

Case Report

Treatment of fever with traditional Chinese medicine according to Zheng on cancer patients (based on case reports)

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ABSTRACT

Fever in cancer patients is often due to the following causes: evil qi and toxicity stagnancy, disorders of qi and blood, deficiencies of zang and fu organs, and the disorder of yin and yang. The treatments given to cancer patients with a fever are according to five: (a) Excessive inner heat and toxicants: remove heat and the toxicant, induce purgation. We use Cheng-Qi-Tang plus Qing-Wen-Bai-Du-Yin. (b) Tangle of damp and heat, and qi stagnancy: remove damp and heat, smooth the qi channel. We use Gan-Lu-Xiao-Du-Dan or San-Ren-Tang. (c) Obvious blood and heat stagnancy: remove heat and blood stasis. We use Xue-Fu-Zhu-Yu-Tang. (d) Deficiency of spleen qi, inner heat caused by a yin deficiency: nourish spleen qi and yin to remove the inner heat. We use Bu-Zhong-Yi-Qi-Tang or Xiao-Jian-Zhong-Tang. (e) Prominent yin deficiency and hectic fever: replenish yin and remove inner heat. We use Qing-Hao-Bie-Jia-Tang or Chai-Qian-Mei-Lian-San. The pathogenesis of fever in cancer patients is complicated. We can see both deficiency and excess in one differentiation. Therefore, we must make sure of it, then we can get the most effective treatment.

Keywords traditional Chinese medicine, fever, zheng, cancer, qi

INTRODUCTION

Fever is a common symptom in cancer. It is divided into two types: infectious and non-infectious fevers. An infectious fever is caused by viruses, bacteria, fungus etc (Rasool Hassan et al., 2010). A non-infectious fever is caused by the mediators of inflammation or toxic producers while the tumor tissue is quickly being destroyed and dissolved (Toussaint et al., 2006). Part of chemotherapeutics can lead to a non-infectious fever, such as bleomycin, L-asparaginase and mitomycin (Mangiarotti et al., 2008). Some cytokines such as interferon, IL-2, granulocyte colony-stimulating factor can lead to a non-infectious fever, and radiotherapy can also lead to a non-infectious fever (Toma et al., 2010).

Fever in cancer patients belongs to internal fever, and it is divided into deficient and excess Zheng (Seki et al., 2005). Deficiency Zheng is caused by long term evil qi which leads to deficient qi, yin, zang and fu organs. Excess Zheng is caused by the stagnancy of qi and blood, gathering of phlegm and dampness. Follow toxicant and fire can't be discharged. The battle of evil qi and healthy qi creates the imbalance of yin and yang, then a fever occurs (Yuan et al., 2011).

DIFFERENTIATIONS AND CASE REPORTS

There are four kinds of treatment by differentiations as following, and each differentiation was explained with a case report.

Remove heat and toxicant, and make purgation

The pathogenesis of this differentiation is excessive heat and toxicant. It's often seen in the early period of cancer or in young patients. The main symptoms include: hyperpyrexia or remittent fever, bitter taste in the mouth, dry pharynx, constipation, scanty dark urine, a red tongue with a thick, yellow and dry coating (Fig. 1), and a strong and rapid pulse (Sun et al., 2010).

The principle of treatment is to remove heat and the toxicant, and induce purgation. We use Cheng-Qi-Tang to remove heat and induce purgation, and at the same time use Qing-Wen-Bai-Du-Yin to remove heat and the toxicant in the Triple Warmer and to cool the blood heat (Ge et al., 2011). Sometimes, we add *Flos Lonicerae*, *Wild Chrysanthemum* and *Hedyotis Diffusa* to strengthen the removal of heat and the toxicant. The heavy cases should be treated with additional An-Gong-Niu-Huang-Wan.

