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Experiential Knowledge of Famous Physicians

Integrative treatment of granulomatosis with polyangiitis based on the traditional Chinese medicine principle of soothing the liver, promoting blood circulation, resolving phlegm, and dispersing nodules

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Abstract

Granulomatosis with polyangiitis (GPA) poses significant therapeutic challenges due to its susceptibility to concurrent infections and frequent relapses. Professor SHI Zaixiang proposed the therapeutic theory of lifting depression and removing blood stasis, resolving phlegm and dispelling nodulation for GPA management. He identified the core pathogenesis as "Qi collapse with collateral obstruction and phlegm-stasis intermingling", establishing the treatment principle of comprehensive intervention through ascending ancestral Qi, activating blood circulation, and resolving phlegm-stasis nodules. In clinical practice, Professor SHI emphasizes maintaining immune homeostasis with herbal medicine to enhance efficiency, while dynamically balancing Qi, blood, Yin, and Yang. Notably, he highlights the critical role of emotional factors in autoimmune disease progression. A representative case was provided to elucidate his clinical reasoning in GPA treatment.

Keywords: Granulomatosis with polyangiitis (GPA), Lifting depression, Removing blood stasis, Resolving phlegm, Dispelling nodulation, SHI Zaixiang, Expert experience

1 Introduction

SHI Zaixiang (born in 1942), former Director of the Department of Integrated Traditional Chinese and Western Medicine at China-Japan Friendship Hospital, is recognized as a national distinguished traditional Chinese medicine (TCM) practitioner, capital eminent TCM master, and doctoral supervisor. As a mentor for the Third to

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Seventh Batches of the National TCM Academic Experience Inheritance Program, he has dedicated over six decades to TCM clinical practice, research, and education. Based on the academic philosophy of being rooted in TCM while integrating western medicine, he pioneered the "Lifting Depression and Removing Blood Stasis" theoretical framework. He specialized in treating cardiovascular diseases and immune-related inflammatory conditions, including antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, nephrotic syndrome, Sjögren's syndrome, and systemic lupus erythematosus.

Granulomatosis with polyangiitis (GPA), a subtype of ANCA associated vasculitis, was historically termed Churg-Strauss syndrome (CSS) or allergic granulomatous angiitis. It is a multisystem disorder characterized by asthma, rhinitis, nasal polyposis, and marked peripheral blood/tissue eosinophilia, predominantly associated with proteinase 3-antineutrophil cytoplasmic antibody (PR3-ANCA) positivity. Pathogenically, activated neutrophils release proteases and oxygen free radicals, triggering vascular endothelial injury and inflammatory vasculopathy[1,2]. Core histopathological features include eosinophilic infiltration, eosinophilic giant cell vasculitis, and necrotizing granulomas in perivascular or interstitial tissues. Although GPA may affect small vessels in nearly all organ systems, the upper or lower respiratory tract and kidney are most frequently involved organs. Severe organ-threatening or life-threatening manifestations may occur, including dyspnea, hemoptysis, and saddle-nose deformity resulting from osteocartilaginous destruction when ear, nose, and throat (ENT) structures are affected[3,4].

The primary therapeutic goal for GPA is achieving sustained remission. Treatment protocols comprise induction therapy to control active disease and maintenance therapy[5]. International guidelines recommend induction regimens combining glucocorticoids with rituximab or cyclophosphamide (rather than glucocorticoid monotherapy) for organ-threatening or life-threatening GPA[6–8]. However, many patients fail to attain clinical remission or low disease activity. Furthermore, conventional therapies (glucocorticoids, cyclophosphamide, rituximab, mycophenolate mofetil) carry significant risks of severe infections, hematologic toxicity, hepatotoxicity, and carcinogenicity[9]. Consequently, emerging strategies aim to reduce or replace glucocorticoids (GCs), such as complement component 5a (C5a) inhibitors[10] and cluster of differentiation 20 (CD20) monoclonal antibodies[11,12], however their long-term efficacy remains suboptimal with persistent immunosuppression-related adverse effects[13–15].

