急性移植物抗宿主病 13 例，慢性 1 例。中位數年齡為 35.0 歲（四分位距 [IQR] 為 26 至 44 歲），而急性移植物抗宿主病皮膚症狀的中位數發病時間為 70 天（四分位距 [IQR] 為 17.0 - 96.5 天）。所有病例均有組織病理學證實。對於急性移植物抗宿主病 (n=13)，全身性皮疹和毛囊周圍紅斑的典型表現是最常見的 (84.6%，n=11)，其中 61.5% (n=8) 和 38.5% (n=5) 的患者分別有第 2 級和第 3 級皮膚受累程度 (n=11)。當中有 76.9% (n=10) 的急性移植物抗宿主病患者有其他器官受累，如肝臟、眼睛和腸道。勒納分級（Lerner grading）第 2 級是急性移植物抗宿主病患者最常見的組織學程度級別（53.8%，n=7），其次是第1級（38.5%，n=5）。一名慢性移植物抗宿主病患者則出現扁平苔癬樣表現。所有患者均在發病前兩個月內接受過各種抗生素治療，皮膚切片檢查俱未顯示明顯的嗜酸性粒細胞浸潤。**結論：**移植物抗宿主病的皮膚表現是接受造血幹細胞移植者當中最早出現的相關反應之一。這些患者中有一半僅出現皮膚移植物抗宿主病，而沒有其他器官受累。因此，臨床相關性再加上活檢對於確認移植物抗宿主病的診斷實為重要。

Keywords: Graft versus host disease, Haematopoietic stem cell transplant, Histopathology of GVHD, Skin biopsy for GVHD

關鍵詞：移植物抗宿主病、造血幹細胞移植、移植物抗宿主病的組織病理學、移植物抗宿主病的皮膚切片

Introduction

Acute and chronic graft-versus-host disease (GVHD) are multisystem disorders that are complications of haematopoietic stem cell transplant (HSCT). These are serious and potentially life-threatening sequelae from allogenic HSCT and can affect between 40-60% of patients receiving HSCT.[1,2] Human Leukocyte Antigens (HLA) incompatibility is the strongest risk factor for developing GVHD in the setting of allogenic HSCT, along with several other risk factors.[3] Cutaneous symptoms are usually the earliest manifestation of acute GVHD and can range from a mild maculopapular eruption to a full-thickness skin loss that resembles toxic epidermal necrolysis.[4,5] Other organs can also be affected, such as the liver and gastrointestinal tract.

Methodology

We performed a retrospective review on patients who received HSCT for haematological malignancy between January 2014 to June 2018 in a tertiary medical centre. We cross-checked the pathology database with the diagnosis of GVHD with the list of patients who had received HSCT. We included the data on age, sex, type of HSCT, histology grade of GVHD from skin biopsy, other organ involvement, stage and grade for the acute GVHD and concurrent drugs history.

Results

Fourteen patients were included in the study. The median age of the patients was 35.0 years (interquartile range, IQR 26 - 44 years) while the median onset of cutaneous symptoms for acute GVHD was 70 days (IQR 17.0 - 96.5 days). All cases were diagnosed by skin biopsy with subsequent histopathological confirmation (Table 1).

For acute GVHD, classical presentation with generalised exanthem and perifollicular erythema was the most common manifestation

Table 1. Clinical characteristics, cutaneous symptoms, stage and grade of GVHD, and histology grade