Case 1 was a 78-year-old female who was diagnosed with lung cancer in the lower right side five months earlier. She also was diagnosed with intracranial and bony metastatic cancer. She received treatment of gamma knife and thirty-three times' radiotherapy. She had a history of pulmonary tuberculosis for ten years. The main symptoms were: (a) Fever: Highest temperature was 39.1°C in recent one week. (b) Cough: Sputum was white and viscous. (c) Pain of the bilateral lower limbs and hips. She was already being treated with anti-inflammation treatment and an external application of indometacin in the anus. It showed temporal pyretolysis. At the

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Fig. 1. Red tongue with thick, yellow and dry coating.

same time, she had dry mouth and dry and hard stools every five days. The tongue was dark red with a yellow and thick coating, but with a thinner coating in the middle of the tongue. The pulse was taut and rapid.

The root of pathogenesis was the deficiencies of the liver, kidneys, qi and yin, and the appearance was internal excessive heat and toxicant. Therefore, we first gave the prescription to remove heat and the toxicant using the herbs as followed :

Radix et Rhizome Rhei (6 g, decocted later), *Fructus Aurantii Immaturus* (10 g), Stir-baked *Radix Scutellariae Baicalensis* (10 g), Stir-baked *Fructus Gradeniae* (10 g), *Radix Scrophulariae* (10 g), *Cortex Mori Albae Radicis* (15 g), *Fructus Forsythiae Suspensae* (10 g), *Rhizoma Typhonii Gigantei* (10 g), *Arisaema Cum Bile* (10 g), *Bombyx Batryticatus* (10 g), *Scorpio* (6 g), *Nidus Vespaee* (10 g), *Pseudobulbus Cremastrae Seu Pleiones* (15 g), *Herba Euphorbiae Helioscopiae* (15 g), *Rhizome Curcumae Longae* (10 g), *Yew* (20 g), *Speranskia Tuberculata* (15 g), *Glycyrrhiza Uralensis Fisch* (5 g). That was each day's dosage. Two days later, the patient defecated everyday.

Then we gave the prescription to replenish qi and yin. That meant replacing *Radix et Rhizome Rhei* by prepared *Radix et Rhizome Rhei* (6 g), and adding *Radix Adenophorae Tetraphyllae* (15 g), *Radix Glehniae* (15 g), *Radix et Rhizoma Cynanchi Atrati* (10 g). Two weeks later the temperature was below 37.5°C.

Remove heat and damp, smooth activities of qi

This kind of differentiation is often seen in digestive system cancer such as hepatoma, pancreatic cancer and gastric cancer (Fang et al., 2011). The pathogenesis of this differentiation is internal stagnancy of heat and dampness. The main symptoms include: (a) Continuing fever, especially a higher temperature post meridiem. (b) Distention feelings in the chest and stomach areas, poor appetite, fatigue and heavy sense of body and head, cutaneous edema. (c) Swollen tongue with a yellow and greasy coating (Fig. 2), and slippery and rapid pulse (Ge and Xu, 2011).

The treatment could remove heat and dampness, and smooth activities of qi (Brusa et al., 2009). We can give the prescription as Gan-Lu-Xiao-Du-Dan or San-Ren-Tang. If the patient has an obvious bitter taste in the mouth, we can add *Radix Gentianae*, *Radix Curcumae Wenyujin* and *Radix Bupleuri Chinensis* to remove the heat and dampness of the liver and gall bladder (Willimott et al., 2009).

Case 2 was a 76-year-old male who had a history of chemotherapy after the operation of descending colon cancer. The main symptoms included: (a) Fever ten days earlier, temperature fluctuating between 37.1 ~ 37.8°C. (b) Itching sense of skin, dry mouth, little drinking, common appetite,



Fig. 2. Swollen tongue with yellow and greasy coating.

loose stools, and yellow urine. (c) Dark tongue with yellow, thick and greasy coating, and a taut, slippery and rapid pulse. The pathogenesis was interties of heat and dampness in the intestines and disorder of qi activity. So we gave the prescription to remove heat and dampness and smooth the activities of qi. The herbs as follow: Stir-baked *Radix Scutellariae* (10 g) (Mu et al., 2009), *Herba Artemisiae Annuae* (15 g, decocted later), *Semen Plantaginis* (15 g, wrapped), *Semen Coicis* (15 g), *Polyporus* (15 g), *Radix Sophorae Flavescentis* (15 g), *Herba Hedyotidis* (20 g), *Herba Scutellariae Barbatae* (20 g), *Radix Stemmactanthae Uniflori* (15 g), *Fructus Akebiae* (12 g), *Fructus Amomi Rotundus* (6 g), Stir-baked *Massa Medicata Fermentata* (10 g). After one week's treatment, the temperature was normal.

