

Malignant intertrigo: A subset of toxic erythema of chemotherapy requiring recognition



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INTRODUCTION

Toxic erythema of chemotherapy (TEC) encompasses a broad spectrum of cytotoxic effects on the skin.¹ Despite increasing awareness of TEC, such eruptions may remain unrecognized and subsequently result in unnecessary hospitalizations. Of the different variants of TEC, intertriginous eruptions have been reported using many terms, such as *intertrigo dermatitis*, *intertriginous eruption of chemotherapy*, *flexural erythematous eruption*, and *intertrigo-like eruption associated with chemotherapy*.¹ *Intertrigo* is a broad term that refers to any inflammatory rash of closely opposed skin, typically presenting with varying degrees of erythema and maceration, and this particular type of TEC has not been identified with consistent nomenclature. We present 6 cases of this distinct subset of TEC, all occurring within a 7-month period at a single institution; these cases were initially unrecognized, resulted in hospitalization, and required inpatient dermatologic consultation to achieve a diagnosis. Although *TEC* is a clinically useful term intended to improve discernment of its noninfectious and nonallergic etiology,¹ the loss of morphologic specificity may prevent its variants from being properly recognized, especially in the intertriginous regions. We therefore propose *malignant intertrigo* (MI) as a useful and encompassing term describing toxic erythema of chemotherapy affecting the intertriginous skin.

Abbreviations used:

MI:	malignant intertrigo
PPE:	palmoplantar erythrodysesthesia
SDRIFE:	symmetrical drug-related intertriginous, flexural exanthema
TEC:	toxic erythema of chemotherapy

REPORT OF CASES

Six patients with various malignancies undergoing chemotherapy presented with intertriginous rashes (Table I and Fig 1). Involved areas included cervical, inframammary and inguinal folds, and axillae, abdomen, antecubital fossae, perineum, buttocks, and thighs. Physical examination found sharply demarcated, erythematous-to-dusky patches and plaques with focal scaling, crusting, and erosions. These lesions were painful and exquisitely tender. Histopathology results showed subtle interface dermatitis with variable epidermal dysmaturation and necrosis, along with perivascular and periadnexal chronic inflammatory infiltrate. Three of these cases showed eccrine squamous syringometaplasia.

Several patients were initially misdiagnosed in the outpatient or emergency setting with infections, contact dermatitis, and, in one case, atypical Stevens-Johnson syndrome, leading to treatments with antimicrobials and corticosteroids, both topical and intravenous. At the time of diagnosis of TEC,

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Table I. Epidemiologic and clinicopathologic findings in the 6 cases

Case	Age/ sex	Malignancy	Prior therapy	Most recent therapy*	Onset of rash (season and chemotherapy cycle)	Clinical findings	Histologic findings	Course and response
1	60 F	AML: 47,XX, +8, t(9;11)	None	Decitabine priming with "7+3" cytarabine and daunorubicin	Autumn, cycle 1	Tender erythematous patches in the bilateral inframammary folds, left axilla, left anterior chest, and cervical skin folds	Atrophic epidermis with prominent interface changes displaying a hydropic pattern of the basal keratinocytes, early squamous metaplasia of the dermal eccrine ducts, and superficial and perivascular lymphocytic inflammatory infiltrate, consistent with interface dermatitis with early associated changes of squamous syringometaplasia	Complete re- epithelialization achieved after application of topical steroids, silver- impregnated mesh gauze, and aluminum acetate soaks
2	43 F	Metastatic rectal adenocarcinoma and renal cell carcinoma	Surgical debulking	FOLFIRI and bevacizumab	Summer, cycle 3 (interrupted because of nausea and vomiting)	Tender, sharply demarcated hyperpigmented and erythematous scaly patches in the inframammary regions and inguinal folds bilaterally, with focal serous crusting in the right inframammary patch	Prominent compact hyperkeratosis of the epidermis with patchy parakeratosis and focal ulceration with a mild chronic inflammatory infiltrate admixed with occasional neutrophils and some impetiginization; mild, predominantly perivascular and periadnexal chronic inflammatory	Initially treated for suspected cutaneous candidiasis, cellulitis, and ACD without improvement. Treatment included nystatin cream, fluconazole (both topical powder and oral), empiric IV antibiotics, and topical corticosteroids. Astringent soaks and higher-potency topical steroids

