Acute Interstitial Nephritis with Polyclonal B Cell Infiltration and Development of Mantle Cell Lymphoma

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Abstract

A 69-year-old man with proteinuria, hematuria and abnormal renal and hepatic function developed acute renal failure. His clinical and laboratory examinations showed splenomegaly, edema, anemia and polyclonal hypergammaglobulinemia with high IgG levels. Renal biopsy showed interstitial nephritis with predominant B cell and plasma cell infiltration without monoclonality. After corticosteroid treatment, the patient showed remission in clinical symptoms and laboratory findings. However, one year later, he developed mantle cell lymphoma (MCL) with typical lymphocyte markers of cyclin D1 and CD5. When evaluated retrospectively, this patient appeared to have multicentric Castleman's disease initially and developed MCL later. (Internal Medicine 41: 1158–1162, 2002)

Key words: acute renal failure, hypergammaglobulinemia, plasma cells, multicentric Castleman's disease

Introduction

Acute interstitial nephritis (AIN) is an important cause of acute renal failure (ARF), and can be induced by drugs, infection, immune-mediated diseases and glomerular diseases (1–4). AIN with no evident pathogenic cause is diagnosed as idiopathic AIN. The most common clinical presentations are skin rash, fever, eosinophilia and eosinophiluria, especially in drug-associated AIN. The typical findings in urinalysis include leucocytes, leucocyte casts and tubular protein (1, 2). Patients with AIN caused by systemic diseases may display clinical characteristics of the primary disease. Kidney size in AIN is normal or enlarged with an increased cortical echo level. Diagnosis of AIN is based mainly on the pathological characteristics of renal biopsy tissues (1). Here, we report a patient with AIN with many clinical abnormalities and numerous renal B cell and plasma cell infiltrations who developed mantle cell lymphoma one year later. These findings suggested that this

patient might have had multicentric Castleman's disease although lymph node swelling was not observed at the beginning of the clinical course.

For editorial comment, see p 1086.

Case Report

A 69-year-old Japanese man was referred to our hospital in 2000 because of ARF. Three months before admission, he had a sore throat, but an otolaryngologic examination was unremarkable. He took a Chinese herbal medication for three weeks because of general fatigue. Two weeks previously, he felt severe fatigue and sought medical attention again. At this time, proteinuria, hematuria, abnormal renal function and hepatic dysfunction were disclosed. His renal function declined rapidly; the serum creatinine level rose from 4.5 mg/dl to 8.0 mg/dl within four days.

On physical examination, his temperature was 36.4°C, pulse 92/min and blood pressure 166/99 mmHg. No peripheral lymph node swelling was observed. The liver was palpated 1.5 cm below the costal margin, smoothly and painlessly. Lungs, heart and spleen were unremarkable. Extremities and neurological examination were normal. Otorhinolaryngologic and ophthalmologic examinations revealed no abnormalities. Chest and abdomen X-rays were normal. Abdominal ultrasonography showed that liver was normal and bilateral kidneys were enlarged with an increased echo level. Laboratory tests revealed normocytic, normochromic anemia (hemoglobin 10.1 g/dl), a white blood cell count of $4.0 \times 10^3/\mu\text{l}$ with a lymphocytopenia (21.2%) and a platelet count of $27.3 \times 10^4/\mu\text{l}$. Serum total protein (TP) was 11.4 g/dl, albumin 3.2 g/dl, blood urea nitrogen (BUN) 50 mg/dl, creatinine (Cr) 8.0 mg/dl and uric acid (UA) 9.9 mg/dl. Liver function tests showed aspartate aminotransferase (AST) 88 IU/l, alanine aminotransferase (ALT) 112 IU/l and lactate dehydrogenase (LDH) 1,380 IU/l. Serum gammaglobulin level was increased to 55.0%. A marked increase in levels of serum IgG (7,540 mg/dl) and IgM (226 mg/dl) was observed, although the serum IgA level was normal

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Figure 1. CD79a immunostaining (A) showed infiltration of a large number of CD79a positive B cells in the renal interstitium. CD3 immunostaining (B) showed that interstitial infiltrating CD3 positive T cells were not the main cell type in this case.

