

Hematopoietic Cell Transplantation and Emerging Viral Infections

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Viral infections remain important causes of morbidity and mortality in hematopoietic cell transplant recipients. More recent developments in preparative regimens and graft manipulations, as well as the control of well-recognized post-transplant infections by the introduction of prophylaxis and preemptive strategies, have influenced the timing and the epidemiology of infections. As new pathogens, such as human metapneumovirus (HMPV), human bocavirus, human coronaviruses HCoV-NL63 and HCoV-HKU1, human herpesviruses HHV-6 and HHV-7, and polyomaviruses, have emerged, it is fundamental to determine the significance of the newly discovered viruses and their role in the transplantation field. This article summarizes recent data on epidemiology and laboratory diagnosis of new pathogens, as well as clinical features and management of the associated infectious complications. *J. Med. Virol.* 82:528–538, 2010. © 2010 Wiley-Liss, Inc.

KEY WORDS: hematopoietic cell transplantation; infection; virus; laboratory diagnosis; treatment

INTRODUCTION

Transplantation of hematopoietic stem cells derived from three sources, bone marrow [Thomas et al., 1975a,b], peripheral blood [Schmitz et al., 1995], or umbilical cord blood [Gluckman et al., 1997], either autologous [Haurani, 1997] or allogeneic [Mathé et al., 1965], has been established over the years as a treatment of choice in a variety of hematological, malignant, or non-malignant diseases. Hematopoietic cell transplantation is defined as the intravenous infusion of progenitor hematopoietic cells, which are capable of establishing long-term, stable myeloid, hematological and immunological functions [Thomas and Blume, 1999]. In some disease entities, hematopoietic cell transplantation corrects the inherited or acquired deficiencies in the normal production of hematopoietic cells or in the immune function. In other cases, it rescues

hemopoiesis after high-dose chemoradiotherapy for malignancy or promotes powerful graft versus leukemia effect through adoptive immunotherapy [Mathé et al., 1965; Kolb et al., 1990].

The aggressive induction regimens utilized in hematopoietic cell transplantation may result in multiple organ toxicity; furthermore, prolonged time to engraftment and use of immunosuppression result in increased risk for bacterial, viral, and fungal infections [Frassoni et al., 1996]. Infection is the main cause of death after stem cell transplantation, especially after allogeneic transplant. Supportive care has been the major concern in order to diminish infectious complications. The use of growth factors for the rapid hemopoietic engraftment has reduced the aplastic phase and consequently the neutropenic febrile episodes [Hughes et al., 2002]. The occurrence of infectious complications roughly follows the pattern of immune reconstitution, which is highly influenced, after allogeneic transplantation, by acute or chronic graft versus host disease (GVHD) [Billingham, 1968]. The increasing use of alternative donors has led to intensified immunosuppressive regimens against acute and chronic GVHD, which further modified the timing of fungal and viral infections. Once a new approach in hematopoietic cell transplant is undertaken, new infectious complications can be observed [Cordonnier and Maury, 2007].

Since the first successful allogeneic transplant in 1968 in three children with severe combined immunodeficiency [Gatti et al., 1968], more than 800,000 patients have been transplanted worldwide. Today 50,000–60,000 patients undergo a type of transplant annually, whereas the registry of European Bone Marrow Transplantation reported that in 2007 there carried out 25,563 hematopoietic cell transplantations, 10,072 allogeneic (39%), 15,491 autologous (61%), and 3,606 additional

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TABLE I. Characteristics of Emerging Viral Infections in Hematopoietic Transplant Recipients

Virus	Incidence	Clinical manifestations	Laboratory diagnosis	Antiviral agents
HMPV (paramyxovirus)	Up to 5% in HCT recipients	URI, pneumonia	PCR techniques; culture/FA rapid culture: research	Ribavirin
HBoV (parvovirus)	Limited data; \approx 5% in immunocompromised patients	Limited data; fever, pneumonia	PCR techniques; culture: research	Not available
HCoV-NL63 HCoV-HKU1 (coronaviruses)	Limited data; 8.8% in immunocompromised patients	Limited data; pneumonia	PCR techniques; culture: research	Not available
HHV-6 (betaherpesvirus)	33–48% in HCT recipients	Skin rash, fever, acute GVHD, myelosuppression, pneumonitis, encephalitis	PCR techniques; antigen–antibody detection tests: available	Foscarnet, ganciclovir, cidofovir
HHV-7 (betaherpesvirus)	10–57% in HCT recipients	Limited data; GVHD, CNS disease	PCR techniques, antigen detection tests	Foscarnet, ganciclovir
BK virus (polyomavirus)	Viremia: 30% in HCT recipients	Hemorrhagic cystitis, nephropathy	PCR techniques, culture, electron microscopy, immunohistochemistry, cytology, histology	Cidofovir, leflunomide
JC virus (polyomavirus)	No data available	PML (14 cases in HCT recipients)	PCR techniques, histology	Cidofovir
KI virus/WU virus (polyomaviruses)	Limited data; KIV: 8%; WUV: 1% in immunocompromised patients	Respiratory pathogens?	PCR techniques	Not available

