·临床病理讨论·

Clincopathological Conference (the 49th case)

An old male patient with pulmonary mucormycosis

(Department of Respiratory Diseases, Guangdong Institute of Geriatrics, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, China)

【CLC number】 R563 【Document code】 A 【DOI】 10.3724/SP.J.1264.2011.00069

Case presentation

The patient, a 75-year-old male, was admitted to the Department of Respiratory Diseases, *Guangdong Institute of Geriatrics, Guangdong General Hosptial*, on March 11, 2008, because of left chest pain, loss of appetite and fatigue for two months.

Two months ago, the patient began to experience left chest pain of unknown cause accompanied with loss of appetite and fatigue. The chest pain was located in subaxillary and scapular area, had no relation with cough and movement, and was described as persistent, dull pain. He had little cough and white sputum, no heamoptysis. He reported no history of fever, chills, night sweats and palpitation. Voltalin (a drug of NASID) could release the pain occasionally. Chest X-ray on March 5, 2008 revealed a space-occupying solitary pulmonary lesion in the left upper lobe. For further diagnosis and treatment, he was transferred to our department with the diagnosis of left lung opacity with unknown origin. He lost body mass of 10 kilograms in the last two months.

Past history: The patient reported previous history of hypertension, type 2 mellitus diabetes for 5 years. Both his blood pressure and glucose were poorly controlled. He had heavy smoking (20 cigarettes per day) for 50 years. No positive family history was found. The patient had no drugs and food sensitive history.

Physical examination on admission: Body temperature was 35.8℃, pulse rate 88 beats/min, respiratory rate 21 breaths/min, blood pressure 108/48 mmHg. The patient had consciousness, anemic appearance and active posture. No jaundice over the skin and mucous membrane, noticeable cyanosis, or clubbed finger was found. No swelling of superficial lymph nodes was found. Trachea was at central position. No chest deformity was found. Respiratory movement of two lungs was symmetrical. Respiration was rhythmic, with normal tactile fremitus, but no friction rub felt. Auscultation revealed dullness and increased fremitus over the left upper part of chest in percussion, and diminished breath sounds of the left upper lobe of lung. No obvious rale, wheeze, or friction rub was heard in both lungs. No obvious pathological murmur was heard in the valve auscultation areas. His abdomen was flat and soft, and no visible intestinal peristaltic wave was observed. No tenderness, rebound tenderness, myotonia, or mass was touched. The liver and spleen were not touched below the costal margin. The abdominal percussion sounded like drum. Murphy's sign was negative. The shifting dullness was negative, and the bowel sounds were about 5 times per minute. No peripheral edema existed and the pulse of bilateral dorsal pedal arteries was normal.

Accessory examination after admission: (1)On March 11. Blood routine: WBC 21.67×10^9/L, N% 0.838, RBC 2.48×10^{12}/L, Hb 65g/L, PLT 344×10^9/L; CRP: 208mg/L; Blood biochemical test: BUN 7.8 mmol/L, CREA 194μmol/L, ALT 16U/L, AST 22U/L, CK 53U/L, CK-MB 9.8U/L; cTnT negative; D-dimer 1080ng/L; Electrocardiogram: sinus rhythm and complete right bundle branch block; Echocardiogram: normal heart size and shape and wall movement, moderate tricuspid regurgitation, pulmonary arterial pressure(47mmHg), LVEF 66%. (2)On March 14. PPD 24h(－), 48h(－), 72h(－). (3)On March 15. Blood routine: WBC 22.73×10^9/L, N% 0.924, RBC 2.53×10^{12}/L, Hb 67g/L, PLT412×10^9/L; Sputum culture: Stenotrophomonas maltophilia, sensitive to Piperacillin sodium / Tazobactam sodium; 99mTc- MIBI tumoraffin: positive in the left upper lobe of lung. (4)On March 19. Chest CT scan showed that there was an thick walled and irregular cavity in the apicoposterior segment of left upper lobe, about 82mm×61mm, no bilateral hilar and mediastina lymph nodes enlargement was found, and pulmonary arteries and bronchial arteries were normal, suspected of "peripheral lung cancer in the left upper lobe involving the pleura", which should be confirmed by needle biopsy. (5)On March 23. Flexible bronchoscopy revealed that the bronchial wall in the apicoposterior segment of left upper lobe was edema, and the opening of apicoposterior segment was obviously narrow. The histopathologic examination for the apicoposterior segment of left upper lobe revealed no carcinoma or epithelioid granuloma. (6)On March 23, 25 and April 1. Sputum culture: Abundant of Candida albicans, sensitive to fluconazole. (7)On April 9. Pathological diagnosis: CT guided transthoracic needle biopsy was done and the definite diagnosis was confirmed histologically. There were

