· 临床病例讨论 ·

Clinicopathological Conference

A 60-year-old male patient with cough, dyspnea and fever

(the 36th case)

Department of Respiratory Disease, Chinese PLA General Hospital

Case presentation

The patient, a 60-year-old male, was admitted to the hospital on Apr 30, 2009 because of cough and dyspnea for 1 month, fever for half a month.

In May, 2005, the patient was diagnosed as chronic renal failure, uraemia. In November, 2005, he received the operation of kidney allograft and took immunosuppressive agents orally after the operation. He used sirolimus and prednisone before hospital admission. On April 2, 2009, the patient had a cough productive of white sputum after catching a cold, with shortness of breath, without chest pain and fever. The symptoms were relieved after taking some cold medicine. On April 13, 2009, the patient started to feel shaking chills with rigor and fever (the highest temperature was 39.1℃), he visited Chinese PLA General Hospital and conducted the blood routine test, chest CT scan and the G test. He was diagnosed as "fungal infection" and took voriconazole for one week then fluconazole before he was admitted. However, he still had fever, the highest temperature reached 37.3℃, without night sweat. The symptom of dyspnea was not relieved. In order to further diagnose and treat the disease, the patient was hospitalized with pneumonia and post-renal transplantation.

Physical examination: the temperature was 37.2℃, pulse 78/min, respiration 17/min, and BP 110/60 mmHg. The patient was fully conscious. His eyelids were swollen. No cyanosis was found. The respiratory sounds were clear and a small amount of moist rales were heard at both lungs. The heart rate was 78/min. Cardiac rhythm was regular and no pathologic murmur was heard at auscultation areas. The abdomen was flat, soft and had no tenderness and rebound tenderness. The transplanted kidney was touched at the right lower quadrant of abdomen. There was mild edema over both legs.

Blood routine examination: white blood cell count 5.16×10^9/L, neutrophil 0.605, lymphocyte 0.279, hemoglobin 71.0g/L, CRP 51mg/L

Chest CT scan(Fig 1): Multiple plaque shadow and ground-glass opacity in bilateral lung fields and under pleura, locally formatted irregular cord shadow, especially in the right lung.

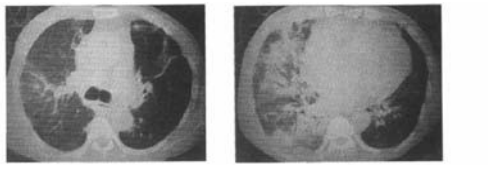

Fig 1 Chest CT on April 21, 2009 revealing multiple plaque shadow and ground-glass opacity in bilateral lung fields and under pleura, especially in the right lung.

Blood gas analysis: pH 7.385, PO_2 72.7mmHg, PCO_2 27.4mmHg, HCO_3^- 16.0mmol/L, BE-7.3mmol/L.

Pulmonary function test: Ventilation reserve percentage was insufficient moderately, and diffusion function declined severely.

After admission, the patient received treatment with antibiotics (meropenem, fluconazole injection), hepatic protectant and antihypertensive agent. Administration of immunosuppressive agents and prednisone (5mg, once

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daily) continued. The temperature of the patient was below 37℃, but the symptoms of cough, dyspnea were not relieved. On May 7, 2009, percutaneous lung biopsy was done to make a definite diagnosis. Pathological diagnosis: Fibrinous exudate, macrophages, foam cells and a small amount of inflammatory cells were seen in alveolar cavity. Loose fibrous tissue was found along the extension of alveolar and small airway (organization). Alveolar septum was widened irregularly, accompanied with interstitial edema and chronic inflammatory cell infiltration. Collagen deposition was seen around the blood vessels. Lung tissue culture: Candida albicans, sensitive to fluconazole. Because the symptoms of cough and dyspnea were not relieved, we considered the diagnosis of cryptogenic organizing pneumonia (COP) according to the patient's clinical manifestation. From May 7, 2009, prednisone was added to 20mg once daily in oral administration, and with continuous use of fluconazole. On May 18, 2009, the patient underwent again chest CT scan and results showed decreased shadows in the lung fields, but not significantly. On May 27, prednisone was added to 30mg once daily. On May 31, the patient was discharged, when the symptoms of cough and dyspena were significantly relieved. On June 22, this patient received the reexamination of chest CT at Out-patient Department, and the results showed that the shadows in the lung assimilated significantly (Fig 2). He had no fever and dyspnea.

