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CASE REPORT

Trastuzumab-Associated Flagellate Erythema: Report in a Woman with Metastatic Breast Cancer and Review of Antineoplastic Therapy-Induced Flagellate Dermatoses

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ABSTRACT

Introduction: Flagellate erythema presents as erythematous, individual and intermingled, linear streaks in a whiplash-like pattern. Several conditions, including antineoplastic agents, have been associated with flagellate erythema. A woman with metastatic breast cancer who developed flagellate erythema after receiving trastuzumab is described and the features of flagellate erythema associated with other antineoplastic agents are reviewed.

Methods: PubMed was used to search the following terms, separately and in combination: agent, antineoplastic, bendamustine, bleomycin, breast, cancer, chemotherapy, dermatitis, dermatosis, docetaxel, erythema, flagellate, Herceptin, pigmentation, peplomycin, therapy, and trastuzumab. All papers were reviewed and relevant manuscripts, along with their reference citations, were evaluated.

Results: The woman's pruritus and skin lesions promptly resolved after treatment with corticosteroids (oral and topical) and antihistamines (oral); premedication with dexamethasone prior to each subsequent trastuzumab treatment prevented recurrence of flagellate erythema. Chemotherapy-induced flagellate erythema was initially described in oncology patients who received bleomycin. In addition to trastuzumab, other antineoplastic agents that have been associated with the development of flagellate erythema include bendamustine, docetaxel, and peplomycin.

Conclusion: Cutaneous adverse events to trastuzumab are uncommon. However, flagellate erythema should be added to the potential side effects of trastuzumab. In addition, trastuzumab should be added to the list of antineoplastic agents that may be associated with flagellate erythema.

Keywords: Agent; Antineoplastic; Bendamustine; Bleomycin; Breast cancer; Chemotherapy; Dermatitis; Dermatosis; Docetaxel; Erythema; Flagellate; Herceptin;

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Pigmentation; Peplomycin; Therapy; Trastuzumab

INTRODUCTION

Flagellate erythema is a distinctive morphologic presentation of linear, whiplash-like pattern, red streaks on the skin [1]. Trastuzumab (Herceptin®; Genentech) is a humanized monoclonal antibody that binds to the human epidermal growth factor receptor 2 (HER2)/neu receptor and has been shown to increase not only overall survival, but also disease-free survival in patients with HER2-positive breast cancer [2, 3]. A woman with trastuzumab-induced flagellate erythema is described and the features of flagellate erythema associated with other antineoplastic agents are reviewed.

PubMed was used to search the following terms, separately and in combination: agent, antineoplastic, bendamustine, bleomycin, breast, cancer, chemotherapy, dermatitis, dermatosis, docetaxel, erythema, flagellate, Herceptin, pigmentation, peplomycin, therapy, and trastuzumab. All papers were reviewed and relevant manuscripts, along with their reference citations, were evaluated. Informed consent was obtained from the patient for being included in the study and for publication of the accompanying images.

CASE REPORT

A 64-year-old woman presented with left axillary lymphadenopathy in December 2014. Metastatic infiltrating ductal carcinoma of the left breast and left axillary and pectoral lymph nodes was diagnosed. The tumor was clinical stage III T2N2, estrogen receptor negative, progesterone receptor negative, and HER2 overexpressed.

She began treatment in 2015 with triple therapy on February 24, March 17, and April 7: paclitaxel, pertuzumab, and trastuzumab. She also received monotherapy with paclitaxel on March 3, March 10, March 24, and March 31. Following her treatment on April 7, she developed eyelid ptosis and peripheral neuropathy with ataxia that was attributed to paclitaxel.

Monotherapy with trastuzumab was resumed on May 9, 2015. On June 1, 2015, 3 days after receiving trastuzumab on May 29, 2015, she developed pruritus. She also noted a rash developing on her chest, abdomen, arms, and legs.

Cutaneous examination on June 3, 2015 showed erythematous, distinct and intermingled (in a lacy pattern), linear streaks on her arms (Figs. 1, 2), chest, and abdomen (Fig. 3). The morphology of the clinical lesions was a flagellate erythema. Similar linear streaks—both erythematous and hemorrhagic—were also noted on her legs (Figs. 4, 5).

