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Original Article

Mirizzi syndrome: A retrospective analysis of 84 patients from a single center

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A B S T R A C T

Background: There is a paucity of literature regarding the prevalence of Mirizzi syndrome (MS) in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) for obstructive jaundice. We aimed to describe the clinical presentation; laboratory, imaging, and ERCP findings; and surgical management of patients with MS at our center.

Methods: A retrospective review was performed of the medical records of 3,852 consecutive patients who underwent ERCP between January 2010 to December 2019 at our center.

Results: MS was diagnosed in 84 (2.2%) of the patients who underwent ERCP, with 45 male and 39 female patients. Jaundice was the most common symptom (100%) followed by abdominal pain (91.6%). Leukocytosis and altered liver function tests were noted in all our patients. Although most of our patients had one or more pre-procedure imaging studies, MS was confirmed and subclassified based on cholangiographic and intraoperative findings. There were 11 post-cholecystectomy MS patients who opted for endoscopic therapy with repeated biliary stenting. Among the remaining 73 patients, 48 with type I and 21 with type II MS underwent open cholecystectomy, 4 with type III MS received cholecystectomy and choledochoduodenostomy, and another 4 patients with type II MS underwent subtotal cholecystectomy and choledochoplasty. Associated cystic duct abnormalities were noted in 20.2% of patients. Bile duct injuries occurred in 3 patients during an attempted laparoscopic procedure; however, no mortality was reported.

Conclusion: Although it is preferable to diagnose MS preoperatively, a preoperative diagnosis is seldom possible. ERCP is both a diagnostic and therapeutic procedure of choice before definitive surgery and helps to identify any associated cystic duct anomalies in these patients.

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Keywords: Cholangitis; Cholecystectomy; Endoscopic retrograde cholangiopancreatography; Mirizzi syndrome; Obstructive jaundice

Introduction

Although Mirizzi syndrome (MS) was first described in the early 1900s, it was not until 1948 that Pablo Luis Mirizzi, an Argentinian surgeon, gave his name to this uncommon complication of long-standing cholelithiasis characterized by common hepatic duct (CHD) and/or common bile duct (CBD) obstruction secondary to mechanical compression by an impacted calculus at the gallbladder neck or within the cystic duct.¹ It is estimated to occur in approximately 0.05% to 4% of all cholecystectomies performed.^{2–4} The impacted gallstone results in an intense inflammatory reaction, which in turn favors the formation of adhesions and fibrosis around Calot's triangle, posing a formidable challenge to the operating surgeon. In 1982, McSherry et al⁵ classi-

fied MS into two types based on endoscopic retrograde cholangiopancreatography (ERCP) findings; in the first type, extrinsic compression of the CHD is caused by a calculus in the cystic duct or Hartmann's pouch, whereas in the second type, there is either partial or complete invasion of the calculus into the CBD resulting in cholecystocholedochal fistula. In 1989, Csendes et al⁶ proposed further subclassifying MS patients into four subtypes: type I with external compression of the CHD; type II with a cholecystobiliary fistula and erosion of less than one-third of the circumference of the bile duct; type III with a fistula involving up to two-thirds of the duct circumference; and type IV with complete destruction of the bile duct. Given its low incidence, limited preoperative recognition, association with cystic duct abnormalities, and the altered anatomy caused by the intense inflammatory reaction around

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the Calot's triangle, MS causes significant morbidity secondary to iatrogenic bile duct injuries, with an overall conversion rate from laparoscopic cholecystectomy to an open procedure ranging from 31.7% to 100%.⁷

The aim of our study was to describe the clinical presentation; laboratory, imaging, and cholangiographic findings; and surgical management of MS patients at St. John's Medical College Hospital.

Methods

This retrospective study was exempted from review by the Ethics Committee of the St. John's Medical College Hospital. From our hospital database, we retrospectively retrieved the medical records of 3,852 consecutive patients who underwent ERCP for obstructive jaundice between January 2010 and December 2019 at our center and identified 84 patients based on imaging, ERCP, and intraoperative features consistent with MS. Patients were further subgrouped using the Csendes classification for MS.⁶ Data were collected on patient demographics, clinical presentation, laboratory and imaging findings, therapeutic interventions, and post-surgical complications, if any. The retrieved data were analyzed using appropriate statistical methods (mean, median, and standard deviation [SD]).

