A patient with oxaliplatin immune-induced syndrome (OIIIS) who also developed leucovorin and palonosetron-associated thrombocytopenia

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ABSTRACT

Objectives: We report a case of an 83 year old man who developed oxaliplatin immune-induced syndrome (OIIIS) after his 19th cycle of FOLFOX (5FU, leucovorin, oxaliplatin). When oxaliplatin was omitted from his next cycle of chemotherapy he continues to show signs of drug-induced immune thrombocytopenia (DITP) and was found to have drug-dependent, platelet-reactive antibodies (DDPA) to leucovorin and palonosetron as well as oxaliplatin.

Methods: The patient was admitted for monitoring but required no transfusions and thrombocytopenia resolved without treatment during his first admission. Drug-dependent antibody testing was performed on his blood by the Blood Center of Wisconsin (Diagnostic Laboratories; Milwaukee, WI).

Results: No RBC or platelet IgG or IgM antibodies were detected in the absence of any drugs, but upon addition of palonosetron, leucovorin, or oxaliplatin, the tests became strongly positive for anti-RBC IgG and anti-platelet IgG antibodies.

Discussion: Repeated administration of oxaliplatin can result in drug-induced immune thrombocytopenia (DITP) or autoimmune hemolytic anemia (AIHA). This phenomenon has recently been termed OIIIS and may additionally include Evan’s syndrome or thrombotic microangiopathy (TMA). Here we describe a patient who developed OIIIS with drug-dependent, platelet-reactive antibodies (DDPA) to leucovorin and palonosetron. To our knowledge, these two drugs have never been described in the literature as a cause of DDPA. We suggest that OIIIS in addition to oxaliplatin-induced thrombocytopenia may be associated with the development of DDPA to other drugs causing clinically significant thrombocytopenia which is important to recognize and manage with discontinuation of provoking agents.

Case

The patient is an 83-year-old man with a history of stage IV rectal cancer with metastasis to the liver. He was treated with eight cycles of FOLFOX (5FU, leucovorin, oxaliplatin) and bevacizumab, which were complicated by mild hypertension, neutropenia (which resolved with pegfilgrastim injections), and thrombocytopenia (with nadir platelets that remained above 50 × 10^9/l). He then underwent partial hepatectomy, followed by capecitabine chemoradiation, and definitive resection of his rectal cancer. Three months later he had a recurrence of his liver metastasis, at which point he resumed the chemotherapy treatment with 10 additional cycles of FOLFOX plus bevacizumab.

He presented for his 19th cycle in his usual state of good health. He was first premedicated with dexamethasone and palonosetron. Then, halfway through his concurrent leucovorin and oxaliplatin infusions, he experienced back pain and rigors. He was treated with famotidine and diphenhydramine; bevacizumab was not given. On complete blood count (CBC), his platelet count, which had been 144 × 10^9/l before the infusions, dropped to 54 × 10^9/l 13 hours after infusion and continued to decline to a nadir of 17 × 10^9/l 31 hours after infusion (Figure 1). His hemoglobin, which had been 10.3 g/dl prior to infusion, dropped to 8.1 g/dl afterwards, with a reticulocyte count of 47 × 1000 cells/μl an increase in total bilirubin from 0.37 to 2.54 mg/dl, a lactate dehydrogenase (LDH) of 642 U/l (normal range: 118 U/l–242 U/l), and a haptoglobin of <10 mg/dl. His white blood cell (WBC) count rose from 4700 to 17,800 μl. His peripheral smear showed normocytic, normochromic anemia with thrombocytopenia and a few schistocytes and microspherocytes. He developed acute kidney injury (AKI), with a rise in his creatinine from 0.9 to 2.0 mg/dl. Prothrombin time, partial thromboplastin time, and fibrinogen were normal. Urinalysis revealed hyaline casts, four red blood cells (RBC) per high powered field, and moderate blood. Blood and urine cultures were negative. No signs of active bleeding were observed.

