临床病例讨论
Clinicopathological Conference

Acute renal failure due to granulomatous interstitial nephritis of renal sarcoidosis

(the 41st case)

Center of Nephrology, China-Japan Friendship Hospital, Beijing 100029, *China*

Case presentation

A 60-year-old male patient was admitted to Department of Nephrology, China-Japan Friendship Hospital in July 6, 2006, because of "asthenia for 4 months, edema for 2 months, and marasmus for 1 month". Four months ago, the patient complained asthenia without known predisposing cause. Two months ago, he complained edema of lower limbs and underwent routine urine examination in Nanchang Medical College. Urinary protein and occult blood were positive. Serum creatinine was 138.2 μmol/L, and hemoglobin (HGB) 102 g/L. One month ago, the patient complained aggravated asthenia and marasmus and visited Peking Union Hospital. At that time, his blood pressure was 125/75 mmHg, HGB 89 g/L, 24-h urine protein 1.45 g, serum creatinine 195μmol/L, and serum calcium 2.94 mmol/L. Antineutrophil cytoplasmic antibody (ANCA) was negative. Previous history disclosed neither apparent infection nor exposure to toxic or allergic substance. At the time of admission, the patient reported a weight loss of 5 kg within 4 weeks and physical examination revealed no remarkable abnormalities. Temperature was 36.1℃, blood pressure was 90/60 mmHg, heart rate was 80 beats per minute and regular. No any uveitis, erythema nodosum, or common macular skin lesions were observed. Routine blood test showed WBC 6.3×10^9/L, HGB 76 g/L and PLT 190×10^9/L. Routine urine test: PRO 1.0 g/L, RBC 0-1/HP, WBC 15-18/HP, and urine glucose 5.5 mmol/L. The 24-h urine protein value was 0.9 g. Laboratory tests revealed renal dysfunction, with serum creatinine level 905μmol/L, blood urea nitrogen level 25.32 mmol/L, uric acid (UA) 485 μmol/L, and creatinine clearance (Ccr) 5.1 ml/min. Urinary α_1-microglobulin was 227 mg/L (reference range <12.5 mg/L). Osmotic pressure after 12-h water deprivation was 298 mOsm/kg · H_2O. Urinalysis showed 1.0g/L proteinuria, moderate glucose (with normal serum glucose), 15 to 18 WBC per high power field, without erythrocytes. Urine cultures were negative. Other admission laboratory values included: HGB of 76 g/L, normal serum calcium and albumin, elevated immunoglobin G of 17.6 g/L without M protein component, normal complement 3, negative ANCA and antinuclear antibody (ANA), elevated plasma angiotensin-converting enzyme (ACE) of 153.7 U/L (reference range 17-55 U/L). ECG was normal. Ultrasound showed kidneys of normal size. A computed tomography (CT) scan of the thorax did not demonstrate enlarged hilar nodes but the pattern of ground-glass at tenuation. Gastric biopsy revealed noncaseous granulomas (Fig 1).

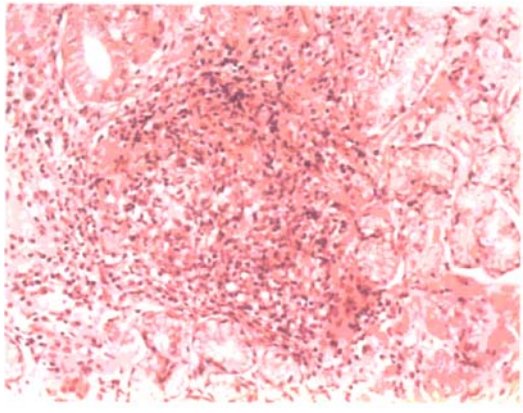

Fig 1 Gastric biopsy showing noncaseous granulomas (HE×200)

作者单位:100029 北京市,中日友好医院肾内科
通讯作者:李文歌,Tel:010-84206172,E-mail:wenge_lee2002@yahoo.com

Admission diagnosis of acute renal failure and acute interstitial nephritis was given. After admission, the patient received hemodialysis and anemia correction.

