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Recent Progress in the Clinical Understanding, Diagnosis, and Treatment of Castleman Disease

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Abstract: Marked by clinical and pathological heterogeneity, Castleman disease (CD) is a lymphoproliferative disorder classified into unicentric (UCD) and multicentric (MCD) types. Distinct subtypes of Castleman disease differ in pathogenesis, pathology, and prognosis, yet diagnosis and treatment remain challenging, requiring standardized approaches. This paper explores the classification, pathological characteristics, diagnostic methods, and treatment strategies of CD, with a focus on the clinical and pathological features of different subtypes. Through analysis of recent literature on clinical presentations, imaging, histopathological diagnostic criteria, and therapeutic outcomes, this study provides evidence-based guidance for clinical practice. The results show that CD can be histologically categorized into hyaline vascular (HV), plasmacytic (PC), and mixed variants. Besides, MCD is further subdivided into HHV-8-associated, POEMS syndrome-associated, and idiopathic (iMCD) subtypes. The diagnostic approach combines clinical presentation, imaging results, and pathological evidence while excluding infectious, autoimmune, and malignant disorders. Treatment for UCD primarily involves surgical excision with favorable prognosis, whereas MCD requires tailored regimens including antiviral therapy, immunosuppression, targeted agents, and chemotherapy. Despite their efficacy in achieving quick symptom relief, corticosteroids are predominantly used as ancillary agents due to the constraints imposed by their long-term adverse effects.

Keywords: Castleman disease, Lymphoproliferative disorder, Diagnosis, Treatment options

1. Introduction

First described by Dr. Benjamin Castleman in 1956, Castleman disease (CD) encompasses a group of rare lymphoproliferative disorders marked by striking clinical and pathological heterogeneity. Despite decades of investigation, standardized diagnostic and therapeutic guidelines remain lacking. This heterogeneity is reflected in the variable patterns of lymph node involvement, either unicentric or multicentric, as well as in the degree of systemic inflammation and the presence or absence of underlying viral infections, such as human herpesvirus 8 (HHV-8). Accurate classification plays a key role in elucidating disease mechanisms, guiding treatment decisions, and assessing prognosis. Recent advances in imaging modalities and molecular diagnostics have significantly improved the ability to distinguish among CD subtypes. Meanwhile, novel targeted therapies tailored to specific

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clinical variants have emerged as a growing focus of research and clinical care. However, gaps remain in the integration of histological, clinical, and etiological factors into a unified diagnostic framework. Besides, therapeutic approaches are still evolving, particularly for the more aggressive multicentric forms and less well-characterized idiopathic variants. Therefore, the paper summarizes the classification systems, diagnostic strategies, and current therapeutic approaches for CD. By synthesizing findings from recent literature, it seeks to provide clinicians and researchers with a comprehensive and practical reference. In particular, the paper explores how diagnostic tools can be refined for accurate subtype classification, examines current treatment strategies for each clinical variant, and identifies ongoing challenges and research gaps through analysis of recent literature. As such, better insight into CD subtypes and pathogenesis can refine diagnosis, guide targeted therapy, and improve patient outcomes.

2. Types and pathological features of castleman disease

2.1. Clinical classification

Due to its marked clinical and pathological heterogeneity, CD requires a classification system that integrates both histological and clinical parameters. From a histopathological perspective, three major variants of Castleman disease have been identified. The hyaline-vascular (HV) subtype, or hypervascular (HyperV) variant, is defined by its histological features of regressed germinal centers, prominent vascular proliferation, and an expanded mantle zone. The plasmacytic (PC) subtype is characterized by hyperplastic follicular centers and a dense infiltration of plasma cells. In contrast, the mixed variant exhibits overlapping histological features of both the HV and PC types, and is generally considered an intermediate form. From a clinical standpoint, the disease manifests in two distinct forms, with unicentric Castleman disease (UCD) involving a single lymph node region and multicentric Castleman disease (MCD) affecting multiple sites [1]. While UCD typically involves a single lymph node region and presents with localized symptoms, MCD affects multiple lymph node areas and exhibits a more systemic clinical profile. Based on etiological and clinical characteristics, MCD can be divided into three major phenotypes. These include human herpesvirus-8-associated (HHV-8-associated) MCD, POEMS-associated MCD, defined by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes, and HHV-8-negative MCD, more commonly referred to as idiopathic MCD (iMCD). Building on this classification, iMCD has been further divided into distinct clinical subsets [2]. iMCD-TAFRO, a notably aggressive clinical subset, involves thrombocytopenia, anasarca, fever, renal dysfunction, and organomegaly. In contrast, cases that do not exhibit the TAFRO constellation of symptoms are categorized as iMCD-NOS (not otherwise specified). Among these, patients exhibiting thrombocytosis, hypergammaglobulinemia, and PC or mixed histology are classified as iMCD-IPL (idiopathic plasmacytic lymphadenopathy), whereas those lacking these features remain categorized as iMCD-NOS without IPL [1,3].

