Epstein-Barr Virus–Induced Infectious Mononucleosis Complicated by Acute Renal Failure: Case Report and Review

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Infectious mononucleosis, most commonly caused by Epstein-Barr virus (EBV), is generally a benign, self-limited illness. Occasionally, however, more severe complications may arise such as acute renal insufficiency. While subclinical renal involvement appears to be relatively common in patients with infectious mononucleosis, patients with significant renal parenchymal dysfunction have rarely been described in the English-language literature. In this report, we review 27 previous cases and present a case of oliguric renal failure complicating heterophil-positive infectious mononucleosis. The patient required hemodialysis but recovered promptly with treatment with the combination of corticosteroids plus acyclovir. Renal biopsy revealed interstitial nephritis, and immunoperoxidase studies demonstrated a predominance of suppressor/cytotoxic T cells, which has been described in only one previous case report. In situ hybridization done on renal biopsy tissue failed to reveal evidence of EBV-encoded RNA-1. Acute renal failure in infectious mononucleosis is rare, often self-limited, and usually caused by interstitial nephritis that is likely the result of immunopathologic injury precipitated by EBV infection.

The clinical spectrum of Epstein-Barr virus (EBV) infections is vast. In addition to infectious mononucleosis, EBV has been associated with lymphoproliferative lesions, most notably B-cell tumors in patients with AIDS and in organ transplant recipients [1–5]. X-linked lymphoproliferative syndrome is another disorder that affects young males in whom fulminant, often fatal infectious mononucleosis follows EBV infection [6]. Other syndromes associated with EBV include nasopharygeal carcinoma, Burkitt's lymphoma, T-cell lymphomas, some thymomas, and hairy leukoplakia [7]. There have also been recent reports linking EBV to smooth-muscle tumors in children following liver transplantation and in children with AIDS [8, 9].

Similarly, the syndromes associated with EBV infection may themselves be quite complex. For example, the presentation of EBV-associated infectious mononucleosis may deviate substantially from the classic triad of fever, pharyngitis, and lymphadenopathy. Although uncommon, the presence of hemolytic anemia, granulocytopenia, encephalitis, pericarditis, hepatitis, and other entities has occasionally made the diagnosis of infectious mononucleosis more difficult.

Acute renal failure is yet another rare complication of EBV-induced infectious mononucleosis. But while true renal parenchymal dysfunction may be uncommon in these patients, abnormalities in urinary sediment have been noted in up to 5%–15% of those affected [10, 11]. In 1946 Wechsler et al. described abnormal urinary findings for 17 of 556 patients during an epidemic of infectious mononucleosis at an army post; these 17 generally presented with microscopic hematuria and proteinuria [12].

In 1978 Lee and Kjellstrand reviewed 128 patients with infectious mononucleosis and found a 14% incidence of proteinuria and an 11% incidence of hematuria [13]. In a series of patients with infectious mononucleosis without clinical evidence of renal disease, renal biopsies revealed glomerular cell swelling and focal interstitial mononuclear infiltrates in 12 of 13 cases [14]. Thus, it is likely that subclinical kidney involvement in infectious mononucleosis is relatively common, whereas significant impairment of renal function is rare.

We encountered a previously healthy individual with clinically and serologically evident EBV-induced infectious mononucleosis complicated by acute renal failure. A kidney biopsy revealed interstitial nephritis and a predominance of suppressor T lymphocytes in the biopsy specimen. Herein we present this case and review the previously reported cases of acute renal failure complicating infectious mononucleosis.

Case Report

In April 1993 a 29-year-old man with no significant medical history presented to another institution because of a 2-day history of fever (temperatures to 103°F), fatigue, shaking chills, headache, anorexia, and vomiting. On presentation he also complained of low-back pain and bilateral flank pain. Emergency department personnel noted a temperature of 103.5°F and orthostatic hypotension.

