

Viral Causes of Lymphoma: The History of Epstein-Barr Virus and Human T-Lymphotropic Virus 1

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ABSTRACT: In 1964, Epstein, Barr, and Achong published a report outlining their discovery of viral particles in lymphoblasts isolated from a patient with Burkitt lymphoma. The Epstein-Barr virus (EBV) was the first human cancer virus to be described, and its discovery paved the way for further investigations into the oncogenic potential of viruses. In the decades following the discovery of EBV, multinational research efforts led to the discovery of further viral causes of various human cancers. Lymphomas are perhaps the cancer type that is most closely associated with oncogenic viruses: infection with EBV, human T-lymphotropic virus 1 (HTLV-1), human immunodeficiency virus (HIV), Kaposi sarcoma-associated herpesvirus/human herpesvirus 8, and hepatitis C virus have all been associated with lymphomagenesis. Lymphomas have also played an important role in the history of oncoviruses, as both the first human oncovirus (EBV) and the first human retrovirus (HTLV-1) were discovered through isolates taken from patients with unique lymphoma syndromes. The history of the discovery of these 2 key oncoviruses is presented here, and their impact on further medical research, using the specific example of HIV research, is briefly discussed.

KEYWORDS: Burkitt lymphoma, human T-cell lymphotropic virus 1, adult T-cell leukemia/lymphoma, Epstein-Barr virus, history

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Introduction

Viral infections contribute to an estimated 15% to 20% of all human cancers.¹ Several viral infections have been found to be associated with increased risk of lymphomas. There is a well-studied association between Epstein-Barr virus (EBV) and the development of Burkitt lymphoma (BL) and Hodgkin lymphoma (HL) and between human T-lymphotropic virus 1 (HTLV-1) and adult T-cell leukemia (ATL)/lymphoma.¹ Likewise, Kaposi sarcoma-associated herpesvirus has been well-documented to be causally associated with the onset of primary effusion lymphoma and Castleman disease.^{1–3} Previously controversial, the association between hepatitis C virus infection and non-HL (NHL) has been supported by a number of case-control and cohort studies published over the past 15 to 20 years.^{4–7} Evidence for an association between hepatitis B virus (HBV) and lymphoma is less clear. There appears to be an increased risk of NHL overall in patients infected with HBV, but the association between HBV and NHL subtypes is less clear.⁸ Several small studies have reported a potential link between HBV and lymphoma^{9–11}; however, large clinical registry studies have not corroborated these findings.^{4,12} Our current understanding of viral causes of human lymphomas continues to change as new evidence becomes available. The identification of EBV and HTLV-1 as causes of lymphoma was a major breakthrough in virology and oncology, and these 2 viruses continue to be the topic of research to this day. This article serves to highlight the historical aspects of the discovery of EBV and HTLV-1.

The First Human Tumor Virus

Although the confirmation of the first human cancer virus did not occur until the mid-20th century, the theory that cancers could be caused by an infectious agent was propagated as early as the 19th century. The observation that married couples would sometimes be affected by similar cancers and that cancers appeared to be transmitted from mother to child lent support to the early theory of an infectious cause of some forms of cancers.¹ Epstein-Barr virus was the first human cancer virus to be discovered, but the discovery of a virus that could cause human *tumors* predates the birth of either Epstein or Barr. Before we can fully explore the history of EBV and HTLV-1, we must briefly explore the history of the common wart.

In 1907 Guiseppe Ciuffo,¹³ an Italian physician, described an experiment involving autoinoculation with a cell-free extract of common warts in humans. He described these warts as “assuredly infectious” and the aim of his experiment was to determine the “specific microscopic germ or invisible virus that is responsible for these lesions.”¹⁴ Earlier experiments involving inoculation with material from warts had been described,^{15,16} but Ciuffo’s experiment was the first to filter wart extract through a pore size small enough to remove bacteria and fungi while allowing viruses to pass.¹⁷ This experiment represents the first published experiment that appeared to confirm the transmission of human tumors in the light of a viral etiology. However, the significance of Ciuffo’s findings were not appreciated at that time, possibly because warts are benign rather than malignant in nature,¹ and perhaps because Ciuffo’s article was published in Italian. In addition, despite significant



