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Case Report

Acute Oxaliplatin-Induced Immune Hemolytic Anemia and Thrombocytopenia; A Case of Oxaliplatin Immune-Induced Syndrome

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Abstract

Oxaliplatin immune-induced syndrome is a rare side effect associated with oxaliplatin-based chemotherapy. This case study describes a 64-years old male with metastatic colorectal cancer who developed acute hemolytic anemia, thrombocytopenia, and acute kidney injury after oxaliplatin infusion. The positive results of direct and indirect globulin tests suggested immune hemolytic anemia. Intravenous steroid and hemodialysis were applied, and the patient fully recovered.

Keywords: Oxaliplatin; Hemolytic Anemia; Thrombocytopenia; Acute Kideny Injury;

Introduction

Oxaliplatin is a third-generation platinum drug that is widely used as an effective adjuvant and palliative chemotherapeutic drug for various gastrointestinal malignancies, particular colorectal cancer [1]. Common side effects of oxaliplatin include hematologic toxicities, gastrointestinal toxicities, and peripheral neuropathy [2]. Oxaliplatin immune-induced syndrome (OIIS) is an uncommon but potentially lethal immune-related side effect that is characterized by acute onset hemolytic anemia and thrombocytopenia, with or without acute renal failure, arising within 24 hours of oxaliplatin infusion [3]. Herein, this case study describes a patient with metastatic colorectal cancer who developed acute immune hemolytic anemia, thrombocytopenia, and acute kidney injury after the administration of oxaliplatin-containing chemotherapy.

Case Presentation

A 64-year-old man was diagnosed with sigmoid colorectal cancer with hepatic metastasis and underwent palliative left hemicolectomy. He completed 18 cycles of chemotherapy with a combination of fluorouracil, leucovorin, and oxaliplatin (FOLFOX). Eighteen months later, new hepatic and peritoneal metastases were detected through imaging studies, and chemotherapy with FOLFOX plus cetuximab was initiated. Treatment was stopped after 16 cycles because the patient did not want to continue chemotherapy. One year later, hepatic metastasis was aggravated, and combination chemotherapy with fluorouracil, leucovorin, and irinotecan (FOLFIRI) was performed. After 15 cycles of chemotherapy with FOLFIRI, imaging studies revealed aggravated hepatic and peritoneal metastases and the new onset of pleural metastasis. The patient was re-initiated with chemotherapy with FOLFOX.

Three hours after starting oxaliplatin during the fifth cycle of FOLFOX, the patient complained of a mild fever and chills. These symptoms subsided after receiving acetaminophen and chlorpheniramine, and oxaliplatin infusion was completed. Sixteen hours after the end of oxaliplatin infusion, the patient presented with gross hematuria and fever. Vital signs revealed a body temperature of 38.8℃, a heart rate of 70 beats/min, a respiratory rate of 23 beats/min, and a blood pressure of 150/80 mmHg. His mental status abruptly changed to confusion. Table 1 shows the laboratory findings before and after oxaliplatin infusion. Complete blood count revealed decreased hemoglobin and platelets, compared with the results before chemotherapy (hemoglobin 11.0 g/dL à 9.0 g/dL, platelets counts 236,000/μL à 127,000/μL). Indirect hyperbilirubinemia (indirect bilirubin; 0.28

mg/dL à 1.65 mg/dL), increased lactate dehydrogenase (LDH) (696 IU/L à >3000 IU/L), and acute renal failure (blood urea nitrogen [BUN]; 15.0 mg/dL à 54.3 mg/dL, creatinine; 0.75 mg/dL à 3.17 mg/dL) were observed. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were prolonged (PT; 12.0 à 22.5 seconds, aPTT; 29.6 à 47.7 seconds). The symptoms and laboratory findings suggested acute intravascular hemolysis, such as microangiopathic hemolytic anemia (MAHA) or immune hemolytic anemia. The patient was immediately transferred to the intensive care unit (ICU) and managed with plasma exchange with fresh frozen plasma. Methylprednisolone (1 mg/kg) was intravenously administered.

