bjh guideline

# The management of Castleman disease

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## Methodology

This 'Good Practice Paper' was compiled according to the British Society for Haematology (BSH) process at (http://www.b-s-h.org.uk/guidelines). The BSH produces Good Practice Papers to recommend good practice in areas where there is a limited evidence base but for which a degree of consensus or uniformity is likely to be beneficial to patient care. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.graded workinggroup.org.

## Literature review details

The PubMed database was searched for English language articles up to June 2021 using the keywords: Castleman, POEMS, HHV8, HIV, lymphoma, lymphadenopathy, investigation, imaging, histology. The references from relevant publications were searched as well.

## Review of the manuscript

Review of the manuscript was performed by the BSH Guidelines Committee Haemato-oncology Task Force, the BSH Guidelines Committee and the Haemato-oncology of sounding board of BSH. It was also on the members section of the BSH website for comment.

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## Introduction

Castleman disease (CD) describes a rare group of lymphoproliferative disorders with characteristic histopathological appearances.[1] Unicentric CD (UCD) presents with isolated lymphadenopathy, usually accompanied by mild or localised symptoms. In contrast, multicentric CD (MCD), presents with lymphadenopathy across multiple sites, usually accompanied by mild to life-threatening constitutional symptoms. MCD represents a constellation of different clinicopathological subtypes that vary in their aetiology, presentation and management.

The incidence of all forms of CD is estimated at 21–25 per million person-years, based on insurance registries in the USA.[2] Application of this rate to the UK adult population provides an estimated incidence of CD in the UK of 1100–1300 patients per year.[3] There is an approximately even distribution of CD between men and women. UCD is most commonly diagnosed in the fourth decade of life, whereas MCD usually presents later in the fifth and sixth decades.[4,5] The introduction of the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code D47.Z2 in 2016 should facilitate the understanding of the epidemiology of the disease.[6]

## Clinical presentation

### *Unicentric CD*

Lymphadenopathy is found most in the chest and neck and less commonly in abdominal nodes or as a retroperitoneal mass.[5,7,8] The clinical presentation of UCD often relates to the localised mass effect on organ function. Systemic symptoms are uncommon with fever in <10% of cases and inflammatory markers including C-reactive


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protein (CRP), erythrocyte sedimentation rate and tests of organ function usually being normal.[7] Severe paraneoplastic phenomena such as pemphigus and bronchiolitis with organising pneumonia have been described very rarely.[7,9] The 5-year overall survival (OS) of UCD has been estimated at 91%.[4]

### *Multicentric CD*

The presentation of MCD is usually with relapsing and remitting systemic symptoms, e.g. fatigue, sweats, weight loss, anaemia, dyspnoea, oedema, pulmonary fibrosis, hepato-splenomegaly and skin-lesions (such as cherry-coloured eruptions).[7,10] Such systemic symptoms may present rapidly with signs of organ dysfunction that require urgent admission to the intensive care unit and the input from a number of clinical specialities including respiratory and renal physicians. Many of the symptoms associated with MCD, have been attributed to the excessive secretion of the cytokine interleukin-6 (IL-6).[11] IL-6 is a key modulator of lymphocyte maturation as well as the acute phase reactants CRP, vascular endothelial growth factor (VEGF), C-X-C motif chemokine ligand 13 (CXCL-13) and the iron regulatory hormone, hepcidin.[12–14] Together with a fall in plasma albumin concentration, these inflammatory mediators contribute to the clinical features of fever, oedema and anaemia that may be observed in MCD. Survival rates for MCD are not clear given changes in in diagnostic criteria, reporting and therapy.[7] Nevertheless, the 5-year OS rate for MCD have been estimated at ~65%.[4]

### *Human herpesvirus 8-associated MCD (HHV8-MCD)*

A proportion of cases of MCD have been attributed to infection with HHV8. HHV8 infection predominantly occurs in the context of immunodeficiency, in particular following infection with human immunodeficiency virus (HIV). HIV negativity should prompt investigations designed to identify other causes of immune suppression.[15,16] Immunodeficient states facilitate the replication of HHV8 in blastic cluster of differentiation 20 $(CD20)^{+}$ lymphocytes, which in turn leads to the secretion of a virally derived analogue of IL-6 (vIL-6) that drives the pathogenesis of MCD.[17] Current assays for IL-6 do not detect vIL-6. Clinically, patients frequently present with fever, splenomegaly and effusions. Blood results may reveal hyperferritinaemia, direct anti-globulin test positive haemolysis and monoclonal gammopathy.[5] HHV8 serology does not necessarily reflect viral activity. HHV8 polymerase chain reaction (PCR) in blood detects circulating viral DNA and detectable expression of the virally encoded protein latency associated nuclear antigen-1 (LANA-1) in the diagnostic lymph node biopsy better reflect active HHV8-driven pathology. Indeed, HHV8 viral load has been found to be positively correlated with relapse.[18]

