CASE REPORT

The unexpected finding of a splenic infarction in a patient with infectious mononucleosis due to Epstein-Barr virus

Catarina Machado,¹ Joana Melo Salgado,² Leonor Monjardino¹

¹Department of Internal Medicine, Hospital de Santo Espírito da Ilha Terceira, Angra do Heroísmo, Portugal
²Unidade de Saúde da Ilha Terceira—Centro de Saúde de Angra do Heroísmo, Angra do Heroísmo, Portugal

Correspondence to
 Dr Catarina Machado,
 machado.cat@gmail.com

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SUMMARY

The authors present a case of a 24-year-old man with infectious mononucleosis (IM) due to Epstein-Barr virus (EBV). Among his symptoms, he reported abdominal pain in the upper left quadrant. An abdominal ultrasound and CT revealed an extensive splenic infarction. During the acute stage of this disease, the thrombophilic screening revealed reduced free protein S and elevated factor VIII, with normalisation on re-evaluation 6 weeks later. Splenic infarction is a very rare complication of IM due to EBV but should be considered in patients presenting abdominal pain. A hypercoagulability state should be investigated. To our knowledge, this is the first described case of a splenic infarction in a patient with IM due to EBV associated with a transient reduction of protein S and elevation of factor VIII. Thus, this work promotes the importance of including these factors in the thrombophilic screening conducted during the investigation of similar cases.

BACKGROUND

Epstein-Barr virus (EBV) is a widespread virus. By adulthood, the prevalence of positive antibodies in the population reaches 90–95%. It is the most common causative agent of infectious mononucleosis (IM), but can induce a wide spectrum of clinical presentations. In children, primary EBV infection is most commonly asymptomatic and the proportion of cases developing a clinically significant disease increases with age. Most cases have an uneventful recovery, but a wide range of complications have been reported.¹

The typical clinical manifestations of IM are fever, sore throat and lymphadenopathy.¹ Although uncommon (9%), abdominal pain can be the result of splenic enlargement and has been associated with splenic rupture,¹ a rare (0.1–0.5%) but potentially critical event.² Pain in the left upper abdominal quadrant is also the most common presenting symptom of splenic infarction, which may alternatively originate pain located in other areas of the abdomen; in some cases, it can even be painless.^{3–4}

Splenic infarction is an uncommon diagnosis.⁴ When a disorder of the spleen is suspected, such as a rupture or infarction, an ultrasound may have an important role in the diagnosis,⁵ as it can be performed quickly and with minimum stress to the patient. However, contrasted CT scan stands out as the best non-invasive diagnostic test for this condition, as ultrasound has demonstrated a low diagnostic capacity in some studies.⁴ The main causes

of splenic infarction are thromboembolism (of cardiovascular aetiology or as a result of a hypercoagulable state) and haematological diseases.⁴

Cases of splenic infarction have been described in patients with IM due to EBV where symptoms of abdominal pain were present. As there are few cases described, it remains a very rare complication of IM,³ and can pass unnoticed in this disease if appropriate investigation is not conducted.

CASE PRESENTATION

A 24-year-old man presented at the emergency department of our hospital, with a history of abdominal pain in the left upper quadrant, nausea and bilious vomiting, which had begun the previous day. He also presented a weeklong history of anorexia, asthenia, fever (39.5°C) (more severe in the afternoon), excessive sweating, headache and choluria, but denied other symptoms.

On examination, he was subicteric, well hydrated and tachycardic (101 bpm). The abdomen was tender at the right iliac region, without peritoneal signs. The remaining physical examination was unremarkable.

He had only a history of a left leg trauma and fracture at the age of nine, submitted for surgical correction, and no other medical conditions and no regular drug habits.

INVESTIGATIONS

Investigations revealed an elevated total white cell count, with a normal neutrophil count and lymphocytosis, slightly elevated prothrombin time and activated partial thromboplastin time, with normal international normalised ratio, elevated total bilirubin and direct bilirubin, aspartate transaminase, alanine transaminase, alkaline phosphatase, γ -glutamyl transpeptidase, lactate dehydrogenase and C reactive protein (table 1). Urine analysis had vestigial traces of bilirubin and was strongly positive for urobilinogen.