	Normal range	Day -1[a]	Day 1[b]	Day 2	Day 7
Hemoglobin (g/dL)	14.0–16.7	11	9	7.4	6.3
Platelets (/μL)	144,000–351,000	2,36,000	1,27,000	74,000	37,000
Bilirubin, indirect (mg/dL)	0.20–0.80	0.28	1.65	0.86	0.27
LDH (IU/L)	200–450	696	>3000	2442	486
BUN (mg/dL)	5–23	15	54.3	91	47.7
Creatinine (mg/dL)	0.80–1.30	0.75	3.17	5.5	4.66
PT (sec)	11.0–15.0	12	22.5	15.3	14.6
aPTT (sec)	27.0–45.0	29.8	47.7	35.7	33
prior chemotherapy; after oxaliplatin infusion; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; PT, prothrombin time; aPTT, activated partial thromboplastin time					

Table 1: The laboratory findings before and after oxaliplatin infusion.

At the laboratory finding, the peripheral blood smear revealed no schistocytes, but helmet cells. The haptoglobin was decreased to less than 20 mg/dL, and the d-dimer and fibrin/fibrinogen degradation products were increased to> 20.0 μg/mL and >120 μg/mL, respectively. The direct and indirect antiglobulin tests were positive, which suggested autoimmune hemolytic anemia. The ADAMTS (A Disintegrin and Metalloproteinase with Thrombospondin motifs) 13 activity was moderately reduced to 33%, but required time to obtain the result.

After starting plasma exchange, the patient's level of consciousness recovered to an alert status and the prolonged PT and aPTT were corrected immediately. Hemoglobin and platelets level decreased to 6.3 g/dL and 16,000/μL, respectively, but gradually recovered by continued management with plasma exchange, transfusion, and steroids (Figure 1). Hemodialysis was continued for one week, and renal function was fully normalized after one month.

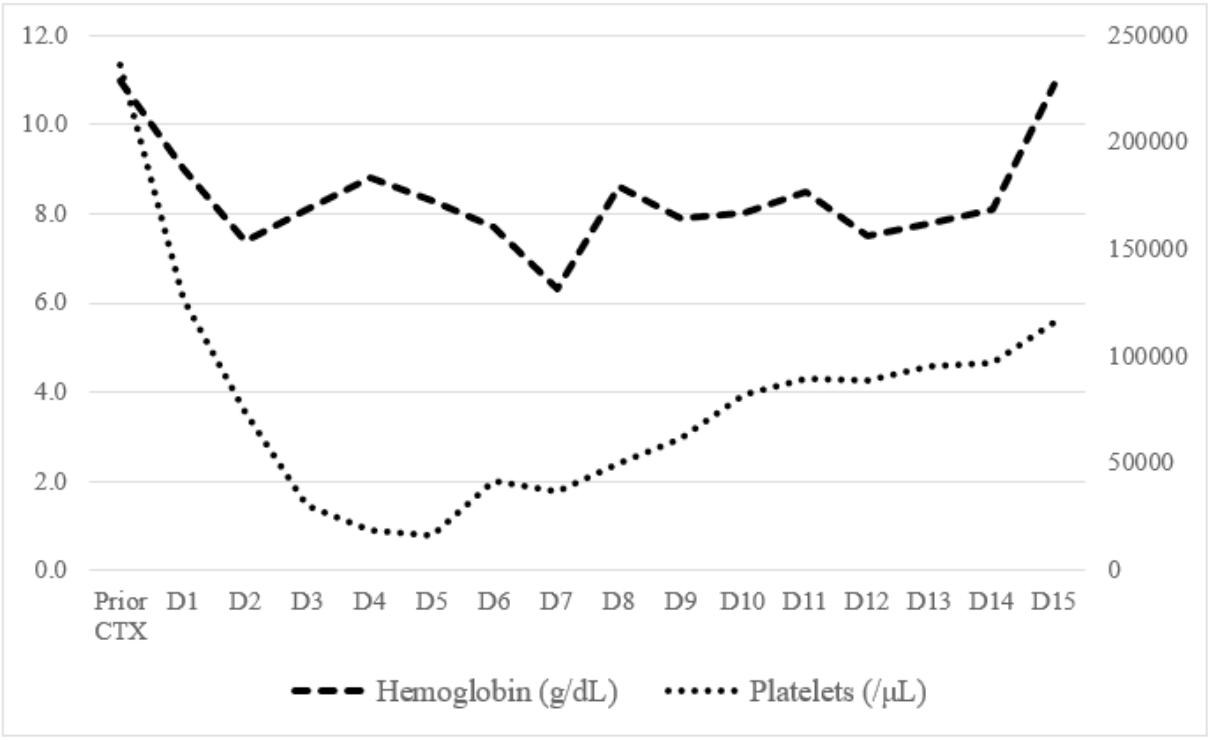

Figure 1: Trends in hemoglobin and platelet during episode. CTX; chemotherapy.