### *Peripheral sensorimotor neuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy and Skin lesions (POEMS)-associated MCD (POEMS-MCD)*

The syndrome of POEMS is a rare disorder with other clinical features frequently encountered including osteosclerotic bone lesions and papilloedema. Occasionally, features of POEMS syndrome may co-exist with MCD. Diagnosis may be challenging in that idiopathic MCD (iMCD), may present with features such as rash, organomegaly and neuropathy similar to those found in POEMS but without evidence of a clonal plasma cell (PC) disorder.[4,7] The malignant PCs of POEMS are thought to drive the CD-like lymphadenopathy and the resulting immunoglobulin (Ig)G or IgA paraprotein is almost always λ light-chain restricted.[19,20] Thrombocytosis and elevated concentrations of VEGF are important features.[4] There appears to be significant overlap in the pathophysiology and presentation of the related disorders of MCD and POEMS. Indeed, a diagnostic criterion of POEMS is the identification of CD histopathology.[21] The complex presentation of these rare conditions emphasises the need for careful discussion with an experienced haemato-pathological multidisciplinary team (MDT). Autologous stem cell transplantation (ASCT) is established as a therapeutic modality in POEMS syndrome. But due to limited data, if ASCT is considered in this overlap POEMS-MCD, they should be conducted in experienced centres and as part of a trial, if available.

### *Idiopathic MCD*

In 2017, the Castleman Disease Clinical Network (CDCN) proposed diagnostic criteria for iMCD, which require the exclusion of HHV8 and POEMS-associated MCD as well as potential mimics of CD histopathology from autoimmune conditions, infections and other haematological disease (Figure 1).[6] IgG4-related disease (IgG4-RD) is a systemic inflammatory disorder that is characterised histologically by a PC-rich sclerosing infiltrate of organs such as the pancreas, bile ducts, lungs and lymph nodes. It may, therefore, bear some resemblance clinically and histologically to CD. Biochemically, the IgG4/IgG ratio is significantly higher in IgG4-RD compared to CD; histologically sheets of PCs favour CD and clinically splenomegaly is found exclusively in CD, whereas IgG4-RD is typified by pancreatitis and sialo-dacryoadenitis.[22]

Patients with iMCD may present with a spectrum of systemic inflammatory symptoms with constitutional symptoms in approximately half of cases.[4] Some patients experience only mild symptoms, whereas others experience severe inflammatory symptoms with multi-organ failure necessitating intensive care support.

A particularly aggressive form of iMCD has emerged that appears to be clinicopathologically distinct from iMCD-not otherwise specified (NOS). It is characterised by

