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Clinical Research

Herpes zoster after COVID-19 vaccination, aspect of pain medicine: a retrospective, single-center study

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Background: Herpes zoster (HZ) is one of the most common cutaneous adverse reactions associated with the coronavirus disease 2019 (COVID-19) vaccine and has been widely reported. This study aimed to evaluate HZ following COVID-19 vaccination from the viewpoint of pain management.

Methods: A retrospective study was conducted on 42 patients with HZ who visited the pain clinic between August 2021 and October 2021. Medical records were reviewed to compare pain severity, treatment methods, treatment duration, and incidence rate of postherpetic neuralgia (PHN) in patients who received COVID-19 vaccination within 6 weeks prior to developing symptoms compared with other patients with HZ.

Results: Fourteen patients developed HZ within 6 weeks after vaccination and were significantly younger than the other HZ groups. There were no significant differences in the frequency of prodromal pain, location of pain, pain severity, treatment methods, treatment duration, or incidence of PHN compared with the other HZ groups.

Conclusions: COVID-19 vaccination-related HZ showed clinical features similar to those of the other HZ.

Keywords: COVID-19; Herpes zoster; Postherpetic neuralgia; Vaccination; Varicella zoster virus.

INTRODUCTION

As coronavirus disease 2019 (COVID-19) was declared a global pandemic, vaccines are being developed rapidly, and mass vaccination has been performed in a short time. Vaccination is an efficient and safe way to resolve the COVID-19 pandemic; however, its adverse reactions have been continuously reported [1]. The most common adverse reactions associated with vaccines include injection site pain, fever, myalgia, headache, and fatigue, which can be treated easily in a short period [2,3]. However, rare, fatal postvaccination adverse reactions, such as myocarditis, thrombosis, and Guillain–Barré syndrome, have been reported [4–7].

Herpes zoster (HZ) is one of the adverse reactions of COVID-19 vaccination and is being continuously reported up to now [8–12]. HZ is caused by the reactivation of varicella-zoster virus (VZV), which remains latent in the dorsal root ganglia. It is characterized by severe pain along the area of the affected nerve with a unilateral skin lesion appearing around its cutaneous distribution [13,14]. HZ, which was reported in relation to COVID-19 vaccination, has been investigated from the perspective of dermatology regarding skin

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lesions [15–17]. However, HZ may induce severe acute pain from nerve damage by the virus and postherpetic neuralgia (PHN), in which pain persists even after skin lesions improve [18]. PHN can affect patients' daily lives and may cause depression, decreased quality of life, and social withdrawal [13,18]. In this regard, HZ should not only be considered a cutaneous adverse effect associated with COVID-19 vaccination. However, to the best of our knowledge, there have been no reports or studies of HZ from the perspective of pain medicine. Therefore, we conducted this study to compare the clinical features of HZ related to COVID-19 vaccination with those of other HZ from the perspective of pain medicine by retrospectively reviewing medical records.

METHODS

This was a retrospective single-center study. This study was approved by the institutional review board of our hospital (no. 2021-11-046) and registered with the Clinical Research Information Service (no. KCT0006864). The present study was conducted according to the ethical principles for medical research of the Declaration of Helsinki 2013.

Patients who visited the pain clinic of our hospital from August 1, 2021, to October 31, 2021, were screened. During the study period, 475 patients visited the pain clinic, of whom 53 were diagnosed with HZ. Patients whose COVID-19 vaccination history was not clearly verified (n = 8), whose medical records were unreliable (n = 2), and who were referred to dermatologists because of chilblain-like lesions (n = 1) were excluded from this study (Fig. 1). Patients were divided into two groups based on 6-week (42-day) postvaccination [1]. Patients who were vaccination-naïve or had received a vaccine more than 6 weeks before were allocated to the control group (n = 28), and those who developed HZ within 6 weeks after vaccination were allocated to the COVID-19 vaccination-related HZ (CV-related HZ) group (n = 14).

