



A child with Kawasaki disease successfully treated with Chinese herbal medicine: A case report with 12-month follow up



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ARTICLE INFO

Keywords:

Kawasaki disease
Chinese herbal medicine
Case report

ABSTRACT

Introduction: Kawasaki disease (KD) is an acute febrile and eruptive disease with systemic vasculitis of unknown etiology presenting predominantly in early childhood, most commonly in those under 5 years old. Although KD has been reported in almost all populations, it is especially common in North East Asia such as Japan, Korea and Taiwan which has the highest incidence worldwide that in contrast to the US, Europe and Australia. It is reported that more than 1 in 100 Japanese have had KD by 12 years of age. KD is a potentially life-threatening condition because it can cause serious pediatric-acquired heart disease such as asymptomatic coronary artery ectasia or an aneurysm. Intravenous immunoglobulin (IVIG) is a routine and effective treatment for KD and significantly reduces risk of coronary artery abnormalities during the acute phase of illness from approximately 15%–25% to 5%–8%. In spite of its effectiveness, some patient do not respond to this therapy and still develop coronary aneurysms. Chinese herbal medicine (CHM) as a therapy alone for KD was rare. The success of this patient with KD treated by CHM provided a new way of thinking for harmonizing Eastern-Western drug for KD and the potential utilization of CHM as a source of new drugs could be an alternative.

Clinical features and outcome: A 17 month-old boy suffered from persistent fever, poor appetite, vomiting diarrhea, slight cough, running nose and throat congestion for 2 days and was diagnosed with an upper respiratory infection. He had taken cefprozil suspension plus anka Huangmin 2 days for his symptoms before his final diagnosis of KD, but it was unsuccessful. He continued to have a fever, in addition, he presented with bilateral bulbar conjunctival congestion without exudate, labial and lingual erythema and was diagnosed with KD before his first CHM visit, his parents refused to continue receiving Western medicine. Therefore, his parents sought CHM for further intervention. His symptoms subsided, and the blood tests, electrocardiogram (ECG) and echocardiographies show completely normal after regular therapy with Xiao Chai Hu Tang (小柴胡汤) combined with Bu Yang Huan Wu Tang (补阳还五汤), Huang Lian Jie Du Tang (黄连解毒汤), and Wu Ling San (五苓散) for approximately 21 days. Neither complications nor side-effects were noted during the CHM treatment.

Conclusions: In this case, CHM may be an effective alternative therapy for the treatment of KD, and furthermore, may also be applied as an option to salvage failed intravenous immunoglobulin procedures. Further controlled trials are warranted to determine whether this is an effective treatment option for other cases of KD.

1. Introduction

Kawasaki disease (KD) is an acute systemic vasculitis most commonly seen in infancy and childhood below 5 years of age. KD is a potentially life-threatening condition because it can cause pediatric-acquired heart disease particularly coronary artery aneurysms [1]. Although the etiology of KD is unknown, the widely accepted consensus is

that one or more environmental triggers especially microbial origin cause genetically susceptible individual's abnormal and exaggerated inflammatory response [2,3]. Diagnosis of KD is based on clinical manifestation including fever persisting for at least 5 days in addition to 4 of the following 5 principal clinical features as defined by Japanese Ministry of Health (JMoH): bilateral bulbar conjunctival congestion without exudate, changes in peripheral extremities (Acute phase:

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<https://doi.org/10.1016/j.eujim.2019.02.006>

Received 4 January 2019; Received in revised form 17 February 2019; Accepted 20 February 2019

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redding of palms and soles, indurative edema; Convalescent phase: membranous desquamation from fingertips.), polymorphous exanthema, changes of lips and oral cavity (Redding of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosa.) and acute nonpurulent cervical lymphadenopathy [4]. Intravenous immunoglobulin (IVIG) is a routine and effective treatment for KD and significantly reduces risk of coronary artery abnormalities during the acute phase of illness from approximately 15%–25% to 5%–8%. [4,5]. However, some patients suffer from KD do not respond to IVIG and coronary aneurysms are still developed [4,5]. Although adding steroids to the 2nd round of IVIG has proven to be the optimal therapy for IVIG non-responsive patients, some patients are still resistant to the second line treatment. For those who present a lack of response to the first and second step of treatment, other approaches have been described such as anakinra, cyclosporine, or infliximab [5,6]. However, there have been no reports describing the role of CHM in the treatment of KD. This case report deals with KD in a boy who was treated solely with CHM. After approximately 21 days of CHM treatment, all symptoms and signs were resolved and all examinations were normal.