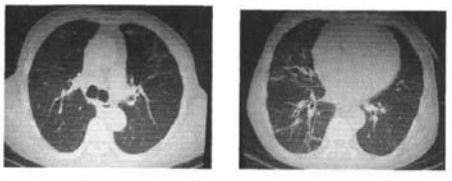

Fig 2 Chest CT on June 22, 2009 revealing the shadows in bilateral lung fields were absorbed obviously after therapy, with irregular cord shadow left

Clinical discussion

Dr. LIANG Zhixin (attending physician): This patient is an old male, who received the operation of kidney allograft 3 and a half years ago. After the operation, he took oral administration of immunosuppressive agents and steroid routinely. The chief complaint of this patient was cough, dyspena and fever. The chest CT scan showed multiple shadows in bilateral lungs. So the diagnosis was considered as pulmonary infection. Gram-negative bacillus was the most common pathogen responsible for pneumonia which occurred after organ transplantation. The G test of the patient was positive twice and the lung tissue culture was Candida albicans positive. Therefore, after admission, the patient received the therapy of meropenem, a broad spectrum antibiotic, and fluconazole as anti-fungal agent, which is really helpful to control the pulmonary infection.

Dr. SHE Danyang (associate chief physician): We should also take the factors beyond infection into consideration during the therapy. The pathological results of percutaneous lung biopsy showed a large number of foam cells and fibrinous exudate, pulmonary fibrosis significantly, hyalinization and accompanied by chronic inflammatory cell infiltration in alveolar cavity. So the diagnosis of COP could not be excluded. COP has a good response to steroid therapy. As we added the dose of prednisone, the clinical symptoms and chest CT scan images were improved. This verified the diagnosis of COP.

Dr. CHEN Liang'an (chief physician): I agreed with the analysis of the above two doctors. Pulmonary infection is a most serious disease after organ transplantation which has high mortality. It is one of the most important reasons which affect the success rate of organ transplantation. As a result of the application of immunosuppressive agents, bacteria, fungi, mycobacteria and viruses can all be the pathogens. The result of lung tissue culture was Candida albicans positive, which provided the evidence for the infection. Although the lung CT images showed diffuse bilateral lung disease, clinical symptoms of the patient were less serious, which was not consistent with the CT images. When reviewing the chest CT after the anti-infection therapy, we found little change in CT images, which suggested the possibility of other combined dis-

ease. The pathological examination of the lung displayed no infectious disorder, and the pathological changes were similar to COP. COP is an inflammatory lung disease, the key pathophysiological findings are related to the inflammatory pathway rather than the fibrosing pathway as in idiopathic pulmonary fibrosis. Histological features include clusters of mononuclear inflammatory cells that form granulation tissue and plug the distal airways and alveolar spaces. COP has good response to steroid therapy. So, as we added the dose of prednisone, the clinical symptoms and chest CT images improved. This verified our judgment. From this case, we can learn that, when treating this kind of patients, it is necessary to combine the clinical manifestations and pathological results together, and take into account not only the possibility of infectious diseases, but also the non-infectious diseases, so that we will not miss diagnosis or make misdiagnosis.

Pathological diagnosis

Results of percutaneous lung biopsy: fibrinous exudate, macrophages, foam cells and a small amount of inflammatory cells can be seen in alveolar cavity. Loose fibrous tissue can be found along the extension of alveolar and small airway (organization). Alveolar septum was widened irregularly, accompanied with interstitial edema and chronic inflammatory cell infiltration. Collagen deposition can be seen around the blood vessel. PAS staining (-). Acid-fast staining (-). Warthin-Starry(-). No bacterous was found. No "Masson Body" was found.