Laboratory data on admission included a WBC count of 8.0×10^9/L, with 27% atypical lymphocytes. The blood urea nitrogen (BUN) level was 34 mg/dL and the creatinine level

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was 4.2 mg/dL. Urinalysis was remarkable for findings of proteinuria (>300 mg of protein per dL) and microscopic hematuria (2–5 RBCs). Tests of liver function yielded values within normal limits. Cultures of blood and urine were negative. A renal ultrasonogram was normal. Treatment with intravenous cefazolin was initiated, and over the next 2 days his urine output diminished while his BUN and creatinine levels rose to 47 mg/dL and 6.8 mg/dL, respectively. A monospot test was positive, and he was transferred to our institution for further evaluation.

Physical examination at the time of admission revealed the following values: blood pressure, 120/90 mm Hg; pulse, 84/min and regular; and temperature, 100.7°F. He was well developed and somewhat edematous. Notable findings were a beefy-red pharynx with palatal petechiae, bilateral posterior cervical lymphadenopathy, and palpable liver edge and splenic tip.

Findings of repeated laboratory tests were notable for a further rise in BUN and creatinine levels, to 50 mg/dL and 7.8 mg/dL, respectively. Urinalysis again revealed proteinuria and microhematuria. A urine myoglobin test was negative, and there was no evidence of eosinophiluria. A monospot test was again positive.

An antistreptolysin O titer was minimally elevated at 240 Todd units. Tests for antinuclear antibody, antineutrophil cytoplasmic antibody, antibody to glomerular basement membrane, and antibody to HIV were all negative. Serum complement (C3, C4, and CH50) levels were normal. Blood, urine, and throat swab cultures were negative as well. A roentgenogram of the chest was unremarkable.

The following day, because of continued oliguria (urine excretion, 350 mL per 24 hours) and worsening renal function, the patient underwent a renal biopsy. He was given a single intravenous dose of methylprednisolone (500 mg), and although his symptoms abated the following day, persistent oliguria and progressively worsening renal function (BUN, 72 mg/dL; creatinine, 8.7 mg/dL) prompted the initiation of hemodialysis. The heterophil antibody titer was 1:896 (after guinea pig RBC absorption, 1:448; after absorption with beef RBCs, 1:14), and treatment with intravenous acyclovir was begun (5 mg/kg every 24 hours).

The patient's condition dramatically improved over the next several days, and resolution of his oliguria and a stepwise decline in his BUN and creatinine levels were noted. He required no further dialysis and received no additional corticosteroids, and he was discharged on hospital day 6 (BUN, 30 mg/dL; creatinine, 1.6 mg/dL) to complete a 10-day course of oral acyclovir.

Further serological testing of plasma samples obtained at the time of diagnosis yielded the following titers: IgM to viral capsid antigen, 1:10; IgG to viral capsid antigen, 1:320; early antigen (diffuse), 1:80; early antigen (restricted), <1:10; and EBV nuclear antigen, 1:2 (with a negative control). The patient was unavailable for determination of convalescent titers. An ELISA for antibody to cytomegalovirus was negative.

The renal biopsy (figures 1A and 1B) showed normal glomeruli and vessels but acute interstitial nephritis with interstitial edema and a cellular infiltrate composed of atypical lymphocytes, occasional plasma cells, and histiocytes. Focally, atypical lymphocytes infiltrated tubules (tubulitis).

Immunofluorescent studies revealed 1+ staining for fibrinogen in the interstitium, but there was no significant reactivity to IgG, IgA, IgM, the C3 component of complement, or kappa or lambda light chains in glomeruli, tubules, or vessels. Immunoperoxidase studies of frozen tissue showed positive staining of the majority of interstitial cells with monoclonal antibody to Leu-1 (pan T cells) and little staining for antibody to BL 26 (pan B cells). Antibody to Leu-2a (suppressor T cells) stained the majority of the cells in the interstitium, while only a few were positive with Leu-3a (helper T cells) (figure 1C). Electron microscopic examination demonstrated normal glomeruli (figure 1D). In situ hybridization done on kidney biopsy tissue did not reveal evidence of EBV-encoded RNA-1 (EBER-1).

