

Prof. Li Zhang, a brisk PUMCH doctor with sunshine

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Introduction

The ancient Greek aphorism “*know thyself*” engraved on the forecourt of the Temple of Apollo epitomizes the human desire for the exploration into the unknown. In fact, never has mankind dragged their feet in understanding themselves, as in the achievements scientists have made all these years in the studies of disease and pathology.

Ere the 2017 WCLC journey, AME Editors were sent across China to conduct in-depth interviews with an army of distinguished experts in the field of lung cancer. Together we learned how these soldiers fought for the nation that has the largest number of patients, and how they dedicated their lives to inventing the most-advanced weapons and probing into the enemy camp. From the past, they reflect and learn from mistakes; At present, they work hard and make changes; For the future, they make plans and improvements.

May this issue take you to the innermost world of these Chinese scholars, where you can delve into their wealth of knowledge and be inspired.

Prologue

As a little girl, Li Zhang was brisk and outgoing, and always spoke cheerfully which made her families believe she was especially congenial to be a doctor. Followed the advices of the elders who were doctors as well, the innocent Li Zhang chose the road of Medicine.

At the university days, Li Zhang has shown her obsession with medicine. In the class of orthopedics, she would silently stood by a box housing a whole set of human bone specimens which were so smooth due to the touch from countless hands, and took a serious look and pondering over the specimens, lost in the inexpressible pleasure.

As a postgraduate mentored by Professor Longyun Li, Li Zhang would have secret happiness when her mentor spoke highly of the medical record written by her own, for instance, “Li Zhang, you have done a wonderful job on the medial record!”

When she was still a green hand, she believed “*It is my responsibility to cure and save life.*” She never thought of

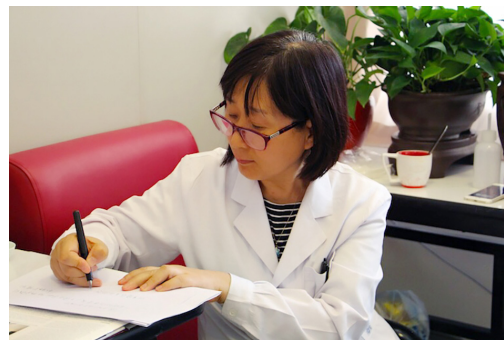


Figure 1 Prof. Li Zhang in the interview.

shirking in face of patients. After the morning shift, when the patients become better in her hands, she would feel extremely proud of herself, and the pride would even spread to her lunch at noon.

Now she will not simply “reject” any patient, because she believes, “If we as the doctors in Peking Union Medical College Hospital (PUMCH, the most renown hospital in China) can not find a resolution to the disease, then whom should the patients ask for help? If I could not figure it out, the patient was supposed to be ‘over’.”

Li Zhang has never thought of quitting the career as a doctor. “What can I do if I gave up the career? I’m not good at anything except being a doctor.” She gave a hearty laugh like a merry child. I have almost forgotten that Professor Zhang is more than 50 years old now (*Figure 1*).

The mentor, who pioneered the road

In 1993, Li Zhang was admitted to Peking Union Medical College Hospital (PUMCH), becoming a postgraduate of respiratory medicine under the tutelage of Professor Longyun Li—Zhang is the first disciples of Professor Longyun Li (*Figure 2*). About Professor Longyun Li, the first word came to Zhang’s mind is “Awful. Especially awful.”

She said, “*Professor Li collected clinical history carefully indeed, and her medical record was really wonderful, which*



Figure 2 Prof. Li Zhang at her age as a postgraduate.

contained clinical history, physical examination, diagnosis as well as her entire logical thinking. Particularly, in the cases of lung cancer her medical record combined words with a lot of diagnostic imaging, like a small album. In each year's outstanding medical records show of PUMCH, there would be Professor Li's work." Professor Li's high standard in profession made young Zhang feel particularly awful, "I feel awful, so I have to write it well in order to earn the praise from my mentor."

Professor Longyun Li keeps perfecting her expertise as a doctor, and this has become the persistent pursuit of Li Zhang in her three decades' medical career. "I have been doing my best to move closer to my mentor in profession. She is like the shadow that I have been chasing," said Li Zhang.

