

## CASE REPORT

# Kampo Extract of Shinbuto Improved Refractory Diarrhea in Milroy's Disease

汉方真武汤提取物 – 缓解米洛病引起的顽固性腹泻

El extracto Kampo de Shimbu-to: mejoría de la diarrea resistente al tratamiento en la enfermedad de Milroy

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## Key Words

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## Disclosure

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and none related to this publication was reported.

## ABSTRACT

Milroy's disease is a hereditary congenital lymphedema caused by lymphatic obstruction. The legs are most commonly affected, but impaired intestinal lymphatic flow can cause loose bowel movements. Here, we report the use of the Kampo extract of shinbuto for successful treatment of and abdominal pain in a patient with Milroy's disease. Milroy's disease was diagnosed because of left leg lymphedema with onset at birth. Conservative therapy with a compression bandage was applied. However, when the patient moved to Manila at 35 years of age, she was exposed to drastic temperature changes between the air-conditioned cold environment in her room and the hot and humid environment outside. She developed a constitutional state of coldness as in *hiesho* (冷之症). Then sudden lower abdominal pain and diarrhea began to occur 3 times per week and lasted at least 1 hour, sometimes accompanied by vomiting. It happened particularly when she was exposed to the cold environment and was not related to meals. Conventional anti-cholinergic or antidiarrhetic drugs had no therapeutic effect. These attacks continued in the same frequency for 3 years, so the patient visited a Kampo (traditional Japanese medicine) clinic, where her diagnosis of Milroy's disease-associated diarrhea and abdominal pain was augmented by the Kampo diagnosis of *hiesho*, *suitai* (body fluid retention). She was prescribed 7.5 g of shinbuto extract per day (TJ-30; Tsumura Co, Tokyo, Japan). The shinbuto extract significantly reduced abdominal pain and refractory diarrhea to about 2 days

per month, and it tapered off completely in 3 months. Shinbuto is usually used against cold-induced diarrhea. Rewarming and water movement by shinbuto resulted in significant improvement in symptoms induced by *hiesho* and *suitai* triggered by the cold environment, though the patient's leg swelling did not change.

## 背景

米洛病 (Milroy's disease) 是一种因淋巴管阻塞而引起的遗传性淋巴水肿。此病最易感染患者腿部，而受损的肠道淋巴流则能够导致稀便。这里，我们报告的是，使用汉方 (Kampo) 真武汤 (shinbuto) 提取物可成功治疗米洛病患者，并缓解其腹痛。米洛病是因患者出生时左腿淋巴水肿发作而被诊断出来的。当时采用的是压缩绷带的保守疗法。但当该患者在 35 岁迁至马尼拉时，她经常在凉爽的空调环境与炎热潮湿的室外环境之间经历极端的温度变化。她随后变成了寒性体质，即寒症 (*hiesho*, “冷之症”)。接着，她突然出现每周 3 次，每次至少持续 1 小时的下腹疼痛和腹泻，有时还伴有呕吐。这种症状在其进入寒冷环境时尤为明显，并且与饮食无关。传统的抗胆碱能药物或止泻药物无任何疗效。此病依同样的频率持续发作了 3 年，于是，该患者前往汉方 (Kampo, 传统日本医学) 诊所就诊，在那里，她患有米洛病相关腹泻和腹痛的诊断得到了汉方寒症，即 *suitai* (体液滞留) 诊断的证实。医生给她开了每天 7.5 克的真武汤提取物 (TJ-30; 日本东京津村株式会社)。真武汤提取物显著缓解了腹痛和顽固性腹泻，将频率降至

每个月 2 天左右，并在 3 个月内完全消失。真武汤通常用于治疗因寒冷引发的腹泻。真武汤可引起复温和体液流动，进而显著改善因寒冷环境触发的寒症和体液滞留而引起的症状，只不过腿部肿胀并无改善。

