临床病理讨论
Clinicopathological Conference

A case of subacute tubulointerstitial nephritis induced by Castleman disease

(the 38th case)

Department 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 on March 13, 2009, because of lymphy node swelling and renal failure for 9 days.

In October, 2004, with swollen submandibular lymph nodes, the patient received lymph node biopsy in the Shunyi District People's Hospital, but the result was unavailable. In August, 2007, he was admitted to the hospital for a trauma. During the hospitalization, he had normal renal function and parameters of routine blood test and urinalysis. In March 4, 2009, the patient received the lymph node biopsy again in the hospital because of right submandibular lymph nodes swelling. He presented no fever, no skin rash, but leanness. The Scr level was 469.3 μmol/L, hemoglobin (Hb) 121 g/L, and ultrasonography examination suggested bilateral kidneys enlargement(left kidney 14.6cm×6.0cm×5.6cm, right kidney 13.2 cm×5.8 cm×5.8 cm). The patient was diagnosed with acute renal failure and referred to our hospital. The submandibular lymph nodes biopsy showed giant lymph node hyperplasia (vascular type), which presented with epithelioid cell nodules.

The patient has a history of hypertension for 1.5 years, with maximum blood pressure(BP) level up to 150/110 mmHg. His BP was currently controlled within 120-130/80-90 mmHg with medication.

Physical examination Body temperature was 36.4℃, BP 130/85 mmHg, and the bilateral submandibular, right preauricular, postauricular and bilateral groin lymph nodes could be touched, which appeared as pea- to bean-sized, well-demarcated mass. There was no tenderness. Heart rate was 72 beats/min. Cardiac rhythm was regular. Bilateral breathing sound was clear. Dry or moist rale was not heard. No enlarged liver and spleen can be touched. There was no sign of ascites, and no leg edema.

Laboratory tests Routine blood test showed a white blood cell count of 7.8×10^9/L, Hb of 121 g/L, blood platelets count of 275×10^9/L, and erythrocyte sedimentation rate of 100 mm/h. Urinalysis showed negative expression of urine protein, urine glucose 2.8 mmol/L, 0-2 red blood cells (RBC) /high power field, 24-hour urine protein 0.84 g, urine α1-microglobulin 238.0 mg/L, osmotic pressure of urine 504 mOsm/kg·H_2O. Hepatic function was normal. Serum total protein concentration was 102 g/L, albumin 41 g/L, SCr 399.0 μmol/L, urea 16.05 mmol/L, uric acid 382 μmol/L. Glucose and electrolytes were normal. CO_2 was 16.5 mmol/L, total cholesterol 4.93 mmol/L, triglyceride 1.05 mmol/L, creatinine clearance rate 15.38 ml/min. The SCr levels were within a range of 352－420 μmol/L in the two following weeks. Parathyroid hormone (i-PTH) level was 234 ng/L, Hb 102g/L. with a positive Coombs test. Ferro protein level was 374.4 μg/L, serum iron 10 μmol/L, transferrin saturability 35.7%, folic acid 4.4 nmol/L, vitamin B_{12} 541pmol/L。Serum protein electrophoresis showed 37.1% of albumin, 2.7% of α1 globin, 7.3% of α2 globin, 6.8% of β globin, 46.1% of γ globin.

