Castleman disease

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Abstract | Castleman disease (CD), a heterogeneous group of disorders that share morphological features, is divided into unicentric CD and multicentric CD (MCD) according to the clinical presentation and disease course. Unicentric CD involves a solitary enlarged lymph node and mild symptoms and excision surgery is often curative. MCD includes a form associated with Kaposi sarcoma herpesvirus (KSHV) (also known as human herpesvirus 8) and a KSHV-negative idiopathic form (iMCD). iMCD can present in association with severe syndromes such as TAFRO (thrombocytopenia, ascites, fever, reticulin fibrosis and organomegaly) or POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder and skin changes). KSHV-MCD often occurs in the setting of HIV infection or another cause of immune deficiency. The interplay between KSHV and HIV elevates the risk for the development of KSHV-induced disorders, including KSHV-MCD, KSHV-lymphoproliferation, KSHV inflammatory cytokine syndrome, primary effusion lymphoma and Kaposi sarcoma. A CD diagnosis requires a multidimensional approach, including clinical presentation and imaging, pathological features, and molecular virology. B cell-directed monoclonal antibody therapy is the standard of care in KSHV-MCD, and anti-IL-6 therapy is the recommended first-line therapy and only treatment of iMCD approved by the US FDA and EMA.

Castleman disease (CD) is a heterogeneous group of lymphoproliferative disorders that share common morphological features on lymph node biopsy[1]. According to the clinical presentation and disease course, CD is divided into unicentric CD (UCD), a localized and reversible disease involving a single lymph node[2,3], and multicentric CD (MCD), a systemic, progressive and often fatal disease with lymphadenopathy in multiple nodes[4]. More recently, an intermediate subtype referred to as 'oligocentric CD' or 'regional CD' has been described[5], which affects a few lymph nodes and is generally considered to have a clinical course similar to that of UCD[5]. Specifically, these patients often have enlarged lymph nodes in two to three adjacent lymph node stations, but they lack sufficient clinical and laboratory abnormalities to meet the MCD diagnostic criteria[5]. On the basis of aetiopathogenic characteristics, MCD can be divided into Kaposi sarcoma herpesvirus (KSHV, also known as human herpesvirus 8 (HHV8))-associated MCD (KSHV-MCD)[6] and idiopathic MCD (iMCD), which is KSHV negative (BOX 1).

KSHV-MCD can occur in both persons living with HIV (PLWH) and in individuals who are immunocompromised for another cause. KSHV-MCD occurring in PLWH may be found in association with other neoplasms, including Kaposi sarcoma, B cell lymphomas (especially primary effusion lymphoma (PEL)) and Hodgkin lymphoma[7,8]. Importantly, these malignancies are consistently associated with KSHV (Kaposi sarcoma and PEL) and frequently associated with Epstein–Barr virus (EBV) infection (PEL and Hodgkin lymphoma). Thus, the interplay between these viruses and HIV may increase the risk of concomitant KSHV-associated and EBV-associated disorders with KSHV-MCD (BOX 2)[9]. In some patients, KSHV inflammatory cytokine syndrome (KICS) may represent a prodromic form of KSHV-MCD[10]. iMCD may also be associated with serious clinical syndromes; iMCD is typically subclassified into iMCD-TAFRO, in which patients also present with thrombocytopenia, ascites, fever, reticulin fibrosis and organomegaly (TAFRO), and iMCD–not otherwise specified (iMCD-NOS), in which patients do not have TAFRO syndrome[11]. These patients often have thrombocytosis, elevated immunoglobulin levels and striking plasmacytosis in bone marrow and lymph nodes. iMCD can occasionally co-occur with POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder and skin changes) syndrome, and these cases are referred to as POEMS-associated MCD[12] (BOX 1).

The clinical presentation may help with the correct recognition of the different subsets of CD (TABLE 1), but the diagnostic work-up is often complex[8]. Importantly, all forms of CD can demonstrate a range of histopathological

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features that have been historically classified into hyaline vascular, plasma cell (plasmacytic and/or plasmablastic) or mixed histopathological subtypes (TABLE 1). All patients tend to have increased vascularity and at least some atrophic germinal centres. Similarities and differences between CD and other diseases involving morphological changes in lymph nodes have been reported[13]. Thus, CD comprises a spectrum of different disorders that can be unravelled thanks to integrated pathological, virological, oncological and internal medicine skills[7]. On these bases, diagnostic and treatment guidelines for CD have been proposed[5,14,15].

This Primer discusses the evolution of our CD understanding since the initial description of unicentric CD and critically evaluates the complexity of the epidemiological and clinical scenario after the discovery of KSHV-associated MCD and the further characterization of iMCD. The diagnostic and therapeutic challenges, especially in PLWH who are immunosuppressed, are also reported.

Box 1 | **Timeline of key definitions in CD**

Several types of Castleman disease (CD) have been discovered and defined on the basis of clinical, pathological and virological features since the 1950s.

1954
Unicentric CD: localized, solitary lesion commonly occurring in the mediastinum[2].

1972
Plasma cell type[3] CD with follicular hyperplasia and interfollicular plasmacytosis; may be associated with blood disorders.

1972
Hyaline vascular type[3] CD with diffuse vascularity, lacking clinical symptoms.

1985
Multicentric CD (MCD): generalized disease[4].

1995
Kaposi sarcoma herpesvirus-associated MCD: a plasmablastic variant of MCD[5].
Idiopathic MCD (iMCD): may display interfollicular plasmacytosis or rich intrafollicular or perifollicular vascularity with hyalinization.

1999
Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes (POEMS)-associated MCD[9].

2008
iMCD–thrombocytopenia, anasarca, fever, reticulin fibrosis, organomegaly (TAFRO)[9].
iMCD–not otherwise specified.

Epidemiology

It should be noted that limited data exist, particularly from low-income and middle-income countries (LMICs) and sub-Saharan Africa[16]. Evaluation of CD was limited by the lack of a specific ICD code or evidence-based consensus diagnostic criteria until a specific ICD-10 code for CD (ICD-10-CM D47.Z2) was created, effective 01 October 2016, and diagnostic criteria for iMCD were established in 2017 (REFS[17,18]). Prior evaluation was based on case series and case reports. The epidemiology of UCD differs notably from that of MCD[5,15,19].

Incidence

Few case series exist; since 2017, data have been informed by the guidelines including diagnostic criteria and classification developed by the Castleman Disease Collaborative Network (CDCN)[15,20].

Approximately 6,500–7,700 cases of CD occur in the USA annually; 75% of these are UCD. In Japan, a similar total incidence of CD was described but MCD accounts for 70% and UCD for 30% of cases; the reason for such a discrepancy is not clear[21]. Few patients with HIV were recorded in this study; a regional difference in the cause of MCD in Japan is suggested possibly also related to the low incidence of KSHV in Japan compared with other countries. A single-centre French study described 273 patients accrued over 20 years[19]. In sub-Saharan Africa, where KSHV infection is seen in >40% of the population in many countries, a series from Malawi described 6 cases of MCD[22] and a small South African case series reported 38 cases (3 UCD and 35 MCD) in 24 years (between 1990 and 2014), with 22 out of 38 individuals included from 2010 to 2014 (all with MCD, all HIV positive and all those tested for KSHV ($n = 19$) were positive)[23]. There is little published information about incidence from other regions.

CD in all its forms may present in childhood and has been documented to occur from <1 year of age to the second decade, with no gender difference[24,25]. In children, UCD is more common than iMCD (~75% of cases). Only 11 case reports exist of KSHV-MCD in children[26].

UCD. The incidence of UCD in the USA has been estimated as 16 per million person-years (PYs); UCD occurs in individuals of all ages, with the median age of onset occurring in the fourth decade; there is no gender preference[18]. In Japan, the incidence is estimated to be 0.6–4.3 per million PYs[27].

MCD. In the USA, the incidence has been estimated at 5 per million PYs, with cases occurring in individuals of all ages and the median age of onset being in the fifth to seventh decades. There seems to be a male preponderance[18]. Another study estimated a higher incidence in the USA, at 21–25 per million PYs[28]. MCD cases are thought to be divided almost evenly between KSHV-associated MCD and iMCD[28]. In Japan, the estimate for MCD is 2.4–5.8 per million PYs[27]. In patients who are HIV negative and have MCD, KSHV-MCD accounts for 2–50% of cases, with variations most likely depending

Box 2 | **Disorders and malignancies concurrent with KSHV-MCD**

KSHV-associated disorder

- Kaposi sarcoma: a neoplastic endothelial proliferation strictly associated with Kaposi sarcoma herpesvirus (KSHV) infection[7].
- Primary effusion lymphoma (PEL; classic and solid variants): PEL is an AIDS-defining disease and one-third of patients are affected by Kaposi sarcoma. PEL, KSHV-multicentric Castleman disease (MCD) and KSHV inflammatory cytokine syndrome overlap clinically. PEL tumour cells, in both classic and solid variants, are positive for LANA1 and are frequently positive for CD45, CD38, CD138, BLIMP1, VS38c (a monoclonal antibody that recognizes a rough endoplasmic reticulum intracellular antigen that strongly labels plasma cells), MUM1, CD30 and epithelial membrane antigen. They are often positive for Epstein–Barr virus (EBV)-encoded small RNAs (EBER)[7,9,10].
- KSHV-positive diffuse large B cell lymphoma: a new lymphoma category usually arising in association with MCD and HIV infection. The tumour cells display plasmablastic features and are usually positive for CD45 and CD20 and express terminal B cell differentiation markers, including MUM1. They are often negative for EBV and/or EBER[9,95].
- KSHV-positive germinotropic lymphoproliferative disorder: patients present with localized lymphadenopathy without immunodeficiency. The clinical course is indolent. A plasmablastic proliferation is confined to expanded germinal centres. Plasmablasts positive for cytoplasmic monotypic light chain, CD38, MUM1, viral IL-6, LANA1, and EBV and/or EBER[95].
- KSHV-positive reactive lymphoid hyperplasia has been reported in the context of HIV infection. The lymph nodes show follicular hyperplasia. Lymphoid cells are positive for LANA1 (REF.[167]).
- KSHV inflammatory cytokine syndrome. Patients have inflammatory symptoms, high KSHV titres and high serum levels of cytokines without KSHV-associated MCD. The prognosis is poor[10].

