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Professor Liu Liangli Treated 1 Case of Pulmonary Alveolar Proteinosis from Phlegm Stasis

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Abstract: ***Pulmonary alveolar proteinosis (PAP) is a rare chronic interstitial lung disease, characterized by the accumulation of a large amount of phospholipoprotein-like substances in the alveoli and bronchioles. It lacks specific clinical manifestations and is mainly manifested as cough, expectoration, and dyspnea. In Western medicine, the main treatments include whole-lung lavage, inhalation/subcutaneous application of granulocyte-macrophage colony-stimulating factor, rituximab, pioglitazone, statins, gene therapy, plasma exchange, lung transplantation, etc. [1]. However, a unified treatment standard has not been established, and the disease cannot be completely cured. It can only relieve the clinical symptoms. Professor Liu Liangli, as a renowned traditional Chinese medicine doctor in Guizhou Province, has been engaged in the diagnosis and treatment of common and difficult respiratory diseases using integrated traditional Chinese and Western medicine for more than 30 years. Based on the theory of phlegm and blood stasis, she believes that the main pathogenesis of pulmonary alveolar proteinosis is the deficiency and decline of the internal organs as the root cause, and the obstruction of phlegm and blood stasis in the lungs as the superficial manifestation. Therefore, this disease mostly presents a situation of both deficiency of the root and excess of the branch, with a mixture of deficiency and excess syndromes. Among them, deficiency of the lungs, spleen, and kidneys is the main aspect. Therefore, in clinical practice, the principle of treating both the root cause and the superficial manifestation is adopted, and the treatment methods are to resolve phlegm and remove blood stasis, and to tonify the lungs, spleen, and kidneys, achieving good clinical curative effects.***

Keywords: Pulmonary alveolar proteinosis, Phlegm stasis, Clinical experience**.**

1. Introduction

Pulmonary alveolar proteinosis (PAP) is a disease caused by abnormal metabolism of pulmonary surfactant. It is extremely rare clinically and was first reported in 1958 [2]. Pulmonary alveolar proteinosis is a heterogeneous disease. According to the different mechanisms of pulmonary surfactant accumulation, it can be divided into three types: primary, secondary, and congenital [3]. The pathogenesis of the three types is different, but it is mainly considered to be related to granulocyte-macrophage colony stimulating factor (GM-CSF) gene defects and the presence of anti-GM-CSF antibodies [4]. Among them, the primary type is the most common clinically. Its clinical manifestations lack specificity, mainly manifested as progressive dyspnea, repeated coughing and expectoration, fatigue, chest tightness, etc. On high-resolution chest CT, it is mainly manifested as the "crazy paving" sign, "geographic" distribution, manifestations similar to pulmonary edema (on X-ray films, the "butterfly-wing shadow" is similar to pulmonary edema), manifestations similar to pulmonary consolidation, and manifestations similar to interstitial fibrosis. At present, the main recommended treatment for this disease in Western medicine in China is whole-lung lavage, but it cannot be cured completely, and most patients need repeated lavage for many times. Other treatments such as inhalation/subcutaneous application of granulocyte-macrophage colony stimulating factor, rituximab, pioglitazone, statins, gene therapy, plasma exchange, etc., have unclear indications. Relapse is also likely to occur after lung transplantation. Therefore, there is no clear and effective treatment method for this disease in Western medicine.

There is no record of the traditional Chinese medicine (TCM) disease name for this disease in TCM. However, based on its clinical manifestations, most TCM practitioners classify it into the categories of "lung wilt" and "lung bi syndrome". In terms of the pathogenesis, it is mainly treated based on the theories of "phlegm, blood stasis, and deficiency" [5, 6]. This disease has an insidious onset, a long course, and its nature is mainly characterized by deficiency of the root cause and excess of the superficial manifestation.

