

## Case Report

# Multicentric Castleman's disease with renal amyloidosis and mesangial proliferative glomerulonephritis: a case report

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**Abstract:** Renal involvement is a significant complication of multicentric Castleman's disease (MCD) and various glomerular involvements have been reported. A 56-year-old Chinese woman presented with proteinuria and skin rash, with lymphadenopathy and hypergammaglobulinemia. Lymph nodes and skin biopsy proven the case was multicentric CD with plasma cell pathological pattern. The renal biopsy was performed and six glomeruli were observed and two of these showed global sclerosis. Moderate increasing of mesangial matrix with mesangial cell proliferation were seen in every glomerulus. In addition, one-segmental sclerosis accompanied by adhesion of the Bowman's capsule was revealed. Two of the glomeruli had crescents formation. Under immunofluorescence microscopy, immunofluorescence for anti-IgA, IgM, C3, C1q and FRA showed coarse and fine granular depositions along capillary walls and sparsely in the mesangium. Staining for anti-IgG was negative. Under electron microscopy revealed indistinct amyloid deposits in glomerular basement membrane. The foot process of glomerular podocytes was fusion. Moderate increasing of mesangial matrix and mesangial cell proliferation were found. Subsequently, she was successfully treated with prednisone combined with cyclophosphamide therapy not only for proteinuria but also for renal function.

**Keywords:** Hypergammaglobulinemia, lymph node hyperplasia, multicentric Castleman's disease, amyloidosis, mesangial proliferative glomerulonephritis

## Introduction

Castleman's disease (CD), also known as giant lymph node hyperplasia or angiofollicular lymph node hyperplasia, is a rare non-neoplastic lymphoproliferative disorder firstly reported by Castleman in 1956 [1]. Three histological variants (hyaline vascular, plasma cell and mixed) and two clinical types (localized and multicentric) have been identified. Asymptomatic mediastinal lymph node mass is the main clinical feature of the localized form and generally has a good prognosis. Approximately 90% of localized CD is of the hyaline vascular type, and almost all the cases occur with the involvement of only one lymphatic organ and without symptoms, while multicentric CD (MCD) is usually the plasma cell type with multiple involvements accompanied by fever, skin rash, weight loss and signs of inflammatory activity (increased

C-reactive protein (CRP), erythrocyte sedimentation rate, anemia, polyclonal hypergammaglobulinaemia). The two major diseases may overlap a hyaline vascular variant that accounts for 80-90% of cases and a plasma cell 10-20% of cases [2].

Renal alterations, such as proteinuria, mild haematuria, decreased glomerular filtration rate (GFR) may be seen in CD; however a true nephrotic syndrome due to amyloidosis and mesangial proliferative glomerulonephritis has rarely been reported. In the present report we describe a patient with MCD and a nephrotic syndrome secondary to amyloidosis and mesangial proliferative glomerulonephritis.

## Clinical summary

A 56-year-old (y.o.) Chinese woman was admitted to our hospital with nephritic syndrome.



**Figure 1.** Brown skin patches on body trunk (A-D).

Hypertension had previously been found in a 1998 health check (41 y.o.), as well as skin rash in 2008 (51 y.o.). On admission, there were no vital abnormalities, but she had brown skin patches on her body trunk (**Figure 1A-D**) and limbs (**Figure 2A-D**). In addition, she showed bilateral cervical, axillary and inguinal superficial lymphadenopathy with no tenderness and good mobility. Urinalysis indicated nephrotic range proteinuria, with urinary protein 4.4 g/day. The cast abnormality was trace, but hematuria was revealed. Blood count indicated severe normocytic anemia (hemoglobin 77.3 g/L) as well as platelets and white blood cell to heighten (platelets  $655 \times 10^9$ /L, white blood cell  $14.4 \times 10^9$ /L), but no hemolysis was suspected (LDH 139 U/L, total bilirubin 3.51 mmol/L). The biochemical serum study was compatible with a diagnosis of lymph proliferative disease with hypergammaglobulinemia (immunoglobulin; IgG 21.1 g/L, IgA 6.18 g/L,

IgM 4.06 g/L, LAM 10.8 g/L, KAP 24.4 g/L), as the complement was in a normal range (C3 1.17 g/L, C4 0.19 g/L) and it could not be matched with nephrotic syndrome (total protein 70.07 g/L, albumin 20.82 g/L). Anti-nuclear antibody and anti-neutrophil cytoplasmic antibody were negative. Renal function was impaired (blood urea nitrogen 9.89 mmol/L, creatinine 125  $\mu$ mol/L). Elevated levels of CRP (17 mg/L) indicated active inflammation. Computed tomography of the neck to pelvis revealed systemic lymphadenopathy (**Figure 3A, 3B**).