HMPV, human metapneumovirus; URI, upper respiratory infection; HCT, hematopoietic cell transplantation; FA, fluorescent antibody; PCR, polymerase chain reaction; HBoV, human bocavirus; HCoV, human coronavirus; HHV-6, human herpes virus-6; GVHD, graft versus host disease; HHV-7, human herpes virus-7; PML, progressive multifocal leukoencephalopathy, CNS; central nervous system.

transplantations in Europe. The main indications were leukemia in 8,061 cases (allogeneic transplants 89%) and lymphoma in 14,627 (89% autologous transplants) [Gratwohl et al., 2009].

The reasons for the global spread of hematopoietic cell transplantation are first the documented or potential efficacy in many disease entities, second the bigger pool of available donors through the alternative options of transplantation (i.e., related, haploidentical, or unrelated transplants and double cord blood transplants), and last the improved supportive care against bacterial, viral, and fungal infections which leads to reduced morbidity and mortality related to the method.

In 1970s, a new era with needs for unrelated donors was initiated as only 25% of the patients have the possibility of a sibling donor. In 1979, the first allogeneic transplant from an unrelated HLA compatible donor was performed [Hansen et al., 1980; Kaminski, 1989; Petersdorf et al., 1998]. Since then, the National Marrow Donor Program (NMDP) has been funded and by now, more than 12 million donors are available. Approximately 3,500 hematopoietic cell transplantations from unrelated donors are carried out annually, 40% of which involve donors from different countries.

An alternative option for a patient to be transplanted is the haploidentical related donor (i.e., with one shared haplotype) as having such a donor is 50% probable, which makes it always easily available. This type of transplant needs to be designed under certain conditions (a) post a highly intensified preparative regimen

and (b) infusion of a megadose of purified CD34 cells so as to avoid rejection and GVHD simultaneously. The major disadvantage of haploidentical transplants is the late immune reconstitution and the high cytomegalovirus (CMV) infection rate. In an effort to enhance immune reconstitution, scheduled genetic engineered donor lymphocyte infusions with herpes simplex virus thymidine kinase suicide gene are administered and can be destroyed by the drug ganciclovir, in the presence of GVHD [Bonini et al., 1997].

In 1989, another valuable graft source was recognized, the cord blood, which was initially used only in pediatric patients due to the limited number of cells [Gluckman et al., 1997]. The main advantages of the cord blood transplantation are: (1) the graft is ready for use as it is already prescreened for infections and HLA before cryopreservation and (2) it can be applied even in HLA disparity due to low immunogenicity. Nevertheless, there are disadvantages of the cord blood graft, which are as follows: (1) the low stem cell counts, prolonged neutropenia, and increase of infections and (2) the lack of access to donor lymphocyte infusions for the management of relapse. The transplantation of double cord blood units was demonstrated, by the team of Minnesota [Barker et al., 2003] to be effective and promising for adults with high body weight.

Since 1995 a major breakthrough has been achieved in the transplantation field with the use of reduced intensity conditioning, which widened the candidate population for an allogeneic transplant not only in the

terms of older age but also in the terms of the disease as well [Niederwieser et al., 2003; Bacigalupo, 2004]. Patients undergoing hematopoietic cell transplantation post reduced intensity conditioning appeared to have shorter neutropenia period, fewer bacteremia episodes as well as viral infections in the first 100 days, compared to those transplanted with myeloablative regimens [Baron et al., 2004]. Furthermore, the number of severe viral infections, such as CMV reactivation and CMV disease, was lower in the first 100 days, while the incidence of invasive aspergillosis was similar between the two types of transplants in the first year [Fukuda et al., 2003]. The CMV infection remains a severe complication in these patients, especially in the late post-transplant period.

CMV infections, the major fatal threat for transplanted patients, are prevented in CMV seropositive patients with either prophylactic or preemptive antiviral treatment with ganciclovir–foscarnet. It is noteworthy that early detection of all viruses is of great importance as the best management policy remains the lowering or gradual tapering of immunosuppression [Kontoyiannis et al., 2008]. In addition, one of the major achievements is the recognition of the importance of risk assessment for the development of post-transplant viral infections. This assessment is made for several viruses through pre-transplant detection of the viral status of the patient and for several viruses of the donor too [Ljungman, 2007].

