

Characteristic features of ulcerative colitis with concomitant primary sclerosing cholangitis

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Abstract

Ulcerative colitis is a chronic inflammatory bowel disease of the colon. The most frequent symptoms include bloody diarrhoea with rectal urgency and tenesmus. It is often complicated by the presence of primary sclerosing cholangitis, a chronic, cholestatic liver disease, characterised by the inflammation and fibrosis of bile ducts. The presence of primary sclerosing cholangitis seems to alter the course of ulcerative colitis, changing its natural course.

Introduction

Inflammatory bowel disease (IBD) is a term used for ulcerative colitis (UC) and Crohn's disease [1]. The diseases are caused by a complex immunological disturbance with both environmental and genetic causes [2]. Ulcerative colitis greatly affects the patient's quality of life due to debilitating symptoms, and patients with UC have a 1.8-fold higher risk of work disability as compared to the general population [3]. Although it is uncertain whether IBD alone affects mortality, mortality is higher in patients who have both IBD and primary sclerosing cholangitis [2, 4]. The presence of primary sclerosing cholangitis alters the course of ulcerative colitis [5]. The pathogenesis of primary sclerosing cholangitis is still unclear [6]. Further research may provide an insight into the natural course of ulcerative colitis in the presence of primary sclerosing cholangitis.

Ulcerative colitis

Ulcerative colitis is a chronic inflammatory bowel disease of the colon that causes a superficial mucosal inflammation in a continuous fashion extending from the rectum to the more proximal colon, to varying extents [7]. The most frequent symptoms include bloody diarrhoea with rectal urgency and tenesmus, and the disease runs a relapsing – remitting course [8]. The peak age of disease onset is 30–40 years, and no sex predominance exists [9, 10]. Thirty-one percent of patients with UC limited at diagnosis will have disease extension

by 10 years, and in 10–15% of patients the disease will lead to colectomy [11]. Younger age at onset (< 40 years), pancolitis, lack of endoscopic healing while in clinical remission, deep ulcerations, and high concentrations of perinuclear antineutrophil cytoplasmic antibodies have been identified as risk factors for aggressive or complicated disease [12]. UC can also cause extra-intestinal manifestations – both gastrointestinal (GI) and non-gastrointestinal. GI extra-intestinal manifestations of UC include primary sclerosing cholangitis, present in between 0.76% and 5.4% of UC patients, depending on the study [8]. In UC patients with higher incidence of acute or chronic pancreatitis, autoimmune hepatitis, primary biliary cholangitis, and atrophic gastritis have been described [8, 13]. Non-GI extra-intestinal manifestations most frequently occur in the musculoskeletal system, integument, ocular, and renal systems, respectively [8]. Rates of extra-intestinal manifestations are higher in children compared to adults [14]. Therapeutic agents, such as mesalamine, immunosuppressants, and biologic agents are used to induce and maintain remission [15].

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is defined by the American Association for the Study of Liver Diseases (AASLD) as a chronic, cholestatic liver disease, characterised by the inflammation and fibrosis of both intrahepatic and extrahepatic bile ducts, leading to the formation of multifocal bile duct strictures [16]. It is a classic hepatobiliary manifestation of inflammatory bowel diseases,

such as ulcerative colitis [17]. The incidence varies geographically, and in northern Europe it is as high as 10 per 100,000 people per year, it is slightly more frequent in men, and the median age of onset is 30–40 years [17, 18]. Some studies suggest the increase in the incidence of PSC, which may partly result from the more frequent application of magnetic resonance cholangiography [19, 20].

The pathogenesis of PSC is unknown, but several groups of theories have been proposed, such as immune-targeted injury, toxic biliary damage, infectious triggers, and vascular insults. Gut microbiota disturbances and recruitment of gut-derived T cells to the liver have also been proposed as possible mechanisms [17, 21].

Most patients are asymptomatic at the time of the diagnosis, and only in 10–15% of patients are fever, night sweats, chills, pain in the right upper quadrant, itching, or jaundice present [22]. The most frequent signs at diagnosis are hepatomegaly (in 44% of patients) and splenomegaly (in 39% of patients) [23]. Sometimes, cholelithiasis, gallbladder carcinoma, pancreatitis, or colorectal cancer may be the first symptom of the disease [24]. Diagnostic criteria include exclusion of secondary sclerosing cholangitis and both laboratory (increase in serum alkaline phosphatase for more than 6 months) and imaging findings (bile duct strictures in either magnetic resonance imaging or endoscopic retrograde cholangiopancreatography) [25].

