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AMERICAN COLLEGE of RHEUMATOLOGY
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EXPERT PERSPECTIVES ON CLINICAL CHALLENGES

Expert Perspective: Diagnosis and Treatment of Castleman Disease

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Castleman disease (CD) is a major diagnostic challenge for rheumatologists. Unicentric CD (UCD) involves one enlarged lymph node region, whereas multicentric CD (MCD) involves multiple enlarged lymph node regions. Both UCD and MCD may exhibit a wide range of symptoms that overlap with other immune-mediated conditions. MCD can be associated with excessive cytokine production due to a plasma cell neoplasm (MCD–polyneuropathy, organomegaly, endocrinopathy, monoclonal paraprotein, skin changes) or uncontrolled human herpesvirus-8 infection (HHV-8) (HHV-8–positive MCD), but more than half of cases are idiopathic. Although they are all driven by excessive cytokines such as interleukin-6 (IL-6), patients with idiopathic MCD (iMCD) often present as a diagnostic mystery with heterogeneous symptomatology that can be classified into three subtypes. The three subtypes are iMCD–thrombocytopenia, anasarca, fever, renal dysfunction/reticulin fibrosis, organomegaly (TAFRO); iMCD–idiopathic plasmacytic lymphadenopathy (IPL); and iMCD–not otherwise specified (NOS). Rapid onset cytokine storm with severe inflammation, anasarca, thrombocytopenia, and small volume lymphadenopathy, similar to hemophagocytic lymphohistiocytosis or sepsis, are the hallmarks of iMCD-TAFRO. Patients with iMCD-IPL present with subacute or chronic lymphadenopathy, anemia of inflammation, and polyclonal hypergammaglobulinemia, often with increased IgG4 in serum and lymph node tissue; these cases can be difficult to distinguish from IgG4-related disease and histiocyte disorders. Those who have iMCD not meeting criteria for TAFRO or IPL have iMCD-NOS, which often mimics indolent lymphoma or autoimmune conditions. Patients with autoimmune disease, lymphoma, and infections can experience Castleman-like changes in reactive lymph nodes, and thus histologic findings must be combined with clinical and laboratory findings to accurately diagnose iMCD. Broadly speaking, treatments for CD can be considered in three categories: immunomodulators such as glucocorticoids, cytokine inhibitors, and sirolimus; antilymphoma therapies such as rituximab, cytotoxic chemotherapy, and BTK inhibitors; and antimyeloma therapies such as thalidomide and bortezomib. The first-line therapy for all subtypes of iMCD is siltuximab, an IL-6 antagonist. Patients with refractory disease have numerous treatment options and consulting treatment guidelines as well as consultation with a center with expertise in CD are recommended.

CLINICAL CHALLENGE

Case 1: A 23-year-old White male presented to the emergency department with a two-month history of progressive fatigue, fever, intermittent abdominal pain, constipation, and dyspnea. He has gained 20 kg over one month, from a baseline of 80 kg. On examination, he had severe lower extremity pitting edema, decreased breath sounds, and dullness to percussion at the lung bases. His hemoglobin was at 85 g/L, platelets were at 45 giga/L, C-reactive protein (CRP) was at 150 mg/L, and creatinine was at 210 μmol/L. Serum protein electrophoresis showed normal gamma globulins at 12 g/L, and autoantibodies were

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negative. Imaging revealed diffuse mild lymphadenopathy to 1.2 cm in short axis and mild splenomegaly with profound anasarca. A bone marrow biopsy showed reticulin fibrosis (grade 1–2) and megakaryocyte hyperplasia. Excisional biopsy of a 1.2 cm axillary lymph node showed atrophic germinal centers and hypervascularity, which are thought to be reactive changes with no evidence of malignancy.

Case 2: A 42-year-old Chinese woman was referred to a rheumatologist for chronic inflammation and a CRP level from 50 to 120 mg/L in the context of a three-year history of enlarged lymph nodes up to 2 to 3 cm in the cervical, mediastinal, abdominal, and inguinal areas on fluorodeoxyglucose positron emission tomography (FDG-PET) computed tomography (CT), with mildly increased uptake in the submandibular and parotid glands. She was diagnosed with lymphocytic interstitial pneumonitis one year from the date of writing of this article. Laboratory tests showed mild anemia (hemoglobin at 100 g/L) and thrombocytosis (platelets at 470 giga/L), with marked polyclonal hypergammaglobulinemia on serum protein electrophoresis and quantitative Igs: IgG 65 g/L (7–16), IgA 10 to 12 g/L, and IgM 4 to 5 g/L. Autoantibodies (antinuclear antibody [ANA], rheumatoid factor, and antineutrophil cytoplasmic antibody) were negative, and complement levels were normal. An excisional cervical biopsy of a 2.5-cm lymph node showed polyclonal plasmacytosis and hyperplastic germinal centers with no evidence of malignancy.

BACKGROUND

The two clinical cases mentioned previously represent distinct subtypes of idiopathic multicentric Castleman disease (iMCD). Castleman disease (CD) is a hematologic disorder characterized by enlarged lymph nodes with characteristic histology and a wide range of clinical presentations.[1,2] Diagnosis and management of CD, particularly iMCD, are a clinical challenge for several reasons. First, CD is rare, and most physicians seldom encounter it. Second, the clinical presentation is very heterogeneous, ranging from asymptomatic lymphadenopathy to chronic inflammation with lymphadenopathy (case 2), to severe, rapidly progressive cytokine storm (case 1). Third, iMCD can mimic rheumatologic diseases with overlapping symptoms and laboratory abnormalities as well as responsiveness to common treatments such as glucocorticoids. Finally, unlike clonal malignant diseases such as Hodgkin disease (eg, Reed-Sternberg cells), the histologic features of CD are not specific to CD and can be seen in infectious, autoimmune, and neoplastic diseases. Thus, many patients with CD present to rheumatologists as diagnostic mysteries. This review will focus on the protean ways in which CD, particularly iMCD, presents and how to distinguish it from key mimickers using expert clinicopathologic correlation.

Classification of CD. CD can be classified both clinically and histologically, but prognosis and therapy are directed by clinical (Figure 1) more so than histologic classification. Historically, clinical classification of CD was based on two factors, both of which were considered binary: number of enlarged lymph node groups and presence or absence of systemic symptoms. Patients with one region of enlarged lymph nodes were classified as having unicentric CD (UCD), and those with more than one region of enlarged lymph nodes were classified as having MCD. UCD is rarely associated with systemic symptoms and often cured by surgical resection, whereas MCD typically includes systemic inflammatory symptoms and requires systemic therapies.[3,4] However, important new subtypes have been added to the canon in the past 15 years that demonstrate a more complex spectrum of both lymph node involvement and pattern of systemic symptoms (Figure 1). We now know that UCD can be associated with systemic immune dysregulation such as an MCD-like inflammatory state,[5,6] paraneoplastic pemphigus (PNP),[7] bronchiolitis obliterans (BO),[8] and AA amyloidosis.[9,10] Further, not all patients with more than one enlarged lymph node regions have systemic symptoms. Asymptomatic patients with a few regions of lymphadenopathy in neighboring regions are now classified as having oligocentric CD (OCD),[11,12] and those asymptomatic patients with more distributed enlarged lymph nodes are classified as having asymptomatic MCD (aMCD).[13]

Symptomatic MCD has three major subtypes (Figure 1): polyneuropathy, organomegaly, endocrinopathy, monoclonal paraprotein syndrome (POEMS)–MCD); human herpesvirus-8 associated (HHV-8) (HHV-8–associated MCD); and iMCD. Diagnosis of POEMS-MCD is aided by the presence of a monoclonal paraprotein (typically an IgA or IgG lambda monoclonal protein in serum) and peripheral neuropathy. Most patients with POEMS-MCD are treated by hematologists, with therapy directed at the plasma cell disorder.[3,14] HHV-8–associated MCD is typically seen in the context of HIV or other immunodeficiencies. Diagnosis is aided by immunohistochemistry (latency-associated nuclear antigen positivity for HHV-8), as well as detectable HHV-8 viremia in blood in some patients. Management of HHV-8–associated MCD typically requires treatment of the HIV/immunodeficiency as well as rituximab or other systemic therapies to manage the MCD.[15] Among the subtypes of symptomatic MCD, iMCD is most likely to present to rheumatologists and will be the focus of this review.

iMCD has three subtypes, all of which have substantial overlaps with autoimmune and autoinflammatory diseases. The key features of these three subtypes are summarized in Table 1. Given their heterogeneity and differing approaches to management, rheumatologists must be familiar with the subtypes of iMCD and how to distinguish them from key mimics:

- iMCD–thrombocytopenia, anasarca, fever, reticulin fibrosis/renal dysfunction, organomegaly (iMCD-TAFRO)
- iMCD–idiopathic plasmacytic lymphadenopathy (iMCD-IPL)
- iMCD–not otherwise specified (iMCD-NOS)

