

ORIGINAL ARTICLE

Atopic dermatitis—like presentation of graft-versus-host disease: A novel form of chronic cutaneous graft-versus-host disease

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Background: Graft-versus-host disease (GVHD) is a systemic disease, and skin is often one of the target organs. An atopic dermatitis (AD)-like presentation has never to our knowledge been reported.

Objective: We sought to describe an AD-like presentation of cutaneous GVHD.

Methods: Data on 11 patients with an AD-like presentation of GVHD were collected. The clinical and laboratory findings were retrospectively studied.

Results: All 11 patients developed skin lesions after hematopoietic stem-cell transplantation. The skin lesions occurred between 2 to 12 months after transplantation. Eight patients received their transplant from a first-degree family member; 3 received their transplant from an unrelated donor. The skin lesions were pruritic and suggestive of AD, whereas the histology showed features of AD and GVHD. The lesions responded to topical and systemic anti-inflammatory and immunosuppressive therapy and phototherapy.

Limitations: The number of patients is small and the study is retrospective.

Conclusions: AD-like GVHD might represent a novel form of chronic cutaneous GVHD and responds well to treatment. (J Am Acad Dermatol 10.1016/j.jaad.2012.12.970.)

Key words: atopic dermatitis; graft-versus-host disease.

Graft-versus-host disease (GVHD) is a systemic disease and the skin is often involved with various manifestations.¹ GVHD is classified into acute and chronic forms. Acute GVHD occurs within the first 100 days after transplantation whereas the chronic form occurs at a later point in time.² Acute GVHD usually presents with fever, rash (diffuse morbilliform macules and papules), pancytopenia, elevation of serum liver enzymes, and gastrointestinal symptoms. On the other hand, chronic GVHD often affects the skin, oral mucosa, liver, eyes, esophagus, and upper respiratory tract. The skin manifestations of chronic GVHD are much more variable. So far, many forms of cutaneous manifestations have been reported such as lichenoid

Abbreviations used:

AD:	atopic dermatitis
GVHD:	graft-versus-host disease
HSCT:	hematopoietic stem-cell transplantation
NB:	narrowband
UV:	ultraviolet

form, scleroderma-like, ichthyosis-like, and dyspigmentation. Over the past years, some rare forms of cutaneous GVHD have also been reported including psoriasiform, erythema multiforme-like, dermatomyositis-like, and lupus erythematosus-like forms.³⁻⁵ In 1999, Tanasescu et al⁶ reported a patient with eczema-like GVHD. In 2007, Creamer

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et al⁷ reported 10 patients with eczematoid GVHD. However, to our knowledge, no atopic dermatitis (AD)-like cutaneous GVHD has been reported. We report 11 patients with AD-like presentations after allogeneic hematopoietic stem-cell transplantation (HSCT) and the clinical features, risk factors, and prognosis in these patients were all different from eczematoid GVHD reported by Creamer et al.⁷ We believe that our patients may represent a novel form of chronic cutaneous GVHD and we propose the name of “atopic dermatitis–like graft-versus-host disease.”

METHODS

All 11 patients (5 male and 6 female; 16–45 years old) underwent allogeneic HSCT at Peking University People's Hospital, Beijing, China, between 2007 and 2010. None of the patients had personal history of atopy before HSCT. Eight patients received HSCT from first-degree family members. Three received HSCT from unrelated donors. Ten donors had no history of atopy (AD, asthma, or eczema). Only 1 donor had a history of allergic rhinitis (the recipient was patient 4). None of our patients received donor lymphocytic infusions. Drug reaction was ruled out through reviewing the medicines they used. All patients had used prophylactic prednisone, immunosuppressive agents, or both for prevention of GVHD. The AD-like lesions occurred when these medications were stopped or during tapering. The primary diseases were chronic myeloid leukemia (4 patients), acute nonlymphocytic leukemia (3 patients), acute lymphoblastic leukemia (2 patients), aplastic anemia (1 patient), and myelodysplastic syndrome (1 patient). Data of patients and donors are shown in Table I.

