Clinical Oncology: Case Reports

Case Reports

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Oxaliplatin-induced Disseminated Intravascular Coagulation. Case report and literature review

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Abstract

Oxaliplatin is a platinum-based chemotherapy drug used to treat colorectal cancer and other gastrointestinal malignancies. It can cause a wide range of common adverse reactions and hematologic adverse events have been described occasionally. Their suspicion is paramount for a proper diagnosis. In this case report, we present the case of a 54-year-old female who developed Disseminated Intravascular Coagulation (DIC) after oxaliplatin infusion. She was receiving FOLFOX chemotherapy for the treatment of metastatic anal canal cancer.

Keywords: Adverse reaction; Disseminated intravascular coagulation; FOLFOX; Hematologic; Oxaliplatin

Introduction

Oxaliplatin is a chemotherapy drug commonly used to treat advanced colorectal cancer and other gastrointestinal malignancies as well as refractory lymphomas. However, it can cause a wide range of adverse reactions, including nausea, vomiting, diarrhea, myelosuppression (particularly neutropenia and thrombocytopenia), and mucositis [1]. In some cases, oxaliplatin can also induce other rare hematologic adverse events, such as Thrombotic Micro Angiopathy (TMA) and Disseminated Intravascular Coagulation (DIC) [2]. DIC is a serious condition in which the body's clotting system becomes overactive leading to the formation of small blood clots throughout the body. They can block blood flow to vital organs and consume clotting factors causing systemic haemorrhages. In this case report, we present the case of a 54-year-old female who developed DIC induced by oxaliplatin.

Case Presentation

We present a fifty-four-year-old female with no significant medical comorbidities and functionally independent for activities of daily living. She has a previous medical history of chronic hepatitis C virus infection without liver dysfunction, which was regularly monitored at the hospital, a discopathy in the dorsolumbar spine and uterine leiomyomas for which she underwent hysterectomy and bilateral adnexectomy 10 years-ago.

Nine years ago on October 2014, the patient was diagnosed with Squamous Cell Carcinoma of the Anal Canal at clinical stage cT3N0. The initial treatment approach involved a combination of intravenous chemotherapy (cisplatin 70 mg/m2 and 5-Fluoro Uracil (5-FU) 3000 mg/m^2 for two cycles) and concomitant radiotherapy (60 Gy). A biopsy was done on march 2015 that was positive for disease persistence. Pelvic magnetic resonance suggested also disease persistence. An abdominal-perineal resection was planned but patient denied surgery. In February 2016, a CT showed progressive metastatic spread with pathological retroperitoneal lymph nodes. She received first-line treatment for advance disease with 11 cycles of FOLFOX6 (folinic acid 400 mg/m^2, oxaliplatin 85 mg/m^2, 5-FU 400 mg/m^2 bolus and 5-FU 2400 mg/m^2 continuous infusion over 46 hours). Approximately two years later, there was further progression of the disease in the lymph nodes, prompting the patient to undergo a second line of 11 cycles of FOLFOX6 chemotherapy. One year later, the disease once again exhibited lymphatic progression and the patient was included in a clinical trial with retifanlimab, a PD-1 inhibitor agent with partial response, during 2 years. Then, due to a new progression on lymph nodes and bone, fourth-line chemotherapy with carboplatin AUC (Area Under the drug concentration Curve): 5 and paclitaxel 80 mg/m^2 was initiated, resulting in partial response.

In December 2022, the patient showed recurrent lymph node progression and a fifth-line treatment was initiated using again the FOLFOX6 chemotherapy regimen. Prior to initiation of the 8th cycle of FOLFOX6, the patient's White Blood Cells count (WBC) was 8.3 x 109/L (Reference Values (RV): 4.5-11 x 109/L), Haemoglobin (Hb) 10.3 g/dL (RV: 12-16 g/dL), platelet count of 139 x 109/L (RV: 150 – 400 x 109/L) and normal liver and renal function with a bilirubin level of 0.2 mg/dL (RV: 0.1 - 1.2 mg/dL) and a serum creatinine of 0.93 mg/dL.

She was admitted at clinics to receive the 8th cycle of FOLFOX. Oxaliplatin was administered without incidence and while the patient was receiving the 5-FU she developed sudden febrile syndrome, reaching temperatures of up to 38.5ºC, along with severe chills and haematuria. She was transferred to the emergency department. On examination, the patient was hemodynamically stable, tachycardic, eupnoeic, and febrile.