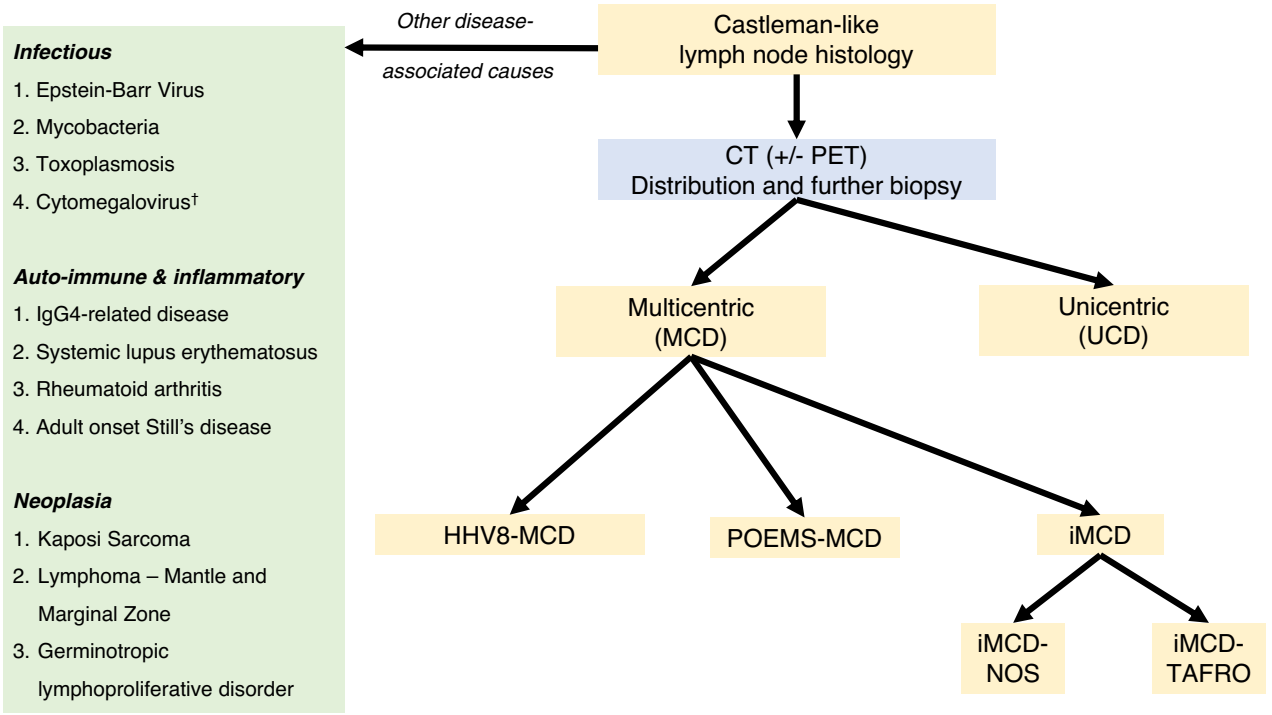


**Fig 1.** Key steps in the diagnosis and classification of Castleman disease (CD). CT, computed tomography; HHV8, human herpesvirus 8; IgG4, immunoglobulin G subclass 4; MCD, multicentric CD where 'i' prefix denotes idiopathic; NOS, not otherwise specified; PET, positron emission tomography; POEMS, Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Proteins and Skin Changes; TAFRO, Thrombocytopenia, Anasarca, myelofibrosis, Renal dysfunction and Organomegaly; UCD, unicentric CD. †Exclusion of cytomegalovirus infection may be complicated by persistence of passively transferred antibody after blood transfusion. [Colour figure can be viewed at wileyonlinelibrary.com]

Thrombocytopenia, Anasarca, Myelofibrosis, Renal dysfunction and Organomegaly (TAFRO). Anasarca is a state of extreme generalised oedema and is more commonly used in North America than in the UK. It occurs predominantly in patients of Japanese and East Asian descent, but this may be due to a reporting bias and data are awaited from the ACCELERATE registry (NCT02817997 http://www.cdcn.org/accelerate). In contrast to iMCD-NOS, renal impairment, peripheral oedema and thrombocytopenia are common.[23] However, the diagnosis of the TAFRO-iMCD syndrome remains clinical, without any specific diagnostic laboratory test.[24] Diagnostic criteria for TAFRO have been proposed (Iwaki et al.[25] 2015). Major criteria comprise at least three out of the five canonical features identified by the acronym with the absence of hypergammaglobulinaemia and small volume lymphadenopathy. Minor criteria include hyperplasia or normoplasia of megakaryocytes in the bone marrow and elevated serum alkaline phosphatase (ALP) in the absence of marked elevation of serum transaminase. In TAFRO, the platelet count tends to reflect iMCD activity, with greater thrombocytopenia correlating with greater disease activity.[25]

Figure 1 shows a summary of the clinical differential diagnosis of CD and its subtypes according to the classification proposed in 2017 by the CDCN.[6]

## Histology and staging

A lymph node excisional biopsy is required to ensure adequate histological assessment of suspected cases of CD. Core biopsy may be the means by which a first suspicion of CD is reached but should be followed-up with excision biopsy if at all feasible. The rare but important situation whereby highly atypical follicular dendritic cells that mimic poorly differentiated malignancy, such as a sarcoma, may be misinterpreted were it not for the context provided by an excision biopsy of a lymph node that reveals more typical features of CD. All cases should be reviewed by an experienced haemato-pathologist and reviewed in a MDT meeting.[26] The CDCN curates online resources to aid in the diagnosis including case examples presented by a panel of expert pathologists (http://cdcn.org/pathology-toolkit/).

As the classical histological findings of CD were first described in 1956 by Dr Benjamin Castleman,[27] a spectrum of histological variants has been identified: hyaline vascular, plasma and mixed type. While follicular centres are classically atretic and traversed by penetrating vessels with perivascular hyalinisation in the hyaline vascular variant of UCD, follicular structures in the rarer PC variant of UCD are typically hyperplastic or normal sized. In the mixed variant of UCD,

hyaline vascular features and prominent PC proliferations can be seen together.

