Hereditary ADAMTS 13 deficiency presenting as recurrent acute kidney injury

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ABSTRACT

We report here a case of 26-year-old male who presented with history of recurrent acute renal failure associated with microangiopathic hemolytic anemia and thrombocytopenia. ADAMTS 13 deficiency due to mutation in the gene encoding for ADAMTS 13 was identified as the cause. After eight episodes of acute kidney injury (AKI), patient started developing hypertension, proteinuria, and renal insufficiency. Treatment with regular monthly plasma infusions prevented further episodes of AKI and stabilized the renal function. Hypertension and proteinuria are controlled with angiotensin II receptor blockers.

Key words: ADAMTS 13 deficiency, chronic kidney disease, plasma therapy, proteinuria, recurrent acute kidney injury

Introduction

ADAMTS 13 deficiency is classically associated with thrombotic thrombocytopenia purpura. We present here a case of hereditary ADAMTS 13 deficincy presenting as recurrent acute kidney injury. Mutation in the gene encoding for ADAMTS 13 was identified as the cause. Therapeutic regular plasma infusion prevented the recurrence and led to stabilization of renal function.

Case Report

A 26-year-old male presented with history of decreased urine output, red urine for past 7 days following an episode of upper respiratory tract infection. There was no history of edema, hypertension, flank pain, fever, and jaundice. On examination, he was conscious and alert, with pulse rate of 86 beats per minutes, blood pressure of 122/76 mmHg with no postural drop. General physical examination was remarkable for pallor and petechial rash over lower limbs with no evidence of icterus, lymphadenopathy. He was clinically euvolemic. Examination of throat was normal. There was no hepatosplenomegaly, chest was clear to auscultation, and heart sounds were normal.

Laboratory evaluation showed anemia (Hb 7.2 g/dl) with reticulocytosis (7%) thrombocytopenia (platelet 52000 / mm^3), azotemia (blood urea nitrogen 56 mg/dl, creatinine 5.2 mg/dl). Transaminases, protrombin time, and bilirubin were normal. Bleeding time, clotting time, and activated partial thromboplastin time was normal. Peripheral smear showed schistocytes, crenated RBCs, and microspherocytosis. LDH was elevated to 1540; serum haptaglobin was depressed to <7.62 (normal 30–200 mg/ dl) Serum creatinine rose up to 8.8 mg/dl. Considering the diagnosis of thrombotic microangiopathy, therapy with plasmapheresis was planned but deferred as patient went into diuretic phase on the third day of illness and creatinine started declining returning to 1.5 mg/dl at day 7. However, during follow up the persistent subnephrotic range proteinuria (2-2.5 gm/day), hypertension, and elevated creatinine (1.5–1.6 mg/dl) was noted. In view of proteinuria and hypertension losartan 50 mg OD was started.

Patient's past medical history was remarkable for episodes of passing red urine associated with renal failure, low

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platelet count, and anemia. First, such episode was at the age of 8 years in year 1993, associated with chicken pox that required hospitalization for approximately 2 weeks. Peritoneal dialysis was performed for 48 h after which patient had a complete recovery of the renal function. Hemoglobin had dropped to 5.7 gm requiring blood transfusion and thrombocytopenia was also noted (platelet count 52000). Serum creatinine at discharge has decreased to 0.9 mg/dl. Recurrence of this episode occurred six times before current admission (year 1993, 2002, 2003, 2005, 2006, and 2009); all the three episodes were characterized by anemia, variable degree of azotemia, thrombocytopenia, and self-resolving course. None of these episodes of AKI required renal replacement therapy. In between the episodes, hemoglobin remained normal but platelet count remained low [Table 1].

Direct and indirect Coomb's tests were negative. Bone marrow examination showed normal erythroid and platelet precursors. Acid ham test and flow cytometry for defect of PNH was negative. Antinuclear antibodies, ANCA, APLA were negative.

