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Prognosis in Patients With Gallbladder Edema Misdiagnosed as Cholecystitis

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ABSTRACT

Background and Objectives: Edema of the gallbladder may pose a diagnostic challenge because it also occurs in patients without an indication for cholecystectomy.

Methods: We evaluated all consecutive patients with gallstone disease who presented for cholecystectomy at the Department of Surgery of Kansai Medical University from January 2006 to April 2019. Using the prospectively collected database in our department, we obtained information on patients whose final diagnoses were gallbladder edema. We identified 12 patients with gallbladder edema who were misdiagnosed with acute cholecystitis among 2661 patients and who presented for cholecystectomy for benign gallbladder diseases. The outcome of these patients was assessed to prevent unnecessary cholecystectomy.

Results: In all 12 patients, computed tomography and ultrasonographic imaging showed gallbladder wall thickening. Acute cholecystitis was suspected, and emergent cholecystectomy was performed for the first 5 patients. Of these 5 patients, 2 patients died of liver failure postoperatively. Based on the misdiagnosis in the first 5 patients, the latter 7 patients did not undergo cholecystectomy; instead, they were treated specifically for their systemic disease. To date, no cholecystitis has occurred in these 7 patients. In all misdiagnosed cases in the present report, mesh-like wall thickening was a distinctive feature of gallbladder edema on ultrasonography. We consider this feature important for distinguishing simple gallbladder edema from cholecystitis.

Conclusion: Careful evaluation of clinical symptoms and imaging findings, especially mesh-like wall thickening on ultrasonography, is necessary in this setting to prevent misdiagnosis and unnecessary cholecystectomy.

Key Words: alcoholic hepatitis, cholecystectomy, cholecystitis, gallbladder edema, misdiagnosis.

INTRODUCTION

Acute cholecystitis is a common clinical entity, and its misdiagnosis can result in significant morbidity and mortality. Diffuse gallbladder wall thickening without cholecystitis can be detected in a number of pathological conditions, including liver cirrhosis, acute viral hepatitis, drug-induced hepatitis, renal failure, hypoproteinemia, and heart failure.[1–12] Edema of the gallbladder may pose a diagnostic challenge because it occurs in patients without an indication for cholecystectomy. Misinterpretation of the cause of gallbladder edema can lead to unnecessary cholecystectomy in patients without intrinsic gallbladder disease. In these patients, cholecystectomy is unnecessary, and gallbladder wall thickening usually resolves after its extrinsic cause has been handled.[2] Thus, accurate diagnosis of simple gallbladder edema is important to prevent unnecessary cholecystectomy.

PATIENTS AND METHODS

We evaluated all consecutive patients with gallstone diseases who presented for cholecystectomy at the Department of Surgery of Kansai Medical University from January 2006 to April 2019. Using the prospectively collected database in our department, we obtained information on patients whose final diagnosis was gallbladder edema. Of 2661 patients with benign gallbladder diseases who presented for cholecystectomy during this period, we identi-

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Informed consent: Dr. Matsui declares that written informed consent was obtained from the patient/s for publication of this study/report and any accompanying images.

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fied 12 patients (0.45%) with gallbladder edema who were misdiagnosed with acute cholecystitis during the observation period. These 12 patients had been referred to our department for emergent cholecystectomy for acute cholecystitis.

Diagnosis of gallbladder edema was made as follows: in patients who underwent cholecystectomy, diagnosis was made using macroscopic gallbladder findings and confirmed by histopathological examinations. In contrast, in patients who did not undergo cholecystectomy, the diag-

Table 1.
Characteristics and Prognosis of Patients with Gallbladder Edema Who Were Misdiagnosed as Having Acute Cholecystitis

