A case of biopsy-proven oxaliplatin-induced acute tubulointerstitial nephritis with thrombocytopenia and anemia

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Abstract

Oxaliplatin, a third-generation platinum agent, has been used for the treatment of colon, pancreatic, and stomach cancers in recent years. It carries a reduced risk of acute kidney injury (AKI) compared to the previous platinum agents, including cisplatin and carboplatin. Several cases of oxaliplatin-induced acute tubular necrosis (ATN) have been reported; however, only one case has been reported as acute tubulointerstitial nephritis (ATIN) histopathologically. Here, we present a case of biopsy-proven and dialysis-dependent ATIN, which dramatically resolved with steroid therapy. The patient was a 67-year-old male who had undergone chemotherapy for colon adenocarcinoma. He suddenly developed shaking chills, fever, and hot flashes at the end of the 18th 5-fluorouracil (5-FU)/L-leucovorin/oxaliplatin administration, and was admitted to our hospital. On the 4th day of hospitalization, severe renal dysfunction (creatinine 6.5 mg/dL) was observed. As oliguria continued, we initiated hemodialysis therapy on the 6th day of hospitalization. Drug-induced ATIN was strongly suspected due to the history of multiple exposures to oxaliplatin with allergic reaction and sterile pyuria. We began steroid therapy on the 8th day of hospitalization. Subsequently, renal biopsy was performed and the diagnosis of ATIN was made. The patient's renal function gradually improved, and 6 months later, it had returned to baseline. Our case demonstrates that we should consider not only ATN, but also ATIN, as potential presentations of oxaliplatin-induced AKI.

Keywords Oxaliplatin · Platinum agent · Acute interstitial nephritis · Drug-induced acute kidney injury

Introduction

Oxaliplatin is one of the third-generation platinum agents, developed after cisplatin and carboplatin. Oxaliplatin has been used for the treatment of colon, pancreatic, and stomach cancers in recent years [1]. Although the most common side effect is peripheral neuropathy [2, 3], with increasing use of oxaliplatin, there have been an increasing number of acute kidney injury (AKI) cases reported. The pathogenesis in most cases of oxaliplatin-induced AKI is acute tubular

necrosis (ATN) confirmed by renal biopsy [4–7]; only one case was reported as acute interstitial nephritis (AIN) histopathologically [8]. Here, we report a case of AKI after repeated doses of oxaliplatin diagnosed as acute tubulointerstitial nephritis (ATIN) by renal biopsy, accompanied by cytopenia (thrombocytopenia and anemia), both of which dramatically improved after steroid therapy.

Case report

The patient was a 67-year-old male who was admitted with fever after several courses of chemotherapy for colon adenocarcinoma. His past medical history included atrial fibrillation and severe mitral valve stenosis status post-mitral valve replacement surgery; he had no history of allergy. His medications included warfarin, aspirin, lansoprazole, bisoprolol, prochlorperazine, alprazolam, digoxin, and duloxetine; there were no changes or new medications, including non-steroidal anti-inflammatory drugs (NSAIDs) or antibiotics,

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during the 6 months prior to his presentation. Lower front anterior resection was performed for rectal cancer 3 years and 7 months prior with P stage (pathologic stage) as IIIa. Liver metastasis was diagnosed 2 years and 9 months prior, and he received chemotherapy consisting of 5-fluorouracil (5-FU)/L-leucovorin/oxaliplatin (mFOLFOX) + cetuximab (eight times). The liver metastasis was resected 2 years and 1 month prior, and a total of six doses of mFOLFOX were administered in the 2 months prior to admission. He was diagnosed to be at stage IV of colon cancer caused by liver metastasis at this point.

