Clinical characteristics of the patients with Hodgkin’s lymphoma involving extranodal sites

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Abstract

Differences between Hodgkin’s lymphoma (HL) patients in China and Western countries are known to exist, but data on Chinese patients with HL are limited. It is not clear whether there are clinical and histological differences in patients with HL involving different extranodal sites. This is the first study to analyze Chinese patients with HL involving different extranodal sites. We selected 22 HL patients with extranodal involvement from more than 250 previously untreated HL patients. Most patients were young males, and 20 of the 22 patients had stage IV disease. The major pathologic types were nodular sclerosis classical HL (NSCHL) and mixed cellularity classical HL (MCCHL). At diagnosis, the most commonly involved extranodal sites were the liver and lung, followed by the bones. There was no significant association between the international prognostic score (IPS) and survival in patients with different extranodal sites. Our data showed the overall survival (OS) and disease-free survival (DFS) rates of low-risk group (IPS = 0–2) were relatively higher than those of high-risk group (IPS ≥ 3), but the IPS did not show predictive power for survival. Although HL with extranodal involvement is rare, it should be considered as a unique form of HL.

Key words  Hodgkin’s lymphoma, extranodal involvement, international prognostic score, survival

In 2010, approximately 8490 new cases of Hodgkin’s lymphoma (HL) (4670 males and 3820 females) were expected to be newly diagnosed in the United States, and 1320 Americans were expected to die of HL[1]. HL accounts for about 30% of all lymphomas and its incidence has been steady. Currently, more than 80% of patients with HL can be cured with chemotherapy and involved-field radiotherapy, and ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) is the most common first-line regimen. HL most frequently involves lymph nodes; primary extranodal involvement is rare[2]. Extranodal organ involvement occurs more often in non-Hodgkin’s lymphoma (NHL) than in HL, and distinct extranodal sites show different incidence of involvement[3,4].

Because of the extremely low incidence, most published studies on HL with extranodal involvement are either case reports or reports of a very small series of cases of a particular extranodal site. Most HL patients have localized disease (stages I and II), and patients with extranodal involvement are often staged as advanced stage. It is not clear whether there exists a clinical and histological difference among patients with HL involving different extranodal sites. As we know, the characteristics of Chinese patients with HL are different from those of patients in Western countries. Indeed, some of these distinct features were found by a previous study in our institution[5]. Moreover, studies about HL patients in China, especially HL patients with extranodal involvement, are limited in number. Here, we retrospectively studied the clinical characteristics and outcomes of HL cases involving different extranodal sites to determine whether different extranodal sites influence clinical features and outcomes and whether treating HL patients with extranodal involvement requires improved treatment strategies.
therapy modalities.

**Materials and Methods**

**Patients**

Between July 1989 and December 2009, more than 250 patients were diagnosed with HL at Sun Yat-sen University Cancer Center. We selected 26 previously untreated patients with HL involving one or more extranodal sites, regardless of regional lymph node involvement; 8 patients with disease only presented at the spleen and lymph nodes were not included. These cases had no previous malignant tumor or severe complications. The pathologic diagnosis of HL was confirmed in all cases by expert pathologists according to the World Health Organization (WHO) classification guidelines. All patients were treated with chemotherapy or chemoradiotherapy and had complete follow-up data. Based on previous definition, lymphomas involving both the spleen and lymph nodes were considered primary nodal HL. Of the 26 patients with extranodal involvement, 4 patients with lymphocyte-predominant HL (LPHL) were also excluded.

After obtaining approval of all patients to use their medical records for research, we retrospectively reviewed the clinical and laboratory data before therapy including gender, age, presence or absence of B symptoms, pathologic subtype, stage, original treatment, time to relapse or death, date of last follow-up, complete blood count, serum lactate dehydrogenase (LDH) level, computed tomography (CT) or positron emission tomography/computed tomography (PET/CT) scans of the neck, chest, abdomen, or pelvis, and bone marrow examination results. 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) was also evaluated for survival analysis. All patients was staged according to the Ann Arbor staging system.