Dissipate the stasis of blood, regulate meridian and remove heat

This kind of differentiation is commonly seen. The pathogenesis of this differentiation is the predominant stasis of blood (Murata et al., 2011). The main symptoms include: (a) Low-grade fever that occurs after noon or during the night. (b) Immovable pain in the area of cancer, dark face. (c) Dark tongue with petechia, or thickening collaterals under the tongue (Fig. 3). We can use Xue-Fu-Zhu-Yu-Tang (Lin et al., 2012). This prescription could impulse the activity of qi while promoting blood circulation. It also can nourish healthy qi while activating blood circulation. Then fever pyretolysis can be seen. *Cortex Moutan* and *Radix et Rhizoma Cynanchi Atrati* should be added especially for fever (Xing et al., 2010).

Case 3 was a 43-year-old male who suffered the operation of the right part of liver and gallbladder because of bile duct cancer one month earlier. Severe right flank pain sensation after the operation didn't allow him to lie on his back. Draining in the tube was increasing from the peritoneal cavity. He took the 5- fluorouracil orally. His main symptoms were (a) Fever especially in the night up to 38.5°C in recent half a month. (b) Severe right flank pain sensations often made him wake up during the night. Uncomfortable sense of the whole body, slim shape with yellow face, rugitus, dry and bitter taste in the mouth, poor sleep. (c) Dark tongue with a slight yellow coating, taut, slippery and rapid pulse. The pathogenesis was stagnancy of qi and blood, tangling of heat and damp in the liver and gall bladder. The principle of treatment was to dissipate the stasis of the blood and qi, to remove heat and dampness in the liver and gall bladder. The prescription of herbs were: Stir-baked *Radix Bupleuri* with Vinegar (5 g), *Radix Paeoniae Rubra* (10 g), *Rhizoma Curcumae Phaeocaulis* (10 g), *Radix Curcumae* (10 g), Shi-Xiao-San (15 g, wrapped), *Cortex Moutan* (10 g), *Radix Salviae Miltiorrhizae* (10 g), *Fructus Citri Reticulatae Immaturus* (10 g), *Rhizoma Corydalis Yanhusuo* (15 g), *Aspongopus* (5 g), *Fructus Akebiae* (10 g),



Fig. 3. Dark tongue with petechia, or thickening collaterals under the tongue.

Rhizoma Cyperi (10 g), *Longcoronate Sage Root* (20 g), *Endothelium Coreneum Gigeriae Galli* (10 g), *Oxalis Articulata Subsp Rubra* (15 g), *Herba Lysimachiae* (20 g).

Changes were seen after one week's treatment: (a) Fever was alleviated, maximal temperature was 37.5°C. (b) Right flank painful sensation was eased. He could lie on the back. (c) Less draining in the tube.

We added *Herba Abri Cantoniensis* (20 g), *Olibanum* (5 g) per day. The temperature was normal one week later after that.

Nourish qi of middle warmer, remove heat with sweet and warm methods

This kind of differentiation is often seen after operation of digestive cancer such as esophageal cancer, gastric cardia cancer and colon cancer (Li et al., 2006). Sometimes it's also seen after chemotherapy (Liu et al., 2009). The pathogenesis of this differentiation is deficiencies of the stomach and spleen. That leads to the low ability of transporting and transforming nutrients from foodstuff. Thus, Yang qi drops into the yin area which causes fever and toxicants and stagnancy tangle in the area.

The main symptoms include: (a) Fluctuating fever or continuous low-grade fever. (b) Fatigue of the whole body, inability to regularly speak with a poor appetite, palpitations, shortness of breath, loose stools having no shape. (c) Swollen and pale tongue with tooth marks (Fig. 4), deep and thin pulse (Saif et al., 2007). The principle of treatment is nourish the qi of the triple warmer, remove heat with sweet and warm methods. We use *Bu-Zhong-Yi-Qi-Tang* (Jeong et al., 2010) or *Xiao-Jian-Zhong-Tang* to lift the spleen's Yang qi to lower the heat in the yin area. Then the fever can disappear.

