

Idiopathic multicentric Castleman's disease: a systematic literature review



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Summary

Background Multicentric Castleman's disease describes a group of poorly understood lymphoproliferative disorders driven by proinflammatory hypercytokinaemia. Patients have heterogeneous clinical features, characteristic lymph node histopathology, and often deadly multiple organ dysfunction. Human herpesvirus 8 (HHV8) causes multicentric Castleman's disease in immunosuppressed patients. The cause of HHV8-negative multicentric Castleman's disease is idiopathic; such cases are called idiopathic multicentric Castleman's disease. An absence of centralised information about idiopathic multicentric Castleman's disease represents a major challenge for clinicians and researchers. We aimed to characterise clinical features of, treatments for, and outcomes of idiopathic multicentric Castleman's disease.

Methods We did a systematic literature review and searched PubMed, the Cochrane database, and ClinicalTrials.gov from January, 1995, with keywords including "Castleman's disease" and "giant lymph node hyperplasia". Inclusion criteria were pathology-confirmed Castleman's disease in multiple nodes and minimum clinical and treatment information on individual patients. Patients with HHV8 or HIV infection or diseases known to cause Castleman-like histopathology were excluded.

Findings Our search identified 626 (33%) patients with HHV8-negative multicentric Castleman's disease from 1923 cases of multicentric Castleman's disease. 128 patients with idiopathic multicentric Castleman's disease met all inclusion criteria for the systematic review. Furthermore, aggregated data for 127 patients with idiopathic multicentric Castleman's disease were presented from clinical trials, which were excluded from primary analyses because patient-level data were not available. Clinical features of idiopathic multicentric Castleman's disease included multicentric lymphadenopathy (128/128), anaemia (79/91), elevated C-reactive protein (65/79), hypergammaglobulinaemia (63/82), hypoalbuminaemia (57/63), elevated interleukin 6 (57/63), hepatomegaly or splenomegaly (52/67), fever (33/64), oedema, ascites, anasarca, or a combination (29/37), elevated soluble interleukin 2 receptor (20/21), and elevated VEGF (16/20). First-line treatments for idiopathic multicentric Castleman's disease included corticosteroids (47/128 [37%]), cytotoxic chemotherapy (47/128 [37%]), and anti-interleukin 6 therapy (11/128 [9%]). 49 (42%) of 116 patients failed first-line therapy, 2-year survival was 88% (95% CI 81–95; 114 total patients, 12 events, 36 censored), and 27 (22%) of 121 patients died by the end of their observed follow-up (median 29 months [IQR 12–50]). 24 (19%) of 128 patients with idiopathic multicentric Castleman's disease had a diagnosis of a separate malignant disease, significantly higher than the frequency expected in age-matched controls (6%).

Interpretation Our systematic review provides comprehensive information about clinical features, treatment, and outcomes of idiopathic multicentric Castleman's disease, which accounts for at least 33% of all cases of multicentric Castleman's disease. Our findings will assist with prompt recognition, diagnostic criteria development, and effective management of the disease.

Funding None.

Introduction

Castleman's disease was first described in case reports published in the 1950s.^{1,2} The initial report featured a constellation of histological findings in one region of lymph nodes; case reports describing more than one affected region of lymph nodes were published in the 1970s.³ The observation that Castleman's disease can arise in more than one region gave rise to the first major distinction in the classification of the disease: unicentric versus multicentric. Unicentric Castleman's disease has been treated by surgical lymph node excision, which is curative for most patients.^{4,5} By contrast, systemic treatment is needed to control multicentric Castleman's disease effectively.

A sharp increase in reported cases of multicentric Castleman's disease emerged in the 1980s, when the disease was noted in immunocompromised patients with HIV-1 infection.^{6–9} In these patients, the disease was frequently associated with Kaposi's sarcoma,¹⁰ leading to the discovery that human herpesvirus 8 (HHV8)—also known as Kaposi's sarcoma herpesvirus—caused multicentric Castleman's disease in this subgroup.^{11,12} Replication of HHV8 in germinal centre lymph node plasmablasts expresses viral interleukin 6, human interleukin 6, and several other proinflammatory proteins, which cause the characteristic histopathological changes noted in patients with multicentric Castleman's

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Research in context

Evidence before this study

Before undertaking this study, we were aware of no attempts in published medical literature to characterise idiopathic multicentric Castleman's disease systematically. Although case reports, case series, and clinical trials in idiopathic multicentric Castleman's disease have been published, analysis of these data in aggregate has not been described for clinical features, treatment responses, outcomes, or associations with cancer. We searched PubMed and the Cochrane database between January, 1995, and May, 2013, with the terms: "castleman", "Castleman's", "angiofollicular hyperplasia", "giant lymph node hyperplasia", "lymph node hamartoma", "follicular lymphoreticuloma", "benign giant lymphoma", "angiomas lymphoid hamartoma", "angiofollicular mediastinal lymph node hyperplasia", "angioimmunoblastic lymphadenopathy with dysproteinemia", "benign giant lymphoma", or "idiopathic plasmacytic lymphadenopathy with polyclonal hypergammaglobulinemia". We retrieved reports published in English and references from relevant reports of all published cases of multicentric Castleman's disease. We searched ClinicalTrials.gov with the terms "Castleman disease" or "Castleman's disease". A smaller set of terms was used for ClinicalTrials.gov because the number of characters in a search field is restricted. We included cases from reports published in English that contained: pathology-confirmed Castleman's disease in multiple nodes; negative testing for HHV8; and minimum clinical and treatment information on individual patients. Reports were excluded if they referred to: unicentric Castleman's disease, presence of only one mass, or complete

remission after surgical resection of one mass, or a combination of these; positive testing for HIV or HHV8; or diagnosis of another disease that could account for the Castleman-like histopathological features—eg, systemic lupus erythematosus or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin abnormalities). 2184 eligible reports were retrieved for review.

Added value of this study

Our study is, to our knowledge, the first and largest systematic characterisation of the clinical features, associated diseases, treatment responses, and outcomes of HHV8-negative idiopathic multicentric Castleman's disease. This information is important because it provides an evidence base with which to establish diagnostic criteria, inform clinical decisions, and focus research efforts. Our review showed that effectiveness of first-line treatment was highly variable across treatment regimens, the disease is deadly, and associated malignant diseases are common.