Case	Age/ Sex	Aetiology	Type of HSCT	Related/ Unrelated	Skin symptom	Sites	Stage of skin involvement	Type of GVHD	Grade of acute GVHD	Days from HSCT to symptoms	Days from symptoms to diagnosis	Histology grade
1	57, F	ALL	PBSCT	Sister	Morbiliform	Face, arms and legs	3	Late onset, acute	2	120	28	1
2	27, M	T-ALL	Haplo-identical	Sister	Morbiliform	Trunk, limbs	2	CA	1	70	14	1
3	42, F	AML-M5	PBSCT	Brother	Blisters, morbilliform, follicular accentuation	Face, trunk, limbs	2	CA	1	90		3
4	20, M	Pre B-ALL	PBSCT	Sister	Morbiliform	Trunk, limbs	2	CA	1	21	19	2
5	28, M	AML	Haplo-identical	Brother	Morbiliform	Trunk, limbs and palms	2	CA	1	100	14	1
6	20, M	AML	Haplo-identical		Erythematous plaques	Face, trunk, neck and limbs	3	Late onset, acute	2	150	60	2
7	46, M	AML	Match related		Morbiliform and vesicles	Face, trunk, neck and limbs	2	CA	1	86	12	2
8	42, F	AML	Haplo-identical		Morbiliform	Face, trunk, limbs	3	CA	3	13	14	2
9	31, M	AML-M4	MUD		Morbiliform and erythematous plaques	Trunk, limbs and palms	2	CA	1	8	14	1
10	37, M	AML	PBSCT	Sibling	Morbiliform	Trunk, limbs and palms	3	CA	1	93	40	2
11	35, M	CML	Haplo-identical		Erythematous plaques	Face, palms, trunk, limbs and intertriginous folds	3	CA	1	67	14	2
12	48, M	AML	PBSCT	Sister	Morbiliform	Face, neck and trunk	2	CA	1	30	90	2
13	25, M	ALL	Haplo-identical		Morbiliform	Face, trunk and limbs	2	CA	2	12	7	1
14	44, F	ALL	PBSCT	Brother	Lichenification and xerosis	Abdomen, legs	1	Chronic	1	129	10	3

Abbreviations: M, male; F, female; AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; CML, chronic myeloid leukaemia; PBSCT, peripheral blood stem cell transplant; MUD, matched unrelated; CA, classic acute

(84.6%, n=11), where 61.5% (n=8) and 38.5% (n=5) of patients had stage 2 and 3 extent of skin involvement, respectively. 76.9% of our acute GVHD patients (10 out of 13 patients) had other organs involvement, such as liver, eyes, oral cavity and gut involvement. Lerner's grade 2 was the most common histological grade for patients with acute GVHD (53.8%, n=7) followed by grade 1 (38.5%, n=5). One patient with chronic GVHD had lichen planus-like presentation. Eleven patients had classic acute GVHD while 2 had late onset, acute GVHD. 76.9% (n=10) patients with acute GVHD had other organ involvement (Table 1). During subsequent follow-up, two patients died of HSCT complications. Around one-third, 30.8% (n=4) of acute cutaneous GVHD progressed to chronic cutaneous GVHD (Table 2). All patients had

Table 2. Conditioning regime, implicating drugs, other organs involvement and patients' outcome for our GVHD case series

Case	Conditioning Regime	Drugs within 60 days	Other organs involvement	Treatment for GVHD	Progression of GVHD	Patient outcome
1	Myeloablative	Voriconazole, cloxacillin	Lungs	Cyclosporin	Chronic skin	Alive
2	Myeloablative	Ethambutol, Isoniazid, Rifampicin, Pyrazinamide	Oral, liver, esophagus, eyes	Prednisolone	Chronic oral	Alive
3	Myeloablative	Voriconazole	Liver, eyes	MMF	Chronic skin, eyes, liver	Alive
4	Myeloablative	Imipenem, tazocin, gentamycin	Liver, oral cavity	Tacrolimus, ruxolitinib	Chronic liver	Alive
5	Myeloablative	Penicllin V, acyclovir	Oral cavity	Tacrolimus, prednisolone, PUVA	Chronic oral	Alive
6	–	Tazocin, vancomycin, bactrim	Liver, gut, eyes	Ruxolitinib, prednisolone	Chronic skin	Alive
7	–	Tazocin, gancyclovir	Gut	MMF, prednisolone	Chronic oral, liver	Alive
8	–	Ethambutol, Isoniazid, Rifampicin, Pyrazinamide bactrim, cefepime	Liver	Methylprednisolone, MMF	Died	Dead
9	–	Cefepime, gentamicin	Nil	CSA	Chronic liver	Alive
10	–	Posaconazole and amphotericin B	Nil	Prednisolone	Chronic skin	Alive
11	–	Clindamycin and pyrimethamine	Liver, lungs	MMF	Resolved	Alive
12	–	Penicillin V	Liver, oral cavity	MMF	Chronic liver, oral	Alive
13	–	Penicillin V	Nil	MMF, prednisolone	Died	Dead
14	–	Bactrim, acyclovir, Penicllin V	Oral cavity	CSA, prednisolone	Chronic skin	Alive

