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Original Article

Clinical characteristics of 26 patients with primary extranodal Hodgkin lymphoma

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Abstract: Background: Most Hodgkin lymphoma (HL) patients present with disease in nodal regions. However, in a small subset, disease develops extranodal sites primarily, such as lung and liver. This study aims to identify the characteristics and outcomes of patients with primary extranodal HL. Methods: A retrospective analysis of patients with HL from 1998 to 2012 was enrolled. We selected 26 HL patients with primary extranodal involvement from 251 previously untreated HL patients. All data analyses were performed with SPSS software version 17.0 and GraphPad Prism 5. Results: We identified 26 patients with primary extranodal HL. Results in the series of young patients, male predominated. Pathologically, the major pathologic types were nodular sclerosis classical HL (NSCHL, 46.2%) and mixed cellularity classical HL (MCCHL, 38.5%). Thirteen patients had early stage (I or II stage). The most commonly primarily extranodal sites were the lung and the stomach and intestine, followed by the liver and bones. Fifteen of 26 received chemotherapy alone and 11 received combination therapy. Finally, primary extranodal HLs in our study have a favorable survival. Furthermore, there was no significant association between the international prognostic score (IPS) and survival in patients with extranodal HL. Conclusion: Our retrospective data in part reflect clinical characteristics of primary extranodal HL in China, and form the basis for further concerning researches.

Keywords: Hodgkin's lymphoma, extranodal, prognosis, international prognostic score, survival, 18F-FDGPET-CT

Introduction

Hodgkin lymphoma (HL) is one of the most frequent lymphomas in the world, with an annual incidence of about 3 cases per 100,000 persons. There is only a mild increase in incidence throughout adolescence and young adulthood. Most of HL patients present with early stages. A majority of HL lesions originate at nodal sites and excellent control rates have been achieved with the use of combination chemotherapy and involved-field radiation therapy (IFRT). However, it is a subset in whom disease develop in some extranodal sites primarily. Most published studies on HL of primary extranodal involvement are case reports [1-3]. Therefore, it is difficult to gain a true grasp of primary extranodal HL's clinical characteristics and consequent outcomes [4]. This analysis attempts to gain some insight into clinical characteristics and outcomes of patients diagnosed and treated for primary extranodal HL.

Materials and methods

Patients

From 1998 to 2012, there were 251 consecutively admitted patients with HL in Tianjin Medical University Cancer Institute and Hospital. Among the 251 HL patients, 26 were found to have disease involving extranodal sites originally. These cases had no previous malignant tumor or severe complications. We retrospectively reviewed the clinical and laboratory data including gender, age, presence or absence of B symptoms, pathologic subtype, clinical stage, original treatment, time of relapse or death, date of last follow up, complete blood count, serum lactate dehydrogenase (LDH) level and so on. The pathologic diagnosis of HL was confirmed in all cases by expert pathologists according to the World Health Organization (WHO) classification guidelines [5]. All patients were staged according to the Ann Arbor staging

Table 1. Clinical characteristics of patients with extranodal involvement

Characteristics	Number (%)
Gender	
Male	16 (61.5%)
Female	10 (38.5%)
Age (years)	
Median years	32.5
Range years	8-64
Histological type	
lymphocyte predominant	2 (7.7%)
Nodular sclerosis	12 (46.2%)
Mixed cellularity	10 (38.5%)
Lymphocyte-rich	1 (3.8%)
Lymphocyte-depleted	1 (3.8%)
Extranodal sites	
lung	11 (42.3%)
stomach and intestine	6 (23.1%)
liver	5 (19.2%)
bones	4 (15.4%)
thyroid	1 (3.8%)
Clinical stages	
stage I-II	13 (50.0%)
stage III-IV	13 (50.0%)
B-symptoms	
with	10 (38.5%)
Without	16 (61.5%)
LDH	
normal	7 (26.9%)
abnormal	19 (73.1%)
IPS	
≤2 scores	14 (53.9%)
>3 scores	12 (46.1%)

