Presentation and Outcome of Castleman's Disease in Immunocompetent Hosts

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Abstract Castleman's disease (CD) is a heterogeneous lymphoproliferative disorder of unknown aetiology. Mostly, this disorder is seen in immunocompromised hosts. It is known to be associated with systemic disorders like HIV, HHV-8, lymphoma, and Kaposi sarcoma. As of today, the clinical behaviour and outcome of CD in immunocompetent host remains suboptimally studied. We analyzed consecutively treated cases of CD presented to our centre in last 12 years. Case record files were studied for patient's characteristics, clinical presentation, baseline laboratory and pathologic parameters, therapy and outcome. This study describes presentation and treatment outcome of CD in immunocompetent patients. Total 16 patients of CD were treated during the study period. The median age of patients at the time of presentation was 40.5 years (range 13–72 years). An equal number of patients (8 each) had unicentric and multicentric CD. Sixty-three percent patients had hyaline vascular subtype while 37 % patients had plasma cell or mixed variant.

Majority of the patients had good performance status (ECOG PS 0, 1 in 10 (62.5 %) patients; PS2–4 in 6 (37.5 %) patients). The median duration of symptoms was 6 months (range 2–36 months). None of the patients in our study had associated HIV infection. Six patients presented with fever, out of which four had plasma cell variant of CD and three of them had multicentric involvement. In comparison to unicentric CD, patients with multicentric CD had lower albumin levels (4.15 vs. 3.38 g/dl, $p = 0.006$), haemoglobin levels (11.3 vs. 9.8, $p = 0.06$), and lower complete remission rates (62.5 % vs. none). Patients were treated according to the stage and clinical status with surgery, chemotherapy or combination of both modalities. Surgery was the predominant treatment for unicentric CD while multicentric CD was treated with various chemotherapy regimens. Eight patients were treated with chemotherapy (CHOP-based regimen-5, melphalan-prednisolone thalidomide-1, chlorambucil-prednisolone-1, and only corticosteroids-1). In the entire study group, ORR was 72 % (CR 36 %, PR 36 %), one patient died of progressive disease during chemotherapy. Two patients lost to follow-up before assessment of treatment response. Five-year overall survival was 100 and 87 % for unicentric and multicentric CD respectively. Castleman's disease is a rare lymphoproliferative disorder amongst Indian patients. It more commonly presents as hyaline vascular variant and affects middle-aged individuals. The most remarkable fact in our analysis was a lack of HIV positivity in any of the patient that is in contrast to the majority of the published literature. With multimodality therapy, high response rates and long-term survival were noted in the entire study group.

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Introduction

Castleman's disease (CD), also known as angiofollicular lymph node hyperplasia or giant lymph node hyperplasia is a lymphoproliferative disorder of unknown aetiology. This rare disorder predominantly involves lymph nodes or lymphoid tissue, and this is mostly seen in immuno-compromised hosts. CD is known to be associated with systemic disorders like HIV, POEMS syndrome, lymphoma and Kaposi sarcoma [1, 2]. CD is linked with high levels of interleukin 6 and identification of human herpes virus 8 in these patients [3–5] which are supposed to be associated with its pathogenesis. Over the last few decades, gradual rise in the incidence of multicentric CD is noted, and this trend is parallel to the rise in HIV infections along with increasing use of antiretroviral therapy [2]. The majority of the published studies on CD discuss presentation and outcome of CD in patients suffering from HIV [1, 2, 6]. The data on presentation and treatment outcome in patients with CD in immunocompetent hosts is very limited. We analyzed consecutive immunocompetent patients of CD treated at our center over last decade, and the results are discussed further in this article.

Methods

By computer-assisted search for patients treated at Postgraduate Institute of Medical Education and Research from the year 2002–2014, we identified all registered case of CD and their data was retrieved from the central record department. Only cases with histologically proven CD were included. Ambiguous biopsies were reviewed to ascertain pathologic subtypes of CD.

Data regarding patient's demographic details, clinical features, physical and radiological findings at baseline, histological details, staging, treatment and outcome were recorded. Treatment response was assessed by contrast-enhanced CT scan or PET-CT scan. The response was stratified by using RECIST criteria 1.1 [7]. Clinical and treatment outcome variables were studied in a comparative manner for unicentric versus multicentric CD.

