Chapter 13
Castleman Disease

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13.1 Introduction

Castleman's disease (CD) was first described in 1954 and further defined in 1956 by Dr. Castleman (1) (Figure 13.1). He reported on patients possessing localized mediastinal lymph node enlargement that was characterized by redundancy of lymphoid follicles with germinal-center involution as well as marked capillary proliferation with endothelial hyperplasia in both follicular and interfollicular regions. Prior cases had been reported, but were anecdotal in nature (2, 3). In 1962, Lattes and Pachter evaluated 12 cases and suggested that these lymph nodes were hamartomatous in nature (4). Lee described refractory anemia associated with CD that responded to surgical resection 5, and by 1967, Tung and McCormack described 5 new cases and reviewed the 62 cases described to that point in the literature (6), highlighting the potential for associated hypochromic anemia, hypergammaglobulinemia, and bone marrow plasmacytosis.

In 1969, in a review of his own 13 patients plus a review of the 92 cases reported in the literature, Flendrig described three types of: benign giant lymphoma": the plasma cell variant,the hyalinized variant, and the "intermediate variant" (7, 8). Flendrig noted that those patients with what is now called the plasma cell variant were more likely to have B-symptoms as well as anemia and hypergammaglobulinemia. He postulated that the plasma cell variant transitions into the hyaline vascular variant, defining what we now call the "mixed" variant, but which he called an intermediate variant (9). In 1972, Keller et al expanded upon Flendrig's work after performing a clinicopathologic analysis of 81 cases of angiofollicular lymph node hyperplasia (8). He coined the expressions plasma cell type (PCV) and hyaline vascular type (HVV), which have superseded Flendrig's: type I" and "type II" nomenclature. Gaba and associates reported the first case of multicentric Castleman disease in 1978 (10). By the mid-1980s, investigators began describing several of the salient differences between HVV and PCV and their respective associations with unicentric (unifocal or localized) and multicentric (multifocal or generalized) presentations (11, 12) (Table 13.1).

Also during this time frame, there were increasing numbers of cases of CD that were associated with peripheral neuropathy (10, 13–17), highlighting the overlap

S.M. Ansell (ed.), *Rare Hematological Malignancies.*

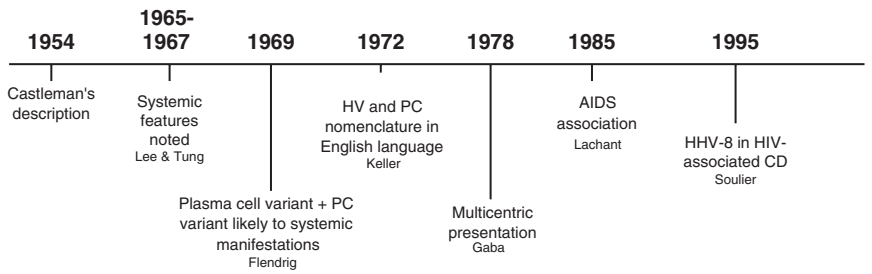

Figure 13.1 Timeline of Castleman disease discoveries.(Compiled from Refs. 1 and 5–10)

Table 13.1 Classification of Castleman disease

	Unicentric	Multicentric
Age	Fourth decade	Sixth decade
Symptoms	Incidental or compressive; occ systemic symptoms	Fever, sweats, weight loss, malaise, autoimmune manifestations; might be associated with peripheral neuropathy and POEMS syndrome
Organomegaly	Rare	Yes
Distribution of lymphadenopathy	Central (mediastinal, abdominal) most common	Peripheral plus central
Laboratory abnormalities	Occasional. Anemia, hypergammaglobulinemia, increased ESR, CRP	Common. Anemia, thrombocytopenia, hypergammaglobulinemia, increased ESR, CRP, abnormal LFTs, low albumin, renal dysfunction
Pathology	HV, occ mixed or PC	PC, mixed, and occ HV
HIV association	No	Some
HHV-8 association	No	Yes (23, 83, 197, 203)
Therapy	Surgery; occ radiation if inoperable	Assorted systemic therapies with variable success (see text)
Clinical course	Benign	Usually aggressive

occ, occasional; POEMS, peripheral neuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes; HV, hyaline vascular variant; PC, plasma cell variant; CRP, C-reactive protein, ESR, erythrocyte sedimentation rate; LFTs, liver function tests.

Source: Data compiled from Refs. 12, 19, 21, 24, 28–30, and 85.

between CD and POEMS syndrome (peripheral neuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes).

Other terminology used historically to describe the entity known as Castleman disease or angiofollicular lymph node hyperplasia included angiofollicular and plasmacytic polyadenopathy, benign giant lymphoma, giant lymph node hyperplasia,

follicular lymphoreticuloma, giant hemolymph node, idiopathic plasmacytic lymphadenopathy with polyclonal hypergammaglobulinemia, lymph nodal hamartoma, lymphoid hamartoma or choristoma, multicentric angiofollicular hyperplasia, and tumorlike proliferation of lymphoid tissue (18, 19).

13.2 Epidemiology

As many men as women are affected. The age distribution is bimodal, with unifocal patients being in their fourth decade versus patients with multicentric disease being in their sisxth decade (11, 20, 21). CD occurs not uncommonly in the pediatric population, and there is a suggestion that the pediatric population might have a better prognosis than that of the adult population (22). There are little data of the actual incidence or prevalence of this disorder, but it is considered to be a rare lymphoproliferative disease. With the AIDS epidemic, the incidence has increased (23); but even in this population, it is a rare condition, with CD lymph nodes accounting for fewer than 2% of lymph node biopsies in HIV^+ patients (24). Nearly all HIV^+ CD patients are infected with human herpes virus-8 [HHV-8; also known as Kaposi's sarcoma virus (KSV]) (23).

13.3 Pathogenesis/Pathology

The underlying pathogenesis of CD is not understood. Early on, it was thought that the HVV tumors were possibly hamartomas (4). An extraordinary case of identical twins who developed CD in the same location 2 years apart from each other (25) supported this notion. However, most authors including Castleman have speculated that CD is a chronic nonspecific inflammatory process in reaction to an unknown stimulus (1, 8). The differential phenotype (HVV vs. PCV) would then be explained by either a continuum of disease, a differential host-dependent immune response, or reactions to two different but closely related stimuli. Further speculation has revolved around which cell type (stromal cells, endothelial cells, lymphocytes, or plasma cells) drives the process. A number of viral pathogens, like Epstein-Barr virus (EBV), cytomegalovirus (CMV), and HHV-8, have been studied looking for a pathogenic link.

13.3.1 Pathology of Hyaline Vascular Variant

On gross pathology these lesions tend to be large, single, rounded, encapsulated masses—more commonly to be found in central than peripheral lymph node regions. Adjacent lymph nodes might be enlarged and involved with the identical process (8, 11). Most masses are between 5 and 10 cm, although lesions as large as

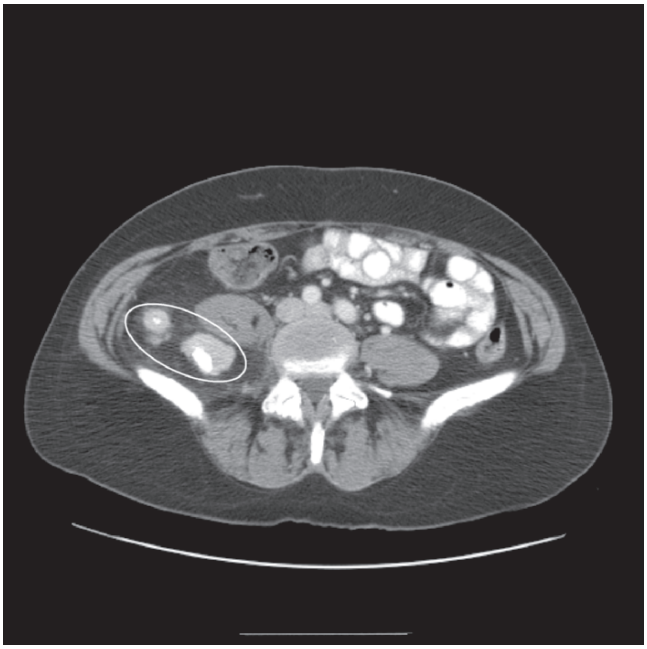

Figure 13.2 CT of a unicentric hyaline vascular variant of Castleman disease displacing the right psoas muscle

Table 13.2 Histology of Castleman disease variants

	Hyaline Vascular Variant (HVV)	Plasma cell variant (PCV)
Follicular size	Small	Normal to large
Capillaries	Increased in number (hyalinized)	No increase
Interfollicular zone	Plasma cells, eosinophils, lymphoblasts	Sheets of plasma cells

Source: Modified from Ref. 87.

