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CASE REPORT

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Epstein-Barr virus genome-positive tubulointerstitial nephritis associated with immune complex-mediated glomerulonephritis in chronic active EB virus infection

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Abstract Renal involvement is rare in chronic active Epstein-Barr (EB) virus infection. We report a case of a 7-year-old girl with recurrent EB virus infection. She had fever, lymphadenopathy, hepatosplenomegaly, and persistently high titres of IgG to EB virus capsid antigen (VCA) and IgG to EB early antigen with low titres of IgM to VCA. She showed mild haematuria and proteinuria, but had no symptoms of renal failure. Renal biopsy revealed immune complex-mediated glomerulonephritis, which may have been due to a persistently high titre of antibody against EB virus. In addition, a peculiar form of tubulointerstitial nephritis was found. The morphology was characterized by a papillary infolding of the tubular epithelial cell layer into the tubular lumen. The interstitium was surrounded by the infolded epithelium and contained a large number of B-cell dominant lymphocytes. EBV-encoded RNA 1 (EBER-1) gene was detected in the nuclei of some tubuloepithelial cells by in situ hybridization and may have been associated with the pathogenesis of tubulointerstitial nephritis.

Key words Epstein-Bar virus · Tubulointerstitial nephritis · Glomerulonephritis · In situ hybridization

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Introduction

Epstein-Barr virus (EBV) is a ubiquitous virus, which is usually asymptomatic [5]. The primary infection causes infectious mononucleosis (IM) in some individuals, who manifest fever, acute pharyngitis, cervical lymph node swelling and hepatosplenomegaly. IM usually takes a self-limiting and benign clinical course, but a clinical syndrome with relapse of the symptoms of IM and a persistently high titre of EBV infection was reported in the early and mid-1980s [27, 30, 33]. This syndrome has been designated chronic active EBV infection (CAEBV). Multi-organ involvement in CAEBV has been reported, including fulminant hepatitis [32], lymphoproliferative disorder [17], parotitis [1], coronary arteritis [15, 22], chronic myelogenous leukaemia [10], interstitial pneumonitis [28], pancytopenia and polyclonal B-lymphoproliferation terminating in acute lymphoblastic leukaemia [6]. Kidney involvement is rare and direct detection of the EBV genome in the kidneys has not often been performed [21–23].

In this report, we present a case of CAEBV showing interstitial nephritis with peculiar morphological findings combined with immune complex-mediated glomerulonephritis. Renal involvement by EBV infection was confirmed by in situ hybridization in renal tissue. Serological analysis of anti-EBV antibodies and phenotypic characterization of infiltrating cells into the interstitium were also performed. The paucity of information on morphology, phenotype of infiltrating cells, and distribution of EBV genome-positive cells in the renal involvement of CAEBV prompted us to present this case report.

Clinical history

A 7-year-old Japanese girl with a recurrent fever of 38°C was admitted to our hospital in June 1995. She had no history of renal disease. She had noticed swelling of the cervical lymph nodes on both sides and had also had hepatosplenomegaly from May 1993. Urinalysis began to show proteinuria and haematuria in August 1994, and this continued. Persistent EBV infection had been noted from

Table 1 Results indicating Epstein-Barr (*EB*) virus infection (*VCA*, viral capsid antigen; *EBEA*, EB early antigen; *EBNA*, EB nuclear antigen; *ANA*, anti nuclear antibody, *HS*, homogenous and speckled pattern; *CIC*, circulating immune complex; *P-ANCA*, perinuclear anti-neutrophil cytoplasmic antibody; *C-ANCA*, cytoplasmic anti-neutrophil cytoplasmic antibody)

	1993/5	1995/5	1995/8	1995/10	1996/1	1996/7
EB virus titre						
EB VCA IgG	640	1280	1280	1280	1280	1280
EB VCA IgA		40		10	<10	<10
EB VCA IgM	40	<10			<10	<10
EBEA IgG	320	160	1280		640	
EBEA IgA	<10	10	40		10	
EBNA	10	80	40		80	40
Immunoserological test						
IgG (mg/dl)			2930	1910	1674	2609
IgA (mg/dl)			145	194	145	140
IgM (mg/dl)			555	497	471	731
C3 (mg/dl)			80.6	74.0	78.6	92.7
C4 (mg/dl)			18.5	17.8	16.3	24.5
CH50 (U/dl)			24.0	31.1	26.0	29.0
Anti-DNA			80 (ssDNAIgG+, dsDNAIgG-)			
ANA			20 HS			
Heterophil antibody					28	
CIC (antiC1q)	–					
P-ANCA	–					
C-ANCA	–					

May 1993, showing IgG to viral capsid antigen (VCA), 1:640; IgM to VCA, 1:40; IgG to EB early antigen (EA), 1:320; IgA to EBEA, less than 1:10, and EB nuclear antigen (EBNA), 1:10 (Table 1). Chronic sinusitis and otitis media were also diagnosed.

