Castleman’s disease

Update on pathogenesis

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ABSTRACT

Castleman’s disease (CD) is an unusual lymphoproliferative disorder that may mimic lymphoma clinically and pathologically. It is classified clinically as localized and multicentric types, and pathologically as hyaline vascular and plasma cell types. It is associated with increased risk of lymphoma and follicular dendritic cell tumors. The pathogenesis of CD is still controversial and complex. Active research is ongoing to highlight more on the etiopathogenesis of this entity. The aim of this article is to review the literature on pathogenesis of CD and to focus on the possible role of viruses in the development of this disease.


Castleman’s disease (CD) also known as angiofollicular lymphoid hyperplasia, angiomatous lymphoid hyperplasia, and benign giant lymph node hyperplasia is a heterogeneous group of hematolymphoid disorders of uncertain cause. This entity was first described by Castleman and associates. There are 2 clinical types, localized and multicentric, and 2 histological types hyaline vascular type (HVT) and the plasma cell type (PCT). The localized hyaline vascular type (LHVT) is the most common clinicopathological form of CD. The pathogenesis of CD is still complex and unclear. Although the disease is not very common, both clinicians and the pathologists should be aware of the clinicopathological types and the underlying etiology of this disease to avoid misdiagnosis at the pathological level, and to avoid mismanagement clinically. In this review, the pathogenesis of CD is reviewed with concentration on the possible role of viruses in the development of this disease including, human herpes virus-8 (HHV-8), Epstein-Barr virus (EBV), human herpes virus-6 (HHV-6) and cytomegalovirus (CMV).

Clinical features. The CD patients can be asymptomatic and can present clinically with symptoms of a mass lesion or, alternatively, with systemic findings such as weight loss, fever, and anemia. There is no gender preference in CD. The CD usually affects adult, however, it is also described in children. Multicentric Castleman disease (MCD) may be divided by clinical features into multicentric CD associated with neuropathy (POEMS-associated or neuropathic multicentric CD) and multicentric CD without neuropathy (non-neuropathic). The MCD is a clinicopathologically defined entity that was first described in 1983 by Frizzera et al. The first case report of CD in a patient infected with human immunodeficiency virus (HIV) was published in 1985, in which MCD was described in 2 homosexual males with acquired immune deficiency syndrome (AIDS). There is a strong association between AIDS and CD. The CD has also been reported in association with many diseases as case reports including immunoglobulin A nephropathy, autoimmune hypophysitis, uveal effusion syndrome,
membranoproliferative glomerulonephritis,24,25 gastric lymphoma,26 chordoid meningioma,27 and peliosis hepatis.28

Pathological features. The CD usually affects lymph nodes. The most common site of involvement by CD in order of frequency is mediastinum, abdomen, neck, axilla, and inguinal region; however, CD has been also described in many other locations including uterus,29 central nervous system,17 liver,18,30 heart,31 kidney,32 skeletal muscle,33 orbit,34 parotid,35 breast,36 spleen37 and lung.38 The 2 main histological types are the HVT and the PCT. Mixed or intermediate forms with features of both have been described.29,33-37 In HVT, the involved lymph nodes usually show follicular and interfollicular vascular proliferation. The follicles are variable in size from small to medium and many of them contain small hyalinized blood vessels that are usually radially penetrating the germinal centers from the perifollicular area. Some of the follicles usually show concentric layering of the cells around the germinal centers giving what is called ‘onion skin’ pattern. The interfollicular areas consist of numerous capillaries and the majority of the cells among these capillaries are lymphocytes admixed with some plasma cells and occasional immunoblasts. The PCT is characterized by sheets of plasma cells and the follicles are usually large and hyperplastic.39

