

TG13 miscellaneous etiology of cholangitis and cholecystitis

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Abstract This paper describes typical diseases and morbidities classified in the category of miscellaneous etiology of cholangitis and cholecystitis. The paper also comments on the evidence presented in the Tokyo Guidelines for the management of acute cholangitis and cholecystitis (TG 07) published in 2007 and the evidence

reported subsequently, as well as miscellaneous etiology that has not so far been touched on. (1) Oriental cholangitis is the type of cholangitis that occurs following intrahepatic stones and is frequently referred to as an endemic disease in Southeast Asian regions. The characteristics and diagnosis of oriental cholangitis are also commented on. (2) TG 07 recommended percutaneous transhepatic biliary drainage in patients with cholestasis (many of the patients have obstructive jaundice or acute cholangitis and present clinical signs due to hilar biliary stenosis or obstruction).

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However, the usefulness of endoscopic naso-biliary drainage has increased along with the spread of endoscopic biliary drainage procedures. (3) As for biliary tract infections in patients who underwent biliary tract surgery, the incidence rate of cholangitis after reconstruction of the biliary tract and liver transplantation is presented. (4) As for primary sclerosing cholangitis, the frequency, age of predilection and the rate of combination of inflammatory enteropathy and biliary tract cancer are presented. (5) In the case of acalculous cholecystitis, the frequency of occurrence, causative factors and complications as well as the frequency of gangrenous cholecystitis, gallbladder perforation and diagnostic accuracy are included in the updated Tokyo Guidelines 2013 (TG13).

Free full-text articles and a mobile application of TG13 are available via <http://www.jshbps.jp/en/guideline/tg13.html>.

Keywords Oriental cholangitis · Calculous cholecystitis · Primary sclerosing cholangitis · Guidelines · Biliary infection

Introduction

Along with the addition of the evidence that has been reported since 2007, we report on the miscellaneous

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etiology of cholangitis and cholecystitis included in the Tokyo Guidelines for the management of acute cholangitis and cholecystitis (TG 07) [1] published in 2007. In view of the presence of miscellaneous evidence that has not so far been touched on, we thought it necessary that the updated Tokyo Guidelines 2013 (TG13) prepare new items, put the evidence so far collected in its due place, and provide explanations. Diseases and morbidities classified in this category include (1) oriental cholangitis, (2) acute cholangitis and cholecystitis associated with pancreaticobiliary malignancies, (3) biliary tract infections in patients who underwent previous biliary tract surgery, (4) primary sclerosing cholangitis, and (5) acalculous cholecystitis.

In this paper, we present comments not only on the characteristics of miscellaneous etiology of cholangitis and cholecystitis but also on diagnostic and therapeutic methods, along with the addition of the newly reported evidence.

Oriental cholangitis (cholangiohepatitis)

Characteristics

Oriental cholangitis (Fig. 1, Supplement Fig. 1) is defined as that type of cholangitis characterized by recurrent right upper quadrant pain, fever, chill and jaundice induced by intrahepatic biliary stricture and intrahepatic stones. It is a pandemic disease observed in Southeast Asian regions, and people in the low-income group are frequently affected by the disease. Involvement of β -glucuronidase due to parasitic and bacterial biliary tract infections is suggested as a causative factor [2–7]. In recent years, however, it is rare that the presence of parasites is confirmed by a resected specimen of the liver [8]. Terms such as “oriental cholangitis,” “recurrent pyogenic cholangitis” and “primary hepatolithiasis” are frequently used in Korea, Hong Kong and Japan. They have been referred to as the terms that describe different aspects of the same morbidities [9]: emphasis is placed on ethnic predilection and the mysterious nature of “oriental cholangitis”, clinical presentation and suppurative inflammation in “recurrent pyogenic cholangitis”, and pathological changes in “primary hepatolithiasis”, respectively [9]. Pathologically, “oriental cholangitis” is characterized by dilatation and stricture of the extrahepatic/intrahepatic bile duct accompanying intrahepatic pigment calculi, and hypertrophy is observed in the bile duct wall accompanied by intrahepatic pigment calculus and thickening accompanied by fibrosis and inflammatory cell invasion [2–5, 7].

