



Review Article

Updates on the diagnosis and management of multicentric Castleman disease

Ya-Ju Wu^a, Kuei-Ying Su^{b,c,*}

^aDivision of Critical Care Medicine, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan, ^bDivision of Rheumatology and Immunology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan, ^cSchool of Medicine, Tzu Chi University, Hualien, Taiwan

Submission : 25-Jan-2020
Revision : 13-Apr-2020
Acceptance : 27-Apr-2020
Web Publication : 29-Jul-2020

ABSTRACT

Multicentric Castleman disease (MCD) is an uncommon systemic lymphoproliferative disease. The diagnosis of this disease is typically challenging and requires collaboration between clinicians and pathologists. Moreover, it is important to exclude other diseases (such as malignancies, autoimmune diseases, and infectious diseases) that have similar clinical manifestations and pathological findings. Patients with untreated severe MCD have high mortality due to devastating cytokine storms. Thus, early diagnosis and prompt treatment is a key imperative. The diagnosis of MCD is based on the clinical signs of systemic inflammation, serological tests, and typical pathological features. In this review article, we provide an overview of MCD with a focus on the emerging evidence pertaining to its diagnosis and treatment.

KEYWORDS: *Anti-CD20 monoclonal antibody, Human herpesvirus-8, Interleukin-6 targeted therapy, Multicentric Castleman disease, Thrombocytopenia, Anasarca, Fever, Reticulin fibrosis, and Organomegaly syndrome*

INTRODUCTION

Multicentric Castleman disease (MCD) is a rare, destructive, and potentially fatal lymphoproliferative disorder [1]. In 1954, pathologist Benjamin Castleman reported the first case of Castleman disease, who had a single enlarged lymph node; the condition was later referred to as unicentric Castleman disease (UCD) [2] with the pathological characteristics of hyperplasia of lymphoid follicles, germinal center formation, and marked capillary proliferation with endothelial hyperplasia [Figure 1] [3]. These features were later recognized as the typical pathological characteristics of Castleman disease [4]. Clinically, Castleman disease can be categorized based on the extent of lymphadenopathy. UCD presents with a single enlarged lymph node, whereas MCD presents with two or more enlarged lymph nodes at different anatomical locations.

Lymphadenopathy and fever are the two common manifestations of advanced MCD; however, these clinical symptoms are nonspecific and occur in several conditions such as infectious diseases, hematological malignancies, and autoimmune diseases. Furthermore, patients may present with various constitutional symptoms that delay the recognition of this disease. Owing to its rarity, the diagnosis of MCD is liable to be missed in clinical settings.

The incidence rate of MCD in the United States is 5.7 per million person-years [5], whereas that in the United Kingdom [6] and Japan [7] is 11.8 and 2.4–5.8

per million person-years, respectively. However, the incidence of MCD may be underestimated in many regions owing to the lack of well-established diagnostic criteria [8]. Although MCD is not a malignancy, the survival rate of patients is lower than that of patients with some malignancies such as non-Hodgkin lymphoma or breast cancer [9]. According to an analysis performed by the Castleman Disease Collaborative Network, a global group that facilitates high-impact research on patient survival [9], the 5-year survival rate of patients with MCD was 60% in 2012 [10]. New therapies targeting CD20 and interleukin-6 (IL-6) have been shown to substantially improve the outcomes of patients with MCD [9]. Thus, increasing the awareness of this disease will facilitate the timely diagnosis and treatment of this condition.

CLINICAL PRESENTATION OF MULTICENTRIC CASTLEMAN DISEASE

Lymphadenopathy is the main presenting feature of MCD [10,11]; other clinical features include fever, night sweats, and unintentional weight loss of >10%. Some patients (12%–30%) may have hepatomegaly, splenomegaly, and pleural effusion (or anasarca) [10,11].

*Address for correspondence:

Dr. Kuei-Ying Su,
Division of Rheumatology and Immunology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, 707, Section 3, Chung-Yang Road, Hualien, Taiwan.
E-mail: kueiying.su@tzuchi.com.tw

Access this article online

Quick Response Code:



Website: www.tcmjmed.com

DOI: 10.4103/tcmj.tcmj_15_20

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How to cite this article: Wu YJ, Su KY. Updates on the diagnosis and management of multicentric Castleman disease. *Tzu Chi Med J* 2021; 33(1): 22-8.