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

Rheumatoid factor level was 188 kU/L (normal value <20 kU/L), C-reactive protein 0.417 mg/dl, immunoglobulin IgG 5010 mg/dl(normal 694—1620 mg/dl), IgA 88.30 mg/dl, IgM 61.1 mg/dl, complement C3 36.4 mg/dl(normal 70—128 mg/dl), C4 4.97 mg/dl, serum ANA 1∶640, nuclear granularity/homogeneity, anti-DsDNA antibody 31 kU/L (normal value <25 kU/L). ENA and ANCA were negative. Peripheral blood smear assessment showed 79% of polymorphocytes, 10% of eosinophils, 8% of lymphocytes, and 3% of monocytes. The size of part of mature red blood cells was abnormally big. There were 500×10^6 eosinophils/L (normal 50—300). Blood κ light chain level was 2710 mg/dl (normal 629—1350 mg/dl), λ light chain 2550 mg/dl(normal 313—723 mg/dl), urine κ light chain 26.3 mg/dl(normal value <1.85 mg/dl), light chain λ30.9 mg/dl (normal value <5.0 mg/dl). M protein was abscent in either serum protein electrophoresis or immunofixation electrophoresis. Urine Bence-Jones protein was negative. Hepatitis B virus markers, hepatitis C virus antibody, HIV antibody, and syphilis antibody were all negative in serum. Chest CT showed inflammation in bilateral lower lungs and lymphatic shadow in mediastinal part. Abdominal ultrasonography showed the enlarged kidneys, right kidney size 14.6 cm×5.4 cm×6.1 cm, left kidney 14.7 cm×5.9 cm×5.9 cm. No abnormality was found both in the X-ray examination of skull and pelvis, and in the bone marrow aspiration and biopsy.

Clinical discussion

Dr. XU Zhihong (attending physician from Department of Nephrology): The patient had normal renal function in August, 2007. This time, he was admitted with renal failure. The Scr level was up to 469.3 μmol/L, while there was no anemia, and the HB concentration was 121 g/L. The patient also presented bilaterally enlarged kidneys. So the diagnosis of acute renal failure (ARF) was established. According to the clinical features and ultrasonography, prerenal and postrenal failure could be excluded, renal parenchyma might be involved. Considering less RBC in urine, 24-hour urine protein of 0.84 g, and marked increase of urine α1-microglobulin, the etiology of the ARF might be explained by acute tubulointerstitial injury.

Dr. Yang Yanfang (chief physician from Department of Nephrology): The diagnosis of ARF was established. There were many evidences supporting that the etiology was an autoimmune disease or blood system disease. The features of renal failure, decreased complement level, ANA and anti-Ds-DNA antibody positivity may meet the diagnosis of systemic lupus erythematosus (SLE). But there were few RBC and little proteinuria in urine, which was different with the ARF induced by SLE in the ordinary pattern. Multiple myeloma (MM) can not be excluded completely too, but no high level of calcium, hyperuricemia, ostalgia, no abnormality in the X-ray examination of skull and pelvis, no M protein band in immunofixation electrophoresis, and urine Bence-Jones protein negativity did not support the diagnosis of MM. Because the patient had a high serum immunoglobulin level, and low complement level, there was another possible diagnosis of cryoglobulinemia, but low urine protein level and hepatitis C virus markers negativity excluded this diagnosis.

Dr. LI Wenge (chief physician from Department of Nephrology): After hospitalization, the patient presented with mild anemia, the Hb level decreased to 102 g/L, and the Coombs test was positive, together with renal impairment, low complement level, ANA and anti-Ds-DNA antibody positivity, all features met the Shanghai SLE clinical diagnosis criteria completely. SLE-induced ARF is mainly the lupous nephritis type Ⅳ, which was characteristic of hematuria and proteinuria, but there were few RBC and little protein in the patient's urine. This was in consistent with the clinical features of acute tubuluointerstitial injury induced ARF. There are only few clinical reports about acute tubuluointerstitial injuries caused by SLE. So, ARF in this patient was not necessarily induced by SLE. The patient had many tumescent body surface lymph nodes, CT scan indicated tumescent lymph nodes in medidetinum, the serum globulin and the immunoglobulin IgG levels re-

markably elevated, rheumatoid factor was positive, and the serum protein electrophoresis showed a high level gamma globulin band. Lymphadenectasis was detected in this patient in 2004, and the lymph node biopsy in the other hospital suggested Castleman disease, therefore, it could not be ruled out that the ARF was the consequences of some lymphoproliferative diseases. Lymph node biopsy and the kidney biopsy were mandatory to reach a definite diagnosis.

