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Vincent Guiraud[1,2], Henri Thévenet[1], David Boutolleau[1,2]

[1]Centre National de Référence Herpèsvirus (Laboratoire Associé), AP-HP. Sorbonne Université, Hôpital Pitié-Salpêtrière, Service de Virologie, Paris, France

[2]Sorbonne Université, INSERM, UMR-S 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique (iPLESP), Paris, France.

Abstract

Objective: To assess whether varicella zoster virus (VZV) DNA can be detected in blood before herpes zoster (HZ) rash onset.

Method: Monocentric retrospective study from January 2019 to March 2023 including patients with HZ and stored blood samples performed during the week preceding the onset of HZ rash. Blood samples were retrospectively analyzed for VZV DNA by quantitative PCR.

Results: Among the 138 patients with HZ during the study period, stored blood samples performed during the week preceding the onset of HZ rash were available for 13 of them. Twelve (92%) patients were immunosuppressed, mostly due to solid organ transplantation (38%), solid malignancy (31%) or autoimmune disease (23%). During the week preceding HZ onset, VZV DNA was detected in blood from 10 (77%) patients, with a median value of 3.6 log (copies/mL) (IQR 3.3-3.9). At the time of HZ onset, all VZV PCR performed in available blood samples were positive.

Conclusion: Our findings demonstrates that VZV DNA can be commonly detected in blood from immunocompromised patients during the prodromal phase of HZ. Early screening of VZV DNA in blood from high-risk immunocompromised patients might improve HZ therapeutic management.

Keywords: VZV, herpes zoster, virus reactivation, blood, viral DNA, immunosuppression.

Introduction

Herpes zoster (HZ), also known as shingles, results from the reactivation of latent varicella zoster virus (VZV) in sensory ganglia [1]. It presents as a characteristic unilateral dermatomal vesicular rash [2], preceded, among 50% to 70% of patients, by pain or abnormal sensations in the affected area for 3 to 7 days [3–5]. The main complication of HZ is post-herpetic neuralgia (PHN), defined as the persistence of pain for at least 3 months after rash onset [6]. Incidence of HZ increases with age, with up to a third of people living in developed countries expected to experience HZ in their lifetime [7,8]. Early antiviral therapy significantly accelerate the resolution of HZ-associated pain [9]. Therefore, early detection of VZV, before the appearance of rash, might improve the therapeutic management and prognosis of HZ.

Detection of VZV genome in blood from immunocompetent or immunocompromised patients with localized HZ is common [2,10–12]. However, data concerning the potential detection of VZV genome during the prodromal phase remain scarce and controversial. Two recent retrospective studies suggested that VZV genome might be detected by PCR before rash onset of HZ [13,14]. The first study assessed VZV detection in bronchoalveolar lavage fluids only, while the second study described a single case of a heavily immunocompromised patient with one VZV positive blood sample. However, another study reported no evidence of a preceding phase of detectable VZV in blood in hematopoietic stem cell transplant recipients [13]. The objective of this study was to assess whether VZV genome could be detected in peripheral blood before rash onset among patients with HZ.

Methods

From January 2019 to March 2023, patients with HZ in Pitié-Salpêtrière Hospital (Paris, France) were identified according to the results of VZV PCR performed on cutaneous swabs in the Virology Department. Patients from whom blood samples had been collected for routine standard clinical management and stored at -80°C during the week preceding HZ rash onset were included in the present study. DNA extraction was performed retrospectively from those stored samples using

QIAsymphony DSP DNA mini kit. Quantitative VZV PCR was performed using HSV1&2 VZV R-GENE kit (BIOMERIEUX), The limit of detection was 2.7 log (copies/mL). Baseline characteristics of patients were collected from the medical records. Statistical analyses were performed using R software. Categorical variables were expressed as numbers (percentages) and continuous variables as medians (interquartile ranges [IQR]). Univariate analyses were performed using Mann-Whitney U test with $p<0.05$ considered to be statistically significant.

Results

During the study period, a total of 15,218 clinical samples were tested by VZV PCR, out of which 268 (1.7%) were positive. These VZV positive samples included 64 blood samples and 173 mucocutaneous swabs, corresponding to 138 distinct patients with HZ. Characteristics of the patients and the samples are summarized in supplementary table 1. Of the 64 blood VZV positive samples (0.98% of blood PCR), 6 (9.4%) were performed after varicella and 47 (73%) after HZ. One (1.5%) patient was hospitalized for encephalitis, 1 (1.5%) for a bilateral retinitis with encephalitis, 2 (3%) patients had acute hepatitis, 2 (3%) toxidermia, 1 (1.5%) was hospitalized for myocardial infarction, and data was missing for the last 4 (6.3%) patients. Stored blood samples performed during the week preceding the onset of HZ rash were available for 13 patients.