Summary

COP is a relatively rare disease. It is defined histopathologically by intra-alveolar buds of granulation tissue, consisting of intermixed myofibroblasts and connective tissue. The etiology and pathogenesis of COP are still unknown, but infection, drugs, transplantation rejection and connective diseases have been postulated. Cough and progressive dyspnea are common manifestations. High-resolution CT has an important value in diagnosis. A mild or moderate restrictive ventilatory defect is the most common abnormality at spirometry. The diagnosis of COP is usually suggested by clinical and radiological findings, but needs to be confirmed histopathologically. Rapid clinical and imaging improvement is obtained with corticosteroid treatment, but relapses are common after stopping treatment. In clinical work, more understanding of COP needs to be raised to avoid misdiagnosis.

(Translator: LIANG Zhixin)

60岁男性咳嗽呼吸困难伴发热患者1例

1 病历摘要

患者，男性，60岁，主因"咳嗽、呼吸困难1个月，发热半月"于2009年4月30日入院。

患者曾于2005年5月在解放军总医院诊断"慢性肾功能衰竭，尿毒症期"，2005年11月在解放军总医院泌尿外科行"右肾同种异体移植术"，术后长期服用抗排异药物，入院时服用西罗莫司和强的松片。2009年4月2日患者受凉后出现咳嗽、咳少量白色痰，时有气短，无胸痛，无发热，自服感冒药后稍好转，但仍有咳嗽。4月13日出现发热伴寒战，体温最高达39.1℃，来解放军总医院门诊查血常规、肺CT平扫和1,3-β-D-葡聚糖实验(G实验)，考虑不能除外真菌感染，给予"伏立康唑"口服1周后改为"氟康唑"口服，但仍反复发热，最高体温37.3℃，无盗汗，但呼吸困难症状无缓解，为进一步诊治，门诊以"肺部感染、肾移植术后"收入院。

查体：体温37.2℃ 脉搏78次/min，呼吸17次/min，血压110/60mmHg，眼睑水肿，口唇无紫绀，双肺可闻及细湿啰音，无干鸣音，心率78次/min，节

律齐，各瓣膜区未闻及杂音。腹平软，无压痛，无反跳痛，右下腹可触及移植肾，双下肢轻度水肿。

血常规：白细胞计数 5.16×10^9/L，中性粒细胞0.605，淋巴细胞0.279，血红蛋白71.0g/L，C-反应蛋白测定51mg/L。

肺CT平扫：双侧肺野内、胸膜下可见多发散在斑片状磨玻璃影，局部形成不规则索条影，以右肺明显。

血气分析：pH 7.385，PO_2 72.7mmHg，PCO_2 27.4mmHg，HCO_3^- 16.0mmol/L，BE -7.3mmol/L。

肺功能检测：通气储量百分比中度不足，弥散功能重度下降。

入院后给予美罗培南、氟康唑注射液抗感染以及保肝、降压等治疗，继续应用免疫抑制剂和强的松(5mg，1次/d)，患者体温波动于37℃以下，但咳嗽、呼吸困难症状未见明显缓解，2009年5月7日在解放军总医院行CT引导下经皮肺穿刺活检术，行病理检查和肺组织培养。病理结果示：肺泡腔内可见纤维素性渗出，巨噬细胞、泡沫状组织细胞及少量炎细胞，部分有疏松纤维组织沿肺泡及小气道伸延(机化)，肺泡间隔不规则增宽，间质水肿，慢性炎细胞浸润，血管周可见较多胶原沉积。穿刺肺组织真菌培养结果：白色念珠菌属，药敏结果对氟康唑敏感。因患者咳嗽、气短症状无明显改变，综合患者临床表现考虑隐原性机化性肺炎(cryptogenic organizing pneumonia，COP)不除外，所以5月7日激素加量为强的松20mg，1次/d，并继续应用氟康唑注射液0.3g，静滴，1次/d，5月18日复查肺部CT示双肺内多发片状影，与老片比较病灶略减少，5月27日强的松加量为30mg，1次/d，5月31日患者好转出院，出院时咳嗽、气短症状明显好转。6月22日患者门诊复诊，精神可，无发热，无咳嗽和呼吸困难症状，复查肺CT示肺部病变明显吸收好转。

