Exceptional Cases

Lethal varicella-zoster virus reactivation without skin lesions following renal transplantation

Jonathan Jantsch1, Barbara Schmidt2, Jürgen Bardutzky3, Christian Bogdan1, Kai-Uwe Eckardt4 and Ulrike Raff4

1Microbiology Institute, Clinical Microbiology, Immunology and Hygiene, 2Institute of Clinical and Molecular Virology, German National Reference Centre for Retroviruses, 3Department of Neurology, University Hospital Erlangen and 4Department of Nephrology and Hypertension, University Hospital Erlangen, Friedrich-Alexander University of Erlangen-Nuremberg, Erlangen, Germany

Correspondence and offprint requests to: Ulrike Raff; E-mail: ulrike.raff@uk-erlangen.de

Abstract
Patients after solid organ transplantation are at increased risk of developing herpes zoster and are more likely to develop major complications such as cutaneous dissemination, post-herpetic neuralgia and visceral organ involvement. We report on a 68-year-old woman being varicella-zoster virus (VZV)-seropositive prior to transplantation, who developed fatal VZV meningoencephalitis after renal transplantation presenting with non-specific neurologic symptoms. The case illustrates that VZV reactivation may occur in renal transplant recipients in the absence of skin lesions. Approaches towards risk assessment pre-transplantation and prophylactic regimens for the prevention of VZV recurrence are needed.

Keywords: renal transplantation; varicella-zoster reactivation

Background
Especially in elderly and immunocompromised patients, sporadic reactivation of varicella-zoster virus (VZV) can lead to herpes zoster (HZ) [1]. Reactivation of VZV is due to a decrease of cell-mediated immunity, and it has been demonstrated that anti-VZV T-cell responder frequency rather than VZV-specific Ig-titre correlates with the resolution of HZ [2]. Patients with immunosuppression after solid organ transplantation are at increased risk of developing dissemination of HZ over several dermatomes, post-herpetic neuralgia and visceral organ involvement.

We report on a patient with cadaveric donor renal transplantation (RTX) who developed lethal VZV reactivation. The case illustrates that VZV reactivation post-transplantation can occur in a wide array of clinical presentations rendering diagnosis difficult and suggests that novel strategies for risk assessment in patients awaiting RTX should be explored.

Case report
A 68-year-old woman presented to her local hospital with deterioration of coordination, somnolence, tremor and increased muscular tone. She had received a kidney transplant 13 months prior to admission. Her immunosuppressive regimen consisted of tacrolimus, prednisolone and azathioprine. An acute humoral rejection 1 week post-transplantation had been treated with thymoglobuline, immunoadsorption and anti-CD 20 antibodies (rituximab).

At the time of transplantation, the patient was positive for VZV-IgG and negative for IgM. She had no known history of HZ.

On admission, neurologic symptoms were attributed to tacrolimus toxicity. Since the patient had schizoid psychosis and was treated with haloperidol, an extrapyramidal syndrome was also considered as a differential diagnosis. When symptoms were aggravated, a cerebral CT scan was performed, which revealed hypodense areas in both basal ganglia, prompting a lumbar puncture for suspected meningoencephalitis. Cerebrospinal fluid (CSF) cell count was elevated, and antiviral therapy with acyclovir 500 mg ter in die (TID) was started (corresponding to 7 mg/kg).

Because of progressive reduction of vigilance, the patient was transferred to our tertiary care centre. At the time of admission she was somnolent, showed meningism and poor cough and gag reflexes, a 2–3/s alternating tremor, increased muscular tone, as well as rigour in all extremities, most pronounced in the upper extremities. Propriocceptive reflexes were symmetrical but weak on the lower extremities and normal and symmetrical in the upper extremities. No pyramidal signs and no paresthesias were present. Importantly, the patient did not develop skin findings pointing to herpes zoster, either before she felt ill, at presentation or during the course of her disease. Lab tests revealed leucopaenia (2.3 * 10^9/L, normal range 4–10) and discrete lymphopaenia (20.5%, normal range 25–40%) as well as elevated C-reactive protein (6.1 mg/L, normal range <5)
and elevated lactate dehydrogenase (429 U/L, normal range <250). CSF showed an elevated white cell count with a lymphocytic pleocytosis, an elevated protein level and a glucose level that was about 53% of the blood glucose level suggesting a viral meningoencephalitis (Table 1).

