



RESEARCH ARTICLE

UNDER RECOGNIZED HUMAN INTESTINAL SPIROCHETOSIS AND ITS CONNECTION WITH IRRITABLE BOWEL SYNDROME AND COLORECTAL NEOPLASMS

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ABSTRACT

Human Intestinal Spirochetosis (HIS) is an infection of colonic epithelial cells by *Brachyspira pilosicoli* and *Brachyspira aalborgi*, which is diagnosed by a characteristic blue haze present on the histological biopsies. The most common clinical manifestation of this infection is chronic diarrhea, but it may contribute to other known clinical entities such as Irritable Bowel Syndrome (IBS) and Sessile Serrated Adenomas (SSA), especially in immunocompromised patients. IBS is an intestinal disorder characterized by an onset of pain with changes in bowel habits, consistency etc. and with no clear etiology. HIS infection may be that etiology in some cases since there is a significant overlap of symptoms and a study in Sweden found that people with HIS were at a three times higher risk of developing IBS when compared to those without it. SSA can be associated with the development of high grade dysplasia and the progression to adenocarcinoma. The development of SSA is linked to a mutation in the BRAF gene, however distinct causes of the mutation have not been established. HIS may be one of those causes due to the induction of chronic inflammation, which would explain why a 2014 study conducted in Japan found that the rate of HIS infection was significantly higher in those with SSA than those that did not have it. Pathologists should have HIS on their mind when helping to treat patients with chronic diarrhea, but should also recognize the contribution this infection can have on people with IBS and sessile serrated adenomas.

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INTRODUCTION

Human Intestinal Spirochetosis (HIS) is an infection of colonic epithelial cells, diagnosed by the presence of *Brachyspira pilosicoli* and *Brachyspira aalborgi*. The most common clinical manifestation of this infection is chronic diarrhea, occasionally associated with blood in the stool and abdominal pain (Alsaigh and Fogt, 2002; Esteve *et al.*, 2006). Although HIS manifests infrequently clinically, it mimics multiple distinct clinical and histopathological entities, especially in patients with compromised immunities such as those with bone marrow or solid organ transplant or under chemotherapies; thus pathologists should be well versed in its diagnosis. The colonoscopy of a patient with HIS varies greatly, with some even being completely normal (Alsaigh and Fogt, 2002). Thus, histopathological inspection must focus on the characteristic blue haze present on the histological biopsies (Esteve *et al.*, 2006). Irritable Bowel Syndrome (IBS) is an intestinal disorder characterized by an onset of pain with changes in bowel habits, consistency etc. and with no clear etiology. HIS may play a

role in the causative factor for some cases of IBS. A study in Sweden found that people with HIS were at a three times higher risk of developing IBS when compared to those without it (Colonic spirochetosis is associated with colonic eosinophilia and irritable bowel syndrome in a general population in Sweden, 2015). The infection can account for many of the symptoms associated with IBS. The bacteria adhere to the microvilli of the colonic epithelium and disrupt the absorptive capabilities, lending a credible explanation for the chronic diarrhea some people with IBS suffer from. HIS has also been linked to other symptoms resembling IBS such as abdominal pain and alternating bowel habits (Alsaigh and Fogt, 2002; Esteve *et al.*, 2006). Also of note was that there was one distinct difference between the individuals that had IBS with HIS and those that just had IBS. This was the concurrent development of eosinophilia and lymphoid follicles in the submucosa. This eosinophilia was also observed in a case-report of acute appendicitis secondary to spirochete infection of the cecum and appendix (Zerhouni *et al.*, 2012). Another association with HIS that has been explored is with the development of polyps, specifically hyperplastic polyps and sessile serrated adenomas (SSA) (Calderaro *et al.*, 2012). The former is recognized as benign, but the latter can be associated

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with the development of high grade dysplasia and adenocarcinomas. A study conducted in 2014 in Japan found that the rate of HIS infection was significantly higher in those with SSA than those that did not have it (Human intestinal spirochetosis is significantly associated with sessile serrated adenomas/polyp, 2014). A mutation of the BRAF gene is suspected as the cause for the development of SSA, but what spurs that mutation has not been clearly established. The author postulates that the spirochetes may be that causative factor, but this retrospective study was not enough to confirm the causality. However, the authors in a case-report published in the Journal of Medicine in 2015 made a causative hypothesis. The patient had been suffering from chronic colitis, which could be secondary to HIS infection (Iwamoto *et al.*, 2014; Infective colitis associated with human intestinal spirochetosis, 2007), which was what the treating physician surmised as well. Metronidazole was administered which did eradicate the bacteria, but the colonic architecture did not fully return to normal, as stricture of the transverse colon persisted. Eventually due to complications, a colectomy was performed and mucinous adenocarcinoma (MC) was found. There are two established etiologies for the development of MC. One is microsatellite instability due to mismatch repair protein dysfunction and the other is inflammation (Akiyama *et al.*, 2015). This patient had normal MMR protein function so the authors inferred that the cause was inflammation, most likely from the HIS colitis (Zerhouni *et al.*, 2012). This is crucial because if this speculation is true, then early detection and elimination of spirochete infection could help prevent the development of certain type of adenocarcinomas. Owing to the rarity of the disease, until more definitive prospective studies have been done, we cannot confidently establish human intestinal spirochetosis as the causative agent in irritable bowel syndrome or sessile serrated adenomas. Nevertheless, their association with one another seems to be significant and is sure to be more accurately illuminated in the coming years. Pathologists should have HIS on their mind when helping to treat patients with chronic diarrhea, but should also recognize the contribution this infection can have on people with IBS and sessile serrated adenomas.

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