

## **Immunopathology of the X-Linked Lymphoproliferative Syndrome\***

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### **A. Abstract**

The immunopathogenesis of 25 kindreds affecting 100 males with the X-linked lymphoproliferative syndrome (XLP) is being studied comprehensively by our registry and laboratory group. XLP is a combined variable immune deficiency with Epstein-Barr virus (EBV) induced phenotypes of: (1) fatal infectious mononucleosis (IM), (2) chronic IM progressive to malignant lymphoma, (3) acute IM progressive to acquired agammaglobulinemia or (4) malignant lymphoma. Cytogenetic studies of peripheral blood lymphocytes from 15 surviving males and 21 carrier females reveal random karyotype errors in several kindreds. Often polyclonal Ig or selective IgM increases and lymphocytosis with plasmacytoid forms typifies the IM phenotypes. Weakly reactive EBV-specific antibodies are found and anti-EB nuclear antigen is lacking. Antibodies to EBV are paradoxically elevated in female carriers. Initially all lymphoid tissues show immunoblastic proliferation with plasma cell differentiation and focal to extensive necrosis. Thymus gland and other lymphoid organs become depleted in T cell regions and Hassall's corpuscles may become destroyed. Multinucleated giant cells may be seen destroying the corpuscles or calcified corpuscles are found. The lymphoid infiltrates and lesions resemble graft-versus-host response in the fatal IM phenotype. Extensive necrosis in lymph nodes and deficient Ig secretion of B-cells characterize acquired agammaglobulinemia phenotypes. The malignant lymphomas span the spectrum of B cell differentiation with most being

immunoblastic sarcomas. One case probably was monoclonal thus far, others are being studied. EBV DNA hybridization of tissues from 7 patients with fatal IM revealed 1 to 20 EBV genome equivalents per cell. The patients lacked appropriate EBV antibody responses. Our studies of XLP support the hypothesis that immune deficiency the EBV permits chronic and fatal lymphoproliferative diseases in XLP following EBV infections. Owing to this knowledge, rational bases for prevention by genetic counseling and by providing high titer gammaglobulin and antiviral therapy is being attempted.

### **B. Introduction**

Our studies of the X-linked lymphoproliferative syndrome demonstrate the interaction between genetic predisposition to oncogenesis triggered by an environmental agent (EBV) in immunodeficient males. Prior to discussing XLP, the immunopathogenesis of Burkitt lymphoma (BL) and IM is reviewed.

The results of studies done by numerous investigators during the past two decades substantiate the view that EBV can be an oncogenic agent in immunodeficient individuals. A brief historical review follows for focusing our discussion of EBV-induced oncogenesis in immune deficient persons. Denis Burkitt, working in tropical Africa, delineated a new malignant lymphoma which often involves the jaws or abdominal organs (Burkitt 1958). Endemic African Burkitt lymphoma (AfBL) is present in areas of hyperendemic malaria. A hematopathology committee of WHO has defined BL pathologically (Berard et al. 1969).

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\* This study was supported in part by a grant from the National Institutes of Health, CA 23561-02

William Dameshek observed that infectious mononucleosis (IM) is a lymphoma-like illness which, though often serious, is rarely fatal (Dameshek and Gunz 1964). Diagnosis of IM requires fulfillment of a triad of clinical, hematologic, and serologic criteria. Werner and Gertrude Henle (1968) demonstrated that EBV was the etiologic agent of IM. Specific antibody responses to EBV form against early antigen and are transient, whereas viral capsid antibodies (VCA) and EB nuclear-associated antigen (EBNA) persist throughout life. Approximately 90% of adults have EBV antibodies to EBV, indicating past infection.