(143 mg/dl). Erythrocyte sedimentation rate was 133 mm/h and C-reactive protein was 3.27 mg/dl (reference range <0.3 mg/dl). Urinalysis showed 24 h urine volume of 860 ml, urinary protein 1.3 g/day, glucose (+) and hematuria (3+), RBC 1-4/HF, WBC 1-4/HF and hyaline casts (+). The endogenous creatinine clearance test showed 8.2 ml/min of GFR. The serum levels of sodium, potassium, chloride, calcium and phosphate were 119 mEq/l, 3.5 mEq/l, 94 mEq/l, 7.3 mg/dl and 4.9 mg/dl, respectively. Tests for HBsAg, HCV antibody, anti-nuclear antibody, lupus erythematosus (LE) cell, anti-ds-DNA, anti-SSA, anti-SSB, MPO-ANCA, PR3-ANCA and rheumatoid factor were all negative. Bone marrow aspiration performed because of suspected multiple myeloma showed normocellular marrow with a slight increase of mature plasma cells (3.4%). No monoclonality of plasma cells was observed in immunohistochemical studies. Bone marrow findings with a negative Bence-Jones protein test ruled out the diagnosis of multiple myeloma. In order to determine the reason for ARF, open renal biopsy was performed. No apparent glomerular abnormality was discerned except for four out of 50 hyalinized glomeruli. The stroma revealed marked and dense infiltration of lymphoid cells and mature plasma cells without formation of lymphoid follicles. Characteristically, lymphoid cells (small and medium-sized centrocyte-like cells) infiltrated among the tubular epithelial cells, resulting in the formation of lymphoepithelial lesions. The majority of infiltrating cells were immunoreactive for the B-cell marker, CD79a (Fig. 1A) and partially for CD20. Small T-lymphocytes were observed sporadically (Fig. 1B). The plasma cells in the interstitium showed predominant IgG production (Fig. 2), but no monoclonality was identified for the light chains. The patient was then diagnosed as having acute interstitial nephritis with predominant B lymphocyte infiltration. Corticosteroid therapy was initiated using 40mg/day of prednisolone. The patient showed good response to steroid therapy and serum levels of IgG, TP, BUN, Cr, UA, AST, ALT

Figure 2. IgG immunostaining revealed many plasma cells in the renal interstitium, which were producing IgG immunoglobulin.

and LDH were all decreased. Serum Cr returned to the normal level and remained at 1.0 mg/dl.

One year after treatment of AIN, the patient again felt fatigue with weight loss, then developed dyspnea and peripheral lymph node swelling. Chest and abdomen CT scans showed enlargement of the hilar, mediastinal, left axillar and inguinal lymph nodes. Flow cytometry of the lymph node indicated cellular characteristics of CD19+, CD20+, CD22+, CD25+, CD5+, HLA-DR+ with λ light chain monoclonality. Together with the histopathological findings of biopsy tissues from skin and bone marrow, a diagnosis of mantle cell lymphoma (MCL) was determined. The test for human T cell lymphoma virus (HTLV-1) was negative. The *in situ* hybridization test for Epstein-Barr virus showed negative results in the skin, lymph node taken at the second admission and kidney tissue taken at the first ad-

Figure 3. Cyclin D1 and CD5 immunostaining. Strong cyclin D1 and CD5 expression was observed in a lymph node (L), while almost no cyclin D1 and CD5 expression was observed in the renal tissue (R).

mission. Serum IL-2R level was significantly increased to 17,500 U/ml (reference range 220–530 U/ml). The patient died of serious pulmonary infection one month after starting radiotherapy and chemotherapy.

Immunohistochemical staining of renal tissue, taken at the initial admission, for cyclin D1 and CD5 was negative for cyclin D1 and only slightly positive for CD5. But, immunohistochemical lymph node staining, taken at the second admission, was strongly positive for cyclin D1 and CD5 (Fig. 3). These findings suggested that MCL developed after recovery from AIN in this patient.

Discussion

We diagnosed our patient as having AIN because his renal tissue showed that almost all glomeruli were normal in appearance except for four out of fifty that were hyalinized, while infiltration of lymphoid cells and mature plasma cells in the tubulointerstitium was marked with occasional findings of tubulitis. The most common pathogenic factor in AIN is con-

sidered to be drugs (1, 2). Our patient had been using a Chinese herb but no other drugs before he developed ARF. Some Chinese herbs were recently reported to pose a risk of interstitial nephritis and some patients using them developed ARF (5–7). The main component of the Chinese herb our patient used was Ginseng, which has not been reported as a cause of AIN. A lymphocyte stimulation test was performed on this herb with negative results. Therefore, we ruled out the herb as a cause of AIN in this case. Infection is the second common cause of AIN. Streptococcal tonsillitis can cause AIN with ARF (4). Our patient had a sore throat three months before development of ARF. However, post-infectious AIN was ruled out because he did not develop tonsillitis and the otolaryngologic examination was normal at that time. AIN caused by systemic diseases such as Sjögren's syndrome, systemic lupus erythematosus (SLE) and sarcoidosis is not rare. Our patient did not have these systemic diseases based on his clinical profile and laboratory results. We could not find the cause of AIN in this patient.

