Case Report / *Olgu Sunumu*

DOI: 10.5578/ced.20219607 • *J Pediatr Inf 2021;15(4):239-e242*

A Rare Cause of Hematuria in Children: Ebstein-Barr Virus

Çocuklarda Hematürinin Nadir Bir Nedeni: Ebstein-Barr Virus

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Cite this article as: Yılmaz S, Bayhan Gİ, Karbancıoğlu EY. A rare cause of hematuria in children: Ebstein-Barr virus. J Pediatr Inf 2021;15(4):e239-e242.

Abstract

A 16.5-year-old male was admitted to the emergency department with fever, sore throat and hematuria. The patient's body temperature was measured as 40°C, there was no edema and his blood pressure was normal. Oropharynx was hyperemic, there was jaundice on the skin and sclera, hepatosplenomegaly, and multiple lymph nodes up to 4 cm in both cervical chains. Laboratory studies revealed prominent lymphomonocytosis and Downey cells in peripheral blood smear. Liver enzymes and bilirubin levels were elevated, kidney functions were normal. Urinary examination revealed hematuria and non-nephrotic proteinuria. His urinary outflow was normal in follow up. Ultrasonography showed hepatosplenomegaly and an increase in renal parenchymal echogenicities. Epstein-Barr Virus viral capsid antigen immunoglobulin M was positive, polymerase chain reaction result was positive with 140.000 copies/μL. In the follow-up, steroid treatment was given due to persistent fever and rapid growth in lymph nodes, and then the fever did not recur. Macroscopic hematuria improved on the fourth day of his hospitalization, and at the third week of control, hematuria and proteinuria disappeared completely.

Keywords: Hematuria, nephritis, Epstein-Barr virus

Öz

16.5 yaşındaki erkek hasta ateş, boğaz ağrısı ve kanlı idrar yapma şikayeti ile acile başvurdu. Vücut ısısı 40°C ölçülen hastanın ödemi yoktu ve kan basıncı normaldi. Fizik muayenesinde orofarenksi hiperemik, ciltte ve sklerada ikter, hepatosplenomegali ve her iki servikal zincirde 4 cm'yi bulan birden fazla lenf nodu saptandı. Laboratuvar tetkiklerinde belirgin lenfomonositozu ve periferik yaymada Downey hücreleri görüldü. Karaciğer enzimleri ve bilirubin seviyeleri yüksekti, böbrek fonksiyonları normaldi. İdrar tetkikinde hematüri ve nefrotik düzeyde olmayan proteinüri mevcuttu. Kolestatik hepatit ve glomerulonefrit ön tanıları ile izlenen hastanın izleminde idrar çıkışı normal seyretti. Ultrasonografide hepatosplenomegali ve böbreklerin parankim ekojenitesi artmıştı. Epstein-Barr virüs viral kapsit antijen immunglobulin M pozitif geldi ve polimeraz zincir reaksiyonu ile Epstein-Barr virüs, 140.000 kopya/μL bulundu. İzleminde direngen ateşi devam etmesi ve lenf nodlarında hızlı büyüme nedeni ile steroid tedavisi verildi, sonrasında ateşi tekrarlamadı. Yatışının dördüncü gününde makroskopik hematürisi düzelen hastanın üçüncü haftaki kontrolünde hematüri ve proteinürinin tamamen kaybolduğu görüldü.

Anahtar Kelimeler: Hematüri, nefrit, Epstein-Barr virüs

Introduction

Infectious mononucleosis (IMN) is characterized with fever, sore throat and lymphadenopathy, and its most common agent is the Epstein-Barr virus (EBV). Epstein-Barr virus infection is usually self-limiting in all age groups and progresses with obscure symptoms especially in infants and young children; however, IMN incidence increases with advancing age. It has been reported that all systems may be affected during IMN caused by Epstein-Barr virus and cardiac, respiratory, neurologic, hematological, and renal complications may develop (1). Renal involvement is rather rare, with severity carrying

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Received: 29.08.2020 **Accepted:** 15.03.2021 **Available Online Date:** 29.12.2021

from hematuria to acute kidney failure (2-6). This study aimed to present and adolescent case presenting with bloody urine and fever and diagnosed with IMN.

