Epstein-Barr virus-associated acute pancreatitis: a clinical report and review of literature

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Abstract

Background: Acute pancreatitis is a disorder of reversible inflammation of the pancreas. Only a few cases are related to infections and the most common pathogens are the viruses responsible for mumps, parotitis, and influenza. Epstein-Barr virus (EBV)-associated acute pancreatitis is a rare condition and it may occur in children and adults.  

Case presentation: A 3-year-old female was admitted to the “G. Di Cristina” Children’s Hospital in Palermo for vomiting and abdominal pain. Laboratory investigations revealed elevated amylase and lipase, with normal liver function tests. Abdominal ultrasound demonstrated an enlarged pancreas, with hypoechogenic areas; no biliary lithiasis was observed. Infectious disease serology was positive for the presence of EBV VCA IgM and IgG. A diagnosis of EBV-associated acute pancreatitis was made. The patient was treated conservatively and recovered.  

Conclusions: Acute pancreatitis is rarely associated with EBV infection; a review of the English literature revealed only 10 pediatric and 6 adult cases. Patients with pancreatitis should always be evaluated for EBV serology, even in the absence of the typical clinical and hematological features of infectious mononucleosis. For these patients, good prognosis is generally expected.  

Keywords: Epstein-Barr virus (EBV), Pancreatitis, Children

Background

Epstein-Barr virus (EBV) infection is a common viral infection, especially in children; it could have an asymptomatic course or may present as flu syndrome characterized by fever, malaise, headache, lymphadenitis, and pharyngitis [1]. EBV infection usually causes an acute self-limiting disease and resolves spontaneously in a few weeks; however, it may be responsible for various complications of the respiratory, cardiovascular, genitourinary, gastrointestinal, and nervous systems, ranging from minor to severe to life threatening. EBV also plays a significant role in the pathogenesis of autoimmune diseases and neoplasms [2].  

As regards gastrointestinal manifestations, enlarged spleen and liver, with elevated transaminase levels, are the most common symptoms. Acute pancreatitis is a disorder of reversible inflammation of the pancreas. Only a few cases are related to infections and the most common pathogens are the viruses responsible for mumps, parotitis, and influenza. EBV-associated acute pancreatitis is a rare condition and it may occur in children and adults. Here we report on a 3-year-old girl with acute pancreatitis due to EBV infection; a review about this topic was also conducted thereafter.
Case presentation

A 3-year-old female, previously in good health, was admitted to the “G. Di Cristina” Children’s Hospital in Palermo for vomiting and abdominal pain. She did not complain of any other symptoms. Vital signs were normal. On physical examination, she appeared sick, with moderate epigastric tenderness. Laboratory investigations showed hemoglobin 13.8 g/dl, platelet 340,000/mm³, white blood cell count 16,600/mm³ (neutrophils 20%, monocytes 11%, and lymphocytes 69%), C-reactive protein 13.1 mg/dl (normal range <0.5 mg/dl), aspartate aminotransferase 40 U/l, alanine aminotransferase 25 U/l, total bilirubin 0.11 mg/dl, amylase 913 U/l (normal range 30–100 U/l), and lipase 6450 U/l (normal range 3–32 U/l). Because of fair general conditions and elevated inflammatory markers, empirical antibiotic therapy with cefotaxime was started. Abdominal ultrasound revealed an enlarged pancreas, with hypoechoigenic areas; no biliary lithiasis was observed. She had no past history of abdominal trauma, surgery or cholecystitis and no familial history of pancreatitis or gallstones was reported. She did not receive any medications known to cause pancreatitis. Serological tests for mumps, parotitis, rubella, EBV, cytomegalovirus, varicella-zoster virus, herpes simplex virus, coxsackie virus, and mycoplasma were all negative, except for the presence of EBV VCA IgM and IgG (EBNA IgG negative). Exudative pharyngotonsillitis, cervical lymphadenopathy, and hepatosplenomegaly were not present. A diagnosis of EBV-associated acute pancreatitis was made; the patient was treated conservatively, including fasting for three days until the resolution of vomiting, peripheral parenteral nutrition support for seven days, and pain management with aceterminophen. An abdominal ultrasound, performed after five days, did not show any complications and antibiotic therapy was discontinued. She improved clinically, lipase and amylase levels progressively decreased, and enteral feeding was gradually resumed. She was discharged home on the fifteenth day of hospitalization.

