Splenic infarction in patients with Epstein-Barr virus infectious mononucleosis-case reports and literature review

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Splenic infarction in patients with Epstein-Barr virus infectious mononucleosis-case reports and literature review

Infarkt slezene u bolesnika s Epstein-Barr virusnom mononukleozom – prikaz slučajeva i pregled literature

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Summary

Introduction: Epstein-Barr virus (EBV) is one of the most common herpes viruses in humans with over 90% of adults demonstrating antibodies to EBV. Infectious mononucleosis (IM) is the most frequently occurring clinical presentation of EBV infection and typically presents with fever, tonsillitis/pharyngitis, cervical lymph node enlargement and tenderness and fatigue. Splenomegaly is also part of the clinical presentation. Splenic infarction (SI) due to IM is rare but its exact frequency is unknown.

Methods: We present two cases of SI accompanying IM caused by EBV in young adults without underlying comorbidities together with a literature review of this topic. Literature search included journal articles describing splenic infarctions confirmed by CT or MRI associated with IM due to EBV infection published in English between 2005 and 2024 in PubMed. A total of 32 case reports presenting 34 patients were selected for detailed analysis.

Results: Among 34 patients, 58,8% were males and the median age was 20.97 years. Only 26.5% of patients had some chronic disease, the most common one being hereditary spherocytosis present in four patients. The most common symptoms were: fever (82.4%), abdominal pain (88.2%) localized mostly in the left upper abdomen and splenomegaly (50%).

Conclusion: Our overall conclusion is that establishing the diagnosis of SI does not change the therapeutic approach in most cases and that symptomatic treatment is sufficient.

In the future, greater availability of abdominal imagining methods and a higher index of suspicion will lead to more accurate data about SI.

Keywords: splenic infarction; Epstein-Barr virus; infectious mononucleosis; case reports; literature review

Sažetak

Uvod: Epstein-Barr virus (EBV) jedna je od najčešćih herpes virusnih infekcija u ljudi, a više od 90% odraslih ima prisutna protutijela na EBV. Infektivna mononukleoza (IM) najčešća je klinička manifestacija EBV infekcije koja se obično manifestira vrućicom, tonzilitisom/faringitisom, povećanim i bolnim cervikalnim limfnim čvorovima, te umorom. Splenomegalija je također dio kliničke slike. Infarkti slezene (IS) tijekom IM pojavljuju se rijetko, a stvarna učestalost nije poznata.

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Metode: U ovom radu prikazana su dva slučaja IS tijekom IM uzrokovan EBV-om u mladih odraslih osoba bez komorbiditeta, zajedno s pregledom literature o ovoj temi. U pretraživanje literature uključeni su članci iz časopisa koji opisuju infarkte slezene potvrđene CT-om ili MRI-om, povezane s IM-om, uzrokovane EBV-om, te objavljene na engleskom jeziku između 2005. i 2024. u PubMed-u. Za detaljnu analizu odabrana su ukupno 32 prikaza slučaja s 34 bolesnika.

Rezultati: Od 34 bolesnika, 58,8% njih bili su muškarci, a medijan dobi bio je 20,97 godina. Samo 26,5% bolesnika imalo je neku kroničnu bolest, a najčešća je bila nasljedna sferocitoza prisutna u četiri bolesnika. Najčešći simptomi bili su: povišena tjelesna temperatura (82,4%), bolovi u trbuhu (88,2%) lokalizirani pretežno u lijevom gornjem dijelu trbuha i splenomegalija (50%).

Zaključak: Postavljanje dijagnoze IS u većini slučajeva ne mijenja terapijski pristup, te je dovoljno simptomatsko liječenje. U budućnosti će sve veća dostupnost slikovnih pretraga abdomena i veća svijest o postojanju te bolesti sigurno dovesti do točnijih podataka o IS.

Ključne riječi: infarkt slezene; Virus Epstein-Barr; infektivna mononukleoza; prikazi slučajeva; pregled literature

Introduction

Epstein-Barr virus (EBV) is one of the most common herpes viruses in humans. It is spread through intimate contact between asymptomatic or symptomatic EBV shedders and susceptible persons. Antibodies to EBV have been demonstrated in over 90% of adults worldwide [1,2]. Most primary EBV infections that occur during childhood are subclinical. Infectious mononucleosis (IM) is the most common clinical presentation of EBV infection and usually occurs in adolescents and adults. After primary infection, both asymptomatic and symptomatic, EBV persists asymptomatically for life by establishing latent infection of B lymphocytes.[1,3,4]

A typical clinical presentation of IM includes fever, tonsillitis/pharyngitis, cervical lymph node enlargement and tenderness and fatigue.[1,3,5]

However, EBV can affect any organ system and has been associated with a variety of clinical presentations, some of which are present more often than others.

Splenomegaly is also part of the clinical presentation of IM, but the frequency of its occurrence is reported unevenly. For example, Rea TD et al. reported that only 8% of observed patients with IM had splenomegaly.[5] In contrast, earlier studies of Domerby H et al. demonstrated that all patients had an enlarged spleen but palpable in only a few [6]. Hosey RG et al. also reported an enlarged spleen in all participants of their study which included young athletes with IM.[7] Somewhere in between are the data published by Hoagland RJ in which splenomegaly was present in about one half of all analysed cases (52%) over the course of the illness.[8]

Splenic infarction (SI) due to IM is rare and its exact frequency is unknown due to underreporting or underdiagnosing.