2 临床病例讨论

梁志欣主治医师：患者老年男性，右肾同种异体移植术后3年半，术后长期应用激素和抗排异药物。本次发病以咳嗽、呼吸困难伴发热为主诉，肺部CT提示双肺野内多发片状阴影，诊断首先考虑肺部感染。革兰阴性杆菌在移植后肺部感染中是常见的病原菌，同时此患者G实验2次阳性，肺组织真菌培养结果阳性，为白色念珠菌，所以入院后及时应用强效广谱抗生素美罗培南抗细菌，同时用氟康唑抗真菌治疗是非常恰当的，为该患者肺部感染的控制提供了保证。

佘丹阳副主任医师：在该患者的治疗过程中还需要注意到感染因素以外的情况，该患者经皮肺穿刺的病理结果为肺泡腔内可见纤维素性渗出和巨噬细胞、泡沫状组织细胞及少量炎细胞，肺间质纤维化显著及玻璃样变伴多量慢性炎细胞浸润。根据此组织病理学改变，临床诊断上要考虑到COP的可能性，COP对激素治疗反应较好，所以该患者在抗感染治疗过程中将强的松加量后临床症状改善，肺部影像学也明显改善，进一步验证了COP的诊断。

陈良安主任医师：同意以上两位医生的分析。肺部感染是器官移植后感染的常见类型，常进展迅速，病死率高，是影响器官移植成功率的重要原因之一，由于免疫抑制剂的应用，细菌、真菌、分支杆菌以及病毒等都有可能成为致病原。本例患者穿刺肺组织培养明确了肺部感染的致病原为白色念珠菌，为感染的控制提供了病原学依据。该病例的特殊之处在于虽然患者肺CT表现严重，为双肺弥漫性病变，但其临床症状较轻，与影像学表现并不一致。抗感染治疗后复查肺CT变化不明显，提示合并其他疾病的可能性。病理学检查结果提示其存在非感染性病变导致的肺脏病理学变化，与COP的病理改变基本一致。COP本质上是一种肺部炎性病变，与以纤维化改变为主的特发性肺间质纤维化不同，组织学改变以单核细胞的聚集形成肉芽组织并阻塞远端气道和肺泡腔为特征。该病激素治疗效果好。基于此，将激素强的松加量，患者临床症状得到了改善，肺部影像学也明显好转，证实了COP的判断。因此，今后在此类肺部弥漫性病变患者的诊治过程中，要将患者临床表现与病理结果相结合，既要考虑到感染性疾病的可能，又要重视非感染性病变并存的可能性，才不会漏诊和误诊。

3 病理诊断

经皮肺穿刺活检病理结果：肺泡腔内可见纤维素性渗出，巨噬细胞、泡沫状组织细胞及少量炎细胞，部分有疏松纤维组织沿肺泡及小气道伸延(机化)，肺泡间隔不规则增宽，间质水肿，慢性炎细胞浸润，血管周可见较多胶原沉积，特染PAS(-)，抗酸染色未见抗酸杆菌，warthin-starry(-)，细菌学检查未见细菌，未见到典型Masson小体。

4 总 结

COP是一种临床少见病，以细支气管以下气道

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2.5.2 对糖尿病及肾脏病的治疗，已累积大量证据，应给予更积极治疗，更早开始，目标血压应更低，早期肾脏损害的标志如微蛋白尿，肾小球滤过率下降应高度重视。指南明确提出利尿剂和β受体阻滞剂可能恶化胰岛素耐受，不宜在糖尿病患者中作为首选，ARB 可能具有更大优势，尤其是对 2 型糖尿病及肾病患者。肾脏病者有时需联合使用降压、他汀及抗血小板活性药。