A diagnosis of viral hepatitis was hypothesised and the patient was admitted for surveillance and further study. Later, the patient developed symptoms of a sore throat and, on examination, a tonsillar enlargement and erythema with no exudate were observed.

Infectious mononucleosis due to acute EBV infection was confirmed by the serological results for EBV viral capsid antigen (EBV-VCA) with a positive IgM and negative IgG. Serologies

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Table 1 Laboratory values on admission

	Results on admission	Normal range
White cell count	17.67	4.1–9.1×10 ⁹ /L
Neutrophils	2.21 (12.5%)	2–7.5×10 ⁹ /L
Lymphocytes	13.99 (79.2%)	1.5–4.0×10 ⁹ /L
Prothrombin time	15.2	9.4–12.5 s
Activated partial thromboplastin time	43.1	25–36.5 s
International normalized ratio	1.2	
Total bilirubin	1.67	0.01–1 mg/dL
Direct bilirubin	1.15	0–0.2 mg/dL
Aspartate transaminase	243	<40 U/L
Alanine transaminase	446	<41 U/L
Alkaline phosphatase	191	35–129 U/L
γ-Glutamyl transpeptidase	226	5–61 U/L
Lactate dehydrogenase	1276	240–480 U/L
C reactive protein	12.87	0–5 mg/L

for cytomegalovirus, hepatitis B and C and HIV, were unremarkable.

As the patient continued to have abdominal pain, an ultrasound was performed, which revealed a normal sized liver, and an enlarged spleen with a heterogeneous and hypoechoic area on the inferior portion (figure 1). An abdominal CT scan was carried out revealing an enlarged spleen with an intact capsule and an extensive area of low density ranging from the hilus to the inferior portion, consistent with splenic infarction (figure 1).

A peripheral blood smear showed leucocytosis with reactive lymphocytes with no other changes. A coagulation profile demonstrated reduced free protein S of 55% (normal range 74–146%) and elevated factor VIII of 179% (normal range 50–150%), with unremarkable results for protein C, lupus anti-coagulant and haemoglobin electrophoresis.

OUTCOME AND FOLLOW-UP

During his hospital stay, the patient received symptomatic treatment with intravenous fluids, analgesia and antipyretics.

His condition improved, his temperature lowered and the fever subsided after 10 days. The abdominal pain markedly decreased in intensity and all other symptoms were resolved in the first week. Blood tests revealed a progressive decrease in the values of total white cell count, lymphocytes and liver function tests. The patient was discharged with an instruction to avoid sports activities, particularly strenuous contact sports, for the next 4 weeks.

Follow-up appointments with internal medicine in our outpatient clinic were scheduled, to which the patient presented completely asymptomatic.

Six weeks after discharge, a reassessment of the blood tests showed a return to within normal range of white cell count, liver function, protein S (78%) and factor VIII (89.9%). At this time, we conducted an autoimmune study and assessment of anticardiolipin, and anti-β₂ glycoprotein IgM and IgG, which were unremarkable. Genetic test results showed the patient to be heterozygous for the methylene tetrahydrofolate reductase (MTHFR C677T) mutation with unremarkable results on mutations of factor V Leiden and prothrombin.

Repeated serologies revealed positive results for EBV-VCA IgM and IgG at 6 weeks, and, at the fourth month, a negative VCA IgM and a higher titre of VCA IgG.

An abdominal ultrasound was repeated 2 months after discharge revealing a smaller but still enlarged spleen, and a small hypoechoic area of infarction in the inferior portion.

DISCUSSION

Infection by EBV complicated with splenic infarction has been reported in rare cases, and an article on a retrospective examination of splenic infarctions over a 10-year period identified EBV infection in 2 of 48 of the selected cases.⁴ The pathophysiological mechanisms leading to splenic infarction in patients with IM due to EBV are not completely clear and need to be further studied, but the small number of cases makes this a difficult task.

