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Two cases of cisplatin-induced permanent renal failure following neoadjuvant chemotherapy for esophageal cancer



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ABSTRACT

INTRODUCTION: We experienced two esophageal cancer patients who developed severe acute renal failure after neoadjuvant chemotherapy with cisplatin and 5-fluorourasil.

PRESENTATION OF CASE: After administration of cisplatin, their serum creatinine increased gradually until they required hemodialysis and their renal failure was permanent. In both cases, renal biopsy examination indicated partial recovery of the proximal tubule, but renal function did not recover. After these events, one patient underwent definitive radiotherapy and the other underwent esophagectomy for their esophageal cancers, while continuing dialysis. Both patients are alive without cancer recurrence.

DISCUSSION: In these two cases of cisplatin-induced renal failure, renal biopsy examination showed only slight disorder of proximal tubules and tendency to recover.

CONCLUSION: Although cisplatin-related nephrotoxicity is a well-recognized complication, there have been few reports of renal failure requiring hemodialysis in cancer patients. In this report, we present their clinical courses and the pathological findings of cisplatin-related renal failure.

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1. Introduction

Cisplatin and related platinum-based therapeutics are used widely in the treatment of a variety of cancers. However, the clinical use of cisplatin can be complicated by myelotoxicity, ototoxicity, nausea and vomiting, and nephrotoxicity [1]. Nephrotoxicity secondary to cisplatin administration is dose-dependent, and the drug-induced renal failure reflects acute tubular necrosis, which is usually reversible.

We experienced two cases of esophageal cancer with therapy-related acute renal failure that developed during neoadjuvant chemotherapy. These patients required dialysis, and their renal failure was permanent. There have been few reports of renal failure in

cancer patients undergoing chemotherapy, though therapy-related nephrotoxicity is a well-recognized complication of chemotherapeutic agents, including cisplatin. In this report, we present two cases with their clinical courses and renal biopsy findings.

2. Presentation of case

2.1. Case 1

A 66-year-old man was referred to our hospital for treatment of his thoracic esophageal cancer. An irregularly elevated lesion (type 0-IIa) occupied the middle thoracic esophagus, and biopsy specimens from the lesion showed well-differentiated squamous cell carcinoma (Fig. 1a–d). Computed tomography revealed wall thickening in the middle thoracic esophagus and swelling of a middle thoracic para-esophageal lymph node. 18F-fluorodeoxy glucose positron emission tomography-computed tomography (18F-FDG PET/CT) revealed high uptake at the tumor and lymph node. We diagnosed the cancer as clinical stage T1bN1M0, stage IIB according to the Union for International Cancer Control (UICC) classification, 7th edition.

Abbreviations: 18F-FDG PET/CT, 18F-fluorodeoxy glucose positron emission tomography-computed tomography; UICC, the Union for International Cancer Control; CTC-AE, the Common Terminology Criteria for Adverse Events; ARB, angiotensin II receptor blocker.

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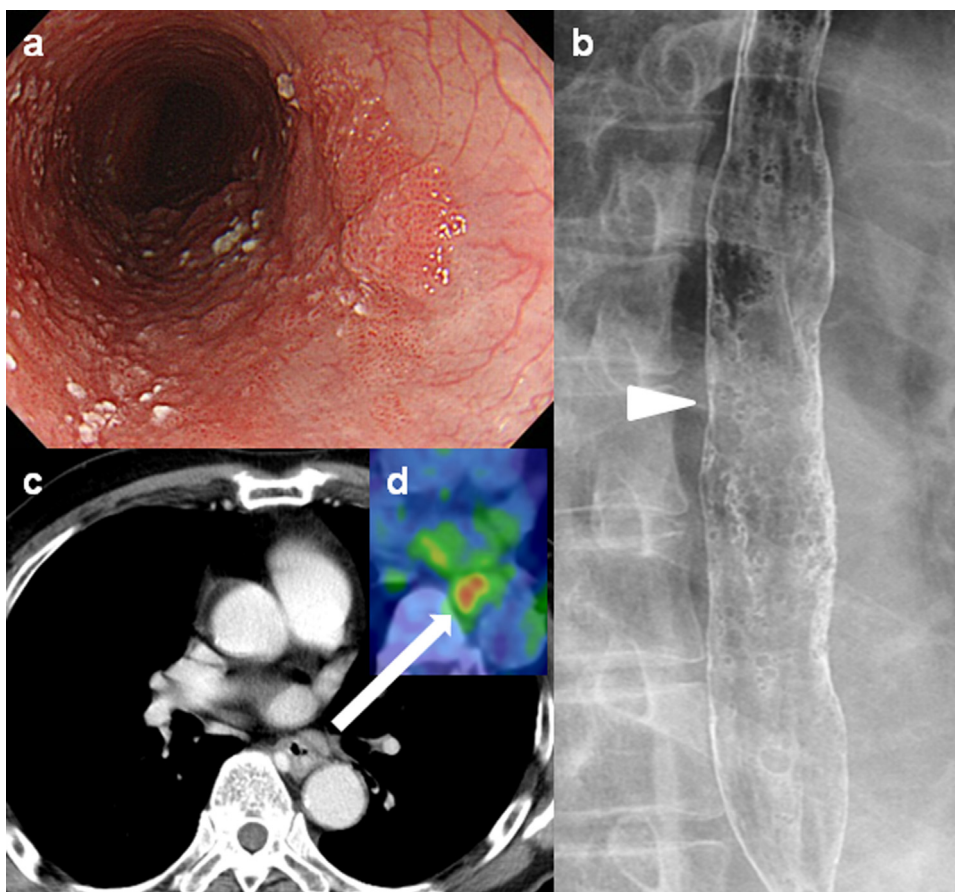