Discussion and conclusions

Acute pancreatitis is an inflammatory disorder of the pancreas; the incidence rate is 3–13 cases per 100,000 per year in the pediatric population [3, 4], and 5–60 cases per 100,000 persons per year in adulthood [5]. According to the American College of Gastroenterology guidelines, the diagnosis of acute pancreatitis is established by the presence of 2 of the 3 following criteria: (i) abdominal pain consistent with the disease, (ii) serum amylase and/or lipase greater than three times the upper limit of normal, and/or (iii) characteristic findings from abdominal imaging [6]. The most common etiology of acute pancreatitis is gallstones or microlithiasis; other causes include alcohol misuse, trauma, metabolic disorders (hypertriglyceridemia, hypercalcemia), infections (parotitis, mumps, influenza, herpes viruses, hepatitis viruses, coxsackie viruses, mycoplasma), systemic disease (hemolytic uremic syndrome, systemic lupus erythematosus, Henoch-Schönlein purpura, Kawasaki disease, inflammatory bowel diseases), and autoimmune pancreatitis [5, 7]. EBV infection is a rare cause of acute pancreatitis; the pathophysiology remains unclear: both direct viral infection and inflammatory process induced by the virus are plausible pathogenic mechanisms [8, 9].

A review of the English literature was performed: a PubMed search, using as keywords acute pancreatitis AND (EBV OR Epstein-Barr virus), revealed only 10 pediatric [8, 10–18] and 6 adult cases [9, 19–23]. As regards pediatric reports (Table I), median age and mean age was 12 and 11.8 years respectively (range 3–18), 36% were male and 64% were female. As regards pancreatitis symptoms, abdominal pain was described in all cases, vomiting in 55%, and nausea in 27%; eight patients (73%) also had mononucleosis symptoms, like fever, lymphadenitis, and pharyngitis. Amylase and/or lipase levels were increased up to three times the normal limit in 100% of the cases. In 5 children, there was evidence of acute pancreatitis on abdominal computerized tomography (CT), while only in our case, ultrasound (US) revealed an enlarged pancreas with a heterogeneous echotexture. The diagnosis of pancreatitis was confirmed in all patients, using the diagnostic criteria of the American College of Gastroenterology. Six children presented other complications related to EBV infection: the most common was cholestatic hepatitis (50%); cholecystitis, pneumonia, proctitis, portal vein thrombosis, and septic shock were also reported. Serological documentation for EBV infection was obtained in 10 cases, while in 1 child, the diagnosis was made clinically. All cases were treated with supportive care, that were fasting, intravenous fluids, parenteral nutrition, and/or pain management; in 1 patient, antibiotics and antivirals (meropenem, teicoplanin, and ganciclovir) were also used [17]. All children recovered.

As regards adult patients (Table II), EBV-associated acute pancreatitis affects mainly young adults (range 21–45 years), with a slight female predominance (66%). All cases presented abdominal pain, associated some times with nausea, fever, and vomiting. In 3 patients (50%), signs and symptoms related to infectious mononucleosis were also observed. The diagnosis of EBV infection was made by positive serology in 5 patients; also in 2 cases, serum EBV-DNA was detected. Abdominal CT was executed in 5 patients, revealing signs of acute pancreatitis, such as enlarged and edematous pancreas; in 1 case, areas of necrosis were also noticed.
All patients except one had complications related to systemic EBV infection, revealing a more severe clinical course in adults than children. The reported complications are hepatitis with or without cholestasis, gastritis, pneumonia with pleural effusion, ascites, pericardial effusion, autoimmune hemolytic anemia, and multi-organ failure. The patients were treated with symptomatic therapy; antibiotics, antivirals, and steroids were also administered in critical cases. All patients except one fully recovered.

