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ORIGINAL RESEARCH REPORT

Clinical and histopathological spectrum of toxic erythema of chemotherapy in patients who have undergone allogeneic hematopoietic cell transplantation

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Toxic epidermal necrolysis

Abstract
Objective/Background: Toxic erythema of chemotherapy (TEC) is a well-recognized adverse cutaneous reaction to chemotherapy. Similar to many skin diseases, the clinical presentations may vary. Our objective is to expand on the typical and atypical clinical and histopathological presentations of TEC.
Methods: Forty patients with a diagnosis of TEC were included from 500 patients who had undergone an allogeneic hematopoietic stem cell transplant. Relevant information and demonstrative photos and pathology were selected.
Results: Classic clinical presentations included hand and foot erythema and dysesthesias; atypical presentations included facial involvement, hyperpigmentation, dermatomyositis-like, and erythroderma associated with capillary leak syndrome.

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Conclusion: The diagnosis of TEC should be considered after a correlation of clinical and histological findings in conjunction with a timeline of chemotherapy administration. Suggested criteria for the diagnosis of TEC may be helpful to dermatologists and clinicians when caring for these patients.

Introduction

Toxic erythema of chemotherapy (TEC), a general term that encompasses hand–foot syndrome, palmar–plantar erythrodysesthesia, and eccrine syringometaplasia, is a cutaneous eruption occurring after the initiation of cytotoxic chemotherapeutic agents [1–6]. Clinical manifestations of TEC present along a spectrum, with typical and atypical variants, similar to sclerodermoid disorders that range from localized morphea to morbid systemic sclerosis. Within that context, TEC also has a clinical spectrum with variants that range from mild palmar erythema to systemically morbid capillary leak syndrome [7,8]. A few of these presentations can be confused with other skin diseases as it occurs during a period where patients receive multiple medications and are susceptible to infections. It can be misdiagnosed as an infectious exanthem, graft versus host disease (GVHD) or acute morbilliform drug eruption. It is important for clinicians caring for affected patients to be aware of these clinical presentations. As the management of TEC is mainly supportive, recognizing typical and atypical presentations will assure appropriate treatment.

In this study, we present a photographic clinical spectrum and histopathological examples, and summarize some of the criteria necessary for diagnosis of TEC.

Materials and methods

After obtaining Mayo Clinic Institutional Review Board (IRB; Rochester, MN, USA) approval, the charts of 500 patients who had undergone allogeneic hematopoietic cell transplant (HSCT) between January 1, 2010 and December 31, 2015 were reviewed for a diagnosis of TEC. The patients who were included were evaluated by a dermatologist and had either photographs and/or a biopsy sent for dermatopathology. Of the 500 patient records, 40 patients were selected. Twelve had skin biopsies taken at the time of diagnosis. Pathology slides were reviewed by a dermatopathologist to confirm and document the histopathological features. Photographs were selected to show typical and atypical clinical presentations to serve as educational examples. The following data was abstracted for each suspected case of TEC: age, sex, race, malignancy type, description of lesions, symptoms, location of the eruption, chemotherapy agent, time to onset of rash from infusion date, duration of eruption, treatment of TEC, and any recurrences.

Results

Patient characteristics

Of the 500 patients who received chemotherapy regimens prior to allogeneic stem cell transplantation, 40 had cutaneous reactions consistent with TEC. A summary of the patient demographics is shown in Table 1. The patients were treated with standard chemotherapy (Table 2). The majority ($n = 25$) underwent treatment with clofarabine and cytarabine for acute myeloid leukemia (AML). Thirteen patients had previously received the same type of chemotherapy and developed TEC only after repeated cycles of chemotherapy with the same agent. The mean age of the patients was 44.1 years (range, 20–71 years). The mean time to TEC was 93.2 days from graft infusion (range, 3–606 days). The mean time of onset of the rash from administration of offending agent was 14.5 days (range, 2–88 days) and the mean time to resolution was 29.3 days. This excludes patients who died prior to resolution of the rash ($n = 5$) and those patients in whom resolution of symptoms of TEC were not documented ($n = 10$). Documented duration of TEC ranged from 4 days to 180 days.

