Association between juxtapapillary diverticulum and acute cholangitis determined using laboratory data

Minoru Tomizawa¹
Fuminobu Shinozaki²
Yasufumi Motoyoshi³
Takao Sugiyama⁴
Shigenori Yamamoto⁵
Makoto Sueishi⁶

¹Department of Gastroenterology, ²Department of Radiology, ³Department of Neurology, ⁴Department of Rheumatology, ⁵Department of Pediatrics, Shimoshizu Hospital, National Hospital Organization, Yotsukaido, Japan

Abstract: The aim of this study was to evaluate the association between juxtapapillary diverticulum (JD) and acute cholangitis (AC), and to analyze laboratory data to reveal the underlying mechanism. We conducted a retrospective review of 139 patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) between April 2008 and March 2013 for diagnosis or treatment of biliary tract conditions. The Wilcoxon signed-rank test was used for comparison of variables between patients with or without JD. The χ² test was used to analyze the association between JD and AC duct dilatation. Logistic regression analysis was performed to identify variables with strong correlation with AC. ERCP was attempted in 139 patients, but in one patient the endoscope did not reach the papilla of Vater because of a partial gastrectomy, and in two patients evaluation for JD was not possible because of duodenal or papilla of Vater cancer. Therefore, 136 patients were included in this study. JD was significantly associated with AC (P<0.0001) and bile-duct dilatation (P=0.0107), and AC was strongly associated with bile duct dilatation (P=0.0013). Alkaline phosphatase levels were significantly elevated in patients with JD (P=0.0237). In AC patients without JD, χ² for C-reactive protein was 4.48 (P=0.0342), whereas in AC patients with JD, χ² values for the white blood cell count, alkaline phosphatase, and aspartate aminotransferase were 2.62, 3.1, and 3.61, respectively (P=0.025, 0.015, and 0.0336, respectively). JD was strongly associated with AC. Logistic regression analysis suggested that bile flow was disturbed with JD.

Keywords: logistic regression analysis, bile-duct dilatation, alkaline phosphatase, bile flow, papilla of Vater, Wilcoxon singed-rank test, χ² test

Introduction

Acute cholangitis (AC) is a bacterial infection caused by obstruction of the bile duct,¹–³ and should be treated promptly to prevent fatal sepsis.⁴,⁵ Biliary drainage is usually performed through endoscopic retrograde cholangiopancreatography (ERCP),⁶ but papillotomy is necessary for biliary drainage in the treatment of AC.⁷ Juxtapapillary diverticulum (JD) is associated with an increased risk of cholangiopancreatic diseases, such as obstructive jaundice, AC, and acute pancreatitis.⁸–¹⁰ The success rate of cannulation is controversial with ERCP for patients with JD,¹¹,¹² the latter being a risk factor for sphincterotomy.⁸ JD is an outpouching of mucosa and muscularis mucosa that arises in the duodenal window, located at the interruption of the duodenal muscle fibers where the common bile duct (CBD) and main pancreatic duct penetrate the duodenal wall.¹³ The mechanism underlying the association between AC and JD, however, is not known. The aim of the present study was to compare laboratory variables in AC patients with or without JD to identify the potential mechanism underlying the association between these two conditions.
Materials and methods

Patients

Patient records were retrospectively analyzed from April 2008 to March 2013. The institutional ethics committee reviewed our study, and determined that it was not a clinical trial because it was performed as a part of daily clinical practice. Written informed consent was obtained for each session of ERCP and from patients who underwent contrast-enhanced computed tomography (CECT) or magnetic resonance CP (MRCP). Patient anonymity was preserved. ERCP was performed for patients with suspected AC, bile-duct cancer, gallbladder cancer, pancreatic cancer, or intraductal papillary neoplasm. ERCP was also performed for patients with bile-duct stricture and other biliary or pancreatic conditions. In this study, JD was not categorized. Bile-duct dilatation was defined as a bile-duct diameter >7 mm as seen on abdominal ultrasonography, MRCP, CECT, or ERCP. The laboratory data analyzed in this study were white blood cell (WBC) count and C-reactive protein (CRP), total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase, and γ-glutamyl transpeptidase (γ-GTP) levels, all important variables for the diagnosis of AC.

