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Refractory Chest Pain in Mild to Moderate Coronavirus Disease 2019 Successfully Treated with Saikanto, a Japanese Traditional Medicine

Ryutaro Arita,[1,2] Rie Ono,[1,2] Natsumi Saito,[1,2] Satoko Suzuki,[1,2] Akiko Kikuchi,[1,2,3] Minoru Ohsawa,[1,2,3] Yasunori Tadano,[1] Tetsuya Akaishi,[1,2,3] Takeshi Kanno,[1] Michiaki Abe,[1] Ko Onodera,[1] Shin Takayama[1,2,3] and Tadashi Ishii[1,2,3]

[1]Department of Education and Support for Regional Medicine, Tohoku University Hospital, Sendai, Miyagi, Japan
[2]Department of Kampo Medicine, Tohoku University Hospital, Sendai, Miyagi, Japan
[3]Department of Kampo and Integrative Medicine, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan

Coronavirus disease 2019 (COVID-19) causes a variety of pain symptoms in the acute phase. Severe chest pain suddenly occurs even without abnormalities on examination and is sometimes refractory to analgesics. Such pain is a clinical concern in care facilities with limited resources, and this is the first report on the use of saikanto for its treatment. In Miyagi Prefecture, Japan, COVID-19 patients with mild symptoms were admitted to a hotel that operated as an isolation facility, and their symptoms were observed. In this article, we report four cases in which chest pain comorbid with mild to moderate COVID-19 was successfully treated with saikanto, a traditional Japanese (Kampo) medicine. The patients presented with chest pain and underwent medical examination at the facility. Two patients had severe chest pain refractory to acetaminophen. Critical cardiopulmonary diseases were ruled out in all the patients, and three patients had features of pneumonia on chest radiograph. Medications, including saikanto, were administered to the patients. The patients' chest pain and other symptoms improved 1-4 days after the administration of saikanto, and they left the care facility without hospitalization. The cause of the chest pain experienced by these patients is unclear, but we speculate that it could be minimal pleural inflammation or neuropathy. Previous pharmacological studies have suggested anti-inflammatory and analgesic properties of the crude drugs that constitute saikanto. This case report suggests that saikanto could be a treatment option for chest pain refractory to analgesics in patients with mild to moderate COVID-19.

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Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The COVID-19 pandemic has spread worldwide since early 2020, and repeated epidemics have been reported. The World Health Organization reported 373 million confirmed cases of COVID-19 and 5.6 million deaths globally as of January 31, 2022 (World Health Organization 2022).

In Japan, COVID-19 cases are classified as mild, moderate I, moderate II, and severe, and it has been recommended that patients with moderate I disease [defined as hypoxia (oxygen saturation; SpO_2 < 96%) or pneumonia diagnosed by imaging] should be hospitalized (Clinical Practice Guidance Review Committee 2022). However, the rapid increase in the number of patients made it difficult to follow these guidelines, and patients with pneumonia had to be treated in isolation facilities. We previously reported a care challenge in an isolation facility (Takayama et al.

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Correspondence: Shin Takayama, Department of Education and Support for Regional Medicine, Tohoku University Hospital, 1-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8574, Japan.
e-mail: takayama@med.tohoku.ac.jp

2021c; Kikuchi et al. 2022). Every day in the care facility, patients recorded their vital signs and subjective symptoms using a Numeric Rating Scale (NRS) ranging from 0 to 10, where 0 indicates no symptoms, and 10 indicates the worst symptom imaginable. The care staff listened to the patients' report of their symptoms, and the doctors visited the patients in poor condition. We performed radiography, electrocardiography, and blood tests and administered treatment, including oral drugs, oxygen, infusion, or glucocorticoid therapy in this facility. The facility was run in collaboration with the government of Miyagi Prefecture, Japan.

COVID-19 patients have various clinical symptoms, such as fever, cough, sputum production, sore throat, diarrhea, vomiting, headache, myalgia, and arthralgia. A retrospective survey of hospitalized COVID-19 patients showed that 82.5% of them had pain during hospitalization, and acetaminophen was usually used to alleviate it (Şahin et al. 2021). The prevalence of chest pain in COVID-19 patients has been reported to be 9-11% in meta-analyses (Li et al. 2021; da Rosa Mesquita et al. 2021; Weng et al. 2021). Some patients initially experienced severe chest pain after infection despite the absence of abnormalities in laboratory data, electrocardiogram, and even plain chest radiograph, and the pain was sometimes refractory to analgesics.

