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Castleman Disease: Insights from a Case Series and Literature Review

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Abstract

Castleman disease (CD), a rare lymphoproliferative disorder with unicentric (UCD) and multicentric (MCD) subtypes, presents significant diagnostic and therapeutic challenges due to its clinical heterogeneity. This case series of four patients highlights rare and diverse clinical presentations of CD, including atypical anatomical sites and paraneoplastic pemphigus. Diagnostic challenges included differentiating CD from malignancies or autoimmune disorders, emphasizing the critical role of histopathology. UCD pathogenesis may involve follicular dendritic cell mutations, whereas MCD subtypes are driven by human herpesvirus (HHV)-8-associated viral interleukin-6 or idiopathic cytokine dysregulation. Treatment strategies varied, with surgery preferred for UCD and immunomodulators (siltuximab, rituximab) for MCD. Challenges such as limited standardized protocols in resource-constrained settings and biomarker variability underscore the need for individualized therapy. Emerging approaches, including cytokine-targeted therapies and bortezomib, show promise for refractory cases. This study reinforces the importance of multidisciplinary collaboration, early histopathological diagnosis, and long-term monitoring to optimize outcomes. By integrating clinical experiences with literature, it advocates for refined diagnostic criteria and context-specific therapeutic algorithms, urging further research to address gaps in managing this complex disease.

Keywords
- case report
- Castleman disease
- unicentric CD
- multicentric CD
- human herpesvirus 8

Introduction

Castleman disease (CD) comprises a group of rare lymphoproliferative disorders with diverse clinical presentations, histopathological features, and treatment approaches. CD is traditionally classified into unicentric CD (UCD), involving a single lymph node or region, and multicentric CD (MCD), which affects multiple lymph node regions. MCD is further categorized into human herpesvirus 8 (HHV-8)-associated, idiopathic MCD (iMCD) and polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell (PC) disorder, skin changes (POEMS)-associated MCD (POEMS-MCD). The

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diagnosis of CD from other lymphoproliferative diseases is pathologically challenging. UCD is typically managed through surgical excision or monitoring, while MCD requires more complex treatment, including immunomodulators or chemotherapy, based on the clinical severity and organ involvement. However, standardized protocols remain elusive, especially in resource-limited settings like India. This case series presents four patients with CD, detailing their clinical presentations, laboratory tests, imaging, treatment, and outcome with comprehensive review of literature. The study underscores the challenges in diagnosis and management while emphasizing the need for individualized care strategies.[1,2]

Case Series

Case 1: A Case of Symptomatic UCD Treated with Rituximab

A 41-year-old female patient with no notable medical or family history presented with a 4-year history of chronic lower back pain. Over the preceding 6 months, she experienced an 8 kg (13% of body weight) unintentional weight loss but denied fever, night sweats, or appetite changes. Physical examination was unremarkable. Laboratory tests revealed a normal complete blood count (CBC) and biochemistry panel, except for an elevated erythrocyte sedimentation rate (ESR). Abdominal ultrasound identified multiple retroperitoneal lymph nodes near the upper pole of the left kidney, the largest measuring 4×3 cm, with normal-appearing liver, spleen, and kidneys. The uterus was structurally normal, but endometrial thickness was 18 mm. Contrast-enhanced computed tomography (CECT) of the chest and abdomen demonstrated several enlarged para-aortic lymph nodes, the largest measuring 5.2×3.8 cm, accompanied by fat stranding. Additional findings included a left thyroid nodule (16×10 mm), a left ovarian corpus luteum cyst, sacralization of L5 (Castellvi type IIIB), diffuse osteopenia, and degenerative vertebral changes. 18-Fluorodeoxyglucose positron emission tomography-CT (^{18}FDG-PET-CT) scan revealed mild hypermetabolism in the para-aortic nodes (maximum standardized uptake value [SUVmax] 4.0), moderate activity in the left thyroid nodule (SUVmax 6.7), physiological endometrial uptake (SUVmax 4.1), and left adnexal uptake (SUVmax 6.8) (►**Fig. 1A–E**). Histopathological examination of a para-aortic lymph node biopsy confirmed unicentric hyaline vascular CD (HVCD), demonstrating distorted nodal architecture, hyperplastic follicles with onion-skinning mantle zones, and interfollicular vascular proliferation (►**Fig. 2**). Immunohistochemistry (IHC) showed CD10 and BCL6 positivity in germinal centers, BCL2 expression in mantle zones,