Clinical signs and symptoms

Clinical signs and symptoms varied from localized cutaneous reactions to more generalized rashes. The most common initial presentations were edema, erythema, and burning dysesthesia of the hands and feet (Fig. 1). These progressed to edema with blisters and bullae that were very painful (Fig. 2). Other acral areas included erythema and edema of the ears and the face (Fig. 3). Symmetric drug-related intertriginous and flexural exanthema (SDRIFE), formerly known as baboon syndrome, was also one of the early manifestations of TEC, as shown in Fig. 4. Atypical presentations included palmar–plantar violaceous plaques on the dorsum of the hand mimicking Gottron papules of dermatomyositis (Fig. 5). TEC in patients with a darker skin type were more likely to present with hyperpigmentation (Fig. 6) with mild to moderate dysesthesia. In most patients, distribution of the rashes were generally symmetric and bilateral in 97%, with the palms of the hands and soles of the feet affected in the majority (65%, $n = 26$) of cases. Capillary leak syndrome (Fig. 7) was diagnosed in two patients. Both patients had generalized erythroderma, with painful skin associated with multisystem failure, anasarca, and fluid leakage from the skin. The two patients with the capillary leak syndrome

Table 1 Summary of demographics and histopathological features (n = 40).

Gender, n (%)	Male	25 (62.5)
	Female	15 (37.5)
Race, n (%)	Caucasian	36 (90)
	Asian	3 (7.5)
	Afro-Caribbean	1 (2.5)
Cytotoxic chemotherapy agents used	Cytarabine	18 (*)
	Clofarabine	11
	Idarubicin	8
	Carboplatin	7
	Cyclophosphamide	7
	Fludarabine	4
	Melphalan	4
	Mitoxantrone	4
	Methotrexate	3
	Busulfan	2
	Etoposide	2
	Flavopiridol	1
	Rituximab	1
	Sorafenib	1
Histopathological features of TEC (number of cases)	Interface vacuolar dermatitis	8
	Dysmaturation of keratinocytes	8
	Dyskeratotic keratinocytes	8
	Epidermal necrosis	3
	Acrosyringeal involvement	2
	Focal eccrine squamous syringometaplasia	2
	Subepidermal bullae	1
	Keratinocyte apoptosis	1
	Perivascular lymphocytic inflammation	1
	Subcorneal blisters	1
	Focal pigment incontinence	1

Table 2 Drugs used pre- and post-allogeneic transplantation.

Pre-transplant cancer treatments	Conditioning regimens	GVHD prophylaxis
Cytarabine	Fludarabine plus Melphalan	Methotrexate plus cyclosporine
Clofarabine	Fludarabine plus Busulfan	Methotrexate plus tacrolimus
Idarubicin	Total body irradiation plus Cyclophosphamide	
Carboplatin	Busulfan plus Cyclophosphamide	
Mitoxantrone		
Etoposide		
Flavopiridol		
Rituximab		
Sorafenib		

had each undergone one cycle of clofarabine and cytarabine.

Histopathology

The histopathological findings are described in Table 1. The most common findings were vacuolar interface dermatitis, dyskeratotic keratinocytes (Fig. 8), and keratinocyte dysmaturation (Fig. 9), as previously described [9]. Epidermal necrosis and acrosyringeal involvement were also observed, albeit less frequently (Fig. 10).

Treatment

Patients were typically treated with topical creams such as Triamcinolone 0.1% and wet dressings. Five patients were treated with systemic steroids.

