AN EPISODE OF ACUTE CHOLANGITIS IN A DEPARTMENT OF INTERNAL MEDICINE: AN UNUSUAL CASE

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[Un episodio di colangite acuta in un reparto di medicina interna: un caso inusuale]

ABSTRACT

Diagnosis of acute cholangitis (AC) is clinical. A definitive diagnosis cannot be established only on the basis of laboratory tests. Thus, a history of biliary tract disease and clinical presentation are important to reach the diagnosis. Pathogenesis of AC is represented by an infection of the biliary tract associated with a partial or complete obstruction of the biliary system due to various causes (bile duct lithiasis, benign or malignant stenosis, malfunction of biliary-enteric anastomosis, etc.). Here we reported the case of a 69-year-old man with recurrent postoperative (laparoscopic cholecystectomy) biliary stricture-related mild acute cholangitis, with presence of biliary sludge in the common bile duct, previously diagnosed by gastroenterologists as acute drug-induced hepatotoxicity. After broad-spectrum antibiotic i.v. therapy the patient subsequently underwent endoscopic retrograde cholangiopancreatography (ERCP), with stent placement, and symptoms and laboratory abnormalities disappeared.

Key words: Acute cholangitis; laparoscopic cholecystectomy; postoperative biliary strictures.

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Introduction

Diagnosis of acute cholangitis (AC) is clinical. A definitive diagnosis cannot be established only on the basis of laboratory tests. A history of biliary tract disease and clinical presentation are important elements in establishing the diagnosis. Classically, the most important clinical manifestation is the so-called "Charcot's triad" (fever and/or chills, abdominal pain and jaundice). According to the literature, 50-70% of patients with AC present this symptomatic triad, but this means that more than one-third do not manifest all the triad components. Laboratory data and the results of imaging studies can provide evidence to support the diagnosis, especially in those patients with clinical manifestations of AC, but without the full triad[1].

The pathogenesis of AC is represented by an infection of the biliary tract associated with a partial or complete obstruction of the biliary system due to various causes (bile duct lithiasis, benign or malignant stenosis, malfunction of biliary-enteric anastomosis, etc.). A biliary tract infection alone may not cause a clinically evident cholangitis, until the biliary obstruction increases intraductal pressure resulting in cholangio-venous or cholangio-lymphatic reflux[2].

Subsequently AC evolves from a localized biliary infection to a systemic inflammatory response syndrome (SIRS), and in the case of advanced disease can lead to sepsis with or without organ dysfunction. In the 1990s mortality rates in severe cases of AC ranged from 11 to 27%, and even now severe forms of AC may be fatal if proper treatment is not received[3,4].

Here we report the case of a 69-year-old man, admitted to our Internal Medicine Department, suffering from recurrent postoperative (laparoscopic cholecystectomy) biliary stricture-related mild acute cholangitis, with presence of biliary sludge in the common bile duct, previously diagnosed by gastroenterologists as acute drug-induced hepatotoxicity. After broad-spectrum antibiotic i.v. therapy the patient subsequently underwent endoscopic retrograde cholangio-pancreatography (ERCP), with stent placement, with resolution of symptoms and laboratory abnormalities.

Case presentation

A 69-year-old man was admitted to our Department of Internal Medicine with night fever. On admission the patient was pyretic (axillary temperature 38.8°C), with pale and dehydrated skin and mucous membranes, soft abdomen with tenderness on deep palpation in the hypo-gastric region, normal bowel sounds. Blood tests showed leucocytosis: white blood cells (WBC) 15.200/mmc, neutrophils 93%, increased hepatic cytolysis: aspartate aminotransferase (AST) 855 IU/ml, reference values 0-37, alanine aminotransferase (ALT) 481 IU/ml, reference values 0-41, and cholestasis indices: alkaline phosphatase (ALP) 669 IU/ml, reference values 40-19, gamma-glutamyl transpeptidase (γ-GT) 552 IU/ml, reference values 8-61, total/direct bilirubin 1.97/1.26 mg/dl, reference values 0.67-1.17/<0.3, and presence of nitrates, bacteriuria and leucocyturia in the urinalysis. A whole-body Computerized Tomography (CT) scan, performed urgently, showed "modest aerobilia and prevalence of left hepatic sections with outcome of cholecystectomy, bladder lithiasis and fecaloma in rectal ampulla". About a week before admission and 3 months before, the patient was hospitalized in a Department of Gastroenterology, with the same symptoms, and discharged with the diagnosis of "acute drug-induced hepatotoxicity" secondary to oral assumption of home antibiotic therapy with penicillin and macrolides to treat a urinary tract infection; during these hospitalizations a "spontaneous" reduction of fever and liver function tests occurred.

Patient's medical history revealed the following. In 1976 a diagnosis of pineal tumor associated with triventricular hydrocephalus, underwent placement of ventricular-peritoneal shunt and subsequent surgical excision of the tumor and cobalt therapy.