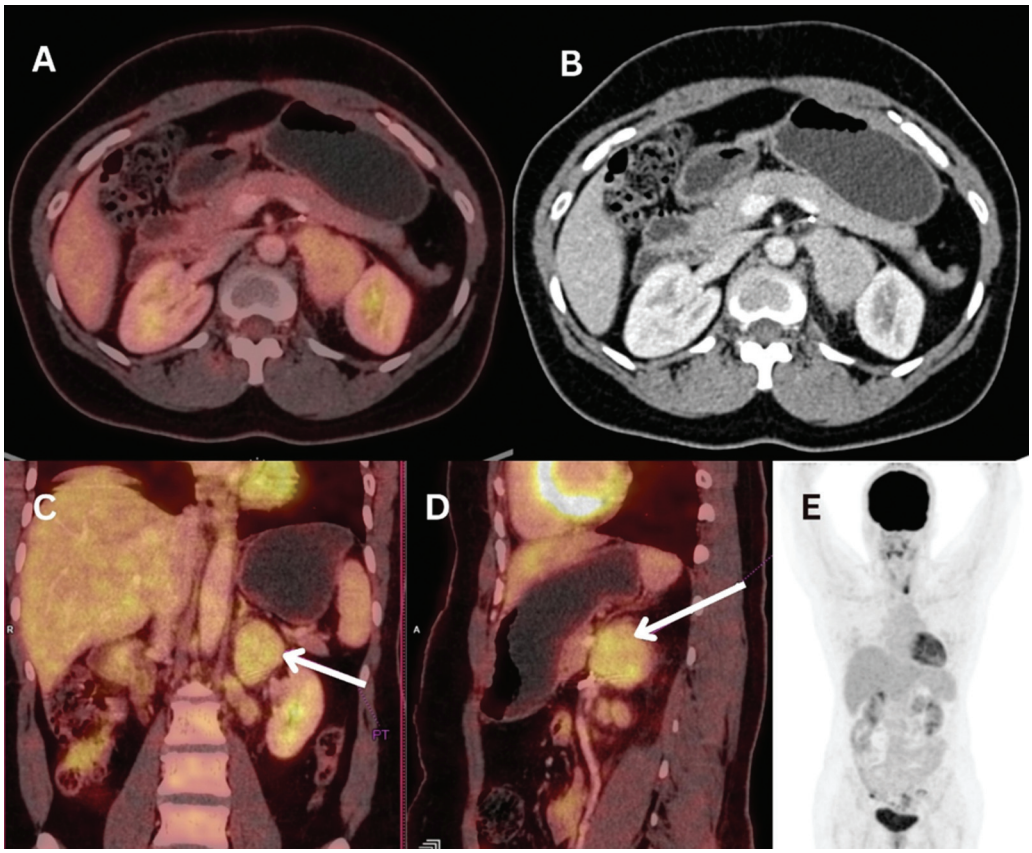

Fig. 1 18-Fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/ contrast-enhanced computed tomography (CECT) findings in a patient with hyaline vascular Castleman disease. (**A**) Axial fused PET/CECT image showing mild to moderate FDG uptake in a near homogeneously enhancing retroperitoneal lymph nodal mass. (**B**) Corresponding axial CECT scan showing a near homogeneously enhancing retroperitoneal mass. (**C**, **D**) Coronal and sagittal PET/CECT images (arrows) indicating the hypermetabolic lymph node. (**E**) Maximum intensity projection (MIP) image highlighting the region of increased tracer uptake.