Traditional Japanese (Kampo) medicines have been used to alleviate various clinical symptoms of the common cold. We also prescribed various Kampo formulae to treat COVID-19 symptoms in the isolation facilities. In particular, saikanto (SKT), a Kampo formula, was used to alleviate coughing and the resultant chest pain (Tsumura & Co. 2013a). Herein, we report some successful cases of mild to moderate COVID-19 with chest pain, in which the patients were treated with SKT and experienced quick pain relief.

Case Presentation

The patients' characteristics are shown in Table 1. All the cases in this report were those of confirmed COVID-19 patients who were admitted to the care facility in Miyagi Prefecture, Japan. This case report was approved by the Tohoku University Ethics Committee (institutional review board number: 2021-1-447). All procedures were performed in accordance with the current version of the Declaration of Helsinki revised in 2013. Informed consent was obtained in an opt-out manner.

Table 1. Patients' characteristics.

	Case 1	Case 2	Case 3	Case 4
Age (years)	29	31	20	51
Sex	Male	Male	Male	Male
Body mass index (kg/m^2)	22.2	28.3	22.9	20.1
Medical history			Asthma	Hypertension Dyslipidemia
Smoking	●		●	
Doctor visiting				
Days from the onset	5	7	7	10
Symptoms				
Chest pain (manifestation)	Entire chest and back pain	Choking pain in the middle chest	Pain on inhalation on the right side	Entire chest pain
Cough	●	●	●	●
Sputum			●	●
Headache			●	●
Body temperature (ºC)	36.5	36.6	36.4	36.5
SpO_2 (%)	97	96	100	95
Chest X-ray abnormality	None	GGO	GGO	GGO
Blood test				
White blood cell count (/μL)	6,100	2,650	4,080	4,730
Lymphocyte count (/μL)	3,000	590	1,680	630
Lactate dehydrogenase (IU/L)	167	220	117	254
C-reactive protein (mg/dL)	0.02	1.00	0.16	2.86
Creatine kinase (IU/L)	545¶1	253	131	76
D-dimer (μg/ml)	Negative¶2	0.24	0.13	0.49
Duration of saikanto administration for improving chest pain (days)	3	1	2	4

●, positive; SpO_2, oxygen saturation; GGO, ground glass opacities.

¶1, creatine kinase-isoenzyme MB was 3 IU/L.

¶2, D-dimer was 0.7 μg/ml, within the normal range at the hospital where he was tested.

The Kampo formulae used in this case report was manufactured by Tsumura & Co. (Tokyo, Japan). Detailed information on SKT is available on the company's website (Tsumura & Co. 2013a). The three-dimensional high-performance liquid chromatography fingerprints of SKT are shown in Fig. 1.

Case 1

A 29-year-old man presented with cough and was diagnosed with COVID-19 by polymerase chain reaction (PCR) test on day 1. The patient was unvaccinated. He had a body mass index (BMI) of 22.2 kg/m^2 and no significant medical history. He underwent medical examinations on day 4 at a nearby hospital. The chest radiograph showed no sign of pneumonia, and blood sampling showed no inflammatory changes [white blood cell (WBC) count (6,100/μL), lactate dehydrogenase (LDH) (167 IU/L), C-reactive protein (CRP) (0.02 mg/dL), and there was no elevation of troponin-T and D-dimer]. He received 600 mg of acetaminophen; however, the chest pain was not alleviated. He was admitted to the care facility on day 5. The patient had severe stabbing pain in his entire chest and back (NRS score = 10), headache, and a slight cough. His body temperature (BT) was 36.5°C, SpO_2 was 97%, blood pressure (BP) was 117/79 mmHg, and pulse rate (PR) was 58/min. We additionally performed electrocardiography, which showed sinus bradycardia (46 bpm) but no findings suggestive of acute coronary syndrome or myocarditis.

We classified him as a mild COVID-19 case with chest pain and prescribed SKT (7.5 g daily; Table 2) and loxoprofen tablet (60 mg when needed). His chest pain was alleviated to NRS score of 7 on day 6 and completely resolved on day 8 (Fig. 2). Loxoprofen was used only two times for chest pain.

