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IFOSFAMIDE INDUCED KARYOMEGALIC INTERSTITIAL NEPHRITIS – A CASE REPORT

Nephrology

Mythri Shankar Assistant Professor, Department Of Nephrology, Institute Of Nephro-urology, Bangalore

Sanjay Rampure* Consultant Nephrologist, Manipal Hospitals, Bangalore *Corresponding Author

Mahesha V Consultant Nephro pathologist, Manipal Hospital, Bangalore

Vishwanath Siddini HOD & Consultant Nephrologist, Manipal Hospital, Bangalore

H. Sudharshan Ballal Chief Consultant Nephrologist, Manipal Hospital, Bangalore

ABSTRACT

Karyomegalic interstitial nephritis is a rare cause of hereditary interstitial nephritis. There are few case reports of Ifosfamide, an alkylating agent causing karyomegalic interstitial nephritis. There are 4 case reports described in children and adolescents. There is only one case report described in adults. Here we present a case report of a 36 year old gentleman, who was treated with ifosfomide as part of chemotherapy regimen for myxoid liposarcoma. He later went on to develop renal dysfunction requiring renal replacement therapy. Evaluation of renal dysfunction with Renal biopsy revealed karyomegalic interstitial nephritis. He had significant improvement with steroid treatment. He was weaned off hemodialysis. This emphasizes the importance of diagnosis of this condition and appropriate therapy with steroids for reversal of renal dysfunction.

KEYWORDS

INTRODUCTION

Ifosfomide (IFO), is a nitrogen mustard and an alkylating agent. It is used for treatment of solid tumours like soft tissue sarcoma, testicular cancer, bladder cancer, cervical cancer, small cell lung cancer and ovarian cancer. Common side effects include alopecia, vomiting, infections,bone marraw supression, reversible fanconi's and acute kidney injury. It was approved for medical use for the first time in the United States in 1987. It is included in the World Health Organization's List of Essential Medicines.

Karyomegalic interstitial nephritis (KIN) is one of the rare causes of chronic interstitial nephritis (CIN), described for the first time 40 years ago. The prevalence of this disorder is <1%. It is a hereditary disease with genetic mutations in HLA- A6 and HLA B35 haplotypes causing the disease.(1)

Here, we present a rare case of karyomegalic CIN secondary to Ifosfomide chemotherapy.

CASE REPORT:

36 years old, male patient was evaluated for lump in the left groin June 2015. The lump was excised and the histopathology was suggestive of myxoid liposarcoma with focal round cell areas. He was treated with chemo radiotherapy. He received 2 cycles of chemotherapy with inj ifosfamide, inj Mesna and inj. Doxorubicin. He attained complete remission following chemotherapy.2 months later, he presented with acute gastroenteritis. He was found to be in volume depleted state. On evaluation, his creatinine was found to be 6 mg/dl. He was treated with I.V hydration and antibiotics. His creatinine reduced to 4 mg/dl. Urine routine was suggestive of sub nephrotic range proteinuria. As the creatinine continued to increase to 15mg/dl on follow up in spite of adequate hydration, he underwent renal biopsy.

Renal biopsy light microscopy (Figure 1) showed ten glomeruli. None of them were obsolescent. They were normal in size.Tubules showed severe degree of acute tubular injury with thinning of the epithelium. There were marked nuclear changes in the proximal tubule lining epithelial cells- in the form of anisonucleosis, nuclear hyperchromasia and karyomegaly. Interstium was edematous and showed scattered foci of lymphocytes. There is mild degree of tubular atrophy and interstial fibrosis, occupying less than 25% of the cortical area. Vessels were normal.

Immunohistochemistry was negative for CMV and BKV. Immunofluorescence was negative for IgG, IgA, IgM, C3 and C1q antisera. Kappa and lambda light chains did not show restriction.

Ki67 staining was positive in proximal tubule cells. (figure 2)

Following the biopsy report, he was started on steroids. His creatinine reduced to 4mg/dl in a month's time with steroid therapy. He was weaned off hemo dialysis as he improved symptomatically and had good urine outputs.

Unfortunately, he developed cavitatory pulmonary Koch's. Hence, steroids were stopped and he was started on ATT. Following which his renal functions continued to worsen and he ended up in ESRD requiring hemodialysis in a span of one month.

