Case Report

An unusual case of CMV cutaneous ulcers in a renal transplant recipient and review of literature

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Abstract

Cytomegalovirus (CMV) infection involving the skin is rare. We present a case of a renal transplant recipient who developed fever and axillary, scrotal and penile skin ulcers after renal transplantation. The skin ulcers did not heal with antibiotics. The skin biopsy revealed CMV inclusion bodies, CMV antigen on immunohistochemistry and high CMV DNA copies. The patient was diagnosed with CMV cutaneous ulcers. The skin ulcers healed after treatment with intravenous ganciclovir and oral valganciclovir. The diagnosis of CMV disease should be considered in the febrile immunosuppressed patient with skin ulcers. The biopsy of the cutaneous lesions may provide the diagnostic clue in such patients.

Keywords: cytomegalovirus infection ; renal allograft recipient skin ulcers

Backgrounds

Cytomegalovirus (CMV) is a common viral infection in renal transplant recipients, affecting more than 50% of recipients of major organ transplants [1]. The most common clinical presentation is a viral syndrome characterized by fever, leucopenia, thrombocytopenia, atypical lymphocytosis and other well-documented manifestations including pneumonia, liver dysfunction and gastrointestinal disease [2]. Skin infection with CMV is rare. Here, we report an unusual case of a renal allograft recipient who developed ulcers over the right axilla, scrotum and penile skin which later developed into ulcers (Figure 1). Both the donor and the recipient were CMV immunoglobulin G (IgG) antibody positive and CMV IgM antibody negative before transplantation. He was on triple immunosuppression mycophenolate mofetil, cyclosporine and prednisolone. He developed new-onset diabetes in the immediate post-transplant period for which he was on insulin therapy. He had C4d-negative acute graft rejection after 20 days of transplant, which was treated with three doses of methyl prednisolone and graft function became normal. On presentation, he had pyrexia of 38.5°C, pulse rate 90/min and BP 130/84 mmHg, and other physical examinations were within normal limits. Laboratory findings revealed a haemoglobin of 10.5 g/dL, total leucocyte count of 17 000/µL with 83% neutrophils, platelet count of 310 × 10^3/mm^3, fasting blood glucose of 69 mg/dL, serum creatinine of 1.71 mg/dL and normal liver function tests. His urine examination showed mild proteinuria and two to four leucocytes per high-power field. Blood and urine cultures were sterile. A chest radiograph was normal. A swab culture from the axillary and scrotal ulcers revealed Pseudomonas infection. The patient was treated with intravenous (IV) cefoperazone–sulbactam combination antibiotic for 7 days. The ulcers were not healing and fever was persisting. Subsequently, the patient was treated with another set of antibiotics, cefuroxime and piperacillin–tazobactam combination for further 7 days. The skin ulcers and pyrexia did not respond to this therapy either and antibiotic treatment was discontinued. Then skin biopsy was done and samples were sent for microbiology and histology. The total leucocyte count at this time was 12 500/µL with 72% neutrophils, and serum creatinine was 1.86 mg/dL. Cultures from the axillary and scrotal ulcers were sterile. The skin biopsies from the axillary and scrotal ulcers revealed intranuclear and intracytoplasmic inclusions positive for CMV antigen on immunohistochemistry. The patient responded to anti-CMV therapy.

Case report

A 52-year-old, live related renal allograft recipient, after a 2.5-month post-transplant period, presented with a history of vesicular eruptions over the right axilla, scrotum and penile skin which later developed into ulcers (Figure 1). Both the donor and the recipient were CMV immunoglobulin G (IgG) antibody positive and CMV IgM antibody negative before transplantation. He was on triple immunosuppression mycophenolate mofetil, cyclosporine and prednisolone. He developed new-onset diabetes in the immediate post-transplant period for which he was on insulin therapy. He had C4d-negative acute graft rejection after 20 days of transplant, which was treated with three doses of methyl prednisolone and graft function became normal. On presentation, he had pyrexia of 38.5°C, pulse rate 90/min and BP 130/84 mmHg, and other physical examinations were within normal limits. Laboratory findings revealed a haemoglobin of 10.5 g/dL, total leucocyte count of 17 000/µL with 83% neutrophils, platelet count of 310 × 10^3/mm^3, fasting blood glucose of 69 mg/dL, serum creatinine of 1.71 mg/dL and normal liver function tests. His urine examination showed mild proteinuria and two to four leucocytes per high-power field. Blood and urine cultures were sterile. A chest radiograph was normal. A swab culture from the axillary and scrotal ulcers revealed Pseudomonas infection. The patient was treated with intravenous (IV) cefoperazone–sulbactam combination antibiotic for 7 days. The ulcers were not healing and fever was persisting. Subsequently, the patient was treated with another set of antibiotics, cefuroxime and piperacillin–tazobactam combination for further 7 days. The skin ulcers and pyrexia did not respond to this therapy either and antibiotic treatment was discontinued. Then skin biopsy was done and samples were sent for microbiology and histology. The total leucocyte count at this time was 12 500/µL with 72% neutrophils, and serum creatinine was 1.86 mg/dL. Cultures from the axillary and scrotal ulcers were sterile. The skin biopsies from the axillary and scrotal ulcers revealed intranuclear and intracytoplasmic inclusions positive for CMV antigen on immunohistochemistry. The patient responded to anti-CMV therapy.
IV ganciclovir 2.5 mg/kg at 12-h intervals for 14 days and then the patient was discharged with advice to continue oral valganciclovir 450 mg daily for 2.5 months as maintenance therapy. He became afebrile with healing and regression of the skin ulcers after 2 weeks of ganciclovir therapy (Figure 1). At the time of discharge, his serum creatinine was 1.61 mg/dL. The intensity of immunosuppression was reduced during the period of CMV treatment by reducing the dose of cyclosporine. On a follow-up visit 3 months later, the patient was completely asymptomatic with a total leucocyte count of 4800/µL and serum creatinine of 1.38 mg/dL. The presence of CMV inclusion bodies,
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Discussion