The patient's clinical course is shown in Fig. 1 and Table 1. The patient developed shaking chills, fever, and hot flashes at the end of the 18th mFOLFOX administration, and he was admitted our hospital on an urgent basis. Renal dysfunction developed and gradually worsened after admission, and on the 4th day of hospitalization, nephrology consultation was requested due to the concern for AKI. Urinalysis at that time showed pyuria [10–19/high power field (HPF)], non-glomerular hematuria (100 or more/HPF), nephrotic-range proteinuria [13.6 g/gram creatinine (gCr) in total and 7.4 g/gCr as albuminuria], and elevated renal tubular damaged markers (NAG (*N*-acetyl- β -D-glucosaminidase) 25.5 U/L (normal range 0.7–11.2 U/L), β 2-microglobulin 13,730 μ g/L (normal range under

230 μ g/L), α 1-microglobulin 19.9 mg/L (normal range 9.7–19.9 mg/L), and L-FABP (liver-type fatty acid-binding protein) 39.2 μ g/gCr). Urine and blood cultures were negative. Serological examination showed an elevated IgG level (1816 mg/dL) without M-peak, abnormal distribution of free light chains (kappa and lambda), and normal IgA/IgM. Urinary Bence-Johns protein and cryoglobulin were absent. Complement levels (C3, C4), MPO/PR3-ANCA, and anti-nuclear antibody were also negative. Tuberculosis, HBV, HCV, and HIV testing were also negative. Computed tomography and abdominal echography did not show any findings related to post-renal causes of AKI including hydronephrosis, nor significant renal atrophy. Drug lymphocyte stimulation test (DLST) for oxaliplatin, gallium scintigraphy, and urine eosinophil count was all negative. Blood pressure was stable without a significant hypo- or hypertension and the patient appeared euvolemic by physical examination and laboratory testing. At consultation, significant renal dysfunction (Cr 6.5 mg/dL), anemia (9.5 g/dL), and thrombocytopenia ($38 \times 10^3/\mu$ L) were observed (Table 1).

Although ATN as a common etiology of oxaliplatin-induced AKI was considered, drug-induced ATIN was also suspected due to the history of multiple exposures to oxaliplatin, appearance of allergic symptoms including rash and fever after its administration, and repeated detection of sterile pyuria. Since oliguria continued, we initiated hemodialysis therapy on the 6th day of hospitalization. In addition, 30 mg of prednisolone (PSL) (0.5 mg/kg body weight) was administered beginning on the 8th day of hospitalization. On the 18th hospital day, his urine output started to improve, and hemodialysis was discontinued. After improvement of his platelet count ($100 \times 10^3/\mu$ L or greater), transcutaneous kidney biopsy was performed on the 17th hospital day. Kidney biopsy revealed global sclerosis in 6 out of 22 glomeruli and moderate to severe tuft collapse without proliferative changes. There was no evidence of thrombotic microangiopathy in the glomeruli or arterioles. On Masson-trichrome staining, 30% of tubulointerstitial injuries were observed. Interstitial cellular infiltrations consisting of lymphocytes and numerous eosinophils were observed (Fig. 2a). Mild renal tubulitis was observed (Fig. 2b). Nuclear irregularities were found in some renal tubular epithelial cells (Fig. 2c). In addition, some tubular epithelial cells showed vacuolization (Fig. 2d). In the electron microscopy findings, no foot process effacement, consequently supposed to be podocytopathy, was present despite high amount of proteinuria. Based on these findings, the patient was diagnosed with ATIN. In addition, due to the presence of tubular vacuolization [8, 9], the diagnosis of acute tubular injury (ATI) characteristic of platinum exposure was made. Serum creatinine, urinary tubular damage biomarkers, and other laboratory data showed improvement (Table 1). The steroid dose was gradually decreased and steroids were discontinued after 6 months. Ultimately, renal function was found to be completely restored

Fig. 1 Clinical course of present case. Clinical course of oxaliplatin-induced acute kidney injury. The patient developed shaking chills, fever, and hot flashes at the end of the 18th 5-fluorouracil (5-FU)/L-leucovorin/oxaliplatin (mFOLFOX) administration. Renal dysfunction gradually worsened after admission. Drug-induced acute tubular interstitial nephritis was suspected. Since anuria continued, we initiated hemodialysis therapy on the 6th day of hospitalization. In addition, 30 mg of prednisolone (0.5 mg/kg) was administered beginning on the 8th day of hospitalization. After improvement of his platelet count ($100 \times 10^3/\mu$ L or greater), transcutaneous renal biopsy was performed on the 17th hospital day. On the 18th hospital day, his urine volume was started to improve, and hemodialysis was discontinued. Cr creatinine, Plt platelet, Hb hemoglobin, PSL prednisolone, RCC red cells concentrate

