# Clinicopathologic Features of Castleman's disease: Experience at King Hussein Medical Center

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## ABSTARCT

**Objective:** To study the clinicopathologic features of Castleman's disease (CD), to review the treatment challenges in a group of Jordanian patients at King Hussein Medical Center, and to compare that with international data.

**Methods:** This is a retrospective review of CD cases conducted at King Hussein Medical Center over 8 years (January 2009 to December 2016). A total of 21 cases of histopathologically diagnosed CD were enrolled in this study. Clinical data and histopathological parameters were analyzed and correlated among different subtypes of the disease with different outcomes and associations.

**Results:** There were 14 males and 7 females. The median age of presentation was 40.1 years. Common symptoms include lymphadenopathy 76%, anemia 35%, abdominal pain 30%, splenomegaly in 19% of cases. Lymphoma was diagnosed in 10% of cases. The disease was localized in 15 cases and multicentric in 6 cases. Univariate analysis showed that most of multicentric CD cases presented with complications compared to localized disease (p value of 0.0002). Of multicentric CD, 2 cases were positive for Human Herpes Virus-8 (HHV-8). The results of Human Immunodeficiency Virus (HIV) were available in 15 patients, and no case was positive. Hyaline vascular morphology was the commonest histopathological pattern observed in 67%, followed by plasma cell 19%, and mixed type in 5%. For all patients with localized disease, hyaline vascular was the only pathologic variant, whereas 4 out of 6 (66.6%) multicentric CD were of plasma cell type. Treatment of unicentric CD consisted of surgical resection, whereas for multicentric it was medical and 19 patients were followed up. Of these, 93.3% of unicentric disease remain symptom free without recurrence, while 2 cases of multicentric CD died, and the 3 others attained partial remission .

**Conclusion:** Unicentric and multicentric CD are different clinical entities with overlapping histologic features. Most of the cases of Jordanian patients with CD exhibit an indolent clinical course with local surgical therapy. Further studies are needed to further elucidate the epidemiology, pathogenesis, clinical behavior, and optimal therapeutic regimens of this rare disease.

**Keywords:** Castleman's disease, lymphoma, Hyaline vascular, Plasma cell

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## Introduction

Castleman's disease (CD) describes a rare heterogeneous group of lymphoproliferative disorders characterized by massive growth of lymphoid tissue of unknown pathogenesis. [1]This entity was first described in 1956 by Dr. Benjamin Castleman who defined it as a distinct pathologic disorder. [1, 2]To date, only a few large series have been published because it is not only a very rare disease, but also a poorly understood entity. [3] The disease usually occurs in the third to fifth decades of life and it appears to have more predilection for men. The most common

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location of CD is the mediastinum, although in about 70% of cases, although it can be found at other nodal or extranodal sites. [1, 2,4] Clinically, CD is categorized into either unicentric or multicentric subtypes. Furthermore, there are three major histological subtypes: hyaline vascular, plasma cell, and mixed variants. More recently, a fourth sub-variant known as plasmablastic has been recognized. [5, 6] The histopathologic findings of CD can also be seen with other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and collagen vascular disease. So exclusion of these reactive entities is crucial before establishing the diagnosis of CD. [3, 4] Of note, multicentric CD overlaps either clinically or histopathologically with POEMS syndrome (Peripheral polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy M-protein and skin changes), which is a very rare syndrome and observed in 24% of CD patients. [3, 7] The clinical spectrum and course of CD varies widely among the different subtypes, ranging from asymptomatic or flu-like illness to multigrain failure and death. This is determined by dysregulated overproduction of interleukin-6. [1, 2, 6, 7] Moreover, several studies have revealed a pivotal role of Human Herpes Virus 8 (HHV8) in the pathogenicity of mutlticentric CD which has been detected in about 50% of this type. [8]It was also proved that HHV8 positive variants of CD have increased the likelihood for development of complications, such as lymphomas and Kaposi's sarcomas. [6, 9] The purpose of this retrospective study is to describe the clinicopathologic features of Castleman's disease (CD), to review the treatment challenges in a group of Jordanian patients at KHMC, and to compare that with international data.

