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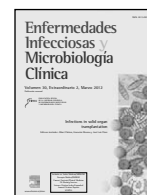
Infections caused by herpes viruses other than cytomegalovirus in solid organ transplant recipients

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Despite great advances in solid organ transplantation (SOT) in recent decades, infection remains a major cause of morbidity and mortality among SOT recipients. Members of the herpesvirus family are the most common viral pathogens causing disease in this patient population. Herpes viruses are large enveloped DNA viruses that commonly reactivate during periods of severe immunosuppression. Currently, infections caused by herpes viruses continue to complicate clinical management of transplant patients. Although cytomegalovirus (CMV) is the most important virus of this family and is the subject of active research, herpes simplex virus (HSV) and varicella-zoster virus (VZV) can also lead to severe disease. Epstein-Barr virus (EBV) associated with post-transplant lymphoproliferative disease is increasingly recognized as a major complication of SOT. There is less information available on the role and impact of other viruses of the herpesvirus family, such as the human herpes virus 6 (HHV-6), human herpes virus 7 (HHV-7) and human herpes virus 8 (HHV-8). This review summarizes current knowledge regarding epidemiology, clinical manifestations, diagnosis, treatment and prevention of infections caused by herpes viruses other than CMV in SOT recipients.

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Infecciones causadas por otros herpesvirus distintos al citomegalovirus en receptores de trasplante de órgano sólido

R E S U M E N

Palabras clave:
Otros herpesvirus humanos
Trasplante de órgano sólido
Trastorno linfoproliferativo postrasplante
Virus herpes simple
Virus varicela-zoster
Virus de Epstein-Barr

A pesar de los grandes avances en el trasplante de órgano sólido (TOS) en las últimas décadas, la infección sigue siendo la mayor causa de morbimortalidad entre los receptores de TOS. Los miembros de la familia herpes virus son los patógenos virales más frecuentes causantes de enfermedad en esta población de pacientes. Los herpesvirus son virus ADN grandes envueltos, que habitualmente se reactivan durante períodos de inmunodepresión grave. Actualmente, las infecciones causadas por herpesvirus continúan siendo un desafío para el tratamiento clínico de los pacientes trasplantados. Aunque el citomegalovirus (CMV) es el virus más importante de esta familia y sobre el que se realiza una investigación activa, el virus herpes simple (VHS) y el virus varicela-zoster (VVZ) pueden también producir una enfermedad grave. La enfermedad linfoproliferativa asociada al virus de Epstein-Barr (VEB) se reconoce cada vez más como una complicación importante del TOS. Existe menos información disponible sobre el papel y el impacto de otros virus de la familia de los herpesvirus, como por ejemplo el virus del herpes humano 6 (VHH-6) y el virus del herpes humano 8 (VHH-8). Esta revisión resume el conocimiento actual respecto a la epidemiología, las manifestaciones clínicas, diagnóstico, tratamiento y prevención de las infecciones causadas por otros herpesvirus distintos al CMV en receptores de TOS.

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Herpes Simplex Virus

Herpes simplex virus type 1 and type 2 (HSV-1, HSV-2) belong to the alpha-herpesvirus family. They are characterized by short replication cycles, rapid growth in culture, lysis of the host cell during replication and latency in nerve root ganglia. Although HSV types 1 and 2 share 40% of their nucleotide sequence, they have different epidemiological profiles and distinct biological and antigenic characteristics.

Epidemiology and pathogenesis

Most of the population is infected with HSV-1 during childhood or early adolescence, usually through saliva. Primary infection is usually asymptomatic (but can cause gingivostomatitis), while viral reactivation typically causes *herpes labialis* (cold sores or fever blisters). Human transmission occurs by direct contact with lesions or secretions of a person actively shedding virus. In the USA the prevalence of HSV-1 has been reported to be 80% by the age of 60. HSV-2 infection is less common; it is usually acquired by sexual transmission and is commonly associated with genital infection. Its prevalence increases with age: in the USA the rate is 1.6% of people aged 14-19 years and 26.3% of those between 40 and 49 years.[1]

During primary infection, the virus replicates in the mucocutaneous epithelium, reaching axonal endings of sensory metameric neurons and remaining latent in the ganglion. The mechanisms by which the virus establishes, preserves or recovers its latency are not known. There is currently no way of stopping or keeping the latency at the molecular level in the cell.[2]