In 2001 diagnosis of Parkinson's disease with vascular genesis. In 2006 received an indwelling bladder catheter due to diagnosis of prostatic hypertrophy with urinary incontinence and recurrent urinary tract infections. In 2007 arterial hypertension was diagnosed, and in the same year he was admitted to hospital for "obstructive jaundice", then submitted to laparoscopic cholecystectomy for biliary lithiasis. During the hospitalization in our Department, broad-spectrum antibiotic i.v. therapy with piperacillin/tazobactam plus levofloxacin was carried out followed by defervescence and resolution of leucocytosis (GB 7.250/mmc, neutrophils 67%). Moreover, since the patient had not reported home use of drugs and in relation to previous laparoscopic cholecystectomy, despite the absence of typical AC symptoms (i.e. upper abdominal pain and jaundice), a mechanical obstruction of the bile flow was suspected. Therefore, cholangio-nuclear magnetic resonance was performed showing "mild dilatation of the intra-hepatic bile ducts and of the common bile duct (1.0 cm), as in the presence of gallstones and biliary sludge".

The patient then underwent endoscopic retrograde cholangio-pancreatography (ERCP), which showed a "scar-like sub-stenosis of the papilla of Vater," which was dilated with spontaneous leakage of biliary sludge from the common bile duct, and in which a stent was placed. After the endoscopic treatment, indices of hepatic cytolysis and cholestasis returned to normal range, with the exception of the γ-GT value (125 IU/ml), which normalized after three months. Therefore we reached a final diagnosis of postoperative (laparoscopic cholecystectomy) biliary stricture-related mild acute cholangitis, with presence of biliary sludge in the common bile duct.

Discussion

Patients with AC are at risk of developing serious infections that can be fatal if appropriate treatment is not received promptly. Unlike other diseases, such as acute cholecystitis or diverticulitis, there is no organ or tissue through which the definitive diagnosis can be reached through histology. Therefore, a diagnostic gold standard must be established using other methods. The update of "Diagnostic criteria and assessment of severity of AC: Tokyo Guidelines" in 2007 (TG07), with the new criteria (TG13), improved sensitivity and specificity in the diagnosis of this disease and allows an early assessment of severity, assuming

that biliary drainage or other surgical procedures can be performed immediately[5].

The three main criteria used in the diagnosis of AC are shown in Table 1.

Table 1: Tokyo Guidelines version 13 (TG13) diagnostic criteria for acute cholangitis.

A. Systemic inflammation			
A-1. Fever and/or shaking chills			
A-2. Laboratory data: evidence of inflammatory response			
B. Cholestasis			
B-1. Jaundice			
B-2. Laboratory data: abnormal liver function tests			
C. Imaging			
C-1. Biliary dilatation			
C-2. Evidence of the etiology on imaging (stricture, stone, stent, etc.)			
Suspected diagnosis: one item in A, + one item in either B or C. *Definite diagnosis: one item in A, one item in B, and one item in C*			
A-2 Abnormal white blood cell counts, increase of serum C-reactive protein levels, and other changes indicating inflammation			
B-2 Increased serum γ-GT, ALP, AST and ALT levels			
Thresholds			
A-1	Fever		BT >38°C
A-2	Evidence of inflammatory response	WBC (x1.000/μL) CRP (mg/dL)	<4 or >10 ≥1
B-1	Jaundice	T-Bil (mg/dL)	≥2
B-2	Abnormal liver function tests	ALP (IU/ml) γ-GT (IU/ml) AST (IU/ml) ALT (IU/ml)	>1.5 x STD* >1.5 x STD* >1.5 x STD* >1.5 x STD*

Other factors which are helpful in the diagnosis of acute cholangitis include abdominal pain (right upper quadrant or upper abdominal) and a history of biliary disease, such as gallstones, previous procedures, and placement of a biliary stent.
In acute hepatitis, marked systemic inflammatory response is observed infrequently. Virology and serological tests are required when differential diagnosis is difficult.

γ-GT: γ-glutamyltransferase; ALP: alkaline phosphatase;
AST: aspartate aminotransferase; ALT: alanine aminotransferase
BT: body temperature; WBC: white blood cells;
CRP: C-reactive protein; T-Bil: total bilirubin;
STD*: upper limit of normal value

From: Kiriyama S, Takada T, Strasberg SM, et al. Tokyo Guidelines Revision Committee. New diagnostic criteria and severity assessment of acute cholangitis in revised Tokyo Guidelines. J Hepatobiliary Pancreat Sci 2012; 19: 548-56. (modified)

Table 2: Tokyo Guidelines version 13 (TG13) severity assessment criteria for acute cholangitis.

