Inflammatory Bowel Disease: Adverse Effect of Isotretinoin

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Isotretinoin (13-cis-retinoic acid) is a well-known vitamin A synthetic analogue used in several dermatologic diseases including acne and various forms of folliculitis [1]. Despite its successful use in these conditions, isotretinoin is associated with many side effects, some of them common and others infrequent like those associated with the alimentary system. One such rare association affecting the gastrointestinal tract is the development of an inflammatory bowel disease [1]. We report the case of a young man diagnosed with ulcerative colitis after prolonged treatment with isotretinoin.

PATIENT DESCRIPTION

A 32 year old man presented to our department with a 3 week history of bloody diarrhea accompanied by abdominal pain relieved by defecation, and weight loss. The patient denied fever, vomiting, skin rashes, arthralgias or vision disturbances. He had not traveled and had not been exposed to sick people or animals. He had no risk factors for sexually transmitted diseases and no family history of chronic disease. The patient's medical history was remarkable for severe folliculitis diagnosed a year and a half earlier that was treated with isotretinoin twice daily.

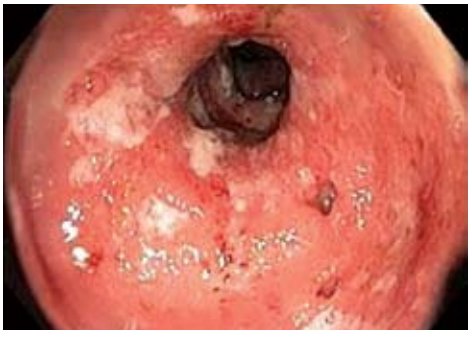
Blood tests revealed normocytic anemia with hemoglobin of 10.59 g/dl, erythrocyte sedimentation rate was 100 mm/hour and C-reactive protein was 156 mg/L. Infectious causes were ruled out by negative stool cultures for bacteria and parasites. Colonoscopy demonstrated ulcerative colitis involving the entire colon [Figure A]. Histological examination of mucosal biopsies taken during colonoscopy revealed severe, chronic, active, crypt-destructive colitis. No dysplasia was seen [Figure B]. Isotretinoin treatment was discontinued and the patient was prescribed 5-aminosalicylic acid. He was followed in an outpatient gastroenterology clinic where he was given a course of steroids with good clinical response. After a few months, steroids were discontinued and the patient is currently in clinical remission.

COMMENT

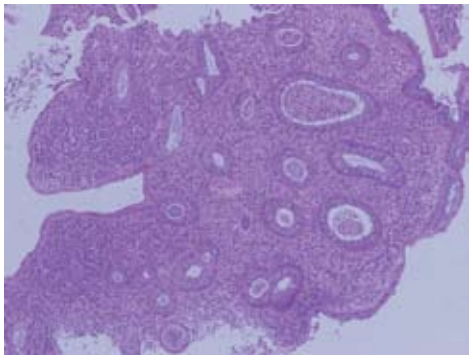
Isotretinoin-induced inflammatory bowel disease has been rarely reported in the literature. Reddy et al. [2] reviewed all reports filed with the U.S. Food and Drug Administration through Medwatch for the period 1997–2002 in an attempt to reveal a possible association of IBD with isotretinoin. In 68% of the cases isotretinoin was a probable cause of IBD, and in 4 cases isotretinoin was strongly associated with the development of IBD. These results show that probably in some genetically predisposed patients isotretinoin may be the trigger factor for the development of IBD. This suggestion is also supported by other case reports in the literature. Passier and co-authors [3] reported three male adolescents who developed IBD after discontinuation of isotretinoin. Two of them developed ulcerative colitis and the third patient Crohn's disease.

Crohn's disease and ulcerative colitis, also known as IBD, are chronic inflammatory diseases affecting the intestinal tract. It is believed that genetic predisposition associated with a dysregulated immune response to endogenous bacteria in the gastrointestinal tract, together with environmental factors, play a significant role in the pathogenesis of these diseases. How isotretinoin causes the

[A] Endoscopic image of ulcerative colitis affecting the entire colon. The image shows inflamed, edematous, fragile colonic mucosa with superficial ulceration and loss of normal mucosal architecture



[B] Colon mucosal biopsy demonstrating chronic, active, crypt-destructive colitis



IBD = inflammatory bowel disease

development of IBD is unclear. Several mechanisms are proposed based on the variety of biological functions that retinoids possess. It is well known that retinoids induce the proliferation and the differentiation of cells. Retinoids have the ability to bind nuclear retinoid receptors and are involved in the induction of apoptosis [1]. Therefore, it is proposed that isotretinoin may cause intestinal tissue injury through inhibition of epithelial cell growth, disruption of glycoprotein synthesis, and activation of killer T cells that eventually result in intestinal inflammation [2,3].

Another hypothesis for the role of isotretinoin in inducing IBD is based on the role of retinoic acid in lymphocyte migration and immunomodulation in the gut. As we know, an important factor in the pathogenesis of IBD is cell trafficking, the migration of circulating T cells into the inflamed intestine. This group of T cells is characterized by the expression of molecules such as integrin α4β7 and the chemokine receptor CCR9, which are essential for homing of T cells to the gut [4]. Recent studies identified retinoic acid as a crucial factor in activating naïve T cells and inducing the expression of homing receptors like α4β7 and CCR9, which leads to accumulation of these cells in the intestinal tract. In a similar way retinoids may play a role in trafficking activated B cells to the gut mucosa [4].

Although published reports suggest that the most probable cause of the development of IBD is the intake of isotretinoin, it is important to not overlook the possibility of coincidence in an undiagnosed patient having a subclinical course of IBD and taking retinoids. In fact the presence of anti-*Saccharomyces cerevisiae* antibodies and atypical perinuclear antineutrophil cytoplasmic antibodies was demonstrated in the sera of Crohn's patients long before the clinical diagnosis, suggesting a prolonged asymptomatic period in some cases of IBD [5]. Another point is the possibility that the dermatological lesions treated with isotretinoin in these reports may represent early dermatological manifestations of IBD in the first place.

In conclusion, IBD should be in the differential diagnosis of every patient treated with isotretinoin and presenting with gastrointestinal symptoms. Therefore, taking into consideration the possible association between isotretinoin and IBD, patients at high risk for developing IBD should be carefully evaluated before being started on isotretinoin treatment.

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