Stevens–Johnson syndrome/toxic epidermal necrolysis in a patient receiving concurrent radiation and gemcitabine

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A patient with stage IV malignant melanoma treated with daily radiotherapy and low-dose (100 mg/m^2) daily gemcitabine developed a blistering skin eruption, fever and neutropenia consistent with overlap Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). The diagnosis was confirmed by skin biopsy of an affected area. The case history is described, and the literature relating to the development of SJS/TEN in association with chemotherapy and radiotherapy administration is reviewed. This report describes a serious potential complication of concurrent gemcitabine and radiotherapy. *Anti-Cancer Drugs* 14:659–662 © 2003 Lippincott Williams & Wilkins.

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Introduction

Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a rare, potentially life-threatening complication of anti-neoplastic therapy. We provide here only the second report of gemcitabine-associated SJS/TEN and the first report in which gemcitabine was the only anti-neoplastic agent involved. Gemcitabine is a deoxycytidine analog pyrimadine antimetabolite with cell-phase specificity, primarily killing cells undergoing DNA synthesis (S phase) and also blocking progression of cells through the G_1/S boundary. The case history and review of the literature suggests that SJS/TEN may be a rare complication of gemcitabine when administered concurrently with radiotherapy.

Case history

Patient RJ, a 54-year-old male, was initially diagnosed with melanoma in January 2000, with skin involvement to the right thigh. Resection of the primary tumor and sentinel node groin dissection was performed in March 2000, revealing metastatic disease in three of four deep and three of 10 superficial inguinal lymph nodes. Postoperatively the patient received the Kirkwood regimen of high-dose interferon [1] from March 2000 through May 2001. A computed tomography (CT) scan in September 2000 revealed a suspicious right pelvic abnormality which was not resected or biopsied. Follow-up CT scan in January 2001 revealed an increase in size of the right pelvic mass. The patient subsequently underwent surgery and the right pelvic mass was found to be recurrent disease which was unresectable. The patient then received six cycles of biochemotherapy consisting of cisplatin, temozolamide, vinblastine, interferon and interleukin-2 [2] without significant change in the pelvic mass. The patient received further therapy with nine cycles of docetaxel and vinorelbine, again without significant improvement of the mass. In April 2002, treatment was change to temozolamide (75 mg/m^2/day) and thalidomide (400 mg/day) according to Hwu *et al.* [3]. The patient's disease continued to progress and the decision was made to utilize radiotherapy (2 Gy daily) to the pelvic mass along with daily low-dose (100 mg/m^2) gemcitabine as a radio-sensitizer.

The patient received 4 days of radiotherapy and gemcitabine without difficulty. On day 5, the patient presented with mild fever, sore throat and a mild non-pruritic erythematic rash confined to the trunk. A complete blood count (CBC) was within normal limits. On day 6, dexamethasone at 4 mg t.i.d. was initiated because the patient reported an increase in severity of the rash and pain in his hands. On day 8, the patient was seen for follow-up and was found to have a painful maculopapular rash, affecting approximately 27% of the body, with blistering eruptions on lips, mouth, hands (Fig. 1A), knees (Fig. 1B) and anal mucosa. A CBC showed profound neutropenia with a WBC of less than 400 cells/mm^3. At this time, gemcitabine and radiation therapy were discontinued and the patient was admitted for close observation, pain control, antibiotic coverage for fever in the setting of profound neutropenia, and possible SJS. Therapy with sargramostim (granulocyte macrophage colony stimulating factor), cefepime and i.v. immunoglobulin (70 g) was instituted. Dexamethasone

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was discontinued. Right knee skin biopsy (Fig. 2) revealed necrolytic dermatitis consistent with SJS. During his hospitalization, the skin rashes and bullae gradually resolved over the course of 14 days. The neutropenia resolved by day 20 following initiation of chemotherapy [absolute neutrophil count (ANC) = 0.7 cells/mm^3]. The patient was discharged on day 21 with an ANC = 2.1 cells/mm^3. Skin and mucous membranes were without bullae or erythema at the time of discharge.