Risk factors

Most infections are due to endogenous reactivation of latent virus rather than to primary exogenous infection. Although rare, infection can be transmitted through the graft, a situation described mainly in renal transplants.[3,4] In the absence of prophylaxis, most infections occur in the first month after transplantation. After initiation of immunosuppressive therapy, HSV reactivates rapidly. The risk of infection depends on the intensity of immunosuppression. Solid organ transplant (SOT) recipients receiving OKT3, mycophenolate or anti-thymocyte globulin have a high rate of HSV disease.[3,5,6] The effect of other drugs such as alemtuzumab, basiliximab, tacrolimus or sirolimus is not well known.

Clinical manifestations

Without antiviral prophylaxis against HSV, 40%-50% of SOT recipients develop the disease,[7] which usually occurs 2-3 weeks after SOT. Mucocutaneous lesions caused by HSV in SOT recipients are similar to those observed in immunocompetent patients, but in the immunocompromised host the disease is usually more severe and of longer duration, showing greater viral clearance and increased susceptibility to spreading. Herpes lesions are localized painful papules on the lips and oral mucosa (gums, tongue and posterior pharynx). They rapidly evolve into clusters of vesicles that may form pustules or break and cause ulcerated or erythematous lesions. Without antiviral therapy, healing of these lesions may be delayed for 4 to 6 weeks. Gingivostomatitis is more common in hematopoietic transplant patients than in SOT recipients.

Anogenital herpes is usually caused by HSV-2, which reactivates from the latent virus in the sacral ganglia. The reactivation of HSV-2 may be complicated by lymphocytic meningitis without progression to encephalitis and with a good prognosis.

Mucocutaneous HSV infections cause some morbidity but are usually mild. Without treatment, patients with disseminated HSV disease and hepatitis have a mortality of 60%-80%, although the figure approaches 100% in cases with disseminated intravascular coagulopathy; liver transplantation or retransplantation is required in a few patients with liver failure due to fulminant HSV hepatitis.[8]

HSV can spread by direct extension from the oropharynx to the gastrointestinal or respiratory tracts, causing herpetic esophagitis or pneumonia, most frequently in lung and heart-lung transplant recipients.[9,10] Colitis in SOT is more commonly caused by cytomegalovirus (CMV) than by HSV, and HSV encephalitis does not appear to occur with increased frequency in SOT.

Prevention

Acyclovir, valacyclovir and valganciclovir prevent most HSV reactivation. HSV prophylaxis should be considered in SOT recipients who are seropositive for HSV-1 and 2 and who are not receiving antiviral prophylaxis against CMV. Some authors argue that HSV-seronegative patients also require such treatment. Prophylaxis has shown efficacy in recipients receiving OKT3. The recommended dose of acyclovir in SOT is 400-800 mg twice/day for at least one month.[10] In patients with a history of severe HSV reactivations, higher doses are recommended. The dosage should be adjusted according to renal function.

Treatment

Patients with extensive cutaneous, mucosal or disseminated HSV disease should receive intravenous acyclovir 5-10 mg/8 h until the complete resolution of lesions. In severe cases reduction of immunosuppression should also be considered. In mild cases oral acyclovir, valacyclovir or famciclovir can be used. In patients with resistance to acyclovir, foscarnet is recommended. Topical or intravenous cidofovir and topical trifluridine have also been used.

Varicella-Zoster Virus

Epidemiology and risk factors

Varicella-zoster virus (VZV) is a human virus that belongs to the alpha-herpesvirus family. Primary infection acquired through direct contact with skin lesions or by the respiratory route usually leads to chickenpox. After initial infection VZV establishes latency in dorsal root ganglia and cranial nerves, and years or decades later can reactivate as herpes zoster (HZ).[11] The seroprevalence of VZV in adult recipients of SOT reaches 90%, while rates are lower in child transplant patients. SOT seronegative adult recipients usually acquire infection through exposure in the community. Although very rare, VZV transmission by donor has been described.[12] Recipients with previous VZV disease or who have received vaccination have an increased risk of HZ. Other predisposing factors are advanced age, being a heart or lung recipient and the use of mycophenolate mofetil.

