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Epstein-Barr Virus İnfeksiyonuna Sekonder Olarak Gelişen Otoimmun Hemolitik Anemi: Bir Vaka Raporu

Autoimmune Hemolytic Anemia Developing Secondary to Epstein-Barr Virus Infection: A case report

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ÖZ
Enfeksiyöz mononükleoz (EM), Epstein-Barr virüsünün (EBV) yayılması ile karakterize bir hastalıktır. Klinik bulgular tonsillofarenjit, lenfadenopati ve atipik lenfositoz ile karakterizedir. EBV'ye sekonder tonsillofarenjit ve genel durum bozukluğu nedeniyle kliniğimizde takip sırasında hemolitik anemi gelişen genç bir hastayı tanımladık.
Anahtar kelimeler: Hemolitik anemi, infeksiyoz mononukleozis, otoimmun

ABSTRACT
Infectious mononucleosis (EM) is a disease characterized by irradiation of the Epstein-Barr virus (EBV). The clinical manifestation is characterized by tonsillopharyngitis, lymphadenopathy and atypical lymphocytosis. We describe a young patient developing hemolytic anemia during follow-up in our clinic due to tonsillopharyngitis secondary to EBV and general condition disorder.
Keywords: Autoimmune, Hemolytic anemia, Infectious mononucleosis

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INTRODUCTION

Epstein-Barr Virus (EBV) is a DNA virus of the Herpetoviridae family, also known as human herpes virus type 4. EBV usually causes infectious mononucleosis in adolescents and young adults, with high fever, sore throat, lymphadenopathy, and lymphomonocytosis. It is often self-limiting, and most patients recover without complications.[1,2] However, it may also present with hepatitis, and respiratory, renal (acute tubular necrosis or tubulointerstitial nephritis), neurological (meningoencephalitis, cerebellitis) and hematological (neutropenia, aplastic anemia, hemophagocytic lymphohistiocytosis, hemolytic anemia, thrombocytopenia) involvement. We describe a young patient developing hemolytic anemia secondary to EBV.

CASE REPORT

Ethics committee approval is not required for this study. The patient's consent was obtained. A 24-year -old man who had previously received oral 2x1 g amoxicillin-clavulanic acid treatment at another health institution due to fever, sore throat and fatigue persisting for 10 days was admitted to our policlinic due to lack of improvement. He had also noticed a swelling in his neck. Physical examination revealed multiple lymphadenopathies covered with exudate membrane on both tonsils, with tonsillar hypertrophy grade 2-3, sensitivity to palpation in the bilateral cervical chain, and a tendency to conglomeration. Respiratory examine were natural, no rash was observed, and hepatosplenomegaly was determined at abdominal examination.

The patient was admitted to our clinic with these findings.

At laboratory tests, white blood cell count was 20.5 mm3 (neutrophil: 5.9 mm3, lymphocyte: 11.9 mm3, monocyte: 2.3 mm3), Hgb: 10.4 g/dL, platelet: 174.000, total bilirubin: 3.6 mg/dL, direct bilirubine: 1.78 mg/dL, AST: 315 U/L, ALT: 635 U/L, ALP: 215 U/L, and LDH: 1009 U/L. The patient reported drinking bottled water, a history of substance use (from mouth to mouth), being in a single-partner relationship for the previous four months, and that his partner had no similar symptoms. He also had no history of working in animal husbandry. No Group A hemolytic streptococcus growth was observed in throat culture, and no growth occurred in blood cultures. Brucella rose bengal and tube agglutination were negative, EBV VCA IgG positive, EBV VCA IgM positive, Parvovirus IgM negative, Anti-CMV IgM negative, VDRL-RPR negative, and hepatitis B and C negative. Neck ultrasound (USG) revealed conglomerated oval-shaped multiple lymph nodes.

The patient was followed-up for tonsillo-pharyngitis due to EBV. During follow-up, Hgb was 8.2 g/dL, reticulocyte 3.57, and total bilirubin 5.2 mg/dl, and an icteric appearance were observed. The internal diseases department was consulted for internal anemia and reticulocytosis, and indirect Coombs, direct Coombs, complement IgG and peripheral smear tests were requested. Peripheral smear showed destruction-induced nucleated erythrocytes, neutrophilic leukocytosis and moderate thrombocytosis. Methylprednisolone was started at 1mg/kg per day with a preliminary diagnosis of immune hemolytic anemia. Hgb at complete blood count after initiation of steroid therapy was 6.4 mg/dL, and the steroid dose was maintained at 2mg/kg/day. Anemia persisted despite the steroid dosage being increased, and the steroid therapy was discontinued. Folic acid and vitamin B12 were started. The patient's fever did not persist, antibiotic therapy was stopped, and Hgb was measured at 7.6 g/dL. He was discharged two weeks later with a recommendation of monitoring by the infectious diseases and hematology polyclinic. A summary of the laboratory values measured during the follow-up of the patient is given in Table 1.