LDH = lactate dehydrogenase, IPS = international prognostic score, B symptoms include unexplained fever above 38°C, night sweats, or unexplained loss of more than 10% body weight within 6 months.

system [6]. In addition, the international prognostic score (IPS) (male, age >45 years, stage IV, albumin <40 g/L, hemoglobin <105 g/L, white blood cells ≥15×109/L, lymphocytes <0.6×109/L or <8% of white blood cells) [7] was also evaluated for survival analysis. Treatment response was assessed using the International Working Group recommendations of standard criteria [8]. All patients were followed-up until May 2013. Overall survival (OS) was calculated from the date of diagnosis to the date of death due to any cause or to the date of last contact. Disease free survival (DFS) was defined as the time from which CR/CRu was achieved to the date of relapse, death, or last followup. Several prognostic factors (gender, age (45 years old or less/>45 years), B symptoms, albumin <40 g/L, hemoglobin <105 g/L, white blood cells ≥15×109/L, lymphocytes <0.6×109/L or <8% of white blood cells, lactate dehydrogenase (>248 u/l), β-2 micro-globulin (>2.7 mg/l), outside the affected area number (<2/≥2), pathological type, Ki-67 (<75%/≥75%), clinical stages (I-II/III-IV), the curative effect for the first time (CR, PR, PD, SD, death) and so on were analyzed by single factor and multi-factor COX regression.

Statistical analysis

OS and DFS rates were estimated by using the Kaplan-Meier method and the log-rank test. A two sided *p* value of <0.05 was considered significant. COX regression was used to analysis prognostic factors. All data analyses were performed with SPSS software version 17.0 and GraphPad Prism 5.

Results

Clinical and pathologic characteristics

The main clinical characteristics of these patients at diagnosis are shown in **Table 1**. Patients with primary extranodal involvement represented approximately 9.6% of all HL cases. Among all patients, most (16/26, 61.5%) were males. Patients with stomach and intestine involvement were most males (5/7, 71.4%), whereas patients with involvement of lung were mainly females (8/11, 72.7%). The major pathologic types were nodular sclerosis classical HL (NSCHL) and mixed cellularity classical HL (MCCHL). The most common sites were lung and gastrointestinal tract. Among the 26 patients, 25 had extranodal involvement at one site and 1 at two sites (bone, intestine). All of our patients presented with no mass and bone marrow infiltration. The median age of males was 34.3 years and female was 30.7 years. Thirteen patients (13/26, 50%) presented with stage I-II. The presence of B-symptoms was more common in patients with lung involvement (6/11, 54.5%). Furthermore, the IPS of all patients with bone involvement was higher. Clinical features were mostly manifestations of viscera itself and the physical examination failed to disclose any evidence of lymphade-

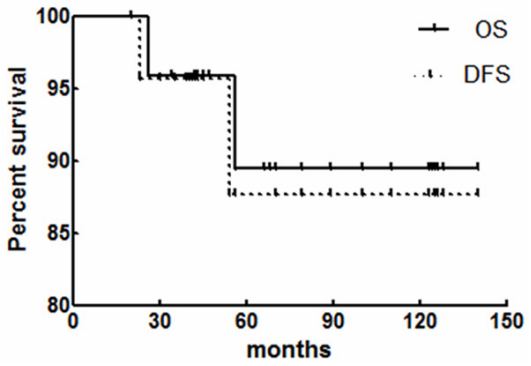

Figure 1. OS and DFS rate of the 24 patients with primarily extranodal HL.

nopathy. Nodal involvement was absent, so were pruritus and the pain cascade after drinking. Ten patients presented with fever, and antibiotic therapy were either temporarily available or ineffectiveness. However, serum laboratory data did not reveal some type of derangement of function in these organs. For the hematological manifestation and most common routine chemistry manifestation, no special modification was found. X-ray, CT and 18F-FDG PET-CT scan revealed lesions of the disease. Finally, 4 patients (3 patients with liver and 1 with small intestine) invaded to node lymph node and were major nearby lymph nodes.

