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Postinfectious Glomerulonephritis and Epstein-Barr Virus Co-Infection

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A B S T R A C T

Contrary to group A β-hemolytic streptococcus as the most common cause of postinfectious glomerulonephritis (PIGN), Epstein-Barr virus (EBV) is only occasionally associated with acute renal involvement. We describe an 11-year-old boy who presented with clinical signs of infective mononucleosis and acute glomerulonephritis characterized by edema, hypertension and dark colored urine with diminished renal function. Serology tests confirmed streptococcal infection and acute EBV infection. Persistently depressed C3 complement and gross hematuria indicated renal biopsy which shows PIGN-type picture and, in addition, acute interstitial nephritis, both conclusive of streptococcal infection. We performed tissue DNA extraction by polymerase chain reaction (PCR) and demonstrated EBV-DNA from the kidney specimen supporting EBV involvement in renal tissue. This is the first reported case of PIGN with serologically-proven streptococcal and simultaneously, acute EBV co-infection. EBV-DNA extraction supported the EBV involvement in renal tissue suggesting that both etiologic agents might have contributed to renal inflammation. Adding serology evaluation for EBV in cases with typical clinical signs of infective mononucleosis and renal symptoms, EBV might be more commonly associated with PIGN than is currently appreciated.

Key words: *β hemolytic streptococcus, Epstein-Barr virus, interstitial nephritis, postinfectious glomerulonephritis*

Introduction

Contrary to the most common group A β-hemolytic streptococcus, Epstein-Barr virus (EBV) is only occasionally associated with postinfectious glomerulonephritis[1]. EBV infection occurring later in childhood usually causes infectious mononucleosis[2]. The diagnosis is based on characteristic clinical features and a positive heterophilic antibody test and serology evaluation. As a self-limited disease EBV infectious mononucleosis has a benign course with mainly subclinical renal involvement with acute renal failure reported in 1.6% and up to 4.8% as recently reported in children[3]. The common pathologic finding in patients with renal failure was interstitial nephritis[4,5].

It is difficult to find the causal relationship between any antigen and renal inflammatory lesions. The search of the literature revealed that the causal relationship between EBV and renal injury was found by polymerase chain reaction (PCR) analysis in different nephropathies[6,7] but it was not yet associated with postreptococcal glomerulonephritis (PSGN).

We report an 11-year-old boy who presented with acute glomerulonephritis and clinical signs of infective monucleosis, serologically-proven streptococcal and acute EBV infection. EBV-specific DNA detected by PCR analysis in renal biopsy specimen suggested a possible EBV involvement simultaneously with streptococcal infection contributing to renal damage.

Case description

A previously healthy 11-year-old boy presented with 12 day history of fever, pharyngitis, cervical lymphadenopathy, hepatosplenomegaly, mild periorbital edema and diffuse maculopapular rush on the trunk, dark col-

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ored urine and hypertension (145/95 mmHg). His family and previous medical history were unremarkable. He had no antecedent pharyngeal infection and denied taking any medications. Laboratory tests showed: increased erythrocyte sedimentation rate, 68 mm/h, and white blood cell count, 13.7x109/l with 23% of atypical lymphocytes, normal hemoglobin and platelet count. Blood urea nitrogen of 11.4 mol/L (normal <6.3), serum creatinine of 111 μmol/L (normal <90) and cistatin-C of 1.16 mg/L (normal <0.95) were all elevated indicating diminished renal function but with sustained diuresis. Serum glucose, electrolytes, bicarbonate, albumine and coagulation profile were normal except elevated total bilirubin, 33.56 umol/L (normal <17.1) and elevated aspartate aminotransferase (AST), 180 IU (normal <31), alanine aminotransferase (ALT), 212 IU (normal <30) and γ-glutamyltransferase (GGT), 110 IU (normal <28). Urinalysis revealed 2+ protein (total urine protein 0.56 g/day), 1+ glucose and 3+ blood, large number of dysmorphic red blood cells (RBC), a few leucocytes and several RBC and coarse granular casts in urinary sediment and sterile urine culture. Serum complement C3 was depressed, 0.25 g/L (normal 0.93–1.88) with normal C4, 0.20 g/L (normal 0.15–0.48). *Streptococcus pyogenes* isolated from throat and nose swabs with high antistreptolysin O titer (ASTO) of 5210 UI/L (normal <250) supported streptococcal etiology. Viral tests performed on the second day of hospitalization yielded an anti-EBV capsid antigen (VCA) IgM titter 109 AU/mL (normal <20), anti-EBV VCA IgG titter 84 AU/mL (normal <20) and EBV early antigen (EA) IgG 72 AU/mL (normal <20) indicating acute primary EBV infection. Other serologic tests for hepatitis A, B and C virus, cytomegalovirus and Hantavirus were negative. Cryoglobulin, anti-neutrophilcytoplasmic antibodies and rheumatoid factor were negative with negative antinuclear antibody excluding systemic disease. Abdominal ultrasound showed enlarged kidneys (>95th percentile for age) with mild splenomegaly. Ophthalmologic examination excluded anterior uveitis. Following treatment with furosemid and oral penicillin V, edema and the rash successively resolved and his blood pressure normalized within a week. Hematological parameters, liver function tests and serum creatinine level spontaneously returned to the normal range with significant decrease of ASTO titer (833 UI/L) within 4 weeks. Since gross hematuria and depressed C3 (0.26 g/L) continued, a percutaneous renal biopsy was performed on 29th day following admission. Light microscopy revealed hypercellular glomeruli with crowded neutrophils within capillary lumens, unchanged vascular area and no crescents. Interstitial tissue showed mild edema with focally condensed infiltrate of mononuclear cells. Immunofluorescence was positive for IgG, IgM and C3 along capillary loops and in mesangial stalks. Immunohistochemical