Haematological findings were as follows: haemoglobin (Hb) 11.9 g/dl; white blood cell (WBC) count 6,600/μl with 4,120/μl (62%) granulocytes and 1850/μl (28%) lymphocytes including 310/μl (3.7%) atypical lymphocytes, and 420/μl (6.4%) monocytes; red blood cell (RBC) count 4,500,000/μl; haematocrit (Ht) 34.8%; platelet count 138,000/μl. The test results for coagulation were in normal ranges except for serum thrombomodulin, which was 6.0 FU/ml (normal 4.5 FU/ml). Serum biochemistry testing revealed a blood urea nitrogen (BUN) level of 18 mg/dl, a serum creatinine (Cr) level of 0.2 mg/dl, and a uric acid level of 4.2 mg/dl. Creatinine clearance was 134 ml/min. IgG was 1910 mg/dl, IgA was 194 mg/dl, IgM was 497 mg/dl, C3 was 74 mg/dl, C4 was 17.8 mg/dl, and CH 50 was 31.1 U/dl. C-reactive protein (CRP) was 0.2 mg/dl. Total bilirubin was 0.3 mg/dl. Hepatic transaminase levels were 203 IU/l for glutamic oxaloacetic transaminase (GOT) and 183 IU/l for glutamic pyruvic transaminase (GPT). In the urine, protein was +1 positive (0.264 g/day), sugar was negative, and occult blood was +2. In the urine sediment, RBC was 10–19/HPF, and WBC was 1–4/HPF. *N*-Acetyl-β-glucosaminidase (NAG) and beta-2 microglobulin in the urine were 15.7 U/g Cr and 412 μg/g Cr, respectively.

Serologically, anti-DNA was positive (1:80). (ssDNA-IgG was positive, dsDNA-IgG was negative). Antinuclear antibody (ANA) was positive (1:20; homogenous and speckled pattern). The titre of heterophil antibody was positive (1:28). The titres of antibodies to EBV-specific antigens were as follows (Table 1): IgG antibody to VCA was consistently 1:1280 in May, August, and October 1995, and in January and July 1996. IgA to VCA was 1:40 in May 1995, 1:10 in October 1995 and less than 1:10 in January and July 1996. IgM to VCA was less than 1:10 in May 1995 and July 1996. IgG antibody to EBEA was 1:160 in May 1995, 1:1280 in August 1995, and 1:640 in January 1996. IgA antibody to EBEA was 1:10 in May 1995, 1:40 in August 1995, and 1:10 in January 1996. EBNA was 1:80 in May, 1:40 in August 1995, 1:80 in January 1996, and 1:40 in July 1996. Antibodies against HTLV-I and HTLV-II were not present, and an assay for cytomegalovirus, syphilis, and toxoplasma gave negative results. The titres for hepatitis B virus surface (HBVs) antigen, HBVs antibody and HCV antibody were in the normal ranges. P-ANCA and C-ANCA were both negative.

Renal biopsy was conducted on the presumptive diagnosis of systemic vasculitis syndrome. After the result of renal biopsy indicating acute aggravation of interstitial nephritis, pulse therapy (1 g/day over 3 days) was conducted with methylpredonosolone.

Method

For light microscopy, kidney tissues from the biopsy were fixed in 0.1 M phosphate-buffered 10% formalin. Paraffin sections (2 μm thick) were stained with periodic acid–Schiff (PAS), Masson's trichome, and periodic acid-methenamine silver (PAM). For electron microscopy, biopsy kidney was fixed in phosphate-buffered 1.2% glutaraldehyde, postfixed in 1% osmium tetroxide, and embedded in Epon 812. Ultrathin sections were double-stained with uranyl acetate and lead citrate. For the immunohistochemical studies, paraffin-embedded sections were processed by the peroxidase-antiperoxidase method. Antisera against IgG (1:1600), IgM (1:1600), IgA (1:2500), C3 (1:1600), C1q/C4 (1:1600), and CD68 (PG-M1)(1:50) (DAKO Japan, Kyoto, Japan) were used to treat the sections after digestion for 15 min at 37°C by 0.05% protease type 8 (Sigma, St. Louis, Mo.).