According to her many years of clinical experience, Professor Liu believes that the occurrence of this disease is mainly due to the deficiency and decline of the internal organs, the endogenous production of phlegm turbidity, the poor circulation of qi and blood, and the formation of blood stasis after a long illness. Eventually, phlegm and blood stasis block the lungs, leading to the dysfunction of the functions of dispersing and descending of the lungs, and the development of lung bi syndrome. Professor Liu Liangli uses a self-formulated prescription with modifications. Adopting the methods of resolving phlegm and removing blood stasis, and tonifying the lungs, spleen, and kidneys, she treats patients with pulmonary alveolar proteinosis. This can significantly improve the patients' symptoms such as cough, expectoration, chest tightness, and dyspnea, increase the patients' oxygen saturation and exercise tolerance, and improve the patients' quality of life.

2. Etiology and Pathogenesis

2.1 The Mutual Binding of Phlegm and Blood Stasis, Obstructing the Lungs, is the Pathological Basis

The formation of phlegm-rheum is derived from the impairment of the body's water metabolism. When the water metabolism goes awry and body fluids cannot be normally distributed and excreted, they will condense into phlegm-rheum. Once formed, phlegm-rheum is like the "evil of yin pathogens" within the body. It not only hinders the normal circulation of qi and blood in the human body, but

over time, it will also prompt the generation of blood stasis. Both phlegm-rheum and blood stasis belong to yin pathogens. They are not only pathological products generated during the disease process, but also further act as pathogenic factors, exacerbating the development and changes of the disease. Both phlegm-rheum and blood stasis belong to yin pathogens. They are pathological products generated during the disease process and will further act as pathogenic factors, aggravating the development and changes of the disease. In terms of pathological mechanisms, there is a close and complex relationship of mutual influence between phlegm and blood stasis. Fundamentally, phlegm is generated from the condensation of body fluids and is the initial stage of the formation of blood stasis. When the metabolism of body fluids is disordered and condenses into phlegm, the phlegm pathogen blocks the collaterals, hindering the circulation of qi and blood. The blood flow gradually slows down, and then blood stasis is formed. Once blood stasis is generated internally, it means that the normal circulation of blood has stagnated, which in turn will affect the body's qi transformation function. When the qi transformation is abnormal, the distribution and metabolism of body fluids will be more disordered, thus exacerbating the generation of phlegm pathogens. As Ye Tianshi, a famous doctor in the Qing Dynasty, expounded: "Over the years, exogenous pathogens linger, both qi and blood are damaged, and they transform into stagnant blood stasis and congealed phlegm, mingling in the meridians and collaterals." This state of the mutual adhesion of phlegm turbidity and blood stasis makes the manifestations of the disease complex and changeable, often presenting many strange symptoms. There is also a saying among the people that "many strange diseases are caused by phlegm. "During the entire pathological process, phlegm, as the initiating factor, takes the lead in breaking the normal physiological state of the human body and triggering a series of pathological changes; while blood stasis is the central link in the progression of the disease. The two are intertwined and mutually reinforcing, jointly constituting the pathological basis of this disease. For patients with pulmonary alveolar proteinosis (PAP), their alveolar lavage fluid appears milky or viscous, a characteristic that highly conforms to the characteristics of "phlegm turbidity" described in traditional Chinese medicine, further confirming the crucial position of the mutual binding of phlegm and blood stasis in the pathology of this disease. PAP patients often have an insidious onset, a long course of the disease, and the disease location is deep in the lung collaterals. When phlegm and blood stasis block the lung collaterals, the functions of dispersing and descending of the lung will be abnormal. The lung dominates qi and is in charge of respiration. When the dispersing and descending functions of the lung are abnormal and the lung qi rebels upward, it can cause coughing. When the qi movement is not smooth and blocked in the chest, the symptom of chest tightness will occur. As the disease further develops, the respiratory function of the lung is severely damaged, and it may even lead to dyspnea. Many scholars have also deeply explored the pathogenesis of PAP, and many believe that the mutual binding of phlegm and blood stasis is the key to its pathogenesis [6]. During the process of clinical syndrome differentiation and treatment, many doctors take resolving phlegm and removing blood stasis as an important treatment principle and have achieved remarkable curative effects. For example, doctors such as Pan Deng [7] take promoting blood circulation and removing blood stasis as the main treatment idea and use the classic formula Xuefu Zhuyu Decoction to treat this disease. Through the effects of promoting blood circulation and removing blood stasis, promoting qi flow and relieving pain, it regulates the circulation of qi and blood and resolves the state of the mutual binding of phlegm and blood stasis, achieving good clinical curative effects. Professor Han Yun [8] often combines Salvia miltiorrhiza with Achyranthes bidentata in clinical practice, and the two work together to play the role of promoting blood circulation and removing blood stasis. Salvia miltiorrhiza promotes blood circulation and removes blood stasis, cools the blood and dissipates carbuncles, while Achyranthes bidentata removes blood stasis and dredges the meridians, tonifies the liver and kidney, and strengthens the tendons and bones. The combination of the two enhances the power of promoting blood circulation and removing blood stasis, promotes blood circulation, and improves the state of blood stasis in the lungs. Based on the theory of "cold-phlegm-blood stasis", Professor Li Guangxi [9] takes warming the meridians and dredging the collaterals, resolving phlegm and removing blood stasis as the principle of formula composition and self-formulates Wensan Tincture for external use. In the formula, Chinese medicinal materials such as Angelica sinensis and Ligusticum chuanxiong are skillfully combined. Angelica sinensis nourishes blood and promotes blood circulation, regulates menstruation and relieves pain, while Ligusticum chuanxiong promotes blood circulation and qi flow, dispels wind and relieves pain. The two together play the role of promoting blood circulation, removing blood stasis and unblocking stagnation. Through the method of warming and unblocking, it disperses the cold pathogen and resolves phlegm and blood stasis. In the treatment, doctor Hu Xuejun [10] combines Aurantii Fructus Immaturus with Salvia miltiorrhiza and Carthami Flos. Aurantii Fructus Immaturus promotes qi flow and widens the middle-jiao, Salvia miltiorrhiza promotes blood circulation and removes blood stasis, cools the blood and dissipates carbuncles, and Carthami Flos promotes blood circulation to dredge the meridians and dissipates blood stasis and relieves pain. The combination of the three promotes qi flow, blood circulation and removes blood stasis, complementing each other's advantages. The ancients said that "a single herb of Salvia miltiorrhiza has the same effect as Siwu Decoction." In the formula, Salvia miltiorrhiza can not only promote blood circulation and remove blood stasis, but also has the effect of cooling and nourishing the blood. On the one hand, it can prevent the heat-toxin from consuming yin blood, and on the other hand, it can restrict the relatively warm nature of drugs such as Aurantii Fructus Immaturus and Carthami Flos, making the nature of the whole formula mild and combining both attacking and tonifying.