Treatment parameters

Patients with stage III-IV (13 /26, 50.0%) and patients with stage II (2/26, 7.7%) in our study were treated only with chemotherapy. The remaining patients were treated with combination therapy (11 of 26, 42.3%). Radiation alone was not used for patients in our study. ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) was the most frequently used chemotherapy regimen, with patients receiving 2 to 6 cycles. For 26 patients of HL with primary extranodal involvement, 16 patients (16/26, 61.5%, 12 with stage I-II and 4 patients with stage III) were treated with ABVD or regimens improved by ABVD; 5 patients (5/26, 19.2%) were treated with BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone); 4 patients (4/26, 15.4%) were treated with MOPP (mechlorethamine, vincristine, procarbazine, and prednisone); the remaining 1 patient was treated with CVPP (cyclophosphamide, vinblastine, prednisone, procarbazine). IFRT (25-36Gy) was used for 10 patients. Extended field radiotherapy (EFRT, 30Gy) was used for only one patient.

Treatment outcomes

Response to entire therapy was assessed in 24 patients (one patients with NSCHL and one with MCCHL were excluded): 14 patients (14/24, 58.3%) achieved a CR/CRu, 3 patients (3/24, 12.5%) had a PR, 3 patients had a SD, and 2 patients had a PD. Moreover, 1 case died of liver cancer and 1 case died of infections caused by bone marrow suppression.

Two of 24 patients had HL recurrences and one of them was MCCHL, another was NSCHL. Both 2 recurrences occurred in patients with stage IV and were treated with single modality chemotherapy. Specifically, a woman who was 67-year-old at initial presentation with stage IVB HL of the thyroid of MCCHL had a recurrence in supraclavicular lymph nodes 3 years after treatment with MOPP. A 29-year-old (on initial presentation) woman with stage IVA NSCHL of the bones were treated with BEACOPP chemotherapy developed a pelvic recurrence 3 years after treatment. Only one patient developed second malignancy without suffering HL recurrences. A woman who was 31-year-old on initial presentation was treated with MOPP alone for stage IIIA nodular sclerosing HL of the lung, later developed second cancer of liver, <1 year after completing treatment, and died soon thereafter. The only one patient with two extranodal sites obtained a SD at last follow-up.

The OS and DFS rates of the 24 patients were 89.6% and 87.7%, respectively, at five years (**Figure 1**). No significant difference was observed in the OS and DFS of patients with involvement of the liver, lung, bone or other extranodal sites. At last, 83.3% (20/24) of patients were without relapse.

Prognostic analysis

Our data showed that the OS and DFS rates of low-risk group (IPS ≤2 scores) were relatively higher than high-risk group (IPS >3 scores), but the difference was not significant (OS: 90.8% vs 87.3%, p=0.504; DFS: 89.5% vs 84.1%, p=0.324, figure not shown). With the single factor of 5-year OS COX regression, our results showed that the age, albumin, LDH, clinical stages and EBER (+) can affect 5-year OS of pri-

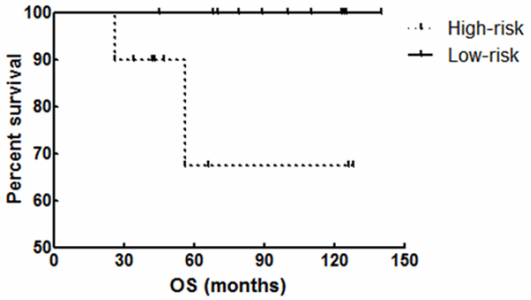

Figure 2. Twenty-four patients were stratified according to the results (albumin, LDH, clinical stages) we acquired by prognostic analysis and each index was one score. Integral <2 scores were divided into low-risk group, integral ≥ 2 scores were divided into high-risk group. OS rate of 24 patients in two groups.

