85377_Auto_Edited-check.docx

Clinical approach to indeterminate biliary strictures: Clinical presentation, diagnosis and workup

Yadlapati S *et al*. Approach to IDBS

Abstract

Despite advancement in cross sectional imaging and endoscopic technology, bile duct strictures remain a challenging clinical entity. It is crucial to make an early determination of benign or malignant nature of biliary strictures. Early diagnosis not only helps with further management but also minimizes mortality and morbidity associated with delayed diagnosis. Conventional imaging and endoscopic techniques, particularly endoscopic retrograde cholangio-pancreatography (ERCP) and tissue sampling techniques play a key in establishing a diagnosis. Indeterminate biliary strictures (IDBS) have no definite mass on imaging or absolute histopathologic diagnosis and often warrant utilization of multiple diagnostics to ascertain an etiology. In this review, we discuss possible etiologies, clinical presentation, diagnosis, and management of IDBS. Based on available data and expert opinion, we depict an evidence based diagnostic algorithm for management of IDBS. Areas of focus include use of traditional tissue sampling techniques such as ERCP with brush cytology, intraductal biopsies, fluorescence *in-situ* hybridization and flow cytometry. We also describe the role of endoscopic ultrasound (EUS) guided fine needle aspiration and biopsies, cholangioscopy, confocal laser endomicroscopy and intraductal EUS in management of IDBS.

Key Words: Biliary strictures; Indeterminate strictures; Biliary sampling; Cholangioscopy; Benign strictures; Malignant strictures; Indeterminate biliary strictures

Yadlapati S, Mulki R, Sanchez-Luna S, Ahmed AM, Kyanam Kabir Baig KR, Peter S. Clinical approach to indeterminate biliary strictures: Clinical presentation, diagnosis and workup. *World J Gastroenterol* 2023; In press

Core Tip: Despite advancements in imaging and endoscopy, bile duct strictures remain challenging. Timely detection of malignant strictures is crucial. Conventional techniques play a crucial role in diagnosis, but indeterminate biliary strictures (IDBS)

require multiple diagnostic tools. This review discusses etiologies, diagnosis, and workup of IDBS, presenting an evidence-based algorithm focusing on traditional tissue sampling techniques and innovative technologies. The importance of future research is emphasized.

INTRODUCTION

Bile duct strictures are commonly encountered in clinical practice and pose a diagnostic challenge to endoscopists. The diagnostic difficulty lies in differentiating malignant strictures from benign strictures. Failure to diagnose malignant strictures or subjecting patients with benign strictures to unwarranted surgery can result in increased morbidity and mortality. Biliary strictures are characterized as indeterminate when no overt mass or differentiating characteristics are seen on cross sectional imaging or after performing endoscopic retrograde pancreatic cholangiography (ERCP) with standard diagnostic tools[1]. At present, up to 20% of biliary strictures are indeterminate. These strictures include both benign and malignant conditions. Biliary strictures may result from intrinsic biliary pathology as well as from extrinsic compression or infiltration from benign or malignant lesions.

Based on previous observational studies, up to one-third of biliary strictures are benign, and two-thirds are malignant in nature[2]. Inflammatory strictures, particularly those related to primary sclerosing cholangitis (PSC), often mimic malignant strictures. Close to 25% of suspected neoplastic strictures are ultimately found to be benign after surgical intervention[2]. Treatment of benign strictures typically involves medical and endoscopic therapy, with only a few patients requiring surgical intervention. Alternatively, malignant strictures often require surgical resection or palliative biliary drainage.

Establishing histological diagnosis is key in determining further management of biliary strictures. ERCP with traditional diagnostics such as brush cytology and forceps biopsies have limited sensitivity in establishing a definite diagnosis[3]. In some cases, it may be necessary to employ additional diagnostic tools such as endoscopic ultrasound

(EUS) guided sampling or cholangioscopy to improve diagnostic yield. Our review aims to explore potential causes of indeterminate biliary strictures (IDBS) and provide guidance on how to use diagnostic testing and technologies to confirm a diagnosis and plan further management. Based on the available data and expert opinion, we depict an evidence based diagnostic algorithm for management of IDBS.

