Epstein-Barr Virus Infection–Associated Renal Disease: Diagnostic Use of Molecular Hybridization Technology in Patients with Negative Serology

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ABSTRACT

There are only a few reports of renal disease associated with Epstein-Barr virus (EBV) infection. The diagnosis of EBV infection in these previously reported patients was based primarily on positive serology. Two patients with renal disease who, despite repeatedly negative serologies, were shown by molecular hybridization techniques—*in situ* hybridization (ISH) and polymerase chain reaction (PCR)—to have EBV infection are reported here. Site-specific molecular probes directed against specific, tandemly repeated EBV genomic regions were used. A synthetic 23-mer terminally biotin-labeled oligonucleotide probe selected from the EBV No/I region was used for ISH. For PCR, oligonucleotide primers were designed from sequences of the highly conserved, long internal direct repeat region of EBV to specifically amplify a 110-base-pair segment. The first patient, a 3-yr-old girl with a 1-yr history of fatigue, fever, splenomegaly, and lymphadenopathy developed hematuria. A renal biopsy revealed widespread glomerular mesangiolysis admixed with segmental mesangial sclerosis; no immune deposits were noted by electron microscopy or immunofluorescence. ISH on paraffin sections of the resected spleen and lymph nodes was positive for EBV. The second patient, a 28-yr-old male renal allograft recipient, received a double dose of OKT3. Seven weeks after transplantation, a renal biopsy revealed a lymphoproliferative disorder. Paraffin sections of the nephrectomy specimen were positive for EBV by both ISH and PCR. It was concluded that (1) EBV cannot be excluded on the basis of multiple negative serologies in some patients, and (2) ISH and PCR may lead to the detection of viral genomic information in renal and nonrenal tissues.

Key Words: Epstein-Barr virus, *in situ* hybridization, polymerase chain reaction, renal transplantation, lymphoproliferative disorder, mesangiolysis

There is only sparse information about the association of Epstein-Barr virus (EBV) infection and renal disease. Nephritis associated with infectious mononucleosis was first described by Pfeiffer (1) in 1889; this, however, probably represented an acute poststreptococcal glomerulonephritis. Poststreptococcal or nonpoststreptococcal acute postinfectious glomerulonephritis after infectious mononucleosis has also been described by others (2,3). Tennant (4) did not note any morphologic signs of renal disease in a patient with infectious mononucleosis and dinnally acute glomerulonephritis. Hematuria in patients with infectious mononucleosis is not infrequent, but cases documented with renal biopsy are rare (5). Occasional occurrences of immunoglobulin A (IgA) nephropathy (3), steroid-dependent minimal-change nephrotic syndrome (6), and hemolytic uremic syndrome (7) in patients with infectious mononucleosis have been also reported. A recent study from France suggested the role of EBV in the pathogenesis of primary IgA nephropathy (9). Taub (8) published a case with glomerular scarring and a vasculitic lesion. However, the most frequently reported renal disease in infectious mononucleosis appears to be interstitial nephritis (2,3,10–12). In addition, in the early and mid-1980s, posttransplant lymphoproliferative disorders (PTLD) have been recognized to be caused by EBV, which frequently involves the graft itself (13–18). Recent studies confirm this data (19–33), and some of them suggest that
OKT3 (CD3) antibody treatment may facilitate the development of PTLD (21,24,26,28,34).

EBV infection is usually diagnosed by serologic examination for the presence of anti-EBV antibodies. Primary EBV infection is defined serologically by circulating antibodies to the viral capsid antigen (IgM and IgG) and to the EBV early antigen (IgG). The EBV early antigen consists of two components, diffuse and restricted, as defined by immunofluorescence staining characteristics. The IgM response to the viral capsid antigen lasts for only a few months, whereas the IgG response is thought to be lifelong. Antibodies to EBV nuclear antigen (EBNA) usually develop several weeks or months after the infection.

We report two patients with EBV infection-associated renal disorders (one with a primary glomerular disease and one with a PTLD) in whom EBV was demonstrated by in situ hybridization (ISH) and polymerase chain reaction (PCR) in routinely processed, formalin-fixed, paraffin-embedded tissue sections, despite repeatedly negative serologies.

