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The clinicopathological features and survival of Castleman disease: a multicenter Turkish study

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Abstract. – OBJECTIVE: In this study, we aimed to investigate the clinicopathological features and survival of CD, which is quite rare and has many unknowns.

PATIENTS AND METHODS: This study was conducted by retrospectively evaluating patients diagnosed with CD in six different centers in Turkey.

RESULTS: The median age of 33 patients included in the study was 49 and 51.5% (n = 17) of these patients were women. 18 (54.5%) patients were in the hyaline vascular subtype and most of the patients were UCD (n = 20, 60.6%). The most common involvement region was head and neck (n = 19, 57.5%). The UCD group was younger than the MCD group (p=0.027). Visceral lymph node involvement was higher in MCD than in UCD (p=0.001). Similarly, it was observed that there was more hepatomegaly (p=0.035) and splenomegaly (p=0.013) in the MCD group. During the median 19.5 months follow-up period, there were no patients who died.

CONCLUSIONS: It was observed that UCD and MCD are different clinical entities. Promising survival times can be achieved with surgical and systemic treatments in both subtypes of this extremely rare disease. However, this result should be supported by well-designed prospective comprehensive studies.

Key Words:
CD, Unicentric Castleman disease, Multicentric Castleman disease, Hyaline vascular.

Introduction

Castleman Disease (CD), also known as angiofollicular lymph node hyperplasia, was first described in 1954 by Castleman et al[1] in a 40-year-old male patient with a mediastinal mass. At that time, it was defined histologically as lymph node hyperplasia characterized by follicles with small, hyalinized foci[1]. In the following years, CD began to be classified as single-center and multi-center according to the area of involvement[2-4]. It has been reported that human herpes virus-8 (HHV-8) and interleukin-6 (IL-6) play a role in the etiology in most of the cases, and human immunodeficiency virus (HIV) may also have an effect on the development of CD[2-7]. Viral, autoimmune, and

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neoplastic processes have all been among the possible etiologies of CD[8-11].

It is estimated that approximately 7000 new CDs appear each year in the United States (US). Approximately 75% of these are thought to be Unicentric Castleman Disease (UCD) and 25% may be HHV-8 related Multicentric Castleman Disease (MCD) or HHV-8-negative/idiopathic MCD (iMCD)[4]. CD can occur at any age, but the disease is typically seen in adulthood and 50-65% of cases are men[7,12,13].

MCD can be seen with polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes (POEMS) syndrome[14]. In Japan, a clinical condition called TAFRO syndrome with low volume lymphadenopathy (usually mixed type, rarely hyaline vascular variant) characterized by CD histology, thrombocytopenia, ascites, myelofibrosis, renal dysfunction and organomegaly has also been defined[15].

Complete surgical resection is curative for UCD and provides excellent long-term results. Based on studies[16,17] conducted with a small number of patients, it can be said that radiotherapy (RT) is an acceptable treatment option in unresectable cases[16,17]. To date, the efficacy of cytotoxic chemotherapies, anti-CD20 antibodies, agents targeting the IL-6 pathway, immunomodulators, bortezomib and antiviral agents in MCD treatment has been investigated. Although all of these agents appear to have an effect on disease activity, the information obtained is limited to case reports or small patient series[17].

In this study, we aimed to investigate the clinicopathological features, factors in etiology and survival of this disease, which is quite rare and has many unknowns.

Patients and Methods

This study was conducted by retrospectively evaluating patients diagnosed with CD in six different centers in Turkey between 2012 and 2020. Patients under the age of 18 and those with missing file information were excluded from the study. Ethics committee approval was obtained prior to the study.

The primary endpoint of our study was to evaluate the clinicopathological characteristics of patients with CD. The secondary endpoint was the comparison of clinical features of UCD and MCD subtypes and, overall survival (OS) in all the cohort.

Demographic and clinical characteristics of the patients (anatomical location, splenomegaly, hepatomegaly, edema, pleural effusion, ascites, endocrinopathy, skin changes, polyneuropathy, papilledema), laboratory parameters (hemoglobin, platelet, sedimentation, CRP, albumin, total protein, creatinine, coombs test, ANA, hypergammaglobulinemia), pathological characteristics (histological subtype, HHV8 and HIV status), treatment modality (surgery, RT, systemic therapy) and survival status were recorded retrospectively using manual patient files and electronic patient registration system.

Head-neck, axillary and inguinal lymph nodes were defined as peripheral lymph nodes, while mediastinal and abdominal lymph nodes were defined as visceral lymph nodes.