As for parasites related to oriental cholangitis, roundworms and Chinese liver flukes have been reported. Adult

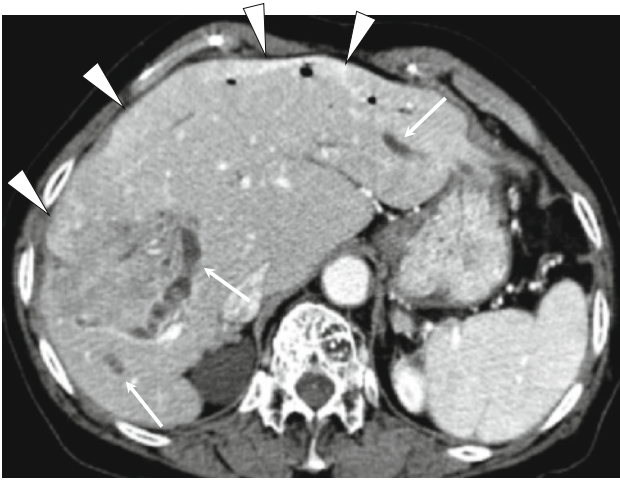


Fig. 1 Oriental cholangitis: dynamic contrast-enhanced CT shows inhomogeneous enhancement (especially of the peripheral portion of the liver: *arrowheads*) and intrahepatic bile duct dilatation (*arrows*)

roundworms sometimes enter the bile duct through the duodenal papilla and give rise to cholangitis in 16–56.6 % of patients [10]. Chinese liver flukes colonize the intrahepatic bile duct and then live there for 20–30 years, causing chronic inflammatory parasitic changes [11].

Q1. What are the imaging findings of oriental cholangitis?

The imaging findings of oriental cholangitis are follows; extrahepatic bile duct dilatation, intrahepatic calculi, localized dilatation / stricture in the biliary tree of the medial segment of the liver, atrophy of the liver segment/decreased blood flow, increased echogenicity (US) of the hepatic portal vein, and liver abscess.

Diagnosis

Ultrasound/computed tomography (US/CT) enables observation of bile duct dilatation and pneumobilia (Fig. 1, Supplement Fig. 1), increased US echogenicity in the portal vein segment of the liver, and atrophy of the liver segment/decreased blood flow [4–6, 8]. However, US does not necessarily depict intrahepatic stones accompanied by acoustic shadow [8]. Calcium bilirubinate calculi are also observed as a high-absorption region on CT; however, due to the low absorption level of cholesterol stones, depiction of cholesterol stones sometimes becomes difficult [8]. Magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) is able to provide better imaging without the risk of aggravated sepsis cholangitis

and is good at depicting lesions on the proximal side of the obstruction and stricture and those outside of the biliary duct [6]. However, when cholestasis is present, a diagnosis of stones can become impossible or it may be impossible to visualize the bile duct because of bile concentration and low signal. Pneumobilia is likely to be mistaken for stones because it presents a low signal [8]. The rate of correct diagnosis of the obstructed location by MRI/MRCP is 96–100 %, a diagnosis of a cause of obstruction is made in 90 % and one of intrahepatic stones is the same as that by endoscopic retrograde cholangiopancreatography (ERCP). Direct cholangiography such as percutaneous transhepatic cholangiography is an invasive test [6] and it has merits in that it simultaneously enables (1) the removal of intrahepatic stones, (2) biopsy of bile duct lesions, and (3) stent placement in the bile duct [8]. The reported imaging findings from direct cholangiography are those of the dilated bile duct and stones, straightening of the bile duct, rigidity, decreased arborization, increased branching angle, acute peripheral tapering and multiple focal strictures [5, 6]. The diagnostic sensitivity of direct cholangiography for making a diagnosis of bile duct obstruction is 100 %, that for stones is somewhat inferior to that of MRCP (90–96 %), and specificity is 98 %. The incidence of liver abscess in oriental cholangitis is 20 % lower; there is often a number of partitions. Abscess should therefore be suspected when the limbus is depicted with CT [6].

