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Long-term maintenance of nutritional status with ninjinyoueito in terminal patients with chronic respiratory disease: Two case reports

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Abstract. Ninjinyoeito, is a traditional herbal (Kampo) medicine which is administered to patients with debilitating diseases in North-East Asia. Ninjinyoeito has been reported to be effective against loss of physical strength, fatigue and loss of appetite in patients with wasting diseases. The present study described long-term maintenance of body weight with ninjinyoueito in 2 terminal patients with chronic respiratory diseases. The first patient was a 75-year-old with chronic obstructive pulmonary disease (COPD) who took ninjinyoueito for ≥5 years and the second patient was a 72-year-old man with metastatic lung cancer with combined pulmonary fibrosis and emphysema (CPFE) who took ninjinyoueito for ≥1 year. Both of them maintained their physique and nutritional status during the terminal stages of disease and there were no adverse effects observed in these 2 patients which could be attributed to ninjinyoueito. The results suggest that ninjinyoueito may be a supplementary treatment for the maintenance of nutritional status in patients with a chronic respiratory disease accompanied by wasting, such as COPD.

Introduction

Several Japanese traditional herbal medicines (Kampo medicines) have favorable nutritional effects in patients with chronic respiratory disease (1-3). However, to the best of our knowledge, only one study has examined the effects of traditional Japanese medicine on body weight gain in a patient with chronic obstructive pulmonary disease (COPD) (3). Ginseng is one of the most well-known herbal medicines and has been administered to patients with chronic wasting diseases (4). Ninjinyoueito, is a Kampo medicine which is comprised of twelve herbs including ginseng and is used to treat various symptoms, such as fatigue, anorexia, night sweats, cough, malaise, insomnia, dry skin and dry mouth (5,6).

In the present case report, the cases of two terminal patients with respiratory disease who maintained body weight and nutritional status with ninjinyoueito are described.

Case reports

Case 1. A 75-year-old man was referred to the University of Tsukuba-Mito Kyodo General Hospital (Mito, Japan) due to an increase in dyspnea and chest pain on his right side. At the age of 69, he had a forced expiratory volume (FEV) in 1 sec (FEV1.0) of 0.83l and FEV% in 1 sec of 58.6% on the pulmonary function test, therefore, he was diagnosed with chronic obstructive pulmonary disease (COPD). He had no other comorbidities. His smoking history included 40 cigarettes per day between the ages of 14 and 69 years. Since the diagnosis of COPD, he had been prescribed a combination of an inhaled long-acting antimuscarinic antagonist, a long-acting β2-agonist, and oral carbocysteine, ambroxol and theophylline. His height was 174 cm and he weighed 46 kg, with a body mass index (BMI) of 15.2. Laboratory results revealed a total serum protein level of 6.4 g/dl and a serum albumin level of 3.6 g/dl. There was no abnormality in liver and kidney function, and no increase in C-reactive protein (CRP) and leukocytosis. A mild pneumothorax on the right side was diagnosed on a CT scan. The pneumothorax improved on bed rest without requiring deaeration. According to the patient's request, ninjinyoueito (2.5 g three times a day; Kracie Pharmaceutical, Ltd.) was prescribed. Nutritional supplement therapy with oral enteral nutrients (Ensure Liquid; Abbott Pharmaceutical Co., Ltd.) was prescribed. The patient visited the hospital every month and was weighed each time. Total protein and albumin were measured once every 10 months. Fig. 1 shows the changes in the body weight, and serum total protein and albumin levels over 5 years from the initiation of ninjinyoueito until his death.