Results

A total of 3,852 ERCP procedures were performed for various causes of obstructive jaundice during the study period extending from January 2010 to December 2019. MS was diagnosed in 84 (2.2%) patients who underwent ERCP. The mean ($\pm$ SD) age of the study population was 49.6 years ($\pm$ 15.77 years; range 21–83 years) with 45 male and 39 female patients. Jaundice (100%) was the most common symptom noted in our patients, followed by

abdominal pain (91.6%). While 52 patients presented with features of cholangitis (the triad of abdominal pain, fever, and jaundice), seven patients complained of jaundice and pruritus (Table 1). Less common symptoms included anorexia, vomiting, abdominal bloating, and hiccups, which were noted in various combinations with the above symptoms.

Abnormal liver function tests (LFTs) in the form of hyperbilirubinemia, transaminitis, and/or raised alkaline phosphatase and gamma glutamyltranspeptidase (GGT) levels, along with leukocytosis, was noted in all our patients on biochemical testing (Table 2). Overall, 17 patients were diagnosed with MS on abdominal ultrasonography, 28 on contrast-enhanced computed tomography (CECT) of the abdomen, 14 on magnetic resonance cholangiopancreatography (MRCP), and two on endoscopic ultrasonography. The remaining 23 patients were diagnosed as having MS based on cholangiographic findings. Definitive surgery was performed in 73 patients, while 11 patients with post-cholecystectomy MS (PCMS) preferred repeated endoscopic biliary stenting. Of note, although the diagnosis of MS in a majority of our patients was made preoperatively with a combination of imaging and ERCP findings, MS was confirmed and the subgrouping was done in all our patients based on the intraoperative findings except in the 11 PCMS patients who opted for repeated endoscopic therapy and biliary stenting.

Based on the imaging, ERCP features, and intraoperative findings of the 73 patients with MS who underwent definitive surgery in our series, 48 patients had type I, 21 had type II, and 4 had type III MS (Table 3). ERCP with biliary sphincterotomy and CBD stenting was performed in all our patients for preoperative biliary decompression. Subsequently, all 48 patients with type I and 17 patients with type II MS underwent open cholecystectomy, and four patients with type III MS underwent cholecystectomy and choledochoduodenostomy. The remaining four patients with type

Table 1 Demographic and Clinical Data of the Study Population

Variable	Value
Total no. of subjects	84
Mean age (yr)	49.6 $\pm$ 15.77 (21–83)
Male : Female	45 : 39
Clinical feature	
Cholangitis (fever, pain, and jaundice)	52 (62.0)
Right upper quadrant pain and jaundice	25 (29.7)
Painless jaundice with pruritus	7 (8.3)
History of previous laparoscopic cholecystectomy (n)	11

Values are presented as mean $\pm$ standard deviation (range) or number (%).

Table 3 Prevalence of Mirizzi Syndrome Subtypes (Based on the Csendes Classification) in Our Study Population

Csendes subclassification (based on imaging, ERCP, and intraoperative findings)	N (%) [*]
1. Type I (external compression on CBD)	48 (65.7)
2. Type II (cholecystocholedochal fistula affecting less than one third of the CBD)	21 (28.8)
3. Type III (cholecystocholedochal fistula affecting up to two thirds of the CBD)	4 (5.5)

ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct.

^{*}N indicates number and percentage of patients with abnormal values. Total number was 73.

Table 2 Laboratory Abnormalities in the Study Population with Mirizzi Syndrome

Laboratory parameter	Normal value	Mean $\pm$ SD	Range	N (%) [*]
Total bilirubin (mg/dL)	0.2–1.2	5.64 $\pm$ 4.214	1.6–15.8	84 (100)
Aspartate aminotransferase (U/L)	5–34	115.603 $\pm$ 95.54	30–301	62 (73.8)
Alanine aminotransferase (U/L)	Up to 55	143.36 $\pm$ 112.83	35–408	78 (92.8)
Alkaline phosphatase (U/L)	40–150	327.568 $\pm$ 206.487	130–889	79 (94.04)
Gamma-glutamyltranspeptidase (U/L)	9–36	323.75 $\pm$ 177.434	30–558	80 (95.23)
White cell count (cells/ μ L)	4,000–11,000	13,972.179 $\pm$ 4,548.895	12.1–21.7	84 (100)

SD, standard deviation.

^{*}N indicates number and percentage of patients with abnormal values.

II MS underwent subtotal cholecystectomy and choledochoplasty. Although laparoscopic cholecystectomy was attempted in 12 patients with type I MS, given the difficult anatomy secondary to severe inflammatory reaction around Calot's triangle and the subhepatic space, all these laparoscopic procedures were ultimately converted to open surgery. During attempted laparoscopic cholecystectomy, three patients sustained bile duct injuries, which were treated successfully with hepaticojejunostomy. No ERCP- or surgery-related mortality was reported in our study. Anatomical variations of the cystic duct were noted in 17 (20.2%) of our patients. While a long and tortuous cystic duct was noted in eight patients, low insertion of the cystic duct was seen in four patients and a combination of a tortuous, long, and low inserting cystic duct was noted in five patients.