Various combinations of all these features can be identified in MCD. However, the presence of HHV8-infected plasmablasts is largely restricted to MCD and is almost always seen in the context of HIV infection.[4,20] These plasmablasts are immuno-positive for organic cation transporter 2 (OCT2) and interferon regulatory factor 4/melanoma-associated antigen (1IRF4/MUM1), but lack paired box 5 (PAX5), B-cell lymphoma 6 (BCL6) and CD138. They express IgM with monotypic λ light-chain expression, but typically demonstrate a polyclonal pattern of immunoglobulin gene rearrangement. HHV8 serology is not specific for MCD pathology. Rather, a diagnosis of MCD requires either histological staining with LANA-1 or quantitative PCR for HHV8 in peripheral blood.[22] The histological appearances of CD are not in themselves pathognomonic of the condition and need to be distinguished from other infectious, inflammatory, autoimmune and malignant conditions that may mimic or co-exist with CD. The key histological differential diagnoses for CD include: non-specific lymphadenitis with polytypic PCs; autoimmune lymphadenitis; reactive follicular and paracortical hyperplasia; lymphoproliferative disorders including lymphoplasmacytoid lymphoma, plasmacytoma, follicular lymphoma and angioimmunoblastic T-cell lymphoma; follicular dendritic cell sarcoma and Kaposi sarcoma.

Cross-sectional, whole body imaging is used to distinguish between UCD and MCD by establishing the extent of lymph node involvement; the presence of extra-nodal disease in the lungs, effusions and lytic or sclerotic bone lesions (POEMS), as well as accurately determine the extent of effusions and ascites. UCD appears on computed tomography (CT) imaging as a solitary node or a lymph node mass with most cases with nodes in the thoracic cavity and a small percentage are reported in the abdomen, retroperitoneal space and extra-nodal sites, particularly in the lung parenchyma. MCD does not have a predilection in distribution.[8,28] Positron emission tomography (PET) allows whole-body imaging and identifies the usually highly metabolically active lymphadenopathy of CD and may help to differentiate it from lymphoma by virtue of a lower, but still elevated, relative metabolic activity in CD.[5,29]

## Recommendation

- Lymph node biopsy specimens should be excisional. If a diagnosis of CD is considered following a core biopsy, an excisional lymph node biopsy should be performed to confirm the diagnosis. Fine-needle aspirates are inadequate to examine lymph node architecture (1A).
- Lymph node biopsy specimens must be reported by a haemato-pathologist with experience of CD (1A).
- Cross-sectional staging imaging (CT or PET-CT) should be performed to identify distribution of lymph node, extra-nodal masses and any pleural abnormality, thereby confirming the classification of the disease into the UCD or MCD variants (1B).

## Management

### *Unicentric CD*

In the absence of symptoms, patients with UCD, may be managed expectantly.[28] There are no reported cases of UCD progressing to MCD, but paraneoplastic phenomena such as bronchiolitis obliterans and pemphigoid eruptions may develop rarely.[7,9] The follow-up of patients with asymptomatic UCD to detect disease progression should be made on a case-by-case basis in discussion with local community services to optimise care. For symptomatic patients, complete surgical resection represents a curative approach.[8] If the affected node or nodal group is not amenable to complete surgical resection, volume-reducing interventions with vascular ablation,[30,31] radiotherapy[32] or a course of weekly 375 mg/m$^2$ rituximab may be considered. These may be effective at symptom control and may act as neoadjuvant therapy to render the nodal mass small enough for reconsideration of complete resection.[33] Prognosis after complete surgical resection is excellent, as only 6% of patients with UCD died due to the disease over a 10-year follow-up.[8] However long-term follow-up is required as recurrence is rare but has been reported up to 14 years after resection.[34]

Where complete resection is not attained, even with neoadjuvant therapy, debulking resection, embolisation or radiotherapy alone may offer adequate control of symptoms.[32,35] Incomplete resection was associated with a worse OS than complete resection but still ~70% at 10 years.[8] Radiotherapy can be effective as primary therapy but is usually reserved for inoperable cases.[32] Given the median age of presentation of UCD being in the fourth decade, particular consideration should be given to limit the dose of radiation to normal tissues.[36] In a proportion of patients, the distinction between UCD and MCD may be challenging due to an oligocentric or regional distribution of pathology. Such patients often run a clinical course like that of patients with UCD.[22]

## Recommendations

- Asymptomatic patients with UCD may be monitored expectantly (2B).
- Symptomatic patients with UCD should be treated as follows:
- A. Curative resection should be the aim (1A).
- B. Unresectable disease may undergo volume reduction therapy by means of vascular ablation (2C), radiotherapy (2C) or rituximab (2C),
- C. Further consideration of surgery if curative resection now achievable after neoadjuvant therapy (2C).

