Enfermedades Infecciosas y Microbiología Clínica

Other viral infections in solid organ transplantation

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ABSTRACT

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Viral infections are a major cause of morbidity and even mortality in solid organ transplant recipients. This article reviews key aspects of infections in solid organ transplant recipients from respiratory viruses, such as influenza, polyomavirus, erythrovirus B19 and measles.

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Otras infecciones víricas en el trasplante de órgano sólido

RESUMEN

Palabras clave:
Erythrovirus B19
Gripe
Poliomavirus
Sarampión
Trasplante de órgano sólido
Virus respiratorios

Las infecciones víricas constituyen una causa importante de morbilidad y, en ocasiones, también de mortalidad en el receptor de un trasplante de órgano sólido. En este artículo se revisan aspectos fundamentales acerca de las infecciones por virus respiratorios, incluyendo el virus de la gripe, poliomavirus, erythrovirus B19 y sarampión en el receptor de un trasplante de órgano sólido.

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Influenza virus infection

The influenza virus is one of the most common human respiratory viruses affecting the general population, with immunosuppression conferring a greater number of complications. However, prior to the emergence of the new A/H1N1 influenza virus in 2009, information available on clinical manifestations and prognosis of influenza in solid organ transplant (SOT) recipients was quite scarce. With the 2009 pandemic, knowledge of the influenza infection's behaviour in transplant recipients has increased markedly, and has highlighted the potential severity and importance of proper treatment.

Incidence and time since transplantation

The incidence of influenza, as with other respiratory viruses, was probably underestimated given the low sensitivity of diagnostic techniques prior to the polymerase chain reaction (PCR) technique. Its incidence is greater in lung transplant patients than in other organ transplants,[1,2] and infection by this virus may occur at any time after transplantation, with a median that varies between 27 and 44 months.[1-4] However, some studies have shown that it can also occur in the first days after transplantation, and when it does, it is associated with greater severity and mortality.[5,6]

Clinical manifestations and prognosis

Clinical manifestations are similar to those that occur in immunocompetent patients: most patients indicate fever and coughing. Between 29% and 40% of patients present images consistent with pneumonia, which generally has multilobar involvement. Laboratory abnormalities are more frequent than in the general population, but only the number of lymphocytes and platelets are significantly reduced after viral infection[2-5,7-9] (Table 1).

Influenza in SOT recipients is a disease with considerable associated morbidity and mortality, clearly higher than in immunocompetent patients. In studies performed in 2009, the proportion of patients who required hospitalisation varied between 73-96%, one of every five patients suffered severe complications and approximately 7-8% died[3,5] (Table 1).

Delays in hospitalisation and in the initiation of treatment with oseltamivir have been clearly associated with mortality, as occurs with the general population.[7,10,11] Another factor that significantly

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Table 1

Clinical and outcome manifestations of 2009 A/H1N1 influenza in solid organ transplantation recipients[2-5,9]

Variables	Values
Duration of symptoms before diagnosis	2 days (1-15 days)
Fever (days)	80-94
Cough (%)	80-91
Purulent sputum (%)	31
Rhinorrhoea (%)	21-30
Sore throat (%)	12-37
Dyspnoea (%)	29
Arthromyalgia (%)	52-62
Cephalea (%)	24-31
Gastrointestinal symptoms (%)	27-43
Septic shock (%)	6
Pneumonia (%)	29-40
Hypoxaemia (PO2<90%, %)	8
Lymphopaenia (<1500/µl, %)	70
Anaemia: (Haematocrit <30%, %)	18
Thrombocytopaenia (<100,000/µl, %)	14
C-reactive protein >20 mg/l (%)	21
Early antiviral therapy (≤48 hours, %)	31-76
Admission to Intensive Care Unit (%)	13-17
Mechanical ventilation (%)	4-12
Bacterial superinfection/coinfection (%)	14
Rejection (%)	6
Graft loss (%)	2
Mortality (%)	7-8

influences prognosis is the presence of bacterial coinfection, which may occur in up to 14% of SOT recipients with influenza. Therefore, patients with influenza and bacterial infections have greater mortality (43% vs. 2%), greater severity (87% vs. 2%) and longer hospital stays (26 days vs. 5 day average stay). Worse outcomes have also been linked to diabetes mellitus, the presence of pneumonia, use of antilymphocyte gamma globulin and infection in the first three months after transplantation.[3,5]

