ResearchTJH-2021-0670.R3

doi: 10.4274/tjh.galenos.2022.2021.0670

Castleman Disease: A Multicenter Case Series from Turkey
Castleman Hastalığı: Türkiye'den Çok Merkezli Bir Olgu Serisi

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December 6, 2021
February 7, 2022

Abstract
Objective: Castleman disease (CD) is a rare disease also known as angiofollicular lymph node hyperplasia. Two main histological subtypes are hyaline vascular and plasma cell variant. It is classified as unicentric (UCD) or multicentric CD (MCD) according to the anatomical distribution of disease and the number of lymph nodes involved. The aim of this multicenter study is to evaluate all cases of CD identified to date in Turkey to set up a national registry aiming to improve CD early recognition, treatment and follow-up. **Materials and Methods:** Both adult (n=130) and pediatric (n=10) patients with a lymph node or involved field biopsy result reported as CD were included in the study. Patients' demographic information, clinical and laboratory characteristics, imaging studies, treatment strategies and clinical outcome were evaluated retrospectively. **Results:** 140 patients (69 male and 71 female) with a diagnosis of UCD (n = 73) and MCD (n = 67) were included. Mean age was 39 in UCD and 47 in MCD. Female patients were more common in UCD. The most common histologic subtype was hyaline vascular for both UCD and MCD. Asymptomatic patients were more common in UCD. Anemia, elevation of acute phase reactants and hypoalbuminemia were more common in MCD. Most commonly used treatment strategies in UCD were surgical excision, rituximab and radiotherapy respectively. All UCD patients were alive at a median 19.5 month follow up. Most commonly used treatment strategies in MCD were methyl prednisolone, R-CHOP, R-CVP and rituximab. Thirteen patients died at a median 34 month follow up. **Conclusion:** Our study is important due to representing the patient characteristics and treatment strategies from Turkey and have a potential of increasing awareness about CD. Treatment data may help making decision particularly in countries who

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can not get access to siltuximab. Larger prospective studies are needed to make definitive conclusions.
Keywords: Castleman disease, unicentric, multicentric, treatment

Öz

Amaç: Anjiyofolliküler lenf nodu hiperplazisi olarak da bilinen Castleman hastalığı (CH), nadir bir hastalık olup başlıca hiyalin vasküler ve plazma hücreli olmak üzere 2 histolojik alt tipi vardır. Hastalığın anatomik yayılımı ve tutulan lenf nodu bölgelerinin sayısına göre unisentrik (UCH) ya da multisentrik (MCH) olarak sınıflandırılır. Bu çok merkezli çalışmanın amacı bugüne kadar Türkiye'de tanımlanan tüm CH vakalarını tanımlamak, ulusal bir veri tabanı oluşturarak CH'de erken tanı, tedavi ve takip sürecine katkı sağlamaktır.

Materyal ve Metod: Çalışmaya lenf nodu ya da tutulan alandan yapılmış biyopsi sonucu CH olarak rapor edilen hem erişkin (n=130) hem de pediatrik (n=10) hastalar dahil edildi. Hastaların demografik bilgileri, klinik ve laboratuvar özellikleri, görüntüleme bulguları, aldıkları tedaviler ve tedavi sonuçları geriye dönük olarak değerlendirildi.

Bulgular: Dahil edilen 140 hastanın 69'u kadın, 71'i erkekti. Yetmiş üç hasta UCH, 67 hasta MCH olarak sınıflandırılmıştı. Yaş ortalaması UCH'de 39, MCH'de 47 yıl idi. Kadın hastalar UCH'de daha fazlaydı. Hem UCH hem de MCH için en sık histolojik alt tip hiyalin vaskülerdi. Asemptomatik hastalar UCH'de daha fazlaydı. Anemi, akut faz reaktanı yüksekliği ve hipoalbuminemi MCH'de daha sıktı. UCH'de en sık uygulanan tedaviler sırasıyla cerrahi eksizyon, rituksimab ve radyoterapiydi. Median 19.5 aylık takipte tüm UCH'li hastalar hayattaydı. MCH'de 1.basamak tedaviler metil prednizolon, R-CHOP, R-CVP ve rituksimab idi. Median 34 aylık takipte 13 hasta kaybedilmişti.