In conclusion, from theoretical discussions to clinical practices, many physicians consider resolving phlegm and removing blood stasis as one of the important treatment principles when treating pulmonary alveolar proteinosis. By resolving phlegm and removing blood stasis, it regulates the circulation of qi, blood and body fluids in the human body, restores the functions of dispersing and descending of the lungs, and provides effective ideas and methods for the treatment of pulmonary alveolar proteinosis, which is worthy of further in-depth research and widespread application in

clinical practice.

2.2 The Deficiency and Decline of the Internal Organs is the Root Cause.

Traditional Chinese medicine classifies this disease into the categories of "Lung Bi Syndrome" and "Lung Wilt Syndrome". In the "Treatise on the True Organs of the Vital Qi in Plain Questions", it is stated: "Therefore, wind is the origin of all diseases. Now, when wind-cold invades a person, it makes all the body hairs stand upright... If not treated, the disease will invade and lodge in the lungs, which is called Lung Bi Syndrome, causing coughing and shortness of breath." The lung, known as the "canopy" and a delicate organ, cannot tolerate the invasion of pathogens. Therefore, when external pathogens invade, the lung is the first to be affected. The main pathogenesis of Lung Bi Syndrome is that, on the basis of lung qi deficiency, the body is again invaded by external pathogens, which causes the lung qi to be stagnated and blocked, the circulation of qi and blood to be unsmooth, the lung to lose its functions of dispersing and descending, and phlegm and blood stasis to mutually bind. After a long illness, the spleen is affected. When the spleen loses its normal transportation and transformation function, the source of qi and blood production is lacking, leading to spleen qi deficiency. Since the mother organ's disease can affect the child organ, a lung disease can involve the kidney, resulting in the kidney's failure to receive qi and its malfunction in governing water. The disorder of water metabolism occurs, and phlegm-rheum accumulates internally, which in turn affects the functions of the lung, spleen, and kidney. Eventually, all three organs, the lung, spleen, and kidney, become deficient. The location of this disease is in the lung, and over time, it can involve the spleen and kidney.

