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LETTER TO THE EDITOR

Stevens-Johnson syndrome in a liver transplant recipient

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The etiology of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) may range from multiple drug toxicities to viral infections. Treatment of SJS involves immunosuppression, such as plasmapheresis, cyclosporine, corticosteroids, and intravenous immunoglobulins (IVIG) [1–4]. In this article, we report the case of SJS in a liver transplant patient under immunosuppressant agents and steroids. This case implies another possible mechanism underlying the pathogenesis of TEN or SJS.

A 62-year-old man with hepatocellular carcinoma (HCC) and hepatitis B-induced cirrhosis was admitted to undergo deceased donor liver transplantation. He underwent hepatic sectionectomy (S5, S6) 17 years earlier resulting from HCC, and there was no evidence of recurrence. The deceased donor liver transplantation was performed using a whole liver. Basiliximab (20 mg) and methylprednisolone (1000 mg) were used for immunosuppressive induction therapy in the operating room. The second dose of basiliximab was administered on the 4th postoperative day. The steroids were steadily tapered and maintained with prednisolone (10 mg/day) 1 month after transplantation. Tacrolimus, as a main immunosuppressive agent, was titrated to achieve a trough of 12–15 ng/ml during the first four postoperative weeks and 8–12 ng/ml during the second and third postoperative months. Prophylactic antibiotics were used with ceftizoxime (3 g/day) and levofloxacin (400 mg/day). Ranitidine (100 mg IV twice a day) was used for ulcer prevention. Oral nystatin syrup (2 cc) was administered four times a day to prevent oral and esophageal candidiasis. Doppler ultrasonography showed parenchymal congestion of the graft liver, but no vascular or biliary complications on the first, second, and fourth postoperative days. Laboratory findings for liver function gradually normalized after transplantation.

On the 12th postoperative day, erythematous rashes erupted on the patient's oral mucosa, face, trunk, back, and both thighs. The skin lesions gradually became aggravated and an abrupt onset of fever occurred on the 13th postoperative day. On that day, vancomycin-resistant enterococcus (VRE) was cultured in the blood and peritoneal fluid. Antibiotic therapy consisting of linezolid (600 mg twice a day) was started. The skin lesions were thought to be drug eruptions and dexamethasone (5 mg/day for 3 days) was started while tapering prednisolone. As the skin eruptions showed improvement, trimethoprim-sulfamethoxazole (TMP-SMX) [sulfamethoxazole (400 mg) and trimethoprim (80 mg)] was administered orally twice daily by the routine prophylactic protocol of our institution. Pancytopenia and a painful erythematous skin rash gradually progressed, therefore TMP-SMX was stopped 4 days later and a full-thickness skin biopsy was performed on the trunk under the diagnostic impression of SJS. Figure 1a,b shows the patient's skin lesions involving the face and forearm respectively. The pathologic report confirmed erythema multiforme with subepidermal blister formation, consistent with SJS (Fig. 1c,d). Therefore, dexamethasone (10 mg/day IV) was administered for 3 days. The skin lesions repeatedly showed signs of progression and recovery. Severe pancytopenia was persistent. The patient expired because of multiorgan failure with sepsis at 104th postoperative day. There was no exact evidence that the patient's mortality was related to SJS; rather, the patient deteriorated because of other complications, such as pneumonia, cerebral infarction, herpes zoster, and septic vegetations of the heart. The function of the transplanted liver graft was well-preserved, however.

Genetically, an increased incidence of HLA-B12 has been found in affected people, leading to the suggestion of genetic susceptibility [5]. The pathogenesis of TEN resembles that of GVHD [6,7]. There are mainly $CD8^+$ lymphocytes in the blister fluids and epidermis, and $CD4^+$ lymphocytes in the dermis [8]. Also, high levels of soluble IL-2 receptor (sIL-2R) are observed in the blister fluids and serum of TEN patients. This is the evidence supporting the role of cytotoxic T lymphocytes in the pathogenesis of TEN [9]. In GVHD, the circulating lymphocytes are donor-derived but we have no evidence indicating whether the patient's circulating CD8+ thymocytes were donor- or recipient lymphocytes. Differentiation of GVHD and TEN is very difficult only in clinical manifestation. Most, but not all, cases of postliver transplant GVHD are accompanied by diarrhea secondary to cytotoxic T-cell attack on the gastrointestinal mucosa [7]. But the patient did not have diarrhea in this case. Calcineurin inhibitors inhibit the synthesis and subsequent release of