A skin biopsy from her left arm showed basket-weave orthokeratosis overlying a spongiotic epidermis. There was edema in the

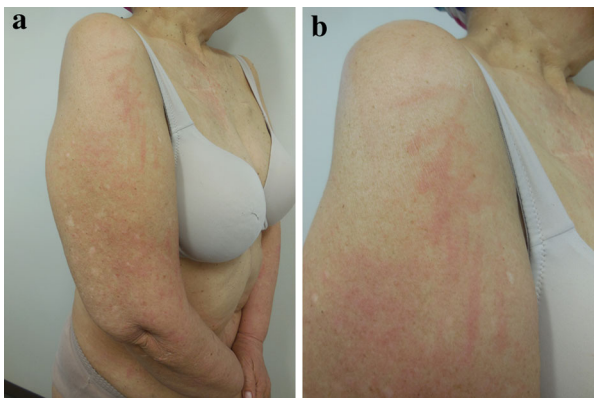

Fig. 1 Distant (**a**) and closer (**b**) views of the proximal extensor *right arm* show flagellate erythema presenting as distinct and intermingled (in a lacy pattern) linear erythematous streaks

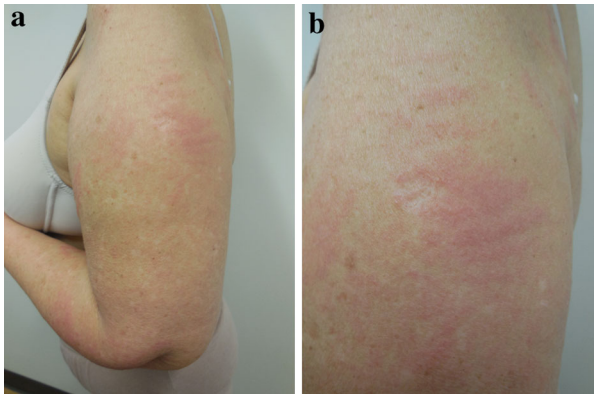

Fig. 2 Distant (**a**) and closer (**b**) views of the proximal extensor *left arm* show flagellate erythema presenting as distinct and intermingled (in a lacy pattern) linear erythematous streaks

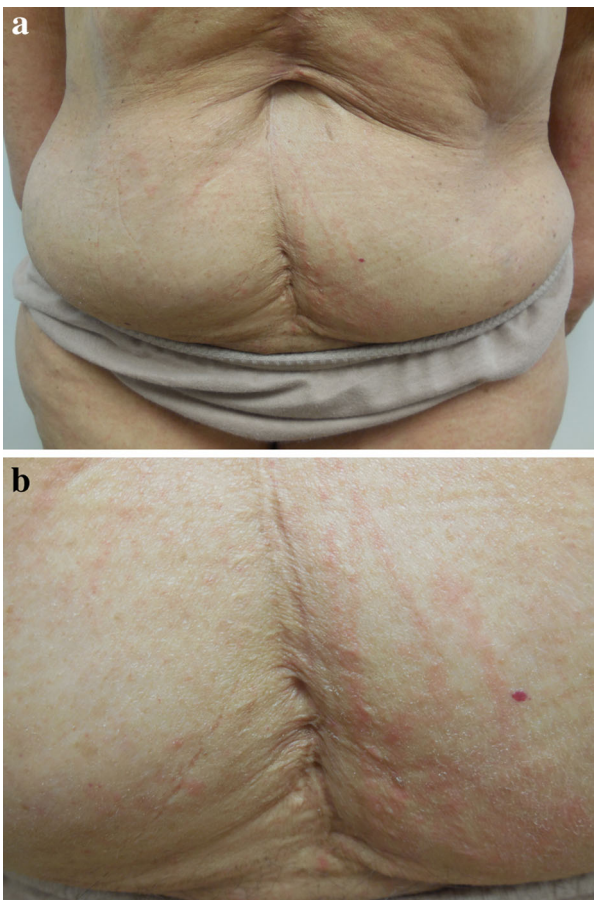

Fig. 3 Distant (**a**) and closer (**b**) views of the *lower abdomen* show flagellate erythema presenting as distinct and intermingled (in a lacy pattern) linear erythematous streaks

dermis with a predominantly lymphocytic inflammatory infiltrate that is present around blood vessels in the papillary dermis. There was exocytosis of small lymphocytes into the overlying epidermis (Fig. 6). The pathologic findings were those of a spongiotic dermatitis, compatible with a medication reaction.