Clinical manifestation of SI includes abdominal pain, fever, and tachycardia but even abdominal pain as the most consistent symptom is present in only half of the cases.[9] Therefore, a high index of suspicion is needed to confirm this diagnosis.

As abdominal pain is uncommon in IM, splenic rupture, which is also a rare but possibly lethal complication of IM, must be strongly considered whenever abdominal pain occurs.[10]

To establish the diagnosis of IM, routine laboratory tests are used together with specific tests for EBV.

In laboratory findings, peripheral blood lymphocytosis with atypical lymphocytes (defined as more than 10% of total lymphocytes), together with elevated aminotransferases (seen in the vast majority of patients), are present.[11]

The detection of EBV-specific antibodies is the gold standard for the diagnosis of IM. EBV serostatus can be defined by the presence of IgM and IgG antibodies against EBV viral capsid antigen (VCA), IgG against early antigen-diffuse (EA-(D)) and IgG against EBV nuclear antigen (EBNA). Acute infection is characterized by the presence of IgM anti-VCA and anti-EA(D) IgG without antibodies against EBNA.[12] EBV deoxyribonucleic acid (DNA) can be detected and quantified by polymerase chain reaction (PCR) assays on blood or plasma [13,14] which is positive in 40-70% of patients at symptom onset and in up to 90% of patients two weeks after disease onset.[15]

If splenic involvement is suspected, abdominal ultrasound should be performed, but to confirm the diagnosis of SI, a computed tomography (CT) or magnetic resonance imaging (MRI) is indicated [9].

We present two cases of SI accompanying IM caused by EBV in young adults without underlying comorbidities together with a literature review of this topic.

Case presentations

Case 1

A 34-year-old male presented with fever of up to 38.5°C starting 11 days prior to admission, accompanied with chills and malaise. He also reported lower back pain and flatulence with loose stools, and two days prior to admission he noticed dark urine and developed scleral icterus.

His past medical history was unremarkable except for obesity, with BMI at admission of 40.6 kg/m^2, and he was smoking up to 40 cigarettes per day.

The physical examination revealed icterus of the sclera and skin as well as hepatos plenomegaly without palpatory tenderness of the abdomen.

Laboratory tests on admission showed elevated acute phase reactants with erythrocyte sedimentation rate of 30 mm/h and C-reactive protein (CRP) of 107.3 mg/L. The white blood cell count (WBC) was 11.6 ×10^9/L with 24% of lymphocytes and 18% of atypical lymphocytes on peripheral blood smear, with red blood cell and thrombocyte counts within normal ranges. Clotting profile showed elevated fibrinogen of 4.4 g/L and D-dimers of >4.30 mg/L with normal values of prothrombin time, activated partial thromboplastin time and thrombin time. Bilirubin was elevated (96 µmol/L, direct 53 µmol/L, indirect 43 µmol/L) along with liver function tests (aspartate aminotransferase (AST) 164 U/L, alanine aminotransferase (ALT) 235 U/L, gamma-glutamyl transferase 478 U/L, alkaline phosphatase (AP) 165 U/L) and elevated lactate dehydrogenase (LDH) of 994 U/L.

A CT scan of the abdomen and pelvis with contrast revealed as teatotic, enlarged liver with a diameter of 25 cm in the medial clavicular line and splenomegaly with a sagittal diameter of 16.5 cm, with multiple subcapsular infarctions ranging from 2 to 4 cm as shown in Figure 1.

Blood cultures were negative while transthoracic and transoesophageal cardiac ultrasound revealed no signs of infective endocarditis.

Extensive screening for infectious diseases was negative for HIV and viral hepatitis, leptospirosis, tularemia, haemorrhagic fever with renal syndrome, bartonellosis, SARS CoV-2 and CMV but revealed an acute EBV infection with positive VCA IgM and IgG and borderline result of EA IgG. Acute EBV infection was confirmed by PCR of blood and 17 300 copies of viral DNA/mL were detected.

Flow cytometry of peripheral blood showed an elevated T lymphocyte count of7219/µL or 93.8% with elevated CD8+ T lymphocytes and lowered B lymphocyte count of 27 or 0.4%, which was consistent with the diagnosis of IM. The screen for thrombophilia was negative. All relevant laboratory findings are listed in Table 1.