**CASE HISTORIES**

**Patient 1**

The clinical symptoms of the 3-yr-old girl started in December 1988 with a mononucleosis-like syndrome (generalized lymphadenomegaly, hepatosplenomegaly, and Coombs negative hemolytic anemia). An evaluation of her anemia included a bone marrow biopsy, which showed lymphoid and erythroid hyperplasia. EBV serology (IgG, IgM against viral capsid antigen, early antigen, EBNA) was negative. In June 1989, a lymph node biopsy was performed and reactive hyperplasia was noted. Her differential blood counts over time showed the following: polymorphonuclear leukocytes, 12 to 43%; bands, 0 to 1%; lymphocytes, 31 to 61%; atypical lymphocytes, 2 to 23%; monocytes, 3 to 15%; eosinophils, 1 to 16%. A T and B cell panel, performed on October 11, 1989, was normal. The serum immunoglobulins were also all within normal ranges for her age. Her sedimentation rate was usually elevated, up to 105 mm/h. Her red blood cell morphology was interpreted as normal in the peripheral blood smears examined. Her platelet count varied between 146 x 10^9 and 730 x 10^9/L, but it was within the normal range during most checkups. EBV serology (IgG, IgM against viral capsid antigen, early antigen, EBNA) continued to be repeatedly negative. The patient was also tested for antibodies to cytomegalovirus, human immunodeficiency virus, toxoplasmosis, mycoplasma, leptospirosis, tularemia, diphtheria, tuberculosis, hepatitis B surface antigen, as well as for the presence of hepatitis B core IgM antibody and hepatitis A IgM antibody—all with negative results. Her antinuclear antibody tests were always negative. In November 1989, she developed macroscopic hematuria with red blood cell casts in the urine. Proteinuria was 0 to 1+ by dipstick. She was admitted to Children’s Hospital of Oklahoma on November 23, 1989, in acute oliguric renal failure, which appeared to be secondary to uric acid nephropathy (serum uric acid, 16.1 mg/dL). Her serum potassium rose to 7.8 mg/dL, BUN was 88 mg/dL, and serum creatinine was 1.5 mg/dL. She received 3 consecutive days of hemodialysis, which resulted in a decrease in her serum uric acid level to 8.8 mg/dL and reestablishment of normal renal function. A renal biopsy was performed on December 12, 1989. In January 1990, the patient underwent a splenectomy because of the persistent generalized hemolytic anemia with hemolytic anemia. Splenic perihilar and mesenteric lymph nodes were also removed for examination. Histology showed sinusoidal congestion and lymphoid hyperplasia in the spleen and parafollicular hyperplasia in the lymph nodes. After the splenectomy, the hemolytic anemia subsided. The hematuria also resolved, and the renal function has remained satisfactory until the present time. However, her general condition did not improve and the malaise and fatigue, as well as the severe generalized lymphadenopathy, persisted. The patient’s whole blood was tested for various adenoviruses and herpesviruses (including human herpesvirus 6) by PCR in the laboratory of Dr. Robert Fox (Scripps Clinic, La Jolla, CA). The results were positive for EBV, and only for EBV. Subsequent workup at the National Institutes of Health (NIH) revealed a peculiar immunodeficiency with the appearance of an increasing percentage of CD3 + CD4− CD8− T lymphocytes without clonal rearrangement in her peripheral blood (Dr. Steve Strauss, NIH, Bethesda, MD, personal communication).