Now Mentor Li has retired. However, every time Zhang reads a new academic view, encounters a skeptical clinical case or the familiar patients of Mentor Li, she will still go to discuss with Mentor Li. Even though Li was Zhang's mentor at her postgraduate time, Zhang believes Mentor Li has a lasting influence on herself. "In my life, Mentor Li is my teacher. She has never left my clinical practice, as if she has been watching me all the time." Professor Zhang said affectionately, with a hand gesture of "watching".

Professor Zhang also recalled her first time to manage

wards. "Young doctor should take charge of a ward for 6 months first"—which is a hundred-year tradition of Peking Union Medical College Hospital. Within the half year, Li Zhang was the commander of the ward, that was to say, when she encountered any problem, she could ask Mentor Li for advices or consult other doctors, but finally Li Zhang had to make the decision on her own. "When you face the patients and find someone is with incurable disease, someone's diagnostic outcome is unclear, someone is worsening with treatment... you are under heavy pressure every day when you go into the ward, but you can't stop, because this is the sky that you are holding, and you have to hold it up and go on. Sometimes you will really feel that all of these stuffs of patients will 'torment' yourself to death." Abruptly, Professor Zhang said with delight, "But one day you will suddenly find a new world because you are able to take the patients out of danger. It seems that the sky you are holding is much higher than before."

In the eyes of Professor Zhang, the mentor's edification and patients' "spur" have played a great role in tempering her strong will.

She always believes it is good to be a doctor with the high standard imposed on herself, just as what her mentor has done.

A doctor, seeing patients

After graduation, Professor Zhang followed her heart to become a doctor of Respiratory Medicine in Peking Union Medical College Hospital. Up to now, she has been in clinic for more than 30 years.

Today, the vast majority of Zhang's outpatient patients take her as the "last stop." "I cannot be more right than now, that is her", this is the hearty word that some patients will speak out directly, while some will show on their faces. In other words, this reflects the patients' trust in Zhang.

How to treat a patient? Zhang has her own set of theory.

Professor Zhang attaches great importance to effective communication with patients, especially the approach to communicate. She believes, there are some key knowledge points that are necessary for patients to learn and understand. "If a doctor told the patient about lung adenocarcinoma, EGFR mutation, and EGFR-TKI treatment at his first diagnosis, normally the patient could not understand these professional terms. However, if the patient is told with his diagnosis outcome, the characteristics of the disease and the upcoming therapeutic schedule, and then go back to learn these knowledges. Gradually, he could understand and will be easier to communicate."

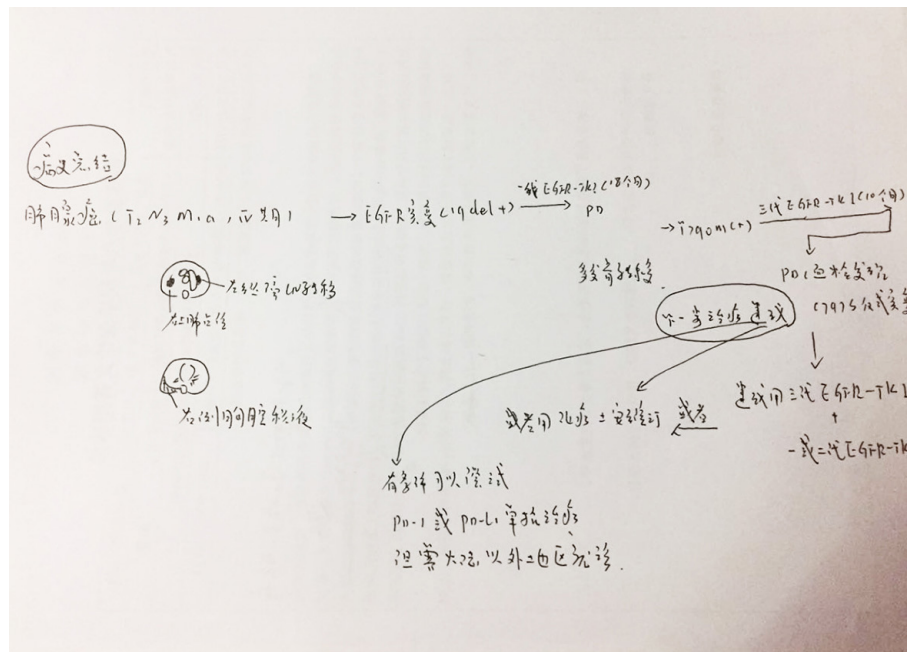


Figure 3 A schedule line of diagnosis and treatment drawn by Prof. Li Zhang.