收稿日期：2011-11-15；修回日期：2011-12-16

通讯作者：吴 健, Tel: 020-83827812-70612, E-mail: wujian67@yahoo.com.cn

large quantities of inflammatory cells infiltrated among the fibrous tissue and alveolar septum, accompanied with focal necrosis, without granuloma and hyperplastic hetercyst bolus. Macronema with septation and blunt angle arborization could be found. Acid-fast staining (－). PAS staining (+) and PM staining (+). Pathological diagnosis: (left upper lobe of lung) consistent with mold fungus infection. (8)On April 22. Blood gas analysis: pH 7.332, PO_2 54mmHg, PCO_2 62mmHg, HCO_3^-18.5 mmol/L, BE 7.2mmol/L.

After admission, some auxiliary tests were arranged for the patient. Firstly, the patient received antibiotics treatment for pulmonary infection with cefamandole nafate and moxifloxacin. And he also received treatment for sputum, blood glucose control, parenteral nutrition and odynolysis. His condition had no improvement and reexamination revealed that leukocytosis was in a left shift. Considering that his pulmonary infection was not well controlled, cefamandole nafate and moxifloxacin were stopped, and Piperacillin sodium / Tazobactam sodium was initiated on March 15. Then Fluconazole was administrated on April 1 according to the sputum culture and susceptibility test. On April 9, the pathological diagnosis of lung tissue by percutaneous lung biopsy revealed mold fungus infection in left upper lobe. Because the symptoms were not relieved yet, fluconazole were stopped and Amphotencin B Liposom (AM Bison 150mg per day) was administrated intravenously on April 9. The symptoms of chest pain were relieved after treatment with AM Bison. Because the patient was always underfed, catheterization of the subclavian vein was performed and the patient was fed with intensive intravenous nutrition on April 17. On April 22, the patient presented tachypnea at 10:00. Oxygen saturation measured by pulse oxymeter dropped to 55% even though he breathed 5-10 liters of oxygen per minute by mask. Moist rales and Rhonchi were heard in the lungs. The blood pressure could not be measured, and the central venous pressure was 2.5cm H_2O. At 10:25 the trachea tube was inserted by nose under the guidance of bronchoscope and the patient was transferred into ICU and was under mechanical ventilation support, received liquid resuscitation, anti-shock treatment with continous infusion of dopamine hydrochloride through central venous line. In order to strengthen the antifungal effects, the patient was treated with combination of Caspofungin with AM Bison. The patient died two days later.

Clinical discussion

Dr. YANG Shifang: The patient was an elderly male. The laboratory test showed that WBC count and neutrophil ratio remained elevated even after active anti-infection treatment. In addition to the common bacterial infection, the possibility of infections caused by rare pathogen and malignant tumor could not be ruled out. Sequentially, the pathological diagnosis of lung tissue by percutaneous lung biopsy revealed mold fungus infection, and AM Bison was administrated. However, his condition was too serious to control. The invasive pulmonary mucormycosis led to his death because of respiratory and circulatory collapse.