As the number of alternative transplants has increased, more profound T-cell depletion is needed. Therefore, viral infections remain the most significant predictors of the transplant outcome, as they are still the main cause of morbidity and mortality. Over the years, major improvements in the post-transplant management of viral infections have been achieved, especially in well-recognized pathogens as CMV, herpes simplex virus (HSV), varicella-zoster virus (VZV), respiratory syncytial virus (RSV), adenovirus, parainfluenza viruses, and influenza viruses. The development of new diagnostic molecular techniques has led to the recognition of new viruses in transplanted patients. This review attempts to describe the role of these emerging viruses, such as HMPV, human bocavirus, human coronaviruses HCoV-NL63 and HCoV-HKU1, human herpesviruses HHV-6 and HHV-7, and polyomaviruses in hematopoietic graft recipients (Table I).

HUMAN METAPNEUMOVIRUS

Basic Characteristics

The discovery of HMPV, a new paramyxovirus, which was first identified in children with respiratory tract disease, was reported in 2001 [van den Hoogen et al., 2001]. It is a negative-sense non-segmented RNA paramyxovirus (family *Paramyxoviridae*, subfamily *Pneumovirinae*). There appear to be at least two major genotypes of HMPV, A and B [van den Hoogen et al., 2004].

Epidemiology

HMPV infections have been identified worldwide. By the age of 5, more than 90% of children are seropositive, with reinfections and winter epidemics occurring throughout life [Health Protection Agency, 2008]. It accounts for approximately 4% of the community-acquired pneumonia in adults [Johnstone et al., 2008] and for 5–15% of bronchiolitis in young children [Kahn, 2007]. HMPV infection has been detected in up to 5% of hematopoietic graft recipients [Peck et al., 2007]. Whether asymptomatic infections occur, it remains to be defined [Debiaggi et al., 2007; Peck et al., 2007]. HMPV was detected in 3–4% of bronchoalveolar lavage samples from hematopoietic transplant recipients with clinical and radiographic signs of pneumonia. Idiopathic pneumonia syndrome had been the initial diagnosis for the majority of these patients [Englund et al., 2006].

Clinical Symptoms

The role of HMPV as a respiratory pathogen has been confirmed after experimental infection of cynomolgous macaques [Kuiken et al., 2004]. Both symptomatic and asymptomatic upper and lower respiratory tract disease occur in immunocompetent young or older adults and residents of a long-term nursing care facility, with clinical features similar to those seen in adults infected with RSV (i.e., infection of the upper respiratory tract, bronchiolitis, pneumonia, otitis media). Severe disease activity has been associated with HMPV infection in immunocompromised patients [Kahn, 2007]. In hematopoietic transplant recipients HMPV disease has been reported to be presented with upper respiratory symptoms, including fever, nasal congestion, and cough. Once pneumonia developed, rapidly progressive pulmonary infiltrates, accompanied frequently by hypotension, septic shock, or both, were observed [Englund et al., 2006]. Recently, Kamboj et al. [2008] found that HMPV infections in cancer patients caused a number of unspecific respiratory symptoms but they did not observe any fatal cases of respiratory HMPV infections in their series. In a recent study, bronchoalveolar lavage samples from 157 immunocompromised patients with atypical pneumonia were examined and HMPV was detected in a male patient undergone allogeneic bone marrow transplantation due to chronic myeloid leukemia. Unfortunately, the patient succumbed because of severe aggravation of the atypical pneumonia and fatal pulmonary failure 10 days after admission [Müller et al., 2009].

Laboratory Diagnosis

Laboratory diagnosis is mainly based on PCR techniques, performed with primers mainly targeting the conserved fragment of 170 nucleotides in the L-polymerase gene [van den Hoogen et al., 2004]. Other primers have also been successfully used, such as those targeting the 150-bp region of the N genes [Debiaggi et al., 2007]. Culture is difficult and inappropriate for

routine diagnosis. Commercial antigen detection tests are in development. Detection by indirect fluorescence assay using a monoclonal antibody (IF) is also a useful test [Manoha et al., 2008]. Regarding the new HMPV detection kit using immunochromatography (SAS HMPV test), overall sensitivity and specificity were 82.3% and 93.8%, respectively, suggesting that this test is useful especially for pediatricians to diagnose HMPV infection in a clinical setting [Matsuzaki et al., 2009].

