DENGUE FEVER WITH ACUTE ACALCULOUS CHOLECYSTITIS

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Abstract. Dengue fever (DF) with acute acalculous cholecystitis is rarely reported. To investigate the incidence, treatment, and prognosis of acute acalculous cholecystitis in DF patients, we retrospectively studied 10 patients with DF and acute acalculous cholecystitis. From October 2001 to July 2002, 131 patients were diagnosed with DF. Ten of 131 DF patients (7.63%) had complications of acute acalculous cholecystitis. Two patients underwent cholecystectomy and one underwent percutaneous transhepatic gallbladder drainage due to poor resolution of acute acalculous cholecystitis. We found acute acalculous cholecystitis in a small proportion of patients with DF. In our experience, closely monitoring vital signs to avoid shock and correct thrombocytopenia to avoid bleeding could be adequate for most patients. In some cases, surgical treatment may be needed for DF fever patients with complications of diffuse peritonitis.

INTRODUCTION

Dengue fever (DF) is a mosquito-borne viral disease caused by the dengue virus and is endemic in large areas of the Southeast Asia. Typically, DF is an acute febrile illness characterized by frontal headache, retro-ocular pain, muscle and joint pain, nausea, vomiting, and rash. Atypical presentations are infrequent and may lead to catastrophic illness if unrecognized. Taiwan has been an endemic area for DF since 1870. A major outbreak of DF occurred in the southern part of Taiwan from 1987 to 1988. A few dengue sporadic cases have been observed in southern Taiwan since October 2001, and an outbreak of type 2 DF occurred in southern Taiwan in July 2002.

Some patients presented with right upper quadrant abdominal pain, fever, a thickened gallbladder wall, and a positive Murphy’s sign on abdominal sonography. Acute acalculous cholecystitis was diagnosed. To investigate the incidence, proper treatment, and prognosis of acute acalculous cholecystitis with DF, a retrospective study was conducted among these patients.

MATERIALS AND METHODS

During a period of 10 months from October 2001 to July 2002, 131 patients were diagnosed with DF according to clinical manifestations and laboratory examinations. The diagnosis of DF was further confirmed by a ≥ 4-fold increase in the titer of an IgG enzyme-linked immunosorbent assay between two separate (acute and chronic) blood samples, or a positive IgM antibody test result for a late acute or convalescent-phase blood specimen.

The diagnosis of acute acalculous cholecystitis was made according to clinical features and sonographic findings. The clinical manifestations were fever, right upper quadrant tenderness, and a positive Murphy’s sign. Sonographic findings were a thickened gallbladder wall (defined as wall thickness > 3.5 mm), a positive sonographic Murphy’s sign (defined as maximum tenderness of the sonographically localized gallbladder), pericholecystic fluid collection, and no stone(s) in the gallbladder. Patients had no recent history of burns, trauma, vasculitis, or recent surgery.

Levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin were measured, and complete blood counts were determined. Symptoms of DF, such as fever, rash, myalgia, arthralgia, headache, abdominal pain, vomiting, chills, and diarrhea, were recorded. Abdominal ultrasonography was performed with a real-time scanner (SSD-2000, 3.5 MHz; Aloka, Tokyo, Japan) in patients with abdominal pain and abnormal results on liver biochemical tests. The splenic volumetric index was measured by timing the distances from hilum to the lower tip of spleen and from hilum to the upper spleen at chest wall site just below the dome. A splenic index greater than 20 cm² was defined as splenomegaly.

RESULTS

Ten of 131 DF patients (7.63%) had complications of acute acalculous cholecystitis. Of the 10 patients with acute acalculous cholecystitis, four were men and six were women, with a mean ± SD age of 48 ± 15 years. The mean ± SD interval from the onset of fever to the hospital visit was 3.3 ± 0.8 days (range = 2–5 days). The clinical symptoms are shown in Table 1. The mean ± SD white blood cell count was 4.9 ± 3.1 × 10⁹/µL. The mean ± SD platelet count was 1.9 ± 1.6 × 10⁴/µL upon presentation to our hospital. All patients had abnormal liver biochemical test results and platelet counts (Table 2). Five patients had abnormal levels of alkaline phosphatase. All 10 patients had a thickened gallbladder wall, a positive Murphy’s sign, pericholecystic fluid collection, and no stone(s) in the gallbladder (Table 3). The mean ± SD gallbladder wall thickness was 9.1 ± 2.3 mm (range = 7–13 mm). The sonographic findings were consistent with acute acalculous cholecystitis. There were more ascites and pleural effusion noted in our cases than in other reports.

During the early period of this DF outbreak since October 2001, two patients underwent cholecystectomy due to severe abdominal pain with a positive peritoneal sign after a platelet transfusion with 10 × 10⁶ platelets/µL. One patient underwent percutaneous transhepatic gallbladder drainage (PTGBD) due to a severely thickened gallbladder wall with a positive Murphy’s sign and severe thrombocytopenia that was not corrected after platelet transfusion. The operative findings of two patients who underwent cholecystectomy were a distended gallbladder with a thickened wall. The gross pathologic finding was congestion of the gallbladder serosa. Upon dissection, the gallbladder contained greenish-yellow bile...
without stones. The wall of the gallbladder had a thickness of 0.7 cm. Microscopically, the gallbladders showed chronic inflammatory cell infiltration and extravasation of erythrocytes into the lumen (Figure 1). The two patients who underwent cholecystectomy had the same pathologic findings. Both of these three patients recovered completely.