25 cm have been described (Figure 13.2). On microscopic examination (Table 13.2), HVV is characterized by the presence of large follicles separated by vascular lymphoid tissue containing lymphocytes (1) (Figure 13.3). There is regressive transformation of the germinal centers, often producing multiple small, burned-out geminal centers within one follicular area. Within and between the follicles there are increased numbers of small vessels with sclerosis and loss of sinuses, which is pathonomic for HVV. The endothelial cells of the capillaries are often plump and mitotic figures might be seen (6, 8). Among the vessels, there is a variable mixture of cells, usually dominated by lymphocytes, but polyclonal plasma cells and eosinophils might also be seen. There is, however, a large variation in the proportions of these components. Large areas of some lesions might be sclerosed, and within such areas, calcification might be present (8). In most cases, there are remnants of lymph node architecture within an affected lymph node. Adjacent lymph nodes

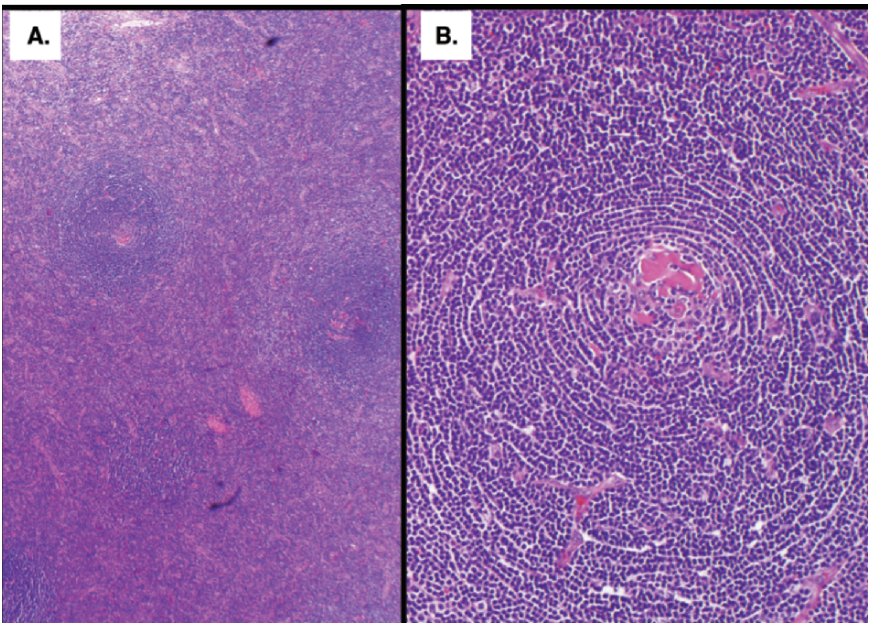

Figure 13.3 Hyaline vacular variant histology. **(A)** Hyaline vascular variant low-power view with reactive follicles and an interfollicular infiltrate of small lymphoid cells and fibrosis as well as increased vascularization of the interfollicular space. **(B)** High-power view showing the B-cell follicle with typical expanded mantle zone showing "onion skin"' pattern and depleted, hyalinized germinal center with increased vascularity. (Courtesy of Dr. Ahmet Dogan)

might be involved, with a spectrum of findings from normal nodal architecture to identical histology to the initial site to somewhere in between (8).

13.3.2 Pathology of Plasma Cell Variant

The gross specimen is that of multiple discrete lymph nodes, comprising the clinically observed "mass." This is distinct from the single rounded mass that is typically seen with HVV (8, 11). Microscopically (Table 13.2), PCV is distinguished by the presence of sheets of plasma cells (PCs) in the interfollicular zone (Figure 13.4) (8). This marked plasmacytosis might be comprised of immunoblastic proliferation along with prominent high endothelial venules, or of mature plasma cells without increased vascularity. Russell bodies are commonly present (8, 26) and binucleated plasma cells might be seen, but mitoses of PCs are rare (26). Some eosinophils and mast cells might also be present (26). There is germinal-center hyperplasia also characterized by sharp borders within the mantle zones and by "polarization" with the light area directed toward the capsular or trabecular sinus (27). Within the follicles, there are mitotic figures, nuclear fragments, histiocytes, and cells resembling lymphoblasts.

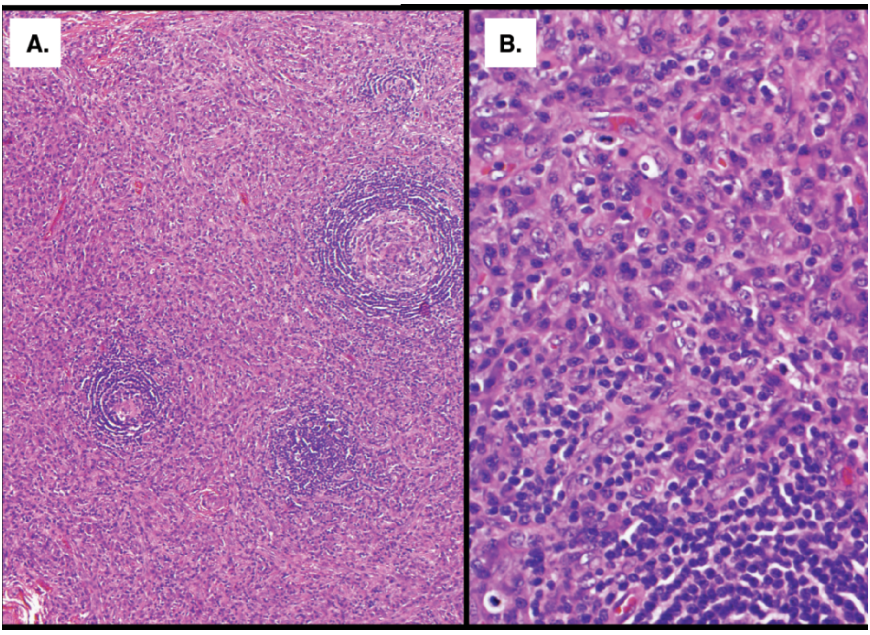

Figure 13.4 Plasma cell variant histology. **(A)** Low-power view with small reactive follicles and an interfollicular infiltrate of plasma cells; lack of vascular proliferation. **(B)** High-power view showing the plasma cell component. Lower left corner contains a small part of a reactive follicle. (Courtesy of Dr. Ahmet Dogan)

13.3.3 Mixed Variant of Castleman Disease

Lymph nodes have characteristics of both HVV and PCV. Focal accumulations of plasma cells next to extensive areas without plasma cells are found in the interfollicular tissue (9). Characteristic lymphoid follicles with normal reaction centers and pseudo-Hassall's corpuscles are found in small areas.

13.3.4 Histologic Differential Diagnosis of CD

The differential diagnoses for CD are broad. Initially, HVV cases were most commonly confused with thymomas because the intrafollicular capillaries with thick hyalinized walls take on a concentric arrangement—the so called "onion skin appearance"—that can be confused for Hassall corpuscle of the thymus (1). More often, HVV might be confused with other conditions in which there is regressive transformation of germinal centers (GCs), like angioimmunoblastic lymphadenopathy, other atypical lymphoproliferative disorders, and advanced phase of HIV-related lymphadenopathy (27–29). In these cases there is a variable

degree of condensation of the germinal center. This condensation is due to the progressive disappearance of the lymphoid component of the GC, crowding and sclerosis of the vessels, and increased prominence of the follicular dendritic reticular cell (FDRC) component. The increase in the FDRC can occur, either by concentration or by proliferation.

The PCV "is an overabused diagnosis for a lymph node pattern of germinal center hyperplasia (with or without some regressive transformation) and marked plasmacytosis" (27). This pattern, which might be associated with either immunoblastic proliferation and prominent high endothelial venules or with all mature plasma cells with no increase of the vascularity, might be seen in several other conditions, like autoimmune diseases, primary or acquired immunodeficiencies, or in association with malignancies (27–29). Increased follicular size, mitotic rate, and numbers of intrafollicular tingible body macrophages per follicle can be used to distinguish nonspecific reactive lymph nodes from CD (30).

13.3.5 Histology of Other Tissues

About 75% of patients with multicentric disease have hepatosplenomegaly. Splenic findings might include altered germinal centers, white pulp or marginal zone fibrosis, and prominent plasmacytosis (11, 31). Splenic findings parallel those found in the lymph nodes.

Liver biopsy results are quite varied. Findings might be nonspecific. Peliosis hepatitis, the presence of blood filled cysts in the liver parenchyma secondary to dilated hepatic sinusoids, has been seen (11, 32–34). Micronodular cirrhosis associated with large fibrotic masses resembling hyaline vascular germinal centers of the lymph node has also been described.