Clinical manifestations

In adult SOT recipients, chickenpox is rare. Clinical features consist of a disseminated pruritic rash, which evolves over several days to papules, vesicles and pustules on the chest and face, without affecting the palms and soles. The rash is associated with malaise and fever. This clinical picture resolves in 7-10 days. Complications such as pneumonitis or hepatitis are rare, but cases with visceral involvement, severe skin disease and disseminated intravascular coagulation have a poor prognosis. HZ occurs in 8%-11% of SOT recipients in the first 4 years after transplantation. Vesicular lesions with dermatomal distribution characterize HZ disease, and skin lesions may be preceded by pain. Common complications are post-herpetic neuralgia, chronic neuropathy or bacterial infections.[11-14]

Diagnosis

In most cases the clinical manifestations of disease by VZV and HZ are the basis for diagnosis. Laboratory tests may be reserved for atypical cases and patients with disseminated or visceral disease. Rapid diagnostic methods, including polymerase chain reaction (PCR) and direct fluorescent assays (DFA), are the methods of choice. PCR is the most sensitive test for HSV and VZV, and both viruses can be detected in vesicle fluid, serum, CSF and other tissues.[15] Culture is specific and can distinguish HSV and VZV from other viruses, but it is less sensitive. Immunochemistry may be useful in the histopathological study. Serological tests are not recommended for the diagnosis of acute infection. In fact, IgM positivity in HSV infection may indicate reactivation and not new infection, and false-negative and false-positive serological testing can result in VZV infection.

Treatment

Patients with primary varicella infection after transplantation are at risk of serious illness and should be treated with intravenous acyclovir.[16] Therapy should be started within 24 hours of the rash in order to improve outcomes. In addition, reducing immunosuppression should be considered. Neither nonspecific intravenous immunoglobulin nor VZV immunoglobulin is recommended.[17,18] Disseminated HZ should be treated as primary chickenpox.[16] When HZ is mild and localized in only one dermatome, it may be treated with oral valacyclovir or famciclovir as an outpatient. Ophthalmicus and oticus HZ should be treated with intravenous acyclovir.

Prevention

Drugs used for prophylaxis of CMV or herpes simplex (valganciclovir, acyclovir) may also be effective in the prophylaxis of VZV in the immediate post-transplant period.[18] There are no reports of long-term VZV prophylaxis in SOT. VZV seronegative transplant candidates should receive attenuated virus vaccination to prevent primary infection 4-6 weeks before transplantation.[19] After the transplant, vaccination is not recommended.[20]

SOT recipients who are seronegative for VZV and are exposed to a case of varicella-zoster or rash after vaccination should receive post-exposure prophylaxis by administration of specific gamma globulin as soon as possible (within 92 hours).[18] After this period, the administration of post-exposure antiviral prophylaxis should be considered. In seropositive recipients, prophylaxis with acyclovir is not recommended because of the good response to treatment and risk of resistance development.

Epstein-Barr Virus and Post-Transplant Lymphoproliferative Disorder

Epstein-Barr virus (EBV) is a human herpesvirus that spreads by exposure to infected body fluids such as saliva. It is also transmitted by leukocyte-containing blood transfusion products, and to SOT recipients through seropositive donor organs. The majority of the population is seropositive before the age of 5 years. In developed countries, seropositivity may be delayed until the fourth decade of life.[21] Post-transplant lymphoproliferative disorder (PTLD) is a serious complication in SOT recipients that is usually associated with EBV. The disease has a clinical spectrum ranging from mild mononucleosis syndrome to EBV-induced aggressive neoplasms. This lymphoid proliferation is the result of immunosuppression, which causes a decrease in the function of specific T cells against EBV, with subsequent uncontrolled proliferation of B cells infected with the virus.[22] The period of greatest risk of PTLD presentation is the first year after transplantation and the median onset of disease in SOT is 6 months. The median onset of primary infection is 6 weeks.

