A Case of Vancomycin-Induced Thrombocytopenia

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Immune thrombocytopenia is a rare complication associated with vancomycin. A 76-year-old male patient who was treated with vancomycin experienced severe thrombocytopenia and refractoriness as a result of platelet transfusion. Vancomycin-dependent antibodies in his thrombocytopenic serum were detected by flow cytometric analysis. The mechanism of thrombocytopenia is probably related to immunological destruction, as strongly suggested by its association with a specific drug-dependent anti-platelet antibody. ***(Korean J Hematol 2009;44:294-297.)***

Key Words: Thrombocytopenia, Vancomycin, Drug-induced

INTRODUCTION

Vancomycin, a glycopeptide antibiotic isolated from *Streptomyces orientalis*, is widely used to treat gram-positive bacterial infections. Vancomycin- induced thrombocytopenia (VIT) is rare and ascribed to an immunological mechanism.[1-3] We report a case of severe thrombocytopenia occurring temporarily during vancomycin therapy with a review of the literature on VIT.

CASE REPORT

A 76-year-old male patient was admitted to the department of internal medicine of our hospital for the evaluation and treatment of diabetic ulcers with purulent exudates formed on the lateral malleolus and the second toe of the right foot. He had a medical history of diabetes mellitus and total hip replacement on the left side. On admission, his body temperature was 36.5°C; blood pressure, 130/90 mmHg; WBC count, 7.5×10^9/L; hemoglobin, 9.9 g/dL; and platelet count, 310.0×10^9/L. Pulmonary edema and pneumonia were suspected on chest X-ray, but abdominal ultrasonogram did not reveal any specific finding, except for the presence of pleural fluid on both sides. On day 3, the second toe was amputated and the ulcers were incised and drained. From the culture of the drained exudates, methicillin-resistant *Staphylococcus aureus* (MRSA) was identified. Treatments with vancomycin and Tazocin (piperacillin sodium tazobactam, Wyethkorea) had been initiated on admission, and the patient had no history of previous use of vancomycin. On day 10, he developed a fever (37.5°C). His body temperature increased to 38.5°C, and on day 11, the laboratory tests indicated thrombocytopenia (platelet count, 69.0×

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10^9/L). He was suspected to have VIT therefore, therapy with vancomycin was replaced that with teicoplanin. Thrombocytopenia ($<15.0\times 10^9$ cells/L) persisted for 3 days after vancomycin administration was discontinued. His platelet counts did not return to normal despite transfusion of 35 units of platelet concentrates (Fig. 1). Immature platelet fraction (IPF) measured on day 15 was 23.5% (IPF reference range: 0.4～5.4%[4]) which indicated that thrombocytopenia was a result of the peripheral destruction of platelets rather than hypoplasia of the bone marrow. Although his platelet counts returned to normal on day 16, the patient expired because of aggravation of pneumonia.

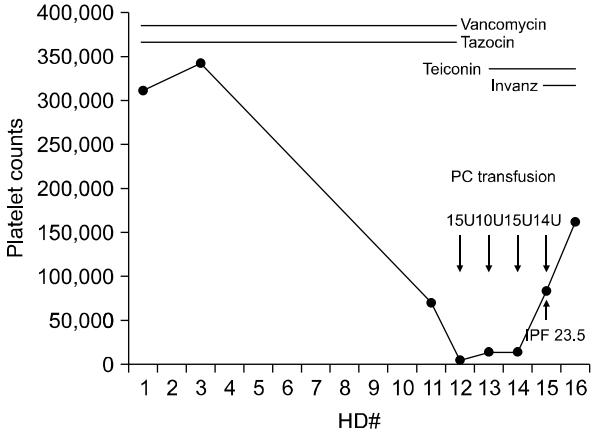

Fig. 1. The course of platelet count, transfusion, and the use of drugs. Thrombocytopenia was detected on day 11, and the use of vancomycin was discontinued on day 12. Abbreviations: HD, hospital day; IPF, immature platelet fraction; PC, platelet concentrates.

1. Identification of vancomycin-dependent antiplatelet antibody

We performed flow cytometric analysis with the patient's serum isolated on day 11 and identified the vancomycin-dependent platelet antibody. At first, we prepared a platelet-rich plasma (PRP) from a healthy volunteer with normal platelet counts, diluted the PRP until the platelet count was 10.0×10^9/L, and then diluted each drugs administered to the patient, including vancomycin and Tazocin, serially from 1 : 1 to