13.3.6 Stromal Cells in CD

The stromal background of CD, especially in HVV, is quite striking. How much stroma is present can be variable, and Krishnan et al. have proposed subdividing HVV into a lymphoid variant, in which the lymphoid follicles largely predominate, and a stromal-rich variant, in which the follicles are almost overrun by the proliferation of vessels and/or stromal cells (27). By immunohistochemistry, these whorled centers contain some factor VIII-positive cells suggesting endothelial origin (35). By electron microscopy (EM), the whorled follicle centers are comprised mainly of dendritic reticulum cells (36). Moreover, these FDRCs might be polyploid and have prominent nucleoli, which connotes dysplasia (37). These cells might also aberrantly express adhesion molecules (38). These dysplastic changes are more common in HVV (27, 37, 38) but mightalso be seen in PCV (37). In the majority of PCV cases, the network these FDRCs form is similar to that seen in normal or reactive

germinal centers. However, two aberrant phenotypes are commonly seen in HVV: an expanded, disrupted follicular dendritic cell network or multiple tight collections of follicular dendritic cells (39). There are data that suggest that the FDRCs are the primary source of interleukin (IL)-6 in CD (40, 41), which drives the lymphocyte infiltrate seen in PCV (41). Finally, there are four reports of clonal karyotypic abnormalities derived from the stromal elements: (1) 46,XX, t(1;16)(p11;p11), del(7)(q21q22), del(8)(q12q22) (42); (2) 46,XX, add(1)(q21), der(6)t(6;12) (q23;q15), add(7)(p22), -9, inv(9)(p11q13), del(12)(q15),+mar (43); (3) t(1;22)qter;q13 44; and 4) t(7;8)(q37.3;q12) (44).

These observations about the FDRCs are compelling for two reasons. The first is that there is an apparent increased incidence of dendritic sarcoma in patients with CD (45) and other non-KSV vascular neoplasms (46, 47). The second is the association of HHV-8 (aka KSV), CD, Kaposi's sarcoma, and lymphoma in AIDS patients.

13.3.7 The Lymphoplasmacytic Compartment

In addition to FDRCs, there are lymphocytes, plasma cells, and eosinophils within CD lymph nodes. The spectrum of distribution can be broad. Frizzera has divided PCV into proliferative and accumulative patterns based on the number and size of germinal centers, their composition, and the extent of immature lymphoid cells (11). Menke et al have speculated that PCV is a immune disorder characterized by proliferation of an immunophenotypically abnormal population of mantle zone lymphocytes (aberrantly lacking Ki-B3 and/or Ki-B5) (37). These lymphocytes might be of $CD5^+$ B-lymphocyte origin (37, 48)—an autoantibody producing subset—which is sustained by local factors such as IL-6 produced by FDRCs (41). In addition, CD45 RA^+ lymphocytes are absent in the mantle zone in CD lymph nodes (37). The T-cell infiltrate are predominantly CD4 cells with a paucity of CD8 cells in PCs (12, 49). T-Cell gene rearrangement studies have been performed by a handful of investigators. The vast majority show no T-cell clones (44, 48, 50, 51).

13.3.8 Is Castleman Disease a Clonal Disorder?

There is contradictory information about whether the interfollicular plasma cells are clonal (Table 13.3) (12, 17, 26, 35, 37, 48–64). The majority of studies are based on immunohistochemical investigations, but some authors have also looked for clonality using molecular techniques. Despite the contradictions, there are a few unifying points. Typically, the PCV cases were more commonly monotypic than the HVV cases. The lymphocytes found in the follicles or the interfollicular regions are not clonal. Plasma cells in the interfollicular zones might sometimes be monotypic—most commonly lambda light-chain restricted—but the majority are not. If plasmablasts

Table 13.3 Defining clonality in Castleman disease

Ref.	Localization	Subtype	Immunohistochemical	Notes
			HIV-negative patients	
17	1 M	1 PCV	Monotypic	
52	1 U	1 PCV	Monotypic	
53	NS	1 Mixed	Monotypic	
54	1 M	1 PCV	Monotypic	No clonal IGH rearrangement
55	1 U; 1 M	2 PCV	1 polytypic; 1 monotypic	
35	9 U	9 PCV	2 monotypic	
12	16 M	3 HVV; 13 PCV	1 PCV monotypic[a]	
48	4 U 1 M	5 PCV	Monotypic × 2; polytypic × 2; Equiv monotypic ×1	First 3 patients had clonal IgH gene rearrangement
26	15 U 3 M	18 PCV	7 monotypic	
56	2 M	2 PCV	1 monotypic; 1 polytypic	1 IgH rearrangement; 1 w/o clonal IGH rearrangement; TCR germline
37	Not stated	9 HVV 21 PCV	1 monotypic 4 monotypic	IgH rearrangements in 4/9 IgH rearrangements in 3/21
57	5 M	5 PCV	2 monotypic All other polytypic	The 2 monotypic cases were only 2 with detectable plasmablasts
51	2 U 3 M 15 U	2 PCV 3 PCV 15 HVV	1 M was monotypic	1 with IgH gene rearrangement
58	4 U 16 M	4 HVV 3 HVV 9 PCV 4 Mixed	Not done	4 w/o clonal IgH rearrangement 2 IgH rearrangement (both NHL) 15 w/o clonal IgH rearrangement 2 IgH rearrangement (1 HD & 1 POEMS)
59	Not stated	4 HVV; 1 mixed; 1 PCV	All polytypic	
60	1 M	1 PCV	All polytypic	
61	1 U	1 PCV	All polytypic	Adjacent monotypic plasmacytoma
62	5 M	5 PC variant	All polytypic	
63	9 M	9 PCV	All polytypic	
50	4 U 4 M	3 HVV; 1 PCV 4 PCV	All polytypic	3/4 multicentric with IgH gene rearrangement
49	1 U	1 mixed	Polytypic	No clonal IgH rearrangement; TCR germline

(continued)

Table 13.3 (continued)

Ref.	Localization	Subtype	Immunohistochemical	Notes
64	25 M	25 PCV[b]	Polytypic	Only the HHV-8+ cases had mantle zone plasmablasts; these cells were monotypic lambda in 4 of 6.
			HIV-positive patients	
58	30 M	1 HVV; 6 PCV; 7 Mixed	Not done	14 w/o clonal IgH rearrangement
57	8 M	8 PCV	8 monotypic (plasmablasts)	2 of 3 had clonal IgH rearrangements

M, multricentric; U, unicentric; HVV, hyaline vascular variant; PCV, plasma cell variant.
[a]Prior LN biopsy 4 years earlier had been polytypic.
[b]Three HIV-positive.

are present in the mantle zone and/or interfollicular regions, these are the cells most likely to express monotypic light chains and/or have clonal immunoglobulin gene rearrangement (57, 64). Plasmablasts are more likely to be present in HHV-8+ cases. It should be noted, however, that not infrequently is there discordance in determining clonality between the immunostains and molecular techniques [polymerase chain reaction (PCR) or Southern blot analyses].

Even in the context of HIV/AIDS, the issue of clonality is contradictory (57, 58). In one study, of eight MCD PC/HIV+ patients studied, all had lambda-restricted plasmablasts, but only two of the three tested by molecular techniques could be confirmed as being clonal (57). However, in another study in which only molecular techniques were used, only 3 of 14 had minor clones identified (58).

Several possible explanations have been postulated. It is possible that a virus (e.g., HHV-8) might infect IgM-positive naïve B-cells and drive them to differentiate into plasmablasts without undergoing the germinal-center reaction (65). Alternatively, HHV-8 or another similar virus, could naturally target both kappa and lambda light-chain-expressing B-cells without bias, but with only lambda cells expanding preferentially due an intrinsic proliferative response to the viral infection (65).

13.3.9 Cytokines

Overproduction of circulating cytokines is implicated in the pathogenesis and symptomotology of CD and its sister syndrome, peripheral neuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes (POEMS) syndrome (66). Serum levels of IL-6 in CD patients are significantly higher than those found in patients with Hodgkin's disease, diffuse large cell lymphoma, or multiple myeloma. The causative association is based on several observations. The first is that

removal of the lymph node masses causes an abrupt drop in IL-6 levels and resolution of symptoms (67). The second is that treatment with IL-6 receptor antibody also relieves the symptoms and signs of the disorder (68). The third is that overexpression of IL-6 in mice produces a phenotype similar to the MCD phenotype (69). High IL-6 levels might contribute to the plasma cell infiltration of lymph nodes, polyclonal hypergammaglobulinemia, increased level of acute-phase proteins, and constitutional symptoms.

Vascular endothelial growth factor (VEGF) is also elevated in CD patients, but less so than in patients with POEMS syndrome (66). Increased VEGF expression has been observed in the interfollicular area of CD lymph nodes and in the supernatant of cultured PCV lymph nodes (70). In one study, five of eight cases of CD, germinal centers containing small vessels expressed VEGF by *in situ* hybridization (71). VEGF, which induces endothelial proliferation and endothelial permeability, could account for the hypervascular skin lesions, the peripheral edema and anasarca.

13.3.10 The Role of Viruses, Especially HHV-8 and HIV

From the initial recognition of CD, it was postulated that a virus might be a driving factor for the disorder. Although there had been initial reports linking EBV to CD (50), this has not been substantiated (56, 72, 73). CMV does not play a role in CD (50). However, HHV-8 and HIV appear to play a significant role in a subset of patients.

