ENDOSCOPIC MANAGEMENT OF CHOLEDOCOLITHIASIS RELATED TO PERIAMPU LLARY DUODENAL DIVERTICULA

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ENDOSCOPIC MANAGEMENT OF CHOLEDOCOLITHIASIS RELATED TO PERIAMPU LLARY DUODENAL DIVERTICULA (Abstract): Aims: Periampullary duodenal diverticula is a subject still widely debated in the literature. Our study aimed to describe the characteristics and the clinical outcomes of a case series of subjects with periampullary duodenal diverticula and bile duct stones, receiving therapeutic endoscopic retrograde cholangiopancreatography (ERCP), by comparison to patients having only bile duct stones. Material and methods: 639 consecutive patients with bile duct stones have been investigated through ERCP during 2011 – 2016 in a single specialized center of gastrointestinal surgery. Periampullary duodenal diverticula (PADD)’s prevalence reached at 16.9% (n=108 cases). The patients with PADD have been compared to those without PADD, by personal characteristics, pathophysiological mechanisms incriminated in producing symptoms and therapeutic outcomes. Results: Patients with PADD showed a predominance of males, and a significantly older age. Most frequent abnormality was angulation of the terminal CBD group and jaundice occurred in a significantly higher proportion compared to non PADD group. The percentages of successful selective cannulation and sphincterotomy were significantly lower in the PADD group, even comparable to the literature; meanwhile mechanical lithotripsy was required in a higher proportion of cases. Main cause of failure of cannulation was the changed distal track of the duct. The frequency of postoperative complications was like patients without periampullary duodenal diverticula. Conclusions: Therapeutic endoscopic retrograde cholangiopancreatography is obviously a more difficult procedure in the presence of periampullary duodenal diverticula, due to the difficult access to the papilla and the common bile duct, but the success rate remains high even in such cases. Keywords: PERIAMPU LLARY DUODENAL DIVERTICULA, CHOLEDOCHOLITHIASIS, ENDOSCOPIC RETRO-GRADE CHOLANGIO-PANCREATOGRAPHY (ERCP).

Duodenal diverticula (DD) are known for more than three centuries, the first descriptions belonging to Chomel (1710), Morgagni (1762) and JT Case (1913) (1). Their implications in biliary pathology, especially in syndromes associated with cholestasis (with or without bile duct stones) are known and studied systematically only after introduction into practice of Endoscopic Retrograde Cholangio-Pancreatography (ERCP) in mid-1980. It is also a still widely debated topic in litera-
ture, which is why we present our experience in this regard. Reporting their occurrence depends on the method of diagnosis: 1-6% in patients undergoing a barium transit, 8-12% during an upper gastrointestinal endoscopy, in 15-17% of patients treated by ERCP, about 20-23% after autopsy studies (1). Obviously, the differences between statistics is due to several factors: specific diagnostic accuracy of the method, the type of pathology to which it is addressed, and not least upon the age groups most frequently investigated. Most DD are clinically latent. They rarely produce symptoms, which are usually the consequences of their complications. Of these, the most common are the biliary-pancreatic and more rarely the inflammatory and drilling complications.

Our study aimed to describe the characteristics and the clinical outcomes of a case series of 108 subjects with periampullary DD (PADD) and bile duct stones, receiving therapeutic ERCP in a single specialized center of gastrointestinal surgery, by comparison to patients having only bile duct stones.

**MATERIAL AND METHODS**

In our clinic, we investigated through ERCP 639 consecutive patients with bile duct stones during 2010 –2015 and we found a prevalence of PADD of 16.9% (n=108 cases). We compared the group of patients with PADD to those without PADD, following the personal characteristics (age and gender), the pathophysiological mechanisms incriminated in producing symptoms and the therapeutic outcomes.

As regard the pathophysiological mechanisms, few abnormalities could induce symptoms in DD: 1) angulation of the terminal common bile duct (CBD) with changes in local anatomy and disturbed excretion dynamics of bile and pancreatic juice; 2) compression and stenosis of the terminal portions of the common bile duct and Wirsung duct, with impaired evacuation and dilated CBD; 3) impaired duodenal peristalsis and 4) incomplete evacuation of the diverticular bag, exacerbating the local microbial flora (2). These abnormalities usually induce biliary-pancreatic symptoms like: jaundice, cholangitis, recurrent acute pancreatitis or diverticulitis and perforation. We considered the presence of all these symptoms in the study, as binary variables.