GRADE III - Severe acute cholangitis	
"Grade III" acute cholangitis is defined as acute cholangitis that is associated with the onset of dysfunction in at least one of any the following organs/systems	
1. Cardiovascular dysfunction	Hypotension requiring dopamine ≥5μg/Kg per min, or any dose of norepinephrine
2. Neurological dysfunction	Disturbance of consciousness
3. Respiratory dysfunction	PaO_2/FiO_2 <300
4. Renal dysfunction	Oliguria, serum creatinine >2.0 mg/dL
5. Hepatic dysfunction	INR >1.5
6. Hematological dysfunction	Platelet count<100.000 mm3
GRADE II - Moderate acute cholangitis	
"Grade II" acute cholangitis is associated with any two of the following conditions	
1. Abnormal WBC count	(>12.000 mm^3, <4.000 mm^3)
2. High fever	(≥39 °C)
3. Age	(>75 years)
4. Hyperbilirubinemia	(T-Bil ≥5mg/dL)
5. Hypoalbuminemia	(<STD* x 0.7)
GRADE I - Mild acute cholangitis	
"Grade I" acute cholangitis does not meet the criteria of "Grade III" (severe) or "Grade II" (moderate) acute cholangitis at initial diagnosis	

Early diagnosis, early biliary drainage and/or treatment for etiology, and antimicrobial administration are fundamental treatments for acute cholangitis classified not only "Grade III" (severe) and "Grade II" (moderate) but also "Grade I" (mild).
Therefore it is recommended that patients with acute cholangitis who do not respond to the initial medical treatment (general supportive care and antimicrobial therapy) undergo early biliary drainage or treatment for etiology.

PaO_2: partial pressure of oxygen in the blood; FiO_2: fractional inspired concentration of oxygen;
INR: International Normalized Ratio; WBC: white blood cells; T-Bil: total bilirubin;
STD*: upper limit of normal value

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The diagnosis is suspected when there is an element in A, plus an element in B or in C, and confirmed if an element is present both in A, in B and in C. In our case, the episode of AC due to biliary outflow obstruction, secondary to postoperative biliary strictures (POBS), was suspected not only because of systemic inflammatory response and laboratory data, but also thanks to important anamnesis information: the previous laparoscopic cholecystectomy. This procedure is considered by the Tokyo 2013 guidelines as another useful factor in the diagnosis of AC.

Laparoscopic surgery has spread rapidly and has been applied not only to the gastrointestinal tract, but also the liver, gallbladder, and pancreas. Laparoscopic surgery was initially applied to cholecystectomy, and laparoscopic cholecystectomy is a standard operation at present. However, it is well known that the transition, since the 90s, from "open" cholecystectomy to laparoscopic has been associated with a significant increase in POBS frequency[6,7]. According to some studies, postoperative benign bile duct strictures occur in 0.2 to 0.6% of cases after laparoscopic biliary tract surgery[8]. In addition it has been reported that after laparoscopic cholecystectomy for cholelithiasis, the recurrence of common bile duct lithiasis is around 2.5%[9]. Several studies argue that POBS adversely and significantly affect the patient's quality of life and are a common cause of lawsuits relating to medical negligence[10,11].

Thanks to improved and increased training in the technique of laparoscopic cholecystectomy, these lesions have become infrequent, but have not disappeared and when they occur, a multidisciplinary approach is essential to ensure the best outcome[12]. The median delay in POBS diagnosis may be months or years, and the belated presentation includes recurrent episodes of AC, as in our case, previously diagnosed as acute drug-induced hepatotoxicity, and secondary biliary cirrhosis[13].

POBS are often identified by endoscopy during ERCP for known or suspected lesions of the biliary tract. When there is strong suspicion of biliary complications, ERCP can be performed immediately after the surgery, or months or years later when a delayed stenosis appears with abnormal liver function values, dilated bile ducts or both[14]. The stenotic outcome of laparoscopic cholecystectomy is a difficult problem to manage. The standard radiological percutaneous and surgical treatments result in significant morbidity[12].

Consequently interest in alternative therapies to surgery has recently appeared[15,16]. Endoscopic dilatation of the postoperative biliary strictures, with or without stent placement, was firstly described by Costamagna et al. in 2001[17]. Many studies considered this surgical technique of dilatation with stent to be less invasive[18,19]. In the Yasuhisa et al. study, endoscopic treatment was associated with low morbidity and excellent long-term outcome. In addition the after-surgery recurrence of the stenosis was only 5% (1/21) during a mean follow-up of more than 120 months[20]. In other studies on the endoscopic management of postoperative stenosis of the bile duct, the success rate varied from 68-89%[18,19,21].

Therefore, the widespread and improved skills of biliary endoscopy have led to a reduction in morbidity and mortality from POBS-related AC. Nevertheless AC remains a potentially fatal disease and early identification of the severity is necessary to choose an appropriate therapy, surgery in particular. The Tokyo 2013 guidelines (see Table 2) allow the early assessment of disease severity on admission, assuming that biliary drainage or other procedures can be carried out rapidly. According to these criteria patients who fall into the moderate or severe category would be candidates for urgent decompression of the biliary tract, while those in the mild category would be initially treated with antibiotics. Many patients in the latter category should undergo biliary drainage within the first 48h, to control the origin of the AC, such as stenosis of the papilla, and extract stones or biliary sludge within the common hepatic duct[5], as our case report has described.

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