CASE REPORT
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Nephrotic Syndrome and Recurrent Infection

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ABSTRACT

Nephrotic syndrome is characterized by the leakage of protein from the blood into the urine along with the triad of proteinuria, albuminuria, and peripheral edema. Loss of protein leads to the loss of immunoglobulin and complements. X-linked agammaglobulinemia (XLA), or Bruton disease, is a primary immunodeficiency disease caused by a defect in the development of B cells in the bone marrow and a low serum level of immunoglobulins. The present case involves a 12-year-old boy with nephrotic syndrome, osteomyelitis, and recurrent infections. We discovered that he had XLA. This report underscores the importance of considering inborn errors of immunity in cases of protein loss, such as nephrotic syndrome.

Keywords: Bruton type agammaglobulinemia; Inborn errors of immunity; Nephrotic syndrome; Primary immunodeficiency diseases; X-linked agammaglobulinemia

INTRODUCTION

Nephrotic syndrome is one of the most common causes of glomerular disease in childhood, characterized by a triad of peripheral edema, significant proteinuria (>40 mg/m^2/h), and hypoalbuminemia (<2.5 g/dL).[1] Nephrotic syndrome can be either congenital or acquired. The acquired form can further be classified as idiopathic or secondary.[2] The secondary type is often associated with systemic diseases such as malignancies, autoimmune disorders, infections (e.g., hepatitis and human immunodeficiency virus [HIV]), and the use of certain medications.[3] These associations are also observed in the context of treating immune deficiencies.[4-7]

Loss of protein and treatment with corticosteroids and immunosuppressive drugs leads to decreased levels of immunoglobulin and complements. This weakening of the immune system, in turn, leads to increased susceptibility to infections.[8]

Agammaglobulinemia and hypogammaglobulinemia result from a heterogeneous group of diseases collectively known as primary B-cell immune deficiencies. Agammaglobulinemia can occur in both X-linked and autosomal recessive forms, with X-linked agammaglobulinemia (XLA), or Bruton disease, being the most common cause.[9]

Patients with XLA typically do not exhibit symptoms during the first few months of life due to transmitted maternal passive immunity. However, after

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this period, they experience recurrent infections, particularly with encapsulated bacteria. They are also susceptible to other infections, such as joint and skin diseases, viral infections like enteroviruses, and parasitic infections such as *Giardia lamblia*.[10]

In nephrotic syndrome, the occurrence of various infections is usually attributed to the aforementioned causes, leading to a lack of serious consideration for immune deficiency diseases. However, the present case report highlights a nephrotic syndrome patient with recurrent, resistant infections who was diagnosed with XLA.

CASE PRESENTATION

A 10-year-old boy with generalized edema presented at the nephrologist's office. Lab tests revealed elevated triglycerides and cholesterol, low levels of albumin and total protein, and proteinuria characteristic of nephrotic syndrome (Table 1). This boy was the first child of consanguineous parents with 4 children. The patient's uncle had died at the age of 7 months due to an unknown infection. In his early years, the patient had recurrent diarrhea and several hospitalizations for intestinal infection, otitis media, and fever. Although he exhibited all the diagnostic criteria of nephrotic syndrome, a kidney biopsy was not performed due to a lack of parental consent. Initial investigations were conducted to rule out common autoimmune diseases, malignancies, and infections such as hepatitis and HIV. Considering that idiopathic nephrotic syndrome accounts for 90% of nephrotic syndrome cases in children,[11] he was treated accordingly and received prednisolone and other medications, including cyclosporine for steroid-resistant nephrotic syndrome, for 3 years.

During treatment, he had a positive urine culture for *Acinetobacter*, developed recurrent otitis media, and was once treated for meningitis. He experienced several seizures and received anticonvulsants such as sodium valproate and phenobarbital. Later, he presented with knee pain and limping; subsequent examinations diagnosed osteomyelitis in the left femur (Figure 1).

Despite various antibiotic treatments for osteomyelitis, the patient did not respond adequately. Consequently, an immunologist was consulted, and he was evaluated for immune deficiency diseases (Table 1).

