Omega-3 fatty acids in the maintenance of ulcerative colitis

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Immunomodulation of the gut associated lymphoid tissue is a key issue in the clinical management of inflammatory bowel disease (IBD). Often toxic drugs are used to obtain clinical remission, sometimes in already immunocompromized patients. The presence of important co-morbidity might also heavily affect the clinical strategy. Polyunsaturated fatty acids (PUFAs) might represent a valid therapeutical option in IBD patients and further controlled clinical studies are warranted.

Case report

This report presents the management of a 38-year-old Caucasian woman with ulcerative colitis who had extra-intestinal manifestations (polyarthritis) and mitral valve prolapse, and whose treatment included essential fatty acids.

In 1998, at the age of 27, she presented to the emergency department with 10 days of bloody diarrhoea and lower abdominal cramping pain. She described up to 15 bowel motions daily with urgency, and approximately 3 kg weight loss. She denied emesis or a family history for IBD and/or colorectal cancer. She was a smoker with no history of medical illness or surgery, and denied recent antibiotic or non-steroidal anti-inflammatory drug use. She had no known sick contacts or exposure to at-risk foods. However, she had experienced increased emotional stress over the past several weeks.

She was clinically dehydrated. Laboratory investigations and inflammatory markers were remarkable only for a moderately low haemoglobin (100 g/L), a low blood ferritin (7 ng/mL) and a high cholesterol (245 mg/dL).

The patient was admitted to the hospital for presumed infectious enterocolitis to start intravenous hydration and symptomatic treatment.

Stool microbiology was negative for pathogens, but faecal leukocytes were present. After 48 hours with minimal response to therapy, she underwent flexible sigmoidoscopy and biopsies, which showed friable and erythematous mucosa in a diffuse circumferential distribution from the anal verge to the splenic flexure. There were no pseudomembranes. Histological evaluation revealed acute inflammation without architectural distortion consistent with either acute infectious colitis or new inflammatory bowel disease favouring ulcerative colitis.

The patient's symptoms substantially resolved over the next 3–4 days, and she was discharged with a course of antibiotics.

However, a few days after discharge, she returned with recurrent bloody diarrhoea and abdominal pain. A working diagnosis of ulcerative colitis was made and she was started on mesalazine 2.4 g daily with oral prednisone 40 mg daily. After three days of this treatment, stool frequency had decreased to twice a day, with rare blood-tinged stools. The abdominal cramping had improved, but still occurred episodically with some tenesmus. Steroid side-effects included depressed mood and insomnia, which resolved as the dose was tapered.

Due to persistent rectal urgency, an ileocolonoscopy was performed after six weeks; this showed mild erythema and granularity from the rectum to the sigmoid colon and in the ascending colon. The transverse colonic mucosa and terminal ileum were grossly normal. However, biopsies

throughout the colon revealed diffuse crypt architectural distortion. A daily mesalazine suppository (1 g) was added with improvement, and at three months she remained in clinical remission on mesalazine monotherapy.

Later onset of fatigue, palpitations, chest pain, anxiety and headaches led to echocardiography which disclosed mitral valve prolapse associated with moderate mitral regurgitation. She was also found to have arthrosis and chondropathy of the right knee. She was prescribed bisoprolol hemifumarate (1.25 mg daily) for the heart, and rizatriptan (10 mg) for the headaches. Her ulcerative colitis then entered a new phase of exacerbation and she was referred to the inflammatory bowel disease clinic of Parma University Hospital. Clinical assessment and proctosigmoidoscopy were carried out and yielded a Mayo Clinic score of 8.

An eight-week course of tapering steroids was started with clinical remission occurring after three weeks. Continuing immunosuppressive and biologic therapy were considered excessively high-risk options given her predisposition to infective endocarditis. She was, however, recruited to the hospital's colonoscopic surveillance programme.

Soon after stopping steroids there was another exacerbation of the colitis, with a Mayo Clinic score of 6. To minimize infective risk she was started on budesonide 9 mg daily with some benefit (Mayo Clinic score 4), but after two weeks the serum amylase became abnormal (426 U/L). Abdominal ultrasound was normal and it was felt that this was a drug-related effect. The budesonide was, therefore, stopped and amylase returned to normal.

Withdrawal of the budesonide precipitated a further relapse comprising diarrhoea and bleeding, with a Mayo Clinic score of 8. Omega-3 unsaturated fatty acid therapy was commenced. The PUFAs (EPA and DHA) were started at the dose of 1 g twice daily, while mesalazine was maintained at 2.4 g daily. The PUFAs were very well-tolerated and no side-effects were identified. Her bowel frequency slowly decreased, and within a week all rectal bleeding had resolved.