*Multicentric CD*

Each patient should be assessed individually as not all patients require therapeutic intervention. Particularly, patients who are asymptomatic should be monitored closely to allow for prompt intervention upon disease progression. This approach, therefore, spares asymptomatic patients from therapies that have not been shown to be curative or alter the natural history of disease. In addition, not all patients will respond; by withholding therapy patients can be spared short- and long-term toxicities, costs and inconvenience of parenteral drug therapy. The choice of therapy in MCD depends on the presentation of the patient as well as identification of drivers of disease: HHV8-MCD, POEMS-MCD, iMCD (NOS and TAFRO). Up to 40% of patients in a Japanese cohort exhibited pulmonary involvement at diagnosis, with fatigue and splenomegaly being other prominent clinical features.[10]

*Human herpesvirus 8-MCD*

Human herpesvirus 8-MCD often, but not always, co-exists with HIV infection. There is conflicting evidence regarding the consequence of anti-retroviral therapy (ART) on HIV-positive HHV8-MCD.[37] Nevertheless, ART treatment is indicated for all patients with HIV. It should be initiated immediately on diagnosis of HIV and should be continued throughout treatment for MCD.[15] The understanding that in HHV8-MCD, $CD20^{+}$ nodal plasmablasts act as a reservoir of pathogenic HHV8, has driven the successful use of rituximab to deplete this pool of B cells that harbour the virus. The introduction of rituximab as a therapy for HHV8-MCD has resulted in an increase in 5-year OS from 33% to 90%.[38] Rituximab may be used as monotherapy at a dose of 375mg/$m^2$ weekly for 4 weeks in patients with mild symptoms. Relapses of HHV8-MCD can be successfully re-treated with rituximab therapy.[39,40]

The topoisomerase inhibitor (etoposide 100 mg/$m^2$ weekly) has been used in addition to rituximab for more severe clinical presentations of HHV8-MCD, e.g. with a poor performance status [Eastern Cooperative Oncology Group Performance Status (ECOG PS) score >2]; signs of end-organ damage or haemophagocytic syndrome. In a case series, the risk-stratified use of etoposide appeared to be well tolerated and was not associated with excess death compared to rituximab alone.[38] All patients responded to therapy, although only 2% achieved a complete response (CR). It is, therefore, reasonable to consider etoposide in higher risk cases. Rituximab ± etoposide therapy also appears to be effective in patients with HIV-negative HHV8-MCD.[16] Around a quarter to a third of patients relapsed in the year after therapy, with a median time to first relapse being 30 months in one study.[40,41] The use of rituximab in this cohort has been associated with a lower risk of HHV8 lymphoma[42] but with an increased risk of exacerbating of co-existent Kaposi sarcoma.[38,41,43] Rituximab in combination with at least three cycles of anthracycline chemotherapy (provided cardiac function is satisfactory) has been used successfully in a cohort of patients with HIV-associated HHV8-MCD who predominantly had undergone some treatment previously. Particularly, this approach has shown efficacy in treating concomitant Kaposi sarcoma.[38,43] Therapeutic intervention should be guided by the presence of constitutional symptoms and organ function, irrespective of HIV status.

## Recommendation

- Rituximab (375 mg/$m^2$ weekly for 4 weeks) should be considered as initial therapy for HHV8-MCD with mild symptoms (2B).
- In the context of severe systemic symptoms or organ dysfunction consider etoposide (100 mg/$m^2$ weekly for 4 weeks) in conjunction with rituximab (2B).
- If symptoms severe and concurrent Kaposi sarcoma, anthracycline therapy (e.g. liposomal doxorubicin 20 mg/$m^2$ every 3 weeks for at least three cycles) may be considered (2B).

*POEMS-MCD*

Patients with MCD may present with some features of POEMS, which are often milder than in classical POEMS. Conversely, patients with POEMS may be found to exhibit some histological features of CD.[21] Given the pathophysiological overlap between POEMS and MCD, patients with simultaneous presentations may require therapy tailored to both conditions depending on the clinical presentation.[44] The high prevalence of sensorimotor neuropathy in POEMS-MCD should warrant caution with bortezomib or thalidomide therapy at induction, but this can be well-tolerated.[45] Given their efficacy and low neurotoxicity compared to thalidomide and bortezomib, lenalidomide-based myeloma regimens may be considered. The role of ASCT in MCD is less clearly defined than for POEMS. Therefore, it may be considered in the experimental setting in a specialist centre.

## Recommendation

- POEMS-MCD should have therapy directed against the underlying PC dyscrasia. This should comprise standard myeloma induction therapy with consideration of consolidation with ASCT (1B).

*Idiopathic MCD-NOS and TAFRO*

The cases of MCD that lack an associated driver such as HHV8 or POEMS, are described as being idiopathic. TAFRO represents a subset of clinically aggressive disease, compared to the remainder of cases having a milder inflammatory

presentation of iMCD, which is referred to as iMCD-NOS (Figure 1). Several therapeutic options have been described in case reports and small cohort studies. These include systemic corticosteroids, monoclonal antibodies and systemic combination chemotherapy. Given the limited evidence underlying many of the therapeutic options, clinical trials should be considered depending on availability as part of a regional MDT discussion.

