Intertriginous Eruption Associated With Chemotherapy in Pediatric Patients

Kathryn A. Webber, BA; Liborka Kos, MD; Kristen E. Holland, MD; David A. Margolis, MD; Beth A. Drolet, MD

**Background:** Cutaneous eruptions commonly occur in children receiving chemotherapy, and the clinical situation often demands immediate diagnosis and initiation of treatment. Several patterns of cutaneous eruptions to chemotherapy have been reported; however, the nomenclature used to describe these entities has been derived from the histologic findings. The morphologic characteristics, distribution, and natural history of these reactions have not been well established.

**Observations:** We report the clinical features of 16 pediatric patients with a distinctive chemotherapy-induced eruption. The eruption is most prominent in or limited to intertriginous regions and areas of occlusion. We were not able to identify any single chemotherapeutic agent or even a group of agents in the same pharmacologic family that seemed to be associated with this reaction. The eruption did not appear to be related to sex, age, ethnicity, underlying malignancy, or genetic disease.

**Conclusions:** Recognition of this distinct clinical pattern can help rule out more serious entities, avoid a biopsy, and reassure the physician and patient of the benign and self-resolving clinical course. This entity may be observed with many chemotherapeutic agents and underlying diseases, but most often with high-dose chemotherapy protocols.

Arch Dermatol. 2007;143:67-71

**METHODS**

Approval from the institutional review board of the Children’s Hospital of Wisconsin, Milwaukee, was obtained. All available inpatient dermatology consultations from August 1999 to December 2005 were reviewed. A dermatologist was consulted for the onset of a cutaneous eruption for 56 patients who were on the hematology-oncology service. We included all patients in whom the current eruption was documented as being related to chemotherapy. The diagnoses given to these patients by the consulting dermatologist included cutaneous toxic effects secondary to chemotherapy, drug reaction, neutrophilic eccrine hidradenitis, and eccrine squamous syringometaplasia. We excluded patients with eruptions limited to palms and soles because this pattern of acral erythema has been well described. The medical records of the 23 remaining patients were obtained and reviewed in detail. One patient was excluded owing to unavailability of medical records from an outside institution. Six patients with red papules not involving the intertriginous areas were also excluded. The information in the 16 dermatology consultations and complete medical records of all cases was analyzed. We noted the clinical appearance, distribution, and morphologic features of the eruption (Table 1). Chemotherapeutic agents, dosages, and timing were

---

**D**iagnosing skin eruptions in immunocompromised patients is often challenging because many of the classic clinical features that aid in diagnosis are dictated by intact immunologic mechanisms. Furthermore, the clinical situation often demands immediate recognition and initiation of treatment, as life-threatening complications such as infection and drug reaction are not uncommon. This challenge is particularly emphasized in the inpatient oncology/bone marrow transplant setting, where multiple medications, including chemotherapy, are administered simultaneously, and there is risk for cutaneous graft vs host disease.

Several unusual patterns of cutaneous eruptions associated with chemotherapy have been described in case reports and small case series, many of which emphasize the histologic pattern rather than the clinical appearance. The morphologic features of these eruptions in the pediatric population have rarely been described. We report the clinical features of 16 patients with a distinct chemotherapy-induced eruption of the intertriginous regions.

---

Author Affiliations: Departments of Dermatology (Ms Webber and Drs Kos, Holland, and Drolet) and Pediatrics (Drs Margolis and Drolet), Medical College of Wisconsin, Milwaukee.
analyzed in an attempt to identify single agents or a class of agents attributable to this reaction (Table 2). To identify a pattern in the timing of this eruption, we noted the first and last days of chemotherapy and the onset of the rash. Rash onset is recorded as the number of days from the last dose of chemotherapy administration to the date of the cutaneous eruption (mean onset, 6.5 days; median onset, 4 days [range, 1-25 days]).

REPORT OF CASES

CASE 1

The dermatology service was consulted to see a 3-year-old white female patient with stage IV neuroblastoma who had developed a cutaneous eruption. She was admitted for a hematopoietic progenitor cell infusion after conditioning with melphalan, etoposide, and carboplatin. She developed an asymptomatic cutaneous eruption that began on her lower abdomen 6 days after the last dose of chemotherapy. The patient had received lower doses of etoposide and carboplatin in the past, with no history of a similar reaction.

On physical examination, she was lethargic and febrile at 39.2°C. There were hundreds of 1- to 5-mm red papules on the arms, chest, and lower abdomen (Figure 1A). Several of these lesions had a dusky violaceous color and were coalescing into large patches in the intertriginous areas including the genital area and inguinal folds, axillary folds, the back of the neck, and antecubital fossae (Figure 1B). No conjunctival injection or oral lesions were noted. Several erythematous papules were scattered over the vertex scalp. Her ears were swollen, and there were a few 1- to 3-mm pustules on the helix. No acral erythema or vesicles were noted.