Discussion

Patients with MS typically present with the clinical features of extrahepatic biliary obstruction. Although there are no pathognomonic clinical, laboratory, or imaging features of MS, obstructive jaundice is the most common presentation (50%–100%) and is often accompanied by pain in the right upper quadrant (50%–100%) or epigastric pain. The presence of fever with chills and rigors suggests cholangitis. A certain preoperative diagnosis can only be achieved in 8% to 63.4% of cases, since MS is easily confused with choledocholithiasis, immunoglobulin (Ig) G4-related scleros-

ing cholangitis, and hilar cholangiocarcinoma given the intense inflammatory adhesions that occur in Calot's triangle.^{7–9} Patients inadvertently referred to surgery often sustain bile duct injuries when laparoscopic cholecystectomy is attempted by a naïve surgeon.¹⁰ The situation is further complicated given the fact that a considerable number of patients with MS have associated cystic duct anomalies.¹¹ While LFTs often reveal an obstructive pattern with high levels of bilirubin, transaminitis, and elevated alkaline phosphatase and GGT levels, the diagnosis of MS is based on clinical features combined with a high index of suspicion and supplemented by radiologic imaging and ERCP findings.^{11,12} Although ERCP is regarded as the gold standard for the diagnosis of MS, MRCP is the preferred imaging modality because it is non-invasive.

The prevalence of MS is estimated to be around 1.5% to 7% in those with symptomatic gallstones, 0.06% to 5.7% in patients during cholecystectomy, and in 1.07% in those undergoing ERCP.^{6,12–14} The prevalence of MS in our cohort of patients undergoing ERCP was higher at 2.2%. MS usually presents in elderly individuals, with a mean age that varies between 53 to 70 years, and 70% of MS patients have been reported to be female.^{3,15–17} However, a study by Tan et al¹⁸ reported a male preponderance (66.7%) in their series of 24 cases, as did another study by Al-Akeely et al,¹⁹ which showed a male-to-female ratio of 58.8% to 41.2%. Our present study concurs with the above two studies, as there was a male preponderance (45 male and 39 female patients).

Fig. 1. MRI/MRCP and cholangiographic findings in a patient who was diagnosed with Klatskin's tumor and referred for palliative ERCP. (A, B) An intense inflammatory reaction around the hilar region mimicking malignancy (arrows). (C) MRCP (inversion sequence) of the same patient showing hilar narrowing (arrow). (D) Cholangiographic image on index presentation (arrow). (E) Coronal computed tomography image 4 months after ERCP and CBD stenting (arrow). (F) Repeat ERCP and cholangiographic image showing resolution of hilar narrowing/stricture (arrow). MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct.

The mean ($\pm$ SD) age of our study cohort was 49.6 ± 15.77 years (range, 21–83 years). The clinical presentation of MS varies from asymptomatic to cholangitis and septic shock. Concurrent with other studies, jaundice and abdominal pain were universal or near-universal findings in our series (100% and 91.6%, respectively). Cholangitis was noted in 62% of patients, while pain and jaundice were seen in 29.7% of patients and 8.3% of patients presented with jaundice and pruritus. Anorexia, nausea, vomiting, abdominal bloating, and hiccups were noted in combination with the above symptoms. The high incidence of cholangitis in our study could have been due to a delayed referral of these patients to our center.

The intense inflammatory reaction accompanied by elevated CA19-9 levels that sometimes occurs in patients with MS is often mistaken for advanced hilar cholangiocarcinoma.²⁰ Two of our patients were erroneously diagnosed with inoperable hilar cholangiocarcinoma based on CECT and MRCP findings. Along with an elevated CA19-9 level, both these patients had such intense inflammatory reaction around Calot's triangle and the subhepatic space that they were misdiagnosed on both CT and MRCP as having a malignant hilar stricture with vascular invasion around the porta hepatis and were referred for palliative ERCP (Fig. 1). Fortunately, following ERCP and biliary stenting, there was marked reduction in the inflammatory mass around the biliary tree and the subhepatic space. The previous diagnosis was revised to MS on repeat MRCP imaging, and both patients underwent successful open cholecystectomy.

The reported incidence of different types of MS subtypes according to the Csendes classification is as follows: type I (the most common), 10.5%–78%; type II, 15%–41%; type III, 3%–44%; and type IV, 1%–4%. Type V (which includes the presence of a cholecystoenteric fistula together with any other type of MS) can be present in up to 29% of patients.⁶ This distribution was reflected in our study with type I MS being reported in 69%, type II in 26%, and type III in 4.7% of the patients.