Discussion

TEC is a skin reaction that can be readily diagnosed when manifesting as typical acral erythema, edema, and dyses-

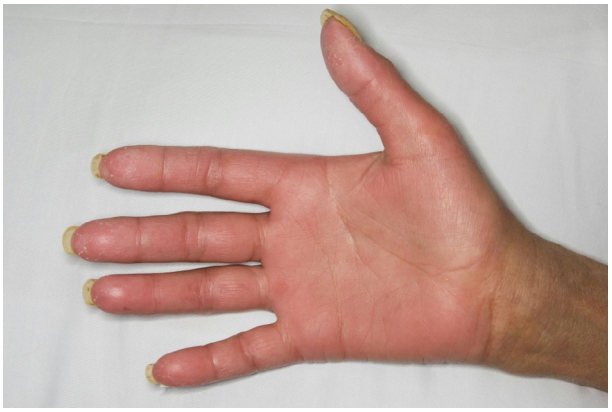

Fig. 1 Erythema and edema of the fingers with dysesthesia.

thesias of the hands and feet arising after administration of cytotoxic chemotherapy. However, this study identified several unusual clinical presentations, thus highlighting the importance of careful clinicopathologic correlation, as well as familiarity by the treating clinicians with this spectrum for accurate diagnosis.

Atypical presentations in patients with Fitzpatrick type IV–V skin are more subtle and can manifest as hyperpigmentation, most commonly associated with neuropathy as reported in three of our patients. A new atypical clinical presentation seen in our case series is violaceous erythema associated with lichenoid violaceous plaques on the dorsum of the hand and elbows similar to dermatomyositis. The term ''baboon syndrome'' (currently referred to as SDRIFE) has previously been used to describe a phenomenon of

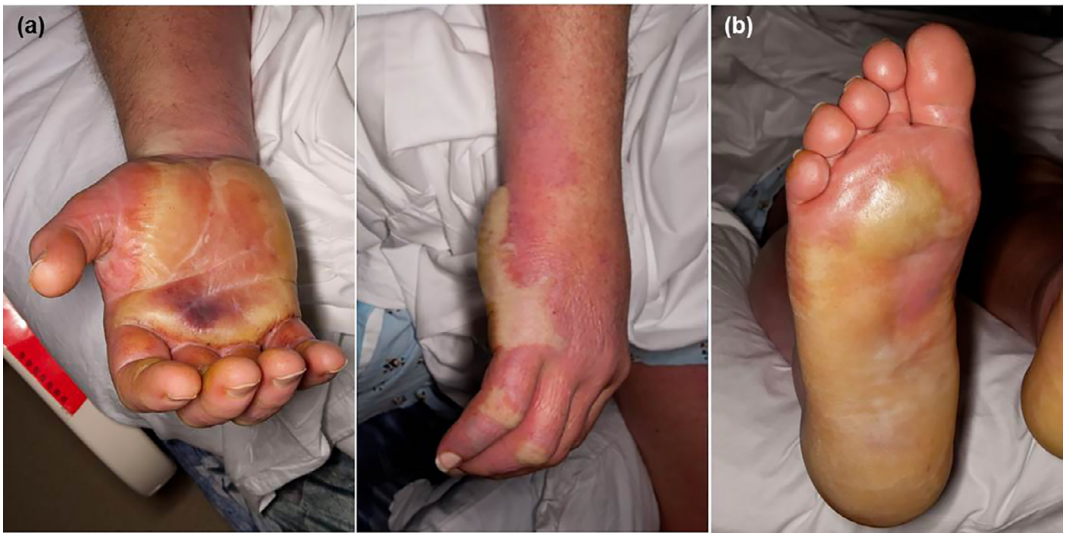

Fig. 2 Severe edema with erythema and bulla formation and pain involving (a) hands and (b) feet.