Consensus guidelines for the treatment of iMCD have been published by the CDCN.[46] The choice of treatment is driven primarily by the urgency for a symptomatic response, rather than histopathological characteristics.[47,48] The burden of symptoms in severe cases may be defined as those with at least two of the following: ECOG PS score of ≥2; severe renal impairment (glomerular filtration rate <30 ml/min/1.73 $m^2$); widespread serous effusions; haemoglobin <80 g/l and pulmonary involvement including pneumonitis.[46] Similar to the approach used in the 2018 consensus guidelines, the iMCD International Prognostic Index (iMCD-IPI) has recently sought to stratify patients according to performance status and organ dysfunction to predict response to therapy.[48] In iMCD, CRP concentration remains closely correlated with IL-6 and may be used to track activity and treatment response.[49] A suggested treatment algorithm for iMCD-NOS is shown in Figure 2.

### *Corticosteroids*

The primary role of corticosteroids is for the rapid control of systemic inflammation or associated phenomena such as autoimmune haemolytic anaemia. Responses to corticosteroids are observed across the spectrum of MCD, but they are not durable. A recommended starting regimen would be a dose of 1 mg/kg prednisolone for 2 weeks followed by a taper.[28] The control of inflammatory symptoms in a patient requiring critical care will likely require a more intense dosage of steroid than for the management of paraneoplastic autoimmune phenomena. Therefore, the dose of steroid should be commensurate with the nature and severity of the primary or concomitant clinical condition.

### *Monoclonal antibody-mediated therapy*

Interleukin-6 has been identified as an important mediator of the inflammatory state that promotes lymphadenopathy in MCD.[11] However, elevated serum concentrations of IL-6 are not found in all cases of active iMCD. Furthermore, circulating concentrations of the cytokine do not predict clinical efficacy from anti-IL-6 therapy.[50] Despite these caveats, IL-6 signalling has been made a therapeutic target in iMCD. Siltuximab is a chimeric human-murine IgG monoclonal antibody that binds human IL-6 (but not virally derived, vIL-6