The mean ± SD duration of hospitalization for the seven patients without invasive treatment was 4.1 ± 1.6 days. The duration of hospitalization of the two patients who underwent cholecystectomy was 18 days and 16 days, respectively. The duration of hospitalization of the patient who underwent PTGBD was seven days. The cause of prolonged hospitalization for the patients with DF complicated by acute acalculous cholecystitis who received surgical treatment was active wound bleeding. All patients who received conservative treatment showed a good response, and there were no complications after discharge.

DISCUSSION

Dengue fever may be asymptomatic or present as a febrile illness with myalgia or as hemorrhagic fever with or without shock syndrome. Some unusual clinical manifestations have been reported, including fulminant hepatitis, encephalopathy, cardiomyopathy, acute pancreatitis, and acalculous cholecystitis.\textsuperscript{9,14} Reports of DF complicated by acute acalculous cholecystitis are rare.\textsuperscript{13,14} In our study, approximately 7.6% of the DF patients had complications of acalculous cholecystitis, which is not an uncommon finding. This could be due to different diagnostic criteria.

The etiology of acalculous cholecystitis is usually well-described in association with burns, trauma, vasculitis, postsurgical conditions, and certain infections such as salmonellosis\textsuperscript{15} or cytomegalovirus in immunocompromised patients.\textsuperscript{16} Fever, right upper quadrant abdominal pain, abnormality of liver biochemical test results, a thickened gall bladder wall without stones, and a positive sonographic Murphy’s sign establish a diagnosis of acute acalculous cholecystitis. In our study, 10 DF patients were diagnosed with acalculous cholecystitis due to these signs. It appears that DF could be an etiology of acalculous cholecystitis.

The exact pathogenesis of acute acalculous cholecystitis is obscure, but cholestasis and increased bile viscosity from prolonged fasting, spasms of the ampulla of Vater, infection, endotoxemia, microangiopathy, and ischemia-reperfusion injury, among other causes, have been suggested.\textsuperscript{17–19} The pathophysiology in the development of acute acalculous cholecystitis from infection with dengue virus is unknown. It may be due to virus invasion of the gallbladder wall causing edematous change,\textsuperscript{16} but we could not identify any specific etiologic agent or finding on histologic examination of the surgical specimens. The main pathophysiologic change in DF could be increased vascular permeability, causing plasma leakage and serous effusion with high protein content (mostly albumin),\textsuperscript{20} which then induces thickening of the gallbladder wall.

Laboratory findings commonly associated with DF include neutropenia, lymphocytosis, increased concentrations of liver enzymes,\textsuperscript{21} and thrombocytopenia. Ten patients in our study had abnormal liver biochemical test results and severe thrombocytopenia. Abdominal sonographic findings of DF are a thickened gallbladder wall, ascites, splenomegaly, and pleural effusion.\textsuperscript{2–5} Bhamarapravati and others found serous membrane edema of the gallbladder wall and peritoneal effusion in DF patients.\textsuperscript{22} There is a significant association between thickening of the gallbladder wall and severity, as well as progression, of DF.\textsuperscript{23} The fact that our patients had more ascites and pleural effusion supports this finding.

Patients who present with fever and a thickened gallbladder wall on abdominal sonography with a positive Murphy’s sign without stones in the gallbladder could be easily diagnosed as having acute acalculous cholecystitis. Cholecystectomy or PTGBD would be then performed. However, in DF patients with acute acalculous cholecystitis, the course of DF could be self-limiting and thickening of the gallbladder wall could return to normal after several days.\textsuperscript{7} Thus, cholecystectomy would not be initially indicated for these patients. Moreover, the resulting tendency for bleeding would be very difficult to manage during and after surgery. Two patients underwent cholecystectomy after an initial diagnosis of acute acalculous cholecystitis with diffuse peritonitis. Oozing of the
wound and shock were observed after surgery. Fortunately, after three weeks of intensive care treatment, the patients were discharged without complications. One patient underwent PTGBD, and his discharge was delayed due to bleeding. The other patients without invasive management remained healthy after discharge. Thus, invasive treatment of dengue fever patients with acute acalculous cholecystitis may not be necessary. The mortality rate of acute acalculous cholecystitis is very high, ranging from 10% to 50%. The rapid progression of acute acalculous cholecystitis to gangrene and perforation has been reported. Therefore, prompt, early recognition and intervention are required. Among our patients, the mortality rate was zero, although three patients underwent intensive surgical treatment. Based on these results, close observation might be adequate for DF patients with acalculous cholecystitis, and invasive treatment may not be initially required. Surgical treatment could be only indicated for DF complicated by diffuse peritonitis.

In our study, we found that acute acalculous cholecystitis occurred in a small proportion of patients with DF. It is important that acute acalculous cholecystitis be considered a complication of DF in area endemic for this disease. When patients present with abdominal pain, fever, a positive Murphy’s sign, and a thickened gallbladder wall without stones, DF with acalculous cholecystitis should be suspected. Based on our small cases series, we suggest close observation and initial treatment of the thrombocytopenia. Surgical treatment might be indicated for DF patients with acute cholecystitis complicated by diffuse peritonitis. However, larger cases studies are needed to justify this recommendation. Thus, it appears that the prognosis of these DF patients was very good compared with patients with other causes of acute acalculous cholecystitis.

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