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Long-Standing Ulcerative Colitis and Sulphasalazine Treatment Complicated by Adult Celiac Disease

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Abstract The risk of celiac disease may be increased in patients with inflammatory bowel disease (IBD), however, the precise pathogenetic mechanisms involved remain controversial. In this report, an elderly man with long-standing and extensive ulcerative colitis was treated with daily salazopyrine for over 30 years. His medication was eventually discontinued although endoscopic surveillance studies showed healed colitis with minimal inflammatory change and no dysplasia. He subsequently volunteered as an IBD control in a celiac disease research study. Endomysial and tissue transglutaminase antibodies were unexpectedly positive and a small bowel biopsy showed changes of celiac disease that later responded to a gluten-free diet. Earlier historical duodenal and ileal biopsies had been normal suggesting that changes were new, developing after cessation of the salazopyrine. This unusual presentation "unmasking" celiac disease after cessation of long-standing salazopyrine for colitis raises the potential that the drug may have acted to suppress the inflammatory process in celiac disease and may offer another alternate and inexpensive therapeutic approach.

Keywords: *celiac disease, Sulphasalazine, ulcerative colitis, serological screening*

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1. Introduction

The risk of celiac disease in inflammatory bowel disease (IBD) patients has been controversial [1,2]. In a further recent review [3], a meta-analysis of 65 studies suggested an increased celiac disease risk in IBD, including ulcerative colitis. Over decades, a number of anti-inflammatory drugs have been used to treat colitis, often as the sole medication for mild to moderate or localized disease [4]. One of these, sulphasalazine, was used largely as a "designer" pro-drug consisting of sulphapyridine, a sulpha-containing anti-bacterial agent, and 5-amino-salicylate (5-ASA), an active anti-inflammatory component thought to be responsible for mucosal healing [5]. Sulphasalazine was thought to target a therapeutic concentration of the 5-ASA component in the colon, largely avoiding (but not excluding) proximal small intestinal release or uptake. Because of reported side effects [5], other 5-ASA-containing drugs were developed (eg., mesalamine) with similar effectiveness, albeit with differing mechanisms of action [6], but also similar adverse effects [7]. The use of these agents has continued to the present day, including sulphasalazine, in spite of the emergence of a number of modern colitis treatment modalities.

Sulphasalazine may cause side effects in the intestinal tract. These contrast with known effects of non-steroidal anti-inflammatory drugs [8], such as duodenitis [9] and diaphragm disease [10] involving the small intestine. Interestingly, one of these, sulindac, was directly implicated in the development of a sprue-like intestinal disease with detection, withdrawal and challenge studies [11].

Sulphasalazine may also cause folate deficiency in ulcerative colitis patients, and folate deficiency *per se* may then cause small intestinal mucosal changes distinct from celiac disease [12]. These include villus atrophy, but with a reduction in crypt mitotic figures and the presence of macrocytic epithelial cells partially mimicking, but distinct from celiac disease [13,14]. Finally, sulphasalazine may induce or exacerbate colitis, possibly on the basis of a direct hypersensitivity-type reaction or indirectly by drug-induced alterations in the intestinal microflora [15,16,17].

In a patient with ulcerative colitis reported here, cessation of long-term sulphasalazine treatment in colitis resulted in coincidental "unmasking" of late onset celiac disease.

2. Case Report

A 69-yr-old male was first referred in July 1983 with a 15 year history of up to 10-12 watery and loose stools daily. No blood or mucus was reported and treatment had consisted of salazopyrin 500 mg daily for many years.

Prior to 1983, a diagnosis of ulcerative colitis was initially made by a surgeon followed by annual sigmoidoscopes and bi-annual barium enemas. His exam was normal with a weight of 73 kg. Flexible sigmoidoscopy and biopsies confirmed colitis with mucosal erythema, friability and histological evidence of diffuse mucosal inflammatory disease, including crypt abscesses. Fecal cultures and toxin assays were negative. A complete blood count was normal, including a serum folate. As his diarrhea seemed to spontaneously resolve during this initial evaluation, he was followed on an outpatient clinic basis but with an increased dose of salazopyrine 1 gram bid.

In December 1983, colonoscopy confirmed extensive disease and multiple biopsies showed histologic evidence of mucosal inflammatory change into the ascending colon but no dysplasia. Cecal and ill biopsies were normal. Intra-epithelial lymphocytes were not increased [18]. Blood studies remained normal, including serum albumin, folate and iron studies.

He continued follow-up in the office on the same medication dose and in January 1986 had a further colonoscopy. Diffuse hyperaemia was present throughout the colon. An inflammatory polyp was resected from the cecum. Multiple biopsies showed chronic mucosal inflammatory changes with crypt loss and disorganization. Similar biopsy changes were detected on further annual colonoscopies from 1986 to 1991. Bloodwork remained normal, including folate and iron studies. He remained on salazopyrine 1 g bid.

Because of an episode of upper abdominal pain, upper endoscopy was was normal in January 1992, including normal gastric and duodenal biopsies without increased intra-epithelial lymphocytes. A colonoscopy in 1992 led to complete resection of a small villous adenoma. He remained on salazopyrine 1 g bid. A further colonoscopy in 1994 revealed minimal erythema and biopsies showed mild inflammatory change with slight crypt architectural distortion. By 1996, a colonoscopy showed a tubular colon with macroscopic mucosal healing, so-called “burned out” colitis and multiple biopsies showed only minimal inflammatory change.