## Methods

This study was conducted at KHMC over a period of 8 years (January 2009 to December 2016), and was approved by the ethical committee of the Royal Medical Services.A systematic search of our histopathology department data-base, revealed 21 cases of clinically and pathologically proven diagnosis of CD during the study period. The diagnosis of CD was established on the basis of light-microscope morphologic analysis of paraffin-embedded lymph nodes or other tissue specimens that were cut into 4 μm and stained with hematoxylin/eosin. Tissue sections were immunohistochemically stained by an automated immunostainer (Ventana system) using the following panels of monoclonal antibodies against: CD3, CD20, CD10, CD23, CD138 and latent nuclear antigen-1 (LANA-1) of HHV8 to identify the presence of HHV8 in CD or lymphomas associated with CD. Furthermore, patients diagnosed to have CD were tested for (HIV) infection, using Enzyme Linked Immunosorbent Assay (ELISA). The Castleman's disease cases were first classified clinically, based on surgical findings and physical examination. Unicentric Castleman's disease (UCD) was defined by the presence of histologic findings of CD at only one single region of lymph nodes, while mutlicentric Castleman's disease (MCD) was considered if there were≥ 2 enlarged nodes stations involved by CD. [8,10] In all patients, CD cases were further sub-classified according to the histopathological characteristics of the involved lymph nodes or other tissue specimens into: hyaline vascular, plasma cell, and mixed variants. Clinical data and histopathologic characteristics of these patients were analyzed and reported, including patient's age at diagnosis, gender, clinical presentation, site of diagnosis, centricity, histopathology type and treatment modalities . Follow up details were collected whenever possible. In this study, Chi square test (Pearson) was used to identify the inter-relationships between clinical parameters, pathologic variants with regards to treatment and clinical course of the disease. A P value of $< 0.05$ was considered as statistically significant difference .

## Results

In total, 21 patients of CD were included in this study, of which 14 (66.7%) were males and 7 (33.3%) were females with more predilection for males. The median age of diagnosis for both males and females was 40.1 years, with 14 patients between 21-60

years. In this study, we only found 2 pediatric cases of CD, one 7 years old whereas the other was 13 years old as shown in Figure 1.Median follow-up was 28 months and the longest follow-up was for 5 years. The study results showed that the most frequent clinical presentation was slowly growing palpable mass which was observed in (76%) followed by anemia and abdominal pain in (35%) and (30%), respectively. Overall, 4 cases (19%) presented with huge splenomegaly,(14%) with B-symptoms (fever, fatigue, weight loss, and night sweats), and others non-specific symptoms like oral ulcers in about (17%) of studied cases. However, 3 patients(14%) exhibited no symptoms and were diagnosed incidentally as shown in Table I. Furthermore, we identified 2 cases of autoimmune hemolytic anemia (AIHA). Importantly, among our patients, 2 cases (10%) had been diagnosed with non-Hodgkin's lymphoma 1 case prior to presentation and the other was high grade peripheral T-cell lymphoma arising in a background of CD).Moreover, because of the relationships between POEMS and CD, there were no sufficient features to diagnose POEMS in our patients, so we excluded this rare entity from the present study. In our series, the most common site of CD was the abdomen in 33.2% (mesentery: 3, retroperitoneal area: 3, peritoneum: 1), followed by cervical and axillary nodes 6 cases (28.6%) for each, thorax and others 1 case (4.8%) for each. Interestingly, one case who underwent radical nephrectomy was found to have a pelviureteric involvement by CD. Of all included cases, 15 (71%) patients were clinically classified as having unicentric CD while only 6 (29%) were diagnosed with mutlicentric disease. Grossly in resected tumors, the size ranged from 0.5 to 7.5 cm with no size relations among different sites of the disease. The Outcome analysis which was performed in the subset of 21 cases, showed a strong relationship between centricity and clinical complications. The MCD subtype was most commonly present in patients with complications including 5 of the 7 cases of anemia, 4 of the 6 patients with abdominal pain, and all cases that presented with splenomegaly, B-symptoms and AIHA were of multicentric type. Furthermore, progression to malignant lymphoma was reported in 2 of 6 MCD cases. In contrast, 10 of the 15 UCD cases presented only with regional lymphadenopathy, 2 patients presented with anemia and abdominal pain, and there were 3 cases of asymptomatic UCD with P value of 0.0002 which indicates a significant difference between the two disease patterns as shown in Table II and III .

