Multicentric Castleman Disease

Francisco Socola
PGY 7, Bone Marrow Transplant fellow at Stanford University, USA

*Corresponding author: Francisco Socola, PGY 7, Bone Marrow Transplant fellow at Stanford University, USA, Tel: 501 400 6651, E-mail: fsocola@stanford.edu

Received date: January 26, 2018; Accepted date: February 01, 2018; Published date: February 06, 2018

Copyright: © 2018 Socola F. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

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 (Figs. 1 and 2)
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 m²) 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

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.

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

<table>
<thead>
<tr>
<th>1. Histopathological criteria (need both)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Compatible with histopathological findings of lymph nodes as TAFRO syndrome</td>
</tr>
<tr>
<td>-Negative LANA-1 for HHV-8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Major criteria (need all)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present at least 3 of 5 TAFRO symptoms</td>
</tr>
<tr>
<td>i. Thrombocytopenia</td>
</tr>
<tr>
<td>ii. Anasarca</td>
</tr>
<tr>
<td>iii. Fever</td>
</tr>
<tr>
<td>iv. Reticulin fibrosis</td>
</tr>
<tr>
<td>v. Organomegaly</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Minor criteria (need 1 or more)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypernephromatosis of megakaryocytes in bone marrow</td>
</tr>
</tbody>
</table>

Table 2: Diagnostic criteria for TAFRO syndrome

February 2018
Volume 6 • Issue 1 • 1000e122
fatigue, night sweats and anemia [7]. POEMS features (sensorimotor polyneuropathy), these patients may
least 18 weeks for the intention-to-treat population. Durable tumor
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 to 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
calganciclovir (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].

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
events was (25 (47%) vs. 14 (54%)

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/m2, 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

References

classification and the spectrum of associated lesions. Adv Anat Pathol. 16:
236-246.
2. Suda T, Katano H, Delsol G (2001) HHV-8 infection status of AIDS-
related and AIDS-associated multicentric Castleman's disease. Pathol
Int. 51:671-679.
(2013) Human herpesvirus 8-related Castleman disease in the absence of
diagnostic criteria for HHV-8-negative/iIdiopathic multicentric
marrow fibrosis accompanied by fever, pleural effusion, ascites and
6. Iwaki N, Fajgenbaum DC, Nabel CS (2016) Clinicopathologic analysis of
TAFRO syndrome demonstrates a distinct subtype of HHV-8-negative
7. Van Rhee F, Casper C, Voorhees PM (2015) A phase 2, open-label,
multicenter study of the long-term safety of siltuximab (an anti-
 interleukin-6 monoclonal antibody) in patients with multicentric
and multicentric Castleman's disease: a report of 16 cases and a review of