Castleman Disease: A Multicenter Case Series from Turkey

Castleman Hastalığı: Türkiye'den Çok Merkezli Bir Olgu Serisi

Eren Gündüz, Hakki Onur Kırkınlar, Elif Gülsüm Ümit, Sedanur Karaman Günsaran, Vildan Özkocaman, Fahir Özaklemka, Ömer Candar, Tugrul Elverdi, Selin Küçükkyurt, Semra Paydaş, Özcan Çeneli, Sema Karakuş, Seren Maral, Ömer Ekinci, Yıldız İpek, Cem Kıs, Zeynep Tuğba Güven, Aydan Akdeniz, Tiraş Celkan, Ayşe Hilal Eroğlu Küçüküler, Günsüm Akgün Çağlıyan, Ceyda Özçelik Şengöz, Ayşe Karataş, Hakkı Onur Kırkınlar, Ömer Ekinci, Ömer Candar, Şule Mine Bakanay Öztürk, Gül Nihal Özdemir, Aylin Canbolat, İbrahim Kartal, Hale Ören, Ersin Töret, Gül Nihal Özdemir, Şule Mine Bakanay Öztürk

1.Eskişehir Osmangazi University Faculty of Medicine, Department of Hematology, Eskişehir, Turkey
2.Tüyk University Faculty of Medicine, Department of Hematology, Edirne, Turkey
3.Uludağ University Faculty of Medicine, Department of Hematology, Bursa, Turkey
4.Istanbul University-Cerrahpaşa Cerrahpaşa Faculty of Medicine, Department of Hematology, Istanbul, Turkey
5.Cukurova University Faculty of Medicine, Department of Hematology, Adana, Turkey
6.Necmettin Erbakan University Meram Faculty of Medicine, Department of Hematology, Konya, Turkey
7.Ankara Başkent University Faculty of Medicine, Department of Hematology, Ankara, Turkey
8.University of Health Sciences Turkey Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital, Clinic of Hematology, Ankara, Turkey
9.Fırat University Faculty of Medicine, Department of Hematology, Elazığ, Turkey
10.Kartal Dr. Lütfi Kirdar City Hospital, Clinic of Hematology, Istanbul, Turkey
11.Adana Başkent University Faculty of Medicine, Department of Hematology, Adana, Turkey
12.Erciyes University Faculty of Medicine, Department of Hematology, Kayseri, Turkey
13.Mersin University Faculty of Medicine, Department of Hematology, Mersin, Turkey
14.Izinye University Faculty of Medicine, Department of Pediatric Hematology, Istanbul, Turkey
15.Adnan Menderes University Faculty of Medicine, Department of Hematology, Aydın, Turkey
16.Pamukkale University Faculty of Medicine, Department of Hematology, Denizli, Turkey
17.Karadeniz Technical University Faculty of Medicine, Department of Hematology, Trabzon, Turkey
18.Hacettepe University Faculty of Medicine, Department of Hematology, Ankara, Turkey
19.University of Health Sciences Turkey Gülhane Training and Research Hospital, Clinic of Hematology, Ankara, Turkey
20.Istanbul Medeniyet University Faculty of Medicine, Department of Pediatric Hematology, Istanbul, Turkey
21.Ondokuz Mayıs University Faculty of Medicine, Department of Pediatric Hematology, Samsun, Turkey
22.Dokuz Eylül University Faculty of Medicine, Department of Pediatric Hematology, İzmir, Turkey
23.Ankara Yıldırım Beyazıt University Faculty of Medicine, Department of Hematology, Ankara, Turkey

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.

Amaç: Castleman hastalığı (CH), nadir bir hastalık olup başlıca hiyalin vasküler ve plazma hücreli olmak üzere 2 histolojik alt tipi vardır. Hastalığın anatominik yayılımı ve tutulan lenf nödu bölgelerinin sayısı göre unisentrik (UCH) ya da multisentrik (MCH) olarak sınıflandırılır. Bu çok merkezli çalışma amacı bugüne kadar Türkiye’de tanımlanan tüm CH olgularını tanımlamak, ulusal bir veri tabanı oluşturmak, erken tanıyı, tedavi ve takip sürecine katkı sağlamaktır.

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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; polynuropathy, 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.

**Table 2. Laboratory characteristics of the patients.**

| Laboratory findings             | Unicentric (n=73) | Multicentric (n=67) | p       |
|--------------------------------|------------------|---------------------|---------|
| 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 not evaluated for 3 patients in this group.

### Table 3. First-line treatments of patients.

| First-line treatment | Unicentric (n=34) | Multicentric (n=38) |
|----------------------|-------------------|---------------------|
| 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  | 2 (2.9%)          | 10 (26.3%)          |
| CVP                  | 0 (0%)            | 4 (10.5%)           |
| CHOP                 | 0 (0%)            | 4 (10.5%)           |
| 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.O., Ş.M.B.Ö.; Concept: E.G., S.Kü., G.N.O., Ş.M.B.Ö.; Data Collection or Processing: E.G.; Analysis or Interpretation: E.G.; Literature Search: E.G.; Writing: E.G.

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