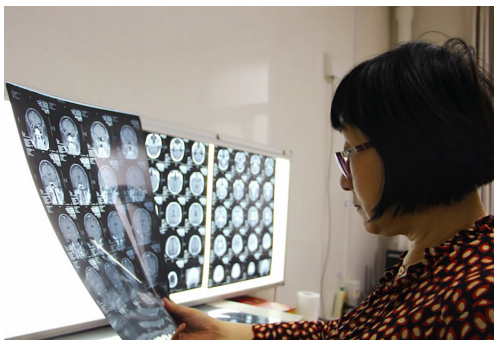


Figure 4 Prof. Li Zhang was working for a patient.

Only after the patients understand their own diseases and the treatments they receive, can they relax their minds and actively cooperate with the doctor's treatments. "However, you have to prevent the patients from feeling crazy in the process of guiding them in learning. As a doctor, you should pay attention to the patients' mood, and control the rhythm and manner of communication with them. If you run into a patient with lung cancer who asked 'How long can I live', you can not go on with this topic. In clinical practice, I often clear my thinking—first diagnosis, then therapeutic schedule, and then follow-up." In order to let the patients better understand and accept her treatment, Professor Zhang even will draw out a schedule

line of diagnosis and treatment (Figure 3).

Professor Zhang was drawing for her patient while speaking in the interview "lung adenocarcinoma → EGFR mutation → 19 exon deletion → to take 2nd generation of EGFR-TKI → drug resistance → T790M mutation → to take 3rd generation of EGFR-TKI → C797S mutation → back to take the 1st or 2nd generation of EGFR-TKI".

In clinic, Professor Zhang is so meticulous that she deeply moves the people around. For example, at the first time she met a lung cancer patient (who has received multiple examinations and treatments in other hospitals), Professor Zhang would unfold the imaging materials according to their time order, and then compared one with another. Initially, she would identify the number of nidi, their sizes and characteristics; with comparison of next image, she would look for the changes of nidi, the point-in-time that these changes occurred, and the treatments during these changes, and explore the reasons for the changes: Is it due to inadequate treatment, or the emerging of a new target for drug resistance, or because the patient missed taking drugs; then next image.... One by one, Professor Zhang reviewed all the information of the patient brought from other hospitals (Figure 4).

Sometimes, Professor Zhang may spend 40 minutes on a patient.

“Lung cancer, is quite complex, and pretty hard”, Professor Zhang said to herself. As long as a doctor treats the patient attentively, the patient will certainly be touched.

In the eyes of Professor Zhang, many patients are smart and interesting. Every time when she encounters such a patient, she will find the joy as a doctor. Once a provincial leader went to see Professor Zhang accompanied by a health physician, bringing a pile of imaging materials. Professor Zhang compared all the imaging and therapeutic schedules, and gave her advice, *“Don’t worry. You don’t need to do anything. Observe first, and come back to check in one year.”* Usually the health physician would first question the doctor, but then the provincial leader said first, *“Well, so goodbye.”* And the health physician had to say “goodbye”. One year later, when they came back to follow up, the health physician said frankly to Professor Zhang, *“Our leader is particularly careful. But last time after you read the imaging, he told me that there was no need to question you with any doubt, just leave as you suggested. I asked why. He said, when he saw you had read every slid so carefully, he believed you must have treated his case seriously. You are so meticulous, much meticulous than him!”*

Professor Zhang does not like to be flattered with the words like *“A goddess bringing the dying back to life”*, *“Superb medical skills”*. She thinks that she is just a “worker”. She prefers to be seen as a “craftswoman”, who builds a clinical case into a small garden, and she thinks this is marvelous. *“I can do a wonderful job as a doctor, I think, I enjoy this kind of feeling.”* Professor Zhang said.

Clinic work and scientific research are inseparable

In addition to clinical work, Professor Zhang is burdened with tremendous clinical researches. *“Put the clinical practice throughout the clinical trials, naturally the research awareness is cultivated”*, this is her daily status at work.

