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Castleman disease: A single-center case series

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ABSTRACT

BACKGROUND: Castleman disease (CD) is a rare lymphocytic disorder. Unicentric CD (UCD) has an excellent long-term prognosis after surgical excision; however, multicentric CD (MCD) has a severe clinical course with poor outcomes.
STUDY DESIGN: We analyzed the clinical presentation of 28 patients treated at a single institution from 1995 to 2017. Demographics, clinical variables, anatomical site, centricity, histopathology, immunochemistry, and surgical approach were reviewed. We evaluated the 5-year recurrence and survival for patients with UCD and MCD.
RESULTS: Of the 28 patients, 57 % (n = 16) were female, with a mean age of 41.6 ± 15.6 years. CD was asymptomatic in 57 % (n = 16) of patients, 21 % (n = 6) presented with local symptoms such as pain, and 21 % (n = 6) of patients also had systemic symptoms, including weight loss and fever. CD was unicentric in 64 % (n = 18) and multicentric in 36 % (n = 10). The hyaline vascular variant was noted in 57 % (n = 16) of the tumors, plasmacytoid variant in 36 % (n = 10), and mixed variants in 7% (n = 2) of tumors. Anatomical distributions included: head and neck (20 %), thorax and axilla (24 %), retroperitoneal (13 %), abdominopelvic (30 %) regions, and other (13 %). Complete surgical resection was performed in 95 % of patients with UCD. Surgical biopsy and medical therapy were provided to all patients with MCD. The recurrence rate for UCD and MCD was 6 % (n = 1) and 14 % (n = 1), respectively. The five-year disease-free survival rate for UCD was 95 % (n = 19) and MCD was 33 % (n = 2). We found 100 % survival in patients with UCD and histology demonstrating the HV variant.
CONCLUSION: CD is rare and often misdiagnosed due to the absence of specific clinical symptoms. Surgeons should include CD in their differential diagnoses when evaluating patients with lymph node hyperplasia. Surgery can be curative in nearly all patients with UCD. Patients with MCD require a combination of surgical therapy, chemotherapy, and immunotherapy; however, cytoreductive surgery benefits for patients with MCD have not been established.

1. Introduction

Castleman Disease (CD), first described in 1954 [1,2], is also known as angiofollicular lymph node hyperplasia or giant lymph node hyperplasia [3,4]. CD is an uncommon disorder that can involve either a single lymph node (unicentric, UCD) or multiple lymph nodes (multicentric, MCD). This distinction is based on the anatomical distribution of disease and the number of lymph nodes involved [5]. The estimated CD incidence is approximately 25 cases per million person-years, which represents under 5200 cases in the United States per year [6,7]. This rare lymphoproliferative disorder has been linked to the human herpesvirus 8 (HHV 8) that infects both B-cells and the lymphovascular compartment of lymph nodes [8]; however, the etiology and pathophysiology of CD remains elusive and may be related to dysregulation of the immune system [7,9]. Although HIV and HHV 8 infections are not associated with UCD, dysplastic follicular dendritic cells and elevated levels of inflammatory cytokines such as IL-6 are associated with the lymph node hyperplasia in UCD [7,9–15]. In a subset of

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patients with MCD, elevated levels of IL-6 and infections with HHV 8 are thought to underlie the pathological lymph node process of MCD [7,9–15].

Two main histological subtypes are described: the hyaline vascular (HV) and the plasmacytoid (PC) variants; occasionally, there are mixed variants (MV) [1,2,9]. Differentiation of the HV versus the PC is based on lymph node morphology and is determined by the pattern of lymph node architectural destruction [16]. The HV histology, characterized by small hyaline-vascular follicles and capillary proliferation penetrating the germinal centers, characterizes nearly all cases of UCD [17]. The plasma cell variant, composed of lymphoid follicles separated by plasma-cell sheets, characterizes most cases of MCD [17].

CD is rare; we report patients' clinical presentation and review the surgeon's role in the care of 28 patients with CD. It is essential to differentiate CD from lymphoma and identify the subtype of CD (UCD or MCD) as each subtype varies significantly in terms of symptoms, clinical findings, disease mechanism, treatment approach, and prognosis. This single-center study aims to report the histopathology, tumor location, centricity, medical and surgical therapy, and long-term outcomes for patients with CD.