Dr. LIN Qi: The patient was admitted to hospital because of left chest persistent and dull pain for two months. Chest pain may have many causes, which may originate from the heart, large vessels, the lung and pleura, mediastina, intercostal pain, joints and the vertebral column, musculoskeletal and so on. Considering the accessory examination results after admission, the patient's chest pain might be attributed to pulmonary disease. The increased D-dimer (1080ng/L) level, complete right bundle branch block in electrocardiogram, and slightly elevated pulmonary arterial pressure (47mmHg) in echocardiogram strongly suggested pulmonary embolism, while which was excluded by pulmonary angiography. A solitary large, irregular, thick walled cavity was found in chest CT scan on March 19, which might indicate cavernous tuberculosis, necrotizing bronchial cancer, or a nonspecific, nontuberculosis pulmonary abscess. Tuberculous cavity is usually featured by predilection site at the apicoposterior segment of upper lobe and apical segment of lower lobe, inequality of size, thick wall and no air-fluid level, with calcification focus. The carcinomatous cavity is usually in particular squamous-cell cancer, and is characterized with uneven thickness, central cavity, and rare fluid. Abscess formation may occur as complication of pneumonia or may be due to hematogenic spread of an infection at another primary location. It is often complicated with cough and foul smell sputum, and etiological evidence can be obtained through sputum cultivation. In CT examination, predilection site is the posterior segment of upper lobe and apical segment of lower lobe, with thin wall(<3mm), multicentricity, and common fluid level. The features of this patient's CT scan strongly indicated lung cancer-induced cavity, which still needs further confirmation by biopsy.

Dr. GAO Xinglin: This patient possessed the following characteristics: (1) elderly male; (2) the main symptom was chest pain, no cough or expectoration; (3) long history of smoking; (4) Radiography tests support lung cancer; (5) diagnosis of mold fungus infection was established by percutaneous lung biopsy. These characteristics suggested that pulmonary mucormycosis had no specific symptoms, signs and radiographic manifestations, and diagnosis could be definitely established in the evidence of characteristic hyphasma and pathological changes by biopsy. Pulmonary mucormycosis is manifested with compact and consolidated umbra with inequality of size in chest X-ray and CT, which could emerge cavitas (air crescentic sign, ACS) or lung embolism. ACS could also be detected in lung abscess, lung tuberculosis, lung cancer, so it should be differentially diagnosed.

Sputum culture had very poor sensitivity for mold fungus. For this patient, multiple sputum culture was all negative for mold fungus. So, for patients suspicious for pulmonary mucormycosis, early biopsy is necessary to get the definite diagnosis. In this patient, flexible bronchoscopy failed to discover mold fungus for the first time, which might be attributed to small tissue coverage. So, tissue samples for biopsy should cover multiple sites. However, if the patient is under serious condition and is not tolerant to lung biopsy, sputum cultivation is preferable. Diagnosis can be established based on consecutive sputum cultivation, together with patient's condition and pulmonary infection features.

Dr. WU Jian: I agree with the above opinions. Mold fungus is conditional pathogenic bacteria, which can survive in the buccal cavity and pharynx nasalis of health adult. When the immune function of organism decreases, mold fungus could encroach bronchus and lung, and result in acute inflammation, which could also involve brain and other organs by hematogenous infection. Tedder *et al* reported that the proportion of malignant blood disease and diabetes in pulmonary mucormycosis was 35.5% and 32.2% respectively, and others included renal failure, organ transplantation and tumor and so on. The diabetes patients are frequently susceptible to mold fungus infection because their immune function is low when the glucose level was poorly controlled. Timely diagnosis of pulmonary mucormycosis remains a great challenge because its symptoms are absent or nonspecific even at the late stage. Sputum smear and culture is simple to manipulate, but has poor sensitivity. So, timely diagnosis of mucormycosis requires definite pathological evidence by transbronchial biopsy, percutaneous needle biopsy of the lung or open lung biopsy. For this patient, repeated sputum smear and culture after admission failed to detect mold fungus, which made his condition out of control although mold fungus infection was diagnosed finally by percutaneous lung biopsy. So, timely diagnosis and treatment is critical to decrease mortality of pulmonary mucormycosis. Currently, the only effective antifungal therapy for pulmonary mucormycosis is Amphotencin B(AMB), usually 0.5 to 0.7 mg/(kg·d), totally 2g at least, 8 to 10 weeks course. The nephrotoxic effects and acute infusional toxic effects of high-dose conventional AMB frequently preclude long-term high-dose therapy. As a result, AMB liposom presents an attractive alternative for treating mucormycosis. It is recently reported that echinocandin could be taken as adjunctive therapy. Additionally, reversal of the underlying predisposing factors (when possible), and early and ideally broad surgical debridement of infected tissue could be also important. Pulmonary lobectomy can also be considered for pulmonary mucormycosis.

