

Toxic epidermal necrolysis-like toxic erythema of chemotherapy: 2 illustrative cases



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INTRODUCTION

Toxic erythema of chemotherapy (TEC) encompasses a spectrum of cutaneous eruptions secondary to the use of antineoplastic drugs presenting as red-purple patches and plaques favoring the hands, feet, and intertriginous skin.¹ Here, we present 2 cases of severe TEC mimicking toxic epidermal necrolysis (TEN).

CASE REPORT

Case 1

A 66-year-old woman with T-cell lymphoma complicated by cytomegalovirus and human herpesvirus 6 viremia presented with a bullous flexural eruption 3 weeks after the initiation of cyclophosphamide and brentuximab. Examination revealed magenta papules coalescing into plaques with central areas of dusky necrosis in flexural and dependent areas (Fig 1). The vulvar and perianal regions developed extensive large flaccid bullae (Fig 2). Fever, severe hypotension requiring pressors, acute respiratory distress syndrome, and diffuse anasarca developed in the patient. In addition, laboratory testing revealed pancytopenia (with no eosinophilia), elevated inflammatory marker levels (C-reactive protein 279.5 mg/L, ferritin >40,000 ug/L), an elevated creatinine level, mild transaminitis, and hypoalbuminemia. The clinical differential diagnosis included bullous TEC, Stevens-Johnson syndrome/TEN, paraneoplastic pemphigus (PNP), and linear immunoglobulin A bullous dermatosis.

The results of biopsies from multiple sites were consistent with a chemotherapy reaction, revealing

Abbreviations used:

aGVHD:	acute graft-versus-host disease
CLS:	capillary leak syndrome
IVIG:	intravenous immunoglobulin
PNP:	paraneoplastic pemphigus
TEC:	toxic erythema of chemotherapy
TEN:	toxic epidermal necrolysis

cell-poor vacuolar interface dermatitis with many single necrotic keratinocytes and many mitotic figures among keratinocytes, without thickening of the epidermis or crowding of keratinocyte nuclei (Fig 3). Direct immunofluorescence result was negative. Extensive skin sloughing and denudation developed in the patient over the following days, and she was treated with a 4-day course of intravenous immunoglobulin (IVIG) (4 g/kg), pyridoxine, and pentoxifylline. Her skin improved over several weeks, although she was transitioned to comfort care because of persistent neutropenia and candidemia with septic emboli.

Case 2

A 19-year-old woman with relapsed pre-B-cell acute lymphoblastic leukemia was transferred to our institution for sibling-matched stem cell transplant. One week prior to the transfer, she was treated with thiotepa and total body irradiation. She received cyclophosphamide 2 and 3 days before the transplant and methotrexate and cyclosporine for graft-versus-host disease prophylaxis. Two days after the transplant, diffuse erythema developed, prompting a

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Fig 1. Case 1. Magenta axillary plaque with a dusky appearance and maceration. Image courtesy of Sally Tan Renehan, MD.



Fig 2. Case 1. Skin fragility with flaccid bullae and positive Nikolsky sign in dependent and occluded areas, accentuated over the buttocks. Image courtesy of Sally Tan Renehan, MD.

dermatology consultation. Upon examination, the patient had diffuse red-brown erythema and gingival leukoplakia, evolving to oral erosions. Five days after the transplant, acral, flexural, and confluent erythema with severe burning pain in the axillae and hands bilaterally developed in the patient (Fig 4). Progression to acral and flexural bullae occurred over the next 1-2 weeks. Laboratory testing revealed pancytopenia, without eosinophilia or viral reactivation. Her course was complicated by veno-occlusive disease of the liver, *Clostridium difficile* infection, and *Streptococcus viridans* bacteremia.

Initial skin biopsy showed a very sparse perivascular infiltrate of lymphocytes, a vacuolar change, and necrotic keratinocytes. Repeat biopsies 1 week later demonstrated keratinocyte dysmaturation, syringosquamous metaplasia, a cell-poor vacuolar interface reaction with squamatization of the basal

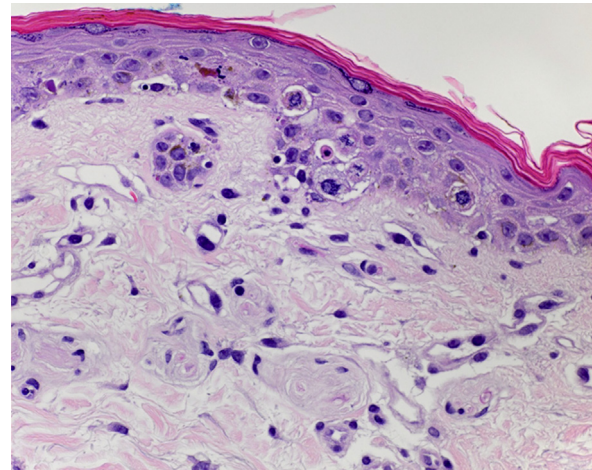


Fig 3. Case 1. Skin biopsy showing a very sparse lymphocytic infiltrate, vacuolar change along the dermoepidermal junction, a few single necrotic keratinocytes, and other mitotic keratinocytes. (Original magnification: $\times 400$.) Image courtesy of Philip E. LeBoit, MD.



