



Three mild cases of coronavirus disease 2019 treated with saikatsugekito, a Japanese herbal medicine

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ABSTRACT

Cases: We report cases of three patients infected with mild coronavirus disease 2019 (COVID-19) treated only with Kampo medicine and discharged from the hospital without symptom exacerbation.

Case 1: A 41-year-old healthy female suffering from headache, sore throat, and fever. **Case 2:** A 16-year-old healthy female suffering from nasal congestion and taste disorder. **Case 3:** A 12-year-old healthy male suffering from nasal congestion and taste disorder.

Outcome: The three patients were prescribed saikatsugekito. Cases 1 and 3 initially presented with white and yellow tongue coating, which disappeared several days after the prescription of saikatsugekito. All three patients were discharged from the hospital without symptom exacerbation.

Conclusion: We believe that treatment with Kampo medicine, which is relatively safe clinically and has few side effects, should be taken at an early stage of COVID-19 along with coping therapy. And we think that saikatsugekito may contribute to prevent the worsening of COVID-19.

KEY WORDS: COVID-19, Kampo medicine, saikatsugekito, white and yellow tongue coating

INTRODUCTION

Countermeasures against coronavirus disease 2019 (COVID-19) are currently underway worldwide, including vaccine development and clinical trials of existing antiviral drugs. However, it is still too early to conclude whether these antiviral drugs are effective against COVID-19, and expansion of their clinical use in the absence of clinical data may result in adverse effects.

On the other hand, general clinicians cannot afford to wait for an effective, evidence-based treatment for COVID-19. In this situation, unlike Western medicine that specifically treats diseases, Kampo medicine can be prescribed for symptoms when the cause is unknown; it is expected to prevent serious illness in mild cases and prevent infections.

We report three mild cases of COVID-19 where the patients were treated only with Kampo medicine and turned virus-negative without symptom exacerbation.

Because of the characteristics of COVID-19, Kampo medicine doctors could not contact the patients directly, so the findings were confirmed only by tongue inspection. In addition, as no extract of saikatsugekito was available, a combination drug consisting of extracts of kakkonto (<http://mpdb.nibiohn.go.jp/stork/>) and shosaiko-ka-kikyosekko was used as substitution and prescribed for seven days.

These three cases are family members and are presented in chronological order below based on the onset date of Case 1 (day X).

CASE PRESENTATION

Case 1

A 41-year-old healthy female (height: 164 cm, weight: 66 kg).

On day X, she used an over-the-counter medication for headache and sore throat. On day X + 1, the same symptoms continued along with nausea, taste disorder, and a fever of 37.5°C. On day X + 4, she visited a nearby hospital. Although there were no abnormal findings on her chest X-ray and head computed tomography, her doctor determined that she needed a polymerase chain reaction (PCR) test for COVID-19. On day X + 5, she underwent PCR at the Akita City Health Center and was confirmed to be positive for

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COVID-19. On day X + 6, she was admitted to the designated infectious-disease hospital. When she arrived at the hospital, she was fully conscious, her body temperature was 36.1°C, her blood pressure was 109/77 mm Hg, her pulse rate was 95/min and regular, and SpO₂ was 96%. She did not exhibit any blood congestion or jaundice. No abnormalities were observed in cardiac sounds, respiratory sounds, or abdominal findings. No superficial lymph nodes were palpable.

The peripheral white blood cell (WBC) count was 5000/μl, and C-reactive protein (CRP) was 0.04 mg/dL.

Eastern medical findings (tongue inspection): pale red; white and yellow tongue coating, without a fissured tongue, with slightly enlarged tongue and tooth marks (Fig. 1a).

Clinical course, Case 1

On day X + 6, she was prescribed saikatsugekito (extracts of kakkonto 2.5 g, three times a day, extracts of shosaiko-kakiyosekko 2.5 g, three times a day). On day X + 9, her taste had improved somewhat; on day X + 10, a dry cough appeared; on day X + 14, the white and yellow tongue coating disappeared (Fig. 1b); on day X + 16, she recovered her appetite and taste; on day X + 19, the PCR result was negative, and she was mostly not suffering from headache; on day X + 22, because the second PCR result was negative, she was discharged from the hospital.