TCM demonstrates dual therapeutic advantages in GPA management. During induction, TCM synergizes with glucocorticoids and immunosuppressants to accelerate remission. In maintenance phases, TCM not only enhances western drug efficacy[16,17], but also mitigates treatment-related toxicities through syndrome differentiation-based modifications. This integrative approach underscores TCM's growing prominence in optimizing GPA therapeutic outcomes.

2 Professor SHI Zaixiang's Understanding of TCM Pathogenesis and Therapeutic Methods in Granulomatosis with Polyangiitis

Professor SHI integrates the dynamic relationship of Qi-blood-phlegm with modern medical understanding of inflammation and immunity in immune-related inflammatory diseases. Based on the pathological characteristics of vascular inflammatory damage and granuloma formation in GPA, he categorizes this condition under "lung impediment (Feibi)" and "lung abscess (Feiyong)" in TCM theory. The TCM pathogenesis belongs to the pattern of "Qi collapse and collateral obstruction, phlegm-stasis interbinding". The core mechanism involves Zong Qi (thoracic vital energy) collapse leading to impaired blood circulation, accumulation of pathological products (blood stasis and turbid phlegm), and subsequent aggravation of inflammatory responses. Through elevating collapsed Qi, removing stasis, resolving phlegm, and dispersing nodules, this approach restores Qi dynamic balance, modulates immune homeostasis, improves vascular endothelial function, and controls inflammatory progression. Professor SHI advocates early integration of TCM with glucocorticoids and immunosuppressants to induce remission, maintain low disease activity during remission phases, and reduce treatment-related toxicities through syndrome differentiation-based modifications. TCM intervention in ANCA-associated vasculitis not only enhances therapeutic efficacy and reduces corticosteroid/immunosuppressant dependence, but also sustains remission, decreases infection/recurrence rates, and ultimately improves clinical cure rates and patients' quality of life.

2.1 Qi Collapse with Collateral Obstruction and Phlegm-Stasis Interbinding as Core Pathogenesis

Professor SHI proposes that GPA pathogenesis correlates closely with Zong Qi collapse and phlegm-stasis obstructing collaterals in TCM, evolving through 4 progressive stages: Major Qi collapse, Qi collapse-induced blood stasis, phlegm-stasis interbinding, and toxic transformation of phlegm-stasis.

TCM holds that Zong Qi accumulates in the thorax, governing respiration, blood circulation, and Qi-blood movement through heart vessels. Zong Qi deficiency or collapse disrupts Qi dynamics, causing fatigue, shortness of breath, and compromised defensive Qi leading to recurrent infections. Impaired blood propulsion results in blood stasis and vascular malnutrition, manifesting as fibrinoid necrosis, vascular stenosis or occlusion, tissue ischemia or hemorrhage, and refractory mucosal or skin ulcers. Dysregulated fluid metabolism causes phlegm stagnation and blood-fluid stagnation, forming necrotizing granulomas through macrophage or multinucleated giant cell aggregation, ultimately leading to bone erosion as well as pulmonary cavities, saddle nose deformity, and hearing loss.

Persistent Qi collapse induces visceral dysfunction and heat-toxin generation from retained phlegm-stasis, disturbing immune homeostasis through T helper 17 (Th17)/regulatory T cell (Treg) imbalance[18]. Th17/Treg imbalance drives promotes proinflammatory cytokine release and complement activation. ANCA-activated neutrophils release PR3 and reactive oxygen species, exacerbating vascular damage and organ dysfunction.

2.2 Therapeutic Principles: Elevating Qi, Removing Stasis, Resolving Phlegm

Professor SHI's treatment strategy emphasizes Zong Qi reinforcement as foundation, phlegm-stasis removal as priority, supplemented by toxin clearance and collateral dredging, embodying the integrative medicine principle of "Supporting Healthy Qi while Eliminating Pathogens".

2.2.1 Zong Qi reinforcement

The Shengxian decoction (Qi-lifting decoction), comprising *Astragali Radix* (Huangqi, 30–60 g), *Cimicifugae Rhizoma* (Shengma, 6–9 g), *Bupleuri Radix* (Chaihu, 6–9 g), and *Platycodonis Radix* (Jiegeng, 9–12 g), serves as core prescription. *Astragalus* replenishes Zong Qi, while Shengma and Chaihu elevate collapsed Qi. Jiegeng regulates lung Qi and water metabolism, achieving "restoring major Qi to resolve stagnation" as described by ZHANG Xichun. This approach improves microcirculation, inhibits ANCA-mediated vasculitis, and prevents granulomatous hyperplasia.