In conclusion, EBV infection is characterized by clinical heterogeneity; multiple organs could be involved, also the pancreas, both in children and young adults. Active surveillance is needed for prompt diagnosis and early treatment. In patients with signs and symptoms of acute pancreatitis, EBV infection should always be considered, even in the absence of the typical clinical and hematological features of infectious mononucleosis. Generally, EBV-associated acute pancreatitis is characterized by a favorable prognosis, with a spontaneous resolution.

Table I Clinical data of pediatric cases with EBV-associated acute pancreatitis reported in literature and our case

| Reference                      | Age/sex | Mononucleosis symptoms | Gastrointestinal symptoms | EBV diagnosis | Amylase-lipase | Imaging | Other complications | Therapy | Outcome     |
|--------------------------------|---------|-------------------------|----------------------------|---------------|---------------|---------|---------------------|---------|-------------|
| Wislocki et al. 1966 [10]      | 18y/M   | Yes                     | Abdominal pain, vomiting   | Heterophil antibody | 480 U/l-NA | NA      | No                  | Fasting, intravenous fluids, analgesics | Recovered |
| Hedstrom et al. 1976 [11]      | 12y/F   | Yes                     | Abdominal pain, nausea     | Clinical       | 8700 U/l-NA | NA      | No                  | Symptomatic | Recovered |
| Werbitt et al. 1980 [12]       | 16y/M   | Yes                     | Abdominal pain, vomiting   | VCA positivity  | 378 U/l-NA | NA      | CT: no pancreatic abnormality | No      | Not available | Recovered |
| Koutras et al. 1983 [13]       | 8y/F    | Yes                     | Abdominal pain, vomiting   | VCA IgM positivity | 300–180 U/l | NA      | Cholestatic hepatitis, proctitis | Symptomatic | Recovered |
| Khawcharoenporn et al. 2008 [14]| 18y/F   | Yes                     | Abdominal pain             | VCA IgM positivity | 620–659 U/l | CT: edematous pancreas, CT: edematous pancreas, peripancreatic fluid accumulation | Cholecystitis, septic shock, DIC | Symptomatic | Recovered |
| Kang et al. 2013 [15]          | 11y/F   | No                      | Abdominal pain, vomiting   | VCA IgM positivity | 4010–4941 U/l | CT: edematous pancreas, peripancreatic fluid accumulation | Cholestatic hepatitis | Fasting, parenteral nutrition | Recovered |
| López-Ibáñez et al. 2013 [16]  | 15y/M   | Yes                     | Abdominal pain             | Heterophil antibody | 1251 U/l-NA | CT: globular pancreas, hepatosplenomegaly, ascites | Bilateral pneumonia, portal vein thrombosis, septic shock | Fasting, parenteral nutrition, meropenem, teicoplanin, ganciclovir | Recovered |
| Galzerano et al. 2014 [17]     | 3y/F    | No                      | Abdominal pain             | VCA IgM positivity | 3880 U/l-NA | CT: enlargement of the pancreatic head | No                  | Not available | Recovered |
| Narchi et al. 2014 [18]        | 8y/M    | Yes                     | Abdominal pain, vomiting   | VCA IgM positivity | 80–1000 U/l | MRI: not visible pancreas | Cholestatic hepatitis, cholecystitis | Fasting, intravenous fluids | Recovered |
| Hammami et al. 2019 [8]        | 18y/F   | Yes                     | Abdominal pain, nausea     | VCA IgM positivity | 327–2016 U/l | CT: signs of acute pancreatitis | Hepatitis | Symptomatic | Recovered |
| Our case                       | 3y/F    | No                      | Abdominal pain, vomiting   | VCA IgM positivity | 913–6450 U/l | US: enlargement of the pancreas | No                  | Fasting, parenteral nutrition, analgesics | Recovered |