Microscopically, hyaline vascular (HV) was the commonest histopathologic subtypes seen in 16 cases (76%), followed by the plasma cell (PC) variant in 4 cases (19%), and only one case (5%) was of the mixed type. Regarding the pathologic findings, all the localized cases were of HV type (100%), while among the 6 MCD cases, 4 cases were of plasma cell type, 1 case of mixed variant, and only 1 case was of HV type. And all the 4 cases of plasma cell type were consistently multicentric in nature. Among the 16 HV subtype, 15 cases were unicentric disease and only one case was MCDas shown in Figure 2. Our study showed a strong relation between the clinical types and the pathologic variants with Chi square of 16.4 and P value of 0.0001 which indicates a significant difference among these types as shown in Table III. Regarding the HHV-8 status, we identified only 2 cases of muticentric disease which were HHV-8 positive in our study (one was of plasma cell type and the other was hyaline vascular). 15 out of 21 patient's results were available for HIV infection and were negative, so HIV status was not reported in all patients. Because of that, data on HIV infection and its association with CD were excluded in this study. Among our patients, all localized cases underwent complete surgical resection of the involved tissues except one case where radiation therapy was used. While 6 muticentric cases, were treated by steroids alone as an initial therapy or in combination with other modalities like: rituximab, which is anti-CD 20 B- cell monoclonal antibody. On follow-up, 14 cases (93.3%) of unicentric disease achieved complete remission with no recurrence of the disease, whereas there was no single documented case of MCD that has entered complete resolution of the

disease symptoms. On the other hand, 2 patients (40%) who had muticentric disease died during the study period, and the 3 other multicentric cases attained partial remission with attributable risk of 0.933, Chi square of 15.5, and P value of 0.0001 which were considered significant values shown in Figure 3.

**Table I:** Characteristics of study patients

| | Number | % |
|---|---|---|
| **Age** | | |
| <60 | 18 | 86 |
| ≥60 | 3 | 14 |
| **Gender** | | |
| Male | 14 | 67 |
| Female | 7 | 33 |
| **Clinical presentation** | | |
| Asymptomatic | 3 | 14 |
| Lymphadenopathy | 16 | 76 |
| Anemia | 7 | 35 |
| Abdominal pain | 6 | 30 |
| Splenomegaly | 4 | 19 |
| B-symptoms | 3 | 14 |
| Others | 4 | 19 |
| **Location** | | |
| Abdomen | 7 | 33.2 |
| Neck | 6 | 28.6 |
| Axilla | 6 | 28.6 |
| Thorax | 1 | 4.8 |
| Other | 1 | 4.8 |
| **Centricity** | | |
| Localized | 15 | 71 |
| Multiple | 6 | 29 |
| **Histopathology** | | |
| Hyaline Vascular | 16 | 76 |
| Plasma cell | 4 | 19 |
| Mixed type | 1 | 5 |

**Table II:** Clinical and histopathological features of the study group

| | Unicentric | Multicentric |
|---|---|---|
| **Clinical presentation** | | |
| Asymptomatic | 3 | 0 |
| Distribution of lymphadenopathy | 10(regional) | 6 (multiple) |
| Anemia | 2 | 5 |
| Abdominal pain | 2 | 4 |
| Splenomegaly | 0 | 4 |
| B-symptoms | 0 | 3 |
| Autoimmune hemolytic anemia | 0 | 2 |
| Malignant lymphoma | 0 | 2 |
| Histopathology type | | |
| Hyaline type | 15 | 1 |
| Plasma cell | 0 | 4 |
| Mixed type | 0 | 1 |
| HHV-8 association | 2 | |

**Table III:** Relation between clinical types, clinical complications and pathologic variants.

| | UCD | MCD | Chi square | P value |
|---|---|---|---|---|
| Clinical complications | 2 | 6 | 13.6 | 0.0002 |
| No complications | 13 | 0 | | |
| HV | 15 | 1 | 16.4 | 0.0001 |
| Non –HV ( plasma cell and mixed types) | 0 | 5 | | |

UCD: UnicentricCastleman's disease
MCD: MulticentricCastleman's disease
P value: Probability value

