Myriad faces of X-linked agammaglobulinemia in a young boy

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To the Editor,

X-linked agammaglobulinemia (XLA) is one of the commonest inborn error of immunity that results in defective antibody production[1]. XLA is characterized by pan-hypogammaglobulinemia resulting in recurrent infections with encapsulated bacteria (such as *Streptococci, Staphylococci* , and*Haemophilus influenzae),* enteroviruses (such as *poliovirus, echovirus, and coxsackievirus*), *hepatitis* viruses and*Giardia* [1]. *Citrobacter freundi* is a normal gut commensal that has mostly been reported as healthcare-associated infection (HCAI) and also in immunocompromised individuals[2,3]. Renal manifestations in patients with XLA are extremely rare and limited to 2 cases of membranoproliferative glomerulonephritis[4] and 1 case of membranous nephropathy.[5] However, the pathophysiology of renal manifestations in XLA is unclear. No case of thrombotic microangiopathy (TMA) has been reported in these patients. Herein, we report a young boy with XLA with myriad clinical manifestations of the disease including TMA. A written informed consent

was taken from the parents and approval for the case report was obtained from the departmental review board.

An 8-year-old boy, presented with history of loose stools and vomiting for 5 days. He also developed reduced urine output and periorbital puffiness for 2 days prior to hospitalization. In the past, he was symptomatic since the age of 9 months when he developed acute flaccid paralysis with anterior horn myelitis. He was suspected to have vaccine-associated paralytic poliomyelitis (VAPP) leading to sequalae of thoracolumbar spine kyphoscoliosis (Figure 1A). However, stool examination did not reveal vaccine derived poliovirus strain. He had had 5 episodes of pneumonia since the age of 2 years (Figure 1B, 1C, and 1D) requiring IV antimicrobials; 1 episode of persistent diarrhoea caused by *Giardia lamblia* ; chronic bilateral ear discharge and 1 episode of bacterial meningitis. At the age of 8, he developed septic arthritis of the right elbow, and pus culture grew *Streptococcus pneumoniae* . His family history revealed death of 3 maternal uncles and 3 maternal grand uncles in early childhood due to repeated sino-pulmonary infections, suggestive of an X-linked recessive pattern of inheritance (Figure 2). On examination, he had hypertension (Blood pressure [118/76 mm of Hg (between 95^{th}-99^{th} centile)], pallor, absent tonsils and lymph nodes, and periorbital puffiness. He also had kyphosis of thoracolumbar spine (Figure 1A) and contractures at bilateral ankle joints and right elbow joint. Rest of the examination was unremarkable.

Laboratory investigations showed anemia (haemoglobin: 62g/L, N:115-145); thrombocytopenia (platelet counts 38x10^9/L; N:150-400) and total leucocyte count 7.54 x10^9/L (Neutrophils-78%, Lymphocytes- 12%, Monocytes- 9%, Eosinophil- 1%) with absolute lymphocyte count of 0.9 x10^9/L (N: 1.88-2.48). Urine examination showed 2 + albumin and microscopic hematuria (-20 red blood cells/high power field). He had deranged renal function [blood urea- 301 mg/dl (N: 14-36); serum creatinine- 8.3 mg/dl (N: 0.2-1); serum sodium- 129 meq/L (N: 135-145) and elevated serum potassium levels (7.4 meq/L, N: 3.5-5). Lactate dehydrogenase was elevated (1939 IU/L, N: <450IU/L) and blood smear examination showed > 25% schistocytes. Alternate complement pathway assay i.e AH 50 activity was 17% (N: 30 – 113%). Anti-complement factor H antibodies was not estimated as the IgG was very low. Kidney biopsy showed features suggestive of TMA (Figure 3A). Urine culture showed growth of *Citrobacter freundi* (> 10^5/colony forming units) that was sensitive only to colistin and polymyxin B. He also had pan-hypogammaglobulinemia (IgG: 0.046 g/L, N: 0.44-1.09; IgA- 0.026 g/L, N: 0.04-0.2 and IgM- 0.031 g/L, N: 0.04-0.24); absent B lymphocytes (0.15%, N: 4-15%) and reduced flow cytometric expression of Bruton tyrosine kinase (Btk) protein on CD14+ monocytes (Figure 3B) when compared to healthy unrelated control (Figure 3C). Btk expression in mother also showed reduced expression, suggestive of carrier state (Figure 3D). He was diagnosed to have XLA with *Citrobacter freundi* infection induced TMA. He underwent 2 cycles of haemodialysis and was initiated on intravenous methylprednisolone pulse therapy (30 mg/kg/dose daily for 5 days) followed by tapering doses of oral prednisolone (initial dose 1 mg/kg/day), intravenous ceftriaxone and intravenous immunoglobulin (1 gm/Kg). He showed prompt clinical improvement in the form of improving urine output, renal function tests, and evidence of haemolysis on peripheral smear. He was discharged with a plan to continue giving replacement IVIg therapy (400 mg/kg/month), azithromycin prophylaxis (250 mg 3 times a week) and tapering doses of oral prednisolone.

