The aetiology and management of Castleman disease at 50 years: translating pathophysiology to patient care

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Summary

Fifty years ago, Dr Benjamin Castleman first described the unusual lymphoproliferative disorder that now bears his name. Over the subsequent decades, astute clinical and pathologic observations coupled with clever molecular biologic research have increased our understanding of the aetiology of Castleman disease (CD). This article proposes three broad CD variants based on both distinctive histopathology and clinical behaviour. The pivotal roles of infection with human herpesvirus 8 and interleukin-6 production in the development of CD are emphasized. Finally, the natural history of CD and the myriad of therapeutic options are reviewed in the context of a unified model of CD pathophysiology, and continued areas of uncertainty are discussed.

Keywords: lymphoproliferative disease, Castleman disease, angiofollicular lymph node hyperplasia, human herpesvirus 8.

Fifty years ago, Dr Benjamin Castleman, a pathologist at Massachusetts General Hospital, first described a rare lymphoproliferative disorder that now bears his name. Also known as angiofollicular or giant lymph node hyperplasia, the clinical manifestations of Castleman disease (CD) are heterogeneous, ranging from asymptomatic discrete lymphadenopathy to recurrent episodes of diffuse lymphadenopathy with severe systemic symptoms. The population prevalence of CD has not been established; based on the proportion of patients presenting to a large cancer centre with lymphadenopathy of undetermined origin later diagnosed with CD, it was estimated that the number of cases in the US ranges from 30 000 to 100 000 (Moore et al, 1996a). The infrequency with which CD is diagnosed has precluded comprehensive clinical studies, leading to an incomplete understanding of the disease. Current knowledge is based largely on case series and histopathologic reviews. Over the last decade, a large body of evidence has supported the importance of infection with human herpesvirus 8 (HHV-8 or Kaposi sarcoma (KS)-associated herpesvirus) in the aetiology and management of CD. This article provides an overview of CD and its variants, proposing a classification system based on both histopathology and clinical findings. Furthermore, recent advances in the pathogenesis, natural history and treatment are summarized, emphasizing the role of HHV-8 infection.

Classification

Dr Castleman initially described a patient who presented with many years of fever and weakness, and was eventually found to have a large mediastinal mass at fluoroscopy. Medical evaluation revealed mediastinal lymphadenopathy, which, upon surgical excision, was found to have strikingly abnormal architecture of the affected lymph nodes that have come to characterize CD (Castleman & Thowne, 1954). One dozen additional patients who were largely asymptomatic but had mediastinal masses detected in the course of other medical procedures were subsequently identified (Castleman et al, 1956). The lymph nodes from these patients showed disarray in all compartments. Most striking were the lymphoid follicles, both markedly increased in number and unique in morphology. The germinal centres varied in their cellularity, ranging from a mostly acellular fibrinous hyalinization of capillaries to proliferations of pale eosinophilic cells with copious cytoplasm. The germinal centre was frequently surrounded by a marginal zone of concentrical lymphocytes. Increased vascularization was noted in the interfollicular space, with vessels traversing between multiple germinal centres. Finally, sinuses rarely appeared in affected lymph nodes. All the initial patients were only mildly symptomatic, if symptomatic at all, and surgical resection resulted in cure.

In subsequent years, additional cases of patients with diffuse lymphadenopathy and the histologically characteristic CD lymph node architecture were identified (Keller et al, 1972; Gaba et al, 1978; Martin et al, 1985). These series also revealed a new variant of CD, which differed from the original in two important ways (Flendrig, 1969). First, the germinal centres in
the involved lymph nodes differed little from normal histology and showed no evidence of hyalinization. However, concentric sheets of plasma cells surrounded the germinal centres and were prominent in the interfollicular space, which also lacked the characteristic hyper-vascularity (Fig 1). In addition, patients uniformly presented with a host of systemic symptoms that were uncommon in the previously described variant. This novel histological variant of CD was termed the 'plasma cell' variant (PCV), to contrast it with the 'hyaline vascular' variant (HVV) that was originally described. The recognition of both patients with localized lymphadenopathy and disseminated disease led to an additional clinical categorization of CD: 'unicentric' (UCD) versus 'multicentric' (MCD).

Most recently, a third 'subvariant', known as 'plasmablastic MCD', has been described in association with particularly aggressive cases of MCD. In the first series to describe such a variant, CD patients with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal proteins and skin changes), also known as Crow-Fukase, were found to have lymph nodes which resembled those in PCV, but also had large plasma cells in the mantle zone with copious cytoplasm and prominent single or multiple nucleoli (Menke et al, 1996, 2000). A second series found the variant to be associated with HHV-8 infection and progression to plasmablastic lymphoma (Dupin et al, 2000).

As the aetiology of CD has not been definitively established, it remains controversial as to whether CD variants represent different ends of the same spectrum of disease or whether they are entirely separate disease entities. The recent association of HHV-8 infection with both HVV and PCV MCD, as discussed below, and the finding of both HVV and PCV in the same lymph node (Flendrig, 1969) argue strongly in favour of a single disease with several variants, as summarized in Table I.

**Pathophysiology**

Careful clinical and laboratory investigations of patients with the different CD variants has enabled a greater understanding of the pathophysiology of CD. From the first reported case series, the unique histological pattern seen in lymph nodes was attributed to a 'chronic non-specific inflammatory process' (Castleman et al, 1956). The similarity between the abnormal nodal histology in both variants of CD and the lymph nodes associated with chronic viral infections spurred a search for a viral pathogen (Keller et al, 1972). The increased vascularity that hallmarks CD suggested to some that an angiogenic factor may play a role in the genesis of the disease (Frizzera, 1988). Similarly, the proliferation of plasma cells was hypothesized to be the result of either exogenous (cytokines) or endogenous (clonal proliferation) stimulation. Investigations over the past five decades have enabled the development of an incomplete model of CD pathogenesis that incorporates each of these aspects.