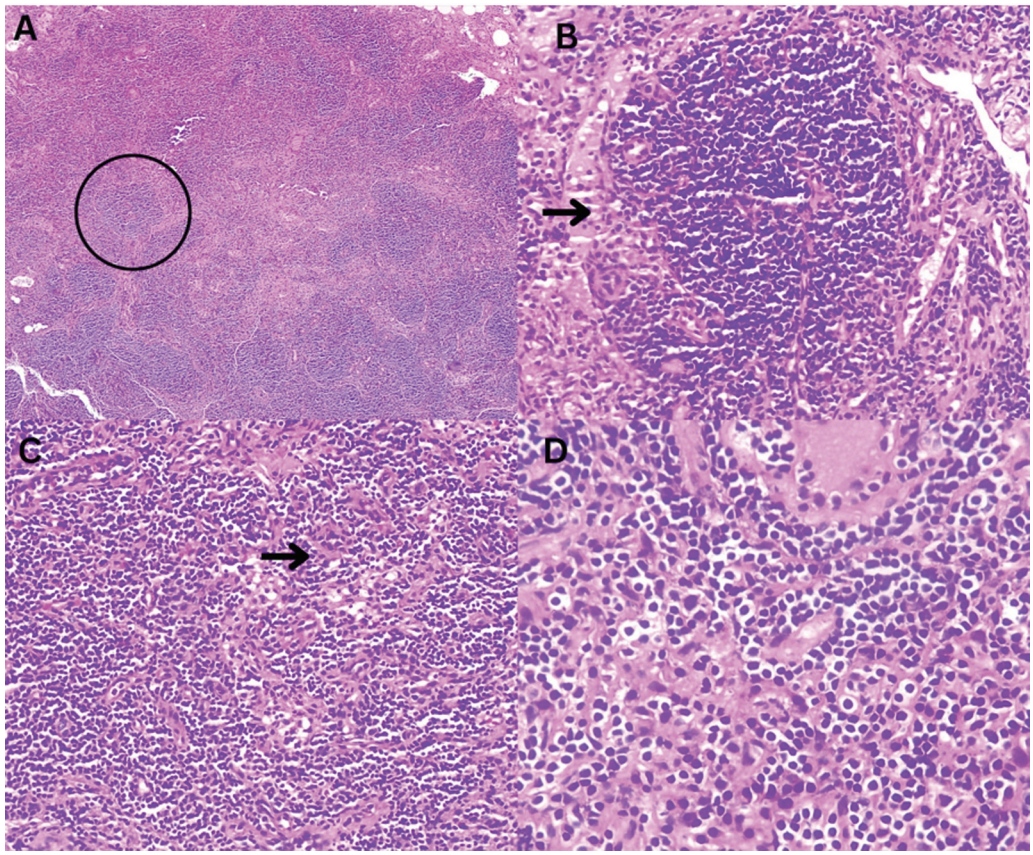

Fig. 2 Histopathological features of the hyaline vascular variant of Castleman disease. (**A**) Lymph nodes showing lymphoid follicles with expanded interfollicular area showing vascular proliferation—4 ×. (**B**) Characteristic "lollipop sign"—penetrating vessel encroaching into the follicle—20 ×. (**C**) Prominent hyaline vascular proliferation—10 ×. (**D**) Image showing pronounced vascular proliferation in the interfollicular area—40 ×.

and a polarized Ki67 proliferation pattern (►**Fig. 3**). Tests for HHV-8 and human immunodeficiency virus (HIV) were negative. The patient received four weekly cycles of rituximab, completed in July 2023, with marked symptomatic improvement. Follow-up CECT scan performed 6 weeks posttreatment showed stable nodal size without progression. At most recent evaluation, she remained asymptomatic and continues routine surveillance to monitor long-term outcomes.

Case 2: A Case of UCD Treated with Surgery

A 29-year-old female patient presented with a 6-month history of menorrhagia accompanied by a 10-kg weight gain, with no comorbidities or family history of malignancy. Initial imaging studies, including ultrasound and CT scan, revealed a 4.5 × 4 cm exophytic lesion arising from the body of the pancreas and abutting the left lobe of the liver, along with bilateral polycystic ovaries. A subsequent CT scan further characterized a 3.7 × 3.7 × 3.4 cm mass in the neck and proximal body of the pancreas, raising the possibility of a nonfunctional neuroendocrine tumor or a solid pseudopapillary tumor. The uterus appeared bulky with a mildly thickened endometrium, and a left adnexal cyst, likely representing a hydrosalpinx. In January 2024, the patient underwent an exploratory laparotomy with excision of the peripancreatic tumor. Postsurgical PET-CT imaging demonstrated low-grade FDG uptake in bilateral level II lymph nodes and subtle nodularity in the thymic tissue, with mild liver enlargement but normal liver parenchyma. The pancreatic region showed postsurgical changes without abnormal FDG uptake or enhancement, and no active disease elsewhere. Histopathological examination confirmed CD, HV type. IHC revealed CD20 positivity within follicles and CD3 positivity in interfollicular areas, with a Ki67 proliferation index of 4% in hotspot areas. CD21 and CD23 highlighted an expanded follicular dendritic cell meshwork. The HHV-8 test was negative, ruling out Kaposi sarcoma-associated herpesvirus involvement. Routine blood tests were normal, HIV serology was negative, and bone marrow evaluation showed moderate euthyroid hyperplasia with normal myeloid maturation. The patient was referred for further management, and follow-up PET-CT imaging, as well as the last clinical and sonological assessment in January 2024, showed no evidence of disease recurrence.

Case 3: A Case of CD Presenting as Paraneoplastic Pemphigus

A 21-year-old female patient presented with a 4-month history of hyperpigmented patches across her body, accompanied by oral and genital ulcers. She had no significant past or family medical history. Examination revealed erythematous and hyperpigmented patches, severe oral and