Of the previously reported cases, some were of patients in whom an underlying prothrombotic disorder was already known or in whom a diagnosis was performed during the study of the case: a patient with hereditary spherocytosis;⁶ a patient with known hereditary spherocytosis and new findings of persistently low levels of protein C activity, and antigen and transient low levels of factor II and VII;⁷ the diagnosis of a sickle cell trait in a previously healthy patient;⁸ and a case where antiphospholipid antibodies were detected during acute infection, and persisted.⁹

In three of the reported cases, the thrombophilic study was unremarkable.^{5 10 11} In two cases,^{12 13} this investigation was not mentioned. Several mechanisms besides a prothrombotic condition have been suggested as potential causes for splenic infarction during IM, such as the possibility of the blood flow being insufficient to provide an adequate oxygen supply when in the presence of an acutely enlarged spleen.^{6 7 10}

Two cases have been reported suggesting that acute EBV infection results in a transient hypercoagulability state, and its

Figure 1 Abdominal ultrasound and CT scan showing an area of infarction on the inferior portion of the spleen.

association to splenic infarction in IM: a case of positive antiphospholipid antibodies during acute illness, with normalisation after 6 months;¹⁴ and a case with decreased activity of protein C and protein S during acute illness, with normalised levels at 3 weeks.³ Other references to the transient increase in thrombotic markers associated with EBV infection have been made.^{10 14}

None of the previously reported cases have mentioned testing for factor VIII, so this is the first case described where a transient elevation of this factor is associated with acute EBV infection. High levels of factor VIII have been demonstrated to constitute a dose-dependent risk factor for thrombosis, both arterial and venous, although the exact mechanisms through which this occurs have not been clearly defined.¹⁵

Also, no other previous case has described decreased protein S with a normal level of protein C. Protein S has an important anticoagulant function and its deficiency has been established as a risk factor for venous thromboembolism.¹⁶ Although there is no evidence that protein S deficiency is a risk factor for arterial thrombosis, this has been suggested by several case reports.¹⁷ Many pathological conditions can induce a transient decrease of protein S levels, such as liver disease, disseminated intravascular coagulation, autoimmune disorders and some infections.^{16 17}

The test for antiphospholipid antibodies in our case was only conducted after the acute phase of the disease, returning normal results. Because of this delayed assessment, we have to consider that a transient elevation of these parameters during the acute illness might have been missed.

In our case, a cardiac ultrasound was not performed during the hospital stay. This examination was planned for after the discharge; but as the patient evolved positively, with no further symptoms or events, the cardiac ultrasound was not performed. This is a limitation of our case report, as a cardiac ultrasound is of importance in the exclusion of thromboembolism of cardiovascular aetiology.

Our case, as others before it, suggests that IM due to EBV results in the induction of a transient hypercoagulable state.

Learning points

- Most patients with infectious mononucleosis due to an Epstein-Barr virus (EBV) acute infection recover uneventfully, but a wide range of complications have been reported.
- Splenic infarction should be considered in patients with infectious mononucleosis due to EBV presenting with abdominal pain, and prompt diagnostic evaluation should be performed early to detect this complication.
- A thrombophilic screening and reassessment on follow-up should be performed on patients with splenic infarction and infectious mononucleosis due to EBV, as this may happen in the presence of a transient procoagulant state or may be the first manifestation of a thrombophilia.

Although we may not infer that this case of splenic infarction was caused by the low levels of protein S or high levels of factor VIII, or both conditions working in conjunction, the knowledge of the thrombotic state that these changes impose is positively suggestive of their influence on our patient's condition. A search for hypercoagulable disorders that includes these parameters should be carried out in all patients with splenic infarction and IM due to acute EBV infection.

Contributors All the authors were involved in the management of the patient, and LM was additionally involved in the follow-up of the patient. CM and JMS were involved in the drafting of the manuscript, and LM critically revised the manuscript for important intellectual content. All the authors read and approved the final manuscript.

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