·临床病理讨论·

Clinicopathological Conference

A 60 year old man with chest upset, breathholding, lower extremity edema and nocturnal dyspnea

(the eighth case)

Case presentation

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The patient, a 60-year-old male, was admitted to CCU of Fuwai Cardiovascular Hospital, Chinese Academy of Medical Science, on Dec 22, 2002, for intermittent chest upset for 10 years, breathholding and edema of lower extremities for 1 year, and nocturnal dyspnea for 2 months.

Ten years ago, he began to suffer from precordial discomfort after exciting and exertion and was suspected to have angina pectoris. The symptom was not alleviated after taking aspirin and traditional Chinese medicine. One year ago, he was diagnosed as old myocardial infarction, anterior, in local hospital and began to take nitrates. Meanwhile, proteinuria (+ + to + + +) was discovered and edema occurred on the lower extremities. Two months ago, the symptom of breathholding became more severe and nocturnal dyspnea occurred. The total volume of 24-hour urine decreased to 1L. He had no history of hypertension, diabetic mellitus, tuberculosis and connective tissue diseases.

Physical examination: BP 100/60 mmHg, clear-mindedness, no conjunctiva pallor, and no macroglossia. His jugular veins could be seen engorged. There was dull percussion on both lower lungs with decreased vesicular breath sound. No rales and pleural friction rub were detected. His left heart realm was a little increased. The heart rate was 88/min with regular rhythm. His heart sound was low, $P_2 < A_2$, and no cardiac murmurs were heard. His enlarged liver was touched without tenderness. Liver-jugular vein reflux was positive. Shifting dullness was doubtfully positive. There was pitting edema on his lower extremities. No abnormality was found in his nervous system.

Laboratory examinations: blood routine analysis: normal; 24-hour urinary protein: 4.2 g; Alb: 23 g/L; urinary RBC: 0-1/HP; SCr: 103 μmol/L; serum urea: 5.7 mmol/L; Glu: 5.3 mmol/L; ALT: 18 IU/L; AST: 29 IU/L; TG and Chol: normal; CK-MB: normal; plasmapheresis: no monoclonal globulin; serum calcium: 2.26 mmol/L; phosphorus: 1.15 mmol/L; HBsAg(-), ANA(-); ESR: 23 mm/h; CRP: 4.6 mg/L; ECG: sinus rhythm with Ⅱ° AVB, Mobitz type Ⅰ, QS wave was showed on Ⅱ, Ⅲ, aVF, and V_1-V_6 leads. Chest X-ray showed mild pleural effusion on both sides and heart enlargement. Echocardiography revealed enlargement of both left and right atrium, mild thickness of left ventricular wall and interventricular septum, and mild to moderate amount of pericardial effusion. The left ventricular end diastolic diameter(LVEDD) was 5.3 cm, , and left ventricular ejection fraction (LVEF) was 53.6%. Abdominal ultrasonography showed enlargement of liver and both kidneys and ascites.

The patient was diagnosed as biventricular heart failure, nephrotic syndrome and was treated with positive inotropic agents, diuretics, nitrates and anticoagulants. The symptom of breathholding and edema were alleviated, but refractory hypotension persisted. High dosage of intravenous dopamine of 10 μg/(kg·min) was needed to maintain the blood pressure at the level of 90/60 mmHg, and massive protein was consistently present in his urine. No significant change was detected in ECG, however, increased thickness and uneven resonance of ventricular wall were found in UCG 15 days later. The amount of pericardial effusion was decreased.

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Clinicopathological Discussion

Dr. Qi Zhe (from CCU of Fuwai Cardiovascular Disease Hospital, Chinese Academy of Medical Science): This is an old patient with intermittent non-specific chest upset for 10 years, and began to receive normal treatment 1 year ago because of his breathholding and edema. According to his symptoms, physical examination and laboratory tests, we tend to believe that the etiology of his biventricular heart failure (mainly rightside) was a special kind of cardiomyopathy. The reasons for excluding the diagnosis of coronary heart disease (CHD) were as follows: ① No typical angina pectoris. ② No ST-T changes in ECG. ③ Nitrates could not alleviate his chest upset. ④ If the QS wave showed on lead Ⅱ, Ⅲ, aVF, V_1-V_6 was a manifestation of an old myocardial infarction, his left ventricular function should be worse than present. Also, abnormal movement of his left ventricular wall was not found in UCG. Therefore, cardiomyopathy may be more suitable to explain his ECG. ⑤ Right heart failure is hard to be explained by CHD if the patient did not have a history of right ventricular infarction. So, I would think it was a kind of cardiomyopathy that caused his cardiac hypertrophy. Typical hypertrophic cardiomyopathy could be excluded because of the age of onset, the symmetric hypertrophy of the right ventricle. Considering his refractory hypotension in combination with normal LVEF and plasma volume, I suspect that the etiology of the heart disease was amyloidosis. But how can it be definitely diagnosed and is amyloidosis the same cause of kidney disease?