ETIOLOGY AND CLINICAL PRESENTATION OF BILIARY STRICTURES

Clinical presentation in these patients is often variable. Strictures may be found incidentally on cross sectional imaging in asymptomatic patients undergoing testing for other reasons or in those who are symptomatic with abdominal pain or jaundice. Clinical presentation can range from lack of symptoms to fulminant cholangitis or sepsis. A detailed history can help determine underlying etiology to some extent. Painless jaundice and rapid weight loss raise suspicion of underlying malignancy, whereas a more progressive course is seen in those with benign strictures.

Biliary strictures can have benign or malignant origins and may arise from either intraductal pathology or external compression on the biliary tract (Table 1). The most frequent causes of benign biliary strictures include postoperative strictures and those associated with chronic pancreatitis. Postoperative strictures can develop after cholecystectomy, bile duct surgery, or liver transplant (Figure 1). These strictures may be caused by several factors: Ischemic injury, mechanical injury, anastomotic leakage, and post-operative infections causing inflammation, underlying autoimmune disease or malignancy. Chronic inflammation and fibrosis of the pancreatic ducts (PDs) in chronic pancreatitis can cause scarring and narrowing of the adjacent bile ducts, leading to the development of biliary strictures. In some cases, chronic inflammation may result in extrinsic compression of bile ducts due to adhesions and fibrosis.

Other causes of benign strictures include systemic or inflammatory diseases such as acquired immunodeficiency syndrome, PSC or immunoglobulin G4 (IgG4) cholangiopathy. PSC is an inflammatory disorder characterized by focal biliary strictures and dilations involving both intra and extra hepatic bile ducts. Close to 13% of

patients with PSC will eventually develop cholangiocarcinoma (CCA). Biliary strictures in PSC can be managed with endoscopic therapy. Oncological treatment is warranted in those with CCA and this highlights importance of endoscopic tissue acquisition for management of biliary stricture[3]. IgG4 disease is a fibro-inflammatory condition characterized by the infiltration of IgG4 plasma cells into the bile duct wall and pancreas, leading to the development of sclerosing cholangitis and autoimmune pancreatitis.

Malignant biliary strictures are commonly associated with pancreatic cancer, CCA, gallbladder cancer, and metastatic cancer. Cross-sectional imaging can detect a mass lesion involving surrounding structures, such as the pancreas, liver, gallbladder, or regional nodes. In some cases of malignant biliary obstruction, a stricture may be visible without an obvious mass in the early stages of the disease. Although rare, malignant biliary strictures can also be caused by biliary lymphoma, sarcoma, or intraductal papillary neoplasm of the bile duct. Biliary strictures in the setting of malignancy occur due to tumor growth and invasion into bile ducts or surrounding structures, inflammation and scarring, or metastases.

DIAGNOSTIC TESTING

Initial testing often involves a combination of laboratory markers and cross-sectional imaging. This is followed by endoscopic procedures for tissue sampling. Although many tests are available to determine the nature of biliary strictures, no single test is considered absolute. A combination of tests may need to be utilized to evaluate indeterminate strictures. Serum markers play a limited role in detection and diagnosis of CCA and pancreatic adenocarcinoma. Carbohydrate antigen 19-9 (CA 19-9) is commonly used but has variable sensitivity and specificity. It is worth noting that CA 19-9 can also be elevated in certain benign conditions that lead to cholestasis, such as biliary tract inflammation, infection, or diabetes. Carcinoembryonic antigen was previously used for colorectal cancer diagnosis but has limited performance in CCA. Elevated IgG4 levels are associated with IgG4-related sclerosing cholangitis and can aid

in diagnosis when used in conjunction with other tests. Other potential tumor markers, such as interleukin-6, transthyretin, mitochondrial-mediated apoptotic pathway-7, mucin-5AC, and microRNA-16 and 21, require further validation through larger studies to determine their clinical utility.

IMAGING

Ultrasound

Transabdominal ultrasound is typically performed early in work up of biliary obstruction. Ultrasound is highly sensitive for detecting biliary dilation however has limited ability to identify biliary strictures. Therefore, follow up cross sectional imaging is generally required. Transabdominal ultrasound is readily available in all institutions, cost-effective, easy to perform, and lacks exposure to radiation, which makes it an optimal screening test.