Abbreviations: y years, M Male, F Female, NA Not available, DIC Disseminated intravascular coagulopathy
| Reference          | Age/sex | Mononucleosis symptoms | Gastrointestinal symptoms | EBV diagnosis | Amylase-lipase | Imaging | Other complications | Therapy                          | Outcome       |
|-------------------|---------|-------------------------|---------------------------|----------------|----------------|---------|---------------------|-----------------------------------|---------------|
| Jahann et al. 2012 [19] | 22y/M   | Yes                     | Abdominal pain            | VCA IgM positivity | 330–2300 U/l | NR      | No                  | Symptomatic                       | Recovered     |
| Cook et al. 2015 [20] | 25y/M   | No                      | Abdominal pain, nausea, fever | VCA IgM positivity | NA-429 U/l | CT: pancreatic edema | Cholestatic hepatitis, pleural effusions, ascites | Fasting, parenteral nutrition, analgesics | Recovered     |
| Singh et al. 2015 [21] | 21y/F   | Yes                     | Abdominal pain, vomiting, nausea | VCA IgM positivity | NA-4301 U/l | CT: pancreatic edema | Autoimmune hemolytic anemia, Hepatitis, pneumonia | Symptomatic, prednisone | Recovered     |
| Zhu et al. 2017 [9]   | 35y/F   | Yes                     | Abdominal pain, vomiting  | VCA IgM positivity | 1300–1450 U/l | CT: pancreatic edema | Cholestatic hepatitis, pneumonia with pleural effusions | Fasting, parenteral nutrition, amoxicillin-clavulanate, acyclovir | Recovered     |
| Fiani et al. 2021 [22] | 35y/F   | No                      | Abdominal pain, fever     | VCA IgM and IgG positivity, serum EBV DNA | 129/408 U/l | CT: enlargement of the pancreas | Cholestatic hepatitis, pneumonia with pleural effusions | Symptomatic, linezolid, meropenem, oseltamivir, acyclovir, methylprednisolone | Recovered     |
| Huang et al. 2021 [23] | 45y/F   | No                      | Abdominal pain             | Serum EBV DNA      | Increased up to three times the normal limit | CT: pancreatic necrosis | Pericardial and pleural effusions, gastritis, MOF | Symptomatic                       | Dead          |

Abbreviations: y years, M Male, F Female, NA Not available, NR Not reported, MOF Multi-organ failure
Abbreviations
EBV: Epstein-barr virus; CT: Computerized tomography; US: Ultrasound.

Acknowledgements
Not applicable

Authors’ contributions
SS and MGua have participated in the diagnostic pathways and treatment. GAR, SS, and MGua wrote the paper. SA, GC, and MGiu revised the manuscript. All authors read and approved the final manuscript.

Funding
No specific fundings were used for the current manuscript.

Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Availability of data and materials
No specific fundings were used for the current manuscript.

Funding
All authors read and approved the final manuscript.

GAR, SS, and MGua wrote the paper. SA, GC, and MGiu revised the manuscript. SS and MGua have participated in the diagnostic pathways and treatment.

Authors’ contributions
Not applicable

Consent for publication
Parent’s informed written consent was provided.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Declarations
The corresponding author on reasonable request.

Ethics approval and consent to participate
The datasets used and analyzed during the current study are available from

Availability of data and materials
No specific fundings were used for the current manuscript.

Funding
All authors read and approved the final manuscript.

GAR, SS, and MGua wrote the paper. SA, GC, and MGiu revised the manuscript. SS and MGua have participated in the diagnostic pathways and treatment.

Authors’ contributions
Not applicable

Acknowledgements
The authors declare that they have no competing interests.

Competing interests
The authors declare that they have no competing interests.

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