Immunoglobulin levels (IgG, IgA, and IgM) were tested using a Biotecnica BT 3000 Plus chemistry analyzer, and IgE was measured using DiaZist, LOT NO: Dlg E 204, Catalog No: DG. Ig E. 01 KIT. Antibody response to tetanus was assessed via enzyme-linked immunosorbent assay. Flow cytometry was performed with a Partec Pas II device (Partec, Germany) using fluorescent-labeled antibodies to analyze T-cell subtypes, which were studied with FlowJo software, version 7.6.2 (Treestar, USA). The patient's immunoglobulin level and antibody responses were significantly low. Given the reduction in protein, which can lead to decreased immunoglobulin levels, and the use of immunosuppressive drugs, such as cyclosporine, CD marker flow cytometry was also performed. Results showed a very small level of B cells (CD19 = 0.12%, CD20 = 0.11%) and a reversed CD4/CD8 ratio. Ultimately, a genetic test was performed for a definitive diagnosis. Whole-exome sequencing identified a mutation in the Bruton tyrosine kinase (*BTK*) gene (chX-100630191 G > A: NM_000061.3: exon2: c.C82T: p.R28c) which was confirmed via Sanger sequencing (Table 2).

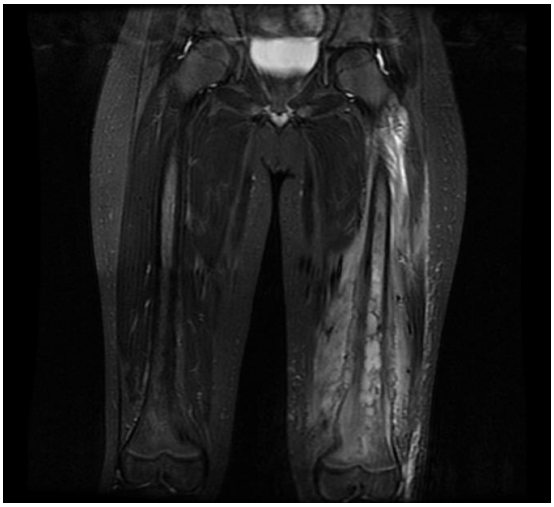

Figure 1. Osteomyelitis in the left femur (magnetic resonance imaging)

Table 1. The patient's lab data

Lab Test	Patient Data	Normal Range
Total protein (g/dL)	3.9	6.5–8.3
Albumin (g/dL)	1.9	3.5–5.3
urine protein (mg/24h)	1240	40–150
Urine protein (mg/m^2/h)	51	<40
Cholesterol (mg/dL)	369	<200
Triglyceride (mg/dL)	226	40–160 mg/dL
C4 (g/L)	0.20	0.165–0.380
Anti-dsDNA (U/mL)	3.6	<12
IgG (mg/dL)	152	700–1400
IgM (mg/dL)	8.5	40–150
IgA (mg/dL)	0.5	44–395
IgE (IU/mL)	19.8	≤115
Anti-tetanus antibody (IU/mL)	0.05 IU/ml	≥0.1 IU/ml
CD45	100%	>80%
CD3	95.43% (4802.5)	68%–82% (1200–2600)
CD4	28.66% (1376.39)	35%–55% (650–1500)
CD8	62.30% (2991.6)	19%–37% (370–1100)
CD19	0.12% (6.038)	5%–15% (270–860)
CD20	0.11% (5.535)	5%–15% (270–860)
CD16	2.48% (124.7)	4%–37% (100–480)
CD56	6.61% (332.6)	4%–37% (100–480)

Anti-dsDNA: anti-double-stranded DNA; CD: cluster of differentiation; C4: Complement 4; Ig: immunoglobin

Table 2. Genetic and clinical characteristics of the identified *BTK* variant

Characteristic	Details
Gene	*BTK*
Variant coordinates	ChrX-100630191 G>A NM_000061.3:exon2:c.C82T:p.R28C
Associated diseases	1. Agammaglobulinemia, X-linked 1 2. Isolated growth hormone deficiency, type III, with agammaglobulinemia
Phenotype MIM numbers	1. 300755 2. 307200
ACMG/ClinVar Classification	Pathogenic/Pathogenic
Zygosity	Hemizygous
Inheritance	X-linked recessive (XLR)

BTK: Bruton tyrosine kinase; MIM: Mendelian Inheritance in Man; ACMG: American College of Medical Genetics and Genomics

Genetic testing confirmed the diagnosis of XLA. Subsequently, the patient began treatment with intravenous immunoglobulin (IVIG) and prophylactic antibiotics, which continued for several months. This regimen, combined with ongoing treatment for nephrotic syndrome, led to a significant reduction in infections.