For the detection of EBV, in situ hybridization was performed with enzyme-linked oligonucleotide probes on the paraffin-embedded section. The probes were chosen from the 40-bp sequence within the EBV-encoded RNA 1 (EBER-1) gene. An alkaline-phosphate (Apase)-conjugated oligonucleotide probe complementary to EBER 1 was used as an antisense probe, while an oligonucleotide DNA probe compatible with the sequence of EBER-1 was used as a sense control probe (Diatron Laboratories, Tokyo, Japan) according to the method of Hironaka et al. [11]. Deparaffinized sections 6 μm thick were placed on side glasses pretreated with 3-aminopropyltriethoxysilane. Raji cells infected by EB virus were used for the control. The sections on the slide glasses were fixed with 4% formaldehyde/0.1 M sodium phosphate buffer (PB, pH 7.2) at room temperature (r.t.) for 10 min. After washing with 0.1 MPB at r.t. for 5 min, the slides were treated with 0.2 M HCl at r.t. for 5 min to inactivate intrinsic Apase, then dehydrated in ethanol and chloroform. A 100-μl volume of the hybridization mixture containing 2× standard saline citrate (SCC, 0.15 M sodium chloride and 0.015 M sodium citrate), 1× Denhardt's solution (0.02% each of bovine serum albumin, Ficoll 400, and polyvinylpyrrolidone 40), 250 ng/ml of sonicated herring sperm single-stranded DNA, 10% dextran sul-

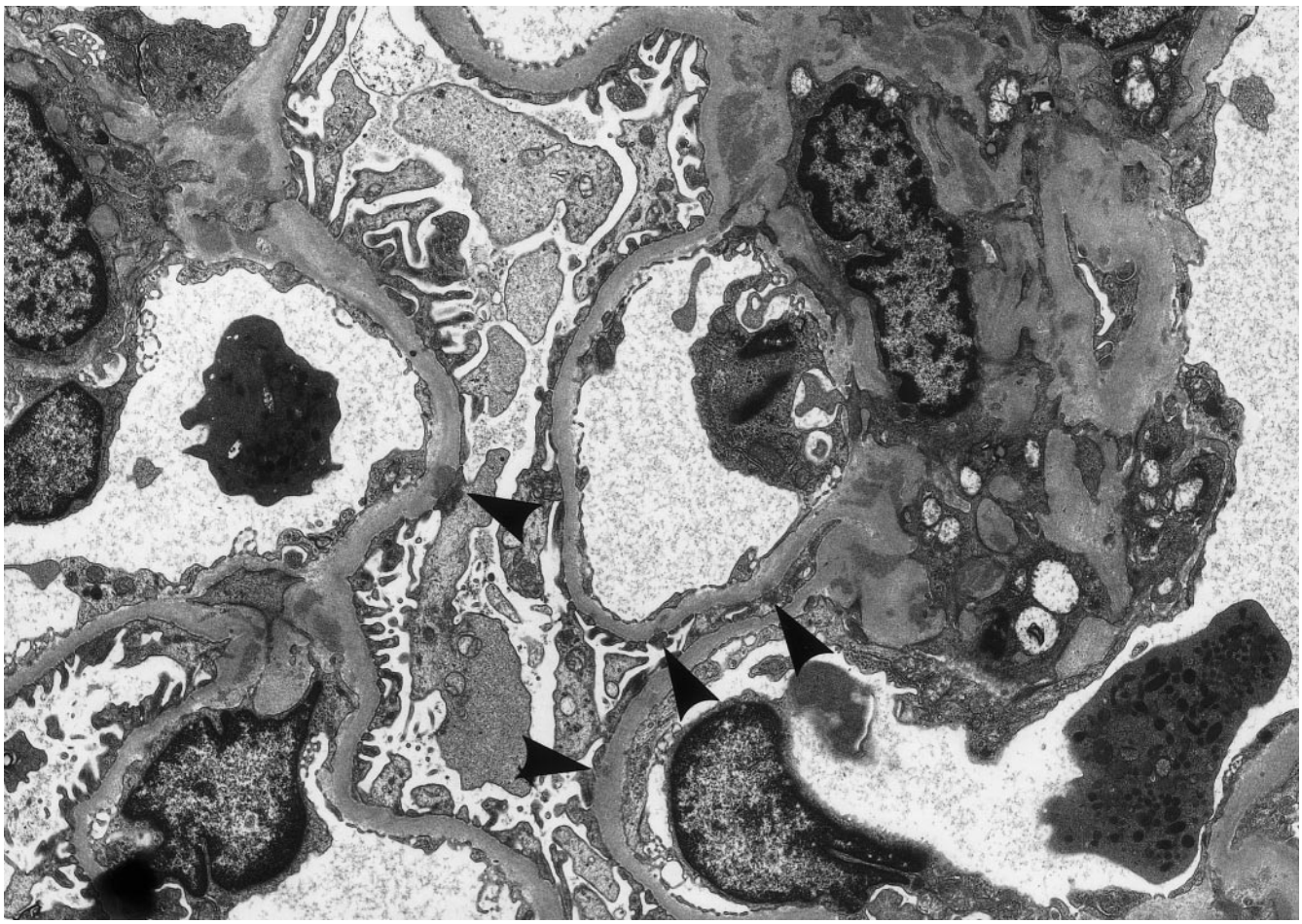
fate, and 2 pmol of the APase-conjugated sense or anti-sense probe was applied to the dehydrated sections. These were then covered with parafilm (American National Can, Conn.) and incubated at 37°C for 12–16 h in a humidified chamber. After hybridization, the slides were washed in 4 × SSC containing 0.1 mM $ZnCl_2$ at r.t. for 10 min, then in 1 × SSC containing 0.1 mM $ZnCl_2$ at r.t. for 3 min. They were then treated with Apase solution (0.1 M NaCl, 10 mM $MgCl_2$, 0.1 M Tris-HCl, pH 9.5) for 3 min. The slides were developed in chloro-3-indoyl phosphate in 1 ml of Apase solution for 15 h at r.t. in a dark room. The reaction was stopped by incubation with 10 mM Tris-HCl (pH 7.5) and 10 mM EDTA for 20 min at r.t., and the sections were mounted in 50% glycerin.