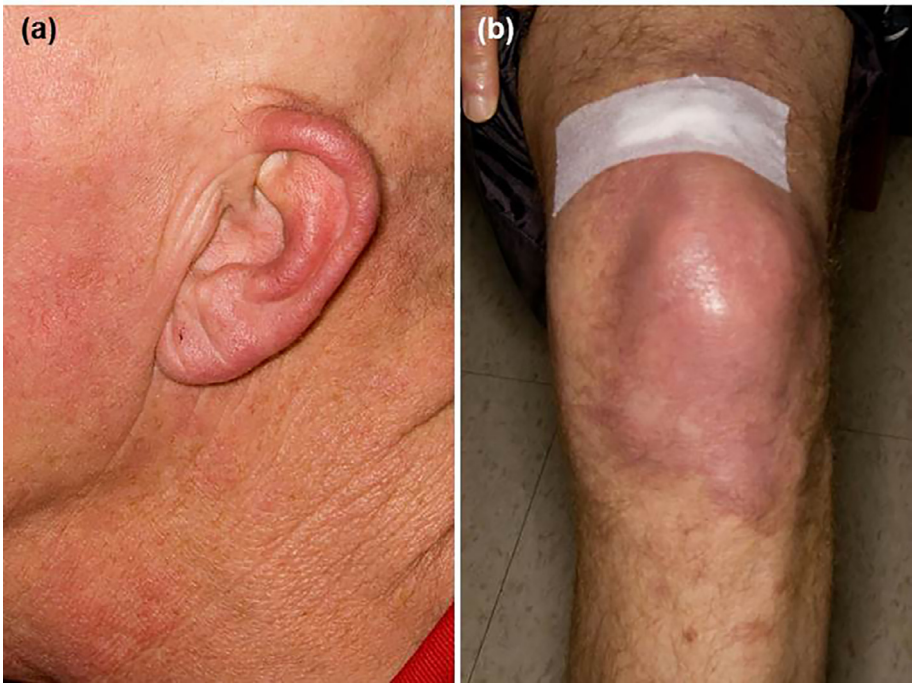

Fig. 3 (a) Acral involvement of the ears. (b) Acral involvment of the knee.

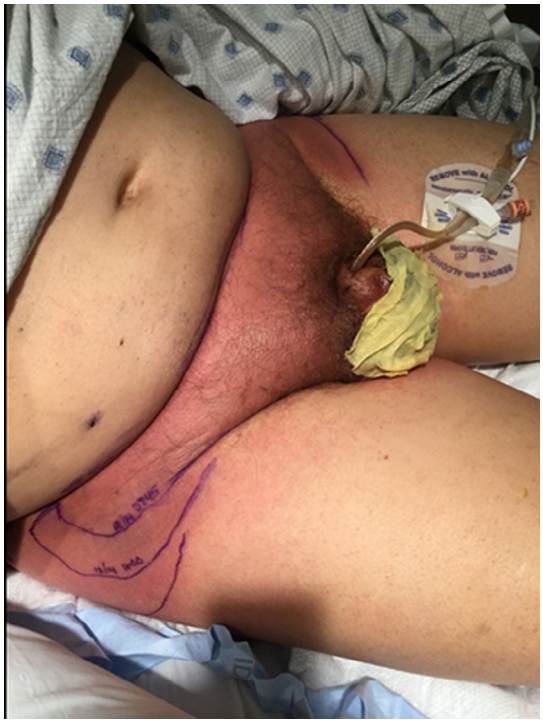

Fig. 4 Symmetric drug-related intertriginous and flexural exanthem (SDRIFE).