DISCUSSION

XLA, caused by mutations in the *BTK* gene, accounts for approximately 85% of agammaglobulinemia cases. BTK, a cytoplasmic tyrosine kinase primarily expressed in hematopoietic cells, plays a crucial role in B-cell development. Mutations in *BTK* impede B-cell maturation in the bone marrow, halting progression from the pro-B to the pre-B stage. The European Society for Immunodeficiencies (ESID), defines XLA patients as typically male with <2% $CD19^+$ B cells, serum IgG levels <200 mg/dL (2 g/L), and IgG and IgA levels usually <20 mg/dL (0.2 g/L). Most patients with XLA develop recurrent bacterial infections, particularly otitis, sinusitis, and pneumonia, in the first 2 years of life.[12,13]

Our patient exhibited numerous infections after his first year. However, his immune deficiency went unnoticed, possibly due to his residence in a remote village.

At the age of 10 years, following the diagnosis of nephrotic syndrome, the patient presented with various infectious diseases, including meningitis and recurrent otitis media. Initially, these infections were attributed to nephrotic syndrome complications, such as hypogammaglobulinemia, complement deficiency, and the effect of corticosteroid and immunosuppressive treatments. However, the patient's treatment-resistant osteomyelitis and family history–his uncle's death from an unknown infection at 7 months–prompted a comprehensive immunological evaluation. Laboratory findings revealed IgG levels<200 (152 mg/dL), inadequate tetanus vaccine antibody titer (0.05), $CD19^+$ B cells <2% (0.12%), decreased $CD4^+$ T cells (28.66%), and increased $CD8^+$ T cells (62.30%). While chronic steroid use can lead to hypogammaglobulinemia and reduced peripheral lymphocytes, particularly $CD4^+$ and $CD8^+$ cells,[14] studies have shown an imbalanced $CD4^+/CD8^+$ T lymphocyte distribution in nephrotic syndrome patients, contributing to disease recurrences and remissions.[15] To establish a definitive diagnosis (Table 3),[13] we performed whole-exome sequencing, which was confirmed by Sanger sequencing and identified a mutation in the *BTK* gene, confirming the diagnosis of XLA.

Patients with agammaglobulinemia do not show significant humoral responses to antigenic stimuli, making antibody-mediated glomerulonephritis unlikely.[16] While rare cases of glomerulonephritis and membranous glomerulopathy have been observed in XLA patients, these manifestations are seen after IVIG therapy. The aggregation and deposition of administered gammaglobulins could potentially trigger glomerulonephritis.[17-20] However, our patient had never received IVIG prior to his nephrotic syndrome diagnosis.

Although the patient showed no evidence of other autoimmune diseases, he suffered from various infections since his first year of life. Repeated subclinical episodes of intravascular coagulation due to recurrent infections and septicemia may contribute to nephropathy.[21] Therefore, the delay in diagnosing his primary immune deficiency and the resulting infections may have played a role in the development of nephrotic syndrome.

Currently, the patient receives monthly IVIG, which has led to a significant decline in infections, effective treatment of his osteomyelitis, and improvement in nephrotic syndrome symptoms. This case highlights the critical importance of considering immunodeficiency diseases in patients with conditions like nephrotic syndrome, particularly when frequent and resistant infections are present.

Table 3. Criteria for definitive diagnosis of agammaglobulinemia (adapted from https://esid.org/WorkingParties/Registry-WorkingParty/Diagnosis-criteria)

X-Linked Agammaglobulinemia **Definitive Criteria**
Male patient with <2% $CD19^+$ B cells and at least one of the following: 1. Mutation in *BTK* 2. Absent *BTK* mRNA on northern blot analysis of neutrophils or monocytes 3. Absent BTK protein in monocytes or platelets 4. Maternal cousins, uncles, or nephews with <2% $CD19^+$ B cells

BTK: Bruton's tyrosine kinase; CD: cluster of differentiation

STATEMENT OF ETHICS

This case report was written with the full and informed consent of the patient's parents. The Ethics Committee of Zahedan University of Medical Sciences approved this study (IR.ZAUMS.REC.1403.123).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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