Tubulointerstitial nephritis complicating IVIG therapy for X-linked agammaglobulinemia

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Abstract

**Background:** Patients with X-linked agammaglobulinemia (XLA), develop immune-complexes diseases such as nephropathy only rarely, presumably because their immunoglobulin (Ig) G concentration is low. We encountered a patient with XLA who developed tubulointerstitial nephritis during treatment with intravenous immunoglobulin (IVIG).

**Case presentation:** A 20-year-old man was diagnosed with XLA 3 months after birth and subsequently received periodic gamma-globulin replacement therapy. Renal dysfunction developed at 19 years of age in association with high urinary beta2-microglobulin (MG) concentrations. Renal biopsy histology showed dense CD3-positive lymphocytic infiltration in the tubulointerstitium and tubular atrophy, while no IgG4-bearing cell infiltration were found. Fibrosclerosis and crescent formation were evident in some glomeruli. Fluorescent antibody staining demonstrated deposition of IgG and complement component C3 in tubular basement membranes. After pulse steroid therapy was initiated, urinary beta2-MG and serum creatinine concentrations improved.

**Conclusion:** Neither drug reactions nor collagen disease were likely causes of tubular interstitial disorder in this patient. Although BK virus was ruled out, IgG in the γ-globulin preparation might have reacted with a pathogen present in the patient to form low-molecular-weight immune complexes that were deposited in the tubular basement membrane.
**Key words:** Burton agammaglobulin tyrosine kinase (BKT) gene; immune complexes; steroid therapy; tubular deposition; tubular atrophy
Background

In X-linked agammaglobulinemia (XLA), Burton agammaglobulin tyrosine kinase (BTK) gene induces a B-cell maturation disorder that causes congenital immunodeficiency in which repeated bacterial infections reflect antibody production failure (1,2). Prognosis for survival is relatively favorable owing to immunoglobulin replacement therapy (intravenous immunoglobulin therapy, or IVIG) (3).

We encountered a patient with BTK gene mutation (p.Gln412X)-induced XLA who developed renal dysfunction associated with increased urinary beta2-microglobulin during IVIG therapy. Renal histology indicated a tubular interstitial disorder. Glomerular immune complex deposition such as in membranous nephropathy (4) and membranoproliferative glomerulonephritis (5) occasionally has been reported in association with IVIG therapy for XLA. To our knowledge, however, tubulointerstitial nephritis (TIN) showing immune complex deposition in the tubular basement membrane has not previously been reported in XLA patients receiving IVIG therapy.

Case presentation

A 20-year-old man who was diagnosed with XLA 3 months after birth was treated periodically with IVIG. Mild renal dysfunction developed at 19 years. Serum creatinine (Cr) and blood urea nitrogen (BUN) were 1.5 and 30 mg/dL, respectively, and urinary beta2-microglobulin was elevated. The
patient was admitted to our department for further evaluation and
treatment.

Urinalysis on admission showed specific gravity of 1.017, 1+
qualitative protein, and 0.14 g/day quantitative protein, 0.14 g/day.
Microscopy showed red blood cells to be 1 to 4 per high power field (HPF).
White blood cells were 1 to 4 per HPF. Urine beta2-microglobulin was 32550
µg/day (normal, below 250), and N-acetyl-β-D-glucosaminidase was 17.9 U/L
(normal, 0.3 to 11.5). Creatinine clearance was 39.2 mL/min/1.73 m²
(normal, 65 to 142). The findings suggested tubular interstitial disorder
causing renal dysfunction. No uveitis was detected. On blood
examinations, the red blood cell count was $548 \times 10^4 /µL$; white blood cell
count, $8400 /µL$; platelet count, $15.5 \times 10^4 /µL$; and erythrocyte sedimentation
rate, 4 mm/hour. By serum examinations, Na was 142 mEq/L; K, 3.9
mEq/L; C-reactive protein, 2.8 mg/dL; BUN, 30 mg/dL; Cr, 1.29 mg/dL; and
cystatin C, 1.96 mg/L (normal, 0.56 to 0.87). In sum, inflammatory markers
were mildly elevated and moderate renal dysfunction was present. The IgG
concentration was 685 mg/dL (normal, 870 to 1700 mg/dL); IgM, below 20
mg/dL (normal, 33 to 190 mg/dL); and complement titers was normal.
Serum IgG4 concentration was below 1% of total serum IgG concentration.
All autoantibodies were absent (antinuclear, anti-DNA, rheumatoid arthritis
hemagglutination antibodies, anti-cyclic citrullinated peptide, anti-SS-A/Ro,
anti-SS-B/La, and myeloperoxidase-ANCA). On investigation for pathogens,
cytomegalovirus pp65 antigen, anti-VCA IgM antibody, and interferon-γ
specific for tuberculosis were not detected. Adenovirus, herpes simplex
virus, and BK virus were not detected by real-time polymerase chain
reaction. Lymphocyte stimulation tests (DLST) with D-mannitol, glycine,
and polyethylene glycol, all contained in the patient’s γ-globulin preparation
were negative. In addition, no physiologic, and laboratory findings
suspecting Castleman’s disease or malignant lymphoma were found.