2.2. Pathological characteristics

Histopathology plays a pivotal role in the diagnosis of CD, despite the absence of pathognomonic features and the necessity to distinguish it from other reactive or neoplastic lymphadenopathies. The classical histological features of CD were first described in 1956 by Dr. Benjamin Castleman, who identified hyaline vascular changes in two lymph node biopsy specimens at Massachusetts General Hospital. Since then, the histopathological spectrum of CD has broadened to include plasmacytic and mixed variants. In UCD, the HV subtype is characterized by atrophic germinal centers traversed

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by sclerotic vessels and surrounded by concentric mantle zones showing perivascular hyalinization. The less common PC subtype demonstrates hyperplastic or normoplastic follicles with prominent interfollicular plasma cell infiltration. The mixed subtype exhibits overlapping features of both HV and PC types [4]. In MCD, histopathological features often resemble those of unicentric CD but present with greater variability. Of these, regressed germinal centers and marked plasmacytosis are particularly characteristic and play a key role in diagnosis. Besides, HHV-8-positive plasmablasts are usually limited to HHV-8-associated MCD, primarily seen in patients with HIV co-infection [5,6]. Localized to the mantle zones and expressing latency-associated nuclear antigen (LANA-1), these cells can be readily identified by immunohistochemical staining, facilitating the diagnosis of HHV-8-associated disease. In addition, immunohistochemical analysis in CD frequently employs markers such as CD20, CD3, CD138, and Ki-67 to assess lymphoid architecture, plasma cell content, and proliferative index. Lack of light chain restriction in most CD cases helps distinguish them from clonal lymphoproliferative disorders like lymphoma or multiple myeloma. In iMCD, recent consensus criteria require histopathological confirmation based on at least two features such as regressed germinal centers, increased vascularity, or interfollicular plasmacytosis.

3. Diagnosis methods and strategies for castleman disease

3.1. Differential diagnosis and common mimics

Establishing a definitive diagnosis of CD remains challenging due to its overlapping features with a range of infectious, autoimmune, and neoplastic conditions. Accurate differentiation from these mimics is crucial to avoid misdiagnosis and inappropriate management. Infectious etiologies that may simulate CD include Epstein-Barr virus, human immunodeficiency virus, and Mycobacterium tuberculosis. Autoimmune or inflammatory disorders, particularly IgG4-related disease, can also present with lymphadenopathy and systemic inflammatory signs, mimicking the clinical and histological features of CD. Among neoplastic conditions, lymphomas and Kaposi sarcoma (KS) are the most common confounders. Notably, KS and CD both involve infection with HHV-8, leading to substantial pathological overlap, especially in immunocompromised patients [5]. In light of these complexities, a multifaceted diagnostic strategy is warranted. Histopathology remains central, with excisional lymph node biopsy offering optimal tissue architecture for evaluation. While core needle biopsy is less invasive, it may not provide sufficient material for definitive diagnosis. In addition, thorough clinical evaluation, including symptom profiling, laboratory investigations (such as IL-6 levels, immunoglobulin profiles, and viral serologies), imaging studies (e.g., CT or PET-CT), and assessment of end-organ involvement, is necessary to support the diagnosis [7].

3.2. Imaging modalities and diagnostic insights

Imaging serves as a pivotal modality in the diagnostic workup of CD, offering both anatomical and functional insights that assist in subtype differentiation and disease assessment. Traditional imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) are widely used in clinical practice. In clinical evaluation, CT provides high-resolution cross-sectional images that help distinguish between UCD and MCD by assessing the extent and distribution of lymph node involvement. In UCD, involvement is typically limited to a solitary lymph node or localized mass, most commonly in the thoracic cavity, followed by the abdomen, retroperitoneum, and occasionally the lung or kidney. In contrast, MCD presents with widespread lymphadenopathy without site predilection [5]. Functional metabolic information can be

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derived from PET imaging, especially 18F-FDG PET/CT, via semi-quantitative parameters such as maximum standardized uptake value (SUVmax), metabolic lesion volume (MLV), total lesion glycolysis (TLG), and uptake ratios like lymph node-to-liver (LLR), lymph node-to-mediastinum (LMR), and spleen-to-liver (SLR). Previous studies have shown that MCD typically exhibits higher values in these parameters compared to UCD. Among histopathologic subtypes, the plasmacytic variant exhibits the highest metabolic activity, followed by mixed and hyaline-vascular types. The spleen-to-liver SUVmax ratio exhibits good diagnostic accuracy, with 77.4% sensitivity and 69.4% specificity in stratifying disease severity. Moreover, PET surpasses CT in detecting involved lymph nodes, with detection rates of 96% versus 78.6%, respectively [7].