Pathological diagnosis

Dr. DA Jiping (chief physician from Department of Pathology): The result of lymphoglandulae submaxillares biopsy on March, 2009 provided by Shunyi District People's Hospital showed lymphadenosis, with obvious plasmacytes and eosinophil infiltration. Cervical lymph node biopsy in our hospital showed the expanded lymph node paracortical area. CD138 staining showed large number of mature plasma cells diffuse infiltration, follicular center expansion or contraction, focal follicular cardiovascular insertion. Immunohistochemisty staining showed CD20 (+), CD79α (+), CD3 (+), CD8 (+), CD34 (blood vessel +), CD138 (plasmacytes +), CD5 (+), bcl-2(-), mum-1(+). Submandibular glands were observed with a large number of lymphocytes and plasma cells infiltration, CD4 +, CD8+, CK (-). Combined with the clinical manifestations, a diagnosis of Castleman disease can be obtained (Fig 1, 2).

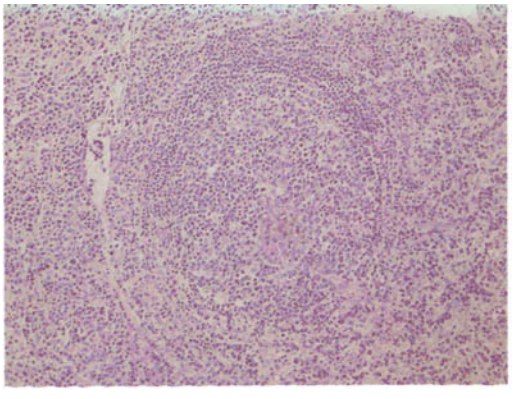

Fig 1 Lymphocytes in follicles shape in a target pattern. Blood vessel proliferation is observed in and around follicles (HE staining ×200)

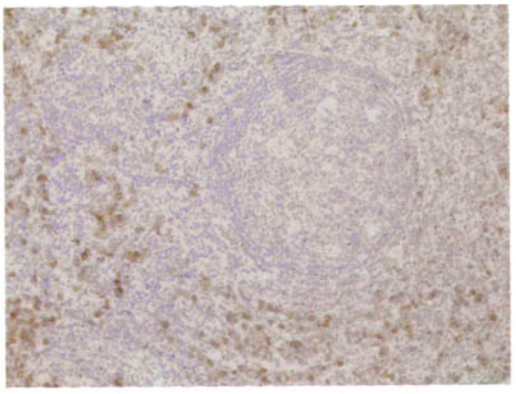

Fig 2 Immunohistochemical staining of CD138 in lymph node. The positive cells are plasmocytes (magnification ×200)

Dr. ZOU Guming (attending physician from Department of Nephrology): Immunofluorescent staining of kidney showed IgA (-), IgM (-), IgG (-), complement C3 (-), C1q (-), FRA (-). Immunohistochemisty of kidney showed some plasma cells (CD138 positive) infiltration in the interstitium. Electron microscopy showed no obvious abnormality in podocytes, mild mesangial cell proliferation, no electron-dense deposition, no significant lesion in GBM, a large number of monocytes, lymphocytes, and a small amount of plasmocytes infiltration, and collagenous fiber accumulation in the interstitium.

Dr. ZOU Wanzhong (professor from Department of Pathology): Light microscopic examination showed that the biopsy specimen contained three glomeruli, of which one was glomerulosclerosis, the other two glomerular mesangium and mesangial matrix diffuse expansion. Renal tubular epithelial cell vacuoles, granular degeneration and diffuse atrophy, protein casts and renal interstitial fibrosis, accompanied by plasmocytes, lymphocytes, monocytes and eosinophil infiltration, and thickening of small arteries were also observed. Combined with the lymph node biopsy results, renal tissue immunofluorescent staining, as well as immunohistochemical study and electron microscopic examination results, Castleman disease induced subacute tubulointerstitial nephropathy in the patient could be diagnosed (Fig 3, 4).