Table 1 Clinical course before hospitalization and throughout hospitalization

	Before hospitalization (day 7)	Day of hospitalization (day 0)	Day 1	Day of consultation (day 4)	Day of discharge (day 26)
Vital signs					
Body temperature (°C)	36.2	37.7 ^a	36.3	36.6	36.0
Body weight (kg)	64.6	N/A	63.8	67.7	53.1
Blood pressure (mmHg)	139/49	135/68 ^a	124/58	149/85	136/59
Laboratory data					
White blood cells (count/ μ L)	7100	7200 ^b	27,800	7600	8200
Neutrophils (%)	61.0	N/A	N/A	81.0	N/A
Eosinophils (%)	1.0	N/A	N/A	0.5	N/A
Hemoglobin (g/dL)	11.6	11.7 ^b	11.2	8.8	11.2
Total bilirubin (mg/dL)	0.6	0.7 ^b	4.6	1.3	1.1
Indirect bilirubin (mg/dL)	0.5	0.5 ^b	1.8	0.7	N/A
AST (IU/L)	21	20 ^b	327	23	18
ALT (IU/L)	11	11 ^b	137	40	18
LDH (U/L)	299	246 ^b	1149	345	249
Total protein (g/dL)	8.4	N/A	7.0	5.5	7.8
Albumin (g/dL)	4.6	4.0 ^b	3.6	2.9	4.0
Creatinine (mg/dL)	0.67	0.65 ^b	2.09	8.5	1.17
eGFR (mL/min/1.73 m ²)	92.0	95.1 ^b	26.5	5.7	50.0
Na (mEq/L)	139	139 ^b	136	133	136
Cl (mEq/L)	103	103 ^b	103	100	102
K (mEq/L)	3.6	4.1 ^b	4.9	5.6	4.2
FENa (%)	N/A	N/A	N/A	18.7	N/A
Urinary protein (g/g Cr)	N/A	N/A	N/A	13.6	0.25
Proteinuria by dipstick test	N/A	N/A	N/A	3+	±
Hematuria by dipstick test	N/A	N/A	N/A	3+ (Non-glomerular hematuria)	2+ (Non-glomerular hematuria)
NAG (U/L)	N/A	N/A	N/A	25.5	10.9
L-FABP (μ g/gCr)	N/A	N/A	N/A	39.2	4.7
β 2-Microglobulin (μ g/L)	N/A	N/A	N/A	13,730	1183
α 1-Microglobulin (mg/L)	N/A	N/A	N/A	19.9	N/A

Before hospitalization, the prior routine outpatient clinic evaluation: data of body temperature and blood pressure were extracted as maximum and minimum of the day, respectively

AST aspartate aminotransferase, ALT alanine aminotransferase, eGFR estimated glomerular filtration, Na serum sodium, Cl serum chloride, K potassium, FENa fractional excretion of Na, NAG N-acetyl glucosaminidase, L-FABP liver-type fatty acid-binding protein, N/A not available

^aAfter administration of mFOLFOX (5-fluorouracil (5-FU)/L-leucovorin/oxaliplatin)

^bJust before the administration of mFOLFOX

to baseline at 2 months after AKI onset in the outpatient clinic (from 0.65 to 0.7 mg/dL).