Implications of all the available evidence

Patients with idiopathic multicentric Castleman's disease should be monitored closely to assess their response to treatment, identify the earliest signs of disease activity, and detect development of malignant diseases. Translational research studies are needed urgently to elucidate the pathophysiology of idiopathic multicentric Castleman's disease and identify novel treatment options for patients who do not respond to anti-interleukin 6 therapy.

disease and lead to multiple organ dysfunction.^{13,14} The pathological role of HHV8—irrespective of HIV infection—has prompted a reclassification of Castleman's disease based on HHV8 status.^{15,16}

A subset of patients show histopathological changes characteristic of multicentric Castleman's disease and clinical features overlapping with HHV8-associated multicentric Castleman's disease but do not have HIV or HHV8 infection.¹⁷ In these cases of so-called idiopathic multicentric Castleman's disease, a hypercytokinaemic proinflammatory state arises similar to that seen in patients with HHV8-associated multicentric Castleman's disease, but the cause and pathogenesis are unknown. Compared with HHV8-associated multicentric Castleman's disease, idiopathic multicentric Castleman's disease is more difficult to diagnose, can have unique clinical features, and responds to different treatments.¹⁸ The previous idea that multicentric Castleman's disease is driven by benign, interleukin 6-secreting lymph node tumours has shifted: the new model of pathogenesis suggests that enlarged lymph nodes and their characteristic histological features are reactive changes to hypercytokinaemia, often including interleukin 6. Current hypotheses for the cause of idiopathic

multicentric Castleman's disease include pathological autoantibodies or germline mutations in genes that regulate the innate immune system (autoimmune/autoinflammatory hypothesis), a small population of malignant cells (paraneoplastic hypothesis), or an undiscovered virus other than HHV8 (viral hypothesis).¹⁶

Scant data exist regarding the epidemiology of idiopathic multicentric Castleman's disease. In a study of the epidemiology of multicentric Castleman's disease,¹⁹ researchers used an insurance claims database and estimated that 6500–7700 new cases of Castleman's disease are diagnosed every year in the USA, with about 1650 cases of multicentric disease. HHV8 status was not specified.¹⁹ Published medical research rarely acknowledges the HHV8-negative subgroup of multicentric Castleman's disease.²⁰

Idiopathic multicentric Castleman's disease is diagnosed clinicopathologically,²¹ yet no official criteria exist for its diagnosis, and symptoms are poorly defined. Typically, idiopathic multicentric Castleman's disease is diagnosed when characteristic Castleman-like lymph node histopathological features are recorded, HHV8 testing is negative, and other well defined diseases that are known to cause these histopathological features are

excluded. Commonly reported clinical features are fever, night sweats, weight loss, lymphadenopathy, ascites, pleural effusions, and hepatosplenomegaly. A subset of patients with idiopathic multicentric Castleman's disease has emerged in the past few years with a syndrome known as TAFRO, characterised by thrombocytopenia, ascites, fever, reticulin fibrosis in bone marrow, organomegaly, and normal amounts of γ -globulin. First described in Japan in 2010,²² TAFRO has gained recognition, with more than 35 cases reported in Japan,^{23–25} Europe,^{26,27} and the USA.²⁸

The four commonly recognised histopathological variants of Castleman's disease are hyaline vascular, plasma cell, mixed pathology, and plasmablastic. Plasmablastic lymph node changes are connected exclusively with HHV8-associated multicentric Castleman's disease and will not be discussed further here. Hyaline vascular lymph node changes are characterised by hyalinised vessels that penetrate small, atrophic, germinal centres. Around these germinal centres are concentric rings of

small lymphocytes that comprise a widened mantle zone. Plasma cell and mixed pathology variants are characterised by hyperplastic germinal centres and a proliferation of plasma cells in interfollicular regions, and some hyaline vascular features.

Various treatments have been used for patients with idiopathic multicentric Castleman's disease (panel). Corticosteroids, immunomodulatory or immunosuppressive agents, and cytotoxic chemotherapy have served historically as the mainstay of treatment, borrowing from regimens in lymphoma and multiple myeloma. More recently, biological anti-interleukin 6 treatments have been developed. Siltuximab, which targets interleukin 6 directly, has been approved for idiopathic multicentric Castleman's disease in the USA, Canada, and Europe, after findings of a double-blind, placebo-controlled, phase 2 trial showing significantly higher durable tumour response (lymph node regression) and symptomatic response (2% complete response and 32% partial response) compared with

Panel: Drugs used for treatment of idiopathic multicentric Castleman's disease

Corticosteroids (off-label)

Corticosteroids are broad-spectrum immunosuppressive drugs that treat both acute and chronic inflammation. They decrease transcription of proinflammatory cytokines and chemokines, adhesion molecules, and key enzymes in the inflammatory process—eg, interleukin 2, interleukin 6, and tumour necrosis factor α (TNF α). They are used commonly as first-line treatment for idiopathic multicentric Castleman's disease; however, patients usually relapse, and corticosteroids are frequently used in conjunction with other drugs for idiopathic multicentric Castleman's disease.

Immunomodulatory agents (off-label)

Bortezomib

Bortezomib is a selective proteasome inhibitor that preferentially targets plasma cells and has been shown to lower the amount of interleukin 6 and induce remission in four patients with idiopathic multicentric Castleman's disease. Another mechanism of action in idiopathic multicentric Castleman's disease might be via direct inhibition of NF κ B by degradation of I κ B kinase.

Anakinra (anti-interleukin 1)

Anakinra is an interleukin 1 receptor antagonist. It has been reported to induce remission in a paediatric case of idiopathic multicentric Castleman's disease and in a patient who did not respond to anti-interleukin 6 treatment.

Thalidomide

Thalidomide is an immunomodulator that inhibits TNF α , interleukins 1, 6, and 12, and VEGF. Moreover, it stimulates T cells (potentially via cereblon inhibition), has shown effectiveness at inducing remission, decreases amounts of interleukin 6, and lowers C-reactive protein in patients with idiopathic multicentric Castleman's disease.

Anti-interleukin 6 treatment (approved)

Siltuximab

Siltuximab is a human-murine chimeric monoclonal antibody that binds with high affinity to interleukin 6. It is the only approved treatment for multicentric Castleman's disease in North America and Europe.

Tocilizumab

Tocilizumab is a humanised interleukin-6 receptor antagonist that is capable of almost completely blocking transmembrane signalling of interleukin 6. It reduces inflammation related to the interleukin 6 signalling cascade. Tocilizumab is currently approved for treatment of multicentric Castleman's disease in Japan and rheumatoid arthritis worldwide.

Anti-CD20 treatment (off-label)

Rituximab

Rituximab is a chimeric monoclonal antibody that binds to CD20—a transmembrane protein present on nearly all B cells. It is currently approved for treatment of non-Hodgkin lymphoma.

Cytotoxic chemotherapy (off-label)

Cyclophosphamide

Cyclophosphamide is an alkylating agent used for the treatment of many cancers. It acts as a potent immunosuppressant, crosslinking DNA by adding an alkyl group to the guanine base of DNA. This mechanism suppresses DNA replication and leads to cell death.

Doxorubicin

Doxorubicin is a cytotoxic anthracycline extracted from *Streptomyces peucetius* var *caesius* that is frequently used in the treatment of many types of cancer. Two mechanisms of action have been suggested for cell death: first, disruption of topoisomerase II-mediated DNA repair; and second, generation of free radicals that damage cellular membranes.

placebo (0%; $p=0.0012$).²⁹ Tocilizumab, which targets the interleukin 6 receptor, was approved in Japan in 2005 and has been used off-label around the world for idiopathic multicentric Castleman's disease. In an open-label prospective study of 28 patients on tocilizumab, ten (43%) of 23 patients with enlarged lymph nodes at baseline saw a decrease in size below 10 mm after 16 weeks.^{30–32}

The presence of clinical and histological features helps to distinguish idiopathic multicentric Castleman's disease from other similar disorders, but an understanding of the frequency of these features is needed to aid accurate characterisation and identification of cases of this disease. Furthermore, an absence of aggregated clinical information and scant understanding of the cause of idiopathic multicentric Castleman's disease has

made treatment and management decisions challenging. The sparseness of data on idiopathic multicentric Castleman's disease is an impediment to the delivery of timely and optimum care. We aimed to do the most comprehensive review to date of published medical literature about idiopathic multicentric Castleman's disease, to summarise diagnostic features, prognosis, and treatment modalities associated with this rare and fatal disease.

