

Gangrenous Herpes Zoster with Multidermatomal Involvement in a Patient after Kidney Transplantation

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Abstract: We present the case of a 66-year-old female after renal transplant with severe course of herpes zoster (HZ). Although HZ represents a common infectious complication of transplant patients, its variable manifestation and ability to disseminate warrants serious consideration. Prompt diagnosis and treatment are essential in preventing further spread and disastrous complications.

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Introduction

Herpes zoster (HZ) is a relatively common after transplant complication second only to infections due to cytomegalovirus (CMV) (Miller and Dummer, 2007). Incidence has been reported between 1–12% for renal transplant recipients representing a 10–100 fold increase above the level seen in the general population. Fehr et al. (2002) reported reactivation rate of varicella-zoster virus (VZV) 18% in adult renal transplant patients. Range of onset of reactivated VZV infection has been reported between 9.0–13.9 months; however infection as early as 9 days after transplant has been observed (Gourishankar et al., 2004). In addition, lifelong immunosuppression makes the disease a likely complication. Salient risks associated with VZV reactivation have been reported as increasing age and mycophenolate mofetil (MMF) immunosuppression (Kotton and Fishman, 2005). Herpes zoster presentation in immunocompromised patients ranges from the classical vesicular eruption along a dermatomal distribution to the severe, but less frequent, disseminated form. Additionally, the after transplant HZ carries disastrous consequences such as severe post herpetic neuralgia (PHN), gangrenous herpes, allograft impairment and increased patient mortality. Thus, HZ in after transplant patients is considered a medical emergency and as such requires rapid diagnosis with immediate institution of antiviral therapy with concomitant reduction of immunosuppressive treatment.

Case report

A 66-year-old female with history of renal transplantation due to chronic renal failure caused by interstitial nephritis and diabetic nephropathy with subsequent long-term immunosuppression was admitted 7 months after transplant due to a severe reactivation of VZV. Previous medical history included varicella and pertussis in her childhood as well as non-insulin-dependent diabetes mellitus on diet since 1999 with diabetic nephropathy and state of bilateral subtotal amaurosis following an episode of cerebral infarction. Immunosuppressive medications included MMF 2 g/day, prednisone 7.5 mg/day and study medication CP 690550 (JAK3 kinase inhibitor). Prior to admission the patient was treated by general practitioner for five days with orally given (PO) co-amoxicillin in dose of 625 mg three times a day (TID) for suspected impetigo. Because the clinical findings did not improve, the patient was referred to the Department of Nephrology. On admission to nephrology, the first vesicular lesions manifested at the site of the patient's left lateral neck region spreading gradually to ipsilateral mandibular, preauricular, retroauricular, external ear, shoulder and nuchal regions corresponding to dermatomes C2, C3, CN XI and CN V/2 (Figure 1). On day 5 new lesions on the oral mucosa emerged followed by headache, anorexia and impaired swallowing. On day 7 the patient was transferred to the Department of Infectious Diseases because of progressive deterioration, including high fever, alteration of mental status,



Figure 1 – Extensive skin involvement of the upper trunk, neck and face.

signs of bacterial superinfection at the auricular lesions, debilitating pain and clinical signs of cerebral irritation. There was neither jaundice nor laboratory signs of liver or renal dysfunction. Lumbar puncture was not performed because of its low expected impact on further treatment. Treatment with intravenous (i.v.) acyclovir (ACV; 750 mg TID), combined with i.v. ceftriaxone – 2 g one a day (QD) due to suspected bacterial superinfection supported by laboratory findings of leucocytosis (10.4×10^9 cells/l) and elevated C-reactive protein (CRP) of 153.7 mg/l was administered; prophylactic treatment with fluconazole (100 mg PO QD) was also initiated. After consulting the Department of Nephrology, both MMF and CP 690550 were discontinued and prednisone was substituted with i.v. hydrocortisone (100 mg TID) for 7 days. For pain management, buprenorphin transdermal patches were administered twice weekly combined with oral gabapentinum (300 mg TID). After a week of hospitalization, the patient's condition stabilized in regards to abatement of zoster lesion spread, normalization of CRP and neurological improvement. On day 14 the antibiotic therapy was discontinued and immunosuppressive treatment was re-established omitting only MMF for the next 21 days. Intravenous ACV was replaced with oral valaciclovir (VCV; 1 g TID). Nevertheless, the patient suffered from severe PHN and complicated healing of pustular lesions leaving painful erythematous superficially epithelizing scars and areas of desquamation in anterolateral areas of face and neck. On day 22, the patient was transferred to dermatology for further local treatment. A year after transplantation, the patient underwent renal biopsy, which demonstrated an

excellent function of the renal transplant with no signs of rejection. Unfortunately, the patient developed circulatory failure of unknown aetiology two months after the biopsy and despite successful resuscitation the patient died in the intensive care unit.