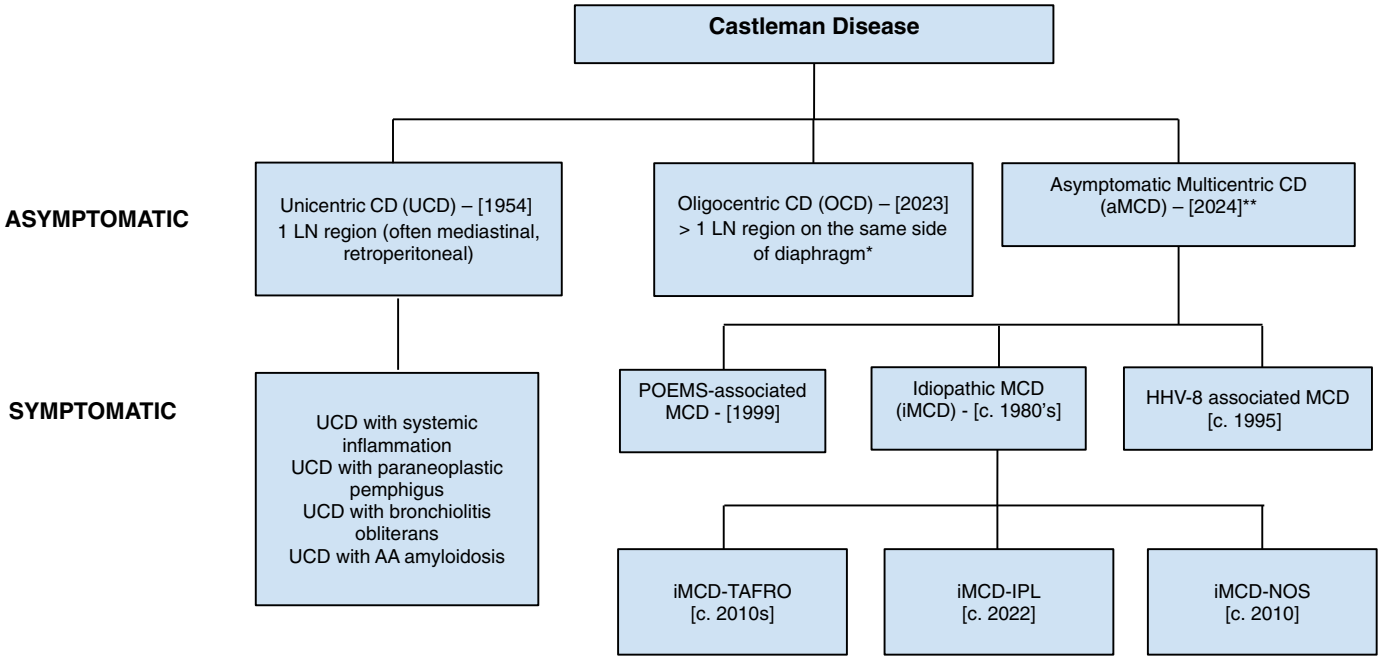

Figure 1. Classification of CD (approximate year entity first described or accepted as a subtype of CD). *Castleman lymphadenopathy in an oligocentric pattern associated with systemic symptoms is classified and treated as iMCD. CD, Castleman disease; HHV-8, human herpes virus 8; iMCD, idiopathic multicentric CD; IPL, idiopathic plasmacytic lymphadenopathy; NOS, not otherwise specified; OCD, oligocentric CD; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal paraprotein, skin changes; TAFRO, thrombocytopenia, anasarca, fever/reticulin fibrosis, renal dysfunction, organomegaly; UCD, unicentric CD.

These three subtypes can be thought of across a spectrum with iMCD-TAFRO on one end, iMCD-IPL on the other end, and iMCD-NOS in between but with greater overlap with iMCD-IPL. Patients with iMCD-TAFRO present with severe and highly morbid cytokine storm syndrome with thrombocytopenia, fluid accumulation (anasarca, edema, effusions), low volume lymphadenopathy, and renal dysfunction, as illustrated in case 1. Patients with iMCD-NOS and iMCD-IPL tend to present with chronic subacute lymphadenopathy, anemia, normal, or elevated platelets; polyclonal hypergammaglobulinemia; and systemic inflammation but with preserved organ function, as illustrated in case 2. Thus, iMCD should be in the differential diagnosis both for patients with lymphadenopathy as well as those with cytokine storm.[16]

Epidemiology of iMCD. One of the first large-scale epidemiologic studies of iMCD in the United States involving insurance claims data estimated an incidence of 994 to 4,216 cases per year in the United States.[17] The estimated prevalence of all CD was 16.2 per million (95% confidence interval 10.5–25.6), UCD was 5.1 per million (95% confidence interval 2.6–11.2) and for iMCD was 9.7 (95% confidence interval 5.6–17.8). Among the patients with iMCD, 53.3% were male and 46.7% were female, with a mean age of 51.4 years. Although this study only identified a small portion of patients younger than 18 years old, we believe this is due to confounders because of data collection and recognition. In our experience, iMCD is remarkably evenly distributed across the age span, with a notable portion of iMCD-TAFRO occurring in pediatric patients.[18,19]

We have also observed differences between regions of the world. Much of the literature on CD comes from East Asia, North America, and Western Europe, and there is a paucity of data on CD from other regions. With these limitations in mind, some trends are that although the overall incidence of CD is similar in Asia, North America, and Europe, the proportion of UCD is higher in the west. In New Zealand, patients with Polynesian descent are overrepresented among patients with iMCD.[20] Most of the early literature on TAFRO came from Asia, and specifically Japan,[21] describing a preponderance of East Asian men in their 20s to 50s, but in recent years, more patients with iMCD-TAFRO have been reported in North America and Europe. A multicenter study of 731 patients with MCD in China showed that the majority of patients (98.3%) were negative for HHV-8, and 19.3% of patients had aMCD.[6] Of the 580 patients with iMCD who fulfilled Castleman Disease Collaborative Network (CDCN) diagnostic criteria,[1] 25.9% of patients had "severe" disease, and 7.1% of patients had iMCD-TAFRO. Likewise, the concept of idiopathic plasmacytic lymphoma as a subtype of iMCD arose in Japan and China, and nearly all reported patients described in the literature as having iMCD-IPL are East Asian.[22] More patients with iMCD-IPL likely exist in North America but have not historically been recognized as iMCD-IPL.

Table 1. Key features of subtypes of idiopathic iMCD*

	iMCD-TAFRO	iMCD-IPL	iMCD-NOS
Key features	Thrombocytopenia, anasarca, reticulin fibrosis, renal dysfunction, organomegaly. In addition, acute, progressive onset, adrenal abnormalities; frequent critical illness, severe hypoalbuminemia and proteinuria.	Severe PHGG, multicentric lymphadenopathy, hyperplastic germinal centers and prominent plasmacytosis (plasmacytic histology), absence of other autoimmune disease. In addition, subacute onset, indolent course, lymphocytic interstitial pneumonitis; platelets normal or elevated.	2017 iMCD criteria, major criteria: multicentric lymphadenopathy ≥1 cm with defined CD histology (see Figure 3); ≥2 minor criteria (clinical criteria such as anemia, PHGG > 17 g/L); exclusion of mimickers (eg, lymphoma, infection, autoimmune disease). In addition, subacute onset.
Key mimics	HLH, sepsis, marrow failure syndrome, systemic lupus erythematosus, severe Still disease	IgG4-RD, Sjögren disease or autoimmune disease, lymphoma	Lymphoma, IgG4-RD, autoimmune disease
CBC and CRP[a]	Anemia, thrombocytopenia, CRP >50 mg/L (may be modestly elevated early but rises rapidly, often to >200 mg/L)	Anemia, thrombocytosis (Chinese criteria: platelets >350 × 10^9/L), CRP 50–200 mg/L (can be very high chronically)	Anemia, thrombocytosis (often >400 × 10^9/L), CRP 30–100 mg/L (prolonged moderate elevation)
SPEP, IgG4	IgG is typically 5–15 g/L (low to mildly elevated; IgG >17 g/L is atypical).	Severe PHGG (Japanese criteria: γ-globulins >40 g/L or IgG >35 g/L; Chinese criteria: IgG > 17.4 g/L), IgG4 is often >5 g/L; IgA and IgM are often elevated.	Moderate polyclonal hypergammaglobulinemia, elevated IgG4 in a subset.
Lung	Nodules, cysts, pleural effusions	Nodules, cysts, lymphocytic interstitial pneumonitis; pleural effusions	Pulmonary nodules, cysts, consolidations, ground glass opacities; lymphocytic interstitial pneumonitis; pleural effusions
Bone marrow	Reticulin fibrosis, megakaryocyte hyperplasia	Polyclonal plasmacytosis/nonspecific	Polyclonal plasmacytosis/nonspecific
Lymph node	Small, but shows Castleman histology. Often hypervascular (hyaline vascular) type. Extramedullary hematopoiesis can be seen.	Often plasmacytic type. Often IgG4-enriched (sometimes meeting thresholds for IgG4-RD, >50/hpf, IgG4/IgG ratio >40%).	Often plasmacytic or mixed (plasmacytic and hypervascular) type.
Management	Aggressive anti-inflammatory therapy; IL-6 inhibition first line, mTOR inhibitors, other cytokine inhibition (IL-1, TNF, JAKi); may also need antilymphoma, myeloma therapies.	IL-6 inhibition or rituximab or thalidomide-based therapies. Other antilymphoma or myeloma therapies.	IL-6 inhibition is the first-line treatment. Relapsed/refractory disease: other cytokine blockade (IL-1, TNF, JAKi); rituximab; antilymphoma or myeloma therapies.

* CBC, complete blood cell count; CRP, C-reactive protein; HLH, hemophagocytic lymphohistiocytosis; hpf, high-power field; IgG4-RD, IgG4-related disease; IL-1, interleukin-1; iMCD, multicentric Castleman disease; IPL, idiopathic plasmacytic lymphadenopathy; JAKi, JAK inhibitor; mTOR, mammalian target of rapamycin; NOS, not otherwise specified; PHGG, polyclonal hypergammaglobulinemia; SPEP, serum protein electrophoresis; TAFRO, thrombocytopenia, anasarca, reticulin fibrosis, renal dysfunction, organomegaly; TNF, tumor necrosis factor.
[a] Approximate interquartile ranges for CRP from a large cohort at Peking Union Medical College Hospital.

Pathophysiology of iMCD. The etiology of most cases of CD, particularly iMCD, remains a mystery. PDGFRβ mutations are present in a small subset of patients with UCD,[23] but otherwise, a contributory clonal abnormality has not been found, particularly in iMCD.[24] HHV-8–MCD is driven by a virus-producing viral[25,26] interleukin-6 (IL-6), and POEMS-MCD is caused by a plasma cell neoplasm. Although the cause of iMCD is not yet known, studies to date have not identified infectious triggers or clonal neoplasms. Although commonly referred to as a lymphoproliferative disorder, a recent study suggests that lymphocyte trafficking may be more important to the development of lymphadenopathy than proliferation.[27]

Inflammation is central to disease pathophysiology in symptomatic MCD. The central role of the IL-6–soluble IL-6 receptor–soluble glycoprotein 130 axis was elucidated more than 30 years ago[28] and demonstrated to be a key driver based on clinical trials showing effectiveness of anti–IL-6 therapies. Siltuximab, an anti–IL-6 therapy, is the only United States Food and Drug Administration– or European Medicines Agency–approved therapy for iMCD or any form of CD. However, it is not effective in all patients; other cytokines including IL-1, CXC13, and tumor necrosis factor (TNF) are likely involved.[29–32] The trigger or cause of this inflammation in iMCD is yet to be discovered.