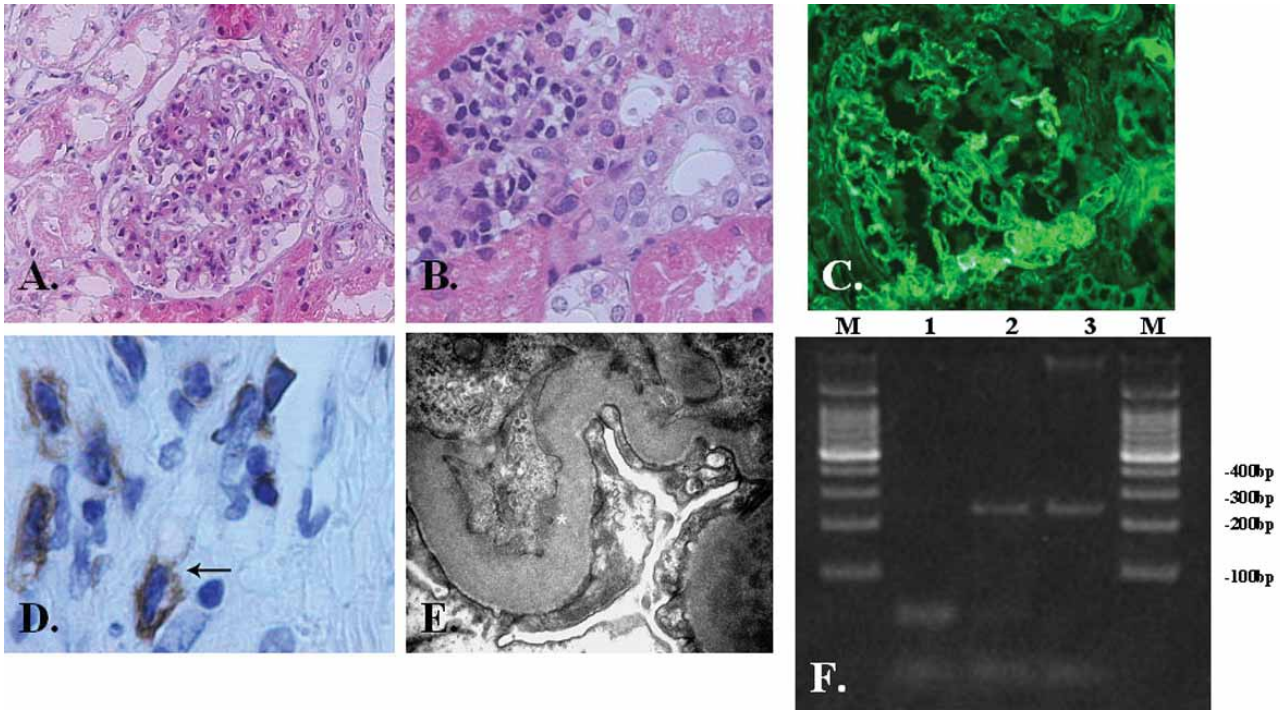

Fig. 1. a) Acute exudative proliferative glomerulonephritis; Light micrograph shows hypercellular glomerulus with numerous neutrophils within capillary lumens (HE, magnification 200x); b) Tubulointerstitial nephritis; the mononuclear cells infiltrate focally condensated in the interstitium (HE, magnification 200x); c) Immunofluorescense with granular deposits of IgG along peripheral capillary loops and mesangium (IF, magnification 1000x); d) Interstitial infiltrate is composed of CD45RD positive T lypmocites; e) Electron microscopy shows electrondense small subepithelial deposit (magnification 18000x); f) Polymerase chain reaction (PCR) revealed that patient's renal biopsy specimen is EBV-DNA positive. M, marker; 1, EBV negative control; 2, patient's renal biopsy sample; 3, EBV positive control.

analysis performed with CD45RD indicated tubulointerstitial involvement characteristic for tubulitis. Electron microscopy revealed small electrodence subepithelial and a few subendotelial deposits (Figure 1). Based on renal biopsy findings consistent with PIGN-type picture and additional, interstitial involvement, we performed tissue DNA extraction with PCR analysis demonstrating EBV genome in the kidney. EBV-specific DNA was isolated from formalin-fixed and paraffin-embedded renal tissue using NucleoSpin®Tissue kit (Macharey-Nagel, Duren, Germany). EBV-DNA positive serum used as positive control and ultra purified water as negative control, demonstrated that patient's renal biopsy specimen was EBV-DNA positive.

Following renal biopsy our patient experienced gradual recovery with normalization of C3 (0.94 g/L) within 4 months, and resolution of hematuria and proteinuria (first morning protein: creatinine ratio <20 mg/mmol) after 12 and 18 months respectively. A few leucocytes in urinary sediment observed from the beginning, eventually disappeared within 6 months. Almost 2 years later, control immune-enzyme tests showed negative anti-EBV IgM and positive anti-EBV IgG titter of 292 AU/mL indicating convalescence. Followed-up for 3 years, he is doing well (without a relapse of infective mononucleosis) and his renal function remained stable.

Discussion

In majority of cases the diagnosis of acute PIGN relay on clinical findings and serological evaluation. Concerning results of either of them, usually rapid decline in renal function indicates renal biopsy[8,9]. Our patient presented with acute glomerulonephritis and serologically--proven streptococcal and simultaneously acute primary EBV infection. Except for negative history of antecedent infection, all other features including clinical presentation with hematuria, hypertension, diminished renal function, low C3 complement and renal biopsy findings of diffuse proliferative immune-complex glomerulonephritis were consistent with PIGN caused by streptococcal infection[1,9]. Accepting that approximately 5% of patients with EBV infective mononucleosis have positive throat cultures for group A streptococcus representing pharyngeal