In the pain clinic of our hospital, we recognize the association between COVID-19 vaccination and HZ [11], and we have been documenting the history of COVID-19 vaccination in patients with HZ since approximately August 2021. The following data were collected from the patients' medical records and analyzed: demographic information: (age and sex), COVID-19 vaccination-related information (vaccination status, types of vaccines, vaccination dose associated with HZ, and time from vaccination to development of HZ), and HZ-related information (time to development of prodromal pain and skin lesions, pain score, location of lesions, treatment methods, treatment duration, and development of PHN). PHN was defined as dermatomal pain persisting for > 90 days after the onset of acute HZ rash [18]. The time

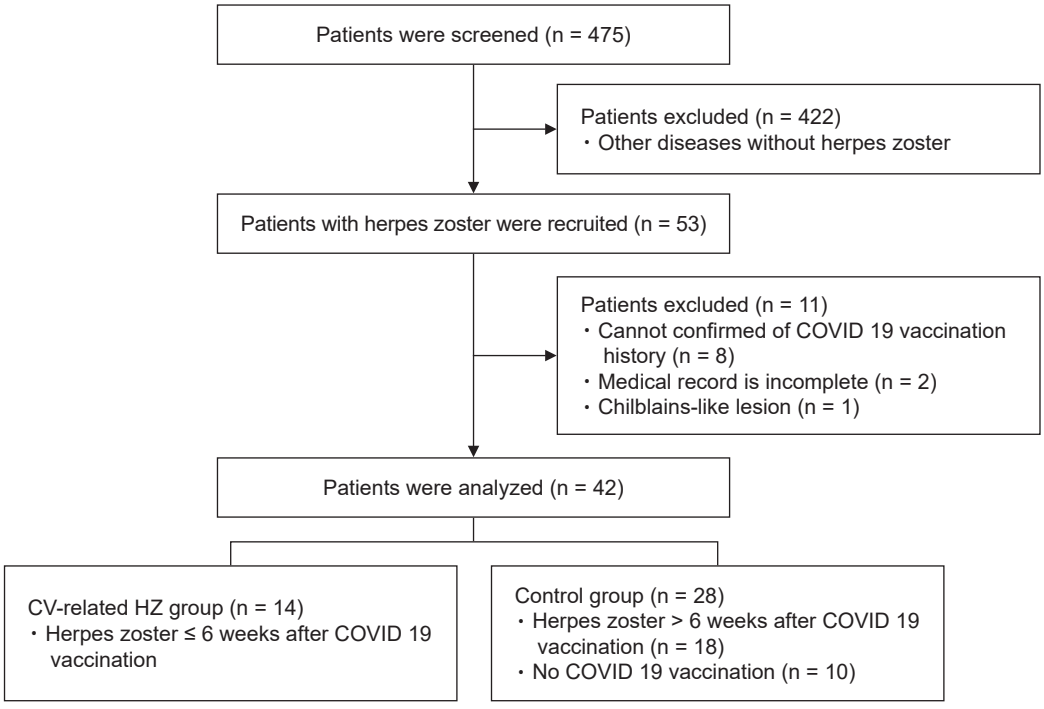

Fig. 1. Study flowchart. COVID-19: coronavirus disease 2019, CV-related HZ: coronavirus disease 2019 vaccination-related herpes zoster.

from vaccination to the development of HZ was defined as the time of onset of pain, not the time of onset of skin lesions. The vaccination date was not included in the calculation. An 11-point numerical rating scale was used to measure pain. In terms of treatment methods, the use of antiviral agents or anticonvulsants and application of nerve blocks were investigated.

Data are presented as mean (standard deviation) or median (interquartile range). The normality of the quantitative data was tested using the Shapiro–Wilk test, and data were analyzed using the independent *t*-test or Mann–Whitney *U* test. The chi-squared or Fisher's exact test was used for categorical data. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using the Statistical Package for the Social Sciences version 23 (IBM Corp., USA).