Case Definitions

Histologically, cases were divided into hyaline vascular and plasma cell subtypes while cases exhibiting overlapping features were labelled as a mixed subtype. The hyaline vascular Castleman's disease (HVCD) variant is characterized by atrophic germinal centres surrounded by expanded mantle zones forming concentric rings ("Onion-skinning"). A hyalinized blood vessel with endothelial

proliferation penetrating into follicles gave it a "lollypop like appearance" (Fig. 1). For the plasma cell Castleman's disease (PCCD) variant, retained lymph node architecture, variable germinal center hyperplasia, with expanded mantle zones with marked plasmacytosis was recorded [8, 9]. On the basis of the extent of organ involvement, two subtypes of CD were classified. Patients with solitary lymph node or a lymph node group involvement were labeled as unicentric CD (UCD). On the other hand, patients with multiple non-contiguous sites of involvement and significant constitutional symptoms were labeled as multicentric CD (MCD). Other definitions in this study included: anaemia, defined as hemoglobin <11.0 g/dl for females and <12.0 g/dl for males; thrombocytopenia, defined as PLT <100 × 10⁹/L; hypoalbuminemia, defined as serum albumin <3.5 g/dl. At our centre, completely asymptomatic patients were kept on close follow-up only. While symptomatic localised disease was surgically excised. Patients with multi-system involvement were treated with combination chemotherapy with or without autologous stem cell transplant depending on the indication. All patients were followed until December 2014. Follow-up data was collected through telephonic calls and cases records. Data was analyzed using PASW Statistics 22.0. (SPSS. Inc) software. Quantitative variables were described using mean ± SD and categorical data using frequency and percentage in the text and figures. A comparison between two groups was analyzed by the Student's *t* test when data were normally distributed. The Kruskal–Wallis test was used when data were not normally distributed. A *p* value of <0.05 was considered to be statistically significant. Overall survival was calculated from the time of diagnosis until death (overall survival). Survival curves were plotted according to the method of Kaplan and Meier [11]. The log-rank method was used to test for the significance of differences in survival distributions.

Results

Total 16 cases of CD were evaluated during the study period. In our data, an equal number of patients (8 in each group) had unicentric and multicentric CD. Histologically, 10 (63 %) patients had a hyaline vascular variant, 5 (31 %) patients had plasma cell variant of CD, and one patient had mixed histological features, therefore, categorized separately. All patients with the plasma cell variant had MCD.

The median age of patients at presentation was 40.5 years (range 13–72 years), and there was no significant difference in the age of presentation in different subtypes of CD as illustrated in Table 1. Male to female ratio was 2.2:1 for the whole group. The same was 2.3:1 and 2:1 for hyaline vascular variant and plasma cell variants,

Fig. 1 Histologic features of Castleman's disease. **a** Low power photomicrograph showing lymphoid follicles with atrophic germinal and a vessel with prominent endothelial cells entering the germinal

center giving “Lolly-pop” appearance. **b** With prominent onion skinning of the mantle zone. **c** CD 34 immunostain. **d** CD 3 immunostain

respectively. Male preponderance was seen in all subtypes, but it was more pronounced for MCD. None of the patients in our study had immune-deficient state or HIV positivity (Table 1).

Lymphadenopathy was the most common clinical finding. In 12 (75 %) cases, patients had lymph node enlargement as the main complaint. Rest of the four cases had pain in abdomen due to pancreatic mass, severe neuropathy due to associated POEMS syndrome, chest pain due to hilar mass, and incidental detection of mesenteric mass during pregnancy-related ultrasound of abdomen, respectively.

All patients with UCD had lymph nodal mass. Three patients (38 %) had cervical lymph nodes, 3 (38 %) with predominant mediastinal lymph nodes and one case each (12 %) with mesenteric and retroperitoneal mass respectively. The average duration of symptoms before the presentation was ten months for UCD in comparison to 4 months for MCD. Majority of the patients had good performance status [ECOG PS 0, 1 in 10 (62.5 %) patients; PS2-4 in 6 (37.5 %) patients]. Higher number of patients

had B symptoms as well as poor ECOG performance status for both multicentric and plasma cell subtypes of CD.