Treatment

With SOT recipients, time to initiation of treatment with oseltamivir has been associated with greater presence of complications, ICU admissions and mortality, and is the only modifiable prognostic factor.[3,5] Therefore, it is essential to have a high level of suspicion of influenza infection in these patients during periods of epidemics. This diagnostic possibility should be assessed in all cases of pneumonia, even when there is a certain diagnosis of bacterial infection, and empiric antiviral treatment initiated as early as possible. It is unclear whether these patients require higher doses than usual or longer treatment times.

Prevention

One of the most effective measures for reducing the incidence and complications of influenza is annual vaccination for seasonal influenza. This measure has been shown to reduce mortality and graft loss risk in the transplant population.[12] However, the response to influenza vaccination in the transplant population is generally lower than in the general population, with a highly variable seroprotection rate ranging from 15% to 90%.[12-17] The vaccination response will depend on the type of immunosuppression, the viral strain involved, the administration route, the use of adjuvant therapy and the presence of baseline antibody titres at the time of the vaccination. Various strategies have been evaluated for improving immunologic response to the vaccination, such as annual vaccination, booster shots and intradermal administration. Despite the hypothetical possibility of rejection after influenza vaccination mediated by the immune response to the vaccine, this has never been clinically relevant. Rejection has, however, been shown to occur in relation to influenza infection.[5,15,17] Due to these safety factors, effectiveness and potential severity of the infection, there is no known reason for delaying vaccination after the sixth month post-transplant. Given that response to the vaccination is not optimal in transplant patients, other measures need to be taken to prevent infection of a SOT recipient, such as vaccination of the recipient's cohabitants and the medical personnel treating the recipient.

Infections by other respiratory viruses

In recent years, the noteworthy role of respiratory viruses has been recognised in infections of SOT recipients; it was previously undervalued due to the limitations of microbiological methods. Molecular techniques have provided a breakthrough in the understanding of the epidemiology and clinical impact of these viruses in SOT.[18-20] There are many respiratory viruses that may affect the respiratory tract, including syncytial respiratory virus (SRV), parainfluenza (PIV), adenovirus (ADV), certain emerging viruses, such as rhinovirus (RV) and metapneumovirus (MPV), and other more recent ones, such as bocavirus (BV) and certain coronaviruses (CoV -OC43, 229E, NL63, HKU1).

Common respiratory virus infections in SOT are as common as in the general population and similarly, they exhibit clear seasonality, although some (PIV and ADV) may appear throughout the year. Although the infections are mainly contracted in the community, they are occasionally nosocomial, which is favoured by the longer elimination of the virus after the acute phase in immunosuppressed patients.[21] ADV transmission through tissues and blood has been reported. Reactivation of certain latent viruses is also possible, as occurs with ADV.[22]

Common respiratory viruses may be involved in upper and lower respiratory tract infections. As with immunocompetent patients, there are no specific clinical manifestations for a specific virus, and therefore diagnostic strategies should consider all possible viruses. Atypical presentations are common in SOT patients, which further hinders diagnosis.[23]

Many common respiratory viral infections in SOT patients are mild, self-limiting and do not require hospitalisation. However, compared to the general population, infections cause longer clinical conditions, greater risk of progression to lower respiratory tract infections and increased mortality.[24,25] They have also been associated with acute and chronic rejection.[18] Although these complications may appear in the context of any type of transplantation, they are more frequently associated with lung and heart-lung transplantation and with the degree of immunosuppression.[5,26] Replication and persistent elimination of the virus over months and even years also favour complications, which have been well documented in PIV, SRV and RV.[27] Coinfections with other pathogens are common, which may contribute to increased morbidity and mortality.[18]

