Not the Usual Viral Suspects: Parvovirus B19, West Nile Virus, and Human T-Cell Lymphotrophic Virus Infections After Kidney Transplantation

Raymund R. Razonable, MD

Summary: Kidney transplant recipients are at increased risk of developing clinical disease due to uncommon opportunistic viral pathogens. Refractory anemia is classically associated with parvovirus B19 infection. West Nile virus has the propensity to cause fever and neurologic symptoms, while spastic paresis and lymphoma can be triggered by human T cell lymphotrophic virus. In this review article, the epidemiology, clinical manifestations, diagnosis and treatment of less common viruses are discussed in the setting of kidney transplantation.

Semin Nephrol 36:428-434

Keywords: Flavivirus, retrovirus, erythrovirus, opportunistic infection, encephalitis, anemia

Kidney transplant recipients are at high risk of developing viral infections, some of which are common such as herpes simplex virus, BK virus, and cytomegalovirus, whereas others are rare and uncommon. For the latter group of viral infections, their clinical suspicion may not be considered initially, resulting in delayed diagnosis and management. This article highlights the epidemiology, clinical manifestations, diagnosis, and treatment of uncommon infections caused by parvovirus B19, West Nile virus, and human T-cell lymphotrophic virus after kidney transplantation.

PARVOVIRUS B19

Virology

Parvovirus B19 is a small, nonenveloped, single-stranded, linear DNA virus that belongs to the family *Parvoviridae* (Table 1). It is one of the smallest DNA viruses known to infect human beings. As the prototype of the genus erythrovirus, parvovirus B19 has a unique trophism for human erythroid progenitor cells.[1] This very limited host range is a unique characteristic of all the erythroviruses, and for parvovirus B19 in particular, its only known host is human beings. Parvovirus attaches to the cellular receptor, the erythrocyte P antigen, a globoside that is found on erythroid cells, erythroid precursor cells, and red cells of the placenta and fetal tissues.[1]

Division of Infectious Diseases and the William J von Liebig Center for Transplantation and Clinical Regeneration, Mayo Clinic, Rochester, MN.

Financial disclosure and conflict of interest statements: none.

Address reprint requests to Raymund R. Razonable, MD, Division of Infectious Diseases, Mayo Clinic, 200 First St SW, Marian Hall, 5th Floor, Rochester, MN55905. E-mail: razonable.raymund@mayo.edu

0270-9295/ - see front matter

http://dx.doi.org/10.1016/j.semnephrol.2016.05.019

Epidemiology

Parvovirus B19 infection is common throughout the world, occurring sporadically and sometimes in clusters. Infection is most common among children, and up to half of individuals aged 15 years will have serologic evidence of previous infection. More than 70% of adults, including adult kidney transplant recipients, will have positive parvovirus B19-IgG antibody.[2–4] Transmission of parvovirus B19 is through contact with infected respiratory secretions. Thus, close person-to-person contact and fomites serve as mechanisms for viral transmission. Nosocomial transmission has occurred. Parvovirus B19 also can be transmitted vertically by the transplacental route, through blood transfusion, and organ and tissue transplantation.[5,6] In a study of pediatric kidney transplant recipients with parvovirus D+/R- serologic mismatch, detection of viral DNA in a kidney allograft biopsy sample was associated with parvovirus B19 viremia after transplantation, suggesting efficient viral transmission by the infected allograft.[7] The incidence of parvovirus infection after kidney transplantation is not defined clearly owing to a lack of surveillance studies. One single-center study reported that 12% of kidney transplant recipients with significant anemia had parvovirus B19 DNA detected in the peripheral blood.[8] Other studies have reported a low rate of 3% (2 of 60 kidney transplant recipients),[9] a modest rate of 10% (6 of 60 kidney transplant recipients tested during the first year),[10] or a rate as high as 58.7% (84 of 143 kidney transplant recipients).[11] Other studies, on the other hand, have not detected the virus. Such a wide variation in reported incidence rates may be related to seasonal variation, clustering of cases, varying diagnostic modalities and sensitivities, variation in transplantation practices, and patient populations. Importantly, however, detection of low-level parvovirus B19 DNA in the blood may not always be meaningful, because only patients with high levels (defined as $>10^6$ copies in one study) have clinically relevant anemia.[2,11]

