CASE REPORT

Epstein-Barr Virus-Associated Acute Interstitial Nephritis

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Abstract

Epstein-Barr virus infection is usually asymptomatic in childhood; however, acute kidney injury may be a rare complication during its course. We reported a case of a 5-year-old female presented with fever, vomiting, abdominal pain, anorexia, anemia, thrombocytopenia, and acute oliguric kidney injury with titer-confirmed Epstein-Barr virus infection. Renal biopsy specimen revealed acute interstitial nephritis and endocapillary glomerulonephritis with Epstein-Barr virus inclusions in renal tubule epithelium. Methylprednisolone pulse therapy was performed, followed by oral corticoid therapy. Hemodialysis was required for 10 days with renal function complete recovery in 17 days. Physicians should be alert of uncommon presentations of Epstein-Barr virus infection in children and consider this differential diagnosis when facing acute kidney injury.

Keywords: Acute Kidney Injury/etiology; Child; Epstein-Barr Virus Infections/complications; Epstein-Barr Virus Infections/diagnosis; Nephritis, Interstitial/diagnosis; Nephritis, Interstitial/therapy

Keypoints

What is known:
- Epstein-Barr virus infection may present with acute kidney injury.
- Simultaneous glomerulonephritis and interstitial involvement can occur due to Epstein-Barr virus infection.

What is added:
- An acute severe kidney injury related to Epstein-Barr virus infection requiring hemodialysis should raise the possibility of an additional kidney insult, especially in the setting of an Epstein-Barr virus reactivation.

Introduction

Epstein-Barr virus (EBV) is a herpes virus responsible for a lifelong latent infection with a wide clinical spectrum.[1,2] Infectious mononucleosis is the prototype of EBV infection in adults and adolescents. Among children, primary infection is usually asymptomatic or produces mild symptoms indistinguishable from other childhood infections.[1-4] It may exhibit numerous rare, atypical, and threatening manifestations including acute kidney injury[1] with the host immune response playing a key role in shaping the clinical manifestations.[1,2] While serious renal parenchymal dysfunction with acute kidney injury is uncommon, subclinical kidney involvement is relatively common (abnormalities in urinary sediment have been reported in up to 5%-15%).[1,3,4,7-9]

Case Report

A previously healthy 5-year-old female was admitted with a five-day history of fever, vomiting, abdominal pain, anorexia, and oliguria. The only medications taken were paracetamol and ibuprofen. There was no family history of renal disease. Physical examination revealed skin pallor, dry lips, a distended and globally painful abdomen, blood pressure of 116/67 mmHg (percentile 95-99), and pulse rate of 120 beats/min. Peripheral edema, lymphadenopathy, or organomegaly were absent. Laboratory investigation revealed acute kidney injury with creatinine 7.43 mg/dL and blood urea nitrogen (BUN) 111 mg/dL, hyponatremia (128 mmol/L), and hyperkalemia (5.8 mmol/L), microcytic hypochromic anemia (hemoglobin 10.5 g/L, mean corpuscular volume 78 fL, mean corpuscular hemoglobin concentration 28

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pg/mL), lymphocytes 1710 cells/µL (22%), eosinopenia (10 cells/µL, 0.1%), thrombocytopenia (65 x 10^9 cells/L), C-reactive protein 22 mg/dL, and procalcitonin 482 ng/mL. Urinalysis revealed glycosuria, nephrotic proteinuria (ratio protein / creatinine 10 364 mg/mmol), and microscopic hematuria (> 100 erythrocytes per field). Blood smears revealed atypical lymphocytes with no schistocytes. The *ADAMTS13* activity was normal. Renal and abdominal ultrasound with doppler flow scan showed renal parenchyma diffuse hyperechogenicity without vessel obstruction. Ceftriaxone was started with fever resolution in less than 24 hours. Vancomycin was added the next day for persistent elevated C-reactive protein and procalcitonin. On day 3 (D3) after admission, a laboratory workup revealed a renal function worsening (creatinine 9.25 mg/dL, BUN 123 mg/dL). Therefore, methylprednisolone pulse therapy was associated, and hemodialysis was initiated. The patient developed severe hypertension with the need for atenolol, amlodipine, and minoxidil.

Anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, and anti-glomerular basement membrane antibody were negative. Serum complements (C3, C4, CH50) and immunoglobulin (Ig) A, G, M and E were normal. Cultures of the blood, urine, and stool were negative. Cytomegalovirus serology was compatible with past infection. Epstein-Barr virus serology revealed a positive viral capsid antigen IgG (16.6 index value) and IgM (20.9 index value) and positive anti-Epstein-Barr nuclear antigen-1 (EBNA-1) IgG (11.9 index value). Epstein-Barr virus deoxyribonucleic acid (DNA) viral load was detected in serum (> 2140 copies/mL).

Renal biopsy performed on D4 revealed an extensive acute interstitial nephritis - diffuse, interstitial infiltrate due to lymphocytes and neutrophils with mild tubular atrophy - and endocapillary proliferative glomerulonephritis, most of the glomeruli with mild intracapillary hypercellularity, mainly due to lymphocytes (Fig. 1). Immunofluorescence studies revealed 1+ staining for IgA, IgM, and kappa light chain in glomeruli. *In situ* hybridization for Epstein-Barr-encoded ribonucleic acid 1 (RNA-1) was multifocal positive in renal tubules epithelium (mainly cytoplasm positive with negative nuclei).

From D9, diuresis progressively improved which led to the suspension of hemodialysis on D13. Methylprednisolone pulse therapy was performed for nine days, and then oral prednisolone (60 mg/m^2/day) was started. Renal function complete recovery occurred on D17 (creatinine 0.76 mg/dL, BUN 31 mg/dL) and urine sediment became normal on D18.

The patient was discharged on D20 under anti-hypertensive triple therapy and oral prednisolone 40 mg/m^2 on alternate days. One month after discharge, hypertension was controlled only with amlodipine and the patient was under corticoid therapy reduction. Epstein-Barr virus DNA viral load was no longer detectable in serum. Epstein-Barr virus serology remained positive for viral capsid antigen IgG and IgM with approximately stable titers (23.8 index value and 19.9 index value, respectively) and EBNA-1 IgG with a decreasing titer (4.7 index value).

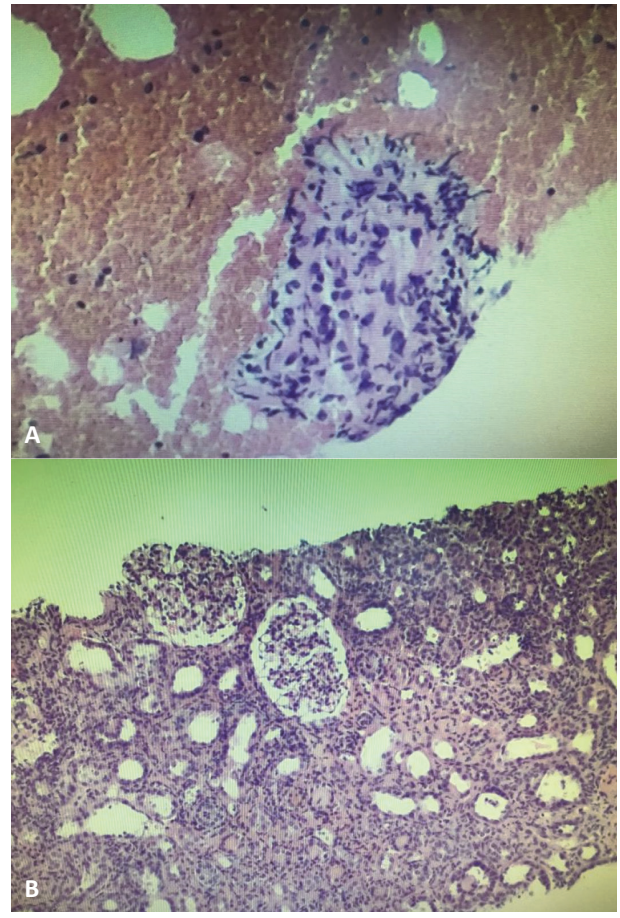

Figure 1. Histologic findings of renal biopsy (hematoxylin eosin staining). Lymphocytic mild glomeruli intracapillary hypercellularity (A). Diffuse extensive interstitial infiltrate due to lymphocytes and neutrophils and mild tubular atrophy (B).