CASE 7

The dermatology service was consulted to see an 18-year-old male patient recently diagnosed with pericardial angiosarcoma. An eruption was noted in his intertriginoous and occluded areas 4 days after the final day of high-dose chemotherapy with ifosfamide, doxorubicin, and vincristine. He was also treated with radiation therapy for 5 consecutive days, which was completed the day after the rash appeared. This was his first course of chemotherapy, and he developed a fever during treatment.

Table 2. Characteristics of Patients With a Distinctive Chemotherapy-Induced Eruption

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Race/Sex</th>
<th>Preexisting Malignancy/Disease</th>
<th>CHEMO Type</th>
<th>No. of CHEMO Cycles</th>
<th>WBC Count at Rash Onset*</th>
<th>CHEMO Agents Used</th>
<th>Days From End CHEMO to Rash Onset, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 y/W/F</td>
<td>Neuroblastoma</td>
<td>BMT, AUT</td>
<td>7</td>
<td>0.1</td>
<td>Melphalan, carboplatin, etoposide</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>3 y/O/F</td>
<td>Neuroblastoma</td>
<td>CHEMO</td>
<td>2</td>
<td>0.1</td>
<td>Cyclophosphamide, doxorubicin</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>4 y/W/F</td>
<td>Neuroblastoma</td>
<td>BMT, AUT</td>
<td>7</td>
<td>0.1</td>
<td>Melphalan, carboplatin, etoposide</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>17 y/W/F</td>
<td>Osteosarcoma</td>
<td>CHEMO</td>
<td>15</td>
<td>2.9</td>
<td>Dextrazoxane, doxorubicin, methotrexate</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>17 y/W/M</td>
<td>Osteosarcoma</td>
<td>CHEMO</td>
<td>13</td>
<td>2.6</td>
<td>Cisplatin, doxorubicin, methotrexate</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>12 y/W/F</td>
<td>Ewing sarcoma</td>
<td>BMT, AUT</td>
<td>21</td>
<td>2.0</td>
<td>Busulfan, melphalan</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>18 y/W/M</td>
<td>Pericardial, angiosarcoma</td>
<td>CHEMO</td>
<td>1</td>
<td>6.8</td>
<td>Ifosfamide, doxorubicin, vincristine</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>17 y/W/M</td>
<td>Malignant germ cell tumor</td>
<td>BMT, AUT</td>
<td>2</td>
<td>0.1</td>
<td>Carboplatin, etoposide, thiopeta</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>10 y/W/F</td>
<td>AML</td>
<td>BMT, ALLO</td>
<td>4</td>
<td>0.8</td>
<td>Busulfex, methotrexate, melphalan</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>6 y/W/F</td>
<td>AML</td>
<td>BMT, ALLO</td>
<td>1</td>
<td>0.1</td>
<td>Cytarabine, cyclophosphamide</td>
<td>10</td>
</tr>
<tr>
<td>11</td>
<td>2 y/W/M</td>
<td>AML</td>
<td>BMT, ALLO</td>
<td>10</td>
<td>6.0</td>
<td>Cytarabine, cyclophosphamide</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>7 y/W/M</td>
<td>ALL</td>
<td>CHEMO</td>
<td>6</td>
<td>11.7</td>
<td>Methotrexate, cyclophosphamide, etoposide</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>5 mo/H/F</td>
<td>ALL</td>
<td>CHEMO</td>
<td>3</td>
<td>2.9</td>
<td>Methotrexate</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>17 y/W/M</td>
<td>Large cell B, lymphoma</td>
<td>CHEMO</td>
<td>1</td>
<td>9.5</td>
<td>Vincristine, cyclophosphamide</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>7 y/B/F</td>
<td>Hgb SS</td>
<td>BMT, ALLO</td>
<td>1</td>
<td>4.4</td>
<td>Methotrexate (low dose), busulfan, cyclophosphamide</td>
<td>25</td>
</tr>
<tr>
<td>16</td>
<td>15 mo/W/M</td>
<td>SCID</td>
<td>BMT, ALLO</td>
<td>1</td>
<td>0.1</td>
<td>Methotrexate, busulfan, cyclophosphamide</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: ALL, acute lymphocytic leukemia; ALLO, allogeneic; AML, acute myelocytic leukemia; AUT, autologous; B, black/African American; BMT, conditioning before transplantation; CHEMO, any chemotherapy; H, Hispanic; Hgb SS, sickle cell anemia; O, other; SCID, severe combined immunodeficiency disorder; W, white/non-Hispanic; WBC, white blood cell.