The therapeutic outcomes included the ERCP performance (with focus on the technical and tactical problems found during sphincterotomy), the occurrence of complications and the length of hospitalization. For measuring the ERCP performance we followed the proportion of patient receiving selective cannulation and sphincterotomy in each group and the proportion of cases which required mechanical lithotripsy. As complications, we followed the acute pancreatitis (classified as mild, medium and severe) and post ERCP hemorrhage.

At admission, all patients were investigated following a protocol that included clinical exam, biochemical tests (blood counts, liver and pancreatic tests, coagulation and renal function), electrocardiogram and thoracic-pulmonary radiography. After ERCP, at 24-48 hours, blood count and serum biochemistry tests were repeated to identify possible post-procedural complications. Antibiotic therapy was indicated in patients with vascular prostheses, heart valves or immunosuppressed status. Piperacillin-tazobactam was administered 12 hours before and 24 hours after ERCP. The endoscopic procedure was performed under sedation with propofol and midazolam (3).
If during the same session laparoscopic cholecystectomy for gallstones was performed, the patients received anesthesia with endotracheal intubation.

The data were analyzed using descriptive statistic techniques. The continuous variables were assessed for normality using the Kolmogorov-Smirnov test. The scale variables were discussed as mean ± standard deviation (SD) and as medians (25th, 75th percentile). T Student-test was used for comparison. A p-value <0.05 was considered for statistical significance (two tailed test). Categorical data were presented as proportions with one decimal. Proportions were compared by using Chi square or Fisher exact tests. Statistical analysis was performed with the SPSS 23.0 and Open Epi.

**RESULTS**

**The personal characteristics:** The subjects with PADD tended to have a predominance of males and to be significantly older compared to the subjects without PADD (males 65% in PADD group vs. 35% in non PADD group, p<0.001). In the PADD group, females tended to be significantly younger compared to males (females median age 54 vs. males median age 64, p<0.001). Generally, it is considered that the clinical manifestations of the presence of DD occur after the age of 60, being correlated with the duration of the biliary disease and the PADD diameter. In our PADD group, only 52.8% of the subjects were older than 60 years, with a clear predominance of the females in younger ages (ratio males/females 0.5-1.9).

PADD had been diagnosed before the endoscopic procedure in only 50 patients, among which 23, 17, 5 after axial upper gastrointestinal endoscopy, computed tomography, barium transit and MRI cholangiography respectively. Of these, five were less than 40 years old. Colonoscopy has been performed in 21 of the subjects due to some digestive symptoms and colon diverticulosis has been identified 17 patients (among which 14 older than 60 years).

The pathophysiological mechanisms incriminated in producing symptoms: We found in our study significantly higher frequency of abnormalities in the PADD group compared to non-PADD subjects (4). Most frequent abnormality in the PADD group was angulation of the terminal common bile duct (CBD), followed by compression and stenosis of the CBD and Wirsung duct, impaired duodenal peristalsis and incomplete evaluation of the diverticular bag.

In the non-PADD group, most common was compression, followed by angulation and impaired peristalsis, but, as mentioned, all abnormalities occurred in a significantly lower proportion (5). Among the symptoms induced by the pathophysiological mechanisms (jaundice, cholangitis and recurrent acute pancreatitis), only jaundice occurred in significantly higher proportion in the PADD group. According to the literature, jaundice is usually moderate (with a bilirubinemia of 4-8 mg/dl), but it can be persistent or wavy, being produced by disturbed bile elimination, compression of CBD, ampulla dysfunction, concomitant bile stones and cholangitis (6). In our study, 77.8% of the PADD subjects had jaundice (moderate in most cases), compared to 42% of patients without PADD. Cholangitis was diagnosed based on clinical symptoms (Charcot-triad: pain, fever, jaundice), clinical investigations and laboratory examinations. It occurred in similar frequency in both groups. Most of the cases with cholangitis had prolonged episodes of low grade fever, occasional vesperal chills – all of them signs of torpid, subacute, slow-
Endoscopic management of choledocolithiasis related to periampullary duodenal diverticula evolving cholangitis. Also, similar frequency was found for recurrent acute pancreatitis. Diverticulitis and perforation - in general, inflammation, ulceration and even perforation of the diverticular wall can occur (commonly retroperitoneal, less intraperitoneal), due to food stasis. We recorded 7 cases of diverticula with intense mucosal congestion, crumbly and easy bleeding. At those specific maneuvers of ERCP these cases had a high risk of bleeding and perforation (7).

