Correspondence

Alternation in the cutaneous microbiome of herpes zoster lesion in a patient with severe coronavirus disease 2019

Dear Editor,

A 57-year-old man with a medical history of hypertension and hyperuricemia with high fever was diagnosed with coronavirus disease 2019 (COVID-19) by polymerase chain reaction from sputum sample. He was hospitalized due to clinical symptoms of cough and fatigue, and findings of slightly patchy ground-glass opacity on chest computed tomography (CT). One day after admission, he received supplemental oxygen due to his worsening respiratory status with rapid progression to segmental mixed consolidation and ground-glass opacity on CT. Three days after admission, he had respiratory failure requiring mechanical ventilation despite receiving several aggressive therapies, including favipiravir with dexamethasone, steroid pulse therapy with methylprednisolone sodium succinate, and remdesivir. He was treated with extracorporeal membrane oxygenation (ECMO) for uncontrolled hemodynamically unstable bradycardia 12 days after admission. Thirty days after admission, erythema developed over the right side of his forehead lesion located in the first division of the trigeminal nerve. The lesion immediately underwent necrosis with exudate but no blisters (Fig. 1a). The patient was diagnosed with herpes zoster (HZ) 33 days after admission. The HZ developed as generalized erythema with vesicles 3 days after the onset of HZ. The damaged face lesion developed into hard black necrotic tissue 40 days after admission despite continuous intravenous acyclovir administration (Fig. 1b). The anti-HZ virus IgG level was elevated at the time of diagnosis (IgM antibody index, 0.09 [normal range,0–0.79]/IgG antibody index, 112.6 [normal range, <2.0]) and after 14 days (IgM 0.27/IgG more than 128). We

