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# Severe Tubulointerstitial Nephritis from Acute Epstein-Barr Virus Infection

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## Introduction

Epstein-Barr Virus (EBV) infection presents with diverse clinical manifestations along a broad spectrum of disease severity.

The classic triad of EBV infection is fever, pharyngitis, and lymphadenopathy. Acute EBV infection may also manifest as hemolytic anemia, granulocytopenia, encephalitis, pericarditis, hepatitis, and other solid organ involvement.<sup>1</sup>

First described in 1889, Acute renal failure from EBV-infectious mononucleosis is a rare disease complication, but subtle abnormalities in urinalysis, such as hematuria and proteinuria have been noted in as many as 15% of patients.1

Renal involvement of EBV typically includes a focal interstial mononuclear infiltrate. Glomerular involvement is uncommon, though both minimal change lesions<sup>2</sup> as well as mesangiolysis have been reported.<sup>3</sup>

The diagnosis of EBV involvement in the kidney has been demonstrated using both in situ hybridization<sup>1,2</sup> as well as PCR assays.3

The pathogenesis of EBV induced renal involvement and its rare occurrence remain unclear.

T-cell activation, and direct injury due to EBV have been proposed mechanisms of renal injury.4

# Case Presentation

A previously healthy, 21-year-old Caucasian woman presents to our center with a complaints of fevers recorded as high as 104°F, nausea with vomiting, malaise, and sore throat. Symptoms had been progressive over the course of the prior four weeks. She had been evaluated by her primary care provider 10 days prior to hospitalization, and had received Azithromycin for a diagnosis of left otitis media.

She denies any difficulties with urination no dysuria, flank pain, hematuria, frothy urine or change in quantity. Oral intake has been maintained.

The patient is an undergraduate student at a local urban university. She resides in a rented row home with seven other classmates and a cat. She otherwise denies any other sick contacts, sexual activity or illicit drugs. Medications include oral contraceptive pill and a recent Azithromycin course.

On physical exam she was noted to have a temperature of 40°C and blood pressure was 107/75. She had evidence of bilateral pharyngeal erythema with pustular, exudative lesions. Tender anterior cervical lymphadenopathy was present.

Cardiopulmonary examination was positive for a regular tachycardia with diffuse and scattered bilateral crackles. The edge of the liver and tip of the spleen were palpable. The remainder of the examination was unremarkable.

TABLE 1. Initial Laboratory Data			
Hematology	Value	Chemistry	Value
WBC (thou/cmm)	14	Sodium (mEq/L)	136
Neutrophil	41%	Potassium (mEq/L)	3.7
Lymphocyte	5%	BUN (mg/dL)	25
Monocyte	4%	Creatinine (mg/dL)	2.34
Bands	11%	Lactate (mm0l/L)	0.7
Reactive Lymphocytes	39%	CO2 (mEq/L)	22
		ALT (U/L)	70
Hgb (g/dL)	14.5	AST (U/L)	70
		CK (U/L)	117
Blood Cultures	Negative		
Urine	Value	Serology	Value
Specific Gravity	1.02	EBV VCA IgG	0.70 (<0.91)
рН	6	EBV VCA IgM	1.68 (<0.91)
Protein (mg/dL)	300-600	Monospot	Positive (Neg)
Blood (mg/dL)	0.03	ASO	947 (<240)
RBC (per hpf)	3 to 5	Mycoplasma IgM	1.27 (<0.91)
WBC (per hpf)	6 to 10	Mycoplasma IgG	4.11 (<0.91)
Granular Casts (per lpf)	>10	HIV	Neg
		Leptospirosis	Neg
Protein: Creatinine ratio	2.34	Resp Viral PCR	Neg
Urine Sodium (mEq/L)	23	Adenovirus Culture	Neg
Urine Culture	Negative		