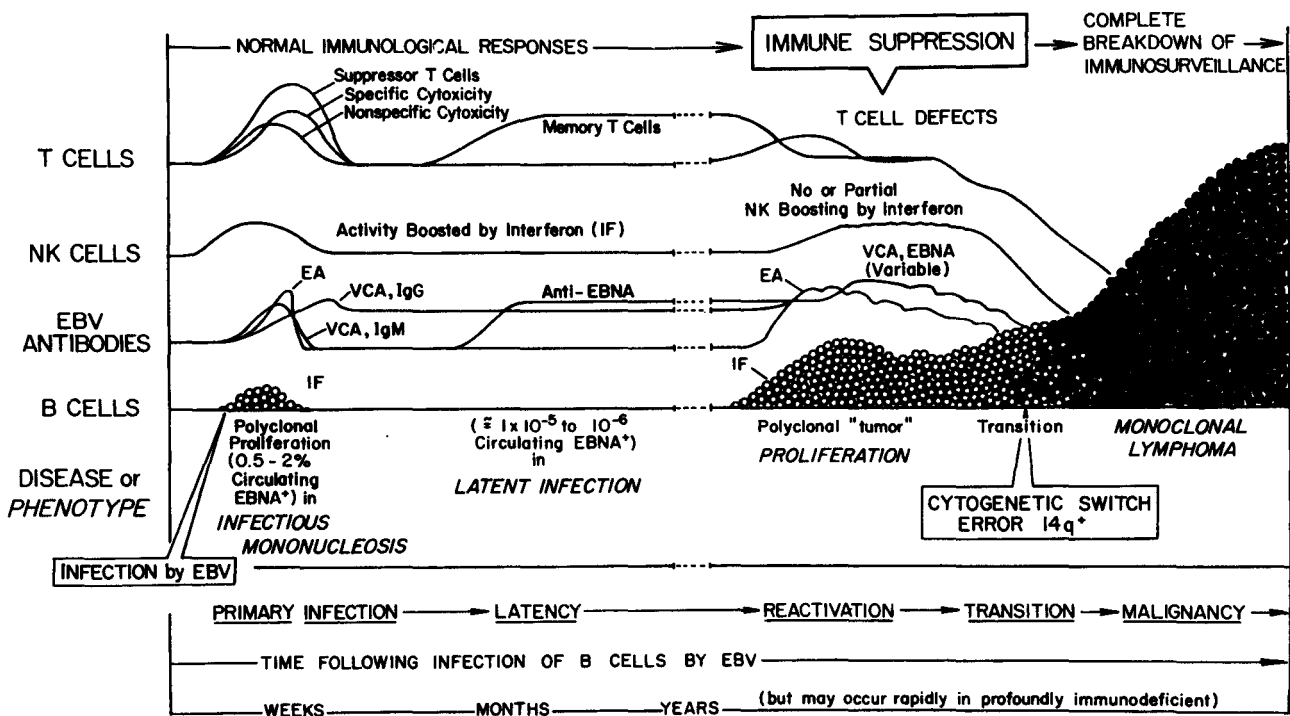
In 1964 Epstein and Barr identified in vitro a unique herpesvirus in a BL-derived cell line (Epstein et al. 1964). EBNA was identified in EBV-transformed B cells by Reedman and Klein in 1973 by immunofluorescence (Reedman and Klein 1973). Many investigators have attempted to determine whether EBV is an oncogenic virus in human beings. Three major EBV-associated diseases occur: IM in adolescents in Western countries, BL in the tropics, and nasopharyngeal carcinoma (NPC) in Southeast Asia. Although EBV has been demonstrated in tumor tissue derived from BL and

NPC, absolute proof that EBV is an oncogenic virus is lacking (Klein 1975)

### C. Immune Responses to Epstein-Barr Virus

Investigators agree that EBV triggers polyclonal proliferation of B-cells. Major questions remaining are: What stops this proliferation? Can IM be regarded as an aborted malignancy of transformed B cells? Figure 1 summarizes immune responses to EBV in primary infection and in reactivation of virus due to acquired immunodeficiency.

A first line of defense against primary EBV infection and reactivation of infection may be natural killer (NK) cells. The role of interferon as an immunomodulator has been the subject of recent intensive studies. Interferon is a potent modulator of spontaneous NK activity in mouse and man (Stebbing 1979; Klein et al. to be published; Saksela et al. to be published). NK show cytotoxic activity for a variety of tumor cell lines as well as normal cell lines infected with certain viruses (Heberman et al.



**Fig. 1.** Hypothesis summarizing humoral and cellular immune responses occurring after primary infection by Epstein-Barr virus (EBV) (*left portion* of diagram). On the *right* acquired immunodeficiency, as in renal transplant recipients, with reactivation of EBV and consequent polyclonal proliferation of B cells is depicted. Males with X-linked lymphoproliferative syndrome who respond or fail to respond to primary EBV infection are displayed on the *right side* of diagram. (Published with the permission of Academic Press)