Case 2

A 31-year-old man, with a BMI of 28.3 kg/m^2 and no significant medical history, developed a fever of 37.3 °C on day 1. He tested positive for SARS-CoV-2 on day 2 and was admitted to the care facility on day 5. He took acetaminophen for fever, but his chest pain and cough worsened on day 7 (NRS scores 6 and 4, respectively). He complained of a choking pain in the middle of his chest. His vital signs were as follows: BT, 36.6ºC; SpO_2, 96%; BP, 114/76 mmHg; and PR, 78/min. A blood test demonstrated inflammatory findings, as follows: decreased WBC count (2,650/μL) and lymphocyte count (590/μL); elevated LDH (220 IU/L), CRP (1.0 mg/dL), and creatine kinase (253 mg/dL) levels. No elevation of D-dimer was noted. Chest radiograph revealed features of pneumonia in the lower lung zones of bilateral lungs.

The patient's creatine kinase level was slightly ele-

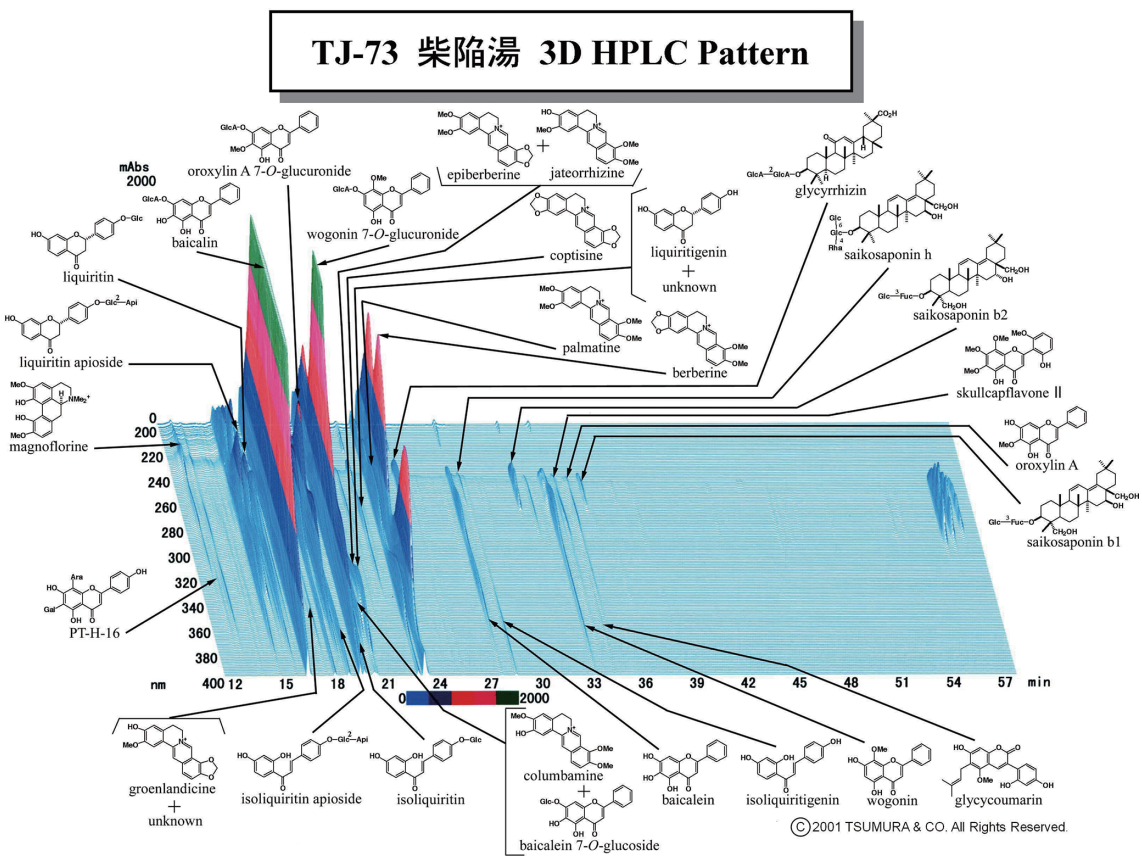

Fig. 1. Three-dimensional high-performance liquid chromatography fingerprints of saikanto.
The figure was provided by Tsumura & Co., the manufacturer of saikanto.

Table 2. Latin names and parts of the crude drugs constituting Kampo medications.