2. Methods

Our inclusion criteria were all patients who presented with CD at our facility for surgical and medical therapy. Our only exclusion criteria were patient refusal to participate in research. We reviewed all patient records for research permission. No patients in our study declined participation in clinical research. We identified a total of 28 patients with CD who presented at our academic medical center over a 22-year period from January 1995 to March 2017. We retrospectively reviewed patients' medical records and evaluated clinical presentation, centricity, anatomic location, diagnostic modalities, and histopathology. We collected laboratory data, viral associations, patient outcomes, and disease recurrence. Our study was approved by our Institutional Review Board (IRB number: 1701M03261) and registered with the research registry (UIN: researchregistry6513) [18]. Our study process aligns with all 2020 guidelines for reporting of case series in surgery [19]. This study's primary outcome was 5-year survival; we also evaluated tumor recurrence rates for patients with UCD.

The term *resective surgery* describes the surgical interventions to resect UCD completely. In MCD, *resective surgery* indicates an attempt to debulk clinically significant tumors; biopsy indicates procedures performed to obtain a tissue diagnosis.

In UCD, *diagnostic surgery* was defined as procedures performed to obtain an incisional biopsy of a lymph node or a solid organ. In MCD, *diagnostic surgery* indicates procedures performed to obtain limited tissue for diagnosis.

2.1. Statistical analysis

We stratified our patient population based on centricity and compared baseline clinical characteristics. Categorical variables are reported as counts and percentages; parametric continuous variables are reported as means and standard deviations. Nonparametric continuous variables are reported as median, interquartile ranges (IQR). To determine differences between cohorts for categorical variables, we used the χ^2 test and Fisher's Exact test. To detect differences for nonparametric continuous variables, we used the Mann-Whitney *U* test To measure differences for parametric continuous variables, we used the Student's *t*-test. We also constructed Kaplan-Meier survival curves for patients with UCD and MCD. All *P* values are two-tailed with a significance of 0.05 to detect statistical significance. We performed statistical analysis using IBM SPSS (version 25.0, Armonk, NY).

Table 1
Baseline characteristics.

Variable	UCD (n = 18)	MCD (n = 10)	*P – Value*
Demographics			
Age (years), mean ± SD	42.1 ± 16.7	41.2 ± 18.8	0.896
Female	13 (72.2 %)	3 (30.0 %)	0.050*
Comorbidities[a]			
Diabetes	6 (33.3 %)	1 (10 %)	0.364
Hypertension	8 (44.4 %)	7 (70 %)	0.254
Malignancy	5 (27.8)	2 (20 %)	0.645
Connective Tissue Disorders	3 (16.7)	3 (30 %)	0.634
Pulmonary Disorders	6 (33.3 %)	3 (30 %)	0.865
Cardiovascular Disorders	9 (50 %)	3 (30 %)	0.434
Gastrointestinal Disorders	5 (27.8 %)	3 (30 %)	1.000
Hypothyroidism	2 (11.1 %)	1 (10.0 %)	1.000
Renal Disorders	2 (11.1 %)	2 (20.0 %)	0.601
Appendicitis	1 (5.56 %)	0 (0%)	1.000
Laboratory values[b]			
Creatinine (mg/dL)	0.85 ± 0.24	2.21 ± 2.52	0.085
WBC	8.23 ± 3.60	12.7 ± 6.5	0.088
Hemoglobin (g/dL)	12.9 ± 1.8	11.0 ± 1.86	0.059
IL-6	3.54 ± 3.63	65.89 ± 80.78	0.022*
Histopathogenic type[a]			
Hyaline vascular	13 (72.2 %)	3 (30 %)	0.050*
Plasmacytoid	4 (22.2 %)	6 (60.0 %)	0.097
Location			
Peripheral	13 (72.2 %)	5 (50 %)	0.412
Visceral	5 (27.8 %)	5 (50 %)	0.412
Other clinical associations			
POEMS	0 (0 %)	2 (20 %)	1
TAFRO	0 (0 %)	1 (10 %)	1
ITP	0 (0 %)	1 (10 %)	1

UCD unicentric Castleman Disease, *MCD* multicentric Castleman Disease, *WBC* white blood cell count, *IL-6* interleukin 6, *POEMS:* Polyneuropathy Organomegaly Endocrinopathy Monoclonal-protein Skin changes, *TAFRO:* Thrombocytopenia Anasarca Fibrosis Renal failure Organomegaly, *ITP:* Idiopathic Thrombocytopenic Purpura.