Clinical discussion

First admission

Dr. FANG Jing: A 60-year-old male had negative previous disease history and had no nocturia, whose serum creatinine increased from 138. 2 μmol/L to 905 μmol/L within 2 months, and his renal function deteriorated rapidly with kidneys of normal size, so we made the diagnosis of acute renal failure. There was no evidence of pre- or post-kidney acute renal failure, so we focused on kidney-related factors. Some characteristics, such as mild proteinuria, without erythrocytes, normal blood pressure, normal urine volume with serum creatinine level of 905 μmol/L, supported neither the diagnosis of glomerulonephritis nor vasculitis. While urinary leukocytes and urinary glucose supported the diagnosis of acute tubulointerstitial nephritis. The patient had no apparent infections and was ever exposed to antibiotics and traditional Chinese medicine, which hints acute allergic tubulointerstitial nephritis.

Dr. LI Wenge: I totally agree with the above analysis and support the diagnosis of acute tubulointerstitial nephritis for the patient. But acute allergic tubulointerstitial nephritis rarely develops so serious anemia, so we should take into account of acute tubulointerstitial nephritis of other causes. This patient displayed higher level of serum creatinine two months ago, which leads to a problem whether the patient developed acute renal failure totally this time or he developed acute renal failure based on the previously existed chronic renal failure. The patient displayed kidneys with normal size and reported no nocturia. Also ultrasound examination revealed normal kidney structures. So the diagnosis of acute renal failure is more acceptable, which needs to be confirmed by renal biopsy. Besides, the patient had elevated serum calcium, which cann't be explained by nephropathy. Further examinations and discussions are still necessary.

Dr. ZOU Wanzhong: The renal biopsy examination was performed. The immunofluorescence studies were negative for immunoglobulin and complement. Among 9 glomeruli in the obtained specimen, four revealed global ischemic sclerosis; the remainder showed wrinkling of the capillary basement membrane with mild proliferation. There was moderate tubular atrophy. Light microscopy revealed 27 noncaseating granulomas in the cortex, each composed of aggregates of epithelioid cells, with giant cells in the interstitium, which contained inclusion bodies (Shaumann bodies) (Fig 2). The vessels showed mild intimal thickening and narrow lumen. All these features are in agreement with sarcoidosis of the kidney. Gastric mucosa biopsy demonstrated moderate chronic inflammations in gastric antrum, decreased glands proper, mild intestinal epithelial metaplasia, and noncaseating granulomas in the lamina propria (Fig 1). The patient was negative for *Helicobacter pylori*.

Dr. LI Wenge: Sarcoidosis is a multisystem-involved disorder of unknown cause, characterized by the accumulation of noncaseous granulomas in multiple organs. Clinical manifestations of sarcoidosis are categorized into two aspects: nonspecific manifestations, including fever, asthenia, weight loss *etc*; and involved-organ related manifestations. Renal dysfunction in sarcoidosis may occur due to a number of causes. (1) Calcium metabolism disorder. Macrophages within sarcoid granulomas have elevated 1α-hydroxylase activity resulting in over-production of 1, 25-dihydroxyvitamin D_3, which in turn leads to hypercalcemia. The hypercalcemia is aggravated after sunlight exposure. The hypercalcemia usually causes renal tubular insufficiency, nephrocalcinosis, and nephrolithiasis. (2) Tubular interstitial nephropathy, such as granulomatous interstitial nephritis, and renal interstitial fibrosis. (3) Glomerulopathy, including membranous nephropathy, focal glomerular sclerosis, intramicrovasular hyperplastic nephritis, membranoproliferative glomerular nephritis, amyloid kidney, IgA nephropathy, and crescentic glomerulonephritis. (4) Retroperitoneal obstructive nephropathy. Sometimes, renal dysfunction in sarcoidosis may be explained by coexistence of more than one disorders. It has long been considered a lower preval-