Specimens were sent for fungal and bacterial cultures, Gram staining, testing for cryptococcal antigen and nucleic acid testing for herpes simplex virus (HSV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), human herpesvirus-6 (HHV-6), picorna and rubella virus and parvo- and adenovirus, which were all negative. However, VZV DNA was detectable (Table 1), and the liquor-serum ratio of VZV-IgG was elevated 10-fold in comparison with CMV, measles, rubella and herpes simplex virus. Thus, a diagnosis of VZV meningoencephalitis was made, and acyclovir therapy was increased to 10 mg/kg body weight TID intravenously. However, the patient's vigilance further deteriorated; she lost cough and gag reflexes and developed pneumonia with subsequent respiratory insufficiency and the need for mechanical ventilation. Additional imaging studies were performed, revealing progressive ischaemic lesions in the pons and the left hemisphere and cerebral vasculopathy. Electroencephalography intermittently showed epileptiform discharges over the left temporooroccipital region. However, clinical signs of seizures were not observed. Magnetic resonance angiography intermittently showed rarefaction of intracranial vessels consistent with VZV vasculopathy (Figure 1). On the basis of these findings, prednisone therapy was increased to 500 mg for 3 days in order to suppress deleterious vasculitic activity. There was no further progression of neurologic symptoms and radiologic findings. VZV DNA was detectable in the cerebrospinal fluid up to week 3 (Table 1). Antiviral therapy was continued until day 30. Unfortunately, the patient showed only very limited recovery from the multiple cerebral lesions. When she was transferred to a neurologic rehabilita-

### Table 1. Cerebrospinal fluid analyses of our patient in the course of disease

<table>
<thead>
<tr>
<th>Cerebrospinal fluid analysis</th>
<th>Admission</th>
<th>1st week</th>
<th>2nd week</th>
<th>3rd week</th>
<th>4th week</th>
<th>Discharge</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (mg/L)</td>
<td>1959</td>
<td>1692</td>
<td>948</td>
<td>1211</td>
<td>1215</td>
<td>n.d.</td>
<td>≤ 500</td>
</tr>
<tr>
<td>Glucose liquor-serum ratio</td>
<td>53</td>
<td>28</td>
<td>59</td>
<td>42</td>
<td>42</td>
<td>46</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>2.95</td>
<td>2.08</td>
<td>4.11</td>
<td>2.71</td>
<td>2.58</td>
<td>2.61</td>
<td>1.21–2.09</td>
</tr>
<tr>
<td>Red cell count (cells/μL)</td>
<td>20</td>
<td>0</td>
<td>9</td>
<td>300</td>
<td>85</td>
<td>405</td>
<td>0</td>
</tr>
<tr>
<td>White cell count (cells/μL)</td>
<td>3</td>
<td>12</td>
<td>3</td>
<td>13</td>
<td>15</td>
<td>9</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>40</td>
<td>1</td>
<td>Not analysed</td>
<td>0</td>
<td>1</td>
<td>Not analysed</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>60</td>
<td>99</td>
<td>Not analysed</td>
<td>100</td>
<td>99</td>
<td>Not analysed</td>
<td></td>
</tr>
<tr>
<td>VZV DNA (copies/mL)</td>
<td>10</td>
<td>18</td>
<td>Not detectable</td>
<td>1</td>
<td>Not detectable</td>
<td>Not detectable</td>
<td></td>
</tr>
<tr>
<td>VZV IgG liquor-serum ratio*</td>
<td>607</td>
<td>61</td>
<td>510</td>
<td>835</td>
<td>640</td>
<td>788</td>
<td></td>
</tr>
<tr>
<td>HSV IgG liquor-serum ratio*</td>
<td>50</td>
<td>48</td>
<td>28.7</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td></td>
</tr>
<tr>
<td>Measles IgG liquor-serum ratio*</td>
<td>46</td>
<td>43</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td></td>
</tr>
<tr>
<td>Rubella IgG liquor-serum ratio*</td>
<td>68</td>
<td>57</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td></td>
</tr>
<tr>
<td>CMV IgG liquor-serum ratio*</td>
<td>27</td>
<td>25</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td></td>
</tr>
</tbody>
</table>