* 2-tailed $P \leq 0.05$.

[a] Categorical variables reported as counts and percentages.

[b] Continuous variables as measured and obtained from the electronic medical record.

3. Results

3.1. Patient demographics

Univariate analysis demonstrated acceptable homogeneity levels among baseline characteristics between the two patient cohorts (Table 1). We observed a significant difference in the distribution of patient sex and serum levels of IL-6; however, we believed that those differences were clinically insignificant or irrelevant to the outcomes we analyzed. Of the 28 patients, 16 were female, and 12 were male with an age range of 16–75 years (mean ± SD, 41.8 ± 17.2 years). 57 % (n = 16) of patients with CD were asymptomatic and diagnosed incidentally by imaging studies. 43 % (n = 12) of patients had nonspecific symptoms such as abdominal pain or discomfort, hematuria, chronic cough, pleuritic chest pain, dyspnea, acute renal failure, and back pain. Retroperitoneal, neck, and abdominal masses were palpated in only 14 % (n = 4) patients. We observed no differences in complete blood counts and biological immunoassays between UCD and MCD. All viral marker results obtained, including HIV, or HHV-8 antibody titers, were negative.

3.2. Tumor location and surgical treatment

Fig. 1 depicts the distribution and anatomical locations of diseased lymph nodes for both UCD and MCD. In patients with UCD, lymph node sizes ranged from 1 to 15 cm (mean, 4.9 ± 3.7 cm). 11.1 % of patients (n = 2) had masses larger than 10 cm in diameter. In MCD, 7 of 10 patients underwent an excisional lymph node biopsy

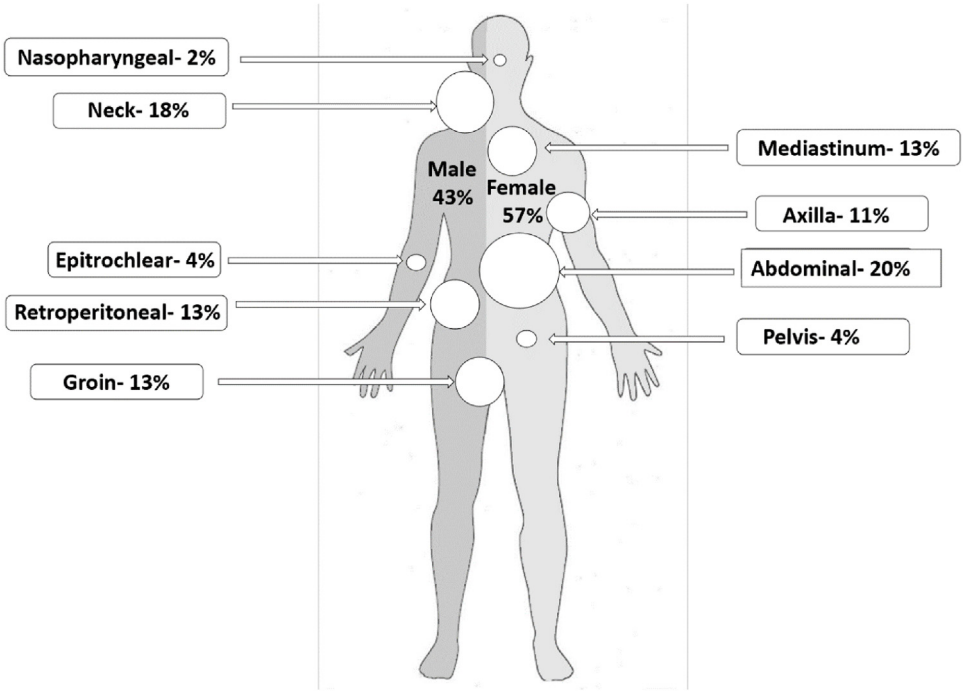

Fig. 1. All anatomical lymph node regions in unicentric Castleman Disease (UCD) and multicentric Castleman Disease (MCD) for a total of n = 46 tumors. The pie graphs indicate the distribution of UCD (n = 18) or MCD (n = 10) in 28 patients.