Age (y)	Sex	Cholecystectomy	Body Temperature* (°C)	White Blood Cell Count* (/μL)	C-reactive Protein* (mg/dL)	Alcohol Intake (g/d × years)	Cause of Gallbladder Edema	Prognosis as in April 2019 After Cholecystectomy or Presentation to Surgical Unit
72	Male	Yes	39.2	10,100	9.5	135 × 45	Alcoholic hepatitis	Died of gastric cancer after 40 mo
46	Male	Yes	Normal†	15,100	Normal§	174 × 26	Alcoholic hepatitis	Died of liver failure after 44 days
34	Female	Yes	Normal	Normal‡	2.6	120 × 14	Alcoholic hepatitis	Bilateral idiopathic osteonecrosis of femoral head after 35 m. Alive after 59 mo
39	Female	Yes	38.3	10,400	2.3	70 × 20	Alcoholic hepatitis	Alive after 5 mo
77	Male	Yes	Normal	Normal	27.2	No	Drug-induced hepatitis	Died of fulminant hepatitis after 2 days
81	Female	No	37.6	9,800	9.2	No	Renal failure	Died of myelodysplastic syndrome after 22 days
28	Male	No	Normal	13,200	6.5	No	Heart failure	Cardiogenic brain embolism after 31 days. Alive after 23 mo
80	Male	No	38.3	15,200	2.6	76 × 60	Alcoholic cirrhosis	Congestive heart failure after 2 days. Died of heart failure after 12 mo
80	Female	No	Normal	Normal	1.2	No	Heart failure	Alive after 22 mo
76	Female	No	Normal	17,500	1.6	No	Hypoproteinemia	Alive after 6 mo
25	Male	No	Normal	Normal	Normal	No	Renal failure, kidney transplantation	Alive after 16 mo
65	Female	No	37.2	12,800	1.2	No	Drug-induced hepatitis accompanied with Stevens-Johnson syndrome	Alive after 3 mo

*Data collected immediately preoperatively or at presentation for surgery.

†<37°C.

‡<8500/μL.

§<0.3 mg/dL.

nosis was made via diagnostic imaging, including computed tomography (CT) scans and ultrasonography. Our study protocol was approved by the Institutional Review Board for Clinical Research of Kansai Medical University Hirakata Hospital (Approval No. 2018017).

RESULTS

In the 12 patients, laboratory findings demonstrated elevated concentrations of transaminases, alkaline phosphatase, and bilirubin. Other initial laboratory tests or physical examinations showed no specific findings that distinguish gallbladder edema from acute cholecystitis (**Table 1**). Tests for viral or autoimmune hepatitis were negative. CT and ultrasonographic imaging showed gallbladder wall thickening. Acute cholecystitis was suspected, and emergent cholecystectomy was performed for the first 5 of the 12 patients immediately after their presentation. Based on macroscopic and microscopic findings after cholecystectomy, 4 of the 5 patients were found to have alcoholic hepatitis as the cause of gallbladder edema, whereas drug-induced hepatitis in the remaining patient was found to have caused gallbladder edema. The presence of alcohol abuse in the patients' histories was identified only postoperatively.

Of the 5 patients who underwent cholecystectomy, 1 patient with alcoholic hepatitis developed liver failure postoperatively. Although this patient had no ascites preoperatively, ascites developed immediately postoperatively, with a volume of approximately 3 L/d. This patient underwent treatment for liver failure in the intensive care unit but died of liver failure 44 days postoperatively. The patient with drug-induced hepatitis died of fulminant hepatitis 2 days after undergoing cholecystectomy. Fulminant hepatitis was noted in this patient intraoperatively based on the macroscopic appearance of the liver, and his gallbladder was confirmed to be edematous and was not affected by cholecystitis. Surgery in this patient triggered disseminated intravascular coagulation, and uncontrollable hemorrhage occurred intraoperatively and postoperatively. These 2 patients died of liver dysfunction, which was apparently triggered by cholecystectomy. Most of the other patients also had a poor prognosis, as shown in **Table 1**. Typical macroscopic and microscopic findings of gallbladder edema are shown in **Figures 1** and **2**. Histological examination revealed marked subserosal edema, but no inflammatory changes were noted in the gallbladder wall.