Fig 4. Case 2. Day 11, after initial dermatology consultation showing bright red-purple erythema of the axillae, with associated bullae, fragility, and focal denudation. Photo courtesy of Eric Meinhardt, MD.

layer, and adnexal epithelial involvement, consistent with TEC. The patient was treated with pentoxifylline and pyridoxine, without improvement. Given the continued progression, she was started on IVIG (4 g/kg) and prednisone 13 days after the transplant, with improvement.

DISCUSSION

Severe TEC mimicking TEN is rare. Isolated reports have suggested that patients with capillary leak syndrome (CLS) may be predisposed to this particularly severe presentation of TEC.² Patients with CLS present with organ dysfunction due to increased vascular permeability to proteins. Triggers, including drugs and infections, may lead to CLS because of cytokines increasing vascular permeability.³ The clinical abnormalities suggestive of CLS seen in our

patients included the acutely elevated creatinine level, fever, hypotension, generalized edema, hemoconcentration, hypoalbuminemia, and multiorgan failure; in both the cases, 1 or more initial infections were considered to be the likely triggers of CLS. It is unclear how CLS predisposes patients to severe TEC, although drug extravasation into tissue spaces and the skin due to increased vasodilation and vascular permeability may play a role.

Sloughed skin, denudation, and ruptured bullae generate a broad range of differential diagnoses, including TEN, PNP, and acute graft-versus-host disease (aGVHD). Although patients with PNP may present with polymorphous lesions, including lichenoid or targetoid lesions and bullae, they classically demonstrate extensive involvement of the lower vermilion lip, which was absent in our cases.⁴ The clinical signs favoring PNP include severe stomatitis, ocular involvement, and lichenoid or erythema multiforme-like targetoid lesions.⁴ aGVHD commonly presents as diarrhea and progresses to a widespread morbilliform eruption.² aGVHD was a major concern in case 2, but the rash presented 2 days after the transplant, before engraftment, making aGVHD unlikely.

TEN was strongly considered in both the cases. TEN has been reported with the use of several chemotherapeutic agents, including cyclophosphamide, brentuximab, and methotrexate.^{5,6} However, it is unclear whether the previous cases that were reported as “TEN” due to chemotherapeutic agents actually represented TEN or exaggerated TEC reactions, as described here. Unlike TEN, TEC is not a hypersensitivity reaction. TEC is thought to be due to the toxic effect of chemotherapy agents on the eccrine ducts, acrosyringia, and epidermis; accumulation of cytotoxic agents in the sweat; and/or release of granulysin by natural killer cells.^{1,7} Both TEN and TEC can occur within days to weeks of initiating the offending agent.^{1,7}

There were many factors favoring TEC over TEN in these cases. The initial presentation involved magenta-colored papules and plaques with a flexural distribution, as is typical of TEC. Furthermore, although the lesions coalesced in the affected flexural areas, more diffuse, confluent erythroderma was absent, and mucosal findings were minimal. Both TEC and TEN can share some histopathologic findings, including sparse lymphocytic infiltrates around the superficial vascular plexus and along the junction, single necrotic keratinocytes, and, in some cases of TEC and most cases of TEN, subepidermal clefting or vesiculation. Increased numbers of mitotic figures among keratinocytes without evidence of

epidermal regeneration (implying mitotic arrest rather than epidermal proliferation), squamatization of the basal layer, syringosquamous metaplasia, and the presence of only scattered single necrotic keratinocytes favor TEC over TEN, a condition in which many necrotic keratinocytes or confluent necrosis are present.⁸

Treatment for TEC is typically supportive, including emollients and topical steroids for symptomatic relief.¹ The other treatment options include celecoxib, pyridoxine, pentoxifylline, and oral corticosteroids.^{1,7} There are also reports of IVIG improving TEC and CLS.^{9,10} The morphology, flexural distribution, and histopathology of the lesions in these cases were felt to be highly suggestive of TEC, and we initially instituted supportive care measures. However, IVIG was initiated after several days of progressive involvement and can be considered as a potential option in addition to supportive care for severe and progressive cases.

Our experience with these cases illustrates several critical points for the diagnosis and management of severe TEC: (1) severe TEC can mimic TEN, PNP, and aGVHD, requiring a careful dermatologic evaluation; (2) marked flexural predominance may be a clinical clue for TEC; and (3) IVIG can be considered for severe TEC and represents an area for further investigation. Lastly, CLS and/or an infection (including bacteremia, fungemia, and/or viremia with cytomegalovirus or human herpesvirus 6) may serve as cofactors for severe TEC, also warranting further study.

Conflicts of interest

Dr Haemel serves as a consultant to CSL Behring and Guidepoint, LLC.

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