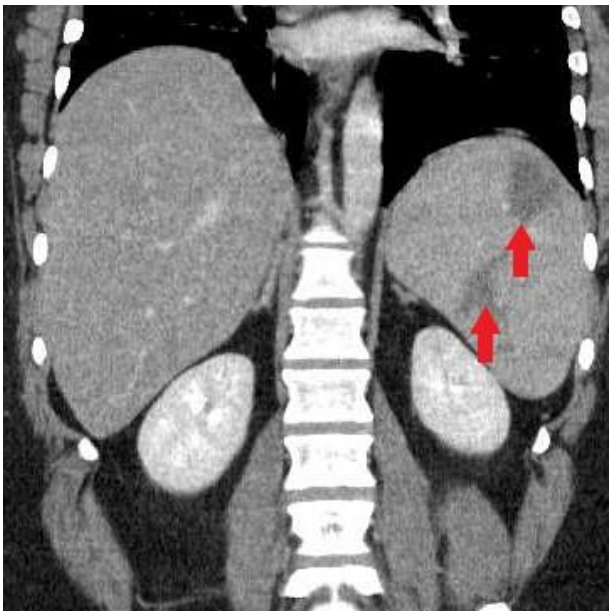

Figure 1 The coronal view of contrast enhanced abdominal CT in a 34-year-old male, demonstrated two well-demarcated wedge shape (arrows) and several small round shape low-density areas (arrowheads) in the spleen, consistent with splenic infarctions.
Slika 1. Koronarni prikaz CT-a abdomena s kontrastom u 34-godišnjeg muškarca pokazuje dvije dobro omeđene klinaste promjene (strelice) i nekoliko malih okruglih područja niske gustoće (vrhovi strelica) u slezeni, koji odgovaraju infarktima slezene.

The patient received empirical parenteral antibiotic treatment with ceftriaxone and metronidazole because intrabdominal infection was suspected, along with thromboprophylaxis with enoxaparin subcutaneously and other supportive measures. He was discharged after 13 days with the recommendation to continue anticoagulant therapy with rivaroxaban for three months and strict bed rest.

On follow-up, three weeks after discharge, the patient was afebrile and feeling better with a decrease in liver function tests and lactate dehydrogenase levels accompanied with a slight decrease of splenomegaly (14 cm) on abdominal ultrasound, but with still visible multiple hypoechogenic infarctions. After six months, the control abdominal ultrasound was normal.

Table 1 Selected laboratory findings of patients
Tablica 1. Odabrani laboratorijski nalazi prikazanih bolesnika

	Case 1 *Bolesnik 1*	**Case 2** *Bolesnik 2*	**Normal range** *Referentne vrijednosti*
C-reactive protein *C-reaktivni protein*	107.3	13.0	<5.0 mg/L
Leukocytes *Leukociti*	11.6	9.3	3.4-9-7 x10^9/L
Lymphocytes *Limfociti*	46 %	38%	20-46 %
Reactive lymphocytes *Reaktivni limfociti*	24%	28%	
Haemoglobin *Hemoglobin*	133	122	119-157 g/L
Platelets *Trombociti*	172	91	158-424 x10^9/L
Bilirubin *Bilirubin*	96	131	3-20 µmol/L
AST *AST*	164	630	11-38 U/L
ALT *ALT*	235	792	12-48 U/L
GGT *GGT*	478	405	11-55 U/L
AP *AF*	165	251	60-142 U/L
LDH *LDH*	994	896	> 241 U/L
PT / INR *PV/INR*	0.75/1.17	0.83/1.12	>0.70
APTT *APTV*	26.1	27.6	23-36 s
TT *TV*	16.6	/	16-21 s
Fibrinogen *Fibrinogen*	4.4	2.4	1.8-3.5 g/L
D-dimers *D-dimeri*	>4.30	>4.28	<0.55 mg/L
EBV VCA IgM	+	+	
EBV VCA IgG	-	+	
EA IgG	Borderline *Graničan*	+	
EBNA IgG	-	-	
EBV DNA PCR blood *EBV DNA PCR krv*	17 300	22 800	<1000 copies/mL of blood *<1000 kopija/mL krvi*

AST- aspartate aminotransferase; ALT- alanine aminotransferase; GGT- gamma-glutamyl transferase; ALP- alkaline phosphatase; LDH- lactate dehydrogenase; PT- prothrombin time; APTT- activated partial thromboplastin time; TT- thromboplastin time; EA – early antigen; EBNA – Epstein Barr nuclear antigen; VCA – viral capsid antigen
AST- aspartatam inotransferaza; ALT- alaninam inotransferaza; GGT- gamma-glutamil transferaza; AF- alkalna fosfataza; LDH- laktat dehidrogenaza; PV- protrombinsko vrijeme; APTV- aktivno parcijalno tromboplastinsko vrijeme; TV- tromboplastinsko vrijeme;EA – rani antigen; EBNA – Epstein Barr nuklearni antigen, VCA – virusni kapsidni antigen

Case 2

A 36-year-old female was admitted on the 9th day of illness which presented with fever of up to 39°C accompanied with sore throat and abdominal pain in the upper left and right quadrant worsening on inspiration. The day before hospital admission, she noticed scleral icterus along with dark urine and

reported several episodes of vomiting.

Except for being a smoker (10 cigarettes per day) and a tonsillectomy in childhood, she had no significant prior illnesses.

On physical examination, she was afebrile, with scleral icterus, pharyngeal injection without exudate and tender, mildly enlarged cervical lymph nodes up to 1.5 cm. Spleen was palpable but without abdominal tenderness.