Treatment

Although there is no established treatment for HMPV disease in hematopoietic cell transplant recipients [Boeckh, 2008], there have been two cases treated successfully with a combination of intravenous ribavirin and immunoglobulin [Bonney et al., 2007; Kamble et al., 2007]. Several candidate HMPV vaccines are under development and each one has shown promising results in experimental animals; however, no studies on human have been performed yet [Kahn, 2007]. An HMPV monoclonal antibody that neutralizes both genotype A and B viruses has been developed and has been shown to protect experimental animals from HMPV infection [Ulbrandt et al., 2006]. Other compounds, such as NMSO3, a sulfated sialyl lipid has potent HMPV antiviral activity in cell culture assays [Wyde et al., 2004]. In a recent study, NMSO3 treatment improved several aspects of HMPV-induced disease in BALB/c mice infected with HMPV and should be considered for further evaluation in other animal models [Spetch et al., 2008].

HUMAN BOCAVIRUS

Basic Characteristics

Human bocavirus (HBoV) was discovered in September 2005 [Allander et al., 2005]. The virus was assigned as a new member of the family *Parvoviridae* (subfamily *Parvovirinae*, genus *Bocavirus*) and has been provisionally termed as human bocavirus, the first human member of this virus genus [Schildgen et al., 2008]. The fact that HBoV was first detected in nasopharyngeal aspirates of patients with respiratory tract infections, while no other pathogen was detected, suggested that the virus may have a pathogenic role in respiratory tract disease [Allander et al., 2005]. Multiple studies have identified the presence of HBoV in respiratory tract samples and recent studies have identified HBoV also in blood and fecal samples [Arden et al., 2006; Arnold et al., 2006; Fry et al., 2007; Qu et al., 2007; Schenk et al., 2007; Costa et al., 2009].

Epidemiology

Reports suggest that HBoV has worldwide endemicity, primarily found in young children. The true incidence and the season of primary HBoV infection remain unknown. Coinfection of HBoV and other common respiratory viruses may be common [Kahn, 2008]. Several clinical research groups have reported

HBoV-positive immunosuppressed/immunodeficient patients [Schildgen et al., 2008]. Disseminated (nasopharyngeal aspirates, serum and feces) HBoV infection was reported in a child after stem cell transplantation, presenting pneumonia with perihilar infiltrates [Schenk et al., 2007]. HBoV was the sole pathogen found in nasopharyngeal aspirate samples of an adult immunosuppressed patient with malignant B-cell lymphoma and a severe infection with long-lasting fever and pneumonia [Kupfer et al., 2006]. Disseminated HBoV infection was also reported in an immunodeficient child with clinical hepatitis and skin manifestations. It is noteworthy that there were no respiratory findings or other concomitant viruses detected [Kainulainen et al., 2008]. The occurrence of HBoV in febrile children with acute lymphoblastic leukemia was 5% [Koskenvuo et al., 2008]. In a prospective study on HBoV prevalence in 341 consecutive bronchoalveolar lavage samples from Italian adult patients, HBoV was detected in 2 out of 12 hematopoietic graft recipients, who developed pneumonia and acute respiratory deficiency [Costa et al., 2009].

Clinical Symptoms

Clinical symptoms most frequently reported in individuals where HBoV is the only isolated virus include cough, rhinorrhea, fever, wheezing, and diarrhea [Arnold et al., 2006]. Gastrointestinal symptoms have been described in up to 25% of HBoV-infected patients [Arnold et al., 2006; Kesebir et al., 2006; Monteny et al., 2007].

Several studies, which have included control groups of asymptomatic children, have found a statistical association between HBoV and acute respiratory symptoms, in a way that is consistent with a causal role [Schildgen et al., 2008]. However, the role of HBoV as a respiratory pathogen remains controversial. HBoV codetections frequencies of 18–90% have been reported [Allander et al., 2005; Fry et al., 2007]. It is also important to note that a high frequency of HBoV detection in asymptomatic children (up to 43%) has been reported in some studies [Longtin et al., 2008]. Furthermore, a recent study has shown the absence of HBoV in bronchoalveolar lavage of a cohort of 53 lung transplant patients [Miyakis et al., 2009].