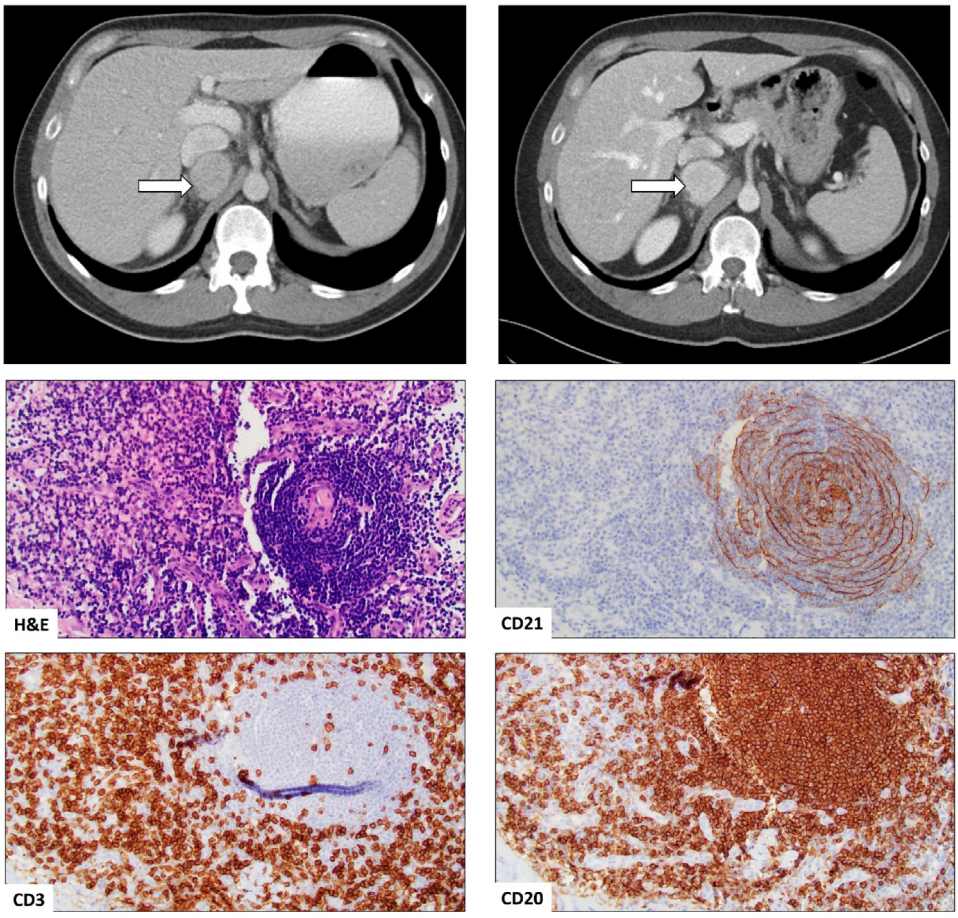

Fig. 2. A 38-year-old female was incidentally found to have a mass in the right upper aspects of the retroperitoneal space deep to the inferior vena cava on CT scan obtained for right lower quadrant pain secondary to appendicitis. The mass was biopsied and demonstrated the HV variant of UCD. The mass was not resected, and the patient has remained asymptomatic. CT scans at presentation and 6-year follow up show no change in the tumor dimensions.

Table 2
Treatment modalities and outcomes.

