

# Antiplatelet antibodies in oxaliplatin-induced immune thrombocytopenia

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## Lesson

Drug-induced immune thrombocytopenia may be potentially fatal; here we report the development of severe thrombocytopenia with strong oxaliplatin-dependent antiplatelet antibodies.

## Keywords

oxaliplatin, thrombocytopenia, drug-induced thrombocytopenia

## Case report

A 78-year-old man with metastatic colon adenocarcinoma receiving his eighth cycle of modified FOLFOX-6 (5-fluorouracil, leucovorin and oxaliplatin) presented with bright red bleeding per rectum and hematemesis. Physical examination was remarkable for a lower extremity petechial rash and several ecchymotic areas on both upper extremities. A complete blood count (CBC) revealed a platelet count of 4000/ $\mu$ L, which had declined acutely from a baseline of 175,000/ $\mu$ L three days prior. The patient denied using any new medications. Given symptomatic acute thrombocytopenia, he was admitted for further evaluation and management.

His medical history was significant for hypertension, dyslipidemia and anxiety. He was originally diagnosed with metastatic colon cancer in 2009, and initially received systemic therapy with 12 cycles of modified FOLFOX-6 in combination with bevacizumab. Oxaliplatin had been dose-reduced and held in the past due to progressive peripheral neuropathy. He subsequently received several other lines of chemotherapy including 5FU/LV (5-fluorouracil, leucovorin), FOLFIRI (5FU, leucovorin, irinotecan), and single agent irinotecan. Most recently, treatment had been resumed with modified FOLFOX-6. Of note, treatment was held for one month after cycle 7, due to a planned family trip, and the patient had just received his eighth cycle of treatment with FOLFOX-6 three days prior to his presentation. Other medications included lisinopril,

hydrochlorothiazide, alprazolam, prochlorperazine and aspirin, none of which were recent additions.

Review of the peripheral blood film revealed no evidence of thrombotic microangiopathy, but severely decreased platelets and normocytic anemia. Coagulation profile and fibrinogen, as well as haptoglobin, bilirubin and lactate dehydrogenase levels were within normal limits, ruling out dissemination intravascular coagulation (DIC) and haemolysis (Table 1). Direct antiglobulin test (DAT) was positive for IgG but negative for anti C3b and C3d. His renal function was normal. The acute onset of thrombocytopenia raised the suspicion of drug-induced thrombocytopenia, and drug-dependent platelet antiplatelet antibody testing was sent to the Blood Center of Wisconsin.

The patient received platelet transfusions and intravenous methylprednisolone that led to a rapid increment of his platelet count. He was discharged on oral prednisone three days after his presentation, with a platelet count of 62,000/ $\mu$ L. Nine days later, his platelet count was 164,000/ $\mu$ L. Drug-dependent antiplatelet antibody testing later confirmed the presence of unusually strong oxaliplatin-dependent antiplatelet antibodies (Figure 1). Re-testing of convalescent sera six weeks later demonstrated the persistence of oxaliplatin-dependent IgG antibodies.

