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Biliary Tract - Disease, Treatment, and Quality of Life

Saraswathi Lakkasani[1]* and Pravitha Jayapratap[2]

[1]Department of Gastroenterology, Gastroenterologist in Richmond, United States

[2]Department of Gastroenterology, Chicago, Illinois, United States

***Corresponding author:**

Saraswathi Lakkasani,
Department of Gastroenterology, Gastroenterologist in Richmond, United States

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1. Abstract

This chapter discusses the most common biliary tract diseases, with particular emphasis on biliary strictures, primary sclerosing cholangitis, and cholangiocarcinoma. The aim is to provide an overview of disease epidemiology, genetic and non genetic risk factors, clinical presentation, treatment options, prognosis and impact on quality of life for each of these conditions. In total, this chapter identifies critical areas for clinicians to recognize a cluster of relatively rare conditions and provides guidance on management, including newly emerging technologies.

2. Introduction

Bile is a digestive fluid produced by the liver that helps break down fat; the term "biliary disease" references conditions that impact the bile ducts, gallbladder, and structures involved in the production and transportation of bile. Biliary disease can be caused by abnormalities in the anatomy or function of bile ducts, composition of the bile, or malignancy involving any portion of the biliary tree. Patients impacted by this cluster of diseases often present with an obstructive clinical picture due to blockage of the bile ducts resulting in abdominal pain, nausea and vomiting. With severe blockages wherein bile cannot drain properly, the patient may develop jaundice, cholangitis, and even cirrhosis. Given the possibility of these conditions leading to severe liver damage and a symptom burden requiring hospital intervention, these conditions cause major issues for patients and can be associated with a poor quality of life [1].

3. Biliary Strictures

3.1. Introduction

Biliary strictures, or bile duct strictures, are narrowed or blocked segments within the ductal system that carries bile from the liver to the small intestine. As the narrowed areas hinder the normal flow of bile, the subsequent collection causes proximal dilatation as well, thereby resulting in the characteristic obstructive clinical picture. There are numerous causes for this condition ranging from pancreatitis, to operative injury, to malignancy [2]. While biliary strictures can be asymptomatic, if untreated they can cause life-threatening complications such as hepatic abscess, ascending cholangitis, and secondary biliary cirrhosis.

3.2. Etiology

This condition is most commonly acquired, however congenital strictures are also possible. Acquired strictures are categorized as either malignant (70%) or benign (30%) [3]. Pancreatic cancer and cholangiocarcinoma are the primary causes of biliary strictures, followed by gallbladder cancer, hepatocellular carcinoma, and liver cancer [4]. Of the benign causes, the most common origin lies within iatrogenic strictures secondary to laparoscopic cholecystectomies wherein the biliary duct is mistaken for the cystic duct. Amongst other interventions, orthotopic liver transplantation and the Whipple procedure can cause anastomotic strictures due to a fibro-proliferative response adjacent to the surgically created connections.[5] Additional benign causes include pancreatitis, bile duct scarring secondary to gallstones, primary biliary cholangitis, primary sclerosing cholangitis, and radiation therapy.

3.3. Epidemiology

The present literature does not claim a concrete consensus regarding the global incidence and prevalence of biliary strictures. However, it is thought to be on the rise in tandem with the increasing frequency of laparoscopic cholecystectomy, as this has also meant an increase in iatrogenic injury to the bile duct [6].

3.4. Pathophysiology

The tumor burden from primary bile duct cancer causes a narrowing of the ductal lumen and thereby obstructs the flow of bile; malignancies in adjacent structures like the gallbladder, pancreas, or liver, cause this narrowing via extrinsic compression. Benign strictures develop secondary to injury like a surgical trauma, a recurring condition like pancreatitis, or a chronic disease like primary sclerosing cholangitis. The injury is followed by an inflammatory response and subsequent collagen deposition, fibrosis, and a narrowing of the ductal lumen. Chronic severe strictures can result in atrophy of the affected hepatic segment, along with hypertrophy of the unaffected areas. In the long term, this can evolve to secondary biliary cirrhosis. Biliary strictures can be categorized according to the Strasberg-Bismuth classification systems [Figure 1&2]. These systems delineate a means to stratify biliary strictures according to anatomic location within the biliary tree and extent of injury, as outlined in the table and diagram below [7].

3.5. Clinical Presentation

Patients with biliary strictures have variable clinical presentations depending on the cause, location, and severity of the strictures; the patient may be entirely asymptomatic. A history of hepatobiliary surgery, pancreatitis, or gallstones in the context of obstructive jaundice like pruritus, pale stools, dark urine, and yellowing skin or mucosa should arouse suspicion for this condition. The patient may also present with constitutional symptoms such as fever, nausea, vomiting, and malaise. A history of weight loss and abdominal pain may point to strictures due to malignancy [9].

3.6. Diagnosis and Testing

Preliminary lab testing for biliary strictures includes liver function tests, wherein the expected results would reflect an obstructive pattern with elevated conjugated bilirubin and liver enzymes. Alkaline phosphatase demonstrates an increase to 3 times normal values, along with increases in gamma-glutamyl transpeptidase and 5' nucleotidase [10].