Abbreviations: MMF, mycophenolate mofetil; PUVA, psoralen ultraviolet A phototherapy; CSA, cyclosporin

received various antibiotics within the two months prior to onset of cutaneous symptoms. None of the skin biopsies showed significant eosinophilic infiltrates.

Cutaneous GVHD presents with different morphologies, ranging from maculopapular eruptions, blisters, erythrodermic plaques and erythroderma (Figures 1-4).

Discussion

GVHD is a major complication of HSCT which affects 20-80% of patients who received HSCT.[6] Several risk factors are associated with the development of GVHD, such as HLA disparity, unrelated HLA-matched donor, parity of the female donor, older age of donor, donor lymphocyte infusion, and intensity of

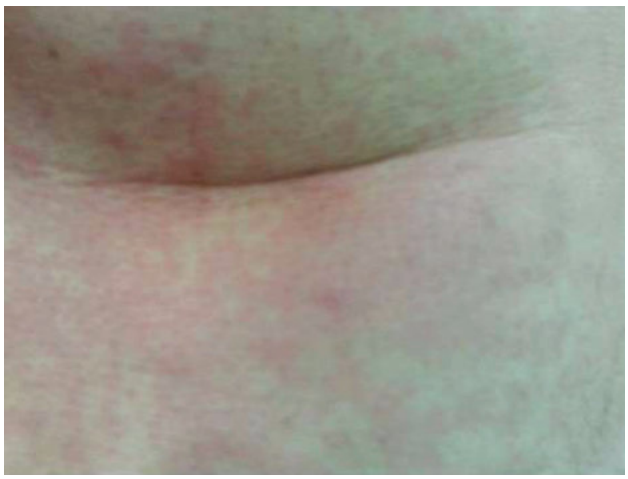

Figure 1. Maculopapular eruptions in acute GVHD.

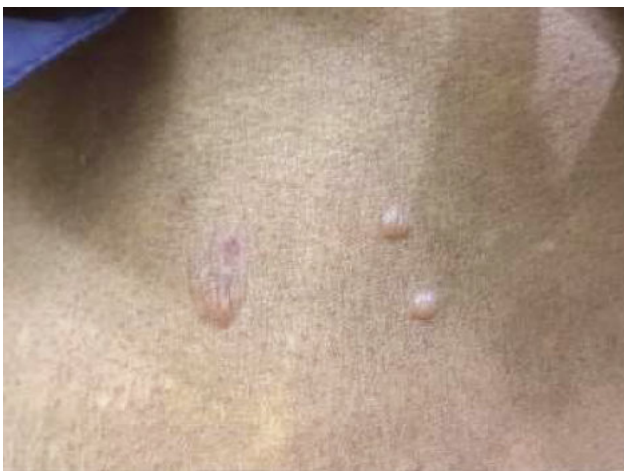

Figure 2. Blisters in acute GVHD.