HIV-associated disorders

- HIV-associated lymphadenopathies: characterized by explosive follicular hyperplasia with huge germinal centres[95].

EBV-associated disorders

- EBV infection: the non-malignant pathological counterpart of EBV infection is usually associated with reactive hyperplastic lymphadenopathy with hyperplastic germinal centres[9].
- Hodgkin lymphoma: in people living with HIV, nearly all cases of Hodgkin lymphoma are associated with EBV infection[7,9].

on the endemicity of KSHV in the region or country; in patients who are HIV positive and have MCD, almost all have KSHV-MCD[15]. KSHV is highly prevalent in sub-Saharan Africa, up to 90% in some countries[29]. In Japan, KSHV-MCD is extremely rare[21,30].

In the antiretroviral therapy (ART) era, KSHV-MCD may now possibly be observed more commonly[31]. A large UK-based prospective database of individuals who are HIV positive (comprising 56,202 PYs) compared the incidence of KSHV-MCD with Kaposi sarcoma in the pre-ART (1983–1996), early ART (1997–2001) and later ART eras (2002–2007)[31]; the incidence of KSHV-MCD was 2.3, 2.8 and 8.3 per 10,000 PYs, respectively, representing a statistically significant increase over time and the overall incidence was 4.3 per 10,000 PYs. The explanation for the increase is uncertain: suggestions include increased awareness of CD, a higher index of suspicion and better diagnostic accuracy. It is postulated that subtle forms of immune dysregulation in ART-controlled HIV disease, together with a complex interplay of HIV with KSHV, are important.

Morbidity and mortality

Life expectancy is not generally changed following a diagnosis of UCD. However, patients may be at increased risk of developing paraneoplastic pemphigus and lymphomas[32]. In MCD, the pattern of MCD presentation and course depends largely on the endemicity of KSHV in the general population[33–35].

A 20-year study of 273 patients with CD in France revealed 2-year survival data of 98.1% in patients with UCD, 100% in those with iMCD, 89.4% in those who were HIV negative and had KSHV-MCD, and 77.7% in those who were HIV positive and had KSHV-MCD. There was no statistical difference between patients with MCD who were HIV negative and those who were HIV positive[19]. These data are similar to those of a retrospective series of 145 Chinese patients (2000–2015)[32]. An important recent US-based trial of 62 participants with KSHV-MCD showed a long-term outcome of overall survival (OS) of 71% at 10 years for all patients[8]. In this study, OS at 5 and 10 years for patients with KSHV-MCD (without Kaposi sarcoma) was 90% and 73%. For those with both KSHV-MCD and Kaposi sarcoma, OS at 10 years was 81%. The presence of concurrent PEL impacted survival negatively. In iMCD, the 5-year OS was found to be ~65% in a US-based study in 2012 (REF.[36]). In a more recent US-based study of electronic medical record data, the 5-year OS was found to be ~75%[17]. Survival is poor in sub-Saharan Africa (probably owing to late presentation and limited definitive and supportive therapies)[16,22].

Risk factors

No known risk factors exist for UCD or iMCD. There seem to be no clear associations with particular ethnicities. Neither family history nor genetic predisposition were noted in a Japanese study[21]. In a retrospective French study of 57 patients with UCD, thymoma, organ transplant, recent vaccination and intrauterine device insertion were reported each in one patient. In the same study, 3 of 27 patients with iMCD were born of consanguineous parents, 2 had hepatitis C virus infection and 1 had inflammatory bowel disease. Among 29 patients who were HIV negative and had KSHV-MCD, consanguinity (2 people), thymoma (2 people), chronic viral hepatitis (2 people) and organ transplant (1 person) were noted and 4 individuals were men who have sex with men; 17 of 29 patients were from an African country, which may reflect the presence of KSHV. Of the group who were HIV positive and had KSHV-MCD, 87 of 144 were men who have sex with men and 60% were Caucasian. A large, prospective UK-based study noted nadir $CD4^+$ T cell count, age >33 years, ART naivety and non-Caucasian ethnicity as risk factors for the development of KSHV-associated MCD in patients who were HIV positive[31].

Mechanisms/pathophysiology

UCD

UCD was originally termed 'giant lymph node hyperplasia' to describe a benign hamartomatous lesion, that is, an abnormal non-neoplastic growth, occurring mainly in the mediastinum. The aetiopathogenesis of UCD is still

Table 1 | **Clinical and histopathological presentation of Castleman disease**

UCD	KSHV-MCD	POEMS-MCD	iMCD-TAFRO	iMCD-NOS
Anatomical location				
Intrathoracic (mediastinum or lung) or extrathoracic (neck, axilla, retroperitoneum or pelvis)	Multiple lymph nodes and tissues	Multiple lymph nodes and tissues	Multiple lymph nodes and tissues	Multiple lymph nodes and tissues
Vascular and lymphatic systems symptoms				
Central lymphadenopathy is the most common, often bulky	Multiple lymphadenopathies (peripheral and central, often of small volume); pancytopenia	Multiple lymphadenopathies (peripheral and central); monoclonal plasma cell disorder; anaemia	Multiple lymphadenopathies (peripheral and central, often of small volume); thrombocytopenia; anaemia	Multiple lymphadenopathies; thrombocytosis; anaemia
Constitutional symptoms				
Clinical symptoms may occur; symptoms related to compression of local anatomical structures are more common	Fever; night sweats; anasarca; weight loss	Fever; night sweats; anasarca; weight loss	Fever; night sweats; anasarca; weight loss	Fever; night sweats; anasarca; weight loss
Organomegaly				
Rarely present	Usually absent	Hepatomegaly; splenomegaly	Hepatomegaly; splenomegaly	Hepatomegaly; splenomegaly
System dysfunction				
Usually, absent	Renal dysfunction; liver dysfunction	Polyneuropathy; endocrinopathy; skin changes	Renal dysfunction; liver dysfunction	Renal dysfunction; liver dysfunction
Histopathological presentation[a]				
Plasma cell type: follicular hyperplasia and interfollicular mature plasmacytosis (that is clinically associated with blood disorders); hyaline vascular type: atrophic germinal centres, diffuse vascularity and hyalinization (with no systemic clinical symptoms)	Distinct pattern characterized by plasmablasts, which are mainly located within the follicle mantle zone	Plasma cell type: interfollicular mature plasmacytosis; hyaline vascular type: rich intraperi-follicular vascularity	Plasma cell type: interfollicular mature plasmacytosis; hyaline vascular type: rich intraperi-follicular vascularity	Plasma cell type: interfollicular mature plasmacytosis; hyaline vascular type: rich intraperi-follicular vascularity

iMCD, idiopathic multicentric Castleman disease; KSHV, Kaposi sarcoma-associated herpesvirus; MCD, multicentric Castleman disease; NOS, not otherwise specified; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes; TAFRO, thrombocytopenia, ascites, fever, reticulin fibrosis and organomegaly; UCD, unicentric Castleman disease. [a]All forms of Castleman disease share a spectrum of histopathological features; the features listed under a Castleman disease subtype are commonly observed in that specific subtype but can be found across all subtypes.

not well known, although some reports have suggested that it may be a neoplastic process involving follicular dendritic cells[37,38]. Mutations in *PDGFRB*, encoding platelet-derived growth factor receptor-β, have been found in 17% of tested patients with UCD[39]. *PDGFRB* mutations have been observed in $CD45^-$ stromal cells by in situ hybridization, thus reinforcing the hypothesis of stromal cell-derived neoplasia[39]. No associations have been found between UCD and viral infections[40].

iMCD

The term iMCD has been proposed to identify cases of MCD that occur in people who are not infected with HIV or KSHV; in these cases, the disease aetiology is still unknown. It has been proposed that iMCD involves polyclonal lymphoproliferation and hypercytokinaemia that are caused by auto-inflammatory or autoimmune mechanisms, paraneoplastic mechanisms secondary to a clonal population, or an unidentified viral infection[41]. Next-generation sequencing has identified several cases of iMCD with somatic alterations and a few cases of germline variants, but the alterations are not consistent across patients and the role of these individual alterations is unknown[42–46]. Substantial effort has been made to search for a virus that could be causative in UCD and iMCD, but initial published work has not identified evidence of a viral aetiology for UCD or iMCD[40]. Nevertheless, it is clear that a cytokine storm involving cytokines such as IL-6 is crucial to pathogenesis as patients have elevated levels of circulating cytokines and symptoms improve with IL-6 inhibition or other forms of immunosuppression; these findings are consistent with those observed in the phenotype of mice with elevated IL-6 levels[41,47]. IL-6 is a multifunctional cytokine produced by various inflammatory cells, fibroblasts, endothelial cells and various types of cancer cells[48,49]. Vascular endothelial growth factor (VEGF), IL-1, IL-2, C-X-C motif chemokine 13 (CXCL13) and tumour necrosis factor (TNF) have also been implicated in the pathogenesis of iMCD[50–54]. Other mechanisms that may be involved in iMCD include T cell activation and the activation of mTOR (mammalian target of rapamycin), JAK–STAT3 (signal transducer and activator of transcription 3) and type I interferon

signalling pathways[55–59]. In the pathogenesis of iMCD, the presence or absence of mutations in genes associated with auto-inflammatory disease has recently been reported to possibly modulate clinical symptoms and inflammasome activity may be associated with disease progression[60–62].

KSHV-MCD

KSHV-MCD is a polyclonal lymphoproliferation that occurs in individuals infected with KSHV who can be either HIV positive or HIV negative[6,63]. KSHV-associated lymphadenopathies, including MCD, are much more prevalent in individuals positive for HIV and KSHV-MCD in individuals positive for HIV generally tends to have the worst prognosis.

Of the B cells in the mantle zones around the germinal centre in a KSHV-MCD lymph node, up to 30% are infected with KSHV[64,65]. These KSHV-infected B cells display IgMλ light chains together with IgM heavy chains[63]; of note, KSHV infection is always restricted to IgMλ light chain-expressing B cells. Indeed, KSHV infection of Igκ-naive B lymphocytes upregulates V(D)J recombination mediated by recombination-activating protein RAG and Igλ expression, resulting in the loss of Igκ over time[66]. One speculation is that this mechanism could enable KSHV to shape the adaptive immune response but there is no definitive evidence of it yet. The KSHV genome encodes for a plethora of viral genes that are involved in modulating cell pathways. The ability of KSHV viral proteins and microRNAs to stimulate cell growth, proliferation and cell survival within the infected cells as well as in a paracrine fashion on neighbouring cells has a central role in the pathogenesis of KSHV-MCD.

