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# Oxaliplatin induced acute immune-mediated thrombocytopenia; a case report

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ABSTRACT

Oxaliplatin is a third-generation platinum anti-neoplastic agent, which is used in the treatment of colorectal, gastric, and biliary tract cancers with combination other chemotherapy drugs. In rare cases, thrombocytopenia may occur suddenly in approximately 24 hours due to immune-mediated reactions. This reaction is usually seen after long term usage of oxaliplatin-based chemotherapy. Here, we present our case of immune-mediated thrombocytopenia associated with oxaliplatin.

A 56 years old man who had stage IV rectum cancer with liver metastasis, had palliative surgery due to bowel obstruction after initial diagnostic approach. After failure of first line treatment, mFOLFOX6 plus Cetuximab (Cetuximab: 500mg/m2 on day 1, Oxaliplatin: 85 mg/m2 day 1, Leucovorin (LV): 400 mg/m2 day 1, 5-FU 400 mg/m2 IV bolus on day 1 followed by 2400 mg/m2 on day 1 infused over 46 hours every two weeks) regimen was started. Before the 21st cycle of oxaliplatin plus cetuximab regimen, the patient had normal thrombocyte, haemoglobin and neutrophile count. Approximately 8 hours after the chemotherapy patient had been taken to the emergency service with petechia, vigorous gastrointestinal and nasal bleeding. The thrombocyte levels were 3000 at μl. The patient was given methylprednisolone for three days. The thrombocyte levels recover quickly in 24 hours. After this reaction, oxaliplatin stopped and the chemotherapy was changed to capesitabine plus cetuximab regimen.

In conclusion, oxaliplatin induced immune-mediated thrombocytopenia is a rare side effect but a life threatening complication. A physician who uses oxaliplatin as a treatment option should keep in mind the possibility immune-mediated thrombocytopenia which may cause life-threatening bleeding. Especially the long term use of oxaliplatin (median >10 cycles) may alert the physician for immune-mediated adverse effects.



## 1. Introduction

Oxaliplatin is a third-generation platinum anti-neoplastic agent, which is used in the treatment of colorectal, gastric, and biliary tract cancers in combination with other chemotherapy drugs. The most common side effects of this agent is peripheral neuropathy, myelosuppression, nausea, and vomiting. In chemotherapy regimens with oxaliplatin, up to 70% of patients had various grades of thrombocytopenia as an adverse effect.[1,9,10] In oxaliplatin monotherapy, thrombocytopenia may be seen about 30% and it is usually moderate, self-limited, and related to myelosuppression.[1] Only 3–4% of patients have grade 3–4 myelosupression related thrombocytopenia with life-threatening bleeding.[1,9,10]

In rare cases, thrombocytopenia may occur suddenly in approximately 24 hours due to immune-mediated reactions.[2] This potentially life-threatening side effect occurs by Type II hypersensitivity reaction. Antibodies against oxaliplatin neoepitope can affect red blood cells, platelets, leucocytes and the other blood glycoproteins [13]. This reaction is usually seen after long term usage of oxaliplatin-based chemotherapy.

Clinical presentation of this drug induced immune thrombocytopenia is quite varied. Patients usually complain of isolated thrombocytopenia related symptoms with or without haemolytic anemia, leucopenia, impairment of renal and hepatic functions, and skin reactions.[2–8]

Here we present a case of immune-mediated thrombocytopenia associated with oxaliplatin.