Sonuç: Çalışmamız Türkiye'deki CH hastalarının özellikleri ve tedavi yaklaşımlarını yansıtması açısından önemli olup hastalıkla ilgili farkındalığın arttırılması potansiyeline sahiptir. Tedavi verileri özellikle ülkemizde olduğu gibi siltuksimaba ulaşımı zor olan ülkelerde tedavi seçimi konusunda fikir verebilir. Kesin sonuçlar çıkarmak için büyük ölçekli prospektif çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Castleman hastalığı, unisentrik, multisentrik, tedavi

Introduction

Castleman disease (CD), also known as angiofollicular lymph node hyperplasia or giant lymph node hyperplasia, was first described in 1954 (1-4). Two main histological subtypes are hyaline vascular and plasma cell variants, mixed variant is seen occasionally (5). It is classified as unicentric (UCD) or multicentric CD (MCD) according to the anatomical distribution of disease and the number of lymph nodes involved (6,7). The estimated incidence is approximately 25 cases per million person-years which represents less than 5200 cases per year in the United States (8,9).

Classically, MCD presents with lymphadenopathy affecting multiple lymph node stations and is associated with systemic symptoms, such as fever, weight loss, and fatigue, driven by interleukin-6 (IL-6) and other cytokines. MCD has been subclassified into human herpesvirus-8 (HHV-8) associated MCD, polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes (POEMS) associated MCD, and idiopathic MCD (iMCD). UCD involves a single enlarged lymph node or multiple enlarged lymph nodes within a single lymph node region. Frequently, the diagnosis of UCD is incidental, and the lymphadenopathy is often asymptomatic. However, some patients present with symptoms resulting from compression of vital structures (eg, airways, neurovascular bundles, or ureters), whereas others will experience iMCD-like inflammatory syndromes. UCD is virtually always HHV-8 negative, but rare positive cases have been reported (6).

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The aim of this multicenter study is to evaluate all cases of CD identified to date in Turkey to set up a national registry aiming to improve CD early recognition, treatment and follow-up.

Methods

We included all patients with a diagnosis of CD based on the histopathological analysis of a lymph node or an affected area. The information about patients were collected retrospectively and included patients' demographic information, treatment strategy, clinical outcome, laboratory and imaging studies. The data was collected between April 2018 and August 2020. The date of diagnoses were between 2002 and 2020.

The study was approved by the local ethical committee of Eskisehir Osmangazi University.

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 Chi Square 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 SPSS for Windows (version 21.0).

Results

A hundred and forty patients (69 male and 71 female) from 21 centers with a diagnosis of UCD (n = 73) and MCD (n = 67) were included in the study. Patients were younger and female patients were more common in UCD than MCD. The most common histologic type on lymph node biopsy was the hyaline vascular. Symptoms at diagnosis were similar between two groups except fatigue, anorexia, fever, diarrhea and inguinal lymph node. Asymptomatic patients were more common in UCD.

Physical examination revealed significant differences between the presence of hepatomegaly, splenomegaly, submandibular, axillary and inguinal lymph nodes in UCD and MCD. Lymph nodes in UCD were most frequently found in the submandibular region (n=5, 17.2%) (Table 1).

Serum C-reactive protein (CRP) level was increased in 15 (36.6%) patients and elevated immunglobulin (Ig) G level was observed in 6 (18.8 %) patients.

Imaging studies were neck computed tomography (CT) in 39 (56.5%), thorax CT in 43 (50%), abdominopelvic CT in 38 (46.9%) and PET/CT in 31 (44.3%) patients. Lymphadenopathy was in the cervical area in 19 (44.2%), intrathoracic in 8 (20.5%), and abdominopelvic in 14 (28.6%) patients (Table 2).

The most common first line therapy in UCD was surgical excision followed by rituximab and radiotherapy. Thirty nine patients were followed without treatment (Table 3). Twenty eight (87.5%) patients were in complete remission and 3 (9.4%) patients were in partial remission after the first line therapy. Response to first line therapy was not evaluated in 2 (6.3%) patients. Only 3 patients needed a second line therapy and the treatment responses were complete remission. Second line therapies were radiotherapy (n=1), cyclosporine (n=1) and chemoimmunotherapy (R-ESHAP) (n=1). At last evaluation after a median follow-up of 19.5 months (range 7-52.5) all patients with UCD were alive (Figure 1).

The most common histologic type of CD on lymph node biopsies was also hyaline vascular type in MCD. Coronary artery disease, chronic renal failure and solid malignancy were more common in MCD possibly due to the older age of this group. Kaposi sarcoma was reported in two MCD patients.