In cases of malignant biliary strictures with complete obstruction, serum bilirubin is staggeringly elevated in comparison with benign causes. This is reflective of the severity of the obstruction, which is more common with a tumor burden and impingement. The first imaging study to check for biliary strictures is a right upper quadrant ultrasound (US), with findings significant for dilated bile ducts. While it is less accurate for determining the level of obstruction, this test is fast, involves no ionizing radiation, is viable for patients with metal implants, pregnant women, and is entirely noninvasive. If the cause of obstruction is not clear on ultrasound, the next imaging option is abdominal computed tomography (CT) scan or magnetic resonance cholangiopancreatography (MRCP). These imaging modalities provide detailed images of the bile ducts, liver, pancreas, and gallbladder. CT scans have the advantage over US given a higher accuracy and visualization of the distal common bile duct, porta hepatis, liver parenchyma, as well as any other areas that may be obscured by gas artifacts. This is a highly sensitive imaging modality particularly when performed with oral and intravenous contrast; the drawbacks include radiation exposure and limitation in those with contrast allergy and poor kidney function [11]. MRCP has become an important imaging tool for assessing biliary strictures; it utilizes the high signal intensity of bile on T2-weighted images. This study is highly sensitive for strictures and provides valuable visualization without requiring ionizing radiation. However, this imaging modality requires substantial patient cooperation and does not allow for concurrent intervention unlike ERCP, which will be discussed next. Endoscopic retrograde cholangiopancreatography (ERCP) utilizes endoscopy along with the injection of contrast media into the bile and pancreatic ducts under fluoroscopy, with the benefit of clear visualization of the ductal system as well as the ability to biopsy and facilitate interventions like stenting, stone extraction, and biliary drainage. Because it is an invasive procedure, this modality comes with risk of complications like pancreatitis in 3-5% of patients. In recent years, endoscopic ultrasonography (EUS) utilizing an ultrasound transducer mounted to an endoscope has arisen as a viable option for guided biliary stenting through the duodenal wall into the bile duct. Further data is necessary in this arena, however the strategy is promising and offers an option that avoids the use of contrast and radiation [12, 13].

3.7. Treatment Modalities

Management of biliary strictures requires a multidisciplinary approach, particularly if the patient presents with obstructive jaundice along with signs of ascending cholangitis. In cases with hypertension or altered mental status, the patient should be started on broad-spectrum antibiotics with gram-negative and anaerobic coverage within an intensive care setting; immediate drainage and decompression of the biliary tree may also be necessary. Interventions for biliary strictures include endoscopic or percutaneous balloon dilatation and placement of a stent, surgical bypass that circumvents the biliary stricture to allow bile to flow directly into the small intestine, or resection to remove the diseased bile duct along with any surrounding tumor burden [14, 15]. Endoscopic balloon dilatation in isolation is insufficient to address biliary strictures and must be followed with stent placement for a durable result. Stents have a low morbidity rate, however this solution has limited efficacy in the long term with the possibility of stent blockage or migration. Use of this modality involves more complex clinical decision making in the context of malignant biliary strictures. The objective in patients with unresectable

disease is relief from obstructive symptoms for palliation. Tumor ingrowth and re-occlusion is possible even in well placed stents; a rising strategy to address this and prolong patency is radiofrequency ablation.

Surgical management varies depending on whether the strictures are benign or malignant in origin. Biliary-enteric anastomosis is a lasting therapy to address strictures; patients with strictures due to pancreatitis may require pancreaticoduodenectomy. In the context of malignant biliary strictures, there may be attempted resection of the tumor or resection for palliation. These patients have a poor prognosis and no survival advantage has been demonstrated when compared with nonoperative interventions.

3. 8. Prognosis

The prognosis for patients with biliary strictures varies depending on the underlying cause of this condition. Patients can expect a good prognosis if their strictures are due to chronic pancreatitis, radiation, trauma, or operative complications. Procedures to open narrowed bile ducts have a good success rate. However, a poor prognosis is more likely for patients with strictures secondary to malignancy, primary sclerosing cholangitis, or HIV cholangiopathy [16].

3. 9. Impact on Quality of Life

In patients with biliary obstruction, as is seen with strictures, there is a range of symptoms that can progress to life threatening complications if left unaddressed. Whereas some signs like jaundice and pruritus are evident, and can therefore be directly addressed, the aggregate of accompanying issues must also be considered in evaluating quality of life in this patient population. In a study assessing symptom relief and quality of life following biliary stenting, [17] patients were given a questionnaire that included assessment of anorexia and indigestion, overall mood, anxiety, depression, changes in appetite, nausea, weight loss, and pain levels. Taken in total, these symptoms give a more accurate picture of the patient with biliary strictures. The study shows improvement in all of these areas following stenting; in the context of malignancy it is relevant to consider that the intent of this intervention is palliation, further underlining the emphasis on quality of life.

3.10. Conclusion

Biliary strictures are a narrowing in the ductal system originating from a wide range of causes from iatrogenic injury to malignancy. Blockages within this critical area can have devastating clinical consequences, particularly if left unaddressed, and can result in significant morbidity and mortality. The cause, location, and distribution of these lesions, along with the clinical status of the patient decide the optimal management and outcome.

4. Bile Duct Stones

4.1. Introduction

Gallstones are the second most common reason for admission in the United States; a complication of this condition is the occurrence of stones in the common bile duct, occurring in up to 15% of patients undergoing cholecystectomy. As suggested by this percentage, the prevalence of bile duct stones is comparatively low. This condition typically results when stones migrate through the cystic duct into the common bile duct (CBD). Infrequently, they may arise within the CBD [18]. Overall, gallstones have a higher prevalence in Western countries, with primary bile duct stones more common in East Asian countries. This condition has a prevalence of 47.3% in Taiwan, 38.0% in China, 17.0% in Korea, and 11.7% in Malaysia. In contrast, the prevalence of these stones in the West is quoted at 0.6–1.3%. [18]. Further, the composition of bile duct stones is primarily calcium bilirubin stones in contrast with cholesterol stones that are typical of gallstones.

4.2. Epidemiology

Overall, gallstones have a higher prevalence in Western countries, with primary bile duct stones more common in East Asian countries. This condition has a prevalence of 47.3% in Taiwan, 38.0% in China, 17.0% in Korea, and 11.7% in Malaysia. In contrast, the prevalence of these stones in the West is quoted at 0.6–1.3%. [18]. Further, the composition of bile duct stones is primarily calcium bilirubin stones in contrast with cholesterol stones that are typical of gallstones.

4.3. Pathophysiology

These calculi are typically bilirubin-pigmented and brown, and can be friable [19], as seen in [Figure 3]. The pathogenesis is not clearly established, however it is thought to be associated with bile infection. There have also been suggestions of associations with nutritional deficiency and ascariasis infection, but these theories require further investigation. Findings for bile duct stones are also associated with dilated intra- and extrahepatic ducts, as well as inflammatory changes along the periportal spaces and hepatic parenchyma.