Primary sclerosing cholangitis is frequently associated with other diseases; the prevalence of ulcerative colitis in PSC patients differs widely in different countries – from 23% in Japan up to 80% in Sweden [26, 27]. The diagnosis of PSC may precede diagnosing the patient with IBD [21, 28]. Also, PSC may present even after colectomy in IBD patients [29]. In up to 25% other autoimmune diseases are present [30]. It is also a risk factor for colon, bile duct, and gallbladder cancers [31]. If primary sclerosing cholangitis is concomitant with inflammatory bowel disease, the risk of colon cancer is 10 times as high as in the general population, and 4 times higher than in patients with IBD alone [32].

Currently there is no effective medical therapy for primary sclerosing cholangitis, despite numerous clinical trials. Poor understanding of the pathogenesis of PSC makes it difficult to identify therapeutic agents [25]. Up to 40% of PSC patients will ultimately require liver transplantation, and PSC may recur in 25% of patients after transplantation [25, 33].

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Previously conducted studies show that when PSC is present, UC seems to demonstrate a characteristic

disease phenotype. PSC-IBD may even be a separate disease entity than IBD alone [34, 35]. Patients with PSC were younger at ulcerative colitis diagnosis and had more extensive disease, but disease activity during acute flares was significantly lower, flares had lower incidence, disease activity was decreased – especially in the first 10 years after the diagnosis – and corticosteroids, anti-tumour necrosis factor, and anti-integrin agents were needed less frequently [36, 37].

In PSC-UC patients, in comparison to UC patients, endoscopic disease activity in the right colon is significantly increased, whereas no differences in endoscopic disease activity in the left colon were observed, which may translate to higher extensivity of the disease, as seen in different studies [37, 38]. Another feature related to right colon disease activity in PSC-UC patients is more frequent presence of so-called “backwash ileitis” – defined as endoscopically described presence of patulous ileocaecal valve with increased granularity of the terminal ileal mucosa [39]. Even in clinical remission of UC, when PSC is present, patients present an increased histologic activity in the right colon, and decreased histologic activity in the rectum – a prolonged course of subclinical inflammatory disease activity may explain the predominance of right-sided neoplasia in PSC-UC patients [37, 40]. Another hypothesis, which might explain the greater presence of the right-sided tumours, is a possible build-up of secondary bile acids, which probably exert a carcinogenic influence on the colon [37, 41, 42].

Another difference is a clearly different gut microbiota species pattern in PSC concomitant with IBD and in UC patients, which suggest that PSC-UC and UC alone have a different pathogenetic mechanism. Microbiotic pattern is suggested to be a potential biomarker and even a therapeutic target in these diseases [43]. Case study reports and some evidence suggest that oral vancomycin induces both clinical and mucosal remission in PSC-UC patients, both adults and children. Although promising, this has yet to be determined by longer prospective, randomised controlled trials [44, 45].

In flow cytometry and immunochemistry tests conducted on biopsy samples, in both UC and PSC-UC the numbers of eosinophil granulocytes were increased, but increased eosinophil activation and increased levels of pro-inflammatory cytokines were only observed in UC groups, not in PSC-UC groups [46]. An interesting speculation arose from these results: activated eosinophils may contribute to the protection against cancer development in UC, and this protection is reduced in PSC, which results in higher incidence of neoplasia. It is not yet clear if the changes in lymphocyte populations result from microbiotic changes, from the presence of

secondary biliary acids, or comprise a different element of disease pathophysiology.

Summary

The course of ulcerative colitis differs significantly when PSC is present, and the impact of PSC is not yet fully understood. The most notable differences are the presence of more extensive presence of inflammation in colitis but lower activity when PSC is present. One must remember the higher incidence of carcinomas in the PSC-UC group, especially in the right-side part of the colon, which implies the need for frequent colonoscopy screening. More research is being conducted to precisely describe the pathophysiology of the disease, which may yet translate to beneficial diagnostic and therapeutic regimes.

Conflict of interest

The authors declare no conflict of interest.

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