**Fig1:** Distribution of CD among different age groups

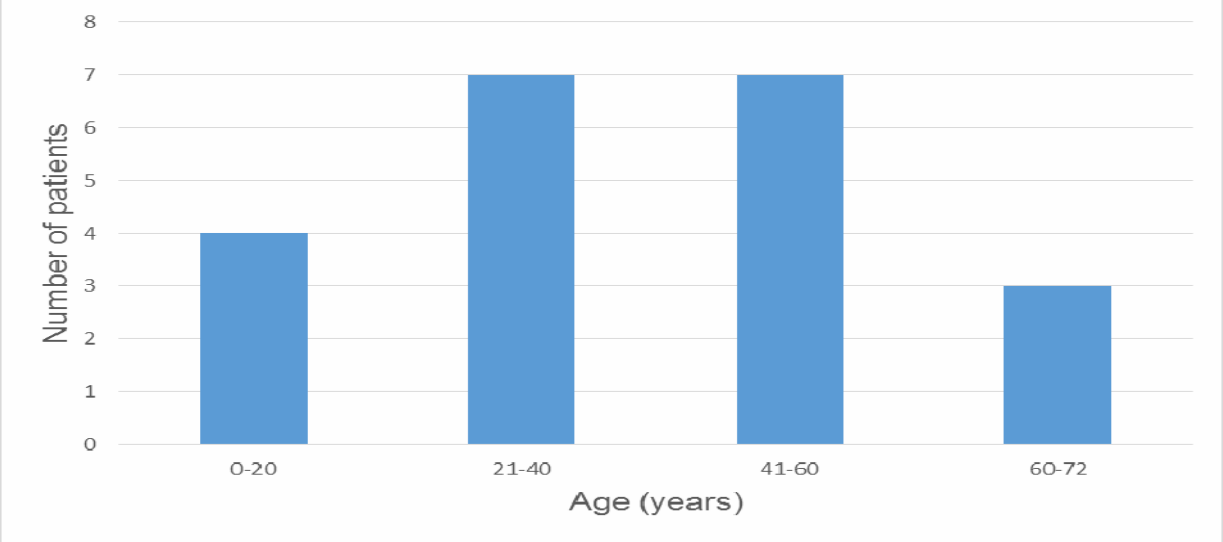
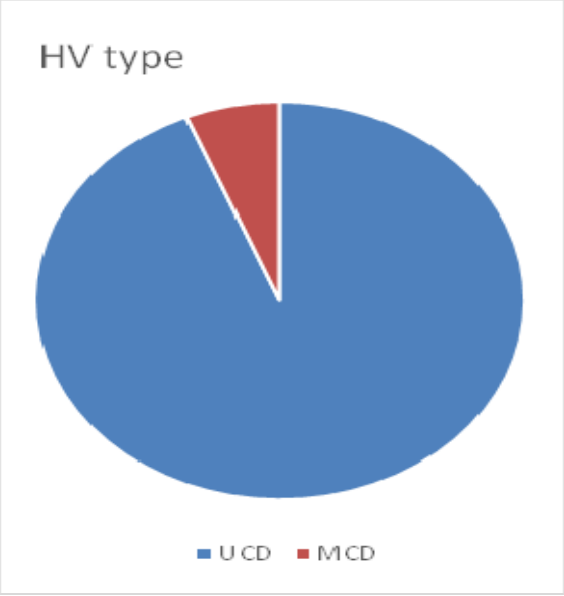