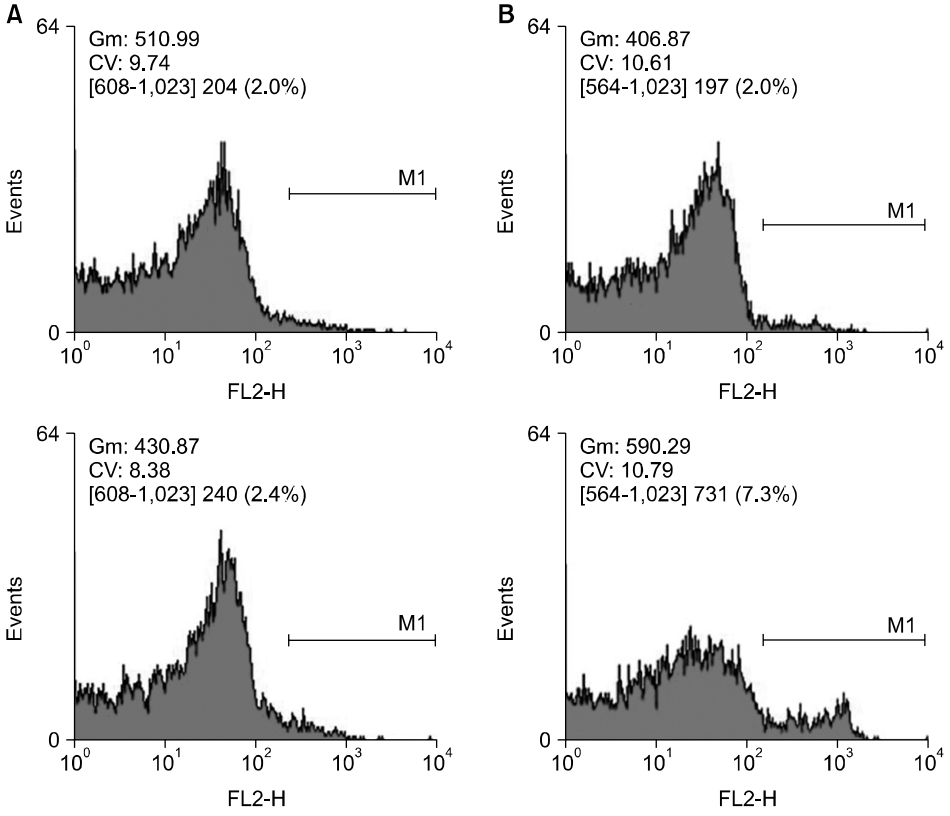

Fig. 2. The results of platelet immunofluorescence test using flow cytometry. The mixture of the patient's sera and serially-diluted vancomycin using drug-free saline in lower histograms generated a fluorescence intensity greater than the control sera in upper histograms. (A) Saline/sera mixture, (B) 1 : 100 diluted vancomycin/sera mixture.

1 : 100 with drug-free saline. Further, we prepared sera of the patient for investigation and used the sera of a healthy person who had not been administered vancomycin as a control. We mixed all the preparations, including PRP, serially diluted drugs, and the sera of the patient and a healthy person. This mixture was incubated for 1 hour at room temperature, labeled that with anti-human immunoglobulin-fluorescein isothiocyanate (IgG-FITC), and then analyzed that using flow cytometry. The analysis revealed that the mixture containing patient's sera and the serial-diluted vancomycin (not Tazocin) generated a higher fluorescence intensity than the control sera (Fig. 2). When the positive threshold of fluorescence intensity was set at 2% in the control serum, the positive rates of 1 : 1, 1 : 10, 1 : 100 diluted sera of the patient were 13.9%, 5.7%, and 7.3%, respectively.

DISCUSSION

The mechanism of VIT is probably related to immunological destruction, as strongly suggested by its association with a drug-dependent antiplatelet antibody (DDPA).[5] The interval between the initial administration of vancomycin and the first occurrence of thrombocytopenia was 11 days. Although the patient's medical history revealed no previous administration of this drug that could account for an anamnestic response, vancomycin-dependent antibodies were detected in the serum of the patient during the first occurrence of thrombocytopenia. Vancomycin-dependent antibodies were detected in many patients who had been exposed to the drug, most of them for at least 6 days; this time period is sufficient to mount an immune response to the drug before the development of thrombocytopenia.[6] However, thrombocytopenia was resolved after the cessation of vancomycin therapy, which could support the diagnosis of immune-mediated thrombocytopenia. It was reported that the platelet levels had returned to the pretreatment values in most of the survivors after vancomycin therapy was discontinued.[6] The increase in the Immature platelet fraction (IPF) value indicated that thrombocytopenia developed due to the peripheral destruction of platelets, and not because of decreased platelet production as is the case in intrinsic bone marrow disease or bone marrow toxicity caused by vancomycin. IPF is the percentage of reticulated platelets to the total platelet counts. It is calculated by using an automated hematologic analyzer (XE-2100, Sysmex Corporation, Kobe, Japan) and is a known marker in the detection of destructive causes of thrombocytopenia, such as immune thrombocytopenic purpura, liver cirrhosis, and disseminated intravascular coagulation.[7]

The identification of drug-dependent antibodies in patients with severe thrombocytopenia is important because of refractoriness to platelet transfusion.[3] In most of the patients who received 1 or more platelet transfusions during the acute phase of thrombocytopenia, no clinically significant rises in platelet counts were detected 6 to 24 hours later.[6] In this patient, more than 40 units of platelet concentrate were transfused, but there was no significant elevation in the platelet count within 6 hours. Therefore, it should be ascertained whether the cause of thrombocytopenia that occurs during antibiotics therapy is a drug-dependent antibody. A recent reports indicate that many antibiotic drugs such as teicoplanin and quinine can also cause immune thrombocytopenia.[8-10] In this patient, the antibody reacted with the platelets only when vancomycin was administered, not Tazocin. However, in some previously reported cases, there was no evidence of the presence DDPA.[2,11]

We conclude that testing for drug-dependent antibodies or the cessation of drug administration can be helpful in identifying the cause of thrombocytopenia in patients who are receiving antibiotics, including vancomycin.

요 약

면역성 혈소판감소증은 반코마이신의 드문 부작용이다. 반코마이신으로 치료받은 76세 남자 환자가 혈소판 수혈에도 회복되지 않는 심한 혈소판감소증을 경험하였다. 환자의 혈청에서 유세포분석을 통해 반코마이신 의존성 항체가 검출되었다. 혈소판감소증은 약물 의존성 항혈소판 항체와 연관되었기 때문에 그 기전은 면역학적인 파괴와 관련된 것으로 추정된다.

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