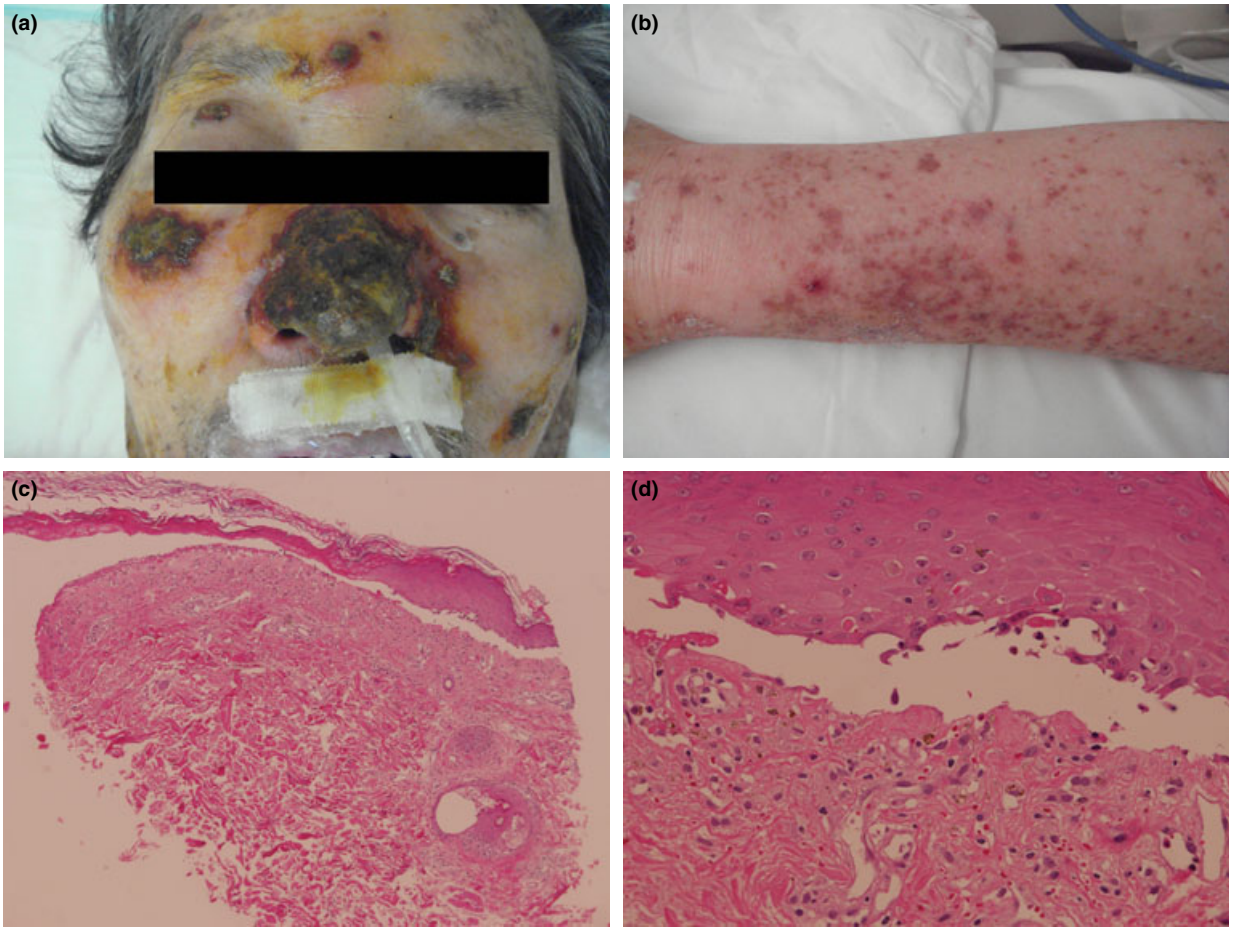

Figure 1 Clusters made from erythematous rash and morbilliform patches on the face (a) and forearm lesions (b). Epidermis shows confluent necrosis and separation from the dermis (c) (hematoxylin–eosin stain × 40). Necrotic keratinocytes shedding, lymphocytes infiltration and erythrocyte extravasations are shown in the dermis (d) (hematoxylin–eosin stain × 200).

IL-2, thus inhibiting activated T-cell proliferation [10]. In this case, tacrolimus was administered in advance before SJS was presented. It is, however, most likely that there is no single responsible mediator in the pathogenesis of SJS and that the pathogenesis of SJS is more complex and multifactorial.

Drug toxicities should be considered because transplant patients are administered a variety of drugs. Drugs can activate T cells by acting as haptens, by acting as prohaptens, or by direct pharmacologic interaction among the drug, MHC molecule, and T-cell receptor [11]. There are hundreds of kinds of drugs associated with SJS. We could not exactly indicate which drug would have likely acted as the cause of SJS in this case. It was revealed that TEN to sulfonamides develops more in HIV patients, who have reduced levels of the cellular detoxifying chemicals, glutathione and cysteine, than the general population because of accumulation of the chemically reactive nitroso product [12]. In this case, however, TMP-SMX was started after the eruption of skin lesions. Basiliximab can also cause hypersensitivity or anaphylactic reaction [13,14]. But most of the cases were anaphylactic shock immediately after injection; however, it was different in this case. Viral infections, such as herpes simplex virus (HSV) and varicella, are also an important etiology of SJS [15].

In this case, there were no exact correlations of above etiologies. Also tacrolimus was administered in advance before SJS was presented. There is little knowledge about the immunopathologic mechanism of SJS in transplant patients. Further study is essential to increase the possibility of developing a directed and effective biologic treatment.

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