3. Examples of Medical Records

Zhang, male, 48 years old, first consultation on May 25, 2023. He visited the outpatient department of our hospital due to "cough, expectoration, wheezing, and chest tightness for 1 month". He had a cough with white and sticky phlegm, which was small in quantity and difficult to expectorate. He experienced wheezing and shortness of breath after activity, which could be relieved after rest. So he went to a local hospital. The chest CT scan showed multiple ground-glass opacities and consolidation shadows in both lungs, distributed in patchy and grid-like patterns, especially in the lower lobes of both lungs, with thickening of the interlobular septa. Pulmonary function tests showed a decrease in pulmonary diffusion function, while the ventilation function was normal. The local hospital considered it as "pulmonary interstitial fibrosis" and completed relevant examinations such as rheumatism and immunity, but no obvious abnormalities were found. After empirical anti-fibrosis treatment (specific details unknown), the patient felt that the above symptoms were not significantly relieved. Later, he visited West China Hospital of Sichuan University. Transbronchial lung biopsy (TBLB) showed that there were pink-stained and granular exudates in some alveolar cavities of the submitted lung tissue, and no definite fibrosis, widening, etc. were found in the alveolar interstitium. The special staining result was PAS (+). Combined with the results of immunohistochemistry with special staining agents, the possibility of pulmonary alveolar proteinosis was highly suspected. After whole-lung lavage treatment, the above symptoms of the patient were relieved.

The current symptoms are as follows: cough, mainly dry cough, occasionally coughing up a small amount of white sticky phlegm, which is difficult to expectorate. There is wheezing and shortness of breath after activity, chest tightness, and sometimes fatigue and dyspnea. The oxygen saturation fluctuates around 88%. The patient is conscious, in good spirits, with a normal appetite and sleep, and normal bowel and bladder functions. The tongue is pale and dark, the coating is white and greasy, there are ecchymoses on the tip and sides of the tongue, and the pulse is deep and stringy. He has a long-term history of smoking and no obvious history of dust exposure. Physical examination: slightly cyanotic lips, coarse breath sounds in both lungs upon auscultation, scattered moist rales can be heard in both lungs, no wheezing sounds, no pleural friction rubs, and no obvious edema in both lower extremities. Western medicine diagnosis: Pulmonary alveolar proteinosis. Traditional Chinese medicine diagnosis: Lung Bi Syndrome. Syndrome differentiation: Syndrome of phlegm and blood stasis blocking the lungs, deficiency of the lung, spleen, and kidney. Treatment method: Resolve phlegm and remove blood stasis, tonify the lung, spleen, and kidney. Prescription: Stemona root 12g, Mulberry bark 10g, Platycodon root 10g, Bitter apricot kernel 10g, Danshen root 12g, Chinese chive bulb 20g, Codonopsis pilosula 15g, Poria cocos 15g, Atractylodes macrocephala 15g, Tangerine peel 10g, Pinellia ternata processed with licorice 9g, Honey-fried coltsfoot flower 10g, Snakegourd peel 10g, Angelica sinensis 10g, Liquorice 6g. A total of seven doses, decocted in water, one dose per day, taken three times a day, 150-200ml each time, taken warm after meals. During the medication period, drinking alcohol is prohibited, and foods such as fatty, sweet, thick, greasy, raw, cold, and dry, fragrant, and fiery foods should be avoided.