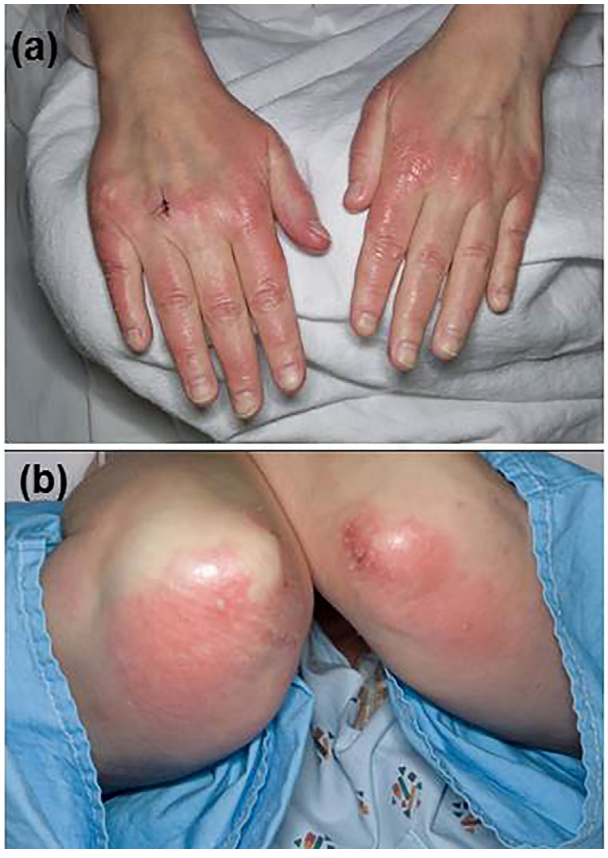

Fig. 5 Dermatomyositis-like violaceous erythema and papules on (a) the knuckles, fingers; (b) elbows.

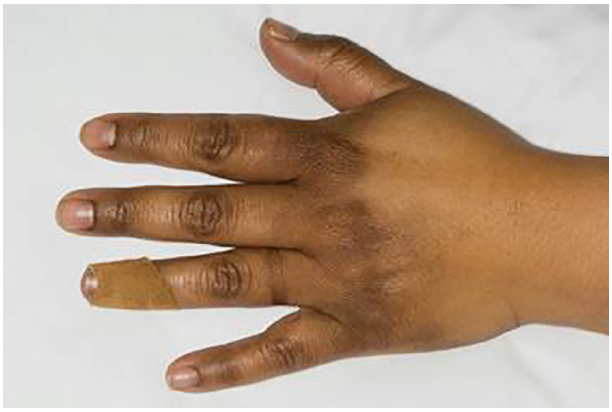

Fig. 6 Sharp, well-defined line of acute acquired hyperpigmentation on the dorsum of both hands without prior erythema, inflammation or edema.

symmetrical, sharply demarcated erythema of the perianal or gluteal region [9], with intertriginous involvement following exposure to a systemically administered drug. Two patients in our series presented similarly, thus further supporting the use of TEC as a unifying term (Fig. 4).

An important entity in the clinical and microscopic differential of TEC is acute GVHD. Both TEC and GVHD have a similar presenting pattern as they initially affect the palms and soles. It is more common for GVHD to progress to a coalescing widespread maculopapular erythema and may present with other systemic symptoms such as diarrhea or liver abnormalities. Table 3 compares the clinical and histopathological features of TEC and GVHD. Based on the findings of this study, we have developed criteria that may be helpful in the diagnosis of TEC (Table 4). Two criteria are required for diagnosis. One criterion must be from the history section and the other from either the clinical or pathology sections.

Among the limitations of this study is its retrospective nature, which may limit the ability to accurately identify all cases of TEC and may not capture the complete spectrum of presentations.

Conclusions

In conclusion, TEC is a clinical diagnosis that is supported by pathological confirmation. We present the clinical manifestations of TEC that ranges from mild hyperpigmentation to generalized erythroderma with bullae, indicating a wide spectrum. Suggested criteria for the diagnosis of TEC may be helpful to dermatologists and clinicians when caring for these patients.

Authors' contributions

REA and MKH designed and conducted the study. MKH, AJR, SKH, AGB, JLS, and REA assisted with data acquisition and analysis. MKH, REA, and SN wrote the manuscript. All authors read and approved the final manuscript.

