·临床病理讨论·

Clinicopathological Conference (the 46th case)

An elderly patient with lung defect caused by ANCA associated small vessel vasculitis

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Case presentation

A male patient, 89 years old, was admitted to our hospital on January 11, 2007 mainly due to "dry cough and nasal congestion for more than half month, and aggravation of the condition for one day". Half month ago, the patient began to suffer nasal congestion and paroxysmal dry cough with unknown cause, accompanied by headache, weakness, left facial pain, joints pain and decreased physical endurance. He had no symptom of hemoptysis, fever, chills, nausea, vomiting, chest pain or chest tightness. The patient visited hospital because of aggravation of the condition for one day. The physical examination revealed moist rales in the left lower lung field. Parameters of routine blood test were as follows: WBC 9.9×10^9/L, NE 75.5%, HGB 120g/L, PLT 270×10^9/L. Chest X-ray showed increased and disordered lung markings in both lungs, multiple small nodules with dense opacity and in reticular shadow, especially in left lower lung field(Figure 1A). The heart shape was full. Interstitial lung disease and infection in left lower lung were suggested. The patient had normal urination, and the body weight had no change. The patient was admitted to our hospital for further diagnosis and treatment.

The patient had 30 years history of hypertension and more than 8 years history of type 2 diabetes. He sufferred from coronary heart disease 4 years ago and anteroseptal myocardial infarction 2 years ago. Stents were transplanted in near and middle left anterior descending artery (LAD) as well as middle right coronary artery (RCA). The diagnosis of chronic bronchitis was established 4 years ago. Two years ago, chest X-ray displayed interstitial changes. History of hepatitis, tuberculosis and other infectious diseases were denied. The patient had a history of smoking and drank occasionally.

Examination at admission Body temperature was 36.1℃, pulse 70 beats/min, breathing frequency 18 times/min, and blood pressure 110/70mmHg. The patient was conscious. Percussion showed clear and symmetric notes in lungs. On chest auscultation, pulmonary sounds were coarse and symmetrical, and crackles were heard in left lower lung at the end of inhalation. His heart rate was in regular pattern. No pathological murmurs were heard in each valve area. Physical examination revealed soft abdomen, no tenderness or rebound tenderness. Liver and spleen were not enlarged. The patient presented with no edema on lower limbs.

Examination after admission Urine routine test: PRO(−), RBC 5-10/HP, WBC 0-3/HP; ESR 58mm/h; blood gas analysis: pH 7.45, PaO_2 95mmHg, $PaCO_2$ 33mmHg; kidney function: Scr 117μmol/L, BUN 7.52 mmol/L; three items of rheumatoid: ASO 47.7IU/mL, RF＜20U/mL, CRP 106mg/L; immune parameters: IgG 15.6g/L, IgA 2.47g/L, IgM 0.63g/L, C3 0.96g/L, C4 0.20g/L; anti-nuclear antibody (ANA) 1:320 (+); anti-glomerular basement membrane antibody (GBM) (−); anti-neutrophil cytoplasmic antibodies (ANCA): positive and type C, 72% of anti-PR3 antibody; urine red blood cell phase: deformed red blood cells in urine. Chest CT scan: interstitial lung disease complicated with infection, indicating pulmonary fibrosis. Echocardiography: normal left ventricular systolic function, LVEF＞50%, reduced diastolic function, higher pulmonary artery pressure(40mmHg), mild pericardial effusion.

Treatment course The patient received active anti-infective treatment immediately after admission. Four days after admission, the patient started to present with fever, and face and joints pain. Six days after admission, the patient's body temperature rose to 38.8 ℃. In addition, emotional agitation resulted in the onset of asthma and shortness of breath. Chest X-ray showed the exacerbation of the situation. Blood gas analysis showed type Ⅰ respiratory failure with pH 7.38, PaO_2 53mmHg and $PaCO_2$ 31mmHg. Bronchial intubation was performed to assist respiratory ventilation(Figure 1B). The patient also presented with bloody discharge from airway. Plasma exchange was performed on January 20, 21, and 23 respectively. Since January 19, the patient received intravenous administration of

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methylprednisolone 40mg for 11 days, 20mg for 2 days, and oral administration of prednisolone 30mg for 11 days sequentially. Additionally, anti-infective treatment and nutritional support were also given with intermittent infusion of plasma and gamma globulin. Following the comprehensive treatment, the patient had decreased ANCA titers, improved respiratory function, more satisfactory blood gas indices, and consciousness recovery, so the ventilator was removed on February 1(Figure 1C). Unfortunately, lung infection was aggravated later and multiple organ dysfunction developed ultimately. The patient died on March 2.

