Iatrogenic cutaneous graft versus host disease

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Abstract

A 65-year-old man with acute myeloid leukemia was treated by bone marrow allograft and developed classic systemic chronic graft versus host disease with hepatic, rheumatologic, ophthalmic, and mucocutaneous involvement. He received systemic corticosteroid, ruxolitinib, and extracorporeal photopheresis, which resulted in complete remission. During follow-up the patient presented with viral cutaneous warts on his neck and submandibular area. After various subsequent topical treatments, he developed localized cutaneous GVHD without any general GVHD reactivation symptoms. To the best of our knowledge, there has been no description in the literature of graft versus host disease developing after local immunomodulatory or cytotoxic treatments. Topical immune-stimulating therapies are commonly used by dermatologists for superficial skin cancers and some viral skin lesions in high-risk populations such as organ transplant patients. Practitioners should be made aware of a possible localized cutaneous GVHD reactivation induced after local therapy.

Keywords: localized cutaneous GVHD, verruca vulgaris, Koebner phenomenon

Introduction

Graft-versus-host disease remains an important complication of allogeneic bone marrow and hematopoietic cell transplantation. The skin is the most commonly affected organ, followed by oral mucosa, liver, eyes, and gastrointestinal tract, but any organ or system may be involved. Cutaneous GVHD is classified into acute and chronic. Acute GVHD is typically characterized by a morbilliform eruption, whereas chronic GVHD usually appears in a lichenoid or sclerodermoid pattern [1]. We describe an atypical case of localized cutaneous GVHD reactivation by local treatment of viral cutaneous warts.

Case Synopsis

A 65-year-old man treated by a bone marrow allograft in July 2015 for acute myeloid leukemia M6 type according to the The French-American-British classification (AML6), or pure erythroid leukemia according to the WHO (World Health Organization) classification, secondary to myelodysplastic syndrome. Less than a month later, he presented with acute digestive GVHD which responded to corticosteroid therapy. During corticoid weaning, he developed classic chronic GVHD with hepatic, rheumatologic, ophthalmic, and mucocutaneous involvement.

Abbreviations:

GVHD	graft versus host disease
AML	acute myeloid leukemia
BID	*bis in die*, two times per day
HPV	human papillomavirus
CMV	cytomegalovirus
FAB	The French-American-British classification
H&E	hematoxylin and eosin stain
HSV	herpes simplex virus
HHV	human herpesvirus
HHV-6	human herpesvirus 6
SCLE	subacute cutaneous lupus erythematosus
VZV	varicella-zoster virus
WHO	The World Health Organization
5-FU	5-fluorouracil

Chronic GVHD was initially treated by systemic corticosteroid and ruxolitinib. In addition, two years later ruxolitinib (10mg BID) was combined with extracorporeal photopheresis owing to incomplete response and persistent flare-ups. Ten months later, corticosteroid treatment was discontinued and ruxolitinib and extracorporeal photopheresis were still ongoing with complete remission.

The patient was treated multiple times for cutaneous warts located in the submandibular and neck region (**Figure 1**). The lesions relapsed after each therapy. He received cryotherapy, two courses of ingenol mebutate, and imiquimod. After this, he received two months of 5-fluorouracil (5-FU), which proved to be effective. Each course of treatment triggered a significant inflammatory reaction.

Three months after the complete resolution of the skin warts, he presented with pruriginous fixed and confluent psoriasiform plaques on the neck and upper chest (**Figure 2**). No other symptoms were present. The skin biopsy revealed an interface dermatitis with keratinocyte apoptosis, lymphocytic infiltrate, and superficial dermal fibrosis. Epidermal hyperplasia and lichenoid infiltrate were not found, ruling out the diagnosis of lichen planus. Otherwise, there was no deep dermal inflammatory infiltrate or dermal mucin deposition and direct immunofluorescence was negative, ruling out the diagnosis of subacute cutaneous lupus erythematosus (SCLE), (**Figure 3**). The clinical and histological appearance was compatible with the diagnosis of localized cutaneous GVHD with the absence of GVHD reactivation in other localizations.