Acute cholangitis and cholecystitis associated with pancreaticobiliary malignancy

Characteristics

Biliary drainage is carried out for pancreaticobiliary malignancies because they are frequently accompanied by obstructive jaundice. However, patients with morbidities accompanied by acute cholangitis requiring urgent biliary drainage are few in number (Supplement Fig. 2). Acute cholangitis requiring urgent biliary drainage is frequently observed in the following patients: (1) those who failed to undergo biliary drainage even if the bile duct at the upper stream of the liver above the obstructed site of the bile duct was depicted, and (2) those in whom drainage was unsuccessful due to catheter obstruction even though a drainage tube had been placed in the bile duct at the upper stream of the liver above the obstructed site of the bile duct due to malignant tumor [1].

The destruction of papillary function due to stent placement and re-obstruction of the bile duct arising from tumor enlargement have been reported as a risk factor for acute cholangitis after metal stent placement for internal

biliary drainage. Furthermore, cancer progression to the cystic duct and cystic duct obstruction due to stent replacement in the bile duct have been reported as risk factors for the development of acute cholecystitis after stent placement [12–15].

Diagnosis

As for the diagnostic accuracy of diagnostic imaging for malignant tumors, there is a report showing that the sensitivity/specificity/rate of correct diagnosis of US for extrahepatic bile duct cancers are 85.6/76.9/84.4 % for cancers of the hilar bile duct; 59.1/50/57.1 % for cancers of the middle bile duct; and 33.3/42.8/36.8 % for cancers of the lower bile duct, respectively [16]. There are reports showing that about 100 % of the tumors of the biliary system, except early cancers, are recognized with multi-detector CT and a judgment of the usefulness of resection can be made in 74.5–91.7 % of the cases [17, 18]. A meta-analysis of MRCP has found that its sensitivity and specificity are 97/88 and 98/95 %, respectively, when the detection of obstruction/malignancy has been set as the end point [19].

Q2. How drainage should be carried out for postoperative acute cholangitis following pancreaticobiliary malignancies?

We suggest a safe and reliable method should be selected at the facility concerned. When it is difficult, emergency transportation to an appropriate facility should take place (recommendation 1, level C).

Treatment

The presence of preoperative cholangitis and cholecystitis without control of pancreaticobiliary malignancies is an independent risk factor for postoperative death during hospital stay and the development of complications, so it is considered that the control of those morbidities is important [20–23]. In recent years, we have occasionally come across opinions that recommend the use of endoscopic naso-biliary drainage for hilar cholangiocarcinoma also, in view of the occurrence of vascular injuries (8 %), peritoneal dissemination (4 %) and recurrence of fistula (5.2 %) [24, 25]. However, there are so far no reports of randomized controlled trials comparing the modalities of preoperative biliary drainage. Therefore, it is thought that what matters at this time will be whether or not there are physicians expert in endoscopic or percutaneous drainage at the facility involved, and the selection of a method

enabling safe and reliable emergency biliary drainage [26]. When the above conditions are not applicable, patients should be transferred to an appropriate facility to undergo biliary drainage.

Due to possible risks associated with preoperative percutaneous biliary drainage for fistula recurrence and carcinomatous peritonitis [1], one-stage radical surgery should be conducted as far as the circumstances allow.

Biliary tract infections in patients who have undergone previous biliary tract surgery

Q3. What is the frequency of cholangitis after biliary tract reconstruction?

Cholangitis occurs in about 10% of the patients after biliary tract reconstruction.