2.2.2 Blood stasis removal

Conventional blood-activating herbs are insufficient for severe stasis GPA. Professor SHI employs potent stasis-removing agents: *Sparganii Rhizoma* (Sanleng, 9–15 g) exhibits dual antithrombotic/thrombolytic effects and microcirculation improvement[19]. *Curcumae Rhizoma* (Ezhu, 9–15 g) contains β-elemene inhibiting platelet aggregation and inducing tumor apoptosis[20]. These are combined with Qi-tonifying herbs (*Astragalus, Codonopsis*) to enhance efficacy while minimizing Qi consumption, aligning with ZHANG Xichun's strategy of "removing stasis without damaging new blood".

2.2.3 Phlegm resolution and nodule dispersion

For GPA's refractory phlegm-stasis complexes, Professor SHI utilizes aggressive phlegm-resolving agents: *Lapis Chloriti* (Qingmengshi, 15–30 g) eliminates stubborn phlegm from collaterals. *Cremastrae Pseudobulbus* (Shancigu, 9–12 g) disrupts granulomatous mitosis *via* colchicine derivatives[21]. Daige San can cool detoxification by *Indigo Naturalis* (Qingdai) and soften hardness by *Meretricis Concha* (Geke).

For pulmonary manifestations (necrotizing pneumonia, bronchiectasis), *Fagopyri Dibotryis Rhizoma* (Jinqiaomai, 15–30 g) clears lung heat and resolves abscesses. *Gleditsiae Fructus* Powder (Zaojia Wan) contains *Gleditsiae Sinensis* (Zaojiao, 3–6 g) for expelling tenacious phlegm, buffered by *Jujubae Fructus* (Dazao) to protect stomach mucosa.

3 Professor SHI Zaixiang's TCM Approach to GPA Emphasizes Personalized Treatment Strategies

3.1 Emphasis on Herbal Combinations to Maintain Immune Homeostasis and Enhance Treatment Efficacy

Professor SHI proposes that the ideal immunomodulatory status for autoimmune diseases should simultaneously suppress pathological autoimmunity while preserving fundamental immune defense functions, achieving dual objectives of immune homeostasis and restoration of self-healing capacity. This concept aligns with the emerging immune reconstitution paradigm in ANCA-associated vasculitis and systemic lupus erythematosus (SLE) management. The unique advantage of TCM lies in its bidirectional regulatory capacity to achieve dynamic immune balance. The classical herb pair Huangqi (*Astragalus membranaceus*) and Shanzhuyu (*Cornus officinalis*) exemplifies this philosophy.

Huangqi, traditionally used for Qi-tonifying and Yang-lifting, exerts critical immunomodulatory rather than purely immunostimulatory effects. Its polysaccharides activate macrophage phagocytosis to enhance anti-infection capacity while promoting Treg cell differentiation to suppress excessive immune responses[22]. This mechanism addresses the Qi deficiency with compromised defense

state in GPA patients caused by long-term immunosuppressant use. Shanzhuyu, nourishing liver and kidney meridians, primarily inhibits pathological immune activation. Its iridoid glycosides downregulate inflammatory cytokines including interleukin-17 (IL-17) and tumor necrosis factor-α (TNF-α)[22], thereby blocking ANCA-mediated vascular endothelial injury. This herb is particularly suitable for suppressing granulomatous proliferation and vasculitic necrosis during GPA active phases characterized by immune storms.

The synergistic combination of strengthening vital Qi by Huangqi to consolidate constitution and restraining hyperactive Yang to control symptoms by Shanzhuyu can achieve dual benefits, which can avoid infection risks from excessive immunosuppression while preventing vasculitis relapse due to uncontrolled immune activation. Compared to the western glucocorticoid combined with immunosuppressant, this approach embodies the TCM principle of simultaneously reinforcing healthy Qi and eliminating pathogenic factors.