Variable	UCD (n = 18)	MCD (n = 10)	*P – Value*
Surgery			
Resective	17 (94.4 %)	0 (0 %)	1.000
Diagnostic	5 (27.8 %)	7 (70 %)	0.050*
Resective surgery alone	13 (72.2 %)	0 (0%)	1.000
Diagnostic Surgery + immunosuppressive therapy	0 (0%)	7 (70 %)	1.000
Immunosuppressive therapy alone	0 (0%)	3 (30 %)	1.000
Chemotherapy			
Cladribine	0 (0%)	1 (10 %)	1.000
CHOP	0 (0%)	1 (10 %)	1.000
VD-PACE	0 (0%)	1 (10 %)	1.000
Immunotherapy			
Tocilizumab[a]	0 (0%)	1 (10 %)	1.000
Siltuximab[a]	0 (0%)	1 (10 %)	1.000
Rituximab	0 (0%)	6 (60 %)	1.000
Cyclosporin	0 (0%)	1 (10 %)	1.000
Methylprednisolone	0 (0%)	6 (60 %)	1.000
Recurrence	1 (5.6 %)	2 (20 %)	1.000
Death due to disease during follow-up to 5 years	1 (6.7 %)	2 (33.3 %)	1.000

Patients were diagnosed using imaging studies such as computer tomography and magnetic resonance imaging.
UCD unicentric Castleman Disease, *MCD* multicentric Castleman Disease.
* 2-tailed $P \leq 0.05$.
[a] Administered in combination with rituximab.

for diagnosis, 2 of 10 patients underwent a core needle biopsy (CNB) for diagnosis, and 1 of 10 patients who had a nondiagnostic CNB required an excisional lymph node biopsy for diagnosis. Four patients with MCD had splenic involvement. One of the four patients underwent a radical excision of tumor that included splenectomy followed by chemotherapy; this patient died following a massive cerebral vascular event, 8-years after surgery. Two of the four patients who had splenic involvement underwent lymph node biopsy for diagnosis followed by chemotherapy; both were alive at 5-years follow-up. One of the four patients with splenic involvement underwent CNB alone and received chemotherapy; this patient died 4-years after diagnosis. 17 of 18 patients with UCD underwent complete tumor excision; 4 of these 18 patients were originally diagnosed with CD by CNB. One of 18 patients with UCD and HV variant underwent only a diagnostic CNB; surgical resection was not performed due to the tumor's unfavorable surgical anatomy and retroperitoneal location. CT scans demonstrated no change in the size of the tumor over six years. The patient remains symptom-free at a total of 8-years follow-up (Fig. 2). Twelve additional patients in our series demonstrated both UCD and HV variants with 100 % survival. Five-year disease-free survival was available for 8 of these 12 patients. Disease-free survival follow-ups for the remaining four patients ranged from 3-months to 3-years.

3.3. Pathological findings

All surgical lymph node biopsies demonstrated histology characteristic of CD. Polymerase chain reaction assays for HHV8 and HIV were negative in the 25 patients tested. The histology of the lymph nodes was characterized as: the hyaline vascular variant in 57 % (n = 16), as the plasmacytoid variant in 39 % (n = 11) and as mixed variant in 11 % (n = 3).

3.4. Patient outcomes

Our treatment modalities and outcomes are summarized in Table 2. Our retrospective review provided patient follow-up for a minimum of 3 months and a maximum of 25 years. Three patients

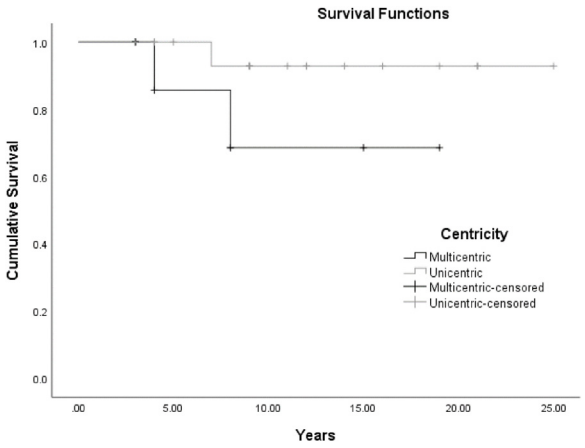

Fig. 3. Outcome in CD depending on centricity. Kaplan-Meier analysis for mortality outcomes. Vertical bars indicate the point in time for which last follow-up information is available for an individual patient who is then considered lost to follow-up. Overall, survival of 28 patients was 89 %.