Computerized tomography

Computerized tomography (CT) has a higher sensitivity for detecting biliary strictures and pancreaticobiliary malignancies. The sensitivity of CT in detecting malignant strictures is 40%-77%[4-6]. With the advent of enhanced detectors and contrast agents, the performance of CT scans has dramatically improved. In initial stages, CCA can present as a biliary stricture without an obvious mass. CT findings in such cases include a hypo-enhancing biliary lesion during the arterial phase and hyperenhancement during the delayed phase. Several studies have concluded that multidetector CT is nearly 100% sensitive in detecting hilar malignancies, but it has low specificity (60%-80%) for identifying malignant *vs* biliary strictures.

Magnetic resonance imaging/magnetic resonance cholangiopancreatography

Magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) can provide high-quality cholangiograms, making it an ideal choice for evaluating biliary strictures. The cholangiogram performed during MRCP is similar in

diagnostic quality to that performed at the time of ERCP. MRCP can help determine the location and extent of a biliary stricture. A large meta-analysis looking at the performance found a sensitivity of 91% and specificity of 98% in determining the presence of biliary obstruction and close to 98% combined sensitivity and specificity in the ability to detect the location of a biliary stricture. The sensitivity and specificity in the ability to delineate benign from malignant strictures were 88% and 95%, respectively[7]. Diffusion-weighted imaging allows for an improvement in the ability to determine the nature of biliary strictures. Compared to ERCP, this test eliminates several risks, including pancreatitis and cholangitis. However, it is not readily available, expensive, and does not allow for tissue sampling.

ENDOSCOPIC MANAGEMENT OF IDBS
ERCP with fluoroscopic imaging, biliary brush cytology and intraductal biopsies
With the increasing availability of MRI, the diagnostic utility of ERCP in detecting strictures has significantly decreased. Nonetheless, ERCP continues to serve as a valuable diagnostic tool for tissue acquisition to determine the nature of these strictures. Cholangiogram performed after successful biliary cannulation is used to evaluate location, anatomy, and extent of strictures. Physical characteristics of a biliary stricture, although indicative, are often inadequate to definitively differentiate between malignant and benign etiologies. Double duct sign, dilation of common bile duct and PD, is more likely to be seen in malignancy. Malignant strictures are often long and irregular with abrupt cut off "shouldering" resulting in upstream biliary dilation (Figure 2A). Whereas benign biliary strictures often appear smoother[2]. Brush cytology and intraductal biopsies during ERCP are routinely performed to establish histological diagnosis. A recent meta-analysis by Navaneethan *et al*[8] showed that brush cytology and biopsies during ERCP had limited sensitivity, 45% and 48% respectively, in establishing diagnosis of strictures. Combining both diagnostic modalities only increased sensitivity to 59% [95% confidence interval (CI): 54%-65%], however, specificity for confirming malignancy was close to 100% (95%CI: 90%-100%)[8]. In this

regard, patients may need multiple ERCPs with brushings and biopsies to establish a conclusive diagnosis.

Several techniques have been proposed to enhance tissue acquisition during ERCP, such as the use of novel brushes, biliary stricture dilation followed by biopsies and brushing, and repetitive brushings. Pörner et al[9] have suggested that balloon dilation of the stricture before forceps biopsies can improve sensitivity from 40% to over 70% without increasing the complication rate. In another study by Sugimoto et al[10] post brushing biliary lavage fluid was obtained by injecting small amount of saline into bile duct. This increased cumulative sensitivity by over 24%. Submucosal tumor growth and presence of extrinsic malignancy with biliary involvement are difficult to detect with standard biliary brushings. Inadequate brushings or biopsy specimens are primary reason for non-diagnostic samples. At present wire guided endo-biliary forceps, free hand biopsies, endoscopic scrapers are available to obtain tissue. Free hand biopsies are performed by using forceps to grasp the stricture and obtain a tissue sample, while wire guided endobiliary biopsies use a wire guide to navigate to the stricture and obtain a tissue sample. There is no clear consensus on whether free hand biopsies have a greater yield than wire guided endobiliary biopsies. Some studies have suggested that free hand biopsies may have a higher yield, while others have found no significant difference in yield between the two methods. The choice between the two techniques may depend on individual factors such as the location and characteristics of the stricture, as well as the expertise and experience of the endoscopist. Endoscopic devices with scraping loops have recently been proposed for sampling of biliary strictures. This type of device can be considered in institutions where cholangioscopy is unavailable. A recent study compared one endoscopic scraper device to cholangioscopy guided tissue acquisition. Sufficient samples were obtained in 87.5% of cases with endoscopic scraping loops compared to 90% with cholangioscopy forceps. This study described 83% sensitivity and 86% specificity with endoscopic scrapers compared to 90% sensitivity and specificity with samples obtained during cholangioscopy[11]. Endoscopic

