Improvement in karyomegalic interstitial nephritis three years after ifosfamide and cisplatin therapy by corticosteroid

Tomokazu Matsuura · Shu Wakino · Ayumi Yoshifuji · Toshifumi Nakamura · Hirobumi Tokuyama · Akinori Hashiguchi · Konosuke Konishi · Takeshi Iwasa · Masaaki Shoji · Ako Hosono · Ken Ohashi · Hirokazu Chuman · Hiroshi Itoh

Received: 6 January 2014 / Accepted: 30 April 2014 / Published online: 4 June 2014
© Japanese Society of Nephrology 2014

Abstract Long-term nephrotoxicity of ifosfamide is occasionally progressive, and, in such case, there has been no specific treatment to prevent progression. It has been reported that the presence of karyomegalic interstitial nephritis, which is rare type of interstitial nephritis, may be related to ifosfamide-induced nephropathy with poor prognosis and resistant to the immunosuppressive therapy. A 15-year-old boy presented with progressive nephrotoxicity 3 years after systemic chemotherapy with ifosfamide and cisplatin for the treatment of osteosarcoma. Renal biopsy revealed the severe tubulointerstitial nephritis with tubular atrophy and focal global and segmental glomerular sclerosis. It also showed tubular epithelial cells with variably sized nuclei, some of which were massively enlarged, abnormal hyperchromatic, irregular shaped, and bizarre-

appearing. These morphological changes were suggestive of the histology of karyomegalic interstitial nephritis. Corticosteroid retarded the progression of nephrotoxicity. The present case is the first report, suggesting that corticosteroid was effective against the late-onset renal toxicity by ifosfamide therapy. Our case also suggests that karyomegalic interstitial nephritis may be the result of long-term nephrotoxicity of ifosfamide. Since concurrent treatment with cisplatin is one of the risk factors for ifosfamide nephrotoxicity, there is a possibility that cisplatin may have a synergetic effect with ifosfamide for producing karyomegalic interstitial nephritis.

Keywords Ifosfamide · Long-term nephrotoxicity · Corticosteroid · Tubulointerstitial nephritis · Karyomegalic interstitial nephritis

T. Matsuura (✉) · T. Iwasa · M. Shoji · K. Ohashi
Division of Internal Medicine, National Cancer Center Hospital,
5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: pm6t-mtur@asahi-net.or.jp

S. Wakino · A. Yoshifuji · T. Nakamura · H. Tokuyama ·
K. Konishi · H. Itoh
Department of Internal Medicine, Keio University School of
Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582,
Japan

A. Hashiguchi
Department of Pathology, Keio University School of Medicine,
35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

A. Hosono
Division of Pediatric Oncology, National Cancer Center
Hospital,
5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

H. Chuman
Division of Orthopedics, National Cancer Center Hospital,
5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

Introduction

Ifosfamide, an oxazaphosphorine alkylating agent and a close analog of cyclophosphamide, is widely used for the treatment of solid tumors, particularly in children. Recently, its use in pediatric solid tumors such as Ewing's sarcoma, rhabdomyosarcoma, lymphoma, neuroblastoma, osteosarcoma, soft tissue sarcomas and Wilm's tumor has rapidly increased owing to greater antineoplastic activity than cyclophosphamide [1]. Improvements in pediatric cancer therapy have led to increasing numbers of long-term survivors. Therefore, the management of late adverse effects of cancer treatment is an increasingly important issue now. Nephrotoxicity of ifosfamide is mainly revealed as proximal tubule damage, and glomerular toxicity is normally secondary to that of tubular [1]. Severe proximal tubular damage manifests as Fanconi's syndrome [1].

Several reports show the long-term renal toxicity of ifosfamide following cessation of its administration, even in glomerular toxicity [2, 3]. In the current report, we describe the case in which oral corticosteroid was effective in the treatment of the long-term nephrotoxicity of ifosfamide and cisplatin. Our case also exhibited karyomegalic interstitial nephritis that was rare form of interstitial nephritis and has been considered to be resistant to the therapy.