## SINOPSIS

La enfermedad de Milroy es un linfoedema congénito hereditario causado por la obstrucción linfática. Suele afectar a las piernas, pero los trastornos del flujo linfático intestinal pueden producir defecaciones blandas. En este texto notificamos el uso del extracto Kampo de Shimbuto (Zhen-Wu-Tang) para el éxito del tratamiento del dolor abdominal en una paciente con enfermedad de Milroy. Esta enfermedad se diagnosticó a causa del linfoedema de la pierna izquierda que había comenzado en el momento del nacimiento. Se aplicó un tratamiento conservador con un vendaje de compresión. Sin embargo, cuando la paciente se trasladó a Manila a los 35 años de edad, se vio expuesta a drásticos cambios de temperatura entre el entorno con aire acondicionado frío de su habitación y el ambiente cálido y húmedo del exterior. Comenzó a sufrir un estado constitucional de frialdad como en el trastorno conocido como *hiesho* «冷之症». Posteriormente, comenzó a sufrir un dolor en la parte inferior del abdomen y diarrea tres veces por semana que duraban al menos 1 hora, en ocasiones acompañados de vómitos. Esto ocurría especialmente cuando se veía expuesta al entorno frío y no se relacionaba con las comidas. Los

fármacos anticolinérgicos o antidiaréticos tradicionales no produjeron efecto terapéutico alguno. Estos ataques continuaron con la misma frecuencia durante 3 años, por lo que la paciente visitó una clínica Kampo (medicina tradicional japonesa) donde se aumentó su diagnóstico de diarrea y dolor abdominal relacionados con la enfermedad de Milroy con

el diagnóstico Kampo de hiesho y suitai (retención de líquidos corporales). Se le recetaron 7,5 g de extracto de Shimbu-to al día (TJ-30; Tsumura Co, Tokio, Japón), con lo que se redujo de forma significativa el dolor abdominal y la diarrea resistente al tratamiento a unos 2 días al mes, para terminar desapareciendo gradualmente por completo en 3 meses.

El extracto Shimbu-to suele usarse contra la diarrea provocada por el frío. El nuevo calentamiento y el movimiento del agua por parte del extracto Shimbu-to obtuvieron mejoras significativas en los síntomas provocados por hiesho y suitai desencadenados por el entorno frío, aunque la hinchazón de la pierna no ha cambiado.

## INTRODUCTION

Lymphedema is characterized by delayed lymphatic flow and excessive fluid retention.<sup>1</sup> Its overall prevalence is 0.13% to 2%, and more men are affected than women (ratio, 10:1).<sup>2-4</sup> Lymphedema can be primary (lymphedema of a single leg or rarely of both legs with onset at birth) or secondary (lymphedema due to excision or destruction of the lymph nodes following surgery for breast and ovarian cancer or lymphangitis following radiation therapy). Diagnosis of secondary lymphedema is excluded on the basis of a combination of history of surgery and radiation therapy, lymphangiography, computed tomography, or magnetic resonance imaging.<sup>5-10</sup>

Milroy's disease is a form of congenital lymphedema caused by genetic abnormality of the vascular endothelial growth factor receptor 3 (VEGFR-3).<sup>11</sup> It is considered to be of autosomal dominant inheritance, but some solitary cases have been reported.<sup>12</sup> In Milroy's disease, lymphedema develops within 2 years of birth. Generally, the symptoms include swelling of the extremities, an oppressive feeling, deep tissue ache, general fatigue, and diarrhea. In Milroy's disease, diarrhea is often induced by protein-losing enteropathy due to dilatation of bowel lymphatic vessels and steatorrhea caused by cholestasis.<sup>1</sup>

Here we report the use of Kampo extract of shinbuto for a successful treatment of refractory diarrhea and abdominal pain in a patient with Milroy's disease.