We obtained the patient's informed consent before each biopsy and histological examination.

#### **Pathological findings**

The lymph node contained folliculus lymphaticus atrophy, vascular follicle arranged as concentric circles and abundant plasma cells in

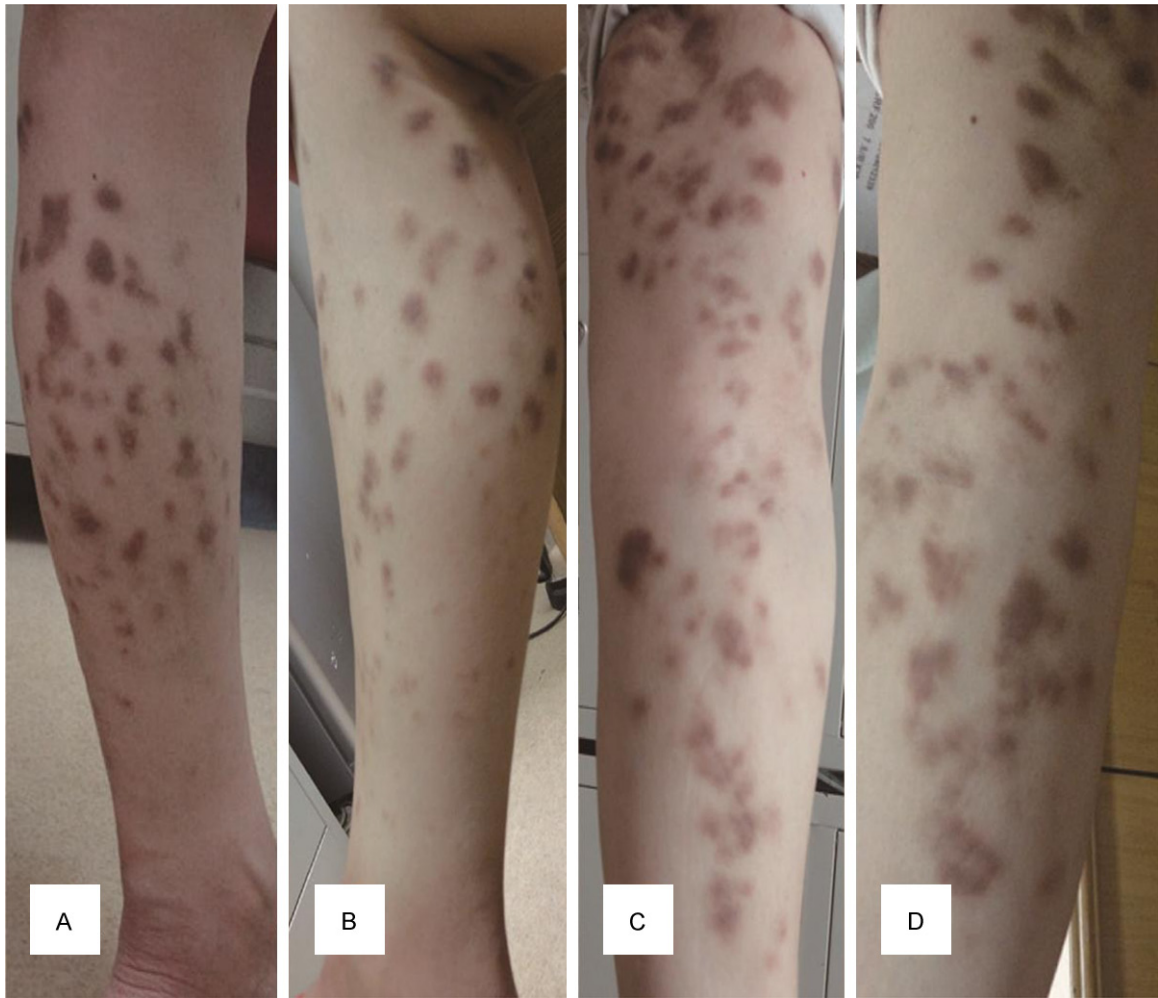


Figure 2. Brown skin patches on limbs (A-D).

