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Approach to the patient with a biliary stricture

Alan Brijbassie, MD, Paul Yeaton, MD*

Section of Gastroenterology and Hepatology, Department of Medicine, Virginia Tech Carilion School of Medicine, 3 Riverside Circle, Roanoke, Virginia

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ABSTRACT

The evaluation of biliary strictures often presents a diagnostic challenge, as missing a malignancy can have catastrophic effects. A variety of diagnostic modalities are available. After a thorough history and physical are obtained, key laboratory information including liver function tests and CA 19-9 levels should be obtained. Radiological imaging, in the form of transabdominal ultrasound, computerized tomography, and magnetic resonance imaging, are instrumental for the determining etiology. Endoscopic evaluation through ERCP with sampling, endoscopic ultrasound, cholangioscopy, and confocal laser endomicroscopy are crucial in the evaluation, and are used as complementary diagnostic tools.

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1. Background

Biliary strictures present a diagnostic challenge and are termed indeterminate when an etiology cannot be ascertained after careful history taking, laboratory evaluation, abdominal imaging, and tissue sampling typically via endoscopic retrograde cholangiography (ERCP). The implications of missing malignancy are grave; however, up to 20% of patients undergoing surgery for suspected biliary malignancy have benign pathology. The diagnostic approach revolves around a detailed history and physical examination; initially ERCP with biopsy was the only modality for securing a tissue diagnosis, however, with the development of endoscopic ultrasound (EUS)-fine needle aspiration (FNA), intraductal ultrasound (IDUS), single-operator cholangioscopy, confocal laser endomicroscopy (CLE), flow cytometry, and fluorescent in situ hybridization (FISH) analysis of the diagnostic approach to biliary strictures has changed.

2. Etiologies of biliary strictures

The incidence of biliary strictures is not known with estimates only available for postcholecystectomy strictures related to bile duct injuries. Strictures defined on ERCP or magnetic resonance cholangiopancreatography (MRCP) are sometimes observed in nonjaundiced patients with or without liver chemistry abnormalities. All bile duct strictures in the setting of obstructive jaundice should be considered malignant unless a benign etiology is confidently apparent.

The most common causes of benign biliary strictures are those related to chronic pancreatitis (CP), choledocholithiasis, primary sclerosing cholangitis (PSC), autoimmune IgG4 disease, ischemic cholangiopathy, human immunodeficiency virus cholangiopathy, recurrent pyogenic cholangitis (RPC), and iatrogenic (postliver transplant or cholecystectomy). Malignant biliary strictures are usually due to pancreatic adenocarcinoma, cholangiocarcinoma, ampullary tumors growing into the bile duct, gallbladder cancer obstructing the bile duct, and metastatic cancer or malignant periportal lymph nodes.

Pancreatic adenocarcinoma is the most important consideration in patients with distal common biliary strictures. An important consideration in these strictures is that a significant percentage do not have a mass lesion demonstrated on computed tomography (CT) or magnetic resonance imaging (MRI) [1,2].

Exclusion of cholangiocarcinoma remains a priority in indeterminate strictures. T1 stage tumors (confined to the bile duct wall limited to the mucosa or fibro-muscular layer without regional adenopathy) undergoing resection have an excellent prognosis with a cumulative 5-year survival rate close to 100% [3]. Most cases, however, are unfortunately diagnosed at an advanced stage. Timely and accurate diagnosis is important not only in terms of patient outcomes but also in appropriately determining surgical candidacy as up to 13%-24% with presumed hilar cholangiocarcinoma undergoing resection are found to have benign disease [4,5]. This difficulty is amplified in patients with PSC as discerning malignant from benign strictures directly affects transplant candidacy.

3. Clinical history and physical examination

In the absence of symptoms of the primary disease, most patients with biliary strictures remain asymptomatic until luminal

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* Corresponding author.
E-mail address: paul.yeaton@gmail.com (P. Yeaton).

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constriction results in resistance to bile flow. Occasionally patients may present with biliary-type pain; however, the clinical manifestations of obstructive jaundice may develop rapidly or slowly depending upon the underlying cause. Patients with jaundice may also report pruritus, dark urine, pale stools as well as steatorrhea. Chronic cholestasis may also be characterized by weight loss and deficiency of calcium and fat-soluble vitamins (A, D, E, and K). Insidious weight loss may suggest malignant obstruction. The etiology of bile duct strictures may be apparent at the time of clinical presentation—in some instances a detailed history is revealed. A history of recent or earlier cholecystectomy should be sought as well as information about the postoperative course especially if complicated should be obtained. Additionally, the history should include information on prior episodes of pancreatitis, known gallstone disease, recurrent episodes of cholangitis (PSC or RPC), cholestatic disorders, prior hepatobiliary surgery, trauma or radiation to the upper abdomen, alcohol abuse, intravenous drug abuse, human immunodeficiency virus infection, and weight loss.

Physical examination may be normal in asymptomatic patients; patients with significant biliary strictures with resistance to biliary flow have apparent jaundice with skin excoriations if associated with pruritus. A palpable nontender gallbladder with jaundice may be observed in patients with malignant obstruction (Courvoisier's sign) and an enlarged nodular liver may indicate malignancy involving the liver or metastatic disease. Patients with postoperative biliary injury and those with recurrent strictures may have evidence of a bile leak in the form of a biliary fistula, biliary peritonitis, or a biloma. These are usually evident in the early postoperative course however may appear weeks to months after.