Bile duct injury	Bismuth	Strasberg
Cystic duct leak or leaks from small ducts in liver bed	–	A
Occlusion of an aberrant right hepatic duct	–	B
Leak from an aberrant right hepatic duct	–	C
Lateral injury to the common bile duct (<50% of the circumference)	–	D
Common hepatic duct stricture, stump >2 cm	Type I	E1
Common hepatic duct stricture, stump <2 cm	Type II	E2
Hilar stricture with preserved biliary confluence	Type III	E3
Hilar stricture with involvement of confluence	Type IV	E4
Stricture to an aberrant right hepatic duct and to common hepatic duct	Type V	E5

Figure. 1: Strasberg-Bismuth classification system.

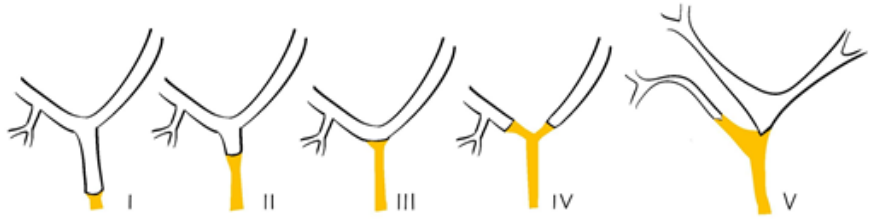

Figure 2: Bismuth classification.

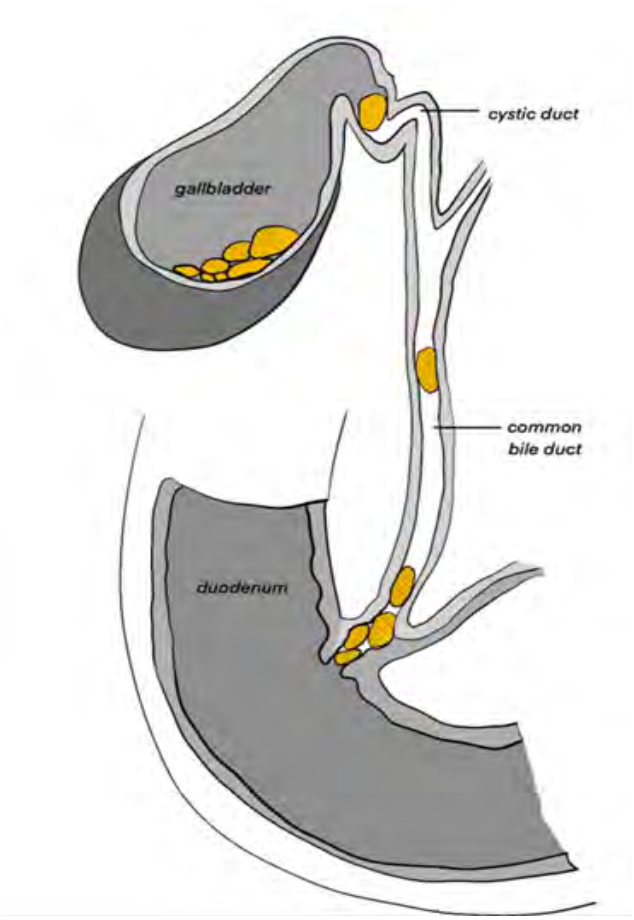

Figure 3: Bile duct stones throughout biliary tree.

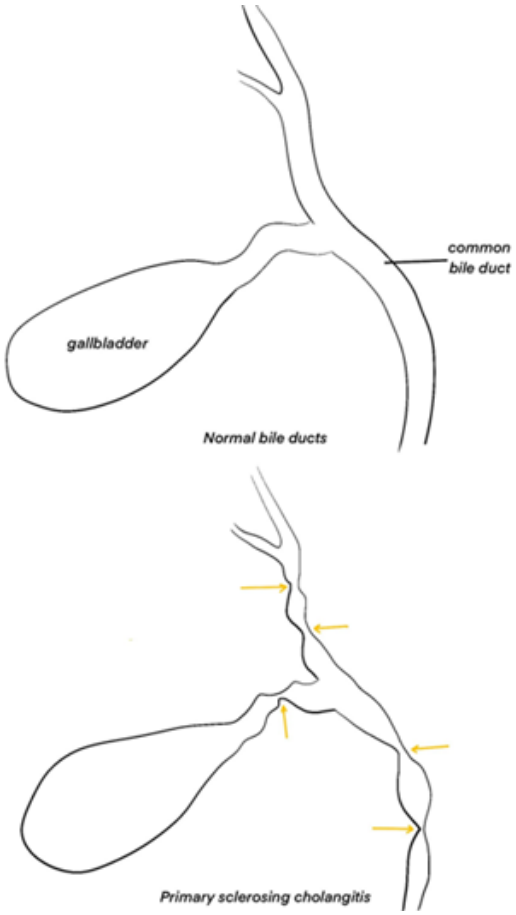

Figure 4: Normal bile ducts in comparison with changes to the biliary seen with primary sclerosing cholangitis.

PSC stages	Histological findings
Stage 1	Degeneration of epithelial cells in the bile ducts and inflammation of the portal triads with mononuclear infiltration and piecemeal necrosis
Stage 2	Fibrosis expanding into the parenchyma with dilation of the portal triads
Stage 3	Bridging fibrosis
Stage 4	Cirrhosis

Figure 5: Primary sclerosing cholangitis histological findings by stage [32].

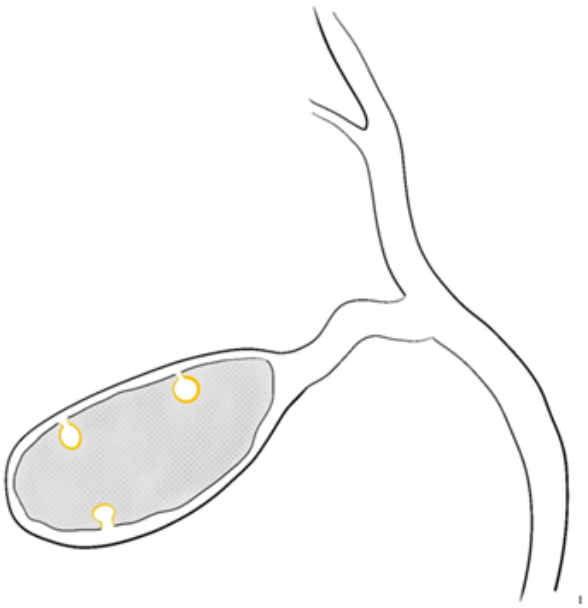

Figure 6: Gallbladder Polyps.