He was admitted for observation and did not require administration of blood products. He was diagnosed with intravascular hemolysis concerning for drug-
induced thrombotic microangiopathy (TMA), with microangiopathic hemolytic anemia, thrombocytopenia, and AKI. ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity was mildly reduced at 43%. Complement C3 and C4 levels were reduced at 68 and 11 mg/dl, respectively. RBC antibody screen was negative. His direct antiglobulin test (DAT) was weakly positive for IgG and negative for C3 when checked 25 hours after chemotherapy infusion, with a negative eluate. With the development of cytopenias after oxaliplatin infusion, oxaliplatin immune-induced syndrome (OIIS) was suspected. He was discharged to home after 2 days of observation with a platelet count of 33 × 10^9/l, a hemoglobin of 7.9 g/dl, a WBC of 3700 μl, and a creatinine of 1.6 mg/dl. Oxaliplatin was discontinued, and the decision was made to continue treatment with 5 FU, leucovorin, and bevacizumab.

Two weeks later he returned for his 20th cycle of chemotherapy. His CBC, total bilirubin, and creatinine had returned to baseline, with a hemoglobin 9.8 g/dl, platelet count 150 × 10^9/l, total bilirubin 0.55 mg/dl, and creatinine 1.0 mg/dl. He was premedicated with dexamethasone and palonosetron, and then received bevacizumab followed by leucovorin. During the leucovorin infusion he complained of chest pressure, felt cold, and developed rigors. Famotidine and diphenhydramine were administered, with resolution of these symptoms. A repeat CBC 5 hours after his leucovorin infusion showed an acute-onset thrombocytopenia, progression of anemia, and leukocytosis (platelet count 43 × 10^9/l, hemoglobin 9.2 g/dl, WBC 20,200 μl); blood chemistries showed a rise in total bilirubin to 2.57 mg/dl and an elevated LDH of 482 U/l, with normal renal function.

He was readmitted for further evaluation. A CBC the following day showed persistent thrombocytopenia, anemia, and leukocytosis (platelet count 30 × 10^9/l, hemoglobin 8.2 g/dl, WBC 13,400 μl). A repeat blood smear showed thrombocytopenia, without schistocytes or microspherocytes. Urinalysis showed no casts, blood, or RBCs. No overt signs of bleeding were observed. He again did not require any transfusions but was treated with 40 mg dexamethasone for 4 days and discharged home in the interim. A follow-up CBC on the day of his fourth dose of dexamethasone showed partial recovery of his blood counts (platelets count 106 × 10^9/l, hemoglobin 9.5 g/dl, WBC 6600/μl).

A repeat DAT was once again weakly positive for IgG and negative for C3, with a negative eluate. Drug-dependent antibody testing was performed on his blood by the Blood Center of Wisconsin (Diagnostic Laboratories; Milwaukee, WI, U.S.A.); no RBC or platelet IgG or IgM antibodies were detected in the absence of any drugs, but upon addition of palonosetron, leucovorin, or oxaliplatin, the tests became strongly positive for anti-RBC IgG and anti-platelet IgG antibodies (Figure 2). Additional testing against chloramphenicol was negative confirming that the antibodies were specific for above-mentioned medications.

After drug-dependent, platelet-reactive antibodies (DDPAs) to oxaliplatin, leucovorin, and palonosetron were identified and these drugs were discontinued, the patient resumed the chemotherapy treatment with bevacizumab and 5 FU and did not experience further reactions during additional 15 cycles of treatment.