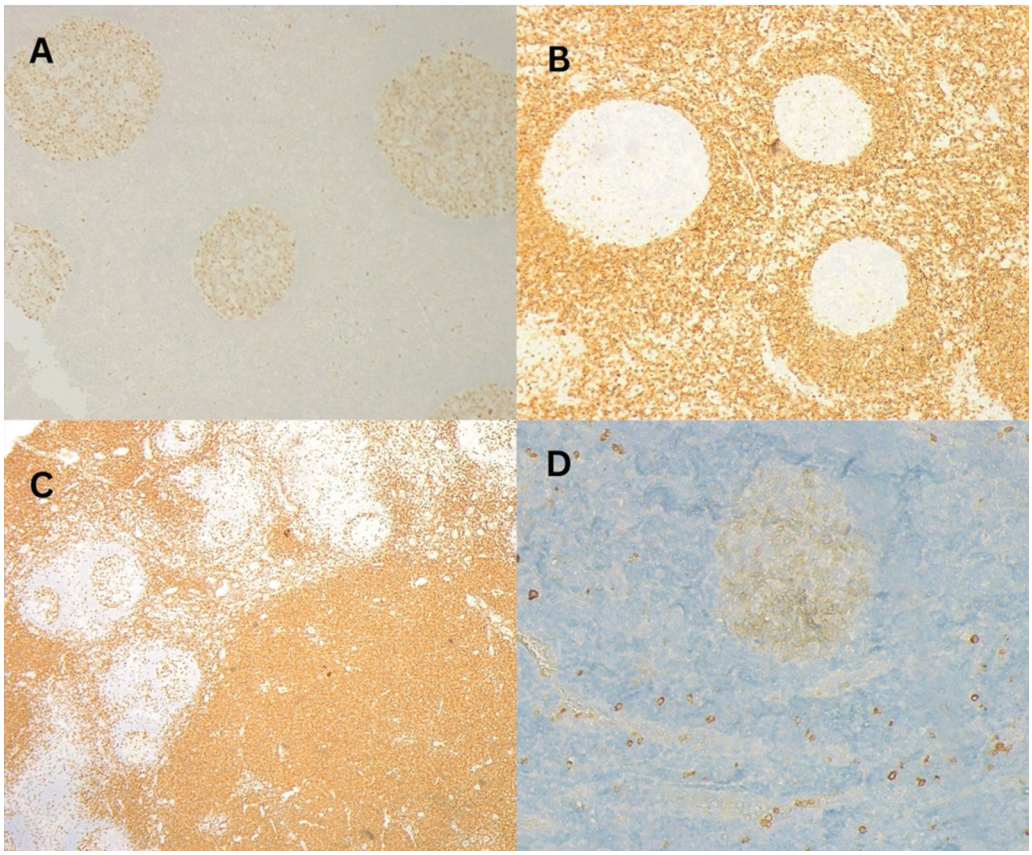

Fig. 3 Immunohistochemical profiles in hyaline vascular Castleman disease. (**A**) BCL6, demonstrates germinal center activity with a characteristic polarized pattern, supporting the diagnosis of the hyaline vascular variant of Castleman disease (HVCD)—20 ×. (**B**) BCL2, showing expanded mantle zone—20 ×. (**C**) CD3, highlights the interfollicular T cell zones, which are notably expanded in HVCD—10 ×. (**D**) CD10, highlights germinal center B cells, confirming follicular hyperplasia in HVCD and aiding differentiation from follicular lymphoma—20 ×.

pharyngeal mucositis, and an extensive, itchy rash with atypical targetoid lesions on the trunk and extremities. Her condition worsened acutely following an episode of herpes stomatitis. A mucosal biopsy from the right cheek revealed lichen planus with acanthosis, hyperkeratosis, basal cell degeneration, and a band-like lymphocytic infiltrate, while a skin biopsy from the abdomen confirmed erythema multiforme. Abdominal ultrasound detected a pelvic mass, further evaluated by CECT and PET-CT, which revealed a low-grade FDG-avid mass in the left paravertebral and presacral region, abutting the left psoas muscle and displacing the left ureter suggestive of UCD. A CT-guided biopsy of a left iliac fossa lesion showed lymphoid tissue with follicles, hyalinized centers, "onion skinning," increased vascularity, and PCs. IHC was positive for CD20, CD3, and CD138, with negative for HHV-8, confirming HVCD. Following four weekly doses of rituximab, an excision biopsy revealed effaced nodal architecture, regressed follicles, and atypical follicular dendritic cells. IHC confirmed CD3, CD2, CD5, and CD7 positivity with dual CD4 and CD8 populations, indicating CD. Enzyme-linked immunosorbent assay for anti-envoplakin was positive and negative for anti-BP 180, anti-BP 230, anti-desmoglein 1, anti-desmoglein 3, and anti-collagen VII suggesting paraneoplastic pemphigus. Her skin lesions resolved and oral mucositis improved but persisted. She is currently on oral prednisolone in tapering doses.

Case 4: A Case of CD on Follow-Up for 9 Years

A 68-year-old female patient was evaluated for central chest pain with mild nonproductive cough in 2015 at an outside hospital. Cardiac workup was negative. An X-ray revealed mediastinal mass. CECT scan of the thorax and abdomen showed a left posterior mediastinal mass of 6 × 4 cm. Biopsy with IHC suggestive of CD HV type. She was treated with low-dose steroids for 5 years and has been in stable disease. Her medical history is otherwise unremarkable, with no significant past or family history and no comorbidities. CT scan done in 2024 showed a heterogeneously enhancing lesion with linear calcifications in the left posterior mediastinum, measuring 5.1 × 3.1 × 5.5 cm. There is no evidence of mediastinal or hilar lymphadenopathy, pleural abnormalities, or pericardial effusion suggestive of stable disease. She was referred to our department for further treatment. A PET-CT scan revealed a metabolically active, heterogeneously enhancing lesion with multiple focal calcifications in the left posterior mediastinum, measuring 5.2 × 3 × 4.9 cm (SUVmax 6.5) with preserved fat plane to the mediastinal structures with no mediastinal and hilar lymphadenopathy.