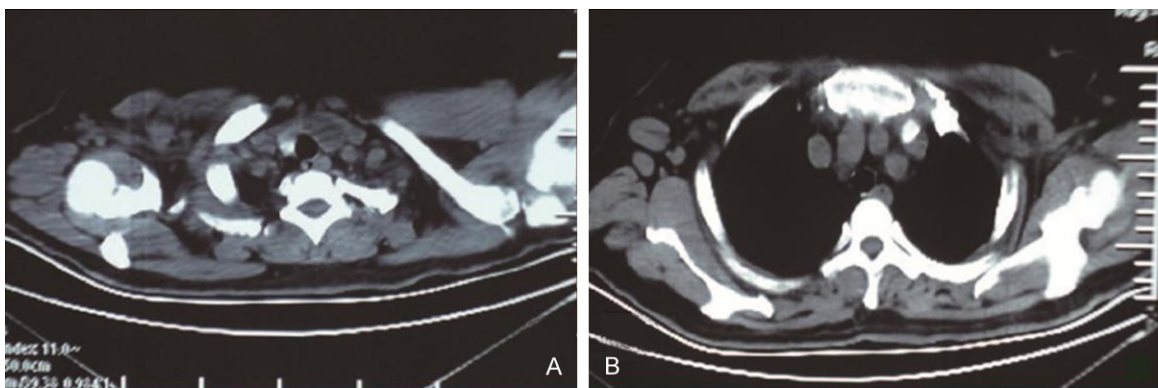
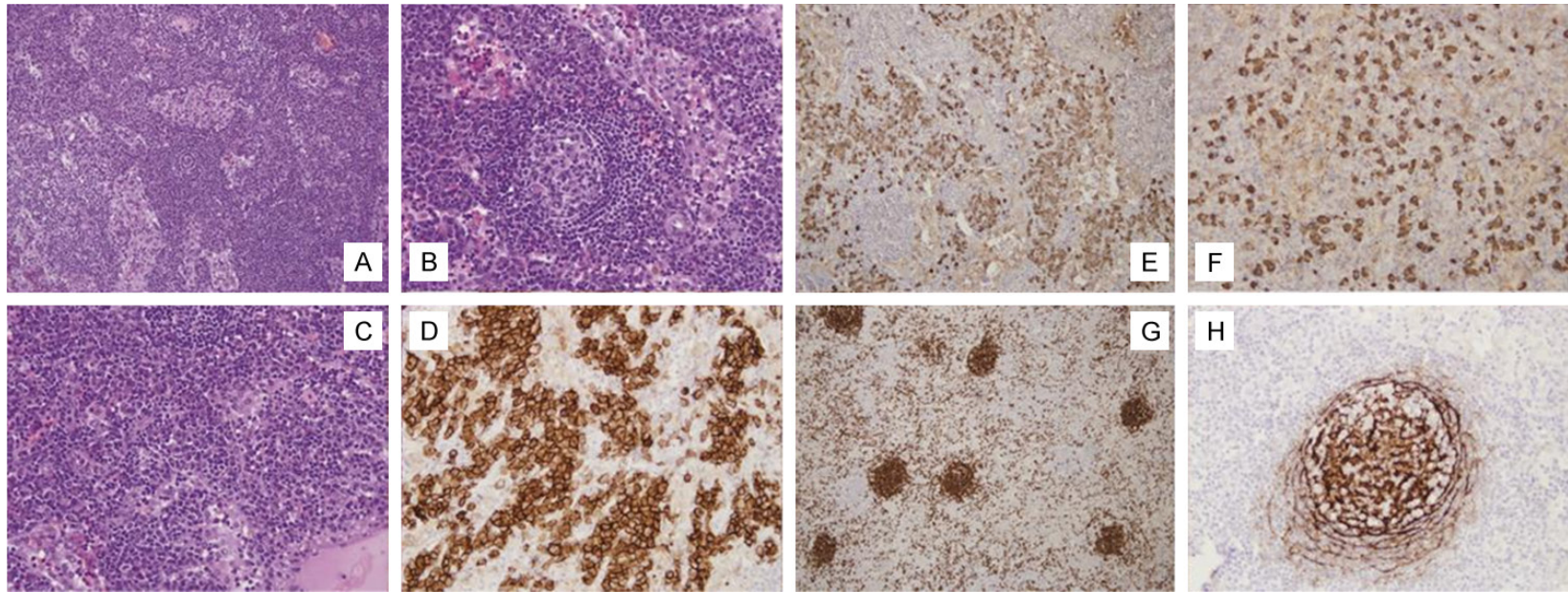


Figure 3. CT shows mediastinum (A) and axillary (B) lymph node.