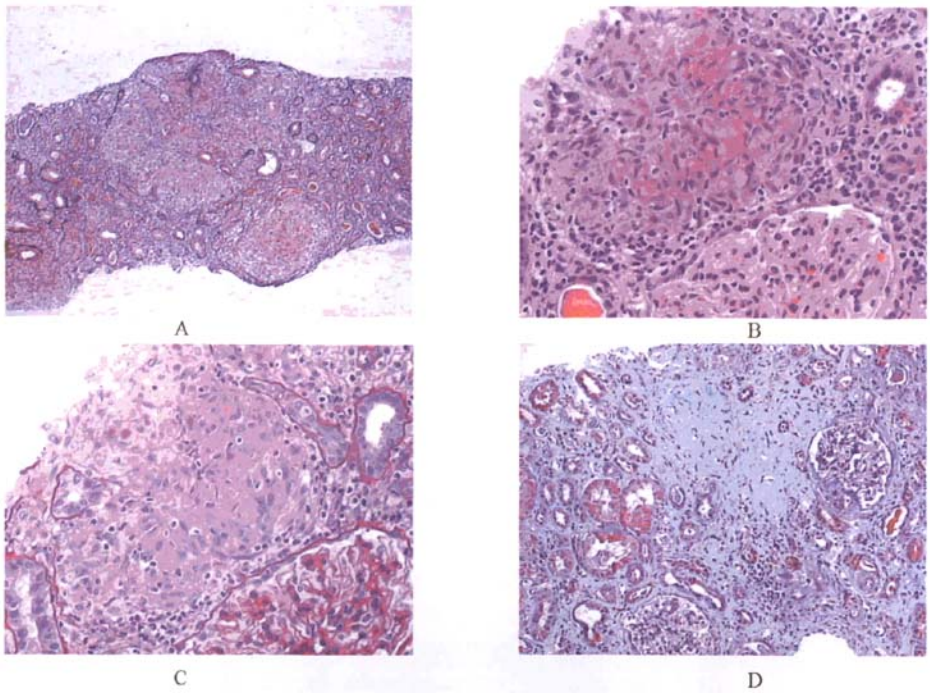

Fig 2 Renal biopsy results

A: two noncaseous granulomas within renal cortex (PASM ×100); B: noncaseous granulomas composed of aggregates of epithelioid cells, with giant cells in the interstitium (HE ×400); C: noncaseous granulomas containing Shaumann bodies (PAS ×400); D: noncaseous granulomas with severe fibrosis in interstitium (PASM ×200)

ence of granulomatous interstitial nephritis in sarcoidosis patients. Actually, it has a high prevalence. It has been estimated from post-mortem series that between 7% and 27% of all patients with sarcoid may have granulomatous interstitial nephritis. However, many of these cases usually clinically silent but may present rarely as acute renal failure, which may result from compression of nephrons as a form of intrarenal obstructive nephropathy. The presence of an occasional granuloma on renal biopsy is unlikely to account for a decrease in glomerular filtration. The functional significance of even more extensive granulomatous infiltration is often difficult to interpret because of the frequent coexistence of calcemic nephropathy. For this patient, although serum calcium was once found elevated in the other hospital, we never found hypercalcemia-caused tubular insufficiency after his admission. So we concluded that renal failure in this patient was associated with granulomatous interstitial nephritis.

Dr. ZOU Wanzhong: Besides sarcoidosis, there are many other agents or conditions which are commonly associated with granulomatous interstitial nephritis, including drugs, infections, immune processes, Wegener's granulomatosis, *etc.* Firstly, sarcoidois should be differentiated from tuberculous granuloma. The two have totally different treatment regimens. Secondly, a variety of drugs may cause granulomatous interstitial nephritis, which is usually characterized by monocytes infiltration. Infection-related granulomatous interstitial nephritis often is caused by some fungi, such as Histoplasma, Candida, Aspergillus, Cryptococcus and other infectious agents. Also, ANCA related nephritis is characterized by small vessel vasculitis. In this patient, there was no evidence of any infection that might cause granulomatous inflammation. Furthermore there was no indication to suggest immune-induced granulomatous interstitial nephritis such as Wegener's granulomatosis. The pathologic hallmark of sarcoidosis is the noncaseous granuloma. In the kidneys, the granuloma is located primarily in the cortex but may be found in the medulla or even in the renal capsule. The mature sarcoid granuloma is composed of a central

follicle of macrophages, epithelioid cells, and multinucleated giant cells, surrounded by a perimeter of lymphocytes, fibroblasts, and plasma cells. The multinucleated giant cells may contain inclusion bodies (Shaumann bodies, and asteroid bodies), which, if present, are strong evidence for sarcoidosis. Renal biopsy revealed primarily multinucleated giant cells in granulomas instead of monocytes, and there was few eosinophils in interstitium. We can make a diagnosis of granulomatous interstitial nephritis due to extensive granulomatous infiltration. Gastric biopsy revealed noncaseous granubomas, confirming the diagnosis of sarcoidosis. Pulmonary CT imaging can not exclude the presence of pulmonary sarcoidosis.