3.3. Clinical presentation and subtype-specific features

The clinical presentation of CD varies substantially by subtype, with distinct patterns observed in unicentric and multicentric forms. In UCD, lymphadenopathy most frequently occurs in the thoracic and cervical regions, with less common involvement of abdominal or retroperitoneal nodes. Clinical symptoms are typically attributable to the local mass effect, and systemic manifestations, such as fever (>38°C), weight loss, anemia, or dyspnea, are uncommon. Rarely, paraneoplastic syndromes like paraneoplastic pemphigus (PNP) may be observed. Due to its localized and indolent nature, UCD is associated with an excellent prognosis, with a 5-year overall survival rate of approximately 91% [5]. By contrast, MCD presents with systemic and rapidly progressive inflammatory symptoms. Patients commonly present with a constellation of systemic symptoms, including fever, night sweats, weight loss, and fatigue, alongside organ-related findings including hepatosplenomegaly, fluid retention, and skin lesions like violaceous papules and eruptive angiomas. Pulmonary involvement, such as lymphocytic interstitial pneumonitis, may also be seen. Multiorgan dysfunction is frequent, often necessitating intensive care and multidisciplinary intervention. With a 5-year overall survival of about 65%, MCD has a notably worse prognosis compared to UCD [5]. In immunocompromised individuals, particularly those with human immunodeficiency virus infection, HHV-8-associated MCD is more common, and viral load has been shown to correlate with disease relapse. iMCD exhibits considerable clinical heterogeneity, with the aggressive iMCD-TAFRO variant marked by thrombocytopenia, anasarca, fever, renal dysfunction, and organomegaly. The diagnosis is based on clinical and pathological findings, with the 2017 Castleman Disease Collaborative Network (CDCN) criteria mandating the presence of at least three out of five key features. Due to overlapping symptoms including neuropathy, organomegaly, and skin rash, differentiating POEMS-associated MCD is challenging; nonetheless, distinctive manifestations such as osteosclerotic bone lesions and papilledema assist in establishing a clear diagnosis [5].

3.4. Laboratory investigations and diagnostic criteria

Laboratory testing constitutes a fundamental component in the diagnosis and management of CD, providing essential biochemical and immunological markers that aid differentiation, classification, and disease severity assessment. Key laboratory parameters assessed in CD typically encompass hemoglobin (Hb), albumin (Alb), erythrocyte sedimentation rate (ESR), hypersensitive C-reactive protein (hsCRP), platelet count (PLT), interleukin-6 (IL-6), immunoglobulin G (IgG), and estimated glomerular filtration rate (eGFR). Although UCD typically lacks specific laboratory abnormalities, MCD diagnosis relies heavily on these findings, except for the TAFRO-iMCD subtype which may present atypically [1]. For HHV-8-negative MCD, quantitative polymerase chain reaction (qPCR) detection of HHV-8 DNA in peripheral blood is critical to confirm viral status [6]. The 2017 CDCN

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consensus diagnostic criteria for iMCD require fulfillment of a three-part framework which includes two major criteria, eleven minor criteria, and relevant exclusion criteria. To establish a diagnosis, at least two minor criteria are needed, one of which must be a laboratory abnormality. These include elevated CRP (>10mg/L) or ESR (>15mm/h), anemia (hemoglobin<12.5g/dL in males, <11.5g/dL in females), thrombocytopenia (<150×10^3/μL) or thrombocytosis (>400×10^3/μL), hypoalbuminemia (<3.5g/dL), renal dysfunction (eGFR<60mL/min/1.73m^2) or proteinuria (>150mg/24 h), and polyclonal hypergammaglobulinemia (IgG>1700mg/dL) [2]. The CHAP score (CRP, hemoglobin, albumin, and performance status) reliably indicates disease severity, while CRP closely correlates with IL-6 in iMCD, serving as a useful marker for disease activity and treatment response [5,8]. Importantly, laboratory parameters also assist in distinguishing CD from other mimics. For example, a clinicopathological comparison between iMCD and IgG4-related disease (IgG4-RD) showed that the IgG4/IgG ratio combined with IL-6 levels can effectively differentiate these two conditions, despite their overlapping multi-organ involvement and histopathological similarities [6].