Treatment and Outcome

UCD was treated with surgical excision in six cases and out of that one patient required chemotherapy for the symptomatic residual disease. One patient was treated with chemotherapy alone. Remaining one patient was completely asymptomatic therefore he was kept on close observation. In this group complete remission (CR) was seen in five cases (62.5 %). One patient each had a partial response (PR) and stable disease (SD). While the patient who was closely observed did not require treatment till the time of data analysis.

Total 7 (87 %) patients with multicentric CD received chemotherapy based therapy. One patient was asymptomatic therefore kept on close follow-up. Out of seven patients treated with chemotherapy, two patients were lost to follow-up before assessment of treatment response therefore chemotherapy outcome is available for remaining

Table 1 Patient characteristic and treatment outcome difference in unicentric versus multicentric Castleman's disease

	Total	UCD	MCD	<i>p</i> value
N	16	8	8	–
Median age (range)	40.5 (13–72)	35 (13–72)	43.5 (18–55)	0.38
Gender M:F	2.2:1	1.6:1	3:1	0.53
Pathologic subtype				0.03
1. Hyaline vascular	10 (63 %)	7 (87 %)	3 (38 %)	
2. Plasma cell variant	5 (31 %)	1 (13 %)	4 (50 %)	
3. Mixed	1 (6 %)	–	1 (12 %)	
Fever	6 (37 %)	2 (25 %)	4 (50 %)	0.44
Weight loss	3 (19 %)	1 (12 %)	2 (25 %)	0.43
Lymphadenopathy	12 (75 %)	5 (62 %)	7 (87 %)	0.24
Hepatomegaly	5 (31 %)	1 (12 %)	4 (50 %)	
Splenomegaly	2 (12 %)	0	2 (25 %)	NS
Haemoglobin (mean $\pm$ SD)	10.5 $\pm$ 2.9 g/dl	11.8 $\pm$ 2.4 g/dl	9.5 $\pm$ 3.0 g/dl	0.06
Platelets [mean $\pm$ SD ($\times 10^5$)]	2.68 $\pm$ 1.5	2.23 $\pm$ 1.3	3.08 $\pm$ 1.6	0.8
Albumin (mean $\pm$ SD)	3.77 $\pm$ 0.58 g/dl	4.15 $\pm$ 0.5 g/dl	3.38 $\pm$ 0.34 g/dl	0.006
Treatment	–	Surgical excision alone-5 Surgery + chemotherapy-1 Chemotherapy-1 Observation-1	Combination chemotherapy-7 Observation-1	–
Response rates	CR 5 (36 %) PR 5 (36 %) PD 2 (14 %) OBS 2 (14 %)	CR 5 (62.5 %) PR 1 (12.5 %) PD 1 (12.5 %) OBS 1 (12.5 %)	CR none PR 4 (67 %) PD/death 1 (17 %) OBS 1 (17 %) (Two cases lost to follow-up)	–
Survival 5-year OS	94 %	100 %	87 %	NS

CR complete remission, MCD multicentric Castleman's disease, NR not reported, OBS observation, PR partial remission, PD progressive disease, SD standard deviation, UCD unicentric Castleman's disease

five cases. Chemotherapy regimens used to treat this group of patients were CVP/CHOP in two cases, melphalan–prednisolone–thalidomide, chlorambucil–prednisolone, and single agent prednisolone in 1 case each. None of the patients with multicentric CD attained CR, 4 (72 %) had a partial response; one patient had progressive disease during chemotherapy and died subsequently due to the same. An asymptomatic patient with MCD also remained on follow up until the time of data analysis. None of the patients in our series received rituximab as first-line therapy.