**Table 1** Lymphedema disease staging according to the International Society of Lymphology (ISL)

ISL stage	Description
0	A subclinical state where swelling is not evident despite impaired lymph transport. This stage may exist for months or years before edema becomes evident.
1	Early onset of the condition where there is accumulation of tissue fluid that subsides with limb elevation. The edema may be pitting at this stage.
2	Limb elevation alone rarely reduces swelling, and pitting is manifested.
Late 2	There may or may not be pitting as tissue fibrosis is more evident.
3	The tissue is hard (fibrotic) and pitting is absent. Skin changes such as thickening, hyperpigmentation, increased skin folds, fat deposits, and warty overgrowths develop.

## CASE PRESENTATION

A 38-year-old woman visited the clinic of the Center for Kampo Medicine at Keio University Hospital, Tokyo, Japan, for refractory diarrhea. She had left leg lymphedema since birth, for which she was diagnosed with Milroy's disease. According to the International Society of Lymphology (ISL) staging system (Table 1),<sup>1</sup> lymphedema was classified as late stage 2 because of chronic edema of the left leg and clearly organized fibrosis. Even though Milroy's disease is known to be a hereditary disorder, this patient did not have a family history of lymphedema. As in a previously reported case, she had been experiencing coldness and occasional abdominal pain without any other symptoms since she was 20 years old. She had undergone plastic surgery to remove fibromatous tissue from her legs twice when she was child. She had been using a compression bandage for the edema in the left leg (Figure 1). When she was 35 years old, she moved to Manila, where she was exposed to significant temperature variations between the cold temperature in an air-conditioned room and the hot temperature outside. Even though the weather outside was hot and humid, she contracted a severe cold and experienced frequent episodes of lower abdominal pain and watery diarrhea (more than six times a day). There was no fever or tenesmus. The abdominal pain



**Figure 1** Patient's legs at 20 years old. The left leg is edematous, and two operations to remove fibromatous tissue had been performed. The patient used bandages for edema all the time. At the first visit, the left leg was bandaged, and the patient said the leg's condition was the same as in this picture.

occurred about 3 days per week for 3 years and lasted for at least 1 hour and was sometimes accompanied by vomiting. Diarrhea was also induced by drinking room-temperature water. When diarrhea and abdominal pain occurred, her left leg lymphedema worsened as well. The symptoms of diarrhea, abdominal pain, and leg lymphedema were relieved by taking a hot bath. The patient had not been diagnosed with allergies, intestinal parasites, infections, or gastrointestinal disorders in the past. Because loperamide hydrochloride or lactomin had not produced results over the previous 3 years, she visited the Kampo clinic.

### Clinical Course

The patient did not present with obvious symptomatology other than Milroy's disease, and she did not have any family history of lymphedema. Physical examination revealed that she was 157 cm in height and 52 kg in weight; her body mass index was 21.1, blood pressure was 123/78 mmHg, and pulse was regular at 72 beats per minute. Physique, complexion, and skin were normal. There was significant pitting edema on the left leg, which was approximately twice the diameter of the right leg (Figure 1). There were no obvious abnormal findings on blood and urine analysis, including analysis of total protein, total cholesterol, hemoglobin, and iron. Stool analysis and imaging studies (eg, computed tomography, magnetic resonance imaging, and endoscopy) were not performed because the patient did not report changes in appetite, body weight, or food intolerance while she was living in Manila.

At the Kampo clinic, tongue inspection revealed dental indentations (*shikon*) caused by body fluid retention (*suitai*) (Figure 2). On abdominal examination



**Figure 2** Dental indentations in the tongue. Dental indentations indicate *suitai* (body fluid retention).

(*fukushin*), abdominal strength (*fukuryoku*) was slightly deficient; there were no other significant abnormal findings. Based on these findings, we diagnosed the patient with coldness (*hiesho*) caused by *suitai* and the body energy deficiency pattern (*kyosho*).