After the 5 misdiagnoses, we adopted a wait-and-see policy for patients who are suspected to have gallbladder edema, even if they presented to our department for urgent cholecystectomy based on a diagnosis of acute cholecystitis. As a result, the latter 7 patients in this series did not undergo cholecystectomy because gallbladder edema was identified, and cholecystitis was excluded based on CT and ultrasonographic findings. These 7 patients were eventually diagnosed with heart failure (2

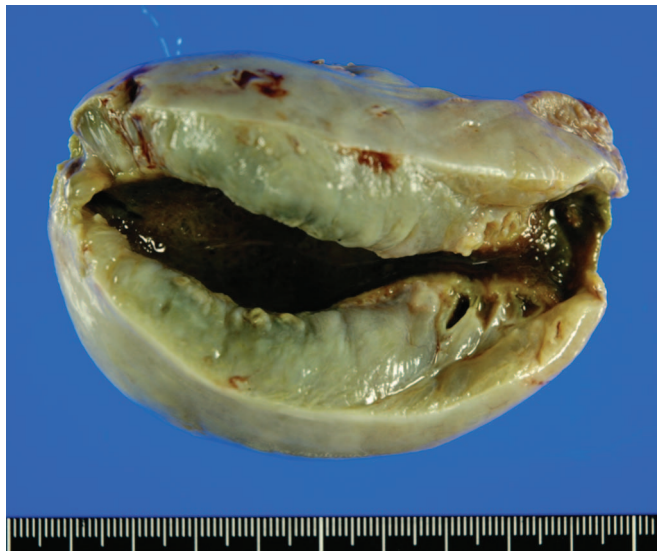

Figure 1. Photograph showing gallbladder edema.

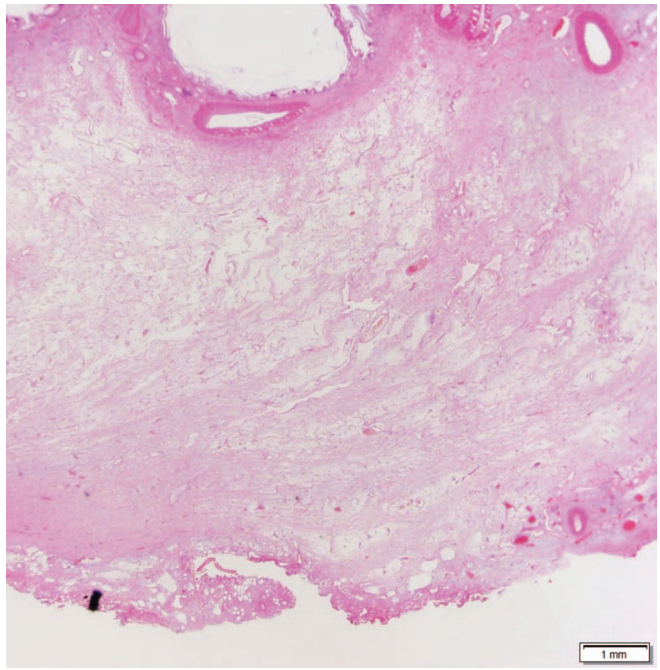

Figure 2. Photomicrograph showing gallbladder edema (hematoxylin and eosin staining, ×12.5).

patients), renal failure (2 patients), alcoholic cirrhosis (1 patient), hypoproteinemia (serum protein level, 34 g/L) secondary to malnutrition from severe depression (1 patient), and drug-induced hepatitis accompanied with Stevens-Johnson syndrome (1 patient). Eventually, the patients were treated specifically for their systemic disease without cholecystectomy. After their discharge, the patients were followed closely at our outpatient clinic during the follow-up period. To date, cholecystitis has not occurred in these patients.