The data obtained were analyzed through IBM SPSS (version 23.0, Armonk, NY, USA). Categorical variables were expressed as numbers and percentages. Parametric continuous variables were reported as median and minimum-maximum. The clinical and laboratory characteristics of the patients classified as UCD and MCD were compared. Chi Square Test and Fisher's Exact Test were used to determine the differences between cohorts for categorical variables. Mann-Whitney U test was used when comparing uncategorical variables. OS was defined as the time from diagnosis to death or last control date. OS was calculated for UCD and MCD using Kaplan Meier survival curve. The p-value of <0.05 was considered statistically significant in all tests.

Results

The median age of 33 patients included in the study was 49 and 51.5% (n = 17) of these patients were women. Histologically, 18 (54.5%) patients were in the hyaline vascular subtype. According to the anatomic classification, most of the patients were UCD (n = 20, 60.6%). The most common involvement region was head and neck (n = 19, 57.5%). None of our patients with CD additionally had POEMS or TAFRO syndrome. All patient characteristics are shown in Table I.

When UCD and MCD subgroups were compared, the median age was found to be 42 (21-67) and 65 (25-84), respectively ($p = 0.027$). Visceral lymph node involvement was higher in MCD than in UCD (92.3% *vs.* 35.0%; $p = 0.001$). Similarly, it was observed that there was more hepatomegaly (46.2% *vs.* 10.0%; $p = 0.035$) and splenomegaly (53.8% *vs.* 10.0%; $p = 0.013$) in the MCD group compared to UCD. In terms of other clinical features, there was no difference between UCD and

MCD (Table II). When the comparison was made in terms of laboratory parameters and serological markers, 4 (30.8%) patients in the MCD group had HHV-8 positivity, while there was no HHV-8 positivity in the UCD group ($p = 0.021$). In terms of other laboratory values, there was no difference between UCD and MCD groups (Table III).

Surgical resection was performed in 15 (75.0%) patients with UCD, whereas surgical excision was not performed in 5 (25%) patients located in the mediastinum and abdomen. In the MCD group, 4 (30.8%) patients had R0 surgical resection. In the UCD group, rituximab monotherapy and glucocorticosteroid were preferred in 1 (5.0%) patient in the first-line treatment. In the MCD group, 5 (38.5%) patients received rituximab monotherapy, 2 (15.4%) patients CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), 1 (7.7%) patient R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), 1 (7.7%) patient R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone), 1 (7.7%) patient glucocorticosteroids, and 3 (23.1%) patients were followed up without treatment. During the median 19.5 (4.96-92.94 months) monthly follow-up period, there were no patients who died in the entire patient group. The 2-year OS was 100%.

Table I. Demographics of the patients.

Variables	(n=33)	%
Age (years), Median (min-max)	49 (21-84)	
Gender		
Male	16	48.5
Female	17	51.5
Anatomic localization		
Head and neck	19	57.5
Mediastinum	12	36.3
Abdomen	10	30.3
Inguinal	5	15.1
Histological subtype		
Hyaline vascular	18	54.5
Plasmacytoid	12	36.4
Unknown	3	9.0
Anatomical subtype		
Unicentric CD	20	60.6
Multicentric CD	13	39.4
Clinical syndromes		
POEMS	0	0
TAFRO	0	0

CD: Castleman disease.

Discussion

In our multicenter study including 33 patients, we investigated the clinicopathological features and survival of CD. In this study, it was observed that the majority of the patients were UCD and hyaline vascular subtype. Looking at the anatomical distribution, the head and neck region was in the first place. Patients with UCD are at a younger age compared to MCD. HHV-8 positivity, visceral lymph node involvement, hepatomegaly and splenomegaly were more common in the MC group. While there was no patient who died during the follow-up period of approximately two years, the 2-year OS was 100%.

Table II. Comparing baseline clinic and demographics of UCD and MCD.

Variable	UCD (n=20)	MCD (n=13)	*p-value*
Age (years), median (min-max)	42 (21-67)	65 (25-84)	***0.027***
Male	8 (40.0%)	8 (61.5%)	0.296
Visceral LAP	7 (35.0%)	12 (92.3%)	***0.001***
Hyaline vascular	10 (50.0%)	8 (61.5%)	1.00
Hepatomegaly	2 (10.0%)	6 (46.2%)	***0.035***
Splenomegaly	2 (10.0%)	7 (53.8%)	***0.013***
Edema	1 (5.0%)	0	1.00
Pleural effusion	1 (5.0%)	0	1.00
Ascites	1 (5.0%)	1 (7.6%)	1.00
Endocrinopathy	4 (20.0%)	2 (15.3%)	1.00
Skin change	2 (10.0%)	2 (15.3%)	1.00
Polyneuropathy	0	1 (7.6%)	0.394
Papilledema	0	0	N/A
Fever	5 (25.0%)	6 (46.2%)	0.270
Night sweats	6 (30.0%)	6 (46.2%)	0.465
Weight loss	3 (15.0%)	4 (30.7%)	0.393

UCD: Unicentric Castleman disease, MCD: Multicentric Castleman disease.