The results of laboratory analysis conducted 1 hour after the onset of clinical symptoms indicated a worsening in the renal function with a serum creatinine of 1.4 mg/dL, leucocytosis of 42.6 x 109/L, a decrease in Hb to 8.9 g/dL, and mild thrombocytopenia (134 x 109/L platelets). It was at this point that the administration of 5-FU was immediately discontinued and empiric antibiotic therapy with intravenous meropenem was initiated while awaiting the results of culture tests. Eight hours later, laboratory tests confirmed leucocytosis (36.3 x 109/L), worsened anaemia (Hb level of 8.2 g/L), and thrombocytopenia (90 x 109/L). Renal function further deteriorated, showing a serum creatinine of 1.89 mg/dL, and increased levels of bilirubin (2.7 mg/dL), Lactate De Hydrogenase (LDH) (3105 U/L (RV: 100–250 U/L)) and decreased haptoglobin (0.02 g/L (RV: 0.5-2.2 g/L), suggestive of haemolytic anaemia, were observed. Prothrombin Time (PT) and activated Partial Thromboplastin Time (aPTT) were 29.1 % and 39.0 s, respectively (RV: PT: 80-100%, PTT 23.5-32.2 s), INR was 2.40 (RV: <1.10), and plasma fibrinogen was low (0.6 g/L (RV: 1.5-4.5 g/L)). The peripheral smear showed noschistocytes. A urinary catheter was inserted, confirming gross haematuria without clots, with 200 red blood cells/ µL in the urinalysis.

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As part of the management plan, since findings were consistent with acute DIC, the patient was transferred to the Intensive Care Unit (ICU). At that moment, clinical pharmacists were consulted regarding the potential involvement of oxaliplatin based on the observed causality in the patient's acute disease onset. Consequently, the Naranjo algorithm was applied [3].

Forty hours after administering oxaliplatin, the patient continued to exhibit worsening of Hb levels (6.8 g/dL), requiring a transfusion of one pack of red blood cells and fibrinogen. It was also accompanied by a significant deterioration in renal function. A peak serum creatinine of 6 mg/dL was reached, so therapeutic renal support with intermittent haemodialysis was initiated. Finally, twenty-four hours after the transfusion and sixty-four hours later of oxaliplatin infusion, the patient's Hb increased to 8.8 g/dL with an improvement in the haemolysis pattern (LDH 834 U/L and normalization of bilirubin levels) and a rise in platelet count to 80 x 109/L. Thereafter, as depicted in Figure 1, both the platelet count and Hb values stabilized.

After five days under empirical treatment with meropenem therapy, and upon receiving negative culture results, antibiotic treatment was discontinued and the patient's clinical presentation was attributed to acute DIC.

Six days after admission at ICU, Hb, platelet and coagulation parameters were stabilized and the patient was discharged to a conventional hospitalization ward.

Twenty-seven days after the oxaliplatin administration, the patient was discharged home, with a serum creatinine value below 2 mg/dL (she required a total of 5 sessions of intermittent haemodialysis during hospitalization), stable Hb levels of 8 g/dL, platelets of 240 x 109/L, no signs of haemolysis and normal coagulation parameters. Finally, forty-two days after receiving oxaliplatin, the patient exhibited an Hb of 9.9 mg/dL in a routine follow-up, which is consistent with values prior to oxaliplatin administration.

In June 2023, a Magnetic Resonance Imaging (MRI) was performed to assess the patient's evolution, revealing the progression of bone metastases causing spinal cord compression despite the 5th line with FOLFOX. Due to the serious drug-related adverse reaction and the confirmation of disease progression, further oncological treatment was not considered. Instead, a surgical approach for spinal cord compression management and palliative radiotherapy was advised.

Discussion

DIC is a serious disorder characterized by the overactivity of proteins that control blood clotting. In DIC, blood clots form throughout the body, blocking small blood vessels. Clinical manifestations include chest pain, shortness of breath, leg pain, speech problems, and bleeding. DIC can occur as an acute complication in patients with severe sepsis, hematologic malignancies or severe trauma. The acute form of DIC develops quickly and is notably serious presenting initially blood clotting followed by bleeding, while the chronic form of DIC develops in a slower way and is more likely to present with thromboembolic complications [4].

After receiving oxaliplatin, the patient developed sudden fever and haematuria (attributed both to haemolysis), and laboratory tests consistent with DIC. It is important to note that in the previous treatment cycles, there were no incidents or signs of hypersensitivity reactions. Due to the clear temporal relationship between the oxaliplatin administration and the rapid resolution of the DIC pattern after discontinuing the treatment, it is highly probable that the DIC was induced by oxaliplatin.

Oxaliplatin is platinum-based chemotherapy with the indication for stage III colon cancer or anal squamous cell carcinoma [5]. It is typically administered in combination with fluorouracil and folinic acid in a regimen known as FOLFOX. Oxaliplatin induces the formation of platinated DNA adducts and then inhibits DNA synthesis and repair resulting in apoptosis [2].