At the second consultation, the patient felt that the frequency of cough had decreased compared with before. The phlegm changed from sticky to thin and was easier to expectorate. He still felt wheezing and shortness of breath after activity, but the chest tightness and fatigue had improved compared with before, and the frequency of the occurrence of dyspnea symptoms had decreased. He sometimes felt dry mouth and itching in the throat. The tongue was pale and dark, the coating was slightly white and greasy, there were a few ecchymoses on the sides of the tongue, and the pulse was deep and stringy. Since the patient had no obvious adverse reactions such as nausea, vomiting, and diarrhea after taking the above prescription, Honey-fried coltsfoot flower and Snakegourd peel were removed from the previous prescription, and 6g of Oroxylum indicum and 10g of Anemarrhena asphodeloides processed with salt were added. Fourteen doses, and the decocting and taking method was the same as before.

At the third consultation, the patient felt that all symptoms had been significantly relieved compared with before. He occasionally coughed, coughing up a small amount of white phlegm, which was easy to expectorate. His exercise tolerance had increased, and he sometimes felt chest tightness, without obvious symptoms such as dyspnea, dry mouth, and itching in the throat. The tongue was pale and dark, the coating was

slightly white and greasy, there were a few ecchymoses on the sides of the tongue, and the pulse was deep. Therefore, Oroxylum indicum was removed from the previous prescription, and 12g of Coix lacryma-jobi and 15g of Chinese yam were added. Seven doses, and the decocting and taking method was the same as before. Follow-up showed that the symptoms of the patient were relieved and the pulmonary function was improved after taking traditional Chinese medicine.

Commentary: The symptoms of this patient improved significantly after traditional Chinese medicine treatment. The patient had a cough, mainly dry cough, occasionally coughing up a small amount of white sticky phlegm, which was difficult to expectorate. There were wheezing and shortness of breath after activity, chest tightness, sometimes fatigue and dyspnea. The oxygen saturation fluctuated around 88%. He was conscious, in good spirits, with a normal appetite and sleep, and normal bowel and bladder functions. The tongue was pale and dark, the coating was white and greasy, there were ecchymoses on the tip and sides of the tongue, and the pulse was deep and stringy, which belonged to the category of "Lung Bi Syndrome" in traditional Chinese medicine. And the pathological changes of the lungs belong to the pathological products such as tangible phlegm and blood stasis in traditional Chinese medicine. The lung dominates qi and is in charge of respiration. When the lung qi is deficient, the lung defense is invaded by external pathogens, and phlegm and blood stasis block the lung collaterals. The lung loses its functions of dispersing and descending, so there are chest tightness and cough. The lung disease affects the kidney. When the kidney qi is deficient and the qi does not return to the origin, there are wheezing, shortness of breath, and dyspnea after activity. Phlegm and blood stasis block, and the qi movement is not smooth, so there is chest tightness. Combined with the signs of phlegm and blood stasis such as a pale and dark tongue, white and greasy coating, ecchymoses on the tip and sides of the tongue, and a deep and stringy pulse. Traditional Chinese medicine uses syndrome differentiation of the zang-fu organs and differentiates it as the syndrome of phlegm and blood stasis blocking the lungs, deficiency of the lung, spleen, and kidney. The location of the disease is in the lung, and it involves the spleen and kidney. The pathogenesis of this patient can be summarized as insufficient healthy qi (deficiency of the lung, spleen, and kidney), mutual binding of phlegm and blood stasis, and blocking of the lung collaterals. The key to the pathogenesis is phlegm, blood stasis, and deficiency, and the deficiency is mainly deficiency of the lung, spleen, and kidney, which belongs to the syndrome of deficiency of the root cause and excess of the superficial manifestation.