Table III. Comparing laboratory values of UCD and MCD.

Variable	UCD (n=20)	MCD (n=13)	*p-value*
Hemoglobin	12.15 (8.1-16.1)	11.60 (5.1-16.0)	0.531
Platelet	277.5 (217.0-554.0)	310.0 (158.0-517.0)	0.825
Sedimentation	25.0 (2-73)	46.0 (2-111)	0.083
C-reactive protein	3.27 (0-38)	5.0 (0.1-161)	0.209
Albumin	4.18 (3.8-4.9)	4.0 (1.8-4.5)	0.131
Creatinine	0.75 (0.2-1.1)	0.80 (0.6-1.2)	0.698
Coombs positive	1 (5%)	1 (%7.7)	1.00
Antinuclear Antibodies	0	0	N/A
Hypergammaglobulinemia	1 (5%)	1 (7.7%)	1.00
HHV-8	0	4 (30.8%)	***0.021***
HIV	0	0	N/A

UCD: Unicentric Castleman Disease, MCD: Multicentric Castleman Disease

CD, which was first described about 70 years ago, is still quite rare. As far as we know, one of the most comprehensive reviews published on CD is the meta-analysis involving approximately 400 patients in 239 studies[18]. In these meta-analysis results, it was reported that 68.8% of the patients had UCD subtype and 61% had hyaline vascular subtype. While 52% of all patients were female, 61% of the MCD group were male. In the results of this study, it could be said that the UCD group was younger than the patients with MCD. Unlike our study, it was observed that visceral lymph node involvement was more common in patients with UCD, while peripheral lymph node involvement was more common in the MCD group. The 10-year OS was found to be better in patients in the UCD group compared to those in the MCD group (95.1% *vs*. 51.8%)[18].

In a recent single-center case-series study conducted in the US, 57% of the patients diagnosed with CD were reported to be female and the mean age was 41 years. It was observed that 64% of the cases were UCD and 57% were hyaline vascular subtype. Anatomical distribution was mostly located in the abdomen (30%), thorax-axilla (24%) and 20% head-neck. While 72% of UCDs were located in the peripheral lymph node, the peripheral and visceral location rates were equal in the MCD subtype[19].

In an experience of 114 patients reported from China, 62% of the cases were UCD and approximately 60% were hyaline vascular subtype[20]. It was observed that 54% of the patients in this study were <40 years old and the same proportion was male. In the same study, 60% of the patients had clinical complications; the most common clinical finding was reported to be paraneoplastic pemphigus (32%). In this study, it was found that 6.1% of the patients with CD also had POEMS syndrome. The 3-year overall survival was 82.4% and 73.5% in the UCD and MCD groups, respectively. Presence of paranaoplastic pemphigus and age> 40 years has been shown to have a negative effect on OS[20].

In a series of 113 patients published by Mayo Clinic and Nebrasca University, the clinical spectrum of CD was investigated[3]. Unlike other studies[18-20], 53% of the cases were found to be multicentric in this study[3,18-20]. While 48% of the patients were male, the median age was found to be 43 years. While hyaline vascular and plasma cell variant were found in equal proportions in all patient groups, it was observed that plasma cell variant was more dominant in patients with MCD and, hyaline vascular variant in patients with UCD. When patients with UCD and MCD were compared in terms of clinical features, it was found that patients with UCD were older. Additionally, organomegaly, neuropathy, B-symptoms, skin changes and edema were reported to be more common in the MCD group. It was observed that 32% of the patients with MCD met the POEMS criteria. Considering the OS results of this study, it was seen that 2-year OS was 92% and 5-year OS was 76% in the whole patient group[3].

In the series we have mentioned so far, the information that CD is seen almost equally in men and women has been confirmed in our study[3,18-20]. When the subtypes of the disease were examined, it was seen that the UCD dominance reported in previous series continued similarly in our study[18-20]. Histologically, it was observed that more than half of the cases in our study were in the hyaline vascular subtype, which is similar to previous studies[18-20]. Anatomically, it was observed that the head and neck region was affected

most frequently in our study, while it was stated that visceral involvement and thorax-axilla region were more affected in other studies[3,18-20]. While it was reported in previous studies that the association of POEMS and MCD could be observed at a rate of up to 30%, accompanying POEMS was not encountered in our patients. In general, it was thought that these differences in clinical features might be due to geographical and ethnic changes and the difference in diagnostic awareness according to the regions where the studies were conducted.