Methods

Search strategy and selection criteria

We did a systematic literature review of clinical features, associated diseases, treatment regimens, and outcomes of idiopathic multicentric Castleman's disease. We identified cases for this review by searching PubMed and the Cochrane database between January, 1995, and May, 2013, with the terms "castleman", "Castleman's", "angiofollicular hyperplasia", "giant lymph node hyperplasia", "lymph node hamartoma", "follicular lymphoreticuloma", "benign giant lymphoma", "angiomatous lymphoid hamartoma", "angiofollicular mediastinal lymph node hyperplasia", "angioimmunoblastic lymphadenopathy with dysproteinemia", "benign giant lymphoma", and "idiopathic plasmacytic lymphadenopathy with polyclonal hypergammaglobulinemia", for reports published in English. We chose 1995 as the initial year for our query because that was when HHV8 testing was introduced for multicentric Castleman's disease.¹⁰ We also searched ClinicalTrials.gov between January, 1995, and December, 2015, with the terms "Castleman disease" or "Castleman's disease". Further, we did a manual search of the reference lists of retrieved articles for relevant additional cases. We excluded duplicate publications; in such instances, we used the report containing the most comprehensive information. Three independent investigators confirmed these inclusion criteria.

We selected cases of HHV8-negative multicentric Castleman's disease. Methods used to report HHV8-negative status included lymph node immunohistochemistry for HHV8 latency-associated nuclear antigen (LANA1), PCR of blood and lymph nodes for HHV8 viral DNA, serological analysis for HHV8, and PCR of non-lymph node lymphoid tissue (appendix p 1). We excluded reports for several reasons: first, if information clearly suggested unicentric Castleman's disease, only one mass was noted, or complete remission occurred after surgical resection of one mass; second, if a positive test was obtained for HIV-1 or HHV8 infection (appendix p 1); and third, if another disease could be diagnosed that could account for the Castleman-like histopathological features—eg, systemic lupus erythematosus or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin abnormalities). POEMS syndrome has been frequently associated with the lymph node features of

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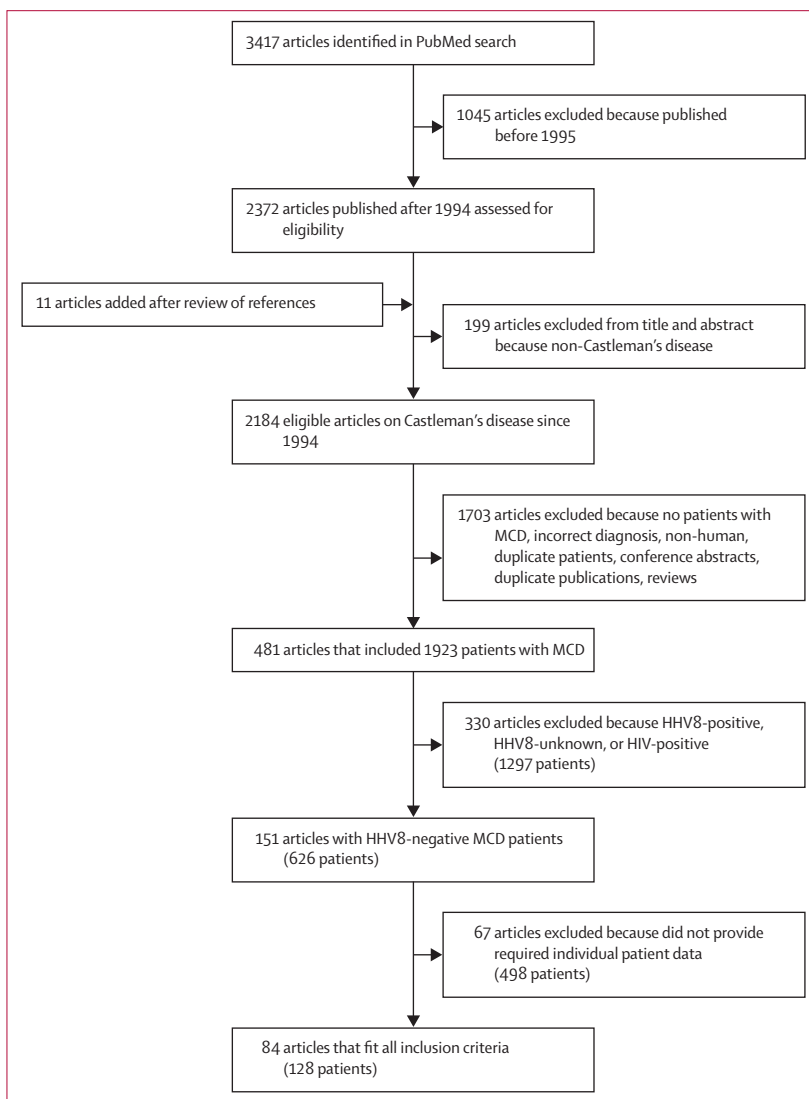


Figure 1: Search strategy and article selection

MCD=multicentric Castleman's disease. HHV8=human herpesvirus 8.

Castleman's disease, but it is unclear whether these Castleman-like features are reactive to POEMS hypercytokinaemia or truly an associated disease.^{33–35} We chose to exclude from our review patients with idiopathic multicentric Castleman's disease and POEMS syndrome because monoclonal plasma cells are known to cause lymphoproliferation and hypercytokinaemia and, thus, the disease is not idiopathic. We included patients with serological abnormalities associated with rheumatological conditions that did not meet criteria for a rheumatological diagnosis.

We excluded studies if clinical, laboratory, and treatment response information was not provided for individual patients. For this reason, we excluded clinical trial data from the primary analysis, but aggregated data for all patients in clinical trials are reported, to allow for comparison. Data for specific variables were not available for all patients. If contact information was available, we contacted authors of case reports and trials to gather additional data and extend the time of follow-up. We judged data missing if they were not available, and we excluded these cases when we calculated summary statistics.

Our primary aims were to record the frequency of clinicopathological features of idiopathic multicentric Castleman's disease; to record associated diseases; to inventory treatment regimens and assess response, including treatment failure, time to treatment failure, and 2-year survival; and to analyse outcomes of patients with idiopathic multicentric Castleman's disease.

Statistical analysis

We calculated summary statistics for different patients' characteristics by tabulation and percentages. We assessed a treatment's effectiveness by the patient's response (ie, no response, partial response, and complete response; appendix pp 4, 5), if treatment failure occurred (ie, relapse, death, or additional treatment needed), the time to treatment failure, and 2-year survival. We calculated survival outcomes based on the time from diagnosis to death or loss to follow-up, using the Kaplan-Meier method, and we compared survival curves at specific times with the log-rank test for survival data up to that point in time. We based hazard ratios (HRs) and CIs on unconditional Cox proportional hazards models, and we censored data artificially at 24 months to ensure comparability with 2-year survival data. We calculated p values with the log-rank test. In view of the exploratory nature of our study, we did not adjust for multiple comparisons. We did all analyses in R, version 3.1.1.