**Fig2:** Relationship between clinical types and pathological variant



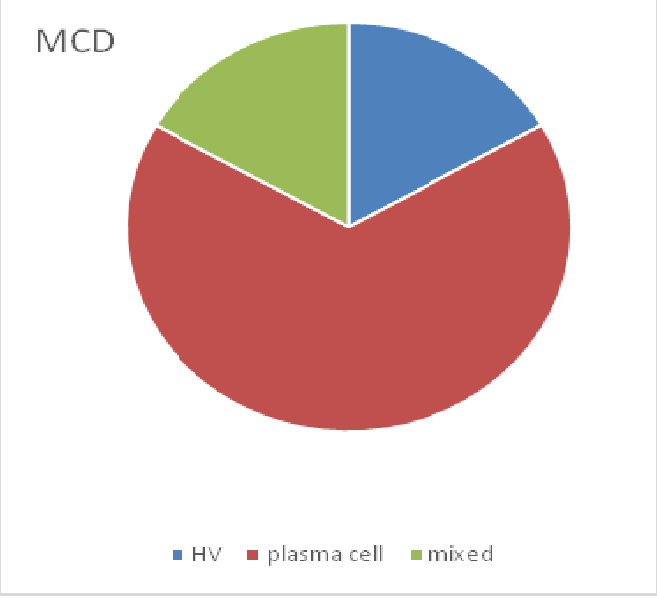
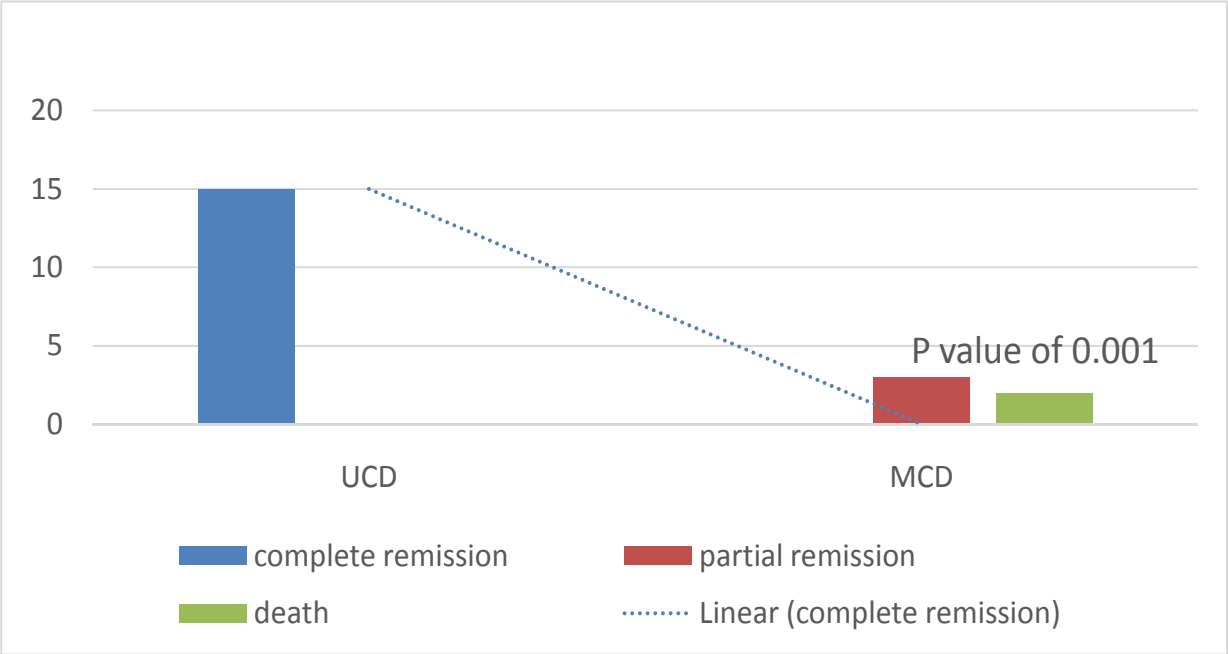



**Fig3:** Outcome analysis based on disease types




## Discussion

Castleman's disease is a rare, atypical clinicopathological entity associated with lymphoproliferation of unknown cause in which, there is massive lymphoid tissue hyperplasia with distinct histologic features.[1,4] Generally, it is considered a benign lymphoproliferative disorder since it's not a cancer, even though, some subtypes of the disease behave in very similar ways to lymphomas. Furthermore, patients with multicentric CD seem to have an increased risk for development of malignant neoplasms particularly lymphomas, and may be treated with chemotherapy. Because of that it is officially included in the American Cancer Society.[5, 8] CD is not only rare but also, a highly controversial and not fully understood disease that makes establishing the diagnosis something complicated, since there is no imaging or laboratory test pathognomonic for this disease.[1, 6] And so far, no genetic factor has been identified in the pathogenesis of the disease.[11] Although CD is a pathological diagnosis that is made by excisional biopsy from affected lymph node tissues, it is crucial to have good communication between pathologists and clinicians, since it sometimes overlaps with several infectious, neoplastic, and autoimmune diseases that create both diagnostic and therapeutic problems.[12] Due to rarity and heterogeneity of the disease, it's population prevalence has not been well established in the literature. However, recent estimates suggest the incidence of 21-25 cases per million person per year, which assigned it as orphan disease status by the National Cancer Institute.[6] Recently, it was estimated that the prevalence rate of all subtypes in the US to be about 6,500 to 7,700 new cases per year. Compared to Western countries, the disease appears to be more common among Asian countries, especially Japan.[3, 8] In population-based studies, the median age at disease onset lies in the fourth decade with more predilection to men which was similar to our results.[6, 7] In children, CD is different from that in adults mainly, because it is not as frequent. When it does occur, compared to adults, the rare occurrence of the muticentric forms in pediatric age group is rare , and the course of the disease in children appears to have more favorable outcome than in adults.[2, 5, 13] We found only 2 cases of children (≤ 14 years) with CD, which were localized and benign . In our series, as also reported in the Canadian and Chinese studies,[10, 13] the most common presenting symptom was lymph node enlargement or tissue mass. Other studies reported that CD can present with mucosal erosions or cutaneous lesions, edema, hematuria, kidney injuries or other general symptoms like fever, weight loss or it may be