Pathogenesis. Clonality in CD. The detection of monoclonality in lymphoid proliferations is considered to be a strong indication of neoplasia. Molecular techniques are the most recent and the most sensitive methods for determining lymphocyte monoclonality. Only a few published studies have used molecular genetics methods to determine the clonality of lymphocytes in CD, and these have provided variable results.40-48 The results of those studies are summarized in Table 1. Soulier et al47 reported molecular genetics analyses using Southern blotting and polymerase chain reaction (PCR) of 34 patients with CD. They detected immunoglobulin heavy chain (IgH) gene monoclonal rearrangements in only 4 of 30 patients with MCD, and in none of 4 patients with localized Castleman’s disease (LCD). Two of the patients with monoclonality had concurrent B-cell lymphoma, and one had concurrent Hodgkin lymphoma, which suggested that the monoclonal populations may have been derived from these disorders rather than the CD. They found one patient with T-cell receptor gene rearrangement, and this occurred in a patient with MCD who was HIV-positive. In a previous study6 on HIV-negative CD, we detected B-cell monoclonality in only one of 17 cases of LCD and in none of 3 cases of MCD.8 T-cell monoclonality was not detected in any of the cases. Hanson et al45 detected monoclonal lymphocyte populations in 3 of 4 patients with MCD, but in none of 4 patients with LCD. The TCR rearrangement was found in 2 patients.

Several investigators have examined CD for cytoplasmic immunoglobulin expression by immunohistochemistry (IHC) for Kappa and Lambda, and have reported both polyclonal and monoclonal findings.44,46,49-52 In our previous study,8 IHC results showed cytoplasmic light chain restriction in only one out of 20 cases. The overall results of most of these studies indicate that the lymphoid component in CD is most commonly reactive. However, rare cases may contain a detectable monoclonal lymphoid population.47

Possible role of viral infection in the pathogenesis of CD. Human Herpes Virus-8. The cause of MCD has remained unresolved for many years. Among the viruses that have been implicated in the pathogenesis of CD is Kaposi’s sarcoma-associated herpesvirus or HHV-8. Horizontal transmission by saliva appears the most common route for HHV-8 transmission; however vertical, sexual, and blood and allotransplant-related transmission remain of significant concern.53-57 The results of the previous studies that discussed the association between CD and HHV-8 are summarized in Table 2. The possible involvement of this virus has been

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<th>Author</th>
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<tr>
<td>Hall et al44</td>
<td>SB</td>
<td>5 CD (all PCT, 4MCD)</td>
<td>IgH rearrangement in 3 patients. No TCR rearrangement</td>
</tr>
<tr>
<td>Hanson et al45</td>
<td>SB</td>
<td>8 CD (4 LCD, 4 MCD)</td>
<td>IgH rearrangements in 3 of 4 MCD. All LCD were negative for IgH rearrangements. TCR rearrangement in 2 patients</td>
</tr>
<tr>
<td>Ohyashiki et al39</td>
<td>PCR</td>
<td>2 MCD</td>
<td>One patient had a clonal rearrangement of the immunoglobulin lambda chain gene</td>
</tr>
<tr>
<td>Soulier et al47</td>
<td>PCR, SB</td>
<td>34 CD, (14 HIV-positive, 4 LCD, 30 MCD)</td>
<td>IgH rearrangements in 4 cases. TCR in one patient</td>
</tr>
<tr>
<td>Al-Maghrabi et al40</td>
<td>PCR, FC, SB</td>
<td>20 HIV-negative CD (15 HVT, 5 PCT)</td>
<td>IgH rearrangements in one case. No TCR was found</td>
</tr>
<tr>
<td>Barozzi et al48</td>
<td>PCR</td>
<td>16 HIV negative CD (11 with LCD and 5 MCD)</td>
<td>No clonal IgH rearrangements were found</td>
</tr>
<tr>
<td>Cummings et al49</td>
<td>FC, SB</td>
<td>One LCD, PCT</td>
<td>IgH rearrangements were detected</td>
</tr>
</tbody>
</table>