Typical CT and ultrasonographic images of gallbladder edema and acute cholecystitis are shown in **Figure 3** and **4**, respectively. These images indicate differences in the features of the thickened gallbladder wall. **Table 2** shows differences in CT and ultrasonographic images between acute cholecystitis and gallbladder edema. The features of gallbladder edema in our patients were as follows: no gallbladder distention, no thickened mucosa, no stones or debris, no inflammatory changes in the surrounding tissues, and a mesh-like appearance of the gallbladder wall on ultrasonography.

DISCUSSION

Systemic diseases, such as liver disorders or heart failure, may lead to diffuse gallbladder edema. Liver cirrhosis, hepatitis, and congestive right heart failure are relatively frequent causes of diffuse gallbladder edema.[1–12] However, it would be difficult to diagnose gallbladder edema without cholecystectomy because the lower incidence of gallbladder edema compared with that of cholecystitis, which requires cholecystectomy, leads to the assumption that the latter is present where related symptoms are identified. Remarkably, the incidence of gallbladder edema was only 0.45% in the current study. In addition, gallbladder edema caused by alcoholic hepatitis has not been previously described, and no study has described the prognosis of patients in whom gallbladder edema was misdiagnosed as acute cholecystitis.

Although the exact pathophysiological mechanism in these conditions is uncertain, the underlying mechanism is considered to be secondary to elevated portal venous pressure, elevated systemic venous pressure, decreased intravascular osmotic pressure, or a combination of these factors.[2] In addition, several reports have indicated that gallbladder wall thickening in patients with acute viral hepatitis may be explained by gallbladder inflammation caused by the hepatitis virus in the bile duct.[11,12] However, the cause of gallbladder edema in patients with hepatitis does not appear to be gallbladder inflammation caused by the hepatitis virus, even in patients with viral hepatitis. This is because the hepatitis-induced gallbladder edema described in the present report was not associated with inflammatory changes in the gallbladder based on microscopic and macroscopic findings. The mechanism of gallbladder