Role of the funding source

No funding was received for this study. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows how we applied our inclusion and exclusion criteria. Our systematic review of work published since 1995 identified 1923 patients with multicentric Castleman's disease. 808 (42%) patients were HHV8-positive, HIV-positive, or both; 489 (25%) were HIV-negative and had unknown HHV8 status; and 626 (33%) patients were HHV8-negative. Thus, HHV8-negative multicentric Castleman's disease accounted for at least a third of all published cases of multicentric Castleman's disease.

	Case reports (n=128)		Clinical trials (n=127)*
	Prevalence†	Minimum possible prevalence‡	
Histological subtype			
Hyaline vascular	23/107 (21%)	23/128 (18%)	35/127 (28%)
Plasmacytic	42/107 (39%)	42/128 (33%)	56/127 (44%)
Mixed	42/107 (39%)	42/128 (33%)	36/127 (28%)
Not reported	21	21/128 (16%)	0
Clinical features			
Fever	33/64 (52%)	33/128 (26%)	NR
Night sweats	13/21 (62%)	13/128 (10%)	41/79 (52%)
Weight loss	21/29 (72%)	21/128 (16%)	24/79 (30%)
Oedema, ascites, or anasarca	29/37 (78%)	29/128 (23%)	27/10 (27%)
Pleural effusions	29/39 (74%)	29/128 (23%)	NR
Lymphadenopathy	128/128 (100%)	128/128 (100%)	127/127 (100%)
Enlarged liver, enlarged spleen, or both	52/67 (78%)	52/128 (41%)	16/48 (33%)
Biochemical features			
Elevated erythrocyte sedimentation rate (>30 mm/h)	44/48 (92%)	44/128 (34%)	NR
Low haemoglobin (<115 g/L)	79/91 (87%)	79/128 (62%)	79/127 (62%)
Thrombocytosis (>500 × 10 ⁹ platelets per L)	16/63 (25%)	16/128 (13%)	NR
Thrombocytopenia (<150 × 10 ⁹ platelets per L)	28/63 (44%)	28/128 (22%)	NR
Hypergammaglobulinaemia (>17 000 g/L)	63/82 (77%)	63/128 (49%)	25/26 (96%)
Hypoalbuminaemia (<35 g/L)	57/63 (90%)	57/128 (45%)	24/26 (92%)
Renal dysfunction (creatinine >106 µmol/L or blood urea nitrogen >7.14 mmol/L)	12/17 (71%)	12/128 (9%)	NR
Positive Coombs test	12/17 (71%)	12/128 (9%)	16/26 (62%)
Positive ANA (>1:40)	15/41 (37%)	15/128 (12%)	17/26 (65%)
Elevated C-reactive protein	65/79 (82%)	65/128 (51%)	26/26 (100%)
Elevated interleukin 6	57/63 (90%)	57/128 (45%)	26/26 (100%)
Elevated soluble interleukin 2 receptor	20/21 (95%)	20/128 (16%)	NR
Elevated VEGF (>100 ng/L)	16/20 (80%)	16/128 (13%)	NR
Elevated tumour necrosis factor α	1/2 (50%)	1/128 (1%)	NR

NR=not reported. *Data are reported for 127 cases from clinical trials in this table and 139 cases in table 2, because an interim analysis of a phase 1 trial was done that included descriptive statistics on 22 of 34 patients with idiopathic multicentric Castleman's disease;³⁶ however, descriptive statistics were not provided for the full cohort,^{37,38} so data are unavailable for 12 patients. †Prevalence is the number of positive cases divided by the number reporting that feature.

‡To account for negative reporting bias, minimum possible prevalence was calculated from positive cases divided by the total number of patients.

Table 1: Main histological subtype and clinical and biochemical features of 128 patients from case reports with idiopathic multicentric Castleman's disease and 127 patients from clinical trials

128 patients with idiopathic multicentric Castleman's disease met all inclusion criteria (table 1); the case reports from which these patients were identified are listed in the

appendix (pp 6–9). Furthermore, 139 patients were identified from three clinical trials of idiopathic multicentric Castleman's disease (table 2).^{29,30,36–38} However,

	Study type	Drug	Patients (n)	Subtype (n)	Histological variant (n)	Previous and concomitant treatments	Study duration	Dose	Control	Clinical response	Adverse events reported in ≥15% of patients
Nishimoto et al (2005) ³⁰	Open-label trial	Tocilizumab	28	Idiopathic MCD (26); HHV8-associated MCD (2)	Plasma cell (28)	Any previous treatment allowed except for radiation therapy or surgery within 4 weeks of entry and immunosuppressants or chemotherapy within 6 weeks of enrolment; 15 patients received concomitant corticosteroids	112 days plus open-label extension study	8 mg/kg every 2 weeks	None	Systematic response not reported; decrease in size of lymph node <10 mm (43%); C-reactive protein returned to normal (64%); fibrinogen returned to normal (71%)	Common cold (57%); pruritus (21%); malaise (21%); pharyngitis (18%); diarrhoea (18%); rash (18%); eczema (18%); low-grade fever (18%)
Kurzrock et al (2013) ^{37,38}	Phase 1, open-label trial	Siltuximab	37	Idiopathic MCD (34), unicentric Castleman's disease (2), HHV8-associated MCD (1)	Plasma cell (17), hyaline vascular (18), mixed pathology (2)	Any previous treatment allowed except for solid-organ, allogeneic bone marrow, or peripheral-blood stem-cell transplantation and murine or human-murine recombinant products or monoclonal antibodies other than rituximab; investigational drugs had to be discontinued more than 30 days or five half-lives before receiving siltuximab	43 days plus option to continue treatment at investigators' discretion	3 mg/kg, 6 mg/kg, or 12 mg/kg every 2 weeks; 6 mg/kg every week; 9 mg/kg or 12 mg/kg every 3 weeks	None	Response on radiological review: CR 3%, PR 39%, SD 56%, PD 3%; clinical benefit response* 86%	Hypertriglyceridaemia (24%); hypercholesterolaemia (21%)
van Rhee et al (2015) ³⁶	Phase 2, open-label, extension study	Siltuximab	19	Idiopathic MCD (19)†	Plasma cell (9), hyaline vascular (10)	Extension study of Kurzrock et al (2013) ^{37,38}	Ongoing (median 5.1 years, up to 7.2 years)	11 mg/kg every 3 weeks	None	All 19 patients alive with sustained disease control (SD or better) by investigator assessment	URTI (63%); diarrhoea (32%); fatigue (21%); arthralgia (21%); pain in extremities (21%)
van Rhee et al (2014) ³⁹	Phase 2, randomised, double-blind, placebo-controlled trial	Siltuximab	79	Idiopathic MCD (79)	Plasma cell (13), hyaline vascular (18), mixed pathology (22)	Any previous treatment allowed except for tocilizumab; 22 patients received concomitant corticosteroids	336 days	11 mg/kg every 3 weeks	Placebo	Durable tumour and symptomatic response: siltuximab 34% (CR 2%, PR 32%) vs placebo 0% (p=0.0012)	Pruritus (42% for siltuximab vs 12% for placebo); URTI (36% vs 15%); maculopapular rash (34% vs 12%); localised oedema (21% vs 4%); weight gain (19% vs 0%); abdominal pain (15% vs 4%); thrombocytopenia (15% vs 4%); nasopharyngitis (15% vs 4%)

Adapted from ref 39, with permission of Future Medicine. CR=complete response. MCD=multicentric Castleman's disease. PD=progressive disease. PR=partial response. SD=stable disease. URTI=upper respiratory tract infection. *Improvement from baseline in one or more of six variables and no worsening in the other variables. Individual response variables included grade 1 or greater decrease in fatigue, ≥25% decrease in bidirectional size of largest lymph node, ≥5% increase in weight, ≥2°C decrease in fever or improvement in night sweats, ≥20 g/L increase in haemoglobin without transfusions, and grade 1 or greater decrease in anorexia. †19 patients reported elsewhere, so total number of patients with idiopathic MCD from clinical trials is 139.