Correlation of the clinical history, symptoms and findings in concert with the pathologic features observed established the diagnosis of drug-induced flagellate erythema. In this patient, the causative agent was trastuzumab.

She was treated systemically with prednisone (60 mg each morning for 3 days, followed by 40 mg each morning for 2 days and 20 mg in the morning for 1 day), and antihistamines for 2 weeks: Fexofenadine 180 mg each morning and diphenhydramine 25 mg each evening. Topical therapy was also initiated: Clobetasol propionate 0.05 % cream twice daily for 10 days and then once daily for 4 days.

Within 2 days, the itching had resolved and the skin eruption had nearly cleared. Follow-up examination after 2 weeks, on June 17, 2015, showed complete clearing of the flagellate erythema on her chest, abdomen, and arms. The erythematous hemorrhagic linear streaks on her distal legs were less prominent and asymptomatic.

The patient has subsequently had a left breast lumpectomy and complete lymph node dissection. There was no residual carcinoma in the breast and 26 lymph nodes were negative for malignancy. She has also received adjuvant radiation therapy.

Her oncologist decided that she would need to receive treatment with trastuzumab, every 3 weeks, for 1 year. She has been receiving dexamethasone prior to each trastuzumab treatment to prevent recurrence of the adverse skin event. Neither pruritus nor flagellate

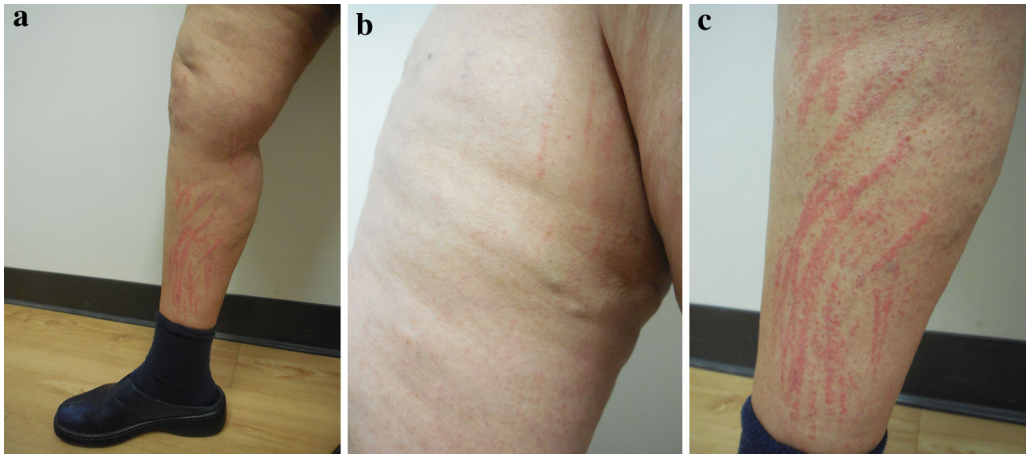

Fig. 4 Distant (**a**) view of the *right* leg and closer views of the *right* medial thigh (**b**) and *right* medial distal leg (**c**) show flagellate erythema presenting as erythematous and hemorrhagic linear streaks