**Viral stimulation**

The information gathered from both clinical and pathological series of patients with CD led early investigators to search for a viral pathogen in the aetiology of CD. The symptoms common to many patients with CD, including indolent fever and lymphadenopathy, as well as the description of mononuclear cells with multiple nucleoli that resembled Reed–Sternberg cells in the lymph node mantle zone (Castleman et al, 1956; Keller et al, 1972), suggested that Epstein–Barr Virus (EBV) could play a causative role in the development of CD.

Hanson et al (1988) sought EBV DNA by viral genomic probes in lymph nodes from eight patients with CD, including four with localized disease and four with systemic symptoms.
Only two of the samples had detectable EBV DNA, both in patients with multicentric disease. These findings were in contrast to a later series, which detected the EBV non-coding early RNA (EBER) in the interfollicular region by in situ hybridization (ISH) in five of 12 (42%) patients with UCD, but not in a single patient with MCD (Murray et al., 1995). Of note, none of the EBER-positive lymph nodes had the latent membrane protein-1 (LMP-1) detected, a staining pattern more consistent with asymptomatic chronic EBV infection. Similar results were reported in a study of 20 human immunodeficiency virus (HIV)-infected persons with MCD, where zero of five patients with PCV and zero of 15 patients with a mixed HVV/PCV CD-variant had LMP-1 detected in lymph nodes with monoclonal antibodies or had EBER by ISH (Oksenhendler et al., 1996). Finally, the use of the highly-sensitive polymerase chain reaction (PCR) paired with Southern blotting of PCR products only identified EBV DNA in two of four patients with PCV and zero of two patients with HVV (Corbellino et al., 1996). It is worth noting that EBV DNA may be found in lymph nodes in conditions other than CD, so its presence falls short of proof of causation. Briefly, these small studies argued against EBV as the aetiological agent for CD.

In 1994, a novel gamma-herpesvirus, HHV-8, was detected in tissue from a patient with HIV-associated KS (Chang et al., 1994). This virus was found to be the HHV, most closely related to EBV, and subsequently was determined to be

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**Table I. Categorization and characteristics of Castleman disease (CD).**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unicentric hyaline vascular variant</th>
<th>Unicentric plasma cell variant (PCV)</th>
<th>Multicentric PCV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histopathology</strong></td>
<td>Germinal centres involved: usually ‘involved’ (hyalinized and lymphocyte depleted)</td>
<td>Germinal centres usually uninvolved, though mantle zone consists of concentric sheets of plasma cells</td>
<td>Interfollicular region normal with sheets of plasma cells</td>
</tr>
<tr>
<td>Vascularity: increased</td>
<td>Interfollicular region: hyperplastic and fibrotic stroma</td>
<td>Vascular proliferation</td>
<td></td>
</tr>
<tr>
<td>Plasma cell infiltration: absent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td>Male = female</td>
<td>Male = female</td>
<td>?Male &gt; female (c. 2:1)</td>
</tr>
<tr>
<td>Wide age distribution, median young adults</td>
<td>Wide age distribution, mostly young adults</td>
<td>Older age distribution (fifth–sixth decade)</td>
<td></td>
</tr>
<tr>
<td><strong>Prevalence</strong></td>
<td>Common (80% of unicentric disease)</td>
<td>Less common (20% of unicentric disease)</td>
<td>Least common (10% of all CD)</td>
</tr>
<tr>
<td>Lymph node involvement</td>
<td>Single lymph node or chain</td>
<td>Single lymph node or chain</td>
<td>Multiple lymph nodes or chains</td>
</tr>
<tr>
<td>Most common in the mediastinum or cervical lymph nodes</td>
<td>Most common in the abdomen</td>
<td></td>
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<tr>
<td><strong>Aetiology</strong></td>
<td>Unknown. May be reactive or developmental</td>
<td>Related to increased levels of IL-6 60–100% of cases may be attributable to infection with HHV-8</td>
<td></td>
</tr>
<tr>
<td><strong>Associated symptoms</strong></td>
<td>Rare</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Fevers</td>
<td>Night sweats</td>
<td>Malaise</td>
<td></td>
</tr>
<tr>
<td><strong>Associated signs</strong></td>
<td>Marked lymphadenopathy</td>
<td>Localized lymphadenopathy</td>
<td>Marked lymphadenopathy</td>
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<tr>
<td>Splenomegaly</td>
<td>Elevated lactate dehydrogenase</td>
<td>Elevated lactate dehydrogenase</td>
<td></td>
</tr>
<tr>
<td>Cytopenias (most commonly anaemia or thrombocytopenia)</td>
<td>Elevated cytoplasmas (most commonly anaemia or thrombocytopenia)</td>
<td>Elevated C-reactive protein</td>
<td></td>
</tr>
<tr>
<td>Elevated interleukin-6 levels</td>
<td>Elevated interleukin-6 levels</td>
<td>Evidence of infection with HHV-8 by serology or PCR</td>
<td></td>
</tr>
<tr>
<td><strong>Associated diseases</strong></td>
<td>Paraneoplastic pemphigus</td>
<td>Amyloidosis</td>
<td>HIV</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura</td>
<td>Renal insufficiency</td>
<td>POEMS Syndrome</td>
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<td></td>
<td></td>
<td>Kaposi sarcoma</td>
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<td></td>
<td></td>
<td>Amyloidosis</td>
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<td></td>
<td></td>
<td>Renal insufficiency</td>
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<tr>
<td></td>
<td></td>
<td>Chemotherapy</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Antiviral medications</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Anti-inflammatory agents</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Monoclonal antibodies to interleukin-6</td>
<td></td>
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<tr>
<td><strong>Treatment</strong></td>
<td>Surgical resection</td>
<td>Radiation therapy</td>
<td></td>
</tr>
<tr>
<td><strong>Long-term sequelae</strong></td>
<td>Rare</td>
<td></td>
<td>Progression to lymphoma is common</td>
</tr>
</tbody>
</table>
necessary but not sufficient for the development of KS. KS had also frequently been reported among patients with MCD. These findings led researchers to investigate the link between HHV-8 infection and CD, as summarized in Table II.