**Patient 2**

The patient, a 28-year-old male with end-stage renal disease from presumed chronic glomerulonephritis (not documented by renal biopsy), received a cadaveric renal allograft on November 11, 1989. The allograft was biopsied pretransplant and was normal. He did well postoperatively except for a transient pancytopenia, which was considered secondary to azathioprine and acyclovir (which he received as prophylaxis to prevent CMV infection), and the acyclovir was discontinued. One month after transplantation, his serum creatinine level began to rise to 6 mg/dL and a fine needle aspirate showed acute cellular rejection. Ultrasound and renogram were consistent with rejection. He was given 5 days of methylprednisolone but failed to respond, and his serum creatinine level rose to 6.3 mg/dL. He was then treated with OKT3, and his serum creatinine diminished to 3 mg/dL. He again received a double dose of OKT3, but in spite of that, his serum creatinine rose to 3.8
mg/dL. On January 3, 1990, a renal transplant biopsy was performed and showed a lymphoproliferative disorder. The diagnosis was confirmed by a bone marrow biopsy. At that time, the differential peripheral blood count showed 24% polymorphonuclear leukocytes, 41% lymphocytes, 6% monocytes, and 29% atypical lymphocytes. EBV serology (IgM and IgG antibody response against viral capsid antigen, early antigen, EBNA) was repeatedly negative. Because of the PTLD involving the renal transplant, the graft was resected on February 9, 1990, and the patient returned to the hemodialysis program. After the cessation of the immunosuppressive therapy, the lymphoproliferative disorder spontaneously regressed. The patient is currently on hemodialysis without any signs of PTLD. The other kidney of the donor was transplanted into a different recipient and is functioning well.

METHODS

The renal biopsy specimen of patient 1 was fixed in 10% buffered formalin and embedded in methacrylate. All other tissue specimens for light microscopy were formalin fixed and paraffin embedded. Direct immunofluorescence on frozen sections was performed in both renal biopsies with antibodies to human IgG, IgM, IgA, kappa and lambda light chains, C3, Clq, fibrinogen, and albumin. For ultrastructural examinations, a small piece of both renal biopsy specimens were fixed in 3% glutaraldehyde, postfixed in osmium tetroxide, contrasted with lead citrate and uranyl acetate, and embedded in Epon.

ISH was performed on paraffin sections of the resected spleen and the splenic hilar lymph nodes of patient 1 and on the removed renal allograft of patient 2. A terminally biotin-labeled oligonucleotide probe (kindly provided by Dr. David Brigati, Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City), composed of 23 consecutive nucleotides selected from the EBV NotI region, was used (35). The NotI region is repeated in tandem an average of 12.6 times in the EBV genome. This synthetic sequence has a 91% homology with another EBV genomic tandem repeat, the PstI region, which is reiterated about 25 times in the EBV genome. The NotI/PstI probe and the hybridization procedure are described in detail elsewhere (35). The UltraProbe Kit (Biomeda, Foster City, CA) was used as a detection system and included streptavidin-conjugated alkaline phosphatase and Fast Red TR chromogen. ISH was performed with the Code-On Automated Molecular Pathology System (Fisher Scientific, Pittsburgh, PA) in the laboratory of Dr. Brigati, according to the procedure described by Montone et al. (35).

PCR was performed on the same tissue blocks as ISH. Templates from EBV genomes were amplified by PCR, as described by Peiper et al. (36). Briefly, oligonucleotide primers were designed from sequences of the highly conserved, long internal direct repeat region of EBV to specifically amplify a 110-base-pair segment. PCR amplification reactions containing extracts from 8-μm sections of paraffin-embedded tissues were subjected to 30 cycles of amplification, each consisting of 1-min denaturation at 94°C, 2 min at 46°C for the annealing of the primers to the template, and 3 min at 72°C for DNA synthesis by Taq polymerase. Nucleic acids present in the amplification reactions were precipitated with ethanol and separated by size on agarose gels. The nucleic acids were then transferred to hybridization membranes by Southern blotting. Amplified EBV sequences were detected by hybridizing the blot with a labeled oligonucleotide probe designed from sequences specific to the targeted 110-base-pair segment. DNA from a Burkitt’s lymphoma cell line (Raji) and a placenta were the positive and negative controls, respectively. Samples were considered positive for EBV templates when an amplification product of 110 base pairs that annealed to the specific oligonucleotide probe was detected. A whole blood sample of the patient was also tested by PCR for various adenoviruses and herpesviruses, including human herpesvirus 6 in the laboratory of Dr. Robert Fox (La Jolla, California). His PCR method for the detection of EBV in whole blood, including the careful controls, is detailed elsewhere (37).