SB - southern blotting, PCR - polymerase chain reaction, FC - flow cytometry, IgH - immunoglobulin heavy chain gene; TCR- T-cell receptor, CD - Castleman’s disease, LCD- localized castleman’s disease, MCD - multicentric Castleman’s disease, HVT - hyaline vascular type, PCT - plasma cell type, HIV - human immunodeficiency virus
proposed mainly in the pathogenesis of MCD, in both HIV-positive and HIV-negative patients.\textsuperscript{38,59} However, there are considerable differences in the proportions of positive cases in these reports. Soulier \textit{et al}\textsuperscript{a} identified HHV-8 sequences in excised lymph nodes in all of 14 patients with HIV-positive MCD and in 7 of 17 HIV-negative MCD. Gessain \textit{et al}\textsuperscript{a} documented the presence of HHV-8 sequences in 3 of 4 HIV-positive and in one of 6 HIV-negative patients with CD. In contrast, there are also reports in which the investigators failed to demonstrate HHV-8 in non-AIDS MCD.\textsuperscript{48,61,62} The association between HHV-8 and LCD in HIV-negative patients has also been reported.\textsuperscript{63} In a previous study,\textsuperscript{64} HHV-8 was identified by IHC in only one of 25 cases of CD (22 LCD, 3 MCD). The only positive case was a patient with MCD, plasma cell variant. Interestingly, this patient showed evidence of coinfection with EBV by PCR analysis. Some authors demonstrated a correlation between the development and exacerbation of the MCD symptoms with the increase in HHV8 viral load.\textsuperscript{65,66} O’Leary \textit{et al}\textsuperscript{a} investigated the cell types infected by HHV-8 in CD and reported that HHV-8 was identified in approximately 10% of the B lymphocytes in endothelial cells, and in subcapsular spindle cell proliferations.

Recently it has been suggested that CD, particularly the plasma cell and the mixed types, may be related to an excess of interleukin-6 (IL-6)-like activity. Because HHV-8 encodes a gene that is highly homologous to human IL-6 (viral IL-6; vIL-6), and because HHV-8-infected lymphocytes can produce vIL-6, it has been suggested that this may be the mechanism by which the viral infection results in MCD.\textsuperscript{67,75} Increases of serum (IL)-6 and vascular endothelial growth factor have been reported in MCD.\textsuperscript{69,74,76-78} These cytokines may play a role in the plasmacytosis and angiosclerosis that are seen in MCD. The level of expression of vIL-6 is much higher in MCD than in either Kaposi’s sarcoma or pleural effusion lymphoma.\textsuperscript{78}

Parravicini \textit{et al}\textsuperscript{a} demonstrated the presence of HHV-8 vIL-6 gene product in 48% of non-AIDS MCD patients by immunohistochemical analysis. It has been suggested that HHV-8 is disseminated throughout the affected tissue, thereby contributing to increased

### Table 2 - Summary of the previous studies on the association between HHV-8 and Castleman’s disease.

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<tr>
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<tbody>
<tr>
<td>Soulier \textit{et al}\textsuperscript{a}</td>
<td>PCR</td>
<td>31 MCD</td>
<td>HHV-8 detected in 14 of 14 cases of HIV-positive MCD, and in 7 of 17 HIV-negative MCD</td>
</tr>
<tr>
<td>Barozzi \textit{et al}\textsuperscript{a}</td>
<td>PCR</td>
<td>16 HIV negative CD (11 LCD and 5 MCD)</td>
<td>HHV-8 detected in one case of LCD and, all MCD were negative</td>
</tr>
<tr>
<td>Parravicini \textit{et al}\textsuperscript{a}</td>
<td>PCR</td>
<td>14 HIV-negative CD</td>
<td>HHV-8 detected in 6 of 14</td>
</tr>
<tr>
<td>O’Leary \textit{et al}\textsuperscript{a}</td>
<td>PCR</td>
<td>16 CD (6 LCD, 10 LCD)</td>
<td>HHV-8 detected in 5 MCD and 2 LCD</td>
</tr>
<tr>
<td>Suda \textit{et al}\textsuperscript{a}</td>
<td>IHC, ISH, PCR</td>
<td>81 MCD (3 are AIDS associated)</td>
<td>HHV-8 detected by IHC and ISH in only 3 out of 82. All positive cases were found to be AIDS associated CD. HHV-8 was detected by PCR in only one out of 43 cases, and this case found to be AIDS associated CD</td>
</tr>
<tr>
<td>Al-Maghrabi \textit{et al}\textsuperscript{a}</td>
<td>IHC</td>
<td>25 HIV-negative CD (21 LCD and 4 MCD)</td>
<td>HHV-8 detected in only one case, and this case was found to be MCD</td>
</tr>
<tr>
<td>Gessain \textit{et al}\textsuperscript{a}</td>
<td>PCR</td>
<td>10 CD (4 with HIV)</td>
<td>HHV-8 detected in 3 of 4 HIV-positive, and in one of 6 HIV-negative CD</td>
</tr>
<tr>
<td>Gujral \textit{et al}\textsuperscript{a}</td>
<td>IHC/ISH</td>
<td>3 HIV positive CD</td>
<td>HHV-8 was not detected in any case</td>
</tr>
</tbody>
</table>