Typical laboratory abnormalities include varying degrees of anemia (hemoglobin <12 g/dL) and/or thrombocytopenia (<150 × 10⁹/μL) and elevated serum levels of C-reactive protein (CRP), immunoglobulin A, and immunoglobulin G. Interestingly, the peripheral blood neutrophil and lymphocyte counts are usually within the normal range; this suggests the involvement of mechanisms leading to plasmacytosis and systemic inflammation. In addition, immune-related cytopenia, cryptogenic organizing pneumonia, paraneoplastic pemphigus, polyneuropathy, and glomerulonephritis have been reported in patients with MCD [12].

Figure 2 shows the approach strategies toward diagnosis for patients with generalized lymphadenopathy combined with constitutional symptoms. Imaging workups are necessary to determine the extent of lymphadenopathy and the existence

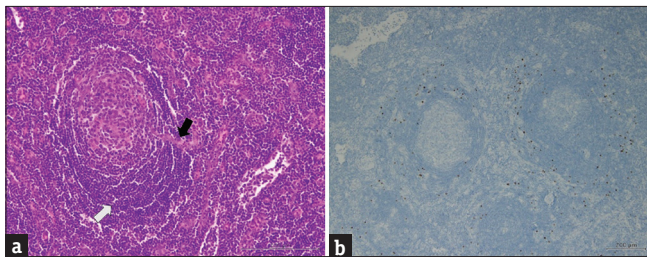


Figure 1: Histologic features in lymph node of Castleman disease. (a) Germinal center hyalinization and onion skin appearance of the mantle zone (white arrow). There is prominent vascular proliferation, the so-called “lollipop” feature (black arrow). The interfollicular area contains abundant plasma cells (hematoxylin and eosin stain). (b) The lymph node is positive for latency-associated nuclear antigen-1 (LANA-1) stain, indicating that plasma cells were infected by HHV-8 virus (×100)

of organomegaly. Serologic and immunologic studies are essential for excluding the possible differential diagnosis of MCD [listed on the right-side panel of Figure 3]. Given the diverse symptoms and laboratory data, lymph node biopsy is indispensable for establishing the diagnosis of MCD. The biopsies of the lymph nodes are evaluated for the histologic features, immunostaining, and special staining for pathogens.

PATHOLOGICAL FEATURES OF MULTICENTRIC CASTLEMAN DISEASE

The key elements of pathological examination of lymph nodes include assessment of the germinal centers (whether regressed or hyperplastic), the degree of vascularity, the aggregations of follicular dendritic cells, expansion of mantle zones, and the presence of abundant interfollicular plasma cells. The vascularity is an important histopathologic characteristic, with various grades of prominent endothelium in the interfollicular space and vascular penetration of the germinal centers [12]. Based on histopathological findings, MCD is further categorized into three major subtypes, i.e., hyaline vascular type, plasmacytic type, and mixed type [9]. Hyaline vascular type is more common in UCD, whereas plasmacytic and mixed types are more common in MCD [1]. Although a consensus statement by experts identified the three main pathologic subtypes of MCD, the clinical utility and prognostic relevance of these subtypes are yet to be determined.

The pathologic characteristics of MCD may mimic those of various diseases, including lymphoproliferative diseases (e.g., lymphoma and multiple myeloma), autoimmune

