Medical Oncology (2024) 41:102
https://doi.org/10.1007/s12032-024-02345-1

REVIEW ARTICLE

Investigating the correlation between prominent viruses and hematological malignancies: a literature review

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Received: 11 January 2024 / Accepted: 23 February 2024 / Published online: 28 March 2024

Abstract
Extensive research has been conducted on the correlation between viral infections and hematological cancers ever since the identification of the Rous Sarcoma Virus as a cancer-causing agent. Numerous viruses, such as the Epstein-Barr virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus, human T-lymphotropic virus 1, and severe acute respiratory syndrome-related coronavirus 2, have been identified as potential contributors to the development and progression of cancer by disrupting normal cellular processes. Different viruses are associated with distinct forms of blood cancers, each exhibiting unique infection mechanisms, pathogenesis, and clinical symptoms. Understanding these connections is crucial for the development of effective prevention and treatment strategies. Healthcare professionals who possess a solid understanding of these associations can offer precise treatments and closely monitor potential complications in individuals with blood cancers and viral infections. By leveraging this information, healthcare providers can optimize patient care and improve outcomes for those affected by both viral infections and hematological cancers.

Keywords Hematology · Malignancy · Oncology · Viral · Viral oncology · Virus

Introduction

Since the Rous Sarcoma Virus (RSV) was identified as the agent that causes the development of cancer, which resulted in the awarding of the Nobel Prize in 1966, there has been a substantial amount of progress made in the investigation of the connection between viral infections and hematological cancers. A great number of viruses have been recognized as factors that contribute to the progression of cancer over the course of numerous years. These may include viruses that are frequently encountered, such as the Epstein-Barr virus (EBV), the hepatitis B virus (HBV), the hepatitis C virus (HCV), the human immunodeficiency virus (HIV), human T-lymphotropic virus 1 (HTLV-1), and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). These viruses have the ability to interact with host cells and throw off the normal functioning of cellular mechanisms, which ultimately leads to the development and progression of cancer.

The relationship between viral infections and hematological cancers is currently being investigated by researchers in the scientific community. Several factors, including inflammation, dysregulation of cytokines, and continuous antigenic stimulation, have been found to be contributors to the increased incidence of cancer in individuals who have been infected with a variety of infections.

The association between viral infections and hematological cancers

Long before viruses were discovered, the very first studies of the role that viral infections play in the development of cancer were already being carried out. The investigation that Peyton Rous conducted in 1911 was one of the earliest to yield an important finding. Rous disseminated the solid neoplasm by means of the inoculation of a cell-free extract of avian tumor into asymptomatic Plymouth Rock chickens. This allowed the tumor to spread. It was discovered that the tumor was made of connective tissue, a sarcoma, and that

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the extract was responsible for oncogenesis [1]. About fifty years later, a viral agent was discovered to be the cause of oncogenesis. This led to the categorization of the virus as the Rous Sarcoma Virus (RSV), and the Nobel Prize was conferred upon Rous in the year 1966 [2].

Since then, a significant amount of research has been conducted to investigate the role that infections caused by viruses play in the development of cancer. The significance of viruses in the formation of hematologic cancers, in particular, has come into much greater focus over the course of time. For example, research conducted on Herpesvirus saimiri by Melendez et al. (1969) [3] and Simian virus 40 by Diamandopoulos et al. (1973) [4] contributed to an improvement in our comprehension of the role that viral infections play in the development of cancer. There is strong evidence available today those numerous viruses are responsible for the development of cancers. It is well known that EBV can cause lymphoma [5]. It is also widely known that infection with the human T-cell lymphotropic virus type 1 (HTLV-1) can lead to adult T-cell leukemia/lymphoma (ATLL) [6]. On the other hand, it would appear that links between viral infections and hematological cancers will be discovered over the course of the next few years. For instance, it is believed that a number of different factors contribute to the increased occurrence of cancers in HIV-infected patients. Several of these, such as inflammation, dysregulation of cytokines, and continuous antigenic stimulation, can be discovered in [7]. Furthermore, a number of pathologic mechanisms, such as a weakened immune system, gene mutations, viral infection, and chronic B cell activation, have been identified for the function of the human immunodeficiency virus (HIV) in HIV-associated lymphoma. A large proportion of these lymphomas are derived from B cells and have clonal rearrangements in their immunoglobulin genes [8].

In our analysis, we searched for studies that analyzed the hematological and biochemical factors in blood samples taken from people who had a specific viral infection and a particular type of hematologic cancer simultaneously and then compared those findings to the results of blood samples taken from control groups. Furthermore, we searched for previously published researches that directly investigated the correlation between viral infections and hematological malignancies to determine whether or not viruses may play a role in hematological cancers.

Methods

We performed a scoping study to identify viral infections linked to hematological malignancies and their suggested mechanisms of oncogenesis. Relevant studies were identified by searching two bibliographic databases, PubMed and Embase. Initial searches of PubMed and Embase yielded 921 papers in total. Titles and abstracts of all papers were reviewed to find studies investigating the connection between viral infections and hematological malignancies. 46 papers were chosen for full-text examination after the screening procedure. The data analyzed in the full-text evaluation led to the creation of a list of six viral infections and their association with hematological malignancies. One of these viral pathogens plays an unproven role in hematologic malignancies, as it has a low viral copy number in hematolymphoid malignancies [9]. Furthermore, the potential involvement of the pandemic-causing virus, Coronavirus, in the process of oncogenesis has been identified [10]. To delve deeper into the suggested pathways of cancer development, focused searches for each of the six selected viral infections were conducted in PubMed and Embase. Table 1 displays an overview of the findings from our study.

