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1 **Detection of varicella zoster virus DNA in blood from immunocompromised patients during the**
2 **week preceding the onset of herpes zoster rash**

3

4 Vincent Guiraud^{1,2}, Henri Thévenet¹, David Boutolleau^{1,2}

5

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

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

10

11

12 **Abstract**

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

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

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

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

27

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

29

30 **Introduction**

31 Herpes zoster (HZ), also known as shingles, results from the reactivation of latent varicella zoster
32 virus (VZV) in sensory ganglia [1]. It presents as a characteristic unilateral dermatomal vesicular rash
33 [2], preceded, among 50% to 70% of patients, by pain or abnormal sensations in the affected area for
34 3 to 7 days [3–5]. The main complication of HZ is post-herpetic neuralgia (PHN), defined as the
35 persistence of pain for at least 3 months after rash onset [6]. Incidence of HZ increases with age, with
36 up to a third of people living in developed countries expected to experience HZ in their lifetime [7,8].
37 Early antiviral therapy significantly accelerate the resolution of HZ-associated pain [9]. Therefore,
38 early detection of VZV, before the appearance of rash, might improve the therapeutic management
39 and prognosis of HZ.

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

49 **Methods**

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

55 QIASymphony DSP DNA mini kit. Quantitative VZV PCR was performed using HSV1&2 VZV R-GENE kit
56 (BIOMERIEUX), The limit of detection was 2.7 log (copies/mL). Baseline characteristics of patients
57 were collected from the medical records. Statistical analyses were performed using R software.
58 Categorical variables were expressed as numbers (percentages) and continuous variables as medians
59 (interquartile ranges [IQR]). Univariate analyses were performed using Mann-Whitney U test with
60 $p < 0.05$ considered to be statistically significant.

61 **Results**

62 During the study period, a total of 15,218 clinical samples were tested by VZV PCR, out of which 268
63 (1.7%) were positive. These VZV positive samples included 64 blood samples and 173 mucocutaneous
64 swabs, corresponding to 138 distinct patients with HZ. Characteristics of the patients and the
65 samples are summarized in supplementary table 1. Of the 64 blood VZV positive samples (0.98% of
66 blood PCR), 6 (9.4%) were performed after varicella and 47 (73%) after HZ. One (1.5%) patient was
67 hospitalized for encephalitis, 1 (1.5%) for a bilateral retinitis with encephalitis, 2 (3%) patients had
68 acute hepatitis, 2 (3%) toxidermia, 1 (1.5%) was hospitalized for myocardial infarction, and data was
69 missing for the last 4 (6.3%) patients. Stored blood samples performed during the week preceding
70 the onset of HZ rash were available for 13 patients.

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

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

80 significantly differ before and at the time of HZ onset (3.6 *versus* 3.3 log[copies/mL], $p = 0.78$, 95%CI
81 for the difference [-1.2;1.2]). Likewise, no statistically significant difference was seen between
82 metameric and disseminated HZ (3.3 *versus* 4.9 log [copies/mL], $p=0.076$, 95% CI for the difference [-
83 2.8;0.15]).

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

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

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

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

102

103 **Discussion**

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

114 From an anatomopathological perspective, VZV reactivation results in infecting and destroying many
115 neurons in the sensory ganglion, together with an hemorrhagic necrosis, allowing the virus to spread
116 throughout the sensitive ganglion and within bloodstream [18–21]. This is why, in contrast to herpes
117 simplex virus reactivation that is restricted to individuals neurons and leads to a reduced number of
118 vesicles on the skin, VZV reactivation leads to vesicles within an extensive portion of a dermatome
119 [22]. In our study, the frequent VZV detection in blood before HZ onset supports the hypothesis that
120 VZV spread to surrounding neurons and into bloodstream happens at an early stage after viral
121 reactivation, several days before skin involvement. It also suggests that VZV DNAemia during HZ may
122 not originate solely from viral replication in the skin, but also directly from the sensory ganglion
123 during early stages of VZV reactivation. This early viral spread allows triggering VZV-specific cellular
124 immunity (CMI). According to the level of CMI, VZV reactivation will result from
125 asymptomatic/subclinical reactivation to metameric and disseminated HZ (Figure 1). Taken together,
126 these observations remarkably align with the hypotheses made by Hope-Simpson regarding HZ in
127 1965 [1]. He postulated that VZV reactivations were frequent and could occur with or without (i.e.,
128 subclinical reactivation) symptoms, depending on the immunity level of individuals.

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

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

140

141 **Ethics**

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

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

147

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149

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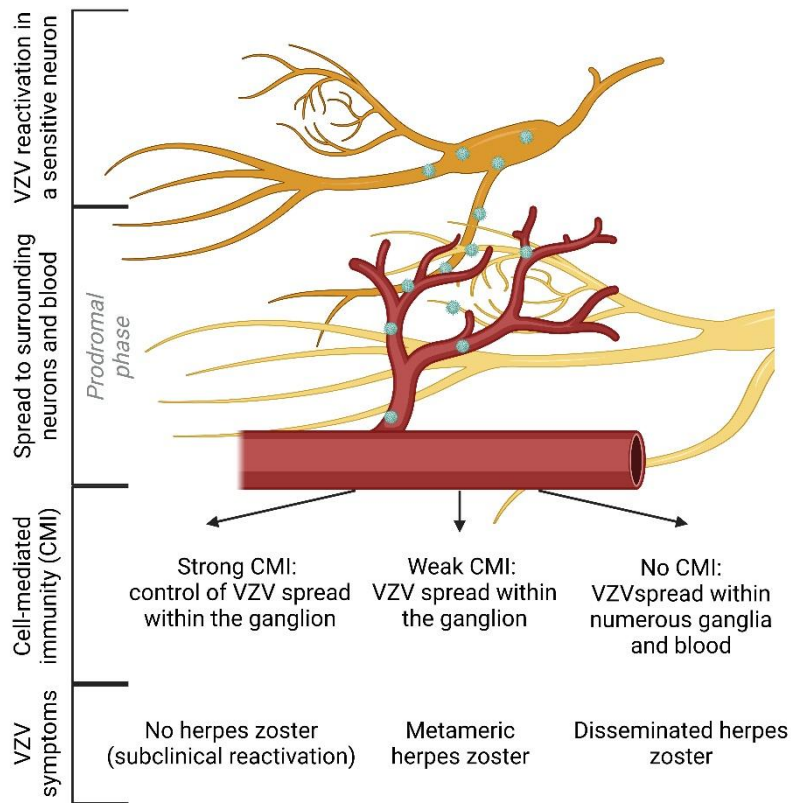
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226 Fig 1: Pathogenesis of HZ. VZV reactivation allows the virus to spread early throughout the sensitive
 227 ganglion and within bloodstream, triggering VZV-specific cellular immunity (CMI). According to the
 228 level of CMI, VZV reactivation result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

230

231 **Table 1: Baseline characteristics of the study population**

<i>Characteristics</i>	Patients (n=13)
Age, years, median (IQR)	60 (51-76)
Male sex, n (%)	10 (77%)
Tobacco smoker, n (%)	2 (12%)
BMI, kg/m ² , 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%)

232

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

235 ^aImmunosuppression: use of corticosteroids, solid organ or hematopoietic stem cell transplantation,
 236 HIV infection, autoimmune disease.

237 ^b expressed in log (copies/mL)

238 BMI: body mass index; HIV: human immunodeficiency virus; HZ: herpes zoster; VZV: varicella-zoster
 239 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

^aprior to HZ; ^bmg equivalent prednisone; ^cexpressed 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