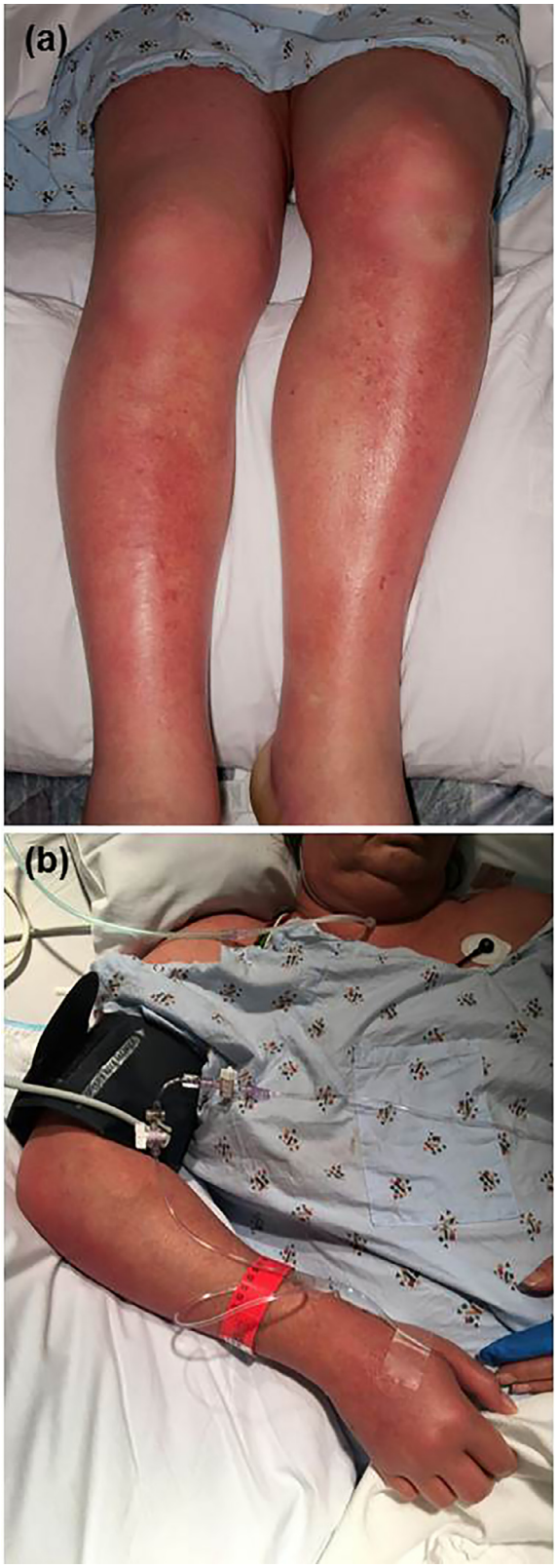

Fig. 7 Diffuse generalized erythema and edema, associated with capillary leak syndrome. (a) The patient's legs. (b) The patient's arm.

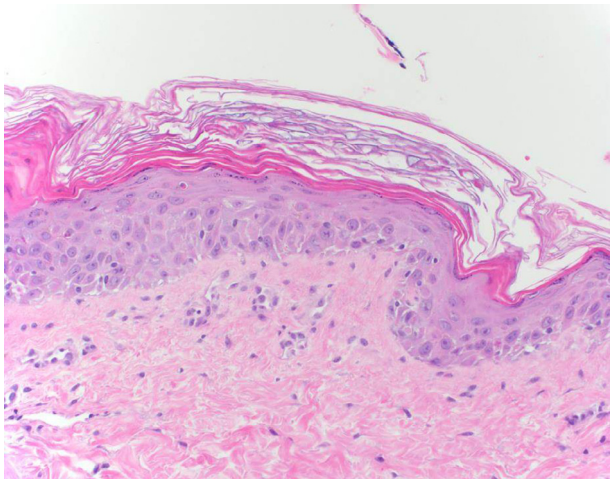

Fig. 8 Vacuolar interface changes with dyskeratotic keratinocytes and mild squamous dysplasia (hematoxylin and eosin stain; original magnification, ×10).