Viral and cellular proteins drive KSHV-MCD pathogenesis. KSHV has two phases of its life cycle. During the latent phase, the virus is dormant and expresses very few latent viral genes. However, during the lytic cycle, the virus expresses multiple lytic proteins that aid in viral replication and the production of infectious virions. Both latent and lytic KSHV viral proteins can be observed in KSHV-MCD lymph nodes, and this finding suggests that abortive or complete lytic replication is occurring in some of the KSHV-infected cells in the lymph node. The KSHV latency-associated nuclear antigen (LANA) and the lytic viral proteins encoded by viral IL-6 (vIL-6), the viral processivity factor ORF59 (also known as PF-8), and viral interferon regulatory factor 1 (vIRF1) can be detected in KSHV-MCD[65]. KSHV viral lytic protein expression is thought to contribute to the pathobiology of KSHV-MCD. Several lytic proteins, including vIRF1, have been shown to downregulate the innate immune response and protect the virus from antiviral immune responses[67,68]. Lytic proteins such as the viral protein kinase (vPK), encoded by ORF36, and the thymidine kinase, encoded by ORF21, are also expressed in KSHV-MCD and these proteins have been successfully targeted to treat KSHV-MCD using zidovudine and valganciclovir, respectively[69]. KSHV ORF36 has been shown to be pro-oncogenic in cell culture and animal models[70,71].

KSHV vIL-6 is the most characteristic viral protein that is expressed at high levels in KSHV-MCD, and it is a homologue of cellular human IL-6 (hIL-6). KSHV vIL-6 expression is generally observed in the plasmablasts surrounding the lymphoid follicles[72–74]. In the follicular mantle zone, 10–30% of cells are positive for KSHV infection as measured by LANA positivity and a subpopulation of these cells (5–25%) demonstrates highly variable (5–25%) expression of KSHV vIL-6 and vIRF1 (REF.[65]). In an independent study in HIV-negative KSHV-MCD, vIL-6 expression was also shown to be variable and was observed in 2–13% of cells in the mantle zone of the KSHV-MCD lymph node[73]. Thus, the expression of vIL-6 in KSHV-MCD is highly variable both in the same individual and between individuals.

KSHV-MCD is also characterized by excessive expression of human cytokines. hIL-6 is highly expressed concomitantly with vIL-6 in this disease. Elevated levels of IL-10 and other inflammatory cytokines, such as IL-1β and TNF, are also observed[75–77], and the increased expression of these proteins may be driven by the virus (for example, KSHV LANA, vFLIP and RTA proteins can upregulate hIL-6 through a variety of different mechanisms[56,78,79]). The hIL-6 receptor is expressed in most KSHV-positive plasmablasts[63]. The induction of the inflammatory cytokines, especially hIL-6 and vIL-6, is likely to be responsible for manifestations of anaemia, fever and hypoalbuminaemia in patients with KSHV-MCD[75]. CD20, a surface protein expressed on mature B cells, is also expressed in the lymph nodes of patients with KSHV-MCD, and KSHV is present in the IgMλ-restricted plasmablasts with variable expression of CD20 (REF.[80]).

Plasma levels of hIL-6, IL-10, vIL-6 and serum C-reactive protein (CRP) are high in KSHV-MCD[75,76,81]. Patients with KSHV-MCD also display much higher viral loads in peripheral blood mononuclear cells than patients with Kaposi sarcoma or PEL[76], a finding indicative of active viral replication. It is thought that HIV-related immunosuppression enables KSHV to replicate in plasmablasts in the lymph node, thereby expressing KSHV viral lytic genes, which elicit the expression of multiple cytokines[82,83]. In patients who are HIV negative and have KSHV-MCD, there may be other factors that cause immunodeficiency and enable KSHV lytic protein expression.

hIL-6 and vIL-6 function in a paracrine fashion in KSHV-MCD. hIL-6 is a multifunctional cytokine that is central to a wide range of biological processes such as cell proliferation, immune regulation and inflammation. hIL-6 also enhances the survival of plasmablasts. Both vIL-6 and hIL-6 have been shown to drive the proliferation of B cells[84–87]. Contrary to hIL-6, KSHV vIL-6 does not need the gp80 subunit of the IL-6 receptor to activate signalling pathways. Instead, it can directly activate the gp130 subunit of the IL-6 receptor to induce signal transduction through the MAPK (mitogen-activated protein kinase), JAK–STAT and PI3K (phosphatidylinositol-3-kinase)–Akt pathways[88].

KSHV vIL-6 has been shown to upregulate the expression of VEGF, similarly to hIL-6 (REFS[89,90]). VEGF

is a potent angiogenic factor that may have a role in the pathogenesis of iMCD and KSHV-MCD as endothelial cell and blood vessel proliferation is an important component of MCD[52,91]. VEGF further induces hIL-6 expression from endothelial cells[63], thereby promoting proliferation in a feedforward loop through a paracrine mechanism. This mechanism is consistent with the histology of MCD as the proliferation of endothelial cells within the lymph node is a characteristic of MCD.

Common aetiopathogenic mechanisms

KSHV-MCD and Kaposi sarcoma. In the literature, MCD has been described as multicentric angiofollicular hyperplasia owing to the presence of a high degree of vascular proliferation, resembling Kaposi sarcoma lesions. In individuals co-infected with HIV and KSHV, it is not unusual to find the mutual presence of KSHV-MCD and Kaposi sarcoma in a lymph node (FIG. 1). The presence of KSHV-positive endothelial cells in KSHV-MCD lymph nodes was demonstrated both in individuals who are HIV negative and in those who are HIV positive[92]. KSHV-infected endothelial cell proliferation and vascularization has a central role in both KSHV-MCD and Kaposi sarcoma and, in both cases, cytokine expression seems to drive disease progression.

In addition to soluble cytokines, extracellular vesicles or exosomes are likely to also be involved in the pathogenesis of Kaposi sarcoma and KSHV-MCD, particularly with regard to endothelial cell dysregulation[93,94]. Exosomes are released by virus-infected cells and transfer KSHV viral microRNAs into neighbouring B cells and T cells. Thus, KSHV infection may contribute to the KSHV-MCD phenotype in a paracrine fashion consistent with the systemic clinical characteristics of KSHV-MCD.

KSHV-MCD and KSHV-associated lymphoproliferation. Patients with KSHV-MCD, which occurs most commonly among PLWH, may present concurrent KSHV-associated lymphoproliferations that are usually complications of KSHV-MCD and less frequently occur in individuals with iMCD. The spectrum of these KSHV-associated lymphoproliferations includes MCD-associated plasmablastic lymphoma (now HHV8-positive large B cell lymphoma, NOS in the 2017 WHO classification[95]), KSHV-associated germinotropic

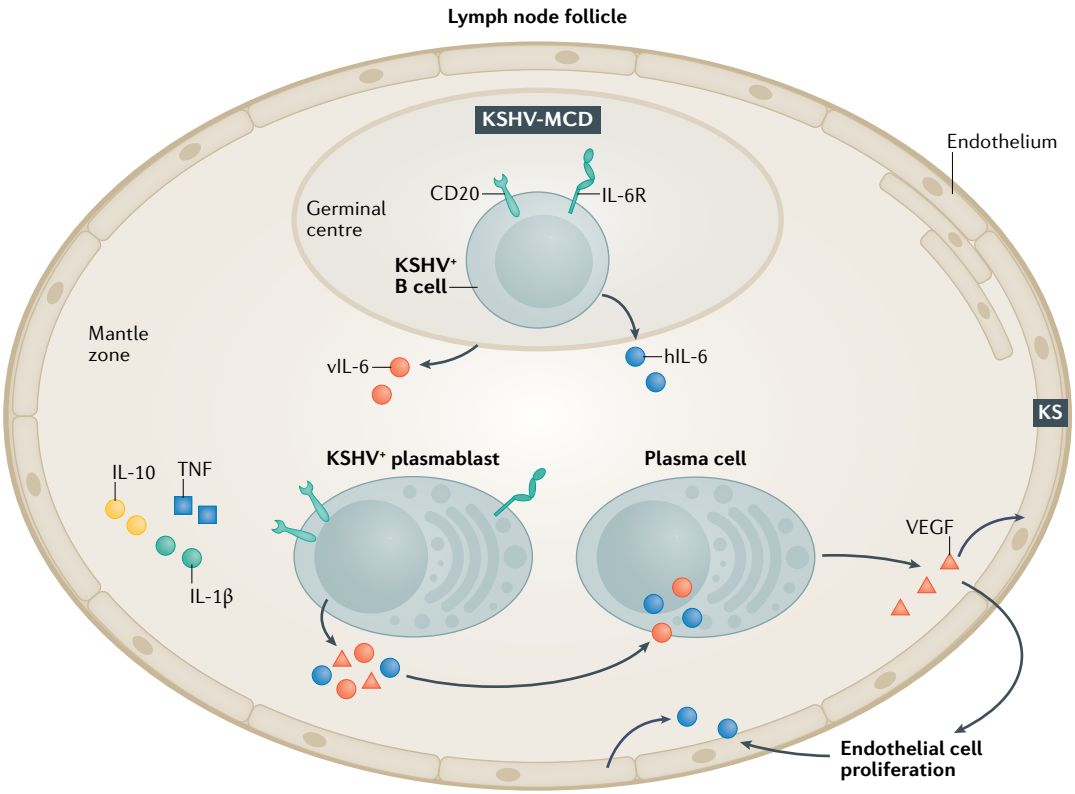

Fig. 1 | **Common pathogenic mechanisms in KSHV-MCD and other KSHV-associated diseases.** Schematic picture of a lymph node follicle with Kaposi sarcoma (KS) herpesvirus (KSHV)-infected B cell plasmablast. These cells express KSHV lytic proteins and some express the cell surface receptor CD20. The KSHV-positive plasmablasts also express high amounts of both human IL-6 (hIL-6) and viral IL-6 (vIL-6). It is hypothesized that both of these cytokines can in turn elicit other cells (for example, plasma cells in the lymph node) to secrete vascular endothelial growth factor (VEGF) or that the KSHV-infected cells themselves express VEGF[90]. VEGF can then induce the endothelial cells that are present in the lymph node to proliferate and to secrete more hIL-6 in a feedforward loop that augments the proliferation of both B cells and endothelial cells in the lymph node. Elevated levels of other cytokines, such as IL-10, IL-1β and TNF, are also observed in KSHV-multicentric Castleman disease (MCD) and other KSHV-associated diseases. KSHV contributes to the development of several lymphoid proliferations, especially primary effusion lymphoma and its variants, through a group of virally encoded proteins (not shown).

lymphoproliferation (now called HHV8-positive germinotropic lymphoproliferative disorder in the WHO classification[95]) and PEL. Neoplastic cells of all these lymphoproliferations show plasmablastic morphology and immunophenotype (that is, with an antigen expression profile MUM1$^+$, CD138$^+$ or CD138$^-$, CD20$^-$ or CD20$^+$, and CD79a$^-$). Moreover, germinotropic lymphoproliferative disorder as well as PEL and its variants exhibit infection by both KSHV and EBV. KSHV exerts an aetiopathogenic role for several lymphoproliferations, especially PEL and its variants, through several virus-encoded proteins. KSHV-encoded vIL-6 is expressed in latently infected cells and during viral replication. As described above, vIL-6 induces VEGF, thereby contributing to angiogenesis and vascular permeability, and probably induces the formation of neoplastic effusions[91,96]. KSHV LANA, in particular, is relevant for tumour cell survival[97].

