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Commentary

# Gut Inflammation in Primary Sclerosing Cholangitis and Autoimmune Sclerosing Cholangitis-Contrasting Pattern of Liver-gut Cross Talk

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Primary sclerosing cholangitis (PSC) is a chronic inflammatory disease of the biliary tree characterized by fibrosis and stricturing of the bile ducts leading to cirrhosis (Navaneethan and Shen, 2010). The coexistence of inflammatory bowel disease (IBD) in 70–80% of PSC patients suggests that immune dysregulation and/or loss of tolerance to gut bacteria may be associated with or promote the disease process (Navaneethan and Shen, 2010; Loftus et al., 2005; Navaneethan, 2014). IBD in patients with concomitant PSC demonstrates a distinct pattern of clinical phenotype with a higher prevalence of rectal sparing, backwash ileitis, pancolitis, lower degree of inflammation and higher risk for colorectal neoplasia (Loftus et al., 2005; Navaneethan, 2014). Thus, IBD in patients with PSC could be considered a distinct clinical entity from classic ulcerative colitis (UC) and Crohn's disease (CD). Autoimmune sclerosing cholangitis (AISC) is a distinctive subset of patients who have clinical overlap features with PSC and autoimmune hepatitis (Floreani et al., 2005; Gregorio et al., 2001). The clinical presentation and the phenotype of colitis in patients with AISC are not known. Understanding the clinical phenotype may help understand the gut-liver axis and provide rational diagnostic and management approach and decisions when confronted with an IBD patient with concomitant liver disease.

In this issue of *EBioMedicine*, Bjarnason and colleagues at Kings College studied intestinal inflammation associated with AISC and compared the findings with those seen in patients with PSC-associated colitis and patients with IBD alone (Bjarnason et al., 2015). The microscopic findings of the colonic mucosa were identical between patients with AISC and PSC. The inflammation was almost invariably more pronounced in the right colon and there were no features suggestive of CD. The authors demonstrated that although the inflammation is histologically mild, the patients had comparable fecal calprotectin levels as patients with IBD alone. However, the findings in the small bowel on capsule endoscopy were different between these entities. Seven of the capsule endoscopy studies in the patients with AISC were abnormal with mucosal breaks which were seen predominantly in the distal ileum. On the other hand, all of the capsule endoscopy studies in the PSC patients were normal except for one patient who had features of backwash ileitis. An interesting observation of the study was that one third of the patients with AISC had small bowel involvement on capsule endoscopy. How do we explain these results and what do they mean? This study highlights the contrasting pattern of liver-gut cross talk in PSC and AISC. What is the significance of these mucosal breaks in the small bowel?

The pathogenesis of PSC in IBD has been suggested to be related to IBD and inflammation in the portal tracts. This 'leaky gut' may be related to gut microbiota contributing to the pathogenesis of PSC (Terjung and Spengler, 2009). Bacterial translocation or absorption of bacterial endotoxins into the portal circulation, through a chronically inflamed bowel with the activation of Kupffer cell, may contribute to the pathogenesis of PSC (Terjung and Spengler, 2009). Another possible liver–gut crosstalk in PSC and UC pathogenesis has been suggested to be related to the enterohepatic circulation of lymphocytes. Gut-activated T-lymphocytes in UC patients may contribute to bile duct inflammation because the adhesion molecule profiles of gut and liver endothelium are similar (Adams and Eksteen, 2006). Since both PSC and AISC share distinct autoantibodies such as atypical perinuclear antineutrophil cytoplasmic antibodies, cross-recognition between microbial antigens in the gut and the immune system through pattern recognition receptors may play a role in the liver–gut crosstalk (Adams and Eksteen, 2006; Liaskou et al., 2011). Since this phenomenon involves gut and the liver, any part of small bowel or colon inflammation may be related to the pathogenesis of PSC. However, the pathogenesis of liver disease in PSC is only related to colon inflammation almost always and isolated small bowel involvement rarely if not never is associated with PSC. Given these observations, the liver involvement seen in AISC with concurrent gut inflammation is predominantly related to colon inflammation seen in these patients. In that case, the importance of small bowel mucosal breaks in the pathogenesis remains unclear. What relevance do these have in understanding disease pathogenesis?

As we know, most patients with PSC have a colitis, which is classified as UC (Navaneethan and Shen, 2010; Loftus et al., 2005; Navaneethan,

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2014). This study clearly shows that in patients with AISC which may be related to PSC have identical forms of colitis; however 39% also have small bowel erosions. This pattern is more representative of CD like presentation. These observations suggest that IBD associated with liver diseases such as PSC or AISC need to be classified as separate disease entity rather than being clustered as classic UC or CD. Also, the pathogenesis and clinical outcomes are likely different from patients with classic UC and/or CD. The study did have limitations as long-term clinical data on outcomes were not available. It would have been interesting if the follow-up clinical data was obtained in all these patients with AISC to understand the long-term disease progression including risks of surgery and cancer in the colon and provide comparison data with PSC patients.

The liver–gut crosstalk could also explain the beneficial effect of oral vancomycin in patients with PSC, which could also work in AISC. A previous study had shown that peripheral levels of regulatory T (Treg) cells are increased in patients treated with oral vancomycin (Davies et al., 2008).

To summarize, the study by Bjarnason et al. (Bjarnason et al., 2015) has given new insight on the potential interaction of the gut–liver axis, and several important clinical observations on the association of AISC and PSC and IBD. We have made progress in understanding liver disease in IBD patients. Until we clarify the pathogenesis, we should consider using the term IBD associated with liver diseases rather than UC or CD until we continue to untangle the mystery of the liver–gut crosstalk in these patients.

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## Conflict of Interest

The author is a consultant for AbbVie, and is on the speaker bureau for Takeda.

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