Diagnosing Biliary Malignancy

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KEYWORDS

- Cholangiocarcinoma (CCA) • Endoscopic ultrasonography (EUS)
- Fluorescence in situ hybridization (FISH) • Intraductal ultrasonography (IDUS)
- Indeterminate biliary stricture • Pancreatic cancer
- Primary sclerosing cholangitis (PSC)
- Probe-based confocal endomicroscopy (pCLE)

KEY POINTS

- Approximately 15% to 24% of biliary strictures are considered indeterminate after standard endoscopic retrograde cholangiopancreatography with sampling and are found to be benign at the time of surgery.
- Combining sampling techniques, including cytology, directed biopsies, and advanced molecular analysis, with fluorescence-in situ hybridization can significantly improve the yield of tissue diagnosis of malignant biliary strictures.
- Advanced imaging techniques such as cholangioscopy and confocal endomicroscopy may assist in improving the diagnosis of biliary strictures and help determine targeted areas for biopsy.

INTRODUCTION

The diagnosis of malignant biliary obstruction remains a significant clinical challenge. Accurately differentiating benign from malignant causes of a bile duct stricture is of obvious clinical importance for therapeutic planning and prognosis. The 2 most common causes of malignant strictures are cholangiocarcinoma (CCA) and pancreatic cancer. Diagnosis of these malignancies at an early stage can allow curative surgical resection or even liver transplantation for early-stage CCA. Tissue diagnosis of pancreaticobiliary malignancies via endoscopic approaches is well known to be limited by poor cellular yield and often requires surgical exploration for definite diagnosis. For cases of suspected pancreatic cancer, in which an extrinsic pancreatic mass is seen on cross-sectional imaging, or a double-duct sign (dilatation of both bile duct and pancreatic duct), endoscopic ultrasonography (EUS) should be the primary

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form of diagnosis and tissue should be sampled with fine-needle aspiration (FNA). This challenge in the evaluation of biliary strictures is made even more difficult in the case of an indeterminate stricture in which preprocedural cross-sectional imaging does not show an overt mass that would be highly suggestive of malignancy. Furthermore, surgical series show that 15% to 24% of patients who undergo resection for suspected malignant strictures based on preoperative imaging or endoscopic retrograde cholangiopancreatography (ERCP) ultimately have a benign diagnosis on pathology.[1,2] This small but significant cohort of patients with benign strictures highlights the importance of accurate preoperative tissue diagnosis to avoid the morbidity and mortality of hepatobiliary surgery. This article reviews the causes of biliary strictures, the initial clinical evaluation of biliary obstruction, the diagnostic yield of ERCP-based sampling methods, the role of newer tools in the approach to evaluating strictures, and ways to address the ongoing challenge of stricture evaluation in patients with primary sclerosing cholangitis (PSC).

CAUSES OF BILIARY STRICTURES

The leading causes of malignant biliary obstruction are pancreatic cancer and CCA.[3] Cholangiocarcinoma is a primary malignancy of the bile duct epithelium, and as such can involve both the intrahepatic and extrahepatic bile ducts. Worldwide, CCA accounts for 3% of all gastrointestinal malignancies and is the second most common primary liver malignancy after hepatocellular carcinoma.[4] When CCA is diagnosed at an early T1 stage, surgical resection can have an excellent prognosis.[5] The difficulty in the diagnosis of CCA is the poor cellular yield from the current first-line method of ERCP with brush cytology and/or biopsy. In addition, there is a known spectrum of benign causes of biliary strictures that can radiographically mimic CCA, making the exclusion of malignancy in these benign disorders clinically challenging.

Pancreatic cancer most often presents as a distal common bile duct stricture caused by extrinsic compression of the extrahepatic duct from a pancreatic head mass. This is in contrast with CCA, which often develops along the length of the bile duct, making its early detection particularly difficult because of the lack of a visible growth or tumor on imaging. Other less common malignant causes of biliary strictures include intraductal hepatocellular carcinoma, metastatic lesion, and extrinsic compression of the biliary tree from an associated visible mass or lymphadenopathy (**Table 1**).

Benign biliary strictures can develop from a variety of causes ranging from recurrent cholangitis, iatrogenic causes (most commonly after cholecystectomy or liver transplantation), to cholangiopathy from autoimmune disease, human immunodeficiency virus, and PSC. One of the least understood mimickers of a malignant process is autoimmune or immunoglobulin G4 (IgG4)–associated sclerosing cholangitis (IgG4-SC). The prevalence and pathogenesis of this disease remains largely unknown but more than 80% of patients have increases of serum IgG4 levels to more than the upper limit of normal and a similar percentage of patients have an associated autoimmune pancreatitis.[6,7] On cholangiogram, hilar IgG4-SC strictures are often indistinguishable from CCA; however, histology can be diagnostic, showing massive infiltration of IgG4-positive plasma cells with fibroinflammatory involvement of the submucosa of the bile duct wall.[6]

LABORATORY EVALUATION

The most common laboratory abnormality seen in patients with malignant biliary stricture is obstructive cholestasis. Direct hyperbilirubinemia is seen more commonly in