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## 2. Case

A 56 years old man who had stage IV rectum cancer with liver metastasis, had palliative surgery due to bowel obstruction after initial diagnostic approach. The pathological specimen of the patient evaluated as K-Ras wild type. The patient was given neoadjuvant FOLFIRI plus Bevacizumab (Bevacizumab: 5 mg/kg on day 1, irinotecan: 180 mg/m2 on day 1, leucovorin: 400 mg/m2 on day 1, 5-FU 400 mg/m2 IV bolus on day 1 followed by 2400 mg/m2 on day 1 infused over 46 hours every two weeks) regimen for the conversion of the border-line resectable liver metastases. After the 6 cycles of chemotherapy (3 months), partial response was seen radiologically. The patient was undergone surgery for the metastasectomy of the liver metastases, but $R_0$ resection cannot be achieved. So FOLFIRI plus Bevazicumab regimen continued for 6 cycles more. Progression was detected radiologically after 12 cycles of FOLFIRI plus Bevazicumab treatment. Second-line mFOLFOX6 plus Cetuximab (Cetuximab: 500mg/m2 on day 1, Oxaliplatin: 85 mg/m2 day 1, Leucovorin (LV): 400 mg/m2 day 1, 5-FU 400 mg/m2 IV bolus on day 1 followed by 2400 mg/m2 on day 1 infused over 46 hours every two weeks) regimen was initiated. After 12 cycles (6 months), partial response achieved. Reduction in marker levels, tumour shrinkage in radiological studies and improvement in clinical performance status was noted. As the maintenance therapy, oxaliplatin and cetuximab regimen was continued for 8 cycles. Before the 21st cycle of oxaliplatin plus cetuximab regimen, the patient had normal thrombocyte, haemoglobin and neutrophile count. Approximately 8 hours after the chemotherapy patient had been taken to the emergency service with petechia, vigorous gastrointestinal and nasal bleeding. (Fig. 2–3) No allergic reactions were seen in the physical examination like urticaria, angioedema, wheezing or rushes. The thrombocyte levels were 3000 at μl. The patient was hospitalized for gastrointestinal bleeding and received 10 random thrombocyte transfusions immediately. He was given 60 mg methylprednisolone for three days. On the 24th hour of oxaliplatin infusion, the thrombocyte levels raised to 38000 at μl. In the second day the thrombocyte levels stabilized and gastrointestinal bleeding stopped. (Fig. 1) Anti-thrombocyte antibodies could not perform because of test unavailability. The fast reduction in thrombocyte count in 12 hours time was considered for oxaliplatin associated immune-mediated thrombocytopenia. After this reaction, oxaliplatin stopped and the chemotherapy was changed to capesitabine plus cetuximab regimen. The thrombocyte levels were normal with this chemotherapy regimen. No adverse reaction was noted.

## 3. Discussion

Myelosuppression is the main cause of thrombocytopenia related to oxaliplatin, which represents generally moderate and asymptomatic thrombocytopenia. In some patients, hepatic sinusoid damage by oxaliplatin leads to portal hypertension and the splenic sequestration of platelets can be resulted thrombocytopenia. Immune-mediated mechanism is the third reason of thrombocytopenia which is quite rarely occurs during oxaliplatin infusion or soon after [11]. This rare side affect occurs by Type II hypersensitivity reactions when antibodies (IgG and/or IgM) recognize surface antigens on host cells and mediate cell lysis via complement and phagocytic cells. Especially, glycoprotein IIb/IIIa or other platelet glycoproteins are targeted by the production of oxaliplatin-dependent specific antibodies. But, mechanism of this drug induced toxicity is not yet clearly understood.

The findings from the clinical evaluation will usually be sufficient for the diagnosis of oxaliplatin induced thrombocytopenia without need for specific antibodies. Sudden onset thrombocytopenia (usually occurs in 24 hours after chemotherapy) and thrombocytopenia related petechia, purpura, and gastrointestinal bleedings are the main clinical findings. Haemolytic anemia, leucopenia, allergic reactions, and or impairment of renal and liver functions were described previously in patients receiving oxaliplatin-based chemotherapy after a prolonged exposure [2–8], [12–13]. The treatment has to initiate rapidly to avoid complications, because fatal cases have been reported in published studies. The treatment includes supportive care and discontinuation of drug. Steroids and intravenous immunoglobulin (IVIG) might be an option for immune mediated thrombocytopenia [12].

