EBV : not your Everyday Benign Virus

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Abstract

***Background* : Epstein-Barr virus infection is common, with seroprevalence of 90% in adults. Clinical presentation of primary EBV infection can be variable and atypical. It is often subclinical or can result in infectious mononucleosis. Clinical course is mostly benign, but in rare cases serious short- and long-term complications may occur.**

***Case presentation* : We present a case of a 19-year-old woman who was admitted to the hospital with general malaise, fever, dyspnea, icterus, vomiting and diarrhea, with acute left upper quadrant pain. She was diagnosed with acute EBV-infection with hepatitis, splenomegaly and spontaneous splenic rupture.**

***Conclusions* : Spontaneous splenic rupture is an uncommon, but potentially fatal complication of infectious mononucleosis. In a patient with suspicion of EBV infection and abdominal pain, we should always be aware of the possibility of spontaneous splenic rupture and emphasis should be put on appropriate counseling.** (Acta gastroenterol. belg., **2020**, 83, **485-487**).

Keywords : Epstein-Barr virus, splenomegaly, splenic rupture, abdominal pain, hepatitis.

Introduction

Epstein-Barr virus (EBV) is a gamma herpesvirus with a double-strand DNA genome. Transmission occurs via saliva droplets and requires close contact. Incubation period is usually four to seven weeks (1,2). Clinical presentation of EBV infection is variable, depending on the age of acquisition and immune status of the host. Clinical course is mostly benign. Primary infection can be asymptomatic, but in adolescence or early adulthood infection is typically associated with acute infectious mononucleosis (IM), a clinical syndrome including fever, lymphadenopathy and pharyngitis. Most of the IM cases are self-limiting, but in rare cases acute and potentially fatal complications may occur (3,4).

Case history

A previously healthy 19-year-old woman visited her general practitioner (GP) with a preceding 2-day history of headache, dry cough, nausea and vomiting, diarrhea, subfebrile state and general malaise. Lab results showed normal white blood cell count with 15% atypical lymphocytes, normal platelet count and hemoglobin. There was elevation of liver enzymes: alanine aminotransferase (ALT) 190U/L (<32) ; aspartate aminotransferase (AST) 200U/L (<32) ; alkaline phosphatase (ALP) 215U/L (35-104); gamma-glutamyl transferase (GGT) 99U/l (5-39), elevated bilirubin 2,4mg/dl (0,2-1,0) and elevated C-reactive protein (CRP) 63mg/l (<5). Hepatitis A, B, C, Toxoplasmosis, EBV and Cytomegalovirus serology was negative. Her GP suspected a benign viral infection and reassured her.

On the fourth day of illness she was admitted to the hospital with new sudden-onset severe left upper-quadrant pain and mild dyspnea for the last 24 hours. She described the pain as continuous and worse with deep breathing. There was no recent trauma or travel, no medication use other than oral contraceptives. Past medical and family history was unremarkable. She didn't smoke or drank alcohol. In the emergency department, she looked icteric, was tachycardic at 122 bpm, normotensive and afebrile. On examination, there was tenderness on the left upper quadrant of the abdomen. Chest X-ray was normal, ECG showed sinus tachycardia. Routine labs demonstrated leukocytosis (17.250/µL) with remarkable lymphocytic predominance. D-dimer levels were elevated >10xULN, with liver test abnormalities (bilirubin 4,9mg/dl (direct 4,4mg/dl), AST 163U/l, ALT 228U/l, GGT 107U/l and ALP 291U/l), elevated CRP 42mg/dl and lactate dehydrogenase 512U/l (135-250), decreased haptoglobin levels <0,10g/L (0,3-2,0). The following results were normal: hemoglobin, platelet count, INR, creatinine, lipase, albumin and HCG. Repeated viral serology showed positive EBV viral capsid antigen (VCA) IgM, with negative VCA-IgG and negative IgG antibody to EBV nuclear antigen (EBNA). Computed Tomography (CT) scan revealed splenomegaly with a splenic rupture and intracapsular bleeding (fluid with high density, +60 Hounsfield Units (HU)) (Fig. 1A) and a large amount of free fluid with a relatively high density (+37 HU) in the pelvis minor, probably resembling hemoperitoneum (Fig. 1B). She was diagnosed with EBV-associated IM with hepatitis, splenomegaly and atraumatic splenic rupture.