Fig. 1. (a) Endoscopic examination showed an irregularly elevated lesion occupying approximately three-fourths of the esophageal circumference 34–36 cm from the incisors. (b) Esophagography showed an irregular outline at the middle thoracic esophagus. (c) CT revealed swelling of a middle thoracic para-esophageal lymph node. (d) 18F-FDG PET/CT revealed high uptake at the lymph node.

The patient underwent neoadjuvant chemotherapy consisting of 80 mg/m² cisplatin on day 1 and 800 mg/m² 5-fluorouracil on days 1–5. On day 5, however, the patient's serum creatinine level had increased to 7.83 mg/ml (Fig. 3a). We diagnosed grade 4 acute renal failure based on the Common Terminology Criteria for Adverse Events (CTC-AE ver. 3.0), after which chemotherapy was stopped, and the patient was administered hemodialysis without delay. On day 36, we performed a renal biopsy, and the specimen contained 24 glomeruli, 3 of which were sclerotic. Light microscopy showed no mesangial proliferation. There was diffuse moderate interstitial infiltration of lymphocytes with tubulitis, mild interstitial fibrosis, and mild arteriolar sclerosis (Fig. 4a). Tubular casts without macrophagic reactions were seen. Immunofluorescence microscopy showed no immunoglobulin or complement deposits, and electron microscopy revealed myeloid body-like particles in the proximal tubules. The patient's renal function was expected to recover, but after 2 months of hemodialysis it had not. We therefore decided to resume treatment of his esophageal cancer while continuing hemodialysis. At that time, the patient was suffering from congestive heart failure and interstitial pneumonia, so we administered definitive radiotherapy (60 Gy). It is 48 months since the radiotherapy, and the patient is currently alive without recurrence of his esophageal cancer.

2.2. Case 2

A 64-year-old man was referred to our hospital for treatment of his thoracic esophageal cancer. Endoscopic examination showed an elevated tumor (type 1) with an irregular mucosal lesion (type

0-IIb) located 35 cm from the patient's incisors (Fig. 2a–f). Biopsy specimens of the lesion showed modified differentiated squamous cell carcinoma. Computed tomography revealed wall thickening in the lower thoracic esophagus and swelling of a lymph node along the left gastric artery. 18F-FDG PET/CT showed high uptake at the tumor and lymph node, and the patient was diagnosed as clinical stage T1bN1M0, stage IIB.

This patient also underwent neoadjuvant chemotherapy consisting of 80 mg/m² cisplatin on day 1 and 800 mg/m² 5-fluorouracil on days 1–5. On day 3, however, his serum creatinine had increased to 3.35 mg/ml (Fig. 3a). We diagnosed acute renal failure at CTC-AE grade 3 and stopped chemotherapy. Then on day 6, we began administering hemodialysis because the patient's serum creatinine had increased to 8.35 mg/ml. On day 36, while continuing hemodialysis, we performed an esophagectomy through a right-thoracotomy and 2-field lymph node dissection, followed by reconstruction with the gastric tube through the ante-thoracic route. It is 49 months since the operation was performed, and the patient is currently alive with no recurrence of his esophageal cancer. At the time of the esophagectomy, a renal biopsy was also performed. Light microscopy showed global sclerosis in 3 of 48 glomeruli with mild ischemic alteration. There was diffuse mild interstitial infiltration by lymphocytes, vacuolar degeneration in the proximal tubules, mild interstitial fibrosis, and moderate arteriolar sclerosis (Fig. 4b). Tubular casts without macrophagic reactions were seen diffusely. Immunofluorescence microscopy showed no immunoglobulin or complement deposits. Electron microscopy revealed enlarged lysosomes and endoplasmic reticulum, and myeloid body-like particles in the tubules. Pathological