We prescribed 7.5 g of shinbuto per day (regular adult dosage) for cold, lymphedema, and diarrhea. The frequency of diarrhea decreased from six to two times per day after 2 weeks of treatment. In addition, abdominal pain and vomiting improved to 2 days per month and tapered off in 3 months, and the lymphedema did not worsen. Four years after her first visit, the patient continues to take the same Kampo medicine exclusively and she does not have diarrhea or abdominal pain.

### DISCUSSION

Congenital lymphedema is a chronic condition with no cure at present. Proper management of the disease with lymph drainage, pressure therapy, and exercise may alleviate symptoms.<sup>13</sup> Further, surgical repositioning of lymphatic vessel anastomosis or waste fluid road may be performed.<sup>14</sup> However, complete healing is not expected. This article presents a case of refractory diarrhea complicated by Milroy's disease that was treated successfully with shinbuto extract.

In Kampo medicine, coldness (*hie*) is a subjective feeling often occurring at the extremities, abdomen, and low back; if the feeling disturbs one's daily living, it is diagnosed as *hiesho* (*hie* means body coldness and *sho* means constitutional pattern). *Hie* is caused by hypometabolism, body fluid retention (*suitai*), or blood circulation disturbance (*oketsu*).

In this case, congenital lymphatic obstruction caused the continuous leg lymphedema, which induced *hie* (body coldness) and *suitai* (body fluid retention). Then the exposure to air conditioning in Manila triggered attacks of sudden diarrhea with severe abdominal pain. Rewarming and water movement by shinbuto resulted in significant improvement in symptoms and quality of life.

Shinbuto is one of the 148 Kampo extract preparations covered by Japan's National Health Insurance Program. It is indicated for chronic gastroenteritis, indigestion, gastropnea, abdominal pain, and diarrhea with watery, foamy, viscous, or bloody stool.<sup>15</sup> According to the well-known Kampo physician Keisetsu Otsuka,

*Shinbuto is used for people with kyosho (energy deficiency pattern) and weak intestines, including loose bowel or chronic diarrhea. However, we can also use it for patients without diarrhea. I have used it for edemas of the paralysis, chronic hypotension, cerebral hemorrhage, gastric atony symptoms, gastropnea and chronic enteritis.*<sup>16-18</sup>

Shinbuto contains *Aconiti tuber* (processed aconite root), *Zingiberis rhizoma* (ginger), *Poria sclerotium*, *Atractylodes lanceae rhizoma*, and *Atractylodes lancea rhizome*

**Table 2** Ingredients of Shinbuto

<i>Poria sclerotium</i>	4.0 g
<i>Atractylodis lanceae rhizoma</i>	3.0 g
<i>Paeoniae radix</i>	3.0 g
<i>Zingiberis rhizoma</i>	1.5 g
<i>Aconiti tuber</i>	0.5 g

(Table 2). Processed aconite root is the most important ingredient in shinbuto. Together with ginger, it warms the body and increases metabolism. *Poria sclerotium* and *Atractylodis lanceae rhizoma* work together to fix the body fluid imbalance. *Paeoniae radix* relaxes the strain of the smooth muscle of the gastrointestinal tract.<sup>19-24</sup> Together, these components ameliorate *hie* and *suitai*.

Kampo medicines other than shinbuto—eg, *goreisan*, *hachimijogan*, and *keishikashakuyakuto*—could have been considered as well. *Goreisan* improves *suitai* and has been shown to be widely effective for dizziness in patients with edema, thirst, decreased urine output, and diarrhea. However, *goreisan* is not effective at warming the body.

*Hachimijogan* improves age-induced *hie*. Indeed, it is frequently used in elderly patients for *jitsusho*. *Keishikashakuyakuto* ameliorates abdominal distension (*fukuman*) caused by retention of stool and gas in the digestive tract of patients with *hie*. Our patient, however, did not have *fukuman*.

## CONCLUSION

Shinbuto, a traditional Japanese herbal product, improved refractory diarrhea and abdominal pain in a patient with congenital leg lymphedema. The mechanism of action of shinbuto can be explained by rewarming and fixing body fluid imbalance.

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