Examination of renal biopsy specimen showed marked mononuclear
cell infiltration in the interstitium (Figure 1a), and loss of tubular epithelial
cells, cloudy degeneration, and irregularity of the basement membrane in
some renal tubules. Some glomeruli showed cellular crescent formation
(Figure 1b) and fibrosclerotic lesions. Fluorescent antibody staining
detected granular depositions of IgG (Figure 1c) and complement component
C3 in the tubular basement membrane. By electron microscopy (Figure 1d),
electron-dense deposits were observed in the tubular basement membrane.
Immune cells infiltrating in the Tubulointerstitium were demonstrated to be
mainly CD3 antigen-positive lymphocytes (T-cell) (Figure 1e) predominantly,
but not IgG4-bearing cells (Figure 1f).

Steroid therapy including methylprednisolone pulse therapy followed
by prednisolone (PSL) was administered. Urinary findings and renal
function slowly improved, and after gradual dose reduction. The patient
still is receiving IVIG therapy, but urinary abnormalities and renal function
deterioration have not recurred.
Discussion

Immune complex-induced nephritis and complement-associated renal impairment are infrequent in XLA patients, most likely because of their very low IgG concentrations (6). We encountered a young man who developed tubulointerstitial nephritis during IVIG for XLA. Glomerular immune complex deposition related to membranous nephropathy (4) and membranoproliferative glomerulonephritis (5) during the course of XLA has been reported occasionally. While TIN associated with IVIG in a child with nephrotic syndrome showing hypogammaglobulinemia was previously reported (7), however the authors assumed that it could be caused by an allergic reaction because of the significant infiltration of eosinophil in the tubulointerstitium. To our knowledge, however, TIN induced by immune complex deposition in the renal tubules, such as that occurring in our patient, has not been reported previously.

In XLA, the course of viral infections is normal except for enterovirus infection, where effective host defense requires antibodies. XLA patients are vulnerable to this infection, which may become persistent, and the progressive (8). In our patient, IgG and complement deposits were demonstrated in the tubular basement membrane by fluorescent antibody staining and electron microscopy, suggesting several possible pathogenetic mechanisms. Complement may have been activated locally after immune complex formation by interactions between an antigen present in the patient and the IgG contained in the γ-globulin preparation, inducing tubular
interstitial disorder. However, no specific infection could be identified in our patient. Although tubulointerstitial immune complex nephritis is very rare condition among TIN, it can be caused by certain drugs such as NSAIDs (9), autoimmune diseases like lupus erythematosus (10), or IgG4-related diseases (11). But our patient had received no long-term drug treatment other than IVIG and he did not have any collagen diseases or IgG4-related diseases by repeated laboratory examinations.

Wegmuller et al. (12) reported that complement activation may occur in both healthy individuals and patients with congenital humoral immunodeficiency. A few B cells are present in XLA patients, and a small amount of IgG is produced in some patients (13). Possibly, the exogenous, non-self IgG infused in the IVIG may have induced autoantibody production against exogenous IgG to cause nephropathy, but this mechanism cannot be proven in our patient because he had been receiving periodic doses of IVIG to prevent fatal infection. Such treatment renders measurement of self-produced IgG impossible. When type III allergy is involved in disease development and the antigen concentration is higher than the antibody concentration, immune complexes will have low molecular weight and likely will be deposited outside the tubular basement membrane (14). However antigen concentrations may be excessive in in many XLA patients and low-molecular-weight immune complexes formed in the circulation could have passed through the glomeruli to be deposited in the tubular basement membrane.
Conclusions

In patients with congenital humoral immunodeficiency patients, vigilance is needed to detect development of renal dysfunction during IVIG therapy. Not only glomerular disease but also TIN may occur, as took place in our patient.

Consent

Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images.

List of abbreviations

XLA: X-linked agammaglobulinemia, IVIG: Intravenous immunoglobulin therapy, Ig: immunoglobulin, BKT: Burton agammaglobulin tyrosine kinase, DLST: Lymphocyte stimulation tests, TIN: Tubulointerstitial nephritis

Competing interest

The authors declare that they have no competing interests of this work.

Authors’ contributions

KS, HN, TM, AI, NW, ET, and MO were the attending physicians of this patient. TT was responsible for the design of this case report, and
manuscript write-up. There were no “ghost writers.”

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References


Figure Legends

Figure 1. Renal histologic findings in the patient.

Marked tubulointerstitial mononuclear infiltration was observed (a) (Masson trichrome stain, x100). Crescent formation was noted in some glomeruli (b) (periodic acid-Schiff stain, x200). Fluorescent antibody staining demonstrated granular deposition of IgG in the tubular basement membrane (c) (x200). Electron-dense materials were present in the tubular basement membrane (d) (original magnification, x6000). Immune cells infiltrating in tubulointerstitial tissue were mainly CD3-positive T-cells (e), but not IgG4-bearing cells (x200).
Additional files provided with this submission:

Additional file 1: Burton-XLA-replying letter.docx, 17K
http://www.biomedcentral.com/imedia/2106280629126516/supp1.docx