At 2 weeks, complete clinical and endoscopic remission had been accomplished, with a Mayo Clinic score of 0. PUFA therapy (1 g twice daily) and mesalazine (2.4 g daily) were continued for six weeks, reducing then to maintenance doses of 1 g and 1.6 g daily, respectively, for the succeeding 18 months. Surgical work-up for mitral valve replacement was commenced.

Discussion

Although the aetiology of inflammatory bowel disease remains unknown, it is believed that an exaggerated intestinal immune response to otherwise innocuous stimuli plays a key role in its pathophysiology. Immune mediators actively contribute to and amplify the pathogenic cascade that initiates and perpetuates the inflammatory response of the gut.[1,2]

Increased dietary intake of certain types of n-3 PUFAs (e.g. EPA and DHA) can divert cell metabolism towards less active eicosanoids, thereby modulating both the inflammatory response and immune reactivity. Previous studies have accordingly proposed a protective role from supplementary dietary intake of (n-3) PUFAs in IBD,[3,4] potentially comparable to the effects of mesalazine, which has clear efficacy in the treatment of acute ulcerative colitis and in the maintenance of its remission.[5–8] Intraepithelial lymphocytes are likely to be essential lymphoid cells that participate in the induction and regulation of the mucosal immune response. The majority of human and murine intraepithelial lymphocytes are classified as T cells. And the presence of large number of CD8+ T cells among these intraepithelial lymphocytes in subjects with ulcerative colitis is quite significant. Evidence exists to prove that attenuation of liberated cytokines, such as leukotriene A4 could affect recruitment of CD8 and CD4 T cells and may beneficially modulate other pro- and anti-inflammatory eicosanoids.[9]

The essential fatty acids are a group of PUFAs that are present in various nutrients but which cannot be synthesized in the body.[10] They are composed of two main types: the n-6 (or omega-6) and n-3 (or omega-3) series. Essential fatty acids have a number of important biological roles, including cell membrane structure and function, and the production of intermediate compounds called eicosanoids. These eicosanoids act as intercellular messengers and mediators of inflammation and immune reactivity.[11] It has been shown that increased dietary intake of certain types of n-3 PUFAs (e.g. EPA and DHA) can divert cell

metabolism towards less inflammatory eicosanoids, thereby modulating both the inflammatory response and the immune reactivity.[11–14]

Previous studies have proposed a protective role from dietary n-3 PUFAs in human IBD,[15–17] given the knowledge that the biological effects of EPA and DHA, encompass improving lipid profiles and reducing blood pressure,[18,19] inhibiting the growth of tumour cells,[20] and modulating symptoms in autoimmune and other inflammatory diseases.[21–24]

EPA and DHA are evidently important as well as essential in the diet, but it is probably not their amount that is directly responsible for the beneficial effects, but rather their influence on the (n-6):(n-3) ratio, because both PUFA types compete with the same enzymes for their conversion to active metabolites.[7] It is, for example, recommended that the human diet should return to a more balanced (n-6):(n-3) ratio of around 4:1 rather than the ratio of over 15:1 provided by many current Western diets. Moreover, it has been shown that dietary supplementation with EPA and DHA produce significant systemic immune suppression. Epidemiological studies in Eskimos reveal a low incidence of IBD compared with other Western populations, thus supporting the protective role of the dietary intake of (n-3) PUFAs, since their diet is rich in fish oils.

Patients with chronic intestinal disorders, such as inflammatory bowel disease, have generally lower plasma n-3 PUFAs than normal subjects.[24] It is possible that the patients are, therefore, compromised, in that the competition for metabolism between n-3 and n-6 moieties will favour the production of the more inflammatory mediators. Eicosanoids such as leukotriene B4 (LTB4), thromboxane A2, or prostaglandin E2, and cytokines are implicated.[7] Most endogenously produced n-3 fatty acids appear to have therapeutic potential in ulcerative colitis and perhaps also in Crohn's disease.[25] LTB4 synthesis in the colonic mucosa of patients with ulcerative colitis and Crohn's disease is increased,[26] and it was proposed that inhibition of its synthesis may contribute to the therapeutic effects of the aminosalicylates used in the treatment of irritable bowel disease.[4] Although the clinical studies dealing with the use of n-3 PUFAs in IBD have yielded conflicting results, this is probably the result of discrepancies in patient selection and the vagaries of the formulations and dosages used in the different protocols. PUFA supplementation in patients with proctocolitis has, however, been associated with a reduction in disease activity.[26] The encouraging findings in the present patient should encourage further clinical evaluation.

Increasing evidence indicates that the fat composition of defined formula diets is critically important in their anti-inflammatory effects. Given that many distinct PPARc ligands (PUFAs, aminosalicylates and rosiglitazone) are effective in ulcerative colitis, and that PPARc is expressed in colonic mucosa,[27] the effect of dietary fat manipulation using natural PPARc ligands is worthy of further investigation in irritable bowel disease.

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