Case report

A 15-year-old boy was referred to the Division of Internal Medicine in National Cancer Center Hospital in June, 2012 because of the gradual deterioration of renal function. He used to be diagnosed with osteosarcoma of the left femur and treated with systemic chemotherapy (cisplatin, doxorubicin, high dose-methotrexate and ifosfamide) along with surgical excision in May, 2009. Radiation therapy was not performed. Treatment was complete in November, 2009, and at that time, his serum creatinine level was 0.8–1.0 mg/dL. A cumulative dose of ifosfamide was 69.7 g/m². Even after cessation of chemotherapy, his renal function continued to deteriorate (Fig. 1). At visit, his serum creatinine level had gradually increased to 3.23 mg/dL until July, 2012. Although he had no history of hypertension and diabetes mellitus, he had been treated with losartan occasionally, which did not change the course of renal dysfunction. CT scan showed normal-sized kidneys with no hydronephrosis. No metastases were found on subsequent radiological staging.

For the evaluation of renal impairment, he was transferred to Keio University Hospital in August, 2012 to be undertaken percutaneous renal biopsy. Laboratory findings at renal biopsy are shown as Table 1. His serum creatinine level was 3.51 mg/dL and urinary protein excretion was 1.10 g/day. His serum phosphate level was 3.3 mg/dL, and tubular threshold of phosphate was 0.98 mg/dL (normal range; 2.3–4.3 mg/dL). Glucosuria with normal serum glucose level and aminoaciduria were evident. Urinary excretion of β 2-microglobulin was high (25,907 μ g/L). These results indicated the presence of Fanconi's syndrome. He had metabolic acidosis with elevated anion gap (16 mEq/L). The causes of metabolic acidosis were evaluated as Fanconi's syndrome and chronic kidney disease. Gallium scintigraphy was performed just before the renal biopsy, and the result was within normal limit.

A percutaneous renal biopsy was performed to assess the cause of his progressive renal damage. Of 34 glomeruli, 18 were global sclerotic, one was segmental sclerotic, and two were collapsed. Thirteen other glomeruli were almost normal. There was severe tubular degeneration and interstitial inflammation (Fig. 2a). Among infiltrate lymphocytes, CD3+ (T lymphocytes) were dominant (Fig. 2b). CD68 staining was not prominent as compared to CD3 staining, indicating that macrophage infiltration was not severe. The tubular epithelia showed severe dysmorphism and anisokaryosis, and epithelial cells with enlarged nuclei were seen occasionally. The foci of Ki-67-positive epithelia were scattered (Fig. 2c), and this implied the regenerative changes in renal tubular epithelium. Marked

Fig. 1 Temporal changes of 1/Creatinine levels and treatment of this case

Table 1 Laboratory findings at renal biopsy

Urinalysis		Blood chemistry			
S.G.	1.005	TP	7.6 g/dL	IgG	1,173 mg/dL
pH	5.5	ALB	4.9 g/dL	IgA	246 mg/dL
Protein	(2+)	TB	0.6 mg/dL	IgM	90 mg/dL
	1.10 g/day	LDL-C	57 mg/dl	C3	95 mg/dL
Glucose	(2+)	BS	90 mg/dL	C4	31 mg/dL
Occult blood	(+)	BUN	25.3 mg/dL	CH-50	50.4 U/mL
		Cr	3.51 mg/dL	RPR	(–)
Urinary sediment		UA	4.3 mg/dL	TPHA	(–)
RBC	1-4/HPF	Na	136.9 mEq/L	HCV-Ab	(–)
WBC	1-4/HPF	K	2.9 mEq/L	HBs-Ag	(–)
		Cl	99 mEq/L	HBs-Ab	(–)
Peripheral blood		Ca	9.8 mg/dL	RF	(–)
WBC	5,400/ μ L	IP	3.3 mg/dL	ANA	<40×
Neutro	55.2 %	GOT	20 IU/L	Anti-dsDNA-Ab	(–)
Lymph	28.9 %	GPT	8 IU/L	PR3-ANCA	(–)
Mono	14.8 %	LDH	191 IU/L	MPO-ANCA	(–)
Baso	0.4 %	CRP	0.18 mg/dL	Anti-GBM-Ab	(–)
Eosino	0.7 %	HgbAlc	5.3 %	Cryoglobulin	(–)
RBC	$464 \times 10^4/\mu$ L				
Hgb	13.4 g/dL	Coagulation system			
PLT	$16.0 \times 10^4/\mu$ L	PT-INR	1.04

