

## INFECTIOUS MONONUCLEOSIS IN SPLENECTOMISED PATIENT

Ljiljana Pašić<sup>1</sup>, Dragan Kasapović<sup>1</sup>, Milan Petrović<sup>1</sup>, Zdravka Kezić<sup>1</sup>, Antonija Verhaz<sup>1,2</sup>, Snežana Ritan<sup>1</sup>

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Ljiljana Pašić  
Dragan Kasapović  
Milan Petrović  
Zdravka Kezić<sup>1</sup>  
Antonija Verhaz  
Snežana Ritan

## ABSTRACT

**Introduction:** Infectious mononucleosis is one of the most common syndromes in our clinical practice. It is characterized by elevated temperature, pharyngitis and generalized lymphadenopathy.

**Objectives:** To describe a clinical characteristics of infectious mononucleosis (IM) caused by the Epstein Barr virus (EBV) in splenectomized patients since in the literature we found insufficient data.

**Subjects and Methods:** Retrospective analysis of medical documentation of the patient treated in the Clinic for Infectious Diseases of the University Clinical Center of Republic of Srpska.

**Results:** We have described the case of infectious mononucleosis, caused by Epstein Barr virus in a splenectomized patient. In support of acute EBV viral infection were the presence of lymphadenopathy, pharyngitis, hepatomegaly, as well as the occurrence of a typical generalized maculopapulous rash, and positive ELISA EBV VCA IgM and anti EBV VCA / EA IgG, were reported. According to the aforementioned patient, it fulfilled most criteria for setting the diagnosis of acute EBV infectious mononucleosis. Our patient showed some atypical signs such as absence of fever during hospitalization, marked leukocytosis with lymphocytosis (with a maximum increase in leukocyte count at  $37.3 \times 10^9$ , in the differential blood sample dominated lymphocytes with  $29.96 \times 10^9$  (reference values 1.1-3.35), i.e. 80.3% (Ref. 20.0-46.0). Due to the maintenance of leukocytosis with lymphocytosis, the range of clinical has been extended trials (US abdomen, US neck, CT neck, chest, abdomen and pelvis, sternal puncture, hematologists' consultation). Based on the aforementioned hematologists' consultation, and post-release and recovery monitoring it is concluded that there has been no sign of acute hematologic disease but it has been just EBV-IM.

**Conclusion:** Because of insufficient data on clinical presentation of Epstein Barr viral infections in splenectomized this we believe that this is one of the clinical variants although the possibility of individual variation cannot be excluded. Briefly, we can conclude that the immune system in the splenectomized patient can greatly modify the clinical presentation of Epstein barr viral infection, with the pathogenic mechanism that are still unclear. However, due to the variety of clinical syndromes and the oncogenic potency of the Epstein-Barr virus, we should be extremely cautious and sometimes expand the diagnostic range beyond conventional examinations.

**Key words:** Infectious Mononucleosis, splenectomy, Epstein-Barr virus, clinical characteristics

## INTRODUCTION

Infectious mononucleosis (IM) is a common syndrome and as such is one of the most frequent reasons of patients visiting their family doctor. Clinical picture of the IM mostly consists of the standard triad: elevated temperature, pharyngitis and lymphadenopathy. The usual laboratory results with IM patients include leukocytosis with atypical lymphocytosis, while elevated serum aminotransferase activity appears in

75% of patients with IM, especially in older children and adults [1, 6]. *Epstein-Barr virus* (EBV) is most commonly associated with IM, while other viruses such as Cytomegalovirus (CMV), Human immunodeficiency virus (HIV) and Human herpes virus 6 also can cause IM [1]. However, little attention is being paid to clinical picture in IM patients with splenectomy. Clinical characteristics in splenectomized patients with IM still are not fully described, especially those caused by EBV. According to

## Affiliations:

<sup>1</sup> Clinic for Infectious Diseases,  
University Clinical Center of  
Republika Srpska,

