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Acute sarcoidosis Löfgren Syndrome treated by Chinese medicinal formula based on Syndrome Differentiation: A case-based review

[Tratamiento de síndrome de Löfgren de sarcoidosis con fórmula medicinal china basada en diferenciación de síndrome: una revisión basada en casos]

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Abstract: Löfgren syndrome (LS) is a unique acute manifestation of sarcoidosis and characterized by erythema nodosum, bilateral hilar lymphadenectasis, and/or bilateral ankle arthritis or peri-arthritis. A 37-year-old female patient with LS presented with fever accompanied by multiple joint swelling and pain, nodular skin erythema, and bilateral hilar lymphadenectasis. The patient had received treatment involving non-steroidal anti-inflammatory drugs and glucocorticoids in other hospitals, but the effects were poor, and the conditions reemerged. The LS duration has lasted for more than 3 months. Following traditional Chinese medicine (TCM) treatment, syndrome differentiation as well as giving patients oral Chinese medicine decoction, the symptoms of the patient were rapidly relieved within one week and did not recur during a six-month follow-up period. This case is the first clinical report of acute sarcoidosis LS treated using TCM and reflects the significant advantages of this form of therapy in emergency treatment.

Keywords: Löfgren syndrome; Arthritis; Erythema nodosum; Arthralgia disease; Traditional Chinese medicine

Resumen: El síndrome de Löfgren (LS) es una manifestación única y aguda de sarcoidosis, caracterizada por eritema nodoso, linfadenectasis hilar bilateral, y/o artritis de tobillo bilateral o periartrosis. Una paciente de 37 años de sexo femenino con LS se presentó con fiebre, acompañada de inflamación y dolor múltiple de articulaciones, eritema nodular cutáneo, y linfadenectasis hilar bilateral. La paciente recibió un tratamiento que consistió en antiinflamatorios no esteroideos y glucocorticoides en otros hospitales, pero los efectos fueron leves y las condiciones reemergieron. El LS ha durado más de tres meses. Siguiendo el tratamiento de medicina tradicional china (MTC), la diferenciación de síndrome, así como darles a los pacientes una decocción de medicina china por vía oral, los síntomas de la paciente rápidamente fueron aliviados en el curso de una semana y no recidivaron durante los seis meses de un seguimiento. El caso es el primer reporte clínico de tratamiento de sarcoidosis aguda asociada a LS usando TCM y refleja las significativas ventajas de esta forma de terapia en el tratamiento de emergencia.

Palabras clave: Síndrome de Löfgren; Artritis; Eritema nodoso; Enfermedad de artralgia; Medicina tradicional china

INTRODUCTION

Löfgren syndrome (LS) is a specific and acute manifestation of sarcoidosis (Castro & Pereira, 2017) that accounts for 5% to 10% of patients with sarcoidosis (Ungprasert *et al.*, 2016). Marked by the characteristics including a sudden clinical onset complicated with fever, LS performed a series of clinical symptoms, for example, erythema nodosum, bilateral hilar lymphadenectasis, and/or bilateral ankle arthritis or periartthritis (Seve *et al.*, 2021), which was also characterized by multisystem damage. Cutaneous symptoms are mainly composed of red subcutaneous plaques and nodules with pressure pain, which accompanied with edema and hypothermia. Acute polyarthritis affects the joints of the lower extremities, with the ankle joint being the most commonly involved. As the disease progresses, the symptoms of LS with self-limiting features will gradually subside in most patients, mostly 3–12 months after onset (Maña *et al.*, 1999). Additionally, when erythema nodosum and arthritis present disabling symptoms, the patients should be treated with drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), with oral glucocorticoids required when NSAIDs cannot be tolerated or when the disabling symptoms reoccur (Karakaya *et al.*, 2017; Castro & Pereira, 2020).

Chinese medicine is the most vital part of the traditional Chinese medicine (TCM) system. Since the Spring and Autumn Period and the Warring States Period to the end of the Eastern Han dynasty, the birth of the Chinese Medical Classics such as *Yellow Emperor's Classic of Internal Medicine*, *Classic on Medical Problems*, *Sheng Nong's herbal classic* and *the Treatise on Typhoid Miscellaneous Diseases* provided tremendous helps for establishing the TCM system of theory, method, Chinese medicine formula, and medicine as well as the principles of diagnosis and treatment of Chinese medicine. Based on continuous summing up of practical experience in treating diseases, a variety of TCM treating strategies consisting of acupuncture, massage as well as Chinese medicinal formula were developed. Of note, Chinese medicinal formula prescribed after the dialectical diagnosis was the common treating strategy in clinic, which has a long applying history for multiple diseases (Zhang *et al.*, 2016). However, there was little information on the clinical case report of using Chinese herbal formulas for treating LS up to now.