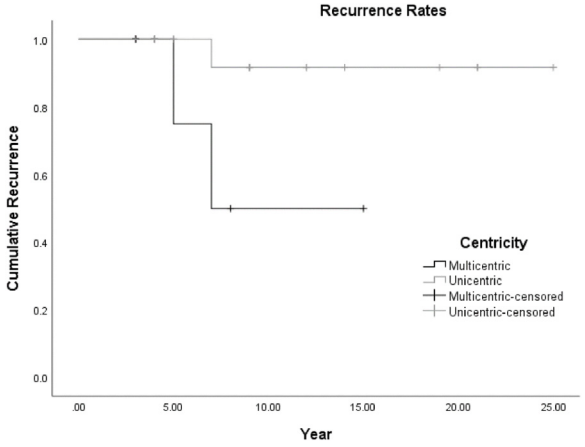

Fig. 4. Overall, recurrence rate of 8 % in CD. Vertical bars indicate the point in time for which last follow-up information is reported for an individual patient who is then considered lost to follow-up.

presented with disease recurrence; two patients with MCD and one patient with UCD.

Overall, patient survival was 89 % (n = 25/28). Survival for patients with UCD was 95 % (n = 17/18) and survival for patients with MCD was 80 % (n = 8/10). Overall, 5-year disease-free survival rate in these patients was 95 % (n = 19/20). The 5-year disease-free survival rate for patients with UCD was 93 % (n = 14/15), and the 5-year disease-free survival rate for patients with MCD was 67 % (n = 4/6). No significant difference in cumulative survival was observed between MCD and UCD on Kaplan-Meier analysis (Mantel-Cox test: $\chi^2 = 2.267$, df = 1, $P = 0.132$, Fig. 3).

Recurrence data was available for 24 of 28 patients (17 UCD & 7 MCD). Overall, recurrence rate was 8 % (n = 2/24); UCD-specific recurrence rate was 6 % (n = 1/17) and the MCD-specific recurrence following chemotherapy was 14 % (n = 1/7). Overall, 5-year recurrence rate was 6 % (n = 1/17); UCD-specific 5-year recurrence rate was 0 % and MCD-specific 5-year recurrence following chemotherapy was 33.3 % (n = 1). Kaplan-Meier curves demonstrated a significant increase in cumulative recurrence rates following MCD (Mantel-Cox test: $\chi^2 = 4.039$, df = 1, $P = 0.044$*, Fig. 4).

4. Discussion

In this single-center review, we describe 28 patients with CD. Our analysis confirms that UCD and MCD are distinct clin-

ical entities, with unique clinical presentations, histopathology, pharmacotherapy, surgical treatment strategies, and long-term prognosis. A surgeon needs to be aware of the clinical spectrum of this disease and specific subsequent therapy. Surgical interventions are primarily dependent on the centricity of disease. As demonstrated in our series, surgical resection is curative for UCD; however, surgery's first role is diagnostic for patients with MCD. The role of additional surgery for patients with MCD remains undetermined.

Our study, consistent with previous literature, confirms the heterogeneity between UCD and MCD. UCD is more prevalent, with a marginal female predominance. Nevertheless, CD is reported to affect both sexes equally [1,20]. In general, patients with UCD tend to present in their 2nd to 4th decade of life, significantly younger than those with MCD who have a peak incidence in their 6th and 7th decades [5,20]. Most patients in our series presented with abdominal masses and were either asymptomatic or had localized symptoms such as back pain, abdominal pain, or shortness of breath secondary to the mass effect. MCD is characterized by systemic symptoms such as fever, fatigue, night sweats, and weight loss (B symptoms) in conjunction with tender lymphadenopathy [2]. It is critical to differentiate CD from lymphoma; however, lymphoma is often an initial working diagnosis. Although histopathology is diagnostic, the laboratory findings are often abnormal (e.g., IL-6, HHV8, ESR, CRP, WBC) and nonspecific. Elevated levels of IL-6 and positive HHV8 antibody titers are associated explicitly with MCD and not with UCD [2]. In our study, elevated C-reactive protein, erythrocyte sedimentation rate, and leukocytosis were all nonspecific. In UCD, lymphadenopathy is typically more substantial than that observed in lymphoma with a mean size of 5 cm [2]. As with every patient with lymphadenopathy, it is essential to perform a complete lymph node examination of all peripheral lymph nodes; this is particularly important when CD is suspected as missing multinodal involvement could result in misdiagnosis and inappropriate therapy. If CD is diagnosed intraoperatively or postoperatively, the surgeon should examine the patient for lymphadenopathy postoperatively using clinical and imaging modalities [2]. Clinical imaging should be pursued regardless of physical examination findings to exclude central lymphadenopathy [2].