discovered incidentally.[14] CD can occur anywhere throughout the body, despite the earlier description that it is confined only to the nodal regions, it may extend even to the extranodal sites.[1, 12] The most common location of CD is the mediastinum (60-70%), followed by the neck (20%), less commonly intra-abdominal (10%), but it also can be found in the retroperitonium, axilla, and various organs like stomach, skin and skeletal muscles as well. [1, 2,15] Our study differs from those reported in the literature in which 33.2% of our cases were found in the abdomen, 28.6% in axilla and neck respectively, and only 4.8% in the mediastinum. On the other hand, our study advocates the possibility of extra lymphatic involvement by CD in which we had one case of CD which involved the pelviureteric junction. One study done at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York, revealed results which were also different from that reported in the literature in which the most common affected area was the retroperitonium. [16] In the present study, the disease was localized in 71% of cases, and multicentric in 29%. Our results were consistent with the results of Dong Y et al. [10], Parez N et al. [13], Bowne W et al. [16] Furthermore, we noticed that 47% of the masses found in unicentric disease were in the abdomen, with no one single case in the thorax. Whereas in the multicentric disease, peripheral lymphadenopathy was found in most patients. Splenomegaly was not identified in any case of unicentric disease, but 4 out of 6 multicentric cases. The distribution of adenopathy and the presence of organomegaly in our study were nearly similar to that reported by Browne W et al. [16] Analysis of association of clinical types and presence of symptoms and complications was performed in the present study. As shown by our study and most studies, patients with two patterns of the disease (unicentric vs. multicentric) differed mainly by clinical manifestations and complications. (4, 9) UCD is usually asymptomatic in over 50% of cases and discovered incidentally or occasionally can present with manifestations secondary to compression. [1,6] Unlike UCD, multicentric CD is always symptomatic; mostly presented with polyadenopathy in 84% and multisystem involvement. [11] It is often associated with splenomegaly and constitutional symptoms such as fatigue, B-symptoms, anemia (either anemia of chronic disease or autoimmune hemolytic anemia). [1, 6, 12] So by comparing UCD to MCD with regards to the clinical manifestations and complications in the present study, there was a statistically significant difference between the two types with a p value of 0.0002. Histologically, CD has been categorized in 1972 by Keller et al. into either hyaline-vascular (HV), plasma cell type (PC). However, it is not always possible to separate these two subtypes so mixed histologic subtype is identified.[12,17] More recently, plasmablastic type was recognized, that is only found in HHV-8 associated MCD and it has the worst outcome.[5, 8]As shown by our study and most studies in the literature, the hyaline vascular variant is by far more common than the plasma cell variant, with less often the mixed variant. [5, 12] Many international studies have shown a strong association between clinical centricity and histopathological type. [1,9] Approximately 90% of unicentric CD have HV pathologic subtype, while the multicentric variety has been associated classically with PC histology, however; HV and mixed pathology have also been reported in MCD as well. [1, 4]This is in agreement with our study that showed a significant relation between clinical and pathological types (p value of 0.0001) in which, all patients with localized disease were of HV type and 4 of 6 MCD cases have PC subtype. Casper C et al. from University of Washington School of Medicine in USA reported that unicentric plasma cell variant accounts for less than 20% of all CD variants. [18] In our study all the 4 plasma cell cases were consistently multicentric .The exact cause of CD is unknown; however, several theories have been proposed to account for the diversity of the disease nature. [2] Immunodeficiency, autoimmunity, and chronic inflammation have been postulated as likely pathogenetic mechanisms. Several studies have shown that excessive secretion of cytokine IL-6 by the hyperplastic lymph nodes plays a central role in the development of both localized and multicentric variants of CD. [12] The main