Table 1
Classification of post-transplant lymphoproliferative disorders (PTLD)

Early lesions
Plasmacytic hyperplasia
Infectious mononucleosis-like lesion
Polymorphic PTLD
Monomorphic PTLD (classify according to lymphoma they resemble)
B-cell neoplasms
Diffuse large B-cell lymphoma
Burkitt lymphoma
Plasma cell myeloma
Plasmacytoma-like lesion
Other
T-cell neoplasms
Peripheral T-cell lymphoma
Hepatosplenic T-cell lymphoma
Other
Classical Hodgkin lymphoma

Risk factors for developing early PTLD (<12 months) are pediatric age, primary EBV infection and type of SOT. Incidence is higher in lung and intestinal recipients (5-32%) and lower in kidney transplant recipients (<1%). Other risk factors for early PTLD are mismatch or CMV disease and anti-rejection therapy, anti-thymocyte globulin or OKT3. Risk factors for late PTLD (>12 months) are prolonged immunosuppression, type of SOT and advanced age of the recipient.[23,24]

Clinical manifestations and diagnosis

The disease usually affects lymphoid organs and it can often become established in the transplanted organ (early cases). However, it may be extranodal and can affect the gastrointestinal tract, central nervous system (CNS), skin or sinuses. Patients may also have infectious mononucleosis (malaise, fever, pharyngitis, hepatosplenomegaly, lymphadenopathy, atypical lymphocytosis), pneumonitis, hepatitis, gastrointestinal symptoms, or blood disorders such as leukopenia, thrombocytopenia, hemolytic anemia or hemophagocytic syndrome.[24]

As symptoms are nonspecific, methods that ensure an accurate and rapid diagnosis are necessary. The detection of EBV DNA by quantitative real-time PCR is now considered the gold standard,[25] and the best sample to use for PCR currently appears to be whole blood. In terms of imaging, positron emission tomography with fluorodeoxyglucose has been shown to be superior to computed tomography and ultrasonography in the study of malignant lymphomas, extranodal lesion detection and evaluation after treatment. Diagnosis of PTLD requires histopathological examination of tissue. Table 1 shows the classification of PTLD according to the World Health Organization.

Prevention

No vaccine of confirmed clinical efficacy is currently available, and the serostatus of recipients should therefore be determined before transplant. It is important to provide correct prophylaxis against CMV for seronegative patients receiving organs from CMV seropositive donors (D+/R−) in order to prevent PTLD, and steps should also be taken to ensure the correct use of the immunosuppressive regimen, especially in high-risk recipients.[26] Pre-emptive therapy has proven effective, and consists of quantitative

monitoring of EBV load in order to reduce immunosuppression when the load turns positive or increases above a certain threshold.[27] The administration of antiviral drugs or EBV-neutralizing antibodies has not proven useful in preventing this infection[28] and data regarding the use of low-dose rituximab or adoptive immunotherapy are limited.[29]

Treatment

There is no consensus regarding treatment for PTLD. Reduction of immunosuppression is considered the first line of treatment and should be individualized for each patient. With this strategy, response rates vary between 0% and 89% depending on prognostic factors. Experience with antiviral drugs (acyclovir or ganciclovir) alone or associated with immunoglobulin is limited.[30] Partial or complete surgical resection and local radiotherapy (CNS) have been used as a therapy associated with reduction of immunosuppression.[24] Experience with rituximab, a chimeric anti-CD20 monoclonal antibody, has been successful. Some authors believe that rituximab should be considered the next step after reduction of immunosuppression in CD20 positive PTLD cases, reserving chemotherapy for patients who cannot receive or do not respond to rituximab.[31] Factors associated with poor prognosis are disseminated illness or CNS disease, EBV-negative PTLD, donor as source of the disease, coinfection with hepatitis B and C viruses, monoclonal disease, T or NK-cell PTLD, poor performance status and the presence of mutations of proto-oncogenes or tumour suppressor genes.[24]

Other human herpes viruses (HHV-6, HHV-7, HHV-8)

In contrast to post-transplantation CMV infection, which is well characterized and associated with high rates of morbidity and mortality, the role and impact of other viruses of the herpesvirus family, such as the human herpes virus 6 (HHV-6), human herpes virus 7 (HHV-7) and human herpes virus 8 (HHV-8), remain unknown. Like other herpes viruses, HHV-6, HHV-7 and HHV-8 establish long-term latent infections that can be reactivated in SOT recipients, who receive intense pharmacological immunosuppression. Reactivation during the post-transplant period is related to the development of symptoms. Even more importantly, in some cases there are indirect effects mediated by viral immune modulating effects, its interaction with other viruses and the effect on the functional activity and rejection of the graft. Due to the limited understanding of the pathogenesis of these viruses, the lack of standardized diagnostic tests and the in vivo effect of antiviral drugs, it is difficult to determine the role of each of these viruses after transplantation.