Literature Review and Discussion

Over the past 3 decades, there have been 27 cases described in the English-language literature in which infectious mononucleosis was believed to be associated with renal insufficiency. In all but two of the cases there was evidence of heterophil antibody, as measured by either the classic Paul-Bunnell test or the monospot test. There was evidence of seroconversion for EBV, however, in both of these patients (table 1). Five of these reports were of individual cases of EBV infection complicated by acute rhabdomyolysis and myoglobinuria [25–27, 31, 33]. Myoglobinuria complicating acute viral illness has also been described in association with herpes simplex virus, influenza virus, and coxsackievirus [26, 36, 37].

There have been additional single case reports of both minimal-change nephrotic syndrome [15] and hemolytic-uremic syndrome [20] complicating infectious mononucleosis. The true etiology of the latter syndrome, however, is unclear since the patient's jaundice, azotemia, and hemolytic anemia ensued only 2 days after the onset of a diarrheal illness but several weeks after the diagnosis of infectious mononucleosis. Finally, hyperuricemia in the setting of infectious mononucleosis has been well described and is a theoretical cause of renal dysfunction in affected patients [38].

Other than these more unusual cases, there have been 18 instances in which renal dysfunction appeared to be due to EBV-induced infectious mononucleosis itself. Fourteen of the 18 patients were male, and their ages ranged from 16–51 years. Thirteen underwent renal biopsy, and the single most common abnormality (10 patients) was interstitial nephritis and/or fibrosis of varying degrees. Glomerular pathology was distinctly uncommon.

Isolated tubulo-interstitial nephritis has also been described in the setting of other viral illnesses, including those due to herpes simplex virus, hantavirus, and BK type polyomavirus