Soulier et al (1995a) used PCR and Southern blot analysis to examine the frequency with which HHV-8 was detected by PCR in formalin-fixed and fresh-frozen lymph nodes excised from persons with MCD. Thirty-one patients with all pathological variants, including 17 HIV-negative and 14 HIV-infected persons, were included in this series. Thirty-four HIV-uninfected individuals with reactive lymph nodes without histopathology, characteristic of MCD, were included as controls. Of the HIV-uninfected participants, seven of 17 (41%) showed evidence of HHV-8 infection, including two of three (66%) with HHV, three of nine (33%) with PCV and two of five (40%) with mixed HHV/PCV. All 14 of the HIV-infected persons had HHV-8 detected in the pathological lymph nodes, including six patients with PCV, one with HHV and seven with mixed variant MCD. Only one of 34 (3%) of persons with reactive lymphadenopathy had HHV-8 detectable in lymph nodes. A larger series of 82 MCD cases from Japan also examined excised, paraffin-embedded lymph nodes for the presence of HHV-8 by monoclonal antibodies, ISH and PCR (Suda et al, 2001). This series found that only three of 82 (4%) patients had detectable HHV-8, all of whom were HIV-infected. Three additional Japanese patients with MCD were found to have HHV-8 DNA detected in peripheral blood mononuclear cells (PBMC) by conventional PCR (Kikuta et al, 1997), but none of the 16 HIV-negative Japanese patients with MCD had HHV-8 DNA detected in lymph nodes or peripheral blood by conventional PCR in a separate series(Yamasaki et al, 1997) leading to false-negative results, while the use of highly sensitive PCR raises the concern for specimen contamination leading to false-positive results.

Six of seven patients with HHV-8 in the lymph node by nested PCR had the virus detectable in peripheral blood. The large discrepancy between these studies is difficult to reconcile, but may be attributable to differences in methodology. The study by Soulier et al (1995a), used PCR on fresh-frozen lymph nodes and the series reported by Kikuta et al (1997) used fresh PBMCs, while the others relied on preserved specimens. The use of paraffin-embedded tissues may markedly reduce the ability to detect genomic DNA in clinical samples (Ben-Ezra et al, 1991) leading to false-negative results, while the use of highly sensitive PCR raises the concern for specimen contamination leading to false-positive results.

Three additional lines of evidence support a role for HHV-8 in the pathogenesis of MCD. First, among HIV-infected individuals, the quantity of HHV-8 DNA in PBMCs or plasma has been found to correlate with symptoms during flares of MCD (Grandadam et al, 1997; Bottieau et al, 2000; Oksenhendler et al, 2000; Corbellino et al, 2001; Boivin et al, 2002; Berezne et al, 2004; Casper et al, 2004). Next, there appears to be a high degree of HHV-8 replication in patients with MCD. All HHVs establish a life-long infection, with the virus alternating between active replication (lytic phase) and quiescent infection with a minimal gene transcription programme (latent infection). The majority of cells infected with HHV-8 in patients with KS contain only latent virus, with a small population of lytic virus (Grundhoff & Ganem, 2004). The viral gene expression profile in MCD tissue shows that mostly lytic genes are active in infected cells (Katano et al, 2000, 2001). Finally, as discussed below, administration of antiviral medications has been associated with the regression of symptoms in HIV-infected patients with MCD (Casper et al, 2004).

It is clear that HHV-8 plays a significant role in the pathogenesis of HIV-associated MCD. Definitively establishing the causality of HHV-8 in the aetiology of CD will prove challenging. To date, there is no animal model suitable for studying infection with HHV-8 and the virus does not actively replicate in cell culture. Prospective studies documenting HHV-8 infection, prior to the development of CD, would support a causative role, but the rarity of CD and its indolent course would require unfeasibly large and lengthy investigations. The best opportunity to examine the role of HHV-8 in CD may come from carefully-designed case–control series, where cases and controls are thoroughly evaluated for the presence of HHV-8 infection using standardized and comprehensive serological and direct virological assessments from freshly excised tissue and blood. Whether HHV-8 is the sole aetiological agent responsible for all variants of HIV-associated CD, HIV-unassociated MCD or UCD remains to be determined and should be the subject of future investigation.

**Angiogenesis**

Since the identification of angiogenesis-promoting cytokines, their role in lymphoproliferative disorders has been debated.
(Folkman, 1995). Perhaps the cytokine which has sparked the greatest degree of interest is the human vascular endothelial growth factor (VEGF). VEGF has been found to specifically promote the growth of endothelial cells and is capable of controlling blood vessel formation. Its role in the generation of the characteristic vascular proliferation in CD has been a target of limited research.

Foss et al (1997) compared the lymph nodes from eight patients with CD (variant not specified) to those in tonsillar tissue from patients with and without infectious mononucleosis. VEGF was detected by ISH in five of eight (63%) germinal centres and not in the controls (interfollicular spaces or tonsillar tissue). Among two patients with CD (one U-PCV and one MCD), both had elevated levels of serum VEGF which fell to normal with nodal resection and chemotherapy respectively (Nishi et al, 1999). The supernatants of the cultured lymph nodes that had been resected from both patients had VEGF levels that were 100-times higher than a control node and nearly all plasma cells from the interfollicular region of both nodes stained strongly positive for VEGF by ISH. No mention was made of the HHV-8 infection status of any participant in these studies.