Fig. 2 Karyomegalic interstitial nephritis. **a** Severe tubular degeneration and interstitial inflammation were evident in renal tissues (Hematoxylin Eosin staining, $\times 100$). **b** CD3+ (T lymphocytes) were dominant among infiltrate lymphocytes ($\times 100$). **c** The Ki-67-positive epithelia were scattered in the tubular epithelium ($\times 400$). **d** Renal

tubular epithelial cells took the form of variably sized nuclei, some of which were massively enlarged, irregular shaped and bizarre-appearing. ($\times 100$, methenamine silver-Periodic acid-Schiff stain). **e** Electromicrograph showing that some tubular epithelia contained an increased lysosome

nuclear cytomorphological change was apparent. This took the form of variably sized nuclei, some of which were massively enlarged, vesicular, irregular shaped and bizarre-appearing (Fig. 2d). These morphological changes were suggestive of the histology of karyomegalic interstitial nephritis. Although these changes were somewhat reminiscent of viral tubulopathy, the tubular nuclei showed no obvious staining for SV40 T-antigen, cytomegalovirus and adenovirus. According to the result of Masson-trichrome staining, interstitial fibrosis was observed in about 50 % of the cortical area. Fluorescent studies for immunoglobulin and complement were negative. Electron microscopy did not give additional morphological information. No viral inclusion could be identified, and some tubular epithelia with an increased lysosome were seen (Fig. 2e). The changes were also thought to represent a form of karyomegalic interstitial nephritis.

Serum creatinine was maximally increased to 3.72 mg/dL. In spite of the global sclerosis in 60 % of glomeruli and the interstitial fibrosis in 50 % of the cortical area, we decided to prescribe corticosteroid to treat the active interstitial nephritis. Since his bone mineral density of spine was 85 % of young adult mean, modest dosage of oral prednisolone (20 mg/day) started in October 2012. Prednisolone apparently improved the course of renal function as shown in Fig. 1. As of November, 2012, serum creatinine level was decreased to 2.55 mg/dL, and serum phosphate level was 3.2 mg/dL. The change of serum creatinine clearance (Ccr) also supported the improvement of renal function. It was 28.6 mL/min before treatment and increased to 42.5 mL/min 2 months after the initiation of prednisolone. His deterioration of renal function was inhibited by the treatment with modest dosage (20 mg/day) of oral corticosteroid. According to the change of serum creatinine, we adjusted the dosage of prednisolone several times and have kept the treatment with it (Fig. 1). The level of Ccr was 39.5 mL/min 17 months after the initiation of prednisolone, and this value was still better than that before prednisolone therapy.

Discussion

This patient suffered from progressive renal damage even 3 years after the completion of chemotherapy. Renal biopsy revealed the focal global and segmental glomerular sclerosis, severe interstitial tubulonephritis and tubular atrophy. Corticosteroid was prescribed to suppress the interstitial nephritis with improved renal function.

Although it is not easy to clarify the direct reason of renal damage, we suggest that it must be a late adverse renal effect of chemotherapy, because no other causes of renal failure were apparent in our patient. Cisplatin, high

dose-methotrexate and ifosfamide are all notorious to cause nephrotoxicity. The review article for renal late effects on patients treated for cancer in childhood [4] revealed that ifosfamide may cause permanent and potentially progressive kidney damage. In contrast, it was also described that the outlook for long-term recovery or stability of renal function caused by cisplatin is generally favorable and that methotrexate-induced nephrotoxicity appears to be entirely reversible. Thus, we speculated that ifosfamide is the major factor for late-onset renal toxicity.

Late renal adverse effect induced by ifosfamide has been reported in several articles [2, 3]. Skinners et al. [2] reported that 13 % of patients suffered glomerular toxicity ($\text{GFR} < 60 \text{ mL/min/1.73 m}^2$) 10 years after ifosfamide treatment in childhood. Prasad et al. [3] also reported that 17.1 % of children underwent glomerular dysfunction appeared to be causally linked to ifosfamide within a median follow-up of 29 months (range 9–135). A follow-up study in 75 patients who had completed ifosfamide treatment also found that subclinical damages developed in the first 2 years after completion of treatment [5]. Since the present case was also treated with ifosfamide 3 years ago, we speculate late onset of ifosfamide nephrotoxicity is the main cause of this renal dysfunction.

The most common manifestation of renal toxicity of ifosfamide is proximal tubular dysfunction and less often decreased GFR [4]. A statistically significant fall in mean GFR of $35 \text{ mL/min/1.73 m}^2$ was observed after completion of ifosfamide therapy [6]. The renal toxicity following ifosfamide treatment is subject to great inter-individual variability [7]. Evidence of renal damage may become apparent immediately after starting treatment or not until after the treatment is completed [1]. Due to these uncertainties, it is hard to predict the late damages by ifosfamide. High cumulative doses ($>60 \text{ g/m}^2$), previous and/or concurrent treatment with cisplatin and prior unilateral nephrectomy are suggested as risk factors [1]. This patient was treated with high cumulative dose (69.7 g/m^2) and with the combination of cisplatin, which enhanced the nephrotoxicity of ifosfamide.