In the field of scientific research, Professor Longyun Li has assigned Zhang to independently preside the research project of IPASS for the hospital even though she was still a green hand at that time. IPASS was a large-scale, randomized, open-label, phase III clinical trial in the pan-Asia-Pacific region, which pushed Li Zhang to regularize herself with the high standard of good clinical trial (GCT) in international clinical research from the very beginning of her clinical study and practice. Finally, the Top 10 research institutes were rewarded, and Peking Union Medical College Hospital happened to rank at No.10. We asked why she was rewarded, she replied, *“Because of the quality and*

quantity. The number of enrolled groups, is quantity; intact data of clinical cases, is quality (only few cases were useless). Moreover, when the IPASS project was inspected by US FDA, my cases in IPASS came out to be the positive examples.”

Professor Zhang said, *“Before we start a clinical study, we must review all the developments of the research field, find an innovative point of the study, determine its objective, and then design the research program—whether it conforms to science and ethic, is feasible or not. Only gone through all the contents, it is a complete clinical study. Through this process, we get to know the forefront of the research field, and the clinical study must be forward-looking.”*

At her young age, Li Zhang was able to manage maximum eight clinical trials at the same time. The work of enrolling patients, filling forms, follow-up, and summary was all completed by herself. *“I am particularly benefited from the training of clinical research, for it has not only trained my research capability, but also my clinical competency,”* said Professor Zhang. Now the clinical researches that Professor Zhang engages in have gradually become the assured brands among peers.

This year a clinical study pertaining to PD-L1 monoclonal antibody was planned to enroll 360 patients. However, when it was enrolled with 240 patients, the therapeutic group showed absolute advantage. If it was continued to enroll, the study would violate the ethic. Then a research staff delightedly came to tell Professor Zhang, *“Good news. This study is going to end up in advance.”* Nonetheless, Professor Zhang did not show any excitement, which made the staff disappointed. *“I have foreseen this result. The study should be terminated much earlier,”* Professor Zhang said peacefully. In fact, Professor Zhang has already concluded the study, and found that patients with lung squamous cell carcinoma acquired a better therapeutic efficacy. The analysis showed an absolute advantage on patients with lung squamous cell carcinoma. Therefore, she decided to follow up the immunotherapy study of lung squamous cell carcinoma.

Clinical Work. Scientific Research. *“Now I feel my mind could not stop turning round and round,”* Professor Zhang said with a sigh.

“PUMCH” is not only pressure and impetus

Professor Zhang told us, the cultural atmosphere of PUMCH and those who have led her in profession are indispensable parts for her growth and achievement. She never directly “expels” patients. *“If it’s hard to diagnose the*

disease right away, I'll ask the patient to come back next time when I have made literature research."

When we asked Professor Zhang, "What PUMCH has brought to you is pressure or impetus?" She answered out of our expectation, "It's convenience."

Not long before, a patient with vulva cancer (squamous cell carcinoma) came to find Professor Zhang out of her fame. "Gynecological tumor is not treated in our department. I'm really not experienced in this field," Professor Zhang said to the patient. However, the patient replied, "You are good at immunotherapy, and immunotherapy is not limited to any tumor type." Professor Zhang had no way but to receive the patient, "Leave your phone number and go home first. I will discuss with you next week after I refer to related materials." According to the literature, there was only one small-sample phase I clinical study which was enrolled with 21 patients, and among them only 7 were with vulvar cancer. Immunotherapy is safe, but its therapeutic efficacy is not high, for its efficiency only reaches 17%. Given the immune drug has not been approved in mainland yet, and the patient was able to get access to the medical treatment overseas, Professor Zhang recommended him to find a doctor in Hong Kong.

In her eyes, if she was not the doctor in Peking Union Medical College Hospital, the patient would not believe in her words, because "everybody can search the literature". It is the Peking Union Medical College Hospital that offers her the "Convenience", which is the trust from patients.

Inflammatory pseudotumor used to be regarded as a benign disease, and so few scholars have researched on it in recent years. Professor Zhang once encountered a patient with inflammatory pseudotumor of pulmonary plasma cell, which was possible a malignant disease after her observation. She questioned, "It is recorded in the textbook that inflammatory pseudotumor is a benign disease, is it true?" Therefore, she went back to search the medical records in Peking Union Medical College Hospital together with her postgraduates and found 17 patients with similar disease. Combining with relevant literature at home and abroad, she finally concluded that inflammatory pseudotumor of pulmonary plasma cell is actually between benign and malignant. Considering that the patient was still a young man under 20 years' old, Professor Zhang advised him to go for surgery with his best effort.