1979). The lymphocyte subpopulation in man responsible for NK activity is currently unknown, although recent evidence favors the T and null lymphocyte subpopulations (Beverly and Knight 1979). Ascertainment of the importance of each of these mechanisms for elimination of EBV-infected or -transformed clones needs further study. Changes in lymphotoxicity of peripheral leukocytes against autologous and allogeneic LCL are demonstrable in IM (Bausher et al. 1973; Junge et al. 1971). The atypical lymphocytes of patients with acute IM reflect an immunologic struggle. EBV infects and causes B-cell proliferation; then T cells respond. The precise magnitude of the B and T cell proliferation is unknown. B cell proliferation is polyclonal, short lived, and precedes the outpouring of T cells (Papermichael et al. 1974; Pattengale et al. 1974). Klein and colleagues have found that approximately 0.5%–2% of circulating B cells contain EBNA during the first week of illness (Klein, et al. 1976). Haynes et al. (1979) have determined that both T and B cells increase in acute mononucleosis and the T cells lack Fc receptors for IgG or IgM.

The subpopulation of B cells infectable by EBV has not been identified; most B cells become transformed by EBV, resulting in a polyclonal proliferation (Pagano and Okasinski 1978). It is noteworthy that bone marrow is not usually involved in IM (Carter and Penman 1969). This finding indicates that a subpopulation of B lymphocytes susceptible to EBV infection traffic to tonsils, lymph nodes, and spleen.

Several laboratories have demonstrated that the atypical T lymphocytes which are characteristic during infectious mononucleosis have cytotoxic activity for EBV-infected lymphoblastoid cell lines (Royston et al. 1976; Hutt et al. 1975; Svedmyr and Jondal 1975). Their data suggest that cytotoxic T lymphocytes may be responsible for the control of EBV-induced B lymphocyte proliferation. Lymphocytes from patients obtained from blood during the initial 2 weeks of overt IM are significantly more cytotoxic than are controls. Cytotoxicity declines proportionately to the number of circulating atypical lymphocytes (Hutt et al. 1975). Results of *in vitro* studies suggest that *in vivo* cytotoxicity aborts B cell proliferation. Exactly how B cells are killed by cytotoxic T cell is not known. In addition, suppressor T cells become activated during B cell prolifera-

tion (Tosato et al. 1979; Haynes et al. 1979). Following primary infection, the virus persists latently throughout life. Repression of reactivation is due, in part, to T lymphocytes: Thorley-Lawson et al. (1978) have shown that T cells suppress the outgrowth of B cells infected by EBV *in vitro*. The suppression of EBV infection occurs after infection but before transformation of the cell (Thorley-Lawson 1980). Perhaps the same subpopulations of T cells prevents the long-term establishment of LCL from seropositive persons (Moss and Pope 1975; Moss et al. 1978; Rickinson et al. 1979). Regression of LCL is probably due to long-term T cell immunity to EBV (Moss et al. 1979; Rickinson et al. 1980).

While cellular immune responses to EBV combat B cell proliferation, antibodies to EBV-specific antibodies neutralize virus and/or kill infected B cells through antibody-dependent cellular cytotoxicity (ADCC). Henle et al. (1979) have recently reported that ADCC activity correlated poorly with the clinical course of IM. Our studies of patients with the X-linked lymphoproliferative syndrome (XLP) have identified affected males, chronically infected by EBV and lacking antibody to EBV, who show relatively normal lymphocytotoxicity (Purtilo et al. 1978a,b,c). Thus, antibodies to EBV do not appear to be required in surviving EBV infection. How ADCC participates to end the proliferative state in immunocompetent persons is not yet determined.

An array of EBV-specific antibody responses occur in normal persons following primary infection (Henle et al. 1974) (Fig. 1). Such antibody determinations have greatly enhanced our understanding of the immunopathology of IM and facilitate differential diagnosis, especially in heterophile negative IM. The latter group accounts for 10% of EBV-induced IM (Evans 1978). Three major antibody responses to EBV deserving mention are EA, VCA, and EBNA. Following infection by EBV, transient IgM antibody responses to VCA appear which later switch to the IgG class and persist for life. Another transient antibody response is against EA. The high titer anti-EA of children with BL shows the restricted (R) component (Henle et al. 1974). In contrast, anti-EA of IM has the diffuse (D) component; recurrent or chronic IM also has the R component (Horwitz et al. 1975). Antibodies to EBNA appear late, after partial

destruction of infected B cells, and persist for life (Henle et al. 1974).