Discussion

Prompt diagnosis of HZ is of paramount importance to effective treatment; the sooner antiviral treatment is initiated, the better is the patient's outcome (Dworkin et al., 2007). High dose ACV and decreasing immunosuppression are the cornerstones of HZ therapy in after transplant patients. Aciclovir may be administered either orally for milder cases or intravenously for patients with disseminated infections or with the head, neck and upper trunk involvement. Recommended dosage of ACV is 10 mg/kg (500 mg/m²) TID. Oral ACV may be switched from i.v. ACV with good control of the infection. Furthermore, the timing of HZ treatment in immunosuppressed patients differs from that in immunocompetent persons and the antiviral treatment is not restricted to 72-hrs window after the onset of rash (Dworkin et al., 2007). In addition, patients should be treated until all lesions are healed, which may extend beyond the regular 7 to 10 day course of therapy. Herpes zoster may also be treated with VCV or famciclovir given orally in milder cases and less immunosuppressed patients (Green et al., 2004). Ganciclovir can be used alone if HZ accompanies CMV infection; however, HZ response may be delayed as compared to ACV (Rodriguez-Moreno et al., 2006). Since ACV has some nephrotoxicity, a close monitoring of renal parameters is required. A reduction of immunosuppressive treatment involves a balance between allowing a competent immune response without compromising graft function. In addition, varicella-zoster immune globulin is not recommended for the treatment of established infection and is reserved only for post-exposure prophylaxis (Gourishankar et al., 2004).

Even though HZ is considered a common viral infection in transplant patients, the disease has the ability to follow an uncommon course. HZ may manifest itself over a greater number of dermatomes as a multidermatomal zoster (Kotton and Fishman, 2005). Additionally, there have been reports of a delay between overt presentation, the classical vesicular rash, and patient complaints of pain (Mortada et al., 2009). Since all patients are considered to be viraemic regardless of evidence of organ involvement, disseminated infection should be always considered. The most common complications documented in the literature are hepatitis (50%), disseminated intravascular coagulation (50%) and pneumonitis (29%). Also, the pancreas or central nervous system may be involved. Central nervous system involvement may present as chronic VZV encephalitis or small vessel encephalitis. Additional complications may include concomitant infections (e.g. CMV or herpes simplex infections), secondary bacterial infection and gangrenous HZ. Post infection outcomes are as varied as the clinical course of HZ. The most common reported

sequela has been PHN (42.7%) as opposed to the PNH rate of 19.6% reported for the immunocompetent persons (Volpi, 2007). The overall reported mortality rate in renal transplant patients is 34%; however, it has been ranging between 53% (prior to 1990) to 22% (post 1990) with the lower mortality rate being attributed to the advent of antiviral therapy (Green et al., 2004). Furthermore, the infection has the potential to impair graft tolerance or survival resulting in early graft failure (Kotton and Fishman, 2005).

Effective prevention remains elusive but may be considered beginning with obtaining pre-transplant VZV serostatus. This will certainly assist with determining, whether the patient is at risk for primary disease or reactivation of VZV, which will also dictate prevention strategies. Aciclovir is a viable option for long term prophylaxis, especially in high-risk patients (e.g. VZV seronegativity, low titres of specific antibody or lymphocytopenia) (Steer et al., 2000). Another effective preventive mean could be active immunization in both the VZV-seronegative and VZV-seropositive patients. The main obstacle to implementing this strategy is the lack of clinical trials. Pre-transplant vaccines have been used in the paediatric population with success (Olson et al., 2001; Weinberg et al., 2006). However, the data in the adult population is scant limited to one study, which was performed in the Netherlands (Geel et al., 2006). A novel approach could be a use of a heat-inactivated Varivax[®] (live attenuated vaccine is contraindicated after transplant), which was tested after autologous bone marrow transplantation (BMT) with a 50–60% reduction in the incidence of HZ during the first year after BMT (Hata et al., 2002). Equally rare is the data regarding a pre-transplant booster with Zostavax[®] (approved for preventing HZ in immunocompetent patients 60 years of age and older), because immunocompromised patients were excluded from the HZ prevention trial.

Conclusion

Herpes zoster poses a serious risk in after transplant patients, which requires careful patients' counselling, rapid clinical diagnosis and intensive antiviral therapy, appropriate reduction of immunosuppression, care for affected skin and good supportive care. These goals can be achieved only in a multidisciplinary cooperation of infectious disease consultants and specialists in transplant medicine. Additionally, the reported case supports the need for routine HZ preventive strategies in transplant patients.

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