

Epstein-Barr Virus (EBV) Infections in Patients

James A. Jackson, MT(ASCP)CLS, Ph.D., BCLD¹,
Hugh D. Riordan, M.D.², Neil Riordan, P. A.², Sharon Neathery, M.T.²

Physicians at The Center see many chronically ill patients with the complaint of "fatigue." If the physical, history and preliminary laboratory tests (e.g., "atypical lymphocytes" on the WBC differential) warrant, the physician will order antibody titers for Epstein-Barr virus (EBV) viral capsid antigen (EBV VCA-IgG) and early antigen (EBV EA-IgG). Elevated EBV EA-IgG anti-bodies suggest recent or chronic-active infection and become undetectable weeks to months after onset. Elevated EBV-IgG antibodies suggest a past infection.

In the patient population treated at The Center, elevated EBV antibody titer is a common finding. During a recent 33 day period, 32 patients seen at The Center had serological evidence of current, recent or past infection with EBV (Table 1).

Epstein-Barr virus (EBV), a member of the herpes group, infects many normal individuals through the B lymphocytes. The data in Table 1 tends to confirm this, 31 of the patients (97%) had antibody titers suggestive of past infection with EBV. If these patients have a competent immune system, the spread of the infection is prevented by T_c cells and antibody which eliminate infected cells and virus. Most normal adults carry EBV throughout life with no ill effects (these patients will usually show an elevated EBV VCA-IgG, Table 1). Exceptions to this, of course, are patients who develop infectious mononucleosis. This disease is spread by healthy viral carriers via oropharyngeal shedding of EBV, usually through close salivary contact.

Of a more serious concern is the association of EBV with several tumor types. These include Burkitt's lymphoma (in Africa), nasopharyngeal cancer (in Southern China), and lymphomas associated with immuno-suppressed individuals. Immunosuppression may be inherited (immunodeficiency), from organ transplantation (cyclosporin), or due to AIDS. In these patients the EBV virus replicates and infects more B cells. The virus is also mitogenic for B cells and these infected B cells tend to proliferate more rapidly. A chromosomal translocation in an infected B lymphocyte may lead to malignant transformation. The chromosomal translocation is usually between chromosome eight and 14, however, it may also occur between eight and two or 22.

An EBV infection can be monitored by the presence of antibodies to the EBV viral capsid antigens (VCA) and the EBV induced early antigen (EA). A current primary EBV infection shows high titers of IgM antibodies to VCA; past infections may show increased EBV VCA-IgG. A recent or chronic-active infection may be identified by elevated EBV EA-IgG. EBV EA-IgG antibodies become undetectable weeks to months after onset. Nineteen of 32 patients (59%), had EBV EA-IgG titers suggestive of active infection; two of these patients were previously diagnosed with Hodgkin's disease. Both patients (M, 13 years old, and M, 47 years old) had evidence of an active infection: EBV EA-IgG of 1:320 and 1:40, respectively (normal <20). There have been several studies in the literature dealing with the association of Epstein-Barr virus in immunodeficiency and lymphomas. In one study, a higher mean titer of EBV-VCA anti-bodies was found in Hodgkin's disease patients when compared to controls. There was no significant difference between non-Hodg-

1. Department of Medical Technology, Wichita State University, 1845 Fairmount, Campus Box 43, Wichita, Kansas 67260-0043.

2. The Center for the Improvement of Human Functioning International, Incorporated, 3100 N. Hillside, Wichita, Kansas 67219.