Epstein-Barr virus

Infecting B lymphocyte cells, Epstein-Barr virus (EBV) is a double-stranded DNA virus. This viral strain is classified within the herpesvirus family and is generally referred to as human herpesvirus 4 [11]. It was discovered in a cell line generated from Burkitt lymphoma by Epstein's group in 1964, and later named after Michael Anthony Epstein and his colleague, Yvonne Bar [12]. Nearly 95% of the adult population in the world is infected with the Epstein-Barr virus [13].

Clinical and hematologic manifestations of EBV infection

When children are infected with EBV, the illness may not manifest any signs at all or may present with symptoms that are difficult to diagnose [13]. EBV infection can cause systemic symptoms such as headache, sore throat, fever, malaise, splenomegaly, and lymphadenopathy [14]. Also, infectious mononucleosis (IM) is typically caused by EBV [15]. The timing of virus exposure affects whether an individual develops infectious mononucleosis. Rarely do young children develop clinical symptoms of infectious mononucleosis [16], whereas up to 70% of adults and adolescents will manifest with the classical triad of fever, pharyngitis, and cervical lymphadenopathy with lymphocytosis for approximately two to four weeks [17].

Grotto et al. (2003) [14] discovered that individuals who tested positive for both EBV and heterophile antibodies had a higher occurrence of leukocyte count exceeding 10,000/ml. Similarly, Son and Shin (2011) [18] discovered a wide range of white blood cell counts in patients, ranging from 2100 to 31,200/mm3. They also observed that 69.1% of the patients experienced leukocytosis. Topp et al. (2015) [19] additionally discovered that 59.1% of the children exhibited

Table 1 A synopsis of our research on hematological oncogenic viral agents, their mechanism of action, and the hematological cancers they induce

Viral agent	Clinical manifestations	Laboratory manifestations	Hematological malignancies	Mechanism of oncogenesis
EBV	Headache, sore throat, fever, malaise, splenomegaly, and lymphadenopathy	Leukocytosis, lymphocytosis, abnormal liver function tests (LFTs), and increased CRP	Burkitt's lymphoma, Hodgkin lymphoma, hemophagocytic lymphohistiocytosis, Systemic EBV-positive T-cell lymphoma of childhood, Extranodal NK/T-cell lymphoma, Nasal type, aggressive NK-Cell leukemia, and Primary EBV-positive nodal T-cell or NK-cell lymphoma	Activating oncogenes like Bcl-2 and MYC and signaling pathways such as NF-B, JNK, JAK/STAT, and the production of cytokines IL2, INFa, and IL6
HBV	Fever, headache, malaise, anorexia, nausea, vomiting, diarrhea, and abdominal pain	Elevation in serum ALT levels and the detection of HBsAg and HBcAg	Non-Hodgkin lymphoma and chronic lymphocytic leukemia	Incompletely defined / Mechanism unclear
HCV	Nausea, fatigue, pain in the abdomen or muscles, weight loss, and mental symptoms like depression and irritability	Anemia, thrombocytopenia, and neutropenia	Non-Hodgkin B-cell lymphoma, peripheral T cell lymphoma, extranodal marginal zone B-cell lymphoma, and diffuse large B cell lymphoma	By E1 and E2 membrane proteins, NS3 proteins, p-53, bcl-2, bcl-6, myc, and beta-catenin genes
HIV	Fever, myalgias, fatigue, pharyngitis, weight loss, and headache	Anemia, neutropenia, reduced CD4 + T-cell counts, and polyclonal hypergammaglobulinemia	Hodgkin and non-Hodgkin lymphoma, Kaposi sarcoma, multicentric Castleman disease, diffuse large B-cell lymphoma, primary CNS lymphoma, and Burkitt lymphoma	Probably by decreasing CD4 + T-cell count
HTLV-1	Hand and foot numbness, arm and leg weakness, frequent nighttime urination, joint pain, bleeding gums, and erectile dysfunction	No significant change in the total number of leukocytes and lymphocytes, presence of atypical lymphocytes	Adult T-cell leukemia/lymphoma	By Tax and Rex proteins
SARS-CoV2	Pyrexia, cough, dyspnea, and exhaustion	Anemia, thrombocytopenia, leukopenia, and lymphopenia	No specific hematological malignancies have been linked	Renin-angiotensin system in neoplastic hematopoiesis, oncogenic pathways such as MAPK, JAK-STAT, and NF-κB

an increased number of white blood cells, whereas Medović et al. (2016) [20] observed that the average leukocyte count was 15.2 × 10^9/l and elevated in 65% of the patients. Regrettably, Çağlar et al. (2019) [21] failed to furnish precise details concerning leukocyte count.

In their study, Grotto et al. discovered that patients who tested positive for EBV and heterophile had a higher incidence of lymphocytes exceeding 50% [14]. Son and Shin discovered that half of the patients exhibited atypical lymphocytosis, and this prevalence remained consistent across all age groups [18]. Topp et al. discovered that 75% of the children exhibited an elevated lymphocyte count [19], whereas Medović et al. observed that 74.7% of the patients had a higher lymphocyte count [20]. Çağlar et al. discovered that 57.5% of the subjects had lymphocyte-to-leukocyte ratios that were greater than 50% [21].

Grotto et al. discovered that patients who tested positive for EBV and heterophile had increased levels of liver enzymes, specifically AST, ALT, and LDH [14]. Son and Shin did not observe any statistically significant variation in the levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) among the three age groups [18]. Topp et al. discovered that the concentrations of ALT, LDH, and bilirubin demonstrated a respective increase of 53.7%, 65%, and 9.3% [19]. Medović et al. discovered that the levels of AST, ALT, and LDH were increased by 74.4%, 66.7%, and 96.3%, respectively [20]. And, Çağlar et al. discovered that 40.9% of the individuals exhibited elevated levels of liver transaminases [21].