Characteristics

After ERCP and biliary tract surgery, there can be latent cholangitis and cholecystitis. According to reports that have examined patients undergoing biliary tract reconstruction, cholangitis occurred during 29–129 months' follow-up in 11.3 % of the patients after papiloplasty, 10.3–10.9 % after choledochoduodenostomy, and 6.4–11.3 % after choledochojejunostomy (Supplement Fig. 3), and in about 4 % of patients in whom cholangitis was recurrent and severe [27, 28]. Although there are no differences between perioperative mortality rate and the incidence rate of complications [28], bile duct carcinomas occurred after biliary tract reconstruction in 1.9–7.6 % of the patients, suggesting the presence of a relationship between inflammatory changes in the bile duct following biliary tract reconstruction and biliary tract cancer that occurs in the late stage [27]. According to a report on patients who were followed up for more than 10 years after surgery for congenital biliary tract dilatation conducted in childhood (mean age 4.2 years), impairment of the liver occurred in 10.7 % of the patients, bile duct dilatation in 10.7 %, and repeated cholangitis in 1.8 % [29].

A systematic review of liver transplantation in adult patients shows that bile duct stricture occurred in 12 % of patients undergoing brain-dead donor liver transplantation and in 19 % of patients undergoing live-donor liver transplantation [30]. According to a discussion of the result according to the surgical techniques of biliary tract reconstruction in 51 patients who had undergone liver transplantation due to primary sclerosing cholangitis (PSC), there were no differences in the survival rate in

patients who had undergone choledochoduodenostomy, choledochojejunostomy or choledochocholedochostomy. However, the incidence of postoperative biliary tract complications that had occurred more than once was 48, 60 and 17 %, respectively [31].

It is reported that the incidence of cholecystitis differs (0.06–12.6 %) according to underlying diseases other than biliary tract surgery or surgical techniques and that the frequency of acalculous cholecystitis is high [32–37].

Primary sclerosing cholangitis

Characteristics

Primary sclerosing cholangitis (PSC) (Fig. 2) causes stricture and obstruction due to progressive and non-specific inflammation of the intra- and extrahepatic bile duct wall and progresses from cholestasis to liver cirrhosis and hepatic failure. Its etiology remains unknown [38, 39]. It is therefore important that secondary sclerosing cholangitis is excluded [40]. PSC is frequently observed in males, Caucasians and Northern Europeans [38]; the incidence rate is 0.41–1.25 patients/100,000 person-years [41, 42], and the mean age at onset is 42 years [38]. There are reports that the age distribution is bipolar in shape with one peak at the 20s and another peak between the 50s and 60s [43, 44]. It is classified into the following 4 stages: (1) small duct cholangitis, (2) progressive cholestasis, (3) cirrhosis, and (4) decompensation [38, 45]. Clinical symptoms differ



Fig. 2 Primary sclerosing cholangitis (PSC): ERCP shows stenosis and beaded appearance

according to the stage of the disease. It is detected by blood test and is often asymptomatic [44]. When the disease has progressed, cutaneous pruritus following cholestasis, jaundice, fever due to cholangitis, and abdominal pain occur. A combination of inflammatory intestinal disease and biliary tract cancer occurs in 4.3–16.6 % of PSC cases [41, 42, 44, 46–51].