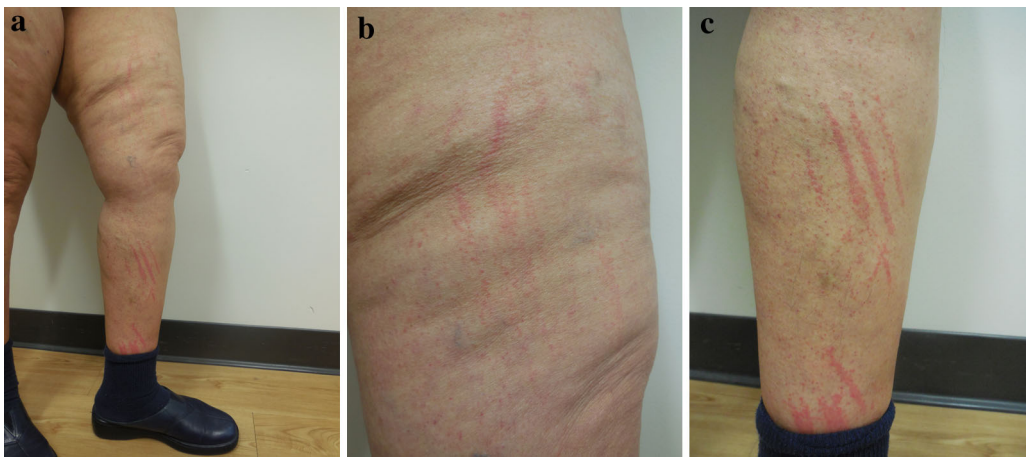

Fig. 5 Distant (**a**) view of the *left* leg and closer views of the *left* anterior thigh (**b**) and *left* medial distal leg (**c**) show flagellate erythema presenting as erythematous and hemorrhagic linear streaks

erythema has occurred with the subsequent administration of trastuzumab.

DISCUSSION

The individual flagellate dermatoses may be referred to as flagellate erythema or flagellate dermatitis or both (Table 1) [1, 4–42]. Flagellate erythema has a unique clinical presentation. It has an intermingled lacy pattern—similar to multiple adjacent flagella; indeed, the morphology of the cutaneous eruption is suggestive of the individual having been whipped. The lesions often are red and macular at presentation. Dermatitis may develop with progression to raised linear plaques. Residual patterned postinflammatory hyperpigmentation may subsequently persist [1].

Antineoplastic agents have also been observed to cause flagellate dermatoses. They include not only bleomycin [5–13], but also bendamustine [4], docetaxel [14], peplomycin [15, 16] and trastuzumab (current report) (Table 2) [4–16].

