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Review Article

Karyomegalic Interstitial Nephritis: a Review of Literature

Vinay KS[1*] and Sujatha Siddappa[1]

[1]Department of Pathology, Institute of NephroUrology Bangalore, Karnataka, India

Abstract

Introduction

Karyomegalic Interstitial Nephritis (KIN) is a rare cause of hereditary chronic interstitial nephritis described first time over 40 years ago. The prevalence of this disorder KIN is less than 1% of all the biopsies examined. KIN term was introduced by Mihatsch et al in 1979, who described 3 cases of systemic karyomegaly associated with chronic interstitial nephritis. Disease presents as slowly progressive chronic kidney disease eventually leading to ESRD before the age of 50 years. Extra renal manifestations are clinically uncommon. They may include recurrent upper respiratory tract infections and transient elevations in liver function tests.

Morphology and Diagnsosis

The presence of karyomegalic tubular epithelial cells on the renal biopsy specimen is the characteristic morphologic picture and it also helps to differentiate from other chronic tubulointerstitial disease. Karyomegalic cells have been identified in various tissues including astrocytes, schwann cells, intestinal smooth muscle and bile duct epithelium, though not diagnostic.

Pathophysiology and Pathogenesis

There has been many case reports and case series published in the literature since the first case reported by Bury A.F, extreme dysplasia in renal epithelium of a young women dying from hepatocellular carcinoma. Since then there has been many insights into the pathogenesis with special reference to hereditary nature of the disease and in identification of genetic mutations. Though uncertain and controversial, HLA – A9 and HLA B35 haplotypes suggest the possibility of genetic susceptibility leading to familial clustering of cases. Karyomegaly is said to be associated with impairment of cell division. Examination of nuclear proliferation markers Ki 67 and PCNA/cyclin, if increased, suggest inhibition of mitosis of these cells. The disease has been recently ascribed to autosomal recessive mutations in the FAN 1 gene, which encodes Fanconi anemia associated nuclease 1(FAN1).This nuclease belongs to Fanconi's anemia DNA damage response pathway and is required for the repair of DNA interest and crosslinks.FAN1 could be more specifically engaged in the repair of a possible renal specific DNA damage. These FAN 1 mutations would render tubular cells more susceptible to environmental genotoxin induced renal DNA damage. Most recent case has been reported by Pierre Isnard in May , 2016 ,who reported 36 yr old Turkish women presenting with chronic kidney disease and high blood pressure. We are herby trying to understand in detail the clinico pathological findings with reference to diagnosis, pathophysiology and pathogenesis by reviewing the Google searched 15 case studies including approximately about 40 cases reported till May 2016, as the last referred case.

Prognosis

Disease usually presents in third decade of life as chronic interstitial nephritis, although slowly progresses Eventually Leading End Stage Renal Disease (ESRD).

Conclusion

KIN is a rare and may be under diagnosed disorder characterized by enlarged tubular epithelial cell nuclei and chronic interstitial nephritis. As pathologists dealing with kidney biopsy with chronic interstitial nephritis, we should always keep KIN in the differential diagnosis especially in younger patients. Identification of mutations in FAN1 gene underscores recent insights linking inadequate DNA repair and susceptibility to chronic kidney disease.

Key Words: KIN; Chronic Interstitial Nephritis; ESRD; FAN1

Introduction

KIN is a rare cause of hereditary chronic interstitial nephritis described first time over 40 years ago [1]. KIN term was introduced by Mihatsch et al [2] in 1979, who described 3 cases of systemic karyomegally associated with chronic interstitial nephritis. Disease presents as slowly progressive chronic kidney disease eventually leading to ESRD before the age of 50 years.

Extra renal features are absent or mild consisting of recurrent upper respiratory tract infections and abnormal liver Function tests.