2. Case report

A 17-month-old boy presented with persistent fever for 2 days, poor appetite, vomiting diarrhea, slight cough, running nose, and throat congestion. He was taken to the Seventh hospital of Ningbo on April 29, 2017. He was being treated with oral cefprozil suspension + ankahuangmin (each pack of ankahuangmin contains 125 mg of paracetamol, 7.5 mg of caffeine, 5 mg of artificial cow-bezoar and 0.5 mg of chlorphenamine maleate) prescribed by the Western medical physician for an upper respiratory infection. He continued to have a fever after medications, in addition, he presented with bilateral bulbar conjunctival congestion without exudate, labial and lingual erythema and he was taken to the Seventh hospital of Ningbo again in the morning on April 30, 2017. Blood tests showed reduced hemoglobin (117 g/L), high white blood cells (15.2×10^9 count/L) and elevated C-reactive protein (CRP) level (56.3 mg/L), as shown in Table 1. The diagnosis of KD was made by the Western medical physician, and hospitalization was suggested for the patient's parents. But the patient's parents do not want to let such a small child hospitalized, and sought CHM treatment for further management on May 1, 2017. Patient's parents deny family history of KD.

Upon examination, the patient presented with fever for a total of 5 days, throat congestion, bilateral bulbar conjunctival congestion without exudate, labial and lingual erythema (strawberry tongue), nonpurulent cervical lymphadenopathy, redding of palms and soles, polymorphous erythema over the trunk and the right axilla, swollen hands and feet, poor appetite, diarrhea, slight cough, running nose, irritability and slippery and rapid pulse (Fig. 1 showed partial clinical features of this patient). We prescribed Xiao Chai Hu Tang combined with Bu Yang Huan Wu Tang, Huang Lian Jie Du Tang, and Wu Ling San, Two times daily dosage by oral administration during the course of treatment. All of Chinese herbal medicine are from Good Manufacturing Practice (GMP)-certified pharmaceutical company called Beijing Tongrentang. Throughout the course of the entire CHM treatment, the

Table 1
The blood test data before and after CHM treatment.

Date	Pre-TCM treatment April 30, 2017	Post-TCM treatment May 31, 2017	1 st follow-up August 6, 2017
WBC White blood cell count	15.2	11.4	9.8
Neutrophil %	72.7	37.5	42.4
Hyper-sensitive C-reactive protein	56.3	2.0	2.0

patient's parents denied receiving any other medication for KD.

The prescription of Chinese medicinal herbs included the compositions listed in Table 2. The preparation and ingestion of the decoction were as follows: for the first decoction, the herbal medicine was soaked for half an hour and approximately four cups (700 ml) of cold water were added to the herbal mixture, which was then boiled for approximately 50 min to reduce the volume to about 150 ml. This decoction was taken in each morning. The remaining herbal mixture was used for making the second decoction which was taken in each afternoon: this was prepared using 500 ml of cold water, boiled for approximately 30 min to reduce the volume to about 100 ml.

Fever subsided gradually from May 2, 2017, and gastrointestinal and respiratory symptom showed improvement, with polymorphous erythema over the trunk receded. In addition, the symptoms of labial and lingual erythema, erythema of the palms and the soles, and the quality of sleep improved gradually. Bilateral bulbar conjunctival congestion receded on May 4, 2017, but other symptoms remained. Polymorphous erythema of the right axilla and the bilateral eyes, and erythema of lips remained on May 5, 2017, but other symptoms receded. The child became high-spirited again started playing with other children and requesting snacks on May 7, 2017, and erythema of lips and polymorphous erythema of the bilateral eyes receded. Desquamation on right axilla and tips of fingers and toes appeared on May 9, 2017, and subsided gradually until May 21, 2017. (Figs. 2 and 3 showed partial clinical features during sub-acute phase)

No relapses appeared after the discontinuation of the CHM. Subsequent blood tests, electrocardiogram (ECG) and echocardiographies on May 31, 2017 and August 6, 2017 were normal. The echocardiographies revealed the z-scores of the left coronary artery and right coronary artery were 2.17 and 1.41 on May 31, 2017, and 1.88 and 1.5 on August 6, 2017. There was no evidence of coronary artery dilatation, ischemic change, or other abnormal findings. ECG also showed a normal sinus rhythm. The patient did not experience any side effects or complications during or after the use of the Chinese herbal medicine. Since August last year up until now, monthly telephone follow-ups with the patient's parents have indicated child is growing healthily. We have obtained written informed consent from the patient's parents for publication of this case in print form for scientific purposes.

