Epstein-Barr virus infection and gastrointestinal diseases

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SUMMARY

Epstein-Barr is a member of the herpesvirus family that infects more than 90% of the world's population. Although primary infection typically occurs within the first few years of life or in adolescence and is generally asymptomatic or results in infectious mononucleosis respectively, in some cases the virus is implicated with the development of a large spectrum of gastrointestinal malignant and benign diseases.

Thus, Epstein-Barr virus is strongly involved in the pathogenesis of non-Hodgkin’s lymphomas and is associated also with some cases of Hodgkin’s disease, Burkitt’s lymphoma, gastric and esophageal cancer and rarely with some benign gastrointestinal diseases.

Key words: Epstein-Barr virus, non-Hodgkin’s lymphomas, Hodgkin’s disease, Burkitt’s lymphoma, gastric cancer, esophageal cancer, esophagitis, gastritis, inflammatory bowel disease.

INTRODUCTION

Epstein-Barr (EBV) is a member of the herpesvirus family with a 184-kbp long, double-stranded DNA genome that encodes more than 85 genes. As with other herpesviruses, EBV is an enveloped virus that contains a DNA core surrounded by an icosahedral nucleocapsid and a tegument.

It is known that EBV infects more than 90% of the world's adult population. Upon infection, the individual remains a life-long carrier of the virus. EBV is transmitted by salivary contact. During acute infection, EBV primarily infects and replicates in the stratified squamous epithelium of the oropharynx. This is followed by a latent infection of the B lymphocytes (although the sequence of epithelial versus lymphoid infection is a matter of debate). EBV infection of B lymphocytes is thought to occur in the oropharyngeal lymphoid organs, and in normal carriers, the virus persists in circulating memory B cells. The B-lymphotropic nature of EBV is evidenced by the ability of the virus to immortalize normal resting B lymphocytes in vitro, converting them into permanently growing lymphoblastoid cell lines. Of interest, once the virus has colonized the B-lymphoid compartment, reactivation from latency can occur at any mucosal site where B cells reside.

Primary infection with EBV typically occurs within the first few years of life and is generally asymptomatic in most undeveloped countries. In more developed areas, primary infection can be delayed until late adolescence or adulthood and results in infectious mononucleosis in some cases. Long-term EBV coexists with most human hosts without overt serious consequences. However, in some individuals, the virus is implicated in the development of malignancy.

Gastrointestinal lymphomas

1. Non-Hodgkin's Lymphomas (NHLs): NHLs were originally defined as neoplastic equivalents of reactions usually occurring in lymphoid tissue after antigenic stimulation. Several studies have shown that tissue-restricted lymphocytes from gut, skin and lymph nodes show preferential homing to their site of origin. Thus, lymphocytes from the gut preferentially home to gut.

Although organ-specific homing receptors play a role in organ-specific homing, the molecular basis of these differential homing patterns is not yet completely understood. Extending the concept of NHLs with this aspect of tissue restriction of lymphocytes, extranodal lymphomas can be considered as neoplastic equivalents of im-
Three populations of tissue restricted T lymphocytes have been recognized: mucosa-associated, cutaneous and nodal T lymphocytes.

T-cell lymphomas of nodal origin have been associated with the presence of EBV. A possible involvement of the virus in the pathogenesis of extranodal T-cell lymphomas is still under investigation.

T-cell extranodal lymphoma cases from different sites, i.e., the nasal cavity, gastrointestinal tract, lung and skin were investigated using several methods (polymerase chain reaction, RNA in situ hybridization, immunohistochemistry, etc) for the presence of EBV, but the results are controversial.

EBV-associated primary gastrointestinal T-cell lymphomas seem to be rare in nonimmunocompromised patients.

In the body of literature there are some case reports and few studies that report detection of EBV genome with a rate ranging between 6% and 14%.

Primary small intestine T-cell lymphomas account for about 5% of all primary gastrointestinal lymphomas and are mostly associated with celiac disease. A considerable number (36%) of enteropathy-associated T-cell lymphoma cases were reported to be EBV-positive. EBV genome was detected also in some cases of colorectal T-cell lymphomas and in some cases of gastric B-cell lymphomas.

The major presenting symptoms in the cases reported above included fever, weight loss, malabsorption, coffee-ground vomitus, diarrhea, tarry stool, gastrointestinal bleeding and intestinal perforation.

Although no data were given about race or geographical origin of the patients, the vast majority of these studies are from Korea, Japan and Netherlands.