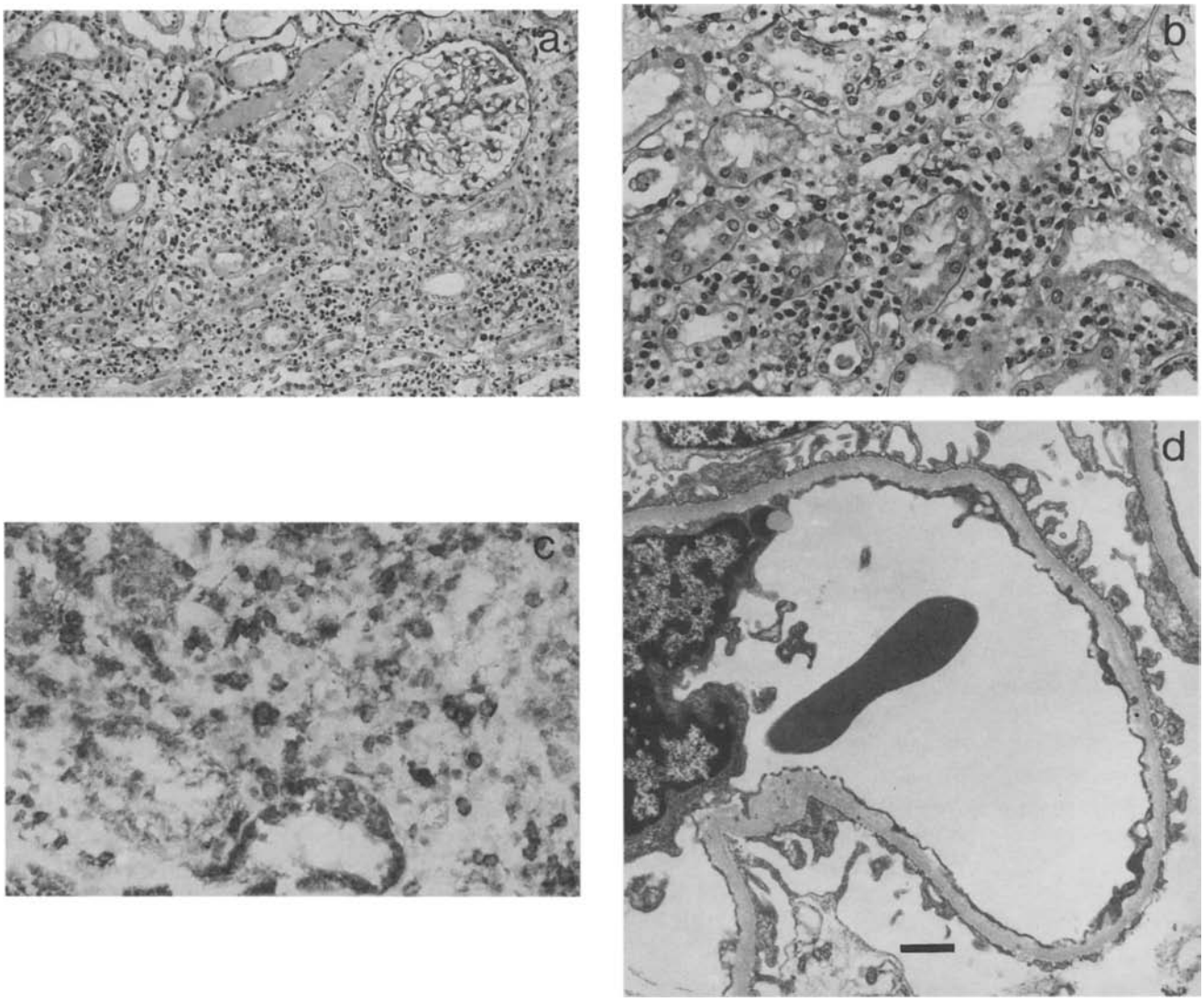

Figure 1. Periodic acid–Schiff stains of a renal biopsy specimen from a man with acute renal failure complicating EBV-induced infectious mononucleosis revealed (*A*) normal glomerulus, interstitial edema, and mononuclear cell infiltrate (original magnification, × 125) and (*B*) atypical lymphocytes in the interstitium and tubules (× 250). An immunoperoxidase preparation (*C*) demonstrated numerous Leu-2a-positive cells (suppressor T cells) in the interstitium (× 320). An electron micrograph of a capillary loop from the normal glomerulus (*D*) showed no electron-dense deposits or foot-process effacement (× 7,500; bar = 1 μm).

[39–42]. A variety of other infectious agents, including *Mycoplasma, Legionella,* and *Leptospira* species, *Rickettsia rickettsii,* and others, have also been reported to cause this entity [43, 44]. The most recently reported biopsy-confirmed case of acute renal insufficiency complicating infectious mononucleosis was from Kopolovic et al. in 1988 [34]. As in our patient, they found an interstitial mononuclear cell infiltrate with tubulitis and normal glomeruli; immunoperoxidase studies revealed a predominance of suppressor/cytotoxic cells, as compared with the number of helper T lymphocytes.

In only two of the patients who underwent renal biopsy was there evidence of immune-complex glomerulonephritis [22, 24]. Electron microscopy revealed electron-dense deposits in the glomerular basement membrane and mesangium. Immunofluorescence studies were performed in one case only and showed granular deposits of IgM and the C3 component of complement in the mesangium of all glomeruli and, to a lesser extent, in the peripheral capillary loops. These are the only cases in which the presence of electron-dense deposits in glomerular structures, as revealed by electron microscopy, has suggested a role for antigen-antibody complexes in the pathogenesis of this disease. Electron microscopy performed in six other cases (inclusive of the present case) revealed essentially normal glomeruli, with no electron-dense deposits.

As for our patient, the outcome for the majority of previously reported patients was favorable. Most cases of oliguric acute

Table 1. Characteristics of our case and of 27 previously described cases of renal disease associated with infectious mononucleosis.