Diagnostic criteria for acute cholangitis

Patients were diagnosed with AC when they had fever, abdominal pain, and jaundice (Charcot’s triad). If a patient did not meet the Charcot’s triad criteria, AC was diagnosed when they showed an inflammatory response, consisting of fever and elevation of WBC count or CRP level, and biliary obstruction involving bile-duct dilatation, biliary stricture, CBD stones, and elevation of ALP or γ-GTP levels. The severity of AC was assessed following the Tokyo Guidelines.

Endoscopic retrograde cholangiopancreatography

ERCP was performed by experienced endoscopists with a duodenoscope (JF-260V; Olympus, Tokyo, Japan). Papillotomy was performed with a pull-type sphincterotome (Boston Scientific, Natick, MA, USA). Stones and sludge were removed with a basket or balloon catheter, and a nasobiliary catheter was inserted for drainage if necessary.

Imaging diagnostics

Patients with suspected AC underwent CECT and abdominal ultrasonography to further investigate biliary dilatation, CBD stones, and cancer. After May 2012, the patients underwent MRCP with a 1.5 T scanner (Achieva Software version 3.2.2; Philips Medical Systems, Best, Netherlands). Before May 2012, some of the patients were referred to Sannou Hospital (Chiba City, Japan) for MRCP. CECT was performed using

Table 1 Comparison of laboratory data between patients with and without juxtapapillary diverticulum

|                      | Without juxtapapillary diverticulum (n=98) | With juxtapapillary diverticulum (n=37) | P-value |
|----------------------|-------------------------------------------|----------------------------------------|---------|
|                      | Mean ± 95% CI                              | Mean ± 95% CI                          |         |
| Age, years           | 69.2 ± 67.2–71.2                          | 69.0 ± 65.7–72.3                       | 0.8989  |
| WBC                  | 7,391 ± 6,551–8,232                       | 8,308 ± 6,940–9,760                    | 0.2610  |
| CRP                  | 6,68 ± 5,157–8,232                        | 6,83 ± 5,157–8,232                     | 0.9592  |
| T-Bil                | 1,23 ± 0.94–1,56                         | 1,23 ± 0.94–1,56                      | 0.6441  |
| ALP                  | 6,68 ± 5,157–8,232                        | 6,83 ± 5,157–8,232                     | 0.9592  |
| AST                  | 1,09 ± 0.84–1,34                         | 1,09 ± 0.84–1,34                      | 0.7268  |
| ALT                  | 1,09 ± 0.84–1,34                         | 1,09 ± 0.84–1,34                      | 0.7268  |
| γ-GTP                | 259 ± 181–316                             | 259 ± 181–316                          | 0.6897  |

Note: P-values were determined by Wilcoxon’s signed-rank test.

Abbreviations: CI, confidence interval; WBC, white blood cell; CRP, C-reactive protein; T-Bil, total bilirubin; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GTP, glutamyl transpeptidase.

Table 2 Comparison of laboratory data between patients with acute cholangitis with and without juxtapapillary diverticulum

|                      | Without juxtapapillary diverticulum (n=27) | With juxtapapillary diverticulum (n=26) | P-value |
|----------------------|-------------------------------------------|----------------------------------------|---------|
|                      | Mean ± 95% CI                              | Mean ± 95% CI                          |         |
| Age                  | 68.8 ± 64.8–72.3                          | 68.8 ± 64.8–72.3                       | 0.5989  |
| WBC                  | 10,122 ± 8,075–12,169                     | 8,075 ± 6,995–11,166                   | 0.0302  |
| CRP                  | 6,19 ± 3,65–8,73                         | 6,19 ± 3,65–8,73                      | 0.6207  |
| T-Bil                | 2,93 ± 1,59–4,27                         | 2,93 ± 1,59–4,27                      | 0.6207  |
| ALP                  | 683 ± 475–804                            | 683 ± 475–804                         | 0.9854  |
| AST                  | 209 ± 123–295                            | 209 ± 123–295                         | 0.2332  |
| ALT                  | 204 ± 131–276                            | 204 ± 131–276                         | 0.3783  |
| γ-GTP                | 350 ± 227–474                            | 350 ± 227–474                         | 0.5591  |

Note: P-values were determined by Wilcoxon’s signed-rank test.