In short, mold fungus infection is not rare in the population with low immunity, such as mellitus diabetes patients. Respiratory tract is the main pathway of infection. Pulmonary mucormycosis is characterized by acute onset, rapid progress, and high mortality. So early diagnosis and timely treatment is the key to elevate survival rate. Early pulmonary biopsy including transbronchoscopic or CT-guided transthoracic is helpful to obtain the definite dignosis, especially in the case of elderly patient with no specific symptoms, signs and images, negative mold results on sputum smear and culture. It is very important to control the elementary disease and administrate antifungal drug as soon as possible. AMB is the first choice to control pulmonary mucormycosis and AM Bison can be used to reduce the side-effect when condition allowed.

(Translators: YANG Shifang, WU Jian)

老年男性肺毛霉菌病 1 例

1 病历摘要

患者男性, 75 岁, 因"左侧胸痛伴纳差、乏力 2 月"于 2008 年 3 月 11 日入院。

患者 2 月前无明显诱因出现左侧胸痛, 为持续性钝痛, 以腋下及肩胛部明显, 疼痛与咳嗽及活动无明显相关, 伴纳差、乏力, 间中有咳嗽, 咳白色黏痰, 无咯血、午后潮热, 无心悸, 自服"双氯芬酸(商品名: 扶他林)"疼痛可稍减轻。3 月 5 日我院胸部 X 线片示: 左上肺病变, 不排除占位。今为进一步诊治来我院就诊, 拟"左上肺阴影查因"收入我科。自患病来, 患者体重下降约 20 kg。

既往史: 既往有高血压病史和 2 型糖尿病史 5 年, 控制不佳; 无药物过敏史; 有长期大量吸烟史; 无特殊家族史。

查体: 体温 35.8℃, 脉搏 88 次/min, 呼吸频率 21 次/min, 血压 108/48 mmHg(1 mmHg=0.133 kPa, 神志清晰, 贫血貌, 自主体位, 全身皮肤、巩膜无黄染, 口唇黏膜无发绀, 无杵状指, 浅表淋巴结未触及肿大。气管居中, 胸廓无畸形, 呼吸 21 次/min, 节律正常, 触觉语颤正常, 无胸膜摩擦感, 右肺叩诊为清音, 左上肺叩诊浊音, 右侧呼吸音正常, 左上肺呼吸音减低, 双肺均未闻及干湿啰音, 听觉语音正常, 无胸膜摩擦音。心率 88 次/min, 律齐, 各瓣膜听诊区未闻及杂音。腹平软, 未触及腹部包块, 未见肠型和蠕动波, 无压痛、反跳痛, 肝脾肋下未触

及，叩诊为鼓音，Murphy's 征阴性，移动性浊音阴性，肠鸣音 5 次/min。双下肢无水肿，双侧足背动脉搏动正常。

入院后辅助检查：3 月 11 日：血常规：WBC 21.67×10^9/L, N 0.838, RBC 2.48×10^{12}/L, Hb 65 g/L, PLT 344×10^9/L；C 反应蛋白 208 mg/L；血生化：BUN 7.8 mmol/L, CREA 194 μmol/L, ALT 16 U/L, AST 22 U/L, CK 53 U/L, CK-MB 9.8 U/L, cTnT 阴性；D-二聚体 1080 ng/L；心电图：窦性心律，完全性右束支传导阻滞；心脏彩超：各房室不大，室壁运动良好，中度三尖瓣反流，轻度肺高压，估测肺动脉收缩压 47 mmHg，左室射血分数 66%。

3 月 14 日：PPD 24h（－），48h（－），72h（－）。

3 月 15 日：血常规：WBC 22.73×10^9/L, N 0.924, RBC 2.53×10^{12}/L, Hb 67 g/L, PLT 412×10^9/L；痰培养：嗜麦芽窄食单胞菌，对哌拉西林钠/他唑巴坦钠敏感；肺亲肿瘤显像：左上肺亲肿瘤显像阳性。

