

Persistent atypical varicella in two renal transplant patients and its relation to mycophenolic acid

Sir,

Mycophenolic acid (MPA) is a recently introduced immunosuppressant for the prevention of graft rejection after various solid organ transplantations. It has significantly decreased the incidence of graft rejection due to its augmented immunosuppressive potential. However, this feature might have led to increased chances of various infections.^[1,2] Though there are a few reports revealing increased incidence of varicella zoster virus (VZV) infections in patients following the use of mycophenolate mofetil (MMF),^[1,2] none have described the altered cutaneous manifestations and the course of varicella as was seen in our patients.

The first patient was a 24-year-old man who underwent renal allograft transplantation following chronic renal failure and was started on oral tacrolimus (12 mg/d), MPA (1.44 g/d), and prednisolone (17.5 mg/d). On the 36th day post-transplant, he developed papules, vesicles, pustules with central necrosis and crust formation all over the body, associated with high-grade fever. At places, lesions were subsiding with pock-like scars. There was neither previous history of varicella in the patient nor of any contact with VZV or herpes simplex virus (HSV). Pre-surgery or post-eruption, VZV or HSV

serology could not be done. Tzanck smear from the vesicle showed giant cells, as well as acantholytic cells. There was no mucosal involvement. Liver enzymes, complete blood cell counts, chest X-ray, and electrocardiograph (ECG) were within normal limits. Serum creatinine level was maintained at the baseline level.

The patient was hospitalized because of high-grade fever and was started on oral valacyclovir, 1 g thrice a day. After 1 week of treatment, he became afebrile, and all the vesicular lesions subsided. While the patient was on the same medications, numerous erythematous well-defined papules and plaques studded with multiple tiny necrotic areas having spiny feel appeared on the sites of subsided vesicles over the face, limbs, and upper back [Figure 1]. Skin biopsy from one of these lesions was nonspecific. He was advised to continue oral valacyclovir in the same dose. Even after 2 weeks of antiviral therapy, none of these papulo-plaque lesions subsided, though no new vesicular lesion appeared. With the suspicion that continuation of MPA could have resulted in the persistence of lesions, mycophenolate was withheld altogether and valacyclovir was continued; tacrolimus dose was adjusted to 10 mg/d. Subsequently, the skin lesions started clearing. At the end of the fourth week of the onset of skin lesions, the patient developed posterior outer retinal necrosis, a known systemic complication of varicella. Valacyclovir was stopped and he was started on intravitreal and intravenous ganciclovir, which was continued for 2 months. Following this treatment, all the skin lesions subsided within 2 weeks, leaving post-inflammatory hyperpigmentation and scarring. The patient maintained a stable graft function throughout the course of the illness. There was no evidence of clinical relapse of varicella after 12 months of follow-up, while the patient continued to take oral tacrolimus and prednisolone. MPA was not restarted later.

The second patient was a 28-year-old man, was a known case of hypertensive benign nephrosclerosis resulting in chronic renal failure, who underwent renal allograft transplantation. The evolution and morphology of the lesions were similar to those in the previous patient [Figure 2]. Even after 2 weeks of antiviral therapy, hardly any of the papulo-plaque lesions cleared, though there was no new vesicle formation or clinical sign suggestive of dissemination of infection. MPA was withheld altogether as in the previous patient, and doses of tacrolimus (8 mg/d) and prednisone (10 mg/d) were reduced. Following 4 weeks of oral valacyclovir use, the patient became lesion free. MPA was not restarted, as in the previous patient.



Figure 1: Papules studded with multiple tiny necrotic areas over thighs in patient 1



Figure 2: Papules with overlying tiny necrotic areas in patient 2

Mycophenolate mofetil (MMF) is a relatively recently approved immunosuppressive agent. Reports on whether MMF increases the incidence of various viral infections, more particularly VZV, have been conflicting. A study by Sollinger *et al.*^[3] revealed no overall increase in the frequency of opportunistic infections or in the incidence of viral (CMV, HSV, VZV) infections in patients treated with MMF compared with those receiving azathioprine. Another study by Fehr *et al.*^[4] in adult renal allograft recipients concluded that no immunosuppressive drug is significantly associated with higher risk of disseminated VZV infection. However, the study by Rothwell *et al.*^[1] in pediatric renal transplant recipients of MMF has indicated otherwise. Out of their 17 patients receiving MMF, 3 developed disseminated varicella as compared to 1 of the 74 children in pre-MMF era. In a single-center study, Lauzurica *et al.*^[2] have observed a significant increased risk of disseminated varicella infection since the introduction of MMF in the immunosuppressive regimens for renal transplant patients.

The manifestations and course of varicella are often altered in immunocompromised hosts. Recurrent varicella or dissemination of herpes zoster is common.^[5] Unusual presentations like verrucous lesions in HIV-infected patients and hemorrhagic lesions have been described.^[5] Persistent varicella, either verrucous or vesicular, has also been reported in immunocompromised patients.^[5] It remains unclear why verrucous varicella may occur in immunocompromised individuals. Altered host response due to decreased cell-mediated immunity (CMI) and altered varicella viral gene expression may precipitate the development of hyperplastic and hyperkeratotic lesions. Formation of verrucous lesions in AIDS patients has been attributed to increase in factor x111a–positive dendritic cells and to decreased VZV g E/g B envelope glycoprotein-expressing keratinocytes, leading to latency-like state of chronic viral infection.^[6]

Chronic/persistent varicella infection is exemplified by continued manifestation of such lesions for more than 1 month after its onset. The first report of chronic VZV infection appeared in the 1980s.^[7] Precise data regarding its frequency is not available. The majority of cases occur in HIV-infected patients with low CD₄ counts.^[5] However, cases have occasionally been reported in organ transplant recipients on immunosuppressive regimens.

Laboratory diagnosis of chronic varicella is often difficult. A variable degree of viral cytopathic changes including Cowdry type A nuclear inclusions, necrotic keratinocytes, as well as slightly swollen eosinophilic cells lacking signs of cytolysis, is seen in histopathology in a proportion of cases.^[5] Differentiation from HSV 1 or 2 can be done by immunohistochemistry or *in situ* hybridization. Viral culture is not an ideal diagnostic tool in chronic varicella.

Altered manifestations and prolonged course of varicella may be encountered more frequently in days to come, as MMF use is increasing in post-transplant patients, autoimmune diseases, and various dermatoses. Thus dermatologists should have greater vigil when confronted with such situations in order to prevent life-threatening complications of a relatively innocuous disease.

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