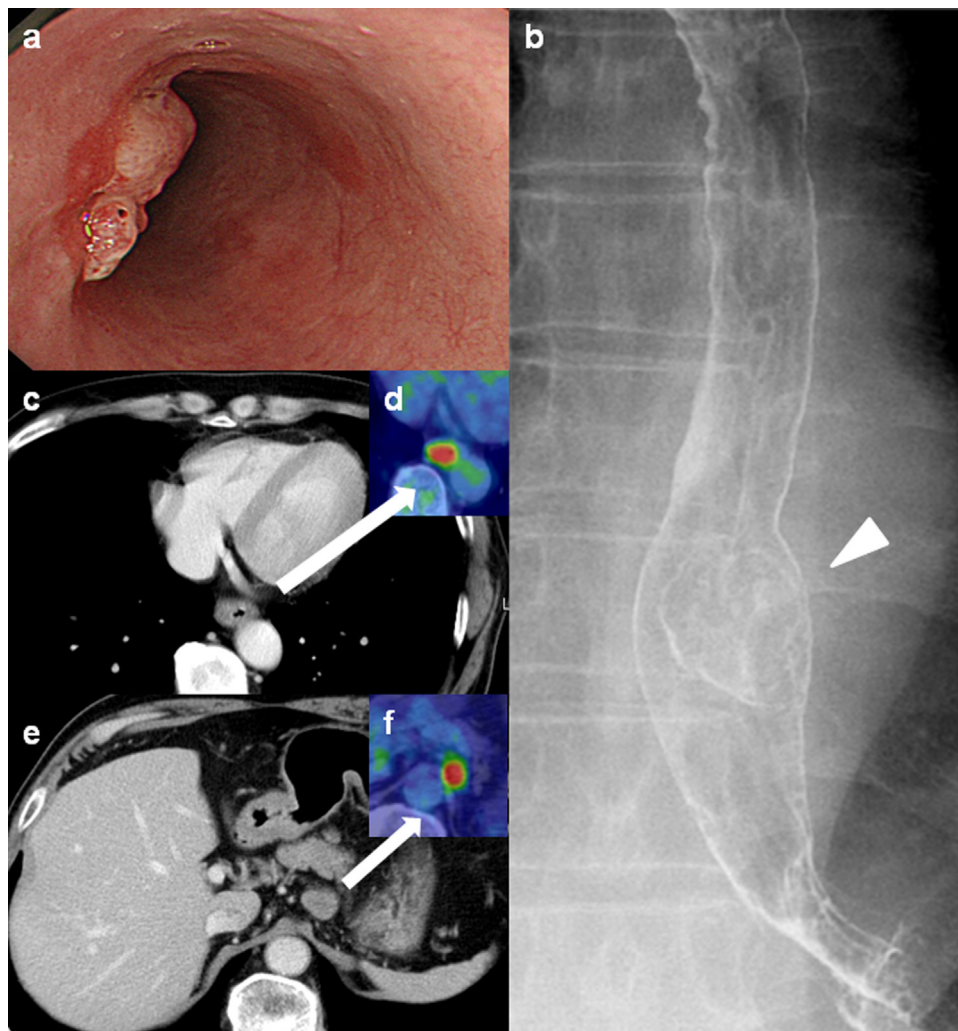


Fig. 2. (a) Endoscopic examination showed an elevated tumor (type 1) with an irregular mucosal lesion located 35 cm from the incisors. (b) Esophagography showed an irregular outline at the lower thoracic esophagus. (c and e) CT revealed wall thickening in the lower thoracic esophagus and swelling of a lymph node along the left gastric artery. (d and f) 18F-FDG PET/CT revealed high uptake at the tumor and lymph node.

images showed only slight disorder of the proximal tubule, which appeared to have partially recovered, though the patient's renal function has not yet recovered.