Table 2: Summary data for 139 patients with idiopathic multicentric Castleman's disease from clinical trials

these patients were excluded from primary analyses because individual patient-level data were not available; summary statistics are provided for 127 of 139 patients reported in the three trials, for comparison (table 1).

The median age at diagnosis among the 128 individual cases was 50 years (IQR 35–61). Overall, a wide range of ages was recorded, with the youngest reported patient aged 2 years and the oldest aged 80 years. 14 (11%) patients were younger than 19 years, and 74 (58%) were male. Male patients presented at a slightly older age than did female cases (figure 2). Because ethnic origin was reported for only 35 (27%) patients, geographic location of the first author was recorded instead: 72 were from Asia (Japan, $n=56$; China, $n=8$; South Korea, $n=6$; Singapore, $n=1$; Thailand, $n=1$), 38 were from Europe and the Middle East (France, $n=15$; Italy, $n=5$; Greece, $n=4$; Spain, $n=2$; Turkey, $n=2$; Hungary, $n=2$; Germany, $n=2$; Sweden, $n=1$; Netherlands, $n=1$; Czech Republic, $n=1$; Lebanon, $n=1$; Israel, $n=1$; UK, $n=1$), 16 were from North America (USA, $n=13$; Canada, $n=3$), one was from South America (Brazil), and one was from Australia.

Histopathological features of patients with idiopathic multicentric Castleman's disease showed an enrichment of the plasma cell and mixed pathology variants, with relatively fewer cases reporting hyaline vascular changes. No major relations were noted between histopathological type and clinical features, treatment effectiveness, or outcomes. We recorded little standardisation with respect to reporting of clinical symptoms and laboratory variables (table 1). An association between idiopathic multicentric Castleman's disease and both systemic inflammation and organ dysfunction was supported by data. Multicentric lymphadenopathy was reported in all patients, because it was a requirement for inclusion. The next most frequently reported clinical features were hepatomegaly and splenomegaly (52/67 [78%]) and fever (33/64 [52%]). Of 79 patients in whom C-reactive protein levels were recorded, 65 (82%) had elevated levels during active disease (table 1). Anaemia was reported in 79 (87%) of 91 patients in whom haemoglobin was measured, and hypergammaglobulinaemia was recorded in 63 (77%) of 82 individuals with reported amounts of γ -globulin. Of 63 patients in whom platelets levels were documented, 44 (70%) had abnormal platelet counts; thrombocytosis was seen in 16 (25%) whereas thrombocytopenia was noted in 28 (44%). Moreover, ANA was positive in 15 (37%) of 41 patients, Coombs test was positive in 12 (71%) of 17 cases, antiplatelet antibodies were reported in 11 (100%) of 11 patients, rheumatoid factor was positive in eight (57%) of 14 cases, and anti-Ro/SS-A antibody was positive in six (86%) of seven patients. Together, 38 (30%) patients with idiopathic multicentric Castleman's disease had positive autoantibodies or reported autoimmune haemolytic anaemia. Patients were also assessed for TAFRO features; 21 (19%) of 110 with sufficient data showed thrombocytopenia and at least two further features. Interleukin 6 levels were reported in 63 patients

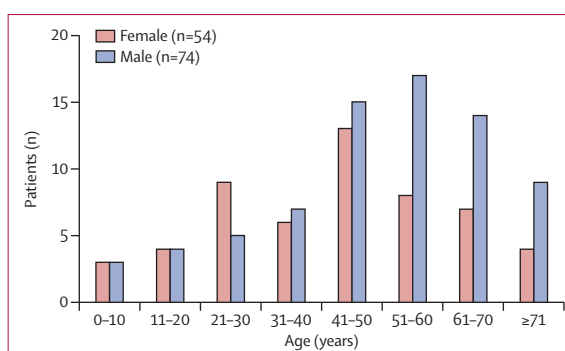


Figure 2: Sex and age distribution of patients

and were elevated in 57 (90%). Soluble interleukin 2 receptor levels were raised in 20 (95%) of 21 cases, and concentrations of VEGF were increased in 16 (80%) of 20 patients reporting that cytokine.

24 (19%) of 128 patients with idiopathic multicentric Castleman's disease were diagnosed with a separate malignant disease before ($n=4$), concurrent with ($n=12$), or after ($n=8$) their diagnosis, a proportion that is significantly higher than the expected age-adjusted prevalence of 6% based on data from the Surveillance, Epidemiology, and End Results programme ($p<0.0001$; appendix p 2). Of these 24 patients, 11 had a haematological malignancy and 13 had a solid tumour. The solid tumours included three cases of adenocarcinoma (two unknown primary site, one gastric), two cases of inflammatory myofibroblastic tumour, and one case each of basal cell carcinoma, dendritic cell sarcoma, metastatic gastric cancer, medullary thyroid cancer, neurinoma, spindle cell sarcoma, squamous cell carcinoma of lung, and tonsil cancer. The haematological malignancies included six cases of non-Hodgkin lymphoma (two diffuse large B cell, one angioimmunoblastic T cell, one mantle cell, one orbital-mucosal associated lymphoid tissue, one not specified), three cases of Hodgkin's lymphoma, one case of acute myeloid leukaemia, and one case of multiple myeloma.

Overall, 66 of 114 patients in the systematic review were alive at 2 years (36 censored); 2-year survival was 88% (95% CI 81–95). Although the median duration of follow-up was only 29 months (IQR 12–50), 27 of 121 patients (22%; 95% CI 15–30) died during their observed follow-up period. The most common causes of death were organ failure ($n=9$, multiple organ systems, renal, pulmonary, cardiac), sepsis ($n=6$), malignant disease ($n=4$), progression of disease ($n=3$), unrelated to Castleman's disease ($n=2$), and paraneoplastic pemphigus ($n=1$); other causes of death were not stated explicitly.