TNM classification	Extent of tumour spread	Stage
T1a	Bile duct mucosa	I
T1b	Muscular layer of bile ducts	II
T2	Periductal connective tissue	III
T3	Vessel or organ invasion	IVA
M1	Distant metastases	IVB
N1a	Lymph node involvement: hepatic, cystic, common duct and hepatoduodenal ligament	
N1b	Distant lymph node involvement	

Figure 7: Staging system by American Joint Committee on Cancer [61].

Stage	Criteria
T1	Tumour involving biliary confluence ± unilateral extension to second-order biliary radicals
T2	T1 + ipsilateral portal vein involvement ± ipsilateral hepatic lobar atrophy
T3	Tumour involving biliary confluence + bilateral extension to second-order biliary radicals; or unilateral extension to second-order biliary radicals with contralateral portal vein involvement; or unilateral extension to second-order biliary radicals with contralateral hepatic lobar atrophy; or main or bilateral portal venous involvement

Figure 8: Staging System by Memorial Sloan-Kettering [61].

4.4. Clinical Presentation

While clinical presentation for this condition can vary, in general patients with bile duct stones can present with fever, abdominal pain, nausea, vomiting, and jaundice, painting an overall obstructive clinical picture [20]. In some instances, bile duct stones may be discovered incidentally along with a dilated common bile duct.

3. 5. Diagnosis and Testing

While they are not definitive and not directly diagnostic for this condition, several lab tests have been associated with bile duct stones including elevations in bilirubin levels, gamma-glutamyl transferase levels, amylase level, and alkaline phosphatase [20]. The first line imaging modality is transabdominal ultrasound, a non-invasive, inexpensive, and easily available option; limitations include confounding artifacts from metallic clips, previous biliary stents, calcifications, and gas. Endoscopic ultrasound involves use of a duodenoscope along with the ultrasound transducer; this provides the benefit of more detailed images but is similarly limited by artifacts and is less easily available than traditional ultrasonography. The next tier of this imaging modality is intraductal ultrasound, wherein an ultrasound transducer is attached to the tip of a catheter that is introduced through a duodenoscope. The resulting images of the biliary tree are limited as stones and air bubbles appear similar. Finally, laparoscopic intraoperative ultrasound involves an ultrasound transducer mounted on a probe and introduced through a laparoscopic port during surgery. This modality is limited by operator ability, patient habitus, and suboptimal visualization of parts of the common bile duct. Because it is tethered to an invasive procedure, accompanying risks and complications must be weighed against possible benefit [21]. Endoscopic retrograde cholangiopancreatography (ERCP) is the gold standard imaging strategy in assessing bile duct stones. This modality involves the injection of a contrast agent into the common bile duct and a combination of xrays and gastrointestinal endoscopy. The primary advantage of ERCP is that it is both diagnostic and therapeutic as common bile duct stones can be managed with ERCP and sphincterotomy in many cases. However, this technique is limited in more complicated cases such as with ductal strictures, peripheral stone impaction, or angulation of the ducts. Given these considerations, magnetic resonance cholangiopancreatography (MRCP) has been rising as an alternative to ERCP as it is non-invasive, allows direct visualization of the entire biliary tract, and allows identification of dominant strictures without instrumentation, while avoiding the risk of complications that accompany ERCP. The visualization of ducts peripheral to stricture is often possible with ERCP but it is important to note that this would require forced injection of contrast dye and therefore increase the risk of cholangitis. Given these elements, MRCP presents a viable alternative to the gold standard technique of ERCP in diagnosing bile duct stones [22].

4. 6. Treatment Modalities

Broadly, the treatment options for bile duct stones are divided into endoscopic or surgical techniques, with the former rising in popularity. Traditionally, open surgical exploration of the common bile duct was combined with intraoperative cholangiography to diagnose and treat bile duct stones in this area. Even with the evolution of laparoscopic cholecystectomy, surgical removal of common bile duct stones is now relegated to cases wherein ERCP has failed. The most favourable management algorithm holds that ERCP should be avoided in causes wherein the probability of stones in the common bile duct is low, and that endoscopic sphincterotomy to allow stones to pass into the duodenum is successful in >90% of patients with a low overall complication rate. Balloon sphincteroplasty may be a viable strategy to keep the sphincterotomy incision small. If stone removal is unsuccessful, biliary decompression can be achieved with a stent [23].

4. 7. Prognosis

The prognosis for bile duct stones is dependent on the extent of the obstruction and the promptness of treatment. Expeditious diagnosis and treatment before severe complications results in a good prognosis for this condition. Patients with severe or chronic obstructions that have been left untreated can become infected and consequently have a higher morbidity, particularly in cases with permanent damage to the liver.

4. 8. Impact on Quality of Life

Quality of life considerations for this condition are dependent on chronicity and complications following intervention. Patients experiencing long bouts of nausea, vomiting, and abdominal pain, as expected, report lower satisfaction scores. Even following treatment, modalities like ERCP can have a substantial impact on quality of life, including clinically significant hemorrhage, prolonged hospital stays, pancreatitis, and post-procedural pain.

4. 9. Conclusion

While this condition is reported primarily in Eastern Asian countries and is not common in western countries, there has been a recent rise in cases in the west. Bile duct stones should be considered in differential diagnoses for patients presenting with an obstructive clinical picture. There are a variety of interventions to address this condition, with continual progress towards advances in minimally invasive procedures. Management of these stones must account for available technology and the cooperation of an interdisciplinary team of gastroenterologists, surgeons, and interventional radiologists to best ensure optimal outcomes.