Case 2

A 16-year-old healthy female (height: 160 cm, weight: 53 kg) who is the eldest daughter of Case 1. On day X + 7, she was admitted to the hospital after a positive PCR test for COVID-19 as a close contact of Case 1. She had a nasal congestion and taste disorder. When she arrived at the hospital, her consciousness was clear, body temperature was 36.0°C, blood pressure was 95/54 mm Hg, pulse rate was 80/min and regular, and SpO₂ was 98%. She did not exhibit any

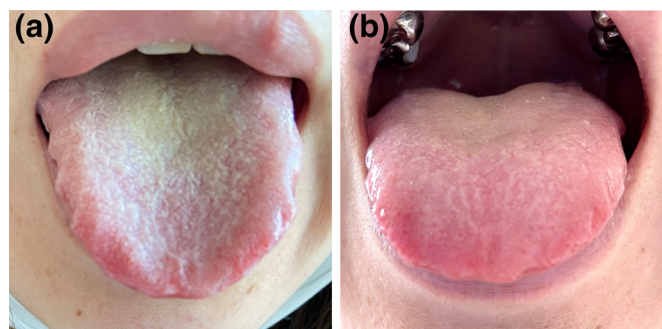


Figure 1 | (a) Findings on the tongue at X + 6 days. The white and yellow tongue coating seen in the late yang stage pattern is present with slightly enlarged tongue and tooth marks. (b) Findings on the tongue at X + 14 days. Tooth marks remain, but the white yellow tongue coating has disappeared.

blood congestion or jaundice. No abnormalities were observed in cardiac sounds, respiratory sounds, or abdominal findings. No superficial lymph nodes were palpable.

The peripheral WBC count was 4900/μl, and CRP was 0.01 mg/dL.

Eastern medical findings (tongue inspection): pale red; no tongue coating; slight tooth marks; she could not adequately stick out her tongue.

Clinical course, Case 2

On day X + 7, she was prescribed saikatsugekito (extracts of kakkonto 2.5 g, twice a day, extracts of shosaiko-kakiyosekko 2.5 g, twice a day). On day X + 11, her nasal congestion gradually improved; on day X + 19, she started to regain her smell, and the PCR result was negative; on day X + 22, because the second PCR result was negative, she was discharged from the hospital, and on tongue inspection, she could get stick out her tongue more, but the other tongue inspection findings were unchanged.

Case 3

A 12-year-old healthy male (height: 175 cm, weight: 74 kg) who is the eldest son of Case 1. On day X + 7, he was admitted to the hospital after a positive PCR test for COVID-19 as a close contact of Case 1. He had nasal congestion and taste disorder. When he arrived at the hospital, he was fully conscious, body temperature was 36.5°C, blood pressure was 122/78 mm Hg, pulse rate was 84/min and regular, and SpO₂ was 97%. He did not exhibit any blood congestion or jaundice. No abnormalities were observed in cardiac sounds, respiratory sounds, or abdominal findings. No superficial lymph nodes were palpable.

The peripheral WBC count was 6300/μl, and CRP was 0.10 mg/dL.

Eastern medical findings (tongue inspection): pale red; white and yellow tongue coating, without a fissured tongue or tooth marks but the tongue was enlarged (Fig. 2a).

Clinical course, Case 3

On day X + 7, he was prescribed saikatsugekito (extracts of kakkonto 2.5 g, twice a day, extracts of shosaiko-kakiyosekko 2.5 g, twice a day). On day X + 10, his nasal congestion gradually improved; on day X + 14, he started to regain his smell, and the white and yellow tongue coating and enlarged tongue disappeared (Fig. 2b); on day X + 19, the PCR result was negative; on day X + 22, because the second PCR result was negative, he was discharged from the hospital.

In addition, all individuals considered as close contacts of each case tested negative for PCR, and no so-called clusters were found thereafter.

The characteristics of these three cases are presented in Table 1.

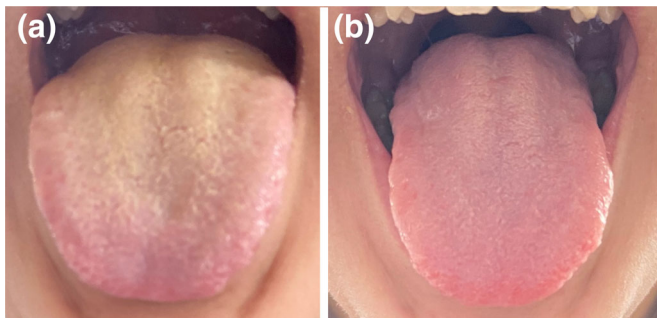


Figure 2 | (a) Findings on the tongue at X + 7 days. The white and yellow tongue coating is present on the enlarged tongue, but no tooth marks. (b) Findings on the tongue at X + 14 days. The white and yellow tongue coating has disappeared, and the enlarged tongue is improved.

DISCUSSION

The original source of saikatsugekito is *Shang Han Yun Yao* by Wu Shou of Ming, but there are three types with the same name [1]. Asada’s father, Seian, removed the jujube and ginseng from the drug combination of kakkonto and shosaikoto and added gypsum to produce a new type of saikatsugekito (Asada family’s original blend). Futsugo yakushitsu hokan kuketsu [2] said, ‘This cures those who complain of a combination of diseases of early and late yang, headache, thirst of nose and mouth, insomnia, tingling pains

in the extremities, and tachycardia’ and ‘Its effect is better than that of saikatsugekito in “shokan rokusho”’.