Dr. Liu Gang (from Department of Nephrology, First Hospital, Peking University): The renal manifestation of the patient is nephrotic syndrome (NS). Several common causes of NS in the elderly should be considered, including diabetic nephropathy, renal amyloidosis, and renal injury due to neoplasm and multiple myeloma. Among them, only the diagnosis of renal amyloidosis could not be excluded: ① it is a high prevalent disease in the elderly, ② myocardial hypertrophy, biventricular heart failure and atrioventricular block are common manifestations of amyloidosis[1], with definite exclusion of hypertensive heart disease and hypertrophic myocardiopathy, ③ refractory hypotension persisted after improvement of left-side heart function, indicating the influence of amyloidosis on blood vessels, and ④ massive proteinuria without hematuria, and enlargement of liver and both kidneys are characteristics of renal and liver amyloidosis. The next step is how to give a definite diagnosis. Amyloidosis needs to be testified by staining the tissue with Congo red to demonstrate the presence of amyloid deposition. Renal biopsy in the hypotension patient is dangerous because severe bleeding is a common complication. Lingual biopsy may not be positive for Congo red stain without macroglossia. Biopsy by proctoscope may not be sensitive without abnormal defecation. It was reported[2] that skin biopsy is sensitive (97%) in finding amyloid in patients with amyloidosis and it is a simple, safe procedure. Refractory hypotension of the patient indicates extensive involvement of his blood vessels, so I believe that amyloid may be found in subcutaneous blood vessels.

Dr. Zou Wanzhong (from Department of Pathology, First Hospital, Peking University): Congo red stain is positive in basement membrane of sweat glands and arterioles of the patient. Coupled with clinical data, diagnosis of amyloidosis in this patient can be confirmed.

Dr. Qi Zhe: Amyloidosis is not a common cause of heart disease and has poor prognosis and poor response to therapy. The median survival time for patients with congestive heart failure is 5 months. Although heart function has been improved in this patient, his blood pressure is still hard to maintain at a safe level. It would be appropriate to give him colloid infusion and to stop using diuretics.

Dr. Wang Haiyan (from Department of Nephrology, First Hospital, Peking University): I agree with the diagnosis of amyloidosis. Next step is to make it clear whether it was primary or secondary. The patient has no history of chronic infection and connective tissue disease. The laboratory data showed a mild elevation of ESR, normal CRP and normal serum immunoglobulin, so we can exclude the possibility of secondary amyloidosis induced by chronic inflammation and multiple myeloma-associated amyloidosis. At present, I prefer the diagnosis of primary amyloidosis, which can be confirmed by potassium per-

manganate oxidation test for skin specimen. It needs to be mentioned that the prognosis of this disease is very poor. The median survival time of diagnosed patients is 17 months. Moreover, for those with congestive heart failure the median survival time is 5 months, and less than 5% of all the patients survive 10 years or longer from the time of diagnosis. At present, there is no satisfactory therapy for these patients. Recently, several studies have showed that stem cell transplantation can improve significantly the prognosis of patients in early stage, but for the patients with heart involved, especially with heart failure, stem cell transplantation may increase their mortality[4,5]. Therefore, it is not appropriate for the patient to receive this therapy. Since the patient is in late stage of amyloidosis, the therapy with melphalan combined with prednisone will not take effect. Also, the patient may not tolerate it well. In this situation, the only thing we can do is to alleviate his symptom, to stop using diuretics, and to maintain his blood pressure at a safe level.

