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Clinical Report

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Severe acute tubular necrosis observed subsequent to oxaliplatin administration

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Abstract
A 67-year-old man known for metastatic colon cancer received treatment with oxaliplatin and developed severe acute kidney injury requiring dialysis. Renal biopsy revealed severe acute tubular necrosis. Acute kidney injury is a rare but severe adverse effect of oxaliplatin administration.

Keywords: AKI; ATN; dialysis; oxaliplatin

Background

Oxaliplatin is a chemotherapeutic agent used for the treatment of colon cancer. It has been in use for over a decade and is generally well tolerated. The drug does not commonly cause renal insufficiency [1]. However, oxaliplatin may rarely result in acute tubular necrosis (ATN) [2], renal tubular acidosis [3, 4] and hemolytic anemia with subsequent renal failure [5]. We present a case of severe ATN observed subsequent to oxaliplatin administration.

Case report

Our patient was a 67-year-old man known for colon adenocarcinoma, for which he received FOLFOX chemotherapy (leucovorin, fluorouracil, and oxaliplatin, 13 cycles) and radiation before undergoing surgery. Three years later, he was treated for two small spinal metastases, receiving 2 years of A-FOLFIRI (bevacizumab, leucovorin, fluorouracil, irinotecan), and a further 6 months of bevacizumab and capecitabine. FOLFOX was restarted in September 2012; a first cycle was well tolerated. During the second cycle, however, shortly after the start of the oxaliplatin infusion, the patient became flushed and complained of chest tightness. The infusion was stopped and these symptoms subsided; when the infusion was restarted 30 min later, they quickly recurred. Oxaliplatin was stopped and the patient received the remainder of his leucovorin and fluorouracil infusions without incident. He denied taking other medications.

Four hours after receiving oxaliplatin, Mr G. voided dark urine which was positive for blood on dipstick. The following day, at home, he became oliguric. He then began to pass bright red blood per rectum. He presented to hospital 3 days after his chemotherapy.

At presentation he had acute kidney injury (creatinine 1072 μmol/L, from a baseline in the 80s). He remained oliguric in response to intravenous fluid administration and hemodialysis was initiated in due course. He had a new normocytic anemia (Hb 123 g/L, previously 144 g/L) and was thrombocytopenic (platelet count 27×10^9/L) and leukopenic (WBC 1.7×10^9/L). A peripheral blood smear revealed polychromatophilia, fragmented cells, burr cells and ovalocytes. Urine dipstick revealed 5 g/L of protein and was positive for blood. Haptoglobin was normal.

His lower GI bleeding continued and his hemoglobin fell to 80 g/L, necessitating transfusion. His absolute neutrophil count continued to decrease, and he was admitted to hematology for febrile neutropenia. Laboratory studies revealed a negative direct antiglobulin test. Haptoglobin, bilirubin and fibrinogen were normal. Anti-nuclear and anti-glomerular basement membrane antibodies were not detected. Screening for hepatitis B and C was negative. A renal biopsy was obtained, revealing severe ATN.

Subsequently, his blood counts recovered. After endoscopy his lower GI bleed was attributed to angiodysplasia at the anastomotic site of his prior bowel resection. Although he was initially dialysis dependent, he gradually recovered his renal function, and by 1 month post-discharge his creatinine had fallen to 97 μmol/L.

Discussion

Oxaliplatin-induced acute kidney injury is a rare event, with only 10 cases previously reported (Table 1). In six, hemolysis and a positive DAT suggested ATN as a consequence of immune-mediated hemolysis [2, 6–10], which has been described as a result of oxaliplatin-dependent anti-RBC antibodies [7, 8]. In the three cases where DAT was confirmed negative, renal biopsy was suggestive of ATN as a direct drug effect [11–13].

Table 1. Previously reported cases of acute kidney injury after oxaliplatin administration

Year	Authors	No. of cycles oxaliplatin previously received	Presenting symptoms	Hemoglobinuria?	Change in creatinine (mmol/L)	Change in hemoglobin (g/L)	Other markers of hemolysis	DAT positive?	Required dialysis?	Outcome (renal function only)	Pathologic diagnosis
2002	Pinotti *et al.*	16	Abdominal pain, fever	Yes	⇑ 7.3 mg/dL	NA	NA	NA	No	Recovered	ATN
2005	Labaye *et al.*	10	NA	NA	73 ⇑ 1126	⇓ 98	NA	No	Yes	Recovered	ATN
2006	Dahabreh *et al.*	4	Discolored urine	Yes	1.1 mg/dL ⇑ 3.1 mg/dL	138 ⇓ 120	Fragmented RBC, elevated LDH, elevated indirect bilirubin	No	No	Recovered	NA
2009	Phan *et al.*	5	Low back pain, dark urine, oliguria	NA	68 ⇑1078	142 ⇓ 107	Increased LDH, schiztocytes	No	Yes	Recovered	ATN
1999	Desrame *et al.*	41	Back pain, fever, chills, schleral icterus, dark urine	NA	⇑ 471	119 ⇓ 48	Elevated LDH, bilirubin, absent haptoglobin	Yes	Yes	No recovery	NA
2003	Hofheinz *et al.*	5	Dark urine, jaundice	NA	⇑ 631	104 ⇓ 67	Elevated LDH	Yes	No	Recovered	NA
2007	Cobo *et al.*	14	Low back pain, dark urine, oliguria	Yes	1.5 ⇑ 7.5 mg/dL	123 ⇓ 84	Elevated LDH	Yes	No	Recovered	NA
2007	Buti *et al.*[a]	10	NA	NA	⇑ 7.08 mg/dL	112 ⇓ 86	NA	Yes	NA	NA	NA
2010	Ulusakarya *et al.*	12	Abdominal pain, fever, chills	Yes	⇑ 359	128 ⇓ 113	Haptoglobin decreased, LDH increased	Yes	Yes	Recovered	NA
2012	Ito *et al.*	33	Back pain	Yes	0.65 ⇑ 8.8 mg/dL	82 ⇓ 56	Low haptoglobin, elevated LDH	Yes	Yes	Recovered	NA