Table 1 shows the baseline characteristics of the study population. Twelve patients (92%) had prior immunosuppression, while the latter was hospitalized in intensive care unit for multiple-organ failure with septic shock due to mesenteric ischemia. Immunosuppression was mainly due to solid organ transplantation (38%), solid malignancy (31%), and autoimmune disease (23%). Therefore, most patients received immunosuppressive drugs: corticosteroids (69%), mycophenolate mofetil (46%).

During the week preceding HZ onset, VZV DNA was detected in blood from 10/13 (77%) patients (Table 2) with a median delay of 4 days (IQR 2.2-5.7) before HZ onset. Median VZV load was 3.6 log (copies/mL) (IQR 3.3-3.9). At the time of HZ onset, all VZV PCR performed in available blood samples (n=11) were positive, with a median value of 3.3 log (copies/mL) (IQR 3.0-4.2). VZV loads did not

significantly differ before and at the time of HZ onset (3.6 *versus* 3.3 log[copies/mL], p = 0.78, 95%CI for the difference [-1.2;1.2]). Likewise, no statistically significant difference was seen between metameric and disseminated HZ (3.3 *versus* 4.9 log [copies/mL], p=0.076, 95% CI for the difference [-2.8;0.15]).

Two patients had several available stored blood samples during the 2 weeks preceding the rash onset. For both of them, VZV loads exhibited an upward trend as they neared the onset of HZ. For patient 3, VZV load was undetectable 15 days before HZ, and then raised to 2.7 log (copies/mL) 8 days before HZ onset and 3.9 log (copies/mL) 5 days before HZ onset. Similarly, VZV load in blood from patient 8 raised from undetectable 8 days before HZ onset to 3.3 log (copies/mL) one day before HZ onset.

Of note, 3 patients had nasal swabs available the week before HZ onset, primarily done for Covid-19 testing (all negative). Patient 1 had a positive VZV nasal swab one day before HZ, Patient 6 a positive VZV nasal swab 7 days before HZ, and patient 3 had a negative nasal swab 3 days before. Since patient 3 had a positive blood VZV PCR 2 days before the nasal swab, and since this type of sample is known to be traumatic, the virus might have come from blood, rather than a local oropharyngeal replication.

Patient 5 developed HZ despite valacyclovir prophylaxis. Treatment of HZ consisted of either intravenous acyclovir or oral valacyclovir, except for patient 10, who received intravenous ganciclovir because of a concomitant cytomegalovirus infection (Table 2).

During the study period, another patient with a low VZV load in blood (2.7 log [copies/mL]) was identified. This immunocompetent patient, hospitalized for myocardial infarction, did not develop HZ despite the lack of antiviral prophylaxis.

Discussion

Our findings demonstrate for the first time that VZV DNA can be commonly detected in blood from immunocompromised patients during the prodromal phase of HZ. Thus, 77% of patients had detectable VZV DNA during the week preceding HZ onset, which is in line with the case of a kidney transplant recipient previously reported [14]. We also observed the constant presence of VZV DNA in blood at the onset of HZ, in accordance with previous studies including both immunocompetent or immunocompromised patients [10–12,15]. In this study, we also described the detection of VZV DNA in blood from an asymptomatic immunocompetent patient who did not develop further HZ despite lack of antiviral prophylaxis. The detection of VZV DNA in blood from patients without symptoms of VZV infection has also been described in immunocompetent children under severe stress [16], or adults with autoimmune diseases or human immunodeficiency virus infection [17].