The patient remains clinically stable and is under regular follow-up.

The cases are summarized in ►**Table 1**.

Discussion

The disease was first described by Benjamin Castleman during mid-1950s. In the course of studying tumors of thymus gland, which presented as enlarged mediastinal lymph nodes resembling thymic tumors grossly, radiologically, and microscopically.[3] Extensive studies followed the discovery in the past five decades, unraveling further disease characteristics. Determining the epidemiology of CD is a challenging feat due to the limited data available about the disease, particularly from low-mid income countries. The incidence of CD varies depending on the region, with the United States reporting an annual incidence of around 7,000 cases, UCD being 70 to 80% of these cases and the rest MCD. The data from Japan gives a similar incidence but with MCD cases more than 70%.[4] A clear gender disparity of the disease is not easily visible, UCD appears to have equal gender distribution while MCD depicts a slight male predominance. HHV-8 though shows a male predominance with around 70 to 80% of the cases while iMCD shows a moderate female predominance. Age distribution of CD is a wide spectrum with the disease occurring at any age, but mostly seen in individuals of between mid-30s and 60s, even though disease have been reported in adolescent age group. Majority of the UCD cases belong to 4th decade whereas MCD cases in comparatively older patients, in their 6th decade of life.[5–8]

The disease is classified based on the proposition of the Castleman Disease Collaborative Network, primarily depending on the extent of lymph node involvement into UCD, where only a single lymph node or a solitary region of lymph nodes and MCD, which involves multiple lymph nodes across different regions. MCD is further classified into HHV-8 virus positive group, subdivided among HIV positive and HIV negative cases. Other variants of MCD includes POEMS-associated MCD linked to a wide spectrum of symptoms and iMCD subdivided into thrombocytopenia, anasarca, fever, reticulin fibrosis of the bone marrow, organomegaly (TAFRO) and iMCD–non-TAFRO.[9]

The pathogenesis of each type varies significantly. UCD usually presents with a slow growing lymph node with characteristic histopathology, mostly harmless.[10] UCD does not usually exhibit systemic symptoms and is often discovered incidentally. Multiple etiological mechanisms have been proposed but the exact mechanism is still obscured. Viral mechanism initially proposed is weakened due to the absence of certain markers like T bet (T-box expressed in T cells), the neoplastic hypothesis involving follicular dendritic cells is currently favored. Mutations in the PDFRB gene encoding platelet-derived growth factor (PDGF) receptor β in CD-45 cells and overexpression of interleukin-6 (IL-6) and epidermal growth factor receptor have been identified in several UCD cases.[1,4,9]

HHV or Kaposi sarcoma-associated herpesvirus is among the key etiological factors of MCD. This virus is found to be present in all HIV associated cases and around half of all the HIV-negative MCD cases. The cells involved belong to B cell lineage, B cells, and plasmablast cells.[1,9] HHV-8 positive plasmablasts which were found to be predominantly localized in the mantle zone of B cell follicles express high levels of cytoplasmic immunoglobulin M (IgM) and are limited to producing a single type of light chain, that is, they are light chain restricted, whereas HHV-8 negative mature PCs in the interfollicular region are IgM negative and produce multiple types of light chain, that is, polytypic. The infected plasmablasts exist as isolated cells, microscopic aggregates also called microlymphomas, or in other cases as frank plasmablastic lymphomas.[11] HHV-8 encodes for viral IL-6 (VIL 6), which is a homologue of human IL-6, and thus contributes to the inflammatory symptoms seen in HHV-8 MCD cases. These cells stain for latency-associated nuclear antigen, VIL 6, B lymphocyte marker CD-20.[1,4,9,11]

POEMS syndrome is found to be linked with MCD and is reported among half of the POEMS cases.[12] POEMS syndrome is a rare paraneoplastic disorder due to underlying PC dyscrasia.[1,4,9] The diagnosis of POEMS syndrome is confirmed when the patient present with both polyneuropathy and monoclonal PC disorder, at least one of the three major criteria which includes CD, sclerotic bone lesions, or elevated vascular endothelial growth factor (VEGF), and minor criteria, that is, organomegaly, extravascular fluid overload, endocrinopathy, and skin changes papilledema of thrombocytosis.[12] Cases where both the mandatory criteria are met but pathologically diagnosed with CD, it must be classified as CD variant of POEMS syndrome if other features of POEMS syndrome exist.[13] Both angiogenic and inflammatory cytokines are found in the condition which are VEGF, IL-1, IL-6, and tumor necrosis factor.[14] Nearly all cases are light chain restricted, which contribute to concurrent MCD and POEMS syndrome.