Due to our best knowledge, there are two published review articles in the literature [12–13].

The review article published by Erdem et al. in April 2016 [12]. Clinical features of 42 cases immune mediated thrombocytopenia due to oxaliplatin use presented. One of the patients was from their institution and the other 41 cases were found in Pubmed screening. According to this review, most of patients were female (54.7%), the age of patients were differ from 38 to 83 years and the emerge of the reaction changed from sudden onset to 24 hours. The infusion numbers of oxaliplatin differed second to thirtieth cycle (average 15

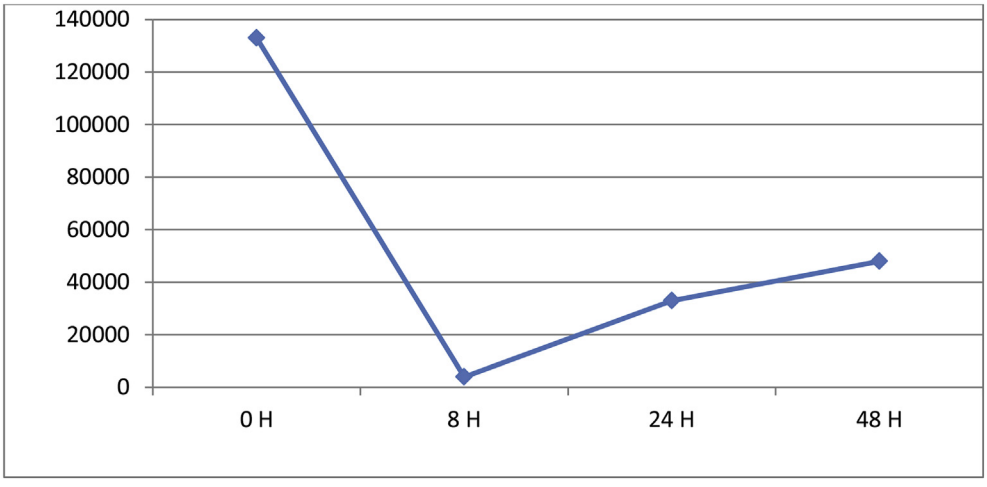


**Fig. 1.** The course of Thrombocyte counts of the patient on the days of chemotherapy and hospitalization.

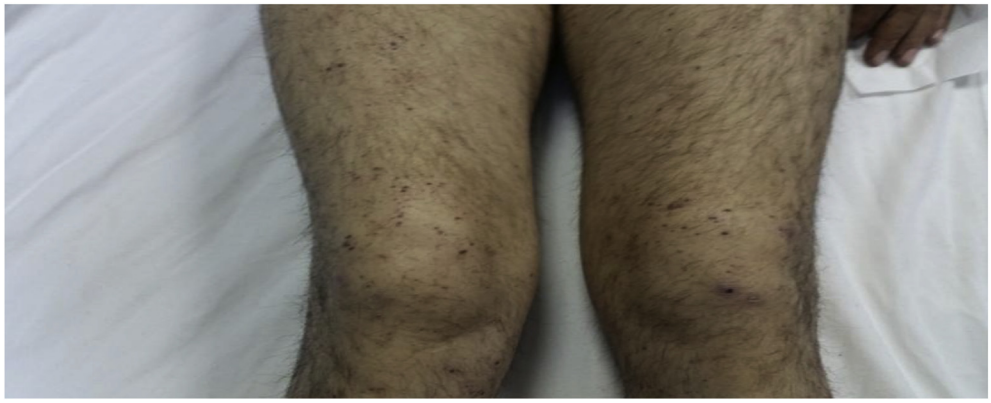

**Fig. 2.** Petechial hemorrhagic lesions.

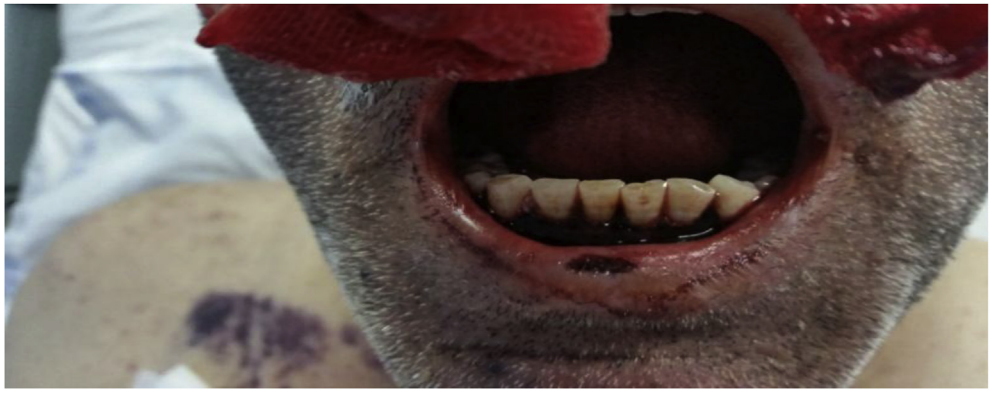

**Fig. 3.** Mucosal bleeding dependent to thrombocytopenia at Emergency service.

cycles). The steroids, thrombocyte transfusion, IVIG, granulocyte stimulating factor (G-CSF), hydration and fresh frozen plasma were used for management. Three patients had been died due to complications of thrombocytopenia while all other cases recover with supportive treatment [12]. Twenty six patient were diagnosed isolated acute immune thrombocytopenia (AIT) and the others were Evan's Syndrome (ES, 9 patients), Haemolytic Uremic Syndrome (HUS, 3 patients), and Thrombotic Thrombocytopenic Purpura (TTP, 3 patients).

In September 2016, a systematic review [13] which had the largest series (61 patients) was published. In this review, oxaliplatin immune-induced syndrome was divided four subgroups; drug mediated thrombotic microangiopathies (TMAs; HUS, TTP, and disseminated intravascular coagulation), Evan's Syndrome (ES), isolated immune haemolytic anemia (IHA), and isolated acute immune thrombocytopenia (AIT). In 7 of cases (11.5%) were