Professor Zhang said, "This is the style how a doctor treat patients in PUMCH." Continued with laugh, "I would have not chosen to be a doctor if I had realized it was a toil."

As a staff in Peking Union Medical College Hospital, like many others, Professor Zhang always keep critical thinking on the diagnosis and treatment by peers, even though that is by her mentor. As to any viewpoint, she will subconsciously compare it with others and then comes up with her own thinking, she said, "Sometimes the perception from other people is more reasonable, while mines is not so comprehensive. Sometimes, I will insist on my mind."

In Professor Zhang's description, it often happens that two experienced professors "almost spark a fight" due to their divergent opinions in the wards' round. Sometimes when a senior expert gives the diagnosis of tuberculosis, a young doctor will even speak out directly, "However, Professor, I do think this is more prone to be lung cancer." Such an interaction is quite normal to see in Peking Union Medical College Hospital. Conversely, it is abnormal if someone does not act in this manner.

Professor Zhang said, "PUMCH has offered a free room for us to think independently, and we have developed a habit of independent thinking."

Young generation should not care for fame or fortune

With the same hope of her mentor Professor Longyun Li, Professor Zhang also hope that her students could pass down the spirit of PUMCH to become an excellent doctor and scholar.

Recently, the hospital admitted a 17-year-old boy from Xinjiang Province, the northwest of China. Recurrent pulmonary shadow was found in his body and had an increasing tendency. A young doctor in Professor Zhang's department independently traced the boy's family history and found that several boys in the patient's latest three generations and seven or eight newly established families of collateral series died young. The patient was the oldest survivor, and there were still two boys who were 2 years old and 3 years old respectively. Later, the young doctor sent the patient's information to test in the genetic center in order to find out whether the patient has got chromosomal abnormalities.

Professor Zhang is gratified to see young people with free and strict logical thinking. In her own words, she likes to see the people around at a positive state, and worries to see frustration and oppression. She likes to encourage young people. Even if they do make mistakes, she will choose to accept and clearly tell the "children" how to do in the future.



Figure 5 In 2017, Prof. Li Zhang was awarded for her outstanding contribution to respiratory research and giving a speech.



Figure 6 A candid photo of Prof. Li Zhang.

Once a postgraduate student of respiratory medicine took her intern rotation to the Department of Hematology. At her night shift, a 70-year-old patient with advanced lymphoma suddenly got a fever at 40 degrees. *“We could not give you the antipyretics because you are at arrear,”* she told the patient. In desperation, the patient scratched her with hands. Afterwards,

the student could not help but kept crying.

Then the Education Department of PUMCH gave a call to Professor Zhang who was still at a meeting out of Beijing. When she came back, she interrogated her students with a series of questions, *“Are you aggrieved because of being ‘Scratched’? In this case, do you think only you are the aggrieved one? Are you the most aggrieved? He is an elderly patient with advanced lymphoma who is also the old patient of the PUMCH. Late at night, you as the doctor on duty however could not resolve a problem of cheap antipyretics. Can’t you coordinate step by step and lend him a piece of antipyretic? He is 70 years old, with high fever staying in hospital, and there is no one to help him bring down the fever. Do you think he is not aggrieved? Have you told his families of arrear when they visited at 8 o’clock in the evening? Have you ever thought whether you would be wrathful if you were the patient or family? Let alone, the patient’s families have apologized to you.”*

“I think your best choice is to go to work with jolly tomorrow. Just treat the old man as if nothing has happened.” Finally, Professor Zhang said with the student.

Nowadays young people face heavy pressure on research. But in Professor Zhang’s view, there is no perfection in the field of scientific research. She will never take the “high-quality” research outcomes as her only pursuit, and will not impose harsh requirements on students. She believes that scientific research should be realistic, and release the valuable findings within a timely scope (Figure 5). Professor Zhang focuses more on training students the ability to extract, analyze, summary and self-improve in a timely and systematic manner, because only one goes through induction and writing, can he understand what to do next.