DIAGNOSTIC APPROACH

UCD, OCD, and aMCD diagnosis and management. Patients with OCD and aMCD and most patients with UCD do not have systemic inflammation or end-organ damage. Thus, diagnosis is based on biopsy and exclusion of mimickers (such as lymphoma, sarcoidosis, and autoimmune disease). UCD can present with localized lymphadenopathy anywhere in the body, but it often presents with deep lymph node involvement in mediastinum and retroperitoneum. Patients and surgeons are sometimes reluctant

to pursue invasive surgery in these cases. However, resection of the mass is both diagnostic and therapeutic and is strongly encouraged.[33] If surgical excision is not feasible (eg, if the lesion is encasing critical vessels) and there are no systemic symptoms, observation is reasonable. In patients with unresectable, symptomatic UCD due to compression of nearby structures, rituximab can debulk UCD, and radiation and cryoablation can also be used.[34] In patients with unresectable UCD causing systemic inflammation, IL-6 inhibition, or other anti-inflammatory therapy may be useful. Paraneoplastic features such as PNP and BO can occur in UCD, and these patients have a worse prognosis.[7,8] Immunosuppressives such as mycophenolate mofetil or sirolimus can be effective for PNP. However, in UCD with BO, neither systemic therapy nor complete surgical resection appear to alleviate BO or prevent progression of BO.[8] In some cases of patients with UCD and BO, lung transplantation may be needed.

OCD is a new concept, first described in 2023, and optimal management is evolving.[11] Some patients may be amenable to surgical resection, and others may benefit from debulking with rituximab.[12] Traditionally, all patients with MCD were thought to be symptomatic. However, a recent Chinese study has described a subset of patients with lymphadenopathy on both sides of the diaphragm who displayed no systemic symptoms and are thus classified as having aMCD. These patients do not appear to benefit from systemic therapy. Over a median follow-up of 46.5 months, only 6 of 114 patients (5.3%) progressed to develop systemic symptoms characteristic of iMCD. Thus, observation may be appropriate for patients with aMCD.[13]

Diagnostic approach to suspected iMCD. The overall diagnostic approach to CD is illustrated in Figures 2 and 3. In patients with acute cytokine storm syndrome and end-organ damage such as renal failure and anasarca with rapid fluid accumulation, iMCD-TAFRO should be considered (Figure 2). In patients with subacute disease (typically seen in the ambulatory setting) characterized by lymphadenopathy and inflammation, both iMCD-NOS and iMCD-IPL are in the differential diagnosis (Figure 3). The 2017 International Consensus criteria[1] for diagnosis of iMCD are shown Supplemental Table 1. Although these 2017 criteria do not distinguish among iMCD-TAFRO, iMCD-IPL, and iMCD-NOS, they remain the gold standard, and all patients with iMCD should fulfill these diagnostic criteria.

Laboratory tests in suspected iMCD. Suggested laboratory tests are indicated in Figures 2 and 3. CRP is a crucial test in the diagnosis and monitoring of iMCD. Although cytokine levels can provide added value, CRP is more reflective of disease activity, can be measured frequently in real time, and can be used to monitor response to therapy. Other simple markers of inflammation such as soluble CD25 (sCD25) (also known as soluble IL-2 receptor, a marker of T cell activation), serum ferritin, and D-dimer can be used as simple biomarkers to help distinguish iMCD from other cytokine storm syndromes (Figure 2) and to monitor response to treatment.[35–37] Measurement of cytokine/cytokine receptor/chemokine levels such as IL-6, vascular endothelial growth factor, and CXCL9 has limited practical value. IL-6 is often not very elevated, even in patients with severe inflammation (IL-6 relies on a buffered signaling pathway in most tissues so serum levels do not reflect intracellular effect), and increases substantially in all patients after IL-6 blockade due to issues with the assay (and should not be interpreted as indicating relapse; it is recommended to no longer test for IL-6 after a blocker has been tried).[38,39] Serum protein electrophoresis, IgG, and IgG4 can be quite useful. If markedly elevated, these suggest iMCD-IPL, whereas in iMCD-TAFRO, IgG is typically normal or slightly decreased or increased. Positive autoantibodies can be seen in iMCD, although very high levels of specific autoantibodies should lead consideration of other diseases. It should also be noted that autoimmune disease such as Sjögren disease, lupus, and autoinflammatory diseases can rarely occur concomitantly with iMCD.[40–42] Serum albumin is often low, and the urine albumin-to-creatinine ratio is often high at the baseline. Viral testing for HIV, viral hepatitis, and HHV-8 should be done at baseline, and Epstein-Barr virus (EBV) viral load should be considered as EBV–hemophagocytic lymphohistiocytosis (HLH) or chronic active EBV, which can mimic TAFRO.

Imaging in suspected iMCD. At minimum, patients with suspected iMCD should have CT imaging from neck to pelvis to examine the extent of lymphadenopathy and assess for hepatosplenomegaly and features and CD mimickers (such as pancreatic swelling or retroperitoneal fibrosis in IgG4-related disease [IgG4-RD]) (Figure 4). Patients with lacrimal gland swelling and suspected IgG4-RD should have CT of the head/orbits, as well. Intracranial involvement and aggressive osseous lesions argue against CD and in favor of aggressive neoplastic, autoinflammatory, or infectious processes. Whereas OCD and MCD typically feature small lymph nodes (typically <3 cm in short axis), lymph node masses in UCD can be quite large, often >5 cm. Lung involvement, such as nodules, cysts, and consolidation, is seen in 30% to 40% of iMCD-NOS cases on CT.[43] Evidence of fluid accumulation including pericardial and pleural effusions and subcutaneous edema or anasarca can be seen in all three iMCD subtypes and is an obligatory feature in iMCD-TAFRO. Perinodal fat infiltration has been recently noted as a helpful feature.[44] Adrenal abnormalities such as adrenal hemorrhage and adrenalitis are frequent in iMCD studies, particularly from Asia,[45] but can be seen in the west, as well.[46,47]

FDG-PET CT can be helpful both for identifying the most PET-avid node for biopsy as well as assessing for mimickers (Figure 4). CD typically demonstrates mild to moderate FDG avidity; very high avidity should raise suspicion for another process

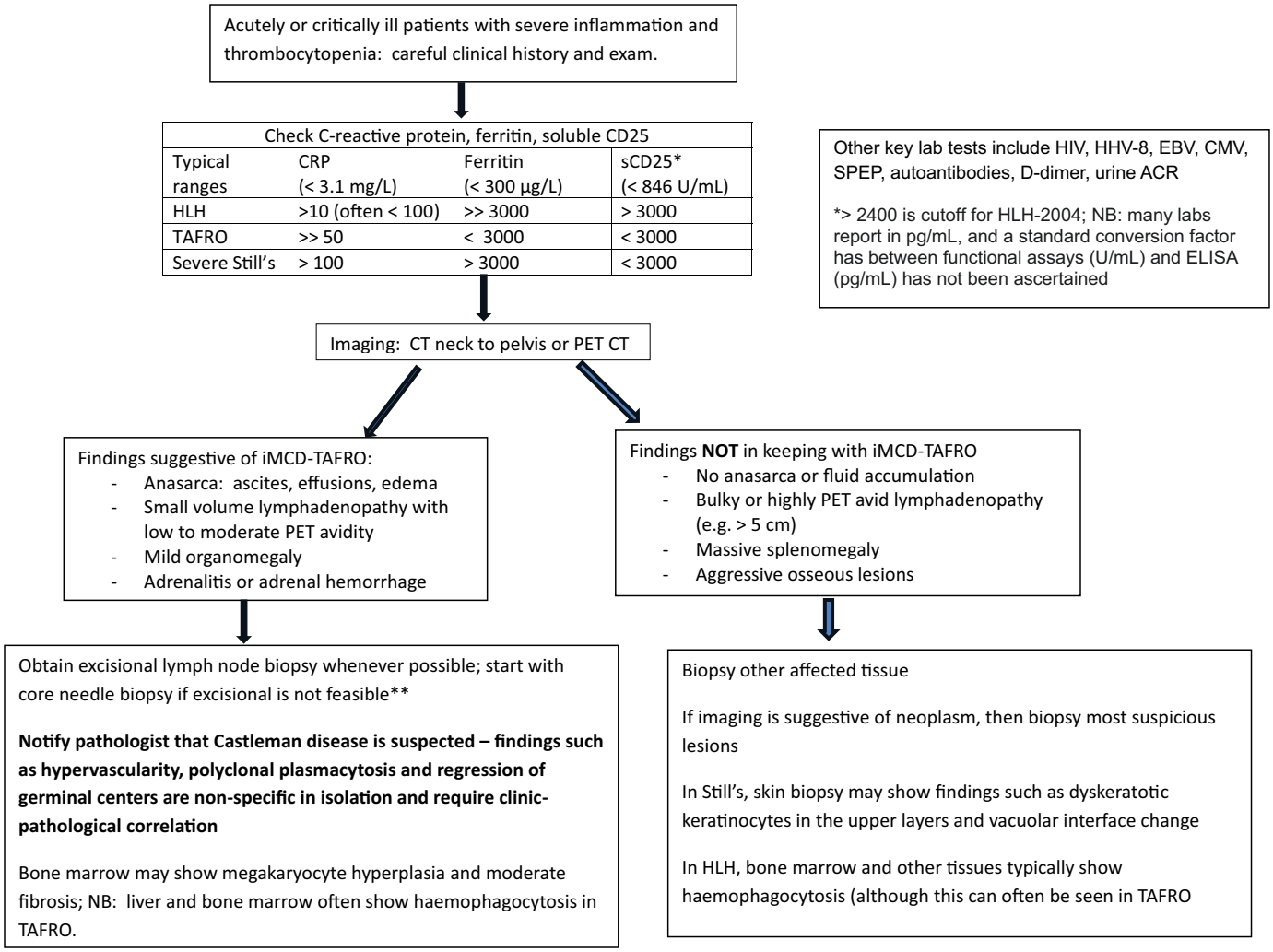

Figure 2. Approach to the acutely ill cytokine storm patient with thrombocytopenia (suspected iMCD-TAFRO). ACR, albumin-creatinine ratio; CMV, cytomegalovirus; CRP, C-reactive protein; CT, computed tomography; EBV, Epstein-Barr virus; ELISA, enzyme-linked immunosorbent assay; HHV-8, human herpes virus 8; HLH, hemophagocytic lymphohistiocytosis; iMCD, idiopathic multicentric Castleman disease; PET, positron emission tomography; sCD25, soluble CD25; SPEP, serum protein electrophoresis; TAFRO, thrombocytopenia, anasarca, fever, renal dysfunction/reticulin fibrosis, organomegaly.

such as aggressive lymphoma or other malignancy. In addition, PET-CT may reveal FDG-avid vasculitis, or bone involvement that would suggest histiocytosis, malignancy, or autoinflammatory disease other than iMCD.