Mechanisms underlying complications of CD

KSHV inflammatory cytokine syndrome. KICS is a more recently described entity in individuals infected with HIV and KSHV[98]. KICS is an inflammatory syndrome with a high KSHV viral load and cytokine profiles similar to those seen in MCD, including hIL-6 and vIL-6 (REF.[10]). Symptoms associated with KICS are also similar to those of patients with MCD, but there is no generalized lymphadenopathy and no histological diagnosis of CD[10,98]. Probably, the absence of lymphadenopathy may be due to the greater rapidity of disease progression in KICS. Similar to KSHV-MCD, patients with KICS have elevated levels of IL-6 and IL-10 (REFS[99,100]) and may also have other KSHV-associated tumours such as Kaposi sarcoma or PEL.

Diagnosis, screening and prevention

Clinical setting and presentation

UCD. The clinical presentation of UCD is usually an enlarging mass, which may be apparent on visual inspection or palpable; in some cases, deeper masses are not clearly apparent but cause symptoms as a result of local compression. These symptoms can include pain associated with local nerve compression or other symptoms associated with disruption of local structures (TABLE 1). Asymptomatic UCD lesions are sometimes identified by imaging tests performed for other purposes[3,15,101]. Systemic constitutional symptoms, such as fatigue and weight loss, are uncommon and usually not severe when present, in contrast with MCD. To fulfil the diagnosis of UCD, lymph node enlargement must be confined to a single lymph node or node region. Hence, diagnostic work-up must include not only histological examination of an excised lymph node but also radiological examination, most commonly by whole-body CT or CT-FDG-PET.

Hepatomegaly or splenomegaly are rare, and their presence should prompt consideration of alternative or additional diagnoses[4]. Similarly, laboratory abnormalities such as anaemia or evidence of inflammation (elevated levels of CRP or prolonged erythrocyte sedimentation rate) may be present but are uncommon[15]. A recent study reported that 16% of 116 patients with UCD had UCD with an MCD-like inflammatory syndrome[102]. Amongst children with UCD, bronchiolitis obliterans is associated with high mortality[103]; thus, lung function tests and high-resolution CT thoracic scans should be performed in those with respiratory symptoms.

MCD. All forms of MCD are characterized by a clinical presentation of systemic inflammatory symptoms and associated organ system dysfunction and laboratory abnormalities, which may be severe or life-threatening[8,15]. These symptoms commonly progress rapidly, although, owing to the rarity of the disease, clinical recognition is sometimes delayed. Whereas asymptomatic UCD is common, asymptomatic MCD is not.

The core symptom complex of MCD includes fever, weight loss, anasarca (severe oedema in the entire body) and generalized lymphadenopathy with splenomegaly (which may be massive) and, in some cases, hepatomegaly[8,15,33,69,104]. Commonly, lymphadenopathy is generalized but of relatively small volume; bulky adenopathy is rare. Anaemia is very common as is hypoalbuminaemia, and other cytopenias may also be present. Elevations in inflammatory markers are almost universal during symptomatic periods. Associated fluid shifts, which result from hypoalbuminaemia and possibly cytokine-induced vascular dysregulation, can lead to intravascular depletion and renal impairment even in the presence of substantial extravascular fluid overload[8]. The inflammatory symptoms may be intermittent, occurring in 'flares', whose precipitants are not clearly established[8,15]. In more severe cases, once the inflammatory flare is established, it becomes self-sustaining and may be life-threatening.

KSHV-MCD is most commonly seen in those with HIV infection (which may be well controlled, with suppressed HIV viral loads and adequate CD4$^+$ T cell reconstitution) but can be found in people without HIV[8,105]. In KSHV-MCD, the KSHV viral load in peripheral blood is almost universally elevated during inflammatory 'flares'[14,106]. Importantly, in patients with HIV or known KSHV infection, the presence of this symptom complex in the absence of substantial adenopathy or organomegaly or the pathological features of KSHV-MCD (see below) should also prompt consideration of other syndromes of KSHV-associated inflammation, including KICS[10,107] or the inflammatory phenomena associated with PEL[108].

Although the core inflammatory symptom complex is broadly similar across all MCD forms, reflecting the underlying role of IL-6 in MCD pathogenesis, for iMCD in particular there are recognized syndromic variants with specific additional clinical manifestations (FIG. 2)[15]. An international consensus diagnostic criteria for iMCD has been described and an alternative diagnostic approach has been proposed by a Japanese study group[109].

Some patients with iMCD experience co-occurring POEMS syndrome, characterized by the features of peripheral neuropathy, organomegaly, skin changes and monoclonal paraproteins (monoclonal excesses of specific immunoglobulins or light chains) in addition

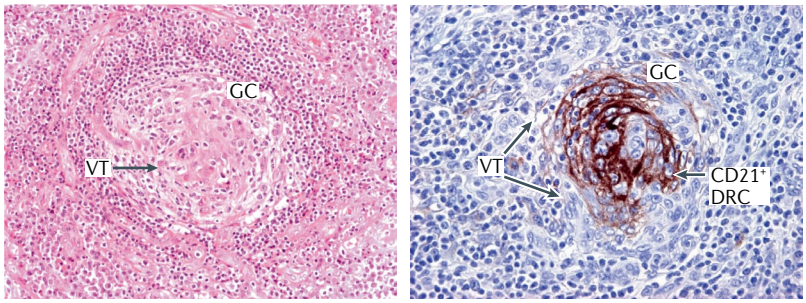

Fig. 2 | **Unicentric Castleman disease. a** | A lymphoid follicle with vascular transformation (VT) of the germinal centre (GC). **b** | Lymphoid follicle in which the GC is replaced by a CD21+ dense meshwork of dysplastic follicular dendritic reticulum cells (DRC) and vascular channels with high endothelium. Magnification x10 (both images).

to features of MCD; of note, POEMS may also occur without MCD[12,50]. In this case, it is likely that an underlying process, perhaps the monoclonal plasma cell proliferation, underlies both POEMS and the clinical features of MCD. Among patients with MCD who do not have KSHV infection or POEMS syndrome, iMCD is sub-divided based on clinical presentation into iMCD-TAFRO (which is sometimes considered a separate disease entity), iMCD-POEMs and iMCD-NOS. Patients with iMCD-TAFRO have thrombocytopenia, ascites, fever, reticulin fibrosis and organomegaly. These patients also tend to have normal immunoglobulin levels and mixed or hyaline vascular histopathological features. Patients with iMCD-NOS tend to have elevated platelet counts, very elevated immunoglobulin levels and plasmacytic histopathological features[15,110]. These features do not precisely distinguish iMCD-NOS from other MCD forms and an assessment of the overall clinical picture is required.

Diagnosis and pathological features

Confirmation of the diagnosis of CD requires pathological review of an affected lymph node, which should ideally be performed from an excisional biopsy (not a core or fine-needle aspirate), given the heterogenous involvement within affected lymph nodes and the need to observe macroscopic architectural features. ^{18}FDG-PET has an important role to play both in excluding alternate diagnoses, such as large cell lymphoma, and in selecting an appropriate target lymph node for surgical biopsy[111]. For KSHV-MCD, the diagnosis is based on the pathology and positive testing for KSHV, whereas an international consensus in which pathological features are integrated with a clinical syndromic assessment has been proposed to confirm the diagnosis of iMCD (BOX 3), which also requires the exclusion of underlying causes such as autoimmune diseases[104]. Specific alternative diagnoses and mimics to exclude in cases with pathological features resembling those of CD include systemic lupus erythematosus and other autoimmune diseases, autoimmune lymphoproliferative syndrome, IgG4 disease, and certain acute viral infections, including EBV and HIV infection. The distinction from lymphoma or an underlying follicular dendritic cell sarcoma is also crucial[13]. Reactive lymphoid hyperplasia without known aetiology, acute infections, autoimmune diseases, lymphomas, and abnormal enlargement of secondary lymphoid follicles as observed in HIV-related lymphadenopathy, PEL and Hodgkin lymphoma are the most common diseases in

Box 3 | **Diagnostic criteria for idiopathic multicentric Castleman disease based on pathological characteristics and clinical features**

Inclusion criteria

I. Major criteria (both needed)

- Histopathological lymph node
- Enlarged lymph nodes in ≥2 lymph node stations

II. Minor criteria (≥2 required, of which ≥1 laboratory criterion) — laboratory criteria

- Elevated erythrocyte sedimentation rate or C-reactive protein
- Anaemia
- Thrombocytopenia or thrombocytosis
- Renal dysfunction or proteinuria
- Polyclonal hypergammaglobulinaemia
- Hypoalbuminaemia

II. Minor criteria (≥2 required, of which ≥1 laboratory criterion) — clinical criteria

- Constitutional symptoms
- Large spleen and/or liver
- Fluid accumulation
- Eruptive cherry angiomata or violaceous papules
- Lymphocytic interstitial pneumonitis

Exclusion criteria

Infection-related disorders

- Kaposi sarcoma herpesvirus infection
- Epstein–Barr virus-associated lymphoproliferative disease
- Inflammation and adenopathy by other infection

Autoimmune or inflammatory diseases

- Systemic lupus erythematosus
- Rheumatoid arthritis
- Adult-onset Still disease
- Juvenile idiopathic arthritis
- Autoimmune lymphoproliferative syndrome

Malignant lymphoproliferative diseases

- Lymphoma
- Multiple myeloma
- Primary lymph node plasmacytoma
- Follicular dendritic cell sarcoma
- POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes) syndrome

Features supportive of but not required for a diagnosis include elevated IL-6, soluble IL-2 receptor (sIL-2R), vascular endothelial growth factor (VEGF), IgA, IgE, lactate dehydrogenase (LDH) and/or β2-microglobulin (B2M) levels, reticulin fibrosis of bone marrow (particularly in patients with TAFRO (thrombocytopenia, anasarca, fever, reticulin fibrosis, renal insufficiency, and organomegaly) syndrome), paraneoplastic pemphigus, bronchiolitis obliterans organizing pneumonia, autoimmune cytopenias, polyneuropathy (in the absence of POEMS diagnosis), glomerular nephropathy and inflammatory myofibroblastic tumour.