Routine laboratory tests revealed a CRP of 13.0 mg/L, a WBC of 9.3×10^9/L with 38% of lymphocytes and 28% of reactive lymphocytes on peripheral blood smear. The red blood cell count was normal with thrombocytopenia of 91×10^9/L. The clotting profile showed elevated D-dimers of >4.28 mg/L while fibrinogen, prothrombin time, activated partial thromboplastin time and thrombin time were within normal ranges. The patient also had elevated serum bilirubin of 131 µmol/L (direct 83, indirect 48 µmol/L) and hepatic lesion with AST 630 U/L, ALT 792 U/L, GGT 405 U/L, AP 251 U/L and LDG 896 U/L. All relevant laboratory findings are listed in Table 1.

A CT scan of the abdomen with contrast revealed hepatomegaly with craniocaudal diameter of 20 cm, without parenchymal lesions and splenomegaly of 18×10.5×7.5 cm with multiple hypovascular and avascular subcapsular zones, the largest of which measured 2x3 cm as shown in Figure 2.

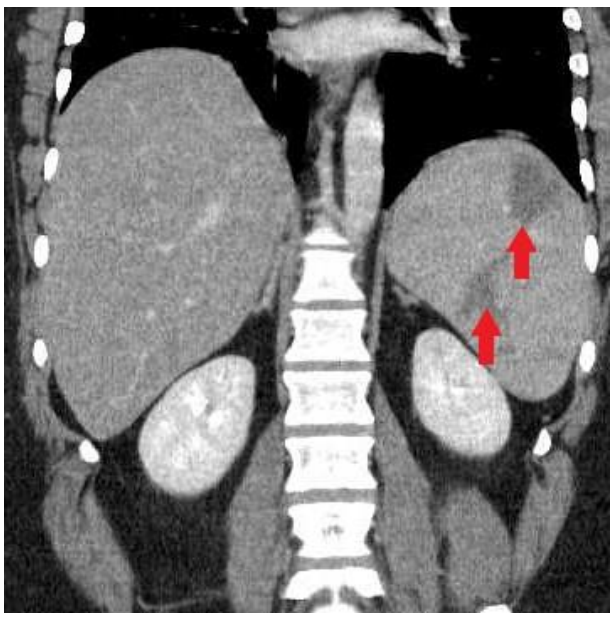

Figure 2 The coronal view of contrast enhanced abdominal CT in a 36-year-old female, demonstrated two well-demarcated triangular hypodense areas in the spleen (arrows), representing splenic infarction.

Slika 2. Koronarni prikaz CT-a abdomena s kontrastom u 36-godišnje žene, pokazuje dva dobro omeđena trokutasta hipodenzna područja u slezeni (strelice), što predstavlja infarkt slezene.

Blood cultures were negative as well as testing for HIV, viral hepatitis viruses and leptospirosis.

Serological testing for CMV and EBV virus revealed borderline IgM for CMV and positive VCA IgM and IgG together with positive EA IgG and negative EBNA IgG which suggested acute EBV infection.

The diagnosis was further confirmed with PCR of blood which revealed 22 800 copies of EBV DNA per ml of blood. The flow cytometry of peripheral blood was also consistent with infectious mononucleosis. The screen for thrombophilia was negative. The patient received only symptomatic treatment and was discharged after six days. After six months, the control abdominal ultrasound was normal.

Literature review

A review of the literature was conducted by searching English articles on splenic infarction confirmed by CT or MRI associated with IM due to EBV infection, published between 2005 and 2024 in PubMed. The keywords „Epstein-Barr virus AND splenic infarction “OR „Infectious mononucleosis AND splenic infarction” were used. A total of32 case reports that presented 34 patients were selected for detailed analysis.[16-47] Characteristics of patients presented in these articles are listed in Table 2.

Among 34 patients, there were 20 males (58.8%) and the median age was 20.97 years (range, 7-40 years). Only nine patients had some chronic diseases (26.5%) with the most common one being hereditary spherocytosis present in four patients. The most common symptoms that were highly suggestive for splenic involvement in EBV IM were as follows: fever in 28 (82.4%) patients; abdominal pain in 30 (88.2%) patients (left upper abdominal pain or tenderness in 22 (64.7%); unspecified abdominal pain in three; epigastric pain in two; right upper abdominal pain in two and upper abdominal pain in one patient); splenomegaly in 17 (50%) patients; nausea/vomiting in five (14.7%); fatigue in eight (23.5%) and general symptoms in four (11.8%) patients.

In all but one patient EBV infection was confirmed by serological testing, and in eight (23.5%) patients also by positive PCR DNA blood test.

The final diagnosis was made by CT in 29 (85.3%) patients and by MRI in five patients.

Only one patient underwent splenectomy, others were only treated using conservative methods and symptomatic treatment.

