Gemcitabine-Induced Linear IgA Bullous Dermatosis

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We describe a 67-year-old man with non-small cell lung cancer in stage IV, who developed palpable purpura with bullae over his trunk and legs 12 days after treatment with gemcitabine. Histologically, a large subepidermal bulla with a mixed cell infiltrate of neutrophils and eosinophils was seen. Direct immunofluorescence of perilesional skin showed linear IgA staining along the dermoepidermal junction, which leaded to the diagnosis of gemcitabine-induced linear IgA bullous dermatosis (LABD). The skin lesions disappeared quickly after discontinuation of gemcitabine. Although chemotherapeutic agents can induce skin lesions with various clinical and histopathological findings, LABD is rarely reported. Clinicians should be aware of this possibility. (Dermatol Sinica 25: 16-19, 2007)

Key words: Gemcitabine, Linear IgA bullous dermatosis

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Accepted for publication: August 31, 2006
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INTRODUCTION

LABD (linear IgA bullous dermatosis) is an uncommon autoimmune disorder characterized by linear IgA autoantibody deposition along the basement membrane zone. It may be idiopathic or drug-related. The clinical presentation of drug-induced LABD, indistinguishable from idiopathic LABD, is heterogeneous with erythema multiforme-like, bullous pemphigoid-like, or dermatitis herpetiformis-like lesions.\(^1,2\) However, absence of mucosal lesions, rapid remission after withdrawal of the offending drug, and fair prognosis are classically seen in drug-induced LABD.\(^2-4\) The most commonly implicated drug is vancomycin. Other causative medications include antibiotics, nonsteroidal anti-inflammatory agents, antiepileptic agents, and others (lithium, furosemide, somatostatin, captopril, amiodarone, cyclosporine, gamma interferon, interleukin-2).\(^1,3\) LABD caused by chemotherapy is rarely reported, and was only described once in the literature.\(^5\) Here we report another patient who developed LABD after gemcitabine treatment for lung cancer.

CASE REPORT

A 67-year-old man diagnosed with lung adenocarcinoma in stage IV was admitted for chemotherapy. He denied major systemic disease and drug allergy history. He received chemotherapy of cisplatin 80 mg m\(^{-2}\) and gemcitabine 1200 mg m\(^{-2}\) on days 1 and 8. At the time of chemotherapy initiation, he was taking the following medications: codeine phosphate, colchicine, medroxyprogesterone acetate, ambroxol, and clonazepam. He has taken these medications for long time, but no cutaneous reactions were reported. Some itchy erythematous papules and macules on the lower trunk and legs appeared on day 5. Topical steroids and oral antihistamine were given with little response. The skin lesions progressed to numerous palpable purpura. Some vesicles and tense bullae in a diameter of 1 to 2 centimeters on the lower trunk and bilateral legs were noted since...
day 12 (Fig. 1). No mucosal lesions were noted. The clinical impression was leukocytoclastic vasculitis, and gemcitabine-induced vasculitis was suspected.

A cutaneous biopsy on day 15 revealed a subepithelial bulla with a mixed-cell infiltrate of neutrophils, eosinophils, extravasated erythrocytes, solitary lymphocytes and fibrohistiocytes. (Fig. 2A.) Direct immunofluorescence of perilesional skin showed linear IgA staining along the dermoepidermal junction (Fig. 2B). C3, C1q, fibrinogen, IgG, and IgM staining were negative. Laboratory studies showed white blood cell count 4.35 K/μL, hemoglobin 10.8 g/dL, and platelet count 64.0 K/μL. Results of anti-DNA antibody, anti-extractable nuclear antibody (scl-70, ribonucleoprotein, Sm, SSa, SSb), anti-nuclear antibody (ANA), basement membrane zone antibody, intercellular substrate antibody, anti-hepatitis C virus antibody, and HBsAg were negative. C3, C4 quantitation and RA factor were within normal limit. C-reactive protein was slightly elevated. Serum protein electrophoresis showed low albumin (3.3 g/dL) and increased alpha 1 and alpha 2 globulins which implied an acute phase reaction.

Scheduled gemcitabine and cisplatin on day 15 were discontinued and we treated the patient with oral prednisolone 40 mg per day for 1 week and then tapered gradually. Blistering ceased in 5 days. Another chemotherapy regimen with navelbine, cisplatin, and high-dose 5-fluorouracil and leucovorin (NP-HDFL) was given on day 22. No new skin lesions were noted.

**DISCUSSION**

The lack of previous attack history, the close relationship between administration of gemcitabine and onset of cutaneous eruption, as well as no recurrence of skin lesions after discontinuation of gemcitabine, all led to the suspicion of a chemotherapy-induced cutaneous reaction. Based on the clinical features and characteristic histopathological findings, a diagnosis of LABD caused by gemcitabine was established.

There was only one case of gemcitabine-induced LABD reported previously. del Pozo J et al. reported a 59-year-old man with LABD 24 hours after receiving cisplatin, vinorelbine, and gemcitabine (1000 mg m⁻²) for treatment of lung cancer. The lesions were symmetric, bullous, herpetiform eruptions on the trunk and upper limbs, and resolved 2 weeks after discontinuing gemcitabine and treatment with topical methylprednisolone. In our case, the eruption was more bullous pemphigoid-like, appeared 5 days after the administration of gemcitabine (1200 mg m⁻²). Rapid resolution after withdrawal of gemcitabine was noted in both cases.

The mechanism of drug-induced LABD may be due to breaking of the self-tolerance to the implicated potential antigens in the basement membrane zone. The structural modification of molecules or the emergence of a previously un-exposed antigenic determinant by the drug may lead to an immune response. Various target antigens are reported, including a 250-kDa dermal antigen corresponding to collagen VII, a 97-kDa antigen as a proteolytic cleavage product of the BP180, BP230, and LAD285. Some authors suggested that other cofactors such as infectious disease, non-lymphoid or lymphoproliferative malignancies, may be associated.

Gemcitabine is a new specific S-phase cytotoxic drug which is well known as its relative low toxicity profile. Cutaneous reactions (24.8%) include skin rash (20.3%), alopecia (14.1%), mucositis (8.4%), urticaria, generalized desquamation, and pruritis. Other rare adverse reactions include scleroderma-like change, radiation recall dermatitis, acute lipo-dermatosclerosis-like reaction, erysipeloid rash, CD8+ CD30+ pseudolymphoma, and vasculitis. Although gemcitabine causes myelosuppression, it does not mean that gemcitabine would not trigger immune response. We review the literature and note that cyclosporine may also cause LABD, and we speculate that an immunosuppressant, such as cyclosporine or gemcitabine, may cause LABD. Besides, gemcitabine is also a drug well-known for causing immune-mediated side effects, like vasculitis.
and diffuse pulmonary infiltrate with good response to corticosteroids.\textsuperscript{14} To our knowledge, there are few chemotherapeutic agents that cause LABD. We suggest that the search of a causative agent, especially chemotherapeutic agent, is mandatory when dealing with lesions of bullae in patients with neoplasm.

REFERENCES