Box 4 | **Disorders that morphologically overlap with unicentric Castleman disease and multicentric Castleman disease**

- Follicular hyperplasia, not otherwise specified
- HIV-associated lymphadenopathy
- Epstein–Barr virus infection
- Autoimmune disorders
- Hodgkin lymphoma
- Angioimmunoblastic T cell lymphoma
- Follicular dendritic cell sarcoma
- Plasmacytoma

the differential diagnosis of CD (BOX 4)[8,112]. In all suspected cases of CD in which there is a suspicion of lymphoma, IgH gene rearrangement studies for B cell clonality, EBV testing, immunohistochemistry and flow cytometry should be performed on the lymph node or effusions (if present) to rule out a clonal disorder.

Pathological features

The pathological categorization of CD is commonly a source of confusion as it aligns imperfectly with the commonly used clinical categorization of UCD, iMCD and KSHV-MCD; we highlight here the pathological features that can lead to differences in the clinical management. For many years, a distinction was made between hyaline vascular (also called hypervascular; HV) and plasma cell (PC) variations of CD, with an additional overall group with pathological features that fall on a spectrum ranging between the two previously defined types. Most (but not all) cases of UCD have been categorized pathologically as being of the HV type (FIG. 2), whereas most (but not all) cases of iMCD were PC type (FIG. 3); all KSHV-MCD is PC type, with some additional features[2,4,7,15]. However, this distinction is increasingly less useful with the recognition that KSHV-MCD is best considered a distinct entity characterized by KSHV involvement in affected lymph nodes (FIG. 4) and that UCD and iMCD may be of any type (HV, PC or mixed); the differentiation of UCD and iMCD is therefore best made by the integration of clinical, imaging and pathological features[15].

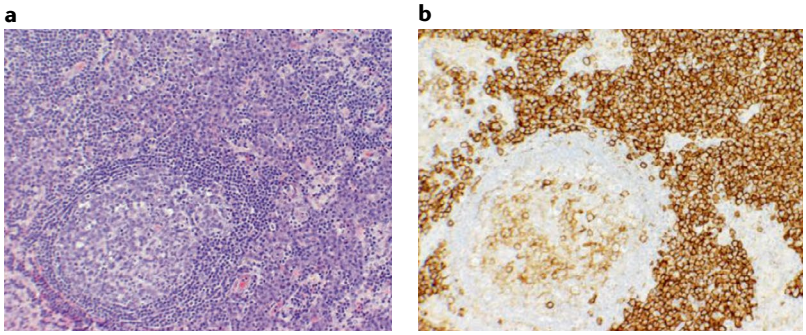

Fig. 3 | **Histological features of the plasma cell variant of iMCD. a** | Haematoxylin and eosin staining shows sheets of plasma cells in the interfollicular areas with relatively well-formed germinal centres in plasma cell variant of idiopathic multicentric Castleman disease (iMCD). **b** | Plasma cells in the interfollicular areas are strongly stained for CD138. Adapted with permission from REF.[166], Elsevier.

The hyaline vascular histopathological subtype of CD is characterized by capsular fibrosis around lymphoid follicles with broad fibrous bands disrupting and crossing the normal lymph node architecture[2,3,19]. In addition, follicular hyperplasia is present, with increased numbers of lymphoid follicles throughout the cortex and medulla. Mantle zones are hyperplastic and composed of concentric rings of small lymphoid cells (the so-called 'onion skin pattern'). By contrast, germinal centres are characteristically depleted of B cells, with remaining hyaline deposits and follicular dendritic cells only; these dendritic cells may be dysplastic in severe cases (FIG. 2). These depleted germinal centres are penetrated by pathological blood vessels (vascular transformation, with so-called 'lollipop lesions'). The interfollicular region is infiltrated by occasional plasma cells, immunoblasts and eosinophils within the stroma but sheets of plasma cells are not seen. This hyaline vascular subtype is the most common pathological presentation observed in cases of UCD and may be seen in cases of iMCD; it is common in iMCD-TAFRO but can be found in other MCD forms, although often with a less severely disrupted lymphoid architecture[3,15].

In the plasma cell histopathological subtype of CD, the key morphological feature is the presence of sheets of plasma cells in the interfollicular zone rather than the occasional cells seen in the HV type[19,113]. These interfollicular regions in the PC type may also exhibit a scattered eosinophil and mast cell infiltrate but these cell populations are much less prominent than the cascading sheets of plasma cells. As in HV type, prominent high endothelial venules may be seen in the interfollicular zone. These nodes are also often characterized by follicular centre hyperplasia with sharply defined mantle zones and polarized, often hypocellular, germinal centres. The pathological 'onion skin' mantle zone is still seen in some cases as are penetrating blood vessels in the germinal centres. The PC pathological type is rare in UCD but common in iMCD with or without POEMS; with the variations described below, it is also the type seen in KSHV-MCD[15,113].

KSHV-MCD. The pathological features of KSHV-MCD differ in some respects from those of PC type iMCD although, broadly, it has been considered a variant of the PC type. The key distinction is the presence of KSHV-infected cells. As in the PC type, affected nodes are characterized by hypocellular germinal centres with a vascularized core. In addition, there is a proliferation of polyclonal but monotypic IgMλ-restricted plasmacytoid cells in the intrafollicular area[19,63,94,113–116]. A proportion of these cells are KSHV infected, demonstrated by the expression of KSHV LANA1, and a subset of these cells also express KSHV lytic genes, including the one encoding vIL-6 (REFS[63,113]). KSHV-infected cells are found predominantly in the mantle zones and centres of the follicles but are also seen scattered as single cells in the interfollicular area[63]. However, the majority of the cellular burden within affected nodes is comprised of uninfected plasmacytoid B cells[116,117]. These plasmablasts can form small clusters (microlymphoma) or confluent sheets (frank lymphoma); the microlymphomas can

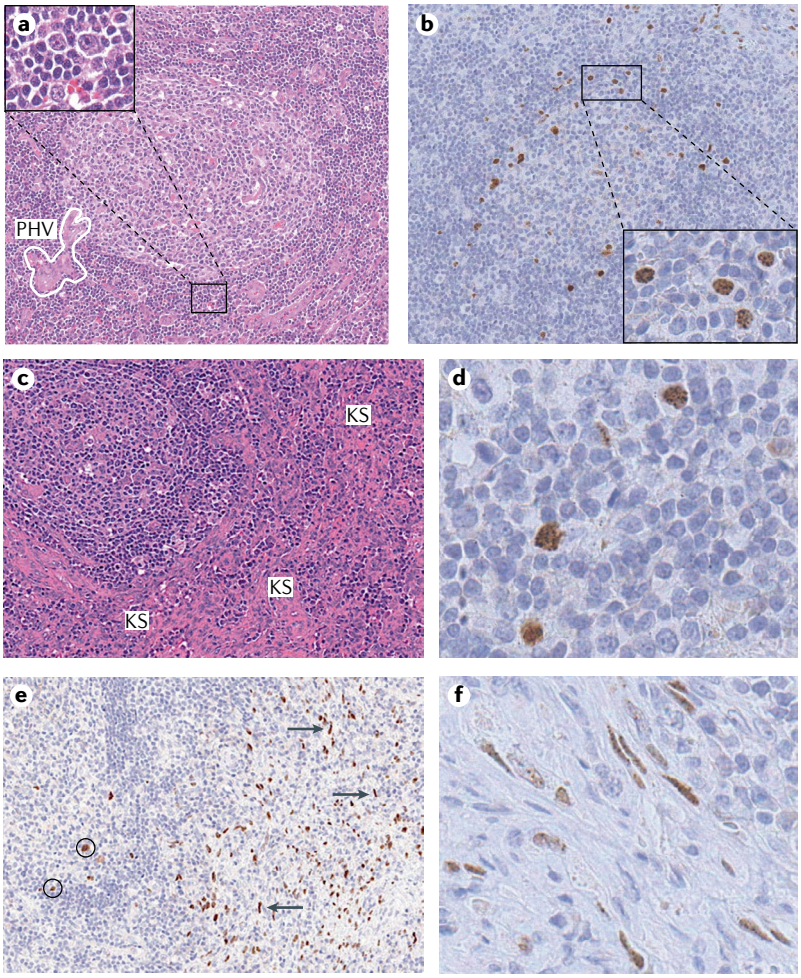

Fig. 4 | **KSHV-MCD and KSHV-MCD with concurrent KS. a** | The lymphoid follicle has a high degree of vascular proliferation. It also has typical penetrating hyalinized vessels (PHV). The inset shows plasmablasts in the mantle zone. **b** | Latency-associated nuclear antigen (LANA1) staining shows the characteristic Kaposi sarcoma (KS) herpesvirus (KSHV)-positive plasmablasts (brown) in the mantle zone. Magnification x10 (panels **a** and **b**); insets magnification x40. **c** | Marked interfollicular endothelial proliferation consistent with KS. **d** | Plasmablast infected cells (brown). **e** | In the mantle zone, typical endothelial cells are positive for LANA1 (arrows). In the follicular mantle, some large atypical cells, consistent with plasmablasts, are also positive for LANA1 (circled). **f** | KS spindle cells (brown) in the tumour. Magnification x20 (panels **c** and **e**); x60 (panels **d** and **f**). MCD, multicentric Castleman disease.

either be polyclonal or monoclonal by molecular genetic studies. Areas of Kaposi sarcoma tumour in affected nodes are also not uncommon (FIG. 4).