Histology in suspected iMCD. High-quality lymph node biopsies are essential. Whenever possible, an excisional lymph node biopsy of the largest and/or most PET-avid lymph node mass should be sought.[48] Fine-needle aspiration should never be used for diagnosis of CD. Core needle biopsy can sometimes provide a diagnosis of CD but is more useful for ruling out other neoplastic and infectious causes of lymphadenopathy.[49] One study showed only 2% diagnostic yield from core-needle biopsies.[50] Determining whether surgical services (otolaryngology, surgical oncology) in one's center are able to excise lymph nodes expeditiously under local anesthetic can help expedite biopsy rather than waiting for operating room time under general anesthetic. Lymph nodes should be sent for "lymphoma processing" including flow cytometry, as lymphoma is often high in the differential diagnosis in these patients (Table 1).

Histopathologic features of CD are illustrated in Figure 5 and occur across a spectrum, with hypervascular and plasmacytic on opposite ends and mixed in between. Hypervascular histopathology is characterized by atrophic germinal centers with fewer germinal center B cells, increased vascularity in the germinal center including penetrating blood vessels called a "lollipop sign," and expanded mantle zones with an "onion-skin" appearance. Hypervascular histology was formerly called hyaline vascular, although the latter term is still used for UCD. Plasmacytic histopathology is characterized by sheets of polyclonal plasma cells in the interfollicular zone and follicle center

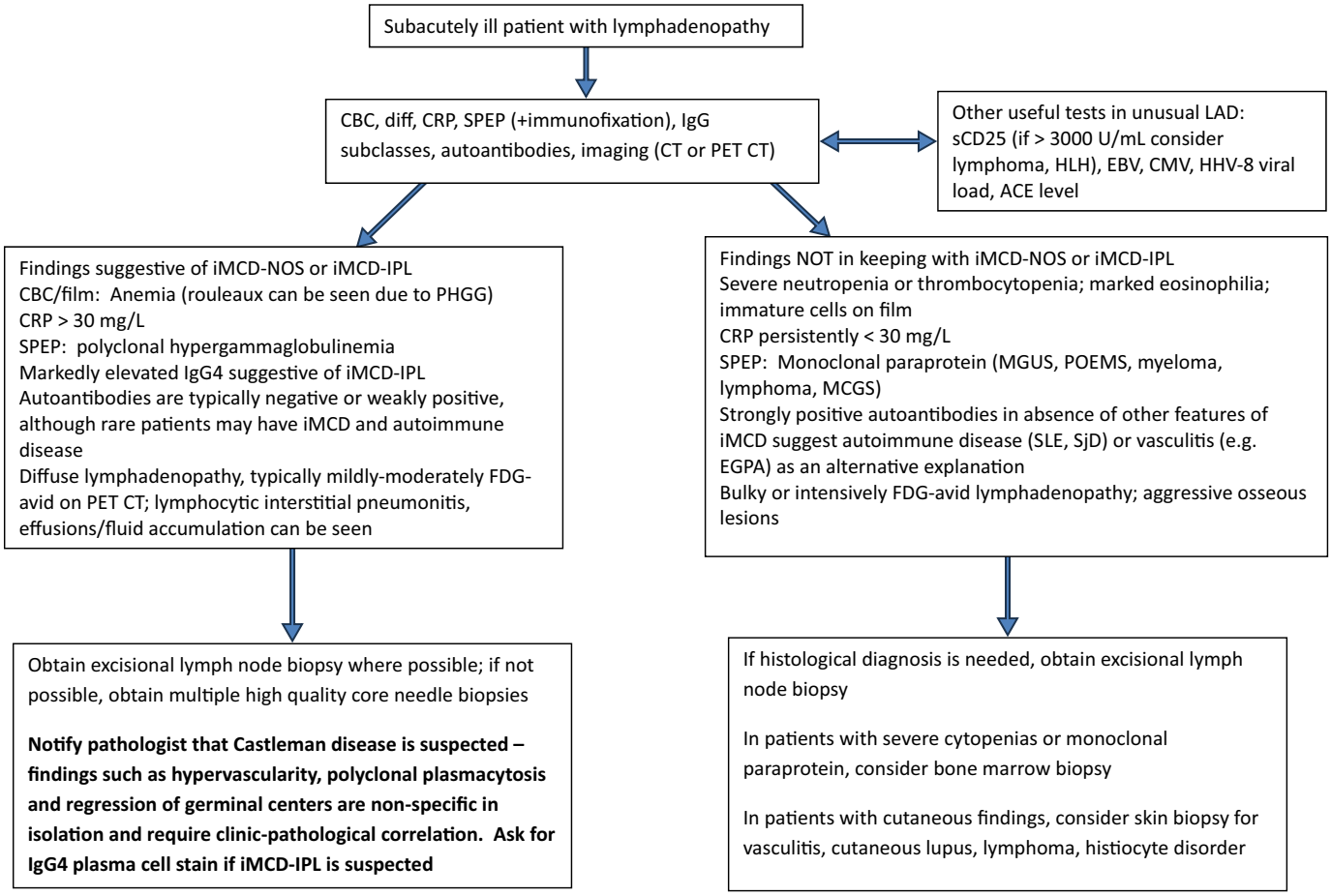

Figure 3. Approach to the ambulatory patient with undiagnosed lymphadenopathy (suspected iMCD-NOS or iMCD-IPL). ACE, angiotensin converting enzyme; CBC, complete blood cell count; CMV, cytomegalovirus; CRP, C-reactive protein; CT, computed tomography; diff, difference; EBV, Epstein-Barr virus; EGPA, eosinophilic granulomatosis with polyangiitis; FDG, fluorodeoxyglucose; HHV-8, human herpes virus 8; HLH, hemophagocytic lymphohistiocytosis; iMCD, idiopathic multicentric Castleman disease; IPL, idiopathic plasmacytic lymphadenopathy; LAD, lymphadenopathy; MCGS, monoclonal gammopathy of clinical significance; MGUS, monoclonal gammopathy of undetermined significance; NOS, not otherwise specified; PET, positron emission tomography; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal paraprotein syndrome; sCD25, soluble CD25; SjD, Sjogren Disease; SLE, systemic lupus erythematosus; SPEP, serum protein electrophoresis

hyperplasia with increased numbers of lymphoid follicles throughout the cortex and medulla. Mixed CD has features of both hypervascular and plasmacytic.

Clinicopathologic correlation is essential. Some degree of hypervascularity and regression of germinal centers are seen in all histologic subtypes, and interobserver variability is high in histologic subtyping. The histologic features of CD can also be seen in reactive lymph nodes in patients with autoimmune and autoinflammatory disease, infection, and malignancy, and thus correlation with clinical and laboratory features is required for diagnosis. This is often best done by clinicians directly communicating with the pathologist(s) interpreting the lymph node. Unless otherwise notified, pathologists are often focused on excluding malignant lymphoma, granuloma, and neoplasm. If the pathologist is not aware that iMCD is high in the differential diagnosis, the specimen may be interpreted as "reactive" (Figure 5).

APPROACH TO iMCD SUBTYPES

Although the three subtypes of iMCD present in distinct ways, they should all meet iMCD diagnostic criteria[1] (Supplemental Table 1). Features of the three subtypes are summarized in Table 1.

iMCD-TAFRO. TAFRO was first described in Japan in 2010, and initially most cases were reported in Asian men[21] in their 30s to 50s. Importantly, iMCD-TAFRO has always been present in patients with CD all over the world but was not specifically classified previously. TAFRO is not restricted by age, sex, or race. The first international definition of iMCD-TAFRO was published[51] in 2021. Although most cases of TAFRO are associated with iMCD, one-quarter of Japanese patients with TAFRO have no lymphadenopathy at all, and thus no CD.[52] The etiology of TAFRO in these cases without CD remains a mystery. The major mimics