<sup>2</sup> Faculty of Medicine, University of  
Banja Luka, Banja Luka, Bosnia and  
Herzegovina

## Corresponding author:

Ljiljana Pašić,  
E mail: ljiljanaipasici@gmail.com

our findings, there is only one published report in literature in the English language. Kunimatsu with his colleagues describes a case of atypical infectious mononucleosis caused by EBV. In this case he highlights that the patient was afebrile, with severe exhaustion, lymphadenopathy was not present, and in laboratory results he had leukocytosis and elevated serum aminotransferase activities [2]. Han and colleagues reported of two cases of postsplenectomy cytomegalovirus infectious mononucleosis (CMV-IM). In this report they describe clinical characteristics of prolonged febrile state, pronounced lymphocytosis in peripheral blood, weakened IgM response to CMV and clonal proliferation of T-cells with redistribution of the T-cell receptor gene [3-4]. Furthermore, based on literature review, Han and colleagues claim that post-splenectomy CMV-IM is a different clinical-pathological syndrome because they had noticed that CMV-IM in asplenic state has some unique clinical characteristics [4]. It is necessary to have it in mind, because we rarely meet end even more rarely recognize this clinical syndrome in splenectomized people.

**AIM:** Describe the clinical picture of infectious mononucleosis caused by EBV in a patient splenectomized due to idiopathic thrombocytopenia because there is not enough data.

**SUBJECTS AND METHODS:** Retrospective analysis of medical documentation of the patient treated in the Clinic for Infectious Diseases of the University Clinical Center of Republic of Srpska.

**RESULTS:** A female, at age 25 comes to our clinic for the first time after the fifth day of the illness because of elevated temperature (maximum temperature 38 degrees Celsius), swollen neck, a feeling of suffocation, night sweating and general exhaustion and weakness. Previously, due to the inflammatory process and tooth extrusion, she was on the antibiotic therapy Cefalexin tablets 5 days, after the neck swelling and lymph node enlargement, Penicillin and Gentamicin injections were introduced for five days. Epidemiological data in terms of contact with similar patients were negative, the patient denied risky sexual behavior, the use of intravenous narcotics, she did not know if she received blood and blood derivatives, and in the fifth year of life the splenectomy was done due to idiopathic thrombocytopenia (she had no medical

record of vaccination). Physically she was subfebrile, hypodynamic, with discrete edema of the eyelids, pharyngitis, and prominent lymphadenopathy on the neck angular where the lymph nodes were 2.5 cm in size, moving, painless to palpation, and with the front and back edge m.sternocleidomastoideus slightly smaller to 1cm as well as axillary and inguinal; skin and visible mucous membranes were without exanthema and erythema. The abdomen was soft, painless to the surface and deep palpation, the liver could be palpated to 1.5 cm. The result on the lungs and heart was orderly. The tooth extraction place in the lower jaw was erythematous and partly edematous. In laboratory results, leukocytosis with lymphocytosis was noticed (Table 1.) as well as moderate increase in aminotransferase activity. Serological examinations showed an acute Epstein-Barr virus infection, and latent cytomegalovirus infection (Table 2). Within the radiological treatment, an ultrasound examination of the abdomen and neck was done (Table 3).

Due to the occurrence of pain and erythema at the place of teeth extraction, and a slightly more prominent submandibular edema, a maxillofacial surgeon was consulted who said that there was no inflammatory process and indications for surgical treatment. Leukocytosis with lymphocytosis was dominated in the blood picture which was checked daily, a hematologist was consulted indicating sternal puncture, CT neck, chest and abdomen, and a regular analysis of bone marrow aspiration excludes acute hematological disease. On the 13<sup>th</sup> day of hospitalization there is a manifestation of maculopapular exanthem partially shown on the skin of the face, upper body and limbs followed by the sensation of itching, subjective feeling of choking, and without the appearance of febrile, angioedema or other deviation in the rest of the physical lab results a dermatologist is consulted, and short-term corticosteroids and antihistamines are introduced in therapy due to suspicion of the toxoallergic component rashes because it was treated with antibiotics (Lincomycin). Following the recommendation of the hematologist, laboratory parameters were followed daily and indicated a gradual normalization of the results so that on the release the leukocyte was  $10.5 \times 10^9$ , while the DKS number of the lymphocytes was 72.1% and the number of monocytes was 12.0%, thrombocytes  $483 \times 10^9$ , AST, ALT, LDH values were in reference values as well as CRP.