In this case study, we report a very rare manifestation of CMV disease, a cutaneous ulcers, in a live related renal transplant recipient. The usual clinical features of active disseminated CMV disease include fever, leucopenia, thrombocytopenia, petechiae, pneumonitis, hepatitis, chorioretinitis, adenitis and encephalitis [3]. Skin involvement is a rare manifestation of CMV disease in kidney transplantation [4]. However, ulcers, mostly around genitalia, perineum, buttocks and thighs, have been described in immunocompromised patients particularly in acquired immunodeficiency syndrome (AIDS) patients [5]. However, to our knowledge, axillary ulcers have not been described in CMV-associated cutaneous lesions in renal allograft recipients. Recently, the true pathogenetic role of CMV in cutaneous lesions has been the focus of interest. It has been thought that CMV may be simply an innocent bystander during herpes simplex virus infection among non-AIDS patients [6]. But the demonstration of CMV antigen on immunohistochemistry, high CMV DNA copies per millilitre and response to anti-CMV therapy indicated CMV as primary causative organism of ulcer in this patient.

Table 1. Summary of review of literature of CMV cutaneous ulcers in organ recipients

| Studies       | No. of cases | Manifestations                                                                 | Outcome                  |
|---------------|--------------|------------------------------------------------------------------------------|--------------------------|
| Lee et al. [6]| 3 transplant recipients | Case 1, wound due to extravasations of inotropes and associated CMV<br>Case 2, mixed Candida and CMV<br>Case 3, CMV pneumonia and purpuric rash | Survived<br>Died due to disseminated herpes simplex virus<br>Died of Pseudomonas sepsis |
| Choi et al. [7]| Non-AIDS immunocompromised patients | Multiple anogenital ulcerations—6/9<br>Solitary nodule—2/9 | 6 survived and 3 died<br>Both kidney recipients survived<br>Maculopapular rash—1/9<br>Both kidney recipients have perineal and penile shaft lesion<br>Only one has coexisting HSV infection |
| Rico et al. [8]| Transplant recipient—1 | Ureterostomy cytomegalovirus infection presenting as stoma ulceration | Survived |

The high leucocyte count and growth of Pseudomonas from the wound at presentation was misleading concerning the diagnosis of CMV and the patient was treated with antibacterial agents. It is known that CMV is an immunomodulatory virus and predisposes the patients to other associated opportunistic bacterial, viral and fungal infection. Our patient also had associated Pseudomonas infection which may be the reason of the high leucocyte count in this patient contradictory to the usual presentation of leucopenia in CMV infection. Recently, Roco et al. [8] reported a case of ureterostomy cytomegalovirus infection presenting as stoma ulceration. The summary of the review of literature of CMV skin ulcers in renal transplant recipients is shown in Table 1.

CMV infection is caused by a virus of the family Herpesviridae and is usually latent and asymptomatic in those with a normal immune system. Infection by CMV may be frequent and severe in children or adults with congenital or acquired defects of cellular immunity, with
underlying malignancy, patients on immunosuppression and AIDS patients. There are three major patterns of CMV infection in transplant patients: (i) Primary infection occurs in seronegative recipient from seropositive donor. (ii) Reactivation of latent virus occurs in seropositive donor after transplant. (iii) Super infection occurs when allograft from a seropositive donor is transplanted into a seropositive recipient. Both our recipient and donor were seropositive and CMV disease appears to be due to either reactivation or super infection of CMV in this patient. Our patient had not been given ganciclovir prophylaxis as per our institute protocol. We used to give ganciclovir prophylaxis if a seronegative recipient receives a kidney from a seropositive donor and with the use of anti-thymocyte globulin for either induction purpose or for the treatment of rejection.

Therapeutic treatment of established CMV disease is primarily with the antiviral agent Ganciclovir IV induces remission of CMV disease in renal transplant recipients in all but rare cases that are ganciclovir resistant. Ganciclovir-resistant strains of CMV are generally sensitive to foscarnet which is otherwise avoided because of nephrotoxicity [9]. Valganciclovir is the L-valyl ester prodrug of ganciclovir which provides an excellent oral alternative to ganciclovir for the prevention of CMV in transplant recipients [10]. Although valganciclovir is an established drug for CMV disease treatment, this is the first case report of the treatment of CMV skin ulcers with valganciclovir.

In summary, CMV-induced skin ulcers, particularly in axillary regions, have not been previously reported in renal allograft recipients. CMV-induced skin ulcers should be added to the list of manifestations of CMV disease in renal transplant recipients. Skin biopsy may be of help in the prompt diagnosis and treatment of CMV skin ulcers.

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Conflict of interest statement. None declared.

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