Reference	Patient's age (y)/sex	BUN/creatinine values (mg/dL)	Findings of urinalysis	Histologic appearance	IF findings
[15]	16/F	14/NA	Proteinuria	Normal	NA
[16]	4–6/F (3 patients)	Moderately elevated/NA	Suggestive of glomerulonephritis	Minimal changes; adhesions between visceral and parietal layers of Bowman's capsule (1 case)	NA
[17]	19/M	Normal	Gross hematuria, proteinuria	Scattered destruction of glomeruli, with dense fibrous scarring; glomerulitis and arteriolitis, with lymphocytic infiltrates	NA
[18]	19/F	7.5/1.1 (clearance, 62 mL per min per 1.73 m^2)	Gross hematuria, proteinuria, RBC casts	Mesangial cell swelling, protrusion of mesangial cytoplasm into capillary lumen	NA
[19]	18/M	111/3.4	Gross hematuria, proteinuria	Slight glomerular mesangial cell hyperplasia; pronounced interstitial edema and infiltrate (histiocytes, lymphocytes, and plasma cells)	NA
[20]	14/M	138/4.5	Microhematuria, proteinuria, casts	NA	NA
[21]	32/M	93/2	Gross hematuria, RBC casts, proteinuria	NA	NA
[21]	19/M	17/1.5	Gross hematuria, RBC casts, proteinuria	Diffuse mesangial proliferation and mesangial interposition	Moderate staining for IgA in mesangium of glomeruli, slight staining for IgG and fibrin
[21]	16/F	17/1	Microhematuria, proteinuria	NA	NA
[22]	24/M	57/1.6	Microhematuria, proteinuria	Electron-dense subepithelial deposits in GBM	NA
[23]	18/M	104/12.1	Microhematuria, proteinuria	Mild increase in quantity of glomerular mesangial cells	NA
[24]	22/M	NA/7.5	NA	Opaque deposits in glomerular mesangium	Granular deposits of IgM and C3 in mesangium of all glomeruli; granular and irregular deposits of IgM and fibrinogen in interstitium and wall of peritubular capillaries
[25]	19/M	8/0.9	Proteinuria, myoglobinuria	NA	NA
[13]	20/M	57/3.5	Microhematuria, proteinuria	NA	NA
[13]	23/M	136/24.6	Microhematuria, proteinuria	NA	Trace IgG, C3, and albumin in GBM (considered to be WNL)

Table 1. (*Continued*)