In the study conducted by Topp et al., it was discovered that 63% of the children displayed increased levels of C-reactive protein (CRP) [19], while in the study conducted by Çağlar et al., approximately 40% of patients exhibited elevated CRP levels [21]. This further demonstrates the utility of CRP levels as a valuable tool for monitoring the advancement of EBV infection in children.

EBV infection and identified associated hematologic malignancies

Burkitt's Lymphoma (BL)

Denis Parsons Burkitt, an Irish surgeon, identified Burkitt lymphoma, an aggressive non-Hodgkin B-cell lymphoma, in 1958 [22]. Six years later, a team led by M. A. Epstein discovered a virus in a Burkitt lymphoma cell line [12], making EBV infection the first viral infection linked to tumor development. Several mechanisms of action for EBV in BL have been described [23]:

1. Apoptosis in B cells is prevented by MYC translocation via the Epstein-Barr nuclear antigen (EBNA) 1 protein, the BHRF1 protein, Epstein-Barr virus-encoded small RNAs (EBER) transcripts, or epigenetic modification, followed by repression of the proapoptotic Bcl-2 interacting mediator of cell death (BIM) protein by the latent transcript EBV latent membrane protein (LMP) 1.
2. The expression of EBNA3A, EBNA3B, and EBNA3C genes results from EBNA2 loss, giving the tumor a survival advantage.
3. Some viral microRNAs have been linked to the development of EBV-positive endemic and AIDS-associated Burkitt's lymphomas.

Hodgkin Lymphoma (HL)

Hodgkin lymphoma (HL) is linked to (EBV), particularly classical HL (cHL) and lymphocyte-predominant HL (LP-HL). The following are some examples of how EBV contributes to HL [24]:

1. Different latency programs (latency 0, I, II, and III) can be expressed by EBV, demonstrating a high degree of adaptation to the B cell physiology.
2. The BCR-mimic LMP2A expression, observed in EBV + Hodgkin/Reed-Sternberg (HRS) cells, is believed to be accountable for the rescue of B cell receptor (BCR)-deficient germinal center B cells by EBV. The reason for this is that LMP2A is also present in cells that express EBV + HRS. The potential contribution of EBV LMP2A to the pathogenesis of HL may involve its involvement in the early stages of lymphomagenesis.
3. The transcription factor known as NF-κB is significantly involved in the preservation of HRS precursor cells. EBV-positive Hodgkin's lymphoma is characterized by a latency II gene expression program, which entails the transcription of EBNA1, LMP1, and LMP2A. The LMP1 protein imitates the behavior of a CD40 receptor that is always active, resulting in a potent stimulation of NF-κB. This protein is believed to be accountable for the persistent expression of NF-κB in cases of Hodgkin's lymphoma that are positive for the Epstein-Barr virus.

EBV-positive hemophagocytic lymphohistiocytosis (HLH)

EBV can cause hemophagocytic lymphohistiocytosis (HLH) by stimulating B cells to trigger over production of cytokines and histolytic cell stimulation. Chronic EBV stimulation can also lead to chronic HLH. EBV can also cause T cell and natural killer (NK) cell generation, leading to the production of cytokines IL2, INFa, and IL6 which may be responsible for HLH [25]. Additionally, EBV can stimulate membrane protein (LMP-1) in cells, leading to INFa secretion and macrophages, similar to XLP, causing acquired immune deficiency and HLH [25].

Systemic EBV-positive T-cell lymphoma of childhood

The cause of systemic EBV-positive T-cell lymphoma of childhood remains unidentified. Nonetheless, the correlation of the previously mentioned phenomenon with initial EBV infection and marked racial susceptibility implies a hereditary anomaly in the host's immune reaction to EBV [26]. The T cells that are infiltrating exhibit monoclonal rearrangements of the T-cell receptor (TCR) genes [26].

Extranodal NK/T-cell lymphoma, nasal type

It is unclear how EBV infection causes extranodal NK/T-cell lymphoma. It's hypothesized that human SINE, LINE, and satellite repeat families incorporate its genomic fragment [27]. By integrating its genomic fragment into its intron, EBV downregulates human non-homologous end-joining factor (NHEJ) 1, which repairs double-stranded breaks. It's believed that extranodal NK/T-cell lymphoma causes genome-wide instability [17]. EBNA1, LMP1, LMP2A, and LMP2B (latency phase II) modulate cell signaling and block apoptotic signals to avoid T-cell-mediated immune response [27]. In extranodal NK/T-cell lymphoma, highly transcribed EBV BART RNAs may cause disease and immune evasion [27].

Aggressive NK-cell leukemia (ANKL)

According to certain reports, cases of aggressive NK-cell leukemia (ANKL) that are positive for EBV exhibit positivity for EBER and negativity for LMP-1, indicating a type I latency pattern of infection [28]. The observed latency pattern is thought to confer a benefit to neoplastic NK cells, as it allows them to avoid recognition and subsequent elimination by virus-specific cytotoxic T cells of the host [28].

Primary EBV-positive nodal T-cell or NK-cell lymphoma (Nodal TNKL)

The molecular mechanisms underlying nodal TNKL remain unclear due to the lack of significant enrichment in pathways commonly implicated in tumor development, such as apoptosis, cell adhesion, and proliferation. The investigation conducted by Siok-Bian Ng (2018) [29] entailed the characterization of gene expression in 19 cases of nodal TNKL, with 12 of these cases undergoing copy number analysis. Their research demonstrated an increase in gene sets linked to the JAK/STAT3 signaling pathway [29]. Also, their findings indicated that the activation of the oncogenic pathway was attributed to the activation mutations of JAK3 and the phosphorylation of STAT3. The observation of nodal TNKL displaying an enrichment of gene sets linked to the cell cycle and genomic instability is significant [29].