Abbreviations: CI, confidence interval; WBC, white blood cell; CRP, C-reactive protein; T-Bil, total bilirubin; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GTP, glutamyl transpeptidase.

Table 3 Correlation between juxtapapillary diverticulum and acute cholangitis or bile-duct dilatation

|                      | Acute cholangitis (P<0.0001) | Bile-duct dilatation (P=0.0107) | Total |
|----------------------|-----------------------------|---------------------------------|-------|
|                      | −                           | +                               | − +   |
| Juxtapapillary diverticulum | 72 ± 27                     | 59 ± 40                          | 99    |
| +                    | 11 ± 26                     | 13 ± 24                          | 37    |
| Total                | 83 ± 53                     | 72 ± 64                          | 136   |

Note: P-values were determined by χ² test.
Table 4 Correlation between acute cholangitis and bile-duct dilatation

| Bile-duct dilatation | Total |
|----------------------|-------|
| –                    | 53    |
| +                    | 19    |
| Total                | 72    |

Note: $P=0.0013$ ($\chi^2$ test).

Table 5 Correlation between juxtapapillary diverticulum and symptoms of acute cholangitis

| Abdominal pain (P=0.2117) | Total | Fever (P=0.6854) | Total | Jaundice (P=0.8928) | Total |
|---------------------------|-------|------------------|-------|----------------------|-------|
| –                         | 8     | 12               | 14    | 27                   |
| +                         | 4     | 13               | 13    | 26                   |
| Total                     | 24    | 25               | 27    | 26                   |
|                           | 45    | 28               | 69    |

Note: $P$ values were determined by $\chi^2$ test.

Correlated with the presence or absence of JD, but ALP level was significantly elevated in patients with JD ($P=0.0237$). No significant differences in baseline characteristics were noted between AC patients with JD or those without JD (Table 2).

Our analysis of the association of JD with AC or bile-duct dilatation (Table 3) revealed that JD was significantly associated with both AC ($P<0.0001$) and bile-duct dilatation ($P=0.0107$). The correlation of AC and bile-duct dilatation was then analyzed with the $\chi^2$ test (Table 4), which revealed a strong association of AC with bile-duct dilatation ($P=0.0013$).

Because symptoms are diagnostic clues to AC, we analyzed the correlation between JD and AC symptoms (Table 5). Although there was a tendency for a correlation of abdominal pain with JD, it was not significant ($P=0.2117$).

To reveal whether any laboratory data variables correlated with AC, logistic regression analysis was applied. The patients with AC were divided into those with or without JD. Table 6 shows the results of logistic regression analysis with AC patients without JD. The $\chi^2$ of CRP was 4.48 ($P=0.0342$). For AC patients with JD, the $\chi^2$ values for WBC count, ALP, and AST were 2.62, 3.1, and 3.16, respectively ($P=0.0251$, 0.015, and 0.0336, respectively; Table 7). No other laboratory parameters correlated with AC patients without JD.

Discussion

JD has been found in 32.8% of consecutive patients subjected to ERCP, and is classified into three types based on the position of the papilla of Vater: type 1, inside the diverticulum; type 2, in the margin of the JD; and type 3, near the JD. In our series, JD was found in 27.2% of patients who underwent ERCP, which is consistent with previous reports.