Dr. YANG Yanfang: The multinucleated giant cells, the epithelioid cells, as well as the macrophages, all can produce ACE, which may be an indicator of active sarcoidosis. But some conflicting results also have been reported that may be related to the influence of renal failure on serum ACE, which suggests that serum ACE values be more useful in following up the clinical course. Corticosteroids (1 mg/kg per day) are effective in treating granulomatous interstitial nephritis. The treatment usually exerts obvious effects within 2 weeks. Quick withdrawal may result in relapse, so long-term treatment with corticosteroids may be recommended. But it has been reported that a repeated corticosteroids administration is usually effective in reversing a relapse.

Dr. LI Wenge: For this patient, the diagnosis is definite, and the mainly involved organs are kidneys and stomach, without exclusion of pulmonary sarcoidosis. The patient was treated with pulsed methylprednisolone (intravenous administration with 1-day interval, 500 mg/d for 3 times), followed by tapering oral prednisone (1 mg/kg daily) with gradual decrease in the dose. The therapeutic effect can be evaluated by monitoring ACE levels.

Second admission

Two weeks after treatment, serum creatinine was 238 μmol/L. The patient was readmitted to our hospital in September, 2006. At this second admission, the patient complained palpitation, and reported a weight increase of 7 kg. Routine urine test showed HGB of 105g/L; routine urine test was negative; renal function test showed Cr of 211 μmol/L, and BUN of 17.03 mmol/L. Plasma ACE decreased to 17.4 U/L(17-55 U/L). Serum calcium was 1.94 mmol/L. Urinary α_1-MG was 187 mg/L. Holter examinaton showed sinus rhythm, frequent ventricular premature beat, ventricualr premature bigemina, trigemina, successive ventricular premature beat, and burst ventricular tachycardia.

Dr. ZOU Wanzhong: The renal biopsy showed that 3 glomeruli revealed global sclerosis among 11 glomeruli in the obtained specimen, and the remainder showed mild proliferation. There were 10 granulomas with severe fibrosis in interstitium, as well as an inflammatory infiltration of mononuclear cells. The tubulae and the vessels showed the similar findings as the first biopsy (Fig 2). Immunofluorescence studies were also negative for immunoglobulin and complement.

Dr. FANG Jing: Granulomatous interstitial nephritis due to renal sarcoidosis responds well to corticosteroids treatment (1mg/kg per day), even for patients with several chronic damage on renal biopsy. But, it can cause renal injury and a repeat renal biopsy often shows progression or persistence of fibrosis and tubular atrophy. In this patient, significant improvement occurred within 2 weeks of commencing corticosteroids therapy: a significant decrease in Scr from 905 to 238 μmol/L, but there was a tendency for his creatinine clearance to fall slowly over time after an initial improvement (from 238 to 211 μmol/L). This is principally due to the development of fibrosis in the interstitium as the granulomatous lesion resolves with corticosteroids therapy. Currently, the serum ACE has recovered to the normal level, indicating the alleviation of sarcoidois. Extensive interstitial fibrosis has taken place of interstitial granulomas.

Dr. LI Wenge: Tapering the dose of corticosteroids slowly to avoid relapse. At second admission, the patient reported arrhythmia, so there is a high possibility of cardiac sarcoidosis. The cardiac involvement can lead to arrhythmic manifestation, including impaired AV conduction, ventricular arrhythmias, and sudden death. The definite diagnosis of cardiac sarcoidosis requires a tissue biopsy