Laboratory Diagnosis

The detection of HBoV has been performed only with conventional and real-time PCR [Choi et al., 2008], since no animal model of infection or antibody preparation for antigen detection has been available. Because of the limited genetic variability of HBoV, multiple suitable PCR targets can be used, including more-conserved genetic regions, such as the NS1 gene, and the frequently targeted NP1 gene [Schildgen et al., 2008]. The culture of HBoV is now possible, as it was first cultured in differentiated human airway epithelial cells [Dijkman et al., 2009]. HBoV DNA, initially found in respiratory secretions, has also been detected in stool

and serum, suggesting that the virus can cause systemic infection [Kahn, 2008]. Application of serology and PCR detection in blood are expected to be very useful diagnostic tools, as HCoV infection seems to be frequently followed by asymptomatic low level virus shedding in the respiratory tract [Allander, 2008].

Treatment

Antiviral drugs active against HCoV have not been applied to date [Nichols et al., 2008]. A rapid HCoV testing method capable of identifying clinically relevant cases could reduce the unjustified and generally ineffective use of antibiotics in these patients. If the pathogenetic role of HCoV turns out to be significant, the need of a vaccine development will probably be investigated [Schildgen et al., 2008].

HUMAN CORONAVIRUSES HCoV-NL63 AND HCoV-HKU1

Basic Characteristics

The coronaviruses consist of an important group of RNA viruses classified in the family *Coronaviridae* in the order *Nirivirales*. Before 2003, only two human coronaviruses had been characterized, HCoV-229E (a group I coronavirus) and HCoV-OC43 (a group II coronavirus). Since 2003, three new HCoVs have been identified, HCoV-NL63 (a group I coronavirus) [Fouchier et al., 2004; van der Hoek et al., 2004; Esper et al., 2005a], HCoV-HKU1 (a group II coronavirus) [Woo et al., 2005], and the SARS coronavirus [Marra et al., 2003].

Epidemiology

HCoV-NL63 and HCoV-HKU1 are found worldwide and seem to be prevalent during winter. Infections occur at all ages, while they are most common in children under 5 years of age [Health Protection Agency, 2008]. The viruses can be detected in 1–10% of patients with acute respiratory tract infection, whereas coinfections with other respiratory viruses are common [van der Hoek et al., 2006]. HCoVs have also been detected in solid organ transplant recipients, patients with underlying malignancies, and individuals infected with HIV [Kumar et al., 2005]. Among 823 patients admitted to hospital with acute respiratory symptoms, 5.7% had HCoV detected. HCoV infections were found in 8.8% of immunocompromised patients and 4.5% of immunocompetent patients [Gerna et al., 2006].

Clinical Symptoms

HCoV-NL63 and HCoV-HKU1 are associated with respiratory tract disease in both children and adults [Chiu et al., 2009]. A clear link between HCoV-NL63 and respiratory diseases has been established [Pyrk et al., 2007]. HCoV-NL63 may be a common cause of croup.

The association of NL63 coronavirus and Kawasaki disease [Esper et al., 2005b] has been put into question by later studies [Rowley and Shulman, 2007]. The respiratory symptoms accompanying a HCoV-HKU1 infection are usually rhinorrhoea, fever, coughing, and wheezing, and disease manifestations include bronchiolitis and pneumonia [Lau et al., 2006; Sloots et al., 2006]. Infection with HCoV-HKU1 may not be limited in the respiratory tract, as the virus has also been detected in fecal samples. HCoV-NL63 and HCoV-HKU1 are common cold viruses that can result in severe clinical manifestations in young children, elderly persons, and immunocompromised patients [Pyrk et al., 2007].

Laboratory Diagnosis

Amplification methods are widely used for respiratory coronavirus diagnosis, as the availability of serological testing and the efficacy of cell culture for many coronaviruses is limited. Pancoronavirus primer sets, which claim to detect all coronaviruses, have been described [Moës et al., 2005]. It has been confirmed that these consensus primers perfectly match HCoV-HKU1 [van der Hoek et al., 2006]. However, the genetic variability among HCoV-OC43, HCoV-229E, and HCoV-NL63 is such that as many as 30% of coronavirus infections are not detected when the available pancoronavirus methods are used [Gerna et al., 2006]. A 237 bp fragment of the ORF1b is used as a specific target gene for HCoV-NL63 [van der Hoek et al., 2004], whereas primers for HCoV-HKU1 are mainly defined in the replicase 1B gene [Woo et al., 2005].

Treatment

The emergence of SARS-CoV intensified antiviral research for CoVs [Nichols et al., 2008]. Antiviral compounds targeting all human coronaviruses, for example, broadspectrum inhibitors of the M^{pro} enzymes, are promising. Several compounds that efficiently inhibit distinct steps of the viral replication cycle of HCoV-NL63 have been described [Pyrk et al., 2007]. Nevertheless, the need to develop antiviral strategies specific for HCoV-NL63 and HCoV-HKU1, as well as HCoV-229E and HCoV-OC43, may be limited due to their low incidence in serious respiratory tract disease [Kahn, 2007].