*Measured as thousands of cells per microliter.
On physical examination, he was afebrile and in no apparent distress. He had 3- to 4-mm bright red papules coalescing into dusky patches on the abdomen and extending into the groin bilaterally. Erythematous papules were noted on the upper thighs, neck, right axilla, back, ears, and scalp (Figure 2). He had no blisters, skin tenderness, or mucosal lesions.

**RESULTS**

There was no sex, age, or ethnic predilection. We found no common predisposing malignancy or disease. Of the 16 patients, 7 (44%) were receiving chemotherapy for treatment of a malignancy; the rest underwent chemotherapeutic ablation of the bone marrow before an allogeneic (5 patients [31%]) or autologous (4 patients [25%]) bone marrow transplantation.

All patients developed the eruption within 25 days of the last dose of chemotherapy, with only 2 patients developing lesions more than 10 days after chemotherapy. The patient who developed the eruption 25 days after chemotherapy was African American and had postinflammatory hyperpigmentation and desquamation at the time of the consultation. We hypothesize that the pigmentation of her skin obscured the erythema at the onset of the rash and delayed the diagnosis.

Of the 16 patients, 4 received total body irradiation and another 2 had limited radiation therapy. Seven patients had received the same chemotherapeutic agents previously, but only 1 had a similar cutaneous eruption previously. Only 1 patient had an underlying skin disease, which was molluscum contagiosum. The analysis of patient white blood cell counts demonstrated that the eruption did not coincide with lymphocyte recovery. Six patients had a fever (body temperature >38.5°C) during chemotherapy administration, and 5 patients had fevers on the first day of the cutaneous eruption.

A striking pattern was noted in the clinical appearance and distribution of the eruptions. All of the patients had dusky, red papules as the primary lesion. All 16 patients had confluent erythematous dusky patches in intertriginous areas, especially in the axillary folds and groin (Figure 3). One patient had a tissue biopsy. Mucous membrane erosions were noted in 3 patients (19%) and were typical of the mucositis observed with chemotherapy.
We believe that cutaneous reactions are common in pediatric patients receiving chemotherapy. Eruptions due to chemotherapy toxicity need to be distinguished from hypersensitivity reactions to either a chemotherapy agent or any of the myriad other medications given to these patients. The nomenclature of cutaneous chemotherapy-related toxic effects has not been well established. The existing literature on chemotherapy reactions is inadequate and often fails to describe the clinical appearance of these eruptions. This is especially true for those eruptions observed in the pediatric population even though they are a frequent reason for dermatology inpatient consultations. These consultations often involve gravely ill patients who could potentially have a life-threatening problem manifested by their skin findings. The consulting dermatologist must be able to evaluate the cutaneous eruption, rule out cutaneous manifestations of systemic infection or graft-vs-host disease and decide whether it necessitates laboratory investigation, treatment, and/or discontinuation of current therapeutic modalities.

We have observed a clinically distinct pattern of cutaneous eruptions in pediatric oncology patients receiving chemotherapy. The morphologic features and distribution are characteristic enough to stand out as a defined chemotherapy reaction. The eruption consists of papules coalescing into patches with an initial deep erythema that progresses to a dusky violaceous hue. The lesions are predominantly located in intertriginous areas, including axillae, antecubital fossae, inguinal folds, and scrotum. Occasionally, they may be found in other areas of occlusion. In spite of the striking eruption, none of the patients had any symptoms such as pruritus or skin tenderness. The clinical course is that of gradual spontaneous evolution into postinflammatory hyperpigmentation and desquamation (Figure 3).

We evaluated the rate, timing, and class of each chemotherapy agent in regards to its potential relation to this eruption. While the rate of administration was standardized in the protocols at our institutions, there was significant variability in the type, dose, and duration of the medications our patients received. We were not able to identify any single chemotherapy agent or even a group of agents in the same pharmacologic family that seemed to be associated with this reaction. The eruption appeared in all patients between 1 and 25 days from the onset of the most recent chemotherapy cycle. Careful analysis of each medication and the number of days from the institution of that medication to the initial appearance of the cutaneous eruption did not reveal a predictable pattern for any single medication. We noted that in patients who received high-dose methotrexate (ie, patients with solid tumors), the eruption appeared to occur sooner, within 1 to 4 days, and the timing was thus more predictable. However, the development of the eruption within a few days was also seen in multiple patients who received multiagent chemotherapy without methotrexate. It also appears that high-dose chemotherapy, such as that used for bone marrow ablation, is more likely to cause this eruption.

Certain chemotherapy reactions are more likely in patients with specific malignancies, such as the association of neutrophilic eccrine hidradenitis with acute myelogenous leukemia. We evaluated the type of malignancy in our patients and found no pattern, since the diagnoses included a variety of solid tumors and hematologic malignancies. No correlation was found with any other parameter, including white blood cell count and peak temperature at the onset of the eruption, prior radiation therapy, and/or a bone marrow transplantation.

