# Varicella Infection After Heart and Lung Transplantation: A Single-Center Experience

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Disseminated varicella-zoster virus infection after organ transplantation in adults is a rare but serious event causing significant morbidity and mortality. We describe our 10-year experience of 13 cases in a single center, including risk factors for infection, lack of protection from pre-existing anti-varicella-zoster virus antibodies, and unusual modes of presentation, including disseminated intravascular coagulation. We also report our preliminary observation of resolution of infection without sequelae in 4 patients with severe disseminated varicella-zoster virus infection who were treated with the combination of intravenous acyclovir and polyspecific intravenous immunoglobulin. J Heart Lung Transplant 2007;26:399–402. Copyright © 2007 by the International Society for Heart and Lung Transplantation.

The varicella zoster virus (VZV) is a common pathogen that causes chickenpox, a relatively benign self-limiting infection of childhood. Up to 90% of the population are infected with VZV in childhood and develop subsequent immunity with circulating anti-VZV antibody. Primary VZV infection in immunocompetent adults is rare but can lead to a much more severe disease, with mortality rates of up to 30%.[1]

VZV is a herpes virus and infection leads to viral latency and a risk of subsequent reactivation. Reactivation usually presents as a painful skin rash in a dermatome distribution commonly known as shingles. After reactivation, however, there is a risk of disseminated infection. Risk factors include increasing age, malignancy, immunodeficiency, organ transplantation, and immunosuppressive drug therapy.[2] Transplant recipients are at increased risk of both primary infection and reactivation, followed by dissemination.[3] There have been few studies of VZV after thoracic organ transplantation, but an incidence of 15% in lung and 17% in heart transplant recipients has been reported.[4]

## METHODS

We retrospectively analyzed 1267 adult heart transplant recipients and 648 adult lung transplant recipients under follow-up at Harefield Hospital, London, United Kingdom, at any time during the study period of 1995 to 2006. Patients were identified from the results of serologic and molecular testing. Medical records were then examined to obtain clinical and laboratory findings as well as the response to treatment.

## RESULTS

Thirteen patients (10 men, mean age 39 years) were identified with disseminated VZV. Eleven (1.7% of the study population) were heart-lung or lung transplant recipients (7 for cystic fibrosis) and 2 (0.15% of the study population) were orthotopic cardiac transplant recipients. All were on triple agent immunosuppression with a combination of cyclosporine or tacrolimus with azathioprine or mycophenolate mofetil and prednisolone (dose range, 5–15 mg) at the time of infection.

Clinical and laboratory features are shown in Table 1. Most had significant comorbidity: coexisting bacterial infection in 4, neutropenia in 3, chronic renal impairment (glomerular filtration rate $<$ 40 ml/min) in 6, small-bowel carcinoma in 1, central pontine myelinosis in 1, recent retransplantation in 1, recent high-dose steroids for acute rejection in 2, and distal intestinal obstruction syndrome owing to underlying cystic fibrosis in 2. Only 1 gave a history of VZV contact. Nine presented with the typical vesicular rash, but 4 did not. Eight cases occurred within the first year after transplantation and 5 at a later stage. Three of the 5 long-term patients died, and 4 of 8 recent transplant recipients died.

VZV infection was demonstrated in the context of the presenting features by combinations of VZV immunoglobulin (Ig) M serology, VZV DNA polymerase chain reaction (PCR) in peripheral blood, and electron microscopy of fluid from skin vesicles showing a characteristic appearance of herpes virus and viral culture. The diagnosis of VZV pneumonitis was made in the context of proven VZV infection by the clinical features as well as the appearance of high-resolution computed tomography (HRCT) scanning of the chest (Figure 1). The diagnosis of VZV encephalitis was made after the

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**Table 1.** Characteristics of Patients Identified With Disseminated Varicella-Zoster Virus