streptococcal carriage, dual action of both etiologic agents causing renal involvement was considered to be possible. At presentation our patient showed features consistent with infectious mononucleosis, atypical lymphocytes, altered liver enzymes and serological profile conclusive of acute primary EBV infection. Renal biopsy findings, beside characteristic PIGN-type picture revealed acute interstitial nephritis that could be associated with PSGN, drugs and other infective agents including EBV as in this particular case.

Infectious mononucleosis commonly caused by EBV is a benign and self-limited disease and occasionally complicated by renal involvement[3,4]. The spectrum of renal manifestations is broad, ranging from mild nephropathy with microscopic haematuria and/or proteinuria to more severe renal failure[4,5]. Although in most cases EBV renal infection is subclinical and found in up to 16% of patients with infective mononucleosis, serious renal involvement like acute renal failure can occur in 1.6% to 4.8% of children as recently reported[4].

Reported renal pathology changes included acute or chronic tubulointerstitial nephritis, immune-complex glomerulonephritis, or hemolytic uremic syndrome[10]. B-cell proliferation is linked to several reports of minimal change disease[3,4,8] and nephrotic syndrome[11]. Pathogenesis of EBV infection complicated with renal involvement has not been clarified. In interstitial nephritis an inflammatory infiltrate is composed of cytotoxic/suppressor T cells and interstitial mononuclear cells nuclei that expressed EBV encoded RNA-1 (EBER-1) mRNA[5]. We performed tissue DNA extraction by PCR analysis demonstrating EBV-DNA from the kidney. DNA extraction supported the EBV involvement in renal tissue, but it did not provide sufficient proof to separate the observed histopathology findings of both acute glomerulonephritis and acute interstitial nephritis. Our performed imunohystochemical analysis with CD45RD only confirmed tubulointerstitial involvement but without any specificity for EBV. If we could demonstrate EBER-1 in interstitial mononuclear cells might be the only means of linking EBV to our patient's interstitial nephritis and even this would be very questionable proof of causation. EBV as a ubiquitous human herpes virus is capable of inducing both replicative and latent infection in lymphocytes and epithelial cells via a receptor designated CD21[8]. Based on serial antibody titers such as elevated anti-EBV capsid antigen (VCA) IgM titer and EBV early antigen at presentation and negative anti-EBV IgM with positive anti--EBV IgG titer at follow-up almost two years later, chronic active EBV infection in our patient was excluded. Replicative form of EBV infection shows apparent clinical signs and symptoms of infective mononucleosis[8] and our results from positive PCR reaction suggest that activated, educated T cells could invade the renal interstitium following the EBV genome-positive lymphocytes and cause an antigen-directed cell-mediated immune response.