Herein, the purpose of this study is to analyze the etiology and pathogenesis of LS according to the four diagnostic means of TCM, following by using

the corresponding Chinese medicinal formula prescribed based on the analysis results of four diagnostic means on LS to treating LS, which aims to provide diagnostic ideas and therapeutic Chinese medicinal formula for syndrome-differentiation-based TCM aimed at the treatment of LS.

CASE REPORT

This study was conducted in accordance with the declaration of Helsinki and approved by the Ethics Committee of Beijing Hospital of Traditional Chinese Medicine, Capital Medical University. Written informed consent was obtained from the patient.

The patient is a 37-year-old female who was admitted to our hospital on April 7, 2021, with the primary complaint of intermittent fever with multiple joint swelling and pain, as well as erythema nodosum for more than three months and aggravated for three days. The patient developed a fever after contracting a cold more than months earlier, with a mean maximum temperature of 38.5°C and presenting a paroxysmal cough. There was no improvement following the self-administration of heat-clearing, detoxifying drugs, and ibuprofen. Later, the patient developed a sore throat and joint pains across the whole body, at which point, they took azithromycin orally for one week. While the peak temperature decreased to a certain extent, the patient continued to experience intermittent low fever, with no improvement in the body-joint pain.

More than two months earlier, the patient developed nodular erythema on the skin of both lower limbs with a size ranging from that of a nail plate to that of a coin (Figure No. 1), with the erythema mostly appearing on the extended side of the lower limbs with bilateral symmetrical distribution and evident tenderness. The patient visited a doctor in the dermatological department of another hospital, where a diagnosis of erythema nodosum was concluded. Following treatment with halometasone ointment (for external use), the condition did not improve, gradually fusing into a larger zone, accompanied by redness, swelling, and pain.

The patient then treated herself using heat-clearing and detoxifying drugs for two weeks, but the treatment was unsuccessful, and the patient experienced severe swelling and pain in both knees and ankle joints and was unable to stand and walk. The patient then received further treatment in another hospital, receiving oral administration of 8 mg of medrol Qd, clindamycin, and loxoprofen, and the external application of polymyxin B ointment and

hasinonide solution. While the swelling and joint pain were relieved and the nodular erythema disappeared, the patient continued to experience some joint pain and discomfort when walking for a long time. The symptoms were further relieved after intramuscular injection with one ampoule of Diprospan.

Three days prior to admission, following

some exertion, the cough symptoms were exacerbated, accompanied by shortness of breath, skin erythema on the limbs, muscle pain in the knees and ankles, and fever. A computed tomography (CT) chest examination revealed multiple enlargements of the lymph nodes in the bilateral hilus of the lung, tracheal carina, and mediastinum.



Figure No. 1

Before treatment: Multiple erythematous nodules in (A, B) bilateral ankle joint and (C) lower limbs swelling and redness (acute sarcoid arthritis)

The patient was then admitted to our hospital seeking TCM-based treatment. At admission, the following symptoms were presented: fever (appearing in the afternoon) and pain, swelling, and heaviness in the muscles of both knees and both ankle joints, while the patient was having difficulty in walking and required help in this regard. The erythema nodosum of the lower limbs had recurred, with new inflammation also appearing on the upper limbs. The patient was experiencing a dry cough without phlegm, chest tightness, and a dry mouth. The patient reported liking hot drinks but did not drink large amounts of water, had a poor appetite, and was experiencing fatigue, smooth urination and defecation, and poor sleep. The patient's tongue was observed to be red, with the tongue coating thin, yellow, and greasy, while the pulse was soft and rapid. Upon a physical examination, the body temperature was 38.5°C, the complexion was yellow, no clear abnormalities were found in terms of the heart, lungs, and abdomen, while all four limbs exhibited scattered erythema nodules with a size ranging from that of a nail plate to that of a coin, with evident tenderness in both ankle joints, resulting in limited movement. During a routine blood test, the

indexes were generally normal, with an elevated erythrocyte sedimentation rate of 83 mm/h and an elevated C-reactive protein level of 85.8 mg/L, while the remainder of the indexes were negative. A CT chest examination revealed enlargement of the lymph nodes in the bilateral hilus of the lung, tracheal carina, and mediastinum, while the endo-bronchial ultrasonic-guided transbronchial needle aspiration (EBUS-TBNA) pathology examination (Figure No. 2) revealed partial lymphocytic infiltration, the formation of granulomatous structures in the small foci, and no definite caseous necrosis.

