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Hematological Cancer and Viral Infection

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Abstract

Hematological cancer patients are particularly vulnerable to the morbidity and death caused by viral infections. But, it is not well known how common viral infections are or what effects they have on patients undergoing traditional nontransplant treatment. How severe and how long T-cell-mediated immune suppression is determines the variation in viral infection incidence and prognosis between patient groups. Topics covered in this mini-review article include late CMV infection, new viral pathogens (human herpesvirus-6, BK virus, adenovirus, and human metapneumovirus), advancements in molecular diagnostics, and the possibility of novel agents for viral prophylaxis (maribavir) or preemptive therapy (valganciclovir). The infections caused by these viruses have been extensively studied. If we want to understand the range of these viral diseases and come up with effective ways to prevent and cure them, we need well-designed prospective trials. Patients undergoing nontransplant treatment for hematological malignancies are at greater risk for viral infections; this is especially important given the rising use of drugs like alemtuzumab, which cause significant T-cell depletion.

Keywords: Hematological Cancer; Viral Infection; Morbidity; Death

Abbreviations

HHV6: Human Haematopoietic Virus 6; GVHD: Graft Versus Host Disease; HD: Hodgkin's Lymphoma Disease; HRS: Hodgkin Reed-Sternberg cells; HSV: Herpes Simplex Virus; ALL: Acute Lymphoblastic Leukaemia; CML: Chronic Myeloid Leukaemia; CLL: Chronic Lymphocytic Leukaemia; PCR: Polymerase Chain Reaction.

Introduction

Patients with a hematological malignancy are at increased risk of viral infections, which can lead to serious complications or even death. However, our understanding of how often and what effects these infections have on patients on traditional nontransplant treatment is lacking. Although T-cell-mediated immune suppression determines

the frequency and severity of viral infections in different patient groups, immune dysfunction can occur in allogeneic transplant recipients depending on factors such as stem cell product, donor-recipient matching, conditioning regimen composition, and the severity of graft-versus-host disease (GVHD). The symptoms of infections caused by influenza, herpes simplex virus, varicella-zoster, respiratory syncytial virus, parainfluenza, and cytomegalovirus are well-known. Emergence of new viral pathogens (such as human herpesvirus-6, BK virus, adenovirus, and human metapneumovirus), as well as advances in diagnostics and treatment, necessitate this Wade JC, et al. [1-3].

The current article will focus on the main viruses that cause infection among hematological cancer patients.

Study Design

The current article is a mini review that primarily focuses on viruses that cause infection among hematological cancer patients, encompassing all studies that address this topic.

Results

Herpesviruses

The herpesviruses are a big family of double-stranded DNA viruses that have distinct biologic characteristics that allow them to enter a dormant state in humans after initial infection and then reactivate at a later time. In terms of taxonomy, nine herpesviruses in humans are classified into three subfamilies: alpha-, beta-, and gamma-herpes-viridiae. Chronic latent and relapsing infections are mostly caused by four herpesviruses: CMV, EBV, HHV6B, and VZV. These patients are among the most seriously immunocompromised and often get allo-HCT from unrelated or mismatched donors. There has been no evidence that HHV-6A virus is harmful thus far [4].

Human Herpesvirus 6 (HHV-6) and Hematological Cancer

In 1986, it was shown that patients with lymph proliferative diseases have human herpesvirus 6 (HHV6). HHV6 belongs to the β-subfamily of herpes viruses. Two main subgroups, HHV-6A and HHV-6B, are used to categorise it. Before becoming two years old, the vast majority of youngsters develop an infection from either grouping A or subgroup B. For HHV-6A, no specific illness has been identified. Exanthema subitum (rose-ola) meningitis, meningoencephalitis, and hepatitis are all caused by HHV-6B. Human haematopoietic virus 6 (HHV6) replicates in cells called CD4+T lymphocytes. Following a first infection, the human herpesvirus 6 can enter a dormant and chronic infection state. It is possible for HHV-6A and HHV-6B to merge their genomes with those of the host. The HHV-6 genes code for the transforming transactivation protein pDR7. In addition to potentially contributing to tumour genesis, the other protein pU94 was discovered to inhibit Ras-induced transformation. Lymphoma, carcinoma, acute lymphoblastic leukaemia, and non-Hodgkin's lymphoma are among the malignant illnesses linked to HHV-6. The presence of extremely large Hodgkin Reed-Sternberg cells (HRS) is a histological hallmark of Hodgkin's lymphoma disease (HD), a prevalent malignant tumour of germinal centre B-cell origin around the globe [5,6].