Discussion

While EBV establishes a lifelong infection, its prevalence increases with age (> 95% of the world's adult population is seropositive) and reactivation may occur.[1,2,4] Epstein-Barr virus is shed in oral secretion consistently at high concentrations for more than six months following acute infection and intermittently at lower concentrations for life. This explains how children can be infected by non-ill people that have been infected in the past. Immunosuppression facilitates the reactivation of latent EBV and such patients are more likely to have complex

manifestations, including multi-systemic damage.[2,5] Although less frequently, immunocompetent individuals can exhibit an EBV reactivation, which is often short and not clinically relevant,[6] or primary infection with a complex clinical course. Serological profiles of EBV antibodies are quite characteristic and necessary for the diagnosis of atypical infections.[2-4] The viral capsid antigen IgM is the most specific serologic test for diagnosing an acute EBV infection, although it may reappear during reactivation and persist for several months after the acute infection. The viral capsid antigen IgG usually peaks late in the acute phase, declines slightly over several weeks to months, and persists at relatively stable titers for life. EBNA-1 IgG is usually undetectable during the first three to four weeks after clinical onset, and therefore, is indicative of past infection. Thus, VCA IgG, VCA IgM, and EBNA-1 IgG may be assumed as reactivation or as a late primary infection (if viral capsid antigen IgM persists, and EBNA-1 IgG has already been produced). To distinguish both, further laboratory tests are required.[2,6] Although these tests were not performed in our case, a positive EBNA-1 IgG in the first week after clinical onset and a decreasing titer one month later instead of an increasing one made it more likely to be a reactivation. It would have been helpful to test viral capsid antigen IgG avidity as low levels are related to recent infection and high levels are found in the course of past infection or reactivation. Although early antigen diffuse staining could have also been required, increased levels are found in primary or past infections and reactivations.[6] In illnesses associated with immune activation, such as interstitial nephritis, serologic EBV reactivation with detectable viral capsid antigen IgM has been described. This way, the described clinical and hematologic features, viral load, and serology seem to be consistent with clinically relevant EBV reactivation.

On the other hand, the EBV genome has been detected in the renal tissue of patients with idiopathic chronic interstitial nephritis and it has also been described in patients with acute infectious mononucleosis presenting with acute interstitial nephritis. It is unknown whether EBV-associated acute interstitial nephritis is a consequence of direct infection or an immunologic phenomenon.[3,4,8-10] Thus, EBV genome identification in renal tissue may not reflect an acute organ involvement. Besides, according to 27 cases reviewed,[7] acute kidney injury in EBV infection is often self-limited.[3,7,8] Thus, the reported acute severe kidney injury requiring sudden hemodialysis may be explained by the combination of two kidney insults. Drugs, such as non-steroidal anti-inflammatory drugs, are another known cause of acute interstitial nephritis.[4,9,10] Therefore, the use of ibuprofen might have been implicated in the clinical course. Although nephrotic range proteinuria is unusual in acute interstitial nephritis, it is often seen in patients with acute interstitial nephritis associated with non-steroidal anti-inflammatory drugs. This fact along with an interstitial infiltrate mainly composed of T lymphocytes supports an acute interstitial nephritis associated with non-steroidal anti-inflammatory drugs; therefore, these were discontinued. In this entity, the full picture of an allergic reaction (fever, rash, eosinophilia, and eosinophiluria) is typically absent, as occurred in this case. Considering all the exposed, two possibilities may be considered: an EBV-associated acute interstitial nephritis or an acute interstitial nephritis in the setting of non-steroidal anti-inflammatory drugs exposure in a patient with an EBV reactivation.