Diagnosis of XLA was suspected in the index child because of strong X-linked recessive family history; repeated sino-pulmonary infections; suspected enteroviral myelitis, *Giardia lamblia* gastroenteritis, and *pneumococcal* septic arthritis. His diagnosis was delayed till 7 years of age which is not unusual in developing countries because of lack of awareness about these diseases. In our previously published experience on XLA, a median delay of 3.25 years (range 0.16-16 years) was reported[7].

Citrobacter freundi is a normal commensal in the intestinal tracts of humans and animals[3]. It may cause serious infections in neonates and immunocompromised individuals. These include neonatal meningitis, urinary tract infection (UTI), bloodstream infections (BSI), gastroenteritis, and respiratory tract infections[2,3]. *Citrobacter sp.* was isolated from 9.4% of healthcare-associated UTI, usually following urinary catheterization and genitourinary instrumentation and *C. freundi*was a common subspecies to be isolated[2]. The index child did not undergo urinary catheterization or any genitourinary instrumentation, hence it was unlikely to

be a health care associated infection (HCAI). Tschape et al[8] reported hemolytic uremic syndrome (HUS) in a cluster of immunocompetent children from a nursery and kindergarten following consumption of sandwich that was found to be contaminated with *C. freundi* . Index case had diarrhoea and *C. freundi* was isolated from urine. Any infection including UTI has been found to precipitate HUS.[9,10]In the index case, *C. freundi* infection is the potential cause for diarrhoea and UTI that precipitated HUS.

Autoimmune and inflammatory complications have infrequently been reported in patients with XLA. These include arthritis, encephalitis, cytopenias and inflammatory bowel disease. It has been postulated that defective B cell tolerance and myeloid cell function in patients with XLA may drive these autoimmune complications. However, exact pathogenesis is still not known. Index patient had TMA which is a complement mediated disease. It may be hypothesized that an immune dysregulatory state triggered by *C. freundi* infection in the index patient lead to overactivation of alternative complement pathway and TMA.

To conclude, we report a spectrum of clinical manifestations of XLA in a young boy whose diagnosis got missed for several years despite having characteristic clinical manifestations of the disease. Renal involvement is rare in XLA. However, infections may trigger TMA in these patients.

Conflict of interest: None

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Figure legends:

Figure 1: (A) Thoracolumbar scoliosis. (B), (C) and (D) Chest radiographs showing left middle zone (B), lower zone (C), and upper zone pneumonia.

Figure 2: Pedigree of the index patient family indicating X-linked inheritance.

Figure 3: (A) Photomicrograph shows glomerulus with mesangiolysis (encircled) and swollen endothelial cells (arrow), the features of thrombotic microangiopathy (Periodic acid-schiff stain, 40x magnification). Flow cytometric expression of Bruton thymidine kinase (Btk) protein on lymphocytes showing reduced expression in index child (B), and mother (D) when compared to the healthy unrelated control (C).