In terms of diagnostic tests, contrast-enhanced, whole-body computed tomography (CT) is the standard for CD diagnosis with a sensitivity and specificity of 89 % and 94 %, respectively [21–25]. The affected nodes in CD typically show homogenously intense contrast enhancement; however, this finding is nonspecific. Magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (PET) can provide enhanced imaging of surrounding tissue if CT scans are inconclusive or contraindicated [20,26–29].

There remains etiologically uncertainty regarding the distinct clinical manifestations between MCD and UCD. It is postulated that viral infections may play a role in its pathogenesis, particularly the association with HHV8 with MCD [9,12,13,30]. Although, in our study, we did not detect HHV8 infections in any of our patients, other investigators have documented this association. In a meta-analysis by Talat et al. [2] 93.9 % of patients (46 out of 49 patients) with positive HHV8 titers had MCD; their mortality with HHV8 infection was also markedly higher than those with a proven negative HHV8 status [2]. HHV8 and HIV coinfection was also commonly observed [9]. A proposed mechanism suggests that coinfection with HIV enhances host cellular invasion by HHV8 [9]. This permits immune evasion, allowing for viral replication in early plasma cells resulting in exaggerated inflammatory responses [9]. TAFRO syndrome is a recently described variant of HHV8-negative MCD with a possible autoimmune etiology [31]. This syndrome is characterized by a more aggressive clinical course that includes severe thrombocytopenia, refractoriness to corticosteroid therapy, increased frequency of anasarca, and normal serum gammaglobulin levels compared to other variants of MCD [31]. CD has also been associated with POEMS syndrome, a rare hematological disease associated with plasma cell dyscrasia characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes [32]. In one study, up to 30 % of patients diagnosed with POEMS syndrome had concomitant evidence of Castleman disease on lymph node biopsy [32]. Peripheral neuropathy and monoclonal gammopathy are essential diagnostic criteria for POEMS syndrome [32].

On histopathologic analysis, UCD predominantly consists of the HV variant (90 %), while in MCD, the PC variant (50 %) is most commonly observed [11,13,14]. Histologic variance is now considered to be of secondary importance in predicting long-term outcomes in CD [2]. Currently, centricity is considered the most important indicator of patient outcomes [2]. In a comprehensive systematic review, before adjusting for confounders, the HV subtype demonstrated a better prognosis than the PC variant; however, after stratifying on centricity, this association disappeared, suggesting that centricity is a better predictor of long-term recurrence and survival [2]. In our series, the combination of UCD and the HV variant was associated with a benign prognosis, and in one patient, no progression of disease at 6-years follow up without resection of the tumor. Resective surgery can be both diagnostic and curative for UCD with negligible rates in recurrence and mortality; the anatomic distribution of lymph nodes determines the surgical approach and complete resection feasibility [1,2,20]. Some authors believe that the feasibility of complete resection explains the lower mortality in patients with peripheral disease versus those with central disease [2]. Other possibilities that explain the higher mortality in patients with central disease include late presentation with advanced disease and the potential impact on vital organs. Although in our study, two patients with UCD had good outcomes with incomplete resection, an incisional biopsy, or an incomplete resection of the affected lymph node is traditionally not recommended [2,30]. Currently, surgical planning involves en-bloc resection of lymph nodes to achieve tumor-free margins; thus, regional lymphadenectomy is advised in patients with multiple lymph node involvement [2,20]. Central lymphadenopathy is usually suggestive of lymphoma unless otherwise proven. If an intraoperative wedge biopsy is suggestive of UCD, then a complete localized resection should be performed [2,30].