He was now over 80 years of age and salazopyrine was electively discontinued after daily use for over 30 years. Another colonoscopy in May 1997 after 1 year off salazopyrine revealed no changes. However, in May 1998, recurrent loose non-bloody diarrhea was noted over 2 weeks, but spontaneously resolved without treatment. During this time, blood studies were normal, including a hemogram, albumin, folate and ferritin, but concomitant celiac serological studies were positive including endomysial antibodies and anti-IgA tissue transglutaminase, 120 U (normal, less than 20 U). These were done as an “IBD control group” in a celiac disease research study. A colonoscopy revealed only minimal mucosal changes with no dysplasia. Endoscopic biopsies of the duodenum from multiple sites showed architectural changes of untreated celiac disease with crypt hyperplastic villus atrophy and increased intra-epithelial lymphocytosis (Marsh 3) (Figure 1).

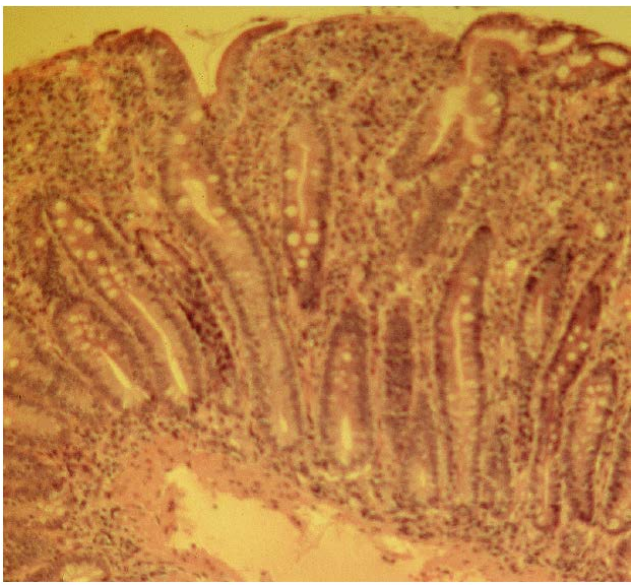

Figure 1. Small bowel biopsy showing typical features of untreated celiac disease with crypt hyperplastic villus atrophy and increased numbers of intra-epithelial lymphocytes (Hematoxylin and eosin stain, endoscopic duodenal mucosal biopsy)

A dietitian reviewed the gluten-free diet with the patient and his wife, and over the next year, he remained well. In 1999, blood studies were normal, including serological studies for celiac disease (anti-IgA tissue transglutaminase, 16 U). Another upper endoscopic revealed that duodenal biopsies had normalized. In 2001, another colonoscopy with biopsies revealed healed colitis with no dysplasia. He remained on a gluten-free diet alone with no medications.

In 2002, he reported epigastric pain. Upper endoscopy showed severe linear ulceration of the distal esophagus, but a normal stomach and duodenum. Duodenal biopsies were normal. He was prescribed pantoprazole and symptoms subsided. Later in 2002, he was seen for abdominal pain, apparently relieved by self-administered enemas. A CT abdominal scan showed an invasive colon cancer in the transverse colon that was resected, but he died with post-operative complications and a cardiac arrest.

3. Discussion

In this report, an elderly man with long-standing and extensive ulcerative colitis had treatment solely with sulphasalazine for more than 3 decades. During the course of his disease, he had regular surveillance colonoscopies with biopsies documenting extensive disease but eventually, a tubular and fibrotic “burned out” colitis, but no dysplasia. Later, it was elected to cease use of salazopyrine but surveillance colonoscopy, readily tolerated, was continued after age 80 years. In 1998, he also volunteered as an “IBD control” in a serological research study. Serological evidence of celiac disease was unexpectedly discovered and then confirmed by a biopsy study showing typical features of untreated celiac disease (despite previously normal duodenal biopsies in 1992), and eventually, in 1999, both a serological and

histological response to a gluten-free diet were documented. Although evidence of ongoing minimal colonic inflammatory disease may have played a role in his eventual outcome, cessation of salazopyrine therapy after decades of daily use appeared to have also "unmasked" celiac disease, even though the small intestinal and microflora effects of salazopyrine have been traditionally considered limited.

As suggested by others [3], future prospective studies in patients with both inflammatory bowel disease and celiac disease might include detailed molecular genetic and biomarker evaluations to more accurately gauge their occurrence. In addition, consideration of other diagnoses is crucial including histological separation from other colonic inflammatory disorders, such as lymphocytic and collagenous collitis, both known to be increased in celiac disease [19,20,21]. Finally, treatment responses or lack of response to modern pharmaceutical and biological agents may be important. In recent years, a number of new forms of treatment for celiac disease have been evaluated in clinical trials [22]. However, there are no published studies on the role, if any, of salazopyrine(or other salicylate-containing agents) in suppression of the serological or histological changes that occur in the celiac disease inflammatory response, with or without a gluten-free diet. The present case suggests that long-term salazopyrine could also suppress the pathological changes of celiac disease, but further research to verify these observations are needed.

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