Hepatitis B virus

The Hepatitis B virus (HBV) belongs to the Hepadnaviridae family and possesses the characteristics of a double-stranded, enveloped, and coated DNA virus. This virus is known to induce both chronic and acute hepatitis, with a particular predilection for the liver [30]. The HBV comprises crucial components, including the hepatitis B surface antigen (HBsAg), the hepatitis B e antigen (HBeAg), and the hepatitis B core antigen (HBcAg) [30]. The virion is composed of a lipoprotein envelope derived from host cells, which encloses the nucleocapsid that contains the viral DNA and hepatitis B surface proteins [30]. The HBcAg is recognized as an icosahedral structure comprising of 240 core protein subunits, which constitute the nucleocapsid [30]. The HBeAg is a soluble antigen that is actively produced from the identical open reading frame as HBcAg. Its presence is indicative of ongoing viral replication [30]. The replication of HBV occurs through the process of reverse transcription of an RNA intermediate by DNA polymerase [30]. However, the lack of proofreading during this process leads to frequent mutations, which in turn results in a high degree of resistance to treatment [30].

The predominant mode of hepatitis B transmission is via exposure to contaminated bodily fluids and blood of an infected individual. Vertical transmission, which occurs from a mother to a neonate, and horizontal transmission, which takes place between children or from a mother to a child, are the prevailing modes of transmission. In nations where sterilization procedures are insufficient or sterile equipment is not readily available, the inappropriate sterilization of medical instruments and the utilization of tainted blood products persist as prevalent modes of transmission. The escalation of the worldwide opioid crisis has resulted in a rise in intravenous drug consumption as a noteworthy avenue for transmission. Finally, participation in sexual practices with multiple partners, irrespective of gender, and male-to-male sexual encounters continue to be significant avenues for the transmission of hepatitis B [31, 32].

Clinical and hematologic manifestation of HBV infection

The manifestation of acute hepatitis B is marked by the abrupt onset of symptoms including fever, headache, malaise, anorexia, nausea, vomiting, diarrhea, and abdominal pain [33]. This is accompanied by an elevation in serum ALT levels and the detection of HBsAg and HBcAg [33]. The diagnosis of chronic hepatitis B infection

necessitates a thorough assessment that includes a detailed medical history, physical examination, and evaluation for indications of cirrhosis [33]. Additionally, it is important to evaluate an individual's alcohol consumption, metabolic risk factors, hepatitis A and B vaccination status, and family history of hepatocellular carcinoma (HCC) [33]. The replication of HBV DNA occurs via the process of reverse transcription, which involves the conversion of an RNA intermediate [34]. In the context of viral infection, it has been observed that the HBV DNA undergoes a transformation from a relaxed circular, partially double-stranded configuration to a circular covalently closed DNA (cccDNA) that functions as a transcriptional template [35]. HBV is responsible for encoding four distinct open reading frames (ORFs), which are identified as the surface, precore/core, polymerase, and X [35]. The production of three surface antigen proteins (small, middle, and large) is facilitated by the surface ORF, whereas the nucleocapsid protein (HBcAg) and the HBeAg protein, which is responsible for evading the host's immune system, are produced by the precore/core ORF [35]. Furthermore, the polymerase open reading frame (ORF) is accountable for the duplication of viral DNA via the operation of reverse transcriptase, Ribonuclease H (RNaseH), and a protein primer [35]. The X ORF ultimately generates the X protein, which serves as a crucial factor in both viral infection and replication [35]. The X protein is known to aid in transcription and promote the expression of genes associated with inflammation, proliferation, immune response, and oncogenesis [35].

There are four possible phases of chronic hepatitis B (CHB), as follows [36]:

1. During the immune-tolerant phase, individuals exhibit high levels of HBV DNA, normal ALT levels (less than 19 U/L for females and less than 30 U/L for males), and liver biopsies reveal no notable inflammation. The duration of this phase is highly variable. The duration of this phase is prolonged in individuals who acquired the virus through perinatal transmission. The process of transitioning from the immune-tolerant phase to the HBeAg-positive immune-active phase is influenced by age.
2. The immune-active phase of HBeAg positivity is distinguished by heightened levels of ALT and HBV DNA, in addition to hepatic impairment. Individuals who contract the infection at a young age typically experience a median age of onset of 30 years. The transition from the HBeAg-positive immune-active phase to the HBeAg-negative immune-inactive phase is characterized by the occurrence of HBeAg seroconversion. The incidence of autonomous seroconversion is comparatively lower in pediatric patients aged below three years, but it escalates during the pubertal phase and is significantly elevated in the adult population.
3. The inactive phase of chronic hepatitis B is characterized by the presence of low or undetectable levels of hepatitis B virus DNA, normal levels of alanine ALT, and the presence of anti-HBe. The liver tissue exhibits a moderate level of necroinflammation, with varying degrees of fibrosis observed based on the extent of liver injury sustained during the HBeAg-positive immune-active phase. The findings indicate that a significant proportion of individuals who undergo spontaneous HBeAg seroconversion remain in this phase, ranging from 67 to 80%. Conversely, a minority of inactive carriers, ranging from 4 to 20%, experience a reversion to HBeAg positive status at least once.
4. The HBeAg-negative immune reactivation phase is applicable to those who have progressed from the HBeAg-positive to HBeAg-negative stages. This phase is observed in approximately 10%-30% of cases and is marked by elevated ALT and high HBV DNA levels. The potential for chronicity arises due to mutations in the precore/core promoter genes of the HBV. Individuals in this particular stage often experience a variable trajectory.