While the elaboration of VEGF may play a role in the pathophysiology of CD, it seems unlikely to account for all of the pathological and clinical manifestations of the disease. Rather, it may be an important step in the causal pathway and should be considered in any unifying model of the pathogenesis of CD.

Interleukin-6 (IL-6)

In parallel to the search for an angiogenic factor in CD, a role for cytokines with lymphoproliferative properties was sought. One potential cytokine with such properties is IL-6, a potent stimulant for the production of B cells. IL-6 had been associated with lymphoid malignancies, such as multiple myeloma and lymphoma, and a series of investigations have led to the recognition of its importance in the pathogenesis of CD.

In the first study to examine the association between IL-6 production and the pathological and clinical findings of patients with CD, Yoshizaki et al (1989) described the elaboration of IL-6 from germinal centres of lymph nodes in patients with both U-PCV and MCD. Furthermore, in this series, serum IL-6 levels were elevated in the patient with U-PCV along with hypergammaglobulinaemia, organomegaly and elevated acute phase reactants. All symptoms and laboratory abnormalities resolved with surgical resection of the node, which was coincident with declines in serum IL-6 levels. The findings in this early study were corroborated by studies in mice, where a murine IL-6 gene expressed in mice via a retroviral vector caused a syndrome indistinguishable from MCD in humans (Brandt et al, 1990). Series of patients observed during symptomatic episodes of MCD have confirmed that serum IL-6 levels are elevated to values seen infrequently with other disease processes and resolve with treatment (Beck et al, 1994; Nishimoto et al, 2000; Oksenhendler et al, 2000).

A number of different mechanisms for the stimulus of IL-6 production have been proposed. Dysregulation of IL-6 production or the cell-signalling pathway downstream of the IL-6 receptor have been hypothesized to play a role in a number of pathologic conditions and may explain the endogenous production of this human cytokine. Another possible source of IL-6 production in CD may be from cells infected with HHV-8. HHV-8 has been shown to produce a viral analogue of IL-6 (vIL-6) with approximately 50% similarity to the human IL-6 (hIL-6) gene on an amino acid level (Moore et al, 1996b). hIL-6 binds the gp130 cellular receptor and activates the Janus kinase/signal transducers and activators of transcription (Jak/Stat) cell signalling pathway through formation of a heterodimer with IL-6 binding protein, IL-6Rα (Kishimoto et al, 1995). vIL-6 may also bind IL-6Rα and complex with gp130 to activate the downstream Jak/Stat pathway (Aoki et al, 2000). The expression of vIL-6 in mice resulted in a similar clinical picture to the expression of hIL-6, with increased haematopoiesis in all lineages, plasmacytosis observed in lymph nodes and organomegaly (Aoki et al, 1999). vIL-6 has been demonstrated to induce the production of hIL-6 in cells harvested from the lymph node of a patient with MCD, providing a link between the higher levels of hIL-6 observed in CD and infection with HHV-8. The expression of vIL-6 may also link the proliferation of plasma cells and vessels seen in CD, as VEGF levels in the supernatant of vIL-6 expressing cells have been shown to be several times higher than the same cells without the expression of vIL-6(Aoki et al, 1999). A role of HHV-8 and vIL-6 in CD has also been corroborated in several observational studies. vIL-6 is expressed in the lymph nodes of HIV-negative (Parravinci et al, 1997; Menke et al, 2002) and HIV-positive (Cannon et al, 1999) persons with CD. In the peripheral blood, elevated levels of vIL-6 in a patient symptomatic with HHV-8-associated MCD regressed with prednisone and foscarnet therapy (Aoki et al, 2001).

Together, these studies provide compelling evidence for the importance of human and viral IL-6 in the pathophysiology of CD, but again raise further questions regarding their exact roles in the variants of CD.

Clonality

Castleman disease is often categorized within the family of lymphoproliferative disorders, among which it is common to find clonal populations of affected cells and cytogenetic rearrangements. Limited studies have failed to uniformly reveal clonal immunoglobulin or T-cell receptor gene rearrangements in tissue from CD (Hanson et al, 1988; Hall et al, 1989; Ohyashiki et al, 1994; Soulier et al, 1995b; Cokelaere et al, 2002) (Table III). A review of four cases of CD did not identify a single case of immunoglobulin gene rearrangement or
cytogenetic abnormality, leading to the conclusion that these factors are unlikely to be a major contributor in the development of CD (Menke & DeWald, 2001).

A unifying model of CD pathogenesis

Important pieces of the chain of events leading to the genesis of CD remain unclear, but a proposed unified model is as follows. The initial step in the development of CD appears to be the production of IL-6 by B cells in the lymph node mantle zone, stimulated in the majority of cases by HHV-8 infection and in a minority of cases by a heretofore unidentified exogenous or endogenous factor. Local elaboration of IL-6, and in turn VEGF, produces the characteristic B-cell proliferation and vascularization of CD. In patients with multicentric disease, systemic symptoms may result from the circulation of IL-6 or IL-6-producing B cells, the generation of excess antibodies or disseminated HHV-8 infection.

Clinical presentation

The clinical manifestations of the CD variants have been well-described in several large case series (Keller et al, 1972; Frizzera, 1988; Peterson & Frizzera, 1993; Herrada et al, 1998) and are discussed individually below.

Unicentric hyaline vascular variant (U-HVV)

Both the first variant of CD to be identified and the most common variant encountered clinically today, U-HVV occurs in approximately 70% of patients with CD (Fig 2). There is no predilection for either gender and while patients present with a range of ages, the median age tends to be in the fourth decade. By definition, a single node or chain of lymph nodes is involved in U-HVV. The involved node is typically large, with a median diameter of 6–7 cm (range of 1–25 cm). Initial case series found the mediastinum to be the most common location for lymph node enlargement, but subsequent series have found

Table III. Summary of studies to determine the clonality of Castleman disease (CD).

