Title: Severe AKI induced by Oxaliplatin: A case report

Running title: Severe AKI induced by Oxaliplatin

Type: Case report

Authors:

Essraa Tala Kouma, Ghufran Abdulrahman Emamaddin, Abdullah Almalki

Affiliation:

Nephrology Department of Medicine, King Abdulaziz Medical City, National Guard Hospital Jeddah, Saudi Arabia

Corresponding author

Essraa Tala Kouma

Nephrology Department of Medicine, King Abdulaziz Medical City, National Guard Hospital Jeddah, Saudi Arabia

Email: izra_1990@hotmail.com
Abstract:

**Background:** Oxaliplatin is used to treat colorectal cancer, and it can be used in combinations with other therapy. Although it is widely used and potentially improves the response and survival rates, it has several side effects. With the increasing use of oxaliplatin, many acute kidney injury (AKI) cases have been reported.

**Case presentation:** Here we report a case of severe AKI after receiving the FOLFOX regimen to treat colorectal cancer. Our patient is a 54-years old male admitted with oliguria after several courses of chemotherapy for metastatic colorectal adenocarcinoma to lung, left kidney, and retroperitoneal mass. He required four hemodialysis sessions; then, his urine output started to improve, and his renal function.

**Conclusion:** Finally, kidney function returned to baseline by six weeks.

**Keywords:** Acute Kidney Injury, Acute Tubular Necrosis, Oxaliplatin.
**Introduction:**

Oxaliplatin is a platinum analog of the third generation with 1,2-diaminocyclohexane substituting the amine group of cisplatin. Oxaliplatin is used widely to treat metastatic colorectal cancer [1], pancreatic and stomach cancers. The combination of oxaliplatin with 5-fluorouracil or capecitabine potentially improves the response and survival rates [2]. Oxaliplatin causes many adverse effects, including moderate myelotoxicity, cytopenia (neutropenia, anemia, and thrombocytopenia), nausea, vomiting, diarrhea, impaired liver function, and impaired kidney functions [3], such as acute kidney injury (AKI) [4], acute tubular necrosis (ATN) [5] and acute tubulointerstitial nephritis (ATIN). It carries a reduced risk of acute kidney injury (AKI) compared to the other platinum agents, including cisplatin and carboplatin [6]. Acute kidney injury (AKI) is a reduction in kidney function; it's a diagnosis based on acute decrease in the glomerular filtration rate (GFR), which is reflected by an acute elevation in the serum creatinine and a decline in urinary output in a given time interval [7]. This case report presents a patient diagnosed with dialysis-requiring AKI induced by oxaliplatin regimen for metastatic colorectal cancer.

**Case presentation:**

Our patient is a 54-years old male admitted with oliguria after several courses of chemotherapy for metastatic colorectal adenocarcinoma to lung, left kidney, and retroperitoneal mass. His past medical history is remarkable for deep vein thrombosis, pulmonary embolism, and prolonged standing hypertension. He is not known to have an allergy, and his medications include Amlodipine and Apixban. In 2019, apixaban was stopped by a hematologist due to severe epistaxis. In 2011, at the time of diagnosis, he underwent a left colon hemicolecetomy followed by eight cycles of XELOX. In 2015, he
had recurrent disease, and he was treated with 32 cycles of the FOLFIRI + Avastin regimen. Then he continued on 5FU (5-fluorouracil) for one year. In 2017, he had disease progression, and the FOLFIRI + Avastin regimen was resumed. In October 2019, he manifested further disease progression and was started on the FOLFOX + Cetuximab regimen; he received fifteen cycles which was later changed to FOLFOX + Avastin and received ten cycles.

Our case was presented on the 19th of Dec 2020 with a history of shortness of breath and decreased urine output for the last four days; another systemic review was unremarkable. Four days before the presentation (15th of Dec 2020), he had a cycle of chemotherapy FOLFOX regimen (Leucovorin, Fluorouracil, and Oxaliplatin) + Avastin. He denied receiving any new medications, including non-steroidal anti-inflammatory drugs (NSAIDs) or antibiotics, for the last 6 months. On examination, he was Afebrile, vitally stable Bp 125/65 with no postural hypotension and Pulse 70. He was conscious, oriented to time, place, and person. Not tachypneic or distressed. His chest was clear, his heart sounded normal, and his abdomen was not distended. There was no neurological deficit.