Previous studies have identified hepatitis B virus reactivation (HBVr) through the examination of antibody titers for HBsAg and anti-HBs [37]. The emergence of quantitative tests for HBV DNA has facilitated the identification of HBVr, which is characterized by the manifestation of hepatitis symptoms and the elevation of HBV DNA levels in patients undergoing immune-suppressive therapies [37]. One of the prevalent techniques for detecting HBVr is through the monitoring of serum ALT [37]. It is typical for ALT levels to experience an elevation of 2–3 weeks prior to the manifestation of a comparable increase in HBV DNA [37].

HBV infection and identified associated hematologic malignancies

During a meeting convened in Taormina, a group of experts delineated occult HBV infection (OBI) as the detection of HBV DNA in the liver (with or without detectable HBV DNA in the serum) among individuals who exhibit negative results for HBsAg [38]. Individuals who were diagnosed with OBI had the potential to transmit the virus through procedures such as blood transfusions and liver transplants. According to the findings, the utilization of OBI has the potential to worsen the advancement of liver fibrosis in patients afflicted with chronic HCV infection. Additionally, it may incite reactivation in patients undergoing immunosuppressive therapy. In addition, due to the ability of HBV to integrate into the host genome and generate proteins that

promote cancer, OBI may play a role in the pathogenesis of hepatocellular carcinoma [39]. Furthermore, it has been postulated that OBI may have an impact on the progression of non-Hodgkin lymphoma and intrahepatic cholangiocarcinoma [40, 41].

Around two billion people exhibit indications of a prior HBV infection and may possess the potential to be carriers of OBI. The association between OBI and heightened susceptibility to lymphoproliferative disorders has recently gained greater clarity [42].

An investigation involved a sample of 240 participants, comprising three groups of 80 individuals each, namely those diagnosed with multiple myeloma (MM), chronic lymphocytic leukemia (CLL), and healthy controls. The results of the study revealed a significant correlation between CLL and OBI, while no such association was observed between OBI and the other two groups. According to the findings of the study, chronic lymphocytic leukemia exhibits an odds ratio of 4.6 (95% CI 1.5–13.9) in relation to the presence of occult hepatitis B infection, as compared to both multiple myeloma and healthy control groups. Remarkably, a majority of 55 percent (44 out of 80) of patients belonging to the CLL cohort exhibited indications of HBV DNA in peripheral blood mononuclear cell (PBMC) [43].

Hepatitis C virus

The Hepatitis C virus (HCV) is an RNA virus that belongs to the Flaviviridae family. It has one serotype, but there are at least six main genotypes and over 80 subtypes [44]. Chronic hepatitis C virus infection is a contagious disease transmitted through blood. It has affected around 3.2 million people in the United States and approximately 3% of the world's population [45].

Clinical and hematologic manifestation of HCV infection

HCV is a virus that primarily affects the liver. However, chronic HCV infection can lead to widespread health problems, with up to 74% of patients experiencing additional symptoms outside of the liver [46]. These symptoms can occur well before the advanced stage of liver disease and include general symptoms like nausea, fatigue, pain in the abdomen or muscles, weight loss, and mental symptoms like depression and irritability. There are also more specific signs like lymphoproliferative disorders, cryoglobulinemia vasculitis, stroke, cardiovascular events, type II diabetes, and kidney disease [47]. These conditions occurring outside the liver can result in elevated mortality rates. As an example, in a study conducted by Lee et al. (2012) [48], a total of 1095 patients who tested positive for HCV antibody (AB) were monitored for an average of 16 years. The study found that HCV AB seropositivity was linked to higher mortality rates from non-liver-related diseases. Over an 18-year period, the cumulative mortality rate from extrahepatic diseases was 19.8% among individuals with HCV AB, compared to 12.2% and 11% among those who never contracted HCV and those who naturally cleared their HCV infection, respectively.

HCV is linked to various hematological manifestations, primarily cytopenias, such as anemia, thrombocytopenia, and neutropenia. Anemia linked to HCV infection is frequently attributed to the administration of peg-interferon and ribavirin during HCV treatment [49]. Nevertheless, it has also been observed in patients who have not received any prior treatment [45]. Additionally, neutropenia frequently occurs in patients infected with HCV who are undergoing antiviral treatment, and this can lead to a decrease in dosage or the discontinuation of peg-interferon therapy [49].

HCV infection and identified associated hematologic malignancies

The correlation between HCV infection and lymphoma, specifically non-Hodgkin (NHL) B-cell lymphoma, has been thoroughly researched and is the most extensively studied subject in relation to HCV infection and malignancies outside the liver. There is a strong correlation between HCV infection and NHL in regions with a high prevalence of HCV infection, such as Southern Europe and Asian countries. Nevertheless, in regions characterized by a low incidence of HCV infection, such as Canada and France, the correlation was not statistically significant [50]. Kang et al. (2010) [51] found a remarkable correlation between HCV infection and certain lymphoma subtypes, including peripheral T cell lymphoma, extranodal marginal zone B-cell lymphoma, and diffuse large B cell lymphoma. Nevertheless, the association between HCV and less prevalent subtypes of lymphoma remains unclear due to the scarcity of HCV-positive cases and the infrequency of these subtypes [51]. Prior studies have shown that HCV seropositivity is more strongly linked to extranodal NHL or specific sites of involvement, such as the liver, rather than nodal NHL. The present findings suggest that the relative risks for extranodal NHL are marginally greater than those for nodal NHL. However, it is important to note that this disparity is mainly attributed to previous investigations. Some reports have indicated that the association between HCV and NHL may only apply to specific histologic subtypes of NHL [52]. A meta-analysis of epidemiological studies found no evidence to support the previous hypothesis that the risk ratios for HCV differ depending on the subtype of NHL. The analysis identified key factors that influenced the variations among the studies, such as the incorporation of age and sex as variables, the study's design, and the geographic location. The heterogeneity in the results across studies may be attributed to the different definitions of