1. Saikanto (SKT)

Ingredient crude drug (English)	Amount (g)	Latin name (family name)	Part (Latin)
JP Bupleurum Root	5.0 g	*Bupleurum falcatum* Linné (*Umbelliferae*)	*Radix*
JP Pinellia Tuber	5.0 g	*Pinellia ternata* Breitenbach (*Araceae*)	*Tuber*
JP Scutellaria Root	3.0 g	*Scutellaria baicalensis* Georgi (*Labiatae*)	*Radix*
JP Jujube	3.0 g	*Ziziphus jujuba* Miller var. *inermis* Rehder (*Rhamnaceae*)	*Fructus*
JP Ginseng	2.0 g	*Panax ginseng* C. A. Meyer (*Panax schinseng* Nees) (*Araliaceae*)	*Radix*
JP Coptis Rhizome	1.5 g	*Coptis japonica* Makino, *Coptis chinensis* Franchet, *Coptis deltoidea* C.Y. Cheng et Hsiao, or *Coptis teeta* Wallich (*Ranunculaceae*)	*Radix*
JP Glycyrrhiza	2.0 g	*Glycyrrhiza uralensis* Fischer or *Glycyrrhiza glabra* Linné (*Leguminosae*)	*Radix*
JP Ginger	1.0 g	*Zingiber officinale* Roscoe (*Zingiberaceae*)	*Rhizoma*
Trichosanthes Seed	3.0 g	*Trichosanthes kirilowii* Maxim. (*Cucurbitaceae*)	*Semen*

2. Gokoto

Ingredient crude drug (English)	Amount (g)	Latin name (family name)	Part (Latin)
JP Gypsum	10.0 g	*Gypsum fibrosum*	-
JP Apricot Kernel	4.0 g	*Prunus armeniaca* Linné, *Prunus armeniaca* Linné var. *ansu* Maximowicz or *Prunus sibirica* Linné (*Rosaceae*)	*Semen*
JP Ephedra Herb	4.0 g	*Ephedra sinica* Stapf, *Ephedra intermedia* Schrenk et C. A. Meyer, or *Ephedra equisetina* Bunge (*Ephedraceae*)	*Herba*
JP Mullberry Bark	3.0 g	*Morus alba* Linné (*Moraceae*)	*Cortex*
JP Glycyrrhiza	2.0 g	*Glycyrrhiza uralensis* Fischer or *Glycyrrhiza glabra* Linné (*Leguminosae*)	*Radix*

The Kampo medications used in this study were extract granules manufactured from various crude drugs through decoction, concentration, drying, and addition of an excipient. The amount (g) is the quantity of crude drug included in the daily dose of extract granules.
JP, The Japanese Pharmacopoeia 17th edition English version.

vated, but other findings did not support the possibility of acute cardiovascular diseases. We classified him as a moderate I case of COVID-19 with chest pain. It was impossible to hospitalize the patient in a large-scale hospital because of the full utilization of inpatient beds in our area. Therefore, he was followed up in the care facility with a real-time SpO_2 monitor (Radius PPG™, Mashimo, Tokyo, Japan). We prescribed 7.5 g of SKT and 30 mg of dimemorfan phosphate daily. He did not experience hypoxia, and on day 8, his chest pain and cough both decreased (NRS score = 2). He was thus able to avoid hospitalization and returned home on day 12 (Fig. 3).

Case 3

A 20-year-old man presented with a fever of 38.1°C, cough, and fatigue, and he tested positive for SARS-CoV-2 on day 2. He was transferred to the care facility on day 5 and underwent examination on day 7. He had stabbing chest pain on inhalation on the right side (NRS score = 5), shortness of breath, cough, sputum production, headache, myalgia, arthralgia, fatigue, and olfactory dysfunction. He had a BMI of 22.9 kg/m^2 and had a history of childhood asthma and was not vaccinated against COVID-19. His vital signs were as follows: BT, 36.4°C; SpO_2, 100%; BP, 126/64 mmHg; and PR, 63/min. Wheezing was not heard. Chest radiograph showed a pneumonia shadow in less than half of both lungs, but a blood test showed no inflammatory changes of WBC count (4,080/μL), LDH (117 IU/L), and CRP (0.16 mg/dL).

We classified him as a moderate I case of COVID-19 with non-specific chest pain. We prescribed two Kampo formulae [7.5 g of SKT daily for chest pain, and 7.5 g of gokoto (GKT) for cough and sputum production], with 30 mg of dimemorfan phosphate, 1,500 mg of L-carbocisteine, and 500 mg of acetaminophen for pain relief. His chest pain severity reduced to an NRS score of 2 on day 9, and it resolved completely on day 11 without the use of acetaminophen. Other symptoms resolved on day 12, and the patient was discharged on day 13 (Fig. 4).