Discussion

We present a case with AKI where oxaliplatin, a third-generation platinum agent, seemed to cause ATIN plus ATI with concomitant cytopenia (anemia and thrombocytopenia). In

this case, renal function was completely restored with the early initiation of steroid treatment. It is reported that kidney dysfunction is not common with oxaliplatin, but case reports have been increasing due to the growing use of oxaliplatin in recent years. Cisplatin-induced AKI has been reported frequently. After administration, oxaliplatin and cisplatin are localized in the vascular basolateral membrane and have been found to be actively transported by human organic cation transporter 2 (OCT2), which mediates drug uptake

Fig. 2 Kidney biopsy findings. **a, b** Interstitial cell infiltrations consisting of lymphocytes, numerous eosinophils, and mild tubulitis (periodic acid methenamine silver stain). **c** Nuclear irregularities

(arrow) in renal tubular epithelial cells (periodic acid-Schiff stain). **d** Vacuolization (arrow) of tubular epithelial cells (periodic acid-Schiff stain)

into the kidney. Cisplatin is minimally excreted by multidrug and toxin extrusion protein (MATE) 1 on the brush border membrane after transferring into the cell. However, oxaliplatin is strongly susceptible to cellular transport via MATE2-K on the brush border membrane, and it is strongly suggested that nephrotoxicity is weak due to low tissue accumulation in the renal tubular epithelial cells [10–12]. However, it is considered that nephrotoxicity due to oxaliplatin develops if patients undergo repeated exposure. Most cases of AKI due to oxaliplatin were diagnosed as ATN in previously published reports [4–7]. Other mechanisms include pigment-induced nephrotoxicity caused by hemoglobinuria [13]. There have been 16 reported cases of AKI and 5 cases were identified by renal biopsy. Of these five cases, only one case was diagnosed as ATIN by renal biopsy [8]; the remaining cases were diagnosed as ATN [4–7]. We reviewed biopsy-proven oxaliplatin-induced AKI for comparison with the present case in Table 2 [4–8].

In the present case, at the end of oxaliplatin administration, allergic symptoms including fever, shaking chill, and facial flushing combined with sterile pyuria were observed, and oliguria subsequently developed. Although the results of DLST for oxaliplatin, gallium scintigraphy, and eosinophiluria were all negative, the possibility of ATIN should be considered, because the sensitivity of these tests for drug allergy

or drug-induced ATIN is not satisfactory [14]. The sensitivity of gallium scintigraphy and DLST for the diagnosis of ATIN was only 69% [15] and 57.9% [16], respectively. Furthermore, eosinophiluria showed moderate sensitivity (62%) for the diagnosis of ATIN [17]. Based on this information, we could not completely rule out ATIN despite the negative results of both DLST and scintigraphy. Therefore, problems concerning sensitivity and specificity in clinical settings are common. We strongly suspected ATIN in the present case due to the allergic reaction and AKI with new onset of sterile pyuria and hematuria. Sterile pyuria and hematuria have been seen in a case of ATIN [17]. In addition, renal tubular damaged markers, NAG and β 2- and α 1-macroglobulin, were reasonably high to support this diagnosis.

Eventually, the patient was diagnosed with ATIN based on renal biopsy, which is the golden standard for the diagnosis of ATIN. In this case, it was difficult to perform transcutaneous renal biopsy before the initiation of steroid therapy because of the bleeding risk due to thrombocytopenia. We often face the same situation, which is represented by an acute deterioration of kidney function, in daily clinical practice, especially in the elderly population. Elderly patients usually tend to refuse transcutaneous renal biopsy to avoid complications. However, the incidence of biopsy-related complications in elderly patients did not increase compared

Table 2 Reported cases of biopsy-proven oxaliplatin-induced acute kidney injury

References	Age/sex	Tumor type	Chemotherapy	Cycle of oxaliplatin	Peak Cr	Dialysis dependence	Specific treatment	Renal outcome ^a (final Cr /time after AKI)	Biopsy finding ^b
[4]	57/M	Colon	De Gramont FOLFOX	17th	7.3	N/A	None	Recovery (detailed information was absent)	ATN
[5]	65/M	Colon	FOLFOX	5th	12.2	Yes	None	Partial recovery (1.4/at 1.5 months after AKI)	ATN
[6]	67/M	Colon	FOLFOX	13th	12.1	Yes	None	Complete recovery (1.1 /at 1 month after discharge)	ATN
[7]	69/F	Ovarian	Oxaliplatin Gemcitabine	10th	12.7	Yes	None	Complete recovery (1.1 /at 1.5 months after AKI)	ATN
[8]	40/F	Colon	mFOLFOX	36th	7.1	Yes	None	Partial recovery (1.6/at 1 month after AKI)	AIN
Present case	67/M	Colon	mFOLFOX	18th	8.5	Yes	Steroid	Complete recovery (0.7/at 2 months after AKI)	ATIN