Laboratory investigations are as follows; CBC shows WBC 1.1 x10⁹/L, neutrophil count 0.21, Hgb 7.4 g/dL, plt 49 x 10⁹/L. Blood film marked leukopenia, moderate thrombocytopenia with no PLT clump and no schistocyte. Mild low levels of Haptoglobin 0.23 g/L, Retics 0.8 % (Normal), LDH 595 (high) unit/L, Bilirubin 20 μmol/L, Direct-bilirubin 11.3 μmol/L, creatinine 818 μmol/L with baseline (80-100 μmol/L), BUN 36.9 mmol/L, Na 121 mmol/L, K 4.4 mmol/L and CO 11 mmol/L. Full viral serology was negative and normal complement levels; C3 0.63, C4 0.28. Urine electrolyte sent by ER showed FeNa 22 and UNa 66. Urine analysis was Unspecific gravity 1.008, Ublood Mod, Uleukocyte -ve, UWBC –ve with scant RBC. Chest x-ray was unremarkable. He was admitted as a case of oligomeric AKI and pancytopenia. A full Septic screen was obtained, and results were negative. Renal ultrasound showed both Kidneys within the normal size with preserved corticomedullary differentiation and a mild increase in parenchymal echogenicity. The hypoechoic mass in the lower pole of the kidney appeared stable 4.1x 4.4 cm; no hydronephrosis or element of obstruction was observed (Figure1). A kidney biopsy was difficult to obtain because the patient was at high risk of bleeding.
On the day of admission, nephrology was consulted for AKI. Foley catheter inserted and started on sodium bicarbonate infusion. On the third day of admission, the patient was clinically unwell. His urine output didn’t improve with hydration, a temporary femoral line was inserted, and he received four hemodialysis sessions. Following that, his kidney function started to improve with increasing urine output and declining serum creatinine. Six weeks later, the kidney function recovered back to baseline serum creatinine (Table 1).

![Ultrasound images of the kidneys](image)

**Figure 1:** Ultrasound of the right and left kidneys

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BP mmHg</td>
<td>135/72</td>
<td>125-110 /65-60</td>
<td>140-120 /70-65</td>
<td>130-120 /65-60</td>
<td>109/73</td>
</tr>
</tbody>
</table>

