

# Toxic erythema of chemotherapy with periorbital and perioral involvement

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**ABSTRACT** Toxic erythema of chemotherapy (TEC) refers to a group of chemotherapy-induced cutaneous toxicities. We present a case of TEC in an 11-year-old girl who received gemcitabine and docetaxel for osteosarcoma of the femur.

*Keywords:* adverse drug reaction, docetaxel, gemcitabine, toxic erythema of chemotherapy, toxicity  
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## INTRODUCTION

Toxic erythema of chemotherapy (TEC) refers to a group of dermatological manifestations that are attributed to the toxicity of chemotherapeutics.<sup>(1)</sup> Cytarabine, anthracyclines, 5-fluorouracil, capecitabine, taxanes, gemcitabine and methotrexate are common causative agents. Entities under TEC include eccrine squamous syringometaplasia, palmoplantar erythrodysesthesia, neutrophilic eccrine hidradenitis, acral erythema, hand-foot syndrome, intertriginous eruption of chemotherapy and others. TEC often presents as an acral or intertriginous eruption of erythematous patches and plaques, which resolve with desquamation and post-inflammatory hyperpigmentation. Histological findings may include vacuolar degeneration of the basal layer, sparse inflammatory infiltrates, cellular atypia, eccrine squamous metaplasia or perieccrine neutrophilic infiltrates.<sup>(2)</sup>

Cutaneous eruptions in paediatric patients receiving chemotherapy are a common cause of inpatient dermatology consultations.<sup>(3)</sup> The diagnosis of TEC is important yet especially challenging in the setting of paediatric oncology, in which possibilities like disseminated infection in an immunocompromised host, drug hypersensitivity reaction, Stevens-Johnson syndrome, toxic epidermal necrolysis and the eruption of lymphocyte recovery have to be considered. We present the case of an 11-year-old Chinese girl who underwent chemotherapy for osteosarcoma of the femur.

## CASE REPORT

An 11-year-old girl with relapsed stage IV osteosarcoma of the right femur was referred to our dermatological service for a cutaneous eruption. She was on Day 3 of Cycle 2 of salvage chemotherapy, which consisted of gemcitabine (900 mg/m<sup>2</sup>) and docetaxel (100 mg/m<sup>2</sup>) (Fig. 1), when the rash started. Apart from the pruritic rash, she had a low-grade fever, non-bloody diarrhoea and painful oral ulcers. The only concurrent medication was co-trimoxazole, of which she had previously taken eight courses without any adverse reaction.

Examination revealed dusky patches and plaques in the periorbital and circumoral regions, axillary and inguinal folds, as well as the antecubital fossae. There were superficial punctate erosions in the left groin crease, but no blisters, acral erythema or peripheral oedema (Fig. 2). Investigations revealed moderate neutropenia with an absolute neutrophil count of 480/mm<sup>3</sup>. Septic work-up was negative for any localising source of infection. A skin biopsy was obtained from her left groin, which revealed focal basal vacuolar degeneration with some apoptotic keratinocytes. There was also a perivascular infiltrate of lymphocytes, histiocytes and eosinophils. However, no eccrine changes were observed (Fig. 3).

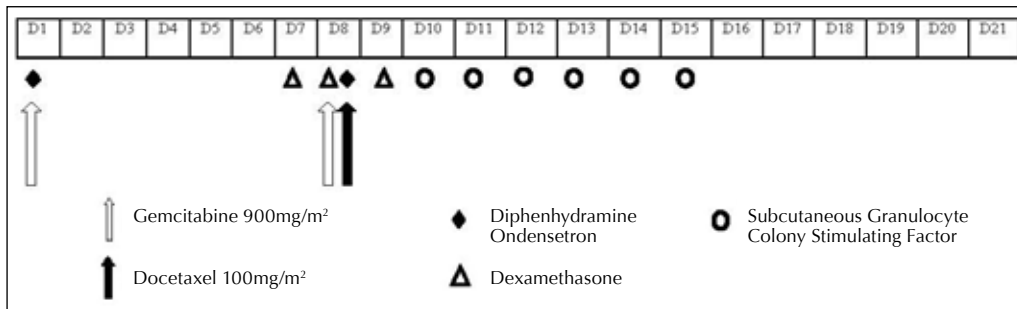
The patient was covered empirically with five days of intravenous antibiotics for neutropenic fever. Topical treatment with corticosteroids and emollient therapy was initiated. Although a hypersensitivity response to co-trimoxazole was deemed unlikely, the patient was switched from co-trimoxazole to nebulised pentamidine. As the rash was recognised as part of the self-limiting TEC spectrum, chemotherapy was continued. An attempt was made to mitigate the cutaneous toxicity by increasing the interval between cycles. With this measure, the rash did not worsen but remained the same. Hence, the dose of gemcitabine was reduced by 25%. After this reduction in dosage, the rash recurred three to four days after each cycle of chemotherapy, but at a lower intensity. The patient eventually responded well to the dose-attenuated chemotherapeutic regime, with repeat scans showing size reduction of her pulmonary metastases.