Diagnosis

ERCP is a standard imaging test. MRCP has shown promise in recent years as a minimally invasive imaging test procedure [38]. Imaging findings in the bile duct include band-like stricture, beaded appearance (Fig. 2), pruned tree-like appearance, and diverticulum-like out-pouching [52]. The Mayo Clinic diagnostic criteria, which are widely used [40] (Supplementary Table 1), make much of the imaging findings of intra/extrahepatic bile duct stricture and the biliary tract. Elevated levels of serum ALP and T-Bil and an increased leukocyte count are findings common to acute cholangitis. An increased eosinophilic count, a serum γ -globulin level, an elevated IgG/IgM level, positive anti-nuclear antibody and positive perinuclear antineutrophil cytoplasmic antibody (p-ANCA) are useful for differentiation from acute cholangitis [38, 43, 44]. The positive rates are ALP 88 %, ALT 73 %, T-Bil 39 %, P-ANCA 7–77 %, and anti-nuclear antibody 33–87 % [38, 44]. According to meta-analyses, MRCP shows 86 % diagnostic sensitivity and 94 % specificity, demonstrating that it is somewhat inferior in terms of the depiction of the intra/extrahepatic bile duct and a diagnosis of liver cirrhosis and cancer at the early stage [53, 54]. However, it is considered that MRCP has sufficient capacity to enable a diagnostic test for various types of diseases [55]. A diagnosis of cholangiocarcinoma occurring in PSC patients without tumor formation remains a challenging task, so the diagnosis of cholangiocarcinoma is made comprehensively by means of diagnostic modalities such as CA19-9, diagnostic imaging and scraping cytology [56–59]. It is reported that the diagnostic sensitivity/specificity of US, CT and MRI for cholangiocarcinoma are about 57/94, 75/80, 63/79 %, respectively [58]. There is a report showing that positron emission tomography (PET)-CT is useful for making a diagnosis of cholangiocarcinoma [49]. On the other hand, there are also reports showing that PET-CT is not useful [60]. Concomitant use of intra-ductal ultrasound is reported to be associated with the elevated sensitivity and specificity of endoscopic retrograde cholangiography [61, 62]. The sensitivity and specificity of scraping cytology for the bile duct are reported to be about 18–73 and 95–100 %, respectively [56, 59, 63, 64].

Acalculous cholecystitis

Characteristics

Patients with acute acalculous cholecystitis (Fig. 3) account for 3.7–14 % of the patients with acute cholecystitis, 12–49 % of which occurs after trauma and major surgery [65, 66]. Acute acalculous cholecystitis occurs in about 1 % of patients admitted to intensive care units (ICUs) [67], about 1.2 % of patients with severe burns [68], 59–63 % of patients with gangrenous cholecystitis, and 15–20 % of patients with gallbladder perforation [65, 69–71] together with frequent multiple organ dysfunction. The mortality rate is 0 % when the patient's general status is maintained [65, 72]; however, it is high (30–53 %) in critically ill patients [67–69]. Early and appropriate diagnosis and treatment are necessary to reduce the mortality rate [69, 71]. Risk factors for the development of acalculous cholecystitis include surgery, trauma, long-term ICU stays, infections, burns and parenteral nutrition [67, 68]. It is reported that ischemia, reperfusion injury and proinflammatory

mediators such as eicosanoids are involved in the mechanisms for developing such conditions [69, 73].

Diagnosis

Patients are under respiratory control and frequently develop consciousness disturbance arising from the use of analgesics. Findings such as an elevated leukocyte count, liver function disorder and clinical symptoms such as sonographic Murphy's sign, right hypochondriac pain and fever that are highly specific for acute calculous cholecystitis presents are not specific for acute acalculous cholecystitis [66, 71]. US/CT findings include thickening of the wall (>3.5 mm), pericholecystic fluid, emphysematous gallbladder, sloughed mucosal membrane, and lack of gallbladder wall enhancement (only for CT). The sensitivity/specificity of US are 30–92/89–100 %, and those of CT are 33–100/99–100 % [70, 74, 75]. When HIDA (hepatobiliary iminodiacetic acid) scan fails to visualize the gallbladder, the case is judged positive. The sensitivity and specificity of HIDA scan are 68–100 and 38–100 %,