Continued

Table I. Cont'd

Case	Age/ sex	Malignancy	Prior therapy	Most recent therapy*	Onset of rash (season and chemotherapy cycle)	Clinical findings	Histologic findings	Course and response
3	68 F	Metastatic breast carcinoma: ER ⁺ , PR ⁺ , Her2/neu	Lumpectomy with axillary node dissection, adjuvant external beam radiation, doxorubicin and cyclophosphamide, paclitaxel, anastrozole, docetaxel, fulvestrant, letrozole, capecitabine	Doxorubicin	Summer, cycle 2	Extensive hyperpigmentation and exquisitely tender, erythematous rash with thin scale on the buttocks, posterior thighs, and inframammary regions	infiltrate in the dermis Interface dermatitis with keratinocyte necrosis and associated squamous syringometaplasia, marked surface hyperorthokeratosis, and superficial and perivascular lymphocytic and histiocytic inflammation	resulted in initial improvement. Treated with topical corticosteroids with lidocaine and an oral prednisone taper with subsequent improvement. Patient discontinued cytotoxic chemotherapy because of severity of the skin reaction and was restarted on hormonal agents
4	26 M	Recurrent HL	ABVD	GND	Winter, cycle 2	Erythematous and dusky papules and plaques intermixed with erosions on the bilateral antecubital fossae, umbilicus, and groin with crusting of the scrotum. Dusky erythema of the palmar and dorsal surfaces of the bilateral hands without evidence of oral mucositis	No biopsy performed	Initially treated for suspected cellulitis with TMP-SMX with subsequent worsening of rash. Supportive treatment with magic mouthwash and aluminum acetate soaks resulted in improvement.
5	52 F	Metastatic ovarian adenocarcinoma	Neoadjuvant carboplatin and paclitaxel, surgical debulking, and adjuvant carboplatin and paclitaxel	Experimental trial of doxorubicin and study drug VTX-2337	Summer, cycle 4	Painful, dusky plaques on the upper abdomen; large, erythematous erosions and desquamation on	Interface dermatitis with alternating hyper- and hypokeratosis, clusters of neutrophils and	Initially treated for suspected atypical SJS with pulse-dosed IV steroids, topical steroids, topical mupirocin, and

						the bilateral posterior thighs, and scattered follicular erythematous papules on the bilateral anterosuperior thighs	parakeratosis in the stratum corneum, lymphoid cells at the dermal-epidermal junction with focal interface reaction, and a superficial and deep dermal, predominantly perivascular and periadnexal chronic inflammatory infiltrate admixed with rare eosinophils	aggressive pain control with gradual improvement over weeks
6	60 F	Metastatic renal cell carcinoma	Nephrectomy, pazopanib, cabozantinib	Axitinib	Winter, cycle 1	Well-demarcated erythema of the intertriginous zones of the panniculus, axillae and perineum with several erosions draining serous fluid	Parakeratosis, mild perivascular dermatitis with red blood cell extravasation; eccrine squamous syringometaplasia identified in several sections	Initially treated with antimicrobial silver complex moisture wicking fabric. Axitinib was stopped. Wounds improved over several days, but patient switched to comfort care because of disease progression.

AML, Acute myelogenous leukemia; FOLFIRI, leucovorin, 5-fluorouracil, and irinotecan; ACD, allergic contact dermatitis; IV, intravenous; ER, estrogen receptor; PR, progesterone receptor; HL, Hodgkin's lymphoma; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; GND, gemcitabine, Navelbine, and doxorubicin; TMP-SMX, trimethoprim-sulfamethoxazole; SJS, Stevens-Johnson syndrome.

*Before or during development of rash.

