Epstein-Barr Virus-specific Serology in Immunologically Compromised Individuals

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Abstract

Since B-lymphocytes are targets and a continuing habitat of Epstein-Barr virus (EBV) and the cell-mediated immune system becomes secondarily involved, one may anticipate that primary and persistent EBV infections in immunologically compromised individuals take unusual courses. Depending on the immunological defect, the clinical, hematological, and serological responses to primary EBV infections may be more or less pronounced than in immunologically competent patients. Infectious mononucleosis has per se an immunosuppressive effect which may enhance a preexisting immune defect. The persistent latent viral carrier state which regularly ensues after the primary EBV infection may become decontrolled by immunosuppressive diseases or therapy, leading rarely to illnesses referable to the virus but often to increases in the titers of antibodies to viral capsid and early antigens and/or declines in the antibody titer to EBV-associated nuclear antigen. Absence or dysfunction of different leukocyte subpopulations may account for the differential changes in antibody patterns.

Primary infections by EBV2 may remain silent or induce IM. In either case, a permanent viral carrier state ensues in the lymphoreticular system (16). It appears that EBV is restricted for its replication to B-lymphocytes since to date no other types of cells have been proven to be infectible in vitro by the virus. B-Lymphocytes are transformed by EBV in vitro into permanently growing lymphoblasts which harbor viral genomes and express EBNA. In most of these cultures, a few of the cells are induced spontaneously at any given time to enter into a productive cycle of viral replication with synthesis of EBV-determined EA's, MA's, VCA and virus particles. The same course of events is thought to occur in vivo, but in that case cell-mediated immune reactions are responsible for the self-limitation of the primary infection, as well as the control of the ensuing viral carrier state in the lymphoreticular system.

Since cells of the humoral immune system are the targets and continuing habitat of EBV and the cell-mediated immune system becomes secondarily involved, one may anticipate that primary and persistent EBV infections in immunologically compromised individuals may take unusual courses. Depending on the types of immunological defects, the clinical, hematological, and serological responses to primary EBV infections may be more or less pronounced than in immunologically competent patients. In fact, IM itself has immunosuppressive effects which could enhance a preexisting defect.

In this review, the EBV-specific serological responses of immunologically competent individuals during primary and persistent infections will be discussed first. An attempt will then be made to summarize the information available on the EBV-specific serology in immunologically compromised patients.

EBV-specific Antibody Responses in Immunologically Compromised Individuals

The antibody responses to EBV-specific antigens in acute IM are characterized by high titers of IgM and IgG antibodies to VCA, transient emergence of antibodies to D in about 80% of the patients, and absence as yet of antibodies to EBNA which arise generally only weeks or even months after onset of illness (3, 18). Antibodies to R may become detectable occasionally in protracted cases of the disease after the anti-D titers have subsided. The majority (>90%) of IM patients develop, in addition, IgM heterophil antibodies of the Paul-Bunnell type which are highly specific for the disease, but the reason for their transient emergence is still unknown.

The antibody responses in silent primary EBV infections of infants under 2 years of age conform to those seen in IM except that antibodies to the EA complex are directed against R instead of D and that heterophil antibodies do not arise or reach at most barely significant titers (3, 10). It is not known as yet whether this pattern extends also to silent primary EBV infections of older individuals.

The IgM antibodies to VCA and the IgG antibodies to D usually decline to nondetectable levels within a few weeks after onset of IM, whereas the heterophil antibodies may remain measurable at gradually diminishing titers for up to 18 months depending on the maximal titer attained (8). During convalescence, the IgG antibodies to VCA decline, and the antibodies to EBNA rise to the moderate titers at which they are maintained without significant fluctuations, as a rule, for many decades (18). Antibodies to EA components, more often to R than to D, are found at low titers only among those individuals who maintain relatively high titers of IgG antibodies to VCA which reflects presumably an enhanced viral carrier state. Continuous EBNA-positive lymphoblastoid cell lines can be established at moderate frequency from peripheral leukocytes and nearly uniformly from lymph nodes of individuals who possess antibodies to EBV (31). Viral carriers excrete EBV intermittently into the oropharynx, which is detected by the capacity of the virus to transform B-lymphocytes in vitro into permanently growing EBNA-positive lymphoblasts (29).

Knowledge of the pathogenesis of IM is still fragmentary (12). During the incubation period of 4 to 7 weeks, complete cycles of viral replication occur in sufficient numbers of cells to yield the amounts of MA, D, VCA, and virus particles needed to evoke near-peak titers of the corresponding antibodies by

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2 The abbreviations used are: EBV, Epstein-Barr virus; IM, infectious mononucleosis; EBNA, Epstein-Barr virus nuclear antigen; EA, early antigen; MA, membrane antigen; VCA, viral capsid antigen; D, diffuse early antigen component; R, restricted early antigen component; HD, Hodgkin’s disease.

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find one which harbors EBV genomes (36). The number of

cated. Among 107 to >108 circulating lymphocytes, one may

be destroyed by T-cell action, yielding enough EBNA for continu

taneous cycles from peripheral leukocytes of IM patients (30). As they are generated during the acute phase of IM, they destroy a large proportion of the EBNA-positive cells which results finally in the release of sufficient EBNA for the late antibody response. Elsewhere in this issue, Klein et al. (23) discuss the contribution of activated killer cells in possibly eliminating virally infected B-cells in vivo.