5. Primary Sclerosing Cholangitis

5. 1. Introduction

Primary sclerosing cholangitis (PSC) - is a rare chronic and progressive liver disorder characterized by multifocal bile duct scarring and strictures; the ducts can become narrowed or entirely occluded, leading to buildup of bile in the liver, with subsequent inflammatory damage. The established subtypes are classic, which impacts small and large bile ducts; small-duct, which impacts strictly small bile ducts; and PSC associated with autoimmune hepatitis, which impacts bile ducts of any size. This condition is associated with cholangiocarcinoma, colorectal cancer, and ulcerative colitis. PSC can lead to end-stage liver disease, ultimately requiring liver transplantation after which recurrence may occur, resulting in a reduced life expectancy.

5. 2. Epidemiology

PSC is most common in men (65%) in the third or fourth decade of life, with the median age of diagnosis at 41 years [24]. The incidence rate ranges from 0.5 to 1.3 cases per 100,000 person-years in North America and Northern Europe, where cases are higher in comparison than Asia [25]. While this remains a rare condition, the incidence rate has been climbing over time. In addition to a higher prevalence in men, this condition is commonly observed in non-smokers, and has a relative risk amongst siblings up to 39 times higher than when compared with the general population.

5. 3. Pathophysiology

Primary sclerosing cholangitis involves inflammation, fibrosis, and cholestasis. The reigning hypothesis posits persistent injury to cholangiocytes, the cells lining bile ducts, following exposure to an environmental stressor. Several genetic pathways are implicated in a hereditary cause in a large cohort study showing a strong association with human leukocyte antigen (HLA) class 1, 2, and 3 regions – specifically HLA-B*08, HLA-DRB1 alleles, and a locus near NOTCH4 [26]. Inflammation and subsequent fibrosis lead to cholestasis, parenchymal injury, biliary obstruction, scarring, and portal hypertension. PSC is also a premalignant condition, with up to 20% of patients consequently developing cholangiocarcinoma; carcinogenesis in this case is thought to originate in the inflammatory processes of PSC.

5. 4. Clinical Presentation

50% of patients exhibit no symptoms and are first assessed for PSC based on abnormal liver function tests performed for other reasons, such as medical or family history of inflammatory bowel disease - particularly ulcerative colitis, autoimmune conditions like type 1 diabetes, or a close relative with PSC [27]. Initial presentation may include right upper quadrant abdominal pain (20%), pruritus (10%), diarrhea, jaundice (6%), fatigue, and fever. Physical exam findings would likely include abdominal tenderness, enlarged liver (44% of patients) or spleen upon palpation, and scratch marks secondary to itchy skin [28]. PSC may be associated with a bile duct infection, which would present with fever and chills, jaundice, and right upper quadrant abdominal pain. With disease progression, the patient may also present with symptoms of cirrhosis like ascites, confusion due to hepatic encephalopathy, and even gastrointestinal bleeding secondary to varices.

The natural history of PSC demonstrates progressively worse clinical features. In the asymptomatic phase, patients would have cholangiographic abnormalities but no clinical symptoms or lab abnormalities. The subsequent biochemical phase would demonstrate lab abnormalities with no accompanying clinical features. In the symptomatic phase, patients would likely experience jaundice, fatigue, pruritus and excoriations, fevers, chills, night sweats, right upper quadrant pain, and diarrhea. The final phase of decompensated cirrhosis would demonstrate ascites, muscle atrophy, peripheral edema, spider telangiectasias, hepatic encephalopathy, and even variceal bleeding.

5. 5. Diagnosis and Testing

Diagnostic criteria for PSC include:

-Increased serum alkaline phosphatase that persists for more than six months [29]

-Bile-duct strictures detected via MRCP or ERCP

-Exclusion of causes of secondary sclerosing cholangitis

Appropriate blood tests to assess this condition include liver function tests, which would show abnormal levels of liver enzymes and indicators of damage to the bile ducts or liver as described above. Bilirubin and albumin levels may be normal initially, but this will change as the disease progresses. Elevated serum bilirubin levels suggest more advanced disease including biliary strictures, or cirrhosis. A cluster of autoimmune markers may also be seen, with positive atypical perinuclear antineutrophil cytoplasmic antibodies in up to 94% of PSC patients. Positive antinuclear antibodies and smooth muscle antibodies indicate possible autoimmune hepatitis-related PSC. Additionally, Serum IgG4 levels of more than four times the upper limit of normal or IgG4:IgG1 ratio of more than 0.24 are suggestive of IgG4-associated PSC [30]. Imaging based diagnosis of PSC is made with the demonstration of characteristic multiple focal areas of stricturing and dilation of intrahepatic or extrahepatic bile ducts

on cholangiography. The first line choice for this is via magnetic resonance cholangiopancreatography (MRCP), as endoscopic retrograde cholangiopancreatography (ERCP) is invasive. However, ERCP and percutaneous transhepatic cholangiography (PTC) are also viable and important options for patients who cannot undergo MRCP, for example those with implanted medical devices [31]. Histopathological findings are characteristic for progressive fibrosis around intrahepatic bile ducts leading to concentric and circumferential laminations known as "onion skin" fibrosis. These changes impact the adjacent circulation, with arterial and capillary ischemia causing further stricturing and circumferential fibrosis.

5. 6. Treatment Modalities

Treatment for PSC ranges from medical management to surgical procedures. While there is no true consensus, ursodeoxycholic acid (UDCA) has been used in moderate doses of 15 to 20 mg/kg daily [33] with some studies showing symptom improvement and survival benefit. While other medications like steroids and antitumor necrosis factor antibodies have been studied as potential treatments, they have not demonstrated benefit. In those patients with pruritus, bile acid sequestrants like cholestyramine can be utilized for symptom relief; if this agent is poorly tolerated, second line options include rifampin and naltrexone. ERCP with balloon dilation is recommended for symptom relief in PSC patients with stenoses measuring less than 1.5mm in the common bile duct or less than 1.0mm in the hepatic ducts, along with pruritus or cholangitis. Additional procedural options include biliary reconstructive procedures like choledochoduodenostomy wherein the common bile duct (CBD) is attached to the duodenum, and choledochojejunostomy, wherein the CBD is connected to the jejunum. Patients with a model for end-stage liver disease (MELD) score of greater than 14 should be referred for liver transplantation, as it is the definitive treatment for decompensated cirrhosis [34]. Additional considerations for patients with PSC include testing for fat-soluble vitamin deficiencies, which are common in patients with advanced liver disease, as well as routine bone mineral density testing as this patient population is at high risk for osteoporosis. Patients may also have steatorrhea, which should be addressed with medium-chain triglycerides. A colonoscopy to assess for inflammatory bowel disease should be considered. Finally, serum CA 19-9 should be evaluated in screening for cholangiocarcinoma given that PSC is a premalignant condition.

