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CYTOMEGALOVIRUS INFECTION AND INFLAMMATORY BOWEL DISEASE

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SUMMARY. Inflammatory bowel disease (IBD) is a general name of two entities: Crohn's disease and ulcerative colitis which represent chronic non-specific inflammation of gastrointestinal tract. Cytomegalovirus (CMV) infection is a common viral infection in humans. It often causes primary infection and later persists lifelong in a latent stage. In different situations of immunosuppression the virus can reactivate and cause disease, affecting multiple organs including the gastrointestinal tract. The etiology of IBD is not clear and CMV infection is often associated with IBD. The pathogenetic link between IBD and CMV infection is discussed in this literature review.

KEY WORDS: inflammatory bowel disease, ulcerative colitis, Crohn's disease, cytomegalovirus.

Introduction. Inflammatory bowel disease (IBD) represents chronic non-specific inflammation of gastrointestinal tract. The etiology of IBD is not clear and Cytomegalovirus infection is often associated with IBD. Early studies indicated that CMV infection can lead to subsequent development of IBD [1]. This may be possible in some susceptible patients but in the most recent reports CMV colitis occurred primarily in patients with pre-existing IBD [2, 3]. The pathogenetic link between IBD and CMV infection was supposed and began to be studied in the last decades.

The **aim** of the study was to evaluate critically literature data on the relationship between CMV and IBD.

Methods. Internet search was conducted in Medline (from 1966 to 2013) and PubMed (from 1980 to 2013) database using words "cytomegalovirus", "inflammatory bowel disease", "ulcerative colitis", "Crohn's disease".

Results and discussion. 419 articles were found. The prevalence of CMV infection is high, ranging from 30–100 %, depending on age and race. Cytomegalovirus is a member of the Herpesviridae family which contains a double-stranded DNA. Most CMV infections are acquired either in the perinatal period and infancy or in adulthood through sexual contact [4]. It often causes primary infection in humans, and later persists lifelong in a latent stage. Primary infection in the immunocompetent hosts is usually asymptomatic or causes syndrome with fever, myalgia and pharyngitis. Gastrointestinal affectation due to primary infection has been described but is rare, and manifests with bloody diarrhea, tenesmus, abdominal pain, fever, anorexia, malaise and weight loss [3]. CMV can cause esophagitis, gastritis, ulcers, terminal ileitis and colitis.

In latent infection principal reservoirs of CMV are fibroblasts, myeloid cells and endothelial cells [5]. Peripheral blood monocytes constitute a major site of viral latency and may be triggered by secreted proinflammatory cytokines and chemokines. They can differentiate into tissue macrophages, leading to CMV reactivation and probably to CMV disease. Endothelial cells are also a common target for CMV in vivo, regardless of the organ involved. The vascular endothelium represents the interface between circulating immune cells and the lamina propria of the gut and this can partially explain the role of CMV in cases of intestinal inflammation.

The association between CMV and IBD was described long ago. The first case report dates from 1961, when Powell and coauthors described a patient with UC and "cytomegalic inclusion" disease. Since then, questions about the role of CMV in these patients remains open [7]. Does CMV reactivation exacerbate the disease in patients with pre-existing IBD or is reactivation a consequence of IBD activity and its treatment with CMV acting as an innocent bystander [3, 8]? Interpretation of existing results is limited because most studies are small and retrospective, with different diagnostic methods of CMV detection and even different classifications of the severity of concomitant IBD.

Patients with IBD are immunosuppressed due to chronic inflammation, medications and poor nutrition [2, 9]. CMV reactivation may be triggered by TNF-ь, catecholamines and proinflammatory prostaglandins [10]. During active IBD, local expression of a wide variety of cytokines including TNF-a, IFN-г, and IL-2 is induced, with activation of transcription factors (NF-Kb) and production of chemokines and adhesion molecules that recruit circulating monocytes and dendritic cells in the area of inflammation. There, these cells differentiate into permissive cells supporting active replication of the virus. Endothelial cells can also serve as permissive cells as they have been shown to stimulate T-cells to produce IL-2 and to proliferate. Activated T-cells consequently produce TNF-β and IFN-γ and perpetuate the inflammation process causing more injury to the gut. These indicate that CMV has tropism for sites of inflammation and confirm the results of clinical studies that have shown presence of CMV in the affected region of the gut in the IBD patients. They also indicate that CMV replication is the result of CMV reactivation rather than primary infection.

Experimental studies have identified three factors that influence the reactivation of CMV infection in active colitis:

– increased cell proliferation in inflamed tissue with ulcers that attract CMV;

– inherent impaired natural killer cell activity presented by patients with IBD;

– use of immunosuppressive drug [6].

The third factor is controversial, since use of steroids may be either a risk factor or a surrogate marker of severity disease [2, 9]. In vitro data suggest that steroids and cyclosporine could support the replication of CMV [11]. Recent studies suggested CMV can appear only in inflamed tissue and is not found in healthy tissue.

Hommes and coauthors proposed the following sequence to explain the pathophysiology of CMV disease in patients with active UC:

– initiation phase, mucosal inflammatory response induces expression of cytokines and chemokines which activates latently infected cells and the migration of monocytes and dendritic cells into the inflamed mucosa;

– reactivation phase, in which infected monocytes differentiate into tissue macrophages and dendritic cells;

– consolidation phase, during which the virus causes an active replication predominantly in endothelial cells that likely exacerbates inflammation [10].

Theoretically, all latently infected IBD patients receiving immunosuppressive treatment frequently produce infectious virus and don't allow antiviral immune responses to develop. In two recent clinical studies, corticosteroids did not seem to be a major factor in the development of CMV infection and disease in IBD patients [12, 13].

There have also been reports of colitis patients with evidence of active CMV infection who improved with steroids and did not require antiviral treatment [14], as well as patients with active colonic CMV infection without active colitis [15]. In these cases CMV seems to behave like an innocent bystander. As it has been mentioned before, CMV has the propensity to infect rapidly growing tissue, especially endothelial cells in granulation tissue. Some studies suggested that CMV represents an opportunistic infection in severely inflamed mucosa rather than a primary pathogen [16].

The most widely held theory is that CMV infects areas of active IBD and causes further tissue injury aggravating the severity of the underlying IBD. In the majority of case-reports patients with severe attacks of IBD and CMV infection had significant morbidity (toxic megacolon 15%, colectomy up to 62%) and mortality (up to 44%). Antiviral treatment prevented colectomy in some but not all of the patients. In more recent series the mortality rate of CMV colitis in UC were 30% and the rate of surgery 40% [9]. CMV disease seems to be less frequent in patients with Crohn's disease compared to patients with ulcerative colitis.

Conclusion. The role of CMV infection in patients with IBD has not yet been clearly defined. In the majority of published studies CMV is considered to act like a true pathogen, complicating the course of IBD, causing the resistance while in the others, CMV does not seem to alter the natural course of the underlying IBD. Further prospective studies are needed to clarify the role of CMV infection

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