breakthroughs in the field of animal cancer viruses in the early 20th century (Ellermann and Bang¹⁸ reported transmission of leukemia in birds through cell-free inoculations in 1908, and Payton Rous¹⁹ demonstrated the transmission of a sarcoma in chickens through cell-free extracts in 1911), many scientists were dismissive of the concept that viruses could cause cancer. It was not until the 1950s, when the transmission of murine cancers via cell-free extract was reported by several sources,^{20,21} that scientists began to accept the theory of oncoviruses.²² It was in this controversial milieu that, in 1949, the confirmation of virus-like particles, later named human papillomavirus (HPV), isolated from skin papillomas, again pointed toward a viral cause of the common wart.²³ However, it was not until 1976 that zur Hausen²⁴ published the hypothesis that certain strains of HPV also play a key role in the cause of cervical cancer. By that time, EBV, first seen in the lymphoblasts of patients with BL in 1964, was already well on its way to claiming the title as the first human cancer virus. Unlike Ciuffo's wart experiment, the impact of BL rapidly propelled the field of human virus studies forward. In the first few decades following its description, more than 10 000 publications relating to BL were published, leading to important discoveries that shape lymphoma research to this day.^{25,26}

BL and the First Human Oncovirus

In 1957, Denis Burkitt, a medical officer with the Colonial Office in Uganda, examined a 5-year-old boy with a tumor of the jaw. A month later, he examined a young girl with a similar jaw tumor. Both children died, and having seen 2 curious and fatal cases in close proximity, Burkitt began to search for records of similar cases.²⁷ In 1961, Burkitt and Gregory O'Connor,²⁸ pathologists at Mulago Hospital, went on to describe a unique lymphoma syndrome characterized by extremely rapidly growing tumors occurring in the jaw, abdomen, and, more rarely, in the salivary gland, bone, or spinal column with a prevalence that appeared to be distributed along central Africa in a "lymphoma belt." O'Connor²⁹ also presented the possibility of a viral etiology for the lymphoma, having noted the similarities in clinical presentation to lymphocytic bovine leukemia, a disease in cows which was known to have a viral cause. Burkitt described the lymphoma as being common in hot, moist, and tropical regions of Africa and rare in colder, dry, elevated regions and raised the possibility of an insect-vectored virus as the cause of the lymphoma,^{30,31} a theory that was eventually proven false when it was determined that EBV was transmitted by saliva and not by insects.²⁵ However, several researchers had previously examined the possibility that malaria and the anopheles mosquito played a role in pathogenesis of BL,^{32,33} and, in 1969, Burkitt published an updated theory stating that mosquitoes transmitting malaria could determine the geographic distribution of the disease while acting as a cofactor with EBV to promote oncogenesis.³⁶ The complicated involvement of both EBV and malaria in the pathogenesis of endemic BL continues to be an active area of research today.^{34,35}

The discovery of EBV itself began in 1961 when Burkitt, while in the United Kingdom for home leave, presented the newly described lymphoma in a lecture at Middlesex Hospital Medical School. The lecture was attended by a medical virologist, Anthony Epstein, whose research had been focused on chicken tumor viruses.³⁶ Fascinated by BL, Epstein asked Burkitt for tumor samples to be sent to him and changed his research focus to isolating the viral cause of BL.³⁷ The publication of the presence of viral particles, later named Epstein-Barr virus,³⁸ in lymphoblasts cultured from a patient with BL would soon follow.³⁹ But the presence of the newly discovered viral particle alone was not enough to conclude that it was involved in the pathogenesis of BL: years of further study were needed before EBV could be called oncogenic. Much of the early research into the characterization and oncogenic potential of EBV can be attributed to Werner and Gertrude Henle, husband and wife virologists living in the United States. In 1967, they published the results of an experiment showing that cocultivation of irradiated BL cells (causing cell lysis and release of EBV) with healthy control leukocytes frequently lead to proliferation of hematopoietic cells, pointing toward an oncogenic potential.^{38,40} The Henles were also part of the team that first published the discovery of EBV DNA within cells taken from BL biopsies, providing strong evidence for the association of EBV with BL.⁴¹ When a laboratory technician working in the Henle laboratory became ill with infectious mononucleosis, it was noted that she developed antibodies to EBV during the course of her illness.⁴² This observation allowed the Henles to investigate the role of EBV in the development of mononucleosis—highlighting both the scope of the Henles involvement in EBV research and the ability of EBV to cause several clinically distinct pathologies.^{42,43} Because of the work of Werner and Gertrude Henle and numerous other researchers, by the late 1970s, enough evidence had been gathered to definitively prove that EBV played a carcinogenic role in humans,⁴⁴ solidifying the place of EBV in history as the first human oncovirus.