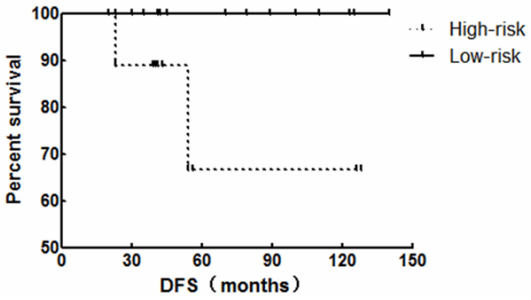

Figure 3. Twenty-four patients were stratified according to the results (albumin, LDH, clinical stages) we acquired by prognostic analysis and each index was one score. Integral <2 scores were divided into low-risk group, integral ≥ 2 scores were divided into high-risk group. DFS rate of 24 patients in two groups.

marily extranodal HL. Furthermore, these meaningful single factors were also tested by multiple factors analysis. Finally, albumin, LDH and clinical stages were associated with 5-year DFS of 24 patients. Similarly, we showed that albumin, LDH, clinical stages and pathological types can affect 5-year OS. Twenty-four patients were stratified according to the results (albumin, LDH, clinical stages) we acquired by prognostic analysis and each index was one score. Integral <2 scores were divided into low-risk group, integral ≥ 2 scores were divided into high-risk group. Finally, the 5-year OS rate was higher in the low-risk group than in the high-risk group (100% vs.67.4%, p=0.016 **Figure 2**). Low-risk patients had a significantly higher 5-year DFS than patients in high-risk group (100% vs. 67.1%, p=0.011 **Figure 3**).

Discussion

HL is a lymphoproliferative neoplasm of lymph node comprising multinucleated Reed Sternberg cells within an inflammatory milieu [9]. However, under some circumstances, those tumors arise from any tissues other than the lymph nodes, simulating other neoplastic or infectious diseases. In this study, we analyzed the clinical characteristics and survival of 26 Chinese patients with primary extranodal HL. Patients with primary extranodal involvement in our study were more commonly young males and major pathologic types were NSCHL and MCCHL, which is consistent with a recent study of 34 cases of HL involving extranodal and nodal sites of the head and neck evaluated at the University of Texas M.D. Anderson Cancer Center [4]. We also found that the epidemiologic and pathologic patterns were similar to previous reports on HL [10, 11] and that the common extranodal sites of involvement were pulmonary system and gastrointestinal tract, which is coincident with previous reports [12, 13]. The most common presentations of patients with primary extranodal HL are caused by visceral organ involved. Consistently the physical examination failed to disclose any evidence of lymphadenopathy. So the correct diagnosis is only reached after extensive and repeated investigations and review of the histology. The practical interest is to make early diagnosis because HL with primary extranodal involvement have a favorable survival compared with recent domestic and foreign report in HL (OS: 87.0% and 80.5%, respectively) [14, 15].

It is worthy to mention that there were 3 patients diagnosed by PET-CT. Several studies suggested that the sensitivity and specificity of 18F-FDG PET-CT for the assessment of nodal and extranodal involvement were higher than those of standard contrast-enhanced CT (CE-CT) including Hodgkin and non-Hodgkin lymphoma patients [16]. PET-CT has a significant advantage for the diagnosis of diffusely infiltrating organs without mass lesions or contrast enhancement compared to CE-CT [17]. Whether PET-CT can be used for the diagnosis of primary extranodal HL is worthy of being explored.

Recently, there are many reports affecting the prognosis of patients with early and late stages of the HL [18]. However, the data in primary extranodal HL are rather limited. The 7 factor IPS is currently the most widely used prognos-

tic scoring tool in patients with advanced HL. Our data didn't show the prognostic value of IPS for 24 HL patients with primary extranodal involvement. So the role of IPS in primary extranodal HL is needed to be analyzed in depth. To date, no conclusion was obtained about the outcome of primary extranodal HLs [12, 13, 19-21]. Our study showed that LDH, albumin, clinical stages and pathological types could be used to evaluate the prognosis of primary extranodal HL. Similarly, many studies have shown that they have individually been suggested to be of prognostic value on HL [22-26].

In conclusion, although relatively rare, primary extranodal HL represents a unique form of the disease. Primary extranodal HLs have a favorable survival and IPS seems unsuitable for evaluating the prognosis of primary extranodal HL patients in our study. Further studies are warranted to analyze the diagnosis and prognosis of primary extranodal HLs.

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Disclosure of conflict of interest

None.

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