demonstrating the characteristic noncaseous granulomas. At the first admission, the patient did not display the arrhythmia, but it appeared after sarcoidosis was well controlled, which seems not in agreement with cardiac sarcoidosis. But it most often involves a small portion of heart and is clinically silent. That may explain why arrhythmia was abscent at the first admission. Immunosuppressive therapy may convert the active granulomatous inflammation to fibrosis, which may lead to aggravation of arrhythmias in some patients like this case. This may be the reason why the patient had regular rhythms with active sarcoidosis at first admission, but developed ventricular arrhythmias when active sarcoidosis was suppressed by immunosuppressive therapy. The response to treatment, including radiofrequency ablation, antiarrhythmic drugs, and immunosuppressive therapy, often was disappointing. As for this patient, we can firstly try antiarrhythmic drugs, and further treatment regimen may depend on the therapeutic efficiency of the drugs.

Follow-up

After two-month follow-up period, the patient's renal function remained stable, with a serum creatinine of 220-280 μmol/L, and ventricular arrhythmia was alleviated significantly.

(Translators: FANG Jing, LI Wenge)

结节病所致急性肾衰竭1例

1 病历摘要

患者男性，60岁，农民，主因“乏力4个月，浮肿2个月，消瘦1个月”，于2006年7月6日入住我院肾内科。患者于4个月前无诱因出现乏力，2个月前间断出现双下肢可凹性浮肿，于南昌医学院查尿常规：蛋白+、潜血+，血肌酐138.2 μmol/L，血红蛋白(HGB)102 g/L。1个月前自觉乏力加重，明显消瘦，于北京协和医院查BP125/75 mmHg，血蛋白HBG 89 g/L，24 h尿蛋白定量1.45 g，血肌酐195 μmol/L，血钙2.94 mmol/L，抗中性粒细胞胞浆抗体(ANCA)(-)，为进一步诊治来我院。发病以来尿量正常，无发热，1个月来体重下降5 kg。既往体健。入院查体：体温36.1℃，BP 90/60 mmHg，消瘦，贫血貌，无皮疹，未及淋巴结肿大，心肺腹未见异常，双下肢无浮肿。入院后查血常规：WBC 6.3×10^9/L，HGB 76 g/L，PLT 190×10^9/L；尿常规：PRO 1.0 g/L，RBC 0-1/HP，WBC 15～18/HP，尿糖5.5 mmol/L(同步血糖正常)，尿培养(-)；24 h尿蛋白定量0.9 g；肾功能：Cr 905 μmol/L，BUN 25.32 mmol/L，尿酸(UA) 485 μmol/L，Ccr 5.1 ml/min；尿 α_1-MG 227 mg/L；禁水12 h尿渗透压298 mOsm/kg·H_2O；血浆白蛋白和血钙正常；免疫球蛋白IgG 17.6 g/L，但血清蛋白电泳中未检出M成分；补体C3正常；抗核抗体(ANA)、ANCA(-)；血中血管紧张素转换酶(ACE)153.7 U/L(17～55 U/L)；B超：双肾大小正常；ECG：大致正常；CT平扫：两肺疑肺泡磨玻璃样变，肺门影不大；胃活检病理：胃窦黏膜固有层见一个非坏死性微小肉芽肿，HP(-)(图1)。入院初步诊断：急性肾衰竭，急性间质性肾炎。入院后给予血液透析、纠正贫血等治疗。

2 临床病理讨论

2.1 **第一次入院** 方静主治医师：中老年男性，既往体健，无夜尿增多病史，2个月内血肌酐由138.2 μmol/L升至905 μmol/L，双肾大小正常，符合急性肾衰竭。肾前和肾后性因素无提示点，考虑肾性因素。患者血尿不明显，尿蛋白<1 g/d，血压正常，血肌酐已905 μmol/L而尿量不少，不支持肾小球肾炎和小血管炎的诊断，考虑为肾小管间质肾病，患者尿中白细胞多，并有肾性尿糖，更支持急性间质性肾炎的诊断。患者无感染征象，2个月前曾在外院应用抗生素和中药，更倾向于过敏因素所致的急性过敏性间质肾炎。