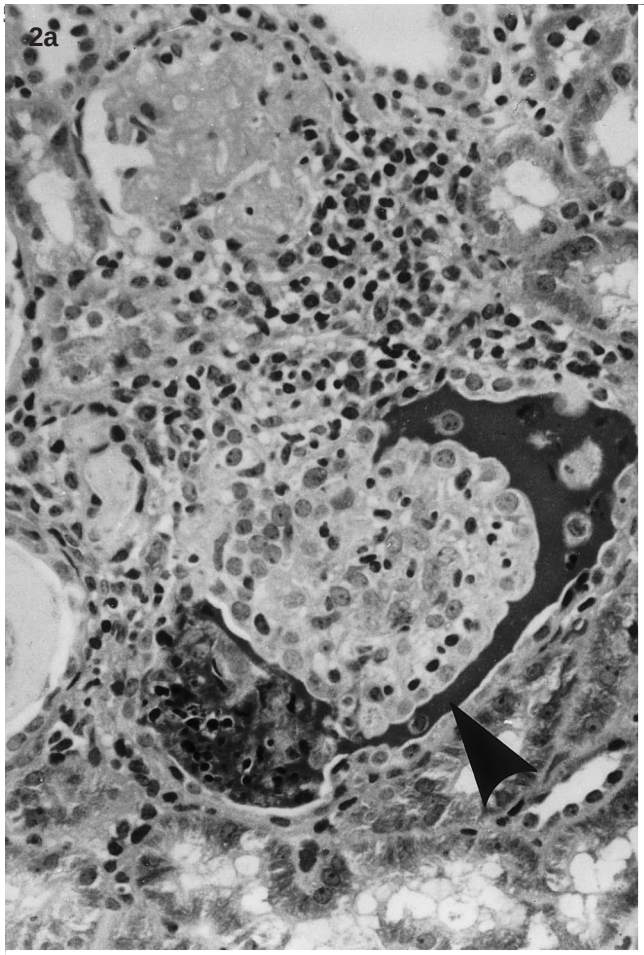
Results

The kidney tissue obtained from the biopsy showed 19 glomeruli, among which global sclerosis was seen in 6, fibrocellular crescent formation in 2, and adhesion in 3. In the other glomeruli, focal segmental proliferation of the mesangial cells and focal segmental spike formation and bubbling on the glomerular basement membrane (GBM) were seen. Immunohistochemical findings revealed that IgG, IgM and C3 were positive on the mesangial area as a diffuse global mesangial pattern as well as on the GBM as a diffuse global peripheral pattern. In the electron microscopy, dense deposits were observed in the mesangial matrix and in the epimembranous region (Fig. 1, arrowheads). In the tubulointerstitial area, regional and massive lymphocytic infiltration was seen where the tubular epithelium was buried showing severe tubular destruction and regeneration (Fig. 2a, b). Lymphocytic cells had infiltrated the tubular systems with rupture of the basement membrane (Fig. 2b, arrow). Papillary infolding of the tubular epithelial cell layer into the tubular lumen was observed. The interstitium was surrounded by the infolded epithelium and contained a large number of lymphocytes (Figs. 2a, b, arrowheads). In the tubular lumen of this lesion, nuclear debris and karyorrhexis were seen. Most of the infiltrating lymphoid cells in the interstitium were L26-positive B cells (Fig. 3a). A very few were UCHL1-positive T cells. Some of the infiltrating cells reacted positively with specific monoclonal antibody against PGM1 (CD68), indicating macrophages (Fig. 3b). The lymphocytes were almost all small, including some lymphocytes with lymphoblastic change. Neither vascular nor granulomatous lesions were seen in the interstitium.

In the next step, EBV-encoded RNA 1 gene was detected by in situ hybridization using enzyme-linked EBER-1-specific sense and antisense probes. This method clearly revealed the presence of this RNA in the nuclei of the the tubular epithelial cells, but not in the cells

Fig. 1 Electron microscopy. Glomerulus showed dense deposits in the mesangial matrix as well as in the epimembranous region (*arrowheads*)