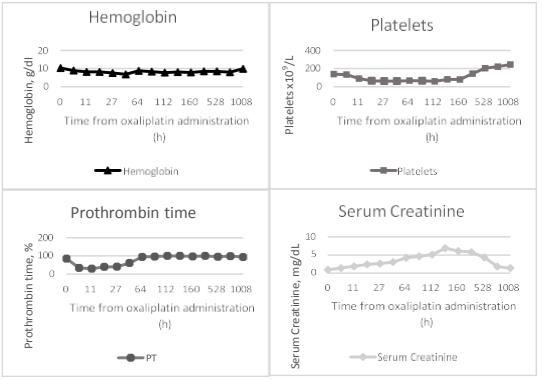

Figure 1. Evolution of hemoglobin, platelet, prothrombin time and serum creatinine values before and after oxaliplatin administration

While it is an effective treatment option, it can cause several hematologic adverse reactions including leukopenia, anemia, thrombocytopenia, and myelosuppression. One rare but life-threatening hematologic adverse reaction that has been associated with oxaliplatin treatment is DIC [6]. The diagnostic criteria for oxaliplatin-induced DIC are not well established due to the rarity of this complication. Therefore, DIC is diagnosed through clinical and laboratory findings, involving the identification of coagulopathy and/or fibrinolysis abnormalities within the relevant context. It is important to note that these laboratory findings are not specific to oxaliplatin-induced DIC, but should be suspected in individuals with unexplained low platelet count, reduced fibrinogen, elevated D-dimer, and prolonged prothrombin time [7]. Thus, a thorough evaluation of the patient's clinical history, physical examination, and laboratory tests are necessary to establish the diagnosis of oxaliplatin-induced DIC and to rule out other potential causes of DIC such as sepsis, malignancies, trauma, obstetric complications, and intravascular haemolysis among other conditions responsible for initiating and propagating the process [7]. Drugs have also been described as a cause of DIC. Bonaldo G et al.[6] conducted a pharmacovigilance study of reported drug-related DIC. Authors conclude that the most frequently reported cases were related with antineoplastic agents, followed by antithrombotic agents and antibacterials for systemic use. Particularly prominent among the frequently linked drugs were dabigatran, oxaliplatin, and bevacizumab.

A differential diagnosis was performed and both sepsis and malignancy were ruled out as causes of DIC in this patient. On the one hand, although the patient presented with an episode of fever, chills, and leukocytosis suggestive of sepsis at admission to hospital, care acute phase reactants such as C-reactive protein did not show a significant increase, and cultures obtained from urine and blood samples consistently came back negative. On the other hand, concerning the

malignancy, despite the patient had recently shown worsening and was on the fifth line of treatment, tests did not reveal extraordinary disease progression. Moreover, the episode was limited after oxaliplatin interruption.

Since drug-induced DIC was also feasible, the Naranjo Algorithm was applied to the two potential drugs administered (oxaliplatin and 5-FU) to assess the causality of the adverse reaction. The algorithm's outcome classified the reaction as possible (5 points) for 5-FU and probable (3 points) for oxaliplatin [3]. Therefore, considering the temporal association, as shown in Table 1; the strongest causal relationship with oxaliplatin based on the Naranjo algorithm, and the absence of reports regarding this reaction with 5-FU, the patient was diagnosed with oxaliplatin-induced DIC after ruling out other potential causes of DIC.

To date, oxaliplatin-induced DIC has been described in four case reports, all of them involving patients with metastatic colon cancer [8–11]. In the first case, a 66-year-old woman developed DIC and severe hematuria after several cycles of FOLFOX, indicating progressive hypersensitivity to oxaliplatin [8]. The second case involved a 76-year-old woman who experienced DIC and acute kidney injury during her sixth cycle of oxaliplatin and bevacizumab treatment [9]. In the third case, a 61-year-old man receiving FOLFOX with bevacizumab developed DIC and acute hemolysis after the 18th-cycle. He was able to tolerate additional chemotherapy cycles without oxaliplatin [10]. Finally, a fourth case featured a 71-year-old man treated successfully with an oxaliplatin-based regimen but experienced disease relapse after three years. Upon re-administration of oxaliplatin, he exhibited signs of an acute hypersensitivity reaction, eventually leading to DIC [11]. The mechanism underlying this reaction has been associated with an immune response mediated by antibodies [11]. The key features of the abovementioned case reports are summarized in Table 2.