3. Discussion

It is recognized that about one-third of patients who undergo chemotherapy that includes cisplatin will experience nephrotoxicity [2]. However, hemodialysis is rarely required. In one study, for example, among 56 patients who developed moderate renal dysfunction (creatinine clearance <60 ml/min), none required hemodialysis, and only two (3.5%) experienced grade 3 or 4 serum creatinine elevations while being treated with cisplatin-containing chemotherapy [3]. In fact, we had administered the same chemotherapeutic regimen, consisting of high-dose cisplatin and 5-fluorouracil, to more than 500 esophageal cancer patients since 2003, and none experienced severe renal failure requiring dialysis. Furthermore, we could not have foreseen the occurrence of renal failure in the two patients described here, as their renal functions were within the normal range (creatinine clearances were 130 ml/min and 122 ml/min, respectively).

Although the exact mechanism of cisplatin-induced nephrotoxicity remains unclear, exposing proximal tubular cells to cisplatin reportedly activates complex signaling pathways and a multifac-

torial process that leads to tubular cell injury and death. Cisplatin has multiple intracellular effects, including altered gene regulation, direct cytotoxicity mediated by reactive oxygen species, induction of apoptosis, and stimulation of inflammation and fibrogenesis [4,5]. In addition, the plasma level of unbound free platinum is an important determinant of cisplatin's antitumor effects and nephrotoxicity. Approximately 98% of cisplatin binds to plasma protein, and the unbound free platinum is rapidly eliminated, mainly via the kidneys such that it becomes undetectable within 2 h after infusing cisplatin [6]. It is therefore important for patients receiving cisplatin to be well hydrated for 2 or 3 h after infusion. Indeed, volume expansion remains the most effective strategy for prevention of cisplatin nephrotoxicity [7–10], though the two patients described here received sufficient drip infusion (3899 ml/day in both) and produced good urine volumes (3220 ml/day, 4830 ml/day) (Fig. 3b). Recent randomized trials showed that addition of magnesium was effective for reducing cisplatin-induced renal toxicity [11,12], and we now add magnesium to the hydration fluid.

A common feature of our two patients was that they were both taking a calcium channel blocker and an angiotensin II receptor blocker (ARB). It is thought that under some circumstances ARBs may contribute to the occurrence of acute renal failure by reducing renal blood flow. After infusion of cisplatin, the blood pressure in case 1's patient fell from 130 mmHg to 80 mmHg, which suggests

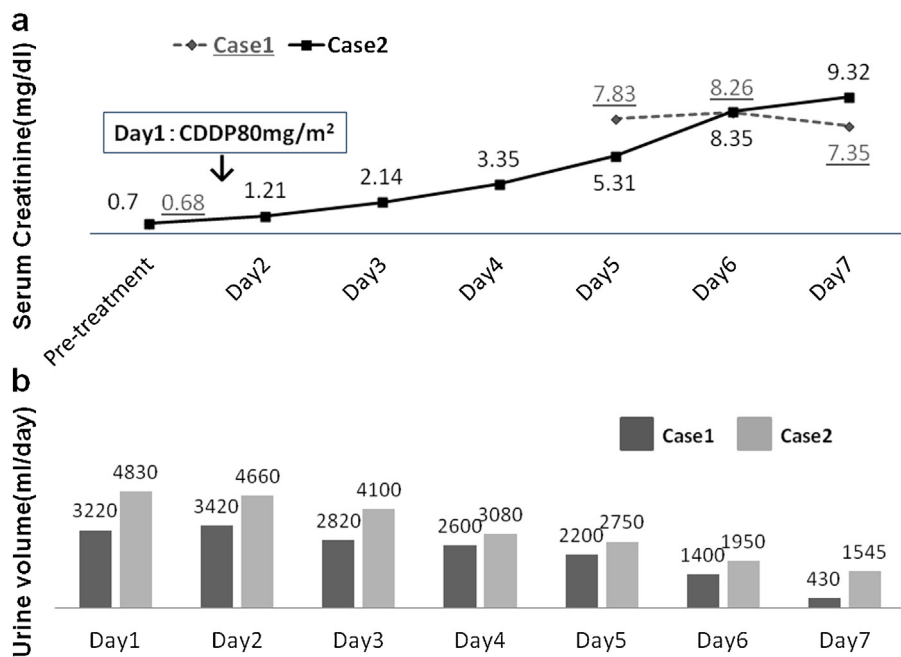


Fig. 3. (a) In case 1, the serum creatinine level was elevated to 7.83 mg/ml on day 5. On day 6, the serum creatinine level reached 8.26 mg/ml. In case 2, the serum creatinine level increased gradually, reaching 3.35 mg/dl on day 4, 5.31 mg/dl on day 5, and 8.35 mg/ml on day 6. (b) Both patients exhibited good urine volumes on days 1–5.

