Techniques in Gastrointestinal Endoscopy 18 (2016) 158–167

Contents lists available at ScienceDirect

Techniques in Gastrointestinal Endoscopy

journal homepage: www.techgiendoscopy.com/locate/tgie

Diagnosis and endoscopic management of primary sclerosing cholangitis

Anthony Razzak, MD, Richard Kozarek, MD*

Digestive Disease Institute, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, Washington 98101

ARTICLE INFO

Article history:
Received 7 March 2016
Accepted 27 May 2016

Keywords:
Primary sclerosing cholangitis (PSC)
Endoscopic retrograde cholangiopancreatography (ERCP)
Magnetic resonance cholangiopancreatography (MRCP)
Cholangiocarcinoma
Fluorescence in situ hybridization (FISH)

ABSTRACT

Primary sclerosing cholangitis (PSC) is a complex, chronic, and progressive fibroinflammatory destructive cholestatic biliary disease. The exact etiology and pathogenesis are unknown and possibly related to an enhanced immune-mediated response and reaction in the biliary system. PSC is closely associated with inflammatory bowel disease and specifically, ulcerative colitis. It can be characterized by both intrahepatic and extrahepatic bile duct stricturing and dilation. Clinical manifestations include abnormal liver tests, jaundice, pruritus, and fatigue. At more advanced stages, PSC can progress to cirrhosis and posttransplant disease recurrence is not uncommon. PSC is associated with an increased risk of cholangiocarcinoma and is an independent risk factor for colorectal cancer in patients with concomitant inflammatory bowel disease. Cholangiography is the mainstay of PSC diagnosis. Improved noninvasive biliary imaging has shifted the role of endoscopic retrograde cholangiopancreatography from disease diagnosis to management of complications, including dominant biliary strictures, bile duct stones, and assisting in the differentiation of benign vs malignant strictures. The role of additional endoscopic modalities, including endoscopic ultrasound, direct cholangioscopy, and probe-based confocal laser endomicroscopy is evolving. At the present time, medical treatment options are limited and the role of endoscopy is mainly supportive.

1. Introduction

Primary sclerosing cholangitis (PSC) is a complex, chronic, and progressive fibroinflammatory destructive cholestatic biliary disease of unclear etiology. Disease complications include recurrent cholangitis, bile duct stone formation, hepatic abscess formation, progression to cirrhosis, and the development of cholangiocarcinoma (CCA).

Endoscopic retrograde cholangiopancreatography (ERCP) is the most common endoscopic intervention to assist with disease diagnosis and management; however, the role of endoscopic ultrasound (EUS), direct cholangioscopy, and probe-based confocal laser endomicroscopy (pCLE) is evolving. At the present time, medical treatment options for PSC are limited and the role of endoscopy is mainly supportive.

2. Epidemiology, pathogenesis, and clinical presentation

A majority of PSC disease burden is thought to occur in North America and Europe, though data on global disease distribution are lacking. A recent systematic review and meta-analysis evaluating North American and European population-based studies projected an incidence rate of 1.00 per 100,000 person years with a near 2-fold increased risk in men as compared to women and a median age of diagnosis at 41 years [1]. In a United States (US)-specific population-based study, the overall incidence of PSC was 0.90 per 100,000 person years and the prevalence estimated at 13.6 per 100,000 persons [2]. More than twice as many men were affected as women, the mean age at diagnosis was 40 years and a significantly lower rate of survival was noted in those with PSC when compared with age and gender matched controls (10-year survival of 65% vs 94%, respectively). It must be acknowledged that these US data are generated from a single geographic location and therefore, may not typify the PSC burden in the United States as a whole.

PSC has a significant association with inflammatory bowel disease (IBD) with an estimated 70%-80% of affected individuals suffering concomitant ulcerative colitis (UC) or Crohn's disease [2,3]. Although the true prevalence is unknown, the more common association is with UC and some data suggest a higher prevalence in those with more extensive colonic involvement [4]. In contrast, approximately 4% of individuals with UC would develop PSC and the rate within the Crohn's population is thought to be lower [3].

The exact etiology of PSC remains unknown. Current theories suggest a complex multifactorial process, which includes both

* Corresponding author.
E-mail address: Richard.Kozarek@virginiamason.org (R. Kozarek).

http://dx.doi.org/10.1016/j.tgie.2016.05.003
0049-0172/

immune and non–immune-mediated biliary injury in those with a genetic predisposition. This is supported by studies that have identified an increased risk of PSC in first-degree relatives and an increased association with autoantibodies [5,6]. Non–immune-mediated injury has been theorized from the association of PSC with IBD and the subsequent potential for bacterial translocation into portal circulation, cholangitis, and ischemic injury [3,7]; however, conclusive data to support this are limited.

Approximately, 50% of individuals are symptomatic at presentation with reported symptoms including jaundice, fatigue, pruritus, weight loss, right upper quadrant pain, and fevers [2,3,8]. Laboratory testing typically reveals a predominant cholestatic liver injury profile with elevated alkaline phosphatase. Complications from PSC and chronic cholestasis include fat-soluble vitamin deficiency, metabolic bone disease, cholangitis, progression to biliary cirrhosis, development of CCA, and an increased risk of colonic dysplasia and colorectal cancer in those with coexisting IBD [3,9]. The lifetime risk of CCA in PSC is approximately 10%. Up to 50% of individuals with CCA would be diagnosed within 2 years of their PSC diagnosis. Cholangiocarcinoma screening is supported by multiple societies [9,10] but there remains no universal screening protocol or high quality data to suggest an impact on overall survival. Individual who are symptomatic at presentation appear to have a significantly lower survival rate [11]. Similarly, those with IBD appear to have a higher rate of malignancy, liver transplantation and death [12]. At the present time, the median transplant-free survival is approximately 10-12 years, and the posttransplant 5-year survival rates are 80%-85% [9].