In between two histological subtypes, patients with HVCD showed a better response to treatment with CR, PR, SD rate of 63, 12 and 12 %, respectively. Patients of PCCD had CR, PR, and PD rates of 0, 67 and 17 %, respectively (Table 1). In our series, two patients had CD associated with POEMS syndrome. One of them had HVCD and was treated with melphalan, prednisolone, thalidomide regimen that led to partial remission in POEMS syndrome as well as in lymph nodal mass of Castleman's disease. The patient remained on regular follow-up for 2 years thereafter. The

other patient with POEMS syndrome had PCCD with poor performance status. The patient showed very aggressive course and succumbed to the illness during the course of chemotherapy with CVP regimen. Another patient with PCCD had aggressive course requiring six courses of CHOP chemotherapy leading to PR. At the time of progression, he was treated with bendamustine + rituximab followed by autologous stem cell transplant. Patient attained CR following transplant and presently is on close follow-up.

For the whole cohort, 5-year overall survival rates were 94 % while individually it was 100 % for UCD and 87 % for MCD (Fig. 2).

Discussion

Castleman's disease has become more relevant in recent decades due to its association with human immunodeficiency virus (HIV) and human herpes virus (HHV)-8 both

Fig. 2 Kaplan–Meier survival curve showing long term survival

of which have shown a steady rise over time. The majority of the case series of CD in the published literature describe this disease in HIV positive hosts and almost all of them have advanced multicentric disease [1, 6, 10–12]. Data on UCD and CD in the immunocompetent host is relatively sparse. The uniqueness of our study is the description of clinical profile and treatment outcome of CD in immunocompetent hosts. A comparative summarisation of our results with other published studies is presented in Table 2.

In our opinion, the contrasting difference in HIV seropositivity rates among various studies indirectly reflects differences in epidemiologically of HIV infections in Western and Asian societies. Use of antiretroviral therapy (ART) significantly modifies immunological status in a

HIV positive individual and brings down the risk of HIV-related Kaposi sarcoma and lymphoma. The widespread use of ART and selective control of HIV-related neoplasm (like Kaposi sarcoma) has reduced HIV-related mortality leading to rise in the incidence of uncommon and late manifestation of HIV like CD in western countries [13]. On the other hand in most Asian countries, ART is still in an early phase. Therefore, many of the HIV positive patients die of other complications before developing uncommon neoplasm-like CD, and this phenomenon can create an impression that CD is uncommon in Asian patients suffering from HIV. Our series and the data from China [8] also reflect the same as none of the patients with CD reported in these studies was positive for HIV. A pertinent question can arise by this observation. Are we looking at different subsets of CD in different parts of the world? This question can only be answered by large-scale studies analysing immunologic milieu of the immunocompetent patients suffering from CD.

As shown in Table 2, the median age of presentation of CD is consistently around 40 years in various studies in immunocompetent as well as in immunocompromised hosts. Usually, it is noted that median age of presentation of most lymphoid neoplasm in India is consistently reported to be lower than the studies from the west [14–16]. However, we did not find such difference in Indian patients with CD. When we compared baseline characteristics between the two subtypes of CD, cases with MCD had a median age of presentation about a decade higher than in the UCD group. A similar difference was also observed by

Table 2 Comparative summarisation of prominent large case series published in the recent past

	Mylona et al. [1]	Gerard et al. [6]	Bower et al. [10]	Luo et al. [8]	Current study
N	84	24	61	48	16
HIV positivity rate	100 %	100 %	100 %	No HIV positive	No HIV positive
Distribution	Majority multicentric	All multicentric	All multicentric	Unicentric 33 % Multicentric 77 %	Unicentric 50 % Multicentric 50 %
Pathologic subtype	HV-4 % PC-45 % Mixed-51 %	NR	NR	HV 39 % PC 50 % Mixed 11 %	HV 63 % PC 31 % Mixed 6 %
Median age	40 (21–67)	43.5 (21–65)	42 (23–69)	37.9 (13–67)	40.5 (13–72)
Male:female	9:1	7:1	NR	1:1.5	2.2:1
Treatment	Various chemotherapy regimen	Rituximab + chemo	Rituximab + chemo	Surgery for unicentric and combination chemotherapy for multicentric CD	Surgery for unicentric and combination chemotherapy for multicentric CD
Survival	Median F/U OS 53 %	1 year OS 92 % 1 year EFS 72 %	5 year OS 90 % 5 year PFS 61 %	Long term survival UC-100 % MC-90 %	5 year OS UC-100 % MC-88 %

Luo et al. [8], who noted median age for UCD at 30 years and for MCD at 41 years.

