Abstract. We treated a 53-year-old man with advanced squamous cell carcinoma of the lung who had developed Stevens-Johnson syndrome, a life-threatening cutaneous reaction, after systemic chemotherapy consisting of carboplatin and paclitaxel. A critical assessment disclosed circumstantial evidence pointing to paclitaxel as the likely cause of this complication. As far as we are aware, this account is the first description of a paclitaxel-induced Stevens-Johnson syndrome. This case serves as an alert for the need to observe patients closely for potentially dangerous cutaneous reactions to paclitaxel therapy.

Paclitaxel (Taxol; Bristol-Myers-Squibb, Princeton, NJ, USA) is a taxane anti-neoplastic agent with activity against a broad range of cancers. Major adverse effects include peripheral neuropathy, myelotoxicity, bradycardia and hypotension, alopecia, nausea and emesis, arthralgia and myalgia, granulocytopenia and hypersensitivity (1). Hypersensitivity reactions are a well-recognized complication of paclitaxel therapy and typically occur following the first or second exposure. These reactions have been attributed to both paclitaxel and its diluent, Cremophor EL, and consist of dyspnea with or without bronchospasm, urticaria, rash, hypotension and angioedema (2). Because of the high risk of hypersensitivity reactions, a standardized premedication regimen using high-dose dexamethasone, diphenhydramine and cimetidine is administered in Japan as prophylaxis against paclitaxel-induced hypersensitivity reactions.

Case Report

A 53-year-old Japanese man with squamous cell carcinoma of the lung (T2N2M1 stage IV) received an initial cycle of chemotherapy at a local hospital. This consisted of carboplatin (area under curve = 6) administered on day 1 and paclitaxel (70 mg/m²) on days 1, 8 and 15. Despite the appearance of a slight skin rash on the abdomen after receiving the first dose of paclitaxel, he was given the second dose 1 week later. Three days later he suddenly developed a generalized pruritic morbiliform rash which varied from erythematous to purplish. This was followed by severe oral, conjunctival and genital mucosal erosions in association with high fever (Figure 1). He was referred to our institution for treatment of this severe adverse effect on October 24, 2002. He had no prior history of drug allergy. Laboratory findings on admission including a white blood cell count of 9460/mm³ with 33.5% neutrophils and 21.5% eosinophil and a C-reactive protein concentration of 12.8 mg/dl. The immunoglobulin E concentration was within normal limits.

The skin lesions rapidly increased in number and size, with partial confluence of the rash over the chest and abdomen (Figure 2). Histopathologic changes in a skin biopsy specimen from the right arm (Figure 3) were predominantly basal and subepidermal, including marked liquefactive basal cell degeneration leading to spongiotic vesiculation or separation at the epidermodermal junction.
Scattered necrotic keratinocytes and cystoid bodies were observed in the epidermis. Eosinophils and neutrophils in the lesion were few, but lymphohistiocytic infiltration and red blood cell extravasation were evident in the lower epidermis and the edematous papillary dermis. These findings were considered to be most consistent with a drug eruption. Leukocyte migration inhibitory tests in peripheral blood were negative for both paclitaxel and carboplatin, but assessment of available evidence suggested paclitaxel as the likely cause of the reaction.

Methylpredonisolone (80 mg/day) and ciprofloxacin were administered. Progression of cutaneous and mucosal lesions ceased after 1 week of therapy. Removal of dead epidermis was repeated as necessary. In the third week of admission, the patient’s condition improved, with resolution of pyrexia, healing of mucosal ulcerations and evidence of cutaneous reepithelization. Methylpredonisolone was tapered off and stopped over 2 weeks. The tumor did not respond to the carboplatin and paclitaxel treatment. No other severe toxicity from this regimen was observed. The patient was next treated with salvage chemotherapy consisting of cisplatin and irinotecan, but had no response. Now he is followed in our outpatients’ clinic monthly.

Discussion

Stevens-Johnson syndrome, an acute, severe, adverse cutaneous reaction to medication, was first described in 1922 in two children with febrile erosive stomatitis, severe ocular involvement, and a disseminated cutaneous eruption of discrete dark red maculae (1). About 50% of these cases were strongly associated with specific medications (2). In
the present patient, although the leukocyte migration inhibitory test in peripheral blood was negative for paclitaxel, this agent still is the most likely cause of his cutaneous reactions based on exclusion of the other etiologies and also on chronology; the reaction developed after the second exposure to paclitaxel.

The mechanism underlying Stevens-Johnson syndrome remains unknown. Some authors have suggested that cutaneous changes related to chemotherapy are usually caused by a direct toxic effect. Most cases supporting this view involve the use of either antimetabolites or alkylating agents, including cytarabine, methotrexate, 5-fluorouracil and mercaptopurine; these interfere with RNA or DNA synthesis. In contrast, paclitaxel is an anticancer drug with a unique mechanism of cytotoxic metabolism (1). Other hypotheses, therefore, must be considered.

In the present case a standardized premedication regimen using high-dose dexamethasone, diphenhydramine and cimetidine [a type I histamine (H1)-antagonist] failed to prevent severe skin toxicity. This prophylactic regimen therefore may be insufficient in some cases.

We believe that our case of Stevens-Johnson syndrome was related to paclitaxel, since extensive investigation disclosed no convincing alternative explanation. It is important to recognize the features of such an adverse effect as reported here in patients given paclitaxel. Several reports have described Stevens-Johnson syndrome induced by other anticancer agents including methotrexate, bleomycin, etoposide, imatinib (STI571) and rituximab (3-6), but we know of no prior report that paclitaxel can induce Stevens-Johnson syndrome. As paclitaxel now is widely used, clinicians should be alert to this possibility.

References


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