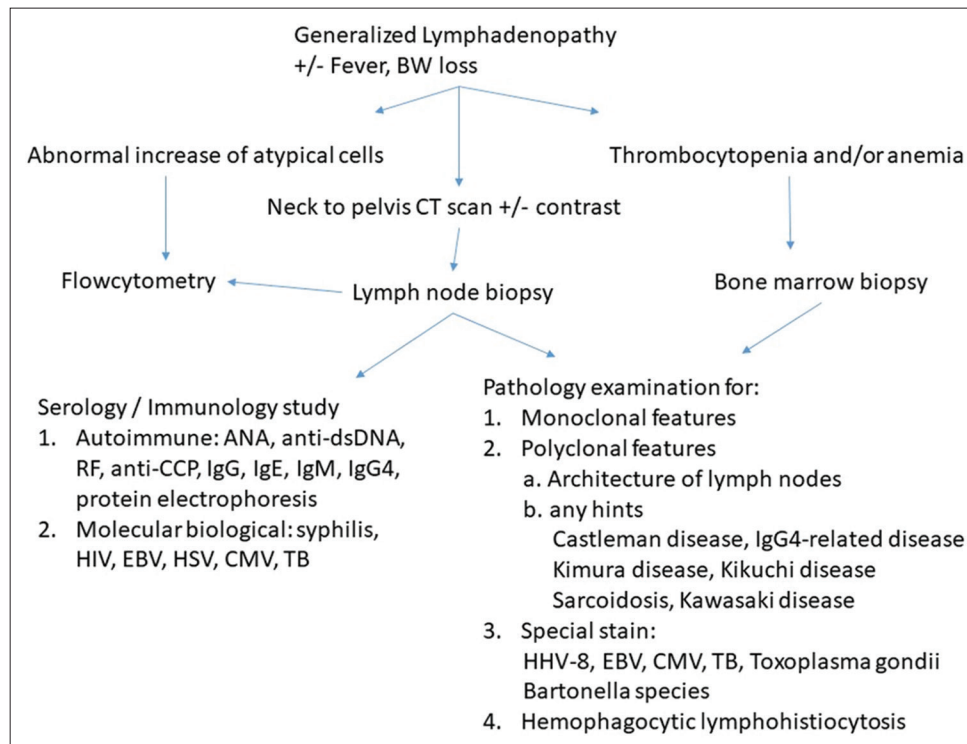


Figure 2: Flowchart of diagnostic strategies for generalized lymphadenopathy with/without fever and body weight loss. ANA: Antinuclear antibody, anti-CCP: Anti-cyclic citrullinated peptide antibody, anti-dsDNA: Anti-double-stranded DNA, BW: Body weight, CMV: *Cytomegalovirus*, EBV: Epstein-Barr virus, HIV: Human immunodeficiency virus, HSV: Herpes simplex virus, Ig: Immunoglobulin, RF: Rheumatoid factor, TB, *Mycobacterium tuberculosis*