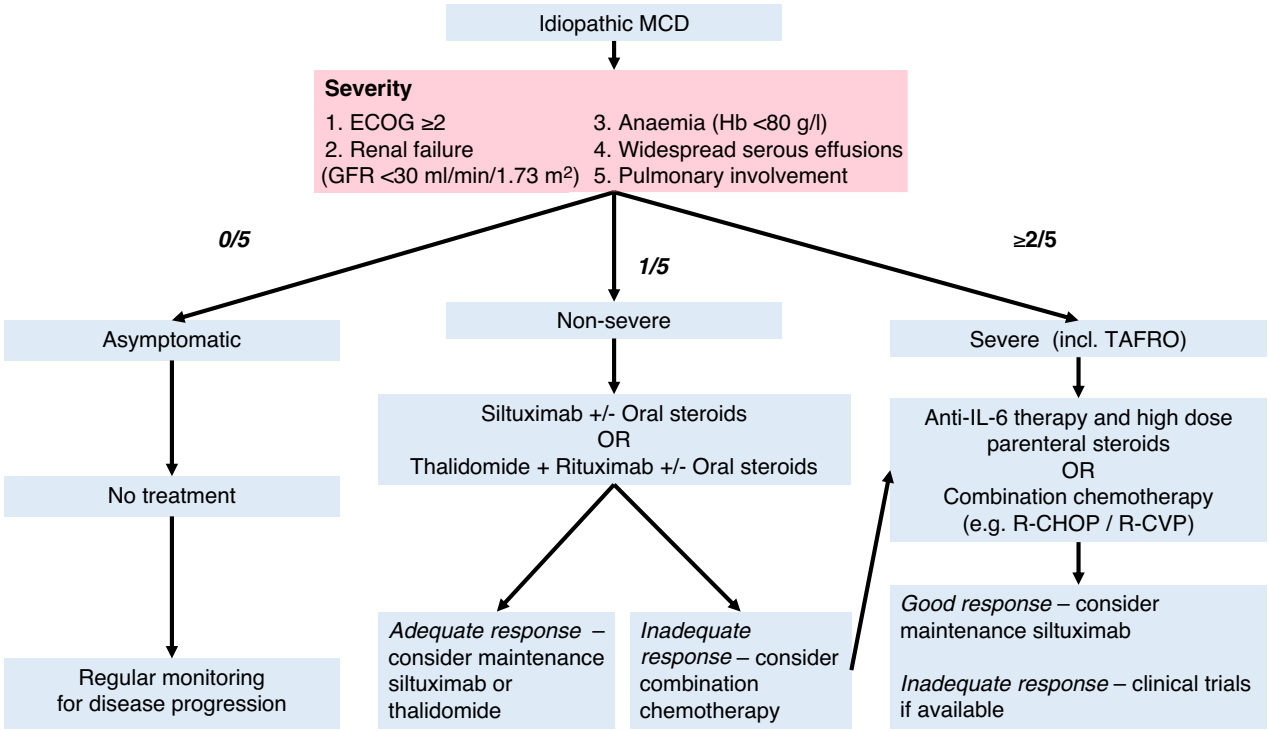


**Fig 2.** Suggested therapeutic algorithm in idiopathic multicentric Castleman disease. Severity scoring derived from the Castleman Disease Clinical Network. Anti-IL-6 therapy, anti-interleukin-6 therapy denotes siltuximab or tocilizumab; ECOG, Eastern Cooperative Oncology Group Performance Status score; GFR, glomerular filtration rate; Hb, Haemoglobin; MCD, multicentric Castleman disease; R-CHOP, rituximab-cyclophosphamide, doxorubicin, vincristine (Oncovin) and prednisone; R-CVP, rituximab, cyclophosphamide, vincristine, and prednisone; TAFRO, Thrombocytopenia, Anasarca, myelofibrosis, Renal dysfunction and Organomegaly. [Colour figure can be viewed at wileyonlinelibrary.com]

as found in HHV8-MCD) to block signal transduction. It is the only drug licensed in the UK for the treatment of iMCD. Siltuximab [11 mg/kg intravenously (IV) every 3 weeks] may be reserved for prompt use on signs of relapse, with the aim to avoid re-induction with high-dose chemotherapy. Siltuximab has a half-life of 17–20 days, necessitating initial dosing every 3 weeks, although extending to 6-weekly maintenance makes treatment more acceptable. A phase I, open-label study demonstrated the safety of siltuximab in several lymphoproliferative disorders including iMCD.[51] The most common side-effects were cytopenias (10–25%) and hyperlipidaemia (15–20%). The cytopenias were generally Grade 1–2, and rarely prompted delay or discontinuation of therapy. CNTO238MCD003, the only blinded randomised controlled trial (RCT) of any therapy in iMCD, compared siltuximab with placebo.[50] Approximately one-third of symptomatic patients with iMCD achieved partial remission, compared to none on placebo (no steroid escalation was permitted). Siltuximab therapy improved symptoms (median time to response 33 days) more rapidly than a reduction in volume of lymphadenopathy (155 days for significant nodal regression). The response was durable whilst on treatment. Importantly, iMCD symptoms of fatigue improve significantly in the siltuximab-treated cohort (68%), compared to placebo or best-supportive care (35%) and the multi-point iMCD symptomatic score improved overall.[52] Patient-reported outcome showed benefit, even though iMCD patients were relatively mildly affected but, due to the screening period, delays for central review of eligibility and placebo-controlled design, the most severe, fulminant cases had been excluded. However, secondary analysis within phase II clinical trial data suggests that patients exhibiting signs of a more moderately increased inflammatory state may benefit the most from siltuximab therapy.[53] The evidence for siltuximab currently supports its use in non-severe cases in need of long-term control. Long-term safety and efficacy have been examined in a follow-on study, whereby 70% of responders sustained a response over a median follow-up of 6 years.[54] The response rates to siltuximab have recently been analysed for those patients who had previously received non-IL-6-targeted therapies. Both newly diagnosed and previously treated patients showed similar levels of response to siltuximab. Very few patients achieved a CR and the majority showed partial response or stable disease.[55] Siltuximab has received regulatory approval in the UK for use in iMCD, but as of November 2020, requires an individual funding request (IFR), which may hamper access.

In the absence of a prospective direct comparison with anti-IL-6-targeted therapy, retrospective series of the use of rituximab in MCD show poorer depth and overall rate of remission compared to siltuximab.[56] However, rituximab is very well tolerated and readily available and, therefore, may be considered as first-line therapy in mild disease or in the presence of immune-mediated cytopenias. Despite the success of IL-6-signalling blockade, there remains a significant unmet clinical need not only for patients who are intolerant of anti-IL-6 therapy, but also for a reliable disease-modifying therapy.[50]

Tocilizumab is a monoclonal antibody that antagonises the IL-6 receptor (IL-6R) to block signal transduction.[57] Tocilizumab is licensed in Japan, but not in the UK, for the treatment of iMCD-TAFRO. iMCD-TAFRO is a relatively recently described condition, which is even rarer than other forms of CD. Only anecdotal reports of response to calcineurin blockade and anti-IL-6 therapies have been reported.[58,59] Although tocilizumab has not been subjected to a RCT, patients have been reported to exhibit significant reductions in lymphadenopathy and resolution of constitutional symptoms and signs.[60] In a small, dose-finding study, humanised anti IL-6R antibody was administered at 50 or 100 mg IV weekly and was associated with a persistent improvement in symptoms and reduction in lymphadenopathy over 1 year.[25] A retrospective study comprising nine cases of TAFRO appeared to suggest that more durable remissions were associated with steroids and anti-IL-6 therapy compared to combination chemotherapy.[7] Nevertheless, tocilizumab is approved in the UK for use in highly inflammatory cytokine release syndromes. Therefore, in the event of a severely unwell patient requiring intensive care support, the authors envisage that tocilizumab may be used on an unlicensed basis given that is more readily available than siltuximab, which usually requires an IFR.