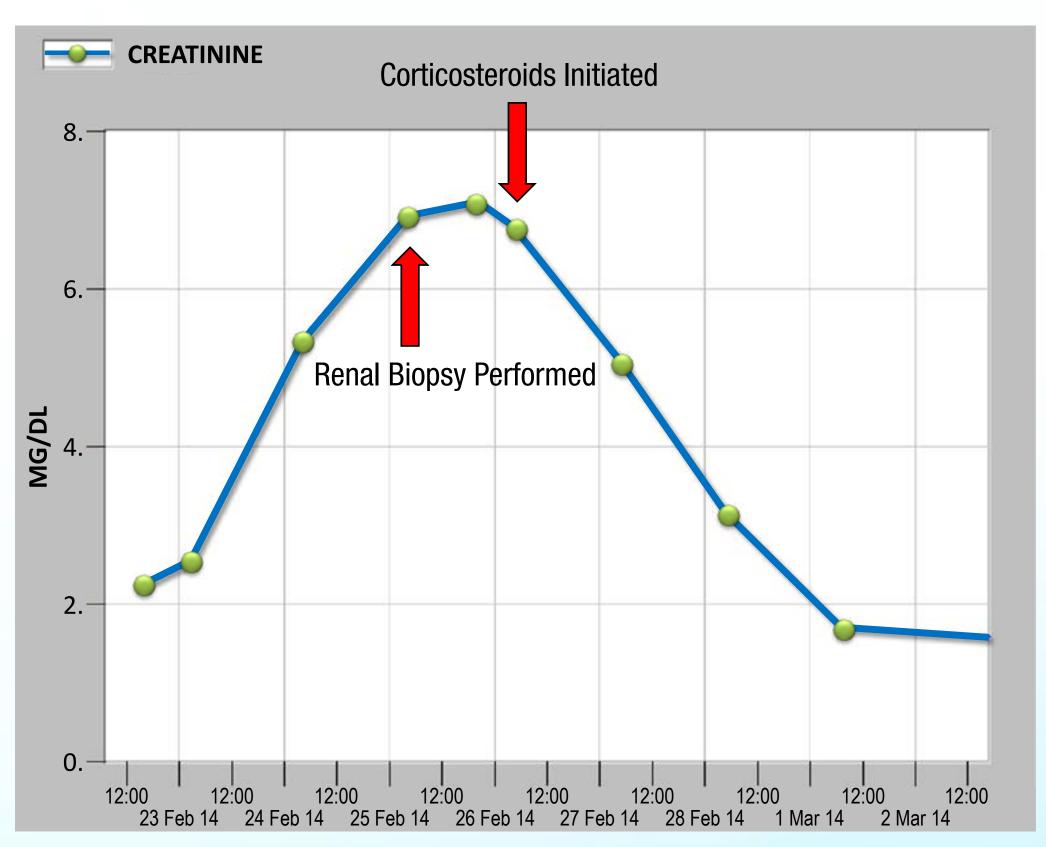


Figure 1. Patient's serum creatinine during hospitalization. Renal biopsy was performed on hospital day 4. The patient did not require renal replacement therapy.

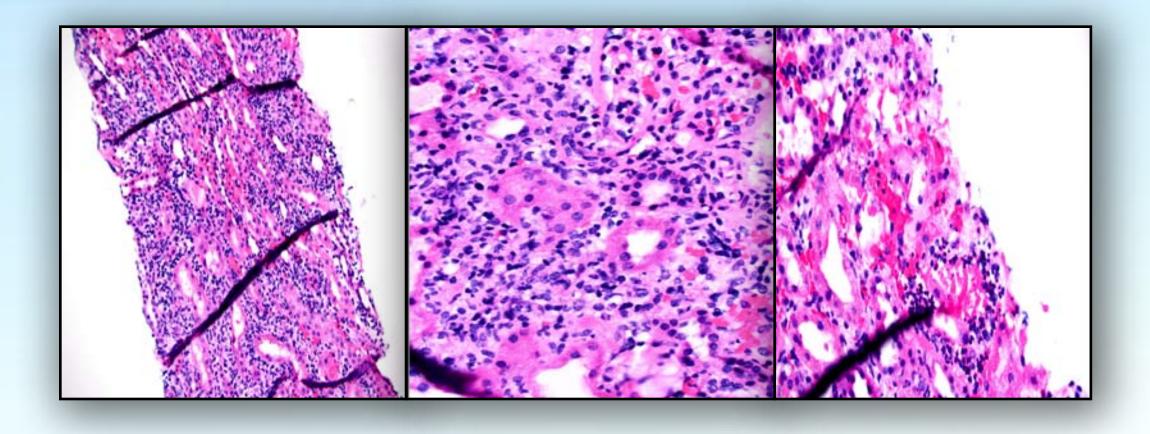
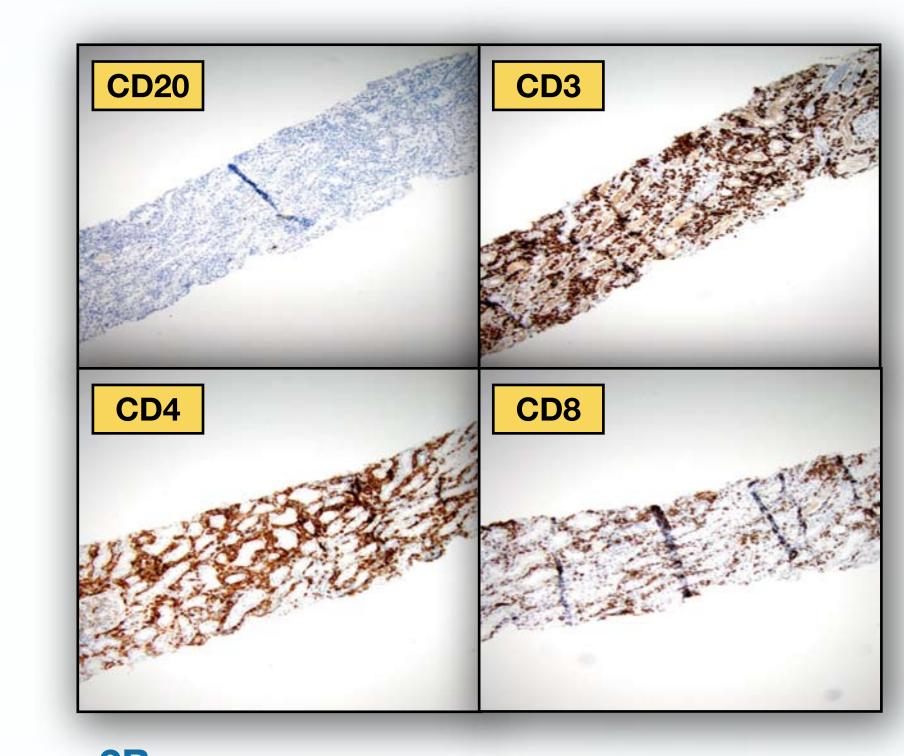