**TABLE I.**

Pathophysiological mechanisms and complication involved in PADD and non-PADD groups

<table>
<thead>
<tr>
<th>Pathophysiological mechanisms</th>
<th>PADD Group</th>
<th>Non-PADD Group</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angulation of the terminal common bile duct</td>
<td>84</td>
<td>90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Compression and stenosis of the terminal portions of the common bile duct and Wirsung duct</td>
<td>62</td>
<td>128</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Impaired duodenal peristalsis</td>
<td>42</td>
<td>54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incomplete evacuation of the diverticular bag</td>
<td>17</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td>79</td>
<td>223</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>37</td>
<td>181</td>
<td>0.972</td>
</tr>
<tr>
<td>Recurrent acute pancreatitis</td>
<td>9</td>
<td>57</td>
<td>0.455</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>7</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Chi² test

**Acute biliary symptoms in pregnant women:** Beside the above-discussed symptoms, we noticed that five patients who required ERCP for biliary pain induced by PADD were women aged between 30 and 43 years. Three of these women were pregnant - one in the first and the other two in the second trimester of pregnancy. For these patients, emergency ERCP was motivated by the presence of CBD stones complicated by repeated episodes of acute cholangitis (two cases) or acute biliary pancreatitis due to intrapapillary impacted stone (one case). Sphincterotomy, clearance of CBD and prosthesis were made without fluoroscopic control. In all three cases, the pregnancy was carried to term without obstetric complications. After birth, the patients were again investigated (biochemical and imaging) and no residual CBD lithiasis was found. Laparoscopic cholecystectomy was performed in the same operating time.

**ERCP performance:** Usually, the first step of ERCP is CBP selective cannulation associated or not with “pre-cut” papillotomy (8, 9). In our study, this step was conducted with a standard pull-type sphincterotomy, which was later replaced by a guide wire. We succeeded to perform selective cannulation in 94.4% and 98.9% of PADD and non-PADD patients respectively. No pancreatic sphincterotomy was done. After performing the cholangiography, most patients require papilo-sphincterotomy for the extraction of stone, especially in patients with
PADD inducing biliopancreatic suffering (10). In our study, papilo-sphincterotomy has been performed in 88.9% and 97% of PADD and non-PADD patients. Normally, this should be followed by appropriate extraction of stones, papilla and terminal CBD prosthesis. Mechanical lithotripsy could be required. As seen in table II, both selective cannulation and papilo-sphincterotomy were performed in slightly lower proportion in the PADD group, meanwhile mechanical lithotripsy was required in a higher proportion of cases.

In four cases from the PADD group we were not able to perform sphincterotomy due to abnormalities in the profound position of the papilla (11). In other two patients, we performed only autostatic balloon dilatation (younger patients, less dilated common bile duct, reduced diameter calculi). Extraction of stones was performed using probes with basket-type slumber. Mechanical lithotripsy was required for calculi over 12 to 15 mm diameter or even less if sphincterotomy was limited by local anatomical changes (12, 13).

**TABLE II.**

<table>
<thead>
<tr>
<th></th>
<th>PADD Group (N=108)</th>
<th>Non-PADD Group (N=531)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective cannulation</td>
<td>102</td>
<td>94.4%</td>
<td>No</td>
</tr>
<tr>
<td>Papilo-sphincterotomy</td>
<td>96</td>
<td>88.9%</td>
<td>No</td>
</tr>
<tr>
<td>Mechanical lithotripsy</td>
<td>17</td>
<td>15.7%</td>
<td>No</td>
</tr>
</tbody>
</table>

* Fisher exact test; ** Chi² test

**Complications.** The frequency of acute pancreatitis was slightly higher in PADD group, but without statistical significance: 24 (22.2%) and 97 (18.3%) cases in PADD and non-PADD groups respectively, p=0.339, Chi² test. They appeared to be attributable to accidental clouding of the Wirsung (12 patients) and to sphincterotomy (12 cases). In both groups (PADD and non-PADD) most cases of acute pancreatitis were mild, limited to biochemical expression and with quick resolution in 24-48 hours (19 and 74 in PADD and non-PADD groups respectively). All patients received indomethacin postoperatively. The medium or severe forms, requiring specific treatment, occurred in similar proportion in both groups (p=0.99, Fisher exact test). Post ERCP hemorrhage occurred in 4 and 13 cases respectively in PADD and non-PADD group (p=0.64, Fisher exact test). Neither other complications specific to ERCP, nor deaths related to ERCP procedure were registered in our study. Length of hospitalization was also similar between groups with a median of 3 days (min 1, max 14 days, p=0.34, Mann Whitney U test).