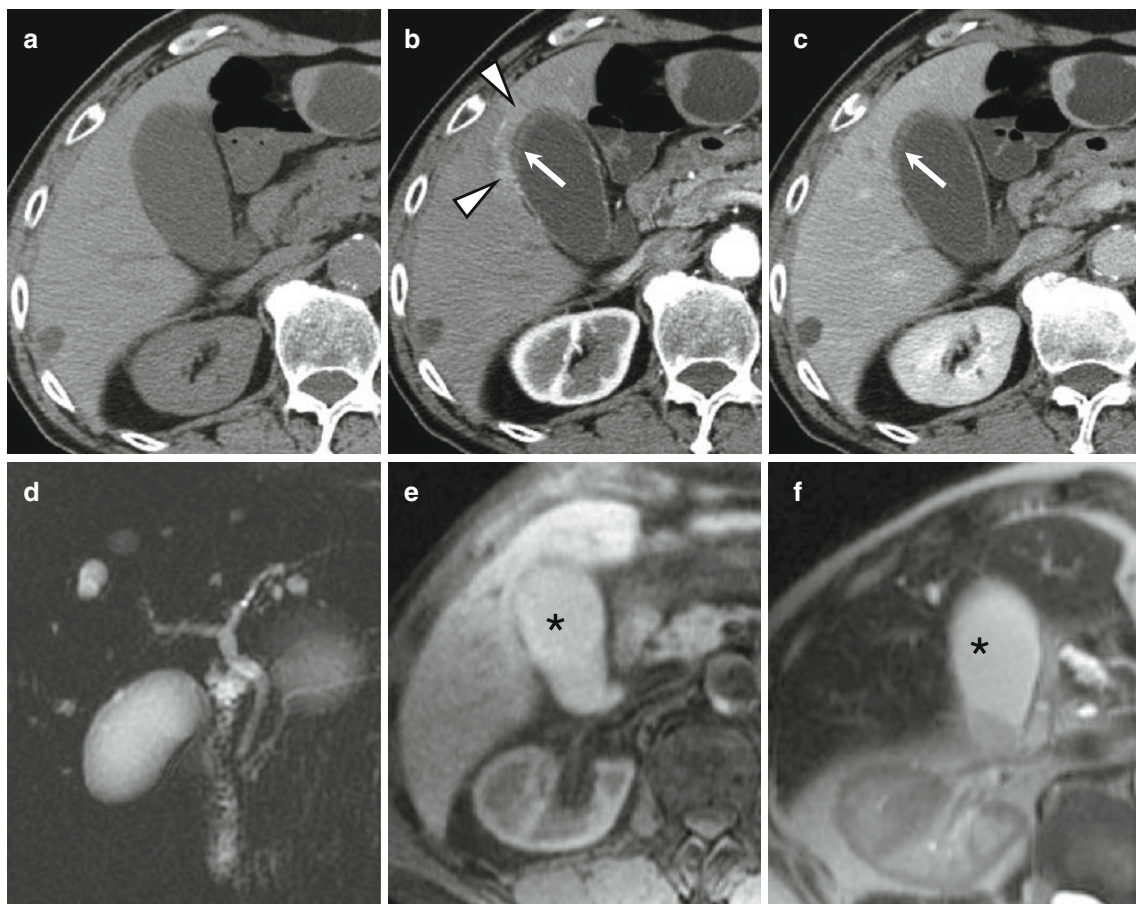


Fig. 3 Acalculous acute cholecystitis: dynamic CT (a–c) shows gallbladder distention, mucosal enhancement (b, c arrows), and transient pericholecystic liver enhancement (b arrowheads). MRCP

(d) shows gallbladder distension. Gallbladder shows marked hyperintensity (asterisk) on fat-suppressed T1-weighted MR image (e) and T2-weighted image (f) indicating inspissated bile juice

respectively. HIDA scan is likely to detect positive cases depending on complications (intravenous hyperalimentation, fasting, hepatic failure) [71]. The rate of correct diagnosis of diagnostic laparoscopy in critically ill patients is reported to be 90–100 % [76].

Q4. What treatment is being carried out for acute acalculous cholecystitis?

Cholecystectomy and/or cholecystostomy (drainage of the GB) are being conducted.

Treatment

Cholecystectomy and/or cholecystostomy (drainage of the gallbladder) are carried out. However, appropriate timing and necessity of cholecystectomy and cholecystostomy are controversial [71]. There are many opinions that cholecystostomy should be conducted in patients with poor general status and that cholecystectomy should be carried out after recovery has been achieved [69, 71, 77, 78]. However, there is a group arguing that cholecystectomy only should be performed [79] and a group asserting that cholecystostomy is the definitive treatment in patients with extremely high risk [80].

Conflict of interest None.

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