sphincterotomy was less frequently needed when sampling was done with endoscopic scrapers[11].

Fluorescence *in situ* hybridization (FISH) is a tissue-based diagnostic tool that uses fluorescent-labeled DNA probes to detect chromosomal abnormalities in cells. It has been found that about 80% of pancreaticobiliary malignancies exhibit abnormalities such as aneuploidy or polysomy of chromosomes[12]. FISH probes typically target chromosomes 3, 7, 9, and 17. FISH has shown a sensitivity of 89% and specificity of 97% for detecting malignancy, especially when combined with other techniques like biopsies and cytology[13,14]. However, false-positive results can occur in chronic inflammatory conditions. Flow cytometry, on the other hand, has lower sensitivity (42%) and moderate specificity (77%) for detecting neoplastic cells in cytology samples[15]. Bile aspirate analysis for mutations and proteomic profiling may aid in distinguishing CCA from benign strictures, but further validation is required for routine use.

EUS guided fine needle aspiration and biopsy and EUS/ERCP combination

EUS can play a pivotal role in evaluation of IDBS. EUS allows for high resolution imaging of pancreaticobiliary system and tissue acquisition by fine needle aspiration and biopsy (FNA/FNB) at the same time. This has been proven to be safe and is considered a primary modality of tissue acquisition from biliary lesions. An overall sensitivity ranging from 47% to 87% has been reported in several studies looking at role of EUS-FNA in work up of hilar strictures[16-18]. EUS has some benefits over ERCP in determining etiology of extrahepatic biliary strictures. In a single center study, EUS-FNA was found to be superior to ERCP with brush cytology and transpapillary biopsies with a sensitivity of 93.8% *vs* 60% and accuracy of 94% *vs* 62%, P = 0.034[19]. However, when ERCP and EUS were combined during a single session, the two procedures reached a sensitivity and accuracy of over 97%[19]. Zaheer *et al*[20] noted diagnostic accuracy of both procedures was over 90% for both benign and malignant strictures. Similarly, in a multicenter retrospective study looking at 263 patients with suspected malignant biliary strictures, combining EUS/ERCP had diagnostic sensitivity and

accuracy of 85.8% and 87.1% respectively[21]. This approach has better outcomes for distal bile duct strictures and those larger than 15 mm[19]. No significant difference in combination procedure *vs* EUS-FNA alone was noted in patients with large biliary or pancreatic mass of 4 cm or more. One advantage of performing both procedures during same session is being able to better triage the need for ERCP in patients with biliary obstruction.

Lee *et al*[16] concluded that sonographic features could provide clues in determining etiology of indeterminate strictures. Presence of pancreatic mass or irregular bile duct wall is suggestive of malignancy. Bile duct wall thickness of 3 mm or more has a sensitivity and specificity close to 79%. Overall EUS-FNA may have low sensitivity but is highly specific for diagnosis of malignancy. Drawback of utilization of EUS-FNA in diagnosis of CCA is concern for potential seeding along needle tract. A small-scale study by Heimbach *et al*[22] revealed peritoneal metastasis was noted in 83% of patients with positive transperitoneal biopsies for CCA. Metastasis was not found in those with negative biopsies and only 8% of patients who did not undergo FNA had peritoneal metastasis. On the other hand, no difference in overall survival was noted among patients who did or did not undergo EUS-FNA. Seeding after EUS-FNA of pancreatic adenocarcinoma is rare with an estimated incidence close to 2%[23]. No large-scale studies are available to investigate EUS-FNA related peritoneal carcinomatosis in cases of CCA. Patients being considered for liver transplant should ideally not undergo EUS-FNA.