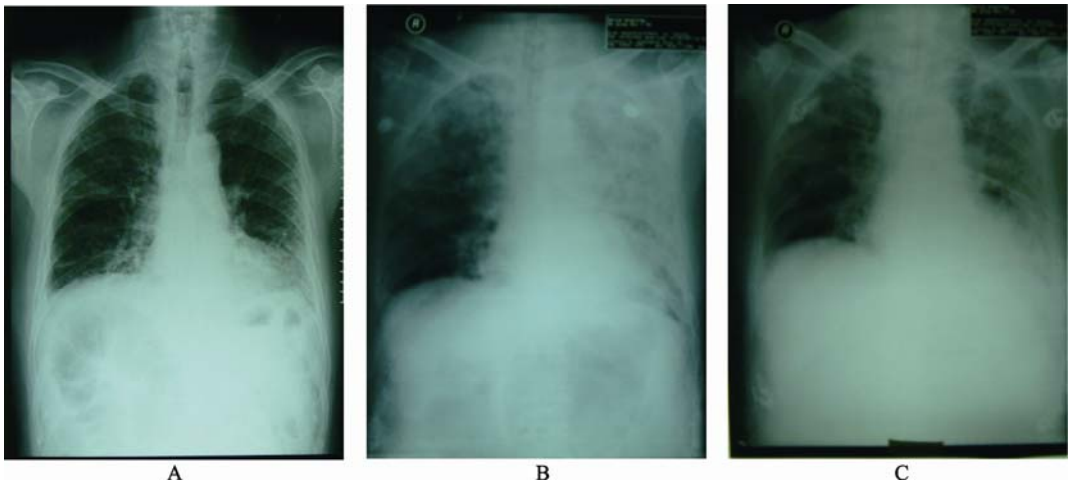

Figure 1 Chest X-ray examination
A: at admission on January 11; B: at intubation on January 18; C: at successful weaning on February 1

Clinical discussions

***Dr. LIN Qing*:** This elderly male patient had acute disease course, and presented with respiratory symptoms, including nasal congestion and dry cough. He sufferred from fever after admission. Physical examination showed moist rales in lower left lung field. Blood test showed increase of total WBC and neutrophils percentage. Chest X-ray showed lung infection. Diagnosis of pneumonia was definitely established. On the other hand, his previous chest radiograph indicated interstitial lung disease. Currently, it was aggravated. The causes of interstitial lung disease should be addressed for differential diagnosis. The patient denied history of exposure to asbestos or dust, keeping pets, or poisons and fibrosis-inducing drugs application. Laboratory test showed that ANA and ANCA were positive. Since ANCA is the specific serological diagnosis marker of vasculitis, the diagnosis of connective tissue disease associated interstitial lung disease was considered. However, there were several questioned points for this case. Kidney was usually involved in small-vessel vasculitis, while for this patient, serum creatinine level was still in the normal range, and lung disease appeared prior to kidney disease. Moreover, the patient did not present with interstitial lung disease until 90-year-old, which was relatively rare.

***Dr. DING Lei*:** It deserves attention that, besides the respiratory symptoms, the patient also complained of headache, weakness, face and joints pain, and decreased body endurance. Together with fast ESR, high CRP, and positive ANCA, it was suggested that the diagnosis of ANCA associated small vessel vasculitis was established. Such diseases mainly include Wegener's granulomatosis(WG), microscopic polyangitis(MPA) and allergic granulomatous vasculitis (CCS). They are also known as ANCA associated vasculitis. ANCA detected by indirect immunofluorescency, was shown in two fluorescence patterns: cytosolic pattern(c-ANCA), with proteinase 3(PR3) as main target antigen, and perinuclear pattern(p-ANCA), with myeloperoxidase(MPO) as main target antigen. For this case, there were several points needing attention. (1)Wegener granulomatosis was suggested according to the indirect immunofluorescency and target antigen test results. For elderly patients with ANCA associated vasculitis, MPA is quite predominant. (2)The symptoms of dry cough and nasal congestion should not only be considered as upper respiratory infections, but also as respiratory symptoms due to Wegener granulomatosis. (3)The patient had the onset of interstitial lung disease two years before this relapse. It was reported that interstitial lung disease can be the first symptom in elderly patients with ANCA associated vasculitis, with no evidence of other connective tissue disease. In some cases, pulmonary fibrosis can exist a few years before diagnosis of ANCA associated vasculitis, and it can progress from mild interstitial lung disease to advanced pulmonary fibrosis. (4)Lung was involved in Wegener's granulomatosis mainly as nodular lesions, occasionally as pulmonary fibrosis. During the active period of the small vessel vasculitis, alveolar hemorrhage can occur. The patient was in critical condition, and glucocorticoid immunosuppression should

be considered for further treatment.