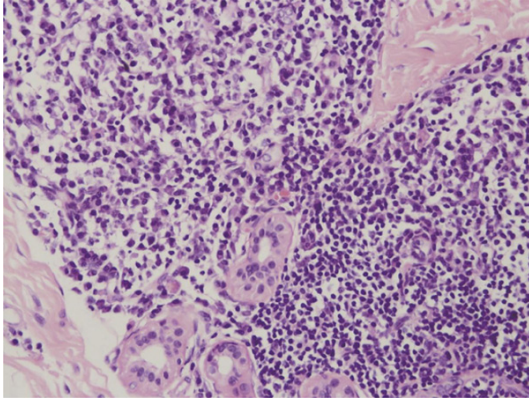
the interfollicular zone (Figure 4A-C). In immunohistochemical analysis, abundant interfollicular infiltrated cells were reacted with anti-CD38 (Figure 4D). As these plasma cells con-

tained both anti-kappa light chain cells and anti-lambda light chain-positive cells (Figure 4E, 4F), they were thought to be of polyclonal origin. Immunoreaction for CD20 was positive

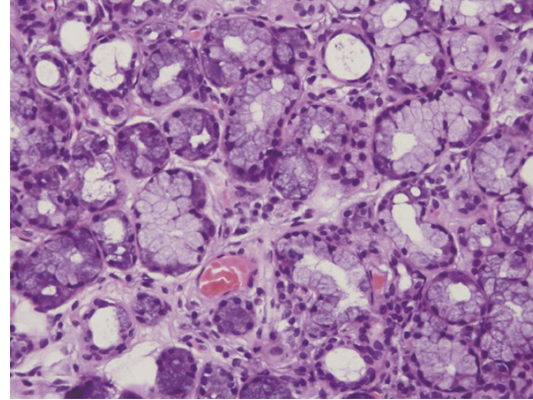
Castleman's disease with renal amyloidosis and glomerulonephritis



**Figure 4.** Histology of the lymph node. A. Folliculus lymphaticus atrophy (HE  $\times$  100). B. Vascular follicle arranged as concentric circles (HE  $\times$  200). C. Abundant plasma cells in the interfollicular zone (HE  $\times$  200). D. CD38-positive. E. Kappa-positive and F. lambda-positive plasma cells or lymphocyte predominantly infiltrated. G. CD20-positive in the lymphoid follicles. H. CD21-positive cells scattered.



**Figure 5.** Histology of the skin. Abundant plasma cells and lymphocytes around small vessels, hair follicle and sweat glands (HE × 400).



**Figure 6.** Histology of glandulae labiales. Plasma cells and lymphocytes were scattered around cryptae (HE × 400).

in the lymphoid follicles (**Figure 4G**). CD21-positive cells were scattered (**Figure 4H**).

These histological features are typical for MCD. It was diagnosed as Castleman's disease, plasma cell type.

The skin contained basal cell pigmentum augmentation, nodule pathological change from corium to subcutaneous, abundant plasma cells and lymphocytes around small vessels, hair follicle and sweat glands, accompany folliculus lymphaticus formation (**Figure 5**). Immunoreaction for CD20, CD38, CD3, CD21, CD4, CD8, anti-kappa light chain and anti-lambda light chain were positive. These histological features are typical for MCD involve to skin.

Plasma cells and lymphocytes were scattered around cryptae (**Figure 6**).