Treatment and outcome

The patient was transferred to the Department of

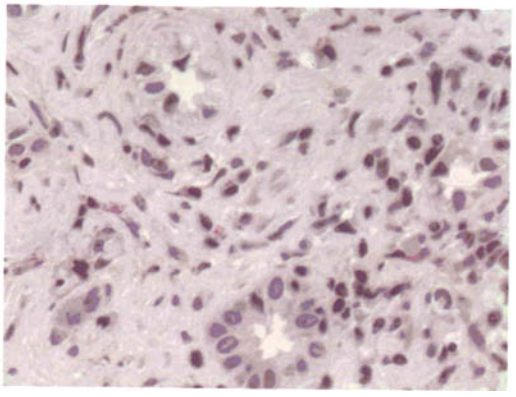

Fig 3 Degeneration and atrophy of renal tubular epithelial cells. Renal interstitial fibrosis and diffuse infiltration of plasmocytes, lymphocytes, monocytes and eosinophil are shown (Masson staining ×400)

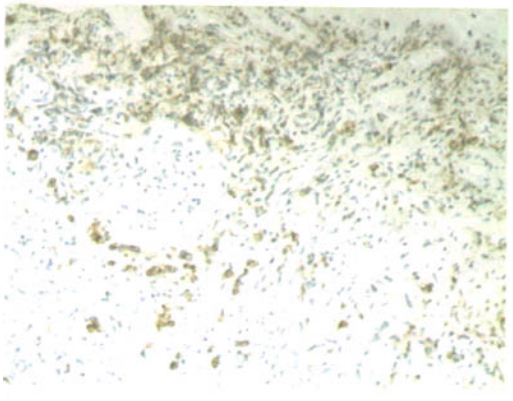

Fig 4 Immunohistochemical staining of CD138 in renal tissue. The positive cells are plasmocytes(×200)

Hematology, bone marrow cytomorphologic examination and pathological study supported the diagnosis of Castleman Disease. After 3-month treatment with R-CHOP (rituximab, cyclophosphamide, vincristine, pirarubicin and prednisone), the body surface tumescent lymph nodes disappeared, and urine protein examination was negative. After 3.5 months treatment, the Scr level reduced to 172 μmol/L, and the serum IgG level returned to normal. The ultrasonography also showed normal size of kidney.

Summary and discussion

Castleman disease is a lymphoproliferative disorder characterized by lymph node enlargement. It was first described by Castleman and other scholars in 1956. Its etiology and pathogenesis has not been entirely elucidated yet. The disease can affect multi-site lymph nodes, such as the mediastinum, neck, axilla, and inguen, *etc*. It is categorized into localized Castleman disease and multi-centric Castleman disease; and had three subtypes pathologically: hyaline-vascular, plasma cell and mixed variants. Plasma cell variant and mixed variant, mostly as systemic disease, accounted for about 10%—20%. Localized Castleman disease (mostly hyaline-vascular variant) usually appears with enlarged lymph nodes asymptomatically. Multi-centric Castleman disease (plasma cell variant and mixed variant) usually manifests as fever, anemia, hepatosplenomegaly, and elevated immunoglobulin and γ-globulin levels, *etc*. It may lead to renal injury, of which the most common one was multi-centric plasma cell variant. The type of renal injury caused by Castleman disease varied, but glomerular diseases are common, including the minimal change disease, mesangial proliferative glomerulonephritis, membranous nephropaty, membrano proliferative glomerulonephritis, rapidly progressive glomerulonephritis, and ANCA-associated nephritis, *etc*. The tubulointerstitial impairment is very rare. This patient presented with subacute tubulointerstitial injuries, and due to the timely diagnosis and treatment, the kidney size and function returned to normal successfully.

Although the clinical manifestations in this case had reached the Shanghai diagnosis criteria of SLE, but the main manifestations of the patient were the lymphadenosis, the anti Ds-DNA antibody titer level was relatively low, and renal pathological immunofluorescence examination was negative; besides, electron microscopy showed no electron-dense deposition, none of which supported the diagnosis of SLE. Therefore, in this case, the primary disease should not be SLE.