***Dr. SONG Yixin*:** ANCA associated small vessel vasculitis can occur at all ages, from 2 years to 90 years old, and multiple organs can be involved. It was reported that lung involvement accounted for 61% to 75%, and lung involvement as the initial presentation accounted for about 44.4%. For elderly patients, lung and kidney involvement was frequent and often in severe condition. Misdiagnosis of ANCA associated small vessel vasculitis was also common in elderly patients, as they had multiple underlying diseases and diverse clinical manifestations. Old age and pulmonary infection are independent predictors of death in patients with ANCA associated small vessel vasculitis. Alveolar hemorrhage cannot be excluded for the rapid deterioration of this patient's condition, which might be related to active vascular inflammation. High-dose hormone therapy was recommended. Additionally, plasma exchange should be carried out to reduce antibody titers. Because elderly patients were vulnerable to secondary infection following immune suppression, especially pulmonary infection, immunosuppressive agents should be reduced appropriately and anti-infective treatment be emphasized. Serum creatinine level was within normal upper limit. Urine test showed deformation of red blood cells. It was indicated that vasculitis caused early renal injury. Routine urine parameters and renal function should be monitored closely.

(Translator: LIN Qing)

高龄老年 ANCA 相关性小血管炎致肺损害 1 例

1 病历摘要

患者男性，89 岁，主因"干咳、鼻塞半月余，加重 1 天"于 2007 年 1 月 11 日入院。患者半月前无明显诱因出现鼻塞、阵发性干咳，伴头痛、乏力、左侧面部疼痛、全身关节疼痛，活动耐力下降。无咯血、发热、畏寒，无恶心、呕吐，无胸痛、胸闷。1 天前症状加重，至我院门诊就诊。查体左肺底少量湿啰音。血常规: WBC 9.9×10^9/L, NE 75.5%, HGB 120 g/L, PLT 270×10^9/L。胸片：双肺纹理增多、紊乱，伴多发小结节状密度增高影，呈网状改变，以左下肺为重，略模糊，心外形饱满，提示双肺间质病变，左下肺感染。自发病以来，排尿如常，体重无变化。为进一步诊治收入院。

既往高血压病 30 余年; 2 型糖尿病 8 年余; 4 年前患冠心病; 2 年前发生前间壁心肌梗死，于前降支近、中段及右冠状动脉中段置入支架; 4 年前诊断慢性支气管炎; 2 年前胸片表现间质性改变。否认肝炎、结核等传染病史。有吸烟史。偶饮酒。

入院查体: 体温 36.1°C，脉搏 70 次/min，呼吸 18 次/min，血压 110/70 mmHg（1 mmHg=0.133 kPa）。神志清，双肺叩诊清音、对称，双肺呼吸音粗、对称，左下肺可闻及吸气末爆裂音。心律齐，各瓣膜区未闻及病理性杂音。腹软，无压痛、反跳痛，肝脾未触及。双下肢不肿。

入院后进行各项检查。尿常规: PRO（–）, RBC 5～10/HP, WBC 0～3/HP 血沉 58 mm/h; 血气分析: pH 7.45, PaO_2 95 mmHg, $PaCO_2$ 33 mmHg; 肾功能: Scr 117 μmol/L, BUN 7.52 mmol/L; 风湿三项: ASO 47.7 IU/mL, RF＜20 U/mL, CRP 106 mg/L; 免疫指标: IgG 15.6g/L, IgA 2.47g/L, IgM 0.63g/L, 补体 C3 0.96 g/L, 补体 C4 0.20 g/L, 抗核抗体（ANA）1∶320（+）; 抗肾小球基底膜抗体（GBM）（–）, 抗中性粒细胞胞浆抗体（ANCA）, 阳性 C 型, 抗 PR3 抗体 72%; 尿红细胞位相: 变形红细胞尿; 胸部 CT 平扫: 双肺间质性病变, 合并感染, 考虑有肺间质纤维化; 超声心动图: 左室整体收缩功能正常, 左室射血分数＞50%, 舒张功能降低, 肺动脉压偏高（40 mmHg）, 少量心包积液。

