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 × 10⁹/L) and leukopenic (WBC 1.7 × 10⁹/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].
| Year | Authors          | No. of cycles | 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             | NA                          | NA                      | NA                                          | NA            | No               | Recovered                    | ATN                 |
| 2005 | Labaye et al.    | 10            | NA                                   | NA              | NA                          | NA                      | NA                                          | NA            | No               | Recovered                    | ATN                 |
| 2006 | Dahabreh et al.  | 4             | Discolored urine                      | Yes             | 1.1 mg/dL                   | 3.1 mg/dL               | Fragmented RBC, elevated LDH, elevated indirect bilirubin | No            | No               | Recovered                    | NA                  |
| 2009 | Phan et al.      | 5             | Low back pain, dark urine, oliguria   | NA              | 68 g/L                      | 107 g/L                 | Increased LDH, schizocytes                   | No            | Yes              | Recovered                    | ATN                 |
| 1999 | Desrame et al.   | 41            | Back pain, fever, chills, sclerical icterus, dark urine | NA              | 471 mg/dL                   | 119 g/L                 | Elevated LDH, bilirubin, absent haptoglobin | Yes           | Yes              | No recovery                  | NA                  |
| 2003 | Hofheinz et al.  | 5             | Dark urine, jaundice                  | Yes             | 631 mg/dL                   | 104 g/L                 | Elevated LDH                               | Yes           | No               | Recovered                    | NA                  |
| 2007 | Cobo et al.      | 14            | Low back pain, dark urine, oliguria   | Yes             | 1.5 g/L                     | 123 g/L                 | Elevated LDH                               | Yes           | No               | Recovered                    | NA                  |
| 2007 | Buti et al."   | 10            | NA                                   | Yes             | 7.08 mg/dL                  | 112 g/L                 | Haptoglobin decreased, LDH increased         | Yes           | NA               | NA                           | NA                  |
| 2010 | Ulusakarya et al.| 12            | Abdominal pain, fever, chills         | Yes             | 359 mg/dL                   | 128 g/L                 | Low haptoglobin, elevated LDH                | Yes           | Yes              | Recovered                    | NA                  |
| 2012 | Ito et al.       | 33            | Back pain                            | Yes             | 0.65 mg/dL                  | 82 g/L                  | NA                                          | NA            | NA               | NA                           | 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.
"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.

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Received for publication: 21.10.13; Accepted in revised form: 19.11.13