3 月 19 日：胸部 CT：左肺尖后段厚壁不规则空洞，大小约 82 mm×61 mm，空洞壁最厚处达到 24 mm，双侧肺门及纵膈未见肿大淋巴结，肺动脉及支气管动脉未见异常，考虑左上肺周围型肺癌并累及左上胸膜，建议穿刺活检。

3 月 23 日：纤维支气管镜检查：左上叶尖后段黏膜肿胀，开口处显著狭窄，于该处行活检送病理，病理未见肿瘤和上皮样肉芽肿结节。

3 月 23 日、25 日及 4 月 1 日：痰培养：白色念珠菌，对氟康唑敏感。

4 月 9 日：经皮肺穿刺活检病理确诊肺毛霉菌感染。镜下所见，纤维组织，间质多量炎症细胞浸润，可见灶性坏死，未见肉芽肿结节，未见增生异形细胞团；特殊染色：抗酸（－）、PAS 和 PM 染色可见粗大菌丝，有分隔，钝角分枝；病理诊断：（左上肺）符合毛霉菌感染，未见肿瘤。

4 月 22 日：血气分析：pH 7.332, PO_2 54 mmHg, PCO_2 62 mmHg, HCO_3^- 18.5 mmol/L, BE 7.2 mmol/L。

入院后完善相关检查。考虑患者存在肺部感染，立即予头孢孟多、莫西沙星抗感染，并予化痰、控制血糖、加强营养及止痛等治疗，后复查血象仍升高，且咳嗽、咳痰增加，考虑患者感染控制不理想，3 月 15 日改为哌拉西林钠/他唑巴坦钠；4 月 1 日根据痰培养药敏结果加用氟康唑抗真菌治疗，患者胸痛未见明显缓解，且咳嗽、咳痰加重；4 月 9 日经皮肺活检病理标本提示毛霉菌感染，停用氟康唑，改用两性霉素 B 脂质体，150 mg 每日 1 次静脉滴注，后患者诉胸痛有所减轻。患者自入院来一直进食少，营养差，为加强静脉营养，4 月 17 日行锁骨下静脉穿刺置管。4 月 22 日 10:00 患者突然出现呼吸急促，指脉氧饱和度进行性下降，最低至 55%，听诊双肺布满湿啰音及痰鸣音，加大吸氧流量（5～10 L/min）指脉氧饱和度无明显上升，血压测不到，CVP 2.5 cmH_2O，10:25 在纤维支气管镜引导下经鼻气管插管，并转入重症监护病房持续呼吸机辅助呼吸，继续液体复苏及多巴胺升压等抗休克治疗，除两性霉素 B 脂质体外并加用卡泊芬净加强抗真菌治疗。2 日后患者死亡。

2 临床病例讨论

杨士芳医师：患者为老年男性，自入院来血象明显升高，但积极抗感染治疗后，血象一直未下降，且病情无好转，故除普通细菌感染外，不排除其他少见感染及恶性肿瘤可能。后经肺穿刺活检提示肺毛霉菌感染，诊断后立即予两性霉素 B 脂质体治疗，但患者病情持续恶化，感染未控制，最终导致呼吸循环衰竭死亡。

林琦医师：患者因左侧胸痛 2 个月入院，胸痛性质为持续性钝痛。很多疾病可以引起胸痛，如心血管系统疾病、肺部疾病、胸膜疾病、纵膈疾病、肋间神经痛、骨骼及关节病变和肌肉病变等。对于此患者，从其入院后检查分析，其胸痛倾向于肺部疾病所致。患者入院后检查发现 D-二聚体升高、心电图提示完全性右束支传导阻滞、心脏彩超提示肺动脉压轻度升高，上述结果提示可能存在肺栓塞，随后行肺动脉造影检查，结果提示肺动脉及支气管动脉无异常，故由此可基本排除肺栓塞。患者入院后，3 月 19 日胸部 CT 扫描发现一巨大不规则厚壁空洞，此种空洞可能由肺结核或支气管肺癌或非特异性非结核性肺脓肿所致。结核性空洞好发于双肺上叶尖后段及下叶背段，空洞大小不一，洞壁厚薄不均，内有或无液体，壁周可出现钙化。癌性空洞大多见于鳞癌，下叶多见，CT 上常表现为厚壁或厚薄不均，以中心空洞多见，洞内壁高低不平，很少有液体存在。肺脓肿常由肺炎或其他部位感染通过血源播散所致，通常有咳嗽，咳大量脓臭痰，通过痰培养可以获得病原学证据，CT 上空洞一般位于上叶后段、下叶背段，多为薄壁空洞，壁厚度＜3 mm，空洞呈多中心性，液平多见。从此患者 CT 空洞特点看，考虑癌性空洞可能性大，但需进一步通过活检明确诊断。

