



Review

Pancreatitis and cholecystitis in primary acute symptomatic Epstein-Barr virus infection – Systematic review of the literature



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ABSTRACT

Acute pancreatitis and acalculous cholecystitis have been occasionally reported in primary acute symptomatic Epstein-Barr virus infection. We completed a review of the literature and retained 48 scientific reports published between 1966 and 2016 for the final analysis. Acute pancreatitis was recognized in 14 and acalculous cholecystitis in 37 patients with primary acute symptomatic Epstein-Barr virus infection. In all patients, the features of acute pancreatitis or acalculous cholecystitis concurrently developed with those of primary acute symptomatic Epstein-Barr virus infection. Acute pancreatitis and acalculous cholecystitis resolved following a hospital stay of 25 days or less. Acalculous cholecystitis was associated with Gilbert-Meulengracht syndrome in two cases. In conclusion, this thorough analysis indicates that acute pancreatitis and acalculous cholecystitis are unusual but plausible complications of primary acute symptomatic Epstein-Barr virus infection. Pancreatitis and cholecystitis deserve consideration in cases with severe abdominal pain. These complications are usually rather mild and resolve spontaneously without sequelae.

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1. Introduction

In immunocompetent subjects, primary symptomatic Epstein-Barr virus infection usually resolves over a period of weeks without sequelae [1]. Cumulative clinical experience, mostly coupled with biologic plausibility and, in some cases, experimental data, indicate that a wide range of complications occasionally occur [1].

Acute pancreatitis [2] and acute acalculous cholecystitis [3] are complications of primary acute symptomatic Epstein-Barr virus infection that have not been included in a detailed analysis [4]. To integrate existing information on this issue, we conducted an extensive review of the literature.

2. Materials and methods

2.1. Search strategy

Between October 2015 and January 2016, we performed a search with no date limits of the Mesh terms (Drüsenfieber OR Epstein-Barr virus OR glandular fever OR infectious mononucleosis OR kissing disease OR Pfeiffer disease) AND (pancreatitis OR acalculous cholecystitis OR cholecystitis) in the US National Library of Medicine and Excerpta Medica database. Personal files and the bibliography of each identified report were also screened. We applied the principles established by the Economic and Social Research Council guidance on the conduct of narrative synthesis and on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

2.2. Selection criteria

For the final analysis, we selected reports published as full-length articles or letters, which include apparently immunocompetent individuals with primary acute symptomatic Epstein-Barr virus infection complicated by acute pancreatitis or acalculous cholecystitis. We exclusively retained well-documented original communications presenting subjects of both sexes and all ages irrespective of follow-up duration. Reports published in languages other than Dutch, English, French, German, Italian, Portuguese or Spanish were excluded. Patients infected simultaneously with Epstein-Barr virus and a second pathogen responsible for infectious mononucleosis were also excluded. When more than one article reported on the same patient, only the more comprehensive one was retained.

The diagnosis of primary acute symptomatic Epstein-Barr virus infection, acute pancreatitis or acalculous cholecystitis established in the original publications was reassessed using recognized criteria. The diagnosis of primary acute symptomatic Epstein-Barr virus infection was made in cases with the characteristic clinical findings of infectious mononucleosis (at least 5 of the following 9: eyelid edema, fatigue, fever, hepatomegaly, jaundice, malaise, sore throat, splenomegaly, swollen cervical lymph nodes), negative past history for infectious mononucleosis and a positive Epstein-Barr virus serology (reactive heterophile antibodies, IgM antibodies directed against the Epstein-Barr viral capsid antigen or IgG antibodies to early antigen) [1]. The diagnosis of acalculous cholecystitis was made in patients with right upper quadrant abdominal pain, imaging studies excluding alternative diagnoses such as calculous cholecystitis or intrahepatic bile duct dilatation and at least two of the following four features: pain on inspiration when the examiner's fingers or the ultrasound transducer were placed under the right costal margin, gallbladder wall thickening (≥ 4 mm), fluid collection around the gallbladder or alternate gallbladder wall density [5,6]. The diagnosis of acute pancreatitis was made in patients with abdominal pain and elevation in lipase or

amylase levels to 3 times or greater than the upper limit of normal irrespective of the imaging findings [5,7]. Patients with chronic alcohol abuse, gallstones or taking drugs implicated as causing pancreatitis were excluded [7].

2.3. Data extraction and analysis

From each report dealing with primary acute symptomatic Epstein-Barr virus infection and either pancreatitis or acalculous cholecystitis, data on pre-existing conditions, gender, age, risk factors for pancreatitis (alcohol abuse, gallstones and prescription of drugs implicated as causing pancreatitis) respectively acalculous cholecystitis (recent surgery, multiple trauma and burn injury), physical findings, laboratory or imaging studies, clinical course and length of hospital stay were excerpted.

Following definitions were also used: absolute lymphocytosis if lymphocyte blood count $\geq 4.0 \times 10^9/l$ ($\geq 6.0 \times 10^9/l$ in subjects ≤ 13 years or age); atypical lymphocytosis if large lymphoid cells $\geq 10\%$ of total lymphocytes; thrombocytopenia if platelet count $\leq 150 \times 10^9/l$; hyperbilirubinemia if total bilirubin $\geq 25 \mu\text{mol/l}$; leukopenia if total white cell count $\leq 4.5 \times 10^9/l$; hemolytic anemia if low hemoglobin count was associated with at least 2 of the following 3 findings: increase in reticulocyte count (or nucleated red blood cells in peripheral blood smear), positive direct antiglobulin test or decreased haptoglobin level.

Because the normal range for enzymes such as aminotransferases, alkaline phosphatase or γ -glutamyltransferase varies with age, sex, and laboratory's own normal values, their ratio was calculated by dividing the value measured in the individual patient by the upper limit of normal. The diagnosis of liver disease was made if the ratio of at least one enzyme was two or more [8]. The diagnosis of hepatocellular liver damage was made in cases with a more than two-fold elevation in aminotransferase ratio compared with alkaline phosphatase or γ -glutamyltransferase ratio and that of cholestatic liver damage in cases with opposite findings. The diagnosis of mixed damage was made in the remaining patients with liver damage [8]. Standard criteria were used for the diagnosis of acute kidney injury, chronic fatigue syndrome, Gianotti-Crosti dermatitis and myocarditis.

The literature search and the data extraction were performed independently by two investigators (L. Kottanattu, G.P. Milani). If the extracted data were incongruent, conflicts were resolved by reaching a consensus. Results are given either as frequency or as median and interquartile range (which includes half of the data points), as appropriate. The Cohen's kappa index was used to assess the agreement between investigators, the Fisher exact test to compare dichotomous variables and the Mann-Whitney-Wilcoxon rank-sum test to compare continuous variables. Statistical significance was assigned at $P < 0.05$.

3. Results

3.1. Search results

The literature search process is summarized in Fig. 1. The chance-adjusted agreement between the two investigators on the application of the inclusion and exclusion criteria was 0.84. For the final analysis we retained 48 scientific reports [2,3,9–54] published between 1966 and 2016 in English (N=45), Spanish (N=2) and German (N=1). They had been reported from the following countries: United States of America (N=12), Italy (N=6), Greece (N=5), Spain (N=4), Turkey (N=3), Japan (N=2), Poland (N=2), South Korea (N=2), Canada (N=1), Czech Republic (N=1), Denmark (N=1), France (N=1), Germany (N=1), Israel (N=1), Peru (N=1), Portugal (N=1), Republic of China (N=1), Sweden (N=1), the

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