3.2 Dynamic Regulation of Qi-Blood and Yin-Yang Balance

Chronic glucocorticoid/immunosuppressant use in GPA frequently induces Qi-blood-Yin-Yang disharmony. Professor SHI emphasizes dynamic equilibrium regulation and preventive intervention against disease progression.

Qi-Yin deficiency syndrome (manifested as weak voice, dry cough, spontaneous or night sweating): Modified Shengmai San (*Radix Ginseng, Radix Ophiopogonis, Fructus Schisandrae*) replenishes Qi and consolidates Yin.

Yin-Yang deficiency syndrome (productive frothy sputum, cold intolerance): Ganjiang Gancao Tang (*Radix Glycyrrhizae, Rhizoma Zingiberis*) warms middle Jiao and transforms Yang.

Yin deficiency with internal heat (low-grade fever, bloody sputum, epistaxis): Beishashen (*Glehnia littoralis*) and Xuanshen (*Scrophularia ningpoensis*) clear lung-stomach heat and resolve phlegm nodules.

Latent heat in collaterals (afternoon fever, subcutaneous nodules, chronic rhinitis): Baiwei (*Cynanchum atratum*) and Biejia (*Carapax Trionycis*) penetrate nutrient-level pathogens and dissipate phlegm-stasis.

These strategies restore holistic homeostasis of the immune-endocrine axis through systemic Qi-blood-Yin-Yang regulation.

3.3 Bidirectional Interaction Between Emotional Factors and Autoimmune Pathogenesis

Professor SHI highlights the pathogenic cycle between emotional disturbances and autoimmune dysregulation. Liver Qi stagnation transforms into fire that damages collaterals (liver stagnation, followed by fire transformation, and finally vessel injury), exacerbating ANCA activation and vascular inflammation. Conversely, GPA-induced pain, facial disfigurement, and dyspnea perpetuate emotional distress and Shen (spirit)-liver malnourishment, creating a disease-depression entanglement.

Clinical interventions focus on Zhizi Chi Tang (*Gardeniae Fructus, Sojae Semen Praeparatum*), which clears liver fire and drains heat downward while dispersing constraint. Ganmai Dazao Tang (*Tritici Semen, Jujubae Fructus, Glycyrrhizae Radix*) nourishes heart Yin, soothes liver urgency, and harmonizes middle Jiao.

These formulas modulate hypothalamic-pituitary-adrenal (HPA) axis activity to suppress stress-induced proinflammatory cytokine release[23], disrupt the neural-immune-endocrine dysregulation loop. This dual approach neutralizes emotion-driven vasculitis exacerbation while breaking the pain-anxiety-immune dysfunction feedback through psychosomatic regulation, embodying TCM's holistic philosophy of calming Shen to stabilize immunity and harmonizing mind to heal body.

4 Therapeutic Case Report

A 29-year-old woman presented with intermittent cough and difficult expectoration for 4 years with aggravation for 3 months sought for medical consultation at 1 March 2024. The patient initially developed fever, cough, nasal congestion, and difficult expectoration of yellow viscous sputum accompanying otorrhea, epistaxis, and ageusia 4 years prior. Bronchoscopic biopsy confirmed granulomatosis with polyangiitis (GPA), treated with prednisolone and mycophenolate mofetil (MMF) resulting in initial remission. Subsequent recurrent infections led to nasal cartilage destruction, hearing loss, and anosmia. Steroid tapering was completed in 2021, with MMF maintained at 0.5 g twice a day.

In January 2024, GPA relapsed with yellow sputum and ineffective antimicrobial therapy. PR3-ANCA rose to 626.3 RU/mL, accompanied by elevated erythrocyte sedimentation rate (ESR) (30 mm/h) and C-reactive protein (CRP) (24.60 mg/L). Computed tomography (CT) revealed pleural effusion. Repeat bronchoscopy showed extensive mucosal necrosis, abundant secretions, and histopathology

demonstrating fibrinous exudate, interstitial fibrosis, granuloma formation, and mixed inflammatory infiltration. Hospitalization at China-Japan Friendship Hospital confirmed ANCA-associated vasculitis with pulmonary infection. Treatment with methylprednisolone 40 mg daily and MMF 0.75 g twice a day showed limited improvement.