3. Discussion

The diagnosis for this child was confirmed as KD from his clinical manifestations and blood tests. Instead of using conventional medical treatment procedures, the patient's parents chose treatment with CHM. In fact, KD doesn't have a direct and equivalent diagnosis in TCM. We considered the KD was belong to the category of epidemic febrile disease, which can be caused by exogenous pathogenic heat and toxin. The pathogenic toxin is trapped inside and the positive Qi fights with it, so there is fever. When the pathogenic toxin lies in skin and mucosa, and combats with Qi and blood, which causing skin flushing, rash and swelling. When the pathogenic toxin further into the blood, the rash merges into purple patches. The pathogenic toxin and heat burns liquid into phlegm, coagulates the meridians and collaterals, and can form phlegm nucleus. Besides, the pathogenic toxin and heat is the most vulnerable to damage Yin, so the tongue produces prickles (like bayberry), vermilion of the lip and chapped, large scale desquamation in the tips of fingers and toes in the later stage. The pathogenic toxin and heat can further injury the Heart-qi which lead to cardiovascular injury.

Hence, we chose Huang Lian Jie Du Tang and Xiao Chai Hu Tang to eliminate the pathogenic heat from the blood, resolving toxin and transforming macules. On the other hand, Bu Yang Huan Wu Tang and Wu Ling San were used to tonify Qi, activate blood circulation and clear damp and promote diuresis, which was aimed to prevent the potential heart damage caused by the pathogenic heat and toxin. While, from the perspective of modern medicine, the patient's symptoms could be



Fig. 1. Partial clinical features of this KD patient. A1 and A2, polymorphous erythema over the trunk. B1 and B2, labial erythema. C, right axilla erythema. D, palmar erythema. E, swollen hand.

divided into three parts including disorder in body temperature regulation, inflammatory reaction of mucosa and vessels, and potential cardiovascular lesion in the process of KD.

The Xiao Chai Hu Tang balances the temperature regulating center to bring down fevers and enhance the body's resistance to disease [7]. The pyrogen effect on the macrophages and monocytes of human body produces IL-1 β , IL-6, TNF- α , etc., these cytokines act on the temperature regulating center of the hypothalamus of the host, which further increasing heat production and temperature through a series of signal transduction and finally lead to fever [8,9,10,11,12]. *Bupleurum chinense* (Chai Hu) has been reported to have anti-inflammatory, antioxidant, antipyretic, analgesic, anti-fibrotic and immunomodulatory effect [13]. Some research reported that *Bupleurum chinense* significantly reduced the body temperature and content of IL-1 β , IL-6, TNF- α in serum induced by lipopolysaccharide (LPS) among fever rat models [7].

The Huang Lian Jie Du Tang inhibits the formation of inflammatory factors and prevents thrombosis [14,15]. *Berberine* and *baicalein* are the

main active ingredients of Huan Lian Jie Du Tang, which significantly reduced TNF- α , IL-6 and COX-2 production in peritoneal macrophages induced by LPS. This observation suggested that the anti-inflammatory effect of Huang Lian Jie Du Tang mainly through inhibiting the production of inflammatory cytokines including TNF- α , IL-6 and COX-2 [16].

The Bu Yang Huan Wu Tang prevents cardiovascular lesion through promoting angiogenesis, improving cardiovascular circulation, and enhancing cardiovascular tissue self-repair after injury [17–19]. *Astragaloside IV* (AST IV), one of the main active ingredients in *Astragalus membranaceus*, has been effectively used to treat coronary artery disease, heart failure, viral myocarditis, and other cardiovascular diseases. The abilities of AST IV in scavenging oxygen free radicals, the regulation of calcium homeostasis, anti-oxidative effect with prevention of mitochondrial damage are associated with its various functions including vasodilating effect, protecting the vascular endothelial cells, anti-inflammatory effect, antiviral effect, and positive inotropism [20].

Lastly, the Wu Ling San acts as a diuretic to reduce the preload of

Table 2
Compositions associated with possible mechanisms.