Case Report

A previously healthy male patient aged 16.5 years presented to the pediatric emergency clinic with fever ongoing four days, sore throat and bloody urine ongoing for two days. It was learned from his medical history that he had presented to another hospital with otalgia and had been diagnosed with otitis and given clarithromycin treatment; however, no amelioration had occurred for his otalgia and upon realizing new symptoms, he presented to our hospital. Family history of the patient, who did not describe any lower urinary system symptoms, was uneventful.

Body temperature of the patient was 40°C and his blood pressure was 115/75 mmHg. On the physical examination of the patient whose general state was moderate, sclera and icterus of the skin were seen. Oropharynx was hyperemic, well-circumscribed lesion, painful lesions were present, one or two on each anterior cervix, 2x3 cm in size, and one on the left anterior cervix, 4x5 cm in size. The liver was 1 cm palpable and the spleen was 2 cm palpable under the jean. There was no costovertebral angle tenderness. Other system examinations of the patient who did not have pretibial edema was normal. Hemogram of the patient was as follows: white blood cell count 30230/µL (4000-10000 /µL), hemoglobin: 16.3 g/dl (11-18 g/dl), platelet: 171x10^3/µL (150-400 x10^3/µL). His peripheral blood smear revealed 42% monocytes, 26% lymphocytes, 12% Downey cells, and 20% polymorphonuclear leucocytes. His biochemical examination resulted as follows: alanine aminotransferase 308 (0-50) IU/L, aspartate aminotransferase 203 IU/L (0-50 IU/L), total bilirubin 3.369 IU/L (0.2-1.2 IU/L) mg/dL direct bilirubin 2.296 IU/L (0-0.2 IU/L) mg/dL, gamma glutamyl transferase 389 IU/L (0-55 IU/L), creatin kinase (CK) 378.5 (30-171) IU/L, and C-reactive protein (CRP) 14.3 mg/L (0-5 mg/L). His renal functions were normal (urea: 22 mg/dl, creatinine: 0.67 mg/dl). Macroscopic examination of the urine showed that it had a tea color. Urine examination showed density 1015, ph 6, and protein (+), blood reaction (++++). Urine microscopy resulted in 222 erythrocytes and 4 leucocytes. Antistreptolysin O and complement C3 levels were normal. The patient was admitted with these findings and preliminary diagnoses of IMN, cholecystitis and nephritis and was started on ursodeoxycholic acid, cefotaxime, fat-free diet, and intravenous fluids. Serologic tests in terms of toxoplasma, cytomegalovirus, EBV, and hepatitis virus (Hepatitis A, B, C viruses) were sent for etiology. Hepatobiliary ultrasonography (USG) demonstrated splenomegaly, hepatomegaly, several lymph nodes located in the portal hilus, with the largest being 20x8 mm in size, and gallbladder edema. Urinary USG did not detect a significant pathology other than mild increase in both kidneys' parenchyma echogenity. 15 mg/m^2/h proteinuria was detected in the patient's 24-h urine collected due to seeing proteinuria in his urine culture. During the follow-up of the patient whose blood pressure was closely monitored, urine output was normal, and his blood pressure measurements were within normal limits for his height and age. No growth was detected in his urine culture. On the fourth day of admission, his macroscopic hematuria was observed to have improved.

The patient was started on methylprednisolone with a dosage of 0.7 mg/kg/day for the first four days and then with 0.1 mg/kg/day for the following six days upon seeing that his fever was resistant on the sixth day of admission, the sizes of the cervical lymph nodes grew distinctively, development of distinct hypertrophy on his tonsils, and findings of respiratory tract obstruction in the way of difficulty in breathing during sleep (10). Following steroid treatment, patient's fever ameliorated and did not regress. Findings of respiratory tract obstruction decreased.