Global variations in diagnosis

The clinical and diagnostic tools necessary to diagnose CD in its various forms are limited or unavailable in many LMICs. In particular, access to functional imaging by FDG-PET is extremely limited, but, in many settings, even access to surgery for biopsy and expert histopathological review may be limited. These challenges are particularly relevant to KSHV-MCD, given its association with HIV and the high rates of HIV infection in certain LMICs, especially in sub-Saharan Africa, where KSHV infection is also endemic. The common occurrence of other inflammatory diseases, including tuberculosis, in these regions further complicates diagnoses. Thus, KSHV-MCD, and perhaps other forms of CD, are probably under-recognized in these settings[16,22]; investments in capacity development in surgery, oncology and radiology resources will be required to address this deficit.

Screening and prevention

There has been no systematic evaluation of the role of screening for any form of CD. In general, they are rare diseases and a broad, population-based approach to screening is unlikely to provide meaningful or cost-effective improvements in diagnosis or clinical outcomes for affected individuals. A possible exception arises for KSHV-MCD, which has increased prevalence in PLWH but, even in this situation, the overall incidence of the disease among PLWH is relatively low; nonetheless, the role of screening with biomarkers such as KSHV viral load warrants exploration[14,106].

Although not a formal screening strategy, education of clinicians and pathologists is key to improving the diagnosis and outcomes for people with all forms of CD. For MCD, delays in diagnosis resulting from failures to recognize these rare syndromes are common and can adversely affect patient outcomes. For iMCD, the CDCN has made substantial investments in addressing this issue through clinician outreach and education activities. Similar efforts are likely to be required for KSHV-MCD, particularly in underserved and resource-limited areas such as the southern USA and sub-Saharan Africa, where HIV infection and AIDS are common and the inflammatory syndrome may not be easily recognized[16,22].

Of note, although it is not clear whether UCD is associated with an increased risk of malignancy, both KSHV-MCD and iMCD seem to be associated with an increased risk of haematological malignancies and screening may be warranted[118].

Prevention strategies for CD are also poorly defined. For KSHV-MCD, given its association with HIV infection, it might be expected that improvements in ART for HIV and consequent improvements in immune function would reduce the incidence of KSHV-MCD; however, the opposite was the case, at least early in the era of highly active ART[31,33]. There are several possible explanations for this trend, including better recognition of the symptoms and pathological features and competing causes of mortality early in the AIDS epidemic. It may also be that a degree of immune preservation is necessary for the development of the spectrum of pathological features defined as KSHV-MCD and that the very severe immune deficiency of the early epidemic did not allow the development of those features. The impact of more recent approaches to immediate, universal initiation of ART remains to be seen. For other forms of CD, a more detailed understanding of the underlying host susceptibilities and environmental triggers may, in the future, inform tailored prevention strategies[54,110,119].

Management

The treatment of patients with CD depends on the disease subtype; consensus has emerged over the past two decades that curative surgery is the gold standard for

UCD and monoclonal antibody-based immunotherapy is the standard of care in MCD.

Management of UCD

Clinical evaluation should be performed for constitutional and other inflammatory symptoms; compression of adjacent structures (airways, neurovascular bundles, ureters); rare complications such as amyloidosis with serum protein amyloid A (AA amyloidosis)[120], paraneoplastic pemphigoid[121], bronchiolitis obliterans[122] and even malignancies (such as follicular dendritic cell sarcoma)[123]; and the feasibility of resection. Complete surgical excision is the optimal therapy for resectable UCD as originally described by Castleman himself[2,124] and confirmed 65 years later by the recently published international consensus evidence-based guidelines[5] (FIG. 5). The great majority of UCD cases can be managed with resection, leading to an OS of >90% at 5 years[5]. Relapse following complete resection is rare and paraneoplastic complications, such as AA amyloidosis, usually resolve gradually following complete resection[125].

Rarely, UCD is unresectable owing to size and location; management is determined by the presence and type (compressive versus inflammatory) of symptoms. Whilst there are no published systematic studies evaluating the optimal treatment of unresectable UCD, consensus opinion suggests that asymptomatic unresectable UCD may be monitored without intervention if no neighbouring structures are threatened by compression as UCD growth may be very slow. In unresectable UCD with symptoms due to compression of adjacent structures, initial treatment with rituximab (a monoclonal anti-CD20 antibody) with or without steroids to reduce the bulk followed by surgical resection if feasible or radiotherapy if not still amenable to surgery is recommended[5]. Patients with unresectable UCD and inflammatory symptoms are managed with treatments used for iMCD.

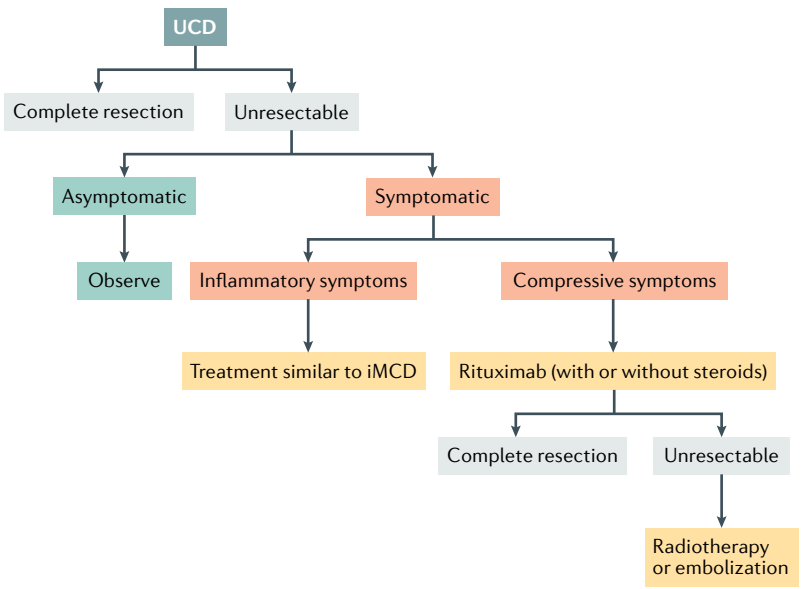

Fig. 5 | **The management of UCD.** The figure highlights the guidelines[5] of the optimal treatment for resectable and unresectable unicentric Castleman disease (UCD). iMCD, idiopathic multicentric Castleman disease.

Management of MCD

Although there is some overlap in the clinical presentation of KSHV-MCD and iMCD, their pathogenesis and clinical management are completely different and are thus discussed separately.

iMCD. The central role of IL-6 in the pathogenesis of a large proportion of iMCD cases was established more than 30 years ago[126] and led to the development of monoclonal antibody therapies directed at IL-6 and its receptor. More recently, the establishment of the CDCN has led to the development of international classification systems[41], evidence-based diagnostic criteria[104] and treatment guidelines that incorporate response criteria[20]. The international consensus published in 2018 recommended anti-IL-6-based therapy as first line for all patients with iMCD, with the addition of steroids depending on disease severity. Siltuximab, a monoclonal antibody against IL-6, is the only drug evaluated in a randomized controlled trial in iMCD and the only drug approved for iMCD by the US FDA, EMA, and more than 40 other regulatory agencies. In a phase II randomized study of 79 patients, 34% of those in the siltuximab arm achieved durable symptom and tumour responses compared with none of the patients in the placebo arm[127]. Intriguingly, although patients with higher IL-6 levels tended to have a higher response rate, some patients with iMCD and normal or low levels of IL-6 responded to siltuximab, whereas some patients with high IL-6 levels did not[128]. Of note, siltuximab non-responders had lower CRP levels than responders[127], suggesting that response to siltuximab may be related to different pro-inflammatory triggers. Tocilizumab is a monoclonal antibody that targets both soluble and membrane-bound IL-6 receptors. It was originally developed for the treatment of iMCD in Japan and is the only approved treatment for iMCD in Japan. An open-label multicentre study of 28 patients (26 with iMCD, 2 with KSHV-MCD) reported a durable reduction in lymphadenopathy in 52% of patients and improvement in laboratory biomarkers in 64–71%[129]. No direct comparison between siltuximab and tocilizumab has been conducted and the consensus guidelines do not favour one over the other but recommend utilization based on regulatory approvals in specific countries. Both siltuximab and tocilizumab are well tolerated; the most common adverse effects with siltuximab are pruritus (itch) (28%) and upper respiratory tract infections (26%) whilst, with tocilizumab, the most common are elevated transaminases (30%) and hyperlipidaemia (20%). Two papers have reported laboratory biomarkers associated with an increased likelihood of response to siltuximab[58,130]. Importantly, insufficient evidence exists for the use of histopathological subtype to guide treatment of iMCD[131].

For patients who fail to respond to anti-IL-6 therapy, there is no clear approach. Most clinicians attempt to avoid cytotoxic chemotherapy in patients who do not have life-threatening disease. However, in severe refractory life-threatening iMCD, combination cytotoxic chemotherapy using either lymphoma or myeloma regimens is often necessary and can be very effective. Rituximab is advocated as second-line treatment for

patients with iMCD who fail to respond to IL-6 blockade and are not classified as having severe disease[20], although this recommendation is based on limited publications on small numbers of patients[132–135] (FIG. 6). A wide variety of third-line immunomodulatory options have been explored in case reports and small case series, including corticosteroids, rituximab, thalidomide, lenalidomide, bortezomib, cyclosporine, sirolimus, anakinra and interferon[20]. Recent reports of mTOR and JAK inhibitors in highly treatment-refractory patients with iMCD have generated enthusiasm and further research[136]. Further research is under way into mTOR, JAK–STAT and other signalling pathways and cytokines found to be increased in iMCD as potential therapeutic targets. Trials of sirolimus in the USA and Japan are currently recruiting patients refractory to anti-IL-6 therapy. The ACCELERATE natural history registry is collecting data on patients with CD.

iMCD-TAFRO. Most studies have not separately investigated the treatment of patients with iMCD-TAFRO or iMCD-NOS and no regulatory bodies recommend treating iMCD-TAFRO differently from other cases of iMCD. In fact, a literature review identified 31 patients with MCD-TAFRO who were treated with tocilizumab and reported that it was effective in half the patients[137]. Furthermore, a retrospective surveillance study from Japan of 229 patients with TAFRO (some with iMCD and others without iMCD) revealed that, following the failure of steroid therapy, cyclosporin A, rituximab and tocilizumab have all been used with some success, although no head-to-head comparisons have been performed[138]. Furthermore, the proposed diagnostic criteria and severity classification have recently been updated following an analysis of cases in Japan[139].