Based on the patient's clinical manifestations and auxiliary examination results, the Western-medicine-based diagnosis was acute sarcoidosis LS, while in terms of TCM-based diagnosis, this was arthralgia disease. Here, the syndrome differentiation was evil wind assailing from the outer body, causing damp-heat obstruction and thermal disturbance of the Yingfen. Therefore, the Chinese medical formula with modification based on the combination of TCM classic formula named Danggui Niantong decoction, Mufangji decoction and Qingying decoction were applied for further treatment via warding the wind and evil, removing the dampness and eliminating the

evil, cooling the Ying, removing the heat. Specifically, the composition of the Chinese medical formula was as follows: 10 g of *Notopterygh Rhizoma et Radix* (Qianghuo), 10 g of *Angelicae Pubescentis Radix* (Duhuo), 15 g of *Stephaniae Tetrandrae Radix* (Fangji), 10 g of *Atractylodis Rhizoma* (Cangzhu), 10 g of *Scutellariae Radix* (Huangqin), 10 g of *Anemarrhenae Rhizoma* (Zhimu), 15 g of *Polyporus* (Zhuling), 10 g of *Tetrapanacis Medulla* (Tongcao), 30 g of *Bubali Cornu* (Shuiniu Jiao, fried first), 30 g of *Rehmanniae*

Radix (Dihuang), 20 g of *Lonicerae Japonicae Flos* (Jinyin Hua), 30 g of *Forsythiae Fructus* (Lianqiao), 15 g of *Scrophulariae Radix* (Xuanshen), 15 g of *Paeoniae Radix Rubra* (Chishao), 10 g of *Armeniacae Semen Amarum* (Kuxing Ren), 10 g of *Peucedani Radix* (Qianhu), and 15 g of *Angelicae Sinensis Radix* (Danggui). A total of five decoctions were administered, one per day, which involved boiling water until a 200 mL solution remained, with this taken orally twice a day, once in the morning and once in the evening.

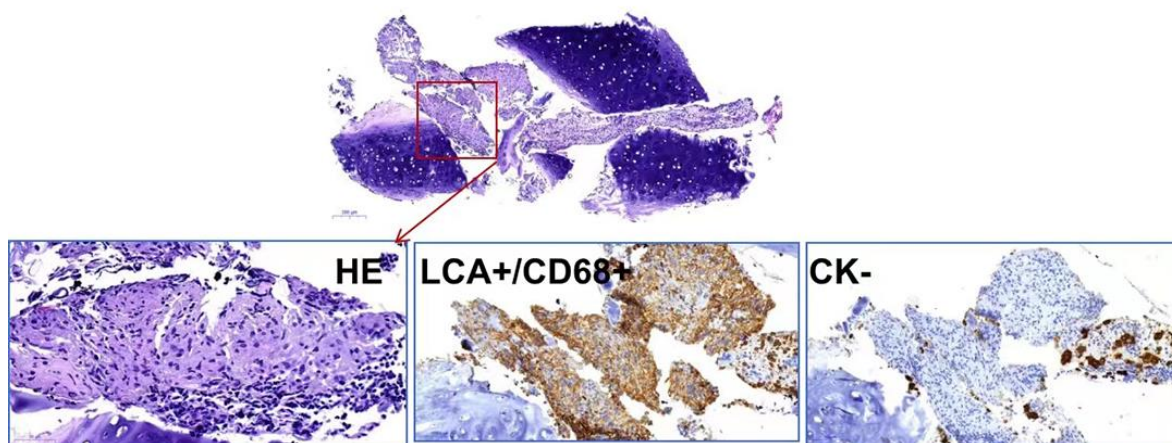


Figure No. 2
Endo-bronchial ultrasonic-guided transbronchial needle aspiration (EBUS - TBNA)

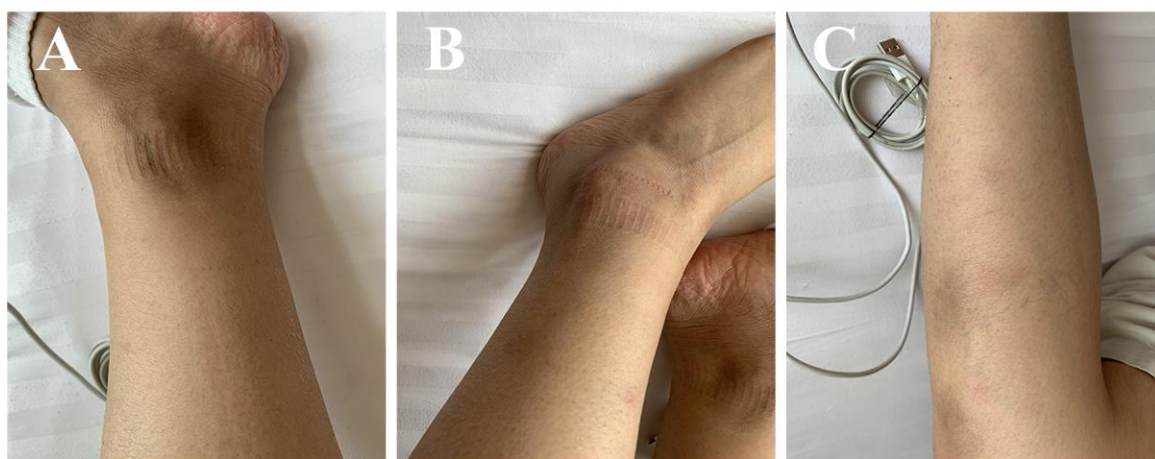


Figure No. 3
After treatment: The erythemas of (A, B) bilateral ankle joint and (C) lower limbs subsided and pigmentation remained