(Translator: Liu Gang, Li Jianping)

Reference

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心前区不适、憋气、肾病综合征、低血压

1 病例摘要

男,60 岁。因发作性心前区不适 10 余年,憋气、双下肢水肿 1 年,加重伴夜间不能平卧 2 个月,于 2002 年 12 月 20 日收入阜外心血管病院 CCU 病房。患者于 1992 年开始在生气、劳累后出现心前区不适感,伴出汗,无心悸,每次约持续半小时,含速效救心丸后数分钟能减轻,每日可发作 2 ~ 3 次,当地医院诊为"冠心病、心绞痛",服偏方及阿斯匹林治疗无好转。2001 年 11 月,因憋气、双下肢水肿,在当地医院查心电图提示"陈旧性前壁心肌梗死",尿蛋白 + + 至 + + +,间断服硝酸酯类药物及阿斯匹林。2002 年 11 月开始,上述症状加重,活动后憋气明显,夜间不能平卧,尿量减少至每日约 1L,纳差,大便尚正常。为进一步诊治收入院。既往无糖尿病、高血压、结核病及风湿类疾病,家族中无类似疾病者。

入院查体:BP 100/60 mm/Hg, 神清,睑结膜不苍白,舌不大,颈静脉充盈,双下肺叩浊,呼吸音略低,未闻及啰音及胸膜摩擦音,左心界稍大,心率 88 次/min,律齐,心音低钝,$P_2 < A_2$,未闻及杂音、附加音及心包摩擦音,腹平,肝于肋下 4 cm 可触及,质中,无压痛,肝颈回流征阳性,移动性浊音可疑阳性,双下肢可凹性水肿,双侧足背动脉搏动正常,神经系统检查未见异常。

辅助检查:血常规正常;尿蛋白定量 4.2 g/d, Alb 23 g/L;尿沉渣镜检红细胞 0 ~ 1/Hp;SCr 103 μmol/L, Urea 5.7 mmol/L;空腹血糖 Glu 5.3 mmol/L, ALT 18 IU/L, AST 29 IU/L,血脂正常;多次查心肌酶正常;血清蛋白电泳未见 M 带,血清钙 2.26 mmol/L,血清磷 1.15 mmol/L;乙肝病毒血清学指标(-), ANA(-);ESR 23mm/第 1 小时,CRP 4.6 mg/L;心电图:窦性心律,QRS 波在 Ⅱ、Ⅲ、aVF、$V_1 \sim V_6$ 导联 QS 型;心电监护可见到Ⅱ度Ⅰ型房室传导阻滞;X 线胸片示双侧少量胸腔积液,心影增大;超声心动:左右心房增大,左室舒张末期内径 5.3 cm,左室壁及室间隔稍厚,左室壁运动欠协调,LVEF 53.6%,各瓣膜形态结构正常,少量至中量心包积液。腹部 B 超:肝大、双肾增大、腹水。

入院初步诊断:全心功能不全待查,蛋白尿待查。

患者入院后,经强心、利尿、硝酸酯类药物及抗凝治疗,憋气水肿减轻,但出现长期顽固性低血压,多巴胺用量在 10 μg/(kg·min)以上才能将血压维持在 90/

60 mmHg，仍为大量蛋白尿，多次复查心电图并与以前比较未见明显变化，半个月后超声心动与前次比较的变化有：室壁增厚，右室壁厚 1.0 cm，左室壁及空间隔厚 1.4 cm，回声增强且不均匀，心包积液明显减少。为明确心血管及肾脏疾病的诊断、决定下一步治疗，两医院相关专业的医师进行了会诊。

2 临床病理讨论

祁哲医师：患者老年男性，先有近 10 年的非特异的发作性心前区不适感，一年来因反复憋气、持续水肿才接受比较正规的诊治，开始有心脏病及肾脏病的医疗记录。根据病史、查体、入我院前后的检查，我们现已倾向于患者所患的是一种心肌病导致的全心功能不全（右心衰竭为主），冠心病的可能性很小，理由是：①病史中没有典型的心绞痛症状。②心电图无明显动态改变。③硝酸酯类药物对于缓解症状效果不明显。④Ⅱ、Ⅲ、aVF、V_1～V_6 导联 QS 型 QRS 波，若源于陈旧心肌梗死，其左心功能应比目前差，超声心动也会发现左室壁节段运动异常，这些在该患者身上都无突出表现；另外，上述心电图改变并不是陈旧心肌梗死所特有的，心肌病也可有类似表现。⑤冠心病患者若右心功能不全，一般出现在右室心梗后，而现有检查表明该患者不存在这种情况。初步除外冠心病之后，结合超声心动显示患者心室壁增厚、回声增强，既往无高血压，因而考虑是一种心肌病变。再根据患者起病年龄大，表现为对称性肥厚且右心功能不全为主，我们已除外典型的肥厚性心肌病，而认为是一种特殊类型的心肌病。结合左室射血分数较好且无血容量不足的情况下，出现顽固性低血压，我们曾考虑过淀粉样变性病（AM）的可能，但应如何确诊？肾脏病是否为同一疾病？能否通过肾穿刺病理诊断？请肾脏专业的医师会诊，帮助我们明确。