Chinese name	Composition in Chinese name	Composition in Latin name	Daily dosage (g)	Mechanism
Xiao Chai Hu Tang	Chaihu	Bupleurum chinense	25	· Bupleurum chinense
	Fabanxia	Pinellia ternata	5	1. anti-inflammatory effect
	Dangshen	Codonopsis pilosula	5	2. immunomodulatory effect
	Shenggancao	Radix glycyrrhizae	5	3. antipyretic and analgesic effect
	Huangqin	Radix scutellariae	10	4. inhibition of IL-1 β , IL-6, TNF- α
	Shengjiang	Fresh ginger	5	5. anti-fibrotic
	Dazao	Fructus jujubae	5	
Huang Lian Jie Du Tang	Huanglian	Coptidis rhizoma	8	· <i>Coptidis rhizoma and Radix scutellariae</i>
	Dahuang	Rheum officinale	8	1. inhibition the production of inflammatory cytokines including TNF- α , IL-6 and COX-2
	Zhizi	Gardenia jasminoides ellis	8	
Bu Yang Huan Wu Tang	Danggui	Angelica sinensis	8	· <i>Astragalus membranaceus</i>
	Chuanxiong	Ligusticum wallichii	8	1. promoting angiogenesis
	Shengdi	Radix rehmanniae	10	2. improving cardiovascular circulation
	Baishao	Radix paeoniae alba	8	3. enhancing cardiovascular tissue self-repair after injury
	Huangqi	Astragalus membranaceus	40	4. protecting the vascular endothelial cells
Wu Ling San	Guizhi	Cinnamomum cassia presl	7	5. anti-inflammatory effect
	Baizhu	Atractylodes macrocephala koidz	5	6. antiviral effect
	Fuling	Poria cocos wolf	15	7. positive inotropism
		Poria cocos wolf		1. diuretic effect

the heart. CHM targeting the skin were added based on the original prescription, including Jingjiesui, Fangfeng, Baizhi, Lianqiao and Tufuling in the sub-acute phase of KD. The combination of these four herbs can strengthen the capillary resistance and antibacterial action, reduce the inflammatory exudation, and repair skin damage [21]. A case report showed that interleukin-1 receptor antagonists (IL-1RA, anakinra) was successfully treated for resistant KD [5]. Lee et al. suggested that IL-1 receptor-deficient mice were protected from induced coronary lesions in a mouse model of KD, and induced coronary lesions were prevented by daily injections of the IL-1RA in normal mice [22].

The combined action of each herb in this Chinese herbal prescription can inhibit the formation of inflammatory factors such as IL-1, TNF- α , and PGE2 [7,15,17,18,23,24]. This observation may explain the possible therapeutic mechanisms of the CHM used and its effectiveness in the management of this case of KD. KD was initially believed to be a

self-limiting illness, but was subsequently recognized to result in potentially fatal changes to the coronary arteries in up to a quarter of untreated KD [24]. This case suggests that the 3 weeks of CHM improved recovery and superior to conventional IVIG treatment for KD. The patient's parents are willing to share their perspective on the treatments their child receive.

Firstly, the patient's fever remained after taking cefprozil for suspension plus ankahuangmin and polymorphous erythema over the trunk with bulbar conjunctive congestion appeared during the period of taking this medicine, but fever and polymorphous erythema over the trunk receded after a day of taking CHM. Secondly, the course of this treatment with CHM was significantly shorter than that of routine treatment (IVIG combined with acetylsalicylic acid) for KD. In routine treatment for KD, acetylsalicylic acid is administered every 6 h during the acute phase of illness, with a total daily dose of 30–50 mg kg⁻¹ d⁻¹

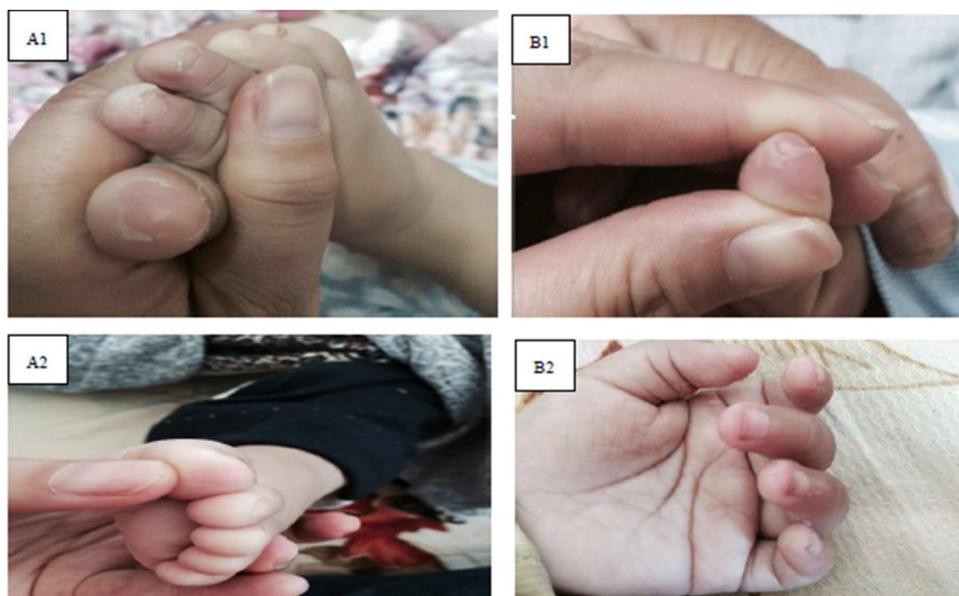


Fig. 2. Desquamation on tips of fingers and toes.