李文歌主任：同意上述分析，患者急性肾衰竭诊断成立，病因倾向于急性间质性肾炎，但是对于感染或过敏所致的急性间质性肾炎，无法解释患者的中度贫血，要警惕一些特殊原因的间质性肾炎。患者2个月前第一次查肾功能就发现血肌酐偏高，是用一元论解释为急性肾衰竭？还是用二元论考虑患者既往有慢性肾功能不全的病史，此次是在慢性肾功能不全的基础上叠加了急性肾衰竭？患者既往无夜尿增多病史，超声显示双肾结构清晰，用一元论来解释更为合理，也需要肾活检来确证。此外，患者于协和医院和我院曾发现血钙偏高，无法用肾脏病来解释，应该多次复查，寻找原因。

邹万忠教授：肾活检病理：免疫荧光全部阴性，

标本中可见9个肾小球，其中4个缺血性硬化，其余肾小球系膜细胞和基质轻微增生，部分缺血性皱缩；肾小管多灶状和大片状萎缩；肾间质可见多数无干酪样坏死的上皮样肉芽肿形成，偶见多核巨细胞和Schaumann小体，纤维化不明显(图2)；小动脉管壁增厚，管腔狭窄。符合结节病肾损伤(renal sarcoidosis)。胃黏膜活检病理：胃窦黏膜中度慢性炎，局灶固有腺体减少，轻度肠上皮化，固有膜内也可见与肾间质相似的非坏死肉芽肿形成(图1)，幽门螺杆菌(-)。

李文歌主任：结节病是一种原因不明的、以非干酪样坏死性上皮细胞肉芽肿为病理特征的、累及全身多系统的疾病，如肺门淋巴结、肺浸润、眼、皮肤、肝、脾、淋巴结、唾液腺、心、神经系统、肌肉、骨骼等。结节病临床表现分为两方面，一方面是非特异性的临床表现，如发热、乏力、体重下降等，另一方面是与特定器官受累相关的临床表现。该患者结节病的诊断目前明确，结节病能以多种形式累及肾脏：(1)钙代谢障碍：结节病肉芽肿的巨噬细胞具有增强的1α-羟化酶活性，造成过度合成1,25α-维生素D_3，导致高钙血症，并在日晒后更严重。而高血钙或高尿钙可以导致肾小管功能障碍、肾钙质沉着症和肾结石。(2)肾小管间质性肾病：如肉芽肿性间质肾炎、肾间质纤维化。(3)肾小球病：膜性肾病、局灶性肾小球硬化症、毛细血管内增生性肾炎、膜增生性肾炎、淀粉样变、IgA肾病、新月体肾炎。(4)腹膜后梗阻性肾病。以上病变可以两种或多种并存。一直以来认为肉芽肿性间质肾炎在结节病患者中发病率不高，其实并不少见，死后尸解显示结节病患者有7%～27%存在肉芽肿性间质肾炎。但是结节病患者出现肾功能受损的主要原因是高血钙或高尿钙所致肾小管功能障碍、肾钙质沉着症和肾结石，肉芽肿性间质肾炎大多数缺乏肾脏疾病的临床表现，它导致肾功能不全的比较罕见，主要是由于弥漫形成的肉芽肿压迫肾单位所致。该患者虽然于协和医院曾发现血钙偏高，但肾活检病理未发现高钙所致肾小管受损表现，可以除外高血钙或高尿钙所致急性肾衰竭，考虑肾功能损害仍与肉芽肿性间质肾炎有关。