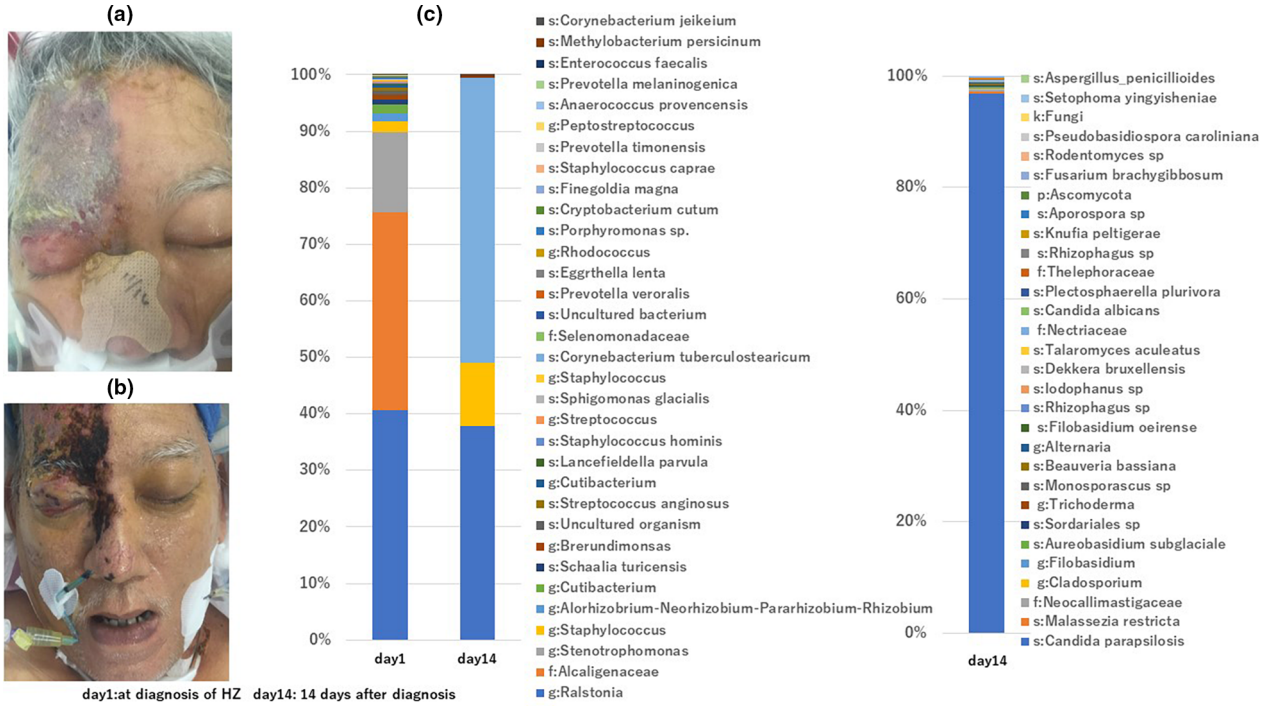

Figure 1 (a) The first division of the trigeminal nerve on the patient's face developed a epidermal erosion with clearly delineated boundaries, 33 days after admission. The patient was diagnosed with HZ using Derma Quick® (Maruho, Osaka, Japan). (b) The herpes zoster (HZ) lesions changed to hard black necrotic tissue 40 days after admission. (c) The rate of bacteria and fungus occupied in HZ lesions investigated by next-generation sequencing at the diagnosis of HZ and 14 days after diagnosis. Healthy skin is characterized by a diverse microbiome, but 14 days after diagnosis, the lesion was predominantly occupied by *Corynebacterium tuberculostearicum, Staphylococcus* genus, and *Ralstonia* genus. Fungus was undetected at the time of HZ diagnosis, but various fungal species were observed 14 days after diagnosis. s: species g: genus f: family p: phylum k: kingdom

then investigated the microbiome of HZ lesions at diagnosis and 14 days after identifying the event outside our experience with HZ. We analyzed the sequence genome data of fungal ITS and bacterial 16S rRNA from the DNA extracted from the necrotic skin by using next-generation sequencing. At the time of diagnosis, the necrotic skin exhibited a high bacterial diversity. Meanwhile, 14 days after diagnosis, the lesion was predominantly occupied by *Corynebacterium tuberculostearicum, Staphylococcus* genus, and *Ralstonia* genus. The proportion of the genus Ralstonia was unchanged between the two points, but the family Alcaligenaceae disappeared. Fungus was undetected at the time of HZ diagnosis, but various fungal species, particularly *Candida parapsilosis*, were observed 14 days after diagnosis. He died despite intensive care 94 days after admission.

The diversity of the skin microbiome is an essential barrier against several antigens.[1] Alternations in the fecal fungal microbiome were observed in patients with COVID-19.[2] In previous reports of COVID-19 associated with HZ, the HZ eruption helped detect latent COVID-19 infections,[3,4] and HZ was detected during the early phase of the COVID-19 infection.[5] In our case, the onset of HZ occurred late after the COVID-19 infection. The patient had sufficient antibody titers against the HZ virus, but HZ progressed rapidly and developed into the generalized type. Compared to previous reports of COVID-19 with HZ,[3–5] this case resulted in mortality despite aggressive and immediate interventions, such as ECMO. The rapid necrotic changes exhibited by the HZ lesion indicated the severity of the cytokine storm caused by the synergistic effect of COVID-19 and HZ. Aggressive treatments against COVID-19 might depress the local immunity of the skin. While the skin microbiome was initially diverse, certain bacterial and fungal species were observed 14 days later. During the onset of HZ, the predominant bacteria found in the facial skin of COVID-19 patients included rare species such as *Ralstonia*, *Alcaligenaceae*, and *Stenotrophomonas*. The dominant species of the *Alcaligenaceae* family and *Stenotrophomonas* genus disappeared after the HZ infection. However, the *Ralstonia* genus survived amidst the rapid skin changes. Controlling *Ralstonia* genus may be a viable treatment for skin necrosis and COVID-19 infection.

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