高兴林医师：该患者具有以下特点：（1）老年男性；（2）症状以胸痛为主，无明显咳嗽、咳痰；（3）有长期大量吸烟史；（4）影像学检查提示肺癌可能性大；（5）通过活检明确诊断。以上特点提示，肺毛霉菌病的症状、体征及影像学检查无特异性，诊断的金标准有赖于活组织检查发现特征性菌丝和病理改变。肺毛霉菌病胸部 X 线或 CT 以大小不一的致密实变影较多见，可形成空洞[新月征（aircrescentsign, ACS）]或肺梗死阴影。ACS 也可在肺脓肿、肺结核及肺癌等疾病中出现，应加以鉴别。肺毛霉菌病患者的痰培养敏感性不高，此例患者多次痰培养均为阴性，故对于怀疑肺毛霉菌的患者应尽早取活检。本例患者经纤支镜活检未能查到毛霉菌，可能与活检组织较小有关，故需多部位取活检。但当患者病情危重不宜行肺活检时，痰液检查简单易行，可连续多次送检痰真菌培养及镜检，结合宿主因素及肺部感染特征及早作出临床诊断。

吴健医师：同意以上分析意见。毛霉菌为条件致病菌，可在正常人口腔和鼻咽部生存，当机体免疫功能降低时，毛霉菌可侵犯支气管或肺，产生急性炎症，并可经血行累及脑及全身各脏器。Tedder 等报道肺毛霉菌病中恶性血液病占35.5%，糖尿病占32.2%，其他有肾功能衰竭、器官移植、实体肿瘤等。尤其糖尿病患者，当其血糖控制不佳时，其免疫力低下，使肺毛霉菌病不再罕见。由于肺毛霉菌病的临床表现无特异性，故及时诊断在临床上是一种挑战。痰液直接涂片、培养是一种简易的初步诊断方法，但其敏感性低，在痰培养或血培养阴性的情况下尽早进行活检（经纤支镜活检、经皮肺活检或开胸肺活检）可能是确诊此类患者的重要手段。此患者入院后曾多次行痰培养检查，均未发现毛霉菌，后尽管通过肺穿刺活检确诊毛霉菌，但对于病情控制可能已来不及，因此，早期诊断和早期治疗是降低肺毛霉菌死亡率的关键。两性霉素B是其唯一有效的药物，剂量为0.5～0.7 mg/（kg · d），疗程8～10周，总量至少2g。但两性霉素B毒性较大，其中以肾毒性和血栓性静脉炎（静脉用药）较常见，对于肾功能不全者可改为两性霉素B脂质体以减少肾脏损害。最近有报道提出，可使用棘球白素作为辅助治疗。另外，积极治疗原发病，手术切除病灶也是重要治疗手段，肺毛霉菌病可考虑肺叶切除。

综上所述，毛霉菌感染常见于免疫功能低下群体，例如糖尿病患者，其常见感染途径是经呼吸道吸入。肺毛霉菌病起病急，进展快，死亡率高，因此，早期诊断，及时治疗是提高生存率的关键。对于临床症状、体征及影像学不典型，痰涂片及培养阴性的患者应尽早进行经支气管镜或CT引导下经皮肺活检以确诊。治疗上控制基础病，及早给予抗真菌药物甚为重要。治疗肺毛霉菌病首选多烯类（两性霉素B），有条件者，可用两性霉素B脂质体，以减少不良反应。

（参加讨论医师：杨士芳，林 琦，高兴林，吴 健）

（杨士芳 整理）

（编辑：任开环）