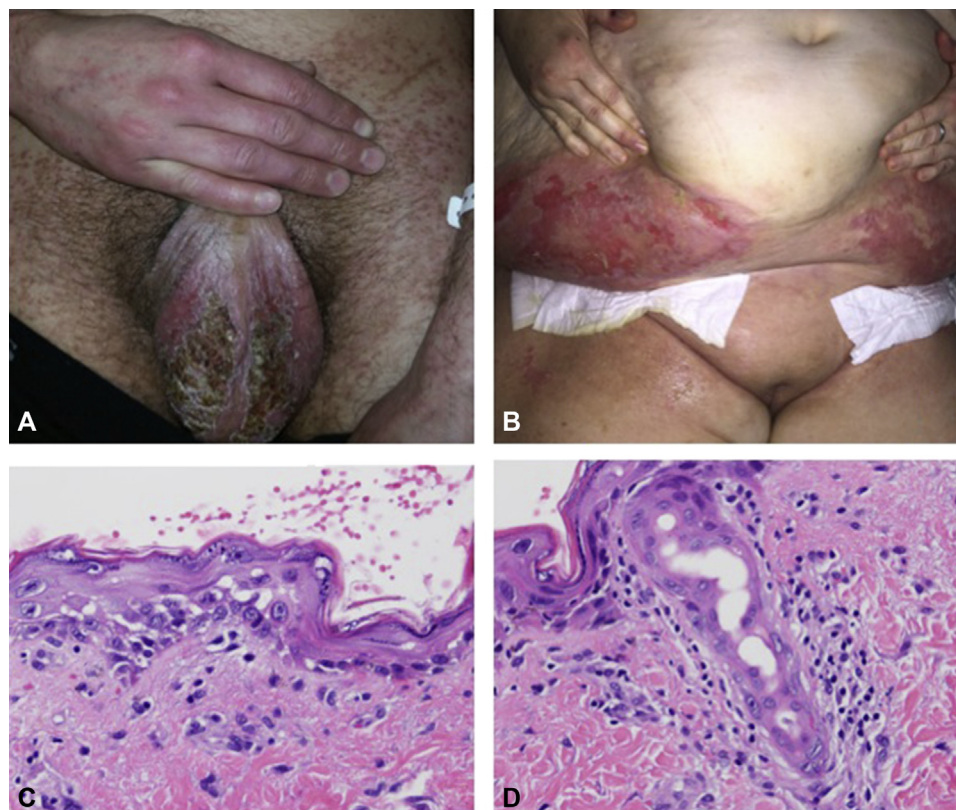


Fig 1. Clinical and histopathologic findings of MI. **A**, Painful dusky macules, papules, and crusts over the scrotum and intertriginous thighs, and overlying PPE changes of hands (patient 4). **B**, Dusky erythema and ulcerations underlying the panniculus without PPE changes (patient 2). **C** and **D**, Epidermal dysmaturation and eccrine squamous syringometaplasia representative of the cohort. (Hematoxylin-eosin stain; original magnification: $\times 400$.)

higher potency topical corticosteroids, astringent wound care, and analgesia were administered for palliation and to aid resolution. Further recommendations included keeping affected areas dry and cool and application of an aluminum chloride solution both after healing and before restarting chemotherapy.

Two of the patients were treated for renal cell carcinoma, one of whom was additionally treated for rectal adenocarcinoma. The other patients were each treated for different malignant diseases, including leukemia, lymphoma, breast cancer, and ovarian adenocarcinoma, in addition to the two other cancers mentioned above. Each patient also underwent a distinct treatment regime; therefore, multiple chemotherapeutic classes are represented in this series, including antimetabolites, anthracyclines, vinca alkaloids, topoisomerase inhibitors, and several others.

