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Multicentric Castleman Disease

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Introduction

Multicentric Castleman disease (MCD) describes a heterogeneous group of disorders with various etiologies that demonstrate episodic systemic inflammatory symptoms, reactive proliferation of morphologically benign lymphocytes, and multiple organ system impairment as a result of excessive interleukin-6 (IL-6) and other proinflammatory cytokine [1]. MCD involves multiple regions of enlarged lymph nodes as opposed to Unicentric Castleman disease that is localized to a single set of lymph nodes. Two-thirds to one-half of MCD are Human herpes virus-8 (HHV-8) positive and the vast majority of these patients are HIV positive or immunocompromised [2].

Idiopathic Multicentric Castleman Disease

There is a group of HIV/HHV8-negative MCD patients who are classified as idiopathic MCD (iMCD). Its etiology is unknown and may be viral, inflammatory or neoplastic [3]. iMCD is sub-classified as hyaline vascular(HV), plasmacytic (PC), or mixed variant (MV) according to histopathologic features. HV is characterized by widened mantle zones composed of concentric rings of small lymphocytes in an "onion skin" pattern around small atrophic germinal centers with penetrating hyalinized vessels and dysplastic follicular dendritic cells. PC has hyperplastic germinal centers, the interfollicular region contains sheets of plasma cells and vascular proliferations, the follicular dendritic cells network is normal, and there is preserved lymph node architecture. MV has features of HV and PC [1.]

Currently there are well defined diagnostic criteria for iMCD that were established in 2016 by the Castleman Disease Collaborative Network (CDCN). It requires the presence of both major criteria (characteristic lymph node histopathology and multicentric lymphadenopathy) and at least 2 of 11 Minor Criteria with at least 1 laboratory abnormality, and exclusion of infectious, malignant, and autoimmune disorders that can mimic iMCD Table 1 [4].

I. Major Criteria (need both):
1.-Histopathologic lymph node features consistent with the iMCD spectrum (Fi
2.-Enlarged lymph nodes (>1 cm in short-axis diameter) in <2 lymph node stations
II. Minor Criteria (need at least 2 of 11 criteria with at least 1 laboratory criterion)
Laboratory
1. Elevated CRP (0.10 mg/L) or ESR (0.15 mm/h)
2. Anemia (hemoglobin, 12.5 g/dL for males, hemoglobin, 11.5 g/dL for females)
3. Thrombocytopenia (platelet count, 150 k/mL) or thrombocytosis (platelet count 400 k/mL)
4. Hypoalbuminemia (albumin, 3.5 g/dL)
5. Renal dysfunction (eGFR, 60 mL/min/1.73 m^2) or proteinuria (total protein 150 mg/24 h or 10 mg/100 ml)
6. Polyclonal hypergammaglobulinemia (total g globulin or immunoglobulin G . 1700 mg/dL)
Clinical
1. Constitutional symptoms: night sweats, fever (38°C), weight loss, or fatigue ($2 CTCAE lymphoma score for B-symptoms)
2. Large spleen and/or liver
3. Fluid accumulation: edema, anasarca, ascites, or pleural effusion
4. Eruptive cherry hemangiomatosis or violaceous papules
5. Lymphocytic interstitial pneumonitis

Table 1: Minor Criteria with at least 1 laboratory abnormality, and exclusion of infectious, malignant, and autoimmune disorders that can mimic iMCD.

There is a newly recognized variant of idiopathic MCD named TAFRO syndrome that was initially identified in 2010 [5]. It involves a constellation of syndromes: thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly. It is important to recognize this new entity because it has a more aggressive course than iMCD [6]. The proposed diagnostic criteria for TAFRO syndrome are summarized in Table 2.

1. Histopathological criteria (need both)
-Compatible with histopathological findings of lymph nodes as TAFRO syndrome -Negative LANA-1 for HHV-8
2. Major criteria (need all)
Presents at least 3 of 5 TAFRO symptoms i. Thrombocytopenia ii. Anasarca iii. Fever iv. Reticulin fibrosis v. Organomegaly
Absence of hypergammaglobulinemia
Small-volume lymphadenopathy
3. Minor criteria (need 1 or more)
Hyper/normoplasia of megakaryocytes in bone marrow

High levels of serum ALP without markedly elevated serum transaminase

Table 2: Diagnostic criteria for TAFRO syndrome.