In 1985, Lachant et al. reported on two homosexual males with the acquired immunodeficiency syndrome (AIDS) who developed multicentric CD followed by Kaposi's sarcoma (KS) (74). More cases followed. In 1995, Soulier reported on the incidence of HHV-8 in 31 multicentric Castleman disease (MCD) patients based on the three following observations: lymphoma and KS were malignancies that had been described in 10–20% of patients with MCD prior to the AIDS epidemic; similar clinical and pathologic features of MCD had been reported in HIV^+ patients with lymph node hyperplasia; and among HIV^+ patients, 75% of MCD patients also had KS during the course of their disease (23). All 14 of the HIV^+ patients tested had HHV-8 DNA sequences in their CD lymph nodes, whereas, 7 of 17 HIV-negative MCD patients had HHV-8 DNA sequences present.

Other investigators have confirmed that nearly all HIV^+ CD cases contain HHV-8^+ and that nearly half of HIV^- MCD are HHV-8^+ (64, 72, 73, 75, 76) (Table 13.4). This is in stark contrast to the roughly 7% HHV-8^+ rate in non-HIV, non-CD, reactive lymph nodes (73). HHV-8 sequences have also been found in the peripheral blood mononuclear cells (PBMC) of some CD patients, more commonly the HIV^+ group (23, 77). HHV-8 has also been found in the bone marrow of HIV^+/$HHV8^+$ CD patients (78). HHV-8 can be found in intranodal B-lymphocytes, in endothelial cells, and in subcapsular spindle cell proliferations. In one study, the highest copy number was in subcapsular spindle cells (75); in contrast, viral IL-6 (vIL-6) is not expressed in KS spindle cells (72). The HHV-8 gene expression

Table 13.4 HHV-8 infectivity and Castleman disease

Ref.	*N*	HIV	HHV-8$^+$	Comments
Soulier et al. 1995 (23)	14 M/PCV	+	14	
Gessain et al. 1996 (77)	6 M	+	5/6	All 5 had cutaneous KS
Suda et al. 2001 (76)	3 M	+	3/3	
O'Leary et al. 2000 (75)	1 U 2 M	+	3/3	
Menke et al. 2002 (80)	PCV	Clinically no	9/15	
O'Leary et al. 2000 (75)	9 U 4 M	–	1/9 3/4	
Suda et al. 2001 (76)	79 M	–	0/79	
Soulier et al. 1995 (23)	17 M/PCV	–	7	
Chadburn et al. 1997 (73)	6 U 5 M	–	0/6 3/5	
Luppi et al. 1996 (204)	7 U (HVV) 5 M (PCV)	–	0/12	
Gessain et al. 1996 (77)	3 U 4 M	– –	0/3 1/4	
Parravinci et al. 1997 (72)	3 U HVV 7 M PCV 6 U PCV	–	0/3 6/7 0/6	4 patients developed KS and 2 patients NHL
Belec et al. 1999 (83)	9 M	–	7/9	All had POEMS
Tohuda et al. 2001 (205)	7 M 3 POEMS	—	3/7 0/3	

U, unicentric; M, multicentric; HVV, hyaline vascular variant; PCV, plasma cell variant.

patterns are different in HHV8-associated CD as compared to the two known HHV-8-associated malignancies, KS and primary effusion lymphoma (PEL). In CD, both latent and lytic proteins are expressed; in KS and PEL, predominantly latent genes are expressed (79). One of these lytic phase proteins is vIL-6. vIL-6 expression occurs in the lymphoid cells of 25–100% of HHV8$^+$ CD patients and is associated with an inferior survival (72, 80).

13.3.11 HIV$^+$ Castleman Disease

There are differences between HIV$^+$ CD and HIV$^-$ CD. The former is almost always associated with HHV-8 (81), whereas only a minority of HIV$^-$ CD case are. In the HIV$^+$ cases, there is a much higher risk of evolution to lymphoma (57) and the MCD course is more fulminant. Morphologically, there are differences as well. HIV$^+$ patients more typically have plasmablasts (CD20$^+$, CD30$^-$) in the mantle zone

(57). These plasmablasts (or immunoblasts) express IgM with lambda immunoglobulin light-chain restriction by immunohistochemistry. These cells also express HHV-8 latent nuclear antigen and are highly proliferative. This type of plasmablast is not commonly observed in HIV$^-$ CD, but when present, it is more likely to be present in the context of HHV-8 infection.

The very remarkable feature of these monotypic plasmablasts—and even some of the resultant plasmablastic lymphomas—is that they are usually shown to be polyclonal by molecular techniques (65). Moreover, they are typically germline consistent with being naïve B-cells, despite their mature phenotype (by morphology and by high expression of cytoplasmic Ig and CD27, which is a marker for memory B-cells) (65).

Castleman disease is has long been thought to be related to overproduction of IL-6 and, to some extent, to hyperresponsiveness to IL-6 (41, 82). The viral homologue of IL-6 exhibits many of the biological activities of human IL-6, but the relative importance of vIL-6 and human IL-6 has not yet been clarified. It appears, however, that the sites of expression of these two types of IL-6 are distinct. Human IL-6 expression can be localized to the germinal centers arising form the follicular dendritic cells, which are located outside the sinuses, but in close contact with blood vessels and plasma cells (41, 81), whereas vIL-6 is localized to the mantle zone and interfollicular regions emanating from lymphoid-derived cells (72, 80, 81). In HIV$^+$ MCD, clinical symptoms correlate with high levels of plasma human IL-6 and IL-10 accompanied by a 1.7-log increment of HHV-8 copy numbers in peripheral blood mononuclear cells (81).

13.3.12 HIV$^-$ CD

There is some suggestion that HIV$^-$ MCD patients who are HHV-8$^+$ have a different disease both clinically (72, 73) and morphologically (64), as compared to their HHV8$^-$ counterparts. In one series, the three HHV-8$^+$ patients had a significantly worse clinical course than did the eight HHV-8$^-$ patients; however, six of the eight HHV-8$^-$ patients had unicentric disease (73), which is known to be associated with a better outcome. In another study of HIV$^-$ CD patients, seven out of eight HHV-8$^-$ patients had localized and limited disease, whereas all six HHV-8$^+$ patients had multicentric PCV with other features of immune dysfunction (72). In yet another study, HHV-8 DNA sequences were present in the tissues of about 88% of HIV$^-$, POEMS associated CD, but fewer than 10% of POEMS patients without CD (23, 83).

In addition, HHV$^+$ CD might have morphologic characteristics that differentiate it from HHV$^-$ CD. After studying the lymph node architecture of HHV-8$^+$ (n = 6) and HHV-8$^-$ (n = 19) patients with PCV, Amin et al. concluded that HHV-8$^+$ PCV is morphologically distinct because there is an accumulation of infected lymphocytes in the mantle zone, which leads to progressive blurring and dissolution of the germinal center and altered regulation of the surrounding stroma (64). Other

HHV8$^+$ cells found in the mantle zone were immunoblasts/plasmablasts, the majority of which expressed lambda light chain. A caveat to this study is that 3 of the 6 HHV-8$^+$ patients were also infected with HIV-1.

13.4 Clinical Presentation

Regardless of the classification system used—unicentric versus multicentric, hyaline vascular versus plasma cell variant, or with peripheral neuropathy versus without—there is considerable overlap of signs and symptoms among populations of CD patients. Part of this blurring of boundaries is a function of the spectrum of disease itself; another part is related to limitations of staging, both past and present. The earliest studies were confounded by the limitations of imaging; therefore, the majority of first reported cases were mediastinal masses (8) detected either because of compressive symptomatology or a mass detected on routine chest radiography. This same limitation of technology also delayed the realization that CD could be multicentric. The actual incidence of (and clinical features associated with) unicentric versus multicentric disease is also confounded by the extent of imaging performed and by the lack of consistency in defining multicentric disease. Given the fact that CD changes can be seen in the spleen (10, 31), should the presence of splenomegaly upstage a patient to multicentric disease? In addition, there are reports in which distant lymph nodes contain only "reactive" tissues rather than CD (11, 26, 84) and other reports in which simultaneous but distant lymph nodes have discordant histology (one with HVV and another with PCs) (10, 12).

With these caveats in mind, there are generalizations that can be made about groups of CD patients, as shown in Table 13.1. The median age of presentation is in the fourth decade for the unicentric and the sixth decade for the multicentric presentations. There does not appear to be any sex predilection. The most common symptoms are malaise/weakness, fever, weight loss, night sweats, and anorexia (12, 19, 21, 24, 28–30, 85). Although the earliest reports suggested that unicentric and HVV accounted for close to 80% of cases, a more modern estimate would be approximately 60%. Most masses occur in typical lymph node regions, but gastric, pulmonary (8), muscle (8), and pancreatic lesions (86) have all been described. By imaging, lesions are often vascular appearing (87), might be heavily calcified (Figure 13.4), especially those found in the pelvis (88), and could be flurodeoxyglucose positron emission tomography (FDG PET) avid (89).

13.4.1 Unicentric Disease

Nearly 90% of patients with unicentric disease have the HV form. These patients often present with either compressive symptoms or a large incidental

mass; however, nearly 40% of patients with HVV will have associated systemic symptoms that promptly resolve after surgical extirpation of the solitary mass. Unicentric disease occurs most commonly in the mediastinum, cervical regions, and abdominal/pelvic cavity, but nasopharyngeal, orbital, dural, and oral occurrences have been described. Laboratory tests might be completely normal, but anemia, hypergammaglobulinemia, and elevated sedimentation rate and liver function tests might be present, again all of which promptly resolves after successful surgical removal of the mass.