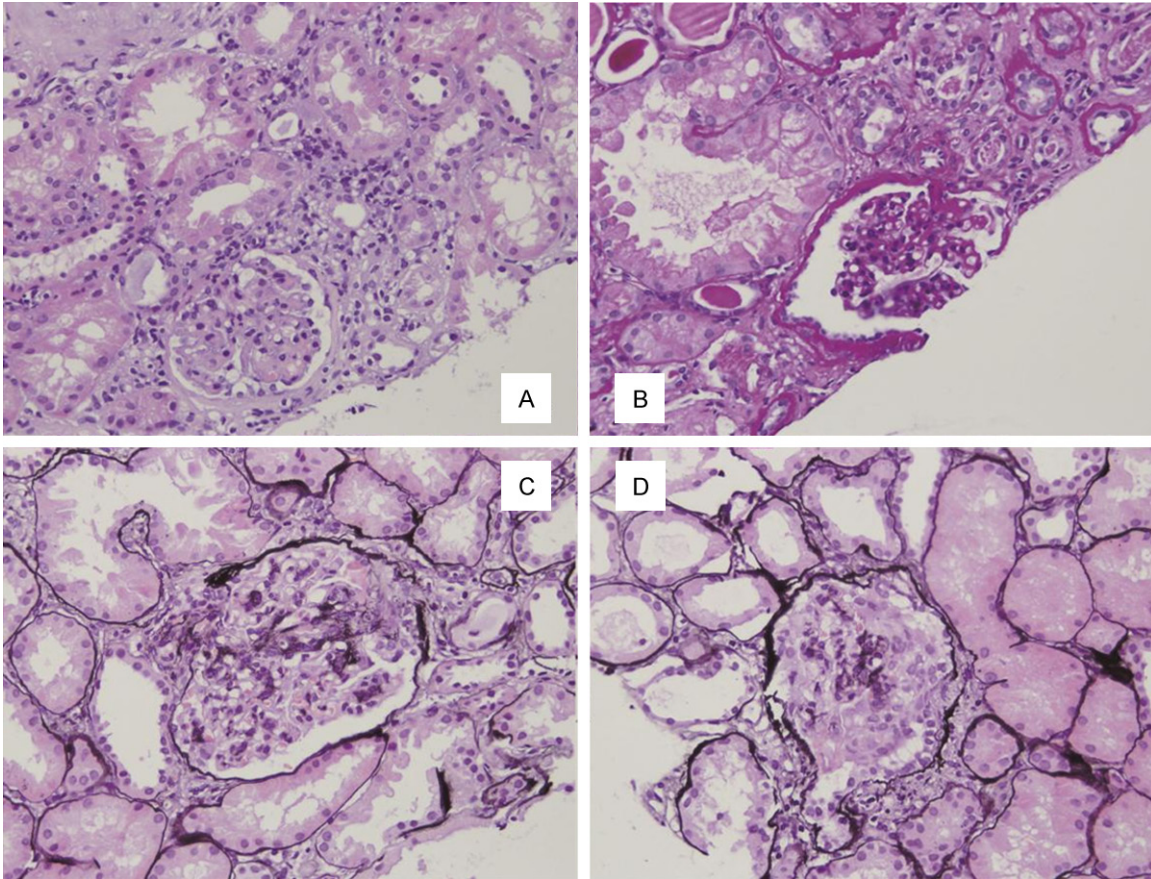
Two cores were taken by needle biopsy under a light microscope. The area of the renal cortex was approximately 90%. Six glomeruli were observed and two of these showed global sclerosis. In PAS staining, moderate increasing of mesangial matrix with mesangial cell proliferation was seen in every glomerulus (**Figure 7A, 7B**). In addition, one-segmental sclerosis accompanied by adhesion of the Bowman's capsule was revealed (**Figure 7C**). Two of the glomeruli had cells crescents formation (**Figure 7D**). In tubulo-interstitial lesions, interstitial fibrosis with tubular atrophy and infiltration of inflammatory cells were seen in the equivalent of 30% of the cortical area. Around the venules, scattering invasion of closely aggregated lym-

phocytes was shown; arteriosclerosis was observed in a proportion of arterioles. Under immunofluorescence microscopy, immunofluorescence for anti-IgA, IgM, C3, C1q and FRA showed coarse and fine granular depositions along capillary walls and sparsely in the mesangium. Staining for anti-IgG was negative. Under electron microscopy revealed indiscriminate amyloid deposits (diameter < 10 nm) in glomerular basement membrane, the foot process of glomerular podocytes were fusion. Moderate increasing of mesangial matrix and mesangial cell proliferation were found. The patient was diagnosed renal amyloidosis (**Figure 8A-C**).