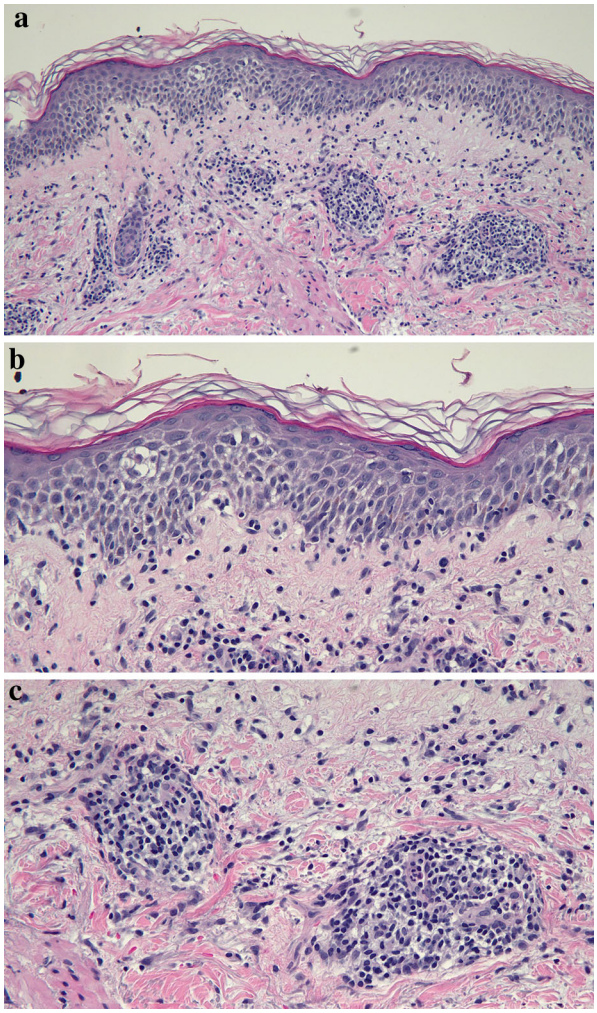

Fig. 6 Distant (**a**) and closer (**b**, **c**) views of a biopsy from the flagellate erythema on the *left arm* shows orthokeratosis (**a**, **b**), spongiosis (**a**, **b**), edema in the upper dermis (**a**, **b** and **c**), and perivascular lymphocytic inflammation (**a**, **c**) with exocytosis of lymphocytes into the epidermis (**a**, **b**) [hematoxylin and eosin; **a** = 10×; **b** = 20×; **c** = 20×]

Antineoplastic therapy-associated flagellate erythema was initially described in oncology patients who received bleomycin by Moulin in 1970 [10, 43, 44]. Bleomycin, a chemotherapeutic antibiotic isolated from the soil fungus *Streptomyces verticillus*, inhibits the uptake of thymidine and thereby resulting in fragmentation of DNA [7, 10, 43]. The adverse reaction has been observed in patients with Hodgkins lymphoma [10–13], and germ cell tumors in both men [5–7] and women [8, 9]. The eruption is often associated with generalized pruritus and has a predilection to occur over bony prominence [7–9, 11, 12]. The erythematous flagellate streaks subsequently develop into hyperpigmented whiplash-like lines. It has been postulated that this unique cutaneous adverse event for bleomycin occurs since the bleomycin hydroxylase enzyme that metabolizes the drug is not found in the skin, allowing the drug to accumulate and cause toxicity. Another hypothesis is that minor trauma to the skin, such as scratches or pressure over bony prominences, results in increased blood flow and accumulation of the drug at these sites [10].

The clinical presentation of bleomycin-associated flagellate erythema is distinctively characteristic; hence, the diagnosis is often established based on the morphologic presentation. When a biopsy has been performed, the findings are variable. They have included fixed drug eruption, hypersensitivity reaction (systemic or urticarial), inflammatory oncotaxis, lymphocytic vasculitis, and perivascular dermatitis with eosinophils [7, 10, 12, 13].

Treatment of bleomycin-induced flagellate erythema typically involves discontinuing the drug; in addition, treatment with antihistamines (oral) and corticosteroids (oral and/or topical) may be initiated. The symptoms and dermatosis typically resolve rapidly. However, residual postinflammatory hyperpigmentation may persist [6–8, 10].

Bleomycin-induced flagellate erythema may not be a therapy-limiting side effect [9]. However, the drug is usually discontinued in patients who develop severe rash [12, 13]. Also, since the overall success of treatment in patients with Hodgkin's lymphoma is not influenced by the exclusion of bleomycin in patients initially

Table 1 Flagellate dermatoses

Antineoplastic therapy-induced erythema/dermatitis
Bendamustine [4]
Bleomycin [5–13]
Docetaxel [14]
Peplomycin [15, 16]
Trastuzumab [current report]
Hypereosinophilia syndrome [17]
Idiopathic
Idiopathic flagellate pigmentation [18]
Infectious diseases
Chikungunya fever [19, 20]
Parvovirus B19 [21]
Infliction-associated lesions [1, 22, 23]
Abuse
Child
Elder
Partner
Self (dermatitis artefacta)
Pleasure
Sexual (sadomasochism)
Punishment
Religious discipline
Torture
Pruritus-related dermatoses [1]
Dermatitis
Allergic contact dermatitis (rhus antigen related)
Phytophotodermatitis (lime associated)
Dermatographism
Excoriations
Rheumatologic conditions
Adult onset Still's disease [24–28]
Dermatomyositis [29–34]
Systemic lupus erythematosus [35]
Toxin-induced conditions
Mushroom-related
Boletus (porcini-grilled) [36]
Shiitake (raw or undercooked) [37–40]
Organism-related
Cnidarian (Portuguese man-of-war and jelly fish) stings [41, 42]
Paederus (Rove beetles) and other insects [1]

treated with bleomycin-containing regimens, the drug is often subsequently avoided in oncology patients who experience bleomycin-induced flagellate erythema [12, 13].