RESULTS

This study included 42 patients with HZ. Of the 32 patients who received COVID-19 vaccination, 14 developed HZ within 6 weeks after the vaccination. Ten patients did not receive any vaccination. The median age of the patients was 63.5 (34.5, 73.3) years, with 17 (40.5%) male and 25 (59.5%) female patients. Patients in the CV-related HZ group (52.0 [30.8, 62.3] years) were significantly younger than those in the control group (66.5 [54.3, 78.8] years) ($P = 0.005$). Prodromal pain was reported in 26 (61.9%) patients; thereafter, skin lesions developed after a median day of 3.0 (0.0, 4.0). The median pain scores were 3.0 (3.0, 4.0) and 4.0 (3.0, 4.0) in the CV-related HZ and control groups, respectively ($P = 0.834$). The most common locations of the lesion were the thoracic (64.3%) and cranial (14.3%) nerves. Antiviral agents (100%), anticonvulsants (87.2%), and nerve blocks (43.6%) were used. Moreover, 87.2% of the patients completely recovered within 12 weeks (Table 1). The other data did not show any statistical difference. In the CV-related HZ group, eight (57.1%) patients completely recovered within 4 weeks after symptom development. Although the difference was not statistically significant, five (12.8%) patients in the control group progressed to PHN ($P = 0.092$) (Fig. 2).

In the CV-related HZ group, five patients received BNT1 62b2 (Pfizer), five received mRNA-1273 (Moderna), and four received ChAdOx1 nCov-19 (AstraZeneca). Ten patients developed symptoms after the second dose. Nine (64.3%) patients developed symptoms within 21 days of vaccination (Table 2).

The clinical information of patients with CV-related HZ and PHN is presented in Tables 3 and 4.

DISCUSSION

In total, 42 patients with HZ were included in the present study, of whom 14 (33.3%) developed HZ within 6 weeks after COVID-19 vaccination. Except for age, demographic and HZ-related data did not show statistically significant differences between the groups. However, five patients in the control group developed PHN, whereas none of the patients in the CV-related HZ group progressed to PHN, but the difference was not statistically significant.

VZV, which remains latent in the ganglia, can be reactivated and replicated, inducing neuritis that directly damages the nerves. It is transported along the microtubules within the sensory axons in the affected nerve to infect the epithelial cells of the skin. This results in severe pain and skin lesions along the cutaneous distribution. Weakened VZV-specific T-cell-mediated immunity reactivates VZV. Its risk factors include immunosenescence, immunocompromised conditions due to disease, trauma, drug use, and psychological stress [14,19]. The outbreak of the COVID-19 pandemic and COVID-19 vaccination have been reported to be associated with the development of HZ [20–23]. Its mechanism of action has been reported to be lymphopenia and T-cell dysfunction due to COVID-19 infection, and immunomodulation associated with COVID-19 vaccination weakens T-cell-mediated immunity, which inhibits VZV from being reactivated. However, its mechanism of action remains unclear [20,23].

Although HZ is accompanied by severe pain and is likely to progress to PHN, a neurological complication, most published cases of HZ after COVID-19 vaccination have been approached from the aspect of dermatology regarding skin lesions [15–17]. Many studies have mentioned HZ in view of skin complications that occur after vaccination [24,25]. Even in studies that directly reported HZ, most described the association between HZ and vaccination or the mechanism [15,16]. In studies published from the aspect of dermatology, it was rare for the treatment and progress of HZ to be clearly described, as in the present study. In cases that clearly described the treatment for HZ and its progress, most treatment outcomes were highly good. Most patients improved with antiviral therapy, and there were no cases lasting > 6 weeks [165. However, five (35.7%) of the 14 patients with HZ required treatment for 6 weeks or longer (6–11 weeks) in the present study (Fig. 1). The reason that the treatment period of the