A second diagnosis was reached on April 12, 2021. On the fifth day following admission, after taking the first decoction as described above, the

patient's body temperature had decreased to a normal range by the following day, the swelling and joint pain were significantly reduced, and the erythema of

the limbs had become pale, without new erythema occurring. After taking the second decoction as described above, the patient was able to walk independently, while following the fifth decoction, the patient's erythema had subsided, with only residual pigmentation observed (Figure No. 3), and the joint muscles were only slightly swollen and painful, but the coughing was more evident. The tongue had turned from red to light red, with the tongue coating turning from yellow to white, and the pulse was soft. Following the administration of the synthesis of the four diagnostic methods, it was deemed that the patient's heat of the Yingfen was eliminated, as had the external contraction of the evil wind, while there was still damp heat blocking the meridians, some impaired dispersion of the lung-qi, and an accumulation of phlegm dampness in the lung.

The patient was then treated with drugs aimed at clearing the heat, removing the dampness and the lung dispersion, and reducing the phlegm. Here, the prescription described above was adjusted as follows: 15 g of *Stephaniae Tetrandrae Radix* (Fangji), 10 g of *Atractylodis Rhizoma* (Cangzhu), 10 g of *Scutellariae Radix* (Huangqin), 10 g of *Tetrapanacis Medulla* (Tongcao), 15 g of *Mori Cortex* (Sangbai Pi), 6 g of *Ephedrae Herba* (Mahuang), 10 g of *Armeniacae Semen Amarum* (Kuxing Ren), 15 g of *Pinellinae Rhizoma Praeparatum* (Faban Xia), 12 g of fried *Sinapis Semen* (Jiezi), 10 g of *Asteris Radix Et Rhizoma* (Ziyuan), 15 g of *Farfarae Flos* (Kuandong Hua), 10 g of *Peucedani Radix* (Qianhu), and 15 g of *Angelicae Sinensis Radix* (Danggui). A total of seven decoctions were administered using the same decocting and administration methods as previously used.

A third diagnosis was then reached on April 19, 2021. Following the administration of the seventh decoction of the prescription described above, the swelling and joint pain disappeared, and the coughing and expectoration were relieved, while the patient continued to experience shortness of breath and chest tightness at times. The tongue was light red with a thin white coating, and the pulse was fine and slippery. In terms of syndrome differentiation, this was concluded to include deficiency of the lung and spleen and an accumulation of phlegm dampness, while in terms of treatment, this included tonifying the lung and spleen, eliminating the dampness, and reducing the phlegm. Here, the prescription was a modified Liujunzi decoction containing 15 g of *Codonopsis Radix* (Dangshen), 15 g of baked *Rhizoma Atractylodis Macrocephalae*-Baizhu, 15 g of

Astragali Radix (Huangqi), 12 g of *Angelicae Sinensis Radix* (Danggui), 15 g of *Poria* (Fuling), 10 g of *Citri Reticulatae Pericarpium* (Chenpi), 10 g of *Pinellinae Rhizoma Praeparatum* (Faban Xia), 10 g of *Fritillariae Thunbergii Bulbus* (Zhebei Mu), 12 g of *Sinapis Semen* (Jiezi), and 10 g of *Cremastrae Pseudobulbus* (Shanci Gu). A total of 14 decoctions were administered using the same decocting and administration methods as used previously.

Of note, the clinical symptoms including fever, nodular erythema and arthritis of the patient have disappeared after treating with Chinese medical formula. The imaging examination result showed that the patient was at stage-I, mainly manifesting as the enlarged mediastinal lymph nodes are at present as well as the not involved lung parenchyma. This is to say that the patient has cured now and no intervention is needed.

The patient was then asked to discharge themselves, with a follow-up set for twice a month. The total follow-up period was six months, during which time the patient experienced no recurrence of fever, joint swelling/pain, or erythema nodosum, while the CT scan revealed no progress of the condition.