RESULTS

The AD-like lesions occurred 2 to 12 months (mean 7 months) after HSCT. In 5 patients, the lesions were found on the back, abdomen, and extremities, presenting with dry skin, erythema, papules, and perifollicular accentuation (Fig 1). In 6 patients, the lesions were widespread. All patients had pronounced itching. One patient also had lichen planus–like and morphea-like lesions. Two patients reported no sweating in the affected area.

Seven patients also had chronic hepatic GVHD. Four had gastrointestinal indisposition. One had both

hepatic and gastrointestinal indisposition. Three patients had preceding cutaneous GVHD. One patient had preceding extracutaneous GVHD. One patient had only cutaneous manifestation. Six patients had extracutaneous involvement. Seven patients had peripheral eosinophilia and 6 patients had increased serum IgE level (Table I). Skin biopsy was performed in 3 patients.

The histology of the lesions showed features of dermatitis and GVHD. The epidermal changes included hyperkeratosis, parakeratosis, focal spongiosis, acanthosis, sparse necrosis of keratinocytes, lymphocyte exocytosis, and basal layer vacuolation. The dermal changes included blood vessel dilation and perivascular lymphocytic infiltration with scattered eosinophils, melanophages, or both in papillary and mid dermis (Fig 2).

All patients were given oral prednisone with or without immunosuppressive

agents to control GVHD. Meanwhile, emollient, topical corticosteroid cream, tacrolimus ointment, or combinations of these were used to control skin lesions. All patients were given antihistamines and 4 patients were also treated with narrowband (NB)-ultraviolet (UV)B. NB-UVB was delivered twice weekly starting at a dose of 0.5 J/cm², increasing the dose by 0.5-J/cm² increments at each treatment to a maximum dose of 5 J/cm². The treatments are summarized in Table II. Most of the AD-like lesions responded well to these treatments (Fig 1, E and F). Three patients achieved long-term remission of AD-like lesions. In 7 patients, the remission and recurrence were observed during follow-up. Four patients treated with NB-UVB responded well and the skin lesions almost cleared. In 1 patient, the AD-like lesions improved upon treatment whereas the scleroderma-like lesions remained.

DISCUSSION

The skin is one of the most frequently affected organs in GVHD and various cutaneous manifestations have been reported. Compared with acute GVHD, chronic GVHD showed much more variable skin manifestations such as lichen planus–like, poikiloderma-like, and scleroderma–like lesions.^{8,9} Over the last years, some rare forms of cutaneous GVHD have also been reported including erythema multiforme–like and eczematoid forms.^{5,7}

CAPSULE SUMMARY

- To our knowledge, atopic dermatitis–like graft-versus-host disease (GVHD) has not been reported.
- We describe 11 cases of atopic dermatitis–like GVHD that presented with pronounced itching, dry skin, and dermatitis; the clinical picture differed from the eczematoid GVHD reported previously.
- Topical therapy and ultraviolet therapy should be considered in addition to anti-GVHD therapy in atopic dermatitis–like GVHD.

Table I. Clinical and laboratory features in patients with atopic dermatitis–like graft-versus-host disease

Patient	Sex	Age, y	Primary disease	History of allergic disease	Donor	History of allergic disease of donor	Prophylactic medication after HSCT	Time of onset after HSCT, mo	Dry skin/itching	Distribution of lesions	IgE* (IU/ml)	EO* (%)	Extracutaneous involvement
1	M	24	AMCL	None	Unrelated	None	CysA, GC	3	+/+	Extremities	+	+	Liver
											226.3		
2	F	21	CML	None	Mother	None	CysA, MTX, GC	4	+/+	Trunk and extremities	–	+	None
3	M	36	ALL	None	Sister	None	CysA, MTX, GC	2	+/+	Widespread	–	–	Liver
4	F	33	CML	None	Sister	Allergic rhinitis	CysA, MTX, GC	4	+/+	Widespread	+	+	Liver
											401.5		
5	M	16	ALL	None	Father	None	CysA, CTX, GC	5.5	+/+	Widespread	–	–	GI
6	M	17	MDS	None	Unrelated	None	CysA, MTX, GC	3	+/+	Widespread	+	+	Liver
											374.9		
7	F	23	AML	None	Mother	None	CysA, CTX	6	+/+	Widespread	+	+	GI
											289.4		
8	F	31	AML	None	Brother	None	CysA, MTX, GC	9	+/+	Extremities	–	–	Liver
9	F	45	AA	None	Sister	None	CysA, MTX, GC	12	+/+	Widespread	+	+	Liver, GI
											231.6		
10	F	28	CLL	None	Unrelated	None	CysA, CTX, GC	3	+/+	Extremities	–	–	GI
11	M	26	CML	None	Brother	None	CysA, MTX, GC	11	+/+	Trunk and extremities	+	+	Liver
											215.8		