邹万忠教授：肾活检病理显示为肉芽肿性间质肾炎的病因很多，不一定就是结节病，可能有药物因素(阿司匹林、庆大霉素)、感染(真菌、结核分枝杆菌)、Wegener肉芽肿等。结节病首先应与结核性肉芽肿鉴别，因为两者的治疗原则截然相反，如果肾脏出现多发结核性肉芽肿结节，应属于血源性播散的粟粒性结核，患者应有高热、衰竭等败血症的临床表现，肺内也有相应的多结节的表现；就结核病的肉芽肿的病理形态而言，结核性肉芽肿以结核菌为中心，各种细胞有一定的排列次序，核心部位是上皮样细胞，混有多少不等的多核的郎罕巨细胞，郎罕巨细胞的细胞核呈马蹄铁样环绕于细胞边缘，外层是淋巴样细胞，最外层是成纤维细胞，结节中心常有干酪样坏死，而结节病的结节性病灶不会有干酪样坏死，组成细胞也无次序，本例的肉芽肿病变完全符合结节病病变。其次，药物过敏性间质性肾炎有时也可出现肉芽肿，这是一种细胞性免疫反应的炎症，常伴有嗜酸性粒细胞，所以，这种肉芽肿样变病一定以弥漫的单个核细胞浸润为背景，本例与之不同。某些真菌感染(组织孢浆菌属、假丝酵母属、曲霉属、隐球酵母属等)也可导致肉芽肿病变形成，但均可在病灶中发现病原体，而且均有明显的中性多形核细胞浸润，显然与本例不同。最后，ANCA相关性多血管炎肾损伤也可出现以损伤的小血管为中心的肉芽肿病变，本例缺乏血管炎的临床指征，也无血管损伤的病理特点。综上所述，本例应诊断结节病性肾损伤，尚属于早期阶段，纤维化现象尚不明显。总之，本例主要的病理特点是以单核巨噬细胞及其衍生细胞组成的上皮样结节，其中上皮样细胞尤为明显，多核巨噬细胞中的Schaumann小体具有一定的诊断价值。本例的肾和胃的上皮样结节完全符合结节病的病理形态，根据肺的CT影像，也不能排除肺结节病。

杨彦芳主任医师：肉芽肿的巨噬细胞、上皮样细胞和多核巨噬细胞都能合成ACE，它的合成增加提示结节病的活动。结节病肉芽肿性间质肾炎和肾外结节病对糖皮质激素〔1 mg/(kg·d)〕治疗敏感，往往2周内就能见效，建议长程激素治疗(6个月～1年)，过快撤药易复发，但是有报道显示复发后重新应用激素仍有效。

李文歌主任：该患者诊断明确，结节病可以累及全身多系统，该患者目前受累器官主要为肾脏和胃，也不能排除肺结节病。该患者治疗选择甲泼尼龙(甲强龙)冲击：0.5 g隔日静点，连续3次，然后泼尼松(强的松)1mg/(kg·d)治疗，逐渐减量。该患者血ACE显著升高，提示目前结节病在活动，可以监测血ACE，观察激素的疗效。

2.2 第二次入院 患者治疗2周时血肌酐238 μmol/L。患者于2006年9月第二次入住我院。患者体重增加7 kg，诉心悸。复查血常规：HGB 105 g/L；尿常规(-)；肾功能：Cr 211 μmol/L，BUN 17.03 mmol/L；血ACE 17.4U/L (17～55 U/L)；血钙1.94 mmol/L；尿α1-MG 187 mg/L；Holter：窦性心律，频发室性早搏，室早二、三联律，连发室早，短阵室性心动过速。

邹万忠教授：第2次肾活检病理：免疫荧光(-)，肾穿组织可见11个肾小球，3个缺血性球性硬化，其余肾小球系膜细胞和基质轻度弥漫增生，肾小管上皮细胞空泡及颗粒变性，多灶状至片状萎

(下转第380页)

duced insulin secretion downstream of granule fusion with plasma membrane[J]. Diabetes, 2007, 53(10): 2610-2616.

[9] Hagman DK, Hays LB, Parazzoli SD, *et al*. Palmitate inhibits insulin gene expression by altering PDX-1 nuclear localization and reducing MafA expression in isolated rat islets of Langerhans[J]. J Biol Chem, 2005, 280(37): 32413-32418.

[10] Solinas G, Naugler W, Galimi F, *et al*. Saturated fatty acids inhibit induction of insulin gene transcription by JNK-mediated phosphorylation of insulin-receptor substrates[J]. Proc Natl Acad Sci USA, 2006, 103(44): 16454-16459.

[11] Kitamura T, Nakae J, Kitamura Y, *et al*. The forkhead transcription factor Foxo1 links insulin signaling to PDX-1 regulation of pancreatic cell growth[J]. J Clin Invest, 2002, 110(12): 1839-1847.

[12] Morgan NG. Fatty acids and cell toxicity[J]. Curr Opin Clin Nutr Metab Care, 2009, 12(2): 117-122.

[13] Laybutt DR, Preston AM, Akerfeldt MC, *et al*. Endoplasmic reticulum stress contributes to cell apoptosis in type 2 diabetes[J]. Diabetologia, 2007, 50(4): 752-763.