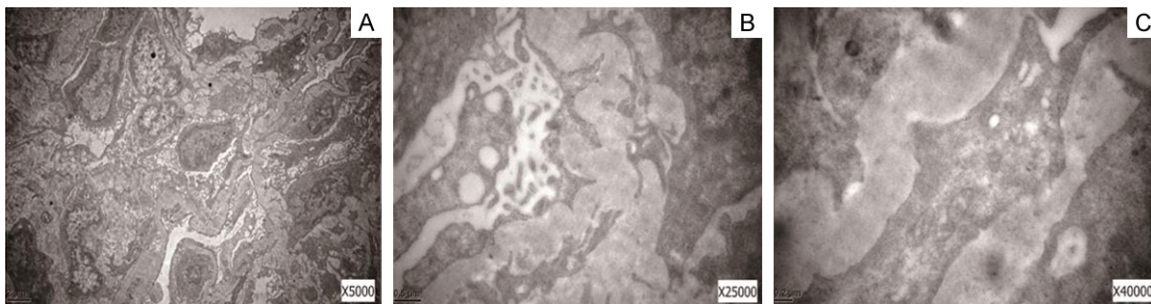
### Discussion

Castleman's disease is a rare clinicopathologic entity among atypical lymphoproliferative disorders. In an analysis of 75 cases of CD between 1954 and 2011, the majority of the cases were reported from Europe (38 cases, 51%) and Asia (28 cases, 37%). In terms of countries, France (21 cases, 28%) and Japan (10 cases, 13%) were on top of the list. Of the 75 cases, 26 cases (35%) were of UCD and 49 cases (65%) of MCD. The mean age was 43.7 years (range 3.5-79 years) when kidney diseases were histologically diagnosed. The proportion between male and female was equal. Renal complications developed previously (9 cases, 12%), synchronously (36 cases, 48%) or later (30 cases, 40%) to CD. Nephrotic syndrome (46 cases, 61%) and chronic renal failure (34 cases, 45%) were the most common renal complications [3]. CD can occur wherever lymph nodes, but the most common location is the thorax (70%) fol-

## Castleman's disease with renal amyloidosis and glomerulonephritis



**Figure 7.** Histology of renal. A. Moderate increasing of mesangial matrix with mesangial cell proliferation accompanied infiltration of lymphocytes in tubulo-interstitial (HE  $\times$  400). B. Moderate increasing of mesangial matrix with mesangial cell proliferation accompanied arteriosclerosis (PAS  $\times$  400). C. Segmental sclerosis accompanied by adhesion of the Bowman's capsule (PASM  $\times$  400). D. Glomeruli cells crescents formation (PASM  $\times$  400).



**Figure 8.** Histology of renal. Under electron microscopy revealed indiscriminate amyloid deposits (diameter  $<$  10 nm) (A-C).

lowed by the neck (14%), abdomen (12%), and axilla (4%) [4]. Multicentric CD (MCD) is usually the plasma cell type with multiple involvements accompanied by fever, skin rash, weight loss and polyclonal hypergammaglobulinaemia. Our patient had mediastinum, bilateral cervical, axillary and inguinal superficial lymphadenopa-

thy mass which was of histologically plasma cell type associate with skin rash and polyclonal hypergammaglobulinaemia. The renal clinical features were nephrotic syndrome.

Amyloidosis was the most common renal histology in CD [3], but nephrotic syndrome due to

## Castleman's disease with renal amyloidosis and glomerulonephritis

amyloidosis and mesangial proliferative glomerulonephritis has rarely been reported. From an analysis of renal histology of 57 MCD patients between 1975 and 2010, they were categorized by amyloidosis (42%, 24 cases), mesangial proliferative glomerulonephritis (12%, 7 cases), MPGN (3.5%), interstitial nephritis (5.2%), MN (3.5%) and a few cases of crescentic glomerulonephritis, focal segmental glomerulonephritis, minimal change nephritic syndrome, plasmacyte invasion and thrombotic microangiopathy [5]. In this case, six glomeruli were observed and two of these showed global sclerosis. Moderate increasing of mesangial matrix with mesangial cell proliferation were seen in every glomerulus, In addition, one-segmental sclerosis accompanied by adhesion of the Bowman's capsule was revealed. Two of the glomeruli had cells crescents formation. Under electron microscopy revealed indiscriminate amyloid deposits in glomerular basement membrane, the foot process of glomerular podocytes were fusion. Moderate increasing of mesangial matrix and mesangial cell proliferation were found.