It is reported that JD is associated with CBD stones and bile-duct dilatation, although JD may be associated with bile-duct dilatation even in patients with normal levels of liver enzymes. Our data are consistent with previous reports. It is speculated that the anatomical abnormalities of JD may play an important role in the formation of bile-duct pigment stones.
Table 6 Logistic regression analysis of patients with acute cholangitis without juxtapapillary diverticulum

|  | OR  | 95% CI of OR | P-value |
|---|---|---|---|
| WBC | 1.61 | 1.0001084 | 0.999709–1.000055 | 0.2052 |
| CRP | 4.48 | 1.176696 | 0.721717–0.979098 | 0.0342 |
| T-Bil | 1.49 | 1.1781629 | 0.580052–1.057499 | 0.2226 |
| ALP | 1.1781629 | 0.999709–1.000055 | 0.2052 |
| AST | 0.19 | 1.001254 | 0.991369–1.004106 | 0.6660 |
| ALT | 0.27 | 1.0018022 | 0.991558–1.005594 | 0.6040 |
| γ-GTP | 0.03 | 1.0002375 | 0.991558–1.002736 | 0.95%

Note: P-values were determined by logistic regression analysis.

Abbreviations: OR, odds ratio; CI, confidence interval; WBC, white blood cell; CRP, C-reactive protein; T-Bil, total bilirubin; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GTP, glutamyl transpeptidase.

The relation between bile-duct dilatation and AC is strong enough for bile-duct dilatation to be a criterion for the diagnosis of AC, possibly suggesting bile-duct obstruction. On the other hand, the mechanism underlying the association between JD and bile-duct dilatation is unclear.

In the present study, ALP levels were higher in patients with JD than in those without JD. With regard to only patients with AC, there was no difference in ALP levels between patients with or without JD. These data suggest that bile flow might be disturbed with JD. Once AC occurs and ALP level is elevated, any difference between patients with and without JD may be obscured. The incidence of positive bacterial bile cultures is significantly higher in patients with JD than in those without, which combined with our data suggests that bile flow might be disturbed with JD and that bacterial infection is present more often in the bile ducts of patients with JD than in those without. Therefore, bile-duct pigment stones formed more often in patients with JD than in those without.

The sphincter of Oddi regulates bile flow and prevents AC. AC is caused by obstruction of the bile duct, mainly by CBD stones. In the present study, the laboratory variables correlating with AC were different between patients with or without JD. CRP was the only variable that correlated with AC in patients without JD, whereas WBC count and ALP and AST levels were correlated with AC in patients with JD. WBC count and CRP level indicate inflammation, whereas ALP and AST levels represent bile-duct obstruction. Our data suggest that bile flow was disturbed in patients with JD. It has been speculated that JD disturbs the motility of the duodenum and pressure of the sphincter of Oddi, leading to increased infection of the bile duct in concert with bacterial overgrowth in the diverticulum. The infection might be enhanced in the presence of edema and partial obstruction of the bile duct with CBD stones. This hypothesis could be demonstrated by measuring bile-duct pressure with a manometer during ERCP. A potential concern is that JD could be a risk factor for complications, such as bleeding, infection, and acute pancreatitis. To reduce this risk, endoscopic papillary large-balloon dilatation is recommended for patients with JD. It would be preferable for AC patients with JD to undergo more frequent follow-ups after treatment, because they could be prone to AC relapse. Further studies measuring the pressure of the sphincter of Oddi using a manometer are needed to provide more details of this association. In conclusion, our study findings showed that JD was strongly associated with AC and that bile flow was disturbed with JD, based on laboratory data.

Disclosure
The authors report no conflicts of interest in this work.

References
1. Mosler P. Management of acute cholangitis. Gastroenterol Hepatol (NY). 2011;7(2):121–123.
2. Sahu MK, Chacko A, Dutta AK, Prakash JA. Microbial profile and antibiotic sensitivity pattern in acute cholangitis. Indian J Gastroenterol. 2011;30(5):204–208.
3. Kim SW, Shin HC, Kim HC, Hong MJ, Kim YJ. Diagnostic performance of multidetector CT for acute cholangitis: evaluation of a CT scoring method. Br J Radiol. 2012;85(1014):770–777.
4. Qureshi WA. Approach to the patient who has suspected acute bacterial cholangitis. Gastroenterol Clin North Am. 2006;35(2):409–423.
5. Yoneyama K, Saito H, Kurihara T, et al. Factors involved in resistance of multidetector CT for acute cholangitis: evaluation of a CT scoring method. Br J Radiol. 2012;85(1014):770–777.
6. Mosler P. Diagnosis and management of acute cholangitis. Curr Gastroenterol Rep. 2011;13(2):166–172.
7. Miura F, Takada T, Kawarada Y, et al. Flowcharts for the diagnosis and treatment of acute cholangitis and choledocholithiasis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg. 2007;14(1):27–34.
8. Zoepf T, Zoepf DS, Arnold JC, Benz C, Riemann JF. The relationship between juxtapapillary duodenal diverticula and disorders of the biliopancreatic system: analysis of 350 patients. Gastrointest Endosc. 2001;54(1):56–61.
9. Boender J, Nix GA, de Ridder MA, et al. Endoscopic papillotomy for common bile duct stones: factors influencing the complication rate. *Endoscopy*. 1994;26(2):209–216.