Clinical Presentation, Morphology And Diagnosis

The prevalence of this disorder KIN is less than 1% of all the biopsies examined. KIN usually presents as slowly progressive chronic kidney disease ,eventually leading to end stage renal

***Corresponding author:** Sujatha Siddappa and Sujatha Siddappa, Department of Pathology, Institute of NephroUrology Bangalore, Karnataka, India, E-mail: sujathasiddappa@gmail.com

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disease in the early adulthood. Patients usually present with mild proteinuria, usually < 1g /day. Whereas less than 1/3 present with urinary sediment abnormalities-mostly consistent with hematuria. The clinical picture has been associated with recurrent upper respiratory tract infections in addition to symptoms of chronic renal impairment beginning in the third decade of life. 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 .Also 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 a rare disorder characterized by enlarged tubular epithelial cell nuclei and chronic interstitial nephritis. Usually these patients presents with renal impairment. Extra renal manifestations are rare. Analysis of the renal biopsy specimen shows presence of karyomegalic tubular epithelial cells, lining the proximal and distal tubules and characterize by markedly enlarged and hyperchromatic nuclei, which is the hallmark of the disease usually associated with non specific glomerulosclerosis, moderate to severe chronic interstitial fibrosis and tubular changes. Karyomegaly has been associated with impairment of cell division. Examination of the nuclear nuclear proliferation ,Ki 67 and PCNA/Cyclin, if increased suggest the inhibition of mitosis of these cells. Some have found the presence of Ki 67 , while more recently others have not. The high ploidy values are indictive 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 other tissues including brain astrocytes, intestinal smooth muscle cells, Schwann cells of peripheral nerves and bile duct epithelium when present remains undetermined considering no clinical sequelae have been identified. In a case published by Vadiaka et al. [5] noted a transient rise in liver enzymes but found no specific pathology on liver biopsy. Case report by Pierre Isnard [6], patient had a history of recurrent upper respiratory tract infections. Extra renal karyomegaly is usually associated with only subtle clinical and biological changes. Karyomegalic cells can also be detected in the urine samples. Renal karyomegally can have other differential diagnosis, including viral infections, immunosuppressive therapy such as alkylating agents and exposure to heavy metals and mycotoxins, particularly Ochrotoxin A.

Pathophysiology of Karyomegalic Interstitial Nephritis

Historically, KIN was thought to be a hereditary disorder because almost half of patients had a family history of nephropathy. Disease has been recently ascribed to autosomal recessive mutations in the FAN1 gene, which encodes for Fanconi anemia associated nuclease 1.Nuclease belongs to the Fanconi anemia DNA damage response pathway and is required for repair of DNA interst and cross links.FAN1 is more specifically involved in the repair of interstand crosslinks induced DNA breaks by being required for efficient of homologous recombination intermediates. Patient with Fanconi anemia usually display developmental abnormalities, bone marrow failure and predisposition to cancers.In contrary to the other FAN genes,FAN1 mutations have not been associated with Fanconi anemia mutations, likely because of a predominant expression of the gene in the kidney, liver and neuronal tissue [7]. In particular, FAN1 could be more more specifically engaged in the repair of a possible renal specific DNA damage. Chaki et al. [8] also 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**.**

Animal Studies

Our DNA does get damaged and our cells have a host of complicated repair mechanisms to deal with such injuries. Of interest is a particular type of DNA damage-repair of interst and cross links, in which two strands of double helix normally twine about each other become physically linked. This type of damage is particularly problematic for the cell because when the two strands stick to each other, DNA cannot replicate and genes cannot be properly expressed. Mutations in many genes that regulate DNA interst and cross link repair cause Fanconi anemia, a rare disorder that can lead to infertility, bone marrow failure, and predisposition to cancer.