<table>
<thead>
<tr>
<th>Study</th>
<th>Castleman variant</th>
<th>Method(s) for determining clonality</th>
<th>Proportion of cases found to be clonal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanson et al (1988)</td>
<td>Unicentric</td>
<td>Immunoglobin and T-cell receptor gene rearrangements</td>
<td>0/4 (0%)</td>
</tr>
<tr>
<td>Hall et al (1989)</td>
<td>Multicentric M-plasma cell variant (PCV)</td>
<td>(1) Lambda/IgA assessment (2) Immunoglobin and T-cell receptor gene rearrangements</td>
<td>3/4 (75%) (1) 2/5 (40%) with lambda/IgA restriction (2) 3/5 (60%) with immunoglobulin gene rearrangements</td>
</tr>
<tr>
<td>Ohyashiki et al (1994)</td>
<td>M-PCV</td>
<td>(1) Lambda/IgA assessment (2) Immunoglobin and T-cell receptor gene rearrangements</td>
<td>2/2 (100%) clonal rearrangement, but only 1/2 (50%) with expression of light chain restriction. 0/2 (0%) with Ig heavy chain or T-cell receptor changes</td>
</tr>
<tr>
<td>Menke and DeWald (2001)</td>
<td>1 U-hyaline vascular variant (HVV) 3 M-PCV</td>
<td>Immunoglobin and T-cell receptor gene rearrangements</td>
<td>0/4 (0%) had immunoglobulin and T-cell receptor gene rearrangements</td>
</tr>
<tr>
<td>Cokelaere et al (2002)</td>
<td>U-HVV</td>
<td>(1) Cytogenetic testing (2) Immunoglobin and T-cell receptor gene rearrangements</td>
<td>Clonal aberration detected on long arm of chromosome 12 without immunoglobulin and T-cell receptor gene rearrangements</td>
</tr>
</tbody>
</table>

Fig 2. Distribution of Castleman variants in the population.
cervical, abdominal and axillary lymphadenopathy to be equally as common (Castleman et al, 1956; Keller et al, 1972; Herrada et al, 1998). The presenting symptoms of patients with U-HVV CD vary according to the site of involvement. Many patients with mediastinal or abdominal lymphadenopathy either are asymptomatic and alerted to their condition via radiographic studies or surgical procedures for other conditions, or come to medical attention because of compressive symptoms. Patients, themselves, often recognize cervical, inguinal or axillary involvement which is then brought to the attention of their health care provider. U-HVV lesions most often present as solitary masses with intense homogeneous contrast enhancement on computed tomography (CT) (Ko et al, 2004) and positron emission tomography may not be useful for distinguishing CD from malignancy (Reddy & Graham, 2003). In contrast to the plasma cell and multicentric variants of CD, U-HVV is rarely (<10%) associated with systemic symptoms. Diagnosis of CD should be established by excisional lymph node biopsy, with the architecture of the entire germinal centre and interfollicular zone preserved for analysis by experienced histopathologists. The normal appearance of cells isolated from the entire lymph node may lead to a failure to diagnose CD with the use of fine needle aspiration (Cangiarella et al, 1997).

Unicentric plasma cell variant (U-PCV)

Unicentric plasma cell variant probably accounts for <20% of all CD variants. It is characterized by the hypertrophy of a single lymph node chain, although involvement of a solitary lymph node is unusual (Keller et al, 1972). Abnormal nodes are most frequently found in the abdomen (Frizzera, 1988). Like U-HVV, the disease occurs equally in men and women, and has been reported among younger patients (third decade). Unlike U-HVV, the majority of U-PCV patients present with constitutional symptoms. Anaemia and elevated sedimentation rates are present in most cases, observed in 90% and 80% respectively. These laboratory anomalies in the setting of lymphadenopathy may raise the suspicion of U-PCV CD, but ultimately an excisional lymph node biopsy showing the characteristic sheets of plasma cells in the interfollicular space is required for diagnosis.

Multicentric plasma cell variant (M-PCV)

Multicentric plasma cell variant CD is the least commonly encountered CD variant, but presents with the most protean manifestations. Affected patients are typically older than those with unicentric disease (median age fifth–sixth decade). A predilection for male sex had initially been reported in the literature (Frizzera et al, 1985; Weisenburger et al, 1985), but the total cases in these series number less than three dozen and subsequent studies have not found that the prevalence of the disease varies by gender (Herrada et al, 1998; Bowne et al, 1999; Chronowski et al, 2001). Patients frequently come to medical attention for the evaluation of systemic symptoms. Fever is reported by most patients, while approximately half will experience weight loss and night sweats (Peterson & Frizzera, 1993; Chronowski et al, 2001). Organomegaly is inconsistent, with splenomegaly reported in 33–79% of patients; hepatomegaly, almost exclusively in the presence of splenomegaly, may occur in up to 63% of M-PCV patients. Thirteen per cent of patients in three case series were found to have KS concurrent with CD, as reviewed in Peterson and Frizzera (1993). A number of abnormal laboratory results are seen, including uniformly elevated sedimentation rates, frequent anaemia (up to 90%), thrombocytopenia or transaminitis (nearly two-third of the patients) (Peterson & Frizzera, 1993). There are no characteristic features of M-PCV on CT and uptake of gallium on scintigraphy is inconsistent (Stansby et al, 1991; Okamoto et al, 2003).