She was managed conservatively with monitoring and supportive treatment including intravenous fluids and analgesics. She remained hemodynamically stable. After a few days she developed a sore throat with pharyngitis and cervical lymphadenopathy. Abdominal pain resolved in a couple of days. Hemoglobin levels dropped to a minimum of 9.7g/dl, liver tests and markers of inflammation improved every day. She returned home

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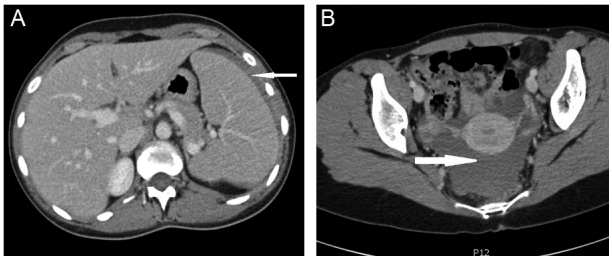

Fig. 1. — CT scan of the abdomen showing (A) splenomegaly with intracapsular perisplenic hematoma (arrow), (B) hemoperitoneum (arrow).

6 days after initial presentation. At follow-up, 41 days after initial presentation, her only complaint was mild fatigue. Lab results and abdominal ultrasound findings had normalized by then.

Discussion

IM is a common disease, classically presenting with a triad of lymphadenopathy, fever and pharyngitis. EBV accounts for 90% of the cases (2,5,6).

Diagnosis is usually made clinically, in conjunction with a positive heterophile antibody test (Paul-Bunnell test) or presence of atypical lymphocytes. Heterophile antibody testing is a specific test for EBV with specificity of 98-100% in the correct clinical setting, but may be negative in the first week of symptoms (25% false-negative) and in children under 12 years of age (2,4,5,7,8). A definitive diagnosis can be made by testing for IgM and IgG antibodies against VCA and EBNA. VCA IgM is a good marker of primary infection and is positive in most cases when symptoms are present. Levels disappear after 4-6 weeks. VCA IgG will increase in the acute phase as well and persists for life. The presence of EBNA IgG suggests past infection, as levels are not detectable until several weeks after the onset of infectious mononucleosis, and persist for life (2,5). In this case, VCA IgM was negative 2 days before hospital admission, which made it more difficult to diagnose EBV.

As shown in this case, clinical presentation of infectious mononucleosis may be highly variable. The classical triad may be absent, whereas fatigue, periorbital or palpebral edema or a morbilliform rash are frequently encountered (2, 4). Hepatosplenomegaly and some degree of hepatitis are common findings. A subclinical increase in ALT is seen in 75% of the patients and splenomegaly is reported in 50%. Jaundice, however, is seen in only 5% of cases of IM. Fulminant liver failure has been reported, but primarily in immunocompromised. In absence of fulminant liver failure, severe hepatic dysfunction due to EBV infection can resolve with only supportive care (1,3,4,9). In this patient there were no signs of severe hepatitis or hepatic failure and liver tests improved spontaneously.

Splenic rupture is an uncommon and feared complication of EBV, seen in 0,1-0,5% of patients, the majority being male. It mostly occurs atraumatic and usually within 3 weeks after diagnosis. It classically presents with acute left upper quadrant pain, but it can present with diffuse non-localizing abdominal pain and nausea or pleuritic chest pain. Palpation of the spleen can lead to radiating pain to the left shoulder tip, known as Kehr's sign (8,10,11). In some cases, splenic rupture is the first sign of IM, making it difficult to diagnose. It can lead to severe hemorrhage and shock. Mortality rates of 9% have been reported (8,10,11). Abdominal ultrasound can be performed to diagnose splenic rupture. Although ultrasound can be performed rapidly bedside and it has no radiation exposure, CT scan is the recommended confirmatory test since it allows diagnosis and grading the severity of splenic injury (6,10). We decided to do a CT scan to rule out pulmonary embolism and vascular liver disease as well, given the pleuritic chest pain, dyspnea, use of oral contraceptives, tachycardia, elevated levels of D-dimer and liver enzymes.