HUMAN HERPESVIRUS-6/HUMAN HERPESVIRUS-7

Basic Characteristics

Human herpesvirus-6 (HHV-6) and human herpesvirus-7 (HHV-7) are members of the genus *Roseolovirus*, subfamily *Betaherpesvirinae* [Berneman et al., 1992]. HHV-6 was first isolated from peripheral blood mononuclear cells of patients with lymphoproliferative disorders [Salahuddin et al., 1986]. There are two subtypes of HHV-6: type A and type B [Braun et al., 1997]. HHV-7 was originally isolated from CD4⁺ T lymphocytes obtained from healthy adults [Frenkel et al., 1990].

HHV-6A, HHV-6B, and HHV-7 are ubiquitous and remain latent in T cells after the primary infection and then can be reactivated in an immunocompromised host [Khanani et al., 2007]. The phenomenon of HHV-6 chromosomal integration (CI), a latent state of the virus in the chromosome, should be kept in mind as an alternative cause of HHV-6 detection in suspected cases [Ljungman et al., 2008].

Epidemiology

HHV-6 and HHV-7 infect 90–95% of the population at the age of 2 and 5, respectively. HHV-6 is thought to be transmitted through saliva, with salivary shedding of the virus being documented in more than 85% of adults [Dewhurst, 2004]. HHV-6 reactivation occurs in 33–48% of transplanted patients, early after transplant. It can be detected in the blood at a median day +20 after transplant, usually before CMV detection [Zerr et al., 2005]. Type B is significantly more common than type A [Boeckh et al., 2005]. The incidence of HHV-6 reactivation is higher after allogeneic cord blood stem cell transplantation than after allogeneic bone marrow transplantation and/or peripheral blood stem cell transplantation [Sashihara et al., 2002; Tomonari et al., 2005]. Younger age, underlying malignancy beyond early phase (i.e., diagnoses other than hematologic malignancy in first remission or CML chronic phase), allogeneic transplants with unrelated, mismatched-related or gender mismatched donors, use of anti-T-cell antibodies or steroids have all been identified as predictors for HHV-6 reactivation [Zerr, 2006].

A positive association of HHV-7 and HHV-6 detection and no relation among HHV-7, CMV, and EBV is shown in studies in pediatric hematopoietic cell transplant recipients [Chan et al., 2004; Hubacek et al., 2008]. A high incidence of HHV-7 viremia (50–55.9%) is detected in pediatric stem cell recipients [Chan et al., 2004; Savolainen et al., 2005]. In studies on both adult and pediatric patients HHV-7 viremia post-transplant is ranging from 10% to 57% [Hubacek et al., 2008]. Nevertheless, in another study on pediatric stem cell recipients, the incidence of HHV-7 was found to be 5.5% [Khanani et al., 2007].

Clinical Symptoms

Primary infection with HHV-6 is most commonly manifested as an undifferentiated highly febrile illness, with approximately 30% of children exhibiting the classic clinical manifestations of exanthem subitum and can be complicated by febrile seizures [Dewhurst, 2004]. In immunocompetent adults, primary infection with HHV-6 can produce a mononucleosis-like illness and, more rarely, severe disease, including encephalitis [Stoeckle, 2000]. In hematopoietic transplanted patients, HHV-6 reactivation has been associated with skin rash, fever, myelosuppression, pneumonitis, and may exacerbate GVHD. Central nervous system disorders, such as encephalitis, have also been linked to

HHV-6, although the causative relationship and incidence have not yet been fully clarified [Boeckh et al., 2005; Yamane et al., 2007]. HHV-6 encephalitis post-hematopoietic cell transplantation is relatively rare, with approximately 40 cases published [Ljungman et al., 2008].

Primary HHV-7 infection can also cause exanthem subitum, although less frequent than HHV-6, and is likely associated with seizures. Furthermore, HHV-7 is detected in some cases of other inflammatory skin disorders, such as psoriasis. Although the data on the detection of HHV-7 in pityriasis rosea have been controversial [Kempf, 2002], recent studies reveal its causal role [Broccolo et al., 2005; Canpolat Kirac et al., 2009]. After allogeneic hematopoietic cell transplantation, HHV-7 has been reported as a cause of severe central nervous system disease [Castagnola et al., 2008]. In addition, HHV-7 was associated with severe GVHD and sepsis secondary to severe immunosuppression after transplantation from matched unrelated donors [Khanani et al., 2007]. The role of HHV-7 has been poorly defined in hematopoietic cell transplant recipients [Ljungman et al., 2008].