In a recent study published in Genes and development, Smogorzewska and her co-workers engineered mice that lack one of the genes involved in the repair of DNA damage. Engineered mice were called knockout mice. The gene that was knocked out was FAN1.In observing the kidney cells from FAN1 knockout mice, the researchers noticed that their nuclei were abnormally large. This phenomenon karyomegaly is thought to occur because the DNA duplicates too many times. They saw enlarged nuclei in the liver as well and the mice developed liver dysfunction. They think FAN1 protein helps to protect the liver function as the animals age. Both the kidneys and the liver need to deal with a lot of toxins in explaining about why FAN1 deficiency affects these tissues in particular.FAN1 helps them to do their lob of detoxification. Without it they can't deal with the toxins. Even though FAN1 interacts with DNA repair proteins implicated in Fanconi anemia, this study demonstrates that it actually doesn't have to do so in order to repair the DNA damage. This may explain why karyomegalic interstitial nephritis and Fanconi anemia cause completly different symptoms in patients. Although FAN1 is clearly necessary for interst and cross link repair, the researchers say it is possible that the kidney and liver dysfunction are not directly related to the problem with this type of repair. Finally the authors concluded that the a lot remains to be learned about FAN1.What activates it, what it interacts with, and the specific type of DNA damage it repairs. The mechanism of genome reduplication in the kidneys and livers is also opaque and an area of intense study [9].

Ochratoxin And Kin

Environmental toxins, including some herbal medicines known to cause kidney disease. Ochratoxin A is a mycotoxin produced by a number of Aspergillus and Pencillium species, which contaminate cereals in particular. Humans are exposed to this toxin through foods of vegetable and animal origin. Ochratoxin A Nis nephrotoxic

to all animal species tested. It causes porcine nephropathy and induces karyomegaly in proximal tubules in rats. Ochratoxin A is regarded as the main causal agent of Balkan endemic nephropathy [10]. Michel Godin [11] presented two cases of brother and sister with KIN. Both had same HLA haplotype A9/B35.A very high concentrations Ochratoxin A was detected in blood and the urine of both the patients. Authors suspected high Ochrratoxin A levels of the condition. They also thought the possibility of a(genetic?) abnormality of ochratoxin metabolism cannot be ruled out.

Kin And Chemotherapy

There are few cases of KIN reported in paediatric and adolescent population following treatment with Ifosfamide (IFO). IFO an alkylating agent used for the management of solid organ tumors, can cause reversible Fanconi's syndrome and acute kidney injury. There is limited data on IFO induced KIN. McCulloch [12] et al. described KIN in three pediatric patients who were survivors of Ewing's sarcoma treated with IFO. Mastuura et al. [13] described a 15 year old boy who developed renal failure and *Fanconi's* syndrome 3 years after receiving IFO. Jayasurya R et al [14] reported a 22 year old man who developed renal dysfunction following treatment with IFO therapy for relapsed Hodgkin's lymphoma. Exposure to cancer chemotherapeutic agent IFO often results in reversible tubular toxicity. *Chloracetaldehyde,* 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%. Younger age ,high cumulative doses, unilateral nephrectomy, renal irradiation and concurrent administration of platinum containing compounds doses enhance the long term nephrotoxic potential of IFO. It is postulated that IFO-induced DNA damage prevents the normal cellular regerative 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.

Our Observations And Conclusion

Out of the total 44 cases we referred (Google searched case reports and case series till December 2016, [1-32], 25 patients were male with slight male predilection. Among these 44 cases ,16 cases had positive family history.31 cases had pure kidney presentation. 15 cases had other associated abnormal liver function tests. About 4 cases had exposure to Ochratoxin A. 6 Cases showed the presence of karyomegalic cells in the urine indicating KIN should be kept in the differential diagnosis while dealing with urine cytology from patients without obvious urological symptoms. KIN is a rare and may be under diagnosed disorder characterized by enlarged tubular epithelial cell nuclei and chronic interstitial nephritis. As pathologists dealing with kidney biopsy with chronic interstitial nephritis, we should always keep KIN in the differential diagnosis especially in younger patients. Identification of mutations in FAN1 gene underscores recent insights linking inadequate DNA repair and susceptibility to chronic kidney disease.

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