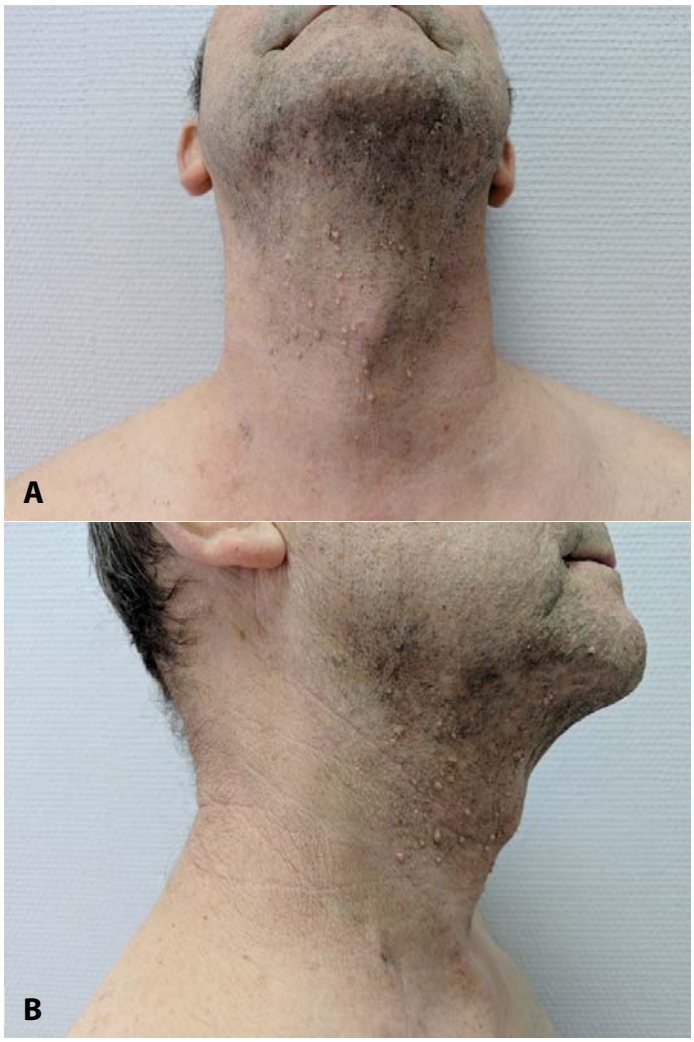

Figure 1. *Cervical verruca vulgaris.*

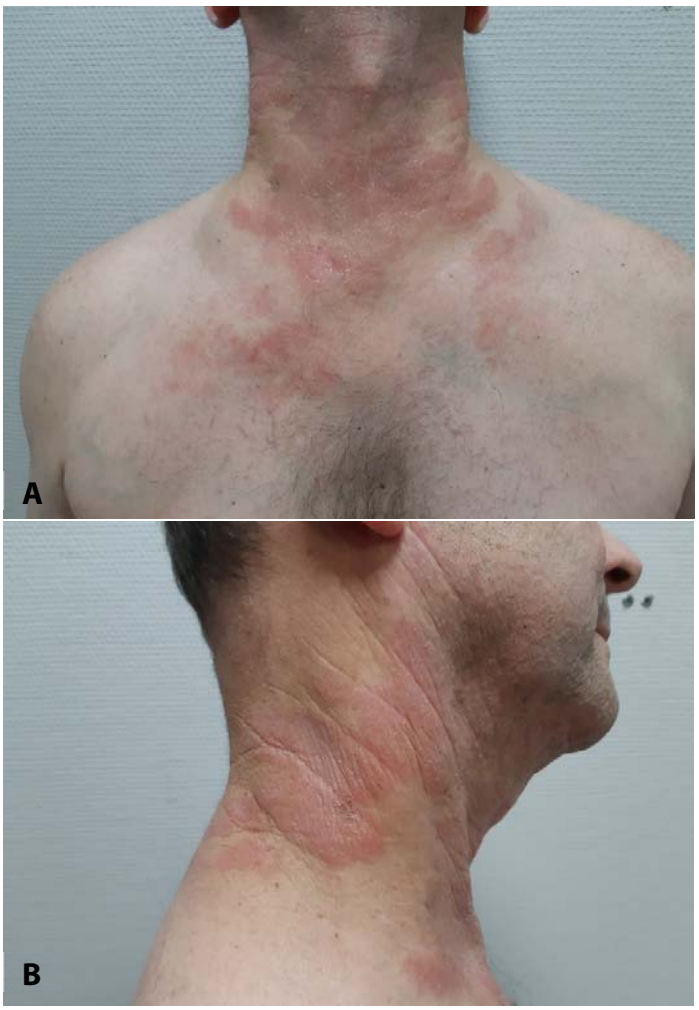

Figure 2. *Psoriasiform erythematous well-defined plaques on the neck and chest.*

All lesions resolved after two weeks of topical corticosteroids. Viral cutaneous warts recurred three months later without the recurrence of localized cutaneous GVHD, which was treated with cryotherapy without further GVHD or GVHD-like eruption.