Diagnosis

Aetiological diagnosis of the infection should be performed as early as possible, especially in the early post-transplant period, in patients with greater immunosuppression and during epidemics. It
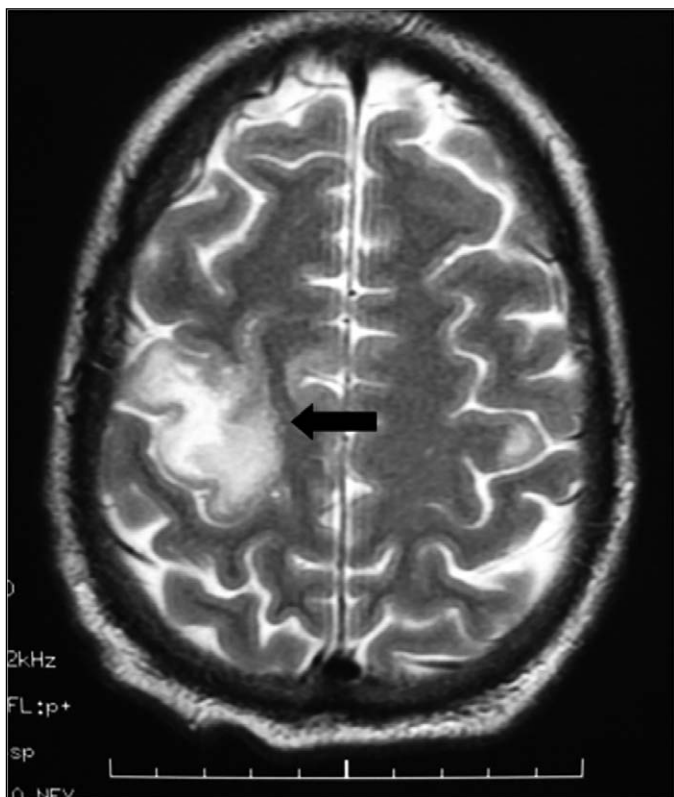
Figure 1. Brain MRI with progressive multifocal leukoencephalopathy due to JC polyomavirus. Subcortical lesion can be seen in the right cerebral hemisphere, which does not trap contrast agents, does not compress adjacent structures and does not produce oedema in its surroundings.

is important to perform them in both upper and lower respiratory tract infections, since the former may promote the onset of pneumonia.[28]

Microbiological study should be performed on respiratory samples. The use of throat and nasal swabs, properly collected and inserted into a special transport medium for viruses, is a good option.[28] If there are complications, bronchoalveolar lavage is the ideal sample since it also allows for the study of other aetiological agents.[23]

Diagnosis can be performed using cell cultures, antigen detection and PCR techniques. For immunosuppressed patients, serology is not useful since the results take too long and the immune response may be impaired. Cell culture has been the reference technique for certain viruses and allows for confirmation of virus viability. However, it is a lengthy, labour intensive methodology that is not available for the growth of all viruses. With shell vial cultures, the incubation time can be reduced to 24-48 hours, but the sensitivity is reduced. Antigen detection techniques are fast and have high specificity, but are only available for specific viruses and their sensitivity is limited.

Currently, microbiological diagnosis is mainly performed using molecular amplification methods. PCR techniques have helped detect viruses that until now could not be studied otherwise. These techniques are highly sensitive, rapid and can simultaneously detect several viruses. Current real-time PCR systems have not only optimised this methodology but have also helped to easily quantify viral DNA or RNA concentrations. The high sensitivity of these methods also has its drawbacks, such as frequent detection of viruses in asymptomatic individuals and prolonged detection of viruses in patients who have already clinically recovered. Undoubtedly, the major challenge is to determine whether a virus detected in the respiratory tract is the cause of the respiratory condition. Culture is the only technique that can report on the infectivity of the isolated virus in a patient. Quantification of the virus may be helpful in

interpreting the results, since high viral loads are associated with the presence of symptoms and may be related to the severity of the clinical picture.[29]