Laboratory Diagnosis

In most studies of hematopoietic cell transplant recipients, diagnosis has relied on detection of HHV-6 since serological methods are generally considered unreliable in severely immunocompromised patients. Most experts agree that isolation of HHV-6 from the blood or detection of viral DNA in serum or plasma indicates active viral infection [Zerr, 2006]. As far as HHV-7 is concerned, PCR and antigen detection are considered to be reliable diagnostic tools [Savolainen et al., 2005]. Amplification of the specific HHV-6 DNA is mainly performed using primers from the U 67 gene [Savolainen et al., 2005], whereas primers for HHV-7 are mainly located in U10 region of HHV-7 [Chan et al., 2004].

Treatment

Only limited data have been published regarding the efficacy of antiviral therapy on HHV-6 [Long et al., 2003]. In a study on the effectiveness of ganciclovir against HHV-6, there was growing evidence that ganciclovir inhibits HHV-6 replication in the salivary glands [Ljungman et al., 2007]. When the *in vitro* activity of acyclovir, ganciclovir, cidofovir, and foscarnet against HHV-6 was compared, cidofovir appeared to be the most potent, and also the most selective, at least against the HHV-6 subtype A in cord blood lymphocytes. In T-cell lines, the highest selectivity score of the four compounds was achieved by foscarnet [De Clercq and Naesens, 2006].

Little is known regarding the treatment of HHV-7-related disease, although *in vitro* studies indicate that HHV-7 is much less susceptible to ganciclovir than

HHV-6 and foscarnet has been suggested as a potentially useful agent [Dewhurst, 2004].

POLYOMAVIRUSES

Basic Characteristics

The first human polyomaviruses, BK virus (BKV) and JC virus (JCV), were coincidentally isolated in 1971 by two independent groups, BKV from the urine of a renal transplant patient who suffered from ureteral stenosis [Gardner et al., 1971] and JCV from the brain tissue of a patient with Hodgkin's lymphoma who developed a progressive multifocal leukoencephalopathy [Padgett et al., 1971]. Recently, two new members of the human polyomavirus family, KI virus (KIV) and WU virus (WUV), were identified in respiratory specimens, mainly from children under 5 years of age with respiratory tract infections [Allander et al., 2007; Gaynor et al., 2007].

Epidemiology

Seroprevalence of BKV ranges between 60% and 80% in the general population. Primary infection usually occurs during childhood at an earlier age than JCV. The route of transmission of both BKV and JCV remains unclear, despite the evidence suggesting respiratory transmission [Jiang et al., 2009]. Asymptomatic reactivation of infection with urinary shedding may occur in immunocompetent individuals [Boeckh et al., 2005]. During immunosuppression BKV infection may reactivate. Asymptomatic BK viruria occurred in up to 5% of immunocompetent individuals and in up to 60% of immunocompromised patients [Hirsch, 2005] and up to 95% of stem cell transplantation recipients [Erard et al., 2005]. In a recent study, BK viruria was related to the pre-transplant detection of anti-BKV IgG antibodies but the relationship between serologic evidence of BKV, BK viruria, and hemorrhagic cystitis remains unclear [Wong et al., 2007].

Primary JCV infection during childhood, which occurs in up to 75% of the population, results in lifelong viral latency in the kidneys and B-cell lymphocytes [Goldberg et al., 2002]. In immunocompromised hosts, JCV associated, progressive multifocal leukoencephalopathy is caused by reactivation of a latent infection rather than de novo exposure [Kharfan-Dabaja et al., 2007].

Reports suggest that KIV and WUV have worldwide endemicity, and infections are common in early winter months. There is gathering evidence that primary infection with KIV or WUV occurs during childhood [Jiang et al., 2009]. KIV and WUV infections have a similar frequency, ranging from 1% to 3% [Norja et al., 2007]. In immunosuppressed individuals their frequency is higher. In a retrospective study of nasopharyngeal aspirates and bronchoalveolar lavage samples from 200 immunocompromised patients with suspected upper or lower respiratory tract infections, the prevalence of KIV and WUV was 8% and 1%,

respectively. Furthermore, KIV infection among hematopoietic graft recipients occurred in up to 17.8%, suggesting that a profound T-cell deficiency could play a role in KIV replication. The high prevalence of KIV among immunocompromised patients (8%) indicates that this population may be more susceptible to KIV, as to JCV and BKV. Respiratory coinfections are common [Mourez et al., 2009].