Table 2 Characteristics of patients with splenic infarction in EBV infectious mononucleosis
Tablica 2. Karakteristike bolesnika s infarktom slezene tijekom EBV infektivne mononukleoze

Reference *Referenca*	**No. of Cases** *Broj bolesnika*	**Age/Sex/Race** Dob/Spol/Rasa	**Symptoms/ Signs of Splenic Involvement** *Simptomi/znakovi zahvaćenosti jetre*	**Chronic Disease/ Concomitant Infection** *Kronične bolesti/konkomitantne infekcije*	**Serology** *Serologija*	**PCR Copies/Ml PCR Kopije/Ml**	**Method of Confirmation of SI** *Dijagnostička metoda za IS*	**Treatment Method** *Način liječenja*
Ma Z et al. (2016)	1	19/F/Chinese *19/Ž/Kineskinja*	Fever, splenomegaly, tenderness in LUA *Temperatura, splenomegalija, osjetljivost u LGA*	Hereditary spherocytosis *Hereditarna sferocitoza*	EBV VCA IgM + EBV VCA IgG + EA IgG + EBNA IgG +	NP *NU*	CT *CT*	Splenectomy *Splenektomija*
Wang XL et al. (2023)	1	8/F/Chinese *8/Ž/Kineskinja*	Fever, splenomegaly, UA pain *Temperatura, splenomegalija, bol u GA*	None *Ništa*	EBV VCA IgM + EBV VCA IgG + EA IgG - EBNA IgG -	281	MRI *NMR*	Conservative *Konzervativno*
Kana T et al. (2023)	1	29/M/NA *29/M/NP*	Fever, general symptoms, fatigue, splenomegaly, LUA pain *Temperatura, opći simptomi, umor, splenomegalija, bol u LGA*	Morbid obesity Acute CMV infection *Morbidna pretilost Akutna CMV infekcija*	EBV VCA IgM + EBV VCA IgG + EA IgG NA/*NP* EBNA IgG +	NP *NU*	CT *CT*	Conservative *Konzervativno*
Jeong JE et al. (2018)	1	16/F/NA *16/Ž/NP*	Fever, fatigue, epigastric pain, splenomegaly *Temperatura, umor, bol u epigastriju, splenomegalija*	None *Ništa*	EBV VCA IgM + EBV VCA IgG NA EA IgG NA/*NP* EBNA IgG NA/*NP*	10828	CT *CT*	Conservative *Konzervativno*
Nishioka H et al. (2021)	1	19/M/Japanese *19/M/Japanac*	Fever, LUA and epigastric pain *Tempertura, bol u LGA iepigastriju*	None *Ništa*	EBV VCA IgM + EBV VCA IgG + EA IgG NA/*NP* EBNA IgG -	NP *NU*	CT *CT*	Conservative *Konzervativno*

Reference *Referenca*	**No. of Cases** *Broj bolesnika*	**Age/Sex/Race** Dob/Spol/Rasa	**Symptoms/ Signs of Splenic Involvement** *Simptomi/znakovi zahvaćenosti jetre*	**Chronic Disease/ Concomitant Infection** *Kronične bolesti/konkomitantne infekcije*	**Serology** *Serologija*	**PCR Copies/Ml PCR Kopije/Ml**	**Method of Confirmation of SI** *Dijagnostička metoda za IS*	**Treatment Method** *Način liječenja*
Heo DH et al. (2017)	1	20/F/NA *20/F/NP*	Fever, abdominal pain *Temperatura, bol u abdomenu*	None *Ništa*	EBV VCA IgM + EBV VCA IgG - EA IgG NA/*NP* EBNA IgG -	NP *NU*	CT *CT*	Conservative *Konzervativno*
Kobayashi K et al. (2023)	1	31/M/NA *31/M/NP*	Fever, RUA pain *Temperatura, bol u DGA*	None *Ništa*	EBV VCA IgM + EBV VCA IgG - EA IgG NA/*NP* EBNA IgG -	NP *NU*	CT *CT*	Conservative *Konzervativno*
Gavriilaki E et al. (2013)	1	17/M/NA *17/M/NP*	Fever, LUA pain, splenomegaly *Temperatura, bol u LGA, splenomegalija*	None *Ništa*	EBV VCA IgM + EBV VCA IgG NA/*NP* EA IgG NA/*NP* EBNA IgG NA/*NP*	NP *NU*	MRI *NMR*	Conservative *Konzervativno*
Gang MH et al. (2013)	1	7/F/NA *7/Ž/NP*	Fever, RUA and periumbilical pain, splenomegaly *Temperatura, bol u DGA iperiumbilikalno, splenomegalija*	None *Ništa*	EBV VCA IgM + EBV VCA IgG - EA IgG NA/*NP* EBNA IgG -	Positive *Pozitivno*	CT *CT*	Conservative *Konzervativno*
Li Y et al. (2014)	1	19/F/Hispanic *19/Ž/Latinoamerikanka*	Fever, general symptoms, severe abdominal pain, vomiting, splenomegaly *Temperatura, opći simptomi, izražena bol u abdomenu, povraćanje, splenomegalija*	Coinfection CMV and *My. pneumoniae* *Koinfekcija CMV i My. pneumoniae*	EBV VCA IgM + EBV VCA IgG NA/*NP* EA IgG + EBNA IgG NA/*NP*	NP *NU*	CT *CT*	Conservative *Konzervativno*
Kobayashi T et al. (2024)	1	17/F/NA *17/Ž/NP*	Fever, fatigue, epigastric pain, splenomegaly	None *Ništa*	EBV VCA IgM + EBV VCA IgG NA/*NP*	NP *NU*	CT *CT*	Conservative *Konzervativno*