The patient had also glomerulonephritis. This additional diagnosis, with a nephrotic proteinuria on admission, surely played a role in the severity of this case. The pathogenesis of glomerular injury in EBV infection is also not well known. The T cells activated by the infiltrating B cells expressing EBV antigens leading to inflammatory response and direct T or B cell-mediated glomerular injury are possible mechanisms.[11] However, Epstein-Barr viral RNA has only been localized in the renal tubules and no glomerular deposition has been demonstrated, as described in other cases.[12] Nevertheless, immunoglobulin chains were detected in glomeruli, which may raise the possibility of glomerulonephritis mediated by immunocomplexes due to cross-reaction (molecular mimicry). There are few reported cases of different types of EBV-induced glomerulopathies, mediated or not by immunocomplexes, which occurred alone or coexisting with interstitial involvement,[13] as in this report.

Renal biopsy should be performed in the early periods of the disease when characteristically shows tubular cell infiltration.

Acute interstitial nephritis treatment is mainly supportive. Removal of any potential offending medication is advisable. Acute interstitial nephritis associated with non-steroidal anti-inflammatory drugs relapse may occur; therefore, patients that suffered from this entity should permanently avoid those drugs administration. Controlled prospective clinical trials of steroid therapy for EBV-associated acute interstitial nephritis is lacking; however, the results of several small studies support its use for unusually severe complications. Acyclovir has been shown to inhibit viral replication and reduce viral shedding; nonetheless, it does not change the course of routine infectious mononucleosis. Although it has limited efficacy and can itself be nephrotoxic, acyclovir

might have a role in cases of fulminant disease.[4,7,9] Acute interstitial nephritis prognosis is often good, with most of the cases completely recovering renal function, as occurred with our patient.[3,4]

Acute interstitial nephritis with oliguric acute kidney injury complicating EBV infection is rare. This possibility should be considered when patients present with acute kidney injury, particularly if other features, such as fever, anemia, or thrombocytopenia, are present, and therefore, serological tests should be performed. Additional insults, such as non-steroidal anti-inflammatory drugs, should also be considered in these cases.

Author Contribuitions

TL and AM participated in the study conception or design. TL and AM participated in acquisition of data. TL and AM participated in the analysis or interpretation of data. TL, AM and CN participated in the drafting of the manuscript. CN, CC and CG participated in the critical revision of the manuscript. All authors approved the final manuscript and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this study.

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Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

Consent for publication

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Nefrite Intersticial Aguda Associada ao Vírus Epstein-Barr

Resumo

A infeção por vírus Epstein-Barr é habitualmente assintomática na infância. No entanto, a lesão renal aguda pode ser uma complicação rara. Descrevemos o caso de uma menina de 5 anos com febre, vómitos, dor abdominal, anorexia, anemia, trombocitopenia e lesão renal aguda oligúrica com infeção pelo vírus Epstein-Barr confirmada serologicamente. A biópsia renal revelou uma nefrite intersticial aguda e glomerulonefrite endocapilar com inclusões de vírus Epstein-Barr no epitélio dos túbulos renais. Foram iniciados pulsos de metilprednisolona, seguidos de corticoterapia oral. Foi requerida hemodiálise durante 10 dias com uma recuperação completa da função renal em 17 dias. Os médicos devem conhecer as apresentações atípicas da infeção por vírus Epstein-Barr em crianças e considerar este diagnóstico diferencial perante uma lesão renal aguda.

Palavras-Chave: Criança; Infecções por Vírus Epstein-Barr/complicações; Infecções por Vírus Epstein-Barr/diagnóstico; Lesão Renal Aguda/etiologia; Nefrite Intersticial/diagnóstico; Nefrite Intersticial/tratamento