Prophylaxis and treatment

As with other infectious processes, immunosuppression reduction is a key element in managing these patients. It is also essential to carry out an early diagnosis that leads to the fastest possible establishment of control measures that avoid transmission and provide appropriate treatment, when possible. There are few data regarding immunoprophylaxis in SOT. Specific monoclonal antibodies (palivizumab) against SRV and SRV-IGIV seem to reduce the frequency and severity of infections.[30]

The options for treatment are very limited. Ribavirin is the only antiviral approved by the FDA for treatment of respiratory viruses other than influenza. It has been used in lower respiratory tract infections due to SRV, PIV and MPV, alone or in combination with intravenous immunoglobulins, with good results.[31] Pleconaril has been used in rhinovirus infections in other clinical situations, although it is not recommended in transplant patients since it may interact with immunosuppressants. The use of systemic interferon is also not recommended since it may predispose the patient to organ rejection. Cidofovir appears to have good results in ADV infections, although significant toxicity limits its use.[30]

Further progress is required to increase our understanding of respiratory viruses in SOT patients. In order to accomplish this, prospective and multicentre studies are needed that include large numbers of patients along with strict and lengthy follow-ups, which will then promote research into new antivirals.

Erythrovirus B19

In 1974, Cossart et al identified a new viral agent, which they called B19 because it was detected in a serum sample with this number in a hepatitis B virus detection trial. In 1985, it was officially classified as a member of the *Parvoviridae* family and recognised using the term B19.[32] It was not associated with any clinical picture until 1981 when viral antigen was detected in the serum of paediatric patients with sickle cell anaemia who had transient aplastic crises. Two years later, it was associated with erythaema infectiosum, and is currently recognised as the aetiological agent in this clinical picture. Subsequently, its vertical transmission was reported as a possible cause of miscarriage or development of foetal hydrops, as well as arthritic conditions in adults.

Erythrovirus B19 infection has worldwide distribution and is very common, as evidenced by seroprevalence studies that show how the percentage of the population that presents antibodies against this virus increases with age, reaching up to 85% in the geriatric population.[33] The virus is transmitted in the community via the respiratory tract, although vertical transmission or transmission through blood products is also possible. Currently, there is evidence that the virus may persist after acute infections in hepatic, synovial and skin tissues, although the clinical significance of this finding has not yet been determined.[34]

The B19 virus belongs to the *Erythrovirus* genus of the *Parvoviridae* family. Until the emergence of the bocaviruses, it was the only member of this family capable of causing disease in humans. The structure of the virus is very simple; its genome consists of a single DNA chain that encodes the synthesis of a nonstructural protein (NS1) and two capsid proteins (VP1 and VP2). The lack of an envelope makes it highly resistant to inactivation by heat and organic solvents. There are three circulating genotypes, with genotype 1 the most common. Two subgroups in genotypes 1 and 3 have also been reported. No association has been found between the various genotypes and clinical manifestations caused by the virus.

Diagnosis

Erythrovirus B19 infection should be suspected in SOT recipients when they present undetermined chronic or recurring anaemia, pancytopaenia and clinical manifestations that include fever, arthralgia or rash. When a patient is infected by the B19 virus, the presence of fever, arthralgia and erythaema is observed in 25%, 7% and 6% of patients, respectively. However, anaemia is present in 99% of cases.[35] The B19 virus has also been involved as an aetiological agent in other clinical manifestations, such as hepatitis, myocarditis, pneumonitis, neurological disorders and vasculitis. It has also been associated with graft dysfunction in renal transplantation. Although there is a lack of prospective studies that include large numbers of patients, the frequency of clinical manifestations attributable to B19 erythrovirus in SOT receptors is estimated at around 2% (35), and some authors have suggested that this figure may be higher.[36]

The first diagnostic step is the determination of IgG and IgM antibodies to the virus, although the production of antibodies in immunocompromised patients may be delayed or may not occur. In recent years, genomic amplification techniques have been used with increasing frequency, most of which are non-commercial and are sometimes incapable of detecting genotypes 2 and 3. Viral DNA may be detected during prolonged periods after acute infection, and therefore results should be interpreted in the appropriate clinical context. Data on the prevalence of viral DNA in blood donors ranges from 0.6% to 0.003%, and reaches a prevalence of 9% in bone marrow donors in one study. Cytological examination of bone marrow shows findings characteristic of this viral infection.