Hepatitis B surface antigen, anti-Hepatitis A virus immunoglobulin (Ig) M, anti-Hepatitis C virus IgM and CMV IgM were negative, EBV viral capsid antigen (VCA) IgM was positive, and anti EBV nuclear antigen (EBNA) was resulted negative. For the diagnosis of acute EBV infection, serology is the standard test and EBV polymerase chain reaction (PCR) of our patient who had an atypical course resulted positive with 140.000 copies/µL (7). On follow-up, it was seen that the lymph nodes and tonsils shrank, liver and spleen sizes returned to normal, and liver function tests improved. On urine examination that was repeated at the end of the first week, it was observed that although microscopic hematuria continued, proteinuria decreased (5.8 mg/m^2/h). On the third week control, microscopic hematuria and proteinuria completely improved. The patient, whose outpatient follow-up is continued, did not have any complaints on the tenth month after discharge, and his examination was normal.

Discussion

Classical symptoms of infectious mononucleosis (IMN) are fever, lymphadenopathy and pharyngitis. In a study evaluation 98 children with IMN, while fever has been found the most common symptom (98%), it was followed by tonsillopharyngitis (85%) and hepatomegaly (77%). It has been reported that complications developed in a total of 13 patients, with hemophagocytic syndrome in one, liver failure in five, hematologic complications in four, upper respiratory tract obstruction in two, and neurologic complication in a case that presented with seizure (8). Important clues for the diagnosis of EBV are edema in the nasopharynx and nasal obstruction and bilateral palpebral edema. It is thought to stem from lymphoproliferation that develop due to replication of the vi-

rus in the nasopharynx or from lymphatic obstruction (9). As a result of nasopharynx edema, secondary otitis may develop. Our patient was diagnosed with otitis at the first hospital he presented; however, he did not have otitis symptoms when he presented to our hospital.

Infection-associated glomerulonephritis can be due to bacterial, viral, and parasitic infection. Even though the most common agents are streptococci (27.7%) and staphylococci (24.4%), it has been reported that many pathogens cause glomerulonephritis. One of the rare agents is EBV (10). The mechanism of renal involvement is not clear. It has been suggested that it could be secondary to the direct renal invasion of the virus during acute infection or that glomerulonephritis may also develop with immune-mediated mechanisms in the long term (6,11). There are limited number of studies studying renal involvement in Epstein-Barr virus infections (10,12,13). Although abnormalities in the urine sediment of 5-15% of the patients have been reported, parenchymal involvement is quite rare (1). Wechsler et al. (14) have reported that they encountered microscopic hematuria and mild proteinuria in only 17 cases out of 556 IMN cases and that renal functions did not deteriorate in any patient. However, there are cases in the literature in which acute renal failure has developed during the course of IMN (6,11,13) .

In a study analyzing acute renal failure (ARF) seen during Epstein-Barr virus infection, 38 cases reported between 1955 and 2015 have been evaluated and macroscopic hematuria and accompanying proteinuria was detected in eight of the patients during presentation. It has been determined that when renal biopsy was performed on the patients, 27 developed acute interstitial nephritis, 7 developed rhabdomyolysis, and 3 developed renal failure secondary to hemolytic uremic syndrome (15). The most commonly reported involvement is acute tubulointerstitial nephritis (TIN) (12). However, there are studies reporting one-case reports of EBV-associated membranoproliferative glomerulonephritis, minimal change disease, focal segmental glomerulosclerosis and crescentric glomerulonephritis in the literature (1,6,11,14).

Many medications and infections can cause acute TIN. Acute TIN is a clinical condition characterized with fatigue, nausea, fever, side pain, rash, hematuria, non-nephrotic proteinuria and deteriorated renal functions. Increase in acute phase reactants and eosinophilia in peripheral smear may be seen. While microscopic hematuria is seen nearly in all patients, macroscopic hematuria is quite rare (13). When it is considered that many medications used today cause TIN, our patient was also thought in differential diagnosis to have generated renal response due to medications. However, medication-associated TIN was excluded since the only medicine our patient used was clarithromycin, which does not have any reported nephrotoxic effects and there were no urine findings suggestive of concentration defect, and eosinophils were not present in peripheral smear (16).

Chronic glomerulonephritis was not considered in our patient in whom hematuria and proteinuria had not been seen before and the finding regressed following infection. Our patient was thought to have EBV-associated renal involvement since he had symptoms of infectious mononucleosis and painless glomerular hematuria and the fact that infection findings ameliorated along with the regression in hematuria and proteinuria even though the location and severity of the involvement could not be determined due to lack of tissue diagnosis. The fact that our patient had both cholecystitis and glomerulonephritis was thought to be due to him being in the adolescent age group.