Diagnosis with a separate malignant disease correlated significantly with negative outcomes. Of patients with idiopathic multicentric Castleman's disease who were diagnosed with malignant disease and had the requisite survival data, 13 of 20 were alive at 2 years (one was censored because of loss to follow-up before 2 years); 2-year survival was 70% (95% CI 52–93). By contrast, 54 of

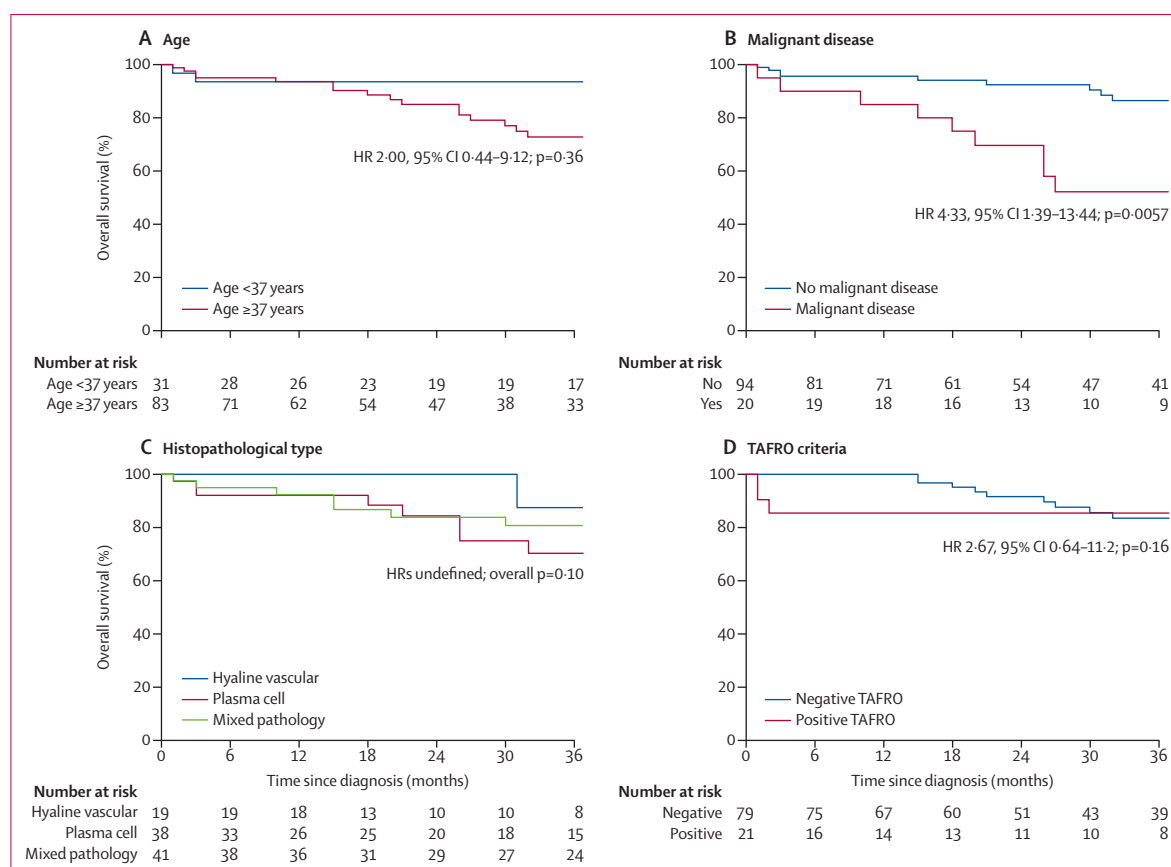


Figure 3: Kaplan-Meier estimates of survival by age, malignant disease, histopathological features, and TAFRO syndrome in patients with idiopathic multicentric Castleman's disease

HR=hazard ratio. TAFRO=thrombocytopenia, ascites, fever, reticulosis in bone marrow, organomegaly, and normal amounts of γ -globulin.

94 patients (34 censored) without malignant disease were alive at 2 years, with 2-year survival of 92% (95% CI 87–99; HR 4.33, 95% CI 1.39–13.44; $p=0.0057$; figure 3B). Additional factors associated negatively with survival included age (>37 years), extravascular fluid overload, plasma cell histopathology, TAFRO features, hypergammaglobulinaemia, and thrombocytopenia. 47 of 83 patients (26 censored) aged 37 years or older were alive at 2 years (2-year survival 85% [95% CI 77–94]) compared with 19 of 31 individuals (ten censored) younger than 37 years (2-year survival 94% [85–100]; HR 2.00, 95% CI 0.44–9.12; $p=0.36$; figure 3A). 13 of 28 patients (ten censored) with extravascular fluid accumulation (ie, oedema, ascites, anasarca, or a combination) were alive at 2 years (2-year survival 79% [95% CI 65–98]) compared with five of eight (three censored) who did not have any reported signs of volume overload (2-year survival 100% [100–100]; HR undefined; $p=0.19$). 20 of 38 patients (13 censored) had the plasma cell histopathological subtype, 29 of 41 (six censored) had mixed pathology, and ten of 19 (nine censored) had hyaline vascular histopathological features. 2-year survival seemed to be worse in patients with the plasma cell histopathological subtype (84% [95% CI 72–99]) and mixed pathology (84% [73–97]) than

in those with hyaline vascular features (100% [100–100]; HRs undefined; overall $p=0.10$; figure 3C). 11 of 21 patients (seven censored) with TAFRO features were alive at 2 years compared with 51 of 79 (23 censored) without these features. 2-year survival was 85% (95% CI 71–100) for those with TAFRO features versus 92% (85–99) for those without (HR 2.67, 95% CI 0.64–11.20; $p=0.16$; figure 3D). The sharp increase in mortality in TAFRO patients within the first 6 months of diagnosis is notable because it reflects the typically highly aggressive phenotype and might portend worse 2-year survival when follow-up is extended. Of 54 patients (19 censored) reported to have hypergammaglobulinaemia, 27 were alive at 2 years compared with 12 of 19 cases (seven censored) with normal amounts of globulin. 2-year survival was 81% (95% CI 70–94) for patients with hypergammaglobulinaemia versus 100% (100–100) for those without increased levels (HR undefined; $p=0.072$). Of 27 patients (nine censored) reported to have low platelets, 14 were alive at 2 years (2-year survival 84% [95% CI 70–100]) compared with 22 of 32 patients (nine censored) with normal or raised amounts of platelets (2-year survival 96% [89–100]; HR 5.32, 95% CI 0.59–47.69; $p=0.095$).

	Patients (n)	Complete response*	Treatment failure†	Median (IQR) time to treatment failure (months)	Proportion alive at follow-up	Survival at 2 years (95% CI)
All treatments	128	47/114 (41%)	49/116 (42%)	6 (1–22)	78%	88% (81–95)
Corticosteroid monotherapy	47	12/44 (27%)	21/45 (47%)	5 (0–15)	74%	83% (71–97)
Cytotoxic chemotherapy (any time used)	47	19/43 (44%)	19/43 (44%)	6 (2–24)	80%	93% (85–100)
Cyclophosphamide regimen (any time used)	23	9/22 (41%)	9/21 (43%)	3 (0–12)	86%	90% (79–100)
Non-cyclophosphamide based cytotoxic regimen	12	5/11 (45%)	7/12 (58%)	17 (7–44)	64%	90% (73–100)
Rituximab (without a cytotoxic agent)	9	5/8 (63%)	1/8 (13%)	2 (2–2)	100%	100% (100–100)
Chemotherapy with radiation therapy	2	0/1 (0%)	1/1 (100%)	120 (120–120)	50%	..
Chemotherapy NOS	1	0/1 (0%)	1/1 (100%)	2 (2–2)	0%	..
Anti-interleukin 6 monoclonal antibody (only without cytotoxic agent)	11	10/11 (91%)	2/11 (18%)	19 (10–27)	100%	100% (100–100)
Tocilizumab with or without corticosteroids	9	8/9 (89%)	1/9 (11%)	1 (1–1)	100%	100% (100–100)
Siltuximab with or without corticosteroids	2	2/2 (100%)	1/2 (50%)	36 (36–36)	100%	100% (100–100)
Surgery (lymph node resection or splenectomy)	8	5/8 (63%)	2/7 (29%)	2 (1–2)	71%	80% (52–100)
Immunomodulators (only when without cytotoxic agent)	5	0/4 (0%)	3/4 (75%)	6 (3–15)	50%	67% (30–100)
Others	3	1/1 (100%)	1/3 (33%)	6 (6–6)	67%	50% (13–100)
No treatment, or follow-up only	7	0/3 (0%)	1/3 (33%)	31 (31–31)	83%	100% (100–100)

Immunomodulatory or immunosuppressive agents—eg, bortezomib, azathioprine, intravenous immunoglobulin, methotrexate, and thalidomide—were used without another agent (n=5) or in combination with cytotoxic chemotherapy (n=3). NOS=not otherwise specified. *Proportion achieving a complete response calculated from number of patients with a complete response divided by the number in whom response to treatment could be assessed. †Proportion failing treatment calculated from the number of patients with treatment failure divided by the number in whom treatment failure could be assessed.