Considering the presence of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure diagnosis of recurrent AKI due to TMA was made. Possibility of atypical HUS was investigated further with serum levels of CH 50, complement factor H, I and MCP-all four were within the normal limits. Patient was further evaluated with level of ADAMTS 13; which turned out to be very low (less than 7%-significant deficiency is considered when the level is less than 10%). Genetic analysis to evaluate congenital deficiency of complement pathway regulatory proteins was performed.

Sequencing of SCR20 of Factor H (SCR20 is the hot-spot mutation region of Factor H), SCRs 1-4 of MCP gene (SCRs 1–4 are the hot-spot mutation region of MCP), and 13 exons of Factor I gene showed no mutation in the hotspot region. Analysis by sequencing all 29 exons of ADAMTS13 gene showed heterozygous mutation in exon 26 (the nucleotide change 3655C>T that causes the amino acid change R1219W). During the molecular screening of ADAMTS13 gene, a homozygous variation of ADAMTS13 gene has been also found in the Intron 8 (987+69A>C), but without a pathogenetic significance.

The results obtained suggest that our patient is affected by a congenital deficiency of ADAMTS13, determined by a heterozygous mutation of ADAMTS13 gene. Monthly plasma infusions 10 mL/kg per month were initiated. Patient showed a good response to plasma therapy in the form of normalization of platelet count (2.4 lac in last follow up), stabilization of serum creatinine to 1.4 mg/dL.

Discussion

Von Willebrand factor (vWF)-cleaving protease activity, or "a disintegrin and metalloprotease, with thrombospondin-1-like domains" (ADAMTS-13) is a plasma metalloprotease that cleaves vWF multimers after excretion by endothelial cells.[1] In its absence, large vWF multimers, cause spontaneous platelet activation in the microvasculature leading to microthrombi formation.

Congenital ADAMTS 13 deficiency is classically associated with inherited TTP with characteristic neurologic features,[2] this is the first report of it presenting as recurrent acute renal failure (without neurological features) and later followed by hypertension, proteinuria and chronic renal insufficiency. This is also the first report of successful use of regular plasma infusion in this setting.

Although liver is the primary site for ADAMTS 13 synthesis, local synthesis of this factor has been demonstrated in kidney[3] which may explain kidney specific manifestations of the disease in some cases. Impaired ADAMTS 13 activity in the podocytes due to genetic mutations has been described.[3]

Heterozygous mutation in exon 26 causing very low levels of ADAMTS 13 was responsible for recurrent renal failure in our case. This mutation has been described as a cause of ADAMTS 13 deficiency in patients with TTP.[4] After repeated episodes of acute kidney injury our patient started developing chronic renal insufficiency as manifested by new onset hypertension, proteinuria and azotemia. Curiously replenishing deficient ADAMTS 13 by institution of regular monthly plasma infusions not only prevented further AKI episodes but also led to control of proteinuria, hypertension and stabilization of renal function. If ADAMTS 13 deficiency can cause chronic kidney disease as evident in our case and in one recent case report;[5] it will be interesting to explore the ADAMTS 13 deficiency as a cause of chronic kidney disease where etiology is not obvious.

Table 1: Laboratory characteristics of seven AKI episodes

Episode no.	1 (1993)	2 (2002)	3 (2003)	4 (2005)	5 (2006)	6 (2009)
Hemoglobin (gm/dL)	7.4	5.3	4.4	9	7.6	7.9
Platelet (per cumm)	46,000	20,000	33,000	08,000	66,000	22,000
Peak creatinine (mg/dL)	5.4	8.1	5.5	7.1	6.2	7.1

To conclude, we have described a case of hereditary ADAMTS 13 deficiency with only renal involvement at presentation (without neurological manifestations) in the form of recurrent AKI- with hypertension, proteinuria and chronic renal insufficiency developing in long run. We also demonstrated a good therapeutic response to treatment with regular plasma exchange.

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