Reference *Referenca*	**No. of Cases** *Broj bolesnika*	**Age/Sex/Race** Dob/Spol/Rasa	**Symptoms/ Signs of Splenic Involvement** *Simptomi/znakovi zahvaćenosti jetre*	**Chronic Disease/ Concomitant Infection** *Kronične bolesti/konkomitantne infekcije*	**Serology** *Serologija*	**PCR Copies/Ml PCR Kopije/Ml**	**Method of Confirmation of SI** *Dijagnostička metoda za IS*	**Treatment Method** *Način liječenja*
			Temperatura, umor, bol u epigastriju, splenomegalija		EA IgG NA/*NP* EBNA IgG NA/*NP*			
Suzuki Y et al (2007)	1	18/M/Japanese *18/M/Japanac*	Fever, splenomegaly *Temperatura, splenomegalija*	Hereditary spherocytosis *Hereditarna sferocitoza*	EBV VCA IgM + EBV VCA IgG + EA IgG + EBNA IgG -	NP *NU*	CT *CT*	Conservative *Konzervativno*
Hasibi M et al. (2021)	1	28/M/NA *28/M/NP*	Fever, splenomegaly *Temperatura, splenomegalija*	None *Ništa*	EBV VCA IgM + EBV VCA IgG NA/*NP* EA IgG NA/*NP* EBNA IgG NA/*NP*	NP *NU*	CT *CT*	Conservative *Konzervativno*
Nofal R et al. (2019)	1	7/M/African American *7/M/Afroamerikanac*	Fever, LUA pain, splenomegaly *Temperatura, bol u LGA, splenomegalija*	Sickle cell trait *Bolest srpastih stanica*	EBV VCA IgM + EBV VCA IgG + EA IgG NA/*NP* EBNA IgG NA/*NP*	NP *NU*	MRI *NMR*	Conservative *Konzervativno*
Li Y et al. (2018)	3	24/F/NA *24/Ž/NP*	Fever, severe LUA pain, nausea *Temperatura, jaka bol u LGA, mučnina*	Crohn's disease, Hashimoto's thyroiditis, sacroiliitis *Chronova bolest, Hashimoto tireoiditis, sakroileitis*	EBV VCA IgM + EBV VCA IgG + EA IgG NA/*NP* EBNA IgG-	NP *NU*	CT *CT*	Conservative *Konzervativno*
		20/M/NA *20/M/NP*	LUA pain, nausea *Bol u LGA, mučnina*	None *Ništa*	Positive heterophile antibody *Pozitivna heterofilna protutijela*	NP *NU*	CT *CT*	Conservative *Konzervativno*
		27/M/NA *27/M/NP*	Fever, LUA pain, general symptoms, nausea, splenomegaly *Temperatura, bol u LGA, opći simptomi,*	None *Ništa*	Positive heterophile antibody *Pozitivna heterofilna protutijela*	NP *NU*	CT *CT*	Conservative *Konzervativno*

Reference *Referenca*	**No. of Cases** *Broj bolesnika*	**Age/Sex/Race** Dob/Spol/Rasa	**Symptoms/ Signs of Splenic Involvement** *Simptomi/znakovi zahvaćenosti jetre*	**Chronic Disease/ Concomitant Infection** *Kronične bolesti/konkomitantne infekcije*	**Serology** *Serologija*	**PCR Copies/Ml PCR Kopije/Ml**	**Method of Confirmation of SI** *Dijagnostička metoda za IS*	**Treatment Method** *Način liječenja*
			mučnina, splenomegalija					
van Hal S et al. (2005)	1	35/F/Caucasian *35/Ž/Bjelkinja*	Fever, LUA tenderness *Temperatura, osjetljivost u LGA*	None *Ništa*	EBV VCA IgM + EBV VCA IgG + EA IgG NA/*NP* EBNA IgG -	NP *NU*	CT *CT*	Conservative *Konzervativno*
Khan S et al. (2019)	1	30/M/NA *30/M/NP*	Fatigue, abdominal pain *Umor, bol u abdomenu*	None *Ništa*	EBV VCA IgM + EBV VCA IgG - EA IgG - EBNA IgG -	Positive *Pozitivno*	CT *CT*	Conservative *Konzervativno*
Machado C et al. (2015)	1	24/M/NA *24/M/NP*	Fever, general symptoms, LUA pain *Temperatura, opći simptomi, bol u LGA*	None *Ništa*	EBV VCA IgM + EBV VCA IgG - EA IgG NA/*NP* EBNA IgG NA/*NP*	NP *NU*	CT *CT*	Conservative *Konzervativno*
Thida AM et al. (2020)	1	19/F/African American *19/Ž/Afroamerikanka*	LUA pain, malaise, nausea, splenomegaly *Bol u LGA, slabost, mučnina, splenomegalija*	Hereditary spherocytosis *Hereditarna sferocitoza*	EBV VCA IgM + EBV VCA IgG + EA IgG + EBNA IgG -	NP *NU*	CT *CT*	Conservative *Konzervativno*
Batista M et al. (2023)	1	20/M/NA *20/M/NP*	Fever, general symptoms *Temperatura, opći simptomi*	None *Ništa*	EBV VCA IgM + EBV VCA IgG + EA IgG NA/*NP* EBNA IgG NA/*NP*	NP *NU*	CT *CT*	Conservative *Konzervativno*
Naviglio S et al. (2016)	1	14/M/NA *14/M/NP*	Fever, LUA pain, splenomegaly *Temperatura, bol u LGA, splenomegalija*	None *Ništa*	NA (Serologic tests confirmed the diagnose) *NP (dijagnoza je potvrđena serološkim testovima)*	19956	MRI *NMR*	Conservative *Konzervativno*