“Some data is missing, but that is the fact, so there is no need to piece up. Take the example of a study five years ago, how to make it up?” Professor Zhang said, *“As long as a scientific research demonstrates its factual results without fraud and is able to illustrate a certain question and provide some clues for future research, it is a good research. If it can not answer a huge question, then just answer a small question.”*

Professor Zhang hopes to see her students surefooted at work and positive in life (Figure 6). Don’t let it go when you are able to do something. *“Today you must compete for the advanced title, tomorrow for promoted position.... This is terrible. You will be promoted sooner or later, as long as you don’t give up.”*

Professor Zhang said, *“I am particularly fearful to foster an utilitarian student.”*

Dialogue with Li Zhang

AME: *Lung Cancer Precision Medicine is at the apex of medical trend. What is the major accomplishment and future direction of researches on EGFR signaling pathway?*

Professor Zhang: One of the milestones in the process of Lung Cancer Precision Medicine is the EGFR signaling pathway. The emergence of EGFR-TKI has extended the survival time of Non-Small-Cell Lung cancer patients from 8–10 months to 36 months, or even longer.

However, the progress of EGFR signaling pathway is as if the police catches the thief. When the drug blocks one section of EGFR signaling pathway, it may come out from another section, or even some new gene mutation will emerge which results in the fleeing of tumor cells eventually.

Now, the latest third-generation EGFR-TKIs has good therapeutic efficacy on 60% of the patients with T790M mutation and drug resistance to the first-generation EGFR-TKI, which shows that the patients' survival period is obviously prolonged. The second-generation EGFR-TKI has brought us the new hope as it is able to cover the rare target which is uncovered by the first and third-generation EGFR-TKIs. Even more, after some patients obtain resistance from the third-generation EGFR-TKI, they show sensitivity to the first and second EGFR-TKIs.

In short, as a doctor of lung cancer, we now have many studies on mechanism and so many new drugs and therapies. We can have a long-term friendship with patients, instead of saying "goodbye" after meeting several times.

We need more exploration in the future and there is still a long way to go.

AME: *What are the characteristics of doctors and patients nowadays?*

Professor Zhang: As the times has changed, the way of how doctors giving treatments are different. I often tell my patients that they need IQ to see a doctor, and should learn how to see a doctor. As a doctor, we need to upgrade ourselves. If we don't keep ourselves in the forefront, we might not be able to understand and answer patients' questions.

The purpose of guiding young doctors, patients and families to learn is to engage everyone into a communication with a common language, so that the communication can be smooth. In this way, doctors, patients and families can have the same expectation on treatment, and they have more to share.

Usually, it is not easy to communicate with the outpatients at the first couple of times. However after a period of time,

the communication will become much smooth because the patients and families keep learning as well, they even understand ahead of our explanation.

Now the relationship between doctors and patients are not only traditional, but also stamped with the stigma of the era owing to the knowledge explosion and internet's popularity, which requires doctors to sort out and remove the fragmented pseudo-scientific knowledge from patients and their families.

AME: *It seems that you disagree with the saying of "Equal information between doctors and patients". Why?*

Professor Zhang: How can you make the information known to doctors also known to patients? It's not necessary and not possible. It depends on the patients whether the information is equal between doctors and patients. To an ordinary patient, do you think he can reach the same information level as the doctor does only through the doctor's explanation? How can a doctor pass his knowledge accumulated in decades to a patient in short time? Impossible. Therefore, there is not such a saying of "Equal information between doctors and patients". Medical science is different from other disciplines. In addition to theories and knowledge in textbooks, what more important is the experience and lessons that doctors have accumulated.

Compared to the patients, doctors must stand at a high ground to schedule the diagnosis and treatment for the patients. If necessary, it just requests the patients to understand a particular part of the knowledge.

AME: *Is your habit "to take everything seriously"?*

Professor Zhang: The whole PUMCH is a place where everyone pursues quality. In the clinical work of PUMCH, only the leaders would not say to us with such words, "Could you please not take it so seriously?" When you get used to taking everything seriously, you will enhance your ability to make decisions at critical time.

In our clinical work, we have lots of similar experience. Every clinical case is permeated with the strict thinking of our PUMCH staffs.

Some time ago, a Chief of a health bureau in China was found with pulmonary shadow. He has visited a number of hospitals for suggestions. Some doctors diagnosed ambiguously while some said there was nothing serious. He came to see me eventually and I gave him the only therapeutic suggestion: surgery. The patient wondered

whether there was a possibility of pharmacotherapy, but was negated by my insist on surgery. Eventually the patient received surgery. Actually, such a “clinical feeling” was not groundless, instead, it was based on years’ accumulation. In a word, be unambiguous at critical moment, and be brave to take responsibilities!

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Footnote

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