Table 3: First-line treatments

Response to first-line treatments varied greatly (table 3). Among 114 patients with sufficient data to assess first-line treatment response, 47 (41%) achieved a complete response, 42 (37%) had a partial response, and 25 (22%) reported no response. 49 (42%) patients eventually failed first-line treatment by follow-up (median 29 months [IQR 12–50]) with a median time to treatment failure of 6 months (IQR 1–22) in these patients. Some patients failed second-line treatment and needed a third, fourth, or even fifth line of treatment. Limited results for the effectiveness of second-line treatments are shown in the appendix (p 3). Corticosteroid monotherapy (47/128 [37%]) and chemotherapeutic regimens (47/128 [37%]) were the most commonly reported first-line treatments (table 3). Chemotherapeutic regimens most commonly incorporated cyclophosphamide (21/45 [47%]) and rituximab (15/45 [33%]). Etoposide, vinblastine, vincristine, doxorubicin, bleomycin, and dacarbazine were also included in regimens. 12 (27%) of 44 patients treated with corticosteroid monotherapy and 19 (44%) of 43 patients treated with cytotoxic chemotherapy achieved a complete response. At 2 years, 22 of 47 patients (16 censored) initially treated with corticosteroid monotherapy were alive, compared with 44 of 81 people (20 censored) treated with another drug. 2-year survival was 83% (95% CI 71–97) for those initially treated with corticosteroid monotherapy compared with 90% (83–98) for those treated with another drug (HR 1.76; 95% CI 0.57–5.45; $p=0.32$). Anti-interleukin 6 agents were used for first-line treatment without a cytotoxic

agent in 11 patients and with cytotoxic chemotherapy in four. Tocilizumab was used for 13 (87%) of 15 patients, with nine cases coming from the same series.⁴⁰ Although based on a limited number of cases, anti-interleukin 6 therapy (tocilizumab and siltuximab) without cytotoxic chemotherapy was the most effective first-line regimen, with ten (91%) of 11 patients achieving an initial complete response; only two of 11 patients subsequently failed first-line treatment by the time of follow-up.

Discussion

The analysis presented here represents the most comprehensive summary, to date, of clinical data in idiopathic multicentric Castleman's disease, advancing our understanding of the disease in many respects. First, our review of the scientific literature shows that at least a third of all published cases of multicentric Castleman's disease are negative for HHV8 and HIV and are, therefore, idiopathic. Thus, idiopathic multicentric Castleman's disease represents a considerable disease entity that has been previously unrecognised by medical reference databases and clinicians. Second, the prognosis of idiopathic multicentric Castleman's disease underscores the importance of prompt recognition: 12% of patients in our study died within 2 years of diagnosis; 35% of patients died within 5 years and 60% died within 10 years of diagnosis in a series by Dispenzieri and colleagues.⁴¹ Furthermore, biases in data reporting suggest that true mortality could be higher than our

observed mortality: the case reports in our series were typically published 24–36 months after diagnosis; thus, deaths and treatment failures in patients occurring after publication have been missed. For survival analyses, patients were censored at the time they were last known to be alive. To minimise the effect of this bias, we only reported 2-year survival and we contacted the authors of every study (if contact information was available) to gather additional follow-up data. Of 237 authors contacted, 67 responded with additional data. Also, there is an accepted negative reporting bias away from patients who do not respond to an experimental treatment and die.⁴²

Although effective treatments for idiopathic multicentric Castleman's disease exist (namely, interleukin 6 blockade), 66% of patients did not meet criteria for a complete response or partial response to treatment in a double-blind, placebo-controlled trial of siltuximab.²⁹ The relatively better response to anti-interleukin 6 treatment (tocilizumab and siltuximab) in our study could be due to a reporting bias towards publishing positive case reports of anti-interleukin 6 agents or could be related to baseline differences in study populations. The side-effect profile of anti-interleukin 6 agents is more tolerable than that for most cytotoxic chemotherapeutic regimens, but anti-interleukin 6 agents might need lifelong administration, because relapse has been reported on cessation.⁴³ For non-responders to anti-interleukin 6 agents, various alternative drugs exist (eg, chemotherapeutic agents, anakinra, sirolimus, bortezomib, azothioprine, intravenous immunoglobulin, methotrexate, and thalidomide), with little data or prognostic guidance with respect to which patients will respond to treatment. Agents that warrant further investigation include anakinra, an anti-interleukin 1 receptor antagonist that has been reported to be effective in several patients, including two who were non-responders to anti-interleukin 6 agents,^{44–46} and the combination of the mTOR inhibitor sirolimus with intravenous immunoglobulin, which has led to extended remission in a patient with idiopathic multicentric Castleman's disease with TAFRO features refractory to many other treatments.²⁸

In previous studies, researchers have noted an increase in the frequency of malignant diseases in patients with idiopathic multicentric Castleman's disease.⁴⁷ In our study, we noted a threefold increased prevalence of malignant disease relative to age-matched controls. Several possible explanations exist for the increased prevalence of cancer. First, the malignant cells might be secreting interleukin 6 and other proinflammatory cytokines that cause the histopathological and clinical features of idiopathic multicentric Castleman's disease. If this possibility is true then these cases of idiopathic multicentric Castleman's disease should be considered to be malignancy-driven multicentric Castleman's disease. Second, idiopathic multicentric Castleman's disease might be a premalignant state that can eventually transform. Third, a common

genetic mutation might make a patient susceptible to both idiopathic multicentric Castleman's disease and malignant diseases. Fourth, excessive cytokine release might promote malignant transformation. Fifth, treatments for idiopathic multicentric Castleman's disease—eg, cytotoxic chemotherapy—might amplify susceptibility to malignant disease. Finally, an unidentified virus might cause both idiopathic multicentric Castleman's disease and the malignant disease.⁴⁶ We suggest that clinicians search for an underlying malignant disease in all patients newly diagnosed with idiopathic multicentric Castleman's disease and monitor individuals with idiopathic multicentric Castleman's disease for development of malignant diseases.