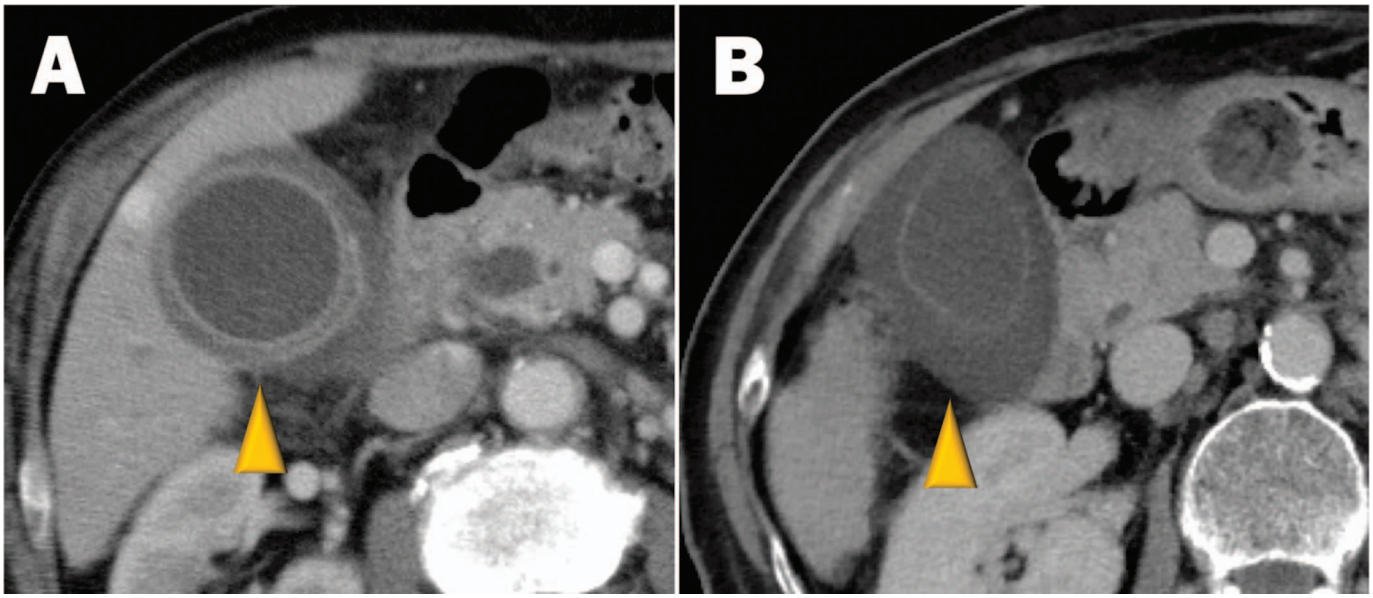

Figure 3. Computed tomographic images showing acute cholecystitis and gallbladder edema. Arrowheads indicate the gallbladder: (**A**) acute cholecystitis amd (**B**) gallbladder edema.