**Table1:** Laboratory tests findings during several time intervals
<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>72</th>
<th>70-80</th>
<th>80-100</th>
<th>90-100</th>
<th>70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature C°</td>
<td></td>
<td>36.6</td>
<td>36.9</td>
<td>37.3</td>
<td>37.3</td>
<td>36.6</td>
</tr>
<tr>
<td>Sat %</td>
<td></td>
<td>100 on RA</td>
<td>98 on RA</td>
<td>98 on RA</td>
<td>97 on RA</td>
<td>99 on RA</td>
</tr>
<tr>
<td>UOP ml</td>
<td></td>
<td>NA</td>
<td>70</td>
<td>Nil</td>
<td>1900</td>
<td>NA</td>
</tr>
<tr>
<td>WCC x10⁹/L</td>
<td></td>
<td>4.4</td>
<td>1.1</td>
<td>1.1</td>
<td>6.2</td>
<td>6.2</td>
</tr>
<tr>
<td>Hgb (g/dL)</td>
<td></td>
<td>9.6</td>
<td>7.4</td>
<td>6.5</td>
<td>9.5</td>
<td>10.5</td>
</tr>
<tr>
<td>PLT x10⁹/L</td>
<td></td>
<td>92</td>
<td>61</td>
<td>41</td>
<td>208</td>
<td>193</td>
</tr>
<tr>
<td>Neut #</td>
<td></td>
<td>NA</td>
<td>0.14</td>
<td>0.07</td>
<td>2.3</td>
<td>NA</td>
</tr>
<tr>
<td>Eosinophil #</td>
<td>NA</td>
<td>0.17</td>
<td>0.12</td>
<td>0.61</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td></td>
<td>NA</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>NA</td>
</tr>
<tr>
<td>BG (mmol/L)</td>
<td></td>
<td>4.8</td>
<td>5.6</td>
<td>5.1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>BUN (mmol/L)</td>
<td></td>
<td>5.9</td>
<td>36.9</td>
<td>37.4</td>
<td>13.2</td>
<td>5.1</td>
</tr>
<tr>
<td>Cr (μmol/L)</td>
<td></td>
<td>100</td>
<td>818</td>
<td>1026</td>
<td>365</td>
<td>129</td>
</tr>
<tr>
<td>Na (mmol/L)</td>
<td></td>
<td>136</td>
<td>121</td>
<td>95</td>
<td>138</td>
<td>138</td>
</tr>
<tr>
<td>K (mmol/L)</td>
<td></td>
<td>3.8</td>
<td>4.4</td>
<td>126</td>
<td>4</td>
<td>4.3</td>
</tr>
<tr>
<td>Co2 (mmol/L)</td>
<td></td>
<td>17</td>
<td>11</td>
<td>13</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Cl (mmol/L)</td>
<td></td>
<td>110</td>
<td>96</td>
<td>95</td>
<td>105</td>
<td>106</td>
</tr>
<tr>
<td>Po4 (mmol/L)</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>1.17</td>
<td>0.99</td>
<td>1.18</td>
</tr>
<tr>
<td>Adjusted Ca (mmol/L)</td>
<td></td>
<td>2.14</td>
<td>NA</td>
<td>1.7</td>
<td>2.17</td>
<td>2.34</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td></td>
<td>31</td>
<td>27</td>
<td>22</td>
<td>22</td>
<td>32</td>
</tr>
<tr>
<td>ALT U/L</td>
<td></td>
<td>22</td>
<td>32</td>
<td>20</td>
<td>16</td>
<td>NA</td>
</tr>
<tr>
<td>AST U/L</td>
<td></td>
<td>25</td>
<td>23</td>
<td>14</td>
<td>49</td>
<td>NA</td>
</tr>
<tr>
<td>T.bili (μmol/L)</td>
<td></td>
<td>12.8</td>
<td>18.3</td>
<td>19.2</td>
<td>21.7</td>
<td>NA</td>
</tr>
</tbody>
</table>
Discussion:

We present a case of reversible AKI where oxaliplatin seemed to cause ATN combined with concomitant cytopenia. However, kidney dysfunction is not common with the use of oxaliplatin. Repeated exposure to oxaliplatin causes AKI in most cases. Most cases develop AKI after multiple sessions, not from the first session. It was reported in a previous study conducted to examine the pharmacokinetics of oxaliplatin, that the clearance of oxaliplatin occurs mainly through the renal mechanism with no increased toxicity [8]. After the administration, oxaliplatin is localized in the vascular basolateral membrane and is actively transported by human organic cation transporter 2, which mediate the drug uptake into the kidney [6]. Oxaliplatin is strongly susceptible to cellular transport through MATE2-K on the brush border membrane. It is supposed that nephrotoxicity is weak due to low tissue accumulation in the renal tubular epithelial cells [4,9,10]. The nephrotoxicity of oxaliplatin develops due to the repeated exposure [6], which was evident in our case, that using the FOLFOX regimen including Oxaliplatin resulted in the development of AKI as he received more than ten cycles.

In a previous case report of oxaliplatin-induced AKI received FOLFOX chemotherapy for 13 cycles, the patient had acute kidney injury (creatinine 1072 μmol/L, from a baseline in the 80s). The patient remained oliguric not responding to intravenous fluid. Hemodialysis was initiated for him, and a renal biopsy was obtained, revealing severe ATN. He gradually recovered by one month, and his creatinine was back to baseline [11]. Naill firewood and Mark Lipman reviewed 10 cases reported as AKI secondary to oxaliplatin. They found half of them had severed AKI, which required HD, and 8 out of 10 had a full renal recovery, as shown in (Figure 2) [11].