A1 showed the tips of toes of this patient started to desquamate. A2 showed the skin of toes of this patient returned to normal. B1 showed the tips of fingers of this patient started to desquamate. B2 showed the skin of fingers of this patient returned to normal.



Fig. 3. Desquamation of the right axilla of this patient.
A to H showed the desquamation process of the right axilla of this patient with KD.

in Japan and Western Europe and $80\text{--}100\text{ mg kg}^{-1}\text{ d}^{-1}$ in the United States. When high-dose acetylsalicylic acid is discontinued, low-dose acetylsalicylic acid ($3\text{--}5\text{ mg kg}^{-1}\text{ d}^{-1}$) is begun and continued until the patient has no evidence of coronary changes by 6–8 weeks after onset of illness [25–28]. While, the course of this treatment with Chinese herbal medicine in this case was 3 weeks.

In addition, the clinical course of KD can be divided into three phases [27,28]. The acute febrile phase lasts for approximately 10 days, which is characterized by fever, conjunctival congestion, erythema, swelling of the hands and feet and erythema of the oral mucosa and lips [27,28]. In this case, the acute phase of this patient lasted from onset of fever until 6 days. In addition, polymorphous erythema over the trunk

receded, gastrointestinal symptom and irritability showed improvement at 6 days after the onset of fever. The subacute phase lasts from day 10 to approximately 6 weeks after the onset of fever, and it begins with fever, rash, and lymphadenopathy resolve, but irritability, anorexia, and conjunctival congestion persist [26–28]. Desquamation of tips of the fingers and toes and thrombocytosis are seen during the subacute phase [27,28]. In this case, the subacute phase of this KD patient lasted from day 6 to approximately 3 weeks. The convalescent phase of KD is from 6 weeks onwards.

On the whole, the course of this patient with KD after taking CHM was significantly shorter than the general course of KD, which also can rule out the possibility of spontaneous recovery of this patient. A repeat

ECG and echocardiography was obtained at 5 weeks following the onset, and again at 14 weeks following the onset, two examinations were both normal. There is no significant evidence to indicate that long-term cardiac complications will develop in those with normal coronary arteries at 2 months after the onset of KD [27,28]. These observations suggested that 3 weeks' treatment of CHM contributed to the recovery.

This is a one-patient case report so that is inadequate in the case number. Thus, we need more cases and experiences to know whether this formula is really applicable to common KD population. Second, we use combination of herbs in clinical practice, so it is difficult for us to understand their effective contribution to relieve the underlying situation [29]. Hence, we reviewed many original articles to clarify the possible mechanisms of herbs we used in this case. We did not test liver and renal function for this case. Liver and renal function were not tested, so we are uncertain whether the three-week treatment caused any potential damage to the child's liver or kidney function and this is a limitation for this case report. Also the cardiac ultrasound in the acute phase was not conducted for this patient, although the final cardiac ultrasound examination was normal.

In conclusion, we claim that Xiao Chai Hu Tang combined with Bu Yang Huan Wu Tang, Huang Lian Jie Du Tang, and Wu Ling San was a safe and effective prescription for KD in this case. It may be applied as an alternative treatment option, or a potential method to salvage IVIG procedures in patients with KD. Further studies such as control trials are warranted to determine whether this regiment of CHM is an effective treatment option for other cases of KD.

Conflict of interest

All authors declare that there are no conflicts of interest.

Authors' contribution

All research done by the authors. ZLB conceptualized and designed the study, drafted the initial manuscript, obtained the patient consent form and approved the final manuscript as submitted; LLX and LJP carried out the initial analyses, helped with the resolution of the clinical case, reviewed and revised the manuscript, and approved the final manuscript as submitted; HYP helped with the resolution of the clinical case and reviewed and revised the manuscript and approved the final manuscript as submitted; LXZ helped with the resolution of the clinical case and reviewed and revised the manuscript and approved the final manuscript as submitted. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Financial support

No.

Acknowledgements

All authors would like to express their gratitude to the kind advice provided by Dr. Fang Zhishan, Director of Zhongdetang TCM clinic of Dongguan, China, for treating this case of KD. The authors would also like to thank the patient's parents, for their support of allowing us to report on this case.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.eujim.2019.02.006>.

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