Siltuximab is the only FDA-approved medication for the treatment of iMCD patients [7]. In addition, there are other therapeutic modalities in the first-line or relapse setting to treat iMCD which include corticosteroids, rituximab, combination chemotherapy, autologous stem cell transplantation (ASCT), novel agents such as bortezomib, thalidomide, the IL1-antagonist anakinra, and immunomodulatory molecules, such as interferon-a and all-trans retinoic acid. The efficacy of these treatment options is only based on small series, case reports, literature reviews, and retrospective analysis of institutional experiences [8].

High dose steroids can be used to decrease the hypercytokinemia and symptoms of iMCD, however it rarely leads to prolong remissions and relapses occur frequently on cessation of therapy. It cannot be given for long period of time because its side effects [9-11]. Rituximab is another common drug used to treat iMCD, in one report describing 25 cases of iMCD treated with rituximab as first-line therapy 20% achieved CR and 48% PR [12]. In another report that described 8 patients treated with this drug alone, 5 patients achieved CR, and 1 patient had disease progression [13]. Siltuximab was tested in a randomized, double-blind, placebo-controlled Phase II study conducted in 19 countries, 70 patients were recruited where 53 patients received siltuximab and 26 patients got placebo (2:1 ratio). The primary endpoint was durable tumor and symptomatic response for at least 18 weeks for the intention-to-treat population. Durable tumor and symptomatic responses occurred in 18 (34%) of 53 patients in the siltuximab group (17 reached PR and 1 CR) and none of 26 in the placebo group (difference 34%, 95% CI 11.1–54.8, p = 0.0012). The median time to symptomatic response was 33 days and time to involution of lymphadenopathy was 155 days. Median time to treatment failure was not reached in the siltuximab arm versus 134 days in the placebo arm. The incidence of grade 3 or more adverse events was (25 (47%) vs. 14 (54%). The most common side effects were fatigue, night sweats and anemia [7].

The first-line treatment for patient who are more severely afflicted and have a clear proinflammatory syndrome should be siltuximab or tocilizumab. If the patient does not respond to IL6 antibodies rituximab + chemotherapy should be started. Patients with milder disease are candidates for a more limited treatment approach with 4 to 8 weekly doses of rituximab 375 mg/m^2, which are often combined with steroids. If this therapy does not work the next step will be either siltuximab or tocilizumab. Some iMCD patients may present with full POEMS features (sensorimotor polyneuropathy), these patients may benefit from high dose chemotherapy with melphalan follow by autologous stem cell transplant [8].

In terms of long term survival, there is a retrospective series of 113 patients treated at the Mayo Clinic and the University of Nebraska. They reported a 5-year overall survival (OS) of 65% for patients with MCD with a median follow-up of 5.8 years. The participants of this study were not formally tested for HIV or HHV8, but none had clinical AIDS at diagnosis or subsequently during follow-up [14].

HIV/HHV-8 positive Multicentric Castleman disease

HIV/HHV-8 positive MCD is a rare lymphoproliferative disorder whose patho-genesis appears to be related to an aggressive immune response against human herpesvirus-8 [15]. The incidence of HIV/HHV8 positive MCD seems to be rising in the combination antiretroviral therapy era, although case-identification bias may play an important role [16]. It presents with a waxing and waning acute febrile illness characterized by various clinical findings, including diffuse lymphadenopathy, splenomegaly, and anemia, this clinical presentation appears to be similar between HIV positive and negative MCD patients. The definitive diagnosis requires histological confirmation [17]. Kaposi's sarcoma (KS) may be diagnosed at the same time in 75% of HIV/HHV8 positive patients [18].

The main upfront treatment for HIV/HHV8 positive MCD is rituximab, it has improved the outcomes of a rapidly fatal illness to a relapsing and remitting disease, in addition it may decrease the risk of developing HHV8-associated lymphomas [19]. In a cohort of 52 patients with HIV/HHV8 positive MCD that were treated with rituximab the median overall survival was 6.2 years and after a mean follow-up of 2.26 years, 19 (40%) of 52 patients died. This study also found superior outcomes of rituximab + chemotherapy versus chemotherapy alone [20]. Combined antiretroviral therapy is necessary to treat the underlying HIV infection and for patients who have not received antiretroviral therapy at the time of MCD diagnosis, 4 cycles of rituximab should be given first and then antiretroviral therapy [17]. The main adverse event of rituximab seems to be a reactivation of KS, which was seen in up to one-third of patients. If the patient is diagnosed with MCD and KS at the same time liposomal doxorubicin in combination with rituximab may be given [20,21]. A short course of valganciclovir (e.g., 3 months) may be useful to control HHV8 replication until the patient's immune system has been partially reconstituted [17]. Finally if the patient relapses rituximab may be used again with high salvage rates [22,23].

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