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Most common symptoms and physical examination findings were reported as fever (n=15, 78.8%), inguinal lymph nodes (n=10; 83.3%), hepatomegaly (n=20, 74.1%), splenomegaly (n=28, 90.3%), arthralgia (n=2, 40%), abdominal pain (n=5, 33.3%), fatigue (n=27, 33.3%) and diarrhea (n=4, 100%). Serum CRP level was increased in 26 (63.4%) patients. Elevated Ig G level was detected in 26 (81.3%) patients. Anemia, thrombocytopenia, elevated erythrocyte sedimentation rate and hypoalbuminemia were more common in MCD compared with UCD.

Imaging studies were neck CT 30 (43.5%), thorax CT 43 (50%), abdominopelvic CT 43 (53.1%) and PET/CT 39 (55.7%). Lymphadenopathy was in the cervical area in 24 (55.8%) patients, intrathoracic in 31 (79.5%), and abdominopelvic in 35 (71.4%). Most of the lymph nodes in thorax and abdominopelvic CT were smaller than 5 cm in diameter.

SUV max values in PET CT were similar in UCD and MCD and most commonly below 6. However, PET CT positivity was more common in MCD.

Patients received methyl prednisolone (n=4, 10.5%) R-CHOP (n=5, 13.2%), R-CVP (n=3, 7.9%), CVP (n=4, 10.5%), CHOP (n=3, 7.9%) and rituximab (n=16, 42.1%) as the first line therapy (Table 2). Thirteen (37.1%) patients were in complete remission and 13 (37.1%) patients were in partial remission after first line therapy. Five (14.3%) patients had progressive and 4 (11.4%) patients had stable disease. Response to first line therapy was not evaluated in 3 patients.

Most patients in the MCD cohort needed a second line therapy compared with UCD (18.8% vs 81.3%, p=0.021). Second line therapies were combined chemotherapy (CVP, CHOP) (n=5), chemoimmunotherapy (R-CVP, R-etoposide) (n=3), rituximab (n=1), lenalidomide (n=1), tocilizumab (n=1) and surgical excision (n=1). Treatment responses were progressive disease (n=1), complete remisison (n=3), partial remission (n=6) and stable disease (n=4). Two patients needed third line (chemoimmunotherapy, tocilizumab) and 2 patients needed fourth line (lenalidomide, methyl prednisolone) therapy. One patient underwent autologous hematopoietic stem cell transplantation as a fifth line therapy and had stable disease at the time of evaluation.

At last evaluation after a median follow-up of 34 months (range 10-59) 13 (34.2%) patients with MCD were died (Figure 1).

Discussion

In this study, our aim was to collect the largest cohort and set up a national registry for a rare disease in Turkey. Another aim of the study was to increase the awareness about CD and to prevent diagnostic delay.

UCD is reported as approximately 75% of patients with CD (10,11). In our study UCD patients were 52% of all patients. Plasmablastic subtype is different from three main histological types and is observed in HHV-8 positive patients (12). Plasmablastic subtype was not reported in our patients but subtype of several patients were not known.

Although Pribyl et al (9) reported a marginal female predominance in UCD, CD generally affects both sexes equally (1,13). We found a significant female predominance for UCD in our patients. Patients with UCD tend to present in 2nd and 4th decade of life, significantly younger than those with MCD who have a peak incidence in their 6th and 7th decades (7,13). Our patients with MCD were also older than UCD patients but younger than MCD patients reported in literature.

Systemic symptoms and laboratory abnormalities are more commonly reported in MCD in literature (2). Our MCD patients also had more systemic symptoms and laboratory abnormalities than UCD.

Viral infections are postulated to play a role in the pathogenesis of CD, particularly an association of HHV-8 with MCD is reported (15-18). In a meta-analysis by Talat et al (2) HHV-8 was reported to be positive in 46 out of 49 (93.9%) patients with MCD. HHV-8 was

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evaluated in 39 of our MCD patients and was found positive in 13 (33.3%) patients. HHV-8 and HIV coinfection was also commonly observed (15) but none of our patients were HIV positive.

On histopathologic examination, UCD predominantly consists of hyaline vascular variant (90%), while in MCD plasmacytoid variant is most commonly observed (17,19,20). Hyaline vascular variant was the most common histopathologic subtype in both of our UCD and MCD patients.

PET CT is the suggested imaging study if it can be performed (21). Maximum SUV max values are reported as 3 to 8 in CD and lymphoma should be suspected in differential diagnosis if found more than 8 (22,23). In our study SUV max values in PET CT were also between 2.5 and 5.