4. Laboratory evaluation

Conjugated hyperbilirubinemia is often present in patients with biliary strictures, but up to 40% of individuals with malignant strictures may have normal serum bilirubin levels and are nonicteric [1,2,6]. Serum alkaline phosphatase (ALP) and gamma-glutamyltransferase are elevated in only 40% of malignant strictures however elevation with isolated biliary ductal dilation was not associated with a greater risk of malignancy [2,7-10]. Serum CA 19-9 levels above 37 U/mL have a sensitivity of approximately 37% in patents with biliary malignancy, however, levels can also be elevated because of benign causes of cholestasis, cholangitis, stomach cancer, and cirrhosis [7-10]. Elevated serum carcinoembryonic antigen commonly used as a marker for colorectal adenocarcinoma has shown a sensitivity of 33%-68% and specificity of 79%-95% for cholangiocarcinoma [11]. Transthyretin (TTR), interleukin 6 (IL-6), matrix metalloproteineise-7 (MMP-7), and mucin-5AC (MUC5AC) have also been used for differentiating cholangiocarcinoma, however, their use is still experimental and rather limited [12-15].

5. Radiological imaging

5.1. Transabdominal ultrasound

Transcorporeal ultrasound is usually the initial diagnostic imaging modality as it is cheap, noninvasive, and widely available. It has a high sensitivity approaching 100% in detecting intrahepatic biliary ductal dilation, however, an unacceptably low yield for the detection of biliary strictures [16-19]. Additionally, owing to the interference of overlying bowel gas, the distal common bile duct cannot reliably examined.

5.2. Computerized tomography

CT as compared with transabdominal ultrasound has a higher sensitivity in detecting biliary malignancy (69% vs 47%) especially for hilar lesions [20]. The sensitivity has improved to date with the development of multidetector helical scanners used with rapid injection of contrast media providing additional information on etiology based upon the rate of contrast uptake and clearance by focal lesions. CT findings in benign strictures include diffuse bile duct dilation and an abrupt narrowing of the dilated duct whereas ductal infiltrating cholangiocarcinoma commonly presents as a biliary stricture that appears as a hypoattenuating lesion during the arterial phase with enhancement during the delayed phase (characteristic of the desmoplastic reaction noted in bile duct tumors) [21,22]. Choi et al [23] retrospectively analyzed the use of multiphasic helical CT for differentiating malignant from benign structures in patients with only focal common bile duct (CBD) strictures and noted that malignant strictures were characterized by strong enhancement or high attenuation during the hepatic arterial or portal venous phase, wall thickness greater than 1.5 mm and a longer involved segment with a more dilated duct proximally than observed in benign cases.

The sensitivity of CT for the detection of cholangiocarcinoma ranges from 40%-63%. Recent studies have quoted a sensitivity of up to 100% in detecting hilar malignancy during the arterial phase [24-26]. An additional advantage of CT scanning is that it provides information about local spread as well as vascular involvement and distant metastases; retrospective studies have reported sensitivity and specificity of 86% and 87%, respectively, for detecting arterial invasion and 85% and 97%, respectively, for portal vein involvement. MCDCT has 53% sensitivity and 95% specificity for preoperative determination of regional lymph node involvement [27].

5.3. Magnetic resonance imaging

Since its introduction in 1991 [28], MRI/MRCP has emerged as an accurate noninvasive modality for biliary imaging [29]. The ability to create an image of the biliary tree without the direct injection of contrast medium has always been an attractive option especially when optimal biliary drainage cannot be provided during ERCP. The disadvantages of MRI include the high cost, motion artifact, claustrophobia in closed stations, longer imaging times, and the inability to obtain material for cytological analysis. The sensitivity of MRCP for bile duct stenosis and filling defects is high, yet the specificity and positive predictive value remains suboptimal, as it cannot reliably distinguish malignant vs benign strictures. In some studies, the reported sensitivity and specificity parallels that of ERCP for assessing the level and morphology of strictures [30-32]. With regard to differentiating malignant from benign strictures, MRCP has a reported sensitivity of 38%-90% and specificity of 70%-85% [26,33,34] along with 88%-96% accuracy in predicting the extent of bile duct involvement by cholangiocarcinoma [32,35] was observed.

MRCP techniques involve the use of heavily weighted T2-weighted sequences to accentuate the high signal from relatively static fluid while suppressing the signal from background tissue including flowing blood [36,37]. Either rapid acquisition with relaxation enhancement (RARE) or a variant (single shot fast spin-echo, half Fourier acquisition singe-shot turbo, or fast recovery fast spin-echo) is used for MRCP [37] obtained using either of the following 2 different techniques: (1) standard two-dimensional (2D) magnetic resonance (MR) cholangiopancreatography, or (2) three-dimensional (3D) isotropic MR cholangiopancreatography [7]. Standard 2D MR cholangiopancreatographic protocols generally consist of the thick-slab single-section sequence

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