Case 4

A 51-year-old man with a BMI of 20.1 kg/m^2 presented with a fever of 38.1ºC, fatigue, headache, and sore throat on the day he received the first dose of COVID-19 vaccine (elasomeran, Moderna Inc., Cambridge, MA, USA). He tested positive for SARS-CoV-2 by PCR on day 2 and was admitted to the care facility on day 5. He had hypertension and dyslipidemia as risk factors for severe disease. He took

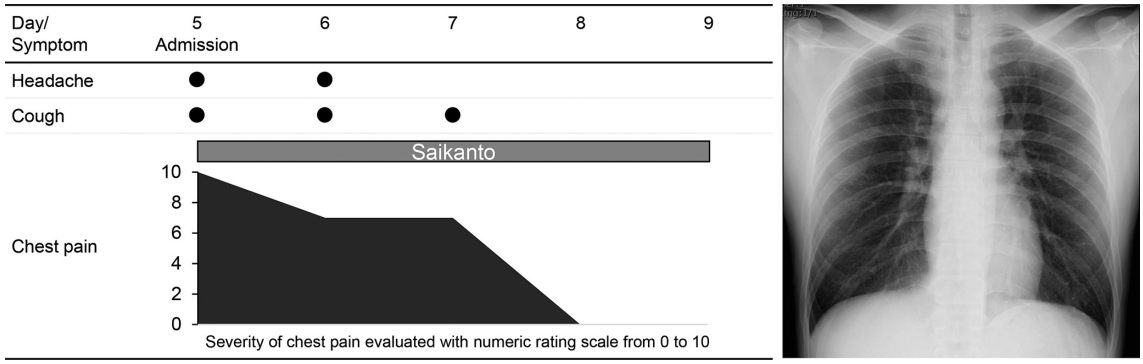

Fig. 2. Case 1 presentation and symptom course.
Black circles indicate symptomatic.

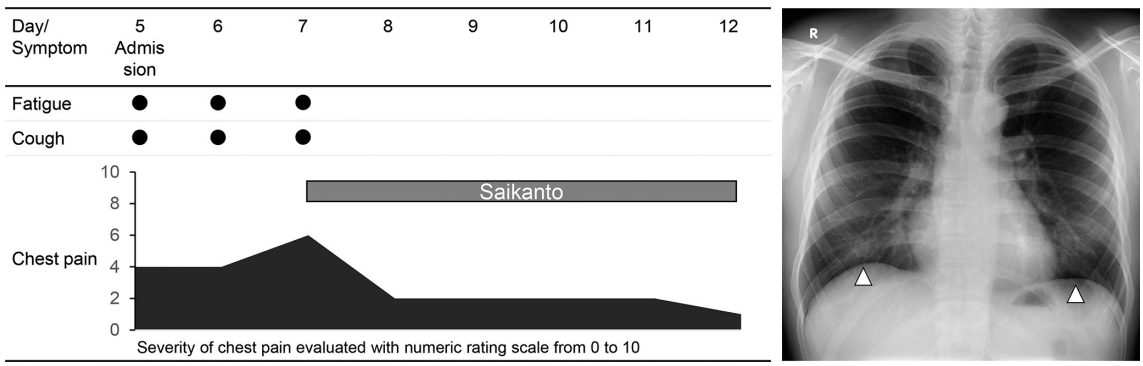

Fig. 3. Case 2 presentation and symptom course.
Black circles indicate symptomatic. White arrows indicate ground glass opacities.