13.4.2 Multicentric Disease

In the case of multicentric disease, the overlap with PCV is about 90%. Approximately 80% of patients with the PCV or the mixed variant have associated protean symptoms. The most common symptoms include fatigue, fevers, night sweats, and weight loss. Hepatomegaly and/or splenomegaly occurs in 75% of patients. Laboratory abnormalities are common, including anemia, low ferritin levels, elevations of the sedimentation rate, antinuclear antibodies, fibrinogen, C-reactive protein, and liver transaminases, and an abnormal urinalysis.

13.4.3 Paraneoplastic Symtpoms and Syndromes

There are a number of paraneoplastic symptoms/syndromes also associated with CD, more commonly with the multicentric form (Table 13.5) (19, 28, 46, 49, 55, 90–116). These include pleural effusions, pericardial effusions, ascites, anasarca, autoimmune hemolytic anemia, immune thrombocytopenic purpura, a multitude of renal disorders, including secondary (AA) amyloidosis or membranoproliferative glomerulonephritis (105, 117, 118), pulmonary abnormalities ranging from infiltrates to restrictive lung disease to lymphoid interstitial pneumonitis (111) to bronchiolitis obliterans (112–114), and skin abnormalities ranging from rash to hyperpigmentation to paraneoplastic pemphigus (99, 100) to Bechet's disease (101) to Kaposi's sarcoma. In one series over the course of the disease, 40% of patients developed central nervous system (CNS) signs, including seizures and aphasia (28). This finding should be tempered by the fact that a number of cases from the 1980s might have been AIDS-associated CD, which is known to have a particularly dismal prognosis (24). Neuropathy occurs in nearly 10% of patients, again more commonly than those with multicentric disease, but it is also possible in patients with unicentric disease. When present, other features of POEMS syndrome (also known as Crow-Fukase and Takatsuki disease) should be sought, including a monoclonal protein and osteosclerotic bone lesions (29, 30) (Figure 13.5).

Table 13.5 Paraneoplastic or autoimmune associations with Castleman disease

Hematologic	Renal
Anemia of chronic disease	Membranoproliferative glomerulonephritis (GN) (93
Pure red cell aplasia (90)	Mesangial proliferative GN (118), mMembranous GN (102, 103)
Autoimmune hemolytic anemia (91)	Interstitial nephritis (104)
Autoimmune thrombocytopenia (92)	Fibrillary glomerulonephritis (105)
Acquired hemophilia (93)	Secondary (AA) amyloidosis (55, 106–109)
Osteosclerotic myeloma (POEMS syndrome) (19, 94)	**Neurologic**
Thrombotic thrombocytopenic purpura (95)	Demyelinating polyneuropathy (POEMS syndrome) (19, 94)
Oncologic	Myasthenia gravis (110)
Non-Hodgkin's lymphoma (96)	**Pulmonary**
Hodgkin disease (96)	Bronchiolitis obliterans (112–114
Follicular dendritic cell sarcoma 97)	Lymphoid interstitial pneumonia (111)
Kaposi's sarcoma98	Pulmonary fibrosis (113)
Mesenchymal spindle-cell neoplasm (46)	**Rheumatologic**
Dermatologic	Systemic lupus erythematosus (115)
Pemphigus (99, 100)	Positive autoantibodies (antinuclear antibodies, antiphospholipid antibodies, Coombs antibodies)
Bechet's disease (101)	**Endocrine**
	Growth failure, delayed puberty (49)
	Adrenal insufficiency (116)

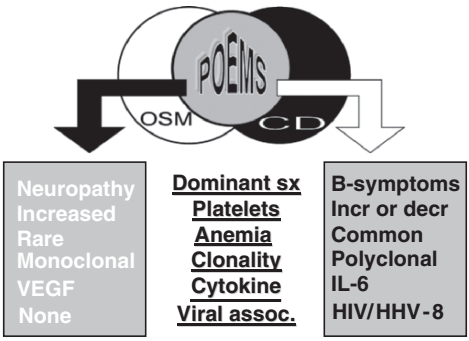

Figure 13.5 Relationship amongn Castleman disease, osteosclerotic myeloma, and POEMS syndrome

13.4.4 CD and POEMS Syndrome

POEMS syndrome is a rare paraneoplastic syndrome most often associated with osteosclerotic myeloma (OSM). The hallmark features of the OSM variant of POEMS are peripheral neuropathy (PN), monoclonal lambda plasmaproliferative disorder, sclerotic bone lesions, as well as the other features shown in Table 13.6, not all of which are required to make a diagnosis. In some cases, the lymph nodes of these patients have Castleman-like (15) or full-fledged CD histology (16, 94, 119). In a series of 30 patients with POEMS syndrome, 19 of 32 biopsied lymph nodes showed angiofollicular hyperplasia typical of CD (16).

Authors have noted that MCD with PN has a different quality to it when compared to MCD without and have even proposed that the presence or absence of PN should be part of the MCD classification system (29, 30). When CD is associated with PN, edema and impaired peripheral circulation are the most common systemic

Table 13.6 Spectrum of multicentric Castleman disease, osteosclerotic myeloma, and POEMS

	MCD	POEMS-MCD variant	POEMS-OSM variant	OSM
Fever/sweats	Defining	+++	+	–
Generalized lymphadenopathy	Defining	+++	++	–
Peripheral neuropathy	–	Defining	Defining	–
Monoclonal PCD	–	+	Defining	Defining
Sclerotic bone lesions	–	+	Defining	Defining
Skin changes[a]	++	++	Defining	–
Papilledema	–	Defining	Defining	–
Edema/ascites/effusions	+	Defining	Defining	–
Endocrinopathy[b]	–	Defining	Defining	–
Interleukin-6 elevation	+++	+++	+	+
VEGF elevation	+	+	+++	+
Weight loss	+++	+++	+++	–
Fatigue	+++	+++	+++	++
Polyclonal hypergammaglobulenima	+++	+++	–	–
Organomegaly	++	++	++	–
Platelets	L or H	L or H	H or N	–
Anemia	+++	+++	–	++
Autoimmune diseases[c]	++	++	–	–
Restrictive lung disease	+	+	++	–
Renal disease	+	+	–	++
Thrombosis	-	+	+	–

MCD, multicentric Castleman's disease; OSM, osteosclerotic myeloma; VEGF, vascular endothelial growth factor; L, low; H, high; N, normal; –: rare or absent; +, occasional; ++, common; +++, very common.

[a]CD-associated skin changes include nonspecific rash, autoimmune pemphigus, and telangectasia; POEMS-associated skin changes include hyperpigmentation, skin thickening, hypertrichosis, cherry angiomata, white nails, clubbing, flushing, and peripheral cyanosis.

[†b]Endocrinopathy should appear to coincide with ongoing illness.[c]See Table 13.5.

abnormalities seen (12, 13, 17, 120–124). In one series, 11 of 12 cases of CD with PN had a monoclonal lambda protein in their serum and/or urine (30). PCV and the mixed HVV/PCV are more like to have associated neuropathy (13, 17, 37, 121–123), but PN has been also seen with HVV (10, 37, 125).

The PN in OSM-POEMS usually has a significant motor component and is one of the dominating features of the syndrome; whereas the PN in CD patients tends to be more subtle and more often sensory. In its most severe form, it is a mixture of demyelination and axonal degeneration, with normal myelin spacing on electron microscopy (121, 123). There might be evidence of abnormal capillary proliferation, similar to that seen in the affected lymph nodes (123).

Table 13.6 presents the spectrum of lymphoproliferative disorder to plasmaproliferative disorder in the context of POEMS. Whereas OSM-POEMS patients have a monoclonal plasma cell disorder, CD is characterized by a brisk polyclonal hypergammaglobulinemia, which, on occasion, also contains a monoclonal protein. Both entities have a proinflammatory cytokine profile, but in the OSM variant of POEMS, VEGF is the most consistently elevated cytokine; in contrast, in CD, IL-6 is the dominant aberrantly overexpressed cytokine. Although renal failure is rare in OSM-POEMS, it is more common when patients have associated CD.

13.4.5 Diagnosis, Classification, and Prognosis

The diagnosis of CD is a pathologic one that can be clouded by discrepant pathology at different sites. It is therefore imperative that more than one biopsy be performed if the clinical level of suspicion is high because of the potential lack of lymph node concordance at distant sites.

Once the diagnosis is made, in addition to a thorough review of systems (B-symptoms, endocrinopathy, peripheral neuropathy) and physical examination (papilledema, skin changes), additional testing is required. Patients should have a complete blood count, erythrocyte sedimentation rate, C-reactive protein, liver function tests, serum creatinine, serum protein electrophoresis with immunofixation, IL-6, VEGF, serology for HHV-8 and HIV, urinalysis, and computed tomography (CT) of the chest abdomen and pelvis. If there are any pulmonary symptoms, the threshold for performing pulmonary function tests should be low. If there is associated neuropathy, imaging of the bones should be done looking for sclerotic bone lesions. If elements of POEMS syndrome are present, then more extensive endocrine testing should also be performed.