*specific IgG levels in CSF divided by specific IgG levels in serum, given as (×10³).
tion centre, she was awake but required supportive ventilation. She died 4 months later.

Discussion

As in the present case, the diagnosis of VZV reactivation can be challenging in particular in the absence of skin manifestations. Peterson and Ferguson reported three renal transplant patients suffering from fatal VZV reactivation affecting the central nervous system. In contrast to our case, in these patients skin lesions appeared during the course of the disease [3]. It is noteworthy that the meningoencephalitis in our patient occurred 13 months after transplantation in the presence of low-dose maintenance immunosuppression.

The likelihood of patients suffering from HZ after RTX to develop post-herpetic neuralgia or a disseminated VZV disease is up to nine times increased compared with the general population [4]. In the majority of patients, HZ infection occurs during the first year after solid organ transplantation [5]. In this respect, it is of great importance to note that VZV vasculopathy may also occur during reactivation up to several weeks and months after HZ infection and after skin lesions have disappeared, rendering diagnosis even more difficult [6]. VZV vasculopathy, which may occur at primary infection or during reactivation, causes ischaemic infarctions, as well as aneurysms and subarachnoidal and cerebral haemorrhage leading to a broad spectrum of neurological symptoms ranging from headaches to acute hemiplegia and changes in mental status.

Given the potentially devastating consequences of VZV disease in patients receiving immunosuppression, the question arises about the efficacy of vaccination and prophylactic therapy and improved risk assessment to identify patients at high risk.

Robust cell-mediated immunity against VZV was correlated with reduced HZ morbidity [2]. One possibility to quantify the patient’s VZV-specific cell-mediated immunity is by determining the VZV-specific T-cell compartment. Therefore, prospective studies should be considered in renal transplant patients to evaluate the role of VZV-specific interferon-gamma-secreting CD8+ T cells from peripheral blood [7].

Considering that cellular immunity in patients with end-stage renal disease (ESRD) on dialysis is impaired [8,9], and that cellular immunity in these patients will be massively suppressed at the time of transplantation by current induction therapies, vaccination of these patients prior to transplantation to boost cellular immunity may only be of limited value. In line with this idea, Arness et al. reported that suffering from HZ pre-transplantation and thereby naturally boosting the anti-VZV-specific cellular immunity does not necessarily protect from HZ post-renal transplantation [4]. Therefore, a history of HZ pre-transplantation does not indicate that the VZV-specific cellular immunity has been sufficiently refreshed to protect from HZ episodes post-transplantation. This might question the rationale to vaccinate ESRD patients on dialysis awaiting renal transplantation with the licensed live-attenuated VZV Oka strain for varicella in order to prevent VZV reactivation post-transplantation. Although after renal transplantation live vaccines are usually not recommended [10], there are studies in solid organ transplant recipients showing that vaccinations using the licensed live-attenuated VZV Oka-strain are safe and immunogenic, safety and efficacy of Zostavax® has not been assessed in solid organ transplant recipients [11,12]. In addition, there are data in bone marrow transplant recipients demonstrating that treatment post-transplantation with valacyclovir is effective [13]. However, in solid organ transplant recipients, efficacy of prophylaxis has not been studied.