[14] Goh TT, Mason TM, Gupta N, *et al*. Lipid-induced cell dysfunction *in vivo* in models of progressive cell failure[J]. Am J Physiol Endocrinol Metab, 2007, 292(2): E549-E560.

[15] Hagman D, Latour MG, Chakrabarti SK, *et al*. Cyclical and alternating infusions of glucose and Intralipid in rats inhibit insulin gene expression and Pdx-1 binding in islets[J]. Diabetes, 2008, 57(2): 424-431.

[16] Poitout V. Glucolipotoxicity of the pancreatic cell: myth or reality[J]? Biochem Soc Trans, 2008, 36(Pt 5): 901-904.

[17] Cusi K, Kashyap S, Gastaldelli A, *et al*. Effects on insulin secretion and insulin action of a 48-h reduction of plasma free fatty acids with acipimox in nondiabetic subjects genetically predisposed to type 2 diabetes [J]. Am J Physiol Endocrinol Metab, 2007, 292(6): E1775-E1781.

[18] Green CD, Jump DB, Olson LK. Elevated insulin secretion from liver X receptor-activated pancreatic beta-cells involves increased *de novo* lipid synthesis and triacylglycerol turnover[J]. Endocrinology, 2009, 150(6): 2637-2645.

[19] Wang X, Zhou L, Li G, *et al*. Palmitate activates AMP-activated protein kinase and regulates insulin secretion from cells[J]. Biochem Biophys Res Commun, 2007, 352(2): 463-468.

[20] Mitro N, Mak PA, Vargas L, *et al*. The nuclear receptor LXR is a glucose sensor[J]. Nature, 2007, 445(7124): 219-223.

(收稿日期:2009-02-27;修回日期:2009-06-22)

(上接第 373 页)

缩,肾间质多数上皮样肉芽肿性结节伴严重纤维化,多灶状淋巴及单核细胞浸润,小动脉管壁增厚,符合结节病肾病(图 2)。与第一次相比,结节纤维化。

方静主治医师:结节病肉芽肿性间质肾炎对糖皮质激素〔1 mg/(kg·d)〕治疗敏感,有时即使肾脏已经缩小或肾活检显示严重慢性化病变,应用激素仍然有效。但是激素治疗虽然有效,却往往遗留肾功能损害,重复肾活检经常呈现进展性纤维化。该患者激素治疗 2 周内血肌酐由 905 μmol/L 迅速下降至 238 μmol/L,此后继续激素治疗,血肌酐 211 μmol/L,变化不显著,血 ACE 目前已经降至正常范围,估计结节病已无活动,肾间质的肉芽肿消失,取而代之的是肾间质纤维化。

李文歌主任:该患者继续激素治疗,缓慢减量,以防复发。本次住院期间患者出现室性心律失常,但既往无心脏病史,高度怀疑是否有心脏结节病。结节病心肌受累主要表现为心律失常,包括房室传导阻滞和室性心律失常,确诊需要心脏组织活检发现非干酪样坏死性上皮细胞肉芽肿。该患者第一次住院期间结节病明显活动时无心律失常,经激素治疗后结节病稳定时却发现室性心律失常,似乎不能用心脏结节病来解释。但是文献报道结节病心肌受累时,大多数病变只累及小部分心肌组织,缺乏明显的临床表现,这就是为什么第一次住院期间无心律失常发作。而心脏结节病用免疫抑制剂治疗后,活动性肉芽肿被纤维组织所替代,提供了形成折返的通路,可能招致难以控制的室性心律失常,这就是为何患者经激素治疗后,病情稳定时却出现室性心律失常。目前室性心律失常的治疗手段主要有免疫抑制剂、除颤起搏器和心脏移植,但效果均不明确,我们可以先用抗心律失常的药物胺碘酮(乙胺碘呋酮)治疗,观察疗效,再决定进一步治疗方案。

2.3 病情追踪 追踪 2 个月,患者血肌酐波动于 200～250 μmol/L,室性早搏明显减少。

(参加讨论医师:方 静,李文歌,邹万忠,杨彦芳)

(方 静,李文歌 整理)