One of the most devastating diseases associated with M-PCV is the POEMS syndrome, seen in up to 15% of MCD cases (Peterson & Frizzera, 1993). POEMS syndrome is thought to result from a plasma-cell dyscrasia and the subsequent production of monoclonal proteins. Lymph node biopsies are not routinely performed as part of the management of POEMS syndrome, but the few large case series have documented MCD in 11–24% of POEMS cases (Nakanishi et al, 1984; Soubrier et al, 1994; Dispenzieri et al, 2003). Patients dually-diagnosed with MCD and POEMS may be more likely to be infected with HHV-8. In a small series of patients with MCD and POEMS, six of seven (85%) had HHV-8 detected in lymph nodes by PCR, and all had serum antibodies to HHV-8 (Belec et al, 1999a). The prevalence of HHV-8 in POEMS patients with MCD is nearly five times that of POEMS patients without MCD (75% vs. 13% in a study of 22 patients) (Belec et al, 1999b). Therefore, it is reasonable to test patients presenting with MCD who have evidence of neuropathy for infection with HHV-8.

Clinical course and prognosis

Few studies exist because of the natural history of untreated CD. The diversity of patients and therapies in the various CD series makes drawing conclusions about natural history and prognosis challenging.

Unicentric CD is almost universally cured after the resection of involved lymph node(s) and has not been associated with increased mortality. Rare patients with U-PCV may require additional therapy after resection for persistent systemic symptoms, but the course of these patients has not been well-characterized.

After the initial presentation of patients with MCD, 33–50% experience symptoms that recur repeatedly over the course of several weeks to over 4 years (Frizzera et al, 1985; Weisenburger et al, 1985). In the four largest series of MCD, median survival ranged from 14 to 30 months, although some patients lived only several weeks following diagnosis, while others were
reported to be alive at 20 years (Frizzera et al., 1985; Weisenburger et al., 1985; Oksenhendler et al., 1996; Herrada et al., 1998). Death in MCD is either caused by sepsis, systemic inflammation leading to multi-organ system failure, or the development of malignancy (most commonly lymphoma). Careful attention to infectious and neoplastic complications, as well as treatment of associated conditions such as HIV may lead to meaningful increases in the life expectancy of patients with MCD.

Special populations

Paediatrics. The clinical manifestations of CD in children that have been reported in the literature differ little from those observed among adults (Salisbury, 1990; Perez et al., 1999). Presentation at <12 years of age is unusual and it has been suggested that the course of MCD among children is less morbid. The proportion of childhood CD cases which may be attributable to infection with HHV-8 has not been determined.

HIV. Lymphadenopathy is frequently encountered among patients infected with HIV and often requires excisional biopsy for aetiological diagnosis. The proportion of HIV-infected patients with lymphadenopathy attributable to CD has not been studied, but a number of published series suggest that the condition is not rare. It also remains to be determined whether the frequent observation of CD in patients with HIV is attributable to the higher prevalence of HHV-8 co-infection among HIV-infected patients or whether HIV-infection itself predisposes to the development of CD.

HIV-associated CD is almost always either M-PCV or multicentric mixed variant (Oksenhendler et al., 1996). Fever and splenomegaly are universal and commonly remit spontaneously after several weeks. Anaemia is present in approximately half of the HIV-infected patients with MCD, but all will have elevated C-reactive protein (CRP) and HHV-8 detected in PBMCs during symptomatic flares (Grandadam et al., 1997; Oksenhendler et al., 2000; Aaron et al., 2002). Symptomatic flares of MCD may occur at any CD4 count, with reports in the literature from 0·001 to >1·0 × 10⁹ T cells/l (Grandadam et al., 1997; Oksenhendler et al., 2000; Aaron et al., 2002; Casper et al., 2004; Loi et al., 2004). There seems to be no clear effect of antiretroviral therapy on the course of MCD, although data are limited. Three patients treated with highly-active antiretroviral therapy were noted to have a `rapidly progressive' course of MCD shortly after initiating treatment (Zietz et al., 1999). Improvements in T-cell count and suppression of HIV replication did not affect the course of MCD in five of seven patients in one series (Aaron et al., 2002) and two of three in another (Casper et al., 2004).

Patients with MCD and HIV-infection are at an increased risk of developing non-Hodgkin’s lymphoma (NHL). Sixty HIV-infected patients with MCD were followed for a median of 20 months and a total of 14 of 60 (23%) developed NHL (Oksenhendler et al., 2002). Of them, three developed primary effusion lymphoma, five developed extranodal NHL and an additional six were diagnosed with an aggressive plasmablastic lymphoma. It was estimated from this series that the 2-year probability of developing NHL after MCD diagnosis was 24% and neither HIV plasma RNA level nor CD4 count was predictive. A similar study of 11 patients followed for 48 months in Australia found that four (37%) developed NHL (Loi et al., 2004).

Treatment

Early interventions in the treatment of CD were iterations of standard therapy for lymphoproliferative diseases, including surgical excision, cytoreductive chemotherapy and radiation therapy. With a greater understanding of CD pathogenesis, therapies directed at specific targets have been developed and show great promise.

Surgical excision

Case series have repeatedly illustrated that surgery is almost always curative for unicentric disease of either the hyaline vascular or PCV (Castleman et al., 1956; Keller et al., 1972; Herrada et al., 1998; Bowne et al., 1999). Because of the disseminated nature of the lymphadenopathy with multicentric disease, complete surgical debulking is rarely possible. The few patients with MCD in whom surgery has been reported have not had meaningful or lasting improvements in their disease symptoms (Herrada et al., 1998; Bowne et al., 1999). As splenomegaly is a constant feature of MCD, diagnostic or therapeutic splenectomy is often performed but has not been shown to be of clinical benefit.