Chemoradiation is not usually indicated in patients with UCD [30]. Recurrence rates are negligible for both central and peripheral UCD; however, the surgical procedure can predispose to various challenges due to the regional anatomy [2,20,30]. There is a lack of consensus on the optimal treatment strategy for unresectable UCD; suggested treatment approaches include observation, corticosteroid therapy, chemotherapy, and radiotherapy [33]. The role of surgery in MCD is debated [2]. Studies have shown that immunochemotherapy provides similar outcomes to surgery, suggesting a limited role for surgery [2,15]. Currently, there is no curative role for surgery; the present consensus is that surgical therapy is primarily diagnostic or palliative. Palliative resection can debulk and alleviate vascular or airway compromise, reduce massive organomegaly, and relieve bowel obstruction [30]. Cytotoxic chemotherapy is often recommended in MCD; however, the evidence is limited, and results on efficacy are mixed [7,34,35]. Chemotherapeutic options include (i) single-agent chemotherapy using daily oral etoposide, vinblastine, or cladribine and (ii) combination chemotherapy using cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) [7]. Other potential treatment options for HIV/HHV 8 associated MCD include antiviral drugs such as valganciclovir and valacyclovir; both have shown promising results [2,36,37]. Other researchers suggest that valganciclovir may prove useful as maintenance therapy. Immunotherapeutic agents such as rituximab, a humanized monoclonal antibody to CD20, have shown significant activity

in HIV-positive or idiopathic MCD when used as monotherapy or in combination with chemotherapy [7]. Future studies may clarify how multimodal therapy can be augmented; the combination of debulking surgery and immunochemotherapy may improve patient outcomes in aggressive disease [15]. Similarly, the combination of immunochemotherapy and antiviral therapy could be prospectively evaluated; preliminary evaluations suggest improved patient outcomes compared to surgery [2,15].

We acknowledge our study's limitations; this was a retrospective single-center review of a very rare disease with a limited sample size. Creating a national registry to capture multicenter data with long-term follow-up may elucidate other factors associated with patient outcomes.

5. Conclusion

Castleman disease is an uncommon lymphoproliferative disorder often misdiagnosed due to atypical or incidental clinical manifestations observed during the workup of other pathological diseases. A surgeon should place Castleman disease in their differential diagnosis when evaluating a patient with local or multicentric lymphadenopathy. Histopathological evaluation is diagnostic. Unicentric and multicentric disease are distinct clinical entities that mandate different therapeutic approaches. In unicentric disease, surgical resection is curative and the standard of care. In multicentric disease, the role of surgery is currently limited to diagnosis or palliative debulking procedures; patients with MCD are likely to benefit from immunochemotherapy and antiviral therapy.

Declaration of Competing Interest

The authors have no other relationships, conditions, or circumstances that present a potential conflict of interest. The authors alone are responsible for the content and writing of this article.

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Ethical approval

Our study was approved by our Institutional Review Board (IRB number: 1701M03261).

Consent

This is a retrospective research study that involved record review only. We will first review patients Fairview's research optout form from the patients EMR. If this box is checked, we will exclude this patient from further review. There was no communication with research participants.

Author contribution

- Kyle Pribyl: Responsible for the data collection, data analysis/interpretation and writing of the manuscript.
- Victor Vakayil: responsible for study design, data analysis/interpretation and writing of the manuscript.
- Najih Farooqi: responsible for data collection and writing of the manuscript.
- Nivedita Arora: responsible for writing of the manuscript.
- Benjamin Kreitz: responsible for data collection and writing of the manuscript.
- Salman Ikramuddin: responsible for writing of the manuscript.
- Michael Linden: responsible for writing of the manuscript and pathological data collection.
- James Harmon: responsible for writing of the manuscript, data analysis/interpretation and writing of the manuscript.

Registration of research studies

Not applicable.

Guarantor

Dr. James V. Harmon MD, PhD.

Provenance and peer review

Not commissioned, externally peer reviewed.

CRediT authorship contribution statement

Kyle Pribyl: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing. **Victor Vakayil:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing. **Najiha Farooqi:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation. **Nivedita Arora:** Formal analysis, Investigation, Resources, Writing - original draft, Writing - review & editing. **Benjamin Kreitz:** Data curation, Writing - original draft, Investigation. **Salman Ikramuddin:** Data curation, Writing - original draft, Investigation. **Michael A. Linden:** Data curation, Writing - original draft, Supervision, Writing - review & editing. **James Harmon:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Supervision, Writing - review & editing.

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