POEMS-associated MCD. When MCD is associated with POEMS, the treatment strategy that is generally adopted is that for POEMS and is based on clinical experience rather than on controlled clinical trials[140–142]. The recommended treatment varies from localized radiotherapy for solitary bone lesions without bone marrow involvement to multiple myeloma approaches, including autologous haematopoietic stem cell transplantation, for more extensive and symptomatic disease.

KSHV-MCD. The choice of treatment for KSHV-MCD was revolutionized by the publication in 2007 of two prospective phase II studies that established the clear efficacy of rituximab[143,144]. Subsequent studies have revealed that life-threatening organ failure, poor performance status and the presence of concurrent Kaposi sarcoma require the addition of chemotherapy to rituximab. For patients with life-threatening disease, etoposide is the most frequently used chemotherapy as an addition to rituximab, whilst pegylated liposomal doxorubicin is usually added to rituximab if there is concurrent Kaposi sarcoma. Rituximab may be associated with hepatitis B virus reactivation, progressive multifocal leukoencephalopathy and progression of Kaposi sarcoma. For all PLWH, ART should be commenced or continued and careful attention must be paid to potential pharmacological interactions. Three large European cohort studies have described the long-term outcomes of this approach

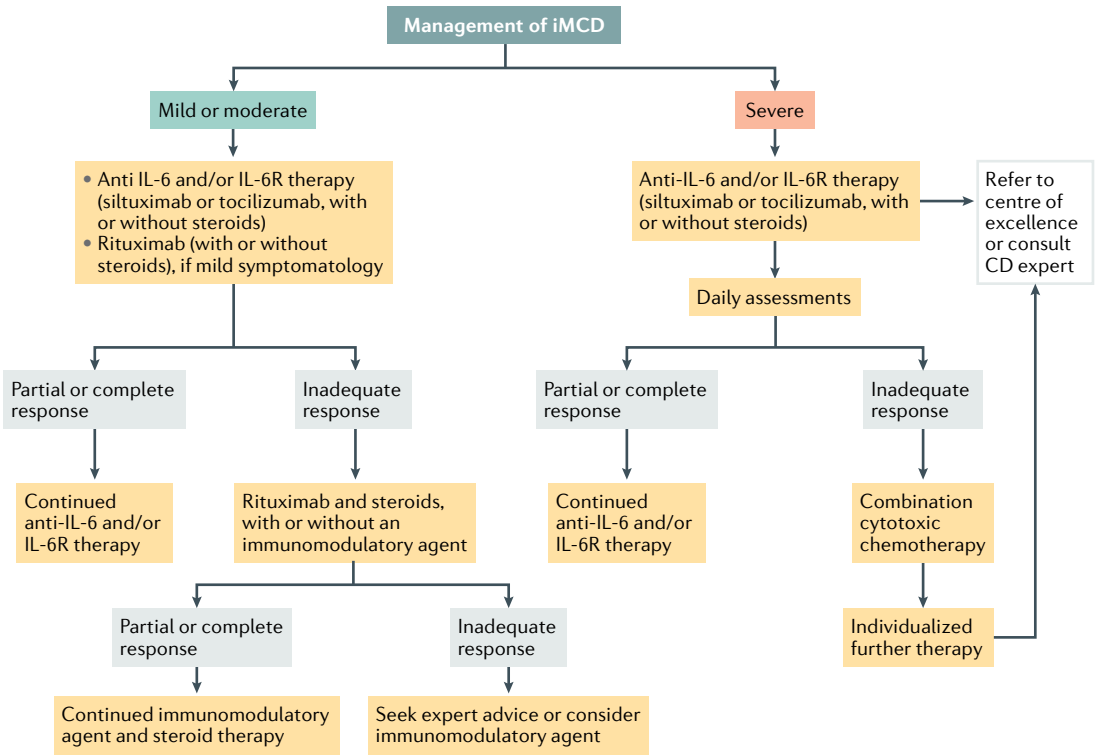

Fig. 6 | **Management of iMCD.** The figure provides an overview of the management of severe and non-severe (mild or moderate) idiopathic multicentric Castleman disease (iMCD) based on available publications[132–135]. Adapted with permission from REF.[20], Elsevier.

Box 5 | **Treatment of PEL and KSHV-positive DLBCL, NOS**

Whether or not it is preceded by Kaposi sarcoma herpesvirus (KSHV)-associated multicentric Castleman disease (MCD), the treatment of primary effusion lymphoma (PEL) in people living with HIV is not based on clinical trial evidence. Nonetheless, there is broad agreement that patients should be treated with antiretroviral therapy and combination chemotherapy with opportunistic infection prophylaxis and careful consideration of the potential pharmacological interactions[168]. The most widely advocated regimens are dose-adjusted EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone). Rituximab may be added to these regimens if the tumour cells express CD20, although this is uncommon. The prognosis is especially poor, with <50% of patients alive at 1 year[108,169,170], leading investigators to explore the roles of molecular-targeting therapies in PEL, including immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide), proteosome inhibitors (bortezomib), and monoclonal antibodies targeting CD30 (brentuximab) and CD38 (daratumumab), albeit with limited success[171].

Human herpesvirus 8 (HHV8)-positive diffuse large B cell lymphoma (DLBCL), not otherwise specified (NOS) usually comprises sheets of large plasmablastic cells that are normally positive for CD45 and CD20, express terminal B cell differentiation markers, including MUM1, and are often negative for Epstein–Barr virus (EBV) and EBV-encoded small RNAs[9,95]. Most of these lymphomas arise in the context of KSHV-MCD in PLWH. Again, there is no consensus regarding optimal treatment and the prognosis is poor[172]. Either cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate (CODOX-M)/ifosfamide, etoposide and high-dose cytarabine (IVAC) (as for Burkitt lymphoma or leukaemia) or dose-adjusted EPOCH are frequently used, whilst CHOP chemotherapy is generally considered inadequate[168].

of rituximab-based immunotherapy in addition to ART in a total of 249 patients with a 5-year OS of >90%[145–147]. Despite the high response rates and good long-term survival, relapse following rituximab-based treatment is frequent and usually salvageable with a further course of rituximab[147].

Nevertheless, other approaches have been explored, including anti-herpesvirus therapies, which have had limited success in Kaposi sarcoma, but the high levels of lytic replication in KSHV-MCD provide a rational basis for this approach. Efficacy has been reported in several small studies, although, in most cases, the responses were brief[59,114,148–150]. A combination of valganciclovir and zidovudine has been the most studied; a recent publication reported progression-free survival (PFS) at 5 years in only 26% of patients when this combination was used as first-line therapy but a more promising 87% (10 patients) 5-year PFS when it was used as maintenance therapy after rituximab-based immunochemotherapy, compared with 62% 5-year PFS (16 patients) with no maintenance therapy[8]. KSHV-encoded vIL-6 is thought to contribute to the pathogenesis of KSHV-MCD and this virokine binds to the gp80 subunit of the IL-6 receptor, the target of tocilizumab; single-agent tocilizumab has disappointingly shown only transient responses in just 5 of 8 PLWH with KSHV-MCD[151].

The risk of lymphoma in patients with KSHV-MCD is extremely high: lymphoma may affect up to one in five patients[146,152] and, in one series, it was the most frequent cause of death[147]. In many cases, the lymphomas were positive for KSHV and most frequently were classified as PEL and plasmablastic lymphoma (HHV8-positive diffuse large B cell lymphoma, NOS in the current 2016 WHO classification), both associated with very poor prognosis (BOX 5). Similarly, Kaposi sarcoma frequently occurs in KSHV-MCD and the diagnosis of Kaposi sarcoma may be made before, at the same time or after the diagnosis of KSHV-MCD. Rituximab monotherapy may exacerbate or expose Kaposi sarcoma[144,153] and this reaction is why pegylated liposomal doxorubicin is added to rituximab if there is concurrent Kaposi sarcoma.

KSHV inflammatory cytokine syndrome. KICS is characterized by the clinical symptoms of KSHV-MCD in association with markedly elevated inflammatory biomarkers and high blood levels of KSHV but without the lymphadenopathy and hepatosplenomegaly seen in KSHV-MCD[107]. The optimal treatment of this novel syndrome is unclear, but the majority of patients have been treated in the same way as individuals with KSHV-MCD[154]. The syndrome has been successfully treated in some cases with immunomodulatory therapy[154].

Quality of life

CD can have profound effects on the life of patients (BOX 6). However, patients with this disease can have a broad range of experiences, principally mediated by disease subtype, which determines symptomatology, clinical course, treatments and risk of death. Patients with UCD are often asymptomatic at diagnosis or present with compressive symptoms, whereas those with subtypes of MCD (iMCD-NOS, iMCD-TAFRO, POEMS-MCD and KSHV-MCD) present with varying degrees of systemic symptoms, such as fever, sweats, weight loss, malaise, effusions and organ dysfunction. Few quality of life studies in patients with CD exist to effectively capture the disease effects across these subtypes, likely owing to the rarity of the disease. However, several inferences can be made from the existing data[15].

UCD typically has a relatively benign clinical course compared with MCD[15]. In a systematic review that included 278 patients with UCD, 262 of whom underwent surgical resection, the 10-year disease-free survival was 95.3%[155]. As the gold standard of treatment for UCD, surgical resection is straightforward and almost always curative. Occasionally, patients report debilitating symptoms, such as persisting pain, fatigue and lethargy, at presentation and after complete surgical excision[5]. Anecdotally, these patients have a substantial decline in quality of life even when all laboratory and imaging studies show no evidence of disease (R.K.J., unpublished work). The cause of these symptoms may include low-grade inflammation, cytokine dysregulation or psychological aspects that are not yet apparent; patients should be evaluated to ensure that an alternative diagnosis was not missed (R.K.J., unpublished work).