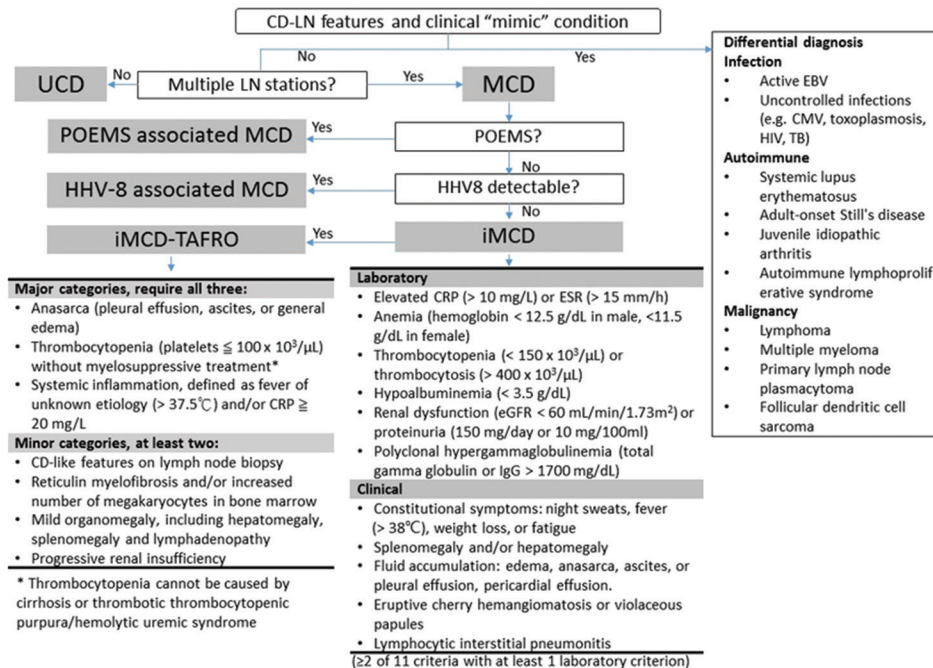


Figure 3: The working flowchart for diagnostic approach of CD-LN features. The major steps toward diagnosis include the number of LN stations, associated features of POEMS, and the concomitant HHV-8 infection. The diagnostic criteria for iMCD [12] and TAFRO syndrome [18] are provided. A differential diagnosis is listed on the right side. CD: Castleman disease, CMV: *Cytomegalovirus*, EBV: Epstein-Barr virus, HIV: Human immunodeficiency virus, HSV: Herpes simplex virus, iMCD: Idiopathic multicentric Castleman disease, POEMS syndrome: Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes syndrome, TAFRO syndrome: Thrombocytopenia, Anasarca, Fever, Reticulin Fibrosis, and Organomegaly syndrome, TB, Mycobacterium tuberculosis, UCD: Unicentric Castleman disease

diseases (e.g., systemic lupus erythematosus and rheumatoid arthritis)-induced lymphoproliferation syndrome, and infectious diseases (Epstein-Barr virus [EBV], human immunodeficiency virus [HIV], tuberculosis, *Cytomegalovirus*, and toxoplasmosis) [4]. Thus, it is important to evaluate these possibilities based on clinical history, physical examination, and serological data while evaluating lymph nodes with CD-like features, before making the final diagnosis [Figure 3]. A definitive diagnosis of MCD should be established after excluding the above diseases.

CLASSIFICATION OF MULTICENTRIC CASTLEMAN DISEASE

Once MCD is diagnosed, further classification of MCD is essential for prognostic assessment and therapeutic decision-making [Figure 3]. The first step is to assess any potential relation of MCD with POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) syndrome [13]. POEMS syndrome is a paraneoplastic syndrome caused by the proliferation of monoclonal plasmacytes. These patients exhibit increased expression of vascular endothelial growth factor (VEGF) on plasmacytes in the bone marrow [14]. Overproduction of VEGF may lead to clinical polyneuropathy, organomegaly, endocrinopathy, and skin changes. About 11%–30% of patients with POEMS syndrome also have Castleman disease. Therefore, patients with MCD who qualify the criteria for POEMS syndrome should be considered as having POEMS-associated MCD [15].

The second step for classification of MCD is to determine

the human herpesvirus-8 (HHV-8) infection status through special staining of lymph node for latency-associated nuclear antigen-1 and serology polymerase chain reaction test [Figure 1b].

Patients with MCD without HHV-8 infection or POEMS syndrome are classified as idiopathic MCD (iMCD). The first consensus diagnostic criteria for iMCD published in 2017 comprise two major criteria and 11 minor criteria [12]. Patients must qualify both the major criteria (typical histopathologic features of MCD in lymph nodes and enlarged lymph nodes at different lymph node stations) and at least two minor criteria (out of six abnormal laboratory findings and five clinical manifestations) to qualify the diagnostic criteria for iMCD [Figure 3].

Thrombocytopenia, Anasarca, Fever, Reticulin fibrosis, and Organomegaly (TAFRO) syndrome, a variant of iMCD, is associated with the poorest prognosis among all MCD subtypes [10,16]. The 2015 proposed diagnostic criteria for TAFRO syndrome included the typical histopathological features of MCD in lymph nodes; negative staining for HHV-8 LANA-1 [17]; and the presence of clinical thrombocytopenia, anasarca, and organomegaly. However, lymph node biopsy is sometimes impossible to detect in patients suspected with TAFRO syndrome. Therefore, the diagnostic criteria and disease severity for TAFRO syndrome were updated in 2019, in which the histopathological features of lymph nodes are considered as a minor category, instead of a necessary histopathological criterion [Figure 3] [18]. All the following three major categories are required: anasarca, thrombocytopenia,

and systemic inflammation. At least two of the four minor categories are required. Furthermore, the disease severity is defined from mild to very severe based on the degree of anasarca, thrombocytopenia, fever, and renal insufficiency.