The course of CD can be quite variable. Typically, those with localized disease are cured by surgical resection. The multicentric form is more difficult to manage and median survival has been reported to be as short as 26 months (12). Frizzera et al. divided patients' courses into two categories—episodic and persistent (28). Those patients with more extensive disease (systemic symptoms, lymphadenopathy, hepatosplenomegaly, and effusions) were more likely to have the episodic pattern of evolution. These authors also found that male gender, episodic evolution, and predominantly

proliferative morphology in involved lymph nodes were associated with worse survival in univariate analysis (28). Weisenberger et al. divided the course for MCD patients into five categories: (1) cure; (2) stable and persistent; (3) relapse and remission; (4) rapidly fatal disease; and (5) evolution to malignant lymphoma (12).

Our group has looked at a prognostic modeling system for survival using the clinical information of 114 patients with CD. We found that after adjusting for age, the multivariable model included organomegaly, respiratory symptoms, and an abnormal platelet count. Depending on whether patients had 0 or 1+ adverse factors, their 10-year survival rates were 80% [95% confidence interval (CI): 65–98%] and 41% (95% CI: 28–59%) (126).

13.4.6 HIV Clinical

Castleman disease in the HIV population distinguishes itself from CD in an HIV-negative population with the following features: (1) more likely to be multicentric; (2) systemic symptoms more common and more intense; (3) adenopathy more likely to be peripheral; (4) pulmonary symptoms more prevalent; (5) leukopenia and thrombocytopenia more common; (6) a much higher incidence of HHV-8 coinfectivity and clinical KS; (7) histologic type most commonly the mixed HV/PC variant; (8) a 15-fold risk of developing malignant lymphoma; and (9) prognosis dismal, with a median survival of 12–22 months (24, 127, 128).

In one series, the duration of known HIV seropositivity before CD diagnosis was less than 2 years in six cases, between 2 and 5 years in eight cases, and more than 5 years in six patients (24). The mean CD4 count was 156×10^6/L. Fifteen of 20 patients had KS: 6 with KS predating the MCD; 6 with concurrent diagnoses; and 3 who went on to develop KS 6–14 months later. This high incidence of KS is mirrored in another smaller series of 11 patients (128). Splenic histology mirrored lymph node histology when evaluated. Bone marrow involvement was observed in 12 of the 15 patients who were tested (24).

The symptoms of MCD might wax and wane for unclear reasons. Often this variability appears to correlate with high HHV8 viral load in peripheral blood mononuclear cells, high level of serum C reactive protein, and high plasma human IL-6 and IL-10 levels (81). The most common symptoms are fevers, sweats, fatigue, fluctuating lymphadenopathy, and hepatosplenomegaly, but patients might also develop pulmonary symptoms (dyspnea and cough) and infiltrates (129). Pulmonary symptoms manifest in approximate 20% of patients (129).

13.4.7 CD in Pediatric Population

Castleman disease is believed to have a more benign course in the pediatric population than in the adult population. Approximately 85% of cases are unicentric (22, 28).

Within the pediatric population, the disease is more common in teenagers, with 72% of cases between ages 10 and 17 years. General symptoms of fever, failure to thrive, weight loss, and fatigue are the presenting complaints in 45% of cases (22).

The distribution of tumor localization is about one-third each in the thorax, the abdomen, and in the periphery (22). Laboratory abnormalities, including anemia, hypergammaglobulinemia, and elevated erythrocyte sedimentation rate, are seen in 23% of the HV cases, in all of the PC cases, and in 82% of the mixed types. Two of the patients with multicentric disease had glomerulonephritis. In a very large review of 83 pediatric cases, patients with localized disease were treated with surgery in all but 4 cases. Two of these patients received radiation and the other two had spontaneous regressions. No relapses were documented in the localized patients. Patients with multicentric disease received various therapies, with half of them achieving a complete response (22).

13.4.8 CD and Lymphoma and Other Secondary Malignancies

Secondary malignancies are not uncommon in CD. This is especially true in the HIV^+ population, who are estimated to have a frequency of lymphoma of 15-fold of an HIV^+ population without CD (127). However, even in the HIV-negative population, as many as one-third of MCD patients develop malignancies, most notably lymphoma (~15%) (28, 30, 64, 96, 130) and Kaposi sarcoma (28). Both unicentric and multicentric patients appear to be a risk.

13.4.8.1 HIV^- Lymphoma

Larroche et al. reviewed the association between CD lymphoma in the HIV^- population by describing 23 cases of non-Hodgkin's lymphoma (NHL) and 27 cases of Hodgkin's disease (HD) (96). They found that NHL is more often associated with multicentric CD, its diagnosis being concurrent with CD diagnosis or occurring within 2 years. In contrast, HD occurs more commonly in localized CD of the plasma cell type (96), but it also occurs in multicentric disease (64). The spectrum of NHL seen includes diffuse mixed cell lymphoma (12), pleomorphic large-cell lymphoma (12), and peripheral T-cell lymphoma (64). Other secondary B-cell neoplasms have included.: γ-heavy-chain disease (131), multiple myeloma (MM) (132), and small B-lymphocytic lymphoma (133).

13.4.8.2 HIV^+ Lymphoma

Within a prospective cohort study on 60 HIV^+ patients with MCD and a median follow-up period of 20 months, 14 patients developed HHV-8-associated NHL: 3 with "classic" EBV^+ PEL) 5 with EBV^- visceral large-cell NHL with a PEL-like

phenotype, and 6 with plasmablastic lymphoma/leukemia (127). All of the plasmablastic cells that were phenotyped expressed IgM lambda on their surface. The estimated 2-year probability of developing NHL after a diagnosis of multicentric Castleman disease (MC) was 24.3%. At the time of NHL diagnosis, the median CD4 count was 248 × 10^6/L. Those patients with the leukemic phase had a dismal outcome and died within 1 week. The overall median survival from NHL in these patients was 1 month (127).

13.4.8.3 Follicular Dendritic Cell Tumor

Follicular dendritic cell (FDC) sarcoma is an extremely rare neoplasm. However, there have been a number of cases reported in patients with CD (97, 134–138). There are even reports of possible progression from CD to FDC malignancies (97, 134). It appears to occur more frequently in patients with HVV.

13.4.8.4 Kaposi Sarcoma

As mentioned, the association between KS and CD became evident during the AIDS epidemic of the 1980s (12, 24, 28, 139–142). Several of these first cases did not have their HIV status specified (12, 28, 139–141). Over ensuing decades there have been reports of the association in patients who are clearly defined as being HIV^- 143. The association has also been in solid-organ transplant recipients (144). Finally, there are sporadic case reports of MCD associated with other carcinomas (145, 146), sarcomas (147) and thymic malignancies. (148).

13.5 Treatment

Treatment options must be considered separately for three different disease presentations: (1) unicentric disease; (2) multicentric disease in patients not infected with HIV; and (3) multicentric disease in HIV-positive patients. Further consideration should be made as to whether patients have coexisting POEMS syndrome.

13.5.1 Treatment of Unicentric Disease

The treatment decision for unicentric disease, regardless of whether it is hyaline vascular, plasma cell variant, or mixed type, is straightforward: surgical removal whenever possible (20, 21, 28, 85, 149). If not possible, irradiation should be considered (Table 13.7) (8, 14, 20, 21, 49, 150–156). For large tumors, embolization of solitary masses prior to surgical removal (157) or neoadjuvant therapy has also

Table 13.7 Role of irradiation in the treatment of Castleman disease

Study	Histology	Response	F/U (months)	Status
		Unicentric Disease		
Fitzpatrick et al. 1968 (150)	—	PR	24+	AWD
Fitzpatrick et al. (1968)	—	CR	72+	NED
Keller et al. 1973 (8)	HVV	Stable disease × 4 patients	—	—
Ernsom et al. 1973 (151)	—	PR	60+	AWD
Nordstrom et al. 1978 (152)	PCV	CR	12+	NED
Weisenburger et al. 1979 (14)	PCV	CR	10+	NED
Stokes et al. 1985 (154)	PCV	Stable	60+	AWD
Massey et al. 1991 (49)	Mixed	CR	26+	NED
Bowne et al. 1999 (20)	HVV	PR	24+	AWD
	HVV	CR	17	DNED
	HVV	CR	12+	NED
Chronowski et al. 2001 (21)	HVV	CR	8	DNED
	HVV	CR	35+	NED
	HVV	Progression	5	DOD
	HVV	CR	23	NED
	HVV	CR	175	NED
Neuhof et al. 2006 (162)	HVV	PR	3	AWD
	Mixed	Stable disease	12	AWD
		Multicentric Disease		
Gaba et al. 1978 (10)	HVV	Mass stable; other symptoms improved	24+	AWD
Nordstrom et al. 1978 (152)	PCV	CR	18+	NED
Marti et al. 1983 (153)	Mixed	CR*	20+	NED
Sethi et al. 1990 (155)	HVV	CR[a]	22+	NED
Veldhuis et al. 1996 (156)	PCV	CR	24+	NED
Bowne et al. 1999 (20)	HVV	CR[b]	—	AWD

HV, hyaline vascular variant; PC, plasma cell variant; CR, complete remission; PR, partial remission; AWD, alive with disease; NED, no evidence of disease.