Table 1. Infections Caused by Parvovirus, West Nile Virus, and Human T-Cell Lymphotrophic Virus After Kidney Transplantation

	Parvovirus	West Nile Virus	Human T-Cell Lymphotrophic Virus
Type of virus	Erythrovirus Single-stranded DNA	Flavivirus Single-stranded RNA	Retrovirus Single-stranded RNA
Epidemiology	Common worldwide;0%-58% of kidney transplant recipients	Endemic in many parts of the world; 10% seroprevalence rate in transplant	Endemic in many parts of the world; uncommon in United States; uncommon after transplantation
Clinical diseases	Pure red cell aplasia; some with leukopenia and thrombocytopenia; some organ-invasive disease	West Nile fever; neuroinvasive disease	Adult T-cell leukemia/ lymphoma; HTLV-1–associated myelopathy or tropical spastic paresis
Treatment	Reduction of drug immunosuppression; intravenous immunoglobulin	Intravenous immunoglobulin; interferon	Chemotherapy for malignancy; corticosteroids; uncertain role of antiretroviral drug
Prevention	Selected; precautions in hospitalized patients to prevent nosocomial transmission	Avoid mosquito bites; selective approach to screen donors with West Nile symptomatology and during active West Nile season	Selective screening of donors from endemic regions

Clinical Manifestations

The clinical manifestations of parvovirus B19 infection are erythema infectiosum (also known as fifth disease—a febrile illness characterized by skin rash in immunocompetent children), arthropathy (especially seen during primary infection in adults), hydrops fetalis (when it infects the developing fetus in utero resulting in fetal death), and profound anemia (causing aplastic crisis and pure red cell aplasia, which sometimes is accompanied by derangement of the other cell lineage such as leucocytes).[12,13] Anemia may be transient among patients with underlying hematologic abnormalities such as sickle cell disease (transient aplastic crisis).[12,13] Parvovirus B19 infection is directly cytotoxic to the erythroid series; the virus replicates in erythroid precursor cells in the bone marrow and the blood, resulting in their destruction. Chronic parvovirus B19 infection occurs in kidney transplant recipients and other immunocompromised patients, where it causes pure red cell aplasia as the most common clinical presentation. In the largest series of 98 transplant recipients with parvovirus B19 infection, the most common manifestation (occurring in 99% of patients) was profound, severe, and recurrent anemia.[14] Leukopenia and thrombocytopenia also were observed in 38% and 21%, respectively.[14] Other clinical symptoms associated with parvovirus B19 infection were fever, arthralgia, and rash.[14] Organ-invasive diseases such as hepatitis, pneumonitis, and neurologic disease also have been reported in transplant recipients.[14,15]

Diagnosis

A high clinical suspicion for the diagnosis of parvovirus B19 infection should be considered in a kidney transplant recipient with profound anemia, especially when it is recurrent despite blood product and erythropoietin support and adjustments (or withdrawal) of myelosuppressive medications. In many instances, anemia is attributed to underlying comorbidity and intake of myelosuppressive medications such as trimethoprim-sulfamethoxazole, valganciclovir, and mycophenolate mofetil. If anemia is severe or does not improve with adjustments of medications, testing for parvovirus B19 should be considered. Serology, nucleic acid detection, and bone marrow examination are the most commonly used methods for diagnosis.[14] During acute primary parvovirus illness, the patients often are viremic. Direct viral nucleic acid detection in the blood, bone marrow, and other organs is a highly sensitive and specific method for diagnosis.[1,14] Serology to detect parvovirus B19-IgM still may be negative at the early stage of infection owing to delayed and impaired ability of kidney transplant recipients to mount a robust antibody production, especially when the degree of drug-induced immunosuppression is intense. In one study, parvovirus B19-IgM was detected in only 75% of all patients with active parvovirus B19 infection.[14] In contrast, nucleic acid detection by polymerase chain reaction is a highly sensitive method for viral detection.[14] Notably, parvovirus B19 viremia often is prolonged, with a duration that extends for a much longer period after resolution of the acute clinical illness. For example, the virus may persist for the lifespan of the infected red cell (ie, 3 months). Hence, the detection of parvovirus B19 DNA alone is not sufficient to indicate disease activity. The gold standard for diagnosis remains bone marrow examination, where the virus can be shown using in situ hybridization and immunohistochemical staining. The bone marrow examination of parvovirus B19 infection