	Reference values	24h before	8h after	11h after	20h after	40h[1] after	64h after	136h after	528h after	696h after[2]	1008h after
Haemoglobin, g/dL	12-16	10.3	8.9	8.2	7.6	6.8	8.8	7.9	8.5	8	9.9
Platelets x10^9/L	150 – 400	139	134	90	66	62	62	80	205	222	245
PT, %	80-100	-	34	29.1	39.4	60.9	94.4	100	95.2	98.6	93.6
aPTT, s	23.5 – 32.2	-	39.1	43.8	38.5	30.1	27.2	22.8	23.1	22.5	-
Fibrinogen, g/L	1.5 – 4.5	-			0.6	1.4					-
Serum creatinine, mg/dL	0.5 – 1.1	0.93	1.41	1.89	2.41	3.05	4.22	6.89	4.35	1.82	1.39
Haptoglobin, g/L	0.5 – 2.2	-	-	-	-	< 0.02	-	-	-	-	-
Lactate dehydrogenase, U/L	100 – 250	-	-	-	3567	1625	834	400	198	172	-
Urine RBC/µL	-	-	-	-	200	-	-	-	-	-	-

aPTT: activated Partial Thromboplastin Time; PT: Prothrombin Time; RBC: Red Blood Cells. 1After administration of one packed red blood cells and 3g fibrinogen. 2Pacient discharged home

Table 1: Laboratory tests before and after oxaliplatin administration.

The therapeutic management of DIC focuses on identifying the underlying cause in order to eliminate the stimulus responsible for initiating ongoing coagulation and thrombosis, in addition to providing supportive measures such as hemodynamic or ventilatory support, red blood cell transfusions, and if required, renal support.

Other complicated and rare hematologic adverse reactions have also been described with oxaliplatin such as immune-mediated hemolytic anemia, immune thrombocytopenic purpura, and thrombotic thrombocytopenic purpura [12,13]. A four-fold higher risk of hypersensitive reactions to platinum drugs has been reported in patients with a history of previous hypersensitivity to chemotherapy, being carboplatin the most common drug within its class with an incidence of 46%, followed by oxaliplatin with an incidence of 15%. These reactions typically occur after 12 months from the initiation of platinum-based treatment and, within the treatment regimen, the reaction is more likely to appear after the 6th dose [14]. In our case, the patient had not shown previous hypersensitivity reactions to oxaliplatin. He received oxaliplatin-based regimens twice before the present episode and the adverse reaction occurred during the 8th dose of the FOLFOX regimen.

By presenting this case, we aim to highlight the value of vigilance for potential adverse reactions, especially in patients with prior exposure to oxaliplatin-based chemotherapy. Prompt recognition and appropriate management are critical in addressing DIC induced by oxaliplatin and optimizing patient outcomes.

Conclusion

This report describes a case of DIC, a rare but significant adverse response that causes extensive blood clotting, caused by oxaliplatin. Because there are no recognized diagnostic criteria, the diagnosis of this disorder depends on clinical evaluation, requiring a comprehensive exclusion of other possible causes such as sepsis or cancer. It was essential to corroborate the adverse reaction to oxaliplatin by using the Naranjo Algorithm to assess the causality of the reaction. Treatment withdrawal, supportive

measures, and close observation for possible consequences are all part of managing oxaliplatin-induced DIC. It is important to recognize this condition early and take necessary action to improve patient outcomes.

the patient's treatment regimen, which enhances our understanding of the therapeutic aspects.

	Patient Age	Cancer Type	Prior Treatments	Current treatment	Cycle of Oxaliplatin	Symptoms	Laboratory findings	Therapeutic Management
Kurian S. et al.[9]	66	Colon cancer	FOLFOX, FOLFIRI, Cetuximab + rinotecan	FOLFOX6 bevacizumab	3rd	Gross hematuria	Anemia, thrombocytopenia low fibrinogen, increased Dimer D and LDH.	Supportive care, requiring RBC transfusion
Meng L et al.[10]	76	Metastatic colorectal cancer	None	FOLFOX + bevacizumab	6th	Nausea, emesis, back pain, and hematuria	Increased LDH, immune hemolitic anemia, trombocitopenia and AKI.	Corticoids and CRRT.
Malkhasyan K et al.[11]	61	Metastasic colon cancer	None	FOLFOX6 + bevacizumab	18th	Rigors, fever, gingival bleeding	Elevated PT and PTT, decreased fibrinogen, elevated dimer-D. Hemolytic anemia and trombocitopenia	Administration of 10 units of cryoprecipitate and 3 units of RBC.
Waddle M et Al.[2]	71	Metastasic colon cancer	FOLFOX, FOLFIRI	FOLFOX + Ramucirumab	1st	Burning sensation, dyspnea, tongue edema	Elevated PT, INR, aPTT, and Dimer-D. AKL.	Supportive care, 3 units of RBC, 1 unit of platelets and hydration.

AKI: Acute Kidney Injury; aPTT: activated Partial Thromboplastin Time; CRRT: Continuous Renal Replacement Therapy; LDH: Lactate Dehydrogenase; FOLFIRI: Bevacizumab, Irinotecan, Fluorouracil and folinic acid; FOLFOX: Oxaliplatin, Fluorouracil and Folinic acid; INR: International Normalized Ratio; PT: Prothrombin Time; RBC: Red Blood Cells.

Table 2: Summary of relevant findings of oxaliplatin induced DIC cases reported in literature.

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