**Table 1.** Spreadsheet of laboratory results according to days of hospitalization

Tests	RVAG	1 <sup>st</sup> DOH	2 <sup>nd</sup> DOH	4 <sup>th</sup> DOH	5 <sup>th</sup> DOH	6 <sup>th</sup> DOH	7 <sup>th</sup> DOH	8 <sup>th</sup> DOH	13 <sup>th</sup> DOH
Leukocytes	3.40-9.70/L	$28.8 \times 10^9/L$	$28.7 \times 10^9/L$	$37.3 \times 10^9/L$	$38.5 \times 10^9/L$	$37.7 \times 10^9/L$	$28.5 \times 10^9/L$	$29.6 \times 10^9/L$	$10.5 \times 10^9/L$
Lymphocytes %	20-60%	69.0%	63.7%	80.3%	66.3%	64.9%	56.3%	57.9%	72.1%
AST (U/L)	<35	26				68			31
ALT (U/L)	<35	19				76			37
LDH (U/L)	<247	215				298			167
CRP (mg/L)	<5.0	1.5				2.1			0.3

Abbreviations : Reference values in adult age (ARVG); day of hospitalization (DOH); Aspartate aminotransferase (AST); Alanine-aminotransferase (ALT); Lactate dehydrogenase (LDH); C-reactive protein (CRP)

**Table 2.** Spreadsheet of serological results

Tests	Reference values in adult age	Result
Anti-EBV VCA IgM (mini Vidas)	>0.19	0.70
Anti-EBV VCA IgG	>0.21	>0.21
Anti-CMV IgM (AbottArchitect)	negative	negative
Anti CMV IgG	>6.0	149.1 AU/ml
Anti Toxoplasmosis IgM (2000SR)	negative	negative
Anti Toxoplasmosis IgG	negative	negative
HIV (OraQuick 1/2)	negative	negative

**Table3.** Spreadsheet of expanded diagnostical methods

Tests Results
<p><b>Neck ultrasound</b> In almost all the groups, enlarged and multiplied lymphonoduses in the neck, diameters up to 1 cm, were seen on both sides, and the largest in the II group of the left shorter diameters up to 14 mm, no pathological changes were seen on soft tissues, submandibular, parotid, and thyroid glands, as well as on vascular structures the door.</p>
<p><b>Abdominal ultrasound</b> An enlarged liver at the expense of the left lobe that reaches to the upper half of the left kidney-anatomic variation; at the boundary line of the liver dimension (13.5x 6.5cm)</p>
<p><b>Neck, chest and abdomen CT scan</b> On the axial sections of the shown structures in the projection of the corresponding part of the group Ia and Ib, both adjacent submental, basically sublingually, as well as submandibular IIa-IIb, as well as the IV group and lower spinal Va, Vb, are enlarged lymphonoduses with a size of about 1-1.2 cm. There were no signs of mediastinal lymphadenopathy, nor of retroperitoneal lymphadenopathy. The remaining result was within the physiological limits.</p>
<p><b>Bone marrow aspiration</b> Cellularity III, megakaryocytes are seen, as well as a productive red blood cell of the normoblast type of ripening, 60% of nuclear elements of the core that make lymphocytes with individual plasma cells.</p>