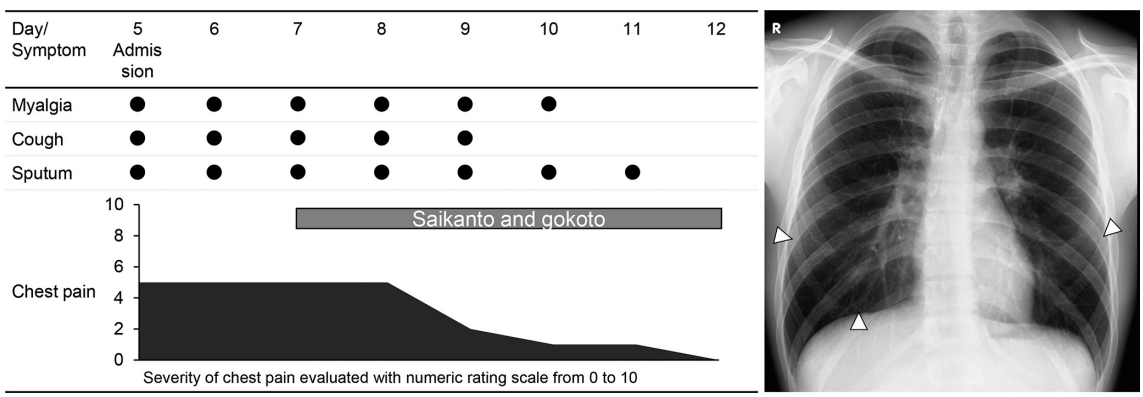

Fig. 4. Case 3 presentation and symptom course.
Black circles indicate symptomatic. White arrows indicate the ground glass opacities.

over-the-counter drugs, including acetaminophen, for fever, headache, and cough. On day 9, his chest pain, headache, and cough suddenly worsened (NRS score = 7 for each symptom). The patient underwent medical examination on day 10. Vital signs were as follows: BT, 36.5°C; SpO_2, 95%; BP, 115/79 mmHg; and PR, 90/min. A blood test revealed the following inflammatory findings: decreased lymphocyte count (630/μL), elevated LDH (254 IU/L) and CRP (2.86 mg/dL). However, no elevation of D-dimer level was noted. Chest radiograph revealed ground-glass opacities in the bilateral lower lung zones. He was equipped with a real-time SpO_2 monitor but demonstrated no signs of hypoxia.

We diagnosed him as a moderate I COVID-19 case with chest pain and prescribed two Kampo formulae (7.5 g of SKT and 7.5 g of GKT, daily), with 30 mg of dimemorfan phosphate, and 1,500 mg of L-carbocisteine. His chest pain decreased on day 12 (NRS score = 3) and resolved on day 16 (Fig. 5).

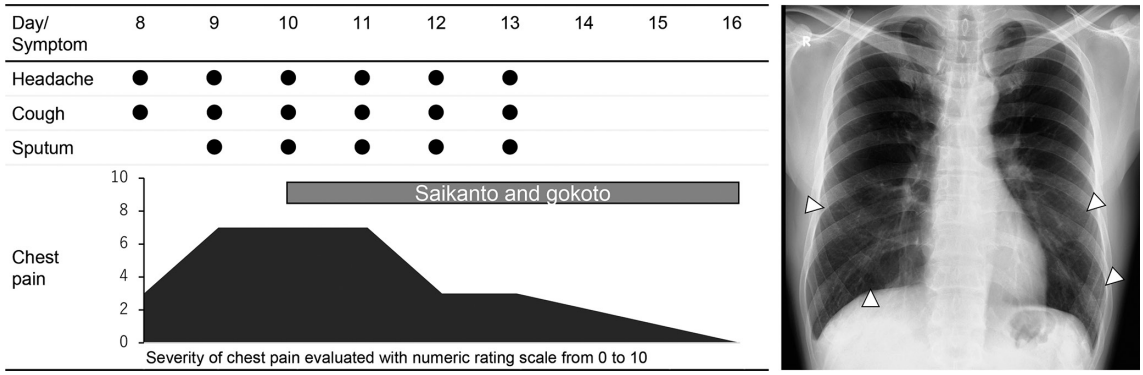

Fig. 5. Case 4 presentation and symptom course.
Black circles indicate symptomatic. White arrows indicate the ground glass opacities.

Discussion

Here, we presented cases of non-specific chest pain in patients with mild to moderate COVID-19 successfully treated with SKT. The chest pain was unclassifiable but refractory to acetaminophen. Refractory chest pain in COVID-19 patients is a clinical concern in care facilities with limited medical resources. This case report suggests that SKT may be a treatment option for non-specific chest pain in patients with mild to moderate COVID-19.

The causes of chest pain comorbid with acute COVID-19 include some critical conditions such as acute pericarditis, myocardial injury, or pulmonary embolism (Baj et al. 2020). We ruled out such critical conditions through medical examinations as much as possible in the care facility. Other common causes can include non-critical conditions, such as myalgia, rib fractures, the gastroesophageal reflux disease (GERD), pleural inflammation, or peripheral neuropathy. Myalgia, rib fractures, and GERD were deemed unlikely due to no effects of analgesic treatment, absence of abnormalities on radiographs, and absence of gastrointestinal symptoms, respectively. The patient in Case 3 experienced pain on inhalation on the right side; however, this pain was not localized, and we could not diagnose the cause of the pain.