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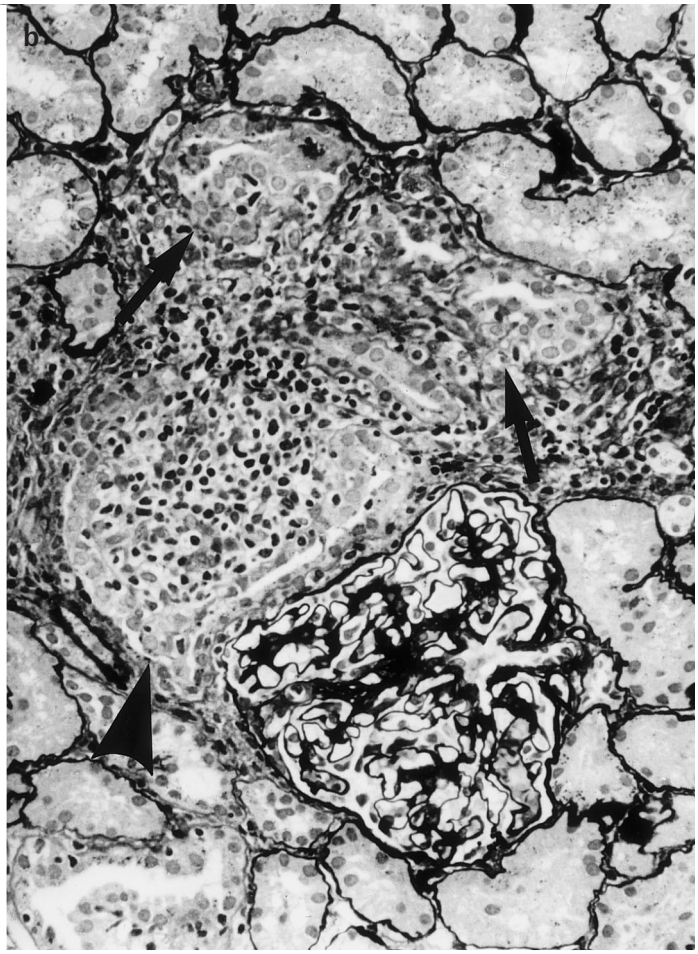