Several trends from this study should inform care of patients. Levels of C-reactive protein should be tracked serially in all patients to assess disease status and response to treatment, because these levels paralleled disease activity in this series. Although the plasma cell variant is said to account for 90% of cases of multicentric Castleman's disease,⁴⁸ our series showed that 45% of patients did not have the plasmacytic variant alone. We did not note substantial variability in clinical features or outcomes based on histopathological subtype. We believe that histopathological features of idiopathic multicentric Castleman's disease are on a spectrum, and the current distinction between histopathological subtypes is of little clinical value. Hypergammaglobulinaemia was not present uniformly in patients who reported immunoglobulin levels, and immunoglobulins are quantified in the workup of nearly all patients with multicentric Castleman's disease, so we suspect that some unreported cases were probably also normal. The greater frequency of thrombocytopenia than thrombocytosis was also not expected; in previous reviews, raised platelet counts have been associated with multicentric Castleman's disease, and excess interleukin 6 was said to cause thrombocytosis.^{49,50} Hyaline vascular or mixed histopathological features, normal amounts of immunoglobulin, and low platelet counts are all reported in patients with idiopathic multicentric Castleman's disease and features of TAFRO syndrome.²⁸

Although we know that clinical features and symptoms of idiopathic multicentric Castleman's disease result from proinflammatory hypercytokinaemia, the role of cytokines other than interleukin 6 is unknown. The presence of autoantibodies in patients with idiopathic multicentric Castleman's disease could suggest that autoimmunity is a pathological cause. Alternatively, these antibodies might be a sign that idiopathic multicentric Castleman's disease was diagnosed incorrectly or they could be a by-product of hypercytokinaemia. Concentrations of interleukin 6 were raised in nearly all (57/63) patients in whom interleukin 6 was measured. Although increased amounts of interleukin 6 are common in patients with idiopathic multicentric Castleman's disease, subsets of symptomatic patients have normal or only slightly elevated levels of

interleukin 6 and some do not respond to anti-interleukin 6 treatment.⁵¹ 66% of patients with idiopathic multicentric Castleman's disease did not respond to siltuximab in a randomised controlled trial,²⁹ suggesting that the disease is not driven purely by interleukin 6 in all patients. Furthermore, none of the 18 patients with the hyaline vascular variant in the phase 2 study responded to treatment.²⁹ Presumably, patients with low levels of interleukin 6 or non-responders to anti-interleukin 6 have other cytokines driving their disease. Concentrations of the soluble interleukin 2 receptor and VEGF were both also frequently raised when amounts were reported. Soluble interleukin 2 receptor is a marker of T-cell activation, but we do not know whether this increase is a bystander effect or whether activated T cells have an important role in pathogenesis of idiopathic multicentric Castleman's disease. VEGF promotes cell survival, angiogenesis, and vascular permeability; it could account for the hypervascularisation in lymph nodes, extravascular fluid overload, and eruptive cherry haemangiomas observed in patients with idiopathic multicentric Castleman's disease.^{52,53} In one patient with idiopathic multicentric Castleman's disease who was receiving anti-interleukin 6 treatment and had serial laboratory data,²⁸ increasing levels of soluble interleukin 2 receptor and VEGF were the earliest indicators of an impending relapse and failure of anti-interleukin 6 treatment. Moreover, these markers paralleled disease status and preceded a decline in platelets and albumin and an increase in C-reactive protein.²⁸ Broad serum proteomics and flow-cytometry studies are needed to better understand the cytokine cascade, early markers of disease progression, activated intracellular pathways, and specific cell types mediating idiopathic multicentric Castleman's disease.

Cautious interpretation of our results is warranted because of several limitations of our systematic review. Most importantly, we analysed a small, non-random sample, sometimes with incomplete data. As a result, analyses were probably underpowered to detect true differences in outcomes or to make definitive recommendations about the relative effectiveness of treatment categories. Also, confounding by indication might have been present; for instance, patients with a more aggressive disease course might have been treated with more aggressive drugs—eg, cytotoxic chemotherapy. Furthermore, median length of follow-up from diagnosis was only 29 months, so longer term survival outcomes could not be assessed adequately. Since our data were obtained from published case reports, selection biases could have been present towards specific types of patients—eg, those with unusual clinical features, treatments, or outcomes. Because our analysis was a retrospective study of published cases, histopathological review by experts and confirmatory testing for HHV8 could not be done. Although guidelines for diagnosis of HHV8-negative multicentric Castleman's disease have not been established, studies of HHV8-associated disease use

LANA1 in lymph nodes (and in some cases, HHV8-encoded viral interleukin 6) to determine HHV8 status.^{54,55} PCR for HHV8 in blood or tissues is typically considered supportive.^{56,57} We recommend that LANA1 staining should be performed in all patients with multicentric Castleman's disease and that serology for HHV8 should not be done. Finally, the relative incidence of symptoms might be inflated artificially by a bias towards under-reporting of negative symptoms. To account for negative reporting bias, in addition to calculating the percentage of positive cases divided by those with reported data, we calculated a second percentage of positive cases divided by all reported cases (n=128). The uncertainty in these data shows the importance of future prospective research with extended follow-up to systematically gather clinical data.

The findings of this systematic literature review illustrate gaps in our knowledge of idiopathic multicentric Castleman's disease and highlight specific areas in which further information will improve patients' outcomes. Learning from the experience of HHV8-associated multicentric Castleman's disease, it was identification of HHV8 as the causative agent that led to the finding that elimination of CD20+ cells, which host the virus, would be highly effective at treating the disease.⁵⁸ In this respect, elucidation of the pathophysiology of idiopathic multicentric Castleman's disease remains vital. We have described a framework for considering potential causes of idiopathic multicentric Castleman's disease.¹⁶ More than one of these mechanisms could account for subgroups of patients, and idiopathic multicentric Castleman's disease might represent a group of disorders that share a final common pathway of proinflammatory hypercytokinaemia. Along with this mechanistic understanding of disease, identification of effective alternative treatments for idiopathic multicentric Castleman's disease is crucial, both during flare and during remission, in view of the variable prognosis associated with disease.

The variable presentation and prognosis of idiopathic multicentric Castleman's disease highlights the need for consensus around diagnostic guidelines. Focused investigation into subgroups of patients with common features—eg, TAFRO—should also help to advance research and clinical care. To address these shortcomings through patient-centred research, the forthcoming ACCELERATE (Accelerating Castleman Care with Electronic Longitudinal registry, E-Repository, And Treatment Effectiveness research) patient registry and natural history study is set to launch in 2016. Patients can enrol with the aid of their treating doctor in Europe or on their own in the USA, Canada, and a few other regions around the world; information from their participation will help to inform prognosis, effective treatments, and disease management. Moreover, the formation of a biobank by the Castleman Disease Collaborative Network will identify patients' samples for translational research into the causes of idiopathic multicentric Castleman's disease.

For more on ACCELERATE see
<http://www.cdcn.org/ACCELERATE>

Contributors

AYL did the literature search, analysed data, and contributed to study design and writing of the report. CSN contributed to study design, data interpretation, and writing of the report. BSF analysed data, developed the figures, and contributed to data interpretation and writing of the report. JRR analysed and interpreted data and contributed to writing of the report. RK, FvR, VPK, DK, and AHR interpreted data and contributed to writing of the report. DCF developed the figures and contributed to study design, data collection, data analysis, data interpretation, and writing of the report.

Declaration of interests

DCF served on an advisory board for Janssen Pharmaceuticals, outside the submitted work. RK received research funds from Genentech, Merck Serono, Foundation Medicine, Pfizer, Guardant, and Sequenom, outside the submitted work; consultant fees from Sequenom, outside the submitted work; and has ownership interest in RScueRX, outside the submitted work. FvR received grants for research from Janssen, during this study; and served on an advisory board for Janssen, outside the submitted work. All other authors declare no competing interests.

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