In conclusion, a careful evaluation of each patient’s history of VZV or HZ pre-transplantation should be performed, and antiviral prophylaxis should be studied in this population. Importantly, a history of HZ in ESRD patients awaiting transplantation may not protect patients from post-transplant HZ. In addition, VZV prophylaxis might be considered in patients receiving enforced immunosuppressive therapy for acute allograft rejection irrespective of prior history of HZ.

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References

A possible rare cause of renal failure in streptococcal infection

Jia-Feng Chang1, Yu-Sen Peng1, Chien-Chen Tsai2, Meng-Shiuan Hsu3 and Chun-Fu Lai1

1Division of Nephrology, Department of Internal Medicine, 2Department of Anatomic Pathology and 3Division of Infectious Diseases, Department of Internal Medicine; Far Eastern Memorial Hospital, Taipei, Taiwan

Correspondence and offprint requests to: Dr. Chun-Fu Lai; E-mail: d954210111@ntu.edu.tw

Abstract

To the best of our knowledge, this is the first biopsy-proven case of streptococcal infection-associated acute interstitial nephritis (AIN) with existence of streptococcal pyrogenic exotoxin B (SPE B) by a controlled immunohistochemical method. Both the intact tubular epithelial cells and oedematous interstitium had strong positive signals, whereas only interstitial inflammation was dominant without tubular necrosis. Reflective of the nature of AIN is that the injury from the hypersensitivity reaction was specific for renal interstitium instead of tubules. SPE B is potentially allergenic and may confuse the clinicians due to its clinical mimicry of drug-induced AIN. Although very rare, AIN might be included into the differential diagnosis of patients with streptococcal sepsis and acute renal failure.

Keywords: interstitial nephritis; renal failure; Streptococcus

Introduction

Acute interstitial nephritis (AIN) was first described as a ‘cellular and fluid exudation in the interstitial tissue’ by Councilman in 1898. This venerable treatise illustrated the pathogenetic link between AIN and a septic state with beautifully hand-drawn images according to the kidneys of patients dying of scarlet fever and diphtheria [1]. Over 100 years have passed since Councilman recognized interstitial nephritis as a distinct disease entity, but no study to date has further demonstrated the pathogenesis by detection of streptococcal exotoxins in renal interstitium.

Streptococcal toxic shock syndrome is defined as an invasive Group A streptococcal (GAS) infection associated with shock, multiple organ failure, and erythematous rash with subsequent desquamation. Acute renal failure (ARF) is present in almost all patients within <72 h, and some of them require haemodialysis. However, the true aetiology of ARF has not been illustrated in detail and is mostly considered to be sepsis-related ischaemic acute tubular necrosis without kidney biopsy. Herein, we report an exceptional case of ARF fulfilling the diagnostic criteria of GAS toxic shock syndrome with biopsy-proven AIN.

Case report

A 22-year-old, previously healthy man experienced an episode of sore throat, diarrhoea and general myalgia for 1 week before admission. He sought medical help, and acetaminophen was initially prescribed. Antibiotic and non-steroidal anti-inflammatory drug (NSAID) exposure was denied. As the symptoms deteriorated, he was admitted due to high fever and chills. On the day of admission, his blood pressure was 80/38 mmHg, heart rate 144 beats per minute, respiratory rate 20 breaths per minute and temperature 38.5°C (101.3°F). Physical examination disclosed injected throat and erythematous rash over the trunk, but was otherwise unremarkable. Biochemical studies revealed the following: serum creatinine, 4.8 mg/dL (424.3 μmol/L); urea nitrogen 32 mg/dL (11.4 mmol/L); and serum sodium, 130 mEq/L (130 mmol/L). The haemoglobin level was 16.9 g/dL (169 g/L), platelet count 8.6 × 109/μL (8.6 × 109/L) and white blood cell count 19.3 × 109/μL (19.3 × 109/L). Urinalysis showed a 3+ positive for urine protein, 167 white