Beltran described at least nine anatomical variations in the cystic duct anatomy that can be associated with MS, and these anomalies are reported to occur in about 18% to 23% of MS patients.^{3,11,19} A long cystic duct running parallel to the bile duct and a low insertion of the cystic duct into the bile duct have been regarded as predisposing factors for MS. A significant and concurrent finding in our study was that 17 of our patients (20.2%) had anatomic variations of the cystic duct; a long and tortuous duct

in eight patients (Fig. 2); low insertion of the cystic duct in four patients; and a combination of a tortuous, long, and low inserting cystic duct in five patients. These anatomic aberrations of the cystic duct make laparoscopic cholecystectomy a challenge even in the hands of an experienced surgeon and should be considered in all patients with MS.

Surgery is the definitive treatment for MS, and the surgical method is determined by the presence and type of cholecystocholedochal fistula. While either open or laparoscopic cholecystectomy is preferred in type I MS, a bile duct intervention should be done via an open surgical method in the presence of a fistula. In type II MS, CBD repair with total or subtotal cholecystectomy can be done through a T-tube. Choledochoduodenostomy or Roux-en-Y hepaticojejunostomy is preferred in type III and type IV MS.²¹ Although laparoscopic cholecystectomy is considered to be a safe approach by some authors, it is technically more demanding, with an overall conversion rate to laparotomy being as high as 31.7% to 100%.^{22–24} Hence, the current evidence does not support recommending laparoscopic treatment of MS as a standard procedure, and open surgery is still the preferred choice among surgeons.¹³ Laparotomy has the advantage of better visualization and gallbladder stone clearance before cholecystectomy (either partial or subtotal) despite being more invasive and associated with a prolonged hospital stay. Partial or subtotal cholecystectomy leaves a cuff of gallbladder or cystic duct that can be used to repair the CBD (choledochoplasty) in cases of type II and type III MS.^{9,25–28} In the present study, all 48 patients with type I and 17 patients with type II MS underwent open cholecystectomy, and four patients with type III MS underwent cholecystectomy and choledochoduodenostomy. The remaining four patients with type II MS underwent subtotal cholecystectomy and choledochoplasty. The rate of conversion to laparotomy from laparoscopic cholecystectomy was 100% (12 out of 12) in patients with type I MS in our series. Three patients with type I MS sustained bile duct injuries during attempted laparoscopic cholecystectomy and underwent hepaticojejunostomy. No surgical mortality was reported in our study, which could be attributed to the fact that the operating surgeons were aware of the diagnosis of MS preoperatively in all our patients and were particularly meticulous during dissection around the Calot's triangle. Post-cholecystectomy residual cystic duct stones have been implicated in MS.^{29,30} There were 11 such cases of PCMS in our series, and all these 11 patients opted for long-term CBD stent exchange rather than surgery. Some authors have

Fig. 2. Imaging features of Mirizzi syndrome. (A) Computed tomography showing a large calculus in a dilated cystic duct (15 mm) causing compression over the proximal common bile duct (CBD) and common hepatic duct (CHD) with resultant upstream dilatation of the right and left hepatic ducts and intrahepatic biliary radicle dilatation (arrow). (B) MRI/MRCP showing a tortuous and thickened cystic duct with constellations of stones at its distal end (enclosed within the oval) causing extraluminal compression of the distal CHD (arrow). (C) Cholangiogram showing a large cystic duct compressing the CHD and proximal CBD, causing upstream CHD dilatation (arrow). MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography.

reported a high association of MS with cancer of the gallbladder; however, no such association was reported in our study.^{4,31}

The main limitations of our study were its retrospective nature and the nonavailability of cholangioscopy, electrohydraulic lithotripsy, or extracorporeal shock wave lithotripsy at our center, although these methods have been used effectively in some studies for the treatment of difficult bile duct stones refractory to conventional extraction techniques.³²

In conclusion, although diagnosing MS preoperatively is ideal, a preoperative diagnosis is seldom possible even with advanced imaging techniques, and MS is often mistaken for hilar cholangiocarcinoma, carcinoma gallbladder causing hilar block, and IgG4-related sclerosing cholangitis. A high index of suspicion should be exercised, particularly in patients with a known history of cholelithiasis. Although surgery is the definitive treatment for MS, ERCP—in addition to its therapeutic role of clearing bile duct calculi and placement of a biliary stent—helps in the intraoperative identification of the CBD, thus reducing bile duct injuries and associated morbidity and mortality. It is also prudent for the operating surgeon to anticipate anatomic variations of the cystic duct in MS patients, necessitating meticulous dissection around Calot's triangle.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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