Treatment

We do not have specific antiviral treatments for B19 erythrovirus infections. Whenever possible, reducing immunosuppression should be considered. Intravenous administration of immunoglobulin has been shown to be beneficial, although the optimal treatment dose and duration has not been well established. The use of 400 mg/kg/day for 5 days is recommended. In some series, up to 28% of patients who received therapy had a recurrence of the infection. In these cases, repeating the administration of immunoglobulin is recommended. Monitoring of treatment response should be clinical.

Measles virus

The measles virus belongs to the *Morbillivirus* genus, within the *Paramyxoviridae* family. Its genome consists of a nonsegmented RNA chain with negative polarity that encodes eight proteins, which include the envelope glycoproteins: fusion protein (F) and haemagglutinin (H), which are important in the pathogenesis of the infection. Before the incorporation of the measles vaccine in the immunisation schedule, the majority of the population contracted the infection in childhood, given the ease of transmission of the virus through contact with nasal and throat secretions from infected patients, which resulted in lifelong immunity. The World Health Organization (WHO) recognises 23 genotypes of this virus, 16 of which were identified after 1990.[37] This variability has no clinical relevance and does not affect the vaccine's efficacy.

The measles virus has reappeared in recent years, affecting both healthy and immunocompromised patients. Once patients have contracted the infection, they present symptoms of fever, cough and runny nose, coupled with the presence of characteristic rash. There may be complications, such as pneumonia and encephalitis, and even systemic disseminated infection in SOT recipients.[38] The infection has also been linked to the presentation of acute rejection.[39]

The diagnosis of choice is based on the determination of specific IgM antibodies to the virus or the seroconversion of IgG. The presence of the viral genome can be detected using RT-PCR in throat swabs, urine and peripheral blood. Typically, this technique is performed in laboratories of the epidemiological surveillance network accredited by the WHO.[37] Pretransplant serological screening is recommended in order to administer the vaccine if necessary. As in the case of B19 erythrovirus infection, we do not have a specific antiviral treatment. Instead, administration of immunoglobulin as postexposure prophylaxis is recommended in unimmunised patients.

BK, JC and other polyomaviruses

The viruses of the *Polyomavirus* genus have a genome consisting of double-stranded DNA. Five species of the polyomavirus are known to infect humans: BK, JC, KI (Karolinska Institute), WU (Washington University) and Merkel cell polyomaviruses. The last one is responsible for Merkel cell carcinoma and possibly other types of neoplasms. The KI and WU polyomaviruses have been isolated mainly in respiratory secretions of various patients, including renal transplant recipients[40] but, so far, its possible pathogenic role in humans is not clear. From the clinical perspective, the most relevant viruses are the JC and BK polyomaviruses.

JC polyomavirus

This virus is the aetiological agent of progressive multifocal leukoencephalopathy (PML), a disease caused by the lytic destruction of glial cells, mainly oligodendrocytes, which affects seriously immunosuppressed subjects and is fatal in most cases.[41] The largest number of cases of this disease was reported in connection to the human immunodeficiency virus infection before the development of highly effective antiretroviral therapy. For SOT recipients, cases of PML have been reported in renal,[42] hepatic,[43] cardiac and pulmonary transplant patients. Although there are early cases, most occur years after the transplantation. In general, these are middle-aged to elderly individuals with organ transplant dysfunction due to recurrence of the underlying disease or development of rejection episodes that require additional immunosuppression. It is important to remember that in recent years, cases of PML have been reported in patients with autoimmune diseases treated with monoclonal antibodies such as natalizumab, efalizumab and rituximab.[41] Rituximab is sometimes used for the treatment of humoral rejection in renal transplant patients.[44]