Human herpes virus 6

Epidemiology

HHV-6 is a ubiquitous beta-herpesvirus that is highly prevalent among humans, and is present in more than 95% of the population.[32] There are two closely related HHV-6 variants, A and B (HHV-6A/B), which are molecularly and biologically different. Although HHV-6B is established as the cause of exanthem subitum (roseola infantum), no disease has been associated with HHV-6A infection. Primary HHV-6B infection usually occurs in the first two years of life, differing from other human herpes viruses because of the unique ability of its genomes to integrate into the host chromosome in a persistent latent state, as well as its vertical transmission from parents to children.[32] The cellular receptor for HHV-6 has been identified as CD46, which is widely distributed in different cell types.[33] Thus, although HHV-6 tropism is mainly directed towards lymphocytes, it can also infect macrophages, megakaryocytes, fibroblasts, epithelial cells and glioblastoma cells.[34]

Because of the high prevalence of HHV-6, it is assumed that the majority of HHV-6 infections after SOT are the result of endogenous

viral reactivation or persistent viral replication in transplanted organs during periods of immune dysfunction, which are characteristic of the post-transplantation period. Between 14% and 82% of SOT recipients experience HHV-6 reactivation, usually variant B,[35-37] with variant A accounting for 2%-3% of events.[38] The high variability in incidence is due to differences in the patient populations studied, the immunosuppressive regimens used, and the methods of detection. Factors associated with HHV-6 reactivation are acute allograft rejection and the intake of high doses of steroids.[39] Primary infection also occurs in a small fraction of susceptible patients undergoing transplantation, usually as a result of the transmission of the virus from the donor through the infected organ or blood transfusion.[40]

Clinical manifestations

The clinical manifestations of HHV-6 infection following transplantation can be classified as direct or indirect. In terms of direct effects, HHV-6 infection can cause disease manifested as a febrile viral syndrome, accompanied by leukopenia, with evidence of HHV-6 in blood samples. Hepatitis due to HHV-6 has been described most frequently in liver recipients,[40] and cases of gastroduodenitis and pancreatitis have also been reported.[41] Encephalopathy is another recognised complication associated with HHV-6, although both HHV-6A and HHV-6B induced encephalitis must be distinguished from encephalopathy induced by cyclosporine, which can also produce non-enhancing white matter lesions on magnetic resonance imaging.[42] Post-transplant acute limbic encephalitis (PALE) is a distinct neurologic syndrome attributed to HHV-6 that has been reported to occur mainly in allogeneic hematopoietic stem cell transplant recipients.[43] Patients with PALE often present with anterograde amnesia, the syndrome of inappropriate antidiuretic hormone secretion, mild cerebrospinal fluid pleocytosis and temporal EEG abnormalities, often reflecting clinical or subclinical seizures.[43]

The most important indirect effect of HHV-6 infection after SOT results from the virus' potential to serve as a cofactor to increase CMV infection and disease.[44] Although several studies in patients with SOT suggest that HHV-6 infection is a marker of CMV disease, they do not demonstrate definitively that HHV-6 modifies the course of CMV infection. The interaction of HHV-6 with CMV and its immune modulating properties are the most important factors in its disease-causing potential, which increases the risk of developing other opportunistic infections.[45] HHV-6 can also cause tissue invasive disease, producing organ dysfunction in the absence of other documented causes. Occasionally, cases of lymphoproliferative disorders have been described in which high copy numbers of HHV-6 DNA have been found, although any role in the etiology of the disorders remains uncertain.

Diagnosis, treatment and prevention

The high seroprevalence of HHV-6 in the human population limits the use of serology, with no tests distinguishing between antibodies against HHV-6A and B.[46] Antigenemia assays have been used for the diagnosis of HHV-6 infection in blood,[39] but there is limited experience as their use has not been widespread. Biopsy specimens should be analyzed for evidence of HHV-6 by demonstrating cytopathological effects and viral antigens. This can be accomplished through immunohistochemistry, using monoclonal antibodies such as those against the structural protein p101 of HHV-6B.[47] The recent availability of quantitative PCR assays offers the advantage of correlating HHV-6 viral load, as has been shown in CMV infection, with clinical manifestations. Its response to antiviral therapy distinguishes between variants A and B.[48] When persistent HHV-6 levels in whole blood are suspected, confirmation can be obtained by checking donor and recipient samples obtained prior to transplant for the characteristic high levels of HHV-6 DNA.