3. Diagnosis of PSC and differential diagnosis

The diagnosis of PSC is based on visualization of the biliary system and identification of characteristic intrahepatic and extrahepatic cholangiographic features. The findings in classic PSC include multifocal strictures and dilations that create a beaded appearance and usually involve both the intrahepatic and extrahepatic biliary system. Less commonly, disease can be isolated to the intrahepatic or extrahepatic biliary system and involve the gallbladder or cystic duct or both [7]. Small-duct PSC, a less prevalent variant found in patients with IBD, is characterized by normal cholangiography with cholestatic liver test abnormalities and typical PSC-related histologic findings on liver biopsy. Some reports suggest that a percentage of small duct patients progress to classic PSC and this may represent an early disease state [13,14].

ERCP had long been considered the gold standard for detecting PSC and favored over percutaneous transhepatic cholangiography owing to the technical difficulties of a percutaneous approach [7] (Figure 1). The availability of a noninvasive diagnostic tool, magnetic resonance cholangiopancreatography (MRCP) has been evaluated with multiple comparative studies that reveal equivalent diagnostic accuracy (80%-90%) with higher interobserver agreement and a favorable cost effectiveness, relative to ERCP [15-17]. Currently, MRCP is preferred over ERCP to establish the diagnosis of suspected PSC when there is no contraindication to magnetic resonance and no indication that would warrant an endoscopic biliary intervention [9] (Figure 2). Limited data are available on the effectiveness of EUS in the diagnosis of PSC, but it may have a role in identifying extrahepatic PSC not identified on MRCP and offer a less invasive diagnostic alternative to ERCP [18].

In patients with cholangiographic features suggesting PSC, a liver biopsy is not necessary to make the diagnosis [10]. However, in the absence of typical imaging features and ongoing clinical suspicion, liver biopsy is indicated and required in cases of the small duct PSC variant. Classic histologic features include ductopenia and concentric periductal connective tissue fibrosis giving an onionskin type appearance [3,10]. Liver biopsy provides the added benefit of staging underlying liver fibrosis in those with advanced disease.

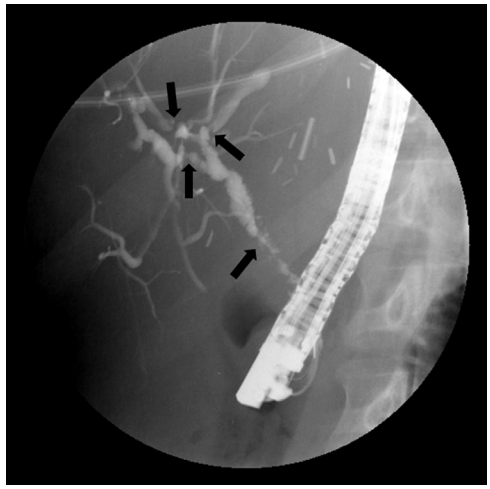

Fig. 1. ERCP cholangiogram in PSC. ERCP cholangiogram revealing Intrahepatic and extrahepatic multifocal biliary ductal stricturing and dilation (arrows highlighting areas of stricturing).

Evaluation to rule out secondary causes of sclerosing cholangitis must be undertaken to ensure the proper diagnosis (Table). Numerous conditions have been associated with secondary sclerosing cholangitis including, malignant and nonmalignant causes of biliary obstruction, toxic biliary injury, biliary ischemia, immune-mediated processes such as IgG4 cholangiopathy, recurrent and chronic biliary infectious, and genetic predispositions [19-34]. A majority of these entities can be evaluated with clinical history, biliary imaging, and a serologic assessment of autoimmune markers, including IgG4.

4. Endoscopic management of PSC and related complications

The preprocedure evaluation of patients with PSC requires specific attention to patient safety and appropriateness of an endoscopic intervention. It is universally acknowledged that expert endoscopists should perform ERCP in patients with PSC. Periprocedural prophylactic antibiotics are recommended because

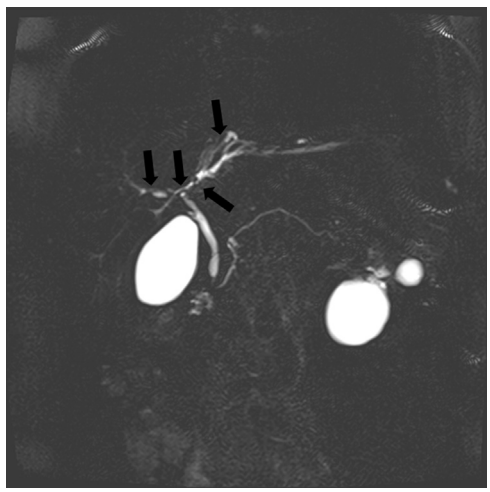

Fig. 2. MRCP cholangiogram in PSC. MRCP cholangiogram in PSC revealing predominately intrahepatic multifocal bile duct stricturing and dilation (arrows highlighting areas of stricturing).