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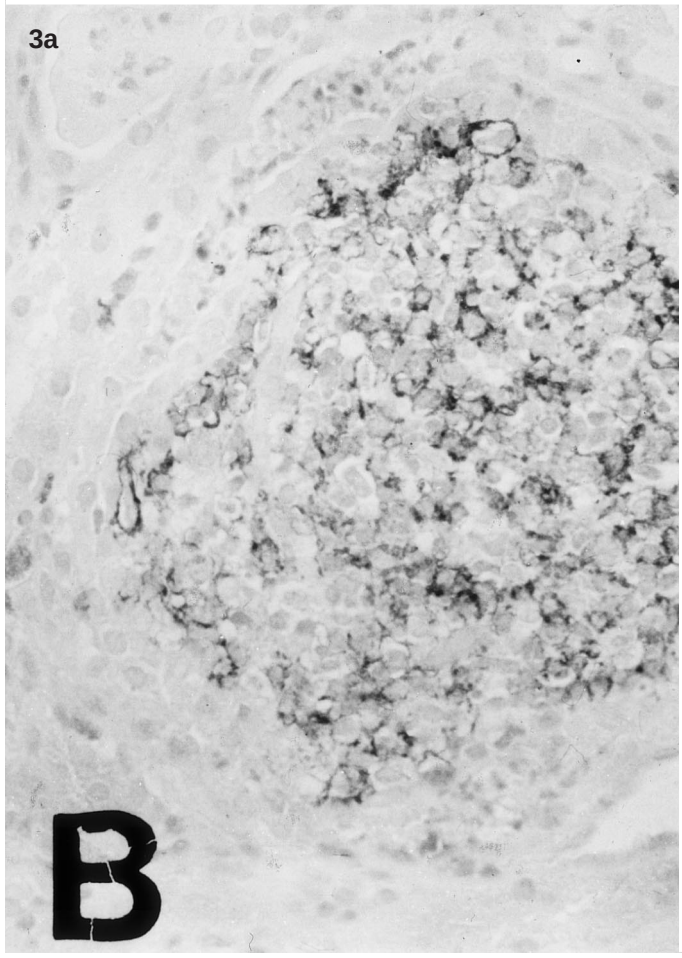
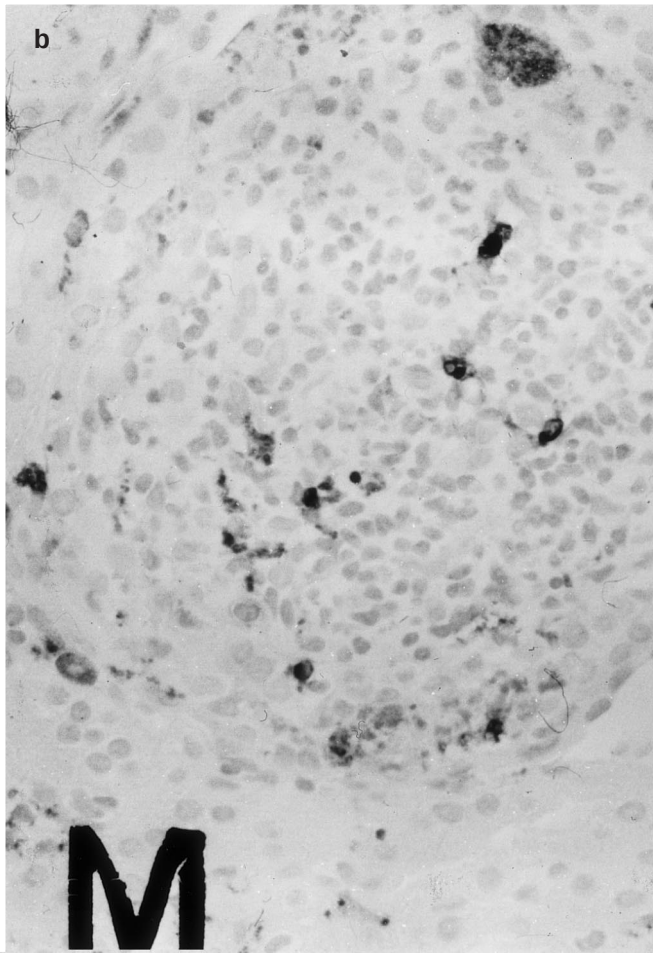