Intraductal ultrasound (IDUS)
A high frequency (12-30 MHz) ultrasound probe is typically placed into extrahepatic bile duct during ERCP to perform intraductal ultrasound (IDUS). This allows for real time imaging of bile ducts and surrounding structures. Features suggestive of malignancy include hypoechoic mass or evidence of infiltration to adjacent structures, interruption of three-layer architecture of a bile duct, eccentric wall thickening, heterogenous or irregular margins, malignant appearing perihilar or periductal lymph

nodes or periportal vascular invasion. A cohort study looking at 397 patients undergoing IDUS concluded that IDUS could differentiate benign from malignant biliary strictures with a sensitivity of 93%, specificity of 90%, and accuracy close to 91%[24]. Other studies have concluded ERCP with IDUS significantly improved diagnostic accuracy in identifying malignant strictures compared to ERCP alone. In addition, IDUS was also found to be superior in sensitivity (91% *vs* 76%), specificity (80% *vs* 75%), accuracy (89% *vs* 76%) and cancer staging (78% *vs* 54%) compared to EUS alone[25]. Limitations of IDUS include inability to obtain tissue to confirm histopathologic diagnosis. Adverse events associated with IDUS include pancreatitis, bleeding, cholangitis, and perforation of the bile duct. It is also challenging to evaluate proximal biliary tree as advancing IDUS probe may be technically difficult.

Cholangioscopy

Cholangioscopy was first introduced in 1976 and has undergone significant technological advancement since time of its inception[26]. Cholangioscopy allows for direct visualization and targeted biopsies of bile ducts. This technique failed to gain popularity a few decades ago due to poor reliability and need for two operators to manipulate the mother-baby endoscopies. Traditional peroral cholangioscopy requires insertion of a dedicated video-cholangioscope through an accessory channel of the duodenoscope and requires two skilled endoscopists to operate the system. However, with development of single operator cholangioscopy (SOC) system, cholangioscopy has gained a renewed interest. At present there are two SOC system: Duodenoscope assisted SOC called spyglass and peroral direct cholangioscopy using an ultrathin gastroscope.

Chen *et al*[27] concluded that sensitivity and specificity of SOC in determining etiology of biliary strictures was 78% and 82% respectively, compared to 51% and 54% with ERCP alone. A meta-analysis conducted by Navaneethan *et al*[28] concluded that pooled sensitivity and specificity for detection of CCA using cholangioscopy was 60% and 98% respectively. Another meta-analysis performed by Korrapati *et al*[29] compared

diagnostic accuracy of SOC based on visual images to histology and reported overall accuracy of 89% for making a phenotypic diagnosis and 79% for making a histopathologic diagnosis. Similar results of higher diagnostic yield with visual impression compared to visually targeted biopsies was seen in multiple other studies[30,31]. This may be a result of sampling error at time of biopsy. Cholangioscopy has also been found useful to differentiate PSC related strictures from those of IgG-4 disease[32].

Cholangioscopy guided biopsies improve diagnosis of IDBS in patients with negative ERCP brushings and biopsies (Figures 2B and C). Gerges *et al* noted increased sensitivity for diagnosing malignant biliary strictures with cholangioscopy compared to conventional ERCP and standard sampling, 68% *vs* 21%. In two meta-analyses performed by Navaneethan *et al*[28] and Wen *et al*[33] pooled sensitivity and specificity of cholangioscopy guided biopsies were 60%, 98% and 74%, 98% respectively. Mean number of biopsies performed in these studies were 2 to 5. A recent prospective trial looking at rapid on-site evaluation (ROSE) of the biopsy specimen in these patients did not significantly alter diagnostic accuracy[34]. Two prior cost analysis studies have shown that cholangioscopy was more cost efficient for establishing CCA diagnosis compared to conventional ERCP[35,36]. One study showed a reduction in number of procedures by over 30% and cost by 5% when cholangioscopy was utilized[36].