Herpes Simplex Virus (HSV) and Hematological Cancer

Nearly of herpes simplex virus infections in people with blood cancer are reactivation infections. They occur often; for example, 15% of CLL patients using fludarabine and 90% of those with acute leukaemia or who have received a stem cell transplant are affected. Early infection and disease with herpes simplex virus (HSV) happens after treatment and often returns with subsequent treatments. An unusual presentation is common in mucocutaneous herpes simplex virus (HSV) disease, which might resemble other infections (such as Candida) or treatment-induced mucositis. Immunocompromised patients often experience more invasive, delayed healing, prolonged viral shedding, and possible dissemination of herpes simplex virus infections [1,7].

Varicella-Zoster Virus (VZV) and Hematological Cancer

Varicella, more often known as chickenpox, and herpes zoster, or shingles, are both caused by the varicella-zoster virus (VZV). The disease-causing varicella virus does not reactivate, but the reactivating varicella zoster virus (VZV) does. Varicella is a harmless, self-limiting illness in well-developed youngsters, but it can cause serious complications or even death in children with impaired immune systems. The immune system is already compromised in children with acute lymphoblastic leukaemia (ALL), and chemotherapeutic medications like steroids, methotrexate, and 6-mercaptopurine can further lower the numbers of B lymphocytes, T lymphocytes, and total immunoglobulins, leaving them more susceptible to infection with VZV. With the improved accessibility of vaccines, the incidence of VZV infection in patients with ALL has reduced dramatically, according to 2 prior multicenter trials. Additionally, VZV's negative effect on ALL prognosis has diminished. Moreover, It is estimated that 2% of patients with chronic myeloid leukaemia (CML) who take imatinib mesylate will get varicella-zoster; 10-15% of patients with chronic lymphocytic

leukaemia (CLL) who take fludarabine or alemtuzumab will; 25% of patients with Hodgkin lymphoma or who receive an autologous stem cell transplant will; and 45-60% of patients who receive an allogeneic stem cell transplant will contract the disease [1,8].

Cytomegalovirus (CMV)

It is unclear whether CMV infection is associated with other malignancies that develop following transplantation. Among around 12,300 people who had solid organ transplants (SOTs) in a UK trial, researchers discovered no correlation between CMV recipient or donor status and the risk of malignancy after the transplant. Nevertheless, for a few results, the sample size was somewhat tiny. In the general population, CMV nucleic acids and proteins have been found in tumour samples from glioblastoma, colon, prostate, and breast malignancies. However, by activating T-cells during acute infection, CMV may indirectly protect transplant recipients from cancer growth, according to one study. An increased risk of acute lymphoblastic leukaemia (ALL), a frequent childhood cancer, has been associated with CMV infection in recent years. Newborn dried blood spot testing revealed the presence of CMV DNA in 9.7% of ALL cases compared to 3.0% of healthy controls in a population-based case-control study (odds ratio: 3.71).20 A second study that looked at data from Swedish registries discovered that haematological malignancies, such as ALL, were eleven times more likely to occur in those with a medically documented history of childhood CMV infection [9].

Adenovirus

It is well-documented that human adenoviruses can cause cancer in mammalian animal models, but the role that these viruses may play in human cancer is still unclear. Adenoviruses appear to be able to avoid immune surveillance while residing in a dormant state in lymphocytes after initial infection. Adenoviral sequences were systematically screened for in over 200 diagnostic specimens of various lymphoid malignancies, including acute lymphocytic leukaemia (n = 50), chronic lymphocytic leukaemia (n = 50), multiple myeloma (n = 11), and various types of malignant lymphomas (n = 100) in the study by Karin, et al. [10]. The researchers used a broad-spectrum adenovirus polymerase chain reaction (PCR) assay. Although the majority of entities evaluated showed negative results in almost all cases, adenoviral DNA was found in fifteen out of thirty-six (42%) mantle cell lymphomas that were examined. Adenoviral species C was found more frequently than B, which was less common. Some of the places where Adenovirus-positive results were found in individuals with mantle cell lymphoma were the intestine (n = 5), tonsillar tissue (n = 1), lymph nodes (n = 2), and bone marrow (n = 7). Individual cells were examined using fluorescence in-situ hybridisation (FISH) to validate the presence of adenoviral sequences that were detected by PCR. Curious about their potential role in the development of mantle cell lymphoma, adenoviruses have been found frequently in this lymphoid cancer [10].

Adenovirus infections have been found to be deadly in patients with B-cell lymphoma, multiple myeloma, and acute myeloid leukaemia, as described by James (2006). Transplantation from an unrelated donor, GVHD, T-cell depletion, total body irradiation, viremia, and younger patient age are all factors that increase the likelihood of infection and illness. Disease affects 5-8% of patients, while the reported prevalence of infection in stem cell recipients ranges from 5% to 29%. Reports indicate that between 30 and 50 percent of cases with viral illness result in mortality [1].