Table 1. Demographic Data and Characteristics of Herpes Zoster-related Data

Variable	CV-related HZ (n = 14)	Control (n = 28)	P value
Demographic data			
Age (yr)	52.0 (30.8, 62.3)	66.5 (54.3, 78.8)	0.005
Sex, M/F	6 (42.9)/8 (57.1)	11 (39.3)/17 (60.7)	0.824
Medical history			
Total	9 (64.3)	20 (71.4)	0.447
Cardiovascular	3 (21.4)	12 (42.9)	
Endocrine	3 (21.4)	8 (28.6)	
Pulmonary	1 (7.1)	2 (7.1)	
Nephrotic	0 (0.0)	2 (7.1)	
Cerebrovascular	0 (0.0)	5 (17.9	
Allergy	3 (21.4)	3 (10.7)	
Malignant	0 (0.0)	4 (14.3)	
Characteristics of herpes zoster			
Prodromal pain	9 (64.3)	17 (60.7)	0.822
Interval between prodromal pain and rash (d)	3.0 (0.0, 4.0)	3.0 (0.0, 4.75)	0.661
Pain score, NRS			
Initial pain	3.0 (3.0, 4.0)	4.0 (3.0, 4.0)	0.843
Peak pain	4.0 (3.0, 4.3)	4.0 (3.3, 5.0)	0.535
Location			
Cranial	2 (14.3)	4 (14.3)	0.689
Cervical	2 (14.3)	2 (7.1)	0.407
Thoracic	9 (64.3)	18 (64.3)	0.629
Lumbar	1 (7.1)	1 (3.6)	0.561
Sacral	0 (0.0)	3 (10.7)	0.285
Patients number	14	25*	
Treatment			
Antiviral agents	14 (100)	25 (100)	
Anticonvulsants	12 (85.7)	22 (88.0)	0.600
Nerve block	6 (42.9)	11 (44.0)	0.945
Recovery time (wk)			
1–4	8 (57.1)	10 (40.0)	0.303
5–8	4 (28.6)	7 (28.0)	0.624
8–12	2 (14.3)	3 (12.0)	0.600
> 12	0 (0.0)	5 (20.0)	0.092
Postherpetic neuralgia	0 (0.0)	5 (20.0)	0.092

Values are presented as median (1Q, 3Q) or number (%). CV-related HZ: coronavirus disease 2019 vaccination-related herpes zoster, NRS: numerical rating scale. *Three patients were excluded: one patient was transferred to another hospital, one was lost to follow-up, and one was transferred to the emergency room at the second visit due to a high fever.

present study was longer than those of previous studies is considered to be the additional treatment for persistent pain that occurs even after skin lesion improvement. We can deduce that such difference can be caused by the possibility of visiting the pain clinic rather than the dermatology department when patients mainly complained of severe pain. Generally, skin lesions of HZ completely recover within 2–4 weeks, and pain is known to last for an average of 45 days [26].

Antiviral therapy is important for the treatment of HZ. Antiviral therapy provided in the acute phase inhibits progression to PHN by inhibiting viral replication and reducing injury to nerve fibers and can also reduce the severity and duration of PHN. In addition, a decreased incidence of PHN was reported when antivirals were administered with gabapentin [27]. On the contrary, nerve blocks are effective in pain control in a short period of time, but their effects on PHN have not yet been clarified [19]. In the present study, all patients received antiviral therapy (100%) for the treatment

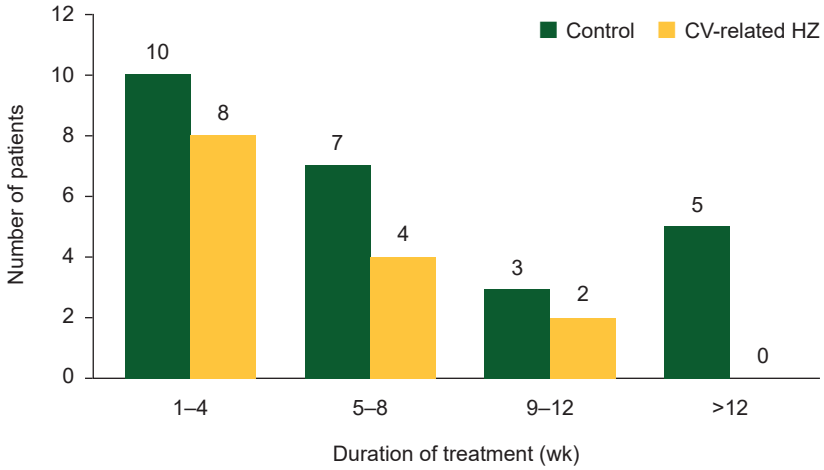

Fig. 2. Recovery time for herpes zoster. The recovery rates within 8 weeks in the CV-related HZ and control groups are 85.7% and 68.0%, respectively. CV-related HZ: coronavirus disease 2019 vaccination-related herpes zoster.