PATHOGENESIS

HHV-8 viral-generated IL-6 triggers systemic inflammation in patients with HHV-8-associated MCD [8]. The virus infects B cells and epithelial cells in the oropharynx and circulates in the bloodstream. While in circulation, the HHV-8 virus in the B cell is in a latent phase. The virus may be reactivated and assume the lytic form with higher expressions of viromes and the viral IL-6 (*vIL-6*) gene [19]. Although the *vIL-6* exhibits only 25% homology with the human IL-6 (*hIL-6*) [20], their functional attributes are similar. *hIL-6* binds to the IL-6 receptor α chain (IL-6R α), which is located in hepatocytes, some leukocytes, and some epithelial cells. The complexes of *hIL-6* and IL-6R α allow further binding of *hIL-6* to the signal transducer glycoprotein 130 (gp130) and subsequently induce activation of the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway. Of note, *vIL-6* can activate gp130 without IL-6R α and induce signal transmission [21]. Therefore, the effects of *vIL-6* are liable to be uncontrolled. However, HHV-8 infection does not always induce the development of Castleman disease. Oxidative stress, hypoxia, simultaneous infection with other viruses, immunosuppression, deranged inflammatory cytokine levels [22], and polyfunctional effector CD8⁺ T cells [23] may lead to the reactivation of HHV-8 and promote the pathogenesis of MCD.

POEMS-associated MCD is comparatively different from HHV-8-induced MCD. VEGF is the main driving cytokine in the POEMS-associated MCD [8] together with IL-6, IL-12, and tumor necrosis factor- α (TNF- α) [24]. IL-1 and IL-6 stimulate macrophages, plasma cells, and megakaryocytes to produce VEGF, which targets the endothelial cells for angiogenesis [15]. There is some overlap between the symptoms of MCD and POEMS syndrome; however, the main difference between MCD and POEMS syndrome is polyneuropathy. The pathogenetic mechanisms by which VEGF causes MCD or POEMS syndrome are yet to be characterized [15].

Unlike the evidence base for HHV-8-related or POEMS-associated MCD, the pathogenetic mechanisms of iMCD are still unclear. Four hypotheses have been proposed. First, case reports suggest that the production of cytokines is triggered by autoimmune disease in about 30% of patients with iMCD [23]. Autoantibodies stimulate the dendritic cells and macrophages in the lymph nodes to produce IL-1, IL-6, and TNF- α . Genetic polymorphisms of IL-6 promoter and NF- κ B were also proposed as pathogenetic mechanisms of autoimmune triggered iMCD [8]. The second hypothesis is oncogenic gene mutation based on the detection of benign or malignant mutated stromal cells, which exhibit continuous secretion of IL-6 and VEGF [8]. The third hypothesis involves infection with viruses other than HHV-8. The most commonly reported viruses are EBV and HHV-6, which may also produce *vIL-6* similar to that by the HHV-8 virus [25,26]. The fourth hypothesis is germline mutations in genes that mediate

the auto-inflammatory process. For example, mutant adenosine deaminase-2 was found in a child with iMCD-like syndrome who had high levels of IL-6 in the serum and lymph nodes. Another example is that a polymorphism in the *IL-6R* gene has also been reported to be associated with higher levels of soluble IL-6R in iMCD [23]. However, these associations are yet to be confirmed.

Among iMCD, TAFRO is a rare syndrome that is not typically induced by excessive production of IL-6. Therefore, polyclonal hypergammaglobulinemia is not observed. The actual pathogenetic mechanism of TAFRO syndrome is not clear [17].

PATHOPHYSIOLOGY

The lymphoproliferative condition in MCD results from abundant production of IL-6 and VEGF [13]. IL-6 is the crucial cytokine for the initiation and development of MCD. IL-6 induces the generation of inflammatory proteins, such as CRP, hepcidin, and serum amyloid A. IL-6 also suppresses the hepatic production of albumin. Therefore, elevated serum levels of CRP and varied degrees of hypoalbuminemia are often detected in patients with MCD. Hypoalbuminemia and tissue inflammation result in anasarca, ascites, pleural effusion, and pericardial effusion [27].

