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Research Article

Inflammatory Bowel Disease and Primary Sclerosing Cholangitis -

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ABSTRACT

Primary sclerosing cholangitis (PSC) and inflammatory bowel disease are strongly related, as 71% of patients with PSC have ulcerative colitis (UC) and it seems that both diseases have shared genetic factors. IBD-PSC has different characteristics than IBD only. In patients with UC and PSC, the more common form of disease is pancolitis, and in Crohn's disease patients with PSC is colitis. Also, IBD with concomitant PSC is less active and occurs at an earlier age. PSC is an additional risk factor for colorectal neoplasia in IBD patients and IBD increases the risk of developing gallbladder cancer and cholangiocarcinoma in PSC.

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic progressive unknown etiology cholestatic liver disease and causes fibroesclerotic stenoses and destructions of intra- and extra-hepatic bile ducts. It can lead to several serious complications and can require liver transplantation. PSC is strongly associated with inflammatory bowel disease (IBD) and especially ulcerative colitis (UC) and less often with Crohn's disease (CD).

EPIDEMIOLOGY

In the Caucasian population, it is estimated that approximately 4% of patients with ulcerative colitis may develop PSC [1] and three quarters of patients with PSC have UC [2]. However, the prevalence of PSC varies among nations. For example, the prevalence of PSC in Korean and in Turks patients with UC is markedly lower, 1.1% and 2.6% respectively [3, 4]. It seems that the association between PSC and IBD is depending on geographical location, with stronger association in Europe and America, and weaker association in Japan [5]. PSC occurs with a 2:1 male predominance [6]. Sano et al. demonstrated association between gender and age distribution of PSC in patients with IBD. The age distribution had two peaks. Male PSC-IBD patients made the first peak in their 20s and the female PSC-IBD patients made the second peak in their 50s and 60s [3]. Furthermore, early onset of UC is associated with high incidence of PSC [7].In CD patients with concomitant PSC, female is the predominant gender and small duct PSC is more common among CD patients (22% of PSC-CD patients vs 6% of PSC-UC patients) [8]. Familial occurrence of PSC and UC and especially the coexistence both diseases in twins show that genetic factors play a role for the development of PSC and UC and there are mutual responsible genes between both diseases [9, 10]. Bergquist et al. described increased risk of PSC and UC in first-degree relatives of patients with PSC [11].

CHARACTERISTICS OF IBD IN PATIENTS WITH PSC

It seems that inflammatory bowel disease with concomitant primary sclerosing cholangitis is a unique form and differs from IBD without PSC. The differences include the clinical course of IBD, the age diagnosis, localization and severity of IBD. In a case-control study, Joo M. et al compared UC patients with PSC and UC patients without PSC. In this study, UC-PSC patients presented at an earlier age (24.5 years vs 33.8 years), had a higher prevalence rate of pancolitis (85% vs 45%), ileitis (35.7% vs 26.9%) and pouchitis (42.8% vs 26.6%) and lower grade of inflammation (a five-point grading system was used, 2.09 +/-0.085 vs 2.59 +/-0.92). So, UC-PSC patients had more extensive but less active disease [12]. Also in another study, Loftus et al. report higher prevalence of rectal sparing and backwash ileitis in UC-PSC patients compared to patients with UC only, 52% and 51% vs 6% and 7% respectively [13]. On the other hand, the most common localization of Crohn's disease-PSC is colitis and followed by ileocolitis. The rate of isolated ileitis in CD-PSC patients is less frequent compared with patients with CD only (6% vs 31%)[8, 14]. Concerning colonic disease activity, Lundqvist et al. report differences in UC activity among UC patients with and without PSC. Patients with UC and PSC receive treatment with systemic and local corticosteroids and hospitalized due to colonic activity less frequently than patients with UC only [15]. It seems that there is an association between progression of PSC and clinical course and type of IBD. Marelli et al studied how the severity of PSC influences the clinical course and treatment of UC. For this reason, they compared UC-PSC patients who underwent or no liver transplantation. The study showed that PSC requiring liver transplantation was associated with a milder activity of UC, less frequently use of steroids and azathioprine, less surgery and reduced incidence of colorectal neoplasia [16]. However, the clinical course of UC changes after liver transplantation and UC become more aggressive. Also, de novo UC development can occur after liver transplantation [17]. Conversely, PSC needing liver transplantation does not influence the clinical course of CD [18]. In addition, there is a correlation between the type of IBD and the course of PSC. Patients with CD and PSC have a milder liver disease than patients with UC and PSC. Perhaps, it happens because small-duct PSC ismorecommoninCDpatients[19].

