

Herpes Zoster and Postherpetic Neuralgia in an Elderly Patient with Critical COVID-19: A Case Report

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Abstract: Critical patients with COVID-19 are thought to be at high risk of developing chronic pain. However, the exact nature and mechanisms of COVID-19-related chronic pain remain largely unknown. Here, we describe clinical features, treatments and outcome of herpes zoster as well as postherpetic neuralgia in a 70-year-old woman with critical COVID-19. The patient had a history of type 2 diabetes and myasthenia gravis. She developed herpes zoster in the right 10 to 12 lumbar dermatomes in the recovery period of COVID-19. Intravenous (250 mg 3 times a day) and then oral (400 mg 5 times a day) acyclovir was used for antiviral therapy. Pregabalin (75 mg orally twice a day) and ibuprofen was used for analgesia. Her skin lesions resolved 21 days after the onset of rash. However, she continued to have persistent pain in the same dermatomal distribution. After the dosage of pregabalin was increased to 150 mg orally twice a day, her pain was partially relieved. During the telephone follow-up 4 months after herpes zoster eruption, the patient still complained intermittent pain in the right 10 to 12 lumbar dermatomes. Our case draws attention to postherpetic neuralgia in COVID-19 patients and provides a targeted suggestion for this kind of patients.

Keywords: SARS-CoV-2, COVID-19, herpes zoster, postherpetic neuralgia, elderly patient

Introduction

Caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the outbreak of coronavirus disease 2019 (COVID-19) has spread quickly across the world. As of July 27, 2020, COVID-19 has been confirmed in 15,785,641 cases and caused 640,016 deaths globally.¹ Although SARS-CoV-2 primarily affects the respiratory system, other organ systems such as cardiovascular, urinary and neurological systems are also involved.² It is likely that COVID-19 survivors will have additional comorbidities requiring further support, including chronic pain.³ Previous studies have suggested that chronic pain is not an uncommon complication following ICU discharge.⁴ Critical patients with COVID-19 are thought to be at high risk of developing chronic pain.⁵ However, the exact nature and mechanisms of COVID-19-related chronic pain remain largely unknown.

Postherpetic neuralgia is a chronic painful condition that can occur following herpes zoster, an extremely painful skin rash caused by the varicella zoster virus. Postherpetic neuralgia occurs most often in elderly people and in people with immunocompromise, who are also susceptible to COVID-19.⁶ Recently, there are case reports of herpes zoster in patients with both symptomatic and asymptomatic

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SARS-CoV-2 infection.^{7,8} However, in these cases, no long-term follow up was performed and no postherpetic neuralgia was observed. Here, we report clinical features and treatments of herpes zoster and postherpetic neuralgia in an elderly patient with critical COVID-19. In addition, we review literatures about pathogenesis of COVID-19 and herpes zoster, and the prevention and treatment of postherpetic neuralgia, in order to provide a targeted suggestion for this kind of patient. This case report was approved by the Research and Ethics Committee of Tongji hospital at Tongji Medical College, Huazhong University of Science and Technology to publish the case details. Written informed consent has been provided by the patient to have the case details and any accompanying images published.

Case Presentation

A 70-year-old woman presented to the emergency department with fever and dry cough of 3 days' duration on January 17, 2020. Her medical history was noteworthy for type 2 diabetes and myasthenia gravis, for which she was taking acarbose (25 mg orally 3 times a day), pyridostigmine (120mg orally 3 times a day), prednisone (20mg orally once a day), and tacrolimus (2 mg orally once a day). The patient had a history of muscle weakness, with no respiratory failure, which was well controlled. In addition, the patient had a history of chickenpox but no previous documented episodes of herpes zoster. Chest CT scans showed multiple ground glass opacities and infiltration in both lungs. Blood examination showed a decreased leukocyte count of $3.4 \times 10^9/L$ and lymphocyte count of $0.6 \times 10^9/L$ (Table 1). The patient was diagnosed as a suspected case of COVID-19 and admitted to an infection isolation ward.

After admission, the diagnose of COVID-19 was confirmed based on positive results of real-time reverse transcriptase–polymerase chain reaction (RT-PCR) tests for nucleic acid of SARS-CoV-2 (Novel Coronavirus PCR Fluorescence Diagnostic Kit, BioGerm Medical Biotechnology). She was treated with arbidol (0.2 g orally every 8 h) and moxifloxacin (0.4 g orally every day). On January 27, 2020, she developed respiratory distress with breath rate > 30 per min and oxygen saturation $< 93\%$ at rest. Low-flow and then high-flow oxygen therapy via nasal cannula was started, but the symptoms did not improve. The patient was transferred to the intensive care unit and noninvasive mechanical ventilation was implemented. Nine days later, noninvasive

mechanical ventilation was stopped and high-flow oxygen therapy via nasal cannula was continued. Her blood examination showed a repeatedly increased leukocyte and neutrophil count, indicating a potential bacterial infection. Thus, tacrolimus was stopped on February 13, 2020. Her clinical condition improved gradually. The patient was transferred to a general ward and oxygen therapy was stopped on February 23, 2020, and tacrolimus was restarted on March 3, 2020.

