PERSPECTIVE

Viruses and Lymphomas

Do viruses cause lymphomas? Yes, at least some viruses can. The first evidence was found in the 1960s, when Epstein–Barr virus (EBV) was detected in an explanted Burkitt's lymphoma. Today's panoply is surprising, ranging from EBV in lymphomas in immunocompromised patients and EBV in Hodgkin's disease to leukemia and lymphoma produced by human T-cell leukemia virus type 1 (HTLV-1) (see Table). Now, in this issue of the *Journal*, Hermine et al. have provided evidence of an association between splenic lymphoma and hepatitis C virus (HCV) (see pages 89–94). What are we to make of these diverse associations, and how will this knowledge benefit us?

Virus and Lymphoma*	Cause or Primary Mechanism	Role of Virus	Other Factors
EBV			
Burkitt's lymphoma	*C-MYC* activation	Cofactor	*Plasmodium falciparum* infection
B-cell lymphoproliferative diseases	EBV	Direct	In immunocompromised hosts
Hodgkin's disease	Unknown	May enhance primary mechanism	Mixed cellularity and lymphocyte-depleted
T-cell lymphomas; lethal midline granuloma	EBV	Uncertain; rarely infects T cells	Especially common in Asia
HTLV-1			
Adult T-cell leukemia and lymphoma	HTLV-1	Direct	Possibly genetic or environmental factors
KSHV			
Primary effusion B-cell lymphoma	KSHV	May be direct	May cooperate with EBV in AIDS
Castleman's disease (plasma-cell variant)	KSHV (polyclonal hyperplasia)	May be direct (KSHV-encoded interleukin-6)	In AIDS
Hepatitis C virus			
B-cell lymphomas	Immunostimulation of B cells	Indirect	Chronic active infection

*EBV denotes Epstein–Barr virus, HTLV-1 human T-cell leukemia virus type 1, and KSHV Kaposi's sarcoma–associated herpesvirus.

Established tumor viruses infect a specific type of tumor cell and cause it to proliferate in vitro. The viral genome is consistently detected in vivo. EBV is lymphotropic and stimulates B cells to proliferate indefinitely in vitro, and in endemic Burkitt's lymphoma in Africa, the viral genome is virtually always detected. By contrast, in sporadic Burkitt's lymphoma in the United States, the EBV genome is detected infrequently. However, there are characteristic chromosomal translocations that reactivate the expression of *C-MYC* that drives cellular proliferation. These abnormalities are the unifying molecular lesion in Burkitt's lymphoma, whether it is positive or negative for EBV. Ironically, its ability to cause transient B-cell proliferation, which then leads to selection for the clonal mutations affecting *C-MYC,* may cause EBV to be downgraded to cofactor status. However, EBV may continue to be seen as contributing to the Burkitt's lymphoma phenotype.

Kaposi's sarcoma–associated herpesvirus also has tropism for B cells, which leads to clonal primary effusion lymphomas in immunosuppressed persons; the lymphomas are often, but not always, coinfected with EBV. Multicentric Castleman's disease results from a polyclonal hyperplasia. Thus, Kaposi's

sarcoma–associated herpesvirus appears to be able independently to stimulate the proliferation of B cells to the point of emergence of monoclonal B-cell lymphomas.

The clearest evidence that EBV can produce lymphomas comes from organ-transplant recipients and patients with AIDS, a large number of whom have B-cell lymphoproliferative conditions. In the early stages, when proliferation is still polyclonal, the process can be reversed by reducing the level of immunosuppression. The origin of the proliferating cells is the latently infected B cells that contain EBV episomes. As the process evolves, the resulting cell population becomes first biclonal and then irreversibly monoclonal, but in neither population is there specific chromosomal translocation or characteristic activation of an oncogene. The neoplasm appears to be driven primarily by the virus. In rare cases, EBV is also found in T-cell lymphomas.

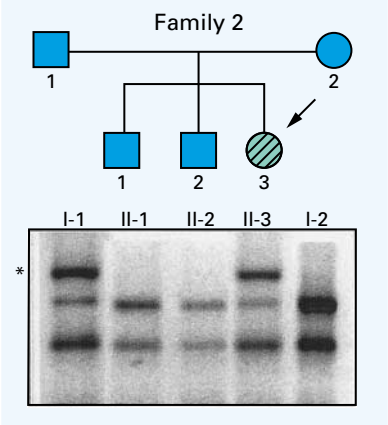
HTLV-1, the only RNA-containing tumor virus affecting humans, also has a direct effect. The T-lymphotropic virus causes T cells to proliferate in vitro and is detected consistently in adult T-cell leukemias and lymphomas. The reasons underlying the endemicity of this disease in Japan have yet to be explained.

The findings of Hermine et al. concerning HCV broaden our perspective. HCV-infected persons are prone to mixed cryoglobulinemia; the virus chronically stimulates the polyclonal proliferation of B cells from which a monoclonal population may emerge. The remarkable regression of lymphoma after the reduction of HCV levels through treatment with antiviral agents is reminiscent of the regression of gastric lymphoma involving mucosa-associated lymphoid tissue (MALT) associated with treatment of *Helicobacter pylori* infection and probably reflects dependence of the disease process on stimulation by viral antigens. However, unlike EBV and lymphoproliferative disease, HCV is not detected in lymphomas. Perhaps more analogous are the EBV-negative B-cell lymphomas in patients with AIDS that are thought to result from immunologic stimulation by infection with the human immunodeficiency virus. However, simian virus 40, which is directly oncogenic, has resurfaced as another possible cause of lymphomas, with its recent detection by the polymerase chain reaction in non-Hodgkin's lymphomas, especially diffuse B-cell and follicular types.