DISCUSSION

Research progress of modern medicine

As a unique manifestation of sarcoidosis, LS was first described by Sven Löfgren, a Swedish medical professor, in 1946 (Castro & Pereira, 2020). Compared with typical sarcoidosis, LS involves an acute onset, is typically accompanied by fever, and is characterized by clinical symptoms that include erythema nodosum, bilateral hilar lymphadenectasis, and/or bilateral ankle arthritis or periartthritis. Although the pathogenesis of LS is unclear, enormous evidences showed that abnormal immune dysfunction and inflammatory responses are involved in this disease (Ungprasert *et al.*, 2016). Globally, the incidence rate of LS varies greatly, which is largely related to genetic background and ethnic differences, with the incidence rate high among Caucasians in Europe but extremely low in Asia (Maña *et al.*, 1999; Seve *et al.*, 2021). At present, there is only two clinical report in China (Sun *et al.*, 2019). The onset age of LS ranges between 25 and 40 years of age, while female patients can experience a second onset peak at the age of 40–60 (Maña *et al.*, 1999). Meanwhile, the clinical manifestations of LS vary according to gender, with ankle arthritis or periarticular inflammation with erythema nodosum mainly affecting women and arthritis without

erythema nodosum mainly found in men. A previous study reported that most of the patients exhibited stage I sarcoidosis on chest imaging (hilar lymphadenopathy only), while a small number exhibited stage II sarcoidosis (involvement of lung parenchyma), with no stage III/IV found (Rubio-Rivas et al., 2020).

The diagnosis of LS is mainly based on clinical and radiological manifestations. For LS patients with typical clinical features, a biopsy is not required, and the condition has high sensitivity and specificity only through the combined diagnosis of acute course, bilateral hilar lymphadenopathy, erythema nodosum, and bilateral ankle arthritis (Karakaya et al., 2017). In terms of the subject of the current study, the patient suddenly fell ill after having contracted a cold three months earlier, with the clinical manifestations including fever, skin erythema nodosum, and swelling and pain of both knees and ankles, accompanied by bilateral hilar lymphadenopathy, all typical manifestations of LS. In fact, with an EBUS-TBNA examination conducted to exclude tuberculosis infection, the final diagnosis was indeed LS.

As noted, although the course of LS is self-limiting, the natural remission cycle is typically 3–12 months following onset (Castro & Pereira, 2020). When the erythema nodosum and arthritis result in disabling symptoms, they must be treated with drugs, mainly NSAIDs that induce analgesia and promote regression, or oral glucocorticoids when NSAIDs cannot be tolerated or when the disabling symptoms (e.g., ankle arthritis) and lung parenchyma involvement co-occur (Karakaya et al., 2017; Castro & Pereira, 2020).

The patient in our case study was treated with antipyretic and analgesic drugs and external or oral administration of glucocorticoids; however, the effect was poor, and the condition was exacerbated, with the increased joint pain meaning the patient could not walk on their own, while the erythema had become more widespread. Following TCM syndrome differentiation and treatment, the clinical symptoms of this patient were quickly eliminated, and there was no recurrence during a six-month follow-up period.

TCM Thinking of syndrome differentiation of LS

At present, there exists no clinical report on LS and no unified name for LS in the field of TCM. In fact, the disease is mainly referred to in terms of the main symptoms or syndrome characteristics at a certain stage of the disease, which is also the essence of the disease differentiation and treatment based on

syndrome differentiation (Jie et al., 2021). In terms of the patient on the first visit reported in this case study, the external symptoms mainly included swelling and pain in the joint muscles and skin erythema, while the internal symptoms were coughing and hilar lymphadenopathy. It can be argued that the most appropriate term for LS is "arthralgia disease," with the external manifestation labeled "muscle arthralgia" or "pulse arthralgia" and the internal manifestation labeled "lung arthralgia".

On the etiology and pathogenesis of arthralgia syndrome, *Plain Question, Arthralgia Theory* recorded that 'Three qi of wind, cold and dampness mix together and combine to form arthralgia,' which essentially describes how the arthralgia is caused by the combination of wind, cold, and dampness. Meanwhile, in the book, *Synopsis of the Golden Chamber*, Zhongjing Zhang proposes that "arthralgia is caused by meridian heat". In *Detailed Differentiation of warm Febrile Diseases*, Jutong Wu suggests that cold, heat, deficiency, and excess present the outline of the syndrome differentiation of arthralgia disease, expanding the system of syndrome differentiation of arthralgia syndrome

The syndrome differentiation of our patient proved to be somewhat complicated. The clinical symptoms of patient on the first visit mainly manifested as a lingering fever, joint muscle pain and swelling, skin erythema, coughing, and chest tightness, accompanied by a sallow complexion, poor appetite, anorexia, dry mouth, a preference for hot drinks but not for drinking too much water, a greasy tongue coating, and a soft and rapid pulse. While this all presents the exterior and interior of hand-foot Taiyin meridians invaded by wind, damp, heat, and pathogenic factors, the condition was dominated by the exterior disease, with both the Weifen and the Qifen suffering from it and affecting the Yingfen, while the location of the disease was predominantly in the meridians, resulting in various symptoms.