Discussion

OIIS may be suspected if fever, chills, back pain, or dark urine suddenly develop during or immediately after oxaliplatin infusion, and the laboratory tests reveal acute hemolytic anemia and/or thrombocytopenia [3-6]. Abrupt intravascular hemolysis causes acute tubule necrosis, which can lead to acute kidney injury [7, 8]. In this study, the patient developed immune hemolytic anemia, thrombocytopenia, and acute kidney injury following oxaliplatin infusion, which is consistent with a diagnosis of OISS.

The mechanism underlying OIIS is not fully understood, however, drug-specific antibody production and drug-induced immune system activation are the most likely causes [9, 10]. Oxaliplatin induces the formation of drug-induced IgG antibodies that target erythrocytes and platelets membranes, which can strongly activate the complement system. These autoantibodies could result acute and severe hemolysis [11]. In several case reports, OIIS occurred within 24 hours of oxaliplatin infusion [3-6]. This syndrome was associated with long-term exposure to oxaliplatin and occurred most frequently upon rechallenge with oxaliplatin. Bencardino et al. analyzed that 61 patients with OIIS and reported that OIIS developed after average of 16th cycles of oxaliplatin-based chemotherapy and occurred earlier when rechallenged after oxaliplatin discontinuation (4.6 cycles after rechallange vs. 13.6 cycles after first-time exposure) [3]. In this case study, the patient received 38 cycles of FOLFOX and OIIS developed at 5th cycles of the third rechallange with of FOLFOX.

OIIS includes various clinical presentations, such as thrombotic microangiopathies (TMA), Evan's syndrome, immune hemolytic anemia, and acute immune thrombocytopenia [3]. The initial clinical symptoms and laboratory findings of the patient in this study were suggestive of acute intravascular hemolytic anemia. He was diagnosed with acute autoimmune hemolytic anemia based on the positive results of the direct and indirect antiglobulin tests. Initially, thrombotic microangiopathy (TTP) was suspected because of a neurological abnormality with a mental status change. However, the peripheral blood smear test did not reveal schistocytes, which are typical of MAHA. In addition, the ADAMTS-13 activity moderately decreased to 33%, but did not reach the diagnostic criteria for TTP (<10%) [12].

It is important to recognize the early signs and symptoms of OIIS. A systemic reviews of 61 patients with OIIS revealed that there were four lethal cases [3]. There are no consensus guidelines for the management of OIIS. The administration of oxaliplatin should be immediately suspended, and aggressive symptomatic managements should be initiated base on the clinical presentations. The administration of steroids is the treatment of choice for autoimmune hemolytic anemia [13]. Hemolysis-induced acute kidney injury is treated with hemodialysis [7, 8]. The patient in this study was successfully treated with intravenous steroids and hemodialysis. He initially underwent plasm exchange with fresh frozen plasma because of the suspicion of TTP. Although it was unclear whether plasma exchange was effective, the patient's neurological symptoms and coagulopathies were resolved after receiving plasma exchange. Plasma exchange is applied to immune-related drug-induced TMA [14]. Oxaliplatin should not be readministered for patients who develop OIIS.

Conclusion

OIIS is an uncommon but potentially lethal side effect associated with oxaliplatin. This syndrome is suspected when acute immune hemolytic anemia, thrombocytopenia, and/or acute kidney injury occur during oxaliplatin infusion. The management of OIIS required the suspension of oxaliplatin and symptomatic treatment including steroids, hemodialysis, and plasma exchange. OIIS frequently occurs with long-term exposure or rechallange with oxaliplatin.

Competing Interests: None

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