2.5.3 对合并脑血管病史者降压可明显减少中风复发与心血管事件，血压应＜130/80mmHg。对急性脑血管病患者的治疗，有多个试验正进行，目前主张应待情况稳定后降压，一般至少在数天后。降压可能对改善认知与痴呆有益。

2.5.4 心肌梗死存活者尽早给与β受体阻滞剂、ACEI、ARB，可减少梗死再发与死亡，主要机制是由于药物的保护作用，小部分与降压有关。最近证实，慢性稳定冠心病降压也有益，包括 CCB 的应用，血压＜140/90mmHg 者也可用药，目标约 130/80mmHg。AHA 2007 的新建议也主张血压应＜130/80mmHg；伴心衰者血压应小心降达＜120/80mmHg；但不主张β受体阻滞剂用于冠心病与中风的一期预防，对指南上述降压目标及β受体阻滞剂应用的建议，国外反馈意见尚不一致。

2.5.5 代谢综合征 目前对其意义的评估认识不一，在欧洲指南中较为重视，并有较深入评述，指南认为代谢综合征之血压正常高值者应考虑降压。

2.5.6 伴随危险因素的治疗 指南推荐对所有伴心血管病或糖尿病者，均应考虑他汀治疗，使总胆固醇＜4.5mmol/L，低密度脂蛋白＜2.5mmol/L 或更低；即使基础胆固醇及低密度脂蛋白不高，无明显心血管病，但属高危患者也考虑使用。对抗血小板药物的使用，指南推荐仅限于已有心血管病事件者，必须使用小剂量阿司匹林、且总心血管危险已为 15%～20%、血压已有效控制（＜140/90mmHg）、并且无出血倾向者。当前国内对阿司匹林常过分强调应用，对出血问题重视不足，尤其脑出血，某些基层甚或三甲医院当患者收缩压高达 170～180mmHg 时仍嘱患者使用，并采用大剂量，值得共同关注。对糖尿病的血糖控制推荐空腹＜6mmol/L，糖化血红蛋白＜6.5%。

3 小 结

在 2003 年欧洲指南及美国 JNC 7 发布以来，正从不同方面改变着高血压的防治。2007 指南集中反映了在高血压的全面评估、检测指标、药物应用与联合用药、特殊人群的处理等方面的进展，尤其是对新近研究成果及汇总分析的科学评估，危险因素及器官损害的标志，药物的合理选择，一些目前有争论的问题，均有正面的、清晰的提示。更新了评估指标，强调了及早降压，更严格更快降压，强化药物治疗，要求防治重心前移。内容贯彻了循证医学的原则，符合临床思维，在许多看似细节的地方，体现了专家组的良苦用心。2007 指南具有教育性、实用性、平衡性、客观性等特点，是高血压及相关领域很有价值的参考资料。我国指南也具有该指南的众多优点，主要观点很接近，且刚发布不久，目前关键是如何贯彻，2009 年将要进行某些更新。JNC 8 已在酝酿中，在 2009 年发布，也值得期待。个人体会 2007 指南的缺点，是某些地方稍显繁琐，如血压分类，单用与联合用药流程等。

（上接第 467 页）

内炎症渗出物机化后形成肉芽组织为病理特征，其病因和发病机制不明，可能与感染、药物、移植排斥和结缔组织病等多种因素有关。临床表现为咳嗽和进行性呼吸困难，高分辨 CT 对临床诊断有重要价值，肺功能检查常提示轻度或中度限制性通气障碍。临床上常根据临床症状和影像学表现考虑到 COP，但需要组织病理学检查来进一步明确，COP 对糖皮质激素治疗反应良好，可以使临床症状和影像学变化迅速改善，但停药常导致复发。在临床工作中要提高对 COP 特征的认识，防止误诊。

（参加讨论医师：梁志欣、余丹阳、陈良安）

（梁志欣 整理）