The patient was usually tired, resulting in damaged spleen qi, endogenous dampness, and the formation of damp abundance due to splenic asthenia, with the dampness heavy and turbid; hence the manifestation of fatigue and the sallow complexion. If a patient is attacked by exogenous pathogenic factors, given that aspects of the same nature always tend to join together, the patient will be most vulnerable to wind and dampness. Here, the weak are easily moved, the Taiyin is directly affected by the external pathogenic factors of wind and dampness above the Taiyin, the dampness is dominant, and the exogenous pathogenic factors quickly humidify,

suppressing the muscle surface and resulting in a loss of Weiqi, all of which results in the patient experiencing a fever (generally in the afternoon) and their body not being warm. Meanwhile, dampness and heat compete with each other, blocking the meridians, with the heat disturbing the Yingfen, while the blood vessels will become obstructed, meaning the patient will exhibit external arthralgia symptoms, such as pain, swelling, and erythema of the skin.

When the disease lies in the skin, and the skin is painful, the condition is termed "muscle arthralgia," which incessantly becomes meridian arthralgia, where meridian qi flows through the meridians. The lungs are connected with hundreds of meridians. If exogenous pathogenic factors invade the vein body, the circulation of qi and blood will not be smooth, thus blocking the qi mechanism, which can further lead to the stagnation of lung qi and the emergence of lung arthralgia, the clinical symptoms of which include coughing and chest tightness. The main cause of the disease is the combination of the three pathogenic factors of wind, dampness, and heat, among which dampness is the most important. Meanwhile, the pathogenesis is spleen deficiency, endogenous dampness, exogenous wind, wetness, arthralgia blocking the meridians, and heat disturbing the Yingfen. The disease locations are generally the exterior and interior of the hand-foot Taiyin meridians, with the locations more inclined to be in the exterior and the meridians and going from the qi to the Yingfen.

Given that dampness lies in the interior, is dried by bitterness and dryness, and is discharged by lightness, the general principle of the attendant treatment is based on warding the wind and removing the dampness, as well as removing the arthralgia, dredging the collaterals, cooling the Ying, and reducing the heat. With this in mind, following the initial diagnosis, the patient was treated with a modified combination of Danggui Niantong decoction, Mufangji decoction and Qingying decoction.

Danggui Niantong decoction firstly recorded by *Medicine Origin* that writing by Yuansu Zhang in Jin dynasty, which has been praised as the "holy formula for treating damp-heat induced pain". Of note, the results of previous pharmacological studies showed that Danggui Niantong decoction could perform anti-inflammatory and analgesic effects via reducing the levels of inflammatory factors as well as inhibiting inflammatory-related signaling pathways. Besides, this formula also exerts others' effects

including inhibiting the expressions of vascular endothelial growth factor, matrix metalloproteinase-9, autophagy-related proteins, inhibiting the proliferation of synovial cells by regulating cell apoptosis (Zhou & Zhang, 2022; Lu et al., 2022).

Recorded by *Item Differentiation of Warm Febrile Diseases* (writing by Jutong Wu), modified Mufangji decoction has been known as the original formula for the treatment of arthralgia syndrome. Previous study exhibited that modified Mufangji decoction performed the beneficial effects on treating gout arthritis by suppressing the inflammation-related signal pathways. The 59 relevant active ingredients of modified Mufangji for treating gout arthritis has been screened, for example, levosorpidine, β -sitosterol, isoglycyrrhiza, stigmastol, glabridine, etc (Du et al., 2022).

As the same as modified Mufangji decoction, Qingying decoction was also recorded by *Item Differentiation of Warm Febrile Diseases* and performed the efficacy of clearing 'Ying' and detoxifying, penetrating heat and nourishing Yin. As the clinical and experimental studies on Yingfen syndrome carried out in recent times have advanced, the pathology changes of blood-heat and blood-stasis under Yingfen syndrome was further revealed. The application of Qingying decoction involved in both acute febrile diseases, emergency and severe disease that were not sensitive to western drugs (Zhang et al., 2009).