Based on these data, the presence of EBV in only a subpopulation of cells suggests that the infection is secondary to malignancy or that the viral genome has been lost from the malignant cell. Additionally, the presence of EBV-positive B-cells in peripheral T-cell lymphomas raises questions about the possible activation of EBV in latently infected B cells by neoplastic T cells and/or the role of the EBV-positive B cells in maintaining the malignant T cell process.

2. Hodgkin’s Disease (H.D.): Although EBV positivity in HD is extremely high in some geographical areas, the role that the virus plays in their pathogenesis is still not fully understood.

On the other hand, gastrointestinal involvement is an extremely rare event in HD and might occur as infiltration from mesenteric lymph nodes. Initial symptoms limited to extranodal tissue are more rare in HD than in NHLs, and only few cases have been described with EBV positive primary gastrointestinal HD. All these cases were associated also with Crohn’s disease and immunosuppression.

3. Burkitt’s Lymphoma: Burkitt’s lymphoma is a B cell lymphoma composed of monomorphic, medium-sized cells with basophilic cytoplasm and a high proliferation fraction, characterized by translocation and deregulation of the c-myc gene on chromosome 8, which is often extranodal and occurs most often in children and immunocompromised hosts.

Three distinct clinical forms of Burkitt’s lymphoma can be recognized: endemic, sporadic and immunodeficiency associated. In sporadic form the distal ileum, cecum, mesentery or both cecum and mesentery are often involved.

Patients typically present with rapidly growing tumor masses and often have a high serum LDH. Burkitt’s lymphoma is highly aggressive but potentially curable with aggressive therapy.

**Gastrointestinal cancer**

1. Gastric adenocarcinoma: EBV presence varies from more than 90% in lymphoepithelial adenocarcinomas (44-55). Whether EBV plays a pathogenic role in either of these two tumors is still unclear.

Given the morphological similarities between lymphoepithelioma-like gastric carcinoma and undifferentiated nasopharyngeal carcinomas, it has been proposed that in lymphoepithelioma-like gastric carcinoma, EBV spreads from the nasopharynx to the stomach. In regard to gastric adenocarcinomas, EBV may enter the gastric epithelium without the use of a receptor. It has been suggested that this is accomplished by the binding of IgA antibody with EBV particles derived from B lymphocytes and the uptake of these particles by gastric epithelial cells. Alternatively, EBV may enter the gastric epithelial cells via a receptor other than the CD21 receptor.

EBV exhibits a novel latency pattern in gastric adenocarcinomas that includes the production of BARF-1, a
homologe to human colony-stimulating factor 1 receptor and intracellular adhesion molecule 1, and the absence of LMP-1.\textsuperscript{57-60} Although any mechanism relating EBV to tumorigenesis in gastric malignancies remains highly speculative, it has been demonstrated that there is a delay in apoptosis in EBV-positive gastric carcinomas and a decrease in cellular differentiation.\textsuperscript{55,60}

2. Esophageal cancer: The etiology and pathogenesis of esophageal cancer (adenocarcinoma and squamous cell carcinoma) is thought to involve a combination of genetic and environmental events which lead to epithelial cell transformation.

A possible association of EBV with undifferentiated esophageal cancer with a lymphoid stroma, just as it is associated with nasopharyngeal lymphoepithelioma, has been proposed.\textsuperscript{61} However, reports concerning a possible relationship between EBV and esophageal cancer are few. Although in some studies a possible association is reported with a detection rate ranging between 6\% and 36\%, further studies are required to establish the implication or not of EBV in esophageal carcinogenesis.\textsuperscript{65-66}

Other Gastrointestinal Diseases

Although EBV is associated with esophagitis and esophageal ulcers, in some cases with AIDS or AIDS-related complex,\textsuperscript{67,68} there are no reports for a possible association of EBV with esophageal diseases in non-immunocompromised individuals.

The association of EBV with a proportion of gastric carcinomas is well established. The role of EBV in conditions predisposing to carcinoma such as chronic gastritis has remained undefined, however. The vast majority of the performed studies argue against a direct involvement of EBV in the pathogenesis of chronic gastritis.\textsuperscript{69-71}

Little is known about EBV infection of colon mucosa, particularly in inflammatory bowel diseases. Crohn's disease and ulcerative colitis are thought to differ in T-helper lymphocyte composition and cytokine secretion patterns. Some of the implicated cytokines are growth factors for EBV-infected cells.

A high detection rate of EBV-encoded small RNA1 (EBER-1) and EBV-DNA in inflammatory bowel disease tissue specimens have been reported\textsuperscript{72,73} with the EBV positive lymphocytes accumulated under and within the epithelium.\textsuperscript{74}

A possible association of EBV with some cases of gastroparesis and intestinal pseudo-obstruction has also been reported.\textsuperscript{75-77}

REFERENCES