Bendamustine, a unique multifunctional alkylating agent that crosslinks DNA and produces single-strand and double-strand breaks, is given intravenously typically at a dose of 100 mg per meter square on days 1 and 2 of a 28-day cycle for chronic lymphocytic leukemia [45]. A 53-year-old man with chemotherapy and radiation therapy refractory transformed chronic lymphocytic leukemia (Richter's syndrome) developed linear pruritic red patches, papules and plaques on his arms, legs, trunk and back a few days after starting the second cycle of bendamustine and rituximab. The chemotherapy was discontinued and topical corticosteroid ointment (triamcinolone 0.1 %) was applied twice daily. The symptoms ceased within a few days and the cutaneous eruption resolved with postinflammatory hyperpigmentation [4].

Docetaxel (Taxotere®; Aventis Pharma S.A.) is an antimicrotubule agent that has been used intravenously to treat solid tumors including breast, gastric, non-small-cell lung, ovarian, and prostate cancer [46]. Cutaneous adverse effects

Table 2 Antineoplastic therapy-induced flagellate erythema/dermatitis

Drug	Cancer	Dose	P	Onset of rash	Path	Treatment	Comment	References
Bendamustine	CLL	NS	+	C2D2+	[a]	D/c drug; TAC oint	[b] Rapidly improved	[4]
Bleomycin	GCT, HL	5 IU to 465 IU	+	<1 day to 9 weeks	[c]	[d]	[e]	[5–13]
Docetaxol	Breast	NS	+	C2D4	NP	None [f]	[g]	[14]
Peplomycin	SCC	?	?	NS	NS	NS	[h]	[15, 16]
Trastuzumab	Breast	6 mg per kg	+	C5D4	[i]	Steroid and antihistamine [j]	Dexa to prevent recurrence [k]	CR

C2D2 + A few days after the second cycle, *C2D4* 3 days after the second cycle, *C5D4* 3 days after receiving the fifth cycle, *CLL* chronic lymphocytic leukemia, *CR* current report, *Dexa* Dexamethasone, *D/c* Stop, *GCT* germ cell tumor, *HL* Hodgkin's lymphoma, *IU* International units, *NP* not performed, *NS* not stated, *Path* pathology, *P* pruritus, *SCC* squamous cell carcinoma, *TAC* oint Triamcinolone 0.1 % ointment twice daily, + present, *?* unavailable

[a] Pathology showed perivascular lymphocytes, plasma cells and scattered eosinophils with minimal epidermal change

[b] Within a few days, the eruption as well as the itching started to improve. At the site of the previous linear red patches, the patient developed digitate postinflammatory hyperpigmented patches

[c] Pathology is variable including fixed drug eruption, hypersensitivity reaction (systemic or urticarial), inflammatory oncotaxis, lymphocytic vasculitis, and perivascular dermatitis with eosinophils

[d] Most affected individuals stop drug [12, 13]; however, bleomycin-induced flagellate erythema may not be a therapy-limiting side effect in all patients [9]. Topical and/or oral corticosteroids, with or without oral antihistamines, are used

[e] The eruption is typically self-limited; it resolves within several weeks to months. The subsequent hyperpigmentation can be permanent (6 months or longer). There are individual reports of treating the hyperpigmentation with either intense pulse light therapy or non-ablative laser

[f] The itch and erythema settled spontaneously, with gradual resolution of the pigmentation over weeks

[g] The investigators postulated that corticosteroid treatment suppressed the flagellate erythema since the symptoms and rash appeared only after discontinuation of the dexamethasone

[h] Five of 23 patients developed an "eruption with skin excoriations or pigmentation along scratch dermatitis [16]."