Cases are divided on the basis of direct antigen test result; highlighted cases are those in which pathological diagnosis was obtained.
NA, not available; RBC, red blood cells.
[a]Abstracted from another reference.

ATN via direct tubular toxicity is most consistent with the laboratory and pathological findings in this case. We believe this to be the fourth case of biopsy-proven ATN as a consequence of oxaliplatin-mediated tubular toxicity.

In common with previously reported cases, our patient eventually recovered the majority of his renal function. In contrast to previously reported cases, our patient was found to be glucose-6-phosphate dehydrogenase deficient. The G6PD deficiency in our patient could potentially have provided an alternative mechanism for hemolysis-induced ATN but the normal serological markers of hemolysis do not support this possibility. It is also unclear whether our patient's prolonged exposure to oxaliplatin placed him at a higher risk of AKI—while prolonged exposure has been implicated as a risk factor for oxaliplatin-dependent immune-mediated hemolysis, previously reported cases of oxaliplatin-induced ATN have been observed after as few as four cycles of treatment [9, 11, 14].

Oxaliplatin-induced ATN is thus a rare but serious complication of the commonly used FOLFOX chemotherapy regimen. Oncologists and nephrologists should be aware of this dramatic adverse effect of oxaliplatin administration.

Conflict of interest statement. None declared.

References

1. Extra JM, Espie M, Calvo F *et al*. Phase I study of oxaliplatin in patients with advanced cancer. *Cancer Chemother Pharmacol* 1990; 25: 299–303
2. Ito I, Ito Y, Mizuno M *et al*. A rare case of acute kidney injury associated with autoimmune hemolytic anemia and thrombocytopenia after long-term usage of oxaliplatin. *Clin Exp Nephrol* 2012; 16: 490–494
3. Linch M, Cunningham D, Mingo O *et al*. Renal tubular acidosis due to oxaliplatin. *Ann Oncol* 2007; 18: 805–806
4. Negro A, Grasselli C, Galli P. Oxaliplatin-induced proximal renal tubular acidosis. *Intern Emerg Med* 2010; 5: 267–268
5. Noronha V, Burtness B, Murren J *et al*. Oxaliplatin induces a delayed immune-mediated hemolytic anemia: a case report and review of the literature. *Clin Colorectal Cancer* 2005; 5: 283–286
6. Buti S, Ricco M, Chiesa MD *et al*. Oxaliplatin-induced hemolytic anemia during adjuvant treatment of a patient with colon cancer: a case report. *Anticancer Drugs* 2007; 18: 297–300
7. Cobo F. Oxaliplatin-induced immune hemolytic anemia: a case report and review of the literature. *Anticancer Drugs* 2007; 18: 973
8. Desrame J, Broustet H, de Tailly PD *et al*. Oxaliplatin-induced haemolytic anaemia. *Lancet* 1999; 354: 1179–1180
9. Hofheinz RD, Nguyen XD, Buchheidt D *et al*. Two potential mechanisms of oxaliplatin-induced haemolytic anaemia in a single patient. *Cancer Chemother Pharmacol* 2004; 53: 276–277
10. Ulusakarya A, Misra S, Haydar M *et al*. Acute renal failure related to oxaliplatin-induced intravascular hemolysis. *Med Oncol* 2010; 27: 1425–1426
11. Dahabreh I, Tsoutsos G, Tseligas D *et al*. Hemolytic uremic syndrome following the infusion of oxaliplatin: case report. *BMC Clin Pharmacol* 2006; 6: 5
12. Labaye J, Sarret D, Duvic C *et al*. Renal toxicity of oxaliplatin. *Nephrol Dial Transplant* 2005; 20: 1275–1276.
13. Pinotti G, Martinelli B. A case of acute tubular necrosis due to oxaliplatin. *Ann Oncol* 2002; 13: 1951–1952
14. Phan NT, Heng AE, Lautrette A *et al*. Oxaliplatin-induced acute renal failure presenting clinically as thrombotic microangiopathy: think of acute tubular necrosis. *NDT Plus* 2009; 2: 254–256

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