The patient subsequently completed radiotherapy, without gemcitabine, to a dose of 40 Gy delivered to the right pelvis in 20 fractions, followed by a 24 Gy boost to the tumor bed delivered in 10 fractions. No further cutaneous reactions were observed. Restaging CT scans of the pelvis obtained 1 month after the completion of radiotherapy were compared with scans obtained 6 months earlier. The pelvic mass had demonstrated a 40% reduction in size from 486 to 292 cm^3.

Discussion

SJS is a blistering disorder that initially presents as a sore throat, malaise and fever. Within a few days, in addition to erosion of multiple mucous membranes, small blisters on dusky or purpuric macules or atypical target (erythema multiforme-like) lesions characterize this eruption. In SJS the total percent of body surface area blistering and eventual detachment is less than 10%. Overlap SJS/TEN shares characteristics of both SJS and TEN, with 10–30% of the body surface area exhibiting epidermal detachment [4]. The disorder is classified as TEN when over 30% of the body surface area is affected. The mortality rate ranges from 1–5% for SJS to 34–40% for TEN [5].

Drugs are the most frequent cause of SJS/TEN. The reaction is independent of dosage. In two large series, the culprit drugs included antibiotics (40%), anticonvulsants (11%) and analgesics (5–23%) [5]. Several antineoplastic drugs have been implicated in SJS/TEN, including alkylating agents [6,7], methotrexate [8–10], thalidomide [11,12], docetaxel [13], mithramycin [14], doxorubicin [15] and L-asparaginase [16]. There are three reports of SJS/TEN associated with cytarabine [17–19], a pyrimidine antimetabolite chemotherapeutic agent in the same pharmaceutical class as gemcitabine. A review of literature revealed only a single case of SJS/TEN possibly associated with gemcitabine. That case involved a pancreatic cancer patient enrolled in a phase I trial of weekly gemcitabine with concurrent radiation therapy and protracted venous infusion of fluorouracil [20]. There have been no reports of SJS/TEN occurring with gemcitabine chemotherapy in the absence of radiotherapy. There are two reports describing radiation recall dermatitis attributed to gemcitabine. In one, a maculopapular confluent erythematous, pruritic rash occurred 6 months following radiotherapy and 2 weeks following institution of gemcitabine [21], and in the other, a recall rash developed 4 weeks after completion of radiotherapy in the second week of gemcitabine therapy [22]. The combination of radiotherapy with anticonvulsants [23,24] and amifostine [25] have also been cited previously as possible etiologies of SJS/TEN in a small number of patients. However, only very rarely have erythema multiforme-like reactions been associated with radiation therapy alone [26].

The patient described in this report developed a potentially life-threatening SJS/TEN overlap syndrome which was attributable to combination therapy with low-dose gemcitabine and radiation administered for the treatment of malignant melanoma. The clinical and pathologic findings, and the time course of onset and resolution, make other blistering diseases of the skin and mucous membranes such as IgA bullous dermatosis, radiation recall and pemphigus vulgaris/paraneoplastic pemphigus less likely. This is the second reported case of SJS/TEN in patients receiving concurrent gemcitabine and radiotherapy. SJS/TEN may represent a rare, but unique, complication of this combination therapy.