RESULTS

Patient 1

The percutaneous renal biopsy contained renal cortex and medulla with 23 glomeruli. Histologically, the majority of the glomeruli showed segmental or global, mild to severe mesangial expansion with sclerosis and moderate mesangial hypercellularity (Figure 1A). In 10 glomeruli, segmental mesangiolysis with microaneurysm formation adjacent to sclerotic segments was noted. In five glomeruli, mesangiolysis dominated (Figure 1B). Central mesangial sclerosis in the glomerular lobules with peripheral microaneurysms also occurred in three glomeruli. One glomerulus with sclerosis contained a cellular crescent. The interstitium was not widened, and no interstitial cellular infiltrate was detected. Some tubules contained red blood cell casts. No prominent vascular changes were observed. Immunofluorescence was negative with the antisera employed. Three glomeruli were examined ultrastructurally. Electron microscopy demonstrated widened and moderately hypercellular glomerular mesangial areas with dissolution of the mesangial matrix and occasional microaneurysm formation (Figure 2). A mild, focal, irregular glomerular subendothelial accumulation of electron-lucent fluffy material was noted. A tubule contained dys-
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Morphologic red blood cells admixed with electron-dense bundles of fibrillar material corresponding to fibrin strands. A few fibrin strands were also observed in a Bowman's capsule. No discrete electron-dense immune-type deposits or viral particles were identified. The diagnosis of a diffuse mesangial glomerulopathy with mesangial sclerosis and mesangiolysis was made.

Both the lymph node and the spleen showed reactive hyperplastic changes (Figure 3). Scattered positive cells for EBV were demonstrated by ISH in the parafollicular areas of the splenic hilar lymph node and in the white pulp of the spleen. The number of positive cells, similarly to the positive control sections, varied between 0 and 5 (usually 1 and 2) per high-power field. The staining was nucleolar or nuclear, but some cells also appeared to show cytoplasmic reaction (Figure 4). PCR in the tissue speci-

Figure 1. Glomerular pathology of patient 1. (A) A glomerulus showing pronounced mesangial sclerosis with moderate hypercellularity. (B) Widespread glomerular mesangiolysis with coalescence of the capillary loops. Jones; magnifications: panel A, x600; panel B, x1,000.

Figure 2. A large dilated glomerular capillary loop with dissolving mesangium. No electron-dense deposits are seen. Uranyl acetate, lead citrate; magnification, x2000.

Figure 3. Paracortical hyperplasia with polymorphic cells in the splenic hilar lymph node from patient 1. Hematoxylin and eosin; magnification, x200.

Figure 4. Two cells in the spleen of patient 1 labeled with the biotinylated oligonucleotide probe for the EBV Nofl region (arrows). Magnification, x400.
mens (lymph node, spleen) were negative (Figure 5). However, PCR performed on whole blood samples in the laboratory of Dr. Robert Fox was positive for EBV and negative for a variety of other herpesviruses (including human herpesvirus 6) and adenoviruses (Dr. Fox, personal communication).

Patient 2

The percutaneous renal biopsy specimen showed renal medulla and cortex with four normal-appearing glomeruli. The interstitium contained a heavy, patchy, lymphoplasmacytic infiltrate with displacement and compression of the renal tubules. In the areas with a slight, diffuse infiltrate, mainly lymphocytes were seen; however, in the heavily infiltrated areas, plasma cells, plasmacytoid lymphocytes, and immunoblasts predominated. Altogether, the infiltrate had a polymorphic appearance. Immunofluorescence showed cytoplasmic positivities for both kappa and lambda light chains in the interstitial plasma/lymphocytic cells and slight granular glomerular mesangial staining with the antibody against C3. No reactions were noted with the other applied antibodies. Electron microscopy demonstrated a number of interstitial inflammatory cells—mainly large lymphocytes and plasma cells. The glomeruli appeared essentially normal by ultrastructural examination; no discrete immune-type, electron-dense deposits were identified, and no viral or viral-like particles were seen. The diagnosis of PTLD was made and was later confirmed by a bone marrow biopsy, which showed a polymorphous polyclonal B cell proliferation.