Table 2. Characteristics of Vaccination-related Herpes Zoster (n = 14)

Characteristics		
Vaccine and dose	1st dose	2nd dose
Pfizer	2	3
Moderna	1	4
AstraZeneca	1	3
Time of symptom onset after vaccination		
1–21 days	9 (64.3)	
22–42 days	5 (35.7)	

Values are presented as number (%).

of HZ, and anticonvulsants, such as gabapentin or pregabalin, were used in 87.2% of the patients. Moreover, 43.6% of the patients underwent nerve blocks. Nevertheless, five patients (male/female: 2/3; age, 66.0 [61.0, 77.5] years) in the control group developed PHN. Although the incidence of PHN in the two groups was not statistically significant, the reason for the absence of PHN in the CV-related HZ group can be deduced from the age of the two groups. Older age is the most potent risk factor for PHN because the nervous systems in the elderly may be less tolerant of the damage associated with HZ. In this study, it can be inferred that progression to PHN was absent in the CV-related HZ group because the patients were significantly younger. However, a large-scale additional study using such a large dataset is required to confirm this because this study has a small sample size.

The window in which the risk of HZ increases remains unclear. The risk window for HZ significantly varied, ranging from 21 days to 3 months, depending on the studies reported [1,22,23,28]. Barda et al. [1] set a follow-up period of 42 days after vaccination in a safety study on the COVID-19 vaccine. They believed that 42 days would be sufficient to identify medium-term adverse events without diluting the incidence of short-term adverse events. In their study, the risk of HZ was substantially higher in the vaccinated group than in the unvaccinated group (risk ratio, 1.43; 95% confidence interval [CI], 1.20–1.73; risk difference, 15.8 events per 100,000 persons; 95% CI, 8.2–24.2). Based on this, the present study used a 42-day risk window [1].

Of COVID-19 vaccines, an association between mRNA COVID-19 vaccination and HZ has been reported more frequently [7,9,16], but postvaccination HZ has been reported in almost all types of vaccines [8,10,29]. In the present study, five patients were in the Pfizer group, five in the Moderna group, and four in the AstraZeneca group. In Korea, there were approximately 75,287,995 vaccination cases by the end of October 2021, and there were 42,927,605 patients receiving Pfizer vaccine, 20,296,861 receiving AstraZeneca vaccine, 10,586,677 receiving Moderna vaccine, and 1,476,852 receiving Janssen vaccine. Since approximately 1.1 million cases in a specific occupational group received the Janssen vaccine in June 2021, the number of vaccination cases was small. Accordingly, there were no cases of Janssen vaccination in the present study.

The association between COVID-19 vaccination and HZ remains controversial. A meta-analysis by Chu et al. [30] reported that there was no evidence that COVID-19 vaccination increased the incidence of HZ (risk ratio, 1.06; 95% CI, 0.91–1.24). Patil et al. [28] also reported that there was no

Table 3. Characteristics of Patients with COVID-19 Vaccination-related Herpes Zoster and Herpes Zoster-associated Data

Characteristics						
Variable	Age (yr)	Sex, M/F	COVID-19 vaccination		Time interval of HZ onset after vaccination (d)	Comorbidities
			Types	Dose		
Patient 1	30	F	Pfizer	1st	31	Food allergy
Patient 2	71	M	AstraZeneca	2nd	1	Hypertension, type 2 diabetes, gastrectomy
Patient 3	63	F	AstraZeneca	1st	1	Nontoxic goiter
Patient 4	57	F	Moderna	2nd	28	None
Patient 5	21	F	Pfizer	2nd	33	Atopic dermatitis, appendectomy
Patient 6	54	M	Moderna	2nd	2	Atrial fibrillation, appendectomy
Patient 7	59	M	Moderna	2nd	30	None
Patient 8	50	M	Moderna	2nd	12	Asthma
Patient 9	31	M	Pfizer	1st	6	Mite allergy
Patient 10	66	F	AstraZeneca	2nd	33	Angina
Patient 11	62	F	AstraZeneca	2nd	5	Gastrointestinal disease, hyperlipidemia
Patient 12	50	M	Moderna	1st	10	Type 2 diabetes, hyperlipidemia
Patient 13	28	F	Pfizer	2nd	14	None
Patient 14	32	F	Pfizer	2nd	3	None