Professor Liu believes that this patient belongs to the syndrome of a mixture of deficiency and excess, with deficiency of the root cause as the main aspect. Therefore, the treatment method is to resolve phlegm and remove blood stasis, and tonify the lung and kidney. In the prescription, Stemona root moistens the lung and relieves cough, which has a good effect on persistent cough. Mulberry bark purges the lung and relieves asthma, and can clear lung fire to relieve cough and asthma. Platycodon root promotes the dispersing of lung qi and removes phlegm, and can carry the medicine upwards to make the medicinal power reach the affected area directly. Bitter apricot kernel descends qi, relieves cough and asthma. Together with Platycodon root, one ascending and one descending, it restores the dispersing and descending functions of the lung. Danshen root promotes blood circulation and removes blood stasis, improves the blood circulation of the lungs, and helps to dissipate the blood stasis in the lung collaterals. Chinese chive bulb promotes yang, dissipates stagnation, promotes qi flow and relieves stagnation, and can unblock the qi movement and relieve chest tightness. Codonopsis pilosula, Poria cocos, Atractylodes macrocephala, and Liquorice are the main drugs of Sijunzi Decoction, which invigorate the spleen and replenish qi, nourish the earth to generate metal, and provide a source for lung qi, enhancing the function of the lung. Tangerine peel and Pinellia ternata processed with licorice dry dampness and resolve phlegm, regulate qi and harmonize the middle-jiao, so that the phlegm-dampness can be resolved. Honey-fried coltsfoot flower moistens the lung, descends qi, relieves cough and resolves phlegm. Snakegourd peel clears heat and resolves phlegm, widens the chest and regulates qi, and helps to remove phlegm pathogens from the lungs. Angelica sinensis nourishes and promotes blood circulation, not only helps Danshen root to remove blood stasis, but also prevents excessive blood stasis removal from injuring the healthy qi.

At the second consultation, the symptoms of the patient such as cough, expectoration, chest tightness, and fatigue had all improved. Since the phlegm changed from sticky to thin, Honey-fried coltsfoot flower and Snakegourd peel were removed to prevent the excessive use of their warm, dry, cold, and cool properties. Oroxylum indicum was added to moisten the lung, soothe the liver, harmonize the stomach, and promote muscle regeneration, improving the patient's dry mouth and itching in the throat. Anemarrhena asphodeloides processed with salt was added to nourish yin and reduce fire, aiming at the patient's deficiency of yin fluid. At the third consultation, the patient's condition further improved. Oroxylum indicum was removed, and Coix lacryma-jobi was added to promote diuresis and remove dampness, invigorate the spleen, and Chinese yam was added to invigorate the spleen, nourish the stomach, promote the production of body fluid, and benefit the lung, strengthening the functions of invigorating the spleen and tonifying the kidney to consolidate the curative effect.

4. Summary

Throughout the treatment process, traditional Chinese medicine pays attention to the holistic concept and syndrome differentiation and treatment. Starting from the comprehensive information such as the patient's symptoms, tongue, and pulse, it accurately grasps the pathogenesis. By adjusting the medication and adding or subtracting according to the symptoms, the medicine is more suitable for the changes of the patient's condition. In terms of eliminating pathogens, resolving phlegm and removing blood stasis are equally emphasized. Since phlegm and blood stasis are mutually adhered, resolving phlegm can make the blood stasis have nothing to rely on, and removing blood stasis can help the phlegm pathogens to dissipate. In terms of strengthening the healthy qi, it focuses on tonifying the lung and kidney. The lung and kidney are the foundation of respiration. When the

lung and kidney are tonified, the respiratory function can be restored. At the same time, by invigorating the spleen and replenishing qi, it enhances the nourishment of the lung by the acquired foundation.

This case fully demonstrates the advantages of traditional Chinese medicine in the treatment of pulmonary alveolar proteinosis. Traditional Chinese medicine regulates the body's functions as a whole, improves the microenvironment of the lungs, relieves the patient's symptoms, improves the quality of life, and can also improve the pulmonary function to a certain extent. Combined with Western medicine treatment methods such as whole-lung lavage, it can complement each other's advantages. After Western medicine relieves the pathological changes of the lungs, traditional Chinese medicine can fundamentally improve the patient's constitution through long-term conditioning, reducing the recurrence of the disease, providing a more comprehensive and effective treatment plan for pulmonary alveolar proteinosis, which is worthy of further promotion and research in clinical practice.

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