Reference *Referenca*	**No. of Cases** *Broj bolesnika*	**Age/Sex/Race** Dob/Spol/Rasa	**Symptoms/ Signs of Splenic Involvement** *Simptomi/znakovi zahvaćenosti jetre*	**Chronic Disease/ Concomitant Infection** *Kronične bolesti/konkomitantne infekcije*	**Serology** *Serologija*	**PCR Copies/Ml PCR Kopije/Ml**	**Method of Confirmation of SI** *Dijagnostička metoda za IS*	**Treatment Method** *Način liječenja*
Breuer C et al. (2008)	1	13/M/Caucasian *13/M/Bjelac*	Fever, LUA pain, splenomegaly *Temperatura, bol u LGA, splenomegalija*	Hereditary spherocytosis *Hereditarna sferocitoza*	EBV VCA IgM + EBV VCA IgG NA/*NP* EA IgG NA/*NP* EBNA IgG NA/*NP*	Positive *Pozitivno*	MRI *NMR*	Conservative *Konzervativno*
Reichlin M et al. (2022)	1	17/M/NA *17/M/NP*	LUA pain, diarrheal *Bol u LGA, proljev*	None *Ništa*	EBV VCA IgM + EBV VCA IgG - EA IgG NA/*NP* EBNA IgG NA/*NP*	NP *NU*	CT *CT*	Conservative *Konzervativno*
Mamo G et al. (2023)	1	32/M/NA *32/M/NP*	Fever, fatigue, LUA pain *Temperatura, umor, bol u LGA*	Obesity, depression, PTSD, migraine *Debljina, PTSP, migrena*	EBV VCA IgM + EBV VCA IgG - EA IgG - EBNA IgG -	NP *NU*	CT *CT*	Conservative *Konzervativno*
Pervez H et al. (2020)	1	20/M/NA *20/M/NP*	Fever, LUA pain, malaise *Temperatura, bol u LGA, slabost*	None *Ništa*	EBV VCA IgM + EBV VCA IgG NA/*NP* EA IgG NA/*NP* EBNA IgG NA/*NP*	NP *NU*	CT *CT*	Conservative *Konzervativno*
Kensey NL et al. (2023)	1	36/M/NA *36/M/NP*	Fever, LUA pain *Temperatura, bol u LGA*	None *Ništa*	Positive heterophile antibody *Pozitivna heterofilna protutijela*	NP *NU*	CT *CT*	Conservative *Konzervativno*
Suzuki Y et al. (2018)	1	22/M/NA *22/M/NP*	Fever, fatigue, LUA pain *Temperatura, umor, bol u LGA*	None *Ništa*	NP *NU*	Positive *Pozitivno*	CT *CT*	Conservative *Konzervativno*
Bhattarai P et al. (2014)	1	16/M/NA *16/M/NP*	Epigastric pain *Bol u epigastriju*	None *Ništa*	Positive heterophile antibody *Pozitivna heterofilna protutijela*	NP *NU*	CT *CT*	Conservative *Konzervativno*

Reference *Referenca*	**No. of Cases** *Broj bolesnika*	**Age/Sex/Race** Dob/Spol/Rasa	**Symptoms/ Signs of Splenic Involvement** *Simptomi/znakovi zahvaćenosti jetre*	**Chronic Disease/ Concomitant Infection** *Kronične bolesti/konkomitantne infekcije*	**Serology** *Serologija*	**PCR Copies/Ml PCR Kopije/Ml**	**Method of Confirmation of SI** *Dijagnostička metoda za IS*	**Treatment Method** *Način liječenja*
Benz R et al. (2007)	1	19/F/NA *19/Ž/NP*	Fever, LUA pain, splenomegaly *Temperatura, bol u LGA, splenomegalija*	None *Ništa*	Positive heterophile antibody *Pozitivna heterofilna protutijela*	NP *NU*	CT *CT*	Conservative *Konzervativno*
Cull E et al. (2012)	1	18/F/NA *18/Ž/NP*	Fatigue, LUA pain *Umor, bol u LGA*	None *Ništa*	Positive heterophile antibody *Pozitivna heterofilna protutijela*	NP *NU*	CT *CT*	Conservative *Konzervativno*
García-Vázquez J et al. (2017)	1	12/M/NA *12/M/NP*	Fever, LUA pain, splenomegaly *Temperatura, bol u LGA, splenomegalija*	None *Ništa*	EBV VCA IgM + EBV VCA IgG + EA IgG NA/*NP* EBNA IgG -	NP *NU*	CT *CT*	Conservative *Konzervativno*
Kim KM et al. (2005)	1	40/M/NA *40/M/NP*	Fever, fatigue, LUA pain *Temperatura, umor, bol u LGA*	None *Ništa*	Positive heterophile antibody *Pozitivna heterofilna protutijela*	Positive *Pozitivno*	CT *CT*	Conservative *Konzervativno*

Only one systemic literature review which investigated SI association with EBV was published in 2023 [48] and included articles published between 1970 and 2022. SI was described in 29 patients, predominantly young males (70%) and underlying haematological disease (hereditary spherocytosis and sickle cell trait) was observed in 21% of patients.