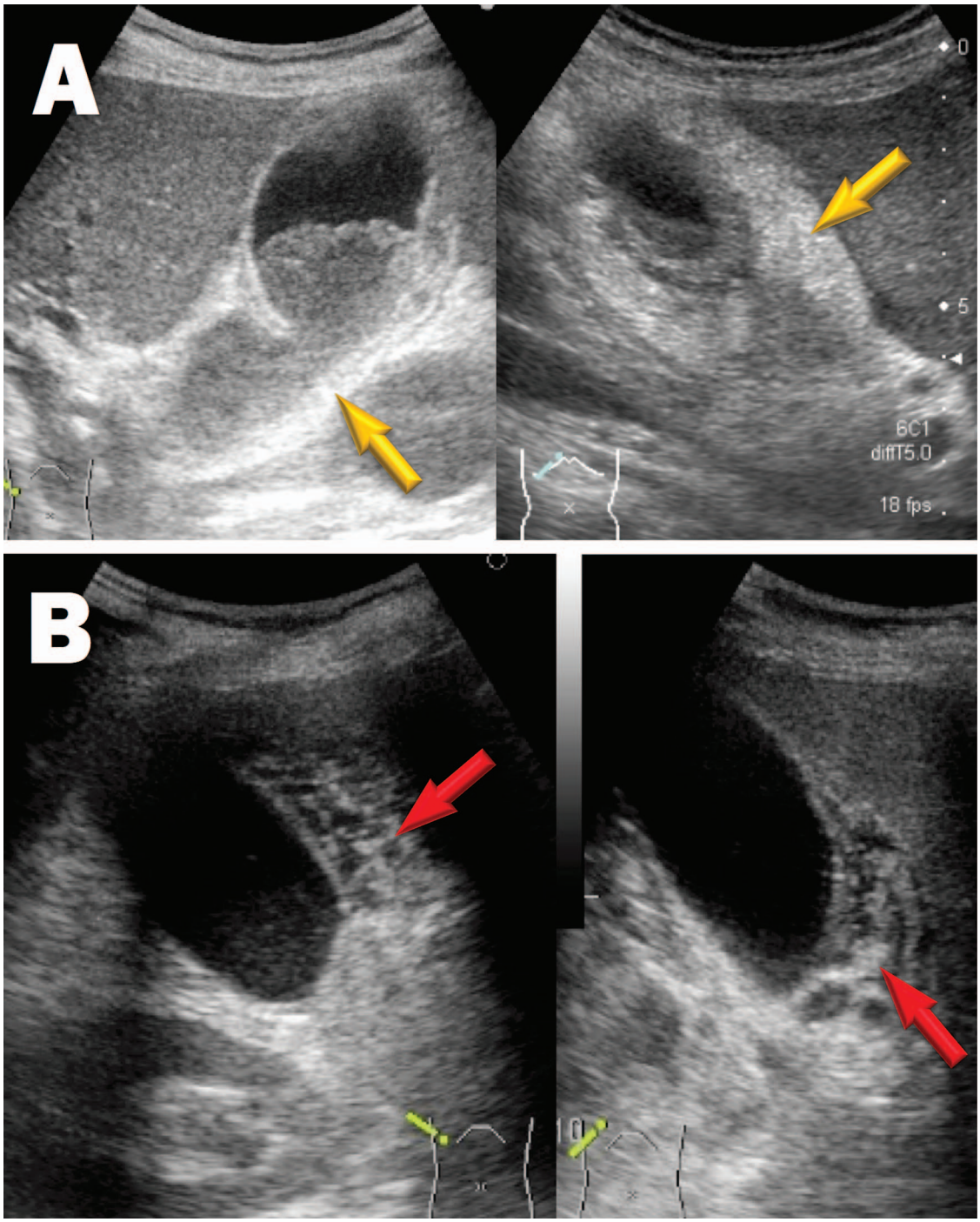

Figure 4. Ultrasonographic images showing acute cholecystitis and gallbladder edema. Arrows indicate the thickened gallbladder wall: (**A**) acute cholecystitis amd (**B**) gallbladder edema. Mesh-like wall thickening is a distinctive feature of gallbladder edema on ultrasonography.

edema caused by all types of hepatitis, such as viral hepatitis, drug-induced hepatitis, and alcoholic hepatitis, may be explained by a single factor—an elevated portal venous pressure.

A contributing factor to the misdiagnosis in our patients was a lack of identification of gallbladder wall edema. In all misdiagnosed cases in the present report, the gallbladder was not distended, the mucosa was not

Table 2.
Differences in Computed Tomography and Ultrasonography Findings Between Acute Cholecystitis and Gallbladder Edema

Gallbladder Imaging	Acute Cholecystitis	Edema of Gallbladder
Computed tomography		
Shape	Distended	Not distended
Mucosa	Thickened	Not thickened
Contents	Stone or debris	No stone, no debris
Surrounding fat	Inflamed	Not inflamed
Ultrasonography		
Shape	Distended	Not distended
Mucosa	Thickened	Not thickened
Contents	Stone or debris	No stone, no debris
Wall thickening	Not mesh-like	Mesh-like

thickened, there was no inflammation in the surrounding fat, and no stones or debris were present on CT or ultrasonography. In the present study, mesh-like wall thickening was a distinctive feature of gallbladder edema on ultrasonography. These features are important to distinguish simple gallbladder edema from cholecystitis, as shown in **Figures 3** and **4** and in **Table 2**. When these features indicate that cholecystitis is unlikely, they suggest that a search for other possible causes should be performed.

It is difficult to indicate cholecystectomy if a gallbladder with silent stones shows gallbladder edema. However, it is better to perform cholecystectomy to decrease the risk of gallstone-related diseases in the future, considering the severity of systemic diseases in patients, especially if they can tolerate surgery and are expected for a long-term prognosis. Patients with silent stones are reported to have a high incidence of gallstone-related diseases when they become older.[13]

There are some limitations to this study. Hepatobiliary scintigraphy, such as hepatobiliary iminodiacetic acid scan, was not used in this study. This modality is not widespread in Japan, and most medical institutions or hospitals do not have the equipment. If the patients with gallbladder edema in the current study had undergone scintigraphy, more accurate diagnoses could have been made. However, the ultrasonography findings demonstrated in this study might be more useful for the diagnosis of gallbladder edema compared with those of hepatobiliary scintigraphy.

CONCLUSION

Careful evaluation of imaging findings and clinical symptoms is necessary in patients with gallbladder edema to prevent misdiagnosis. Understanding the diagnostic findings and common pitfalls, along with a knowledge of the differential diagnoses of gallbladder wall thickening, can improve diagnostic accuracy and prevent unnecessary cholecystectomy.

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