Patients with MCD experience more severe symptoms, laboratory abnormalities and treatment-related adverse effects than those with UCD; patients with iMCD-TAFRO tend to experience the most severe symptoms. Additional comorbid diseases can also be seen in MCD, such as HIV infection or Kaposi sarcoma in KSHV-MCD or progressive motor neuropathy in POEMS-MCD. Furthermore, therapies for MCD are often intense and prolonged with some patients requiring lifelong maintenance therapy[5,20,156]. Many of the common treatments that include corticosteroids,

Box 6 | **Living with Castleman disease**

Male patient with idiopathic multicentric Castleman disease (iMCD)-TAFRO
I was a very healthy, active guy for a long time and 27 years a carpenter, when iMCD knocked me down in just a few days to the point of struggling for my life on a ventilator and feeding tube in the intensive care unit, with every major organ in my body failing. The fight from that hospital room back to a life in which I can laugh and enjoy, as I do today, has been the hardest I have ever known.

Mother of a paediatric patient with unicentric Castleman disease (UCD)
K. has been battling unresectable UCD since she was 18 months old. At the time of K.'s diagnosis, there were no clear answers to many questions and not much in-depth data or research available, making finding a solution very difficult. K. has struggled for the past 5 ½ years with night sweats, fatigue, headaches, tummy aches and a lack of appetite. She has endured countless hospital stays and different forms of treatments, including multiple surgeries. Eventually, she responded to cytoxan (cyclophosphamide), and it helped alleviate her symptoms. Unfortunately, we had to stop the treatment after 18 months, when she developed haemorrhagic cystitis. The thought of having no other options was terrifying. Struggling to figure out the next steps was one of the most difficult times in our life. Today, she is on an experimental treatment (sirolimus), which has dramatically improved her quality of life and given her some of her childhood back.

Mother of a paediatric patient with iMCD–not otherwise specified
Over the past 2 years, D. has undergone a lymph node biopsy, several CT and PET scans, endless blood tests, bone marrow biopsy, several chemotherapy and immunosuppressive therapy treatments, and he is currently being treated with CHOP chemotherapy. He continues to struggle daily, but keeps on smiling!

Mother of a patient with UCD
E. was a 13-year-old vibrant, beautiful girl that embodied strength and life. She was diagnosed with UCD and later developed paraneoplastic pemphigus, an extremely rare and severe complication. E.'s whole family struggled with her diagnosis. We were told it was 'benign', rare and that surgery should be a cure. CD already had such a grip on E. that they were not able to beat the disease. E. lost the battle for her life in February, 2014. Our family continues to work together with others through the Castleman Disease Collaborative Network in our daughter's memory to find a cure for CD, so that no other family has to endure such a devastating loss.

Female patient with iMCD–not otherwise specified
I battle iMCD. I was told in 2013 I would not live to see the age of 35. I have had 14 major surgeries in 3 years to remove lymph nodes. I work a full time job and go to chemotherapy at night, right after work. This has been one of the biggest challenges of my life. My body is riddled with disease and I have pain every day, but I push through anyway. My three kids saved my life. Without them, I would have given up. But because I'm all they have, I decided that day I was diagnosed that I was going to fight this.

chemotherapy and thalidomide have substantial adverse effects. New anti-IL-6 therapies for iMCD have proven to be more effective with fewer adverse effects, but we are aware of anecdotal reports of patients describing psychological challenges associated with being on lifelong therapy (R.K.J., unpublished work). In our experience, the enhancement in quality of life associated with improved symptoms and organ function tends to outweigh the burden of continued therapy for these patients. The advent of rituximab as well as ART for comorbid HIV infection has changed KSHV-MCD from an almost uniformly fatal condition to a disease with >90% 5-year OS[147]. For iMCD, traditional treatments have previously achieved a 5-year OS of ~65% as of 2012, whereas subsequent data suggest an ~75% 5-year OS with newer therapies[17,36,147]. Among patients who respond to siltuximab, a sub-analysis suggests a substantially increased 5-year OS of >95% with few serious adverse effects[156]. In addition to inducing remission, multiple clinical trials, including one with a validated patient-reported outcome (PRO) instrument, have shown that siltuximab is efficacious in alleviating symptoms such as fatigue and pain[156,157]. Quality-adjusted life-years also increased in patients who receive this treatment[158].

More research is needed into the quality of life of patients with CD. Based on data from other rare diseases, patients also likely suffer from unmet clinical needs owing to delays in diagnosis, misdiagnosis, difficulty accessing CD specialists, sparse treatments options, considerable financial burdens and social isolation (R.K.J., unpublished work). Data collection and statistical analysis issues related to the small sample sizes and heterogeneous study population likely also contribute to the shortage of quality of life and PRO data in CD[159]. The only known validated PRO tool for CD, the MCD-Symptom Scale (MCD-SS), was developed in 2014 to quantify iMCD symptoms and responses to therapy and has been used once in the siltuximab clinical trial[157,160].

ACCELERATE (NCT02817997), an international, observational registry for patients with CD, aims to improve understanding of the natural history and burden of CD[161]. In addition to obtaining real-world demographic, clinical, laboratory and treatment data to enhance our understanding of CD, it is currently gathering PROs from ~500 patients worldwide in its first 5 years to strengthen our understanding of the disease's impact on patients[53]. Through continued patient enrolment into ACCELERATE, use of the MCD-SS, and the development and use of additional PRO instruments, we can expect to see improved patient satisfaction, symptom management, quality of life and survival rates in CD[159].

Outlook

Pathogenesis

Many unresolved issues and unanswered questions in the pathophysiology and therapy of CD remain. Benjamin Castleman described the hyaline vascular unicentric variety of CD, but the full spectrum of CD may not have a unifying pathogenic basis. Numerous different processes seem likely to account for the different subsets of CD, which remains an area of active research seeking potential mechanistic explanations.

In UCD, somatic mutation of *PDGFB* in $CD45^-$ stromal cells has been detected in nearly 20% of studied patients[39]. This gain-of-function mutation in the kinase domain could contribute to the observed clonal expansion of stromal follicular dendritic cells[38]. Germline mutations in the same domain of this gene are associated with Penttinen premature ageing syndrome and infantile myofibromatosis[162]. Penttinen premature ageing syndrome is characterized by lipoatrophy, skin atrophy, thin hair, proptosis and acro-osteolysis. Infantile myofibromatosis is the development during childhood of multiple myofibromas in any organ of the body but without local invasion or metastasis. Although neither syndrome resembles UCD, functional analysis of the mutant PDGFRB suggests similar constitutive activation of downstream signalling pathways. This observation may provide clues into the pathophysiology of UCD, but the molecular basis of most cases of UCD

remains obscure and the relationship between UCD and Penttinen syndrome is not widely accepted.

The pathogenesis of MCD is even less clear and numerous hypotheses have been proposed. A virus-driven response is the clear aetiology in KSHV-MCD, so other potential infectious pathogens have been sought to account for KSHV-negative MCD. However, RNA-hybrid, deep sequencing and bioinformatics virome capture sequencing failed to identify novel pathogens in iMCD or UCD[40]. The central role of IL-6 in iMCD is supported by the success of IL-6-blocking monoclonal antibodies in controlling disease signs and symptoms as well as from transgenic animal models[163,164]. However, a wide array of cytokines seems to be elevated in iMCD[54,110] and ~50% of patients with iMCD do not respond to IL-6 blockade and some patients with iMCD flares do not have elevated levels of IL-6. Thus, it is clear that IL-6 is a causative driver in some patients with iMCD but not in all. Uncovering the disease driver in patients with anti-IL-6 refractory iMCD is one of the most important goals of research in CD.

Similarly, the roles of vIL-6 and hIL-6 in the pathogenesis of KSHV-MCD are not fully clear. Murine transgenic models suggest that overexpression of either murine IL-6 or vIL-6 produce an MCD-like syndrome[163,164]. However, if the murine IL-6 is knocked out, the vIL-6 transgene alone cannot induce this syndrome.

The links between CD and several other, rather disparate illnesses (such as AA amyloidosis, paraneoplastic pemphigoid, bronchiolitis obliterans and malignancies, such as follicular dendritic cell sarcoma and POEMS) remain to be explored and could elucidate the pathogenic mechanisms of both CD and the linked disease.

Diagnostics

The histopathological diagnosis of KSHV-MCD became relatively straightforward following the introduction of immunohistochemical staining for LANA1 and the recognition that the plasmablasts in this subtype are IgMλ restricted. By contrast, the histopathological diagnosis of iMCD remains more subjective, although the establishment of diagnostic criteria has mitigated this limitation[104]. Nevertheless, a diagnostic cytokine signature in plasma that could rapidly confirm the diagnosis and identify iMCD flares would be a welcome advance for clinicians often faced with an extremely sick patient. Furthermore, in Japan, a substantial number of patients meet the criteria for TAFRO who either do not have lymphadenopathy that could undergo biopsy, have lymph nodes that do not demonstrate iMCD-like features, or have other co-occurring diseases. An international definition for iMCD-TAFRO has been published in 2021 (REF.[165]), but it remains important to further determine the differences in aetiology, treatment and prognosis between patients with iMCD-TAFRO and those with TAFRO without histopathological evidence of iMCD.

Therapy

The curative role of surgery in UCD was originally suggested by Benjamin Castleman himself and the introduction of rituximab in the management of KSHV-MCD in the early 2000s dramatically improved the outcome of patients with this disease subtype. However, even though IL-6-directed monoclonal antibodies have benefited some patients with iMCD, most do not achieve durable remission and new treatments for iMCD are required. Intracellular signalling pathways have been suggested as suitable therapeutic targets, focusing on the three main pathways associated with IL-6: JAK–STAT3 pathway, MAPK pathway and PI3K–mTOR pathway. Some reports advocate using agents targeting these pathways, such as bortezomib and sirolimus, in iMCD, and high-quality clinical trials are urgently required, recalling that about two-thirds of patients with iMCD do not achieve remission with anti-IL-6 monoclonal antibodies. The establishment of both diagnostic and response criteria should make trial design more straightforward[20].

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