PCR - polymerase chain reaction, HVT - hyaline vascular type, CD - Castleman’s disease, PCT - plasma cell type, LCD - localized Castleman’s disease, ISH - in situ hybridization, HHV-8 - human herpes virus-8, HIV - human immunodeficiency virus, AIDS - acquired immune deficiency syndrome

### Table 3 - Summary of the previous studies on the association between Epstein-Barr virus and Castleman’s disease.

<table>
<thead>
<tr>
<th>Author</th>
<th>Technique</th>
<th>Patients</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Murray \textit{et al}\textsuperscript{a}</td>
<td>ISH/ISHC</td>
<td>13 CD (12 LCD and 1 MCD)</td>
<td>EBV was detected in 5 LCD and not in MCD</td>
</tr>
<tr>
<td>Oksenhendler \textit{et al}\textsuperscript{a}</td>
<td>ISH/ISHC</td>
<td>16 HIV positive MCD</td>
<td>EBV was not detected in any patient</td>
</tr>
<tr>
<td>Barozzi 1999 \textit{et al}\textsuperscript{a}</td>
<td>PCR</td>
<td>16 HIV negative CD (11 LCD and 5 MCD)</td>
<td>EBV was detected in only 7 of LCD and 2 MCD</td>
</tr>
<tr>
<td>Cummings \textit{et al}\textsuperscript{a}</td>
<td>PCR</td>
<td>One LCD, PCT</td>
<td>EBV was not detected</td>
</tr>
<tr>
<td>Al-Maghrabi \textit{et al}\textsuperscript{a}</td>
<td>PCR</td>
<td>20 HIV-negative CD (17 LCD and 3 MCD)</td>
<td>EBV was detected only in 2 cases; both were PCT</td>
</tr>
<tr>
<td>Chen \textit{et al}\textsuperscript{a}</td>
<td>PCR</td>
<td>19 CD (18 LCD and 1 MCD)</td>
<td>EBV was detected in all cases</td>
</tr>
<tr>
<td>Gujral \textit{et al}\textsuperscript{a}</td>
<td>IHC/ISHC</td>
<td>3 HIV positive CD</td>
<td>EBV was detected in 2 cases</td>
</tr>
</tbody>
</table>

PCR - polymerase chain reaction, CD - Castleman’s disease, LCD - localized castleman’s disease, MCD - multicentric Castleman’s disease, PCT - plasma cell type, ISH - immunohistochemistry, ISH - in situ hybridization, EBV - Epstein-Barr virus, HIV - human immunodeficiency virus
vascularity (via v-IL-6 production) and the development of CD.\textsuperscript{67,79}

**Epstein-Barr virus.** Authors reported variable results regarding the role of EBV in CD.\textsuperscript{45,48,80-91} The results of the previous results that discussed the association between CD and EBV are summarized in Table 3. The EBV genomes were detected in the small lymphocytes of 2 of 3 cases examined by in situ hybridization studies.\textsuperscript{83} The EBV was not detected by some authors.\textsuperscript{62} In our previous study,\textsuperscript{89} the EBV genome was detected only in 2 cases out of 20. One patient with MCD and the other one had LCD that was associated with clonal IgH rearrangement. Hanson et al\textsuperscript{115} detected copies of the EBV genome in 2 of 3 patients with CD with clonal rearrangement. No linkage between CD and EBV could be demonstrated by other authors using immunohistochemically for an anti-latent membrane protein-1 monoclonal antibody (n=16), or by RNA in situ hybridization with an EBV-encoded RNA transcript-specific probe (n=3).\textsuperscript{85}