HCV infection. Several studies have provided varying definitions, with some defining it solely as the presence of HCV antibodies, while others have included the identification of both HCV antibodies and RNA. Most studies regarded either of these markers as indicative of HCV positivity [52]. The precise etiology of lymphoproliferative diseases in HCV infection remains unclear despite the existence of multiple theories. According to a proposed theory, the continuous existence of the virus in the immune system results in the proliferation of identical B-cells. This theory is substantiated by evidence indicating that the predominant NHL cells in patients infected with HCV exhibit similarities to germinal and post-germinal center B-cells. Furthermore, patients who are positive for HCV and have B-cell non-Hodgkin lymphoma (NHL) show specific genetic changes, indicating the influence of antigenic selection. The viral envelop protein E2 triggers the stimulation of antigens by interacting with the CD81 receptor which can be found on hepatocytes, T-lymphocytes, and B-lymphocytes. CD19, along with CD21 and CD81, facilitates the transmission of activating signals that reduce the threshold of stimulation required for B-cells to respond to antigens. Alternative hypotheses propose that HCV infection triggers destruction of DNA and gene mutations, while concurrently inhibiting apoptosis in infected lymphocytes. The NS3 proteins and viral core induce the expression of the inducible nitric oxide synthase gene, resulting in the production of nitric oxide. This can subsequently lead to the occurrence of double-stranded DNA breaks and DNA mutations. HCV infection has been demonstrated to cause enzymatic changes, leading to the creation of double-stranded DNA breaks, an elevation in mutations of immunoglobulin heavy chains, and mutations in genes that suppress tumor growth and genes that promote tumor growth, such as p-53, bcl-6, myc, and beta-catenin genes, in B cell lines infected with HCV. Amplification of mutated proto-oncogenes has been observed in lymphomas associated with HCV infection. In addition, the mutation of immunoglobulin heavy chains can diminish the immune response to the viral infection. Lymphocytes infected with HCV also undergo chromosomal translocation t(18;14), leading to the excessive expression of the bcl-2 oncogene, which hinders programmed cell death. The development of B-cell lymphoma can be attributed to the combined impact of inhibition of apoptosis, diminished immune response to the viral infection, amplification of proto-oncogenes, and mutation of tumor suppressor genes [45].

Human immunodeficiency virus

In order to comprehend the correlation between human immunodeficiency virus (HIV) disease and hematological malignancies, it is imperative to initially contextualize the current knowledge regarding the HIV disease and its immunological impacts. The etiology of HIV disease involves the retroviral infection of a human host, which is primarily transmitted via blood or unprotected sexual contact. This results in a gradual deterioration of the immune system, leading to a heightened susceptibility to opportunistic infections and malignancies [53]. Upon entering a susceptible host, the virus utilizes its viral envelope spikes, which are comprised of viral protein trimers, to bind to the CD4-positive (CD4þ) receptor and chemokine receptor-5, a coreceptor of immune system cells, specifically T-helper cells. This binding process facilitates the virus' entry into the cells via membrane fusion, following transmission through sexual contact or blood [54]. The dysregulation of oncogenic viruses and molecular alterations linked to malignant transformations in AIDS are attributed to the immune system's mechanism [55].

Clinical and hematologic manifestation of HIV infection

The human immunodeficiency virus (HIV) has the potential to impact all bodily systems. The onset of acute viral syndrome typically occurs within a timeframe of 2–4 weeks following the initial exposure to the Human Immunodeficiency Virus (HIV) [56]. The duration of the illness that is linked with acute infection is typically 10 days [56]. The symptoms of fever and myalgias were frequently observed at a rate of 94% and 60%, respectively. Additionally, fatigue, pharyngitis, weight loss, and headache were also commonly reported, with rates of 90%, 72%, 70%, and 55%, respectively [56]. The infection of HIV is linked to several disruptions in metabolic function, particularly hyperlipidemia, lipodystrophy or lipoatrophy causing body fat redistribution, hyperglycemia, insulin resistance, and lactic acidosis. During the progression of their illness, a minimum of 90% of individuals who are afflicted with HIV will experience at least one manifestation in the oral cavity. Ocular diseases are prevalent indications of HIV infection, exhibiting a diverse range of etiologies that span from a harmless HIV retinopathy to severe viral opportunistic infections that pose a risk to vision. Dermatological conditions manifest with high frequency among individuals infected with HIV. The pulmonary symptoms of HIV infection may be categorized into three primary categories: malignant, infectious, and noninfectious. Cardiac abnormalities are prevalent in approximately 70% of individuals who have contracted HIV.

Hematologic irregularities represent a prevalent indication of progressed HIV infection and acquired immunodeficiency syndrome (AIDS). Cytopenias are the most frequent of these abnormalities [57]. The incidence of cytopenia is infrequent during the initial phases of HIV infection, however, the prevalence and intensity of cytopenia escalate during the later stages of the ailment [56].