## DISCUSSION

Our patient with TEC had perioral and periorbital involvement. To the best of our knowledge, this feature has not been previously reported in the literature. TEC is believed to occur as a result of the toxic accumulation of chemotherapeutic agents in the eccrine glands.<sup>(1)</sup> The timing to the onset of TEC is highly variable, ranging from one day to a few months after the initiation of chemotherapy.<sup>(1)</sup> Multi-agent chemotherapy or high-dose

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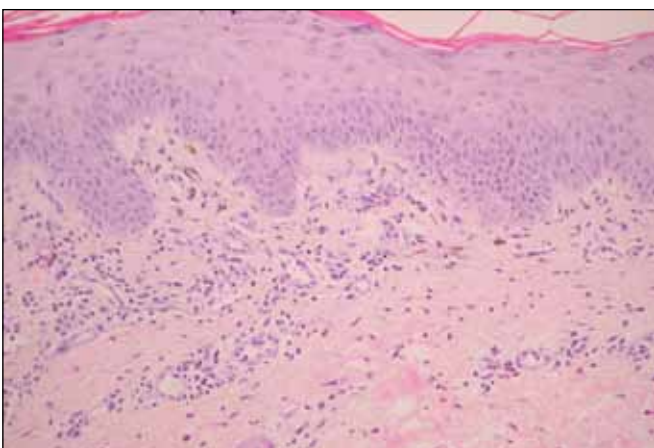
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**Fig. 1** Figure illustrates the patient's chemotherapeutic regimen, which consisted of seven 21-day cycles of gemcitabine, docetaxel and other premedications. This was a novel and potent chemotherapeutic regimen used in paediatric sarcomas that had failed first line chemotherapy.<sup>(4)</sup>



**Fig. 2** Photographs show (a) periorbital erythematous-brown patches; (b) an erythematous patch with early desquamation at the chin, and post-inflammatory hyperpigmentation above the lip; (c) a brown hyperpigmented patch in the left axilla, with accentuation of the skin creases; and (d) superficial erosion and accentuation of the rash in the left inguinal crease.



**Fig. 3** Photomicrograph shows focal basal vacuolar degeneration with a few apoptotic keratinocytes, and scant perivascular infiltrate of lymphocytes, histiocytes and eosinophils (Haematoxylin & eosin, x 40).

chemotherapy are likely to cause the earlier induction of TEC.<sup>(3)</sup> TEC may mimic a drug hypersensitivity response, as it may not appear on first exposure to the chemotherapeutic agent.<sup>(3)</sup> We postulate that this might be due to the time needed for toxic levels of the drug or its metabolites to build up in the eccrine glands.

The diagnosis of TEC is supported by the histological findings of eccrine squamous syringometaplasia, keratinocyte apoptosis and necrosis, and cellular atypia in entities grouped under TEC.<sup>(1,3)</sup> Clinical observation of the accentuation of rashes in skin creases and occlusive sites, where sweat production is increased, concurs with such a pathomechanism in TEC.<sup>(1)</sup> However, eccrine glands are not only found in abundance in the acral and intertriginous sites, they are also present in high density in the periorbital and perioral regions.<sup>(5)</sup> This would explain the peculiar distribution of

the rash in our patient. The lack of inflammatory infiltrate from intensely erythematous lesions in TEC suggests cytokine-induced reactive vasodilatation from keratinocyte damage rather than from a direct inflammatory process.<sup>(6)</sup>

From a clinical standpoint, the recognition of TEC avoids inappropriate interventions, such as the discontinuation of useful prophylactic antibiotics and the mislabelling of drug allergies, which may restrict future treatment. As the name suggests, TEC is not a hypersensitivity response but a self-limiting toxic reaction. Chemotherapy should be allowed to continue, with the caveat that there might be an increase in the severity of the rash should the dose be escalated. Dose reduction and lengthening of the dosing interval have been reported to mitigate the cutaneous toxicity. Meanwhile, the rash can be managed supportively with emollients, topical steroids, cool compresses and analgesics.<sup>(1)</sup> The appearance of TEC may parallel the onset of other toxicities associated with chemotherapy, such as gut toxicity, severe oral mucositis and neutropenia. A work-up for increased immunosuppression and concomitant infection should thus be initiated when TEC is manifested.

In summary, we report an unusual case of TEC involving the periorbital and circumoral skin, and highlight the importance of

recognising this clinical entity, which is usually self-limiting and should not be confused with a drug hypersensitivity reaction.

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