Considering the studies on CD treatment, it has been observed that complete surgical resection is curative for UCD and provides excellent long-term results with a 10-year overall survival rate of over 95%[18]. In cases where complete resection is not possible, debulking operation should be considered if there are local symptoms. Systemic therapies, which are mostly used in MCD treatment, can also reduce lymph node size and make complete resection possible[19]. Based on studies with a small number of patients, it can be said that radiotherapy (RT) is an acceptable treatment option in unresectable cases[17].

In our study, it was observed that 75% of our patients with UCD could undergo complete surgical resection, and 25% were evaluated as unresectable. Rituximab and glucocorticosteroid therapy were used in unresectable patients. With surgical and systemic treatments applied to our patients with UCD, 100% OS was achieved in two years of follow-up. This result was consistent with the known clinical course of UCD.

In the treatment of MCD, many systemic treatment options have been tried, including cytotoxic chemotherapy, anti-CD20 antibodies, IL-6 and IL-6 receptor targeting agents, immunomodulators, and antiviral agents[17,21,22]. Although all of these agents appear to have an effect on disease activity, the information obtained is limited to case reports or small patient series. Therefore, direct comparison between regimes is not possible[17].

Although low-dose single-agent chemotherapies such as daily oral etoposide, intermittent etoposide or vinblastine alleviate symptoms, the disease tends to quickly get out of control after cessation of therapy[11,23]. In a limited number of patients, a complete response rate of around 40% was achieved with CHOP and similar combination chemotherapies, and it was reported that approximately 90% of the patients survived after a median 3-year follow-up[17].

Anti-CD 20 humanized monoclonal antibody rituximab has been shown to be effective in the treatment of HIV positive and idiopathic MCD. In the phase II study, when rituximab was used as monotherapy in the HIV-positive population, long-term remission was achieved in the majority of patients[24]. In the same group of patients, when combined with rituximab with etoposide or liposomal doxorubicin, it was observed that the 2-year survival exceeded 80%[8].

There are trials on a limited number of patients with antiviral agents targeting HIV and HHV-8, which are involved in MCD etiology. In a study of 14 patients, major clinical response was obtained in 86% of patients with high dose zidovudine and valganciclovir, and biochemical response in half of the patients[25]. It has been shown that ganciclovir similarly achieved clinical improvement in small patient groups[26]. However, the role of antiviral agents in the treatment of CD is still unclear.

The current and most promising results in CD therapy belong to agents targeting the IL-6 pathway[27]. The emergence of these agents has significantly affected the treatment of patients with idiopathic MCD. Siltuximab, an IL-6 monoclonal antibody, and tocilizumab, a monoclonal antibody blocking IL-6 receptor, are new generation agents that have shown efficacy in the treatment of MCD. Patients with MCD other than Non-Hodgkin lymphoma and multiple myeloma were also included in the first phase 1 study investigating the efficacy and safety of siltuksimab[28]. The results of this study, which included a total of 37 MCD patients, showed clinical response in approximately 90% of the patients. The 2-year OS achieved with siltuximab in this study was found to be above 90%[28]. Siltuximab has been approved for the treatment of idiopathic MCD in the US and Europe.

Unlike siltuksimab, tocilizumab stops intracellular signal transduction by binding to IL-6 receptors. In the study of Tocilizumab, which included 28 MCDs, clinical response was obtained in more than half of the patients, while it was reported that almost all patients were followed for three years without progression[27].

In our study, more than half of the patients with MCD were administered rituximab therapy in combination with chemotherapy or monotherapy for the first-line treatment. There was no patient who received new generation IL-6 targeted therapies. It was observed that all of our patients were alive at the end of a two-year follow-up with treatment options such as cytotoxic chemotherapy, rituximab, glucocorticosteroid.

Limitations

Our study had some limitations. Among these limitations were the small number of patients and the relatively short median follow-up period. Although patients diagnosed with CD between 2012 and 2020 were included in the study, the fact that some patients were excluded from clinical follow-up caused a short median follow-up period. At the same time, the lack of access to new treatment options in our country has prevented us from sharing our experience with these treatments. However, our study is very valuable with the clinicopathological information and treatment results it gave about this very rare disease, which is mostly reported as a case report in the literature.

Conclusions

We observed that UCD and MCD are different clinical entities. Promising survival times can be achieved with surgical and systemic treatments in both subtypes of this extremely rare disease. However, this result should be supported by well-designed prospective comprehensive studies.

Conflict of Interest

The authors declare that they have no conflict of interests.

Ethics Approval

HSU Dr.A.Y. Ankara Oncology Training and Research Hospital Ethics Committee approval was obtained prior to the study.

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