5. 7. Prognosis

Patients with small duct PSC have a good prognosis, and progression to advanced liver disease is uncommon. Otherwise, PSC is typically a progressive disorder with complications leading to liver failure. The median survival from time of diagnosis to death without liver transplantation in these cases is approximately 10 years [35]. The Primary Sclerosing Cholangitis Risk Estimate Tool (PREsTo) is a prediction tool for clinical outcomes consisting of nine variables including bilirubin, albumin, platelets, AST, hemoglobin, sodium, patient age, and the number of years since PSC was diagnosed.

5. 8. Impact on Quality of Life

Many of the studies performed to assess quality of life for PSC patients are limited by the small number of participants due to the rarity of the condition. Given the lack of a definitive cure, patients with PSC can live for years with debilitating symptoms like fatigue, pruritus, and pain, as well as a substantial mental burden given the uncertainty of the clinical course. Pruritus especially can be severely disabling, resulting in severe excoriations and a decreased quality of life [36]. Overall, the findings from the studies point to reduced quality of life with increased disease severity, particularly with respect to symptoms of IBD and cirrhosis.

5. 9. Conclusion

Primary sclerosing cholangitis is a progressive liver condition with chronic inflammation eventually resulting in cirrhosis, and with a concerning complication of cholangiocarcinoma. There are numerous causes including autoimmune and environmental factors that may contribute to the pathogenesis of this disease. While there are some proposed management strategies to address PSC, there is a lack of efficient and effective curative medical treatment thereby necessitating invasive interventions. Outcomes for future patients may show improvement with advancements in early detection biomarkers, as well as possible treatment options involving molecular-targeted therapy.

6. Gallbladder Polyps

6. 1. Introduction

Gallbladder polyps are abnormal tissue growths that extend out of the inner mucous lining of the gallbladder. While they are generally not harmful, they are of clinical importance because the small percentage that develop malignancy have a very poor prognosis if treatment is not expeditious.

6. 2. Epidemiology

Gallbladder polyps (GBPs) are one of the most common lesions in the biliary system, and are frequently detected because of unrelated ultrasound testing. The incidence of this condition is roughly equal in both genders and most common in those over the age of 40. GBP prevalence has been on the rise among patients with hypertension, diabetes, and of increased age. Risk factors associated with GBPs include gallstones, cholecystitis, cholangitis, high cholesterol, advanced age, and Peutz-Jeghers Syndrome [37, 38].

6. 3. Pathophysiology

Cholesterol polyps are the most common of GBPs and have no neoplastic features. Accounting for 50% of these polyps, [39] these lesions originate as a consequence of phagocytosis of cholesterol esters and triglycerides by macrophages in the lamina propria, with cholesterol-filled histiocytes subsequently covering the columnar epithelium. These lesions are generally asymptomatic and more common in multiparous women between the ages of 40-50. They typically occur in multiples (64%), pedunculated, and 2-10mm in di-

ameter [40]. Inflammatory polyps account for 5-10% of GBPs; they result from chronic inflammation and are therefore associated with cholecystitis and gallstones. These structures are typically solitary, pedunculated, and 5-10mm in diameter, without risk for malignant transformation [41]. Adenomyomatosis involves an abnormal overgrowth of the lining of the gallbladder. These lesions are the second most common benign polyps (25%) following cholesterol polyps. These lesions are primarily seen in women over the age of 50 and thought to develop secondary to the mucosal hyperplasia following cholecystitis [42]. While these growths are considered non-neoplastic, some studies have stated this has a potential risk for malignant transformation [43]. Other benign polyp formations in this area include lymphoid and granulomatous polyps, however these are far less common lesions. On the other hand, malignant lesions include adenocarcinoma, melanoma, and clear cell; malignant formations are thought to originate from dysplastic epithelium along the gallbladder wall [44]. Solitary formations with increased size are thought to be indicative of malignant lesions with a high risk of cancer when the diameter surpasses 1 cm.

6. 4. Clinical Presentation

Most gallbladder polyps do not show clinical symptoms and are, in fact, incidentally found on ultrasound during examinations for other causes. In the event that a polyp causes an obstruction, the patient may develop cholecystitis, cholangitis, or even pancreatitis; these patients would present with abdominal pain, nausea, vomiting, fever, or jaundice [45].

6. 5. Diagnosis and Testing

There are no specific findings for this condition on lab testing. They are incidentally found on ultrasound examination for other causes, with features showing hyperechoic lesions of protruding soft tissue extending into the lumen along with no acoustic shadowing. There is variance in multiplicity, the presence of a stalk, echogenicity, and size [46]. The presence of stones and sludge impact the visual integrity of this examination, so better results may require an endoscopic ultrasound (EUS) study [47].

Additional imaging studies include CT and MRI. These modalities may be especially useful in providing a more complete visualization of the gallbladder and can rule out other conditions on the differential list, without being impacted by artifacts to the same level as ultrasound studies [48, 49].

6. 6. Treatment Modalities

The management strategy for asymptomatic GBPs depends on the size of the lesion. Polyps under 10mm require close monitoring with scheduled ultrasound studies to assess for growth rate every 3-12 months [50]. If this monitoring identifies a wide-based solid lesion, rapid growth in size or number, or segmental adenomyomatosis, then the next step would be cholecystectomy. Similarly if an asymptomatic lesion is large (>10mm), the patient is over the age of 50, with a history of gallstones, or adenoma, the prudent next step is cholecystectomy. Lastly, if the patient presents with symptomatic GBPs, the best management is proceeding with cholecystectomy [51]. Open cholecystectomy is the traditional route and may be required in cases of malignancy, as there may be a need to remove additional tissue and lymph nodes. This procedure is a higher risk and longer recovery in comparison with the minimally invasive laparoscopic cholecystectomy. This method has been increasingly preferred as a treatment modality, as with other minimally invasive advances.

