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EDITORIAL

The role of infections in refractory inflammatory bowel disease

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The etiology and pathogenesis of inflammatory bowel disease (IBD) including ulcerative colitis and Crohn's disease is still unknown, but derangement and imbalance between the host immune system and microbial flora has been proposed. We know that IBD may occur in a section of gut which has a high proportion of bacteria; genetically-engineered mouse model requires bacteria for developing IBD and also IBD patients may improve by antibiotics therapy. Many research studies have been done regarding the role of infection in IBD patients including *Mycobacterium avium*, *E. coli*, *Campylobacter*, and *salmonella*. Bacterial infection may have a protective role in IBD patients especially in patients with antibiotic-associated diarrhea induced by *Clostridium difficile*. We also are aware of post infectious IBS and IBD. In order to clarify the role of infection in IBD, we need to know in which stage in IBD, infections may intervene.

Firstly, infections may mimic IBD. Bacteria causing acute diarrhea and colitis similar to IBD include *Salmonella*, *Shigella*, and *Campylobacter*. *Yersinia* infection can cause chronic diarrhea, ileocolitis, and granulomas in ileum and colon resembling Crohn's disease. Infected persons with parasites including *Entamoeba histolytica* and *Strongyloides stercoralis* may have severe inflammation and ulceration mimicking IBD.

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Secondly, studies have shown that the rate of IBD in post infection phase of acute gastroenteritis is higher compared with control. This has been documented in amebic dysentery and *salmonella* and *campylobacter* gastroenteritis.

Thirdly, infection may aggravate the course of IBD patients. One of the problems in treating IBD patients is prevention and controlling flares of the disease. Infection with different pathogens can exacerbate the course or cause acute dysenteries mimicking IBD. Studies have shown that the rate of positive cultures in flares of IBD is about 10% to 20% which may lead to hospitalization due to flares of IBD. Most of infections documented in multiple studies are *Clostidium difficile*, *campylobacter*, and *salmonella*.

Other infections including viral infection have been shown to aggravate IBD. Among viral infections, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and Herpesvirus have been shown to play a role in flare of the disease. CMV infection is more prevalent than the two others. This infection presents in tow types. Acute form, resembling Ebstain- Barr virus infections, presents with myalgia, fever and lymphadenopathy. The second form is latent type. After acute infection, CMV probably remains in myeloid cells. Primary mechanism for controlling replication is T-Cell mediated response. Therefore, severe CMV infection will occur in patients with cellular immunodeficiency.

Most common CMV infections present in immunosuppressed patients, including solid organ

transplant recipients, stem cell transplants, and human immunodeficiency virus (HIV) patients who progress to Aids. In these patients, acute CMV infection presents with malaise, fever, arthralgia, and low white blood cell count.

There are two types of primary infections occurring in 30% of seronegative patients. The second type or reactivation occurs almost in 80% of seropositives before transplant.

The CMV role in IBD is not completely clear, as it is in post-transplant patients. The patients with IBD, especially with steroid refractory colitis or on immunosuppressive therapy, have increased risk of developing CMV infection. Pathogenesis of CMV is also less clear, either acute type or reactivation of CMV. But, there are many published articles about CMV in severe and refractory colitis, and flares of colitis. In one report, five cases had extensive diseases and one required colectomy. Some of the cases improved with antiviral therapy. The rate of CMV proven colitis in biopsy ranges between 21% and 36%. In a recent case series study in steroid resistance colitis, CMV was found in 8 out of 23 patients. The question rises whether the risk of CMV infection depends on the type of IBD. Studies suggest that colonic disease is a major predisposing factor. One of the important issues in CMV infection in IBD is that the risk increases with the disease activity and steroid dependency. The patients with IBD whose diseases are in control usually never develop infection. Acute cytomegalovirus infection has been shown to exacerbate inflammatory bowel disease. Latent infections commonly do not induce IBD, but can aggravate the severity of intestinal inflammation, if colitis is already present. New researches suggest that latent CMV infection may also exacerbate the disease. Also, a research in animal model revealed that latent infection with CMV and probably other viruses may modulate mucosal immunity and consequently, alter susceptibility for developing severe acute colitis. Our patients' experiences denote their IBD gets worse and exacerbate after viral infection.

Diagnosis of CMV in IBD patients depends on correlation of symptoms and document of CMV in tissue. CMV can be diagnosed in IBD patients with detecting antigen in blood, detection of CMV DNA viral load by PCR, and also by histologic detection of inclusion bodies and immunohistochemistery in biopsy specimens. The best method of detecting CMV in IBD is immunohistochemistry which can lead to positive rates up to 93%.

There are still many questions regarding CMV in IBD. What criteria we should use for diagnosis of the disease? What is the best therapy? Should we use antiviral therapy? Whether we should stop or continue steroid and immunosuppressive therapy? Whether to screen patients with IBD for CMV infection? At present time, we don't know much about the role of CMV in IBD, its role in natural history of disease, and the role of antiviral therapy. We need more studies to clarify these issues.

SUGGESTED READING

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