A Case of Imatinib Induced Nephrotic Syndrome in a Child with Chronic Myeloid Leukaemia

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Abstract:

Background: *Tyrosin kinase inhibitors (TKI) are used as a targeted therapy for the treatment of chronic myeloid leukaemia and Philadelphia chromosome positive acute lymphoblastic leukaemia. Increasing use of TKI has been associated with hypertension, proteinuria and acute kidney injury. There are only afew reports of adults with TK -inhibitor associated nephrotic syndrome.But TK inhibitor associated Nephrotic syndrome is very rare in paediatric age group.*

Case: *A -6- year old boy presented with fever, anaemia, splenomegaly, leucocytosis and finally diagnosed as accelerated phase of chronic myeloid leukaemia (CML) by bone marrow study.He achieved clinical and haematological remission with Imatinib. But developed generalized oedema and was found to have massive proteinuria and microscopic haematuria after three and half months. Renal biopsy revealed focal segmental glomerulosclerosis. Imatinib along with Prednisolone, 60 mg/m2/ day was added to treat nephrotic syndrome. Imatinib discontinued as the patient did not achieve complete remission. After one week of Imatinib withdrawal and five weeks of daily prednisolone the boy attained complete remission of nephrotic syndrome.*

Conclusion: *Tyrosine Kinase inhibitors are important therapies in paediatric cancer and their use is expanding. Timely recognition of renal adverse effectsfor TK inhibitors can aid in the proper management of cancer patients.*

Key words: *Imatinib, Nephrotic Syndrome, Chronic Myeloid Leukaemia.*

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Introduction:

Chronic myeloid leukaemia is a clonal myeloproliferative disorder of haematopoietic stem cell origin. It is caused by Bcr – Abltyrosin kinase induced by the reciprocal chromosomal translocation t(9;22) (q34;q11) called Philadelphia Chromosome.[1] The introduction of imatinib, a Bcr-Abl tyrosine kinase inhibitor is the major progress in the treatment of CML.The outcome of Ph+ ALL before the imatinib era was very poor, with a five year event free survival rate of 25% and an overall survival rate of 36%.[2]The addition of 1st generation tyrosine kinase, imatinib has improved the five year event free survival to 80%[3] which was more than double the event free survival of the patients treated without imatinib.The emergence of effective and well-tolerated therapies targeting specific genes allowing chemotherapy-refractory malignancy to be treated, but increased the occurrence of kidney-related adverse events.[4]Clinical manifestations may include acute kidney injury, glomerular injury with proteinuria, electrolyte disturbances, hypertension, thrombotic microangiopathy, tubular dysfunction, and at times chronic kidney disease. The nephrotoxicity profiles of thesetherapies are qualitatively different from those observed with conventional cytotoxic chemotherapy.[5]There are some reports shows TKI associated nephrotic syndrome in adults but it is rare in

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children. Here we discuss about a case of TKI induced nephrotic syndrome. The relationship of nephrotic syndrome onset to TK-inhibitor therapy and resolution of nephrotic syndrome with cessation of therapy strongly imply an association in this patient.

Case summary:

A 6-year- old boy presented with fever, anaemia, splenomegaly, leucocytosis and finally diagnosed as accelerated phase of chronic myeloid leukaemia (CML) by bone marrow study. He achieved clinical and haematological remission with Imatinib, a first generation TKI at a dose of100mg/m^2. The patient was irregular on treatment and lost to follow-up. Later on, at the age of 7 year he presented with respiratory tract infection, anaemia, splenomegaly and leucocytosis. Again, Imatinib was started and he got remission. After three and half months of starting imatinib he developed generalized oedema, massive proteinuria and microscopic haematuria. Serum concentration of albumin was 1.5 g/dl, cholesterol was 420 mg/dl, and a urine protein to creatinine ratio was 17 mg protein/mg creatinine. Serum creatinine concentration was normal 0.6 mg/dl. She had normal C3 and C4.His ANA, C-ANCA, P-ANCA, HBsAg, Anti HCV were negative.Renal ultrasound was normal. A renal biopsy was performed.On light microscopy, there were 18 glomeruli; and found FSGS (three glomeruli had segmental sclerosis andmost of the remaining glomeruli showed segmental increase of mesangial cells and matrix. Capillary basement membrane thickness appeared normal). No deposit of IgA, IgG, IgM, C3 or C1q was found in DIF. Prednisolone was started at a dose of 60 mg/m2/day, added on the day after renal biopsy to treat nephrotic syndrome. Patient did not achieve complete remission even after 4 weeks of adequate daily dose of prednisolone. Imatinib was discontinued. After one week of imatinib withdrawal and five weeks of daily prednisolone the boy attained complete remission of nephrotic syndrome. Later on switched over to Dasatinib, a second generation TKI. Since then he was on complete remission of CML and nephrotic syndrome. After 6 weeks of daily prednisolone, it was given 40 mg/m2 every alternate day.Unfortunately we lost him after 3 months due to severe respiratory tract infection and septic shock.