刘刚医师：患者目前肾脏病临床表现为肾病综合征（NS），对于老年男性，应首先注意几种常见的继发病因。患者血糖正常可以除外糖尿病肾病；没有实体肿瘤证据可以除外实体肿瘤所导致的肾病；没有单克隆免疫球蛋白血症及骨痛、高钙血症等溶骨表现，可初步除外多发骨髓瘤肾病。但另一个常见继发 NS 的病因——AM 在该患者中却有很多比较确凿的支持点。一是患者正处于本病的高发年龄；二是心肌肥厚、全心功能不全、房室传导阻滞不能用临床上常见的高血压心脏病、肥厚性心肌病解释，而这些都是心脏淀粉样变性病的很常见的表现[1]；三是经治疗左心功能改善后，血压更低，不易纠正，提示 AM 已累及了全身血管；四是患者以大量蛋白尿、双肾增大为主，没有血尿，符合肾淀粉样变性病的特点；最后，肝大虽然可能是右心功能不全造成的，但也不除外 AM 的参与。最后还需要鉴别一种情况，在很少的患者中，右心功能不全可以引起短暂的大量蛋白尿，但达到 NS 程度毕竟更少，且心功能改善后患者的尿蛋白未减少，再者毕竟同时还有多系统损害，因此可以除外这种可能。经分析推断，最后只有 AM 的可能性最大。那么，该如何确诊呢？本病需要病理刚果红染色检查才能明确。但是肾淀粉样变性病肾穿刺后大出血的可能性很大，目前患者的血压尚不稳定，处于危险期，因此应慎行肾穿刺；患者舌不大，舌活检的阳性率可能不高；无排便异常，经直肠镜活检阳性率也可能不高，且患者也不易耐受；有报道[2]表明皮肤活检的阳性率可高达 97%，虽然在另一些学者的工作中未予证实，但其创伤最小是不争的事实，而且本例患者顽固性低血压表明其全身大小动脉都广泛受累，皮下的小血管很可能有淀粉样物质沉积，使刚果红染色阳性而得到确诊，因此，我们推荐患者接受了腹部皮肤活检。

邹万忠医师：（北京大学第一医院病理科）皮肤标本可见真皮及皮下组织中汗腺基底膜及小动脉壁刚果红染色阳性，结合临床符合 AM。

祁哲医师：AM 诊断现已明确，这是心脏病的少见病因，自然预后及疗效均很差。有报道累及心脏者中数存活时间约为 5 个月，而该患者 10 年“心脏病史”不好解释，可能近一年才是患者本病真正的病程。目前患者心功能虽有改善，但难以维持血压稳定，通过慎重的补充胶体、停用利尿剂，可能会有所好转。对于本病及肾脏损害，肾脏专业的医师还有什么诊治意见？

王海燕医师：（北京大学第一医院肾内科）在诊断方面同意前面几位医师的分析，仅补充几点：①这是一例通过紧密结合临床资料、缜密推理与合理选择病理检查手段使患者得以确诊的很好案例，对于如何能够建立正确的诊断思路具有借鉴意义。通过诊断本例患者，更进一步表明，扎实、广泛的内科学基础以及跨学科合作在临床工作中的重要性。②虽然 AM 已确诊，但还应进一步区分是原发性还是继发性。患者无长期感染及结缔组织病表现，ESR 仅稍高，CRP 正常，可以除外慢性炎症引起的继发性淀粉样变性病。现有临床资料已初步除外多发性骨髓瘤，也就除外了由它伴发 AM 的可能，必要时可做颅