The most common antiviral prophylaxis regimens used for treating HHV-6 are foscarnet, ganciclovir and cidofovir, all of which

have been shown to inhibit HHV-6 replication in vitro. Despite a lack of controlled trials, some experts recommend foscarnet or ganciclovir, either alone or in combination, for the treatment of HHV-6 disease. Foscarnet or ganciclovir are also recommended as first-line therapies for HHV-6 encephalitis, while cidofovir is recommended as a second-line therapy. Some authors propose the initiation of treatment in transplant recipients with clinical features of HHV-6 infection and a confirmatory diagnostic test by PCR, viral culture or immunohistochemistry. However, since many patients with HHV-6 infection have no significant clinical symptoms, and given the low risk of HHV-6 disease and the toxicity of available antiviral drugs, anti-HHV-6 prophylaxis is not currently recommended to prevent HHV-6 disease.[47] More research is needed to determine the optimal drug regimen and duration that will effectively inhibit HHV-6 replication following transplantation.

Human herpes virus 7

Epidemiology

HHV-7 was first identified in 1990 and is another ubiquitous virus acquired early in life, usually during the first five years through contact with oropharyngeal secretions. Like HHV-6, HHV-7 infection affects more than 95% of the human population, with an incidence of infection ranging from 0% to 46% in renal transplant recipients.[36] HHV-7 cell tropism appears to be restricted to CD4+ T-lymphocytes.[49] Although lymphocytes and epithelial cells of salivary glands are the principal sites of HHV-7 latency, the observation that the HHV-7 tegument phosphoprotein pp85 is present in cells other than lymphocytes in frequently transplanted tissues (including lung, liver and kidney) is intriguing.[50]

Clinical manifestations

The direct clinical manifestations of HHV-7 post-transplantation are poorly defined. However, it is believed to cause diseases similar to HHV-6, including a roseola-like illness and, more rarely, fever with evidence of HHV-7 in blood samples, with coexistent CMV detection.[50] However, in contrast to HHV-6, there is no evidence of chromosomal integration. HHV-7 may have immunomodulatory effects and it appears to be a risk factor for CMV disease and other opportunistic infections, and may also have effects on graft function.[44,45]

Diagnosis, treatment and prevention

Infection with HHV-7 is defined by evidence of replicative virus regardless of the presence of symptoms. Clinical evaluation of quantitative PCR assays in the diagnosis and management of HHV-7 reactivation in transplant recipients is currently under evaluation. There are no randomized and controlled trials assessing the efficacy of antiviral drugs for the prevention and treatment of HHV-7 infection after transplantation. Data on the susceptibility of HHV-7 to ganciclovir are conflicting, probably due to the lack of a widely accepted standard definition of HHV-7 disease, of a specific antiviral agent for HHV-7 and of a standard diagnostic assay to monitor response to treatment. Due to the concurrent coinfection of these viruses with CMV, it is difficult to design studies that assess the efficacy of antiviral drugs against these viruses in the post-transplantation period.

Human herpes virus 8

Epidemiology

HHV-8, also called Kaposi sarcoma–associated herpesvirus (KSHV), is a γ-herpesvirus (rhadinovirus) closely related to EBV and various rhadinoviruses infecting macaques and African green monkeys. Like all herpesviruses, the HHV-8 lifecycle includes a latent and lytic phase but, in contrast with other widely distributed herpesviruses, HHV-8 is not ubiquitous and has a heterogeneous global distribution. The incidence of HHV-8 after SOT ranges from 0.5% to 5% depending on geographical location and other epidemiological factors.[51] Transmission of the virus is sexual in homosexual and bisexual men, but non-sexual, probably via saliva, in areas of high endemicity. HHV-8 may be transmitted by blood transfusions and by SOT.[52] There is significant worldwide variation in the prevalence of HHV-8. The prevalence of HHV-8 infection is very high (50%) in older children and adults in Africa and parts of the Amazon basin, intermediate (5%-20%) in the Mediterranean and in Middle-Eastern countries and the Caribbean and low (5%) in North America, Northern Europe and Asia (5%).[53]