[a]Local irradiation to dominant mass resulted in shrinkage of distant lymphadenopathy.

[b]Treated with resection followed by irradiation.

been applied. Although there is a low rate of recurrence, these patients appear to have a higher risk of developing HD and NHL. Long-term follow-up should be recommended. A number of patients have seemingly done well with observation alone, but one must be vigilant about subtle development and progression of associated paraneoplastic entities like bronchiolitis obliterans.

If there are associated paraneoplastic or autoimmune conditions associated with CD, these generally resolve within months of the surgery—most notably laboratory abnormalities like anemia, hypergammaglobulinaemia, and high sedimentation rate, C-reactive protein (CRP), and liver function tests. If present, associated pemphigus often (99, 112), but not always (158), improves within the year. NonAA-related

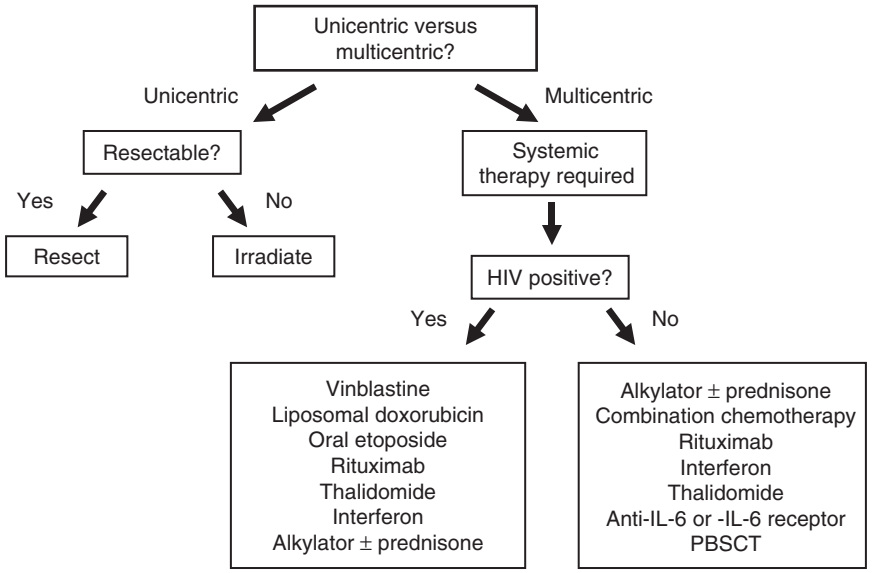

Figure 13.6 Treatment algorithm for patients with Castleman disease

renal disease has also been reported to resolve within 12 months of surgical removal (159). Symptoms from associated AA amyloid typically improves over the ensuing years after removal of unicentric disease (160, 161). Reports of lack of recovery of bronchiolitis obliterans after definitive surgery (112, 113) are difficult to interpret because it is unclear whether earlier intervention (i.e., at a lymphoid interstitial pneumonitis stage or before fibrosis) could reverse pulmonary changes.

Of the 21 patients with unicentric disease treated with irradiation (Table 13.7), 10 had a complete response, 4 had a partial response, 6 had no clinical response, and one had progressive disease (8, 14, 20, 21, 49, 150–155, 162). Even in those patients whose mass does not clearly shrink, the tumors histology changes in that lymphocytes are depleted and nuclear atypicality and hyperchromatism are seen in the plump endothelial cells of the proliferating capillaries (8). Gulati et al. reported on the use of adjuvant radiation therapy in a patient with isolated leptomeningeal disease (163).

13.5.2 Treatment of Multicentric CD in HIV⁻ Patients

For HIV-negative multicentric CD, the best choice of therapy is uncertain because available treatment data are limited to small retrospective series (12, 21, 28, 85, 140) and single case reports. Interpretation of each of these reports is confounded by the absence of uniform response criteria. If B-symptoms abate without shrinkage of lymph node groups, is that a response? If some, but not all, of the autoimmune

manifestations abate, is that a response? Is it a meaningful response if it lasts only 2 months? These are just some of the limitations of the available data. With these caveats in mind, therapy to date has been corticosteroid and alkylator based. Small numbers of patients have been treated with alternative therapies like interferon-alpha (IFN-α), thalidomide, rituximab, bortezomib, and anti-IL-6 receptor antibodies (Table 13.8). High-dose chemotherapy with hematopoietic stem cell transplantation has also been used with good effect in a limited number of cases. Exactly where these treatment plans fit into the overall treatment is uncertain.

No prospective studies support the use of corticosteroids in the treatment of CD. Although they have clinical activity (19, 21, 29, 85) and are not infrequently used to maintain clinical improvement, it is unclear whether this strategy is in the best interest of these patients.

Alkylators (cyclophosphamide or chlorambucil) have been used as single-agent therapy, along with low-dose prednisone (85, 164), or as part of combination chemotherapy. Most reports of improvement are from individual or small case studies (19, 21, 29, 85).

Combination chemotherapy (20, 128, 165), including chlorambucil/prednisone, cyclophosphamide/prednisone, cyclophosphamide/vincristine/prednisone (COP) ± doxorubicin (CHOP) or procarbazine (COPP), and rituximab with either COP (166) or CHOP (165) have all been tried in patients with multicentric disease. Some authors suggest that responses are more durable using the high-dose combination chemotherapy (21), but the evidence does not clearly justify this conclusion. Patients with multicentric CD commonly died of infections related to therapy.

Additional anecdotal cases treated with other agents have been reported. An HIV^- patient developed MCD and KS associated with active human HHV-8 infection. He was treated initially with sequential antiviral therapy (foscarnet) without clinical benefit or improvement in his HHV-8 viremia (143). Subsequent treatment with chemotherapy and corticosteroids led to clinical improvement. Methotrexate provided benefit in a patient with MCD and rheumatoid arthritis (167). Suramin provided long-lasting response in one patient (20), but it was not effective in another five patients (165).

There is limited experience with anti-CD20 antibodies in patients with CD. There is one report of benefit with single-agent rituximab in a young man with an aggressive form of CD with autoimmune hemolytic anemia and positive outcome (168). A man with orbital CD responded to single-agent rituximab (169). There are two single case reports of treating HIV-negative patients with relapsed CD with rituximab along with cyclophosphamide and prednisone with favorable response (166, 170, 171). Not only did the B-symptoms and lymphadenopathy improve, but the renal failure secondary to CD-related glomerulonephritis in one patient normalized after therapy.

Reports of the use of 2-Chloro-2'-Deoxyadenosine (2-CDA) in patients with CD are limited (172, 173). In a series of three patients with CD (two with multicentric and one with unresectable HV), two patients responded with relapse-free survivals of 24 and 20 months. Both responding patients, however, later devloped NHL (diffuse large B-cell lymphoma and peripheral T-cell NHL, respectively) (172). This

Table 13.8 Novel treatment strategies for MCD

Ref.	Drug	*N*	Outcomes
Patients Not Infected with HIV			
Jacobs et al. 2006 (167)	MTX	1	HHV8+, rheumatoid arthritis patient—remission × 54+ m
Senanayake et al. 2003 (143)	Antiviral	1	No benefit from antiviral despite HHV-8.
Ide et al. 2003 (169)	Rituximab	1	CR+ 10 m
Ocio et al. 2005 (168)	Rituximab	1 mixed	CR of lymph node, hemolysis, and Raynaud's at 14+ m
Hudnall et al. 2003 (166)	Rituximab, CTX, Pred		CR of lymph nodes and constitutional symptoms; persistant hypergammaglobulinemia at 12+ m
Abdou et al. 2004 (170)	Ritux, CTX, Pred	1	CR of lymph nodes andw acute renal failure at 24+ m
Gholam et al.2003 (171)	Rituximab after chemotherapy	1	PR 2 months, but death secondary to AA amyloidosis
Bordealeau et al. 1995 (173)	2-CDA	2	1 unresectable HV received 2-CDA + XRT resulted in CR 9+ m; 1 MCD had PR
Colleoni et al. 2003 (172)	2-CDA	3	2 MCD patients had response lasting 20–24 m; both patients evolved to NHL (DLBCL; PTCL); 1 unresectable unicentric HVV did not respond
Pavlidis et al. 1992 (174)	Interferon-α	1	CR 11+ m
Tamayo et al. 1995 (175)	Interferon-α	1	CR 32+ m
Strohal et al. 1998 (101)	Interferon-α	1	CR of lymphadenopathy, B-symptoms, and Bechet's disease 25+ m
Simko et al. 2000 (177)	Interferon-α	1	Long-term disease stabilization (8+ years) in 11-year-old with Klinefelter syndrome & HCV.
Andres et al. 2000 (176)	Interferon-α	1	CR 42+ m
Bowne et al. 1999 (20)	Suramin	1	CR 46+ m
Starkey et al. 2006 (179)	Thalidomide	1	Near total resolution of all symptoms and LA 40+ m
Lee et al. 2003 (178)	Thalidomide	1	Improvement of ascites, anemia, albumin, CRP, platelet count, pulmonary hypertension at 13+ m
Hess et al. 2006 (180)	Bortezomib	1	Improved anemia, constitutional symptoms, IL-6, CRP, but stable lymphadenopathy
Beck et al. 1994 (181)	Murine anti-IL-6 monoclonal Ab	1	Response while on therapy, but rapid relapse upon cessation.
Nishimoto et al. 2005 (68)	Humanized anti-IL-6 receptor Ab	28	Improvement of LA and B-symptoms in all for 36+ m
Repetto et al. 1986 (84)	ASCT	1	CR 15+ m