The pathophysiology of CD remains unclear. The plasmablastic variant is characteristic of human herpes virus-8 (HHV8)-associated CD, which is always multicentric. HHV8-associated CD occurs mainly in human immunodeficiency virus (HIV)-infected patients but may represent about 40% of MCD affecting HIV-negative patients. Dysregulated IL-6 production and increased vascular endothelial growth factors (VEGFs) have been demonstrated to play an important part in the development of both CD and renal complications [6, 7]. CD exhibits a polyclonal lymphoproliferative process. When monoclonality develops, transformation to a malignant lymphoma must be suspected. Immunohistochemical and gene-rearrangement studies can be used to identify such clonal cell populations [8]. Decreased CD57-positive cells in the germinal centers and increased CD21-positive follicular dendritic cell networks in the mantle zone supported the diagnosis of CD [9].

In this case, a dose of 1 mg/kg/day prednisone combined with cyclophosphamide was administered and proteinuria partial remission was achieved. At the last follow-up in December 2013, the disease was stabilized. At present, there is no consensus on optimal treatment for the renal complications of CD. Their therapies

always contain two parts: treatment for renal symptoms and treatment for the primary disease CD. The former is similar to the symptomatic treatment for these primary renal diseases. The latter is essential, which may help improve renal symptoms [3]. Treatment of unicentric Castleman's disease is largely surgical and post-operative prognosis is excellent. Up to 95% of the patients with unicentric Castleman's disease are cured with surgical resection and the prognosis is excellent with a 5 years survival of close to 100% [10]. For MCD, there are no standard therapeutic regimens today. Corticosteroids, chemotherapy, radiotherapy and immune therapy have been helpful [11, 12].

### Disclosure of conflict of interest

None.

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### References

- [1] Castleman B, Iverson L, Menendez VP. Localized mediastinal lymphnode hyperplasia resembling thymoma. *Cancer* 1956; 9: 822-30.
- [2] Keller AR, Hochholzer L, Castleman B. Hyaline-vascular and plasma-cell types of giant lymph node hyperplasia of the mediastinum and other locations. *Cancer* 1972; 29: 670-83.
- [3] Yuan XG, Hu W, Chen FF, Huang BF, Zhao XY. Renal complications of Castleman's disease: report of two cases and analysis of 75 cases. *Clin Exp Nephrol* 2011; 15: 921-6.
- [4] Frizzera G. Castleman's disease: more questions than answers. *Human Pathology* 1985; 16: 202-5.
- [5] Nagai K, Usui J, Noguchi K, Unai K, Hiwatashi A, Arakawa Y, Togashi A, Morito N, Saito C, Yoh K, Tsuruoka S, Kojima H, Aita K, Nagata M, Yamagata K. A case of multicentric Castleman's disease with membranoproliferative glomerulonephritis type 3-like lesion. *Pathol Int* 2011; 61: 686-90.
- [6] Casper C. The aetiology and management of Castleman disease at 50 years: translating pathophysiology to patient care. *Br J Haematol* 2005; 129: 3-17.
- [7] El Karoui K, Vuiblet V, Dion D, Izzedine H, Guitard J, Frimat L, Delahousse M, Remy P, Boffa JJ, Pillebout E, Galicier L, Noël LH, Daugas E. Renal involvement in Castleman disease. *Nephrol Dial Transplant* 2011; 26: 599-609.

## Castleman's disease with renal amyloidosis and glomerulonephritis

- [8] Greiner T, Armitage JO, Gross TG. Atypical Lymphoproliferative Diseases. Hematology Am Soc Hematol Educ Program 2000: 133-46.
- [9] Pham TT, Harrell JH, Harrell JH, Herndier B, Yi ES. Endotracheal castleman disease: A case report. Chest 2007; 131: 590-2.
- [10] Bandera B, Ainsworth C, Shikle J, Rupard E, Roach M. Treatment of unicentric Castleman disease with neoadjuvant rituximab. Chest 2010; 138: 1239-41.
- [11] Dispenzieri A, Gertz MA. Treatment of Castleman's disease. Curr Treat Options Oncol 2005; 6: 255-66.
- [12] Chronowski GM, Ha CS, Wilder RB, Cabanillas F, Manning J, Cox JD. Treatment of unicentric and multicentric Castleman disease and the role of radiotherapy. Cancer 2001; 92: 670-6.