COLORECTAL NEOPLASIA

Patients with UC and patients with CD colitis are at increased risk for colorectal cancer (CRC). For this reason, it recommends interval surveillance colonoscopy [20]. According to the literature, it seems that PSC increases the risk for CRC in patients with UC or with Crohn's disease colitis (CC), although the data for PSC and CC are still unclear [21]. Colon cancer surveillance guidelines for IBD-PSC patients recommend annual colonoscopy after the diagnosis of PSC [20]. A meta-analysis showed that the patients with UC and PSC have a higher risk for the development of CRC compared with patients with UC only; OR= 4.79 (95% CI: 3.58-6.41) [22]. Also, the proximal part of the colon in patients with UC and PSC has a higher risk for CRC compared with the rest part of the colon [13]. About the association between CD with PSC and colorectal neoplasia, the studies are conflicting. A case-control cohort study showed that CC patients with concomitant PSC and patients with CC only have the similar risk of developing colon neoplasia. Furthermore, all cases with colon neoplasia and concurrent PSC occurred in the right colon [23]. However, another study showed that PSC is a risk factor for the development of colorectal neoplasia in CD patients; OR 6.78, 95% CI (1.65-27.9) P=0.16 [24]. Thacherray et al found that the rate of developing colon neoplasms within 2 years of diagnosis of IBD and

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PSC is similar to the rate after 8 to 10 years from diagnosis of IBD and PSC. This study justifies the colon cancer surveillance guidelines of beginning colonoscopy after PSC and IBD diagnosis [25]. Because colon cancer in patients with UC and PSC is more common in the proximal colon where concentrations of secondary bile acids are highest, the chemo preventive role of ursodeoxycholic acid (UDCA) was investigated. The results are unclear and contradictory. For example in a multicenter randomized placebo-control trial, Eaton et al examined the effects high dose UDCA (28-30mg/kg/day) on the development of colorectal neoplasia in PSC-UC patients. Patients who received UDCA have a higher risk of developing colorectal neoplasia compared with those who received placebo; HR 4.44, 95% CI 1.3-20.1, P=0.02 [26]. On the other hand, in another randomized placebo-control trial, UDCA therapy decreases the risk of developing colorectal neoplasia; OR 0.26, 95% CI, 0.06-0.92, P=0.034 [27]. In a retrospective cohort study, UC patients with concurrent PSC who received UDCA or not have the similar risk of developing cancer or dysplasia; OR=0.59, 95% CI 0.26-1.36 [28].

GALLBLADDER CANCER AND CHOLANGIO-CARCINOMA

A serious complication of primary sclerosing cholangitis is the development of carcinomas from bile ducts [29] and gallbladder [30]. The data on the role of IBD as an additional risk factor are still scant. In a prospective study, Rudolph et al described that in PSC patients with dominant bile duct stenosis, IBD is associated with increase of cholangiocarcinoma and gallbladder cancer but not in PSC patients without dominant stenosis [31]. However, Jance et al found that IBD irrespective of dominant bile duct stenosis increases the risk of developing biliary tree carcinoma in PSC [32]. Notably, cholangiocarcinoma occurred to a 17 years old with PSC and IBD [33].

CONCLUSION

IBD and especially UC are closely associated with PSC. It seems that both diseases interact. IBD with PSC has earlier age diagnosis, milder active disease and different localization compared with IBD only. Also, there is dramatic increase in the risk of developing CRC and the clinical course of PSC affects the clinical course of IBD. On the other hand, IBD increases the risk for development of carcinoma from biliary tree. Therefore, IBD patients with PSC require different monitoring and perhaps treatment than patients with IBD only. In the future, more studies should be made on this subgroup of IBD patients.

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