EM findings	Outcome	Findings related to diagnosis	Comments
NA	Recovery with 6 mo of prednisolone therapy	Heterophil antibody test, positive (1:996)	4+ Proteinuria, reversed albumin/globulin ratio (1.3:1), hypercholesterolemia, severe generalized edema
NA	Recovery	PBT, positive (high titer in all 3 cases)	Stool viral culture negative in all cases
NA	Recovery	Heterophil agglutinin titer, 1:896	Complicated by bone marrow granulomas
Focal fusion of glomerular foot processes; no marked alteration in epithelial cells	Recovery	Heterophil agglutinin titer, 1:448 (1:224 after guinea pig RBC absorption)	...
Normal	Recovery	Monospot and PBT, positive	...
NA	Recovery s/p therapy with iv heparin (×4 d after admission) and then prednisone (days 4–10)	Mononucleosis test, positive; EBV antibody titer, 1:40 on admission and 1:160 2 mo later	Hemolytic uremic syndrome
Hypercellular glomeruli; focal collections of inflammatory cells in the interstitium, with patchy tubular atrophy and necrosis	Recovery	PBT, positive (1:56)	Followed poststreptococcal glomerulonephritis
Glomerular mesangial proliferation, one small epithelial crescent, few foci of tubular atrophy, with interstitital fibrosis	Recovery	PBT, positive (1:1,792)	Berger's IgA disease triggered or uncovered by infectious mononucleosis
Occasional areas of mesangial prominence in the glomeruli; small foci of tubular degeneration and necrosis, associated with acute and chronic inflammatory cells in interstitium	Recovery	PBT, positive (1:224)	...
Glomerular mesangial proliferation	NA	PBT, positive (1:320)	Biopsy performed 5 mo after initial illness for persistent proteinuria
Interstitial nephritis (monocytes, histiocytes, eosinophils), mesangial proliferation, periglomerular fibrosis	Progressive azotemia despite prednisone therapy (×6 w), ultimately necessitating renal transplantation	Mononucleosis slide agglutination test, positive; heterophil antibody titer, 1:112 (1:56 after absorption with guinea pig kidney and 0 after beef RBC absorption)	...
Moderate glomerular mesangial cell proliferation, with increased mesangial matrix; focal infiltrates of lymphocytes, monocytes, and atypical lymphocytes in the interstitium around the tubules	Death despite therapy with broad-spectrum iv antibiotics and oral prednisone	Monospot, positive; heterophil antibody titer, 1:896 (same after absorption with guinea pig kidney and 0 after absorption with bovine erythrocytes)	Associated gram-negative septicemia and disseminated intravascular coagulation
NA	Recovery	Heterophil test, positive (1:56 initially; rose to 1:448 by week 3); EBV titer was >1:320 during week 3	Rhabdomyolysis
NA	Recovery	Monospot, positive; heterophil antibody titer, 1:1,792 (1:112 after guinea pig kidney absorption)	Associated hemolytic anemia
15 Normal glomeruli, moderate interstitial fibrosis, significant interstitial edema, chronic inflammatory infiltrate with neutrophils and eosinophils	Recovery, s/p hemodialysis (×5 over 10 d)	Monospot, positive; heterophil antibody titer, 1:448 (0 following absorption with bovine RBCs)	No evidence of EBV antigen-antibody complex on incubation of biopsy material with convalescent sera from several patients with documented EBV infection

Table 1. (*Continued*)

Reference	Patient's age (y)/sex	BUN/creatinine values (mg/dL)	Findings of urinalysis	Histologic appearance	IF findings
[26]	18/M	Normal	Myoglobinuria, rare WBCs	NA	NA
[27]	16/M	113/10.3	Proteinuria, myoglobinuria	NA	NA
[28]	17/M	Plasma urea, 53 mmol/L; creatinine, 555 μmol/L	NA	NA	NA
[29]	20/M	101/7	Microhematuria	NA	NA
[30]	29/M	plasma urea, 29.5 mmol/L; creatinine, 985 μmol/L	NA	Expansion of mesangium, suggestion of mesangial deposits	Negative for IgG, IgA, and complement but positive for IgM involving GBMs and mesangium
[31]	6/F	86/3.3	Proteinuria, myoglobinuria	NA	NA
[32]	51/F	92/13.1	Proteinuria	NA	NA
[33]	23/M	Normal	Proteinuria, myoglobinuria	NA	NA
[34]	24/M	NA/10.8	Proteinuria	Interstitial lymphocytic infiltration	Glomerular staining negative for IgG, IgA, IgM, C3; staining positive for C3 in blood vessels, staining positive for interstitial fibrin
[35]	17/F	28/3.1	Microhematuria, proteinuria	NA	NA
[PR]	29/M	34/4.2	Microhematuria, proteinuria	Normal	Staining of glomeruli, tubules, and vessels negative for IgG, IgA, IgM, C3; fibrinogen staining 1+ in interstitium

NOTE. BUN = blood urea nitrogen; EA = early antigen titer; EBNA = EBV nuclear antigen titer; EM = electron microscopy; GBM = glomerular basement membrane; IF = immunofluorescence; NA = not available; PBT = Paul-Bunnell test; PR = present report; s/p = status post; VCA = viral capsid antigen; WNL = within normal limits.