AA, Aplastic anemia; ALL, acute lymphoblastic leukemia; AMCL, acute monocytic leukemia; AML, acute myelomonocytic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelocytic leukemia; CTX, cyclophosphamide; CysA, cyclosporine; EO, eosinophils; F, female; GC, glucocorticoid; GI, gastrointestinal indisposition; HSCT, hematopoietic stem-cell transplantation; M, male; MDS, myelodysplastic syndrome; MTX, methotrexate.

*IgE+, > 200 IU/ml; EO+, >5%.



Fig 1. Cutaneous manifestations of patients with atopic dermatitis-like graft-versus-host disease. **A**, Lesions of neck and chest. Erythema, papules, scaling, and scratches were seen. Skin was dry with fine flakes. **B**, Arm of same patient. Erythema, papules, perifollicular accentuation, scaling, and slight lichenification were seen. Skin was very dry.

We reported 11 patients with AD-like skin lesions that developed after allogeneic HSCT. The striking features in these patients include pronounced itching, dry skin, dermatitis, and perifollicular accentuation. Seven patients had peripheral eosinophilia and 6 patients had increased serum IgE level. The histologic changes showed features of dermatitis (spongiosis, acanthosis, and lymphocytic infiltrations). These clinical and laboratory findings are quite similar to spontaneous AD. In some patients, other skin lesions (eg, morphea-like lesions, hyperpigmentation, and hypopigmentation) or other organ involvements were also seen. The disease was usually chronic, requiring both anti-GVHD treatments and dermatologic treatments. We believe that the AD-like skin manifestation in our patients may represent a novel form of chronic cutaneous GVHD. We propose the name “atopic dermatitis-like graft-versus-host disease.”

Eczema-like GVHD was reported earlier⁶; the large case series was reported by Creamer et al.⁷ They reported 10 patients with “eczema-like” skin lesions after allogeneic HSCT. The onset of skin lesions of their patients was very similar to that of our patients. However, weeping in involved skin was common in their patients, whereas in our patients, no weeping was found and all patients had dry skin and perifollicular accentuation, quite similar to spontaneous AD. Moreover, all their patients developed erythroderma, whereas none of our patients developed erythroderma. In their patients, 6 of 10 patients died whereas in our series, none died, suggesting a different prognosis. Also, high serum IgE level, peripheral eosinophilia, or both were common in our patients, whereas they did not mention the serum IgE level or eosinophilia. All these differences indicate that these 2 groups of

patients may represent distinct forms of chronic cutaneous GVHD. Furthermore, all their patients developed erythroderma and the photographs of their patients suggested an erythroderma-like rather than an eczema-like skin presentation, thus their cases could be called “erythroderma-like graft-versus-host disease.”

As for the risk factors, our patients also differed from theirs. In their patients, 8 of 10 had received a transplant from an unrelated donor and 7 had a history of acute cutaneous GVHD. Whereas in our patients, only 3 had received transplant from unrelated donors and only 1 had a history of acute cutaneous GVHD. These differences might be related to the different clinical features and prognosis of these 2 groups of GVHD.