The most prevalent form of cytopenia is anemia. The predominant manifestation of anemia in individuals with AIDS shares the features of anemia associated with chronic diseases. A study reported that the average hemoglobin levels of individuals diagnosed with AIDS were found to be within the range of 9 to 10 g/dL, which is consistent with other types of anemia that are associated with chronic diseases. The erythrocytes exhibit normochromia and normocytosis, often accompanied by anisocytosis [57].

During the initial stages of the AIDS epidemic, thrombocytopenia was identified as a symptom of HIV infection among individuals who were HIV-seropositive homosexuals and intravenous drug abusers. The patients exhibited clinical manifestations and therapeutic outcomes that were akin to those observed in individuals with conventional autoimmune thrombocytopenic purpura [57]. The correlation between advanced age and reduced CD4 + T-cell counts is a more prevalent association [56].

The prevalence of neutropenia is high in the advanced phases of AIDS and is frequently induced or intensified by concurrent myelosuppressive pharmacotherapy. The primary etiology of neutropenia in progressive AIDS is the inhibition of bone marrow progenitor cells [57].

An indication of AIDS is the presence of polyclonal hypergammaglobulinemia, which is characterized by elevated levels of IgA, IgG, and IgM [57] The sustained polyclonal activation of B-cells is the underlying cause of hypergammaglobulinemia, which is observed to be parallel to generalized lymphadenopathy [58].

HIV infection and identified associated hematologic malignancies

HIV is associated with an excess cancer risk [59]. Lymphomas are a commonly occurring type of cancer in individuals who have contracted the HIV. Individuals who are HIV-positive or have AIDS are more susceptible to Hodgkin and non-Hodgkin lymphoma in comparison to those who are HIV-negative [60]. The frequency of various lymphomas, such as Burkitt lymphoma, primary effusion lymphomas, and plasmablastic lymphoma of the oral cavity, has remained constant [61]. However, there has been a rise in the occurrence of multicentric Castleman disease associated with Kaposi sarcoma-associated herpesvirus (KSHV) [61]. Multicentric Castleman disease is a developing condition that precedes the growth of high-grade B-cell lymphoproliferation in individuals with HIV, particularly those who are undergoing long-term combination antiretroviral therapy and have well-managed HIV [60]. Despite not being a neoplastic condition, it poses a potential risk for the development of neoplastic high-grade B-cell lymphoproliferation in this population [60]. The employment of combination antiretroviral therapy has significantly decreased the hazards associated with diffuse large B-cell lymphoma, primary CNS lymphoma, and Burkitt lymphoma, and to a minor degree, Hodgkin lymphoma [60].

The available data regarding the potential risk of developing multiple myeloma or leukemia is characterized by inconsistencies and low quality [60]. However, the evidence suggests that there is no significant increase in risk [60]. The utilization of combination antiretroviral therapy does not exhibit any impact on the incidence or progression of multiple myeloma or leukemia [60].

The susceptibility to lymphoid neoplasm is influenced by the immunologic status [59]. The role of immunological risk in the onset of lymphoid cancer is intricate and subject to variation based on the specific type of tumor [59]. The favorable modulation of immunologic status by combination antiretroviral therapy (cART) seems to account for the altered epidemiology and clinical outcomes of these tumors in the context of HIV infection [59].

Non-Hodgkin lymphoma (NHL), also referred to as AIDS-related lymphoma (ARL), is a medical condition categorized as an AIDS-defining illness [56]. It is commonly observed in individuals with advanced immunosuppression, characterized by a CD4 + T-cell count of less than 150 cells/mm3 [56]. Moreover, a CD4 + T-cell count that approaches less than 50 cells/mm3 is associated with an increased risk of developing CNS lymphoma [56]. The predominant type of ARL is derived from B-cells and is characterized by a high-to-intermediate grade, displaying an undifferentiated diffuse large cell, small cell (Burkitt and Burkitt-like) histology, or immunoblastic large cell [56].

Human T-lymphotropic virus 1

Human T Cell lymphotropic viruses, also known as HTLVs, a group of retroviruses, can lead to the development of adult T-cell leukemia/lymphoma or ATLL in 5% of those infected. [62, 63]. HTLV-1, one of the four types of HTLV, was first identified in the early 1980s by two separate research teams in the United States and Japan [64]. The World Health Organization (WHO) estimates that 5–10 million individuals worldwide are infected with HTLV-1, however the actual number is likely greater due to insufficient data [65].

Clinical and hematologic manifestation of HTLV-1 infection

Individuals infected with HTLV-I are susceptible to experiencing symptoms such as hand and foot numbness, arm and leg weakness, frequent nighttime urination, joint pain, bleeding gums, and erectile dysfunction [66]. HTLV-I-infected patients may also experience xerostomia, dry eyes, sore eyes, shortness of breath, and cough as additional symptoms [66].

In paraclinical settings, Ribeiro et al. found that HTLV-1-infected patients show no significant change in the total number of leukocytes and lymphocytes. However, the presence of atypical lymphocytes in HTLV-1-infected lymphocytes is significantly higher compared to non-infected lymphocytes [67]. Platelet count was shown to be irrelevant in relation to HTLV-1 infection according to their findings [67].

HTLV-1 infection and identified associated hematologic malignancies

As mentioned before, HTLV-1 primarily causes ATLL. HTLV-1 infection typically occurs through the transfer of infected lymphocytes, although it has been shown that free virus particles can also infect dendritic cells [68]. Upon infection, CD4 + cells secrete CCL22, a ligand for CCR4, which then attracts CD4 cells expressing CCR4, known as the virological synapse This strategy enhances the selective spread of HTLV-1 within a specific group of CCR4 + CD4 + T cells [69].