(Translator: SHI Xiaohu, YANG Guannan)

Castleman病导致亚急性肾小管间质损害1例报告

1 病历摘要

患者张某，男性，60岁，农民。主因淋巴结肿大、肾衰竭9d，于2009年3月13日转入中日友好医院肾内科。

患者于2004年10月因左颌下淋巴结肿大，曾在当地区人民医院行淋巴结活检，病理结果不详。2007年8月因外伤住院，住院期间曾检查血常规、尿常规、肾功能，未告知异常。9 d前，因右侧颌下淋巴结肿大，再次在当地区人民医院行穿刺活检时发现肾衰竭，无发热、皮疹、消瘦等，血肌酐为469.3 μmol/L，血红蛋白121 g/L，B超示双肾体积增大(左肾14.6 cm×6.0 cm×5.6 cm，右肾13.2 cm×5.8 cm×5.8 cm)，诊断为急性肾衰竭，转入肾内科。颌下淋巴结活检病理结果为巨大淋巴结增生症(血管型)，可见上皮样细胞结节。患者1年半前发现血压升高，最高达150/110 mmHg(1 mmHg=0.133 kPa)，服降压药治疗后，血压维持在120～130/80～90 mmHg。

查′ 体温36.4℃，血压130/85 mmHg，双侧颌下、 -前、耳后以及双侧腹股沟均可触及多个肿大的 ，巴结，约黄豆至蚕豆大小，边界清楚，无压痛。 率72/min，律齐，双肺呼吸音清晰，未闻及干、湿啰音，肝脾未触及肿大，腹水征阴性，双下肢无水肿。

辅助检查：血常规示白细胞7.8×10⁹/L，血红蛋白121 g/L，血小板275×10⁹/L。血沉100 mm/h。尿常规示蛋白(－)，尿糖2.8 mmol/L，红细胞0～2/高倍视野，24 h尿蛋白定量0.84 g。尿α1微球蛋白238.0 mg/L，尿渗透压504 mOsm/kg·H_2O。肝功能正常，血清总蛋白102 g/ L，白蛋白41 g/L，血肌酐399.0 μmol/L，尿素16.05 mmol/L，尿酸382 μmol/L，血糖正常，电解质正常，CO_2 16.5 mmol/L，总胆固醇4.93 mmol/L，甘油三酯1.05 mmol/L，内生肌酐清除率15.38 ml/min。随后2周内多次查血肌酐波动在352～420 μmol/L，甲状旁腺激素(i-PTH)234 ng/L，血红蛋白最低降至102 g/L，Coombs试验阳性。铁蛋白374.4 μg/L，血清铁10 μmol/L，转铁蛋白饱和度35.7%，叶酸4.4 nmol/L，维生素B_{12} 541pmol/L。血清蛋白电泳：ALB 37.1%，α1球蛋白2.7%，α2球蛋白7.3%，β球蛋白6.8%，γ球蛋白46.1%。类风湿因子188 kU/L(正常<20 kU/L)，C反应蛋白0.417 mg/dl，免疫球蛋白IgG 5010 mg/dl(正常694～1620 mg/dl)，IgA 88.3 mg/dl，IgM 61.1 mg/dl，补体C3 36.4 mg/dl(正常70～128 mg/dl)，C4 4.97 mg/dl，血清ANA 1:640，核颗粒型/均质型，抗Ds-DNA抗体31 kU/L(正常<25 kU/L)，ENA阴性，ANCA阴性。外周血涂片：分叶核细胞79%，嗜酸细胞10%，淋巴细胞8%，单核细胞3%，成熟红细胞部分胞体偏大。嗜酸细胞计数500×10⁶/L(正常50～300)。血κ轻链2710 mg/dl(正常629～1350)，λ轻链2550 mg/dl(正常313～723)，尿κ轻链26.3 mg/dl(正常<1.85 mg/dl)，轻链λ 30.9 mg/dl(正常<5.0 mg/dl)，血清蛋白电泳未见M蛋白，免疫固定电泳中未检出M蛋白，尿本周蛋白阴性。乙型肝炎病毒血清五项阴性，丙型肝炎病毒抗体阴性，艾滋病毒抗体阴性，梅毒血清特异性抗体阴性。胸部CT：双下肺炎性病变，纵隔内可见淋巴结影。腹部B超：双肾增大，右肾14.6 cm×5.4 cm×6.1 cm，左肾14.7 cm×5.9 cm×5.9 cm。头颅和骨盆X线检查未见异常。骨髓穿刺结果未见异常。