Simultaneously, excessive amounts of IL-6 activate B cells, T cells, and macrophages, which in turn generate more IL-6, IL-1, and TNF- α . These pro-inflammatory cytokines induce constitutional symptoms such as fever and weight loss. The accumulation of lymphocytes, hyperplasia of lymph nodes, and the subsequent activation of the reticuloendothelial system cause lymphadenopathy and hepatosplenomegaly. Of note, polyclonal gammopathy is the main feature that distinguishes MCD from plasmacytoma and multiple myeloma [27]. This is because IL-6 stimulates the generation of plasma cells with consequent overproduction of serum polyclonal immunoglobulins. Although MCD is considered as a nonmalignant disease, a small amount of monoclonal proteins may occasionally be detected; this is attributable to the overproduction of immunoglobulins from the predominantly HHV8-infected plasmablasts. However, with respect to the immune repertoire and molecular characteristics, the plasma cells are polyclonal [28].

Thrombocytopenia and anemia are commonly observed in patients with MCD. Anemia results from chronic systemic inflammation and decreased production of erythrocytes in the bone marrow. IL-6 increases the production of hepcidin, which traps the iron within the macrophages and hepatocytes. Moreover, hepcidin decreases iron absorption from the gut. Reduced levels of serum iron further affect the production of erythrocytes [27]. Normal to increased megakaryocytes are commonly observed in the bone marrow of patients with MCD, which indicates the immunologic nature of the acute consumption of peripheral platelets [17,29]. Besides the above mechanisms of cytopenia, MCD may be associated with autoimmune thrombocytopenia [30,31] and hemolytic anemia [32,33], which are attributable to the generation of anti-platelet and anti-RBC autoantibodies.

Variable degrees of kidney injury have been reported in patients with MCD [34]. Thrombotic microangiopathy-like glomerulopathy is a key characteristic [35-37]. Some reports suggest that the proliferative endothelial cells in MCD with renal involvement may result from the oversecretion of VEGF [38]. Case reports have documented mesangial proliferative glomerulonephritis, membranoproliferative glomerulonephritis, and amyloidosis nephropathy in patients with MCD [39]. Better estimated glomerular filtration rate (eGFR) at the time of MCD diagnosis was shown to be associated with a better 5-year survival rate [34]; however, the underlying mechanism of this phenomenon is yet to be elucidated.

TREATMENT AND PROGNOSIS

Currently, there are four common therapeutic options for MCD, i.e., glucocorticoids, cytotoxic chemotherapy, anti-CD20 monoclonal antibody (rituximab), and anti-IL-6-targeted monoclonal antibodies (siltuximab [12] and tocilizumab [40,41]). Due to the distinct natural course and pathogenetic mechanisms of MCD subtypes, the therapeutic strategies are different. We summarize the current recommendations and suggestions on the management of each MCD subtype below.

For HHV-8 related MCD, four doses of weekly rituximab 375 mg/m² are effective in patients with mild disease. However, this treatment regimen may deteriorate concurrent Kaposi sarcoma. In patients with aggressive symptoms or those with concurrent Kaposi sarcoma, rituximab combined with chemotherapy (e.g., cyclophosphamide and doxorubicin) is recommended. Recent evidence showed that the rituximab-based regimen has improved the 5-year survival rate from 60% to up to 90% [9,42].

Nevertheless, relapse is common. A cohort study in the United Kingdom in 2017 examined 84 patients with MCD with HIV and HHV-8 infection; the relapse rate was 22.5%, and some patients relapsed more than once [43]. Careful follow-up of patients, at least once every 3 months, is a key imperative for early detection of relapse [43]. The rituximab-based regimen with or without additional chemotherapy is recommended for relapsed cases. There is limited evidence of the benefit or risk of long-term rituximab therapy.