It has been noted that drugs can be concentrated in the eccrine glands. Accumulation of a chemotherapy agent or its toxic metabolite in the eccrine gland and subsequent excretion in sweat may explain the striking clinical distribution of this eruption to natural sites of occlusion. We hypothesized that the eruption may have been related to an increase in body temperature and thus an increase in the amount of sweat produced. However, no correlation was found between body temperature and the onset of the eruption. Local temperature and friction in these naturally occluded intertriginous areas could play a role.

A biopsy to assess histologic features was not performed in most of our patients owing to the grave clinical status of our patients as well as the noted benign course of the eruption. The one histologic specimen obtained from a lesion on the arm demonstrated an interface dermatitis with scattered necrotic keratinocytes and a scant perivascular lymphocytic infiltrate. The eccrine glands appeared normal.

A similar clinical eruption has sporadically been described in the literature in adult patients under various names, including neutrophilic eccrine hidradenitis (NEH) and eccrine squamous syringometaplasia (ESS). These 2 entities are histologic patterns encountered in a variety of clinical settings. What has been called NEH in
chemotherapy patients has a variable clinical presentation with no classic morphologic features or location. It can occasionally occur in intertriginous areas but is usually not confined to those locations. Eccrine squamous syringometaplasia has also been associated with multiple settings outside of chemotherapy, including chronic ulcerations and medications. Valks et al published a case series of 10 patients with chemotherapy-induced reactions localized to intertriginous areas with a clinical pattern strikingly similar to our patients. All biopsy specimens taken from their patients showed ESS, as well as an interface dermatitis and a sparse perivascular lymphocytic infiltrate. Prussick et al published another case series of 8 patients with erythematous patches in an intertriginous distribution, with histologic findings of ESS.

On review of the literature on NEH and ESS, we noted that the timing and location of the biopsy are often not specified, both of which could have an impact on the histopathologic features of the specimen. Both NEH and ESS are thought to be part of a spectrum of chemotherapy-related eccrine gland toxic effects. In addition, there are isolated reports describing intertriginous cutaneous eruptions from chemotherapy, without histologic evidence of NEH or ESS.

The differential diagnosis for this eruption includes infection, graft-vs-host disease, drug hypersensitivity, or radiation dermatitis. Acute cutaneous graft-vs-host disease differs both in clinical characteristics and distribution. It initially appears as erythematous macules or folliculocentric papules on the face, ears, palms, soles, periungual areas, upper back, and neck. The macules and papules rarely become confluent and only in severe graft-vs-host disease, in which they are frequently associated with tense bullae. The eruption of acute graft-vs-host disease occurs at the time of engraftment. None of our patients who underwent a bone marrow transplantation were engrafted at the start of the eruption as evidenced by their white blood cell count. In addition, not all of our patients underwent a bone marrow transplantation. Chemotherapy hypersensitivity reactions tend to be diffuse and symptomatic and tend not to resolve until treatment with the causative medication is discontinued. Eruption of lymphocyte recovery presents as erythematous macules and papules coincident with a fever and rise in white blood cell count. It occurs after chemotherapy without bone marrow transplantation. No correlation between the white blood cell count and the onset of the eruption was observed. We also found no correlation between irradiation and this eruption, since patients who received chemotherapy without previous radiation therapy developed the same findings. In addition, the affected intertriginous areas were unlikely to be the areas of highest radiation exposure.

We believe that it is important to be aware of this response to chemotherapy when one is evaluating a pediatric oncology patient with a new rash. Unlike other reports of cutaneous chemotherapy toxic reactions, we did not find an association with a specific medication or malignancy. However, discontinuation of treatment with or avoidance of the potential causative agent may not be necessary because of the consistent spontaneous resolution and lack of symptoms noted in these patients. Recognition of this pattern can help rule out more serious causes and reassure the physician and patient of the benign and self-resolving clinical course.

Accepted for Publication: June 22, 2006.
Correspondence: Beth A. Drolet, MD, Department of Dermatology, Medical College of Wisconsin, 9200 W Wisconsin Ave, Milwaukee, WI 53226 (bdrolet@mail .mcw.edu).

Author Contributions: Study concept and design: Kos, Holland, and Drolet. Acquisition of data: Webber and Drolet. Analysis and interpretation of data: Webber, Kos, Margolis, and Drolet. Drafting of the manuscript: Webber, Kos, and Drolet. Critical revision of the manuscript for important intellectual content: Webber, Kos, Holland, and Margolis. Study supervision: Webber, Kos, Holland, Margolis, and Drolet.

Financial Disclosure: None reported.

REFERENCES

(REPRINTED) ARCH DERMATOL/VOL. 143, JAN 2007 WWW.ARCHDERMATOL.COM

©2007 American Medical Association. All rights reserved.