DISCUSSION AND CONCLUSION

Primary EBV infection is usually asymptomatic in childhood, although the probability of symptomatic progression increases with age. In societies with low socioeconomic levels, much of the population is infected with EBV in childhood, whereas in developed countries EBV infection is most commonly seen in the 15-25 age range. In Turkey, 80-86% seropositivity has been reported in the adult age group. Fever, sore throat and lymphadenopathy are the most common findings in EBV infection. Hepatic involvement is frequently observed, and spontaneous resolution of liver enzyme elevation is seen in 80-90% of these patients.[1-3] Patients with infectious mononucleosis usually recover without complications within two to three weeks. Rare complications are often self-limiting. Hematological complications include autoimmune hemolytic anemia, thrombocytopenia, neutropenia, aplastic anemia, and disseminated intravascular coagulopathy. Aplastic anemia is one of the rare complications that may require bone marrow transplantation. Severe thrombocytopenia (<20.000 platelets / mm3) is very rare, while mild thrombocytopenia (<100.000-150.000 platelets/mm3) occurs in 25-50% of patients. The mechanism involved in thrombocytopenia is unclear. However, it has been reported to occur as a result of increased peripheral destruction due to antiplatelet antibodies and splenomegaly with a normal or increased megakaryocyte count in bone marrow. Pancytopenia is a rare complication. Corticosteroids are frequently used in the treatment of infectious mononucleosis with severe autoimmune hemolytic anemia, thrombocytopenia, neutropenia or aplastic anemia.[1,4-6] Acute EBV infection causes hemolytic anemia in approximately 3% of patients.[7] Corticosteroids are the drug of choice for the treatment of acute immune hemolytic anemia, irrespective of etiology.[8] Although this is not very common, intravenous immunoglobulin (IVIG) has also been used for treatment in published case series.[9]

In our case, corticosteroid therapy was started, and IVIG treatment was initiated due to lack of clinical and laboratory improvement.

The main reasons for this case being regarded as infectious mononucleosis due to EBV werea positive VCA IgM titer, absence of any other etiology of hepatitis, and positive pharyngeal findings consistent with acute primary EBV infection, often seen as mononucleosis. These symptoms resolved spontaneously, suggesting that the pathological etiology in our patient involved acute viral infection, rather than a bacterial or malignant neoplastic process. When other infectious agents including HIV were screened, no positivity was determined other than EBV IgM. The patient's history revealed no additional hematological malignancies that might ac-

count for lymphocytosis, although high-risk sexual behavior and mouth-to-mouth substance use were present for EBV transmission. Accordingly, we concluded that our patient had an EBV infection which resulted in a mononucleosis-like condition.

However, our analysis had certain limitations and uncertainties. First, the viral load of EBV could not be measured. However, EBV is diagnosed based on history and laboratory findings. The presence of more than 10% atypical lymphocytes in peripheral blood helps narrow differential diagnosis to EBV infection with 75% sensitivity and 92% specificity.[10] In addition, hematological neoplastic conditions such as lymphoma, leukemia and lymphoproliferative disease cannot be totally ruled out since bone marrow biopsy cannot be performed. If clinical suspicion of IM is present, and no hemophagocytic syndrome or neurological involvements are determined, then follow-up is preferable to bone marrow biopsy.[8] Since flow cytometry has not been evaluated for lymphocytes, the increased clonality of lymphocytes is unknown. These are the principal limitations to our analysis. At clinical follow-up in our case, hemoglobin and ferritin levels returned to normal after two weeks, consistent with the diagnosis of infectious mononucleosis and secondary autoimmune hemolytic anemia.

In conclusion, infectious mononucleosis organomegaly secondary to EBV, bicytopenia and hemolytic anemia, may present with different clinical findings such as acute lymphoblastic leukemia, Hodgkin lymphoma, hemophagocytic syndrome, carcinoma, and chronic active EBV infection.

Ethics Committee Approval: Ethics committee approval is not required for this study. The patient's consent was obtained.

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

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Table 1: Laboratory values during patient stay.

Laboratory parameters	0.day	7.day	14.day	28.day
WBC(10^3/µL)	20.5	14.6	7.4	4.9
Neutrophile(10^3/µL)	5.98	5.22	1.69	1.40
Lymphocyte(10^3/µL)	11.95	7.88	5.15	3.15
Monocyte(10^3/µL)	2.35	1.39	0.49	0.34
Haemoglobin(g/dL)	10.4	6.4	7.6	10.4
Platelet(10^3/µL)	174	215	296	181
AST (U/L)	315	199	75	42
ALT (U/L)	635	310	90	55
LDH (U/L)	1009	790	467	429
Total bilirubine (mg/dL)	3.61	5.2	1.36	1.43
Direct bilirubine (mg/dL)	1.78	3.12	0.60	0.47
CRP (mg/dL)	1.81	2.31	-	-
Reticulocyte %	4.659	14.887	8.578	6.239
Direct coombs (IgG)	Positive	Positive	Positive	Negative
Indirect coombs	Negative	Negative	Negative	Negative
EBV VCA IgM	Positive	-	-	-
EBV VCA IGG	Positive	-	-	-
EBV EA	Positive	-	-	
EBV DNA PCR	Positive	-	-	-