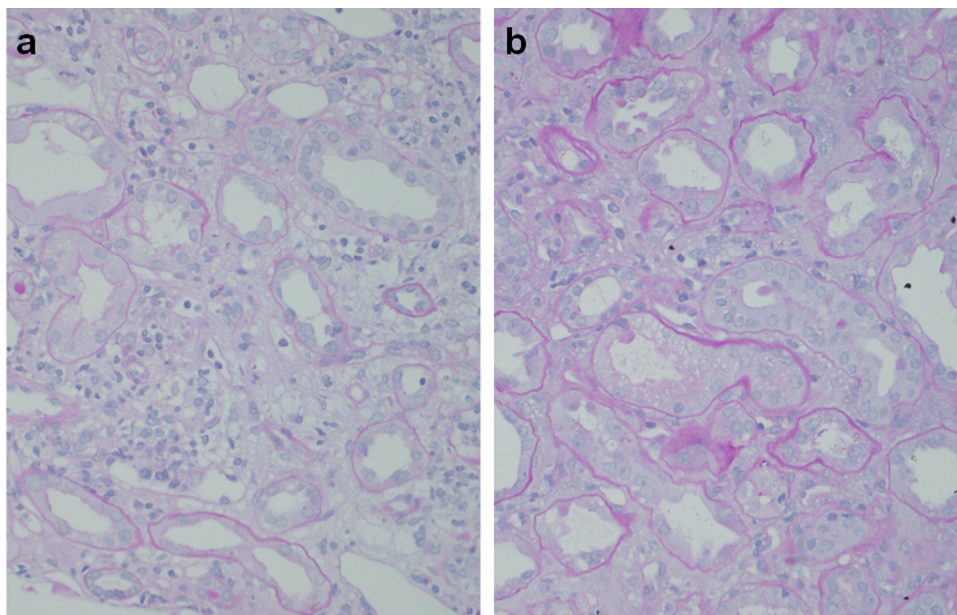


Fig. 4. Light microscopic examination of a renal biopsy sample from case 1's patient showed diffuse moderate interstitial infiltration of lymphocytes with tubulitis, mild interstitial fibrosis, and mild arteriolar sclerosis (a). Light microscopic examination of the biopsy from case 2's patient showed diffuse mild interstitial infiltration of lymphocytes, vacuolar degeneration in the proximal tubules, mild interstitial fibrosis, and moderate arteriolar sclerosis (b). Periodic acid-Schiff staining ($\times 400$).

the possibility that diminished renal blood flow contributed to his renal failure.

It is also noteworthy that renal toxicity was slightly more severe in patients treated with a generic cisplatin formulation than in those treated with an innovator formulation, especially in male patients [13]. In our hospital, a generic cisplatin formulation was adopted 5 years ago, and 49 patients administered the generic cisplatin formulation exhibited elevations in serum creatinine to more than 2 mg/dl (the total treated population was about 2500). We are now investigating the relationship between the generic cisplatin formulation and nephrotoxicity.

In these two cases of cisplatin-induced renal failure, renal biopsy examination showed only slight disorder of proximal tubules and tendency to recover.

4. Conclusion

It is deeply regrettable that our two cancer patients suffered permanent renal failure caused by preoperative treatment with cisplatin. In these two cases of cisplatin-induced renal failure, renal biopsy examination showed only slight disorder of proximal tubules and tendency to recover. To prevent occurrences of per-

manent renal failure in cancer patients administered cisplatin, we suggest it is highly important to maintain sufficient hydration, with frequent measurement of urine volume, serum creatinine and strict control of the blood pressure.

Conflicts of interest

All authors state that they have no financial competing interests to disclose.

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Ethical approval

This study was approved by the Ethics Committee of Akita University School of Medicine. All of the participants provided informed consent and signed a human subject institutional review board consent form.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Authors' contributions

TS made substantial contributions to acquisition of data and to draft the manuscript. SM and AK participated in its design and coordination and helped to draft the manuscript. HS, YS, KY, AW, HS, AA, MJ and YM participated in the design of the study.

Ethical statement

This article does not contain any studies with human or animal subjects performed by any author(s) as it is a post-mortem pathology study.

Guarantor

Satoru Motoyama.

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