iMCD, which accounts for one-third of all MCD cases, is a polyclonal lymphoproliferative disorder with an unknown etiology. They are negative for both HIV and HHV-8.[1,15] Two clinical subtypes of iMCD are iMCD-TAFRO and iMCD–non-TAFRO. iMCD TAFRO presents with features of thrombocytopenia, anasarca, fibrosis of bone marrow, renal dysfunction, organomegaly, and normal immunoglobulin levels. while the latter presents with thrombocytosis hypergammaglobulinemia and less severe fluid accumulation.[9,15] Elevated IL-6 levels are detected in some patients while being normal or marginally raised in other cases, suggesting that other factors may too be involved in the pathogenesis.[1,9,15] Studies also state a history of autoimmune disease in 30% of iMCD patients making a possibility that iMCD may be due to an underlying autoimmune condition triggering a cytokine storm. Hypotheses of an unidentified virus causing the disease also have been considered.[15]

The disease diagnosis is only confirmed when the lymph node is pathologically reviewed after an excisional biopsy.[1,4] Histologically, the disease is classified into subtypes HV, PC, and rarely a mixed variety, based on the lymph node morphology and architectural destruction pattern.[1,16] Predominantly seen in UCD, that is, 90% of UCD is of HV subtype and is

Table 1 Summary of cases

Sl. no.	Age	Sex	HIV status	HHV-8 status	Castleman type	Histopathologic type	Immunohistochemistry	FDG PET findings (SUVmax)	Treatment	Current disease status
1	41	F	Negative	Negative	Unicentric	Hyaline vascular type	CD10/BCL6 + (germinal centers), BCL2 + (mantle zones), Ki67 polarized	Para-aortic nodes (4.0)	Rituximab × 4 cycles	Stable on surveillance
2	29	F	Negative	Negative	Unicentric	Hyaline vascular type	CD20 + (follicles), CD3+ (interfollicular), Ki67 4%, CD21/CD23+ (dendritic cells)	Low-grade FDG uptake in lymph nodes	Surgical excision	Stable on surveillance
3	21	F	Negative	Negative	Unicentric	Hyaline vascular type	CD20/CD3/CD138 + , post-Rituximab:CD3/CD2/CD5/CD7 + with dual CD4/CD8 populations	Low-grade FDG-avid paravertebral/presacral mass	Rituximab + prednisolone	Skin lesions resolved, mucositis improved (on steroids)
4	68	F	Negative	Negative	Multicentric	Hyaline vascular type	CD20 + (follicles), CD3+ (interfollicular), Ki67 4%, CD21/CD23+ (dendritic cells)	Mediastinal lesion (SUVmax 6.5), para-aortic/paratracheal nodes (SUVmax 3.7)	Low-dose steroids (5 years)	Disease stable on latest PET-CT scan

Abbreviations: BCL2, B cell lymphoma 2 protein; BCL6, B cell lymphoma 6 protein; CD10, cluster of differentiation 10; CD138, cluster of differentiation 138; CD2, cluster of differentiation 2; CD20, cluster of differentiation 20; CD21, cluster of differentiation 21; CD23, cluster of differentiation 23; CD3, cluster of differentiation 3; CD4, cluster of differentiation 4; CD5, cluster of differentiation 5; CD7, cluster of differentiation 7; CD8, cluster of differentiation 8; FDG, fluorodeoxyglucose; HHV-8, human herpesvirus 8; HIV, human immunodeficiency virus; Ki67, proliferation marker K_i-67; MCD, multicentric Castleman disease; PET, positron emission tomography; SUVmax, maximum standardized uptake value; UHVCD, unicentric hyaline vascular Castleman disease.
Note: Clinicopathological and radiological features of Castleman disease cases.
Reference; Dispenzieri A, Fajgenbaum DC. Overview of Castleman disease. Blood. 2020;135(16):1353–64.

mostly benign in nature. Histologically characterized by distinctive follicles with expanded mantle zones of small lymphocytes forming concentric rings forming the so-called "onion skinning" around the atretic germinal center, penetrated radially by hyalinized vessels creating a lollipop follicle appearance. This is also associated with vascular proliferation, perivascular hyalinization with occasional intravascular calcification. Evidences suggest follicular dendritic cell dysplasia within germinal centers may lead to proliferations or even malignancies. PC variant is more commonly seen in MCD. Histologic features of PC are less distinctive. Histologically, PC shows lymph node with preserved architecture with expanded mantle zones, hyperplastic germinal centers, and sheets of PCs in the interfollicular areas. Vascular proliferation is mild with hyalinization may be present. Mostly the PCs are polytypic but light chain constrictions may occasionally be seen.[1,4,16] Mixed variant exhibiting histologic characteristics of both HV and PC variants. HV is found to be less aggressive than its PC counterpart and offers a better prognosis even though histologic subtype is a less suitable prognostic indicator[16] (►**Fig. 4**).