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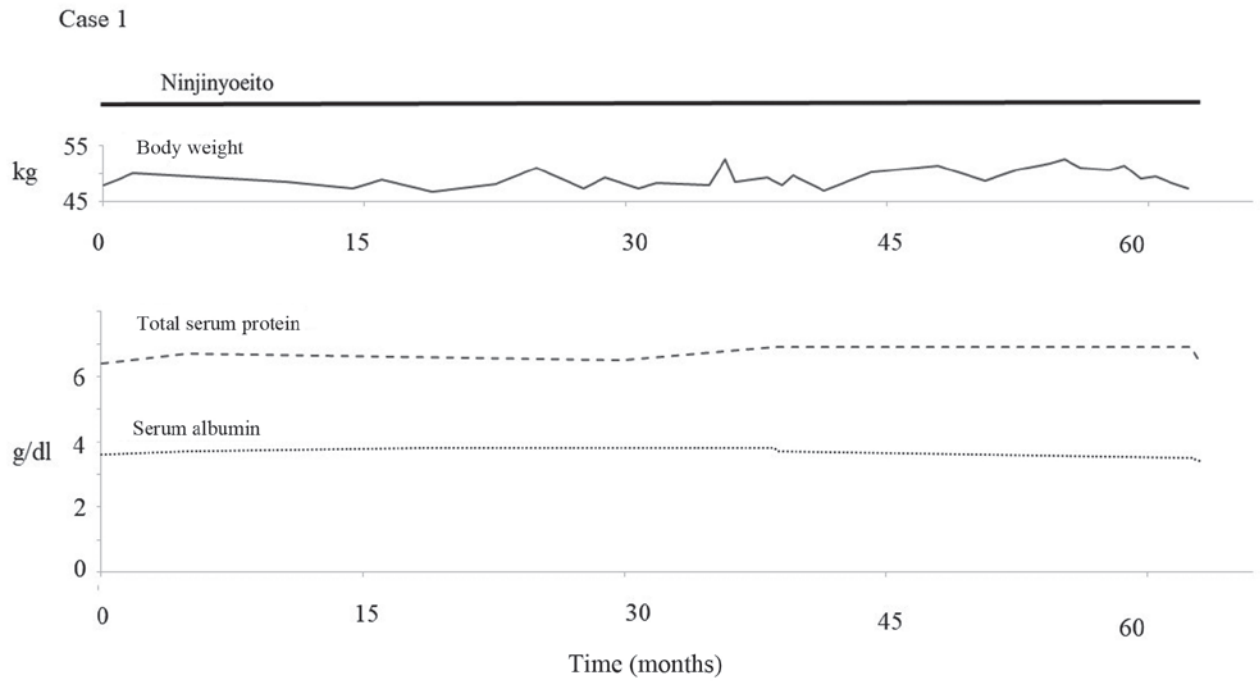

Figure 1. Changes in body weight, and serum total protein and albumin levels of the patient described in case 1 over a 60-month period, from initiation of ninjinyoueito administration until his death.

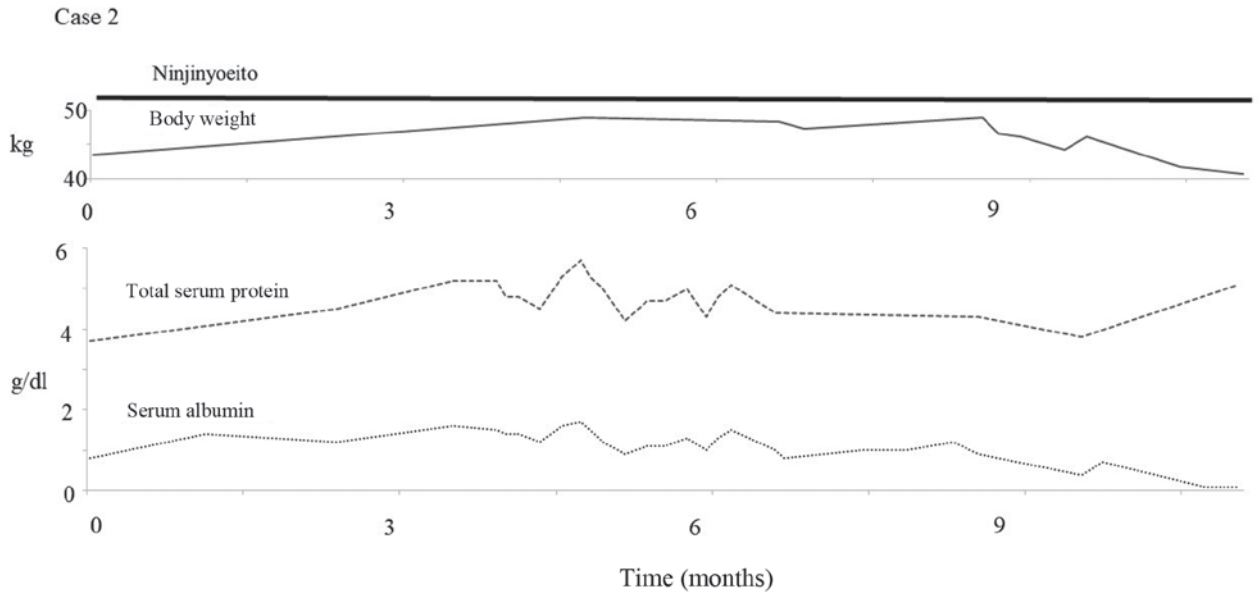

Figure 2. Changes in body weight, and serum total protein and albumin levels of the patient described in case 2 over a 12-month period, from initiation of ninjinyoueito administration until his death.

There were several acute exacerbations during the 5 years. Despite the presence of COPD, the weight, total serum protein levels and serum albumin levels did not change significantly. Throughout the clinical course, the patient did not receive corticosteroids or hormonal therapy.