HTLV-1 and ATL/Lymphoma

Through BL and EBV, the discovery of a unique lymphoma syndrome had propelled cancer research forward. After decades of study, researchers had isolated the first virus proven to cause cancer, leading to renewed interest in the field of human oncoviruses.¹ It was in this environment the discovery of another unique lymphoma syndrome, this time in Southern Japan, again led to a key discovery—the isolation of the first human retrovirus.

In the 1970s, clinicians in Japan noted that many cases of hematological malignancies in Japan did not appear to conform to the patterns described in the literature. In Japan, presentations of chronic lymphocytic leukemia were rare, whereas more aggressive, acute T-cell malignancies were more abundant, particularly in the southern island of Kyushu.^{45,46} The impression of a unique pathology that had

yet to be described led to a concerted effort to investigate and characterize this disease. In 1977, the first formal descriptions of this disease, dubbed ATL, were reported by Kiyoshi Takatsuki and his colleagues in *Blood*⁴⁶ and at the International Congress of Hematology in Kyoto.⁴⁷ They described a disease characterized by its aggressive course with frequent skin lesions, lymphadenopathy, hepatosplenomegaly, and leukocytosis with abnormal lymphoid cells that characteristically display lobulated or indented nuclei.^{45,46,48} Perhaps having learned from BL, the highly geographical incidence of ATL immediately pointed researchers toward a potential viral etiology—a potential that was mentioned in one of the earliest descriptions of ATL.⁴⁶

While researchers in Japan were describing ATL, in the United States researchers were searching for a human retrovirus. Following the discovery of mammalian retroviruses in the 1950s,⁴⁹ there had been considerable effort expended in the search for a human retrovirus. By the 1970s, the failure of researchers to discover a human retrovirus led to significant skepticism from many prominent researchers.^{50,51} Robert Gallo, the head of the team who eventually discovered HTLV-1, described the study of human retroviruses in this period as “unpopular.”⁵⁶ However, the discovery of gibbon ape leukemia virus in 1972⁵² and bovine leukemia virus in 1975,^{53,54} as well as significant technical advances in laboratory techniques,⁵⁶ breathed life into the field of human retroviral studies. In 1979, the first human retrovirus, at that time called human cutaneous T-cell lymphoma virus (HTLV), was isolated from cells taken from a patient diagnosed with cutaneous T-cell lymphoma in Gallo’s lab at the National Cancer Institute.⁵⁶ These results were published in 1980,⁵⁵ followed by confirmation of the findings through isolates from other patients.^{57,58} Soon afterward, in 1982, Gallo’s group isolated a distinct but related retrovirus in a patient with T-cell variant hairy cell leukemia, leading to HTLV being categorized as either HTLV-1 (the prototype isolate) or HTLV-2 (the new isolate).⁵⁸

Although the cell lines used to isolate HTLV-1 came from patients who were contemporarily diagnosed with mycosis fungoides or Sézary syndrome, in retrospect it is likely that these cases represented ATL with cutaneous manifestations,^{45,59} as clinicians in the United States at that time had not made the distinction between HTLV-1-associated T-cell malignancies and other hematologic malignancies.⁵⁶ In 1981, in Japan, where ATL was recognized, Yorio Hinuma and his colleagues in Kyoto discovered that the serum samples of patients with ATL contained an antibody against viral antigens, and that this antigen was not found in human lymphoid cell lines taken from patient without ATL.⁶⁰ Soon after, Yoshida et al⁶¹ reported the isolation of a retrovirus in ATL cells, which they called ATL virus (ATLV). Japanese researchers had characterized a distinct lymphoma (ATL) and isolated a potentially causative retrovirus (ATLV), whereas researchers in the United States had previously described a human retrovirus (HTLV-1) isolated from

