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Herpes Zoster in Kidney Transplant Recipients: Detection of VZV DNA in Blood During the Prodromal Phase

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Herpes zoster (HZ) usually begins with radicular pain in 1 to 3 dermatomes followed by the appearance of a vesicular eruption over the affected area. In transplant recipients who are at high risk of life-threatening visceral dissemination of varicella zoster virus (VZV), neuropathic pain (the prodrome) may precede the appearance of a rash by weeks and shingles may be absent.[1] We aimed to investigate whether VZV DNA detection in plasma could have value for an early diagnosis of HZ during the prodromal phase.

We evaluated 11 kidney transplant recipients who developed HZ in the first year after transplantation and from whom 2 to 7 blood samples had been systematically collected in the first 6 months and stored in our transplant biobank, approved by the local Institutional Review Board (BH 07-002). Plasma VZV DNA was retrospectively analyzed by a qualitative real-time PCR analysis[2] of these stored samples.

The 11 subjects (Table 1) underwent transplantation between 2009 and 2013. The mean time from transplantation to the onset of shingles was 129 days (range, 12-307 days). Prodromal symptoms occurred at 5.5 days on average (range, 0-19 days) before skin eruptions. A total of 41 blood samples from our study cohort were available for analysis, at a median of 4 specimens per patient. Plasma VZV DNA was not detected in 7 individuals. It was detected during HZ infection, at 2 to 53 days after rash onset, in 3 patients. Varicella zoster virus replication was also noted during the prodromal phase, in 1 of these 3 subjects (patient 10, who was diagnosed with HZ ophthalmicus 6 days later) and in another recipient (patient 8, who developed VZV vasculopathy 12 days later).

Our retrospective analysis of available archived blood specimens in a small number of patients had obvious limitations but our findings provide interesting PCR evidence of VZV reactivation during HZ in transplant recipients. These data document the presence of VZV in the plasma of 4 patients diagnosed with HZ. In 3 of these cases, VZV DNA was detectable in blood taken up to 53 days after the onset of shingles. Blood VZV DNA has previously been detected during acute HZ,[3,4] in 16% to 100% of the patient populations analyzed by molecular assays. Some previous studies have revealed a higher VZV load in immunocompromised patients. In addition, VZV DNemia can be documented up to 6 months after skin eruptions. An even more interesting observation from our results was the detection of VZV DNA before rash onset in 2 individuals. In both of these patients, the prodromal phase was particularly painful and prolonged, and the clinical features of HZ were quite severe, particularly in 1 patient who developed a VZV vasculopathy as described elsewhere.[5] Analysis of VZV DNA in plasma could therefore be used for the early diagnosis of atypical HZ and avoid delayed initiation of treatment. However, the precise diagnostic value of this marker for these purposes requires additional research.[3]

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All the authors participated in the study design and had access to the data. A.D. was responsible for coordinating the collection, management and analysis of the data, and drafted the article. E.R. participated in data analysis and in the writing of the article. M.R. participated in the performance of the research, analyzed and discussed data. M.-J.H. was a major contributor to the conception of the study. All the authors read and approved the final version of the article.

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TABLE 1.

VZV DNA detected by PCR in plasma in 11 kidney transplant recipients with herpes zoster

	Patient										
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Age, y	47	51	56	62	61	72	51	65	36	52	67
Sex	M	F	M	M	F	M	M	F	M	M	M
VZV serology (IgG titre)[a]											
Before transplantation	+ (ND)	+ (ND)	+ (ND)	+ (2.84)	+ (1.86)	+ (3.41)	+ (ND)	+ (1.53)	+ (1.43)	+ (ND)	+ (>1.1)
At transplant	+ (2.74)	+ (2.3)	+ (ND)	+ (2.51)	+ (1.88)	+ (2.16)	+ (3.10)	− (0.70)	+ (1.60)	+ (3.10)	+ (>1.1)
CMV serostatus D/R	−/−	−/+	+/−	−/−	+/+	−/+	−/−	−/+	−/−	−/−	−/−
Antiviral prophylaxis	None	None	Yes[b]	None	None	None	None	None	None	None	None
Days between transplant and prodrome onset	22	126	227	12	131	177	302	18	188	22	110
Days between prodrome onset and skin rash	2	4	7	0	2	0	5	16	7	19	1
VZV replication											
Time[c] (result)	1 (negative)	27 (negative)	1 (negative)	0 (negative)	0 (negative)	34 (negative)	0 (negative)	3 (negative)	48 (negative)	0 (negative)	5 (negative)
Time[c] (result)	13 (negative)	79 (negative)	8 (negative)	28 (negative)	33 (negative)	91 (negative)	30 (negative)	28 (positive)	97 (negative)	9 (negative)	35 (negative)
Time[c] (result)	26 (positive)	163 (negative)	27 (negative)		82 (negative)	209 (negative)		93 (negative)	167 (negative)	29 (positive)	89 (negative)
Time[c] (result)		183 (positive)	35 (negative)		89 (negative)				184 (negative)	49 (positive)	179 (negative)
Time[c] (result)			61 (negative)							84 (negative)	
Time[c] (result)			91 (negative)								
Time[c] (result)			189 (negative)								
VZV presentation											
Single dermatome			Yes	Yes		Yes	Yes		Yes	Yes	Yes
Contiguous dermatomes		Yes			Yes						
Generalized HZ (skin)	Yes							Yes			
Ophthalmic zoster										Yes	
VZV vasculopathy								Yes			

[a] In accordance with manufacturer's instructions, a test value of at least 1.1 is considered positive.

[b] CMV prophylaxis with valganciclovir during the first 100 days after transplantation.

[c] Time (days) from transplant to blood sample.

CMV, cytomegalovirus; D, donor; M, male; F, female; ND, no data; R, recipient.