From a clinical perspective, PML may present a varied combination of neurological manifestations, such as motor or sensory disorders, visual field disorders, cognitive dysfunction, aphasia, instability and gait disorders. Multiple lesions are often observed on magnetic resonance imaging in the subcortical white matter or in the cerebellar peduncles, which do not produce oedema or trap contrast agents and show no mass effect. The presence of characteristic radiological lesions along with positive PCR detection of virus DNA in the cerebrospinal fluid (CSF) is usually considered sufficient for confirming the diagnosis. However, in a non-negligible percentage of cases (6-26%), detection of the genetic material in the CSF is negative and, in that case, cerebral biopsy is required for diagnosis.[45]

There is no truly effective antiviral therapy for the JC virus. The most significant therapeutic measure is drastic reduction of immunosuppression. For SOT, this measure is especially feasible in renal transplantation, since there is the possibility that the patient will return to a haemodialysis programme. Some therapeutic success has recently been reported with the use of mirtazapine, a serotonergic receptor blocker. These receptors are the route of entry into cells for the JC virus.[41] Isolated clinical cases with favourable outcomes have been reported, and there is a clinical trial under development using the antimalarial drug mefloquine as treatment.[46]

BK polyomavirus

Human infection occurs almost universally and asymptomatically in the first decade of life. As a result, a latent infection is established in the urinary system and its excretion in urine may be occasionally detected in healthy subjects. Renal transplant recipients are the group in which active infection by this virus is usually detected, although the active infection has been occasionally reported in other types of SOT.[47]

The most characteristic clinical picture of the infection in renal transplantation is BK polyomavirus nephropathy. The following risk factors of this nephropathy have been reported: cadaveric donor, ischaemia-reperfusion damage, HLA donor-recipient incompatibility, rejection episodes and their treatment, cumulative doses of steroids, drugs that cause depletion of lymphocytes, high levels of immunosuppressant drugs, and treatment with tacrolimus versus that was performed with cyclosporine or mTOR inhibitors.[47,48]

Initially, the infection may progress asymptomatically and may only be detected by the presence of decoy cells (epithelial cells with characteristic intranuclear inclusions) in urine, by high levels of viruria (defined as the excretion >7 $\log_{10}$ geq/ml) and by the presence of viraemia (detection of BK DNA in the patient's blood samples).[47] In later stages, nephropathy usually manifests as elevated serum creatinine. Diagnostic confirmation requires a biopsy of the transplanted kidney in which the characteristic intranuclear inclusions are observed in the tubular epithelium and in the parietal cells of the glomerulus. These lesions are accompanied by variable degrees of inflammation, fibrosis and tubular atrophy.[49] It is important to remember the need for differential diagnosis of the BK nephropathy and the nephropathy caused by graft rejection, because they may present clinical and even histological similarities, and their corresponding therapeutic approaches are completely opposite.

Treatment of BK virus nephropathy is based mainly on reduction of the patient's immunosuppression, so as to stimulate the immune response against this virus.[47] Various immunosuppression reduction regimens have been suggested. Monitoring of treatment response is performed using measurements of serum creatinine and levels of viraemia and viruria. In the event of persistent infection, various alternatives have been suggested but, to date, none of the studies have been conclusive in favour of one or the other.[47] These alternatives include the use of cidofovir, leflunomide, intravenous immunoglobulins and quinolones.

Currently, a prophylactic approach is advocated for this infection, using periodic measurement of viruria and the presence of decoy cells in urine. Monthly measurement is recommended during the first three months and quarterly until 12 months have elapsed since transplantation. Positive cytology and detection of 7 $\log_{10}$ geq/ml are indications for determining viraemia. Plasma DNA levels greater than 4 $\log_{10}$ for more than three weeks indicate a presumptive diagnosis of nephropathy due to the virus. In this case, the physician may choose confirmation through biopsies of the transplanted kidney or directly by reduction of immunosuppressive therapy.[47] Some studies have suggested that periodic monitoring directly in the blood may be useful.[50] Recent research has demonstrated the protective role of quinolones in the development of BK virus nephropathy.[51] Although conflicting experiences have been published, recent studies suggest a favourable prognosis for patients who receive a new renal transplant after failure of the previous kidney due to BK polyomavirus nephropathy, especially if viraemia is eliminated before the new transplantation.[52]

Conflict of interest

The authors declare that they have no conflict of interest.

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