From an anatomopathological perspective, VZV reactivation results in infecting and destroying many neurons in the sensory ganglion, together with an hemorrhagic necrosis, allowing the virus to spread throughout the sensitive ganglion and within bloodstream [18–21]. This is why, in contrast to herpes simplex virus reactivation that is restricted to individuals neurons and leads to a reduced number of vesicles on the skin, VZV reactivation leads to vesicles within an extensive portion of a dermatome [22]. In our study, the frequent VZV detection in blood before HZ onset supports the hypothesis that VZV spread to surrounding neurons and into bloodstream happens at an early stage after viral reactivation, several days before skin involvement. It also suggests that VZV DNAemia during HZ may not originate solely from viral replication in the skin, but also directly from the sensory ganglion during early stages of VZV reactivation. This early viral spread allows triggering VZV-specific cellular immunity (CMI). According to the level of CMI, VZV reactivation will result from asymptomatic/subclinical reactivation to metameric and disseminated HZ (Figure 1). Taken together, these observations remarkably align with the hypotheses made by Hope-Simpson regarding HZ in 1965 [1]. He postulated that VZV reactivations were frequent and could occur with or without (i.e., subclinical reactivation) symptoms, depending on the immunity level of individuals.

Our study has several limitations. First, only a small fraction of patients with HZ had a blood sample available during the week preceding the onset of HZ. As a consequence, few patients were included. Moreover, it included patients with heavy comorbidities. Therefore, our results should be extrapolated to other population of patients with caution. Moreover, prodromal symptoms were not reported in most medical records, so we were unable to establish a link with VZV DNAemia before HZ onset.

In conclusion, VZV DNA can be commonly detected in blood during the week preceding HZ onset in immunocompromised patients, suggesting that viral diffusion through the sensitive ganglion and into the bloodstream happens at an early stage of VZV reactivation. Further studies are needed to address the relevance of an early screening of high-risk immunocompromised patients by blood VZV PCR.

Ethics

This study complies with Good Clinical Practices and ethical principles of the Helsinki declaration. All data were anonymized before analysis. Patients were systematically notified of any supplementary biological analyses on frozen samples, initially collected as part of routine clinical practice.

Declaration of competing interests: The authors declare no conflict of interest in relation with this study.

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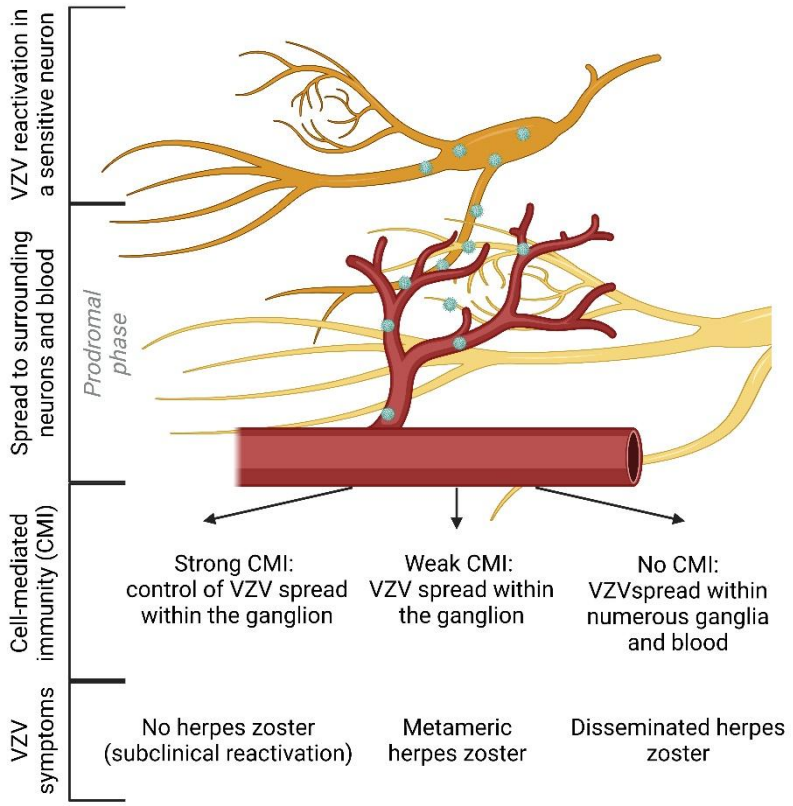

Fig 1: Pathogenesis of HZ. VZV reactivation allows the virus to spread early throughout the sensitive ganglion and within bloodstream, triggering VZV-specific cellular immunity (CMI). According to the level of CMI, VZV reactivation result from asymptomatic/subclinical reactivation to metameric and disseminated HZ.

