Case Report

Multicentric Castleman disease as a rare cause of nephrotic syndrome: a case report

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Received January 30, 2019; Accepted April 8, 2019; Epub June 15, 2019; Published June 30, 2019

Abstract: Castleman disease (CD) is a benign lymphoproliferative disorder that is clinically divided into two types: multicentric Castleman disease (MCD) and unicentric Castleman disease (UCD). Herein is presented a case of MCD characterized by edema, proteinuria, anemia, and renal insufficiency. The patient did not respond well when initially treated as nephrotic syndrome. After systematic evaluation, a final diagnosis of MCD was established by lymph nodes biopsy. The patient received 4 cycles of rituximab and prednisone. The edema resolved significantly, and his condition improved with normalized renal function and hemoglobin. Based on the case of MCD mimicking nephrotic syndrome, the diagnostic dilemma MCD may present to clinicians is discussed, with an emphasis on definitive diagnosis of MCD.

Keywords: Multicentric Castleman disease, lymphoproliferative disorder, nephrotic syndrome, diagnosis, rituximab

Introduction

Castleman disease (CD) is a rare atypical lymphoproliferative disorder first reported by Castleman in 1954 [1]. Clinically, unicentric CD (UCD) involves one lymph node or one group of localized nodes, whereas multicentric CD (MCD) affects more than one lymph node areas [2, 3]. The prognosis of UCD is better than MCD [4]. Histopathologic variants of CD include the hyaline vascular (HV), plasma cell (PC), and mixed type [5]. The HV type occurs in the majority of UCD, and the PC type is more common in MCD [6].

The pathogenesis of CD remains poorly understood. MCD has been shown to frequently correlate with HIV or HHV-8 infection [7]. Those without HHV-8 are called idiopathic Castleman disease, a subset of MCD [3, 8]. Yoshizaki first demonstrated the causative role of interleukin 6 (IL-6) overexpression in the MCD [9]. Human IL-6 is triggered by infection or auto-immune response, and the variant IL-6 is produced by HHV-8 virus [10]. IL-6 overexpression can activate both B cells and T cells and lead to abnormal immune response and systemic inflammation, which contribute to the development of MCD [11, 12]. Therefore, anti-IL-6 antibody is an effective agent for MCD treatment [13].

An evidence-based, expert consensus diagnostic criterion of idiopathic CD [14] was provided by an international working group supported by the Castleman Disease Collaborative Network (CDCN) from June 2015 to September 2016. Later, a tentative diagnostic and classification criteria of CD was established by a Japanese working group [3]. It is often difficult to establish a prompt and reliable diagnosis of MCD based on some atypical clinical manifestations.

Here, an MCD case is presented that is characterized by nephrotic syndrome. To the best of our knowledge, renal manifestations could be seen in some CD patients, though as a complication, nephrotic syndrome rarely occurs.

Case report

A 47-year-old man suffered from progressive generalized edema. Six months before admission, he was seen at the local hospital because of his swelling face, the doctors found he had
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pleural effusions, splenomegaly, proteinuria (+++), mild anemia (111 g/L), and increased levels of serum creatinine (117 μmol/L), but a clear diagnosis was not established.

Following symptomatic treatment, his condition worsened, and then he was referred to the Department of Nephrology for further evaluation. On physical examination, lymphadenopathies were found in bilateral axillary and inguinal regions. The abdomen was distended with shifting dullness, and splenomegaly was also identified. Pitting edemas were seen in his face and lower extremities. Computed tomography scan showed bi-lateral hydrothorax and mild pericardial effusion. Ultrasound demonstrated splenomegaly, ascites and swollen lymph nodes in bilateral axillary and supraclavicular fossa. Laboratory results were as follows: hemoglobin 102 g/L, serum albumin 26.9 g/L, IgG 8.66 g/L, IgA 5.66 g/L, IgM 4.07 g/L, urea nitrogen 3720 mg/24 h, creatinine 140 μmol/L, uric acid 846 μmol/L, antinuclear antibodies were negative, and infectious pathogens were not found. HIV antibody was negative, while the results of HHV-8 and IL-6 level were not available.

Further, ultrasound revealed a mild axillary lymphadenopathy, but 18Fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) detected no SUV-increased lesions (Figure 1). In addition, bone marrow aspiration and trephine biopsy showed no evidence of malignancy. The diagnosis was initially nephrotic syndrome until an ultrasound-guided core needle biopsy of a right axillary lymph node was performed. Pathology showed that hyperplastic lymphoid follicles with vascular proliferation were surrounded by onion-skin-like lymphocytes, and plasma cell infiltrates in the interfollicular area, and which was consistent with CD of plasma cell type (Figure 2). Thus, a final diagnosis of nephrotic syndrome secondary to MCD was established.