**DISCUSSION**

In our study, the patients with PADD were cured using ERCP in slightly lower proportion compared to those without PADD, the results being still comparable to the literature. Few factors could contribute to this lower performance of ERCP.

Firstly, we should consider the position of the diverticula. In terms of relations with the papilla of Vater the diverticula may be juxta-ampullary - when the papilla is adjacent 1 to 2 cm to the diverticulum, or peri-
ampullary - containing both the papilla and bile duct intramural. The chance of generating biliary diseases is more reduced in juxta-ampullary diverticulum, but the periampullary one is most common variety and correlated directly with extrahepatic biliary pathology. Papilla can be located anywhere in the diverticulum, but most commonly it is on the floor. More rarely, we can find one of the side walls of DD. In our case series, all DD were located periampullary (14).

The first step of ERCP, the selective cannulation of CBD, is potentially more difficult in patients with PADD (15). In our study, CBD catheterization average time was 6.6±3.14 minutes compared to only 4.0±2.12 minutes in patients without PADD. Sometimes the papilla of Vater is “pulled” into the DD, its pore is often hidden, diverted down or sideways. The direction of the sphincterotomy is essential to be properly judged in relation to the common bile duct intramural axis, and its length to be correlated with the projection of the papilla. The terminal juxta-ampullar CBD is often strongly angled, making selective cannulation difficult. In our study, this was observed in 48 patients diagnosed with PADD (44%), compared to only 14% in the overall group of non-PADD patients. The changed path of the distal CBD represented the main cause of cannulation failure (16).

We faced technical and tactical problems during sphincterotomy: The correct orientation of sphincterotomy in a distorted papilla, with deeply modified anatomical ratios – 81 (75.0%) versus 59 (11.1%) PADD and non-PADD groups respectively (p<0.001, \( \chi^2 \) test). The hardest part was the approach of a deeply located papilla (in the cavity of a DD) - 39 patients, (36.1%). The room for maneuver in this case is very narrow. The second difficult selective catheterization was when the papilla was located on one of the side walls of the PADD - 42 patients, (38.9%). The depth of the sphincterotomy was difficult to assess, due to the thin DD wall. The landmarks are the ridge of the actual papilla and the cholangiographic appearance of the juxta-ampullary region. The classical landmark for the limit of incision is the mucosal suprapapillary. The depth of sphincterotomy is generally limited, which explains the lower rates of stones extraction. The average time for sphincterotomy was 4.9±2.17 minutes in the PADD group versus 3.2±1.56 minutes in non-PADD group.

**CONCLUSIONS**

In our study PADD were associated with an obvious predominance in males but seemed also to become symptomatic in younger age for females.

The mechanisms implied most frequently in the biliary-pancreatic pathology were angulation, compression and stenosis of the terminal portions of the common bile duct and Wirsung duct, with impairment of bile drainage and pancreatic secretion. By this, favorable conditions for lithogenesis, cholangitis, jaundice and chronic pancreatitis are created. Incomplete evacuation of the diverticular bag exacerbates local microbial flora, becoming a possible source of colonization upward the CBD.

Performing ERCP was obviously more difficult in the presence of PADD. The percentages of successful selective cannulation and sphincterotomy were slightly lower in the PADD group compared to patients having only CBD stones, even comparable to the literature. Proportion of post ERCP complications was similar in both groups. These results can be reached only by accuracy, experience and meticulous execution of maneuvers. Our experience with the pregnant women showed that,
when necessary, ERCP can be performed safely during pregnancy and without important risk for mother or child.

Our experience proved that therapeutic endoscopic retrograde cholangio-pancreatography obviously a more difficult procedure in the presence of periampullary duodenal diverticula, due to the difficult access to the papilla and the common bile duct, but the success rate remains high even in such cases.

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All authors had equal scientific contribution.

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