The most famous example of the use of saikatsugekito is that of Kimura during the Spanish flu epidemic about 100 years ago. Michifumi Takahashi [3] wrote in his book *Asada-ryu Kampo Shinryo No Jissai*:

In the early days, those who developed a high fever were treated with the perspiration and anti-febrile treatment of saikatsugekito and daiseiryuto. ... they were spared from death.

Some Spanish-flu patients were found to have a course of fulminant illness [4]. In such a situation where the disease progressed from the beginning to an intermediate or interior pattern all at once, it was not possible to improve the disease using only medicines releasing the exterior, such as kakkonto and maoto, but at the same time, it was thought that crude medicines for late and middle yang stage patterns were needed.

According to the report by Kashima *et al.* [5] regarding the use of gypsum in patients with COVID-19, large doses of platycodon root and gypsum promptly improved the anti-pyretic and inflammatory reactions and oxygenation. Since the timing of prescription discontinuation and resumption was also consistent with the disease, it is likely that gypsum would be more effective, which is why we chose saikatsugekito for treatment.

Table 1 | Patient characteristics

	Age (years)	Sex	Symptom	*MBT (°C)	*WBC (10 ² /μl) *CRP (mg/dL)	*DOD (day)	*DOA (day)	*DOH (day)	Tongue inspection
Case1	41	F	Headache; sore throat; nausea; taste disorder; fever	37.3	50 0.04	20	7	17	<ul style="list-style-type: none"> • Pale red • White and yellow tongue coating • Slightly enlarged tongue and tooth marks
Case2	16	F	Nasal congestion; taste disorder	36.9	49 0.01	13	7	16	<ul style="list-style-type: none"> • Pale red • Slight tooth marks • Patient could not adequately stick out her tongue
Case3	12	M	Nasal congestion; taste disorder	36.9	63 0.10	8	7	16	<ul style="list-style-type: none"> • Pale red • White and yellow tongue coating • Without a fissured tongue and tooth marks but with enlarged tongue

* CRP, C-reactive protein; DOA, duration of administration; DOD, duration of disease; DOH, duration of hospitalization; MBT, maximum body temperature; WBC, white blood cells.

On tongue inspection of the three patients, Cases 1 and 3 had a white and yellow tongue coating, as seen in late yang stage patterns, and we considered it appropriate to use kakkonto as the medicine releasing the exterior in the acute phase while simultaneously using bupleurum root groups. It is unclear if this is the effect of gypsum, as none of the three patients had fever at hospitalization or worsening symptoms, and PCR results were negative.

Prescriptions of Kampo medicine should be determined based on eastern medical findings; however, in this case, the number of healthcare providers who could come in contact with the patients was limited, making it difficult to prescribe according to each patient's pattern. However, symptoms did not worsen during the treatment, but instead, gradual improvements were observed, suggesting that prescription by the disease name has a certain effect on this disease, and future investigations are needed.

In contrast, the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7) [6] includes seihaihidokuto as an indication for mild to severe patients. Seihaihidokuto is a Chinese medicine, a combination of yakanmaoto, shosaikoto, and goreisan, and is a new medicine for the treatment of COVID-19. Because there are no extracts of this in Japan, Ogawa [7] advocates simultaneous combination of three extracts, makyokansekito, ireisan, and shosaiko-kakiyosekko. However, the basic formulas recommended by this guideline include a total of 21 kinds of crude medicines, with a minimum of 196 g. Considering that even the largest amount of crude medicines in common extracts in Japan is about 30 g, it may be difficult to secure such a large number and amount of crude medicines in Japan, where the production of these remains fragile. Thus, we consider it a great advantage that saikatsugekito can be substituted with kakkonto and shosaiko-kakiyosekko and that we could obtain a therapeutic effect.

Most patients with mild COVID-19 can be discharged from hospital without exacerbation. Our three cases had no particular risk factors and were in their teens and 40s (ages with low mortality), so it is unclear how much saikatsugekito contributed to their recovery. An uncontrolled observational study of seihaihidokuto [8] reported that it may prevent severity in mild or moderate cases of COVID-19. Antiviral drugs currently undergoing clinical trials at a fast pace are viral antigen-specific and have poor versatility, along with the problem of resistance; it will take a long time before they can be used clinically. Furthermore, a pandemic may occur at any time, and like the case of COVID-19, it is impossible to prevent it with border quarantine alone. We believe that Kampo medicine, which is relatively safe clinically and has few side effects, may have an antiviral effect by autoimmune activation and should be taken at an early stage along with general treatment [9].

In particular, because saikatsugekito has the potential to inhibit symptom exacerbation in mild patients, it would be very meaningful to prescribe saikatsugekito early in patients

with mild COVID-19 to determine whether intubation management can be avoided for respiratory symptoms after day 7 of onset, when deterioration is expected.

AUTHOR CONTRIBUTIONS

NH gave conceptual advice. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

NH: lecture fee (Tsumura & Co.)

INFORMED CONSENT

We obtained consent from the family of the patients for treatment and for publication of this report.

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