UCD cases mostly presents with no elaborate clinical symptoms unlike MCD where the patients present with significant symptoms.[17] UCD usually presents with solitary lymphadenopathy commonly in the mediastinum but also in other regions such as the cervical, axillary, abdomen, etc. Some cases may rarely present with signs of inflammation, anemia, hypergammaglobulinemia, and pulmonary findings in approximately 18%. Patients with MCD presented almost always with systemic symptoms. iMCD and HHV-8 MCD present with an overlap of symptoms, including enlarged lymph nodes, signs of inflammations, anemia, hypoalbuminemia, hypergammaglobulinemia, and renal dysfunction. Thrombocytopenia, fluid accumulation, pulmonary findings, cutaneous abnormalities, and neuropathy were also reported in patients even though infrequently.[1,4,18,19] iMCD is further classified into iMCD TAFRO, clinically more aggressive, and iMCD NOS. Evidences also suggest the association of iMCD with autoimmune disorders with these cases presenting with rash, mucosal injury, and positive autoantibodies.[20] Paraneoplastic pemphigus, an autoimmune bullous disease affecting the skin and mucous membrane causing painful bullae; ulcers were found to be associated in some cases of CD, mostly found in HV variant and UCD subtype.[4] Anemia, polyclonal hypergammaglobulinemia, thrombocytopenia, hypoalbuminemia, elevated C-reactive protein (CRP), etc. are the common laboratorial findings. Rise in the levels of cytokines such as IL-6 and VEGF are also detected. Patients require a thorough evaluation, including history, physical examination, and tests such as CBC, ESR, CRP, direct Coombs test, liver function tests, creatinine, serum protein electrophoresis, HIV serology, and urinalysis. Imaging, such as CT or PET/CT, is essential, with pulmonary function tests for those with respiratory symptoms. ^{18}FDG-PET-CT aids in identifying disease activity, guiding biopsy, and monitoring response. Biopsies should target areas of highest uptake. Imaging may reveal lymphadenopathy, organomegaly, sclerotic bone lesions, or pulmonary infiltrates. Lymphoma is the key differential, requiring FDG-PET and pathology for confirmation.[4,21]

Regular monitoring with yearly CT scan is indicated in asymptomatic patients with normal laboratory values and currently no chances of compression-related symptoms. Complete surgical excision remains the mainstay treatment for symptomatic UCD. The clinical and laboratory abnormalities may return to normal after excision. It provides an excellent 10-year survival of 90%. Debulking surgery is an alternative when a complete excision is not feasible especially in cases with compression of critical structures.[4,21] Radiotherapy can be used in symptomatic cases when surgery is not feasible.[22] Inflammation-related disease can be treated with anti-IL-6 agents like siltuximab or tocilizumab, which provide symptomatic relief and arrest lymphadenopathy.[4] We generally use rituximab as the other two agents are costly. The prognosis of peripheral lymphadenopathy is

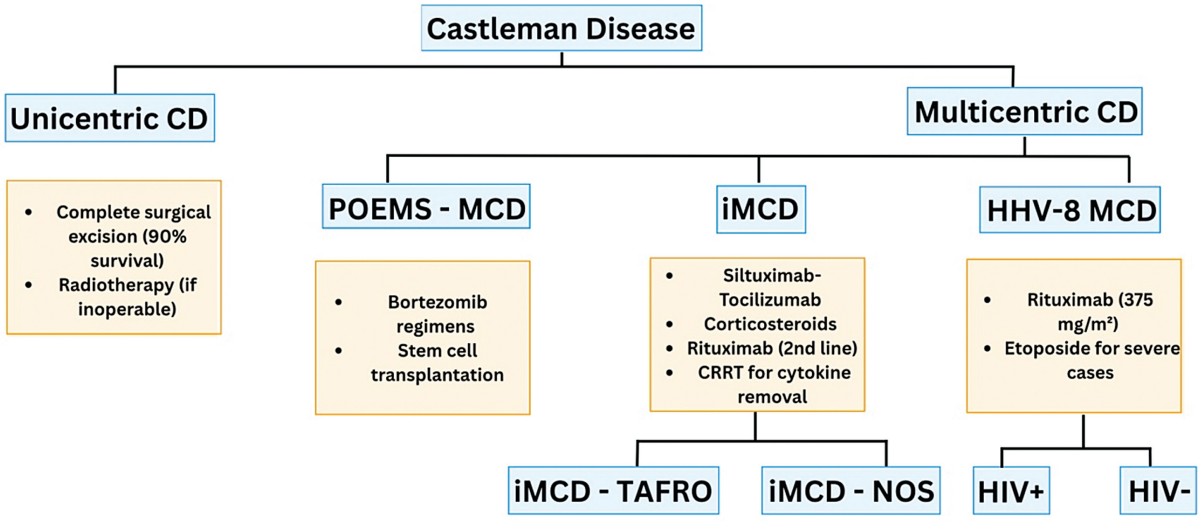

Fig. 4 Classification and treatment of Castleman disease.