Case 4 was a 51-year-old female who suffered one operation for squamous cell cancer of the vagina three years earlier, and another operation for an anal colostomy because of rectum infiltration. The main symptoms were: (a) Intermittent fever: 38.0°C for three days twenty days earlier. The fever disappeared without any treatment. Fever occurred again five days later with the same temperature. (b) Painful sensation of the stoma area, and unclear pain of abdomen, fatigue and sleepiness, loose stools occasionally, too dry a mouth to drink water, frequent discharge of little urine. (c) Pale and dark tongue with thin and yellow coating, and a thin pulse.

The pathogenesis was that qi and blood in the triple warmer was too deficient to remove heat, toxicant and stagnancy. The principle of treatment was to nourish qi of the triple warmer, to remove heat with sweet and warm methods accompanied by removing toxicant and stagnancy. The prescription of herbs were: *Radix Pseudostellariae* (10 g), *Radix Codonopsis* (10 g), *Radix Astragali Mongolici* (15 g), *Semen Coicis* (15 g), *Rhizoma Atractylodis Macrocephalae* (10 g), *Radix Angelicae*

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Fig. 4. Swollen and pale tongue with tooth mark.

Sinensis (10 g), *Herba Agrimoniae* (15 g), *Caulis Spatholobi* (15 g), *Fructus Akebiae* (12 g), *Fructus Ligustri Lucidui* (10 g), *Nelumbo Nucifera Gaertn* (15 g), *Herba Hedyotidis* (20 g), *Shi-Xiao-San* (10 g, wrapped), *Herba Scutellariae Barbatae* (20 g). Fever had already lowered when she returned to visit us, and the other symptoms above were lessening.

Directly replenishing yin to remove heat

This kind of differentiation is often seen as follows: (a) In middle/advanced stage of cancer such as lung cancer, nasopharyngeal cancer and esophageal cancer. (b) Aged patients with cancer. (c) After several times' radiotherapy or chemotherapy.

The main symptoms include: (a) Continuous low or medium fever, especially in the afternoon or during the night. (b) Lazy sense and fatigue with four limbs, burning sensation in the extremities, dry feeling in the throat and on the tongue, occasional polydipsia to drink, and poor appetite. (c) Red tongue with cracks and less or no coating (Fig. 5) (Lin et al., 2009), a thin and rapid pulse. The principle of treatment is replenishing yin and qi to remove heat. We use *Qing-Hao-Bie-Jia-Tang* or *Chai-Qian-Mei-Lian-San*. Sometimes we add *Rehmannia Dried Rhizome*, *Cortex Moutan* and *Humulus Scandens* to cool blood to help remove heat.

Case 5 was a 49-year-old male who had accepted chemotherapy and γ -knife treatment because of lung cancer. He got the diagnosis of metastatic in mediastina and hilum of the lung one and a half years earlier. He was found metastatic of the absorbent gland behind the peritoneum and with heavy pleural effusion in the left side forty days earlier. He twice received the treatment of drawing out pleural fluid twice for total of two thousand milliliter. He also suffered from a lung inflammation because of pleural effusion. The main symptoms were: (a) Continuous fever for one month even with using many kinds of antibiotics. The temperature fluctuated between



Fig. 5. Red tongue with cracks and less or no coating.

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37.1 ~ 38.5°C. (b) Severe cough, small white phlegm which was hard to hawk, and feelings of dizziness and fatigue, limited sweating, dry mouth, burning sensation of the palms and feet. (c) Red tongue with less coating, and a taut, thin and rapid pulse. Sputum culture showed the infection of *Bacillus aeruginosus*.