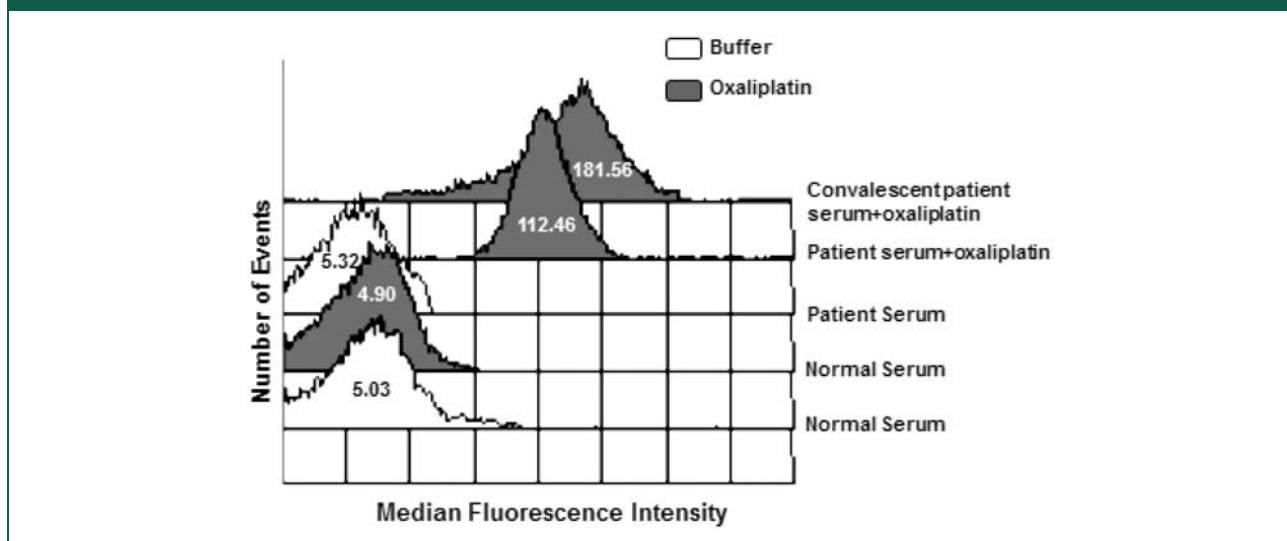
## Discussion

We performed a review of literature using the search terms 'oxaliplatin' and 'thrombocytopenia' as well as 'oxaliplatin induced thrombocytopenia' in Pubmed (see supplementary file). Most patients developed thrombocytopenia within 24 hours of drug exposure. Hematologic abnormalities other than thrombocytopenia were seen in many cases of oxaliplatin-induced thrombocytopenia. DAT was positive in 15 (46.8%) patients, though not all of them developed haemolysis. Three patients developed thrombotic thrombocytopenic purpura and or haemolytic uremic syndrome (TTP/HUS), and one developed DIC.

**Table 1.** Laboratory studies obtained at the time of initial work-up of thrombocytopenia.

Laboratory test	Reference values	Test result
Leukocyte count (k/ $\mu$ L)	3.7–11.0	5.38
Haemoglobin (g/dL)	13–17	12
Prothrombin time (PT) (s)	8.4–13.0	11.8
Activated partial thromboplastin time (PTT) (s)	23.0–32.4	24.9
Fibrinogen (mg/dL)	200–400	258
LDH (U/L)	100–220	374
Haptoglobin (mg/dL)	37–246	163
Coomb's test		Polyspecific: POS Anti-IgG: POS Anti-C3b,C3d: NEG

POS = positive, NEG = negative.

**Figure 1.** Serum from the patient reacted with platelets in the presence of oxaliplatin. Convalescent serum, tested six weeks later, demonstrated persistence of strong oxaliplatin-dependent antibodies.

Systemic symptoms accompanied acute symptomatic thrombocytopenia in 20 patients. Most patients received transfusion support and steroids. Plasmapheresis/plasma exchange, dialysis, or immunoglobulin administration were also utilised in some cases. All patients had favourable outcomes except two who presented with intracerebral haemorrhage and expired.<sup>1,2</sup> All other patients demonstrated normalisation of platelet counts after drug cessation and with supportive treatment. All patients who were re-challenged with oxaliplatin developed recurrence of

thrombocytopenia and previously experienced systemic symptoms. Platelet antibody testing was performed in 17 patients, of whom 11 (64.7%) were positive. Of these, nine patients specifically underwent oxaliplatin-dependent antibody testing, and all had detectable antibodies. High titres of drug-dependant antibodies were noted in three patients. Some patients demonstrated concomitant drug-dependent antibodies against erythrocytes and granulocytes. Oxaliplatin-dependant anti-erythrocyte antibody alone was detected in one patient.