This syndrome of current case was identified as dampness-heat blockaging meridians accompanied by affecting the yingfen at the first consultation. Therefore, Danggui Niantong decoction combined with Mufangji decoction were selected for removing arthralgia and obstruction in the meridians due to the clearing heat and removing dampness effects of them, which Qingying decoction was applied for clearing heat and cooling Ying. In terms of this formula combined with Danggui Niantong decoction, Mufangji decoction as well as Qingying decoction, *Notopterygh Rhizoma et Radix* (Qianghuo) and *Angelicae Pubescentis Radix* (Duhuo) serve to ward off wind and reduce dampness, and *Stephaniae Tetrandrae Radix* (Fangji) serves to clear dampness, eliminate arthralgia, and relieve pain, which were used as principal medication in this formula. *Atractylodis Rhizoma* (Cangzhu) and *Scutellariae Radix* (Huangqin) are bitter and can eliminate dampness, enhancing the function of this formula on clearing damp. *Polyporus* (Zhuling) and *Tetrapanacis Medulla* (Tongcao) serve to clear dampness and promote diuresis, and *Armeniacae Semen Amarum*

(Kuxing Ren) performed the effects on ventilating lung Qi. The function of *Armeniacae Semen Amarum* (Kuxing Ren) on transforming Qi promoting dampness being eliminating help to achieve the efficacy of ventilating lung Qi and elimination of pathogens through purgation and diuresis after combined with the application of *Polyporus* (Zhuling) and *Tetrapanacis Medulla* (Tongcao). *Yi Yuan Theory of Dampness* written by Mr. Shi have recorded that 'opening the upper gate and the branch river to guide the dampness downward to get out of the way, then Qi will run smoothly' (Zhang *et al.*, 1985).

Angelicae Sinensis Radix (Danggui) disperses any stagnation in the blood, the *Bubali Cornu* (Shuiniu Jiao) serves to clear the heat in the Yingfen, the *Rehmanniae Radix* (Dihuang) and *Paeoniae Radix Rubra* (Chishao) serve to cool the blood, *Anemarrhenae Rhizoma* (Zhimu) and *Scrophulariae Radix* (Xuanshen) have the function of nourishing the Yin, *Lonicerae Japonicae Flos* (Jinyin Hua) and *Forsythiae Fructus* (Lianqiao) serve to clear the heat of the Yingfen to the Qifen, and *Peucedani Radix* (Qianhu) and *Armeniacae Semen Amarum* (Kuxing Ren) have the function of guiding the qi down and eliminating phlegm. The synthesis of the whole prescription has the function of eliminating pathogens through phlegm elimination and purgation and regulating both the qi and the blood, which could be are used for removing wind, dampness, heat, deficiency and stasis.

At the time of the second diagnosis, the ailments had been relieved, and the Yingfen-heat had been removed, while there remained some swelling and pain in the joint muscles, as well as coughing and expectoration. The syndrome differentiation was dampness and heat blocking the meridians, impaired dispersion of the lung-qi and phlegm-dampness accumulation. Therefore, a prepared product for removing the wind and clearing Yingfen-heat was applied, while ephedra was used to promote the dispersing function of the lung and to relieve the coughing, the root bark of white mulberry was used to purge pathogenic fire from the lung and to promote diuresis, white mustard seed and pinellinae ternata were used for reducing the phlegm, and asters and coltsfoot flower were used to relieve the coughing.

At the time of the third diagnosis, the swelling and pain of the patient's joints had disappeared, but there remained some coughing and expectoration, as well as some shortness of breath and chest tightness. At this time, the pulse condition had changed from a soft pulse to a fine and slippery

pulse. With the development of the disease, the deficiency in origin became obvious: "the spleen is the source of the production of phlegm, and the lung is the reservoir of phlegm." Therefore, the patient was treated with a modified Liujunzi decoction, tonifying the lung and spleen on the basis of eliminating the dampness and addressing the phlegm to eliminate the source of the phlegm dampness.

The importance of interior and exterior syndromes differentiation in disease location according to syndrome differentiation of eight principles

For this patient mainly with exterior syndrome, attention was paid to the treatment of the exterior syndrome from the beginning, which was the key to success. Through clinical observation, the disease or a certain stage is generally found to exhibit an exterior syndrome. However, when diagnosing and treating diseases, many people neglect their exterior syndrome and do not understand its nature, causing pathogens to penetrate deep into the body layer by layer, resulting in chronic and difficult-to-treat diseases. In the process of syndrome differentiation and treatment of disease, it is vital important to clarify what is the cause and internal pathogenesis of the disease and where the disease is located. If the patient exhibited cold and heat features, the cause of his disease could be divided into Yin and Yang. The disease location or pathogenesis also could be divided into yin and yang when the patients have the features of interior and exterior syndrome or deficiency and excess. Of note, interior and exterior syndrome differentiation is the compendium of the yin and yang of the disease location (Liu, 2010).

Traditional Chinese Medicine Diagnostics (Li, 2017) defines exterior syndrome as follows: 'The initial stage of six evil qi, epidemic disease and other evil qi invading the body through the skin, mouth and nose...the syndrome mainly manifests the new onset of aversion to cold and fever'.

