



## A case of oxaliplatin-induced immune-mediated thrombocytopenia

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### Abstract

Oxaliplatin is a platinum compound used in patients with gastrointestinal malignancies. It is known to evoke a drug-induced immune-mediated thrombocytopenia, which has not been reported in Korea. We describe a 53-year-old man who developed oxaliplatin-induced immune-mediated thrombocytopenia during chemotherapy for colon cancer. Oxaliplatin-dependent IgG platelet antibodies were detected in his serum on flow cytometry. He was treated with immunoglobulin and corticosteroids without any complications. Physicians should consider oxaliplatin-induced immune-mediated thrombocytopenia, when a sudden, isolated thrombocytopenia develops during chemotherapy with oxaliplatin.

**Key Words** Oxaliplatin, Thrombocytopenia, Immune, Drug-dependent platelet antibody

## INTRODUCTION

Oxaliplatin is a third-generation organoplatinum compound, used for the treatment of patients with colorectal carcinoma. Peripheral neuropathy, diarrhea, and mild myelosuppression, including a moderate degree of thrombocytopenia, are common toxicities of oxaliplatin and are mostly mild and self-limited. Recently, oxaliplatin has been reported to induce a rare life-threatening immune-mediated thrombocytopenia [1-3]. Although oxaliplatin has been used widely, oxaliplatin-induced immune thrombocytopenia (OIIT) has never been reported in Korea. We report a case of OIIT confirmed by the presence of oxaliplatin-dependent anti-platelet antibodies and review the literature.

## CASE REPORT

A 53-year-old man with type 2 diabetes mellitus and hy-

pertension was diagnosed with stage IIIB transverse colon cancer in February 2011. He underwent a right hemicolectomy and subsequently received 10 cycles of adjuvant chemotherapy with oxaliplatin and 24-hour infusions of fluorouracil (5FU) and leucovorin (FOLFOX). Before starting the 11th FOLFOX cycle, a complete blood count (CBC) showed the following values: neutrophils,  $3.38 \times 10^9/L$ , platelets,  $113 \times 10^9/L$ , and hemoglobin, 14.8 g/dL. During the 11th FOLFOX cycle, he experienced mild fever ( $37.6^\circ C$ ) and pain in his injected arm. Gum bleeding and petechiae on his legs also developed. The CBC showed: platelets,  $3 \times 10^9/L$ , neutrophils,  $4.18 \times 10^9/L$ , and hemoglobin, 13.8 g/dL. The patient's prothrombin time (PT, 10.5 seconds) and activated partial thromboplastin time (APTT, 25.5 seconds) were within normal range. There were no relevant abnormalities in total bilirubin, aminotransferase, blood urea nitrogen (BUN), creatinine and complement factors (C3 and C4). He was hospitalized and treated with platelet transfusion, immunoglobulin 55 g/day for 2 days and corticosteroids. His platelet count recovered to  $83 \times 10^9/L$ , and his gum bleeding

and petechiae resolved (Fig. 1). The liver and spleen were not palpable. Human immunodeficiency virus testing, hepatitis B and C screening, viral marker of Epstein-Barr virus early antigen (EBV-EA) IgM and cytomegalovirus (CMV) antigen (Ag), antinuclear antibody analysis and thyroid function tests were all negative. The results of bone marrow aspiration and biopsy were unremarkable. Because all other causes of thrombocytopenia were excluded, we concluded that oxaliplatin was the only cause of his thrombocytopenia. He was discharged with oral prednisone, and his platelet count recovered completely without further treatment in 2 months.

## MATERIALS AND METHODS

### Reagents

Oxaliplatin, 5-FU, and leucovorin were purchased from Sigma Chemical (St. Louis, MO), and dissolved using acid citrate dextrose/phosphate buffered saline/bovine serum albumin (ACD, 0.02M Na<sub>2</sub>HPO<sub>4</sub>, PBS 0.145 M NaCl, 0.02% BSA, pH 7.2) as buffer. F(ab')<sub>2</sub> fragment of goat fluorescein isothiocyanate(FITC)-labeled anti-human IgG, Fcγ chain

specific, phycoerythrin (PE)-labeled anti-human IgM, Fcμ chain specific were from Jackson Immuno Research Labs (West Grove, PA).