骨 X 线平片、骨穿进一步明确。目前能诊断原发性 AM，可在病理标本上做高锰酸钾试验予以验证。③关于治疗的问题，需要指出的是本病预后很差[3]，患者的中数存活时间 17 个月，心脏受累者约为 5 个月，目前尚没有满意的治疗方法。近来一些临床研究表明，早期进行骨髓移植可明显改善患者预后，但同时显示心脏受累后、特别是心功能不全者死亡率反而增加[4,5]，因此，该患者不能接受这种治疗。传统的马法兰和泼尼松化疗方案疗效并不满意，恐对患者的心、肾病变难有疗效，因此，目前只能对症治疗。停用利尿剂，可能有利于改善血压。

（参考文献见第 54 页）

·论著摘要·

慢性阻塞性肺病合并多器官功能障碍综合征 PMN 凋亡和 IL-8 水平检测

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中性粒细胞（PMN）、白细胞介素-8（IL-8）是参与多器官功能障碍综合征（MODS）的重要细胞和分子[1]。我们于 2000 年 10 月至 2002 年 3 月检测了慢性阻塞性肺病（COPD）合并 MODS 患者的 PMN 凋亡、IL-8 水平，旨在揭示其病理生理机制，为 COPD 合并 MODS 防治提供依据。

1 对象与方法

选择 COPD 患者 65 例，合并 MODS 26 例，其中男 47 例，女 18 例，年龄 60～86 岁。正常对照组 19 例，男 12 例，女 7 例，年龄 60～78 岁。COPD 患者以及正常对照组分别空腹采血制备血清和分离 PMN。调细胞数为 1×10^6/ml，10%小牛血清 RPMI1640 培养液，37℃、5% CO_2 培养 24 h。收集培养后的细胞，PBS 洗两次，用 75%乙醇固定 4 h，经 RNA 酶作用30 min，用流式细胞仪分析凋亡发生率[2]。血中 IL-8 测定：由解放军总医院科技开发中心提供放射免疫药盒，按说明书步骤测定。数据以 $\bar{x}\pm s$ 表示，采用 t 检验和直线相关分析。

2 结 果

表 1 表明，COPD 合并 MODS 患者 PMN 凋亡率明显低于单纯 COPD 和正常对照组（$P<0.05$），IL-8 明显高于单纯 COPD 和正常对照组（$P<0.05$），并且 PMN 凋亡率与 IL-8 二者之间呈负相关（$r=0.48$，$P<0.05$）。

表 1 老年 COPD 合并 MODS 患者与对照组 PMN 凋亡率及 IL-8 比较（$\bar{x}\pm s$）

组 别	人数	PMN 凋亡（%）	IL-8（ng/ml）
合并 MODS	26	$29.45\pm12.82^{\triangle *}$	$0.98\pm0.17^{\triangle *}$
单纯 COPD	39	$42.28\pm18.64^{\triangle}$	$0.72\pm0.11^{\triangle}$
正常组	19	56.31 ± 16.69	0.67 ± 0.09

注：与正常组比较 $^{\triangle}P<0.05$，与单纯 COPD 比较 $^{*}P<0.05$

3 讨 论

COPD 是以气流阻塞为特征、严重影响人民健康的常见病和多发病，尤其容易合并 MODS，病死率高。近年来，国内外研究进展十分迅速，但是其发病机制复杂，某些环节尚不十分清楚，这给治疗带来了一定困难。已知 COPD 病理生理机制与其内环境改变有关[3]。本研究结果表明，老年 COPD 患者 PMN 凋亡延迟，血中 IL-8 水平增高，尤其合并 MODS 者更明显。机体在感染后，血清中细胞因子适量释放，可延迟 PMN 凋亡，这样有利于局限性炎症的改善，提高机体防御能力，但持续过度释放会加剧炎症反应。PMN 在气道聚集、激活，发生脱颗粒，释放溶酶体酶、炎症介质、自由基，促进炎症进展过程，一旦炎症反应失去控制造成多组织器官受损，则发展为 MODS。PMN 凋亡是维持组织、器官和血循环 PMN 数目、功能的主要机制，适时适度清除 PMN 可控制炎症的发生、发展和转归[4]。因此，从降低 IL-8 水平，调节 PMN 凋亡，来抑制气道炎症，防治 COPD 合并 MODS，是具有广阔前景的研究方向。

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