[i] Pathology showed dermal edema and perivascular lymphocytes with exocytosis of lymphocytes into the overlying spongiotic epidermis

[j] Oral prednisone for 6 days (60 mg for 3 days, then 40 mg for 2 days and then 20 mg for 1 day), oral antihistamines for 2 weeks (fexofenadine 180 mg each morning and diphenhydramine 25 mg each evening), and topical clobetasol propionate 0.05 % cream (twice daily for 10 days and then once daily for 4 days)

[k] The patient has been premedicated with dexamethasone prior to receiving each subsequent trastuzumab treatment and there has been no recurrence of trastuzumab-associated pruritus or flagellate erythema

include acral erythema (also referred to as hand–foot syndrome), photodermatoses (including subacute lupus erythematosus), and hemorrhage of the nail plates [46–48]. A 58-year-old woman with metastatic breast cancer developed pruritic linear erythematous hyperpigmented streaks on her central back and flanks 3 days after her second intravenous course of docetaxel; the onset of her rash occurred with the conclusion of 3 days of oral dexamethasone that is routinely given to prevent hypersensitivity reactions and fluid retention from the docetaxel. There was spontaneous resolution of her itch and

erythema; the hyperpigmentation gradually resolved over the following weeks [14].

Peplomycin, an analog of bleomycin that was discovered by Professor Hamao Umezawa, has been administered intravenously for treatment of breast cancer, Hodgkin's lymphoma, prostate cancer, and squamous cell carcinoma of the cervix, head and neck, and skin [49]. Combination chemotherapy—consisting of cisplatin, vincristine, and peplomycin—was given to 23 Japanese patients with squamous cell carcinoma. The peplomycin was either administered by continuous intravenous infusion or continuous subcutaneous infusion (using a microinfustion pump). Five of the patients developed an "eruption with skin excoriations or pigmentation along scratch dermatitis [16]."

Trastuzumab (Herceptin) is a human monoclonal antibody. It binds selectively and with high affinity to the extracellular domain of the HER2/neu receptor. Treatment with trastuzumab increases survival, in both the metastatic and the adjuvant setting, of patients with HER2-positive breast cancer; the sooner trastuzumab is initiated, the greater its potential benefit. The agent is administered intravenously, as monotherapy or in combination with chemotherapy, usually every 3 weeks (8 mg/kg followed by 6 mg/kg) for 12 months [2, 3, 50, 51].

Cutaneous adverse reactions to trastuzumab are rare (Table 3) [50–59]. Tufted hair folliculitis was observed in one woman who received monotherapy with trastuzumab [59]; also, albeit uncommon, rash associated with a serious infusion reaction was noted in less than 0.3 % of patients [52]. Combination of trastuzumab and chemotherapy resulted in an increase of mild to moderate signs and symptoms of infusion reactions compared to patients receiving chemotherapy alone [53]. Photosensitivity was described in two women; however, in addition to trastuzumab, they were also receiving a taxane to which the skin reaction was likely caused [57, 58, 60]. In contrast to other investigators, a study of 51 Japanese women with metastatic breast cancer who underwent trastuzumab-containing chemotherapy observed both skin (49 %) and nail (27.5 %) toxicity; however, these adverse events may have been secondary—in part or in total—to the concurrent chemotherapy [56]. The incidence or severity of acute radiation-associated skin toxicity was not increased in women who received concomitant trastuzumab and radiation therapy [50, 51].

Trastuzumab-associated flagellate erythema, to the best of my knowledge, has not previously been described. The described patient had erythematous, distinct and intermingled (lacy) linear plaques; her pathology findings showed dermatitis. Her pruritic lesions promptly resolved, without postinflammatory hyperpigmentation, after corticosteroid (oral and topical) and antihistamine (oral) treatment.

Trastuzumab was an integral component of the reported patient's tumor treatment. In contrast to patients with bleomycin-induced flagellate erythema in whom the drug is usually discontinued, she continued to receive trastuzumab and was premedicated with dexamethasone prior to each subsequent treatment. With this management, there was no recurrence of the flagellate erythema when she received subsequent doses of trastuzumab.