10. Tsujino T, Sugita R, Yoshiida H, et al. Risk factors for acute suppurative cholangitis caused by bile duct stones. *Eur J Gastroenterol Hepatol*. 2007;19(7):585–588.

11. Kirk AP, Summerfield JA. Incidence and significance of juxtapapillary diverticula at endoscopic retrograde cholangiopancreatography. *Digestion*. 1980;20(1):31–35.

12. Boix J, Lorenzo-Zúñiga V, Añaños F, Doménech E, Morillas RM, Gassull MA. Impact of periampullary duodenal diverticula at endoscopic retrograde cholangiopancreatography: a proposed classification of periampullary duodenal diverticula. *Surg Laparosc Endosc Percutan Tech*. 2006;16(4):208–211.

13. Avise C, Flament JB, Delattre JF. Ampulla of Vater. Anatomic, embryologic, and surgical aspects. *Surg Clin North Am*. 2000;80(1):201–212.

14. Adler DG, Baron TH, Davila RE, et al. ASGE guideline: the role of ERCP in diseases of the biliary tract and the pancreas. *Gastrointest Endosc*. 2005;62(1):1–8.

15. Lee JG. Diagnosis and management of acute cholangitis. *Nat Rev Gastroenterol Hepatol*. 2009;6(9):533–541.

16. Kiriyma S, Takada T, Strasberg SM, et al. New diagnostic criteria and severity assessment of acute cholangitis in revised Tokyo Guidelines. *J Hepatobiliary Pancreat Sci*. 2012;19(5):548–556.

17. Kim CW, Chang JH, Kim JH, Kim TH, Lee IS, Han SW. Size and type of periampullary duodenal diverticula are associated with bile duct diameter and recurrence of bile duct stones. *J Gastroenterol Hepatol*. 2013;28(5):893–898.

18. Malik S, Kaushik N, Khalid A, et al. EUS yield in evaluating biliary dilatation in patients with normal serum liver enzymes. *Dig Dis Sci*. 2007;52(2):508–512.

19. Bruno M, Brizzi RF, Mezzabotta L, et al. Unexplained common bile duct dilatation with normal serum liver enzymes: diagnostic yield of endoscopic ultrasound and follow-up of this condition. *J Clin Gastroenterol*. 2014;48(8):e67–e70.

20. Wu SD, Su Y, Fan Y, et al. Relationship between intraduodenal periampullary diverticulum and biliary disease in 178 patients undergoing ERCP. *Hepatobiliary Pancreat Dis Int*. 2007;6(3):299–302.

21. Shinagawa N, Fukui T, Mashita K, Kitano Y, Yura J. The relationship between juxtapapillary diverticula and the presence of bacteria in the bile. *Jpn J Surg*. 1991;21(3):284–291.

22. Liu YF, Saccone GT, Thune A, Baker RA, Harvey JR, Touuli J. Sphincter of Oddi regulates flow by acting as a variable resistor to flow. *Am J Physiol*. 1992;263(5 Pt 1):G683–G689.

23. Kakuyama S, Nobutani K, Masuda A, et al. Sphincter of Oddi manometry using guide-wire-type manometer is feasible for examination of sphincter of Oddi motility. *J Gastroenterol*. 2013;48(10):1144–1150.

24. Kim KH, Kim TN. Endoscopic papillary large balloon dilation in patients with periampullary diverticula. *World J Gastroenterol*. 2013;19(41):7168–7176.