Cytoreductive therapy

Chemotherapy for MCD has been modelled on regimens designed for the treatment of NHL. Accordingly, the most common regimen reported in the literature is the use of cyclophosphamide, vincristine, doxorubicin and either prednisone (CHOP) or dexamethasone (CVAD), both with mixed success. Two series documented the induction of remission with chemotherapy lasting from 1 to 10 years in four of six (67%) treated with CVAD and two of four (50%) patients treated with CHOP (Herrada et al., 1998; Chronowski et al., 2001). Other series have documented minimal success with cyclophosphamide, vincristine and prednisone, and cyclophosphamide, vincristine, procarbazine and prednisone (Frizzera et al., 1985; Weisenburger et al., 1985). A host of other regimens have been described in case reports, but in the absence of larger case series or controlled trials, efficacy is difficult to assess. The HHV-8 infection status was not reported for any patient in these case series and whether HHV-8 infection influences the response to chemotherapy is not known.
Interferon. Interferon has both immunoregulatory and antiviral properties, making it a plausibly effective therapy for patients with MCD. Two patients with HIV-associated MCD have been reported to have lasting remissions after administration of interferon-α chronic therapy, one HIV-8 infected patient with a dose of 5 million units thrice weekly (Kumari et al, 2000) and the other with 5 million units weekly whose HHV-8 infection status was not stated (Nord & Karter, 2003). One HIV-negative patient with MCD (HHV-8 status unknown) was observed to relapse 4 years after receiving 3–5 million units of interferon-α (Nord & Karter, 2001). Only three of the 13 responders (23%) had multicentric disease; the benefit in these patients may have been attributable to adjuvant chemotherapy or corticosteroids that was concurrently administered.

Immune modulators

Steroids. The use of corticosteroids to control the intense inflammation associated with multicentric disease is common, but has not been subjected to clinical trials. Six of 15 (40%) patients in one series were treated with glucocorticosteroids, of whom two had ‘control of disease’ during long-term administration and four saw no lasting response (Frizzera et al, 1985). Prolonged therapy with low-dose prednisone (10 mg/d) was successful in two patients with M-HHV (Summerfield et al, 1983), but failed in a patient with aggressive M-PCV (Bertero et al, 2000). Long-term corticosteroids may be associated with a high risk of bacterial infection in MCD patients, as a large number were noted to die of sepsis during therapy (Frizzera et al, 1985; Bowne et al, 1999).

Interferon-α. Interferon-α has both immunoregulatory and antiviral properties, making it a plausibly effective therapy for patients with MCD. Two patients with HIV-associated MCD have been reported to have lasting remissions after administration of interferon-α chronic therapy, one HIV-8 infected patient with a dose of 5 million units thrice weekly (Kumari et al, 2000) and the other with 5 million units weekly whose HHV-8 infection status was not stated (Nord & Karter, 2003). One HIV-negative patient with MCD (HHV-8 status unknown) was observed to relapse 4 years after receiving 1 year of 3–5 million units of interferon-α thrice weekly (Andres & Maloisel, 2000). All patients in these reports tolerated the drug well. The relative importance of the antiviral and immunomodulatory properties of interferon has not been characterized and therefore it remains to be seen whether it is an effective therapy for MCD in patients who are not infected with HHV-8.

All-trans retinoic acid. All-trans retinoic acid (ATRA) has been shown to have antiproliferative effects (Kane et al, 1996) and may also decrease IL-6-dependent cell signalling (Zancal et al, 2004). It was hypothesized that both these properties could be beneficial in the treatment of MCD, and a case report describing its successful administration in a HIV and HHV-8 uninfected woman has been described (Rieu et al, 1999).

Thalidomide. Similar to interferon-α and ATRA, thalidomide also has immunomodulatory properties (Franks et al, 2004). Thalidomide, however, may act specifically to decrease the production of IL-6, but also possess anti-angiogenic properties. Two patients have been reported to receive thalidomide. One HIV- and HHV-8 infected man had improvements in platelet count but persistent constitutional symptoms with thalidomide and etoposide (Jung et al, 2004), and one HIV-negative woman (HHV-8 infection status not stated) had a complete response lasting over 1 year with 300 mg of thalidomide daily (Lee & Merchant, 2003).

Monoclonal antibodies

Anti-IL-6 monoclonal antibody. A 27-year-old man with M-PCV CD was the first patient to receive anti-IL-6 antibodies for the treatment of CD (Beck et al, 1994). Administration of a murine monoclonal antibody (BE-8) led to a rapid improvement in symptoms and CRP, haematocrit, platelet count and albumin, while levels of serum IL-6 rose to over 10,000 pg/ml. After 84 d of continuous administration, the drug was discontinued; symptoms and laboratory abnormalities quickly returned. It was hypothesized that the generation of mice anti-IL antibodies failed to completely neutralize hIL-6 in serum, resulting in an increase in the serum IL-6 level via homeostatic mechanisms. Therefore, a new product (atlizumab, Roche Pharmaceuticals, Basel, Switzerland) with two substantial changes was developed: the target of this new drug was the IL-6 receptor and it was engineered to be a hybrid between mouse and human antibodies to avoid the development of auto-antibodies with repeated administration (Sato et al, 1993). Treatment of seven HIV and HHV-8 negative patients with once- or twice-weekly intravenous infusions resulted in resolution of symptoms and normalization of laboratory values over 2 months, but discontinuation of the infusions led to relapse within 2 weeks (Nishimoto et al, 2000). Re-exposure did not result in the generation of antibodies to the drug. The long-term effects of IL-6 receptor blockade are not known, but none was reported in this series.