DISCUSSION

Among the many presentations of TEC, the most common is palmoplantar erythrodysesthesia (PPE),

which is becoming increasingly recognized.² In contrast to PPE, intertriginous involvement continues to be frequently misdiagnosed, resulting in hospitalization, inappropriate treatments, and inaccurate labeling of drug allergies,^{1,2} as in the cases described in this report. As awareness of TEC increases, the rate of dermatologic consultations and biopsies decreases.³ As such, characterization of the manifestations of TEC is paramount for prompt, accurate diagnosis and treatment and to avoid invasive procedures (eg, biopsies) and inappropriate pharmacotherapy. We thus propose the term *malignant intertrigo* (MI) to discriminate the intertriginous pattern of TEC. We find this term useful, as it is brief, describes the locations involved, indicates the associated malignancy, and alludes to its significant pain and tenderness.

The presumed pathophysiology of TEC is excretion of cytotoxic agents into eccrine sweat ducts, yielding localized toxic effects.^{1,2,4} Areas with high concentrations of eccrine ducts and those vulnerable to sweat trapping are at increased risk. Numerous nucleoside metabolic inhibitors and cytotoxic agents

have been implicated in TEC, and this trapping of chemotherapeutic agents results in eccrine squamous syringometaplasia and epidermal dysmaturation.^{1,2,5} TEC is most commonly associated with anthracyclines, cytarabine, and other antimetabolites.¹ Interestingly, however, similar eruptions may also occur with tyrosine kinase inhibitors, despite their lack of cytotoxicity.^{1,4-6} The cohort in this case series is too small and their treatments too varied to determine additional correlations among types of chemotherapy or malignancy and the subsequent rash.

Although biopsy supports the diagnosis, certain clinical findings help raise suspicion for MI when diagnosing a flexural eruption. In particular, MI should be distinguished from mechanical or infectious intertrigo (including candidiasis) and from drug exanthemata, cellulitis, and graft-versus-host disease.^{1,2,6} Marked pain and tenderness are among the more prominent clinical features that can help identify MI from among other intertriginous rashes, and the absence of a history of organ or marrow transplant will rule-out cutaneous graft-versus-host disease. MI does not display the satellite lesions commonly seen in candidal intertrigo, and neither potassium hydroxide cytology nor bacterial cultures will be positive, unless superimposed infection arises from the associated skin breakdown. Symmetric drug-related intertriginous and flexural exanthema (SDRIFE), with its characteristic erythema on the gluteal or inguinal areas, may also be in the differential diagnosis, requiring distinction from MI. SDRIFE, however, is most commonly associated with systemic antibiotics rather than chemotherapeutics and is presumed to be a delayed T-cell-mediated reaction rather than an accumulation of locally cytotoxic chemicals.⁷ As a type IV hypersensitivity reaction, SDRIFE presents just hours to days after the offending drug administration,⁷ whereas MI presents days to weeks after drug exposure.¹ Therefore, the onset of symptoms can help distinguish SDRIFE from MI.

Cytarabine is one of the agents most frequently associated with TEC.¹ A recently published case series reported on a generalized and benign papular purpuric eruption associated with cytarabine in 16 patients.⁸ This rash also displayed some predilection for intertriginous areas; however, the purpuric eruption was not mostly confined to the flexural areas,

where accumulation of secreted cytarabine may exert its cytotoxic effect; rather, the eruption was hypothesized to result from vascular toxicity and frequently spread to the face, chest, back, and extremities. Additionally, other than mild pruritus, the generalized rash was asymptomatic, lacking the exquisite pain that accompanies MI. Both presentations exhibit some overlapping features, and although both are associated with cytarabine, the generalized purpuric eruption and MI appear to be distinct processes with different symptoms, presentations, and etiologies.

MI is a self-limiting eruption that resolves spontaneously with desquamation; however, severe cases may impact quality of life and may prompt providers to suspend chemotherapy or reduce dosage. Thus, appropriate intervention with topical or oral corticosteroids, astringent soaks, and analgesics is prudent for palliation and the perpetuation of cancer treatment. Prophylactic measures, such as suppression of hidrosis with anticholinergics and application of physical barriers to sweating, may additionally prevent chemotherapy interruption or dose reduction, and, therefore, may warrant further study.

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