Figure 2A. Shows light microscopic findings. There is a moderately severe lymphocytic interstitial infiltrate. Eosinophils are minimal. There are associated patchy foci of active lymphocytic tubulitis, necrotic tubules with neutrophils and many tubules with granular cell casts, suggestive of ATN.



Shows direct immunofluorescence using antibodies to CD20, CD3, CD4, and CD8. The infiltrate is predominately CD4 T-helper cells (CD4:CD8 ratio around 4:1) However, there is virtually absent CD20 positive B lymphocytes among lymphoid infiltrate.

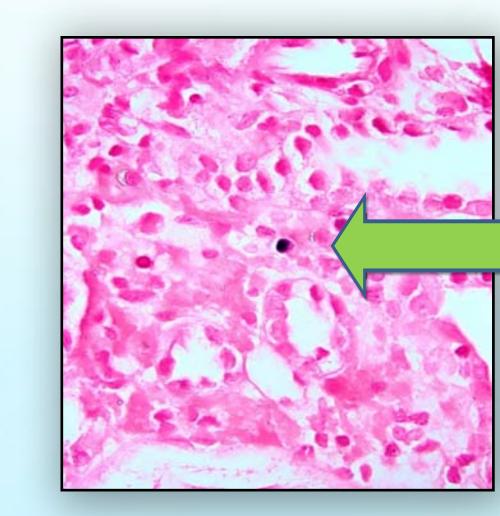


Figure 2C. Epstein-Barr Encoded RNA (EBER) positive lymphocyte staining in the

## Discussion

Acute Epstein Barr virus infection resulting in severe renal impairment is rare and is typically characterized by acute tubulointerstial disease.

Our case contrasts with previously reported cases<sup>1</sup> as the majority of lymphocytes in the interstitium were CD4+ T-Lymphocytes. Consistent with prior studies, the glomeruli were unremarkable.

Epstein-Barr encoding region (EBER) in situ hybridization is the methodology of choice for the detection of the Epstein-Barr virus (EBV) in tissue sections.6

Epstein-Barr Encoding Regions (EBERs) are secreted from EBV-infected cells and are recognized by toll-like receptor (TLR)<sup>3</sup>, leading to induction of type-I Interferons and inflammatory cytokines, and subsequent immune activation.7

This case was complicated by evidence of a recent strep infection (elevated ASO titer) but no evidence of deposits suggestive of post-infectious glomerulonephritis were noted on electron microscopy. Prior cases of EBV induced renal failure have been preceeded by streptococal infection. In addition, the patient had a recent/concurrent Mycoplasma infection, and it is unclear what role, if any, this had in her renal insufficiency.<sup>1</sup>

Therapy is supportive, with anecdotal evidence supporting parenteral corticosteroids as well as acyclovir to inhibit viral replication.<sup>1</sup>

The patient was treated supportively in regard to her renal manifestations, not requiring renal replacement therapy. Corticosteroids were initiated for severe tonsilar swelling, at that time her creatinine had already begun down-trending. She reached a nadir serum creatinine of 0.64mg/dL in follow up four months following the acute illness.

This case underscores the spectrum of EBV disease beyond the classic manifestations, the difficulty in identifying the specific pathogenesis of the mechanism of renal dysfunction, and the heterogeneity of host immunologic responses.

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