^aComplete recovery was defined as recovery of final creatinine levels within 0.3 mg/dL compared to baseline serum creatinine. Partial recovery was defined as no recovery of final creatinine levels within 0.3 mg/dL compared to baseline serum creatinine

^bDescription of biopsy finding was based on each original article

M male, *F* female, *De Gramont* fluorouracil (5FU) in combination with folinic acid, *FOLFOX* 5-fluorouracil (5-FU)/L-leucovorin/oxaliplatin, *mFOLFOX* modified FOLFOX, *Cr* Creatinine (mg/dL), *N/A* not available, *AKI* acute kidney injury, *ATN* acute tubular necrosis, *AIN* acute interstitial nephritis, *ATIN* acute tubulointerstitial nephritis

to non-elderly patients, according to a prior report [18]. If there is a possibility of administration of steroid and immunosuppressant therapy for the patient, biopsies should be attempted regardless of age. We diagnosed ATIN based on typical findings including interstitial cellular infiltration consisting of lymphocytes and eosinophils and mild tubulitis. Tubular vacuolization was also observed on kidney biopsy, which is one of the findings associated with cisplatin toxicity, and similar features were observed in only one case of ATIN due to oxaliplatin [8]. Glomerular sclerosis (6 out of 22 glomeruli) would be an age-appropriate change, and tuft collapse without proliferative changes might be caused by acute ischemia secondary to interstitial cellular infiltration. Furthermore, no foot process effacement on electronic microscopy existed in this case despite proteinuria in the nephrotic range or albuminuria. Unfortunately, the cause of the extremely high level of proteinuria was not diagnosed, even though a kidney biopsy was performed.

Hemodialysis is reportedly required in approximately 40% of ATIN cases [19]. In this case, we decided to initiate steroid therapy immediately, beginning 8 days after hospitalization. In ATIN, the recovery of renal function is reportedly better with the early initiation of steroid therapy [20]. In our patient, it seems that the early initiation of steroid

therapy led to complete recovery of renal function. A prior report of AIN after the administration of oxaliplatin was followed with no specific therapy including steroid. The kidney function did not completely return to baseline in this case [8], as described in Table 2. In the present case, the platelet count recovered first, and we then decided to perform renal biopsy. Subsequently, the results confirmed the diagnosis and validated the steroid treatment.

Both thrombocytopenia and hemolytic anemia were observed. There have been many reports of thrombocytopenia and hemolytic anemia associated with oxaliplatin [13]. The mechanisms of cytopenia are speculated to include the production of anti-platelet and red-blood cell antibodies and thrombotic microangiopathy (TMA) via endothelial dysfunction [21]. Unfortunately, the direct Coombs test and PA-IgG were not measured in the present case; therefore, we could not diagnose an auto-immune etiology. Furthermore, the finding of TMA on the glomeruli and small vessels was absent, as well. However, both thrombocytopenia and anemia dramatically improved after the discontinuation of administration of oxaliplatin and steroid therapy; therefore, we strongly suspect that this patient's cytopenias were due to an auto-immune mechanism. We considered that the cytopenia and ATIN were due to oxaliplatin. 5-FU and

L-leucovorin, administered with oxaliplatin, are not reported to cause ATIN. This patient had undergone the other chemotherapy including 5-FU and L-leucovorin after this episode. However, no symptoms occurred.

In conclusion, we describe our experience with respect to a case of AKI due to oxaliplatin-induced ATIN with autoimmune anemia and thrombocytopenia, which responded very well to steroid treatment. Although many reported cases of oxaliplatin-induced AKI are diagnosed as ATN, we should also consider ATIN as an etiology of AKI and administer steroids as early as possible.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

Human and animal rights This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from the patient described in the study.

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