3a
B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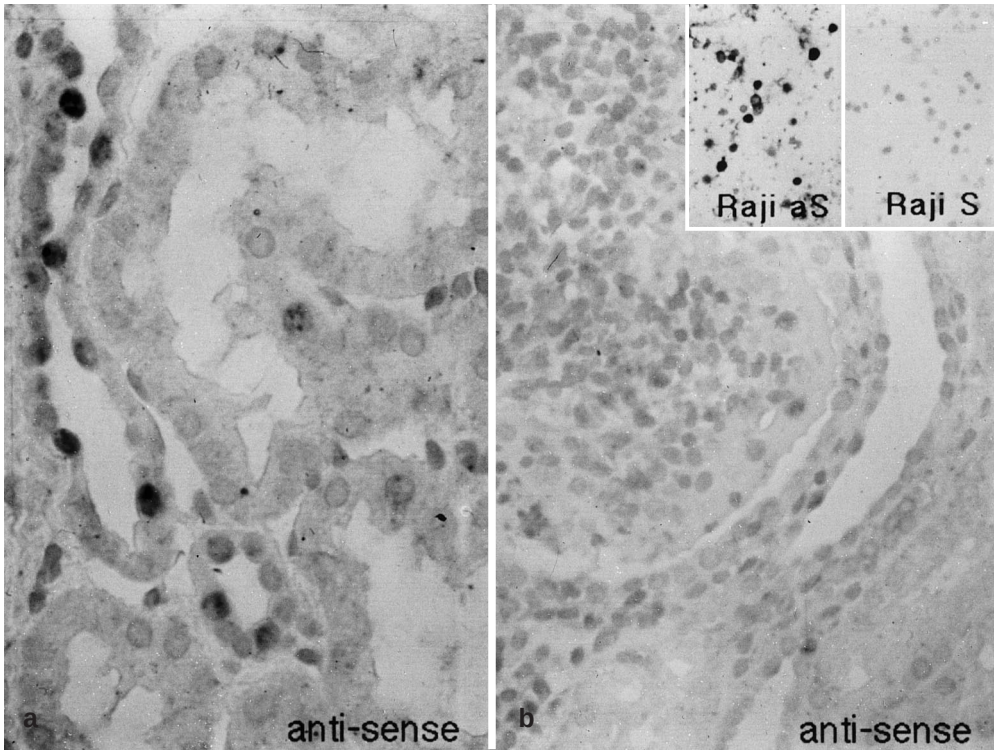

Fig. 4a, b In situ hybridization using Epstein-Barr virus-encoded RNA 1 gene (EBER-1) as an antisense probe on the tubulointerstitial lesion. **a** EBER-1 was positive in the nuclei of tubular epithelial cells. ×100 **b** The infolded tubular epithelial cell layer associated with lymphocytic infiltration was negative for EBER-1. ×100 *Inset*: in the control, Raji cells infected by EB virus were used, showing a positive antisense and negative in sense

of the glomeruli (Fig. 4a). EBER-1-positive cells were almost all tubular epithelial cells in some areas, but cells of the infolded tubular epithelium layer associated with lymphocytic infiltration were negative for EBER-1 (Fig. 4b). In contrast to the large number of infiltrating cells, there were very few EBER-positive interstitial cells or lymphocytes. In the controls, Raji cells infected by EB virus were used and gave positive antisense and negative sense findings (Fig. 4b, inset).

Discussion

The course of our patient was not self-limiting, but showed recurrent symptomatic EBV infection, which was defined by the clinical triad of fever, lymphadenopathy, and pharyngitis combined with the transient appearance of heterophil antibody and atypical lymphocytosis. Serological tests for EBV-associated antibodies were performed during the 3-year clinical course and consistently revealed high titres of IgG to VCA and IgG to EBEA with low titres of IgM to VCA, whereas patients with typical IM had low titres of IgG to VCA [19]. Moreover, testing for anti-EBNA antibody, IgA to VCA, and IgA to EBEA gave positive results. These clinical and serological characteristics of our patient appear to be consistent with CAEBV [9, 14, 24].

There have been rare reports on tubulointerstitial nephritis in CAEBV [22, 23], as in the cases of IM [2, 3, 21]. Mayer et al. investigated 27 patients in whom IM was believed to be associated with renal insufficiency. There have been 18 cases whose renal dysfunction appeared to be due to EBV-induced IM. Thirteen underwent renal biopsy, 10 of which showed interstitial nephritis and/or fibrosis of varying degree [21]. However, the actual incidence of kidney involvement may not be reflected by urinalysis, as renal parenchymal abnormalities can occur in the absence of alteration in function or urine sediment [35]. In a series of patients with IM, but without clinical evidence of renal disease, renal biopsies revealed glomerular cell swelling and focal interstitial mononuclear infiltrates in 12 of 13 cases [26]. Accordingly, it is likely that subclinical kidney involvement as seen in the present case may be relatively common. In contrast, significant impairment of renal function due to tubulointerstitial nephritis is rare, at approximately 1.6% of the total number of cases of EBV infection [20].