The differentiation of exterior and interior syndromes is mainly based on specific clinical manifestations. However, this method cannot fully reflect the connotations of TCM exterior syndrome, with various problems emerging, such as the narrowness and limitation of the concept of the exterior syndrome. For example, in terms of arthralgia disease, spasm, and malaria, the exterior syndrome may dominate at a certain stage of the disease, but these conditions are not fully reflected in the concept of the exterior syndrome (Liu *et al.*, 2014; Fang *et al.*, 2020). However, with the academic development, medical professionals have redefined

the concept of the exterior syndrome, with Professor Xiangru Xiao defining it as a clinical syndrome characterized by aversion to cold that is caused by cold evil invading the muscle surface and encircling the wei qi (Fang *et al.*, 2020). Elsewhere, Yougen Lou distinguishes the exterior syndrome in hierarchical terms, believing that the "exterior" in the term exterior syndrome indicates the concept of "shallow, deep, exterior and interior" in the syndrome differentiation of eight principles (Lou & Tong, 2006). Meanwhile, Professor Yingfeng Liu defines exterior syndrome in terms of an umbrella term for the diseases around the human body caused by exogenous pathogenic factors, including "skin and hair, muscle, orifices, meridians, blood vessels, muscles and bones" (Liu *et al.*, 2014). In the *Dictionary of Traditional Chinese Medicine*, the note on "exterior" is as follows: "appearance, superficial or slight, is relative to the inside (Li *et al.*, 2004; Zeng *et al.*, 2022; Wei *et al.*, 2021; Wei *et al.*, 2022). For example, the skin, muscles, and collaterals of the human body are external, belonging to the exterior." It can be argued that when exogenous pathogenic factors invade the body, the syndrome of the conflict between the vital qi and the pathogenic qi in the above sites can be termed "exterior syndrome." As Professor Yuejun Zhou explains, the exterior syndrome is a kind of syndrome wherein evil qi comes from the outside and invades the body, resulting in the competition between vital qi and the pathogenic qi in the skin, muscles, orifices, meridians, joints, and other tissues, which is regarded as the main contradiction of the disease (Fang *et al.*, 2020). According to the classification of above - mentioned medical doctor for exterior syndrome, we proposed that exterior syndrome is the symptoms induced by struggling between vital qi and pathogenic factors in various location such as skin, hair, muscles, striae, meridians and bones after pathogenic factors attacking the body.

Additionally, we should give attention to distinguishing interior and exterior syndromes from exterior syndromes of patients in clinical practice. For example, superficial symptoms of exterior syndrome mean that the disease location located at skin, hair, striae and muscle, which should be treated by resolving the flesh, sweating and opening the striae. Besides, interior symptoms of exterior syndrome indicated that the location of disease located at bones and muscles, meridian, and orifice, which were suggested to intervened by the strategies of dredging meridian, releasing orifices and

regulating the function of body (Liu, 2010).

The patient in this case developed arthralgia due to dampness and heat, with the disease pertaining to the exterior and interior of the hand-foot Taiyin, and mainly inclined toward exterior syndrome and mainly located in the meridians. When the wind, damp, and heat pathogenic factors invade the muscle surface, the primary means of eliminating any pathogenic factors involves penetrating the surface. However, when the meridians are the dominant disease sites, the core of the disease location lies in the meridians between the muscle surface and the internal organs, and simply using the method of warding the wind on the surface and dispersing the dampness of the internal organs cannot effectively remove the diseases and pathogenic factors remaining in the meridians. Therefore, the prepared medicine was used to clear the dampness and heat the evil qi that was mainly located in the exterior and the meridians, as well as to remove the dampness of the meridians and enhance the function of eliminating the arthralgia. In addition, the patient developed skin erythema nodosum, suggesting that the damp and heat pathogenic factors had spread to the Yingfen, which called for appropriately adding herbs for clearing the Yingfen.

SUMMARY

This case study involved a patient with acute sarcoidosis LS. On undergoing Western medicinal treatment, the patient was treated with antipyretic analgesics and glucocorticoids; however, the symptom control remained unsatisfactory, and the condition was exacerbated. Meanwhile, on undergoing TCM treatment, after one decoction, the fever had subsided, after two decoctions, the patient could walk independently, and after five decoctions, the erythema had disappeared, the effect was both excellent and rapid, and the patient experienced no recurrence during the six-month follow-up period. This was mainly due to the accurate syndrome differentiation, the clear targets, and an accurate grasp of the core etiology and pathogenesis, reflecting the significant advantages of TCM in emergency treatment. This case presents the first clinical report of acute sarcoidosis LS treated with TCM. However, the related study of applying Chinese medical formula for treating LS was still in the preliminary exploration stage, more exploration such as applying large-scale and multi-center clinical research to verifying the efficacy of the treatment needs to be carried out in further work.

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