The resected renal allograft showed similar morphologic findings to those described in the renal biopsy specimen. The polymorphic interstitial infiltrate was widespread with displacement of the renal tubules (Figure 6). Scattered infiltrating cells had eosinophilic cytoplasm and pyknotic nuclei with occasional karyorrhexis. A slight-to-moderate cellular intimal proliferation in the arteries was also detected. ISH revealed 2 to 25 (average, 12) positive cells per high-power field in the heavily infiltrated areas. The positive cells appeared to be mainly lymphocytes, plasmacytoid lymphocytes, and cells showing pyknosis and karyorrhexis. Some of the cells showed only nucleolar or nuclear positivities, but cytoplasmic staining was also frequently seen, particularly in cells with pyknotic nuclei, and occasionally karyorrhexis (Figure 7). Tubular epithelial cells and glomeruli did not stain with the NotI/PstI probe. PCR performed on the resected kidney was also positive for EBV genomic material (Figure 5).

DISCUSSION

Results from our two patients indicate that renal disease can be associated with EBV infection. The pathogenetic role of EBV in PTLD is well known; however, the relationship of EBV infection with glomerular diseases is less well established. We believe that the glomerular disease of our first patient is related to her chronic, devastating EBV infection. In addition to the clinical signs and symptoms, the diagnosis of EBV infection is usually made by the detection of the patient’s antibody response to a variety of different viral antigens of EBV. Of particular interest in our two patients is that neither of them

Figure 5. PCR on tissue samples from patients 1 and 2. Lanes: 1, placenta; 2, buffer; 3, Raji cell; 4, transplanted kidney from patient 2; 6 and 7, spleen and lymph node, respectively, from patient 1.

Figure 6. The resected renal transplant of patient 2 shows widespread tumor-like infiltrate consistent with PTLD. Note the many plasmacytoid cells and the cell showing pyknosis and karyorrhexis (arrow). Hematoxylin and eosin; magnification, ×200.
developed detectable antibody responses to EBV antigens by the routinely used serologic methods, despite their characteristic clinical symptoms. Molecular hybridization methods (ISH, PCR), however, revealed the presence of EBV in both patients.

There are occasional reports on deficient immune responses in immunologically compromised individuals (17,25,26,38–43), such as patients with X-linked lymphoproliferative disorder (39,41), renal transplant patients developing PTLD after cyclosporine and OKT3 treatment (25,26), patients with ataxia telangiectasia (17,38,40), patients with chronic EBV infection (42), and bone marrow transplant recipients (33). It is speculated that the presence of low or undetectable levels of antibodies to EBV signifies a T cell deficiency (40). This might be particularly true in transplant patients, because the immunosuppressive regimen, including cyclosporine and OKT3, primarily suppresses T cell responses. There is both in vitro (34) and in vivo (21,24–26) evidence that OKT3 treatment may facilitate the development of PTLD.

No signs of immunodeficiency were detected before and at the time of the renal biopsy in the first patient. Recent examinations, however, revealed that the patient developed a peculiar immune defect characterized by the appearance of an increasing percentage of CD3+ CD4- CD8- T lymphocytes without clonal rearrangement (Dr. Steve Strauss, NIH, Bethesda, MD, personal communication). This resembles the lpr and gld single gene models in the mice (44). The clinical syndrome in the mice with each of these two nonallelic genes is very similar and includes the appearance of nonmalignant CD3+ CD4- CD8- T lymphocytes with systemic lymphoproliferative disease and autoantibodies. This type of immune disorder could explain the patient’s negative serology for EBV but not the renal disease. The lpr/gld mice develop immune complex glomerulonephritis, whereas in our case, no glomerular immune complexes were noted.