Interobserver variability is often noted when it comes to performing a visual diagnosis during cholangioscopy. This variability exists due to a lack of consensus on what constitutes a malignant stricture. The Mendoza criteria is a set of guidelines used to describe high-risk features during cholangioscopy, and these features have been found to be statistically associated with presence of malignancy. Based on this criteria, high risk features include presence of neovascularization or dilated tortuous vessels, irregular or nodular biliary mucosa, tumors or masses, irregular surface with ulcerated, infiltrative, or friable appearance (Figure 3). Diagnostic accuracy using this method has been found to be close to 77%[37].

Limitations to the use of the Spyglass Visualization System include cost, specialized training requirements for endoscopists and technical staff, and associated risks. An extended biliary sphincterotomy is required to allow for cholangioscopy equipment to advance into biliary tree and this increases risk of cholangitis, pancreatitis, bleeding. Sethi *et al*[38] reported an increase in overall complication rate to 7% with use of cholangioscopy compared with 2.9% with ERCP alone. Rate of cholangitis was significantly higher in patients undergoing cholangioscopy in this study. Similar data was also reported by Korrapati *et al*[29]. Risk of infection after cholangioscopy is attributed to bacterial accumulation in setting of biliary obstruction and disruption of microbial flora with introduction of cholangioscope. For this reason, prophylactic antibiotics are usually given prior to procedure. Cholangioscopy should therefore be used in conjunction to ERCP when conventional techniques fail to provide a diagnosis despite high suspicion for malignancy.

Confocal laser endomicroscopy

Confocal laser endomicroscopy (CLE) is an imaging technique that allows for real time optical biopsies during ERCP. A contrast agent is typically injected intravenously, and the biliary tissue is imaged with a CLE probe. This technique results in specific patterns that correlate with histology and help differentiate between malignant and normal biliary mucosa. Miami classification is used to differentiate probe-based CLE visual findings as benign or malignant strictures. Presence of thick dark bands (> 40 micrometer), thick white bands (> 20 micrometer), dark clumps, epithelial strictures, villous glands, and contrast leakage can differentiate nature of strictures[39]. Paris classification is a newer classification which includes additional features like vascular congestion, dark glandular patterns, interglandular spaces and thickened reticular structures[40]. A multicenter study found that CLE provided higher diagnostic accuracy (90% *vs* 73%) for identifying malignant biliary strictures than conventional ERCP[41].

Use of CLE in clinical practice is limited by several factors. One limitation is that CLE quires specialized equipment and trained personnel to operate it. Cost of the equipment

can be prohibitive for some healthcare facilities. Another limitation is the need for specialized training for endoscopists to ensure that the procedure is performed correctly and safely.

Investigational and less widely used techniques: Chromoendoscopy, narrow band imaging, autofluorescence and optical coherence tomography

During chromoendoscopy different stains are applied to surface of biliary mucosa at time of cholangioscopy. Methylene blue can be used to delineate malignant lesions and ischemic strictures. High risk lesions concerning for malignancy such as increased vascularity and infiltrative or irregular mucosal surface can be better examined using narrow band imaging. Initial studies looking at use of autofluorescence during cholangioscopy have been less promising given lack of specificity and high false positive rates seen with this method of testing. This technique is not widely use.

Optical coherence tomography (OCT) is an imaging technique that allows acquisition of high-resolution images of the intra and extrahepatic bile ducts. OCT is performed by advancing a probe through accessory channel of a duodenoscope. Disturbed bile duct layers and non-reflective areas, indicating presence of tumor vessels are indicative of malignant strictures. A second-generation OCT system using volumetric laser endomicroscopy was recently introduced. Tyberg *et al*[42] reported findings of epithelial thickening, hyper-reflective surfaces with shadowing and haziness of inner mucosal layers in patients with CCA. A pilot study noted at least one such finding in 79% of study population[43]. However, large, randomized trials are necessary to confirm clinical utility of adding this technique to ERCP and conventional tissue acquisition techniques.