2 临床病例讨论

徐志宏主治医师(肾内科)：患者于2007年8月曾检查肾功能正常，此次入院前9d发现肾衰竭，血肌酐为469.3 μmol/L，当时无贫血，血红蛋白121 g/L，双肾增大，因此。诊断急性肾衰竭成立。根据临床表现和B超检查，肾前性和肾后性因素导致的急性肾衰竭除外，考虑为肾实质疾病。尿中红细胞比较少，24 h尿蛋白量0.84 g，也不多，尿α1微球蛋白显著增多，病因考虑急性肾小管间质损害。

杨彦芳主任医师(肾内科)：患者诊断急性肾衰竭成立，病因考虑继发自身免疫疾病或血液系统疾病的可能性较大。患者有肾脏损害、低补体，以及ANA和抗Ds-DNA抗体阳性，系统性红斑狼疮已达到诊断标准，因此，不除外狼疮性肾损害，但患者尿中红细胞少、尿蛋白也不多，与系统性红斑狼疮通常导致的急性肾衰竭不符。多发性骨髓瘤不除外，但患者无高钙、高尿酸血症，无骨痛，头颅和骨盆X线检查未见异常，免疫固定电泳中未检出M蛋白，尿本周蛋白阴性，均不支持多发性骨髓瘤诊断。患者血清免疫球蛋白升高，有低补体，冷球蛋白血症也不除外，但患者尿蛋白少，丙型肝炎病毒检查阴性，不支持该诊断。

李文歌主任医师(肾内科)：患者入院后出现了轻度贫血，血红蛋白降至102 g/L，Coombs试验阳

性，加之有肾脏损害、低补体，以及 ANA 和抗 Ds-DNA 抗体阳性，如果按照我国上海系统性红斑狼疮的诊断标准，该患者已达到了系统性红斑狼疮的临床诊断。系统性红斑狼疮导致的急性肾衰竭主要是狼疮性肾炎Ⅳ型，通常血尿和蛋白尿表现突出，但该患者尿中红细胞少，尿蛋白量也不多，符合急性肾小管间质损害导致急性肾衰竭的表现，系统性红斑狼疮单纯导致急性肾小管间质损害虽有临床报告，但非常罕见，该患者急性肾衰竭是否为系统性红斑狼疮所致现在还不能完全肯定。患者有多处体表淋巴结肿大，CT 检查纵隔也可见肿大淋巴结，血清球蛋白和免疫球蛋白 IgG 水平明显升高、类风湿因子阳性，血清蛋白电泳 γ 球蛋白显著升高，患者早在 2004 年即发现淋巴结肿大，院外淋巴结活检为巨大淋巴结增生症。因此，急性肾衰竭病因不排除淋巴组织增生性疾病所致，确诊有赖于再次行体表淋巴结活检和肾活检。