### *Systemic combination chemotherapy*

Standard cytotoxic lymphoma regimens, such as cyclophosphamide, vincristine, prednisone (CVP)/cyclophosphamide, hydroxydoxorubcin, vincristine (Oncovin) and prednisolone (CHOP), with or without rituximab have been described in multiple cases studies but no randomised prospective data exist to guide their routine use.[61] A retrospective cohort study of MCD revealed that a CR was achieved in just under half of patients but the median time to relapse was 6 months.[12] Despite significant myelo-, neuro- and cardio-toxicity, combination chemotherapy may achieve rapid control of severe cases refractory to anti-inflammatory therapy.

Thalidomide has been shown to exert its anti-inflammatory effects partly via suppression of IL-6 signalling.[62] The long-term continuation of thalidomide has been reported to be associated with prolonged disease control in MCD.[63,64] Rituximab (4 weeks) and thalidomide (1–3 months) in combination have been observed in a retrospective mixed cohort of MCD to show complete regression of lymph nodes and symptoms in 91% of patients, which was maintained after discontinuation of treatment with a 2-year progression-free survival of 60%.[65] The TCP regimen (thalidomide 100 mg daily for 2 years; oral cyclophosphamide 300 mg/m$^2$ weekly for 1 year; prednisone 1 mg/kg twice weekly for 1 year) has undergone a phase II study in a cohort of 25 patients with newly diagnosed iMCD. The primary end-point was durable

tumour and symptomatic response for at least 24 weeks and was achieved in 48% of patients but failed in 40% of patients. The remainder (12%) exhibited stable disease. There were three deaths in total, two of which were after disease progression. OS at 1 year was 88% but a control arm was not recruited.

Therefore, thalidomide therapy for at least 3 months and up to 2 years based on current long-term follow-up data in combination with weekly rituximab for 4 weeks, and steroids as required at induction, is suggested when siltuximab is neither available nor tolerated.

## Recommendations

- Treatment of iMCD should be determined by the burden of symptoms experienced by the patient, with asymptomatic patients offered monitoring alone (1A).
- Severely symptomatic and critically ill patients, including those with suspected TAFRO, should receive parenteral corticosteroids and anti-IL-6 signalling therapy. If anti-IL-6 signalling therapy is not readily available or achieves an adequate response, it should be replaced by combination chemotherapy with rituximab [e.g. rituximab (R)-CHOP/CVP]. Once symptoms subside, subsequent maintenance with siltuximab may be considered (2B).
- In the absence of severe symptoms, patients may be offered the following long-term:
  - i Siltuximab with or without a short course of corticosteroids (e.g. prednisolone 1 mg/kg daily) (1A).
  - ii Rituximab and thalidomide especially in the presence of immune cytopenias (1B).
- Maintenance therapies require regular monitoring for adverse effects.
  - iii Siltuximab requires regular monitoring for cytopenias, polycythaemia, occult infection and hyperlipidaemia (2B).
  - iv Thalidomide for a minimum of 3 months up to 2 years. This class of drug requires regular patient counselling for teratogenicity, monitoring for cumulative neuropathy, cytopenias and regular assessment of thrombotic risk (1A).

## Conclusion

Castleman disease remains a diagnostic and therapeutic challenge. It is now clear that UCD and the subtypes of MCD have different presentations and pursue different clinical courses, which should guide the choice of therapy offered to the patient. Despite the success of surgery for UCD, rituximab for HHV8-MCD and IL-6-antagonism in iMCD, there remains a significant unmet clinical need for definitive therapy, particularly in the cases of iMCD. All patients with CD should be encouraged to self-enrol in the ACCELERATE natural history registry of the CDCN (#NCT02817997, http://www.cdcn.org/accelerate). Thanks to such collaborative efforts, the field has advanced more in the last 15 years than in the preceding half-century and the authors, therefore, look forward to further advances in our knowledge and in therapy for this heterogeneous disease.

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## Conflict of interest

The BSH paid the expenses incurred during the writing of this good practice paper.

All authors have made a declaration of interests to the BSH and Task Force Chairs that may be viewed on request. The following authors have conflict of interest to declare: Karthik Ramasamy: EUSA Pharmaceutical Advisory Board. The following members of the writing group: Oliver C. Lomas, Daniel Royston, Jim Cavet, Guy Pratt, Matthew Streetly and Stephen Schey have no conflict of interest to declare.

## Review process

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (http://www.b-s-h.org.uk/guidelines).

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