RESEARCH ARTICLE

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Castleman Disease: A Multicenter Case Series from Turkey

Castleman Hastalığı: Türkiye'den Çok Merkezli Bir Olgu Serisi

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Abstract

Objective: Castleman disease (CD) is a rare disease also known as angiofollicular lymph node hyperplasia. The two main histological subtypes are the hyaline vascular and plasma cell variants. It is further classified as unicentric CD (UCD) or multicentric CD (MCD) according to the anatomical distribution of the disease and the number of lymph nodes involved. The aim of this multicenter study was to evaluate all cases of CD identified to date in Turkey to set up a national registry to improve the early recognition, treatment, and follow-up of CD.

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 olgularını tanımlamak, ulusal bir veri tabanı oluşturarak CH'de erken tanı, tedavi ve takip sürecine katkı sağlamaktır.

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Abstract

Materials and Methods: Both adult (n=130) and pediatric (n=10) patients with lymph node or involved field biopsy results reported as CD were included in the study. Patients' demographic information, clinical and laboratory characteristics, imaging study results, treatment strategies, and clinical outcomes were evaluated retrospectively.

Results: A total of 140 patients (69 male and 71 female) with a diagnosis of UCD (n=73) or MCD (n=67) were included. The mean age was 39 years in the UCD group and 47 years in the MCD group. Female patients were more common in the UCD group. The most common histological subtype was hyaline vascular for both UCD and MCD patients. Asymptomatic patients were more common in the UCD group. Anemia, elevations of acute phase reactants, and hypoalbuminemia were more common in the MCD group. The most commonly used treatment strategies for UCD were surgical excision, rituximab, and radiotherapy, respectively. All UCD patients were alive at a median of 19.5 months of follow-up. The most commonly used treatment strategies for MCD were methyl prednisolone, R-CHOP, R-CVP, and rituximab. Thirteen MCD patients had died at a median of 34 months of follow-up.

Conclusion: This study is important in presenting the patient characteristics and treatment strategies for CD from Turkey, with the potential of increasing awareness about CD. Treatment data may help in making decisions, particularly in countries that do not have access to siltuximab. However, larger prospective studies are needed to make definitive conclusions.

Keywords: Castleman disease, Unicentric, Multicentric, Treatment

Öz

Gereç ve Yöntemler: Çalışmaya lenf nodu ya da tutulan alandan yapılmış biyopsi sonucu CH olarak rapor edilen hem erişkin (n=130) hem de pediyatrik (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 MCH'li 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 Sözcükler: 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 [1,2,3,4]. The two main histological subtypes are the hyaline vascular and plasma cell variants, and a mixed variant is seen occasionally [5]. It is further classified as unicentric CD (UCD) or multicentric CD (MCD) according to the anatomical distribution of the disease and the number of lymph nodes involved [6,7]. The estimated incidence is approximately 25 cases per million person-years, which represents fewer 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 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, on the other hand, involves a single enlarged lymph node or multiple enlarged lymph nodes within a single lymph node region. The diagnosis of UCD is frequently incidental and the lymphadenopathy is often asymptomatic. However, some patients present with symptoms resulting from compression of vital structures (e.g., the 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].

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

Materials and Methods

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

The study was approved by the local ethics committee of Eskişehir 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 medians and interquartile ranges. To determine differences between cohorts for categorical variables, we used chi-square and Fisher exact tests. To determine differences for nonparametric continuous variables, we used the Mann-Whitney U test. Finally, to determine differences for parametric continuous variables, we used the Student t-test. We also constructed Kaplan-Meier survival curves for patients with UCD and MCD. All p-values are two-tailed with a significance level of 0.05 reflecting statistical significance. We performed the statistical analysis using IBM SPSS Statistics 21.0 for Windows (IBM Corp., Armonk, NY, USA).

Results

A total of 140 patients (69 male and 71 female) from 21 centers with a diagnosis of UCD (n=73) or MCD (n=67) were included in the study. Patients were younger and female patients were more common in the UCD group than the MCD group. The most common histological type by lymph node biopsy was hyaline vascular. Symptoms at diagnosis were similar between the two groups except for fatigue, anorexia, fever, diarrhea, and affected inguinal lymph nodes. Asymptomatic patients were more common in the UCD group.

Physical examinations revealed significant differences between the presence of hepatomegaly, splenomegaly, and affected submandibular, axillary, and inguinal lymph nodes in the UCD and MCD groups. Affected lymph nodes in the UCD group 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 immunoglobulin (Ig) G was observed in 6 (18.8%) patients.

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

Table 1. Clinical characteristics of the patients.