The surge of evidence that EBV is associated with Hodgkin's disease suggests a new paradigm for viruses in lymphomas, mainly because only some cases of Hodgkin's disease are EBV-positive (approximately 50 percent overall), usually the mixed-cellularity and lymphocyte-depleted subtypes. However, no type is excluded from infection. Strikingly, the Reed–Sternberg cells harbor clonal EBV genomes and express the principal EBV oncoprotein latent membrane protein 1 (LMP-1). One way to interpret these findings is to think of the role of EBV in Hodgkin's disease not as causative but as accentuating some pivotal molecular process in the cellular pathogenesis of the disease. In fact, LMP-1 can modify cellular behavior by inducing cellular invasiveness and metastasis factors that alter cell phenotype. This ability may account for the fact that EBV is present in some, but not all, breast cancers, and mainly in the aggressive, invasive forms of the disease. Thus, EBV need not only be causative, it may also enhance the effects of an oncogenic mutation or modify a malignant phenotype.

It may be possible to exploit the viral associations therapeutically. Rarely, antiviral or antimicrobial therapy may cause a dramatic regression of polyclonal and clonal proliferation resulting from immunologic stimulation by an infectious agent rather than by viral transformation. In the EBV-driven lymphoproliferative diseases, viral antigens are recognized in the transformed B cells by specific cytotoxic T cells. The adoptive transfer of autologous EBV-sensitized T cells has produced stunning remissions in immunocompromised patients with otherwise refractory EBV lymphomas. Researchers are trying to extend this success to EBV-positive Hodgkin's disease in the hope that, even if EBV is not causative, a viral latency antigen may make the Reed–Sternberg cells targets for EBV-sensitized T cells. A holy grail in cancer is the discovery of cellular markers that are distinct from those found in normal cells. Thus, virus-associated cancers that express viral neoantigens serve as inviting targets for specific therapeutic interventions.

JOSEPH S. PAGANO, M.D.
University of North Carolina
Chapel Hill, NC 27599-7295



THOX2-Inactivating Mutations and Congenital Hypothyroidism

Untreated congenital hypothyroidism leads to severe developmental difficulties. The authors of this report sought to identify defects in the thyroid oxidase system in infants with iodide-organification defects because two proteins, thyroid oxidase 1 and thyroid oxidase 2, are involved in that process. Biallelic loss-of-function mutations in *THOX2*, the gene for thyroid oxidase 2, were found in one patient with permanent congenital hypothyroidism, and monoallelic mutations were found in three patients with transient congenital hypothyroidism.

Inactivating mutations in the THOX2 *gene that result in total disruption of thyroid hormone synthesis are associated with severe, permanent congenital hypothyroidism, whereas monoallelic mutations lead to a milder, transient form of the disease. This may represent the first genetic mutation causing transient congenital hypothyroidism that has been discovered.*

see page 95

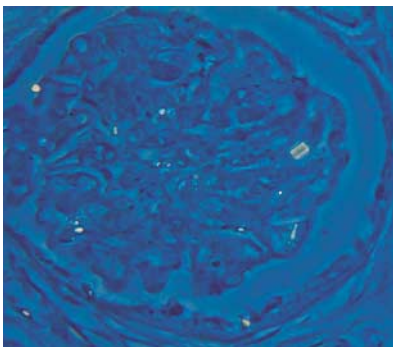
"We predict that recurrent glomerulonephritis will be an increasingly important cause of allograft loss as overall allograft-survival rates continue to improve."

Risk of Allograft Loss from Recurrent Glomerulonephritis

Recurrent glomerulonephritis after renal transplantation is a serious complication that can result in allograft loss. This study, based on data from the Australia and New Zealand Dialysis and Transplant Registry, determined the incidence and timing of risk factors for allograft loss due to recurrent glomerulonephritis in 1505 patients with biopsy-proved glomerulonephritis that had led to end-stage renal disease and primary transplantation. Allograft loss due to a recurrence of glomerulonephritis occurred in 52 recipients. Ten years after transplantation, recurrence was the third most frequent cause of allograft loss, after chronic rejection and death with a functioning renal transplant.

No risk factors were identified that warrant changing the approach to renal transplantation in patients with primary glomerulonephritides.

see page 103



Medical Progress: **Cystinosis**

Cystinosis, a rare autosomal recessive lysosomal storage disease, is due to impaired transport of cystine from lysosomes. The disease results in deposition of crystals throughout the body; if untreated, it leads to failure to thrive, profound metabolic imbalance, early end-stage renal disease, thyroid failure, and multiorgan dysfunction. As this review describes, substantial progress has been made in our understanding and treatment of this disorder. The administration of cysteamine, each molecule of which can combine with a half-molecule of cystine (cysteine) to facilitate the exit of cystine from the lysosome, has greatly improved the course of the disease. In addition, the gene for cystinosis, *CTNS*, which encodes a protein called cystinosin, was isolated in 1998, opening new avenues for understanding this condition.

see page 111