## DISCUSSION

We have described the case of infectious mononucleosis, serologically verified primoinfection of EBV, in a splenectomized patient with a slightly slower recovery and maintenance of pronounced leukocytosis with lymphocytosis, moderately elevated aminotransferase activity, and generalized maculopapular exanthem [1, 6-7]. We think that, as seen in patients with CMV-IM and EBV-IM, the asplenic condition can significantly alter the classic clinical IM image [2]. In fact, our patient showed some atypical symptoms such as absence of febrile during hospitalization, moderate increase in serum aminotransferases, and pronounced leukocytosis with lymphocytosis (with a maximal increase in the leukocyte count to  $37.3 \times 10^9$ ; in the differential blood count dominated by lymphocytes with  $29.96 \times 10^9$  (reference values of 1.1-3.35), ie 80.3% in DKS (ref., value 20.0-46.0), while normal values of  $1.400 \pm 5.400 / \mu\text{L}$  and  $4.000 \pm 3.200 / \mu\text{L}$  up to 30% of

lymphocytes usually occur [2]. As the spleen represents the place of replication of early immunity against viral infection, and the immune response of patients without spleen is compromised, it can also speed up the antiviral immune response elsewhere, for example, bone marrow. As a result, leukocytes, lymphocytes, and atypical lymphocyte counts in peripheral blood can be distinctively increased [2-4]. According to the aforementioned patient, she fulfilled most of the criteria for diagnosing of acute Epstein Barr viral infectious mononucleosis. On the other hand, our analysis has certain limitations and our case of some uncertainty. Firstly, we do not have direct evidence of EBV infection; EBV viral load was not measured (there was no possibility for PCR diagnosis) [5]. In general, a typical IM with primary EBV infection is benign syndrome and can be self-limiting so it does not in any case require the determination of viremia, other than fulminant flow in viral hemophagocytic lymphohistocytosis or neurological complications [1, 8-10].

However, the main differential diagnostic problem after verification of acute EBV infection by methods available, and the exclusion of acute toxoplasmosis, acute CMV infection, acute HIV infections was still the maintenance of leukocytosis with lymphocytosis, the presence of lymphadenopathy, with night sweats and exhaustion, as well as the absence of febrile. For this reason, we have expanded the diagnostic treatment in terms of observing the acute haematological non-infectious disease [1, 8]. Bone marrow biopsy, CT, chest and abdominal analysis of the bone marrow was performed, and acute hematological events were excluded (no further analysis of aspirates-flow cytometry, Southern blot was performed) (Table 2). On the basis of the performed tests, we decided on the watchful waiting model of treatment and continued to monitor the patient's condition after release when all troubles were withdrawn, as well as the normalization of the blood picture. Considering the changed patient's immune response, a possibility occurred to investigate the further course of the EBV infection, or whether EBV nuclear antigen (EBNA) would be formed as a sign of a chronic infection and to what extent the viremia of the EBV virus would be expressed, unfortunately the method for which we were deprived of: such as serological monitoring of anti EBNA, and PCR EBV. [2-4,8-10]. We find in literature that Kunimatsu and associates describe the case of atypical infectious mononucleosis caused by EBV. In his report, he noted that the patient was afebrile, with prominent exhaustion, lymphadenopathy was not prominent, and in laboratory results he had leukocytosis with lymphocytosis and elevated serum aminotransferase activities [2]. Han and associates reported two cases with postsplenectomy cytomegalovirus infectious mononucleosis (CMV). In his report, he describes the clinical characteristics of a prolonged febrile state, a prominent peripheral blood lymphocytosis, a weakened IgM response to CMV and clonal proliferation of T cells, with the redistribution of the T cell receptor gene [3,4]. Furthermore, on the basis of literature review, Han and associates argue that post-splenectomy CMV mononucleosis is a different clinical-pathological syndrome because they have noticed that CMV-IM has some unique clinical characteristics in asplenic condition [4]. Although the possibility of individual variation cannot be excluded, the atypical factors described herein can characterize the clinical features of EBV-IM in asplenic patients. In short, we can conclude that the immunological system in the splenectomized patient can greatly alter the clinical presentation of the Epstein Barr virus infection, with the pathogenetic mechanism remaining unresolved [2-4,8-10].