A strong predilection of CD for male patients was reported in earlier studies with M:F ratio as high as 9:1 [1, 6, 17]. We also found M:F ratio to be in favour of males (2.2:1). But this ratio is much lower than the ratio reported in HIV-positive patients (Table 2). On the contrary, a study from China found female preponderance in CD [8]. The reasons for lower male to female ratio in our study and female predominance in a study from China remain unclear. When we compared gender predilection in between UCD and MCD, then male preponderance was noted in patients with MCD (M:F = 3:1).

We found that constitutional symptoms like fever/weight loss, the extent of lymphadenopathy and hepatosplenomegaly were higher in MCD group. These patients also appeared sicker with poorer performance status than the UCD patients. This observation goes along with the widespread nature of illness in MCD, which behaves like a systemic disease. Serum albumin and hemoglobin values were lower in patients with MCD. This difference was statistically significant for S. albumin ($p = 0.006$). For haemoglobin levels, it came very close to the level of significance ($p = 0.06$). Another statistically significant difference between UCD and MCD was found in the proportion of cases with hyaline vascular and plasma cell variant. Significantly higher number of patients with MCD had plasma cell variant ($p = 0.03$). Luo et al. also showed similar trends in differences in between UCD and MCD [8].

There is no standard treatment for Castleman's disease. A wide range of options ranging from observation, wide local excision, single-agent chemotherapy to multi-agent chemotherapy with or without stem cell transplants are described in the literature [1, 6, 8, 10] with relatively satisfactory outcome (Table 2). In our study, there was a significant difference in treatment response amongst UCD and MCD. Around 62.5 % patient with UCD attained CR after treatment. In contrast, none of the patients with MCD could attain CR. Luo et al. also observed unsatisfactory outcomes in MCD. In their series, all patients of UCD were declared cured while no cure was noted in patients with MCD and the best response was reported as "improvement in disease status".

Only one death was noted in our patient cohort in a case with PCCD due to progressive disease and chemo-toxicity. In a large study of cancer-related mortality in India no CD related death was reported [18], and this observation also reiterate favourable outcome of this disorder.

Published studies on treatment outcome in CD vary in the reporting of survival outcome. In a review of 84 cases of CD by Mylona et al. [1], a contrasting observations were made. They found that case fatality rate of HIV-associated

MCD was lower than that reported for HIV negative MCD (44 vs. 65 %). Median survival for HIV related MCD was only 12 months in comparison to 29 months for HIV negative MCD. Possibly this observation is related to higher case fatality rate of HIV positive patients due to causes other than CD. The fact that many of the cases reviewed by Mylona et al. were treated in the pre-ART era may have contributed to the poorer survival of HIV-related CD. In the current era with the advent of modern ART survival rates of MCD in HIV-positive patients have considerably improved, and they are nearing survival reported in immunocompetent patients [6, 8, 10, 13] (Table 2).

Our study is not without limitations. All the biases inherent to retrospective study design may limit generalisation of our results. Only patients with adequate biopsy were included which could lead to selection bias. Important immunogenic tests for HHV-8 and serum interleukin-6 levels were not done in any of our patients as these tests were not carried out in our hospital during the study period. Sample size of 16 patients is also relatively small for robust statistical analysis.

Conclusion

CD is a rare disease in immunocompetent patients. Equal numbers of UCD and MCD patients were seen in our study. The hyaline vascular variant was the predominant subtype in UCD while plasma cell variant was more common in MCD. Serum albumin was significantly low in patients presenting with MCD. With localized surgical excision and need based chemotherapy patients with UCD had 100 % survival. Chemotherapy was not found to be very effective in patients with multicentric CD and its plasma cell variant. However, their long-term survival was only marginally lower than patients with MCD probably due to the low malignant potential of this illness.

Compliance with Ethical Standards

Conflict of interest There is no potential conflict of interest of authors writing this article.

Research Involving Human Participants and/or Animals This is a retrospective data analysis and does not involve any human or animal intervention or experiment.

Informed Consent Informed consent was obtained before data analysis from participating subjects.

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