Discussion

OIIS is a well-reported phenomenon in the literature. In the largest case series of 61 patients, OIIS usually developed within 24 hours of oxaliplatin-containing chemotherapy, typically after four or more cycles [1]; drug-induced immune thrombocytopenia...
(DITP) occurred in 28, autoimmune hemolytic anemia in 13, Evan’s syndrome in 7, and TMA in 13 patients. AKI has also been reported and thought to be due to TMA or due to acute tubular necrosis caused by the accumulation of hemolysis products in renal tubules [2,3]. Presenting symptoms include fevers, chills, rigors, back or chest pain, hematemesis, hematuria, or dark urine. Treatment includes cessation of oxaliplatin, platelet, and RBC transfusions as needed, and management of bleeding [4]. Oxaliplatin should be permanently avoided in affected patients as re-exposure leads to recurrent reactions that may be more rapid or severe than the index event [5,6]. The reason for clearly recognized delay in the development of OIIS after initiation of oxaliplatin is not clear.

Standard evaluation for OIIS and other forms of DITP includes testing for DDPA, most commonly performed at the Blood Center of Wisconsin [7–9]. There are many different mechanisms proposed for the formation of DDPA, including a hapten mechanism, a neo-epitope mechanism, an autoantibody mechanism, a drug specific mechanism, and a quinine-type mechanism [9]. Although the exact mechanism(s) for DDPA formation to oxaliplatin remains unproven, it is postulated that the mechanism in OIIS is similar to the neoepitope mechanism, whereby interactions of oxaliplatin and various erythrocyte antigens (e.g. Rh) or platelet surface glycoproteins (e.g. GPIIb/IIIa, GPIb/IX) form targets for DDPA formation. The alternative explanation may be quinine-type mechanism when drug facilitates the interaction between the DDPA complementarity-determining region and its target on the cell membrane. Upon clearance of oxaliplatin from the blood, these DDPA are unable to interact with RBCs or platelets, allowing for restoration of normal hemoglobin values and platelet counts [9].

In most cases of OIIS, the DDPA formed are exclusive to oxaliplatin. Our case is unique in that no other published cases of OIIS have observed the concomitant development of additional DDPA to other drugs, and no cases of DDPA to leucovorin or palonosetron have been reported. To our knowledge there is only one case report describing the formation of DDPA to more than one medication [10]. Oxaliplatin is a third-generation platinum derivative with a variety of cytotoxic effects which it causes by forming cross links in DNA which prevent cell replication [11]. Leucovorin is a derivative of tetrahydrofolic acid, a naturally occurring substance, with few known side effects [11]. Palonosetron is a second-generation 5-HT3 antagonist, also with relatively few side effects [12]. These medications do not share similarities in their chemical structure and as leucovorin and palonosetron have never previously been associated with DDPA, we speculate that this

![Fluorescence histograms generated from immunofluorescence detection of immunoglobulin G (IgG) drug-dependent platelet antibodies (DDAbs) by flow cytometry.](image)

Figure 2. Fluorescence histograms generated from immunofluorescence detection of immunoglobulin G (IgG) drug-dependent platelet antibodies (DDAbs) by flow cytometry. Isolated normal donor platelets were incubated with patient’s serum in the presence (dark histograms) and absence (light histograms) of drug, washed, and platelet-bound antibodies were detected with fluorescent anti-human IgG. Results showed patient’s serum contained strong DDAs with leucovorin (MdFI = 95.6, 15× control), palonosetron (MdFI = 39.9, 6× control), and oxaliplatin (MdFI = 85.1, 9× control). As a negative control, the patient’s serum was also tested with a drug (chloramphenicol) he was not exposed to and showed negative results for DDAs (MdFI = 6.7 vs. 6.5 control), MdFI = median fluorescence intensity (MdFI).
rare antibody development may be a part of OIIS and wonder if oxaliplatin-induced immune activation may sometimes be associated with the generation of DDPA to other drugs. The mechanism by which OIIS leads to the formation of additional DDPAs remains unclear.

Clinicians taking care of OIIS patients should be mindful of the possibility that DITP may still develop after withdrawal of oxaliplatin because of additional DDPA related to other concurrently used medications, which may warrant further testing and drug discontinuations.

Disclosure statement
No potential conflict of interest was reported by the authors.

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