Table 1. (*Continued*)

EM findings	Outcome	Findings related to diagnosis	Comments
NA	Recovery	Heterophil test, positive; ox cell hemolysin titer, 1:160 acutely (convalescent titers, 1:80 and 1:40); VCA antibody titer, 1:200 acutely and on 2 consecutive weekly determinations	Rhabdomyolysis
NA	Recovery, s/p peritoneal dialysis (×72 h) and therapy with iv dexamethasone (×96 h)	Monospot and differential heterophil antibody tests, positive	Rhabdomyolysis
NA	Death despite therapy with prednisone (×4 d before admission) and mechanical ventilation (×10 d after admission)	Monospot, positive; PBT titer, 1:320 (same after absorption with guinea pig antigen and 1:10 after absorption with ox RBC antigen); titer of IgG to EBV capsid antigen, 1:512; specific IgM found after density-gradient fractionation	Associated jaundice, upper gastrointestinal bleeding, pulmonary edema
NA	Recovery	Monospot, positive; heterophil titer, 1:3,584; EBV acute-phase titer, 1:10; ox cell hemolysin, >1:1,280	...
Intense interstitial nephritis, mostly in the cortex (lymphocytes and occasional neutrophils); mild proliferative glomerular changes with increased mesangial matrix	Recovery, s/p peritoneal dialysis (×6 d) and therapy with methylprednisolone (×2 d)	Monospot, positive; EBV IgM and IgG detected	...
NA	Recovery	Qualitative mononucleosis slide agglutination test, negative; acute EBV antibody titer, 1:160 on hospital day 2 (rose to 1:640 19 d later)	Rhabdomyolysis
NA	Recovery	Monospot, negative; rise in EBV titer (from 1:56 to 1:512) with finding of specific IgM	...
NA	Recovery	Monospot, positive; VCA IgG titer, 1:1,280 (1:2,560 4 w later); VCA IgM, negative; EA, 1:10; EBNA, ≥1:8	Rhabdomyolysis
Unremarkable glomeruli; diffuse interstitial mononuclear cell infiltration, with minimal tubulitis	Recovery following "emergency dialysis" (×5 d)	Monospot, positive; heterophil antibody test, positive (1:224)	...
NA	Recovery	PBT, positive (1:128)	...
Interstitial nephritis and edema, atypical lymphocytic infiltration with focal tubulitis; glomeruli, WNL	Recovery, s/p hemodialysis (×1 d) and therapy with iv methylprednisolone (×1 d) and a course of acyclovir	Monospot, positive; heterophil antibody test, positive (1:896; 1:448 after guinea pig RBC absorption and 1:14 after absorption with beef RBCs); VCA IgM titer, 1:10; VCA IgG titer, 1:320; EA (diffuse), 1:80; EA (restricted), <1:10; EBNA (nuclear), 1:2; EBNA (control), negative	...

renal failure resolved spontaneously after 1–2 weeks. Five of the six patients who underwent hemodialysis or peritoneal dialysis required it for only a brief period (1–5 days), and their azotemia completely resolved [13, 23, 27, 30, 34].

Corticosteroid therapy was given to eight patients and was variably successful. Two of the patients died, although both had particularly severe disease; one had gram-negative sepsis and disseminated intravascular coagulation, and the other had associated jaundice, upper gastrointestinal bleeding, and pulmonary edema [24, 28]. A third patient's 6-week course of prednisone failed, and the patient later required transplantation [23]. The patients with nephrotic syndrome and hemolytic-uremic syndrome, however, appeared to respond to prolonged courses of corticosteroids [15, 20]. The conditions of two other patients, both of whom had interstitial nephritis, also improved after steroid therapy, but these patients received only brief courses (1 and 2 days, respectively) [27, 30].