DISCUSSION:

One of the rare causes of hereditary chronic interstitial nephritis is KIN. KIN term was introduced by Mihatsch et al [2] in 1979, who described 3 cases of systemic karyomegally associated with chronic interstitial nephritis. Disease manifests as slowly progressive disease chronic kidney disease in second or third decade. Usually reaching end stage renal disease (ESRD) before 50 years of age. Extra renal features are usually absent. If present, it manifests as recurrent upper respiratory tract infections and hepatic dysfunction. Patients usually present with sub nephrotic range proteinuria. Less than 30% present hematuria. In a case series (6 cases) KIN published by Sunil Bandari et al. [3] Three of the patients did not have any recurrent respiratory infections and there was no evidence of karyomegaly in organs other than the native kidney. In a case report described by Sclare [4], patient presented with pneumopathy but he failed to identify pulmonary karyomegalic changes at autopsy.

KIN is characterized by enlarged tubular epithelial cell nuclei predominantly in proximal and distal tubule and chronic interstitial nephritis. Karyomegaly is associated with impairment of cell division and inhibition of mitosis of these cells. Marked by the presence of Ki 67. The high ploidy values are indicative of increased degree of karyotypic abnormalities and are recognized as marker of malignant potential and/or poor prognosis in a number of disease status. In contrast presence of karyomegalic cells in other tissues including brain astrocytes, Schwann cells of peripheral nerves, intestinal smooth muscle cells and bile duct epithelium when present remains undetermined considering no clinical sequelae have been identified. Vadiaka et al.[5] noted only a transient rise in liver enzymes. Extra renal karyomegaly is usually associated with only subtle clinical and

biological changes.

Historically, KIN was thought to be a hereditary disorder because almost half of patients had a family history of nephropathy. Disease has been recently attributed to autosomal recessive mutations in the FAN1 gene, which encodes for Fanconi anemia associated nuclease type1. FAN1 is more specifically involved in repair of interstand crosslinks induced DNA breaks by being required for efficient of homologous recombination intermediates. Patients with Fanconi anemia usually manifest osteomalacia, bone marrow failure and predisposition to cancers [6]. Chaki et al. [7] identified mutations in 2 other genes of the DNA damage response pathway in patients with renal ciliopathies, reinforcing the concept of a potential link between defective DNA damage repair and the pathogenesis of chronic kidney disease.

There is limited data on Ifosfamide induced KIN. There are few cases of KIN reported in pediatric and adolescent population following treatment with Ifosfamide (IFO).Data on adult population are lacking . McCulloch [8] et al. diagnosed KIN in three pediatric patients who were survivors of Ewing's sarcoma treated with IFO. Mastuura et al. [9] described a 15-year-old boy who developed renal failure and Fanconi's syndrome 3 years after receiving IFO. Jayasurya R et al [10] reported a 22-year-old man who developed renal impairment following treatment with IFO for relapsed Hodgkin's lymphoma. Younger age and higher doses increase the long term nephrotoxic potential of IFO. It is postulated that IFO-induced DNA damage prevents the normal cellular regenerative process resulting in karyomegaly. This suggests 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.

To the best of our knowledge, this is the 2nd only case report of ifosfamide induced KIN in adults. Our patient improved significantly with steroid treatment. The genetic studies for KIN are not widely available. This case report emphasizes 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. Early diagnosis of this complication and prompt initiation of treatment with steroids may recover the kidney function.

CONCLUSION:

KIN is a rare form hereditary interstitial nephritis. KIN secondary to IFO in adults is even rarer. This case study emphasizes the early treatment with steroids to prevent progression to ESRD

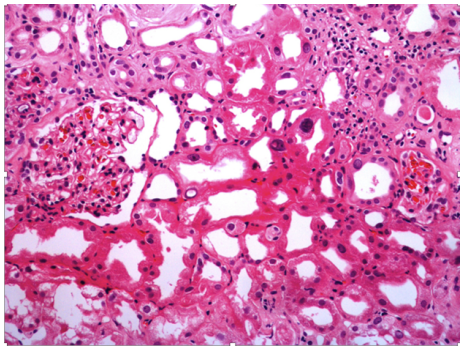

Figure 1 : light microscopy

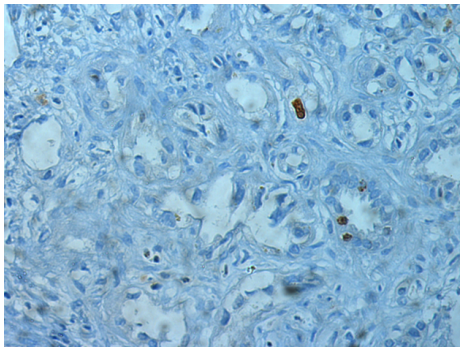

Figure 2: ki 67 staining

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