治疗经过: 入院即给予积极抗感染治疗。入院第 4 日患者开始发热，面部和关节仍然疼痛。入院第 6 日患者体温升至 38.8°C, 并且情绪激动后发作喘憋、气促，胸片明显加重，血气分析示Ⅰ型呼吸衰竭 pH 7.38, PaO_2 53 mmHg, $PaCO_2$ 31 mmHg, 予气管插管呼吸机辅助通气，气道内吸出大量血性分泌物。于 1 月 20, 21, 23 日进行三次血浆置换。1 月 19 日起依次给予甲泼尼松龙静脉滴注 40mg×11d, 20mg×2 d, 泼尼松龙口服 30 mg×11 d。并给予抗感染及营养支持治疗，间断输注血浆、丙种球蛋白。综合治疗后患者 ANCA 滴度下降，呼吸功能较前恢复，血气指标好转，神志恢复，于 2 月 1 日撤除呼吸机。但后来肺部感染加重，最终发生多脏器功能衰竭，于 3 月 2 日抢救无效死亡。

2 临床病理讨论

林箐主管医师：患者老年男性，急性病程，有

鼻塞、干咳的呼吸道症状，入院后发热，查体有左肺底湿啰音，化验血 WBC 总数和中性粒细胞比例升高，胸片有肺部感染，考虑肺炎诊断明确。另一方面，该患者既往胸片显示有明确的双肺间质病变，目前病情加重，应针对肺间质病变的原因进行鉴别诊断。该患者无石棉、粉尘职业接触史，无饲养宠物史，无毒物和致纤维化药物应用史。实验室检查抗核抗体（ANA）和抗中性粒细胞胞浆抗体（ANCA）阳性。ANCA 是小血管炎特异性的血清学诊断依据，因此可能为结缔组织病相关的肺间质病变。疑问之处：小血管炎多表现为肾脏受累，但该患者血清肌酐水平尚在正常范围；肺脏病变先于肾脏起病。而且患者近 90 岁高龄才出现肺间质病变，相对少见。

丁磊主治医师：该患者起病除了具有呼吸道症状外，需注意还伴有头痛、乏力、面部及关节疼痛、活动耐力下降的全身表现。结合血沉快、CRP 高、ANCA 阳性，考虑 ANCA 相关小血管炎诊断成立。该类疾病主要包括韦格纳肉芽肿（WG）、显微镜下型多血管炎（MPA）和变应性肉芽肿性血管炎（CCS），又称为 ANCA 相关性小血管炎。用间接免疫荧光法检测 ANCA，显示两种荧光形态：一种为胞浆型（c-ANCA），其主要靶抗原为蛋白酶 3（PR3）；另一种为环核型（p-ANCA），其主要靶抗原为髓过氧化物酶（MPO）。该病例要注意几点：（1）依据患者的间接免疫荧光及靶抗原检测结果，考虑为 WG 但老年 ANCA 相关小血管炎中，MPA 所占比例较年轻人多；（2）患者的干咳、鼻塞症状不能仅被视为上呼吸道感染，也有可能为 WG 所致的呼吸道症状；（3）患者在此次发病前 2 年就有肺间质病变，据文献报道，老年 ANCA 相关性小血管炎患者可以肺间质病变为首发表现，而且无其他结缔组织病的证据，有些病例在诊断 ANCA 相关性小血管炎前数年就有肺间质纤维化，可随病程从轻度肺间质病变进展至晚期肺间质纤维化；（4）WG 的肺脏受累最常见为结节性病变，少数可以为肺间质纤维化，在小血管炎活动期，可发生肺泡出血。目前患者病情危重，下一步治疗要考虑给予糖皮质激素免疫抑制剂。

宋以信主任医师：ANCA 相关性小血管炎可发生于各个年龄段，从 2 岁到 90 岁不等。该疾病可累及全身多个脏器，文献报道肺脏受累达 61%～75%，以肺受累为首发表现者约占 44.4%。老年患者肺脏、肾脏受累多见且严重，肺脏与肾脏病变的发生顺序可能有三种情况：（1）同时发生；（2）肾脏病变发生过程中出现肺损害；（3）先发生肺损害后出现肾脏病变。老年患者由于基础病多，临床表现复杂多样，故容易漏诊，另外，高龄和肺部感染是 ANCA 相关性小血管炎患者死亡的独立预测因子。该患者病情急剧恶化原因不除外肺泡出血，考虑与血管炎活动相关，应积极给予激素冲击治疗，同时血浆置换降低抗体滴度。要注意强化免疫抑制后，老年患者容易继发感染特别是肺部感染，临床应适当减量免疫抑制剂并加强抗感染治疗。患者血清肌酐水平在正常高限，尿红细胞位相示变形红细胞尿，考虑与血管炎导致早期肾损伤有关，应密切监测尿常规、肾功能。

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