Another defining trait of HTLV-1 is its notable genetic stability, maintained through its replication process [70]. When the HTLV-1 genome enters the cell, it undergoes reverse transcription, which integrates the DNA product into the host genome. Then the virus can proliferate in two ways: infectious replication, in which the integrated provirus generates a new intracellular virion, and mitotic division, in which the integrated provirus replicates. Viral replication is inextricably related to host cellular reproduction, rather than independent viral DNA polymerase [71]. This results in a modest viral replication rate yet with accurate transcription. The outcome is a genetically stable product, distinct from HIV, and immunological escape resistant [72]. HTLV-1 can control its own transcription, leading to the temporary expression of gene products that could help it avoid the host's immunological response [73]. Two regulatory proteins involved are Tax, which promotes transcription, and Rex, which suppresses transcription [74]. Integration of the provirus and translation of viral proteins is connected with cellular proliferation and increased survival, hence imparting viral protection. HTLV-1 infection does not cause cell death, unlike HIV. Instead, T cells avoid apoptosis and convert easily [75].

Severe acute respiratory syndrome coronavirus type 2

Clinical and hematologic manifestation of SARS-CoV2 infection

The prevalent clinical presentations of SARS-CoV2 infection comprise pyrexia, cough, dyspnea, and exhaustion. Frequently encountered hematologic observations encompass the presence of anemia, thrombocytopenia, leukopenia, and lymphopenia. Individuals diagnosed with hematologic malignancies are susceptible to heightened susceptibility to severe complications arising from SARS-CoV2 infection, including sepsis and acute respiratory distress syndrome (ARDS).

SARS-CoV2 infection and identified associated hematologic malignancies

The immune response triggered by the COVID-19 infection is coordinated by proinflammatory cytokines, including but not limited to TNF-α, IL-1, IL-6, and IL-8. Cytokines have been identified as drivers of tumorigenesis [76]. The COVID-19 disease has been linked to the activation of oncogenic pathways such as MAPK, JAK-STAT, and NF-κB, which may pose a potential risk for the development of cancer [77]. Furthermore, it has been frequently observed that individuals with COVID-19 exhibit low-grade inflammation, prompting inquiries into the potential correlation between COVID-19, specifically long COVID-19, and an elevated susceptibility to cancer [78].

The renin-angiotensin system (RAS) is known to have a noteworthy association with SARS-CoV-2. The role of the RAS in neoplastic hematopoiesis has been proposed [79]. According to in vitro studies, the imbalance of the renin-angiotensin system (RAS) caused by the SARS-CoV-2 virus may have the potential to facilitate the development of leukemia [80]. Angiotensin II (Ang-II), a component of the renin-angiotensin system (RAS), has been discovered to act as a growth factor for acute myeloid leukemia (AML) cells in an autocrine mechanism [80]. This phenomenon can be impeded by the administration of losartan, thereby suggesting that it is facilitated via the angiotensin II receptor type 1 (AT1R) receptor [80]. Furthermore, the signaling of AT1R has the potential to enhance pro-survival and anti-apoptotic signaling in neoplastic cells [80]. Numerous studies have demonstrated that the administration of captopril, trandolapril, losartan, and telmisartan can induce apoptosis in leukemic myeloid cell lines and adult T-cell leukemia cells [80]. Furthermore, the co-administration of losartan and doxorubicin resulted in an augmentation of the drug's antineoplastic properties [80]. Thus, the local bone marrow RAS imbalance induced by SARS-CoV-2 infection may be linked to the development of hematologic malignancies in some infected individuals. It is crucial to conduct more research to determine if a direct association between the two conditions exists.

Individuals diagnosed with hematologic malignancies exhibit a greater susceptibility to the development of severe COVID-19 illness, increased mortality rates, and heightened viral shedding in comparison to other

populations with compromised immune systems [81]. The heightened susceptibility is predominantly ascribed to the immunomodulatory impact of hematopoietic malignancy [81]. The heightened susceptibility can be attributed significantly to the impairment of both humoral and cellular immunity [81]. It is worth noting that COVID-19-specific evaluation of the prevalent treatments for hematological malignancies in this demographic has yet to be conducted [81]. The examination of individuals with hematologic malignancies has yielded significant understanding regarding the immunopathogenesis of COVID-19, and it is recommended that they be incorporated in forthcoming randomized controlled trials investigating therapeutic interventions for COVID-19 [81].

Based on the cited research, there is currently no established causal relationship between the incidence of cancer and contracting COVID-19. The theories mentioned above claim that individuals who have undergone severe illness are more prone to developing cancer, particularly hematologic cancers, in the future. The progression of cancer is a prolonged phenomenon, and substantiating these hypotheses will require a considerable duration.

Conclusion

The correlation between viral infections and hematological cancers is intricate and diverse. Several viruses, including hepatitis B virus, Epstein-Barr virus, hepatitis C virus, human immunodeficiency virus, human T-lymphotropic virus 1, and SARS-CoV2, have been associated with different types of blood cancers. The viruses exhibit diverse infection processes, pathogenesis, and clinical manifestations. However, they collectively contribute to the onset of cancer in susceptible individuals.

Gaining a comprehensive understanding of these relationships is important for the formulation and implementation of efficacious prevention and treatment strategies. This knowledge can assist clinicians in delivering precise therapies and overseeing the detection of potential complications in patients with viral infections and hematological cancers. Research on viral infections and their connection to hematological cancers is progressing, yielding important knowledge about the development of these diseases and guiding the creation of successful methods for prevention and treatment.

Author contributions All authors contributed to the study conception and design. The first draft of the manuscript was written by all the authors and reviewed and edited by Arian Haghtalab, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding The authors have not disclosed any funding.

Data availability No datasets were generated or analyzed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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