Discussion

EBV infection is one of the most common infections in humans. In IM, which is the most common clinical manifestation of primary EBV infection, the spleen, as the largest lymphatic organ in the body, is always involved. Although the spleen is not always palpable, splenomegaly can be detected by ultrasound. Complications affecting the spleen during IM, such as splenic rupture or SI, are extremely rare.[48]

SI occurs when splenic circulation (arterial and venous) is compromised, causing tissue ischemia. The vessel occlusion is usually caused by emboli as well as venous congestion by abnormal cells. The anatomic structure of the distal branches of the splenic artery which are noncommunicating end arteries leads to development of spleen infarcts when these distal branches occlude.

In IM, SI is caused by the infiltration of splenic parenchyma with lymphocytes and rapidly enlarging spleen with structural changes.[48] IM is among the causes of non-iatrogenic SI. The size and distribution of SI in patients with IM are variable, from small, focal infarcts to complete SI.

SI can be also associated with other infectious diseases, but studies are limited. In the retrospective study made by Im JH et al. (2020) that included 101 patients in a 10-year period, the most common causes of SI were: bacteremia (in 26 patients), malaria (in 12 patients), respiratory tract infections (in 11 patients), infective endocarditis (in 10 patients) and EBV infection confirmed in only one patient.[49]

SI is in general a very rare disease. The exact prevalence is unknown and a high index of suspicion is needed during the diagnostic process. The diagnosis of SI starts either with symptoms that indicate splenic involvement (usually abdominal pain), or the diagnosis of underlying diseases (cardioembolism, hypercoagulable state, hematologic disease). Due to increased availability of abdominal imaging, such as CT and MRI, SI is being diagnosed more frequently in patients with less specific symptoms, sometimes even in patients without symptoms. To illustrate this shift from symptomatic to asymptomatic SI, the results of two studies published with a gap of 11 years can be used. In a large multicentric study published in 2009, Antopolsky M et al.[50] reported that 80% of patients with SI during a 10-year period had characteristic symptoms such as abdominal pain, while in a retrospective observational study published in 2020, Brett AS et al.[51] reported that 33% of patients with SI presented without abdominal pain in a five-year period.

Imaging has a very important role in the diagnostics of SI. In our clinical settings, usually, the first routine diagnostic method in abdominal examination in patients with IM is ultrasound. This method has limited sensitivity and is operator-dependent, so very often splenic lesions are not detected. When they are visible and reported, they present as ill-defined, nodular, or wedge-shaped hypoechoic areas. Contrast-enhanced CT is the preferable diagnostic method, because of its high sensitivity. In the acute phase, the SI appears as a wedge shaped, hypodense area with no enhancement or poor enhancement. In the subacute phase, it may look like a cystic lesion, if liquefaction occurs. In the chronic phase infarct may completely disappear, or the involution of the non-functional parenchyma may be seen with fibrotic contraction of the infarct and progressive volume loss.[52] A MRI is not often used as an initial diagnostic method of SI. The infarcted area is usually wedge-shaped. The signal intensity is varying, according to the phase of the infarct.[52]

The treatment approach to SI depends on the underlying causative disease.[53] Since there is no specific treatment for EBV infection, patients can only be treated with symptomatic measures and means of supportive care.

The necessity of anticoagulant therapy in SI patients is still questionable due to the difference in pathogenic mechanisms. This therapy aims to achieve vessel recanalization and decrease mortality by preventing subsequent thromboembolic complications. Wand O et al.[54] demonstrated in their study that anticoagulant therapy in patients with SI was associated with decreased long-term mortality, but patients with active non-hematologic malignancy, hematologic disease and infective endocarditis were excluded. The use of anticoagulant therapy is even more questionable in patients with SI and EBV infection since there is no available data on the subject. One of our patients was treated with anticoagulant therapy and one was not, and the final result in both patients was the same in six months follow up-disappearance of the lesions.

The results of our literature review are similar to the results of other researchers; the majority of cases were young males, the most common underlying disease was hereditary spherocytosis and the most frequent symptoms indicating splenic involvement during IM were diffuse or left upper abdominal pain, splenomegaly and fever.[21,48]

Conclusion

SI in EBV infections is an uncommon and rare complication of IM and the available knowledge is mainly based on case reports. We describe two patients; one without characteristic symptoms of IM or splenic affection and one with classical symptoms of IM and left upper abdominal pain. The literature review indicated that fever, left upper abdominal pain and splenomegaly together with other symptoms of IM must arouse suspicion of a SI. Establishing the diagnosis of SI does not change the therapeutic approach in the majority of SI cases in EBV infection and symptomatic treatment is sufficient.

In the future, greater availability of abdominal imagining methods and a higher index of suspicion will lead to more accurate data about SI including underlying conditions/diseases, symptoms, diagnostic methods, treatment and prognosis.

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