There are several reports of the finding of renal biopsy for ifosfamide-induced late nephropathy [3, 8–12]. Most of reports show the chronic tubulointerstitial damage, although segmental glomerular sclerosis was also reported [8], which were also found in the present case. We also found the lesion typical of karyomegalic interstitial nephritis, which was also recently reported in ifosfamide-induced late-onset nephrotoxicity [9]. The authors presented three cases that were treated with ifosfamide, but without cisplatin. In this rare form of interstitial nephritis, systemic karyomegaly can affect other organs [13] and renal failure may be progressive [13, 14]. Although at present there is no specific treatment to prevent progression

of renal impairment, the present patient responded well to the small amount of oral corticosteroid therapy with the favorable clinical outcome.

Ateşşahin et al. [15] revealed that a single dose of cisplatin led to karyomegaly in rat tubular cells, and concurrent treatment with cisplatin is one of the risk factors for ifosfamide nephrotoxicity [1]. Therefore, there is a possibility that cisplatin may have a synergetic effect with ifosfamide for producing karyomegalic interstitial nephritis. In contrast, as far as we know, there is no case report that shows the relationship between methotrexate and karyomegalic interstitial nephritis.

Karyomegalic interstitial nephritis is sometimes regarded as the heredity disease [16], so there is the possibility that this patient had the subclinical karyomegalic interstitial nephritis before initiation of the chemotherapy. However, it is not the case because there were no sign of renal dysfunction and Fanconi's syndrome at least before the initiation of the chemotherapy. His serum creatinine was 0.5 mg/dL, and Ccr was 160.5 mL/min just before the first chemotherapy. In addition, there were no hypokalemia, hypophosphatemia, proteinuria, hematuria and glucosuria. Thus, we speculated that karyomegalic interstitial nephritis was also induced by the chemotherapy.

Since karyomegalic changes of tubular epithelia were believed to be associated with the cell cycle disturbance, the immunohistochemistry for the proliferation marker Ki-67 was performed. Some large nuclei were positive for Ki-67, but negative large nuclei were also observed. There was no different reactivity for Ki-67 between large and small nuclei. The level of positivity for Ki-67 staining is not so high as compared with usual interstitial nephritis, and the localization of Ki-67 positive cells was not regional. Therefore, we were unable to show the existence of the cell cycle disturbance in our case.

In summary, this case report described rare histological finding of karyomegalic interstitial nephritis after the treatment of ifosfamide. There is a possibility that cisplatin may have a synergetic effect with ifosfamide for producing karyomegalic interstitial nephritis. Our case can provide a novel therapeutic choice, corticosteroid, against the progressive nephrotoxicity several years after the ifosfamide therapy.

McCulloch et al. [9] prescribed corticosteroids to ifosfamide-induced chronic tubulointerstitial nephritis, without noticeable effect. Morland et al. [8] speculated on the possible effect of steroid in ifosfamide-induced nephrotoxicity. They, however, did not use steroid because the renal function was stable after renal biopsy. At present, the main strategy against late nephrotoxicity was its prevention by antioxidants therapy [1]. Our case is the first that corticosteroid was possibly effective for the

long-term nephrotoxicity after the completion of the ifosfamide therapy. As shown in Fig. 1, the 1/Creatinine slope for a year before the prednisolone administration is -0.0009 , whereas the slope for a year after the administration is -0.0002 . Thus, the prednisolone seemed to retard the progression of nephrotoxicity, and this effect did not look transient. It was, however, impossible to estimate this effect statistically, because the data were derived from one patient. In our case, steroid only retarded the deterioration of renal function because the basic renal function had already been impaired. We speculate that steroid is more effective to an earlier stage of ifosfamide-induced nephrotoxicity.

The mechanism of ifosfamide long-term nephrotoxicity is not fully understood. The residual nephron after the initial decrease in nephron mass experiences compensatory overuse injury, which causes a further decline in renal function. Another mechanism is the sustained inflammatory response. Schirli et al. [17] demonstrated an increase in serum concentration of cytokines, TNF- α , IL-1 β and IL-6 in the patient treated with ifosfamide. These inflammatory changes induce further tubular damage. We speculate that corticosteroid can break off the part of this self-continuing process.