Case Discussion

We report an atypical case of localized cutaneous GVHD possibly induced by successive applications of local treatments, including ingenol mebutate, imiquimod, and 5- FU for recurrent cutaneous warts. These lesions do not fit classic clinical descriptions of chronic GVHD [2] and could be a variant of chronic GVHD.

It is possible that the localized chronic GVHD may have occurred by direct stimulation of innate and adaptive graft immunity by the topical treatments: imiquimod and ingenol mebutate. His other treatment, 5-FU) is an antimetabolite, which does not lead to immune-modulatory mechanisms, unlike the other two. A Koebner response could also arise indirectly by dermal injury induced by severe inflammatory reactions caused by the different topical treatments (ingenol mebutate, imiquimod, and 5-FU). Moreover, it is known that the dermal reactions in the Koebner phenomenon can occur several weeks to several years after the injury.

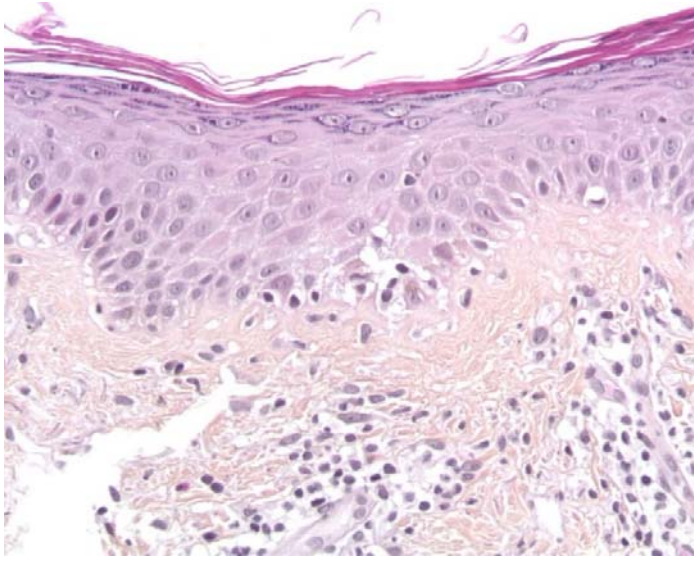

Figure 3. *Focal vacuolar interface dermatitis with superficial perivascular lymphocytic inflammation. H&E, 200×.*

Our patient's eruption could also be a clinical and histological "GVHD-like" reaction, as Hermanns-Lê et al. showed in 2003 [3] following the publication of a three case series treated with prolonged application of imiquimod, who had histological lesions similar to low-grade immunosuppressed GVHD. However, given the patient's history of chronic GVHD, it is less likely a "GVHD-like" condition mimicking clinical and histological GVHD lesions.

Nevertheless, other diagnostic hypotheses can be argued in this case. We could also hypothesize an isotopic response by HPV. However, there was no recurrence of cutaneous GVHD lesions despite the reappearance of cutaneous warts three months after the end of the treatment by topical corticosteroids. Besides, there is an absence of data in the literature on isotopic response by HPV in GVHD, so this hypothesis remains unlikely.

Finally, it could be a result of cryotherapy treatments. However, cutaneous GVHD did not reappear during the second treatment after relapse.

Certain risk factors are known for the development of GVHD: HLA compatibility between donor and recipient, stem cell source, patient's age, type of conditioning, and the anti-GVHD prophylaxis used. However, GVHD can also be: photo-induced [4], virally induced [5] (rhinovirus, BK virus, CMV, parainfluenza virus, VZV, HSV, HHV-6), or even radiation-induced [6].

In the literature, several cases of localized cutaneous GVHD triggered by external factors have been described. These include a few localized chronic cutaneous sclerodermiform GVHD induced by skin injury [7], one case of chronic cutaneous lichenoid GVHD localized to the site of vaccine injection [8], and a localized acute GVHD reactivation on stretch marks [9]. There are no previously reported cases of cutaneous GVHD reactivation following the application of topical treatments.

Localized GVHD did not lead to GVHD reactivation in other locations in our case. Indeed, Ulrich et al. showed that topical immunomodulatory treatment for actinic keratosis, such as imiquimod, could be a potential triggering factor for solid organ rejection or GVHD in organ transplant recipients. However, it has

not progressed to solid organ rejection or GVHD in controlled trials [10].

Conclusion

We report a case of cutaneous GVHD reactivation after immunomodulatory and cytotoxic treatments, commonly used for patients with bone marrow allograft who may develop superficial skin tumors or viral lesions. Our case, and the published literature have not shown any reactivation of generalized GVHD after local treatments. Practitioners must keep in mind the possibility of such occurrences

Potential conflicts of interest

The authors declare no conflicts of interests.

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