### Detection of drug-dependent platelet antibodies on flow cytometry

In September 2011, oxaliplatin-dependent platelet antibodies were detected in the patient's sera by using flow cytometry as previously described [3]. In brief, normal group O platelets were incubated with test serum, in the presence and absence of the drug, and were washed three times in buffer containing the drug at the same concentration as in the primary incubation mixture. Platelet-associated immunoglobulins were then detected by flow cytometry (FACSCanto II, Becton Dickinson, San Jose, CA) using fluorescein isothiocyanate (FITC)-tagged anti-human IgG (Fcγ-specific) and phycoerythrin (PE)-tagged anti-human IgM, (Fcμ-specific). Sera from normal, healthy donors and sera containing previously identified oxaliplatin-dependent platelet antibodies served as negative and positive controls, respectively. A positive reaction was defined as a value of median platelet fluorescence intensity (MFI) at least twice that of platelets processed identically, but without the addi-

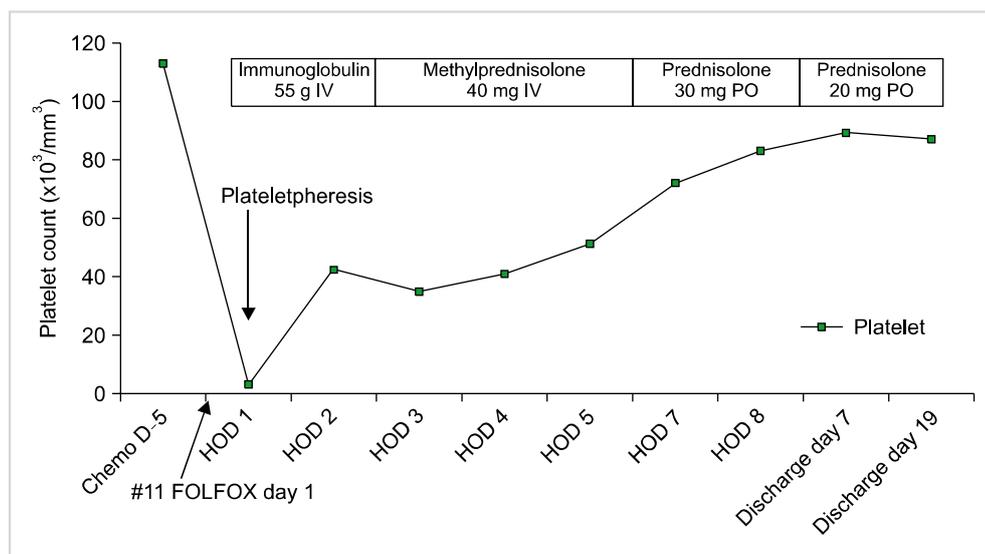


Fig. 1. Clinical course of the patient.

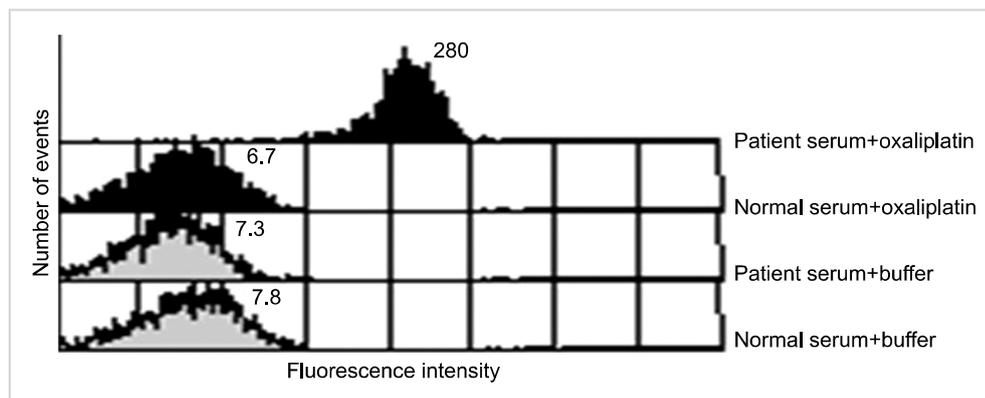


Fig. 2. Detection of oxaliplatin-dependent platelet antibodies by using flow cytometry. Patient's serum, but not normal serum, reacted with group O platelets in the presence of oxaliplatin 0.1 mg/mL (black histograms) but not in its absence (gray). No reactions were obtained with fluorouracil (5-FU) or leucovorin (not shown). Numbers shown above for each histogram represent the median fluorescence intensity (MFI) values, in log scale.

tion of the drug. For this range values the reactions always exceeded control values by at least three standard deviations. The patient's serum showed a positive reaction for IgG platelet antibodies in the presence of oxaliplatin (Fig. 2).