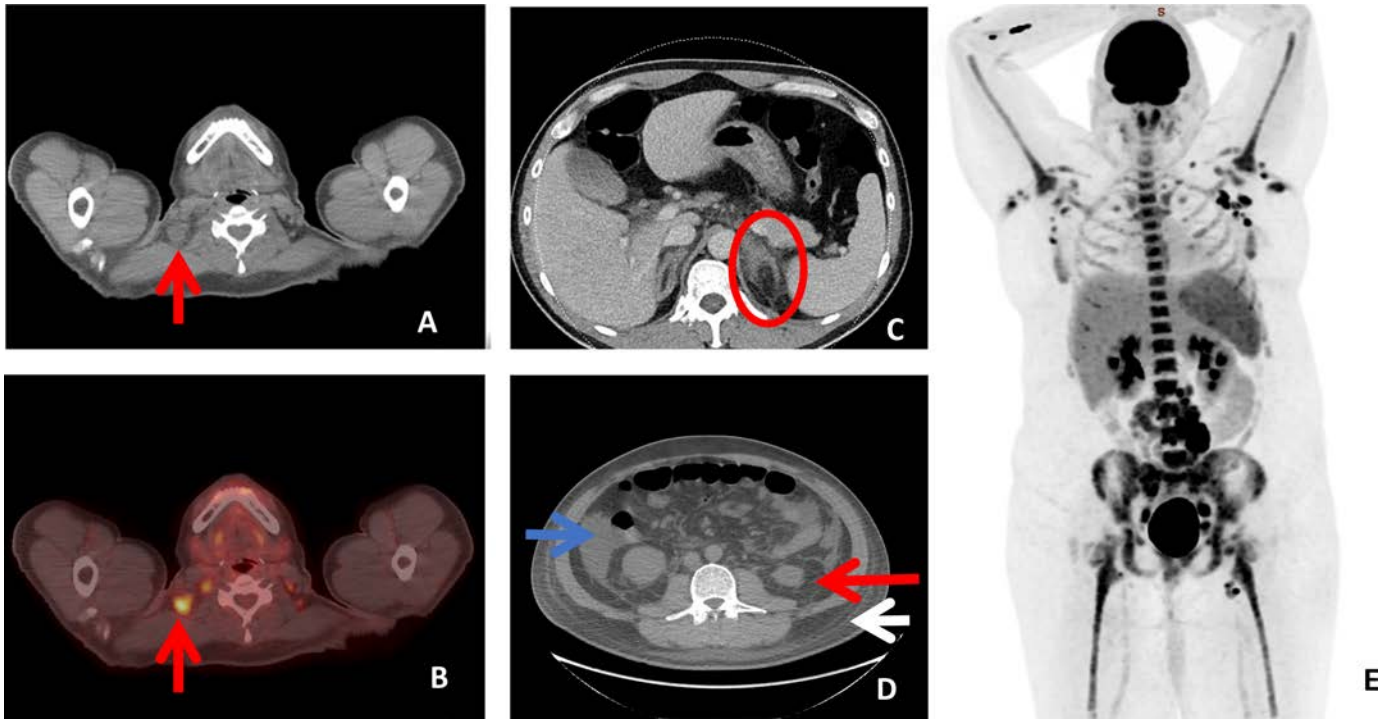

Figure 4. Radiologic findings in idiopathic multicentric Castleman disease (iMCD). (A) Cervical lymphadenopathy on computed tomography (CT) (arrow, largest lymph node). (B) Moderate 18 F-fluorodeoxyglucose positron emission tomography (PET) avidity (arrow) of lymph node in panel A. (C) CT scan showing prominent adrenalitis with adjacent fat stranding (circle) in a patient with thrombocytopenia, anasarca, fever, renal dysfunction/reticulin fibrosis, organomegaly (TAFRO). (D) CT images demonstrating ascites (blue arrow), retroperitoneal standing (red arrow), and subcutaneous edema (white arrow) in a patient with TAFRO. (E) Diffuse axillary, intra-abdominal and inguinal moderately PET-avid lymphadenopathy in a patient with iMCD–not otherwise specified. *Source:* courtesy of Drs Don Wilson and Steve Burrell.

for TAFRO are HLH and sepsis (Table 1). Of note, hemophagocytosis in bone marrow, liver, lymph node, and other biopsies can be seen in TAFRO.[53,54] However, ferritin and sCD25 are only modestly elevated in TAFRO, whereas CRP is typically higher than in HLH (Figure 2). Other autoinflammatory syndromes such as Still disease and vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome can present with lymphadenopathy, fluid accumulation, and thrombocytopenia mimicking TAFRO.[55,56] Adrenal involvement on CT or magnetic resonance imaging is common in TAFRO,[46,47,57] and the alkaline phosphatase is often much more elevated than the other liver enzymes and bilirubin.[21,58] In iMCD-TAFRO, the CRP and D-dimer are simple markers of inflammation that can be useful for tracking a patient's response to therapy.[53]

Case 1. The patient's ferritin level was 950 μg/L (reference <300 μg/L; in HLH the ferritin is typically more than 3,000 μg/L),[36] and his sCD25 was only 620 U/mL (reference <852 U/mL), but his D-dimer was 5,500 μg/L (reference <500 μg/L). His urine albumin creatinine ratio was elevated at 150 (<3.1), and his serum albumin was 17 g/L. His lymph node was rereviewed by the pathologist with the understanding that iMCD-TAFRO was suspected, and hypervascularity including lollipop lesions, regressed germinal centers with onion-skinning were noted, consistent with hypervascular CD. He was diagnosed with iMCD-TAFRO.

iMCD-IPL. IPL was first described in 1980 in Japan among patients with MCD. Similar to iMCD-TAFRO, iMCD-IPL has always been present in patients with CD all over the world, but it was just never specifically classified previously. Patients have lymphadenopathy, anemia, severe inflammation, and profound polyclonal hypergammaglobulinemia. Over the ensuing decades, the disease received little attention in the western literature. With the discovery of IgG4-RD[59] in the early 2000s, it was soon found that many cases of IPL had elevated serum IgG4 and IgG4-positive plasma cells in lymph nodes. Japanese investigators proposed that IPL is a subset of iMCD. Chinese investigators defined iMCD-IPL as (1) eligibility for the diagnostic criteria of iMCD-NOS according to CDCN 2017 criteria; (2) elevated IgG level (>17.4 g/L); (3) plasmacytic or mixed pathologic subtypes; and (4) elevated platelet count (>350 × 10^9 giga/L). The Japanese use a higher polyclonal hypergammaglobulinemia (PHGG) threshold, gamma globulins >40 g/L or IgG >35 g/L, but in practical terms, Chinese and Japanese studies both demonstrate profound PHGG with median IgG levels >40 g/L.[60]

Patients with iMCD-IPL have a distinct natural history; although the degree of systemic inflammation is higher than in iMCD-NOS (median CRP 130 mg/L vs 42 mg/L), the disease behaves surprisingly indolently and those with iMCD-IPL may have longer survival (estimated five-year overall survival 97% vs

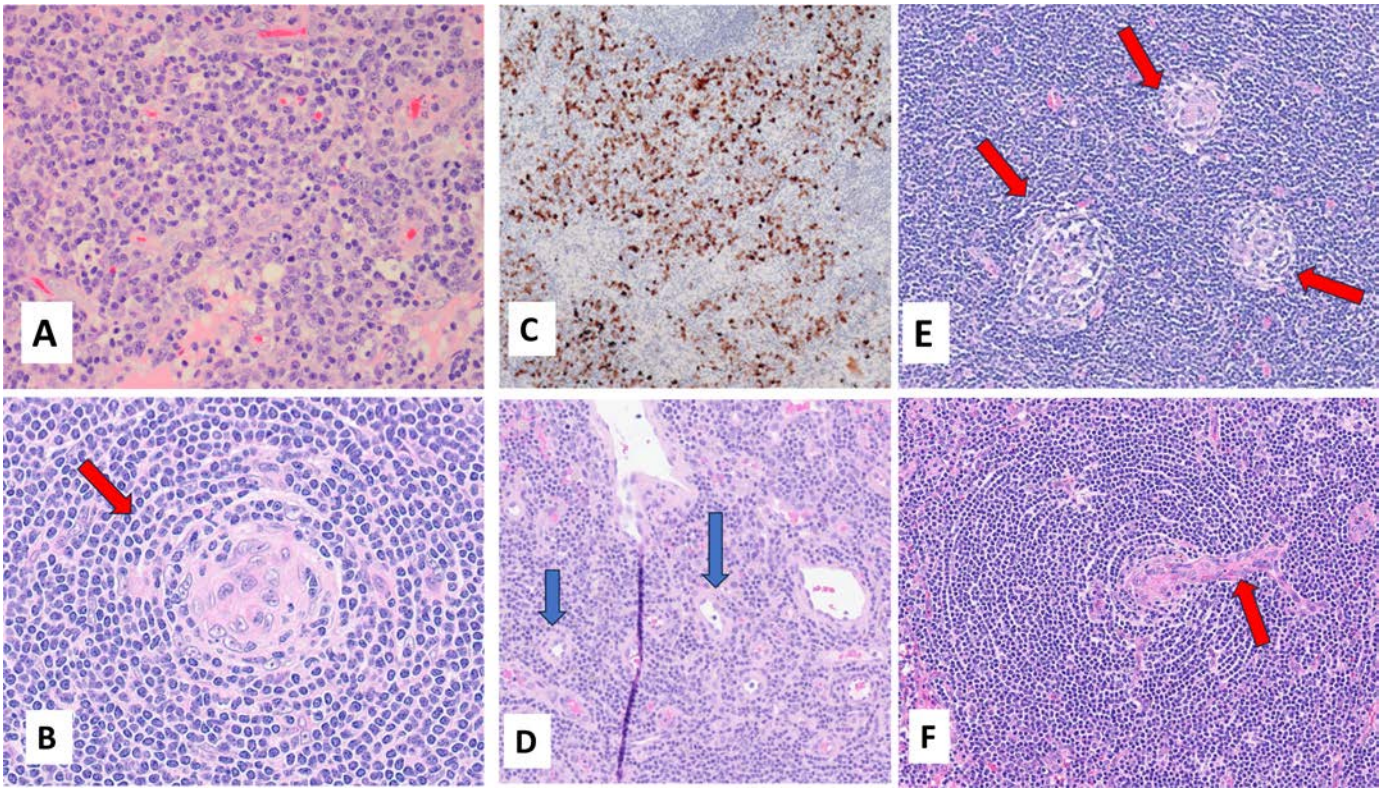

Figure 5. Lymph node histologic features of idiopathic multicentric Castleman disease (iMCD). (A) Plasmacytosis (polyclonal) in a patient with iMCD–not otherwise specified (NOS) and plasmacytic histology. (B) Most of this atrophic germinal center is replaced by a population of dendritic cells; mantle zone expansion with lymphocytes distributed as concentric rings (onion skin, arrow) in a patient with iMCD-NOS and plasmacytic histology. (C) Increased IgG4$^+$ plasma cells >100/high-power field in a patient with iMCD–idiopathic plasmacytic lymphadenopathy and plasmacytic histology. (D) High endothelial venules (teal arrows) in a patient with iMCD–thrombocytopenia, anasarca, fever, renal dysfunction/reticulin fibrosis, organomegaly (TAFRO) and hypervascular histology. (E) Multiple germinal centers in a follicle, known as "twinning," or, in this case, a "triplet" in a patient with iMCD-NOS. (F) Prominent vascularity including a follicle with a radial vessel (arrow) reaching the germinal center—the lollipop sign in a patient with iMCD-TAFRO and hypervascular histology. *Source:* courtesy of Drs Brian Skinnider (A, C, and D) and Sorin Selegean (B, E, and F).