To conclude, we would like to emphasize with this case that renal response may rarely develop during EBV infection and have a quite different clinical course. It should be kept in mind that renal involvement may develop in EBV-associated IMN patients and that the agent might be EBV in patients detected to have glomerulonephritis.

Informed Consent: Patient consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - SY; Design - EYK; Supervision - GİB; Resources - SY; Data Collection and/or Processing - EYK; Analysis and/or Interpretation - GİB; Literature Review - GİB; Writing - SY; Critical Review - GİB.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. *Jenson HB. Acute complications of Epstein-Barr virus infectious mononucleosis. Curr Op Peadiatr 2000;12(3):263-8.* ***[CrossRef]***
2. *Dettmar AK, Oh J. Infection-related focal segmental glomerulosclerosis in children. BioMed Res Int 2016;2016.* ***[CrossRef]***
3. *Helin K, Ekroos H. A case of mononucleosis complicated by acute nephritis. Scandinavian J Urol Nephrol 2002;36(2):152-3.* ***[CrossRef]***
4. *Lee S, Kjellstrand C. Renal disease in infectious mononucleosis. Clin Nephrol 1978;9(6):236-40.* ***[CrossRef]***
5. *Mayer HB, Wanke CA, Williams M, Crosson AW, Federman M, Hammer SM. Epstein-Barr virus-induced infectious mononucleosis complicated by acute renal failure: case report and review. Clin Infect Dis 1996;22(6):1009-18.* ***[CrossRef]***
6. *Mikhalkova D, Khanna S, Vaidya R, Sethi S, Hogan MC. Epstein-Barr virus-associated nephrotic syndrome. Clin Kidney J 2012;5(1):50-2.* ***[CrossRef]***

7. *Long Katz BZ. Epstein-Barr Virus (Mononucleosis and Lymphoproliferative Disorders). In: Long SS PC, Fischer M (eds). Principles and Practice of Pediatric Infectious Diseases, 5th ed. Philadelphia: Elsevier; 2018:1088-95.* **[CrossRef]**
8. *Tsai Ming-Han, Hsu Chih-Yi, Yen Meng-Hsiu, Yan Dah-Chin, Chiu Cheng-Hsun, Huang Yhu-Chering, et al. Epstein-Barr virus-associated infectious mononucleosis and risk factor analysis for complications in hospitalized children. J Microbiol Immunol Infect 2005;38(4):255.* **[CrossRef]**
9. *Bass MH. Periorbital edema as the initial sign of infectious mononucleosis. The Journal of pediatrics. 1954;45(2):204-5.* **[CrossRef]**
10. *Williams E, Bhagani S, Harber M. Infectious diseases and the kidney. Practical Nephrology: Springer 2014;257-68.* **[CrossRef]**
11. *Woodroffe AJ, Row PG, Meadows R, Lawrence JR. Nephritis in infectious mononucleosis. Q J Med 1974;43(171):451-60.* **[CrossRef]**
12. *Lei PS, Lowichik A, Allen W, Mauch TJ. Acute Renal Failure: Unusual complication of Epstein-Barr Virus-Induced Infectious Mononucleosis. Clin Infect Dis 2000;31(6):1519-24.* **[CrossRef]**
13. *Ruebner RL, Fadrowski JJ. Tubulointerstitial nephritis. Pediatr Clinics 2019;66(1):111-9.* **[CrossRef]**
14. *Wechsler HF, Rosenblum AH, Sills CT. Infectıous mononucleosis: Report of an epidemic in an army post: Part I. Ann Int Med 1946;25(1):113-33.* **[CrossRef]**
15. *Moretti M, Lava SA, Zgraggen L, Simonetti GD, Kottanattu L, Bianchetti MG, et al. Acute kidney injury in symptomatic primary Epstein-Barr virus infectious mononucleosis: Systematic review. J Clin Virol 2017;91:12-7.* **[CrossRef]**
16. *Eddy AA. Drug-induced tubulointerstitial nephritis: hypersensitivity and necroinflammatory pathways. Pediatr Nephrol 2020;35(4):547-54.* **[CrossRef]**