The use of corticosteroids for routine management and, to a lesser degree, for complications of infectious mononucleosis is controversial. In a recent consensus statement from the Infectious Diseases Society of America, the authors advised against their routine use in cases of uncomplicated infectious mononucleosis [45]. In addition, the results of several small studies do not indicate that corticosteroids provide significant benefit for hepatosplenic involvement or for lymphadenopathy [46–48]. Similarly, two-thirds of the patients outlined in this review were not treated with steroids and did well nonetheless.

The problems with regard to drawing any conclusions from these data, however, are the small number of cases, the absence of a controlled design, the lack of uniformity in histopathologic diagnosis, and the bias caused by using steroids preferentially in the more critically ill patients.

Acyclovir inhibits EBV replication both in vitro and in vivo, and several small trials have assessed its efficacy in uncomplicated infectious mononucleosis [1, 49–52]. While oropharyngeal shedding of EBV was temporarily inhibited, no overall clinical benefit was demonstrated in any of the studies. The use of acyclovir for the treatment of more complicated infectious mononucleosis has not been well studied, although its use in combination with prednisolone resulted in the dramatic improvement of several patients with fulminant infectious mononucleosis [53]. We therefore chose to administer it to our patient, but to what extent it contributed to the ultimate resolution of the illness is unclear.

The pathogenesis of infectious mononucleosis–induced renal insufficiency and the reason for its rare occurrence remain enigmatic. One might speculate that these few patients were perhaps at particular risk because of underlying or even unrecognized renal disease. One reported case of interstitial nephritis due to infectious mononucleosis was preceded by an episode of poststreptococcal glomerulonephritis [21]. In fact, the first case of infectious mononucleosis complicated by nephritis, described by Pfeiffer in 1889, was also likely to have been in association with poststreptococcal glomerulonephritis [54]. In yet another instance, infectious mononucleosis with associated renal insufficiency appeared to "uncover" Berger's IgA nephropathy several months later [21]. Most of the cases, however, have not been associated with underlying renal pathology, so it is unlikely to be a unifying explanation.

An understanding of the immunopathogenesis underlying EBV-induced infectious mononucleosis helps in postulating some potential mechanisms of renal injury. Although an HLA-1 (human leukocyte antigen 1) class-restricted cytotoxic T cell response has been described, the kidney as an "innocent bystander" seems the most likely explanation, since the primary suppressor/cytotoxic T cell response in acute infectious mononucleosis is neither HLA- nor EBV-specific [55–57]. However, cytotoxic T cell clones that are capable of recognizing several EBV antigens can also be recovered from the blood of patients with infectious mononucleosis [57].

The importance of antigen-directed cell-mediated immune mechanisms in tubulo-interstitial nephritis due to other factors (e.g., methicillin or antibodies to glomerular basement membrane) [58] suggests that activated T cells in patients with interstitial nephritis due to infectious mononucleosis may similarly be reacting to one or several EBV antigens expressed by infected infiltrating lymphocytes within the kidney. However, whereas the EBV genome has been noted in renal biopsy specimens from patients with related diseases—such as posttransplantation lymphoproliferative disease involving the renal allograft and chronic EBV infection with interstitial nephritis [59, 60]—in situ hybridization on renal biopsy material from our patient was negative.

Whatever the exact mechanism involved, renal injury in infectious mononucleosis appears to be a rare event but may be underrecognized because of its largely self-limited nature. Although the case reports have been heterogeneous, more often than not renal biopsies reveal interstitial infiltrates with little involvement of glomeruli. As noted above, in only one previous case were immunohistochemical analyses performed that demonstrated (as ours did) that these cells were primarily suppressor T lymphocytes [34].

Fatal infectious mononucleosis due to severe hepatic failure has also been associated with extensive Leu-2a (CD8)–positive lymphocytic infiltration in the liver, along with the lymph nodes and spleen [61, 62]. This suggests that a common factor in end organ disease due to EBV-induced infectious mononucleosis may be infiltration by circulating CD8 lymphocytes. Why these lesions develop in only a few individuals remains to be investigated.

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