patients diagnosed contemporarily with cutaneous T-cell lymphoma. However, both groups were investigating the same disease, and in 1983, it was shown that ATL and HTLV-1 were, in fact, the same virus, leading researchers to use HTLV-1 universally when describing the virus.^{59,62} Following the isolation of HTLV-1, several studies, including collaborations between American and Japanese researchers, provided convincing evidence that HTLV-1 was the cause of ATL,^{50,63,64} solidifying the place of HTLV-1 as the first pathogenic human retrovirus.⁶⁵

Impact of EBV and HTLV-1

As with BL and EBV, the discovery of HTLV-1 and ATL influenced further studies in a surprising range of fields. An example of the influence of these discoveries can be seen in AIDS research. In the early 1980s, AIDS began to be clinically recognized, beginning with the publication of several cases of *Pneumocystis pneumonia* and Kaposi sarcoma in young homosexual men.^{66–68} At the time, there were less than 2000 physicians in the United States with specialized training in infectious diseases and there were no Food and Drug Administration (FDA)-approved antiviral drugs for long-term suppression of viral infection. Prior to the discovery of human immunodeficiency virus (HIV), viral diseases endemic to the United States were largely self-limiting or controllable with vaccinations.⁶⁹ In light of the lack of training, therapies, and experience available in treating AIDS patients in the early years of the epidemic, it is not surprising that many physicians felt powerless⁷⁰: they could manage some of the complications of AIDS, but they could do little to treat the disease itself.⁷¹ Despite these challenges, research into HIV and AIDS quickly led to results. By 1983, the first report of isolation of a causative retrovirus was published by Luc Montagnier and François Barré-Sinoussi⁷²; this new virus was determined to be in the same family as HTLV and was initially called HTLV-III.^{72–75} The laboratory protocols used in Gallo’s lab during the discovery of HTLV-I and HTLV-II directly contributed to the ability of researchers to characterize HTLV-III,⁶⁵ which was renamed HIV in 1986.⁷⁶ Zidovudine, the first antiretroviral designated to treat HIV, achieved FDA approval in 1986.⁷⁷ Although early retroviral therapy for HIV was not widely effective,⁶⁹ it remains impressive that in less than 6 years international research effort had led to the recognition and characterization of AIDS, the isolation of the causative retrovirus, and the ability to offer treatment. The rapid advancements made in AIDS research owe much to the previous knowledge gained through the isolation of HTLV-1 and HTLV-II.^{59,61}

Both BL and EBV played a role in furthering HIV research. As the AIDS epidemic developed, it became clear that homosexual men were at greater risk of certain cancers.^{78–80} One of the first cancers to be tied to the new outbreak of immunosuppression was Burkitt-like lymphoma, first by a case report⁸¹ and, a month later, by the publication of 4 cases of BL occurring in homosexual men in San Francisco in 1982.^{82,83} Further

reports of high rates of NHL occurring in patients with AIDS followed.^{83–85} Burkitt lymphoma was the most common type of AIDS-related NHL,⁸⁶ and many AIDS-related NHL cases are EBV positive.⁸⁷ In the early 1980s, previous treatment experience with endemic BL gave clinicians a starting point for treating AIDS-related BL—although unfortunately AIDS-related BL does not share endemic BL sensitivity to chemotherapy.⁸⁸

The experience that clinicians and researchers had with diseases caused by EBV and HTLV-1 compensated, at least in part, for the lack of experience in the treatment of the newly described pandemic of AIDS and HIV. The impact of the discovery of EBV and HTLV-1 on cancer and virology research cannot be overstated. Roughly 75 years separate Ciuffo's early experiments investigating the transmission of warts through inoculation of cell free extracts and the discovery of the first human retrovirus, HTLV-1. In contrast, when the AIDS epidemic began to be clinically recognized in 1981, it took only 2 years for a potentially causative retrovirus to be isolated—an achievement that would not have been possible without the key discoveries that came before.

Author Contributions

DE conceived the topic, performed the literature review, and wrote the article.

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