CONCLUSIONS

Flagellate erythema is a distinctive morphologic reaction pattern. Chemotherapy-associated flagellate erythema was initially observed in oncology patients treated with bleomycin. However, flagellate erythema has subsequently been observed with other antineoplastic agents,

Table 3 Cutaneous adverse reactions in patients receiving trastuzumab

Reaction	Comments	Ref
XRT skin reactions	Adverse events included radiation therapy-associated acute skin toxicity (dermatitis) and late skin reactions (telangiectasias, local pain, and fibrosis) [a]	[50, 51]
Flagellate erythema	A 64-year-old woman with breast cancer developed pruritus and linear erythematous streaks of flagellate erythema on her arms, chest, abdomen, and legs 3 days after receiving her fifth cycle of trastuzumab. She was treated with corticosteroids (oral and topical) and antihistamines (oral); symptoms resolved within 2 days and there was clearing of the lesions on her arms, chest and abdomen within 2 weeks. Premedication with dexamethasone prior to each subsequent trastuzumab treatment successfully prevented recurrence of flagellate erythema	CR
Infusion reaction	These occur in 30–40 % of patients, usually present as chills or fever, with the first infusion; they occur only in 3–5 % of patients with subsequent infusions. Severe infusion reactions are uncommon (about 0.3 %) and may include rash	[52–55]
Nail toxicity	In a group of 51 patients, nail toxicity included softening, thinning, or loss (13 patients), paronychia (4 patients) and discoloration (2 patients) [b]	[56]
Photosensitivity	Two women with metastatic breast cancer developed cutaneous photosensitivity associated with aberrations in porphyrin biosynthesis while receiving concurrent taxane and trastuzumab therapy; the lesions resolved and the porphyrins normalized following taxane withdrawal: a 40-year-old woman, following treatment with paclitaxel and trastuzumab, presented with photodistributed erythema multiforme and onycholysis [57] and a 63-year-old woman, receiving treatment with docetaxel and trastuzumab, presented with photodistributed dermatitis consisting of erythematous patches on her hands and face and widespread papules and pustules on her scalp after sun exposure [58] [c]	[57, 58]
Skin toxicity	In a group of 51 patients, skin toxicity included eruptions on the face and body (14 patients), skin detachment or thinning on hands and feet (9 patients) itching (8 patients) and skin drying (7 patients) [b]	[56]
Tufted hair folliculitis	A 47-year-old woman with breast cancer had significant hair loss after treatment with doxorubicin and cyclophosphamide. During treatment with trastuzumab, she noted scalp hair regrowth. However, she also experienced scaling and pruritus of her scalp. Examination of the scalp showed perifollicular erythema and hyperkeratosis. In a patch of alopecia, a few scattered central and peripheral tufts of hair were noted. Tufts of 3–8 hair shafts emerging from dilated follicular openings were observed with dermoscopy. These findings established a diagnosis of tufted hair folliculitis. There was complete resolution of the scalp scaling and itching following twice daily treatment with clobetasol propionate 0.05 % topical solution	[59]

CR current report, *XRT* radiation therapy

[a] Concurrent trastuzumab and adjuvant breast radiotherapy did not increase adverse events associated with radiotherapy

[b] In a retrospective study of 51 Japanese patients with breast cancer who underwent trastuzumab-containing chemotherapy, 27 patients had skin and/or nail toxicity: 13 patients had only skin toxicity, 12 patients had both skin and nail toxicity, and 2 patients had only nail toxicity. However, some of the observations—in part or in total—may be attributed to the concurrent chemotherapy the patients were receiving

[c] In both women, the acquired photosensitivity is likely to be secondary to the taxane they were receiving and not caused by the trastuzumab

including bendamustine, docetaxel, and peplomycin. A woman with metastatic breast cancer developed flagellate erythema after receiving trastuzumab. Her lesion promptly responded to treatment with corticosteroids (oral and topical) and systemic antihistamines. The adverse cutaneous reaction was subsequently prevented by premedicating her with dexamethasone prior to each future treatment of trastuzumab. In conclusion, trastuzumab should be added to the list of potential etiologies associated with flagellate erythema and flagellate erythema should also be included in the potential adverse events that can be caused by trastuzumab.

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Disclosures. Dr. Cohen has nothing to disclose.

Compliance with ethics guidelines. Informed consent was obtained from the patient for being included in the study and for publication of the accompanying images.

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