7. 7. Prognosis

The post-operative recovery period for laparoscopic cholecystectomy is approximately two weeks, with most patients progressing well without major changes other than limiting fat intake during the recovery period. Overall, this condition has a good prognosis following removal of the gallbladder.

7. 8. Impact on Quality of Life

While there is a negative impact on quality of life in the short term following cholecystectomy, 90% of patients reported an improvement within the year in one study, and no association with lower quality of life in another that assessed for anxiety, depression, constipation, and acid reflux. Overall, reduced quality of life was associated with post-operative pain and diarrhea, which typically resolve gradually over the recovery period [52].

7. 9. Conclusion

Gallbladder polyps are often incidentally found on ultrasound examination and typically benign lesions. In instances of symptomatic polyps or concern for malignancy, the condition is addressed with cholecystectomy, and has a low overall morbidity. With continued improvements in diagnostic technology, these lesions are increasingly discovered and treated quickly, with good outcomes.

8. Cholangiocarcinoma

8. 1. Introduction

Cholangiocarcinoma, also called bile duct cancer, is a rare and aggressive malignancy arising from cholangiocytes, the epithelial cells of the biliary tree. It is further categorized into intrahepatic cholangiocarcinoma, and extrahepatic which includes distal bile duct tumors along with hilar cholangiocarcinoma. Intrahepatic cholangiocarcinoma occurs within the small or medium bile ducts inside the liver. Extrahepatic or distal cholangiocarcinoma occurs outside the liver, as the name suggests, after the hepatic bile ducts have joined to form the common bile duct. Hilar cholangiocarcinoma occurs where the right and left hepatic ducts join up to the junction with the gallbladder.

8. 2. Epidemiology

There are approximately 2500 cases in the United States each year; the highest rates occur within Native Americans with an annual incidence of 6.5 cases per 100,000 people [53]. Incidence rates outside North America are particularly elevated in regions like Thailand, Japan, Israel, South Korea, and China. Worldwide, cholangiocarcino-

ma is the second most common primary hepatic malignancy, with incidence and mortality rates increasing steadily over the past several decades. Most cholangiocarcinomas arise in the absence of underlying risk factors. However, known risk factors include: age, primary sclerosing cholangitis (PSC), chronic choledocholithiasis, bile duct adenoma, biliary papillomatosis, Caroli's disease, choledochal cyst, smoking, parasitic biliary infestation, chronic typhoid carrier state. Occupational factors include exposure to high concentrations of 1,2-dichloropropane and dichloromethane in printing companies [54]. Infestation by liver flukes endemic to Asian countries like China, Korea, and Vietnam, have also been linked to the development of cholangiocarcinoma.

8. 3. Pathophysiology

These lesions arise from the intrahepatic or extrahepatic biliary epithelium. >90% are adenocarcinomas, the remaining 10% are squamous cell tumors. While the etiology is undetermined, the long-standing inflammatory state seen with primary sclerosing cholangitis or chronic parasitic infection may play a role via hyperplasia, cellular proliferation, and finally malignant transformation. There is also a possible correlation between intrahepatic cholangiocarcinoma and chronic ulcerative colitis and chronic cholecystitis. Cholangiocarcinomas are slow growing and infiltrate the walls of the ducts, with local extension into the liver, porta hepatis, and regional lymph nodes within the celiac and pancreaticoduodenal chains.

8. 4. Clinical Presentation

Cholangiocarcinoma is a rapidly progressive disease with a median survival of months if left untreated. Presentation varies by anatomic location; for example, intrahepatic cholangiocarcinoma would typically present with right upper quadrant pain. On the other hand, extrahepatic lesions would present with features of biliary obstruction, jaundice, pale stool, dark urine, and pruritus. In the absence of cholangitis, the patient may present with fever, night sweats, and weight loss [55]. The presence of the six clinical criteria that are highly predictive for the diagnosis of this condition include isolated jaundice, age over 60 years, no gallstones, no biliary tract surgery, stenosis limited to the hilum, and a normal common bile duct [56]. Classification for this condition is based on anatomy, with 10% under the umbrella of intrahepatic and the remainder as extrahepatic. Extrahepatic cholangiocarcinoma is further divided into hilar (50-60%) and distal bile duct (around 30%). The Bismuth-Corlette system is commonly used to delineate between the types of hilar cholangiocarcinoma. Type I impacts the common hepatic duct, distal to the confluence of the left and right hepatic ducts. Type II impacts the confluence of the right and left hepatic ducts. Type IIIa impacts the right hepatic duct in addition to the confluence. Type IIIb impacts the left hepatic duct in addition to the confluence. Type IV involves the confluence and both right and left hepatic ducts; it can be referenced as multifocal cholangiocarcinoma [57].

Pathology is useful in categorizing many disorders, particularly in the context of planning and choosing treatment programs, and predicting prognosis. 95% of cholangiocarcinomas are histologically adenocarcinomas. Further morphology-based classification does not have a true consensus with various groups proposing different features for the basis of their systems. Amongst these suggestions is a system from the Liver Cancer Study Group of Japan with the types identified as mass-forming, periductal-infiltrating, and intraductal-growing types. Broadly, surgical planning varies based on morphology. For example, intraductal-growing cholangiocarcinomas are sufficiently addressed with tumor resection with a tumor-free margin, whereas cholangiocarcinomas of the periductal-infiltrating type require aggressive measures, including extensive liver resection, lymph node dissection, and adjuvant anticancer therapy.