better than those cases with central lymphadenopathy. Rituximab administration for cases with HHV-8 positive cases significantly improved the prognosis and survival rate up to 90%. The drug targets the B cell CD20 antigen. Regimen involves weekly rituximab 375 mg/m^2 for 4 weeks in mild cases, administration of etoposide along with rituximab for severe cases. Suppression of B cell by rituximab therapy may lead to the activation of latent HHV-8 and hence there is a risk for development of Kaposi sarcoma.[1,4]

Based on the severity, the disease is classified into severe iMCD and nonsevere iMCD. TAFRO subtype being commonly presented as severe subtype. The disease is categorized as severe subtype if the patients present with two or more out of the five criteria, which includes performance score, that is, Eastern Cooperative Oncology Group ≥ 2, stage 4 renal dysfunction, anasarca/ascites/pleural or pericardial effusion, hemoglobin ≤ 8, and pulmonary involvement.[23] Siltuximab, which acts through an anti-IL-6 mechanism, is the first-line drug for both severe and nonsevere iMCD. Regimen involves 11 mg/kg once every 3 weeks. Corticosteroids are given as an added therapy. Tocilizumab, which is given at a dose of 8 mg/kg every 2 weeks along with corticosteroids, is given if siltuximab is not available. Response toward the treatment must be assessed by symptomatic, biochemical, and radiological criteria. Patients with nonsevere disease and not reacting to first-line therapy must be given rituximab at a dose of 375 mg/m^2 once a week for 4 to 8 weekly doses, supplemented with corticosteroids, immunomodulatory, and suppressive agents including cyclosporine and thalidomide. Patients with severe disease and no response to first-line therapy, concurrent high-dose corticosteroid therapy may be given. A standard therapy for iMCD TAFRO is still not established.[4,24] The POEMS-associated cases must be treated like myeloma therapy. Commonly used regimens are bortezomib, cyclophosphamide, and dexamethasone/bortezomib, lenalidomide, and dexamethasone. High-dose melphalan with autologous peripheral stem cell transplantation is an effective treatment modality for consolidation therapy in severe cases.[1,4]

Continuous renal replacement therapy (CCRT), an extracorporeal blood purification technique, effectively removes inflammatory cytokines, including IL-6, endotoxins, and other mediators, while optimizing fluid balance and restoring homeostasis. Utilizing high cutoff and medium cutoff membranes, CRRT targets cytokine-mediated inflammation and multiorgan dysfunction. It can be used as a bridge therapy for patients unresponsive to cytotoxic chemotherapy or anti-IL-6 therapies.[25] Bortezomib with dexamethasone can be used in the second line for refractory iMCD unresponsive to siltuximab.[26] Testing for markers like VEGF, PDGF, and mutations in PDGFRB gene could help differentiate UCD from other similar disorders. For MCD, its complex nature has led to the discovery of subtype-specific biomarkers, for example, IL-6. CXCL13, a key player in immune regulation, has been found to rise during iMCD flares and could predict how patients respond to treatment. Meanwhile, the mammalian target of rapamycin pathway and serum IP-10 are tied to the hypervascular iMCD-TAFRO type, and IL-6 has been linked to the PC iMCD-NOS type[27–31].

This study highlights the clinical heterogeneity of CD through four diverse cases, emphasizing histopathological and imaging-driven diagnosis, multidisciplinary collaboration, and long-term follow-up insights. However, its retrospective design, small sample size, and institutional bias limit generalizability, particularly for off-label therapies like rituximab in UCD. Future multicenter studies should validate treatment protocols, explore molecular drivers (e.g., PDGFRB mutations, cytokine pathways), and standardize biomarkers (CXCL13, IL-6) for risk stratification. Research must address unresolved areas: HHV-8's role in HIV-negative MCD, autoimmune-CD interplay, and long-term safety of immunomodulators. Findings are most applicable to resource-constrained settings, underscoring the need for adaptable algorithms and equitable access to advanced therapies globally.

Conclusion

CD is a rare lymphoproliferative disorder that poses a challenge even today due to its clinical and pathological heterogeneity. Clinically, CD is a heterogeneous disease which requires individualized treatment with surgery, radiotherapy, immunomodulators, and chemotherapy. We discussed four different scenarios of CD with different presentations treatment and outcome. This case series is to supplement the inadequate existing literature to improve patient outcomes and reduce delays in diagnosis.

Declaration of GenAI Use

Artificial intelligence was used exclusively to enhance language and readability; no data or content was generated solely by AI.

Patients' Consent

All figures in the article were obtained from the patient's medical record with proper consent. These are original images captured during the clinical evaluation.

Ethical Approval

This case report was granted institutional ethics committee clearance by the Institutional Ethics Committee, Government Medical College, Kozhikode, approval number GMCKKD/RP 2025/ IEC/26, written informed consent was obtained from the patient for publication.

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None.

Conflict of Interest

None declared.

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