MCD is a rare disease and there are no prospective randomized controlled trials. Therefore, treatment strategies are heterogenous particularly in iMCD (24). This heterogenity was also observed in our study and our results were not enough to make definitive conclusions. Although siltuximab is commonly suggested as a first line therapy, no experience with siltuximab was reported in our study because we are unable to access this drug due to reimbursement obstacle in Turkey. Central pathological revision was not performed and this may be another limitation of our study.

In conclusion, here we reported a multicenter retrospective study including patients with CD which is a rare disease. The reported data is important due to representing the patient characteristics and treatment strategies from Turkey and have a potential of increasing awareness about CD. Treatment data may help making decision particularly in countries who can not get access to siltuximab. Larger prospective studies are needed to make definitive conclusions regarding the optimal therapy option.

Keywords: Castleman disease, unicentric, multicentric, treatment
Financial Disclosure: The database project of the study was supported by Turkish Society of Hematology
Conflict of Interest: Authors have no financial interests
Acknowledgement: We would like to thank Associate Professor Cengiz Bal from Eskişehir Osmangazi University Faculty of Medicine Department of Biostatistics for statistical analysis.

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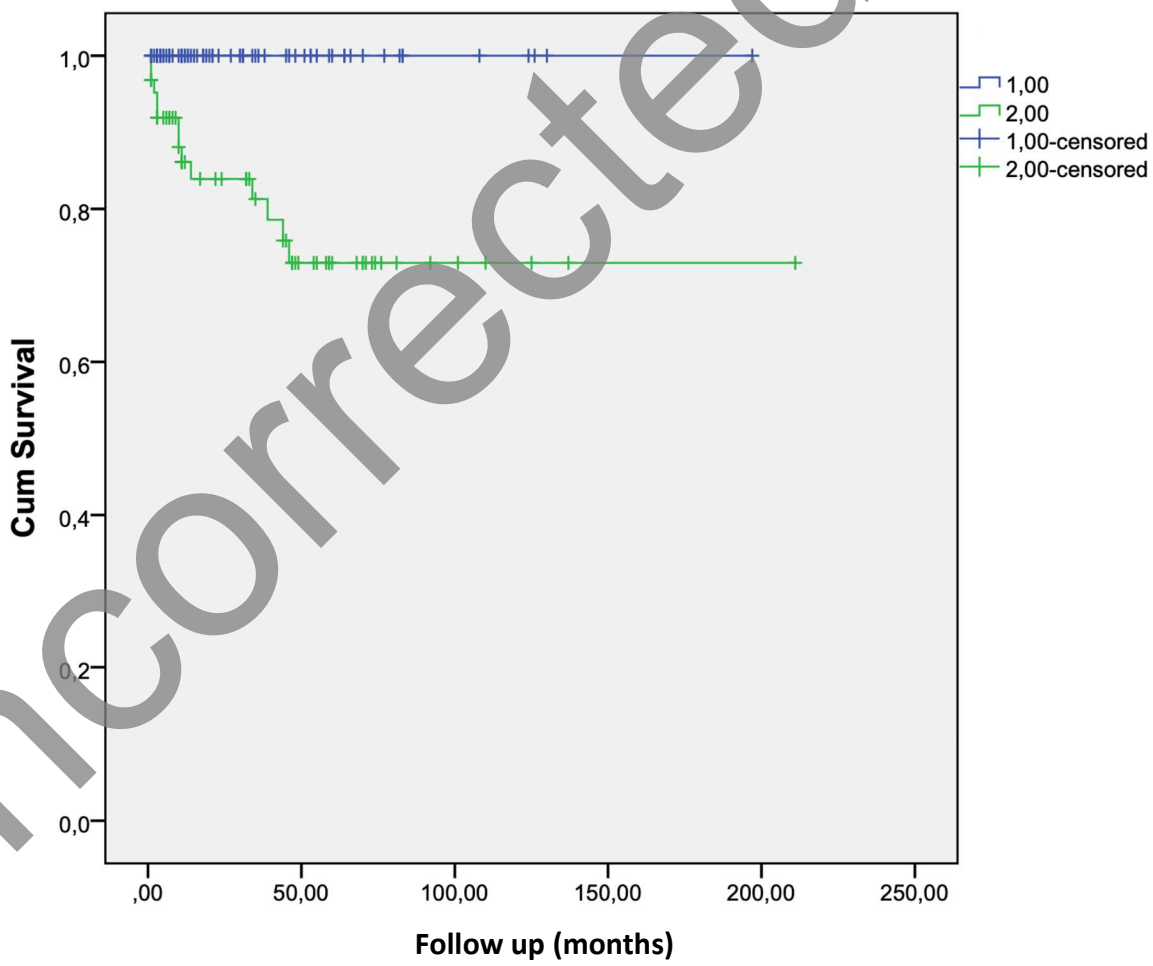
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Figure 1: Survival curves of patients