The infiltrating lymphocytes in the tubulointerstitium have been reported to be T cell dominant [16, 21, 22] or

◀ **Fig. 2a, b** Light microscopy of the kidney. Papillary infolding of the tubular epithelial cell layer into tubular lumen. The interstitium was surrounded by the infolded epithelium and contained a number of lymphocytes (*arrowheads*). **a** Nuclear debris and karyorrhexis were seen in the tubular lumen of this lesion. Masson trichrome, ×400 **b** Regional lymphocytic infiltration was seen in the tubulointerstitial area, where the tubular epithelium was buried. Severe tubular destruction and regeneration with rupture of the basement membrane were observed (*arrow*). PAM, ×300

Fig. 3a, b Immunohistochemical investigation of tubulointerstitial lesion shown by arrowhead in Fig. 2b. **a** The infiltrating lymphoid cells in the interstitium were almost all L26-positive B cells. PAP with anti-L26 antibody, ×100 **b** Some of the infiltrating cells on the serial section reacted positively with specific monoclonal antibody against PGM1 (CD68), indicating macrophages. PAP with anti-PGM1, ×100

B cell dominant [23]. EBV infects B cells through the CR2 receptor against C3d, but the proliferation is controlled by cytotoxic T cells or NK cells. When the regulation of the proliferation is uncontrolled, extensive proliferation of B cells and polyclonal B cell proliferative disease will be induced [31]. However, the analysis of general and EBV-directed immunological reactivity shows heterogeneity of the immune defects in patients of CAEBV [18]. In the present case, the lymphocytes associated with lymphoblastic change infiltrating the renal tubulointerstitium were predominantly B cells mingled with CD68-positive macrophages, whereas UCHL-1-positive T cells were rarely found. Interstitial infiltrate of predominant B cells may be related to EBV infection-associated lymphoproliferative disorder.

To confirm the direct relationship between EBV infection and the renal disease in our patient, viral investigation was performed in the kidney tissues obtained at biopsy. We detected the EBER-1 genome by in situ hybridization using an enzyme-linked antisense probe. EBER-1 is one of two EBV-encoded small nonpolyadenylated RNAs, about 107 copies of which are found in EBV-infected cells [12, 13]. Because of its abundance, this RNA is a good marker of EBV infection. In the present study, the localization of EBER-1 in the nuclei of some tubular epithelial cells, but not of the glomerular cells, was demonstrated. This result suggested that at least some tubular epithelial cells were infected with EBV and may have been associated with tubulointerstitial nephritis, even though the lesion with a peculiar infolding of the tubular epithelium layer and lymphocytic infiltration did not show evidence of an association with direct viral infection. In the literature, the EBV genome has been demonstrated in infiltrating lymphoblastic cells showing pyknosis and karyorrhexis in the interstitium of post-transplantation lymphoproliferative disease involving a renal allograft [23]. It has also been found in the lymphocytes during CAEBV with interstitial nephritis [22], and in the nuclei and cytoplasm of proximal tubular cells in EBV-infected IgA nephropathy [29]. Thus the EBV genome-positive cells in the kidney have differed among the cases in the literature. Future investigations may shed further light on the relationship with EBV infection.

In our patient with microscopic haematuria and mild proteinuria, immune complex-mediated glomerulonephritis was found in addition to tubulointerstitial nephritis. The pathogenesis of the glomerular disease in EBV infection is unknown, but the aetiology is probably multi-factorial. Spontaneous recovery and disappearance of the urinary abnormalities is usual. Immune complex injury or direct viral cytopathic effect is one of the potential mechanisms. In the literature, heterogeneity of glomerular involvement including immune complex-mediated glomerulonephritis [2, 7, 21, 34, 35] and focal segmental glomerulosclerosis [8] has been reported. Andres et al. reported the case of a 22-year-old white man with IM, who had jaundice and oliguric renal failure and showed mesangial granular deposition of IgM and C3 corresponding to a dense deposit on electron microscopy [2]. They found that the IgM mesangial deposits were associated with IgM heterophil antibody and C3, presumably Paul-Bunnell antigen–antibody complex, because eluted IgM contained PB antibody. In another report, circulating IgM-containing immune complexes were demonstrated during the acute and convalescent phases of IM [4]. There has been no substantial evidence implicating EBV-induced immune complex glomerulonephritis in the present case, though a continuous high titre of antibody against EB virus may have been associated with secondary glomerulonephritis.

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