Karyomegalic interstitial nephropathy following ifosfamide therapy

R. Jayasurya, B. H. Srinivas[1], M. Ponraj[2], S. Haridasan, S. Parameswaran, P. S. Priyamvada

Departments of Nephrology, [1]Pathology and [2]Medical Oncology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India

ABSTRACT

Ifosfamide (IFO), an alkylating agent used for the management of solid organ tumors, can cause reversible Fanconi's syndrome and acute kidney injury. Karyomegalic interstitial nephropathy (KIN) is a rare form of chronic tubulointerstitial nephritis, initially described as a familial nephropathy in adults. So far, four cases of KIN have been reported in pediatric and adolescent population following treatment with IFO. We report a 22-year-old man who developed renal dysfunction following IFO therapy for relapsed Hodgkin's lymphoma. Renal biopsy revealed chronic tubulointerstitial nephritis with atypical tubular epithelial cells showing nuclear enlargement and hyperchromasia, consistent with a diagnosis of KIN. The renal function improved following a short course of corticosteroids.

Key words: Cancer chemotherapy, chronic interstitial nephritis, karyomegaly

Introduction

Karyomegalic interstitial nephropathy (KIN) is a rare form of chronic tubulointerstitial nephritis, characterized by atypical tubular epithelial cells with large hyperchromatic nuclei having irregular outlines.[1] It was originally described as a familial nephropathy. Later similar lesions were described in long-term survivors of malignancies treated with the alkylating agent ifosfamide (IFO).[2,3] To the best of our knowledge, only four cases of IFO-induced KIN (one case series and a single case report) have been published so far, and the optimal therapeutic strategies are unclear.

Address for correspondence:
Dr. P. S. Priyamvada,
Department of Nephrology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry - 605 006, India.
E-mail: priyamvadaps@gmail.com

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Case Report

A 22-year-old man with relapsed Hodgkin's lymphoma (HL) was referred to our hospital for impaired renal function. HL was diagnosed in 2007 and was successfully treated with chemotherapy (adriamycin, bleomycin, vinblastine, and dacarbazine). He remained in complete remission (CR) for 7 years, after which the disease relapsed. His renal function testing done 6 months prior to the relapse was normal.

On evaluation, he had a serum creatinine of 2.1 mg/dl (estimate glomerular filtration rate $[eGFR]_{CKD\ EPI}$ 43.4 ml/min/1.73 m^2) and right hydroureteronephrosis (HUN). There were no obstructive lesions, and etiology of HUN was not obvious. A double J (DJ) stent was placed on right side, following which creatinine came down to 1.8 mg/dl within a week. Considering the

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aggressive nature of malignancy, it was decided to start chemotherapy before normalization of GFR. He received three cycles of chemotherapy with IFO, carboplatin, and etoposide (cumulative IFO dose: 18 g), following which he attained CR. Serum creatinine remained at 1.8 mg/dl throughout the course of chemotherapy. The DJ stent was removed in view of complete resolution of HUN. One week later, the serum creatinine rose to 2.4 mg/dl; a repeat imaging revealed re-appearance of HUN. A retrograde pyelogram showed no filling defects, and a DJ stent was re-inserted. Follow-up imaging 1 week later showed complete resolution of HUN. The serum creatinine came down to 1.9 mg/dl ($eGFR_{CKD\ EPI}$ 46/min/1.73 m^2) and remained at the same level for the next 2 months. A repeat abdominal ultrasound showed normal sized kidneys with DJ stent *in situ*. There was no HUN. He had evidence of a partial Fanconi's syndrome [Table 1]. A kidney biopsy was performed in view of incomplete recovery of renal function even after 2 months of cessation of IFO therapy and relief of ureteric obstruction. Kidney biopsy showed normal glomerular morphology, moderate interstitial inflammation composed of mainly lymphocytes and tubular atrophy amounting to 30–35% of the core. The proximal tubular epithelial cells showed markedly enlarged hyperchromatic nuclei with irregular margins. Immunohistochemistry for cytomegalovirus (CMV) and SV 40 were negative. The Ki 67 index was low. The histopathologic features were consistent with karyomegalic interstitial nephritis [Figure 1]. Even though there was evidence of chronicity, we decided to proceed with a trial of prednisolone 1 mg/KBW. The patient responded to corticosteroids, and his serum creatinine came down to 1.5 mg/dl ($eGFR_{CKD\ EPI}$ 65 ml/min/1.73 m^2) by the end of the 2nd week. His DJ stent was removed, and steroids were continued for another 2 weeks. His serum creatinine is remaining stable at 1.5 mg/dl after 3 months of follow-up.

Table 1: Biochemical parameters at the time of biopsy

Parameter	Value
Urine routine	
Protein	++
Sugar	++
Microscopy	Plenty of pus cells 3-5 RBC/hpf No casts
Blood biochemistry	
Sodium (mEq/L)	128
Potassium (mEq/L)	2.8
Calcium (mg/dl)	8.4
Phosphorus (mg/dl)	1.0
Uric acid (mg/dl)	2.1
ABG	
pH	7.2
HCO_3 (standard) (mEq/L)	14.8
Anion gap	22.22
SBE	−10
24 h urine protein (mg/day)	184
24 h urine potassium (mEq/day)	76
24 h urine phosphorus (mg/day)	880
TMP/GFR	0.02 mmol/L (normal 0.80-1.35 mmol/L)

RBC: Red blood cell, ABG: Arterial blood gas, SBE: Standard base excess, GFR: Glomerular filtration rate, TMP: Tubular maximum phosphate