**Other viruses.** There are few studies in the literature that evaluate the association between CD and other viruses. Hanson et al\textsuperscript{115} tested the presence of CMV DNA in 8 CD patients (4 LCD and 4 MCD) and all the cases turned to be negative. Immunohistochemistry for CMV has a very high sensitivity and specificity for detection of CMV.\textsuperscript{92-95} In our previous study,\textsuperscript{96} the presence of CMV infection in HIV-negative CD was tested. This virus could not be demonstrated by IHC in any of the 25 cases of CD that were tested. Persistent CMV antigenemia may induce chronic inflammatory processes leading to tissue injury.\textsuperscript{97} Barozzi et al\textsuperscript{118} demonstrated the presence of HHV-6 in 2 cases out of 16 HIV-negative CD.

**Prognosis and association with malignancy.** There is increased risk of Hodgkin and non-Hodgkin lymphoma in patients of CD. The increase risk includes both HIV-positive and HIV-negative patients.\textsuperscript{20,43,52,85,98-100} The association is clearer and well documented with non Hodgkin lymphoma than Hodgkin lymphoma.\textsuperscript{43,71,84,101-117} The current World Health Organization classification of hematopoietic tumors now distinguishes large B-cell lymphomas arising in CD as a separate entity, called “large B-cell lymphoma arising in HHV-8-associated multicentric CD”.\textsuperscript{118} Oksenhendler et al\textsuperscript{119} demonstrated that there is 15-fold increased risk of lymphoma among HIV-positive patients with MCD over case-matched HIV-positive patients without CD. The LHVT, which is the most common clinicopathological type of CD has good prognosis and patients usually achieve complete remission after surgery, while the prognosis of systemic MCD is poor, with the disease tending to persist for months or years, associated with more complications and patients may die as a result of renal or pulmonary complications.\textsuperscript{120} The prognosis is even worse in HIV positive MCD.\textsuperscript{121,122} Although no standard treatment has been established for MCD, symptomatic recurrences are often managed with corticosteroids and/ or chemotherapy.\textsuperscript{123} Treatments targeted at HHV-8 and the cytokine cascade such as anti-IL-6 receptor antibody (Tocilizumab) show promising results, although the evidence is still limited to case reports.\textsuperscript{24,123,125-129}

In conclusion, it is clear that CD is a morphologic entity that includes a group of diseases with related and often overlapping pathogenesis. The large majority of cases of CD do not show lymphocyte monoclonality and therefore are more in keeping with reactive than neoplastic processes.\textsuperscript{8,47,48} Detection of a monoclonal lymphoid population in CD suggests the possible outgrowth of a neoplastic lymphoid clone, and in the absence of frank morphological evidence of lymphoma; those patients should be followed closely. The HHV-8 is most likely play a significant role in the pathogenesis of HIV-positive MCD, while it is less likely to play a similar role in HIV-negative CD. The role of EBV in the pathogenesis of CD is still controversial, however, it seems that it may play a role in the pathogenesis of a subset of CD and possibly associated with clonal progression. Other viruses including CMV and HHV-6 are unlikely to play any significant role in the etiology of CD. The rare reported association between CD and these viruses most likely represents coincidental findings.\textsuperscript{130,131} The reported association of CD with cytopenias and proteinuria raise the issue of a possible role of immune disturbances in CD pathogenesis, which need to be evaluated in a large study.\textsuperscript{132,133} In this context, the recently proposed CD classification\textsuperscript{134} into 4 histopathogenic subtypes criteria (hyaline-vascular CD, plasma cell CD, HHV-8-associated CD, and multicentric CD not otherwise specified) is suitable to understand this entity and predict the behavior of this disease. Clinicians and pathologists should be aware of the pathogenesis of CD, and in particular the viral role, which may determine disease behaviors and the management plan.

**References**


Pathogenesis of Castleman's disease... Al-Maghrabi


Pathogenesis of Castleman's disease ... Al-Maghrabi