3 病理诊断

笪冀平主任医师（病理科）：阅读 2009 年 3 月顺义区人民医院颌下淋巴结活检组织病理：淋巴组织增生，可见浆细胞和嗜酸细胞浸润。本次住院颈部淋巴结活检：淋巴结副皮质区扩大，CD138 染色显示大量弥漫成熟浆细胞浸润，滤泡中心可见扩大或萎缩，局灶滤泡中心血管插入，免疫组化 CD20（+），CD79α（+），CD3（+），CD8（+），CD34（血管+），CD138（浆细胞+），CD5（+），bcl-2（-），mum-1（+）。颌下腺：腺泡内见大量淋巴细胞、浆细胞浸润，腺泡萎缩。CD4+，CD8+，CK(-)。结合临床表现，诊断为 Castleman 病（图 1，2）。

邹古明主治医师（肾内科）：肾脏病理免疫荧光 IgA（-），IgM（-），IgG（-），补体 C3（-）和 C1q（-），FRA（-）。肾组织免疫组化：肾间质内可见较多浆细胞浸润，CD138+。电镜：肾小球脏层上皮细胞足突无明显异常，系膜细胞和基质轻度增生，未见电子致密物沉积，基底膜无明显病变，肾间质水肿，可见大量单核、淋巴细胞以及少量浆细胞和胶原纤维。

邹万忠教授（病理科）：光镜：肾穿组织可见 3 个肾小球，其中 1 个为球性硬化，2 个肾小球系膜细胞和基质轻度弥漫增生。另外，可见肾小管上皮细胞空泡及颗粒样变性，弥漫性萎缩，并可见蛋白管型，肾间质纤维化，伴弥漫浆细胞、淋巴、单核细胞、嗜酸性粒细胞浸润，小动脉管壁增厚。结合院内外淋巴结活检结果，以及肾组织免疫荧光检查、组化检查和电镜检查结果，诊断为 Castleman 病所致亚急性肾小管间质肾损害（图 3，4）。

4 治疗及预后

患者转入血液科，骨髓细胞形态学和病理检查符合 Castleman 诊断，给予了 5 个疗程 R-CHOP（美罗华、环磷酰胺、长春新碱、吡柔比星和泼尼松）方案化疗治疗，累计约 3 个月，体表肿大淋巴结逐渐消失，尿常规蛋白阴性，化疗 3.5 个月时血肌酐降至 172 μmol/L，血清 IgG 水平恢复正常。B 超检查双肾大小恢复正常。

5 讨论与小结

Castleman 病是一种淋巴组织增生性疾病，由 Castleman 等学者于 1956 年首次报道，病因和发病机制仍不完全清楚，该病可累及多部位的淋巴结，其中以纵隔、颈部、腋窝和腹股沟等处多见。分为局限性和多中心性两大类。病理分为透明血管型、浆细胞型和中间型三个类型，其中浆细胞型和中间型多为系统性病变，占 10%～20%。局限性（多为透明血管型）一般为无症状的淋巴结肿大，多中心性（浆细胞型和中间型）可表现为发热、贫血、肝脾肿大、免疫球蛋白和 γ 球蛋白升高等。Castleman 病可导致肾脏损害，以多中心性浆细胞型常见，该病导致肾脏损害的类型多种多样，以肾小球疾病多见，包括肾小球微小病变、系膜增生性肾炎、膜性肾病、膜增殖性肾炎，以及新月体性肾炎、ANCA 相关性肾炎等，以肾小管间质损害为主的肾脏损害较少见，本例 Castleman 患者表现为少见的亚急性肾小管间质损害，由于诊断和治疗及时，治疗后肾脏大小及功能基本恢复正常。

按照我国上海系统性红斑狼疮的诊断标准，本例患者虽已经达到系统性红斑狼疮的诊断，但主要表现为淋巴组织增生，抗 Ds-DNA 抗体的滴度水平也比较低，肾脏病理免疫荧光检查阴性，电镜也未见电子致密物沉积，均不支持系统性红斑狼疮的诊断，因此，本病例的原发病不应诊断为系统性红斑狼疮。

（参加讨论医师：芦建华，李文歌，徐志宏 邹古明，杨彦芳，笪冀平，邹万忠）

（芦建华，史晓虎，杨冠男，李文歌 整理）

（收稿日期：2009-12-24；修回日期：2010-01-27）