Herpes zoster-associated data									
Variable	Interval between prodromal pain and rash (d)	Pain score, NRS (0–10)		Skin lesion severity	Location	HZ treatment			
		Initial	Peak			Antiviral agents	Anticonvulsants	Antidepressants	Nerve blocks
Patient 1	4	3	3	Mild	T1, T2	+	+	–	–
Patient 2	0	3	3	Mild	T10	+	+	+	+
Patient 3	3	6	6	Mild	L4, L5	+	+	+	+
Patient 4	4	3	3	Mild	T6, T7	+	+	+	+
Patient 5	0	4	4	Severe	T7, T8	+	+	+	+
Patient 6	0	3	3	Mild	T10	+	+	–	+
Patient 7	0	3	3	Mild	V1	+	+	–	–
Patient 8	0	4	4	Mild	C2	+	+	–	–
Patient 9	4	3	3	Mild	V1	+	+	+	+
Patient 10	4	4	4	Mild	T10, T11	+	–	–	–
Patient 11	7	4	4	Mild	T6, T8	+	+	–	–
Patient 12	3	2	2	Mild	T11	+	+	–	–
Patient 13	4	5	5	Mild	T5	+	+	+	–
Patient 14	2	3	3	Mild	C3	+	–	–	–

HZ: herpes zoster, NRS: numerical rating scale, COVID-19: coronavirus disease 2019.

difference in the frequency of HZ before and 3 months after vaccination. In contrast, a case-control study by Alhasawi et al. [22] reported a significant association between COVID-19 vaccination and varicella zoster activation (odds ratio, 4.87; 95% CI, 2.40–9.89). Hertel et al. [23] also reported that the risk increased in the group who received vaccination, with a risk ratio of 1.802 (95% CI, 1.680–1.932). Temporal compatibility and biological plausibility should be confirmed to evaluate the causal association between HZ and COVID-19 vaccination in terms of adverse events following immunization. Future studies should investigate temporal compatibility and biological plausibility.

The present study has a strength in that it was conducted from the aspect of pain medicine, but its limitations are clear as it was a single-center, retrospective study that included a small sample size.Another limitation of this study is that the incidence of HZ associated with COVID-19 vaccination could not be evaluated. To overcome this limitation, a multicenter, prospective, large-scale study targeting a large population must be conducted in the future.

In the present study, patients with HZ associated with COVID-19 vaccination showed similar manifestations to

Table 4. Characteristics of Patients with Postherpetic Neuralgia

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (yr)	73	66	58	82	64
Sex, M/F	M	F	F	F	M
COVID-19 vaccination, yes/no	Yes (AstraZeneca 1st dose)	No	No	No	No
Time interval of HZ onset after vaccination (d)	60				
Comorbidities	Hypertension, asthma	Osteoporosis	Breast and thyroid cancers	Diabetes, cerebral infarction, dementia	Hypertension, diabetes
Interval between prodromal pain and rash (d)	5	0	0	0	7
Pain score, initial/peak/PHN pain, NRS (0–10)	3/4/2	5/5/2	4/4/3	3/4/2	4/5/4
Skin lesion severity	Severe	Moderate	Severe	Severe	Severe
Location	C3, C4, Lt	T3, T4, Lt	T3, T4, Rt	T4, T5, Lt	S1, S2, Rt
HZ treatment					
Antiviral agents	+	+	+	+	+
Anticonvulsants	+	+	+	+	+
Antidepressants	+	–	+	–	+
Nerve blocks	+	–	–	+	+

HZ: herpes zoster, PHN: postherpetic neuralgia, COVID-19: coronavirus disease 2019, NRS: numerical rating scale, Lt: left, Rt: right.

general patients with HZ. They recovered after treatment with antiviral agents, anticonvulsants, and nerve blocks, and none of the patients developed PHN.

FUNDING

None.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

Conceptualization: Ji Hye Lee. Data curation: Hyun Joo Heo, Ji Hun Park, Hyung Gu Cho, Geonbo Kim. Writing - original draft: Yu Yil Kim. Writing - review & editing: Ji Hye Lee. Supervision: Yu Yil Kim. Validation: Hyun Joo Heo.

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