diagnosed ES, in 13 of cases (21.3%) TMA, in 13 of cases (21.3%) IHA, and in 28 of cases (45.9%) AIT. No information had been reported about diagnosis of only one case. Of the 61 patients, 56 (91.8%) had received oxaliplatin based chemotherapy for metastatic colorectal cancer. The median age of patients was 60 years and most of the patients were female (57.9%). Anti-thrombocyte antibodies were positive in 87.7% (49 patients) of the patients. The average number of oxaliplatin cycles was 16.7. When oxaliplatin was administered as a rechallenge treatment, the chemotherapy cycles number until the onset immune induced syndrome was threefold lower than first time exposure to oxaliplatin. Three of patients have been died due to thrombocytopenia.

In our case, the patient was male and received palliative maintenance biweekly oxaliplatin plus cetuximab chemotherapy regimen for metastatic rectum carcinoma. Acute thrombocytopenia developed 8 hours later from exposure to 21st cycle's oxaliplatin. Leucocytes count, renal and hepatic functions tests were normal and no allergic reactions observed. Other drugs usage which cause thrombocytopenia did not identified in patient's clinical history. The sudden onset thrombocytopenia with Very low levels fits to the acute isolated immune-mediated thrombocytopenia. Also the quick recovery of thrombocyte levels with steroid treatment was supported the diagnosis.

In conclusion, oxaliplatin induced immune-mediated thrombocytopenia is a rare but life threatening complication. Also the allergic reactions, renal and hepatic failure can accompany the immune-mediated thrombocytopenia. A physician who uses oxaliplatin as a treatment option should keep in mind the possibility immune-mediated thrombocytopenia. Especially the long term oxaliplatin usage (median >10 cycles) may alert the physician for immune-mediated adverse effects.

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