85.5%).[61] Thus, over the past three years, iMCD-IPL has become accepted as a distinct and important subtype of iMCD.[22,60,61] Given the profound polyclonal hypergammaglobulinemia with elevated serum IgG4 and lymphadenopathy with increased IgG4-positive plasma cells, the most important mimic for iMCD-IPL is IgG4-RD. The lymphadenopathy of IgG4-RD has five classic subtypes, one of which is "iMCD-like," which cannot be distinguished from iMCD based on histology alone. The key differentiating feature is that patients with iMCD-IPL have severe inflammation, often with fever and CRP >50 mg/L and anemia, which are both rare in IgG4-RD.[59,62] Moreover, IgG4-RD often has extranodal lesions and is typically much more steroid responsive than iMCD-IPL. Sjögren disease can present with anemia, PHGG, lymphadenopathy, and lymphocytic interstitial pneumonitis, as well (Figure 3 and Table 1).

Case 2. This patient had IgG subclasses sent, and the serum IgG4 was very elevated at 9 g/L (reference <1.25 g/L). Her lymphocytic interstitial pneumonitis had been diagnosed on a wedge biopsy of the lung and adjacent lymph nodes one year ago; the pathology report mentioned hypervascularity and polyclonal plasmacytosis. The case was discussed with the pathologist, and the clinical suspicion for iMCD-IPL was mentioned, along with the serum IgG4 level. The pathologist reviews the specimen and finds features in keeping with CD in the excised lymph nodes, plasmacytic type, with increased IgG4-positive plasma cells up to 105/high-power field and IgG4/IgG ratio of 40%.

In this context, the clinicopathologic diagnosis is iMCD-IPL. Although patients with iMCD-IPL can exceed the diagnostic thresholds of IgG4$^+$ plasma cells in lymph node for IgG4-RD, the diagnosis of iMCD-IPL supersedes that of IgG4-RD, particularly given there were no other extranodal IgG4-positive lesions.

iMCD-NOS. Patients with iMCD who do not meet criteria for TAFRO or IPL have iMCD-NOS. iMCD-NOS involves diffuse, typically small volume (<3 cm) lymphadenopathy, inflammation with elevated CRP or erythrocyte sedimentation rate, mild to moderate anemia, and mild polyclonal hypergammaglobulinemia. Pulmonary abnormalities including nodules, cysts, consolidations, interstitial thickening, and ground glass opacites are frequent.[43] Most patients follow a more indolent course but a subset may have

more rapid end-organ damage and critical illness. Major mimics include autoimmune disease, infection, and IgG4-RD (Table 1).

THERAPEUTIC APPROACH

Treatment of iMCD should follow the 2018 CDCN or 2020 NCCN guidelines.[63,64] A complete review of therapy is beyond the scope of this article, but some basic principles are outlined herein. IL-6 inhibition with siltuximab is the first-line therapy. However, many classes of anti-inflammatory and immunomodulatory medications as well as cytotoxic chemotherapy, have activity in this disease. Because iMCD is a disease characterized by lymphoid and plasma cell proliferation causing inflammation, the systemic therapy of iMCD can be considered in three major categories:

1. Anti-inflammatory/immunomodulatory therapy:
   a. Anticytokine therapies: IL-6 inhibitors are the recommended first-line treatment for all patients and is the most well established. Others include IL-1 inhibitors[65] and TNF inhibition.[32]
   b. JAK inhibitors (JAKi) such as ruxolitinib[66]
   c. Mammalian target of rapamycin inhibitors such as sirolimus[30,67,68]
2. Cytotoxic, antilymphoma therapy:
   a. Rituximab is commonly used alone or in combination with other therapies such as chemotherapy and bortezomib.[69]
   b. Multiagent chemotherapy such as cyclophosphamide, hydroxy doxorubicin, vincristine, and prednisone can be used in severe, refractory cases of iMCD-TAFRO.
   c. Etoposide is often used in the cytokine storm of iMCD-TAFRO, often in combination with rituximab and bortezomib.
   d. BTK inhibition (BTKi): orelabrutinib has been shown to have slow onset of action but can produce durable responses in iMCD-IPL.[70]
3. Antimyeloma therapy:
   a. Thalidomide in combination with cyclophosphamide and prednisone (TCP) has been used in Asia.[71] The use of other immunomodulatory drugs (IMiDs) such as lenalidomide are less well studied.
   b. Proteosome inhibitors such as bortezomib have activity in iMCD.[72]

The first prospective study in iMCD, a randomized phase 2 study of siltuximab, an IL-6 inhibitor, showed that 34% of patients achieved a durable remission with IL-6 blockade.[73,74] However, there were no patients with TAFRO in this study, although they have been shown to be responsive in subsequent studies, and response rates will likely be higher with more modern selection criteria excluding OCD and aMCD. IL-6 inhibition with intravenous siltuximab at 11 mg/kg is the recommended first-line therapy in the CDCN guidelines[63] published in 2018. If siltuximab is not available, the IL-6 receptor antibody, tocilizumab, at 8 mg/kg (up to 800 mg) can be used.

For patients with severe disease (patients with two of the following: Eastern Cooperative Oncology Group performance status ≥2, glomerular filtration rate <30 mL/min, anasarca, hemoglobin <80 g/L, or symptomatic pulmonary involvement with interstitial pneumonia), weekly IL-6 inhibition for the first several weeks of treatment as well as additional therapies such as glucocorticoids are recommended. If there is evidence of progressive organ dysfunction in these severe cases while receiving IL-6 inhibition, combination cytotoxic chemotherapy is recommended. Treatment according to guidelines is associated with improved outcomes.[75]

A prospective study in China treated 25 patients newly diagnosed with iMCD with TCP.[71] TCP was well-tolerated, and 48% of patients achieved durable tumor and symptomatic response for at least 24 weeks. Patients who are refractory to IL-6 inhibition are a clinical challenge, and optimal second-line therapies should be determined on a case-by-case basis, preferably in consultation with a center of excellence in CD. Some patients may respond to a simple maneuver such as switching from one cytokine inhibitor to another, whereas other refractory cases warrant a more aggressive approach with addition of cytotoxic chemotherapy.

Case 1. The patient was treated with siltuximab with excellent response. He had some mild persistent fatigue and brain fog, but his lymphadenopathy had resolved, his laboratory parameters had normalized, and he had been able to return to work.

Case 2. The patient was treated initially with siltuximab for three months with inadequate response. She was then transitioned to TCP, with excellent clinical and biochemical response after four months of treatment.

DISCUSSION

Great progress has been made in the past 15 years, yet many urgent questions remain. The etiology of CD remains an enigma. Characteristic histologic features in lymph nodes remain the unifying diagnostic thread through all subtypes of CD, yet the great heterogeneity of clinical syndromes encompassed by CD, and the fact that these changes are also seen as reactive findings in autoimmune disease and infection, raises the question of whether CD is truly one disease or many distinct entities. Moreover, TAFRO syndrome can occur without lymphadenopathy, and thus by definition without CD in as many as 25% of cases, raising questions about the relationship between iMCD and TAFRO syndrome, and whether there are distinct causal factors in TAFRO with and without CD.[52,76]

Dysregulation of both the innate and adaptive immune systems clearly play a role in idiopathic multicentric CD. Although current diagnostic criteria require the exclusion of autoimmune and autoinflammatory disease, this criterion is intended to ensure other diseases that can mimic iMCD are considered and ruled in or out.[77] In general, for patients presenting with discrete

autoimmune disease and Castleman-like histology in lymph nodes, the autoimmune diagnosis should take precedence. However, both in the authors' experience, and in the literature, rare cases of iMCD can present with concomitant Sjögren disease,[40] systemic lupus erythematosus (SLE),[41] and other autoimmune diseases. There is overlap in the pathophysiology of these diseases; for example, type I interferon response up-regulated in both TAFRO and SLE.[30,78] The association of lymphocytic interstitial pneumonitis (LIP) with both iMCD-IPL and autoimmune diseases such as Sjögren disease and SLE is not surprising given that studies of LIP show strong association both with diseases of hypergammaglobulinemia and autoimmune disease.[79] Sjögren disease antibodies are found in TAFRO and several cases of Sjögren disease with concomitant TAFRO have been reported.[40,80] A recent study reported enrichment of common connective tissue disease autoantibodies such as ANA, anti-SSA, and direct antiglobulin test, as well as anticytokine antibodies (such as anti-TNF and anti–interferon-λ2) in patients with iMCD.[81]

CD is now recognized by the World Health Organization (WHO) in two important arenas. In October 2016, CD received its first distinct *International Classification of Diseases, Tenth Revision* (ICD-10) code; CD has an ICD-10 code of D47.Z2 under the category "Other neoplasms of uncertain or unknown behavior of lymphoid, hematopoietic and related tissue." In the 2024 fifth edition of the (WHO) classification of lymphoid neoplasms, CD is included for the first time in a chapter on "tumour-like lesions with B-cell predominance."[82] Notably, IgG4-RD is also included in this chapter. Both diseases are characterized by B cell/plasma cell enriched enlargement of lymphoid tissues, often with increased IgG4-positive plasma cells and polyclonal hypergammaglobulinemia. Both the common and distinguishing features of the two enigmatic entities may inform future investigations into etiology, pathophysiology and treatment.[43] Although iMCD always involves lymphadenopathy and autoinflammation, IgG4-RD displays lymphadenopathy in two-thirds of patients with much more pleiotropic organ regional body involvement and very rarely has severe systemic inflammation or B symptoms. Approximately 25% to 55% of patients with iMCD treated with rituximab achieve response,[69,75] whereas B cell depletion with rituximab or inebilizumab is effective in more than 85% of patients with IgG4-RD.[83,84]

Several unmet treatment needs remain. The most urgent is what to do with treatment failure, particularly in patients with TAFRO. In our own experience, responses in TAFRO can be quite rapid and complete after finding the right therapy, but with the many targeted therapies available, rational decision-making about serial treatment is difficult. We recently demonstrated the potential of combining a multiomic and machine learning (artificial intelligence) approach to identify TNF as a potential target in iMCD-TAFRO and then used adalimumab to induce a durable remission in a patient with severe iMCD-TAFRO refractory to multiple lines of therapy.[32] Identifying other novel targets and repurposing drugs to these targets in the context of clinical trials will be crucial. A prospective clinical trial to study the JAKi ruxolitinib in iMCD is being planned.