**Response assessment criteria**

Treatment response was assessed using the International Working Group recommendations of standard criteria for complete remission (CR) or unconfirmed complete remission (CRu), partial remission (PR), stable disease (SD), and progressive disease (PD). 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 follow-up.

**Statistical analysis**

The differences in clinical characteristics of patients with different extranodal sites were analyzed using the Chi-square or Fisher’s exact test. OS and DFS rates were estimated using the Kaplan-Meier method and the log-rank test. A two-sided P value of <0.05 was considered significant. All data analyses were performed with SPSS software version 16.0.

**Results**

**Clinicopathologic characteristics**

Twenty-two HL patients with extranodal involvement were selected for the present study, representing approximately 8.8% of all HL cases evaluated for inclusion in the study. The main clinical characteristics of these patients at diagnosis are shown in Table 1. At diagnosis, the involved extranodal sites were as follows: the liver (9 cases, 40.9%); the lung (9 cases, 40.9%); the bones (7 cases, 31.8%); and the breast, kidney, parotid, thyroid, and bone marrow (1 case each). Of the 22 patients, 15 had extranodal involvement at one site, 6 at two sites, and 1 at three sites. The median age was 28 years (range, 13–76 years), with 13 (59.1%) patients younger than 30 years and 2 over 60 years old. Fifteen patients (68.2%) were males and 7 were females, and the male-to-female ratio was 2.1:1. The average age of males was 33.3 years, the same as the average age of females. Almost all patients (20 of 22, 90.9%) had stage IV disease; 2 presented with stage II disease. Serum LDH levels were elevated in 7 patients (31.8%), and 12 patients presented with B symptoms. Based on the IPS, 7 patients (31.8%) were classified into a low-risk group (IPS = 0–2) and 15 (68.2%) into a high-risk group (IPS ≥ 3).

The clinical characteristics of patients with involvement of different extranodal sites were also compared. The median age of patients with lung involvement (31 years) was greater than that of patients with involvement of all other extranodal sites. Patients with bone involvement were predominantly females (P = 0.026), whereas patients with involvement of other sites were predominantly males. The presence of B symptoms was more common in patients with liver involvement (6/9, 66.7%) and bone involvement (6/7, 85.7%). Furthermore, the IPS of all patients with bone involvement was higher. There was no association between extranodal sites and IPS.

Pathologically, 14 patients (63.6%) were classified as having nodular sclerosis classical HL (NSCHL) subtype, 5 as having mixed cellularity classical HL (MCCHL), 2 as
having lymphocyte-depleted classical HL (LDCHL) and 1 as having lymphocyte-rich classical HL (LRCHL). No significant association was found between histological types and extranodal sites.

Therapeutic modalities

Sixteen patients (72.7%) underwent chemotherapy alone because the majority had stage IV disease. The remaining 6 patients underwent chemotherapy followed by radiotherapy. Most patients (18 of 22, 81.8%) were treated with ABVD regimen, which is considered a standard chemotherapy regimen for HL; 3 patients with stage IV disease were treated with BEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone); 1 patient with stage IV disease was treated with MOPP regimen (mechlorethamine, vincristine, procarbazine, and prednisone). Consolidation radiotherapy with a median dose of 45.8 Gy was given to 6 patients. Response to chemotherapy was assessed in 19 patients: 10 (52.6%) achieved a CR/CRu, 6 (27.3%) had a PR, 1 had SD, and 2 had PD.

Survival and prognostic power of the IPS

The 5-year OS and DFS rates of the 22 patients were 86.8% and 76.5%, respectively (Figures 1 and 2). No significant difference was observed in the OS and DFS of patients with involvement of the liver, lung, bone, or other extranodal sites. Table 2 summarizes clinical features, initial treatment, and outcome of 3 patients who developed relapses. These patients had NSCHL, MCCHL, and LDCHL, respectively. Two patients had disease-related deaths. None developed secondary malignancies within follow-up (median, 35.7 months; range, 10.5–97.6 months).