Table 1.
Patients Showing Positive Serological Response to Epstein-Barr Virus

Sex	Age	EBV EA-IgG (normal <1:20)	EBV VCA-IgG (normal <20)
F	48	1:20	114
F	59	neg.	>170
F	45	neg.	31
M	13*	1:320	135
F	52	1:40	>170
F	25	neg.	46
M	68	1:20	>170
F	36	neg.	104
F	38	1:80	>170
M	58	1:40	neg.
M	47*	1:40	>170
M	77	neg.	102
F	48	1:40	137
M	76	1:80	>170
M	72	1:320	>170
F	39	1:40	>170
F	78	neg.	>170
F	56	neg.	>170
M	53	neg.	111
M	33	neg.	>170
F	49	1:20	56
F	32	1:20	151
M	33	neg.	>170 (CMV-IgG positive)
F	55	1:80	>170
M	63	1:80	>170
F	36	1:20	>170
M	13*	1:160	139
F	50	neg.	>170
F	41	neg.	154
M	47*	1:20	>170
F	49	neg.	>170
F	63	1:40	>170

*= Patients have Hodgkin's disease

* = Antibody titer repeated 30 days after the first test.

kin's lymphoma EBV-VCA antibody titers and the controls.¹ Another study listed three indications for the involvement of EBV in the Burkitt tumor: identification of EBV-transformed lymphoblastoid tumor cells, which contain mostly viral nucleic acid; all tumor patients have EBV antibodies; and it is primarily children

who have had no previous EBV infection who develop Burkitt tumors.² Antibody levels to EBV VCA, EBV EA, to measles and rubella viruses, to CMV (cytomegalovirus), and to *Toxoplasma gondii* were measured in 100 patients with Hodgkin's disease (HD). Anti-EBV antibody titers for VCA and EA were significantly higher in

HD patients than in controls. Anti-CMV and anti-*T. gondii* were also greater in HD patients than in controls.³ In a case report, investigators reported that a patient developed a non-Hodgkin's lymphoma in the right tonsillar fossa six months following renal transplantation. The development of the lymphoma was associated with seroconversion for the EBV VCA and EBV nuclear antigen. The patient was receiving cyclosporin A alone as immunosuppression.⁴

As mentioned before, two of the patients listed in the Table 1 had been diagnosed previously with Hodgkin's disease. Also, 12 of the patients (37.5%, Table 1) were over 50 years of age (immunity tends to decrease with age). In examining this and other data, several items need to be considered. One, which came first? Is it the EBV infection causing the chronic fatigue shown in many of these patients (and, possibly lymphoma), or is it the depressed immunity in the lymphoma and chronically ill patients allowing the opportunistic EBV to infect the patient? Perhaps the EBV can act as either an initiator or promoter of lymphoma. In any case, there seems to be more than just a casual association between EBV and the patients listed in Table 1.

The patients at The Center having positive EBV titers are usually treated with high dose intravenous vitamin C in Ringer's Lactate (15 grams or more depending on other findings). The vitamin C is an excellent viricide and also restores the energy and immunity to many of the patients suffering from EBV infection. After treatment with high dose intravenous vitamin C, the two patients with Hodgkin's disease, one (M, 13 years old), showed a decrease in the EBV EA-IgG titer from 1:320 to 1:160. The other patient (M, 47), showed a decrease in EA-IgG antibody titer from 1:40 to 1:20. The EBV VCA-IgG titer did not show this response. Physicians at The Center find the Epstein Barr virus antibody test to be a valuable adjunct test to the other diagnostic tools used in patient treatment.

References

1. Napel T, et al: Discordance of Epstein Barr Virus (EBV) Specific Humoral and Cellular Immunity in Patients With Malignant Lymphomas: Elevated Antibody Titers and Lowered in vitro Lymphocyte Reactivity. *Clin Exp Immunol*, 1978; 34(3): 338-346.
2. Schmitz H: Correlation Between EBV Infections and Malignant Lymphomas. *Recent Results Cancer Res.*, 1974; 46: 55-58.
3. Rocci G, et al: Antibodies to Epstein-Barr Virus -Associated Nuclear Antigen and to Other Viral and Non-viral Antigens in Hodgkin's Disease. *Int. J. Cancer*, 1975; 16(2): 323-328.
4. Walker RJ, et al: Malignant Lymphoma in a Renal Transplant Patient on Cyclosporin A. *Aust & NZ J Med.*, 1989; 19(2): 154-155.