The pathogenesis was the tangle of phlegm and heat, and the loss the qi and yin. The principle of treatment was to replenish yin to remove heat, to dissipate phlegm and clear the heat. The prescription of herbs was: *Radix Bupleuri Chinensis* (10 g), *Radix Peucedani* (10 g), *Rhizome Picrorhizae* (10 g), *Fructus Mume* (4 g), *Radix et Rhizoma Cynanchi Atrati* (15 g), *Radix Pseudostellariae* (15 g), *Radix Asparagi Cochinchinensis* (10 g), *Radix Ophiopogonis Japonica* (10 g), *Rhizoma Anemarrhenae* (15 g), *Herba Euphorbiae Helioscopiae* (15 g), *Carapax Trionycis* (15 g, decocted first), *Cortex Mori Albae Radicis* (15 g), *Nidus Verspae* (10 g), *Herba Houttyniae Cordatae* (30 g).

After one week's treatment, the cough and phlegm lessened although the phlegm was white and sticky. The temperature fluctuated between 37.1 ~ 37.5°C. The burning sensation of the hands and feet was much better. We added *Cortex Lycii Radicis* (15 g), *Herba Humuli Scandentis* (20 g), *Rhizoma Fagopyri Dibotrydis* (15 g). The temperature was normal one week later. The feeling of dry mouth lessened, but the burning sense of the hands and feet and lessened cough and phlegm remained. The treatment was continued.

DISCUSSION

Fever includes infectious and noninfectious reasons. The former means pathogenic microorganisms including bacteria, viruses and fungus. Agranulocytosis after chemotherapy is also an infectious reason. The latter means abundant inflammation mediators or toxic substances from tumor histoclasia and histolysis during the development or treatment of tumors. Inflammation mediators and toxic substances are endogenous pyrogens which stimulate body temperature regulating the center to cause fever. Fever in cancer refers to noninfectious reasons in this paper. Some kind of chemotherapeutics could lead to fever. Cytotoxic drug such as cyclophosphamide and 5-fluorouracil, biologic agent such as IL-2 and IFN- γ , molecular targeted drug such as Iressa® and Gleevec® all could lead to fever.

The western treatment of fever in cancer focuses on etiological factors, for example, if the etiological factor is chemotherapeutics, we reduce the dosage of chemotherapeutics or change chemotherapy programs to treat fever. If the etiological factor is unknown, we give symptomatic treatment such as physical cooling or NSAIDs. COX-2 inhibitors such as celecoxib are sometimes used in fever treatment. But celecoxib has side effects in the gastrointestinal, cardiovascular and hematological systems. Thus it is of limited used because of its toxicity (Fiorucci and Distrutti, 2011).

There are different characteristics in treatment between western medicine and traditional Chinese medicine. Western medicine has a quicker effect at the beginning. But the fever reoccurs easily and there could be more side effects with western medicine. Traditional Chinese medicine takes longer to control the fever, but with less reoccurrence and less side effects. Traditional Chinese medicine, however, has a slower effect at the beginning. So we select the proper method to treat fever in cancer according to the patient's condition.

The study showed that Chinese medicine could reduce the side effects of chemotherapeutics such as nausea, vomiting and bone marrow depression et al. Chemotherapeutics could also be

coordinated with Chinese medicine in antitumor treatment. However, there is no evidence to show that herbs could inhibit a fever in cancer with chemotherapeutics (Cui and Sun, 1987; Liu et al., 1991).

The treatment on fever in cancer with Chinese medicine is based on the individual differentiation of each patient. Fever in cancer includes five differentiations as above. First of all, we should ensure the kind of patient's differentiation, then select the principle of treatment and herb prescription. After that we add proper herbs according to minor symptoms. The treatment of fever in cancer with Chinese medicine is a kind of individual treatment in contrast to western medicine (Yu et al., 2010).

We focus on the condition of whole body in the treatment and the use the principle that remove evil qi, reinforce healthy qi and regulate yin and yang. The five cases in this article show us the individual treatment in addition to the normal principles of the five differentiations. That means not all of the patients with the same differentiation use the same herbs. We should add or subtract some herbs according to the individual condition.

Fever in cancer patients is a complicated problem with several differentiations in the same syndrome. For example, the tangle of heat and dampness with toxicants at the same time, or with the deficiencies of qi and yin, or with the stasis of blood and qi, or with the deficiencies of qi and blood (Hu et al., 2004). So we should give the treatment from differentiations of asthenia-sthenia Zheng complications because of the pathogenesis of cancer.

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CONFLICT OF INTEREST

The authors have no conflicting financial interests.

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