The search of the literature revealed not even a single case with PIGN with concomitant streptococcal infection that coincided with the onset of a primary EBV infection. Pathophysiological mechanism remains speculative in the absence of direct demonstration of both antigens in the glomeruli and interstitial tissue. As most evidence now suggests, infectious agents induce glomerulonephritis by triggering autoimmune response that results in formation of immune-complex deposits in glomeruli or elicits a cell-mediated immune response to antigens in or of the glomerulus[9]. Besides insufficient evidence provided to support the possibility of EBV inducing acute interstitial nephritis, we suspect that EBV co-infection simultaneously triggered the development of PIGN. Importantly, EBV co-infection might have influenced the prolonged recovery of PIGN not typical for glomerulonephritis caused by streptococcal infection[12]. Still, both

persistent haematuria and proteinuria with low complement C3 have been described in PIGN of poststreptococcal etiology[9] and are not necessarily due to the EBV co-infection. Hence, we speculate that the overall clinical picture and both acute glomerulonephritis and interstitial nephritis were associated with streptococcal infection in addition to acute EBV co-infection that contributed to renal inflammation, in particular to interstitial rather than glomerular damage.

Conclusions

The presented case of PIGN with convincing clinical and laboratory evidence for both streptococcal and acute EBV infection, to our knowledge is the first reported case with demonstrated EBV DNA in kidney tissue. EBV--DNA extraction supported the EBV involvement in renal tissue suggesting that both etiologic agents contributed to renal inflammation, but insufficient to separate the observed histopathology findings of acute glomerulonephritis and acute interstitial nephritis. Adding the serology evaluation for EBV in cases with renal symptoms, EBV might be more commonly associated with PIGN than is currently appreciated.

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POSTINFEKCIOZNI GLOMERULONEFRITIS S ISTOVREMENOM EPSTEIN-BARR VIRUSNOM INFEKCIJOM

SAŽETAK

Infekciozna mononukleoza se iznimno rijetko povezuje s akutnim oštećenjem bubrega za razliku od beta-hemolitičkog streptokoka grupe A koji je najčešći uzročnik postinfekcioznog glomerulonefritisa. Prikazujemo 11-godišnjeg dječaka sa kliničkim znacima infektivne mononukleoze uz serološku potvrdu akutne EBV infekcije,te akutnog posthemolitičkog glomerulonefritisa karakteriziranog edemima, hipertenzijom, tamno obojenim urinom te smanjenom bubrežnom funkcijom. Obzirom na perzistiranje hematurije i proteinurije uz niske vrijednosti C3 komplementa učinjena je biopsija bubrega. Uz tipični patohistološki nalaz za postinfekciozni glomerulonefritis nađen je i akutni intersticijalni nefritis s T limfocitima pozitivnim za CD45RD marker. Učinjena je ekstrakcija tkivne DNK putem PCR-a čime je dokazana virusna DNK u bubrežnom tkivu, što potkrijepljuje EBV zahvaćenost bubrega. Ovo je prvi prikaz postinfekcioznog glomerulonefritisa s istovremenom serološki dokazanom streptokoknom i akutnom EBV infekcijom. Izoliranje Epstein-Barr virusne DNK iz bubrežnog tkiva govori u prilog hipotezi o istovremenom učinku dvaju etioloških čimbenika u nastanku upalnih promjena na bubregu. U bolesnika s bubrežnom bolesti te tipičnim kliničkim znakovima infektivne mononukleoze dodatna serološka dijagnostika na EBV mogla bi pridonijeti češćem povezivanju postinfekcioznog glomerulonefritisa i Epstein-Barr virusa.