For POEMS-associated MCD, the main goal is prompt treatment to eliminate monoclonal plasma cells [44]. The commonly used treatment regimens for POEMS syndrome are high-dose melphalan (140–200 mg/m²) and dexamethasone or cyclical cyclophosphamide 750 mg/m² every 3 weeks with glucocorticoids. Autologous stem cell transplantation has also shown promising outcomes [15]. Interestingly, although elevated serum levels of VEGF are observed in 60% of patients with POEMS syndrome, the results of treatment with anti-VEGF monoclonal antibodies are mixed in these patients [15].

Treatment of iMCD is more challenging than HHV-8-related MCD. In 2018, an international Working Group of experts reviewed 344 patients with iMCD and arrived at an evidence-based consensus [45]. Assessing the severity of iMCD is the first step to tailor the treatment. The criteria for severe

iMCD include five parameters: ECOG \geq 2, eGFR $<$ 30 mL/min/1.73 m², anasarca (or ascites, pericardial effusion, and/or pleural effusion), hemoglobin \leq 8.0 g/dL, and pulmonary involvement. Patients with at least two of the five criteria are classified as severe iMCD.

Regarding the treatment of nonsevere iMCD, siltuximab 11 mg/kg every 3 weeks is strongly recommended [46]; 34% of patients achieved radiographical and symptomatic responses, compared to 0% in the placebo arm in a randomized, double-blind, placebo-controlled trial. Significantly, the number needed to treat in this study was 2.9. If siltuximab is not available, IL-6 receptor antagonist (tocilizumab) is considered.

Patients with severe iMCD experience a higher mortality rate and often require critical care. The overstimulated immune system leads to cytokine or chemokine storm, which is potentially fatal. In a cohort study conducted in 2017, siltuximab was found to confer greater benefits than rituximab, and the number needed to treat for complete remission was 4.3 [10]. However, the steady-state concentration of siltuximab is achieved after several weeks; therefore, concomitant high-dose glucocorticoids are necessary. Since the FDA approval for the use of siltuximab in the United States, the associated mortality rate over a mean observation time of 6.6 years substantially decreased to 6.4% [10]. Cytotoxic chemotherapy is recommended for patients who exhibit signs of deterioration or show no response after 1 week of anti-IL-6-targeted therapy. Promising response (78% overall response rate) can be achieved with this strategy.

Before the targeted therapy reaches the therapeutic level, glucocorticoids can help control the symptoms of iMCD [45]. In patients with milder disease, glucocorticoids (prednisolone 1 mg/kg/day or equivalent doses for 4–8 weeks) are used as an adjunctive treatment. For patients with more severe symptoms, an initial dose of prednisolone 2 mg/kg/day or equivalent is recommended.

Of note, among the iMCDs, TAFRO syndrome shows the poorest response even with siltuximab or tocilizumab. In a retrospective case series, 9 out of 31 patients with iMCD were diagnosed with TAFRO syndrome. The survival rate of TAFRO patients was $<$ 80% at 20 months, while those of non-TAFRO patients was 100% during the same period [10].

Some patients do not respond to anti-IL-6 therapy [13,46]. This indirectly indicates that IL-1, VEGF, IL-2, or other cytokines may also play a role in the pathogenesis of iMCD [41,47]. Patients who do not respond to anti-IL-6-targeted therapy have limited therapeutic options. No large randomized studies have been conducted for patients with iMCD who are refractory to IL-6-targeted therapy. Although VEGF overexpression has been reported in iMCD, especially in the hyaline vascular type and TAFRO syndrome [12,48], there are no promising reports of VEGF-targeted therapies.

CONCLUSION

MCD is a rare lymphoproliferative disease with a poor prognosis if left untreated. A definitive diagnosis is critical to improving the overall survival of these patients. Lymph

node biopsy is essential to establish a definitive diagnosis and to exclude its mimics. With current target-therapy regimens, the 5-year overall survival rate has improved to up to 90%. Greater awareness of the disease among clinicians would facilitate early diagnosis of this disease. More cohort studies and randomized studies are required for a better characterization of the pathogenetic mechanisms of this disease entity and to provide insights for treatment.

Acknowledgments

The authors thank professor Yu Ru Kou for comments that improved the manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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