(continued)

Table 13.8 (continued)

Ref.	Drug	*N*	Outcomes
Advani et al. 1999 (182)	ASCT	1	Failed steroids & chemotherapy, but developed follicular lymphoma. CR 48+ months after ASCT
Dispenzieri et al. 2004 (119)	ASCT	2	Associated POEMS; CR 13+ and 18+ m
Ganti et al. 2005 (124)	ASCT	1	Associated POEMS; response of all manifestations × 24+ m
Lerza et al. 1999 (183)	Splenectomy	1	CR for 12+ m for autoimmune hemolysis, systemic symptoms, and lymphadenopathy
Frizzera et al. 1985 (28)	Splenectomy	1	CR for 78+ m
Patients Infected with HIV			
Lanzafame et al. 2000 (186)	HAART	2	Improvement in both for 12+ m
Aaron et al. 2002 (184)	HAART	7	No response to HAART, but perception that immune reconstitution allowed for better chemotherapy response & overall survival, median 38 m.
Corbellino et al. 2001(188)	Cidofovir	1	No response
Berezne et al. 2004 (189)	Cidofovir	5	No response
Casper et al. 2004 (190)	Ganciclovir	3	Fewer flares of MCD in 2; improvement in acute renal and respiratory failure in one patient who got 12 days of treatment, but who d/c'd Rx due to leucopenia in context of fungal infection–died on day 30.
Nord et al. 2003 (194)	Interferon-α	1	Successful maintenance
Kumari et al. 2000 (193)	Interferon-α	1	Improvement
Jung et al. 2004 (195)	Thalidomide	1	Improvement of hypergammaglobulinemia, thrombocytopenia and constitutional symptoms × 38 weeks
Casquero et al. 2006 (198)	Rituximab	1	CR × 10+ m, but possible aggravation of cutaneous KS
Marcelin et al. 2003 (196)	Rituximab	5	CR × 3 lasting 4+–14+ m, but possible aggravation of cutaneous KS in 2; 2 early deaths
Kofteridis et al.	Rituximab	1	CR 12+ m
Marrache et al. 2003 (206)	Rituximab	1	CR 6+ m
Corbellino et al. 2001(188)	Rituximab	1	CR 14+ m remission of symptoms and HHV-8 viremia

(continued)

Table 13.8 (continued)

Ref.	Drug	*N*	Outcomes
Newson-Davis et al. 2004 (201)	Rituximab	1	Near CR: HHV-8 viral load, IL-6, and TNF-α levels decreased.
Neuville et al. 2005 (200)	Rituximab	2	No significant response, and exacerbation of KS
Revuelta et al. 1998 (202)	Splenectomy & foscarnet	1	CR of LA, B-symptoms, pulmonary infiltrates, and pancytopenia × 12+ m
Oksenhendler et al. 1996 (24)	Splenectomy	9	Prompt, but transient (1–3 m) improvement in fever and cytopenias.

CR, complete response; KS, Kaposi sarcoma; LA, lymphadenompathy; 2-CDA, 2-chlorodeoxyadenosine; HAART, highly active antiretroviral therapy.

brings into question whether the use of 2-CDA accelerates the transformation of CD to lymphoma (172), reminiscent of the high risk observed in HIV-positive patients (127).

Interferon-α has been reported to control disease in five separate cases (101, 174–177). Novel agents like thalidomide have been used with dramatic success in two patients (178, 179). Bortezomib has been shown to improve the cytokine and biochemical profile in addition to clinical symptoms (180).

Beck et al. demonstrated that an HIV-negative patient with multicentric CD could have his systemic manifestations of multicentric CD alleviated by the use of a monoclonal anti-IL-6 antibody. The patient developed extremely high levels of IL-6, and symptoms of multicentric CD promptly reoccurred after the therapy was discontinued (181). This study demonstrated proof of principle (i.e., that many of the systemic symptoms of multicentric CD are IL-6 mediated). Subsequent studies have focused on blocking the IL-6 receptor. A humanized anti-IL-6 receptor antibody (rhPM-1; aka MRA) was used to treat two patients with multicentric PC or mixed-type CD (82).

These same authors have reported on a prospective multicenter clinical trial employing humanized anti-human IL-6 receptor monoclonal antibody in 28 patients with MCD (68). Within 16 weeks of treatment, fatigue, lymphadenopathy, and all of the inflammatory parameters were alleviated. Hemoglobin, albumin, and total cholesterol levels, high-density lipoprotein cholesterol values, and body mass index all increased significantly. Histopathologic examination revealed reduced follicular hyperplasia and vascularity after treatment (82). Eleven (73.3%) of 15 patients who had received oral corticosteroids before study entry were able to do well on a reduced corticosteroid dose (68). Ninety-six percent of patients remain on therapy for more than 3 years.

High-dose chemotherapy with hematopoietic stem cell transplantation has also been used with good effect in five patients, three of whom had coexisting POEMS syndrome (84, 119, 124, 182).

Somewhat surprisingly, on occasion, localized therapies have provided clinical responses in patients with multicentric disease. There are six reports of using radiation in this setting with dramatic clinical benefit in five (Table 13.8). In two of these cases, radiation of the dominant lymph node group resulted in nodal response at remote locations (153, 155). Even in those patients in whom there was no clear response after irradiation, there was a histologic change [i.e., depletion of lymphocytes, causing nuclear atypia and hyperchromatism in the plump endothelial cells of the proliferated capillaries (8)]. For those patients with POEMS syndrome, radiation to a solitary sclerotic lesion can have resolution of lymphadenopathy (30. In a similar vein, splenectomy has provide durable clinical benefit in two patients with multicentric disease (Table 13.8) (28, 183).

13.5.3 Treatment of Multicentric CD in HIV⁺ Patients

The approaches used for the HIV-positive population are slightly different than the approaches for those not infected with this virus. Because these patients are already severely immunosuppressed, high-dose combination chemotherapy is a riskier prospect. Unlike the dramatic improvements in active KS after the institution of highly active antiretroviral therapy (HAART), MCD does not regress by mere immune reconstitution (184, 185) with only a few exceptions (186). There was one report, which has not been substantiated, that HAART might aggravate the symptoms of MCD (187). The use of HHV-8 directed antivirals, like ganciclovir, foscarnet, and cidofivir in HHV-8-positive patients has yielded conflicting results (188–190), with the majority of cases suggesting no benefit (188, 189).

Singly or in combination, liposomal doxorubicin, oral etoposide, and vinblastine have produced remission—sometimes durable—in HIV-positive patients (24, 128, 184, 191). Vincristine, bleomycin, vinblastine combinations have been used with success (128). Alkylator-based treatment including low-dose chlorambucil have occasionally been helpful (128). More intensive alkylator-based therapies can result in responses, but they should be used with caution because of their extreme immunosuppressive effects (192). Interferon-α has also provided modest benefit (193, 194). There is one case report of the benefit of thalidomide in an HIV-positive patient with multicentric CD (195).

Twelve patients with HIV-associated CD have been treated with rituximab with mixed results (188, 196–201). In the largest series, Marcelin et al. (196) reported on five patients infected with HIV with CD. Two died very quickly after the beginning of rituximab therapy. Three had complete remission with no more clinical symptoms related to CD with a follow-up of 4–14 months. In two of the

responders, clinical remission correlated with a dramatic decrease of HHV-8 viral load as well as a transitory but sharp decrease of CD19 cell count and an aggravation of KS (196).

Painful splenomegaly or peripheral cytopenias might trigger splenectomy, which results in a prompt, albeit transient (1–3 months), effect on fever and cytopenia (24), although on occasion the benefit may be durable (202).

13.6 Conclusions

The field of CD has come a long way since it was first described in 1954, but much work is yet to be done. A uniform histologic and clinicopathologic classification system has been the first step. Further advances will come as investigators use the clues imparted from its relationships to AIDS, lymphoma, and the POEMS syndrome. A better understanding of the cytokine networks and the preeminent cell type driving the disease will provide a clearer, more reproducible means to prognosticate, treat, and perhaps even prevent this condition.

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