	Unicentric (n=73)	Multicentric (n=67)	p
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			
Fatigue	15 (35.7%)	27 (64.3%)	**0.015**
Anorexia	4 (22.2%)	14 (77.8%)	**0.012**
Fever	4 (21.1%)	15 (78.9%)	**0.007**
Weight loss	11 (40.7%)	16 (59.3%)	0.266
Sweating	6 (40%)	9 (60%)	0.451
Cough	6 (37.5%)	10 (62.5%)	0.311
Diarrhea	0 (0%)	4 (100%)	**0.048**
Cervical lymph node involvement	22 (53.7%)	19 (46.3%)	1.000
Axillary lymph node involvement	6 (31.6%)	13 (68.4%)	0.085
Inguinal lymph node involvement	2 (16.7%)	10 (83.3%)	**0.021**
Abdominal pain	19 (66.7%)	5 (33.3%)	0.359
Physical examination			
Hepatomegaly	7 (25.9%)	20 (74.1%)	**0.004**
Splenomegaly	3 (9.7%)	28 (90.3%)	**0.012**
Submandibular lymph node involvement	5 (17.2%)	24 (82.8%)	**<0.001**
Submental lymph node involvement	1 (14.3%)	6 (85.7%)	0.053
Supraclavicular lymph node involvement	4 (26.7%)	11 (73.3%)	0.064
Axillary lymph node involvement	7 (15.9%)	37 (84.1%)	**<0.001**
Inguinal lymph node involvement	3 (7.9%)	35 (92.1%)	**<0.001**

The most common first-line treatment in cases of 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 first-line treatment. Response to first-line treatment was not evaluated for 2 (6.3%) patients. Only 3 patients needed a second-line treatment and their treatment responses were complete remission. Second-line therapies were radiotherapy (n=1), cyclosporine (n=1), and chemoimmunotherapy (R-ESHAP) (n=1). At the last evaluation after a median follow-up of 19.5 (range: 7-52.5) months, all patients with UCD were alive (Figure 1).

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

The most common symptoms and physical examination findings were reported as fever (n=15, 78.8%), affected 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 levels were increased in 26 (63.4%) cases. Elevated IgG levels were detected in 26 (81.3%) patients. Anemia, thrombocytopenia, elevated erythrocyte sedimentation rate, and hypoalbuminemia were more common in the MCD group than the UCD group.

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

SUV_{max} values in PET/CT were similar between the two groups and most commonly below 6. However, PET/CT positivity was more common in the MCD group.

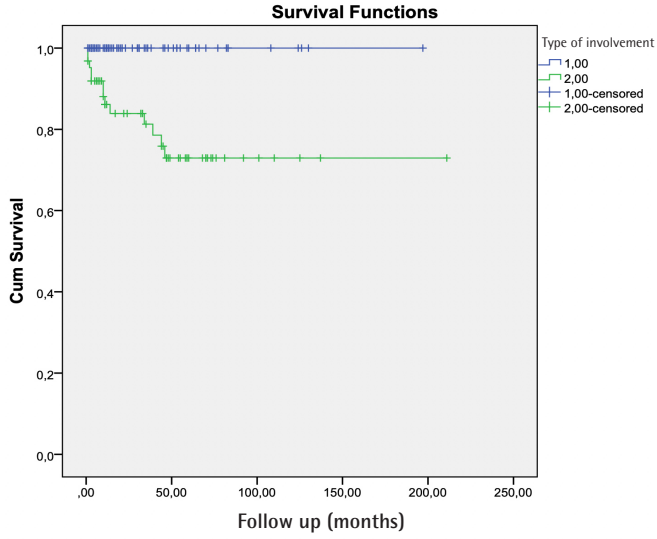

Figure 1. Survival curves of patients.
1: Unicentric Castleman disease, 2: Multicentric Castleman disease.

Table 2. Laboratory characteristics of the patients.

	Unicentric (n=73)	Multicentric (n=67)	p
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 β2 microglobulin	11 (25.6%)	32 (74.4%)	**<0.001**
Hypoalbuminemia	3 (9.1%)	30 (90.9%)	**<0.001**
Elevated IgG	6 (18.8%)	26 (81.3%)	**<0.001**
Elevated IgA	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**

ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; IgG: immunoglobulin G; IgA: immunoglobulin A; HHV-8: human herpesvirus-8; HIV: human immunodeficiency virus; CT: computed tomography; PET: positron emission tomography.

Patients in the MCD group 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 first-line treatments (Table 2). Thirteen (37.1%) patients were in complete remission and 13 (37.1%) patients were in partial remission after first-line treatment. Five (14.3%) patients had progressive and 4 (11.4%) patients had stable disease. Response to first-line treatment was not evaluated for 3 patients in this group.