AD presents as a chronic skin disease with a characteristic phenotype, which often make the diagnosis easy and clear-cut.¹⁰ Genetic and environmental factors were considered to be involved in the pathogenesis of AD. The immunologic hallmark of AD is a helper T cell 1/ helper T cell 2 (Th1/Th2) dysbalance.¹¹ The Th2 cells and their cytokine interleukin-4 and -5 favors IgE production and eosinophilia, which are essential to the atopic diathesis.^{12,13} It has been recognized that both alloreactive and autoreactive T cells play a role in mediating tissue damage.¹⁴ In our patients, none had allergic disorders before HSCT, nor was the patients’ history suggestive of an atopic susceptibility. Moreover, only 1 donor had a history of atopic disorders, suggesting that AD-like GVHD is an acquired disease, although it was reported that atopy could be transmitted by HSCT.¹⁵

All our patients had dry skin when they developed AD-like lesions. In spontaneous AD, the dry skin is often associated with the defect of epidermal molecules such as filaggrin, hence the defect of skin barrier function. It is likely that donor-derived immunoactive cells might cause the defect of skin barrier function,^{2,16} thereby induce dry skin. One patient experienced no sweating on some affected areas and the histologic examination revealed sparse eccrine glands in the dermis, suggesting that immunoreaction might destroy eccrine glands, leading to loss of sweating or hypohidrosis. The mechanism of peripheral eosinophilia and high serum IgE level is not clear.

We treated our patients with anti-GVHD treatment (systemic steroid and immunosuppressive agents) and dermatologic treatment (emollients, topical steroid, topical tacrolimus, and NB-UVB). All the skin lesions responded well to these treatments, suggesting AD-like lesions are not difficult to treat and this form of cutaneous GVHD might represent a good prognosis.

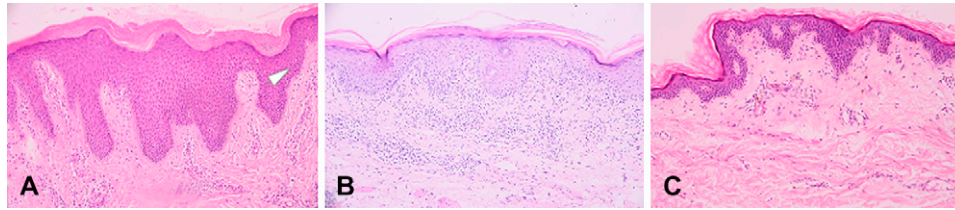


Fig 2. Histologic findings of skin lesions in patients with atopic dermatitis–like graft-versus-host disease. **A**, Hyperkeratosis, parakeratosis, acanthosis, scattered keratinocyte necrosis, and focal spongiosis were found in epidermis. Blood vessel dilation and lymphocytic infiltrations were seen in papillary and mid dermis with scattered infiltration of eosinophils. **B**, Histology in second patient showed parakeratosis, lymphocyte exocytosis, basal layer vacuolation, and perivascular lymphocytic infiltrate with scattered eosinophils. **C**, Histology in third patient showed hyperkeratosis, slight irregular elongation of rete ridges. Sparse lymphocytic infiltrations with melanophages were seen in papillary dermis. Blood vessel dilation was also seen. (Hematoxylin-eosin stain; original magnification: $\times 20$.)

Table II. Treatment of patients with atopic dermatitis–like graft-versus-host disease

Patient	Initial dose of prednisone	Immunosuppressants (initial dose)	Antihistamine	Emollient	Topical corticosteroid	Topical tacrolimus	NB-UVB	Duration of treatment/follow-up, mo	Response
1	30 mg/d	CysA 200 mg/d	+	+	+	+	–	5/24	Good
2	30 mg/d	CysA 200 mg/d	+	+	+	+	–	2/6	Good
3	30 mg/d	MTX 17.5 mg/w							
4	30 mg/d	CysA 200 mg/d	+	+	+	+	–	5/20	Good
5	30 mg/d	MTX 17.5 mg/w							
6	30 mg/d	CysA 200 mg/d	+	+	+	+	+	6/24	Good
7	30 mg/d	CTX 1.0 g/w							
8	30 mg/d	CysA 200 mg/d	+	+	+	+	–	5/18	Good
9	30 mg/d	MTX 15 mg/w							
10	30 mg/d	CysA 200 mg/d	+	+	+	+	–	4/15	Good
11	30 mg/d	CTX 1.0 g/w							
		CysA 200 mg/d	+	+	+	+	–	2/18	Good
		MTX 17.5 mg/w							
		MMF 2.0 g/d							
			+	+	+	+	+	18/36	Poor

CTX, Cyclophosphamide; CysA, cyclosporin; MMF, mycophenolate mofetil; MTX, methotrexate; NB, narrowband; UV, ultraviolet.

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