Most data suggest that therapy with anti-inflammatory agents such as IL-6 should not be stopped. However, thalidomide-based therapy is potentially a time-limited option in iMCD. In a study of patients discontinuing TCP in China, the median PFS had not yet been reached due to few progression events, yet the estimated three-year progression free survival (PFS) serum rate[85] (after drug discontinuation) was 88.4%. How aggressively to treat patients with iMCD-NOS and iMCD-IPL who have partial response is an important question. As more oral options (JAKi, IMiDs, BTKi) become available, determining the most effective and least toxic ways to achieve deeper responses will be crucial. Quality of life and patient perspectives are now being examined in prospective studies and will add an important dimension to treatment decisions.[86]

In summary, iMCD presents to rheumatologists as subacute lymphadenopathy and inflammation in the ambulatory setting (iMCD-NOS, iMCD-IPL) or severe cytokine storm in the hospital setting (iMCD-TAFRO). Simple laboratory tests such as CRP, SPEP, IgG, and IgG4 can be quite helpful in the diagnosis of the disease. Diagnosis of iMCD requires an excisional lymph node biopsy and review by a pathologist with experience in CD. CD is a clinicopathologic diagnosis; clinicians and pathologists must combine clinical, laboratory, and histologic findings to make a diagnosis. Although IL-6 inhibition works for a substantial subset of patients, other cytokines and chemokines play a key role in the pathophysiology, and prospective clinical trials are needed. The rapid progress made in this disease over the past 15 years shows what can be done in rare diseases. Patient driven research and education through networks such as CDCN will provide important patient-centered perspectives for ongoing work.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Drs Chen and Fajgenbaum confirm that all authors have provided the final approval of the version to be published and take responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Fajgenbaum DC, Uldrick TS, Bagg A, et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. Blood 2017;129(12):1646–1657.
2. Carbone A, Borok M, Damania B, et al. Castleman disease. Nat Rev Dis Primers 2021;7(1):84.
3. Dispenzieri A, Fajgenbaum DC. Overview of Castleman disease. Blood 2020;135(16):1353–1364.
4. Chen L, Fajgenbaum DC. Castleman disease. In: Stone JH, ed. A Clinician's Pearls & Myths in Rheumatology. Springer International Publishing; 2023:727–735.
5. Zhang MY, Jia MN, Chen J, et al. UCD with MCD-like inflammatory state: surgical excision is highly effective. Blood Adv 2021;5(1): 122–128.
6. Zhang L, Dong YJ, Peng HL, et al; China Castleman Disease Network (CCDN). A national, multicenter, retrospective study of Castleman disease in China implementing CDCN criteria. Lancet Reg Health West Pac 2023;34:100720.
7. Dieudonné Y, Silvestrini MA, Dossier A, et al. Paraneoplastic pemphigus uncovers distinct clinical and biological phenotypes of western unicentric Castleman disease. Br J Haematol 2023;202(2):267–278.
8. Liu YT, Zhen JF, Gao YH, et al. Unicentric Castleman disease complicated with bronchiolitis obliterans: a single-centre retrospective study from China. Br J Haematol 2025;206(4):1129–1135.
9. Bernabei L, Waxman A, Caponetti G, et al. AA amyloidosis associated with Castleman disease: a case report and review of the literature. Medicine (Baltimore) 2020;99(6):e18978.
10. Zhang MY, Li J, Wang YN, et al. Unicentric Castleman's disease presenting as amyloid A cardiac amyloidosis: a case report. Ann Hematol 2024;103(1):367–368.
11. Pierson SK, Bagg A, Alapat D, et al. Characterization of Castleman disease reveals patients with oligocentric adenopathy and clinicopathologic characteristics similar to unicentric Castleman disease. Blood 2021:138(suppl 1):1622.
12. Pierson SK, Brandstadter JD, Torigian D, et al. Characterizing the heterogeneity of Castleman disease and oligocentric subtype: findings from the ACCELERATE registry. Blood Adv 2025;9(8):1952–1965.
13. Zhang L, Liu QH, Zhou H, et al. Asymptomatic multicentric Castleman disease: a potential early stage of idiopathic MCD. Blood Adv 2024; 8(21):5598–5602.
14. Dispenzieri A. POEMS syndrome: update on diagnosis, risk-stratification, and management. Am J Hematol 2023;98(12):1934–1950.
15. Gérard L, Bérezné A, Galicier L, et al. Prospective study of rituximab in chemotherapy-dependent human immunodeficiency virus associated multicentric Castleman's disease: ANRS 117 CastlemaB Trial. J Clin Oncol 2007;25(22):3350–3356.
16. Nijim S, Fajgenbaum DC. Identifying Castleman disease from non-clonal inflammatory causes of generalized lymphadenopathy. Hematology (Am Soc Hematol Educ Program) 2024;2024(1):582–593.
17. Mukherjee S, Martin R, Sande B, et al. Epidemiology and treatment patterns of idiopathic multicentric Castleman disease in the era of IL-6–directed therapy. Blood Adv 2022;6(2):359–367.
18. Gao YH, Yao JF, Li SY, et al. Clinical characteristics and prognosis of pediatric idiopathic multicentric Castleman disease. Am J Hematol 2025;100(3):539–541.
19. Johnson AK, Goteti S, Devald B, et al. Pediatric TAFRO syndrome: a multi-institution case series illustrating clinical challenges and excellent outcomes. Pediatr Blood Cancer 2024;71(10):e31234.
20. Simpson D. Epidemiology of Castleman disease. Hematol Oncol Clin North Am 2018;32(1):1–10.
21. Iwaki N, Fajgenbaum DC, Nabel CS, et al. Clinicopathologic analysis of TAFRO syndrome demonstrates a distinct subtype of HHV-8-negative multicentric Castleman disease. Am J Hematol 2016; 91(2):220–226.
22. Nishikori A, Nishimura MF, Nishimura Y, et al. Idiopathic plasmacytic lymphadenopathy forms an independent subtype of idiopathic multicentric Castleman disease. Int J Mol Sci 2022;23(18):23.
23. Li Z, Lan X, Li C, et al. Recurrent PDGFRB mutations in unicentric Castleman disease. Leukemia 2019;33(4):1035–1038.
24. Goodman AM, Jeong AR, Phillips A, et al. Novel somatic alterations in unicentric and idiopathic multicentric Castleman disease. Eur J Haematol 2021;107(6):642–649.
25. Suthaus J, Stuhlmann-Laeisz C, Tompkins VS, et al. HHV-8-encoded viral IL-6 collaborates with mouse IL-6 in the development of multicentric Castleman disease in mice. Blood 2012;119(22):5173–5181.
26. Miller I, Mumau MD, Shyamsundar S, et al. No evidence for active viral infection in unicentric and idiopathic multicentric Castleman disease by Viral-Track analysis. Sci Rep 2025;15(1):1676.
27. Mumau MD, Lavery CLM, Irvine A, et al. Trafficking, not lymphoproliferation, promotes lymphadenopathy in idiopathic multicentric Castleman disease. Blood 2024;144(suppl 1):3924.
28. Brandt SJ, Bodine DM, Dunbar CE, et al. Dysregulated interleukin 6 expression produces a syndrome resembling Castleman's disease in mice. J Clin Invest 1990;86(2):592–599.
29. Pierson SK, Stonestrom AJ, Shilling D, et al. Plasma proteomics identifies a 'chemokine storm' in idiopathic multicentric Castleman disease. Am J Hematol 2018;93(7):902–912.
30. Pai RL, Japp AS, Gonzalez M, et al. Type I IFN response associated with mTOR activation in the TAFRO subtype of idiopathic multicentric Castleman disease. JCI Insight 2020;5(5):5.
31. Pierson SK, Katz L, Williams R, et al. CXCL13 is a predictive biomarker in idiopathic multicentric Castleman disease. Nat Commun 2022;13(1):7236.
32. Mumau MD, Gonzalez MV, Ma C, et al. Identifying and targeting TNF signaling in idiopathic multicentric Castleman's disease. N Engl J Med 2025;392(6):616–618.
33. van Rhee F, Oksenhendler E, Srkalovic G, et al. International evidence-based consensus diagnostic and treatment guidelines for unicentric Castleman disease. Blood Adv 2020;4(23):6039–6050.
34. Nishimura Y, Atwell T, Callstrom M, et al. Cryoablation for unresectable unicentric Castleman disease. Am J Hematol 2025;100(1): 149–151.
35. Hayden A, Lin M, Park S, et al. Soluble interleukin-2 receptor is a sensitive diagnostic test in adult HLH. Blood Adv 2017;1(26):2529–2534.
36. Goubran M, Spaner C, Stukas S, et al. The role of C-reactive protein and ferritin in the diagnosis of HLH, adult-onset still's disease, and COVID-19 cytokine storm. Sci Rep 2024;14(1):31306.
37. Goubran M, Chen L. Hemophagocytic Lymphohistiocytosis and Other Cytokine Storm Syndromes in Adults. Canadian Hematology Today 2025:37–46.
38. Chen LYC, Biggs CM, Jamal S, et al. Soluble interleukin-6 receptor in the COVID-19 cytokine storm syndrome. Cell Rep Med 2021;2(5): 100269.
39. Rose-John S, Jenkins BJ, Garbers C, et al. Targeting IL-6 trans-signalling: past, present and future prospects. Nat Rev Immunol 2023; 23(10):666–681.
40. Grange L, Chalayer E, Boutboul D, et al. TAFRO syndrome: a severe manifestation of Sjogren's syndrome? A systematic review. Autoimmun Rev 2022;21(8):103137.
41. Pan Y, Cui Z, Wang S, et al. Idiopathic multicentric Castleman disease with Sjögren's syndrome and secondary membranous nephropathy: a case report and review of the literature. BMC Nephrol 2020; 21(1):528.