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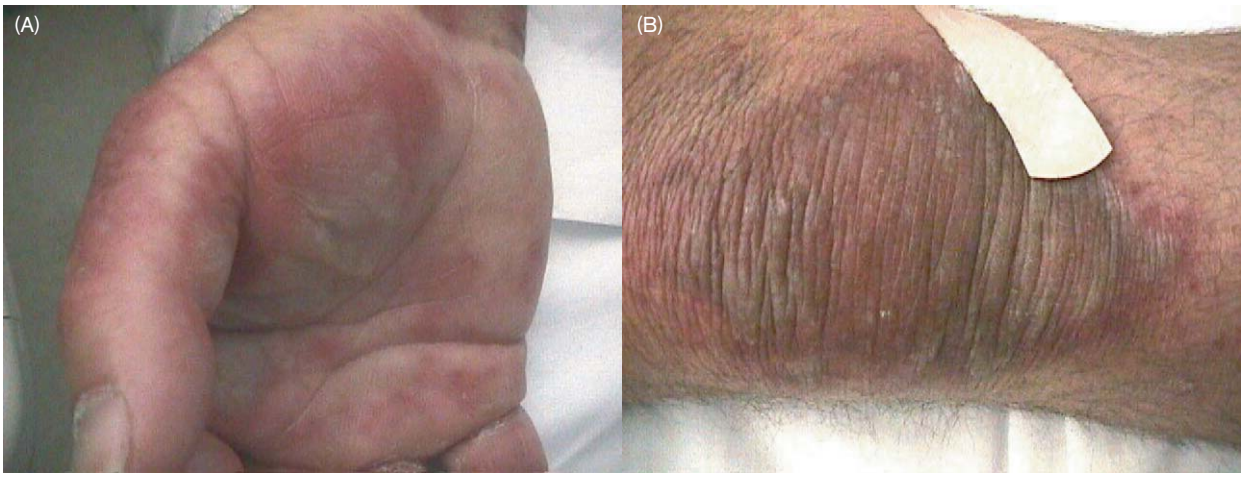
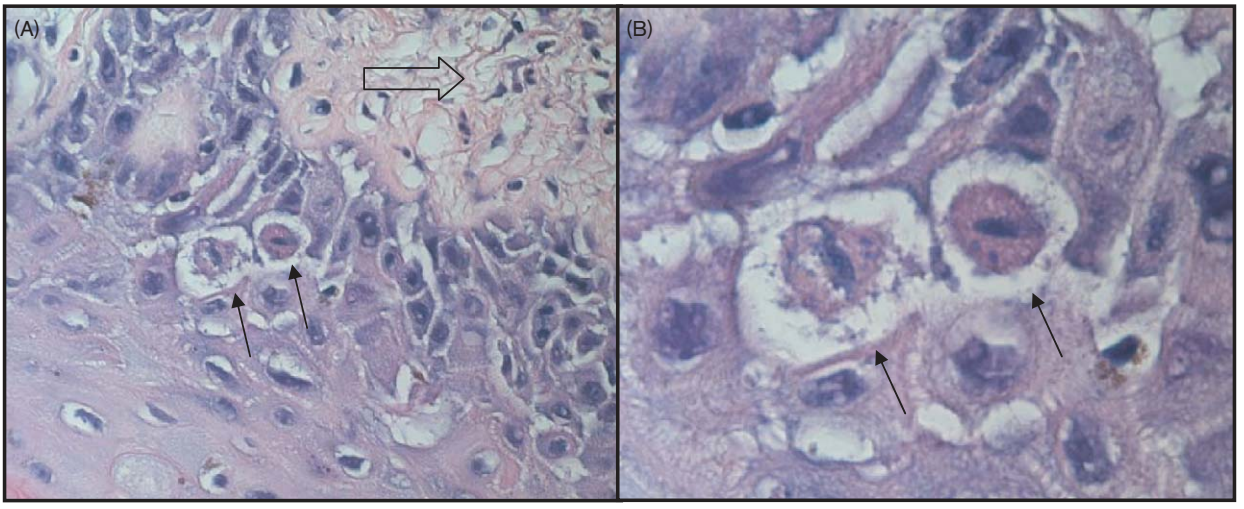
Fig. 1



Bullous and desquamating cutaneous reaction on the hand (A) and knee (B). The trunk, extremities and mucocutaneous surfaces were diffusely affected.

Fig. 2



Histologic evidence of SJS/TEN on skin biopsy. Photomicrographs captured at × 280 (A) and × 700 (B) depict dyskeratotic keratinocytes (solid arrows). These dyskeratotic cells are close to the basal layer consistent with an early-to-intermediate SJS lesion. Lymphohistiocytic infiltration into the vascular spaces is shown in (A, block arrow).

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