More patients in the MCD group needed second-line treatment compared to the UCD group (18.8% vs. 81.3%, p=0.021). Second-line treatments included 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 in these cases were progressive disease (n=1), complete remission (n=3), partial remission (n=6), and stable disease (n=4). Two MCD patients needed third-line (chemoimmunotherapy, tocilizumab) and 2 patients needed fourth-line (lenalidomide, methyl prednisolone) treatment. One patient underwent autologous hematopoietic stem cell transplantation as a fifth-line treatment and had stable disease at the time of evaluation.

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

Discussion

In this study, our aim was to review 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 prevent diagnostic delays.

UCD is reported in approximately 75% of cases of CD [10,11]. In our study, UCD patients accounted for 52% of all patients. The plasmablastic subtype is different from the three main histological types and is observed in HHV-8-positive patients [12]. The plasmablastic subtype was not reported among our patients, but the subtypes of several patients were not known.

Although Pribyl et al. [5] reported a marginal female predominance among patients with UCD, CD generally affects both sexes equally [1,13]. We found a significant female predominance among our patients with UCD. Patients with UCD tend to present in the second and fourth decades of life, being significantly younger than those with MCD, the latter of which has peak incidence in the sixth and seventh decades of life [7,13]. Our patients with MCD were older than the UCD patients but generally younger than MCD patients reported in the literature.

Systemic symptoms and laboratory abnormalities are more commonly reported in cases of MCD in the literature [2]. Our MCD patients also had more systemic symptoms and laboratory abnormalities than those with UCD.

Viral infections are postulated to play a role in the pathogenesis of CD; in particular, an association of HHV-8 with MCD is reported [14,15,16,17]. In a meta-analysis conducted by Talat et al. [2], HHV-8 was reported to be positive in 46 of 49 (93.9%) patients with MCD. HHV-8 was evaluated for 39 of our MCD patients and was found to be positive in 13 (33.3%) cases. Coinfections of HHV-8 and HIV are also commonly observed [14], but none of our patients were HIV-positive.

Upon histopathological examination, UCD predominantly consists of the hyaline vascular variant (90%), while in MCD the plasmacytoid variant is most commonly observed [16,18,19]. The hyaline vascular variant was the most common histopathological subtype in both our UCD and MCD groups.

PET/CT is the suggested imaging method if it can be performed [20]. Maximum SUV_{max} values are reported as ranging from 3 to 8 in cases of CD and lymphoma should be suspected in the differential diagnosis if the value is above 8 [21,22]. In our study, PET/CT SUV_{max} values were between 2.5 and 5.

MCD is a rare disease and no prospective randomized controlled trials have been performed. Therefore, treatment strategies are heterogeneous, particularly in cases of iMCD [23]. This heterogeneity was also observed in our study and our data were

Table 3. First-line treatments 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, doxorubicin, vincristine, methyl prednisolone; CVP: cyclophosphamide, vincristine, methyl prednisolone.

not sufficient for definitive conclusions. Although siltuximab is commonly suggested as a first-line treatment, no experiences with siltuximab were reported in our study because we are unable to access this drug due to reimbursement obstacles in Turkey. Central pathological revision was not performed and this may be another limitation of our study.

Conclusion

We have reported the results of a multicenter retrospective study of patients with CD, which is a rare disease. The data reported here are important as they represent the patient characteristics and treatment strategies from Turkey and have the potential of increasing awareness about CD. Such treatment data may also help in making decisions, particularly in countries that do not have access to siltuximab. However, larger prospective studies are needed to draw definitive conclusions regarding optimal treatment options.

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Ethics

Ethics Committee Approval: The study was approved by the local ethics committee of Eskişehir Osmangazi University.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: E.Ö., H.O.K., E.G.Ü., S.K.G., V.Ö., F.Ö., Ö.C., T.E., S.Kü., S.P., Ö.Ç., S.Ka., S.M., Ö.E., Y.İ., C.K., Z.T.G., A.A., T.C., A.E.H.K., G.A.Ç., C.Ö.Ş., A.K., T.B., A.Ö., F.B.B.A., A.C., İ.K., H.Ö., E.T., G.N.Ö., Ş.M.B.Ö.; Concept: E.G., S.Kü., G.N.Ö., Ş.M.B.Ö.; Design: E.G., S.Kü., G.N.Ö., Ş.M.B.Ö.; Data Collection or Processing: E.G.; Analysis or Interpretation: E.G.; Literature Search: E.G.; Writing: E.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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