42. Demirkan FG, Doğan S, Kalyoncu Uçar A, et al. Systemic lupus erythematosus complicated with Castleman disease: a case-based review. Rheumatol Int 2021;41(2):475–479.
43. Zhou J, Zhang L, Liu X, et al. Evolution of pulmonary involvement in idiopathic multicentric Castleman disease-not otherwise specified: from nodules to cysts or consolidation. Chest 2023;164(2):418–428.
44. Pickhardt PJ, Wong VK, Mellnick V, et al. Abdominal CT findings characteristic of Castleman disease: multi-centre review of 76 adult cases with abdominopelvic nodal involvement. Br J Radiol 2024;97(1160): 1431–1436.
45. Iguchi T, Nishikori A, Sato Y, et al. Computed tomography findings of idiopathic multicentric Castleman disease subtypes. J Clin Exp Hematop 2024;64(4):292–296.
46. Rowe S, Collins BW, Pirzada A, et al. TAFRO subtype of idiopathic multicentric Castleman disease in a 22-year-old man. CMAJ 2024; 196(37):E1262–E1265.
47. Chen LYC, Skinnider BF, Wilson D, et al. Adrenalitis and anasarca in idiopathic multicentric Castleman's disease. Lancet 2021; 397(10286):1749.
48. Bitektine E, Hagh-Daoust H, Michel RP, et al. The value of a pet scan in selecting the best lymph node to biopsy, and confirming the diagnosis of idiopathic multicentric Castleman disease with HLH and EBV viremia in a previously healthy adult. Eur J Case Rep Intern Med 2024;11(12):004908.
49. Wu D, Lim MS, Jaffe ES. Pathology of Castleman disease. Hematol Oncol Clin North Am 2018;32(1):37–52.
50. Sarmiento Bustamante M, Lavery CLM, Bagg A, et al. The development of diagnostic criteria and utilization of excisional lymph node biopsies shorten time to diagnosis for idiopathic multicentric Castleman disease. Blood 2024;144(suppl 1):1156.
51. Nishimura Y, Fajgenbaum DC, Pierson SK, et al. Validated international definition of the thrombocytopenia, anasarca, fever, reticulin fibrosis, renal insufficiency, and organomegaly clinical subtype (TAFRO) of idiopathic multicentric Castleman disease. Am J Hematol 2021;96(10):1241–1252.
52. Otsuka M, Koga T, Sumiyoshi R, et al. Exploring the clinical diversity of Castleman disease and TAFRO syndrome: a Japanese multicenter study on lymph node distribution patterns. Am J Hematol 2025; 100(4):592–605.
53. Campbell CM, Owen DR, Montazeripouragha A, et al. Idiopathic multicentric Castleman disease with arteriolar endotheliopathy and secondary haemophagocytosis. Lancet Haematol 2022;9(7):e546.
54. Blommers M, Selegean S, Wood RK, et al. Idiopathic multicentric Castleman disease with marrow fibrosis and extramedullary hematopoiesis. Eur J Haematol 2024;113(6):833–841.
55. Philip R, Cadro V, Aouba A, et al. VEXAS syndrome: a new mimicker of idiopathic multicentric Castleman disease. Joint Bone Spine 2024; 91(4):105731.
56. Staels F, Betrains A, Woei AJF, et al. Case report: VEXAS syndrome: from mild symptoms to life-threatening macrophage activation syndrome. Front Immunol 2021;12:678927.
57. Yonezaki S, Nagasaki K, Yamaguchi H, et al. Bilateral adrenal infarctions as an initial manifestation of TAFRO syndrome: a case report and review of the literature. Intern Med 2022;61(5):743–747.
58. Nishioka H, Nishino S, Yoshizaki A, et al. TAFRO syndrome presenting as intrahepatic cholangitis on autopsy. Clin Case Rep 2021;9(4): 2254–2258.
59. Chen LYC. IgG4-related disease for the hematologist. Hematology (Am Soc Hematol Educ Program) 2024;2024(1):594–603.
60. Nishikori A, Nishimura MF, Fajgenbaum DC, et al. Diagnostic challenges of the idiopathic plasmacytic lymphadenopathy (IPL) subtype of idiopathic multicentric Castleman disease (iMCD): factors to differentiate from IgG4-related disease. J Clin Pathol 2024. jcp-2023-209280.
61. Gao YH, Liu YT, Zhang MY, et al. Idiopathic multicentric Castleman disease (iMCD)-idiopathic plasmacytic lymphadenopathy: a distinct subtype of iMCD-not otherwise specified with different clinical features and better survival. Br J Haematol 2024;204(5):1830–1837.
62. Zhao EJ, Cheng CV, Mattman A, et al. Polyclonal hypergammaglobulinaemia: assessment, clinical interpretation, and management. Lancet 2021;8(5):e365–e375.
63. van Rhee F, Voorhees P, Dispenzieri A, et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood 2018;132(20):2115–2124.
64. NCCN Clinical Practice Guidelines in Oncology: Castleman Disease. 2025. https://www.nccn.org/professionals/physician_gls/pdf/castleman.pdf.
65. Lanzillotta M, Sant'Angelo M, Kaneko N, et al. Treating life-threatening TAFRO syndrome with interleukin-1 inhibition. Eur J Intern Med 2021; 87:121–123.
66. Kakutani T, Nunokawa T, Chinen N, et al. Treatment-resistant idiopathic multicentric Castleman disease with thrombocytopenia, anasarca, fever, reticulin fibrosis, renal dysfunction, and organomegaly managed with Janus kinase inhibitors: a case report. Medicine (Baltimore) 2022;101(48):e32200.
67. Fajgenbaum DC, Langan RA, Japp AS, et al. Identifying and targeting pathogenic PI3K/AKT/mTOR signaling in IL-6-blockade-refractory idiopathic multicentric Castleman disease. J Clin Invest 2019;129(10): 4451–4463.
68. Arenas DJ, Floess K, Kobrin D, et al. Increased mTOR activation in idiopathic multicentric Castleman disease. Blood 2020;135(19):1673–1684.
69. Dong Y, Zhang L, Nong L, et al. Effectiveness of rituximab-containing treatment regimens in idiopathic multicentric Castleman disease. Ann Hematol 2018;97(9):1641–1647.
70. Gao YH, Li SY, Dang Y, et al. Efficacy and safety of orelabrutinib in relapsed/refractory idiopathic multicentric Castleman disease: a single-centre, retrospective study. Br J Haematol 2025;206(1):152–158.
71. Zhang L, Zhao AL, Duan MH, et al. Phase 2 study using oral thalidomide-cyclophosphamide-prednisone for idiopathic multicentric Castleman disease. Blood 2019;133(16):1720–1728.
72. Zhang L, Zhang MY, Cao XX, et al. A prospective, multicenter study of bortezomib, cyclophosphamide, and dexamethasone in relapsed/refractory iMCD. Leuk Lymphoma 2022;63(3):618–626.
73. van Rhee F, Wong RS, Munshi N, et al. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. Lancet Oncol 2014;15(9):966–974.
74. van Rhee F, Rosenthal A, Kanhai K, et al. Siltuximab is associated with improved progression-free survival in idiopathic multicentric Castleman disease. Blood Adv 2022;6(16):4773–4781.
75. Pierson SK, Lim MS, Srkalovic G, et al. Treatment consistent with idiopathic multicentric Castleman disease guidelines is associated with improved outcomes. Blood Adv 2023;7(21):6652–6664.
76. He T, Zhao A, Zhao H, et al. Clinical characteristics and the long-term outcome of patients with atypical POEMS syndrome variant with undetectable monoclonal gammopathy. Ann Hematol 2019;98(3): 735–743.
77. González García A, Fernández-Martín J, Robles Marhuenda Á. Idiopathic multicentric Castleman disease and associated autoimmune and autoinflammatory conditions: practical guidance for diagnosis. Rheumatology (Oxford) 2023;62(4):1426–1435.
78. Maisonobe L, Bertinchamp R, Damian L, et al. Characteristics of thrombocytopenia, anasarca, fever, reticulin fibrosis and organomegaly syndrome: a retrospective study from a large Western cohort. Br J Haematol 2022;196(3):599–605.

79. Cha SI, Fessler MB, Cool CD, et al. Lymphoid interstitial pneumonia: clinical features, associations and prognosis. Eur Respir J 2006; 28(2):364–369.
80. Shirakashi M, Nishida Y, Nakashima R, et al. TAFRO syndrome is associated with anti-SSA/Ro60 antibodies, in contrast to idiopathic castleman disease. Sci Rep 2024;14(1):2889.
81. Feng A, Gonzalez MV, Kalaycioglu M, et al. Common connective tissue disorder and anti-cytokine autoantibodies are enriched in idiopathic multicentric castleman disease patients. Front Immunol 2025; 16:1528465.
82. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: lymphoid neoplasms. Leukemia 2022;36(7):1720–1748.
83. Carruthers MN, Topazian MD, Khosroshahi A, et al. Rituximab for IgG4-related disease: a prospective, open-label trial. Ann Rheum Dis 2015;74(6):1171–1177.
84. Stone JH, Khosroshahi A, Zhang W, et al; MITIGATE Trial Investigators. Inebilizumab for treatment of IgG4-related disease. N Engl J Med 2025;392(12):1168–1177.
85. Dang Y, Gao Y, Li S, et al. Potential opportunity for drug discontinuation in idiopathic multicentric Castleman disease: evaluating the efficacy of TCP protocol. Blood 2024;144(suppl 1):6310.
86. Mukherjee S, Shupo F, Wayi-Wayi G, et al. Symptom burden in patients with idiopathic multicentric Castleman disease and its impact on daily life: an international patient and caregiver survey. EClinicalMedicine 2023;64:102192.