The EBV antibodies and cellular cytotoxicity directed specifically against EBV antigens serve to stop B cell proliferation, but immunoregulatory mechanisms often short circuit during the chaotic immune struggle of IM, and thus, a hoard of autoantibodies can erupt in IM (Sutton et al. 1974; Thomas 1972; McKinney and Cline 1974; Carter 1975; Steele and Hardy 1970; Purtilo 1980; Langhorne and Feizi 1977). The autoimmune reactions and misdirected lymphocytes are devisive and they injure tissues, as in graft-versus-host response (GVHR) (Purtilo 1980).

#### D. Immunopathology of the X-Linked Lymphoproliferative Syndrome

During the decade since I autopsied an 8-year-old boy in the Duncan kindred who had died of infectious mononucleosis, research efforts have revealed immunopathogenetic mechanisms of EBV-induced fatal lymphoproliferative disorders (Purtilo et al. 1974a,b, 1975, 1977a,b, 1978a,b,c, 1979a,b; Purtilo 1976a,b, 1977). XLP thus serves as a prototype for studying persons at high risk for fatal EBV infection, especially opportunistic malignant lymphomas in immune deficient patients.

Our international registry of XLP has registered more than 25 kindreds involving 100 male patients (Purtilo 1979). Approximately 50% of the affected males thus far have succumbed to IM (Fig. 2) and 15% to IM complicated by immunoblastic sarcoma; 19% have survived IM but acquired agammaglobulinemia or developed dysgammaglobulinemia, and 25% have experienced malignant lymphoma (Hamilton et al. 1980). Only 20 of the 100 affected males survive (Purtilo et al. 1979a,b).

The clinical and pathologic manifestations of the XLP syndrome mimic GVHR, especially in the IM phenotype. Following EBV infection, lymphoid tissues initially undergo hyperplasia followed by depletion and occasionally by malignant lymphoma, as in experi-

mental murine GVHR (Purtilo 1980). In addition, tropism of aggressor lymphocytes in XLP for epithelial tissues – thymic, skin, liver, and gut – resemble GVHR (Seemayer et al. 1977). The acquired aroliferative phenotypes following EBV have consisted of aplastic anemia and hypo- or agammaglobulinemia. In the latter phenotype profound necrosis in lymph nodes and other lymphoid tissues is found (Purtilo 1980; Purtilo et al. 1979a,b). The differential diagnosis of XLP can be achieved by pedigree analysis and laboratory studies, as discussed elsewhere (Purtilo 1980).

We have attempted, in addition to our hematopathology studies, to characterize comprehensively the immunologic, virologic, and genetic defects in the 20 surviving males and 25 carrier females.

#### E. Chromosomal Breakage

Our cytogenetic studies of families with XLP have revealed differences in various kindreds with XLP. The initial two families with the syndrome have not shown appreciable defects. In contrast, a recent kindred has shown extensive aneuploidy in both peripheral lymphocytes and in early passage LCL (Paquin et al. 1980). Carrier females as well as affected males have shown a propensity to chromosomal damage. We have tentatively concluded that cytogenetic changes may be a phenotype of XLP and that increased clastogenic activity could predispose to induction of fatal lymphoproliferative disorders induced by EBV. Other environmental carcinogens could also initiate the lymphoreticular malignancies; however, none have been found.

#### F. Immune Deficiency of XLP

Immunologic studies of 14 affected males with XLP show relatively normal numbers of T and B cells. However, significantly depressed ( $P < 0.05$  compared to controls) lymphocyte transformation responses to phytohemagglutinin, conconavalin A, pokeweed, and strepto-

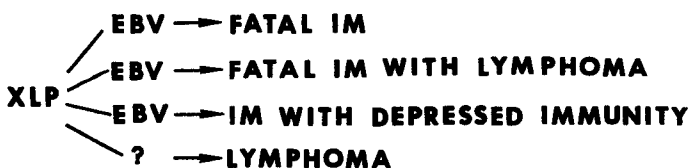


Fig. 2. Phenotypic expression of X-linked lymphoproliferative syndrome following infection by Epstein-Barr virus (reproduced with permission of C.V. Mosby Company, United States)

lysin 0 antigens are found, and mixed leukocyte responses are diminished (Sullivan et al. 1980). Carrier females often show diminished responses to plant mitogens, but the magnitude of the depression is usually less than their sons. Affected males fail to develop a secondary IgG antibody response to  $\Phi$ X 174 (a bacteriophage). This diminished responsiveness indicates that the immunodeficiency of XLP is not limited to EBV (Purtilo et al. 1979a,b) and that helper T cells may be defective. However, most surviving males have dysgammaglobulinemia. We are presently studying several affected males with relatively normal Ig Levels. Profound hypogammaglobulinemia has occurred in six surviving males who had a well-documented antecedent history of IM. Other survivors have shown selective IgA deficiency with or without elevated IgM (Purtilo et al. 1979a,b). Our preliminary studies of NK cells in XLP reveal defective activity in 80% of the patients who survive EBV infection but have other immune defects. Our studies indicate defective T lymphocytes and NK cell subsets which allow uncontrolled EBV-induced lymphoproliferation (Sullivan et al. 1980).