Table 1: Baseline characteristics of the study population

Characteristics	**Patients (n=13)**
Age, years, median (IQR)	60 (51-76)
Male sex, n (%)	10 (77%)
Tobacco smoker, n (%)	2 (12%)
BMI, kg/m², median (IQR)	26.1 (20.7-29.8)
Prior immunosuppression[a], n (%)	12 (92%)
Solid organ transplantation, n (%)	5 (38%)
HIV infection, n(%)	1 (8%)
Solid malignancy, n (%)	4 (31%)
Hematological malignancy, n (%)	1 (8%)
Autoimmune disease, n (%)	3 (23%)
Corticosteroids, n (%)	9 (69%)
Calcineurine inhibitor, n (%)	4 (13%)
Mycophenolate mofetil, n (%)	6 (46%)
Chronic kidney disease, n (%)	5 (38%)
Arterial hypertension, n (%)	8 (61%)
Diabetes mellitus, n (%)	3 (23%)
Dyslipidemia, n (%)	9 (69%)

Results are expressed as numbers (n) and percentages for categorical variables or medians and interquartile ranges (IQR) for continuous variables.

[a]Immunosuppression: use of corticosteroids, solid organ or hematopoietic stem cell transplantation, HIV infection, autoimmune disease.

[b] expressed in log (copies/mL)

BMI: body mass index; HIV: human immunodeficiency virus; HZ: herpes zoster; VZV: varicella-zoster virus

Table 2: Demographic, clinical, virological and therapeutic features of the 13 patients from whom blood samples were tested for VZV during the week preceding HZ

N°	1	2	3	4	5	6	7	8	9	10	11	12	13
Patients													
Age, y	22	58	51	73	49	84	29	58	76	85	60	78	70
Sex	F	M	M	M	M	M	F	M	M	F	M	M	M
BMI (kg/m^2)	21.8	29.1	19.9	26.1	20.7	31	39.8	29.8	18.1	34.9	24.6	18.3	27.6
Prior immunosuppression[a]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cause of immunosuppression	Lupus	Kidney Tx and prostate cancer	Kidney and heart Tx	No	Hemato-poietic stem cell Tx	Anti-synthetase syndrome	HIV infection	Heart Tx	Metastatic prostate cancer	Metastatic epidermoid carcinoma	Heart Tx	Vesical carcinoma	Kidney Tx
Corticosteroid dose[b]	5	5	10	No	No	10	No	20	10	150	40	No	17.5
Calcineurine inhibitor	No	No	Yes	No	No	No	No	Yes	No	No	Yes	No	Yes
Mycophenolate mofetil	No	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes	No	Yes
History of cardiovascular event	No	Ischemic heart disease	No	Peripheral artery disease	No	No	No	No	Ischemic heart disease	No	No	No	Ischemic heart disease
Hypertension	No	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes
Dyslipidemia	No	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes
Diabetes mellitus	No	No	No	Yes	No	Yes	No	No	No	No	No	No	Yes
Death	No	No	No	Multiple organ failure	No	No	No	No	Acute respiratory failure	No	No	Multiple organ failure	No
Herpes zoster (HZ)													
Localization	Sacrum	Disseminated	Arm	Abdomen	HZO	Disseminated	Thorax	Sacrum	Arm	Genital	Thorax	Leg	Shoulder
Time from blood VZV PCR to HZ onset (days)	1	4	5	7	3	7	6	1	6	4	5	2	3
Blood VZV load[c] before HZ onset	3.6	4.2	3.9	3.3	2.7	3.7	Neg	3.3	3.7	4.7	Neg	2.7	Neg
Blood VZV load at HZ onset[c]	3.3	5.5	4.1	4.5	2.7	4.3	NA	2.9	NA	3.1	3.6	2.7	3.3
Pre-eruptive symptoms	NA	Abdominal pain	NA	NA	None	Fever, dysphagia, oral pain	NA	None	NA	Genital pain	NA	None	None
Antiviral prophylaxis	None	None	None	None	VACV	None	None	None	None	None	None	None	None
Antiviral treatment	ACV	VACV	ACV	ACV	VACV	ACV	VACV	VACV	VACV	GCV	VACV	VACV	ACV

[a]prior to HZ; [b]mg equivalent prednisone; [c]expressed in log (copies/mL);

ACV: acyclovir; BMI: body mass index; F: female; GCV: ganciclovir; HIV: human immunodeficiency virus; HZ: herpes zoster; HZO: herpes zoster ophthalmicus; M: male; NA: not available; Neg: negative; Tx: transplantation; VACV: valcyclovir; VZV: varicella-zoster virus