Rituximab. Plasma cells in the mantle zone of some patients with HHV-8 positive and HHV-8 negative M-PCV CD have been shown to express the cell surface marker CD20 (Hall et al, 1989; Dupin et al, 2000; Gholam et al, 2003). The drug rituximab is a monoclonal antibody to CD20 that targets cells expressing this surface marker for death by either complement or cytotoxic cells. Successful therapy with rituximab has been reported in a small number of patients with and without HIV and HHV-8 infection. Eight patients with HIV and HHV-8-associated MCD received infusions of rituximab (Corbellino

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Antiviral therapy

Several antiviral medications have shown the ability to effectively inhibit the replication of HHV-8 in vitro, including ganciclovir, foscarnet and cidofovir (Kedes & Ganem, 1997; Medveczky et al., 1997; Neyts & De Clercq, 1997). A handful of HHV-8-associated MCD patients have been treated with antiviral medications, with mixed success. Of four patients treated with foscarnet, two had no improvement (Bottreau et al., 2000; Senanayake et al., 2003) and two had persistent remission for 12–24 months (Revuelta & Nord, 1998; Nord & Karter, 2003). Seven patients treated with a combination of cidofovir and chemotherapy exhibited no response in either symptomatology or HHV-8 viraemia (Corbellino et al., 2001; Senanayake et al., 2003; Berezne et al., 2004). The use of ganciclovir or the oral derivative valganciclovir, however, reduced HHV-8 viraemia in three patients and led to remissions lasting 12–18 months (Casper et al., 2004). A number of factors may explain the heterogeneity in the response to antiviral therapy for HHV-8-associated MCD. First, as the current in vitro models may not adequately characterize the in vivo efficacy of these drugs, clinical studies to determine which of the antiviral medications has the greatest effect on HHV-8 are needed. Next, if the symptoms of HHV-8-associated MCD are attributable, at least in part to the production of vIL-6, then the current medications that inhibit DNA synthesis may fail to uniformly abort the production of this early-lytic gene product (Zoeteweij et al., 1999). Finally, the optimal time to administer antivirals is not currently understood. If the relationship between MCD and HHV-8 is akin to that of post-transplant lymphoproliferative disorder and EBV, then the use of antivirals prior to cell transformation may be a successful strategy.

Conclusions

Drawing definitive conclusions regarding the optimal treatment of CD from the current medical literature is limited by the small number and heterogeneous characteristics of patients receiving any one therapy, the use of multiple therapies together, the relapsing and remitting nature of CD and continuing uncertainties regarding the pathophysiology of the disease. It seems clear that patients with unicentric disease are almost always cured by surgery alone and that radiotherapy may be a viable option for patients who are poor surgical candidates. A myriad of treatment options exist for patients with MCD and one approach to treatment may be to consider other factors associated with MCD. Ganciclovir, interferon-α or rituximab may be the best treatment options in patients with HHV-8 infection, while CHOP or CVAD may be most appropriate for patients with severe systemic manifestations of MCD. Randomized trials are desperately needed to determine those treatment regimens that are most effective.

Approach to the patient with suspected CD

A diagnosis of CD most often is not entertained until its characteristic features are noted on an excisional lymph node biopsy. Prior to biopsy, however, clinical suspicion for CD should be elevated in patients who have diseases often associated with CD, including KS and POEMS syndrome. A suggested algorithm for the evaluation and management of patients suspected to have CD is shown in Fig 3. Patients with lymph node histology consistent with CD should first have other causes of similar-appearing reactive lymphadenopathy ruled out. These include rheumatoid arthritis, lupus, Sjögren syndrome, HIV infection, lymphoma and drug sensitivity. To differentiate between localized and systemic disease, obtaining a complete blood count (CBC), CRP, and liver function tests (LFTs) are helpful along with a radiologic assessment of cervical, thoracic, abdominal and pelvic lymphadenopathy. Testing for serum interleukin-6 and plasma or PBMC HHV-8 levels are not uniformly available at all laboratories, but should be strongly encouraged in patients with systemic symptoms to help select the most appropriate therapy. Appropriate follow up should be tailored to CD variant and symptoms. Patients with unicentric disease without systemic involvement should have an additional radiological assessment 6–12 months after therapy to verify cure, with additional testing or therapy only pursued with new symptoms. Patients with MCD need to be followed more closely, with repeat CBC, LFT, CRP and radiology at regular intervals or when symptoms suggest recurrence. A suggested algorithm is depicted in Fig 3.

In summary, five decades of steady research into the aetiology and management of the unusual and fascinating lymphoproliferative disorder named after Dr Benjamin Castleman has resulted in many answers, but generates a myriad of questions. Meticulous review of the histopathology in affected lymph nodes in conjunction with astute clinical observations has enabled the categorization of CD into variants with meaningful treatment and prognostic implications. Basic science work has elucidated many of the important components of CD pathophysiology, including

et al., 2001; Marcelin et al., 2003; Kofteridis et al., 2004; Newsom-Davis et al., 2004). In the largest series, three of five (60%) achieved a complete response, which was durable for as long as 14 months and the other two died of multi-organ system failure (Marcelin et al., 2003). It is notable that the two patients who did not respond, both presented with ‘severe haematologic autoimmune phenomenon’, and that two of the four patients with KS saw a worsening of their KS while receiving rituximab. Three HIV-negative MCD patients, including two without evidence of HHV-8 infection, also have been reported in the literature to respond to rituximab. All three patients, however, received either previous or concurrent therapy, including steroids (Ide et al., 2003), chemotherapy (Gholam et al., 2003) and cidofovir (Marietta et al., 2003).

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the role of IL-6 production, HIV and HHV-8 infection and angiogenesis. Innovative treatment strategies have been developed that appear to meaningfully affect the natural history of CD. In the coming years, however, fundamental questions remain to be answered. Why is CD seen only in a small proportion of patients infected with HHV-8? Are all variants of CD caused by HHV-8 infection? What is the stimulus for the production of IL-6 and angiogenesis in the absence of HHV-8 infection? Why do some patients present with localized disease and other systemic? How are
recurrences of CD initiated, and can they be clinically predicted? Which therapeutic regimens are best, are there subsets of patients who benefit more from one over another, and do any prevent the development of lymphoma or death in the most serious cases? The next half-century promises to bring great advances in understanding the aetiology of CD, in turn translating to novel therapeutic approaches for patients afflicted with this disease.

Acknowledgements
I am indebted to Dr Anna Wald for her thoughtful comments and review of the manuscript, as well as her infectious enthusiasm for advancing our understanding and treatment of Castleman Disease.

Grant support: National Institute of Health, K23 1AI054162.

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