The EBV genome-carrying cells are never completely eradi-
cated. Among 102 to >106 circulating lymphocytes, one may

find one which harbors EBV genomes (36). The number of such cells in lymphoid tissues is probably somewhat greater. A few of these cells enter spontaneously into productive cycles of viral replication at any given time, as they do in culture, and synthesize enough MA and VCA but rarely sufficient EA components to maintain production of the corresponding anti-
bodies. Other EBV genome-carrying cells are continuously destroyed by T-cell action, yielding enough EBNA for continu

ing antibody stimulation. Yet, a few of these cells always escape and continue to divide so that the various interactions are perpetuated indefinitely under apparently well-balanced conditions as evident from the stability of the antibody titers over prolonged periods of time. This equilibrium may be upset, however, by a variety of immunosuppressive conditions, as will be discussed in the following section.

EBV-specific Antibody Responses in Immunologically Com-

promised Patients

There are a few reports in the literature concerning IM in patients with immunodeficiencies. This may denote that primary
usual parameters of cell-mediated immunity have reached normal ranges. In an occasional marrow recipient, the antibody spectrum and titers may never exceed those seen in healthy persons after long-past primary EBV infections.

The bone marrow recipients discussed straddle in part the border between primary and persistent EBV infections. In many malignant and nonmalignant diseases, the viral carrier state may become enhanced to a greater or lesser extent. An over-representation of high titers of VCA-specific IgG (≥1:320) has been noted in HD and other malignant lymphomas, in chronic lymphocytic and several other leukemias, and in a variety of other cancers, as well as in ataxia telangiectasia, sarcoidosis, systemic lupus erythematosus, rheumatoid arthritis, and patients with organ transplants (15, 17). High titers of anti-VCA are often accompanied by antibodies to R, less frequently to D, usually at only low titers. In all of these conditions, one finds a number of patients who have not as yet been infected with EBV, excluding an etiological role of the virus. The common denominator in the diseases mentioned is that they all have immunosuppressive effects or require immunosuppressive therapy which may unbalance the control of the persistent EBV infection. A few examples will be presented below.

In ataxia telangiectasia, one may find, aside from the over-representation of high titers of antibodies to VCA and an increased incidence of anti-EA responses, no or barely detectable levels of antibodies to EBNA even if the other antibodies are not elevated (2, 21). Serial follow-up studies of juvenile HD patients have shown a gradual increase during and following chemo- and/or radiotherapy in anti-VCA titers and emergence of anti-EA but no significant changes in anti-EBNA titers (26). High titers of antibodies to VCA were found to correlate with multiple evidence of impaired cell-mediated immune responsiveness (20). Occasional patients with HD or chronic lymphocytic leukemia (≤1%) may gradually develop extraordinarily high anti-VCA titers (up to 1:20240) which then may be accompanied by substantial titers of VCA-specific IgA and D-specific IgG and IgA (28), a pattern seen at high frequency, in nasopharyngeal carcinoma with lymph node metastases (19). Injection of antithymocyte globulin into renal transplant recipients often increases the VCA-specific IgG titers within a month by a factor of 4 or more and calls forth also low titers of antibodies to R, but the levels of antibodies to EBNA remain unchanged (6). Antithymocyte globulin also enhances preexisting antibody titers to other herpes-group viruses, measles, and BK virus and increases the frequency of excretion of EBV into the oropharynx.

From these examples, it is evident that activation of the EBV viral carrier state enhances the production of IgG antibodies to VCA and EA components but not to EBNA. It also increases viral excretion (5, 6, 38), but it rarely is accompanied by illness referable to the virus. When excessively high IgG antibody titers are attained, IgA antibodies to VCA and EA components also become detectable, but IgM antibodies do not. Any reaction measured in tests for VCA-specific IgM turned out to be due to interaction of rheumatoid factor (14). In some patients with ataxia telangiectasia or Behcet's disease, production of antibodies to EBNA is reduced or abolished, whereas antibodies to VCA remain within the normal range. These various results indicate that the control mechanisms for anti-VCA, anti-EA, and anti-MA production are different from those for anti-EBNA synthesis, which has been suggested also by the striking difference in the temporal appearance of these 2 sets of antibodies in the course of primary EBV infection (13).

The mechanisms which control or decontrol production of the various antibodies remain to be elucidated. Several possibilities can be listed. (a) A deficiency in or dysfunction of suppressor T-cells fails to shut off antibody production. (b) A deficiency in or dysfunction of nonspecific killer cells or of cells reactive in antibody-dependent cellular cytotoxicity permits productive cycles of viral replication in spontaneously induced B-lymphocytes to go to completion with a full yield of antigens, whereas normally such cells are rapidly destroyed as soon as virus-determined antigens (MA) are inserted into the membranes. (c) A deficiency or dysfunction of killer T-cells specific for lymphocyte detected MA- (EBNA-) positive cells may have 2 effects; i.e., few or no EBNA-positive cells are destroyed so that production of antibodies to this antigen is reduced or abolished, and EBV genome-carrying B-lymphoid cells increase in number, and if spontaneous induction of productive cycles of viral replication continues at the usual frequency, more of all virus-determined antigens (except EBNA) become available for antibody stimulation. Elsewhere in this issue, Rickinson et al. (35) discuss long-term T-cell-mediated immunity to EBV.

These various possibilities are not mutually exclusive and might well occur in combinations. To assess the contributions of the individual mechanisms will be difficult and slow because patients with highly abnormal EBV-specific antibody patterns are rare (excessively high anti-VCA titers in HD), or the required number of peripheral leukocytes for the test procedures might not be easily sparred by the patients (bone marrow transplant), or for other logistic reasons. However, a study of HD and chronic lymphocytic leukemia patients with excessively high titers of IgG and IgA antibodies to VCA and D is now in progress in collaboration with Drs. Johansson and Klein and others at the Karolinska Hospital and Institute. It has been shown already that no single immunological defect accounts for all of these patients.

References
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