Splenic rupture and hemorrhage can be managed conservatively or surgically or with splenic embolization, depending on hemodynamic status, splenic injury grade, presence of comorbidities and resource availability (6,10). In a recent systematic review of published case reports, 67% of the 85 cases underwent splenectomy (11). Splenic embolization is increasingly used, and suggested for stable patients with active contrast extravasation on CT scan, allowing preservation of the spleen (6,10).

Emphasis should be put on appropriate counseling of those with suspected or confirmed IM. We should warn them about the risk and symptoms of splenic rupture. We should advise them to avoid contact sports or heavy lifting for at least 1 month following onset of infection (10,11).

Infectious mononucleosis is associated with several other acute complications, it can affect virtually any organ (Table 1). Tonsillar abscess and cervical lymphadenopathy may cause airway compromise, leading to stridor and cyanosis (4). Hematological complications, such as hemolytic anemia illustrated in this case, are generally mild, but severe thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome may occur. Meningoencephalitis and Guillain-Barre syndrome are examples of severe neurological complications. EBV is a common trigger of hemophagocytic lymphohistiocytosis (2,4).

Latently EBV infected memory B lymphocytes serve as lifelong viral reservoirs, and EBV has a well-established oncogenic potential (Table 1) (2,12). EBV is associated with lymphoproliferative disorders such as Hodgkin lymphoma, Burkitt lymphoma and nasopharyngeal carcinoma (2,4,13). Chronic active EBV infection is rare, leading to persistent IM-like symptoms and progressive immunodeficiency, with a poor prognosis (4,12).

The majority of the patients with primary EBV infection fully recover spontaneously. Infection is managed mostly in primary care and rarely requires more than supportive therapy, including analgesics, antipyretics, adequate fluid intake and limitation of activities. Bed rest is not advised, special precautions against transmission are unnecessary

Table 1. — **Acute and chronic complications of infectious mononucleosis**

Acute complications	Chronic complications
Hematological (25-50%) - Hemolytic anemia - Thrombocytopenia - Aplastic anemia - Neutropenia - Thrombocytopenic purpura - Hemolytic-uremic syndrome - Disseminated intravascular coagulation - Hemophagocytic lymphohistiocytosis - Splenomegaly (50%) - Splenic rupture (0,1-0,5%)	Lymphoproliferative disorders and malignancy - Hodgkin lymphoma - Non-Hodgkin lymphoma - Burkitt lymphoma - Smooth muscle tumors - Nasopharyngeal carcinoma - Post-transplant lymphoproliferative disease - Diffuse large B-cell lymphoma - T-cell lymphoma - Lymphomatoid granulomatosis - X-linker lymphoproliferative disease
Neurological (1-5%) - Guillain-Barré syndrome - Facial nerve palsy - Meningoencephalitis - Aseptic meningitis - Transverse myelitis - Peripheral neuritis - Cerebellitis - Optic Neuritis	Neurological - Multiple sclerosis (?) (controversial)
Hepatological - Hepatomegaly - Elevated aminotransferase (75%) - Icterus (5%) - Fulminant liver failure	Chronic active Epstein-Barr virus infection
Other - Airway obstruction (1%) - Peritonsillar abscess - Rash - Oral hairy leukoplakia - Pneumonia - Myocarditis - Pancreatitis - Mesenteric adenitis - Myositis - Glomerulonephritis	

(2,4,5,8-12). Routine use of antivirals, such as acyclovir, is not advocated because significant clinical benefit has not been shown (2,5). The use of corticosteroids is relatively common practice but is only recommended for management of severe complications such as airway obstruction (2,12).

Conclusion

Splenic rupture is a rare, but potentially fatal complication of primary EBV infection. It should be considered in any patient with infectious mononucleosis presenting with abdominal or pleuritic chest pain. Typical symptoms of infectious mononucleosis may be absent. CT scan is recommended for diagnosis. It can be managed surgically or conservatively. Counseling patients on the risk of splenic rupture and the associated symptoms is pivotal, as most of the cases are atraumatic.

Conflict of interest

No potential conflict of interest was reported by the authors.

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