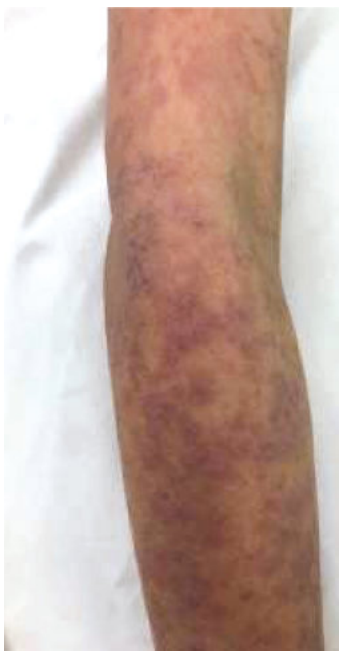

Figure 3. Erythematous plaques in acute GVHD.

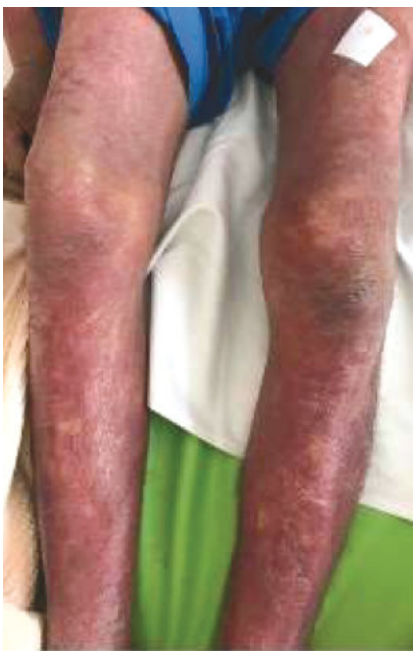

Figure 4. Erythroderma in acute GVHD.

conditioning regime.[7] Conventionally, GVHD has been classically divided into acute and chronic forms based on the days of onset of symptoms, where acute GVHD occurs within 100 days post-HSCT and chronic GVHD occurs after 100 days post-HSCT.

However, the timeline of the presentation of GVHD may change and result in delayed or late acute disease due to the use of reduced-intensity conditioning regimen or donor lymphocyte infusion. Based on the National Institutes of Health (NIH) consensus working group, acute GVHD is defined by the characteristic skin findings, gastrointestinal tract or liver abnormalities, and the absence of any diagnostic or distinctive features of chronic GVHD, regardless of the time of disease onset after HSCT.[4] Further distinction includes: (a) classic acute disease that occurs within 100 days of HSCT, and (b) persistent, recurrent or late-onset acute disease which occurs 100 days after HSCT. In chronic GVHD, time of onset has no role in the definition of chronic disease with the two distinct classes being classic chronic GVHD and overlap syndrome. In this case series, 3 patients had onset of acute GVHD from day 100 and above, which did not fully conform to the classical picture and timeline of acute GVHD presentation. The most common cutaneous presentation was maculopapular exanthem. These findings did not differ from other studies done previously but emphasis should be put on the new NIH classification when considering the diagnosis of GVHD.[8]

In this case series, all the patients had received antimicrobials that could potentially cause drug hypersensitivity reactions prior to the onset of GVHD. Cutaneous manifestations of acute GVHD have many clinical mimickers, most importantly being drug hypersensitivity reactions (DHR). Clinically, the involvement of specific sites on the body such as palms, face, and soles may favour acute GVHD.[9] DHR is a common problem in patients receiving HSCT as they are susceptible to infectious complications of the underlying immunosuppressive state. For patients with acute GVHD, the skin biopsy specimens showed lack of dermal eosinophils with various degree of vacuolar alteration of basal cells.[10] According to the Lerner classification for acute GVHD, the changes observed on the histopathology examination were classified into grade 1 to 4.[11] Our case series findings of lack of dermal eosinophils on skin biopsy was similar to a case series conducted by Lehman et al where they looked into the microscopic features of acute GVHD versus drug hypersensitivity reaction and observed significantly less spongiosis and dermal eosinophils in the skin biopsy samples from patients with GVHD.[12]

In a study done by Weaver et al found that there was a significant difference between the number of eosinophils found in the DHR skin biopsies compared to acute GVHD skin biopsies.[10] However, only an extremely lower number of eosinophils can confidently rule out acute GVHD. Hence, there is potential room for further research to find a way to improve the sensitivity and specificity of skin biopsy in ruling out acute GVHD.