Informed consent Informed consent was obtained from the mother of this patient for publication of this case report and any accompanying images, because this patient was under 16 years of age.

Conflict of interest The authors have declared that no conflict of interest exists.

References

1. Hanly L, Chen N, Rieder M, Koren G. Ifosfamide nephrotoxicity in children: a mechanistic base for pharmacological prevention. *Expert Opin Drug Saf*. 2009;8:155–68.
2. Skinner R, Parry A, Price L, Cole M, Craft AW, Pearson AD. Glomerular toxicity persists 10 years after ifosfamide treatment in childhood and is not predictable by age or dose. *Pediatr Blood Cancer*. 2010;54:983–9.
3. Prasad VK, Lewis IJ, Aparicio SR, Heney D, Hale JP, Bailey CC, Kinsey SE. Progressive glomerular toxicity of ifosfamide in children. *Med Pediatr Oncol*. 1996;27:149–55.
4. Jones DP, Spunt SL, Green D, Springate JE. Renal late effects in patients treated for cancer in childhood: a report from the children's oncology group. *Pediatr Blood Cancer*. 2008;51:724–31.
5. Rossi R, Pleyer J, Schäfers P, Kuhn N, Kleta R, Deufel T, Jürgens H. Development of ifosfamide-induced nephrotoxicity: prospective follow-up in 75 patients. *Med Pediatr Oncol*. 1999;32:177–82.
6. Skinner R, Cotterill SJ, Stevens MC. Risk factors for nephrotoxicity after ifosfamide treatment in children: a UKCCSG late effects group study. *United Kingdom Children's Cancer Study Group. Br J Cancer*. 2000;82:1636–45.
7. Rossi R, Gödde A, Kleinebrand A, Riepenhausen M, Boos J, Ritter J, Jürgens H. Unilateral nephrectomy and cisplatin as risk factors of ifosfamide-induced nephrotoxicity: analysis of 120 patients. *J Clin Oncol*. 1994;12:159–65.

8. Morland BJ, Mann JR, Milford DV, Raafat F, Stevens MC. Ifosfamide nephrotoxicity in children: histopathological features in two cases. *Med Pediatr Oncol*. 1996;27:57–61.
9. McCulloch T, Prayle A, Lunn A, Watson AR. Karyomegalic-like nephropathy, Ewing's sarcoma and ifosfamide therapy. *Pediatr Nephrol*. 2011;26:1163–6.
10. Friedlaender MM, Haviv YS, Rosenmann E, Peylan-Ramu N. End-stage renal interstitial fibrosis in an adult ten years after ifosfamide therapy. *Am J Nephrol*. 1998;18:131–3.
11. Berns JS, Haghighat A, Staddon A, Cohen RM, Schmidt R, Fisher S, Rudnick MR, Tomaszewski JE. Severe, irreversible renal failure after ifosfamide treatment. A clinicopathologic report of two patients. *Cancer*. 1995;76:497–500.
12. Willemse PH, de Jong PE, Elema JD, Mulder NH. Severe renal failure following high-dose ifosfamide and mesna. *Cancer Chemother Pharmacol*. 1989;23:329–30.
13. Monga G, Banfi G, Salvatore M, Amatruda O, Bozzola C, Mazzucco G. Karyomegalic interstitial nephritis: report of 3 new cases and review of the literature. *Clin Nephrol*. 2006;65:349–55.
14. Bhandari S, Kalowski S, Collett P, Cooke BE, Kerr P, Newland R, Dowling J, Horvath J. Karyomegalic nephropathy: an uncommon cause of progressive renal failure. *Nephrol Dial Transplant*. 2002;17:1914–20.
15. Ateşşahin A, Ceribaşı AO, Yuce A, Bulmus O, Cikim G. Role of ellagic acid against cisplatin-induced nephrotoxicity and oxidative stress in rats. *Basic Clin Pharmacol Toxicol*. 2007;100:121–6.
16. Spoendlin M, Moch H, Brunner F, Brunner W, Burger HR, Kiss D, Wegmann W, Dalquen P, Oberholzer M, Thiel G, Mihatsch MJ. Karyomegalic interstitial nephritis: further support for a distinct entity and evidence for a genetic defect. *Am J Kidney Dis*. 1995;25:242–52.
17. Sehirli O, Sakarcan A, Velioğlu-Oğünç A, Cetinel S, Gedik N, Yeğen BC, Sener G. Resveratrol improves ifosfamide-induced Fanconi syndrome in rats. *Toxicol Appl Pharmacol*. 2007;222:33–41.