On March 5, 2020, there were clusters of small red papules occurring on her right side of the waist accompanied by spontaneous sharp pain (rated as 8–9 on an 11-point numeric rating scale (NRS, 0–10), and a clinical diagnosis of herpes zoster was made. The patient received antiviral treatment with intravenous acyclovir (250 mg 3 times a day), and prednisone (20mg orally once a day) was restarted. Meantime, infrared therapy were applied for promoting rash absorption, and pregabalin (75 mg orally twice a day) and ibuprofen was used for analgesia. A follow-up RT-PCR test for nucleic acid of SARS-CoV-2 was performed and the results were positive. On March 7, 2020 (day 3 of herpes zoster), most papules were replaced with clear vesicles and the pain was slightly relieved. On March 20, 2020 (day 16 of herpes zoster), the clear vesicles had become cloudy and some eventually crusted. Intravenous acyclovir was replaced with oral acyclovir (400 mg 5 times a day) and discontinued 7 days later. On March 25, 2020 (day 21 of herpes zoster), her skin lesions resolved (Figure 1). However, she continued to have persistent pain in the right 10 to 12 lumbar dermatomes. She experienced constant burning pain (NRS 5), intermittent electric shocks (NRS 7, >20 times a day, a 5-minute duration each). The dosage of pregabalin was increased to 150 mg orally twice a day. The constant pain decreased to 3/10 within 2 weeks. The intensity of intermittent pain also decreased to 5/10 (3 times a day, a 3-minute duration each). On April 23, 2020, the patient was discharged to an isolation centre for 14 days of quarantine after recovery from COVID-19. On July 6, 2020 (4 months after the onset of rash), the patient received a follow-up telephone call and reported that she still had intermittent pain in the right 10 to 12 lumbar dermatomes (NRS 3, 1–2 times per day, seconds for each episode).

Discussion

Postherpetic neuralgia is one of the most common causes of neuropathic pain, which affects up to a third of patients with herpes zoster.⁹ It is reported that herpes zoster cases

Table I Clinical Laboratory Results of the Patient

Day of illness		Admission	ICU				Herpes zoster					Discharge
		D4	D14	D23	D29	D41	D52	D55	D59	D64	D74	D99
Measure	Reference range	1/17	1/27	2/5	2/11	2/23	3/5	3/8	3/12	3/17	3/27	4/23
hs-CRP (mg/L) (<1)	<1	67.6	248	1.3	1.8	0.4		58.9	5.5	1.3	0.3	
WBC ($\times 10^9/L$)	3.50–9.50	3.4	13.8	13.12	12.62	14.77	5.37	9.66	6.1	8.86	7.99	6.05
NEUT (%)	40.0–75	73.3	92	86	80.6	83.4	61.3	75.7	52.9	61.7	52.1	48.7
NEUT ($\times 10^9/L$)	1.8–6.3	2.42	12.87	11.29	10.18	12.32	3.29	7.31	3.23	5.46	4.17	2.94
LYM (%)	20.0–50.0	<i>18.1</i>	<i>5.3</i>	9.7	<i>10</i>	<i>10.4</i>	28.9	<i>19.6</i>	42.5	35.9	35.8	43.8
LYM ($\times 10^9/L$)	1.10–3.20	<i>0.6</i>	<i>0.74</i>	1.27	1.26	1.54	1.55	1.89	2.59	3.18	2.86	2.65
MONO (%)	3.0–10	8.8	<i>1.9</i>	3.7	8.8	6	8.4	4.2	3.9	2.1	11.4	6.9
MONO ($\times 10^9/L$)	0.1–0.6	0.59	0.27	0.49	1.11	0.88	0.45	0.41	0.24	0.19	0.91	0.42
PLT ($\times 10^9/L$)	125–350	222	240	234	246	353	135	137	199	268	250	199
IL-1beta (pg/mL)	<5.0			8.1		8.1	12.3			16	25.1	
IL-2 receptor (U/mL)	223–710			368		368	305			318	241	
IL-6 (pg/mL)	<7			6.31		6.31	2.53			<1.5	1.8	
IL-8 (pg/mL)	<62			19.7		19.7	21			12.5	10.6	
IL-10 (pg/mL)	<9.1			5.9		5.9	13			<5.0	7.5	
TNF alpha	<8.1			6.4		6.4	8.2			7.4	7.5	
total T-lymphocytes (%)	50–84									67.51		72.8
total T-lymphocytes (cells/ul)	955–2860									1999		1774
total B-lymphocytes (%)	5–18									8.63		6.42
total B-lymphocytes (cells/ul)	90–560									255		158
Th (%)	2–51									40.17		45.32
Th (cells/ul)	550–1440									1189		1115
Ts (%)	15–44									26.24		25.22
Ts (cells/ul)	320–1250									777		621
NK cell (%)	7–40									22.94		20.6
NK cell (cells/ul)	150–1100									679		507
Alanine aminotransferase (U/L)	≤ 33			8	5	13				19	18	16
Aspartate aminotransferase (U/L)	≤ 32			16	16	19				23	20	16
Creatinine ($\mu\text{mol/L}$)	45–84			54	54	50				41	47	45

Note: values in bold were above normal; values in italics were below normal.