Case 2. A 72-year-old man was referred to the University of Tsukuba-Mito Kyodo General Hospital due to an increase in dyspnea. At the age of 68, he was diagnosed with combined pulmonary fibrosis and emphysema (CPFE) and was treated with inhaled corticosteroid/long-acting β-agonist since then. At the age of 70, he was diagnosed with squamous cell carcinoma of the lung and underwent left lower lobectomy. Lung metastases were found on a chest computed tomography scan taken 6 months after surgery. He received 4 courses of chemotherapy with carboplatin and taxol, but the treatment was changed due to progressive disease (PD). The patient smoked 30 cigarettes a day for 30 years. There were no complications other than CPFE. He was 173 cm tall and weighed 43.5 kg, and thus had a BMI of 14.5. Laboratory exams revealed a total serum protein levels of 5.7 g/dl and a serum albumin level of 2.7 g/dl. There was no abnormality in liver and kidney function, and

no increase in CRP and leukocytosis. He underwent a surgical resection of ruptured bullae that had led to right pneumothorax. As his body weight decreased >10 kg in 1 year, the patient wished to take ninjinyoueito (2.5 g three times a day). For squamous cell carcinoma of the lung, 7 courses of docetaxel (60 mg/m^2, day 1, every 28 days) and 3 courses of vinorelbine (20 mg/m^2, dasy 1 and 8, q28) were administered, but these therapies were discontinued due to PD. The patient visited the clinic once every 2 weeks and was weighed each time. Total protein and albumin were measured at each visit. The changes in body weight, and total protein and albumin levels in serum over 1 year from the initiation of ninjinyoueito to his death are shown in Fig. 2. Despite the deterioration of squamous cell carcinoma of the lung, the values of these indicators did not change notably. Throughout the clinical course, the patient did not receive corticosteroids or hormonal therapy.

Discussion

Chronic respiratory diseases such as COPD is considered a systemic disease. It affects a wide range of functions throughout the body and causes impairment of nutrient absorption (7), muscle loss (8) and depressed mood (9) amongst other symptoms. Assessment of body weight, BMI and nutritional status is important in understanding the status of patients with COPD (8). The negative effect of a low body weight on survival can be reversed by appropriate therapy in some patients with COPD (10). In addition, malnutrition in patients with lung cancer is an independent factor associated with poor prognosis (11).

Ninjinyoueito is a Kampo medicine derived from twelve crude drugs; rehmannia root, Japanese angelica root, atractylodes rhizome, Poria sclerotium, ginseng, cinnamon bark, polygala root, peony root, *Citrus unshiu* peel, astragalus root, glycyrrhiza and schisandra fruit (5,6). Ninjinyoueito is used to treat appetite loss, weight loss and respiratory symptoms, and improves nutritional status and immune function in patients with COPD, one of the major underlying causes of cachexia (12). *Panax ginseng* is a therapeutic herb with potential benefits for patients with COPD (13). Recently, Shergis *et al* (14) reported results from a 12-month randomized controlled trial of ginseng extract for treatment of moderate COPD. The primary endpoints of their study were scores on the St George's Respiratory Questionnaire (15), the COPD Assessment Test (16) and the Short Form Health Survey (17). Secondary outcomes included lung function, exacerbation rate and use of relief medication. However, body weight or nutritional status were not assessed in their study (13). Kuniaki *et al* (3) reported improved strength in a patient with severe COPD (but not terminal) following ninjinyoueito therapy, and administration of ninjinyoueito increased body weight and muscle mass without affecting body fat percentage in the 76-year-old male patient during the 6 months of administration. The patients described in the present study were terminal patients, one with COPD and one with CPFE and squamous cell carcinoma of the lung. They took ninjinyoueito for 5 years and 1 year, respectively, so the observation period was longer than that reported by Kuniaki *et al* (3). Assessment of the specific indicators of cachexia could not be performed in our patients during follow-up due to the limits of daily medical care, but body weight and total serum protein and albumin levels, which are indicators of nutritional status, were repeatedly measured.

Thus, the present study describes long-term maintenance of body weight with the Kampo medicine, ninjinyoueito, in terminal patients with chronic respiratory diseases. To the best of our knowledge, this is the first case report showing long-term maintenance of body weight and nutritional status with ninjinyoueito in terminal patients with chronic respiratory diseases. Ninjinyoueito is becoming an increasingly commonly prescribed medication for patients with chronic respiratory disease such as COPD (3,14,18). Although the underlying mechanism by which ninjinyoueito counteracts weight loss and induces maintenance of nutritional status remains unclear, this Kampo medicine may be used as a supplementary treatment for terminal patients with respiratory diseases.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

YS, SO, GO and KK obtained the data. YS and HS designed the study, acquired, analyzed and interpreted the data. KK performed the data analysis and constructed the figures. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Mito Medical Center, University of Tsukuba-Mito Kyodo General Hospital (Mito, Japan; approval no. 19-66). Comprehensive written informed consent was obtained from each patient.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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