The interesting point in this case was that the interstitial infiltrating cells were different from those in most reports, in

which the interstitial infiltrates consisted mainly of T cells, followed by monocytes and B cells in patients with AIN associated with nonsteroidal anti-inflammatory agents and beta-lactam antibiotics (1–3, 8), with tubulointerstitial nephritis-uveitis syndrome (1, 9) and with idiopathic AIN (1, 10). Plasma cells and eosinophils were relatively rare (2, 8) although in rare cases eosinophils were the main infiltrating cells in drug-induced AIN (11). In the present case, the interstitial infiltrating cells were mostly CD79a positive B cells and mature plasma cells with predominant IgG production. CD3 positive T lymphocyte infiltration was observed much less frequently.

This patient developed MCL one year after AIN. To determine if lymphoma had been present when AIN appeared, we studied cyclin D1 and CD5 expression, characteristic markers of MCL (12, 13), in a lymph node and renal tissue immunohistochemically. The renal tissue showed no cyclin D1 positive and only a few CD5 positive cells (T cells), but the lymph node was strongly positive for cyclin D1 and CD5. These findings suggested that this patient had not developed MCL at the time of AIN.

Castleman's disease, also called angiofollicular lymph node hyperplasia, is a rare atypical lymphoproliferative disorder of unknown cause. Diagnosis is based on histologic characteristics of lymph nodes. Castleman's disease can be divided into three histologic subtypes (hyaline vascular type, plasma cell type and mixed type) (14) and two clinical types: localized Castleman's disease and multicentric Castleman's disease (15). Localized Castleman's disease usually occurs in young patients and presents with masses mainly in the abdomen and mediastinum (16–18). Most patients with localized forms have no systemic symptoms (15, 16, 18, 19). In the contrast, patients with multicentric forms are older and have systemic symptoms such as fatigue, fever, weight loss, night sweats, nausea, and physical abnormalities such as splenomegaly, hepatomegaly, edema, polyneuropathy and skin rash (15, 16, 19–23), and laboratory abnormalities such as anemia, hypergammaglobulinemia, elevated IL-6, hypoalbuminemia, elevated erythrocyte sedimentation rate, proteinuria, elevated creatinine, elevated liver function tests and thrombocytopenia (16, 19–23). In this case, general fatigue before ARF, hepatomegaly and edema (after correction of dehydration) were observed. Except for thrombocytopenia and untested IL-6, all of the above laboratory abnormalities were found. The serum gammaglobulin in our patient was considered polyclonal according to immunoelectrophoresis and the renal immunohistochemical examination. Patients with multicentric Castleman's disease are at an increased risk of developing Kaposi's sarcoma, Hodgkin's disease and non-Hodgkin's lymphoma (NHL) (20, 21, 23–28). Larroche et al (24) found that NHL, especially MCL, was more often associated with multicentric Castleman's disease. The present patient developed MCL in the terminal stage. Diagnosis of multicentric Castleman's disease is based on histological features of lymph nodes. Our patient did not display lymph node swelling in the initial admission with ARF due to AIN, and we were unable to diagnose multicentric Castleman's disease initially. The infiltrating cells in renal tissue of our patient produced

polyclonal IgG. This is quite similar to the clonality present in the majority of Castleman's disease cases, in which the accumulating lymphoid cells are mainly polyclonal (28). Interstitial nephritis has been described in two patients with multicentric Castleman's disease. The renal infiltrating cells were T lymphocytes and plasma cells in one case (29) and mainly IgG produced polyclonal plasma cells with some lymphocytes in the other (30). Our case showed the similar features. In these two cases, the same histologic changes were found in different involved tissues such as in lung and in kidney in the first case and in kidney and in lymph nodes in the second case. Taken together, the present patient had most of the characteristics of multicentric Castleman's disease during the clinical course and he developed a B cell lymphoma in the terminal stage.

In this patient acute interstitial nephritis with predominant B cell infiltration appeared to be a prelymphoma state, with a strong possibility of multicentric Castleman's disease before development of definite MCL.

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