The utility of skin biopsy in acute GVHD varies in different clinical centres. The reasons for this discrepancy in practice are due to: (a) skin biopsies being performed in cases of acute GVHD depending on stage and clinical course; (b) skin biopsies can be avoided due to characteristic clinical features of acute GVHD except in cases with atypical clinical features; (c) personal experience that skin biopsy does not assure distinct discrimination between acute GVHD and other diagnoses. The current consensus recommends that skin biopsy to be done in cases for chronic GVHD but the value of skin biopsy in acute GVHD and subsequent biopsy during therapy need to be further evaluated.[13]

In our centre, we perform skin biopsy for patients with suspected acute or chronic skin GVHD. This is because skin biopsy in acute GVHD may offer some diagnostic significance, especially when there is no diagnostic sign as compared to chronic GVHD. A skin biopsy in acute GVHD may also consolidate the diagnosis in the presence of other tests, such as liver function tests.[14] Also, about 40% of patients with late onset acute GVHD may observe a concomitant histological feature of chronic lichenoid GVHD, which may indicate a higher risk of progression to fully developed chronic GVHD.[15]

Meanwhile, cases of chronic cutaneous GVHD may be under-diagnosed. Majority of the patients with acute or chronic GVHD will have other organ involvement and commonly prescribed systemic immunosuppressants such as the JAK-2 inhibitor ruxolitinib.[16] For cutaneous chronic GVHD, several skin-directed therapies are available and may be indicated as monotherapy or as adjuvant treatment for more severe cases in order to allow faster tapering of systemic immunosuppression by improving local responses.[17,18] The role of dermatologists and the adoption of a multidisciplinary approach are indispensable.[19]

Our case series findings are similar with other studies worldwide (Table 3) where patients were generally young with the most common diagnosis of acute myeloid leukaemia. We had more acute GVHD compared to other centres with more hyperacute GVHD cases and only small proportion of our cases progressed to chronic cutaneous GVHD.

Conclusion

Cutaneous manifestations of GVHD are among the earliest presenting complaints among patients who have undergone HSCT. Half of these patients only had skin GVHD without any other organs involvement. Hence, biopsy is

Table 3. Comparison of our case series findings with other case series worldwide

	Yong et al, Malaysia (n=14)	**Shiohara et al, Japan (n=19)[8]**	**Kaminska-Winciorek et al, Poland (n=13)[20]**	**Bridge et al. Indiana, U.S.A (n=20)[15]**
Median age (year)	35	39	42	57.5
Most Common diagnosis	AML	AML	AML	AML
Hyperacute GVHD	3	19	4	NA
Acute GVHD	10	NA	4	20
Progression to chronic cutaneous GVHD	5	16	NA	NA
Most common cutaneous presentation	Maculopapular rash	Maculopapular rash	Maculopapular rash	Maculopapular rash
Histology	Lerner's grade 1	Lerner's grade 2	NA	Lerner's grade 2
Treatment	Prednisolone, mycophenolate mofetil	Cyclosporin, methotrexate	NA	NA
Patients' outcome	12 alive, 2 death	8 alive, 11 death	NA	17 alive, 3 death

AML, acute myeloid leukaemia; NA, not available

important to confirm the diagnosis of GVHD along with clinical correlation.

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Statements and declarations

All authors declare that they have no conflict of interest that are directly or indirectly related to the work submitted for publication.

Ethical approval statement

This study received ethical approval from University of Malaya Medical Centre-Medical Research Ethics Committee (UMMC-MREC) (2018530-6338) on 11 June 2018.

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