Pleural inflammation is a possible cause of chest pain. Most COVID-19 pneumonia lesions are located in the peripheral lung zone, closer to the pleura (Lin et al. 2021). Pleural thickening was noted in 32% of the pneumonia cases (Shi et al. 2020). Furthermore, a similar case of pleural chest pain as an initial symptom of COVID-19 (Oleynick 2020) was reported previously. The presented three cases (Case 2, 3, and 4) showed pneumonia shadows in the bilateral lower lung zones on plain chest radiographs, and the chest pain was localized to the center or on both sides. We could not find a match between the site of pain and frontal radiographs.

Mechanistically, the entry of SARS-CoV-2 cells into pneumocytes depends on binding to angiotensin-converting enzyme 2 (ACE2)—the main cellular receptor—and priming by the cellular serine protease TMPRSS2 (Hoffmann et al. 2020). Moreover, neuropilin-1 (NRP1), which is known to bind furin-cleaved substrates, potentiates SARS-CoV-2 infectivity (Cantuti-Castelvetri et al. 2020; Daly et al. 2020). ACE2 is expressed in the pleural mesothelial cells of COVID-19 patients. The mesothelial cell line expresses ACE2, TMPRSS2, and NRP1, through which SARS-CoV-2 can infect cells *in vitro* (Matusali et al. 2021). This molecular mechanism suggests that COVID-19 may cause pleural inflammation.

Neuropathy could also cause chest pain due to SARS-CoV-2 infection. ACE2 and NRP1 are expressed in the human dorsal root ganglion nociceptors (Shiers et al 2020; Cantuti-Castelvetri et al. 2020; Daly et al. 2020), and SARS-CoV-2 could enter the nociceptor neurons. Recent studies have revealed that SARS-CoV-2 has a direct neuroinvasive capacity with respect to the central and peripheral nerve systems, and could cause neurological inflammation and pain (Song et al. 2021; Wan et al. 2021; McFarland et al. 2021). Clinical case reports of acute transverse myelitis (Román et al. 2021) and the Guillian-Barré syndrome (Abu-Rumeileh et al. 2021) associated with COVID-19 in the acute phase of the disease have been published. While neuropathic chest pain associated with COVID-19 has not been reported yet, viral neuroinvasion may cause chest pain. Further studies could clarify the pathophysiology of acute chest pain.

After we ruled out critical conditions, we had to prescribe drugs to and follow up the patients in the care facility because the hospitals providing COVID-19 inpatient care were fully occupied by more severely ill patients. The chest pain in Case 1 and 3 was refractory to acetaminophen, but after treatment, including administration of SKT, the four cases improved without hospitalization.

SKT was originally prepared in Japan by blending shosaikoto (Xiao-Chai-Hu-Tang) and shokankyoto (Xiao-Xian-Xiong-Tang). A daily dose of 7.5 g of SKT is administered through an extract granule; this granule is made from nine crude drugs through decoction, concentration, drying, and addition of an excipient, as described in Table 2 (Tsumura & Co. 2013a; Ministry of Health, Labour and Welfare 2016). It has been used to treat coughing and the

resultant chest pain. There has been one case report of subacute bronchitis with chest pain refractory to nonsteroidal anti-inflammatory drugs (NSAIDs); the patient was successfully treated with SKT (Ogawa-Ochiai 2016). The present study is the first report on the use of SKT for chest pain in the acute phase of COVID-19.

SKT is supposed to exert a therapeutic effect on COVID-19 and pain based on its pharmacological activity. We previously reviewed the potential antiviral effect of shosaikoto, a component of SKT (Arita et al. 2020). Shosaikoto administration enhances the production of CD4 (+) T-cell cytokines, including interferon-γ and interleukin-4, in anti-CD3 antibody-treated mice (Kang et al. 2009). Shosaikoto also has multiple reactive oxygen species (ROS)-scavenging activities, especially against hydroxyl radicals and singlet oxygen (Hirayama et al. 2018). Respiratory viral infections enhance ROS production in epithelial cells and macrophages (Khomich et al. 2018), and excessive oxidative stress caused by ROS is associated with acute lung injury (Imai et al. 2008). Coptis rhizome exhibits antiviral activity against several viruses, including SARS-CoV. Kim et al. (2008) reported that Coptis rhizome inhibits the replication of SARS-CoV in a dose- and time-dependent manner *in vitro*. Coptis rhizome water extract inhibited the replication of respiratory syncytial virus *in vitro* and *in vivo* through the induction of type I interferon-related signaling (Lee et al. 2017). Berberine, which is a component of Coptis rhizome, produces anti-inflammatory and analgesic effects through modulation of the μ-opioid receptor (Dong et al. 2019), suppression of NF-κB pathway activation (Lu et al. 2019), and reduction of cyclooxygenase-2 and inducible nitric oxide synthase mRNA expression (Li et al. 2019). The components of Bupleurum root (Shin et al. 2019), Scutellaria root (Kim et al. 2009), jujube (Tran et al. 2019), ginseng (Yang et al. 2022), Glycyrrhiza (Yang et al. 2017), and ginger (Grzanna et al. 2005) also have anti-inflammatory activities. Such anti-inflammatory, ROS-scavenging, and analgesic activities of these crude drugs may contribute to the alleviation of chest pain and other symptoms.