Discussion

Karyomegalic interstitial nephritis is a rare form of familial chronic tubulointerstitial nephritis described by Burry in 1974. The disease presents in the second or third decade of life with progressive renal impairment, subnephrotic proteinuria, and bland urinary sediment often with a history of recurrent respiratory tract infections. Histology shows chronic interstitial nephritis with abnormally enlarged hyperchromatic, irregular nuclei in the tubular epithelial cells. It is postulated that the disease results from defective cell division due to multiple events including exposure to toxins, viruses, or genetic predisposition. The cells demonstrate a high DNA ploidy and low index of proliferation as evidenced by low Ki 67 and proliferating cell nuclear antigen expression.[1,2] Similar lesions are described in other organs, but usually do not produce organ dysfunction. Urine cytology is reported to show large pleomorphic cells mimicking carcinoma.[4] The exact genetic basis of KIN is not clearly known. Recently, mutations in fanconi anemia-associated nuclease 1 protein leading to defective DNA repair has been documented in multiple kindreds with familial KIN.[5]

Exposure to cancer chemotherapeutic agent IFO often results in reversible tubular toxicity. Chloroacetaldehyde,

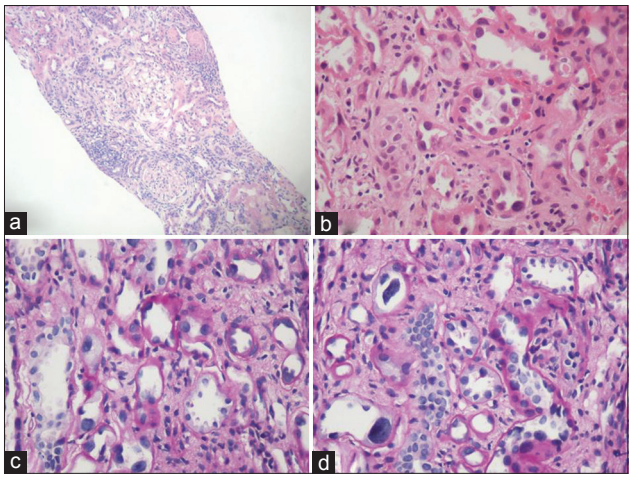

Figure 1: (a) Light microscopy showing normal glomeruli with diffuse moderate degree of lymphocytic infiltration (H and E ×100); (b) H and E staining showing tubules with enlarged nuclei (H and E ×200); (c and d) PAS staining showing enlarged hyperchromatic nuclei in the tubules (PAS ×400)

a metabolite of IFO, acts by depleting glutathione and thus making cells vulnerable to oxidative stress. The reported prevalence of long-term nephrotoxicity following IFO therapy in children varies from 4.6% to 42%.[6,7] Younger age, higher cumulative doses, unilateral nephrectomy, renal irradiation, and concurrent administration of platinum-containing compounds enhance the long-term nephrotoxic potential of IFO. Farry *et al*. observed that the first cycle of IFO leads to an eGFR decline of 15 ml/min/1.73 m^2, followed by a slower but steady long-term decline in adults.[8] There are a few reports of acute and chronic tubulointerstitial nephritis following cancer chemotherapy. Airy *et al.* reported that up to 40% of the patients who developed acute interstitial nephritis following chemotherapy showed a favorable response to corticosteroids, whereas those with chronic interstitial nephritis had a poor response.[9]

There is limited data on IFO-induced KIN. McCulloch *et al*. described KIN in three pediatric patients who were survivors of Ewing's sarcoma treated with IFO.[2] All three patients had renal dysfunction documented between 15 months to 5 years following IFO therapy. The histological picture was similar, characterized by chronic interstitial nephritis and karyomegaly. All had evidence of proximal renal tubular acidosis. Two patients maintained stable renal function without any specific therapy whereas one patient rapidly progressed to ESRD in spite of receiving corticosteroids. Matsuura *et al*. described a 15-year-old boy who developed renal failure and fanconi's syndrome 3 years after receiving IFO.[3] In spite of significant chronicity in the biopsy, the patient showed improvement in GFR following corticosteroid therapy. It is postulated that IFO-induced DNA damage prevents the normal cellular regenerative process resulting in karyomegaly. The Ki 67 staining index in tubular cells is low, reflecting a reduced rate of cellular proliferation. Other causes for nuclear enlargement such as BKV and CMV infection needs to be ruled out in suspected cases of KIN.

In our patient, the histopathological changes were documented at 2 months post-IFO therapy, which is quite early when compared to the previous reports. The concomitant admission of carboplatin could have accelerated the DNA damage in the renal tubular cells. It seems that the histopathological changes may precede the onset of clinical renal dysfunction. Radha *et al.* reported KIN with normal renal function in a child who received cyclophosphamide (CYC) therapy for FSGS.[10] KIN has not been reported with chemotherapeutic agents other than IFO and CYC.

To the best of our knowledge, this is the first report of IFO-induced KIN in adults. In spite of significant chronicity in biopsy, the GFR showed a sustained improvement of 16 ml following steroid therapy. It is possible that KIN might be under-diagnosed as the disease remains asymptomatic in the early stages. Since familial KIN can occur in the second decade, it is possible that the patient might have carried a mutation with IFO acting as the second hit. Genetic testing for KIN is not yet available for routine clinical application. This case report shows the importance of performing a kidney biopsy in patients who develop persistent renal dysfunction secondary to the use of chemotherapeutic drugs which acts by interfering with multiplication of DNA. Identifying this complication and prompt initiation of treatment with steroids may arrest the progression to chronic kidney disease.

Conclusion

KIN is a rare form of chronic tubulointerstitial nephritis, which can develop secondary to IFO therapy. The condition can be diagnosed only with a high index of suspicion and careful pathologic examination. This case report highlights the importance of a trial of corticosteroid therapy in diagnosed cases.

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Conflicts of interest
There are no conflicts of interest.

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