| Patient | Diagnosis | Type of transplant | Age at presentation (years) | Time post-transplant (months) | Immunosuppression | | | | | VZV IgG | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Cyclosporin | Tacrolimus | Azathioprine | Mycophenolate | Prednisolone | Pre-transplant | At Presentation |
| 1 | CF | HLT | 52 | 7 | ● | | ● | | ● | ? | – |
| 2 | CF | BSSLT | 31 | 6 | ● | | ● | | ● | – | – |
| 3 | CCHD | OCT | 21 | 84 | ● | | | ● | ● | + | + |
| 4 | DCM | OCT | 61 | 9 | ● | | | | ● | + | + |
| 5 | Bronch | BSSLT | 49 | 84 | | ● | | ● | ● | + | + |
| 6 | CF | HLT | 40 | 96 | | ● | | ● | ● | + | + |
| 7 | CF | HLT+SLT | 30 | 0.25 | ● | | | | ● | ? | + |
| 8 | CF | HLT | 22 | 11 | | ● | ● | | ● | + | + |
| 9 | Emphysema | BSSLT | 62 | 108 | ● | | ● | | ● | ? | + |
| 10 | Emphysema | SLT | 55 | 9 | ● | | ● | | ● | ? | + |
| 11 | CCHD | HLT | 22 | 11 | ● | | ● | | ● | ? | + |
| 12 | CF | HLT | 29 | 108 | | ● | ● | | ● | ? | + |
| 13 | CF | BSSLT | 30 | 7 | ● | | | ● | ● | + | + |

CF, cystic fibrosis; DCM, dilated cardiomyopathy; Bronch, bronchiectasis; CCHD, complex congenital heart disease; VZV, varicella zoster virus; Ig, immunoglobulins; DIC, disseminated intravascular coagulation; MP, methylprednisolone; ?, unknown; CRI, chronic renal impairment (GFR < 40 mls/min); SLT, single lung transplant; BSSLT, bilateral sequential single lung transplant; HLT, heart-lung transplant; OCT, orthotopic cardiac transplant; HLT+SLT, subsequent single lung transplant following heart-lung transplantation.

*Other comorbidities: patient 6, small-bowel carcinoma; patient 7, retransplantation; patient 8, distal intestinal obstruction syndrome; patient 9, central pontine myelinosis; patient 12, distal intestinal obstruction syndrome.

discovery of CT findings consistent with encephalitis and after cerebrospinal fluid VZV DNA PCR.

Eleven patients were treated with high-dose intravenous (IV) acyclovir (10 mg/kg thrice daily; mean duration, 12.8 days). Patient 9 was treated with IV ganciclovir. Patient 6 was only diagnosed with varicella infection at autopsy. Patient 5, who had persistently raised varicella viral load and had relapsed on oral acyclovir after IV treatment, was treated for 6 months with oral valacyclovir (Valtrex, Glaxo-SmithKline, Uxbridge, Middlesex, UK) with PCR monitoring of the viral load. Four patients (2, 5, 12, and 13), who were suffering rash, pneumonitis, and/or encephalitis, were also treated with IV polyspecific immunoglobulin (1g/kg IV daily Flebogamma, Grifols, Cambridgeshire, UK). Three of these 4 patients (2, 5, and 13) had no long-term sequelae, and the fourth (patient 12) died from bowel perforation owing to distal intestinal obstruction syndrome after resolution of the varicella infection.

Seven lung transplant recipients died, 4 early after diagnosis (mean, 9 days). Three of these patients presented with a pyrexial illness and were found to have disseminated intravascular coagulation without a typical varicella rash. Two late deaths (patient 10 and 11) occurred at 10 and 36 months from respiratory failure owing to VZV-related pulmonary fibrosis. Neither heart transplant recipient died or experienced sequelae of VZV infection.

## DISCUSSION

Disseminated VZV infection caused considerable morbidity and mortality in our thoracic organ transplant patients. In the general population, shingles without further disseminated infection is common. The incidence increases with age: about 1 in 4 adults will experience an attack in their lifetime.[5] Shingles is also common in transplant recipients. It is diagnosed after noting the characteristic dermatomal rash, often without further laboratory investigation, and therefore its incidence could only be determined in a prospective study. Treatment of the rash without systemic symptoms with oral acyclovir may reduce the severity and the duration of the rash but does not require hospitalization.

The incidence of disseminated infection was 10 times higher in lung transplant recipients than after heart transplantation. The reasons for this are uncertain; however, possibilities may include the increased comorbidity in lung transplant recipients with disseminated infection (see Table 1), the different intensity of the immunosuppression between the heart and lung transplant recipients according to local protocol, and possible immune dysregulation in the lung graft.

The presence of anti-VZV antibody did not prevent disseminated disease. The clinical presentation was often atypical, with no vesicular rash. Presentation with disseminated intravascular coagulation was associated with a uniform mortality. This may be attributable partly to a delay in diagnosis caused by this presentation and thus delayed anti-viral therapy. Varicella infection should be considered in the differential diagnosis in transplant recipients presenting with disseminated intravascular coagulation, pneumonitis, or encephalitis.

Varicella infection was more common in the first year after transplantation when immunosuppression was greatest; neutropenia, recent high-dose corticosteroid