OUR APPROACH TO MANAGEMENT OF IDBS

Management of biliary strictures can be complex and requires a personalized approach that considers the specific clinical presentation and the diagnostic techniques available at the institution (Table 2). Biliary strictures can have a variable presentation and can be caused by a variety of underlying conditions, which can make it difficult to have a

standardized approach to their management. Drawing on the data available, we propose an approach to address IDBS (Figure 4). Additionally, it can be challenging to rule out neoplastic biliary strictures prior to surgery, despite the evolution of endoscopic techniques for diagnosis and treatment. It is important for healthcare providers to carefully evaluate each patient and consider the complete clinical picture to develop an appropriate plan of care.

During the initial evaluation of biliary strictures, it is important to obtain a detailed history and physical examination to assess the patient's risk factors and determine the type of biliary stricture. Basic laboratory tests, particularly liver function tests, should be performed. In cases with clinical suspicion of certain conditions such as PSC, IgG4 or human immunodeficiency virus (HIV), additional testing for tumor markers, HIV antibodies, and IgG4 levels may be necessary. Imaging studies, such as ultrasound and CT with IV contrast, can be useful in the evaluation of biliary strictures. If intra- and extrahepatic biliary dilation is visualized on ultrasound, this is more suggestive of a distal bile duct stricture, which may be caused by an ampullary or pancreatic mass. CT with IV contrast is the preferred imaging modality in such cases. If intrahepatic biliary dilation is seen on ultrasound, this is more suggestive of a proximal biliary stricture, for which MRI/MRCP is the preferred imaging modality.

In instances where extrahepatic biliary strictures are suspected to be a result of a pancreatic mass, EUS-guided fine needle sampling is the preferred method to assess for presence of malignancy. EUS guided FNB or EUS with FNA plus ROSE is recommended over EUS with FNA without ROSE. EUS can help identify minute lesions, in about 40% of cases that may not be readily visible on CT. Single session EUS and ERCP may be warranted in cases where biliary decompression is warranted in addition to establishing diagnosis. Cholangioscopy guided biopsies or intra ductal ultrasound may be needed if conventional ERCP is unable to determine nature of stricture. Maintaining stable positioning of cholangioscope is key to performing targeted biopsies and this can often be challenging if there is a distal bile duct stricture. Endoscopists may use techniques such as balloon dilation to widen the stricture and

improve access to the bile ducts. In cases of proximal or hilar lesions, ERCP is often the primary diagnostic and therapeutic procedure. In the assessment of hilar strictures, multimodal sampling during ERCP is preferred over relying solely on brush cytology. EUS may be warranted if ERCP and traditional sampling techniques, cytology and FISH are inconclusive. Since the location of proximal biliary strictures tends to be more intra-hepatic and away from duodenal wall, it may be challenging to adequately visualize using EUS and obtain biopsies. In cases that are being considered for liver transplant, caution should be exercised before perming biopsies of biliary or hilar lesions. Lymph nodes may be biopsied safely with low concern for seeding.

Lee *et al*[16] conducted a study of 181 patients with suspected malignant biliary strictures. Accuracy of cholangioscopy in diagnosis of malignancy in proximal strictures was 93.6% whereas accuracy of EUS-FNA or biopsy in diagnosis malignant biliary strictures was 96.3%. Currently there are no randomized control trials comparing cholangioscopy guided biopsies and EUS-FNA in cases of IDBS where conventional ERCP based tissue sampling is inconclusive. However, based on available data and expert opinions this could be considered a diagnostic approach.

CONCLUSION

Despite advancement in diagnostic testing, non-surgical evaluation of biliary strictures is often challenging. Management of IDBS often involves employing a multidisciplinary approach and utilizing multiple diagnostic modalities. Entire clinical picture should be considered to come up with a management strategy. Goal of management should be early establishment of diagnosis in cases of malignant strictures and avoidance of unnecessary surgical exploration in cases of benign biliary strictures. A single test may be inadequate to diagnose IDBS. However, a combination of validated serum or bile-based markers, imaging and endoscopic testing will improve diagnostic yield.

85377_Auto_Edited-check.docx