Discussion:

Imatinib was the first signal transduction inhibitor (STI), used in a clinical setting. It prevents a Bcr-Abl protein from exerting its role in the oncogenic pathway in chronic myeloid leukemia (CML). Imatinib directly inhibits the constitutive tyrosine kinase activity, which results in the modification of the function of various genes involved in the control of the cell cycle, cell adhesion, cytoskeleton organization and finally in the apoptotic death of Ph(+) cells.[6] Common adverse effects of imatinib are thrombocytopenia, acneifom rash, petechial spot, leukopenia and anaemia.Nephrotic range proteinuria is a rare side effects of imatinib. Dasatinib, the second generation TKIs and a multi-kinase inhibitor has 325-times stronger activity against Bcr-Abl than imatinib. Nephrotic range proteinuria is the toxicity of dasatinib therapy. Incidence rate is unexpectedly high while nephrotic range proteinuria is rare with exposure to other TKIs.[6] Till to date, seven cases of dasatinib induced nephrotic syndrome have been reported in the scientifc literature.[7] To the best of our knowledge a very few cases have been reported with imatinib induced nephrotic syndrome in children. Herein, we found a rare case of nephrotic syndrome associated with imatinib therapy.

Ruebner et al. reported four cases of nephrotic syndrome associated with tyrosine kinase inhibitors (imatinib, dasatinib,sunitinib, quazertinib). Among the four patients one was a CML patient and the other two were ALL patients. Their ages ranged from 3 months to 15 years. Nephrotic Syndrome developed on an average one and half to two years of starting treatment with Dasatinib in two cases &imatinib in one case[9]. In this case the time interval was three and half months. Only one of the four patient had a renal biopsy which showed glomerular sclerosis, and a few segmental areas of increased mesangial cellularity and matrix which is consistent with this case. On immunofluorescence, immunoglobulin M (IgM) and C1q stained 1+ in a partial granular mesangial and loop pattern was seen.One patient also had clinical features of TMA (hypertension, AKI, microangiopathichemolyticanemia, and thrombocytopenia). Three of the four patients had resolution of nephrotic syndrome after cessation of TK inhibitor therapy[9].

Young Tae Lim et al. described a 5 year old boy with Ph (+) ve ALL who developed nephrotic syndrome after Dasatinib therapy. Renal biopsy revealed no abnormality except fused foot processes of podocyte through electron microscopy[10]. As in other cases resolution of

nephrotic syndrome achieved after discontinuation of imatinib.

The mechanism of glomerular injury by TK inhibitors leading to nephrotic syndrome is not completely understood. Inhibition of VEGF expression in podocytes by TK inhibitors has been suggested in the pathogenesis of glomerular injury. Abnormalities in VEGF expression have been implicated in the pathogenesis of minimal change disease and other glomerulopathies[11].Another potential mechanism of renal injury by TK inhibitors is reduction of nitric oxide production by endothelial cells, leading to hypertension, which in turn may increase proteinuria[12].There are several other reports of nephrotic syndrome in adults caused by Dasatinib are available. In all cases, discontinuation or reduction of the dose of Dasatinib or a switch to a first-generation TKI improved proteinuria[13, 14]. Hirano et al. proposed that the severity of proteinuria was dose-dependent, because reducing the dose by half was efficient in their study[15].

Conclusion:

With increasing use of these medications to treat childhood cancers, it is important forpediatric oncologists and nephrologists to be aware of the potential renal side effects of tyrosin kinase inhibitors.The rapid cessation of proteinuria following drug discontinuation indicated that proteinuria was induced by the administration of Imatinib. Proteinuria and renal function should be regularly monitored during tyrosin kinase inhibitor therapy, because they are reversible if earlyintervention is performed.

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