## RESULTS

Oxaliplatin-dependent platelet antibodies were detected in the patient's serum at the Platelet & Neutrophil Immunology Laboratory, Blood Center of Wisconsin (Milwaukee, USA) using the previously described flow cytometry assay [3]. The patient's serum showed a positive reaction for IgG platelet antibodies only in the presence of oxaliplatin (Fig. 2). The MFI obtained with undiluted serum in the presence of drug (280) was 42 times that obtained with the addition of the drug (6.7), when tested by flow cytometry against normal group O platelet (Fig. 2). The flow cytometry tests using the patient's serum and 5-FU or leucovorin were negative (results not shown).

## DISCUSSION

Hematologic toxicities and thrombocytopenia are frequently identified during chemotherapy with oxaliplatin. So far four different mechanisms have been proposed for the development of OIIT: 1) myelosuppression, 2) splenic-sequestration, 3) immune-mediated, and 4) microangiopathy [1]. Among them, myelosuppression-induced thrombocytopenia through direct toxicity of oxaliplatin is the most frequent cause of OIIT. It is frequently associated with neutropenia or anemia with spontaneous recovery. A second type of oxaliplatin-induced thrombocytopenia, splenic-sequestration induced oxaliplatin-induced thrombocytopenia, has been reported in 24% of patients treated with oxaliplatin and is caused by oxaliplatin-induced sinusoidal injury leading to portal hypertension [4]. The presence of splenomegaly and features of portal hypertension during oxaliplatin administration are necessary to confirm this mechanism. The third type of thrombocytopenia related to oxaliplatin administration is immune-mediated thrombocytopenia or OIIT, which is caused by oxaliplatin-dependent antibodies which target specific platelet glycoprotein (GP), most often GPIIb/IIIa [2, 3]. OIIT is well known but rare, and only a few cases have been reported so far. The typical clinical feature of OIIT is the presence of bleeding caused by the development of sudden and isolated severe thrombocytopenia. The detection of oxaliplatin-dependent platelet antibodies is necessary to confirm this mechanism. Isolated oxaliplatin-induced autoimmune hemolytic anemia [5], or Evan's syndrome [6] which are sharing a similar immune-mediated mechanism have also been rarely reported. The fourth type of oxaliplatin-induced thrombocytopenia is hemolytic-uremic syndrome where the mechanism of thrombocytopenia is due to non-immune microangiopathy [7].

All clinical and laboratory findings in our patient met

the criteria for the establishment of an OIIT diagnosis, since the presence of oxaliplatin-dependent antibodies was detected but not myelosuppression or splenomegaly. In our case, OIIT developed after the 11th administration of oxaliplatin. This is consistent with previous observations where OIIT developed in patients receiving more than 10 cycles of oxaliplatin [8]. OIIT is self-limiting and generally resolves within a few months with conventional treatment [1, 8]. Our patient was managed with platelet transfusion, prednisolone, and IV-immunoglobulin after discontinuation of oxaliplatin, and he recovered without complications within two months.

The most frequent targets of antibodies detected in patients with OIIT are the platelet GPIIb/IIIa, while other types of antibodies reacting with GPIb/IX or GPIa/IIa have also been reported [2]. OIIT is thought to be caused by one of several mechanisms, including hapten-dependent antibody response, autoantibody production, or immune-complex type reactions [3].

Desensitization protocols to manage oxaliplatin hypersensitivity and make rechallenge with oxaliplatin possible have been reported [9], and may be considered for patients who do not have the option of an alternative chemotherapeutic agent. However, because drug sensitivity usually persists indefinitely and readministering the same drug can be hazardous in patients having previously experienced drug-induced immune thrombocytopenia, readministration of oxaliplatin after OIIT is generally not recommended [7, 8].

In summary, we describe a colon cancer patient with OIIT, caused by oxaliplatin-dependent platelet antibodies. Immune-mediated thrombocytopenia should be considered when a sudden, isolated severe thrombocytopenia develops during chemotherapy with oxaliplatin.

## Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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