BK Virus

Over the last 30 years, there has been a steady accumulation of reports on the presence or lack of BKV sequences and proteins in human tumours. Recent developments in polymerase chain reaction (PCR) technology have enabled very sensitive DNA and RNA detection in very small biopsy samples, as well as the ability to differentiate BKV sequences from JCV and SV40 sequences. However, a PCR-based technique for viral sequence detection requires meticulous attention to detail. False positives caused by laboratory contamination become more likely when the number of PCR cycles is increased in an effort to create a more sensitive assay. Additionally, a tiny number of normal cells harbouring BKV in a tumour sample can cause the tumour to seem BKV-positive when PCR-based screens of biopsy samples evaluate a heterogeneous population of cells. Alternatively, methods such as in situ hybridisation (ISH), immunohistochemistry (IHC), Southern blotting, and in situ polymerase chain reaction (PCR) are being utilised, which are less prone to contamination. And to make sure researchers don't get false positives from normal BKV-infected cells nearby, in situ analysis helps pinpoint exactly where the virus resides in tissue sections. Many investigations have failed to resolve the ongoing controversy about BKV's potential involvement in human neoplasia. When it comes to human tumour tissues, there are conflicting data about the existence of BKV DNA and proteins.

Notably, Dilek et al brought up One of the key underlying conditions that might cause hemorrhagic cystitis (HC) in haematopoietic stem cell transplantation (HSCT) recipients is polyoma BK virus (BKV) infection or reactivation [11]. Nevertheless, infections linked to BKV can arise in extremely rare cases in patients with acute leukaemia who do not have HSCT. Here, they detail the cases of 12 children diagnosed

with acute leukaemia who contracted BKV while undergoing treatment for their disease. Results showed that Ten out of the twelve individuals tested positive for acute lymphoblastic leukaemia (ALL). Out of the 10 instances of ALL, 7 were T cell ALL. There were ten patients total, ten of them were male and all aged ten and up. Eleven individuals went through HC, and one person developed epididymitis. Between 470 and 1.3 trillion copies/mL was the range of BKV. Hydration, ciprofloxacin, and bladder irrigation were among the treatments administered to seven individuals. All patients showed improvement in their clinical condition, with the exception of one with refractory T cell ALL. According to their findings, BK virus infection can happen in children with acute leukaemia when they are receiving therapy, even though it is a serious problem with HSCT and solid organ transplantation. Male gender and advanced age appear to be risk factors in leukaemia patients, similar to those in HSCT recipients. T cell ALL patients may be at increased risk for BK virus activation due to the full depletion of virus specific T cells [11,12].

Respiratory Viruses

Infections pose a significant risk to the immunocompromised patient and are among the most important problems in cancer patients and those undergoing haematopoietic stem cell transplantation (HSCT). The lower respiratory tract infections (LRTIs) are associated with the greatest severity and fatality rates in this population, and infections affecting the respiratory system are common overall. In the context of haematological cancer patients, community-acquired respiratory viruses (CRVs) are an important cause of morbidity and death among the many etiological agents. Haematological patients are more likely to survive and recover because to advances in therapeutic interventions; yet, the widespread use of immunosuppressive medicines and chemotherapy has further raised the infective risk for these individuals. Biomolecular testing have allowed for the rapid and reliable detection of viral infections, removing a long-standing barrier to conducting epidemiological studies on the topic due to the lack of readily available, precise diagnostic tools. A rising number of research articles assessing the function of community-acquired viruses in the context of respiratory illnesses in immunosuppressed patients has likely contributed to the meteoric rise in the topic's profile. Given these facts, it's obvious that infections are still a common concern and, in some instances, the leading cause of mortality for these patients; so, it's crucial to find ways to avoid these complications [13].

Human Metapneumovirus (hMPV)

In healthy and immunocompromised individuals, human metapneumovirus (hMPV) causes upper respiratory tract infections (URIs) and lower respiratory infections (LRIs), respectively. However, the clinical burden of hMPV in cancer patients is unknown.

Human metapneumovirus infections in cancer patients may cause considerable morbidity, according to Firas and colleagues. This is particularly true for individuals with underlying haematologic malignancies, as they are more likely to acquire a lower respiratory infection. As with other respiratory viral infections, hMPV infection places a heavy strain on cancer patients. Death rates from hMPV infections are lower, nevertheless, compared to those from related viruses such respiratory syncytial virus (RSV). There needs to be strict surveillance for the possibility of LRI advancement in patients with haematologic malignancies (HMs), nosocomial infections, and hypoxia upon presentation. We should emphasise the importance of universal hand cleanliness and strict adherence to infection-control measures because hMPV can be acquired nosocomially, which can lead to worse outcomes and increased morbidity [1,14].

Conclusion

Since the advent of new molecular diagnostic tools, the range of viral infections that patients with haematological malignancy can contract has grown, and the rate of diagnosis has accelerated. To better understand the range of viral infections, illness risk factors, and how to prevent and cure them, well-designed prospective studies are required. To ensure that patients undergoing traditional T-cell-depleting therapy with drugs such as alemtuzumab get the most out of these treatments, clinical management guidelines are required.

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