Clinical Symptoms

The most frequently reported manifestation of BKV infection following hematopoietic cell transplantation is hemorrhagic cystitis [Fioriti et al., 2005], which is characterized by dysuria, varying degrees of hematuria, and affects up to 10% of hematopoietic cell transplant patients [Dropulic and Jones, 2008]. BKV nephropathy after allogeneic hematopoietic cell transplantation is reported in both the adult and the pediatric setting cases even without the evidence of hemorrhagic cystitis. T-cell depleted (ex- or in vivo) grafts and GVHD with its associated profound immunosuppression, exacerbated by its treatment, are potential risk factors, which must be further validated [Verghese et al., 2008; Lekakis et al., 2009].

JCV causes progressive multifocal leukoencephalopathy through the infection of oligodendrocytes and astrocytes [Dubois et al., 1997]. In the literature, there are six reported cases of progressive multifocal leukoencephalopathy after allogeneic transplantation and eight after autologous transplantation. The disease may present with a variety of neurological manifestations, that is, hemiparesis, visual impairment, aphasia, headaches, vertigo and seizures, among others. Outcome is fatal in most cases [Kharfan-Dabaja et al., 2007].

Despite their clear presence in specimens of patients with respiratory illnesses, the pathogenic role of KIV and WUV remains unclear. In studies that included defined non-respiratory disease control groups, KIV and WUV were detected at similar frequencies in asymptomatic patients. KIV and WUV are detected in asymptomatic patients, as well as patients with upper or lower respiratory tract infections. In immunocompromised patients the spectrum of disease in KIV- and WUV-infected patients is ranging from a common cold to acute respiratory distress [Mourez et al., 2009].

Laboratory Diagnosis

Evidence of viral multiplication (lytic or active infection) can be detected by viral culture, electron microscopy, immunohistochemistry, PCR methods (expression of mRNA, viral DNA at non-quiescent sites such as plasma), cytological, or histological examination. Whether infectious WUV and KIV particles can be isolated and grown in the laboratory remains unclear [Jiang et al., 2009]. Primers targeting the VP1 and VP2 region are used to detect KIV and WUV, respectively [Allander et al., 2007; Gaynor et al., 2007]. Although the two viruses differ substantially in amino acid sequence

for VP1 and VP2 proteins, they are more closely phylogenetically related to each other than to BKV and JCV [zur Hausen, 2008].

BKV plasma levels greater than 10,000 copies/ml were highly associated with post-engraftment BKV-associated hemorrhagic cystitis among patients undergone hematopoietic cell transplantation [Erard et al., 2005]. Screening hematopoietic cell transplant patients for BKV would be beneficial in assessing the need for early supportive intervention before overt clinical disease is evident. The definitive diagnosis of BKV nephropathy requires a biopsy [Verghese et al., 2008].

Although PCR of the CSF has emerged as a promising tool for detecting JCV, a negative result does not rule out progressive multifocal leukoencephalopathy. Therefore, brain biopsy remains the gold standard diagnostic tool. The significance of JCV viremia and its potential role as a progressive multifocal leukoencephalopathy screening tool in hematopoietic transplant recipients remains to be assessed [Kharfan-Dabaja et al., 2007].

Treatment

At this time, effective and specific antiviral treatments for BKV do not exist. The best choice of therapeutic intervention from the currently available (fluoroquinolones, leflunomide, cidofovir, IVIG, combination therapy) and optimal timing of treatment initiation is currently unknown. The efficacy of each treatment option remains to be explored [Jiang et al., 2009; Lekakis et al., 2009].

There is no established treatment against progressive multifocal leukoencephalopathy after autologous or allogeneic transplantation. Treatment options include IL-2, cytarabine, cidofovir, combination therapy, and withdrawal of immunosuppressants [Kharfan-Dabaja et al., 2007]. Chlorpromazine and new-generation atypical antipsychotics such as ziprasidone, risperidone, and olanzapine may be useful therapies for progressive multifocal leukoencephalopathy [Pho et al., 2000; Atwood, 2001; Altschuler and Kast, 2005].

CONCLUSIONS

It is apparent that the spectrum of viral infections in hematopoietic transplant recipients is expanding. Well-designed prospective studies focused on both diagnostic tools and management are needed to define the disease burden of newly discovered viruses, such as bocavirus, novel coronaviruses, and polyomaviruses, and to eliminate the risk of morbidity and mortality of the emerging viral infections in hematopoietic graft recipients. Furthermore, effective vaccines and specific antiviral compounds against new pathogens are warranted.

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