Abbreviations: ICU, intensive care unit; hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell; NEUT, neutrophil; LYM, lymphocyte; MONO, monocyte; PLT, platelet; IL, interleukin; TNF, tumor necrosis factor; Th, helper T cell; Ts, suppressor T cell; NK, nature killer.

substantially increase during COVID-19 pandemic.⁸ Because of limited knowledge about pathogenesis of SARS-CoV-2 infection, it is challenging to treat acute herpes zoster and prevent postherpetic neuralgia in COVID-19 patients. Here, we report the clinical features, treatment and prognosis of herpes zoster in an elderly patient with critical COVID-19, indicating the importance of early antiviral therapy.

Herpes zoster is caused by reactivation of latent varicella zoster virus. A decline in cell-mediated immune response is thought to play an important role in the pathogenesis of herpes zoster.¹⁰ Decreased cell-mediated

immune responses can be induced by advancing age, medical treatments or immunosuppressive illnesses.¹¹ In COVID-19 patients, SARS-CoV-2 infection may decrease primarily T lymphocytes, especially CD4⁺ and CD8⁺ T cells.¹² In addition, the current patient had a history of myasthenia gravis and had been receiving tacrolimus therapy. Myasthenia gravis is the most common humoral and cellular immune-mediated neuromuscular disorder. Dysregulation of regulatory T cells and elevated levels of pre-inflammatory cytokines such as IL-6 have been noted in myasthenia gravis patients.¹³ Tacrolimus, a calcineurin



Figure 1 Herpes zoster in a right-sided T10-12 dermatomal distribution. The vesicular crusts has fallen off leaving temporary pigmentation.

inhibitor, is one of the most effective agents in controlling the overall regulatory T cells, which can result in the inhibition of expression of IL-6. Earlier reports have described herpes zoster occurs before or after onset of COVID-19 symptoms with lymphopenia.^{7,8} However, in this patient, herpes zoster occurred in the recovery period of COVID-19 and the results of clinical laboratory measurements were almost normal. This observation indicates the variety of COVID-19 and herpes zoster co-occurrence, and the complexity of the underlying mechanisms.

Although herpes zoster is mostly self-limiting, antiviral therapy needs to be considered in patients with severe diseases such as COVID-19. Among antivirals for treatment of herpes zoster licensed by the Food and Drug Administration (FDA), acyclovir is most commonly used. In the previous studies, acyclovir has been shown to reduce virus shedding, stop new lesion formation and hasten resolution of lesions.^{14,15} In the current report, the administration of acyclovir was started within 24 hours of rash onset and lasted for 21 days. It is recommended that antiviral treatment initiate within 72 hours of onset of the rash, and is usually given for 7 days.¹⁴ The principle of

antiviral treatment in COVID-19 patients with herpes zoster might be the same as in other patients with the condition. In patients with complications of herpes zoster, which might be more common in COVID-19 patients, the course of treatment needs to be extended. Considering the side effects of acyclovir such as hepatotoxicity and nephrotoxicity, liver and kidney function should be monitored regularly. Under certain circumstances such as contraindications of acyclovir, vitamin C and quercetin might be considered as alternative treatments, which have been proved to display immunomodulatory function and anti-viral effect.¹⁶ In addition, the patients with herpes zoster should be placed on contact precautions to avoid varicella zoster virus transmission to susceptible persons such as other COVID-19 patients.

Pain management is one of the cornerstones of treatment of both acute herpes zoster and postherpetic neuralgia. For mild to moderate pain, analgesics such as paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) are appropriate. For severe pain, opioid analgesics such as oxycodone or morphine are options.¹⁵ In the first line treatment of postherpetic neuralgia, tricyclic

antidepressants (like nortriptyline or amitriptyline), anticonvulsant (like gabapentin or pregabalin) and topically administered lidocaine may be used.¹⁷ Because the patient in the current report has a history of myasthenia gravis, drugs affecting the neuromuscular junction like anticonvulsants need to be used with caution. Although one anticonvulsant gabapentin has been widely reported to induce an exacerbation of myasthenic symptoms,^{18–20} another anticonvulsant pregabalin is well tolerant in the current case. Thus, in patients with COVID-19, the comorbidity and the side effects of analgesics should worth further attention to and be treated case by case. Where a single treatment alone is ineffective, combined modalities are recommended.

In summary, this case draws attention to postherpetic neuralgia in COVID-19 patients. For COVID-19 patients with herpes zoster, antiviral treatment should be started as early as possible and last longer than a typical course. The use of analgesics should be based on the dermatome involved, severity of pain and the comorbidities. Our report indicates that longer term outcomes of pain management in COVID-19 patients should be monitored in future studies.

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Disclosure

The authors report no conflicts of interest in this work.

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