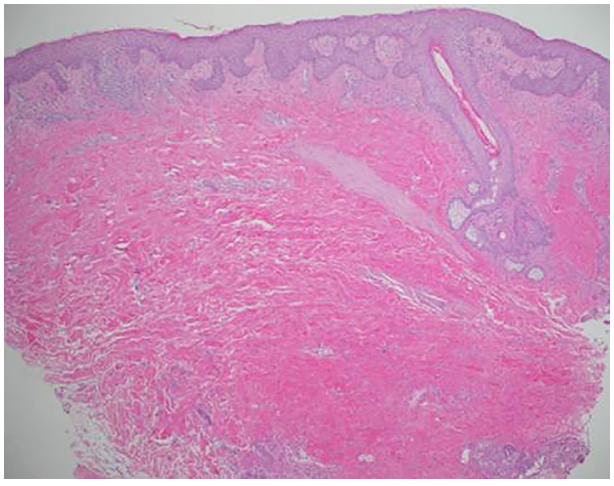

Fig. 9 Vacuolar interface changes with squamous dysmaturation (hematoxylin and eosin stain; original magnification, ×10).

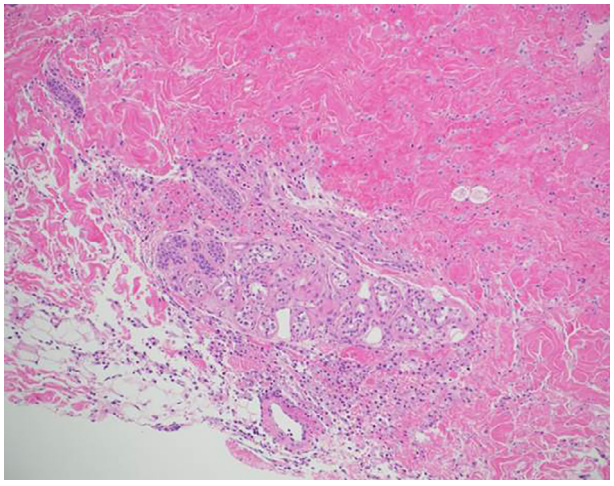

Fig. 10 Vacuolar interface changes and eccrine syringometaplasia (hematoxylin and eosin stain; original magnification, ×10).

Table 3 Clinical and histopathological differences between TEC and GVHD.

	TEC	GVHD
Clinical features		
Acral erythema	++++	++++
Dysesthesia	++++	+
Morbilliform eruption	++	++++
Violaceous erythema	+	++++
Swelling and blistering	++++	+
Sunburn-like erythema	+	++++
Accompanying systemic features: liver abnormalities, diarrhea	+	+++
Timeline related to chemotherapy or recurrence with chemotherapy	++++	—
Palmar involvement	++++	++++
Intertriginous involvement	++++	+
Follicularly based lesions	—	++
Histopathological features		
Eccrine squamous metaplasia	++++	—
Epidermal dysmaturation	++++	—
Vacuolar interface changes	+++	++
Keratinocyte apoptosis	++++	++
Neutrophilic eccrine hidradenitis	++++	—

— = none; + = rare clinical presentation; ++ = common clinical presentation; +++ = more common clinical presentation; ++++ = frequent presentation; GVHD = graft versus host disease; TEC = toxic erythema of chemotherapy.

Table 4 Suggested criteria for diagnoses of toxic erythema of chemotherapy.

History	1. Rash occurring after initiation of chemotherapy 2. Rash recurring or worsening after each cycle of chemotherapy
Clinical	1. Palmar-plantar or acral involvement with or without dysesthesia 2. Rash with or without dysesthesia 3. Generalized erythroderma with anasarca and multisystem failure
Histopathology	1. Vacuolar interface dermatitis plus keratinocyte dyskeratosis or dysmaturation of keratinocytes 2. Acrosyringeal involvement

Conflicts of interest

The authors declare no conflicts of interest.

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