1: Unicentric Castleman disease, 2: Multicentric Castleman disease

Table 1. Clinical characteristics of patients			
	Unicentric (n=73)	**Multicentric (n=67)**	***p* value**
Age at diagnosis (years)	38,95± 16.06	48.61 ± 19.45	**0.002**
Sex ratio (Female/Male)	45/28	26/41	**0.009**
Histological subtype			
Hyaline vascular	53 (72.6%)	26 (37.9%)	**<0.001**
Plasma cell	11 (15.1%)	22 (33.3%)	**<0.001**
Mixed	5 (6.8%)	5 (7.6%)	**<0.001**
Unknown	4 (5.5%)	14 (21.2%)	**<0.001**
Most frequent symptoms at diagnosis	15 (35.7%)	27 (64.3%)	**0.015**
Fatigue	4 (22.2%)	14 (77.8%)	**0.012**
Anorexia	4 (21.1%)	15 (78.9%)	**0.007**
Fever	11 (40.7%)	16 (59.3%)	0.266
Weight loss	6 (40%)	9 (60%)	0.451
Sweating	6 (37.5%)	10 (62.5%)	0.311
Cough	0 (0%)	4 (100%)	**0.048**
Diarrhea	22 (53.7%)	19 (46.3)	1.000
Cervical lymph node	6 (31.6%)	13 (68.4%)	0.085
Axillary lymph node	2 (16.7%)	10 (83.3%	**0.021**
Inguinal lymph node	19 (66.7%)	5 (33.3%)	0.359
Abdominal pain			
Physical examination			
Hepatomegaly	7 (25.9%)	20 (74.1%)	**0.004**
Splenomegaly	3 (9.7%)	28 (90.3%)	**0.012**
Submandibular lymph node	5 (17.2%)	24 (82.8%)	
Submental lymph node	1 (14.3%)	6 (85.7%)	**<0.001**
Supraclavicular lymph node	4 (26.7%)	11 (73.3%)	0.053

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Axillary lymph node	7 (15.9%)	37 (84.1%)	0.064
Inguinal lymph node	3 (7.9%)	35 (92.1%)	**<0.001**
			<0.001

Table 2. Laboratory characteristics of patients

	Unicentric (n=73)	**Multicentric (n=67)**	***p* value**
Laboratory findings			
Anemia	19 (34.5%)	36 (65.5%)	**0.002**
Lymphopenia	8 (50%)	8 (50%)	0.884
Thrombocytopenia	2 (13.3%)	13 (80.9%)	**0.003**
Elevated ESR	9 (19.1%)	38 (80.9%)	**<0.001**
Elevated CRP	15 (36.6%)	26 (63.4%)	**0.048**
Elevated beta 2 microglobulin	11 (25.6%)	32 (74.4%)	**<0.001**
Hypoalbuminemia	3 (9.1%)	30 (90.9%)	**<0.001**
Elevated Ig G	6 (18.8%)	26 (81.3%)	**<0.001**
Elevated Ig A	1 (5%)	19 (95%)	**<0.001**
HHV-8 positivity	0 (0%)	13 (100%)	**<0.001**
HIV positivity	0 (0%)	0 (0%)	1.000
Imaging studies			
Lymph node in neck CT	19 (44.2%)	24 (55.8%)	**0.012**
Lymph node in thorax CT	8 (20.5%)	31 (79.5%)	**<0.001**
Lymph node in abdominopelvic CT	14 (28.6%)	35 (71.4%)	**<0.001**
Activity in PET CT	22 (36.1%)	39 (63.9%)	**<0.001**

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Table 3. First line treatment characteristics of patients

	Unicentric (n=34)	**Multicentric (n=38)**
First line treatment		
R-CHOP	1 (2.9%)	5 (13.2%)
Rituximab	2 (5.9%)	16 (42.1%)
R-CVP	0 (0%)	3 (7.9%)
Surgical excision	28 (82.4%)	2 (5.3%)
Methyl prednisolone	1 (2.9%)	4 (10.5%)
CVP	0 (0%)	4 (10.5%)
CHOP	0 (0%)	3 (7.9%)
Radiotherapy	2 (5.9%)	1 (2.6%)

R:rituximab; CHOP: cyclophosphamide, doxorubicine, vincristine, methyl prednisolone; CVP: cyclophosphamide, vincristine, methyl prednisolone

Uncorrected proof

uncorrected proof