He received 4 cycles of rituximab (375 mg/m², d0) plus prednisone (45 mg/m², d1-5). The lymphadenopathies, pleural effusions, edema and ascites resolved significantly, and his condition improved with normalized renal function and hemoglobin. He has been followed up every 3 months and remains disease-free for more than 12 months.

Discussion

The symptoms or signs in MCD are variable, including malaise, lymphadenopathy, edema, weight loss, night sweats, and fever. The common laboratory and imaging features are anemia, proteinuria, hypoaalbuminemia, hypergammaglobulinemia, high level of IL-6 and CRP, splenomegaly and lymphadenopathy, which are non-specific for MCD, since they can also be found in autoimmune disease, malignancy, infectious disease and kidney disease [15].

The nephrotic syndrome is usually caused by primary kidney diseases or secondary to other systemic diseases. The clinical manifestations of nephrotic syndrome are largely overlapping with those of MCD or lymphoma, such as anemia, lymphadenopathy, proteinuria, hypoalu-
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Figure 2. On hematoxylin-eosin stain section of axillary lymph node biopsy specimen, (A) reactive follicular proliferation was characterized by concentric layers of lymphocytes (“onion-skin pattern”), ×200; (B) plasma cells were present in the interfollicular area, ×400.

minemia, and edema. Therefore, systemic evaluation is important for differential diagnosis, and lymph node biopsy is essential when lymphoproliferative disease is suspected.

The criteria established by an international working group for the diagnosis of idiopathic CD has to meet both major criteria (typical lymph node histopathology and involvement of multiple lymph node stations) and at least 2 of 11 minor criteria and rule out the whole exclusion criteria [14]. Later tentative diagnostic criteria in Japan consist of item A and item B based on laboratory findings and clinical features. Item A requires lymphadenopathy and typical histopathological features. Item B includes the disease that must be excluded (malignant neoplasms, infectious diseases, autoimmune diseases and other diseases manifesting similar symptoms). In this case, both A and B diagnostic criteria were met [3].

MCD cases with atypical clinical features could be easily misdiagnosed, which may result in repeated examinations and ineffective treatment. For example, Stephanie reported that a patient with HIV presented as episodic fevers and vasodilatory shock, mimicking urosepsis, finally diagnosed as MCD, suggesting that possibility of MCD should be considered in sepsis-like episodes in HIV infected patients [16]. In addition, the difficulty increases especially when MCD occurs in children [17, 18].

Renal involvement is common in MCD, but it is rarely manifested as nephrotic syndrome. For physicians specialized in nephrology, MCD is often neglected as an underlying nephrotic syndrome. This case was characterized by anasarca, proteinuria and an elevated creatinine, resembling nephrotic syndrome accompanied by renal insufficiency. The patient was initially diagnosed and treated as primary nephrotic syndrome. However, the response was unsatisfactory, and the consultation with hematology was initiated. Pathological examination of an axillary lymph node biopsy eventually led to the correct diagnosis. The symptoms of nephrotic syndrome disappeared after appropriate treatments, confirming that nephrotic syndrome was secondary to MCD. The limitation is that renal biopsy was not performed, which could have helped to clarify the pathogenesis of kidney involvement. The diagnosis process also highlights the necessity of multidisciplinary collaborations.

Due to the rarity of the disease, optimal treatment of CD is still under investigation. Surgical resection is often chosen to treat UCD [19]. Recurrence is rare, but can happen [20]. On the other hand, MCD often requires systemic treatment. Rituximab, an antibody against CD20, is a suitable choice for MCD, especially in HIV+MCD at the standard dose of 375 mg/m² four-weekly treatment [21-23]. Since IL-6 is strongly linked to MCD, IL-6 antibodies such as siltuximab and tocilizumab are alternative options for MCD. The patients who are not sensitive to the therapies above may benefit from combination chemotherapy, irradiation, gluco-
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corticoid, anti-IL-1 therapy [24], anti-viral therapy or steroids, alone or in combination [25].

In summary, a case of MCD is presented that is characterized by nephrotic syndrome, which was successfully treated by rituximab containing chemotherapy. Although nephrotic syndrome is much more common than CD, the accompanying lymphadenopathy should not be neglected, especially when nephrotic syndrome-directed treatment is ineffective, and lymph node biopsy becomes essential for revealing underlying CD as a rare cause of secondary nephrotic syndrome.

Acknowledgements

The authors would like to thank Dr Xiuzhen Li for her assistance in pathological diagnosis. This work was supported by National Natural Science Foundation of China (No. 81572920), Natural Science Foundation of Zhejiang Province of China (No. LY15H160038) and National Basic Research Program of China (No. 2013CB911303).

The patient, or parent, guardian or next of kin provided written informed consent for the publication of any associated data and accompanying images.

Disclosure of conflict of interest

None.

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