**Figure 2:** Previously reported cases of acute kidney injury after oxaliplatin administration [11]
Our patient was at risk of bleeding in the present case, so he didn't perform a biopsy. However, the US showed a mild increase in parenchymal echogenicity of the kidney. Urine electrolyte showed high FeNa and high UNa at presentation goes with ATN. Also, urine analysis and microscopy didn’t show WBC cast or eosinophilic, which goes against ATIN. Our patient was diagnosed with AKI (ATN). He was started on NaCHO3 infusion. However, the oliguria wasn't improved with hydration, and hemodialysis therapy was initiated on the third day. After four sessions of hemodialysis, his urine output and renal function started to improve. Six weeks later, he returned to the baseline.

His pancytopenia was observed. There were no signs of hemolysis as relics count was average and bilirubin within normal range. We considered this cytopenia is due to chemotherapy. However, it was dramatically improved after the discontinuation of the administration of the chemotherapy. The hematological analysis showed thrombocytopenia and anemia; thrombocytopenia and hemolytic anemia were reported in many studies associated with oxaliplatin [12]. Cytopenia mechanism is suggested to include the production of anti-red blood cells, anti-platelet antibodies, and thrombotic microangiopathy via endothelial dysfunction [13]. Our case was tested for a complement which is part of the innate immune system. Its major function is the recognition and elimination of pathogens via direct killing or stimulation of phagocytosis. Activation of the complement system is involved in the pathogenesis of systemic autoimmune diseases. The results showed normal C3 and C4 reflecting no auto-immune etiology of the
cytopenia, supporting that it may be associated with repeated exposure to oxaliplatin. Cytopenia is dramatically improved after cessation of oxaliplatin administration [6].

A similar case was reported from Japan, where a woman with an age match to our case was treated with 34 cycles of FOLFOX. She required plasmapheresis and HD as a treatment for AIH with AKI (ATN) based on presentation urine volume, high FeNa, high FeUrea & urine sediments which revealed granular cast with a small number of WBC [4]. Another cause of a man who presented with a history of fever, shivering, and hot flashes treated with a-5flourouracil/ Leucovorin/oxaliplatin was severe renal dysfunctions on the 4th day after the 18 cycles of administration. He was admitted and diagnosed based on renal biopsy with acute tubulointerstitial nephritis [6]. The patient underwent a renal biopsy and was diagnosed with acute tubulointerstitial nephritis (ATIN) [6]. It was reported that oxaliplatin clearance occurs mainly through the kidney with no increased toxicity [8]. Pinotti has suggested that the renal damage could have been caused by the cumulative dose of oxaliplatin [14].

Our case and the other cases reported that the kidney was affected by the prolonged administration of oxaliplatin and different chemotherapy combinations. So further investigations should be conducted to determine the cause of this toxicity that occurred to the kidney.

**Conclusion:**

The repeated exposure to oxaliplatin in combination with 5-FU and LV resulted in kidney adverse effects, represented as AKI, that may require hemodialysis to be resolved.

**List of abbreviations:**

AKI Acute kidney injury
ATIN Acute tubulointerstitial nephritis
ATN Acute tubular necrosis
BP Blood pressure
CBC Complete blood count
GFR Glomerular filtration rate
HD Hemodialysis
Hgb Hemoglobin

HR Heart Rate

LDH Lactate Dehydrogenase

NSAIDs Non-steroidal anti-inflammatory drugs

PLT Platelets

WBC White blood cell

**Conflict of interest:**

The authors declare that there is no conflict of interest regarding the publication of this case report.

**Funding:** None.

**Consent to participate:**

Informed consent was obtained from the participant.

**Ethical approval:** Ethical approval is not required at our institution for an anonymous case report.

**References:**


9- Yonezawa A, Masuda S, Yokoo S. Cisplatin and oxaliplatin, but not carboplatin and nedaplatin, are substrates for human organic cation transporters (SLC22A1-3 and multidrug and toxin extrusion family). J Pharmacol Exp Ther. 2006;319:879-86. https://doi.org/10.1124/jpet.106.110346