4. Treatment approaches and management of castleman disease

4.1. Treatment of unicentric castleman disease

Effective management of UCD relies on accurate diagnosis supported by a thorough evaluation, including hematopathological analysis, imaging studies, symptom assessment, laboratory testing, and evaluation of organ involvement [7]. UCD typically manifests as a single enlarged lymph node and is often asymptomatic, frequently detected incidentally during imaging for unrelated conditions. In asymptomatic cases, observation may be appropriate, as UCD has not been shown to progress to MCD, and paraneoplastic syndromes are rare. To detect potential disease progression, consistent follow-up is necessary. For symptomatic patients, complete surgical excision remains the first-line treatment and is considered curative, with reported relapse-free survival (RFS) rates exceeding 90%. Long-term surveillance is still recommended to detect recurrence. In situations where the lesion is not amenable to resection, alternative approaches such as vascular ablation, localized radiation therapy, or medical therapies (e.g., rituximab and/or corticosteroids) may be employed to alleviate symptoms or serve as neoadjuvant treatments to facilitate eventual surgery [5]. However, if these interventions fail to sufficiently reduce tumor size, clinicians should recognize the typically benign and non-progressive nature of UCD to avoid unnecessary or excessive treatment [9].

4.2. Treatment of multicentric castleman disease

With its diverse clinical features and underlying causes, effective management of MCD depends on tailored treatment strategies. Though few asymptomatic patients can be observed to avoid treatment side effects, most demonstrate systemic inflammation and organ dysfunction, demanding urgent and intensive treatment [5,9].Treatment approaches are primarily guided by the underlying subtype. HHV-8-associated MCD, often observed in patients with human immunodeficiency virus infection, requires initiation of highly active antiretroviral therapy (ART), though ART alone is insufficient. Rituximab, targeting CD20-positive HHV-8-infected plasmablasts, is the first-line biologic therapy, boosting clinical outcomes and raising five-year survival by almost 60% [5]. iMCD, including both NOS and TAFRO variants, is driven by a pro-inflammatory cytokine storm, particularly involving IL-6. Siltuximab, an anti-IL-6 monoclonal antibody and the only FDA- and EMA-approved therapy for iMCD, provides durable tumor and symptom control. Its efficacy is greatest in plasmacytic or mixed histopathology, leading NCCN to recommend siltuximab as first-line therapy except for HV

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cases [10]. Patients with HV pathology may benefit more from systemic combination chemotherapy regimens including thalidomide, cyclophosphamide, and prednisone, which are also applicable in relapsed plasmacytic or mixed cases [9]. POEMS-associated MCD, as a rapidly progressing plasma cell neoplasm, requires urgent treatment. The standard approach includes four cycles of proteasome inhibitor-based induction therapy using bortezomib, cyclophosphamide, and dexamethasone (BCD), followed by autologous stem cell transplantation to enhance survival. For patients ineligible for transplantation, two additional BCD cycles are suggested. This treatment achieves a 100% VEGF response rate, underscoring VEGF's importance as a prognostic biomarker. Due to bortezomib's neurotoxicity, careful dose adjustment is necessary to prevent peripheral neuropathy [11].

4.3. Function of corticosteroids in castleman disease

In MCD, corticosteroids are widely used for their potent anti-inflammatory and immunosuppressive properties, providing rapid relief of systemic symptoms like fever, fatigue, and lymphadenopathy. Although effective for acute symptom relief, corticosteroids seldom achieve lasting remission or prevent relapse [4]. The therapeutic approach with corticosteroids depends on disease severity. Mild to moderate cases usually respond to oral prednisolone at 1 mg/kg/day for around two weeks, followed by a gradual tapering to minimize rebound inflammation. In contrast, patients with severe or refractory manifestations may require high-dose intravenous pulse therapy to rapidly suppress the intense cytokine-driven inflammatory response. They are generally used as adjunctive agents rather than definitive monotherapy, often combined with targeted biologics such as anti-IL-6 antibodies or chemotherapy regimens, depending on the underlying disease subtype and clinical context. Such combination strategies aim to improve long-term control by targeting both inflammatory symptoms and underlying pathogenic mechanisms in MCD. Long-term corticosteroid therapy is limited by a range of significant adverse effects, including immunosuppression leading to increased infection risk, metabolic complications such as hyperglycemia and osteoporosis, adrenal insufficiency, and psychological disturbances. These risks demand close monitoring and precise dose management. Efforts focus on minimizing steroid use through alternative immunotherapies and optimized dosing.

5. Conclusion

Due to its diverse pathological and clinical manifestations, CD requires accurate classification and diagnosis to guide personalized treatment strategies. UCD is mainly managed with surgical excision and has a favorable prognosis, whereas MCD requires a combination of antiviral therapy, targeted immunotherapy, and chemotherapy, with treatment efficacy depending on the underlying etiology and disease severity. Corticosteroids serve as adjunctive agents for rapid symptom relief but must be used cautiously in the long term. In the future, precision diagnostics incorporating biomarkers and the development of safer, more effective immunomodulatory therapies are expected to further improve treatment outcomes and quality of life for patients with Castleman disease.

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