Clinical manifestations

HHV-8 is the etiological agent of Kaposi's sarcoma (KS), but has also been associated with primary effusion lymphoma (PEL) and multicentric Castleman's disease.[54-56] A strong association between HHV-8 and KS has been observed in SOT patients, particularly in kidney recipients.[57] It is still unknown whether this results from the reactivation of HHV-8 or from HHV-8 transmission via organ transplantation.[57,52] Although low in absolute terms, the incidence of KS in organ transplant recipients is 54- to 500-fold higher than in the general population.[57,58] KS risk increases with recipient age at transplantation, the number of mismatches at the HLA-B locus and the use of more aggressive immunosuppressive regimens, and it is also more predominant in males.[58,59] The risk peaks in the 0 to 2-year period after transplantation and decreases thereafter.[58] The mean delay between organ transplantation and KS onset is 13 months, ranging from a few weeks to 18 years.[60] Most cases of post-transplant KS apparently develop as a result of HHV-8 reactivation, with an increased risk of KS development in organ recipients infected by HHV-8 before graft.[61,62] In more than 90% of cases, KS is reported with mucocutaneous lesions, mainly located on the lower limbs, as well as on the trunk and the upper limbs.

Visceral KS predominantly affects the lymph nodes, gastrointestinal tract and lungs in up to 20%, 50% and 20% of subjects, respectively.[63] Because of the possibility of an associated lymphoma, histological analysis of enlarged lymph nodes is recommended. The lesions caused by KS are rarely associated with clinical symptoms, such as nausea, hemorrhage, perforation or obstruction syndrome and anemia.

Apart from KS, HHV-8 is also associated with two varieties of B-cell lymphoproliferative disorders: PEL and its solid variants, multicentric Castleman's disease and HHV-8-positive plasmablastic lymphomas arising from multicentric Castleman's disease.[55,56] Recently, HHV-8 has also been associated with a spectrum of post-transplantation plasmacytic proliferations.[63]

Diagnosis, treatment and prevention

There are currently no generally accepted diagnostic techniques for HHV-8. Antibody tests are useful for screening donors and recipients, but show low sensitivity and specificity.[64] Other available methods, such as quantitative PCR using whole blood, plasma or serum, are based on the detection of viral DNA, but no general recommendations can be made due to the lack of related studies. Because of its characteristic histopathological changes, the diagnosis of cutaneous or visceral KS should be based on biopsy, demonstrating the presence of HHV-8 in the lesions by immunohistochemistry or in situ hybridization.[65] In cases where KS is suspected and the site of malignancy is not accessible for biopsy, HHV-8 detection in blood may be helpful, although a negative result does not rule out the diagnosis.

The HHV-8 virus is only susceptible to the effects of anti-viral agents during the lytic phase of the infection.[65] In KS lesions, however, only a small percentage of cells are infected with HHV-8 in the lytic phase, with the great majority occurring in the latent phase. Several antivirals, including ganciclovir, foscarnet and cidofovir, have been

shown to inhibit HHV-8 replication in vitro, and the efficacy of valganciclovir in reducing HHV-8 replication was recently established in a randomized controlled trial.[66] Variable activity of antiviral therapy has been shown for each of the HHV-8-associated diseases, which may be related to the relative proportion of viruses in the lytic phase present in each disease.[66] Histone deacetylase (HDAC) inhibitors are able to induce lytic replication in latently infected cells,[67] which supports the need for further research into more potent HDAC inhibitors over longer treatment courses in patients with KS. In the same context, new therapeutic targets related to the restoration of immune competence and signal transduction pathways utilized by HHV-8 in the propagation of KS are being studied.

Because of the increased risk of KS development in organ recipients infected by HHV-8 before transplantation, prevention should focus on these transplant recipients regardless of the date of seroconversion. Administering sirolimus early after transplantation may have a preventive effect on KS. Importantly, several studies have found that conversion from cyclosporine to sirolimus in patients with KS favors regression of KS lesions without increasing the risk of graft rejection.[68,69]

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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