8. 5. Diagnosis and Testing

Lab testing for patients with cholangiocarcinoma would indicate extrahepatic cholestasis via increased levels of direct bilirubin, alkaline phosphatase, and gamma- glutamyltransferase (GGT). Some indicators of liver function like albumin and prothrombin time (PT) remain normal early in the disease course; with prolonged obstruction, PT can become elevated due to vitamin K malabsorption. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) may be normal or slightly elevated [56, 57]. Some tumor markers are also associated with this condition in a secondary fashion. For example, CA 19-9 greater than 100 U/mL (normal < 40 U/mL) has been identified in PSC patients who have cholangiocarcinoma. Elevated levels of this marker have also been predictive of increased mortality [58]. Several imaging options are useful in diagnosing cholangiocarcinoma. Typically, the first study due to wide availability is ultrasonography [59]. Typical findings include biliary duct dilatation and larger hilar lesions. Patients with underlying PSC may not show dilatation due to ductal fibrosis. This imaging modality is also limited when examining small or distal lesions. For these lesions, endoscopic ultrasonography (EUS) is especially useful as it provides direct intraductal visualization and also permits aspiration for cytologic studies. It is important to note that if EUS-guided fine needle aspiration is used, the benefit of the additional data must be weighed against the risk of peritoneal tumor seeding [60]. CT imaging studies have additional benefit beyond demonstrating ductal dilatation and larger mass lesions as they also show lymphadenopathy and biliary obstruction. Similarly, hepatic involvement is detected on MRI; staging can be completed as well if MR angiography is performed. Lastly, endoscopic retrograde cholangiopancreatography (ERCP) evaluates obstructions via dye injection and endoscopic evaluation. This strategy has the added advantage that numerous diagnostic modalities can be performed in tandem such as brush cytology, biopsy, needle aspiration, and even palliative stenting. Staging for this condition is separated broadly by location. For intrahepatic lesions, staging correlates with survival after hepatic resection. Stage I refers to solitary tumors without vascular invasion. Stage II references solitary tumors with

vascular encasement or invasion. Stage IIIA involves multiple tumors with or without vascular involvement. Stage IIIB includes regional lymph node metastasis. Finally stage IV applies to tumors with distant metastasis. For extrahepatic tumors, two systems are suggested. The first system by the American Joint Committee on Cancer staging does not correlate with resectability and is found in the figure below [61].

8. 6. Treatment Modalities

There are several options to address cholangiocarcinoma, however surgical resection is the mainstay of treatment with curative intent. Unfortunately, this is only an option for 10% of patients as resection is discouraged in a number of circumstances. General criteria for unresectability for cholangiocarcinoma include the presence of adjacent organ invasion, presence of disseminated disease, presence of retropancreatic or paraceliac metastatic lymph nodes, presence of distant liver metastases, and invasion of portal vein or hepatic artery. For hilar tumors, criteria for unresectability includes atrophy of one lobe of the liver with encasement of the contralateral portal vein branch, atrophy of one liver lobe with contralateral secondary biliary radical involvement, involvement of bilateral hepatic arteries, or encasement or occlusion of the main portal vein proximal to its bifurcation. For patients with unresectable locally contained cholangiocarcinoma, recent data has suggested transplant as a viable treatment option. While the disease-free 5-year survival was reported at 82%, this data is from a single center study [62], with stringent patient selection, and also involved neoadjuvant external beam radiation therapy, trans-catheter intrabiliary radiation, and chemotherapy. Far more research is required to ascertain the utility of this treatment modality and its feasibility for broader application. External beam radiation therapy and chemotherapy have been utilized as adjuvants to surgical resection. However, in patients undergoing complete resection, radiation does not improve survival; in fact, adverse events like cholangitis, gastroduodenitis, and longer hospitalizations, may actually outweigh benefit. Additional treatment options include endoscopic biliary stenting and decompression; while this has been shown to relieve obstructive jaundice, it has not been shown to improve survival. The addition of chemotherapy to biliary decompression has included gemcitabine and cisplatin as first line agents; futibatinib, pemigatinib, ingifratinib, and ivosidenib have been utilized as targeted agents. Unfortunately, these have demonstrated overall minimal improvement in survival [63]. Given that such a high proportion of the patient population present with advanced disease with survival measured in months even following biliary decompression, palliative management is a significant option to address unresectable lesions. Photodynamic therapy (PDT) involves administering a photosensitizer, porfimer sodium, followed by local irradiation with laser therapy. The mechanism of action of this therapy involves the laser transforming the drug from neutral to excited state. Cytotoxic radical species are formed in the presence of oxygen, which subsequently destroys dysplastic cells by directly inducing apoptosis and tumor necrosis. PDT and stenting have been shown to have a significant improvement in quality of life and survival benefit in patients with unresectable cholangiocarcinoma [64].

8. 7. Prognosis

The median survival rate is low because 90% of patients are not eligible for curative resection. The overall survival is approximately 6 months [65]. In the 10% of the patients who are eligible for resection due to absence of primary sclerosing cholangitis, curative surgical resection has 5-year survival rates range from 2-43%, higher survival observed in patients with clear surgical margins and concomitant hepatic resection for hilar tumors. Liver transplantation is considered for some patients in cases of unresectable cholangiocarcinoma with a single center reporting a 5year survival of 82%. [66].

8. 8. Impact on Quality of Life

Cholangiocarcinomas are tumors with a poor prognosis and low quality of life. A single center study investigating quality of life for these patients utilized questionnaires filled in at the moment of diagnosis, one month after treatment, and subsequently at three-month intervals. They were asked 30 questions that aimed to quantify the patient's overall emotional, cognitive, physical, and social status, as well as questions focused on pain, fatigue, nausea and vomiting, insomnia, appetite loss, difficulty breathing, and financial difficulties. Given the silent nature of the developing tumor and diagnosis typically in advanced stages, quality of life improvement typically follows endoscopic biliary decompression with significantly decreased symptoms of fatigue, nausea, and vomiting particularly in the first month following treatment [66].

8. 9. Conclusion

Cholangiocarcinomas are rare and aggressive malignancies of the biliary duct system. While treatment modalities for this condition continue to evolve and advances have been made with interventional strategies, medial survival rate remains low with most patients ineligible for curative resection. The focus is often supportive care and strategies for symptom relief. Comprehensive long term management for this condition should therefore also consider lifestyle modifications like a well-balanced diet and supplementation with calcium and vitamin D to prevent osteoporosis. Additional supplements that may be necessary include fat-soluble vitamins A, D, E, or K. [67] Given impact on the liver, patients should be encouraged to limit or stop drinking alcohol, particularly in PSC cases with cirrhosis. Lastly, patients with liver disease should be counseled regarding increased risk of severe bacterial infections from eating raw or undercooked meat, shellfish, and fish.

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