## CONCLUSION

Because there is little data on acute EBV infection in splenectomized patients, we think that the presentation of a clinical picture of our patient could be one of the variants of the presentation of acute EBV infection in splenectomized patients, as well

as the greater possibility of complications due to an impaired immune response. Although the possibility of individual variation cannot be excluded, the atypical factors described herein may be characterized by the clinical features of EBV-IM in asplenic patients. In short, we can conclude that the immunological system in the splenectomized patient can greatly alter the clinical presentation of Epstein Barr viral infection, with the pathogenetic mechanism remaining unresolved. However, due to the wide variety of clinical syndromes and oncogenic potency of the *Epstein-Barr virus*, it should be extremely cautious and sometimes extend the diagnostics beyond normal searches.

## SAŽETAK

**Uvod:** Infektivna mononukleoza je jedan od najučestalijih sindroma koji se sreće u kliničkoj praksi. Karakteriše ga prisustvo povišene temperature, faringitisa i generalizovane limfadenopatije.

**Cilj:** Opisati kliničku sliku infektivne mononukleoze uzrokovane Epstein Barr virusom (EBV) u pacijentkinje splenektomirane zbog idiopatske trombocitopenije s obzirom da u literaturi nema dovoljno podataka (svega tri rada na navedenu temu).

**Isplanici i metode:** Retrospektivna analiza medicinske dokumentacije pacijentice liječene u Klinici za infektivne bolesti Univerzitetsko kliničkog centra Republike Srpske.

**Rezultati:** Prikazali smo slučaj infektivne mononukleoze, serološki verifikovane primoinfekcije EBV, kod splenektomirane pacijentkinje. U prilog akutne EBV virusne infekcije govorili su prisustvo limfadenopatije, faringitisa, hepatomegalija, te pojava tipičnog generalizovanog makulopapuloznog egzantema, kao i serološki verifikovani pozitivni anti EBV VCA IgM i anti EBV VCA/EA IgG. Prema navedenom, pacijentkinja je ispunjavala većinu kriterija za postavljanje dijagnoze akutne EBV infektivne mononukleoze. Naša pacijentkinja je pokazala neke atipične simptome kao što je odsustvo febriliteta tokom hospitalizacije, izrazitu leukocitozu sa limfocitozom (sa maksimalnim porastom vrijednosti leukocita na  $37.3 \times 10^9$ ; a u diferencijalnoj krvnoj slici dominirali su limfociti sa  $29.96 \times 10^9$  (referentne vrijednosti 1.1-3.35), tj. 80,3% (ref. vrijednosti 20.0-46.0). Zbog održavanja leukocitoze sa limfocitozom proširen je dijapazon kliničkih pretraga (UZV abdomena, UZV vrata, CT vrata, grudnog koša, abdomena i male karlice, sternalna punkcija, konsultacija hematologa). Na osnovu učinjenih pretraga i konsultacije, te praćenja po otpustu dolazi do potpune regresije laboratorijskih analiza i oporavka pacijentkinje.

**Zaključak:** Zbog nedovoljno podataka o kliničkoj prezentaciji Epstein Barr virusne infekcije u splenektomiranih mišljenja smo da je ovo jedna od kliničkih varijanti iako mogućnost individualne varijacije ne može biti isključena. Ukratko, možemo zaključiti da imunološki sistem u splenektomiranog pacijenta može uveliko izmjeniti kliničku prezentaciju EBV infekcije s tim da je sam patogenetski mehanizam i dalje nerazjašnjen. Međutim, zbog šarolikosti kliničkih



sindroma i onkogene potentnosti Epstein-Barr virusa treba biti izuzetno oprezan i ponekad proširti dijagnostiku van uobičajenih pretraga.

**Ključne riječi:** Infektivna mononukleoza, splenektomija, Epstein-Barr virus, kliničke karakteristike

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