Interestingly, acute thrombocytopenia related to transcatheter hepatic chemoembolisation with oxaliplatin eluting microspheres has also been reported.<sup>3</sup>

While myelosuppression is believed to be the main mechanism of oxaliplatin-induced thrombocytopenia,<sup>4</sup> increasing evidence of acute thrombocytopenia has brought to attention the risk of drug-induced immune thrombocytopenia (DIT). Previously described common models of DIT include immune complex formation, drug-induced autoantibody production or drug-specific antibody production with reactivity against platelet membrane glycoproteins (Gp).<sup>5</sup> Bougie et al.<sup>6</sup> have demonstrated that in addition to anti-platelet antibodies specific for GPIIb/IIIa or GPIb/IX, 'drug-specific' antibodies that are not platelet reactive may also exist. Jardim et al.<sup>4</sup> have described putative mechanisms of oxaliplatin-induced thrombocytopenia, which include bone marrow toxicity, immune mediated process, or sinusoidal injury leading to portal hypertension and splenomegaly. Furthermore, reports of haemolytic anemia in conjunction with thrombocytopenia raise the possibility of oxaliplatin-induced microangiopathy. It has been speculated that oxaliplatin may act as a hapten, and recurrent exposure may lead to immune activation, resulting in hypersensitivity reactions.<sup>7</sup> In reports of oxaliplatin-related DIT, antibodies identified include those reactive with Gp IIb/IIIa,<sup>8</sup> Gp Ia/IIa and Gp Ib/IX.<sup>9</sup>

Our case unveils some unique aspects of oxaliplatin-induced thrombocytopenia. Our patient developed strong drug-induced antibodies despite significant prior exposure to the drug. Yet, there were no systemic symptoms reported, which argues against a hypersensitivity type reaction. Anecdotal evidence from prior reports suggests that re-challenge with oxaliplatin may lead to recurrent thrombocytopenia. Our patient demonstrated the presence of strong drug-dependent antiplatelet antibodies on serial testing six weeks later (Figure 1), which is a novel finding that has not been reported previously. This is relevant to clinical practice since it suggests an immunologic basis for the recommendation against future re-challenge with oxaliplatin.

The acute onset of severe thrombocytopenia in patients with sparing of red cells and normal coagulation studies should raise the index of suspicion for DIT, in addition to other differential entities. While testing for drug-dependent antibodies may take several days, clinicians should be cognizant of DIT, since the initial diagnosis is clinical and warrants

immediate drug withdrawal. Drug sensitivity can persist indefinitely, and permanent drug withdrawal should be recommended.

#### Declarations

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**Guarantor:** KM

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#### References

1. Shao YY and Hong RL. Fatal thrombocytopenia after oxaliplatin-based chemotherapy. *Anticancer Res* 2008; 28: 3115–3117.
2. Teng CJ, Hsieh YY, Chen KW, Chao TC, Tzeng CH and Wang WS. Sudden-onset pancytopenia with intracranial hemorrhage after oxaliplatin treatment: a case report and literature review. *Jpn J Clin Oncol* 2011; 41: 125–129.
3. Poggi G, Quaretti P, Montagna B, Sottotetti F, Tagliaferri B, Pozzi E, et al. Acute thrombocytopenia: an unusual complication occurring after drug-eluting microspheres transcatheter hepatic chemoembolization. *Cardiovasc Intervent Radiol* 2011; 34(Suppl 2): S190–194.
4. Jardim DL, Rodrigues CA, Novis YA, Rocha VG and Hoff PM. Oxaliplatin-related thrombocytopenia. *Ann Oncol* 2012; 23: 1937–1942.
5. Aster RH and Bougie DW. Drug-induced immune thrombocytopenia. *N Engl J Med* 2007; 357: 580–587.
6. Bougie DW, Wilker PR and Aster RH. Patients with quinine-induced immune thrombocytopenia have both 'drug-dependent' and 'drug-specific' antibodies. *Blood* 2006; 108: 922–927.
7. Chen VM, Thrift KM, Morel-Kopp MC, Jackson D, Ward CM and Flower RL. An immediate hemolytic reaction induced by repeated administration of oxaliplatin. *Transfusion* 2004; 44(6): 838–843.
8. Curtis BR, Kaliszewski J, Marques MB, Saif MW, Nabelle L, Blank J, et al. Immune-mediated thrombocytopenia resulting from sensitivity to oxaliplatin. *Am J Hematol* 2006; 81(3): 193–198.
9. Pavic M, Moncharmont P, Seve P, Rigal D and Broussolle C. Oxaliplatin-induced immune thrombocytopenia. *Gastroenterol Clin Biol* 2006; 30(5): 797–798.