We additionally prescribed GKT in Case 3 and 4 for the treatment of strong cough and sputum, according to the traditional concept. We previously reported a case wherein cough and sputum in the acute phase of COVID-19 were successfully treated using GKT (Takayama et al. 2021c). The therapeutic indications for GKT treatment are cough and bronchial asthma (Tsumura & Co. 2013b). According to the traditional concept, GKT is empirically used for symptoms of respiratory infection, such as coughing and sputum discharge without chest pain. We administered a combined treatment with SKT and GKT when a patient had cough, sputum, and chest pain.

The benefits of non-steroidal anti-inflammatory drugs (NSAIDs) in the management of COVID-19 are controversial. Despite their anti-inflammatory effects, NSAIDs have been shown to upregulate ACE2 expression, which may exacerbate SARS-CoV-2 infection (Fang et al. 2020). However, a meta-analysis showed that NSAIDs were not associated with increased risk of severe outcomes (Moore et al. 2021). Further studies are therefore required to determine the effectiveness and safety of NSAIDs in COVID-19 patients. There should be multiple treatment options for pain in COVID-19 patients, including SKT, which may relieve inflammation and pain through multiple mechanisms.

This case report has some limitations. First, the patients could not undergo computed tomography or magnetic resonance imaging, and they were not evaluated for inflammation in the pleura and pericardium. This is because they were treated in a facility with limited medical resources. Second, there were no control cases of chest pain that were managed without the use of SKT, so it is possible that the presented cases improved even without SKT. Third, we prescribed several other drugs besides SKT. Therefore, this report did not clarify the effectiveness of SKT for chest pain by accounting for the possible confounding effects of the other drugs, and further studies are required to make this clarification.

Recently, the Japan Society of Oriental Medicine has been conducting clinical trials to investigate the effectiveness of Kampo medicine in the treatment of COVID-19 (Takayama et al. 2020, 2021b). Moreover, we previously reported the use of Kampo medicine for the treatment of several symptoms in COVID-19 patients. For example, olfactory dysfunction in the acute phase was treated with kakkontokasenkyusin'i (Takayama et al. 2021a), and its rapid improvement could be associated with the use of Kampo medicines (Ono et al. 2022). Fever and nasal discharge were treated using saikatsugekito (Irie et al. 2021). It is important to note that several granule-type Kampo formulae can be applied to treat several COVID-19 symptoms. In cases of undefined and refractory chest pain despite acetaminophen administration in COVID-19 patients, SKT could be a treatment option.

In conclusion, to the best of our knowledge, this is the first report of cases of chest pain comorbid with COVID-19 successfully treated with SKT. The chest pain was unclassifiable but sometimes refractory to acetaminophen, and our results show that SKT is a treatment option for chest pain in patients with COVID-19.

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Author Contributions

All authors performed the medical examinations at the care facility. R.A. drafted the manuscript. R.A., R.O., N.

S., S.S., A.K., M.O., and S.T. discussed Kampo medicine treatment. S.T. and T.I. supervised the manuscript writing and acquired funding for this study.

Conflict of Interest

A.K., M.O., T.A, S.T., and T.I. belong to the Department of Kampo and Integrative Medicine, Tohoku University School of Medicine. The department received a grant from Tsumura & Co., a Japanese manufacturer of Kampo medicines; however, the grant was used per the Tohoku University guidelines. Potential conflicts of interest were addressed by the Tohoku University Benefit Reciprocity Committee and managed appropriately. The authors declare that they have no other competing interests.

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