### **G. EBV-Specific Antibodies in XLP**

Antibody studies for EBV in the 15 affected males reveal variable responses. Four patients entirely lacked antibodies to VCA, EA, and EBNA (Sakamoto et al. 1980). A second group of six XLP patients show normal anti-VCA titers but lack anti-EBNA and EA. In contrast, carrier females show a fourfold higher VCA antibody titer than do our normal adult controls; all carriers have anti-EBNA. EA antibodies were found in 11 of the 21 carriers, suggesting active infection. One carrier exhibited low grade, chronic lymphoproliferation (D. Purtilo, unpublished observations).

These serologic studies suggest that the B target cells of XLP are permissive of EBV infections. The lack of antibodies against EBNA in infected males suggests they have T cell defects against EBV. These latter findings corroborate our in vitro assays of defective T lymphocyte function and the hematopathologic findings of depletion of T cell zones in lymphoid tissues. Alternatively, helper T cell populations are lacking. In contrast,

the carrier females have approximately one-half defective B cells which are apparently permissive of EBV infection. Evidence substantiating this speculation is that their markedly high anti-VCA and normal anti-EBNA titers indicate vigorous response by normal lymphocytes to EBV infection. The elevated anti-EA activity in several carriers indicates chronic active infection. Thus, the women defend against the EBV infections and only manifest the XLP immunodeficiency in vitro.

### **H. Malignant Lymphomas in XLP**

Documentation of EBV infection in immune deficient patients requires EBV antibody studies, transformation of peripheral blood lymphocytes or cells from lymphoid tissues, transformation of cord lymphocytes by throat washings in vitro, or demonstration of the genome in tissue by EBV DNA hybridization (Purtilo 1980). Employment of these techniques has resulted in the identification of EBV in numerous patients with inherited or acquired immunodeficiency who died of lymphoproliferative disease. In patients with XLP we have evidence suggesting that IM can progress to malignant lymphoma in immune deficient patients. We hypothesize that for the polyclonal proliferation characteristic of IM to become a monoclonal proliferation, a karyotypic abnormality appears which leads to a malignant monoclonal tumor cell. For example, the 14q+ marker chromosome of Burkitt lymphoma (Purtilo 1980) may be present. We are testing this hypothesis by testing affected males over many years (Fig. 1).

The malignant lymphomas in males with XLP have ranged the spectrum of B cell lymphomas (Paquin et al., to be published). In many cases, IM and immunoblastic sarcoma have occurred concurrently. Regrettably, cell surface marker studies for clonality and EBV DNA hybridization studies have not been possible on fresh lymphomas. However, EBV DNA hybridization of 7 cases of the fatal IM phenotype has revealed 7–20 EBV genome equivalents per cell in patients who lacked EBV antibody responses (Purtilo et al. 1981). Similar attempts to document EBV in opportunistic lymphomas in children with immunodeficiency (Kersey and Spector et al. 1978) and in renal transplant recipients ought to be attempted (Hanto et al. 1981).

## I. Summary

We have developed a registry and laboratory of XLP dedicated to conducting multidisciplinary studies to provide:

1. Consultation to clinicians, families, and pathologists seeking diagnosis, treatment, evaluation, and genetic counseling;
2. Collection of data to define diagnostic criteria;
3. Further delineation of the diverse immune deficiencies and the basic genetical-immunologic defects responsible for the various phenotypic expressions;
4. The establishment of lymphoblastoid cell lines from patients with XLP and related lymphoproliferative disorders which occur on genetic or sporadic bases for comparative studies;
5. Testing of the hypothesis that the common ubiquitous EBV can produce lethal lymphoproliferative diseases in individuals with inherited or acquired (renal and cardiac transplant recipients) immunodeficiency; and
6. Development of rational immunoprophylaxis (high titer EBV-specific gammaglobulin) and therapy (interferon and/or antiviral drugs) against EBV-induced oncogenesis.

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