Key symptoms at presentation: Persistent yellow viscous sputum, postnasal drip, dry nasal crusts, otorrhea, emotional lability, palpitations, cold intolerance. Menstrual cycle: 2–3 d per 30–45 d, scanty flow with clots (LMP: February 21). Bowel movements regular. Tongue: Dark with red tip, yellow greasy coating, enlarged with teeth marks. Pulse: Thready, rapid, slippery.

Traditional Chinese medicine diagnosis: Feiyong (lung abscess) with Qi collapse and blood stasis, phlegm-blood stasis interaction, liver fire invading lung.

Prescription: modified Shengxian Quyu decoction and Daige San.

Components: *Astragalus Root* (Huangqi) 30 g, *Salvia Miltiorrhiza Root* (Danshen) 20 g, *Anemarrhena Rhizome* (Zhimu) 15 g, *Cimicifuga Rhizome* (Shengma) 10 g, *Platycodon Root* (Jiegeng) 10 g, *Bupleurum Root* (Chaihu) 10 g, *Sparganium Rhizome* (Sanleng) 12 g, *Zedoary Rhizome* (Ezhu) 15 g, *Motherwort Herb* (Yimucao) 30 g, *Cornus Fruit* (Shanzhuyu) 30 g, *Glehnia Root* (Beishashen) 20 g, *Mulberry Root Bark* (Sangbaipi) 15 g, *Pleione Pseudobulb* (Shancigu) 10 g, *Chlorite Schist* (Qingmengshi) 30 g, *Clam Shell* (Haigeke) 30 g, *Natural Indigo* (Qingdai) 15 g, *Trichosanthes Fruit* (Quangualou) 15 g.

Therapeutic outcomes: By day 7 post-treatment, experienced an 80% improvement in sputum expectoration as well as cough and palpitations. Steroid tapering initiated (starting from 9 tablets with reduction of 1 tablet every 2 weeks). Modified prescription: Increased *Trichosanthes Fruit* (Quangualou) to 30 g, *Anemarrhena Rhizome* (Zhimu) to 20 g. Replaced *Salvia Miltiorrhiza Root* (Danshen) with *Pseudostellaria Root* (Taizishen) 30 g. Added *Phellodendron Bark* (Huangbai) 15 g, *Scrophularia Root* (Xuanshen) 15 g, *Ophiopogon Root* (Maidong) 20 g. Adjunctive therapy: *Golden Buckwheat Rhizome* (Jinqiaomai) 200 g decocted with rice wine. By 24 June 2024: Significant clinical remission with sustained steroid tapering and no recurrence. Follow-up evaluation demonstrated that by January 2025, repeat testing revealed the ANCA titer turned negative, and the ESR returned to normal (5 mm/h), along with CRP normalization (<5 mg/L) and the disappearance of pleural effusion.

Clinical commentary:

This refractory GPA case demonstrated persistent mucosal necrosis despite standard immunosuppression. TCM analysis revealed fundamental Qi collapse with phlegm-blood stasis accumulation. The therapeutic strategy emphasized Qi elevation (Shengxian Quyu decoction) combined with liver-clearing and phlegm-resolving agents (Daige San). Notably, enhanced sputum clearance occurred following TCM intervention, suggesting improved local immunity and tissue repair. This case highlights the importance of addressing underlying Qi deficiency patterns in refractory autoimmune conditions, particularly when conventional immunosuppressants may paradoxically impair endogenous healing capacity. The integration of TCM mechanistically targeting both pathological products (phlegm-stasis) and constitutional deficiency (Qi collapse) achieved synergistic therapeutic effects.

Author Contributions

SHAO Mingjing and SHI Zaixiang conceived the study. ZHU Tingting and CHEN Zhenjie wrote the manuscript. BIAN Yan and CUI Hailan extracted data. CHEN Xiaowei, LIU Yingying, GAO Wei, HAN Xueding and WANG Liyan contributed to the revision of the manuscript. All authors have read and approved the final manuscript.

Ethical Approval

Informed consent for publication was obtained from the patient and authorization was obtained from the Ethics Committee of Beijing No.6 Hospital.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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