We are unsure whether the glomerulopathy of patient 1 is specific for chronic EBV infection. Mesangial sclerosis is not specific to any particular glomerular disease; rather, it is generally considered to be a sign of chronic glomerular injury. Mesangiolysis may heal by mesangial expansion and later sclerosis (45). Morita and Chung (44) gave a detailed review on mesangiolysis and suggested that it may be the consequence of a number of injuries such as toxic effects, glomerular ischemia, hypertension, thrombotic microangiopathy, malignant nephrosclerosis, transplant rejection, radiation nephritis, glomerulonephritis, and diabetic glomerulosclerosis. Mesangiolysis was also recently described in graft versus host reaction after bone marrow transplantation (46), Takatsuki’s syndrome (47), Takayasu’s arteritis (48), and sickle cell disease (49). Huang and Wegenstein (50) published a case of mesangiolytic glomerulonephritis associated with systemic echovirus infection. Of interest is that their patient was an infant with combined immunodeficiency who subsequently developed a devastating disease that led to death. These authors did not note if their patient was tested for EBV or other viral pathogens. Mesangiolysis followed by mesangial sclerosis is usually seen in thrombotic microangiopathies (51). The light and electron microscopic changes in the renal biopsy of patient 1 could be consistent with a late stage of the glomerular type of thrombotic microangiopathy; the hemolytic anemia of the patient, however, was not of the microangiopathic type clinically. We are uncertain whether the glomerular pathology with the concomitant appearance of marked mesangial sclerosis and mesangiolysis, noted in patient 1, is the direct consequence of EBV infection or the action of various viral-associated mediators (e.g., interferons) produced during the devastating illness. Further studies are needed to directly resolve this issue.

The history of our second patient is very similar to that of the patient of Denning et al. (25); this patient was also on cyclosporine and OKT3 treatment and developed PTLD despite entirely negative serologies for EBV. ISH in the renal transplant revealed the presence of the viral sequences in both Denning et al. (25) and our second patient. The lack of immune response against EBV antigens in their and our transplant patients could be explained by the high doses of OKT3 and cyclosporine. The defective immune response to EBV in PTLD appears to be the consequence of deficient immunosurveillance rather than the down-regulation of immunogenic EBV-encoded antigens (52). After transplant nephrectomy and the cessation of immunosuppressive therapy, the PTLD regressed in both the patient of Denning et al. (25) and our second patient, which is not un-
usual, particularly if the disease is polyclonal (17,19,20,23,30).

ISH yielded strongly positive reactions in the tissue specimens of both of our patients, particularly in the renal transplant of patient 2. In the latter case, most of the cells demonstrating signs of necrobirosis (some infiltrating interstitial cells with pyknotic nuclei, eosinophilic cytoplasm, and occasionally, karyorrhexis), were strongly reacting with the NotI/PstI probe and displayed not only nuclear but also cytoplasmic positivities. Some indistinct cytoplasmic staining was also seen in the spleen and lymph node of patient 1. These cells, particularly those with necrobolic features, probably represent cells in the lytic cycle of EBV infection with a high number of viral DNA copies in both the nucleus and cytoplasm, as has been noted before with this nucleotide probe (17,35). This is supported by the experimental evidence that the NotI/PstI tandem repeat is among the most transcribed regions in the EBV genome during the extreme early and late stages of chemically induced, experimental, lytic EBV infections (53). Strong nuclear as well as cytoplasmic staining of lytic cells for EBV sequences was also demonstrated recently by Bashir et al. (54). The difference in the number of EBV-positive cells between our two cases is not surprising; it may vary from case to case, and not infrequently, only a few cells show positive signals (55–57). In our positive control, which was a spleen from the same patient reported in the publication of Montone et al. (35), the number of positive cells did not exceed the number of positive cells in the sections of patient 1. PCR in the renal transplant tissue was obviously positive, but the paraffin blocks of the spleen and the lymph node from patient 1 were negative with the same primers and probe. This is in contradiction to the positive ISH on the tissue sections and the positive PCR performed on whole blood. PCR, although a very sensitive method, may occasionally show false-positive or false-negative results (58). In patient 1, either the ISH was false positive or the PCR on the tissue was false negative. The clinical symptoms, the positive ISH, and the positive PCR on the whole blood suggest that probably the PCR on the tissue specimen was false negative. An explanation for that could be that we may be dealing with an aberrant or mutant EBV strain and the primers were not suitable for performing PCR, and the results on the frozen sections were uninterpretable because of the small piece of tissue, the poorly preserved structure, crush artifacts, and some background staining.

In summary, results from these two patients confirm the usefulness of molecular hybridization methods in the diagnosis of human viral disease in two renal conditions. We were able to demonstrate the presence of EBV genomic sequences by both ISH and PCR in the tissues of two patients with repeatedly negative EBV serologies. Thus, the absence of detectable antibody response does not necessarily exclude EBV infection, even in individuals with an apparently normal immune system.

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