role of IL-6 is to increase proliferation, survival and differentiation of B-cells and it is at least responsible for lymph node hyperplasia in CD. [2, 19] Symptoms of CD wax and wane in relation to the extent of IL-6 secretion. [4, 15] In our study, only two patients of multicentric CD were positive for HHV-8; a known etiologic agent in MCD. This incidence and the reported in other Asian countries were much lower than those in western populations. [3, 20] HHV-8 encodes a viral IL-6 gene, which is a human IL-6 homolog, that is directly implicated in the pathogenesis and systemic manifestations of HHV-8 associated MCD.[2, 3, 20] So blockade of IL-6 signaling using an anti-IL-6 receptor monoclonal antibody is considered a potential therapeutic target in MCD. [2, 3, 9, 20] In fact, HHV-8 is found in virtually all HIV-positive cases of MCD and 50% of HIV-negative MCD which may contribute to poor outcome, as in the presence of HIV infection, MCD is considered a potentially fatal lymphoproliferative disorder. [5, 9, 11, 21, 22]Furthermore, CD associated with HIV is mostly plasma cell type or plasmablastic. [9] 15 of the present patients were negative for HIV infection, 6 patients' results for HIV infection were not available, and most had an indolent clinical course. According to literature, MCD has been associated with increased risk for the development of certain malignancies; [8, 19, 23, 24]most notably non-Hodgkin's lymphoma (NHL) in about 18% of MCD in one series. [9] Weisenburger et al. reported that 4 of 16 patients with MCD developed NHL. [23] Similarly in our series, 2 of 6 patients with MCD had been diagnosed with NHL. Vasef M et al. from the Mount Sinai Medical Center in Ohio, reported one patient with localized HV-CD who developed lymphoma, although progression to malignant lymphoma is rare in localized CD.[23] In addition, Hodgkin's lymphoma has been found to be associated with CD. [6, 9] It seems that the pathogenesis of these lymphomas is due to somatic mutation responsible for the monoclonality process and this is also influenced by HHV-8 infection that leads to abnormal IL-6 production. [15, 21] In addition, there is an increased risk for developing Kaposi's sarcoma in about 32% of patients with MCD. [16] The association between HIV, MCD and NHL is especially strong, since the incidence of HHV-8 related non-Hodgkin's lymphoma in HIV-positive MCD was15 fold higher than that in the general HIV-positive population. [15, 25] Castleman et al, Keller et al, herrada et al, and Browne et al. had illustrated that surgery is the mainstay treatment for localized disease, however; it has a limited role in MCD. (6, 15, 16, 18)In fact, complete surgical resection is almost always curative in approximately 95% of unicentric CD. [1, 4, 19] Rarely, unresectable cases can be treated with radiotherapy as an alternative option with response rate up to 72%. [4, 9]In this series, complete surgical resection of unicentric disease was curative for all patients, regardless of the histopathologic type, except for only one case that was treated by radiotherapy because of its difficult surgical access. Unlike patients with UCD, surgical intervention provides no long term benefit in multicentric disease. [9,16]Instead, different treatment modalities can be used in MCD such as; steroids alone to control symptoms and partially improve lymphadenopathy, or in conjunction with Rituximab especially for HHV-8 associated MCD, which depletes the reservoir of B-cells and significantly reduces the risk of lymphoma. [2, 6, 19, 26] These modalities were used in our center for treatment of CD. Regarding the followed up cases; 93.3% of UCD cases entered complete remission with no recurrence, whereas 50% of MCD cases attained partial remission with p value of 0.0001 which indicates a significant correlation between clinical types and predicting the disease outcome. So, the localized CD seems to have a more favorable course than the multicentric disease. This is in agreement with another study identified in British patients by Talat et al. who demonstrated an association between clinical centricity and response to treatment as well. [24]

### *Limitations of the study*

This study had some limitations. First, some laboratory data were missed and not available because of the retrospective nature of this study. Second, the present study is performed on the experience of one single center in addition, the disease is very rare that created

a bias. Therefore, nationwide scale study's need to be conducted to assess the epidemiology, clinical spectrum, optimal therapeutic strategies, and possible targeted therapy for Jordanian patients with CD.

## Conclusion

Unicentric and multicentric CD are different clinical entities with overlapping histologic features. Most of the cases of Jordanian patients with CD exhibit an indolent clinical course with local surgical therapy. Further studies are needed to further elucidate the epidemiology, pathogenesis, clinical behavior, and optimal therapeutic regimens of this rare disease.

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