The 5-year OS rate was higher in the low-risk group than in the high-risk group (93.3% vs. 83.3%), but no significant difference was found (P = 0.841). Low-risk patients had a slightly higher 5-year DFS than did high-risk patients (75.0% vs. 73.8%, P = 0.841). In these two groups, there was no significant association between IPS and survival of patients with different extranodal sites (P > 0.05).

| Characteristic | Number of patients (%) |
|----------------|------------------------|
| Gender         |                        |
| Male           | 15 (68.2)              |
| Female         | 7 (31.8)               |
| Age (years)    |                        |
| Median         | 28                     |
| Range          | 13–76                  |
| Histological type |                    |
| Nodular sclerosis | 14 (63.6)            |
| Lymphocyte-rich | 1 (4.6)                |
| Mixed cellularity | 5 (22.7)              |
| Lymphocyte-depleted | 2 (9.1)            |
| Involved extranodal sites\(^*\) |                   |
| Liver          | 9 (40.9)               |
| Lung           | 9 (40.9)               |
| Bone           | 7 (31.8)               |
| Others\(^*\)   | 5 (22.7)               |
| B symptoms\(^\d\) |                    |
| Elevated serum LDH | 12 (54.5)          |
| IPS            |                        |
| 0–2            | 7 (31.8)               |
| ≥3             | 15 (68.2)              |

LDH, lactate dehydrogenase; IPS, international prognostic score. \(^*\) More than one extranodal site was involved in 7 patients. \(^\d\) Other extranodal sites include the breast, kidney, parotid, thyroid, and bone marrow (1 case each). \(^\d\) B symptoms include unexplained fever above 38°C, night sweats, or unexplained loss of more than 10% body weight within 6 months.
Figure 1. Overall survival (OS) of 22 Chinese patients with Hodgkin’s lymphoma (HL) with extranodal involvement. The 5-year OS rate was 86.8%.

Figure 2. Disease-free survival (DFS) of 22 Chinese HL patients with extranodal involvement. The 5-year DFS rate was 76.5%.

**Table 2. Relapses in HL patients with extranodal involvement**

| Gender  | Histological type   | Stage | Extranodal site | Initial treatment | Relapse site¹ |
|---------|---------------------|-------|-----------------|-------------------|--------------|
| Male    | Lymphocyte-depleted | IVB   | liver           | ABVD              | Multiple lymph nodes at both sides of the diaphragm at 22 months |
| Female  | Nodular sclerosis   | IVB   | liver, bone     | ABVD              | Lung at 2 months |
| Male    | Mixed cellularity   | IVA   | liver           | ABVD-MOPP         | Cervical lymph nodes at 7 months |

ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; MOPP, mechlorethamine, vincristine, procarbazine, and prednisone. ¹Months were calculated from the date complete remission (CR) or unconfirmed complete remission (CRu) was achieved to the date of relapse.
Discussion

Although HL patients in China and Western countries are known to have different clinical features, data of Chinese patients with HL are limited. Extranodal involvement is relatively rare in patients with HL. Most previous studies are case reports or reports on a particular site. In this study, we analyzed the clinical characteristics and survival of 22 Chinese patients with HL involving different extranodal sites. We found that the epidemiologic and pathologic patterns were similar to previous reports on HL. Patients with extranodal involvement in our study were more commonly young males compared with HL patients in Western populations. Our results showed the major pathologic types were NSCHL and MCCHL, which was 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. At diagnosis, the most common extranodal sites of involvement were the liver and lung, followed by the bone. Although the number of patients with extranodal involvement of each site was small, patients with different extranodal sites appeared to have some distinct clinical characteristics. A possible characteristic was observed in patients with bone involvement: a female predominance and a higher IPS score in contrast with other sites.

The 7-factor IPS is currently the most widely used prognostic scoring tool in patients with advanced HL. We evaluated the prognostic value of IPS for HL patients with extranodal involvement. Our data showed that the OS and DFS rates of low-risk group were relatively higher than high-risk group, but the difference was not significant. Moreover, we found no significant association between IPS and survival in patients with HL involving different extranodal sites. Although the majority of these patients had advanced disease, IPS did not show predictive power for survival. These results may be because most patients in our study had a high IPS score.

A previous report of 137 patients with HL analyzed in our institution showed that the estimated 5-year OS and DFS rates were 97.7% and 94.0%. In the present study, patients with HL involving extranodal sites had relatively poor survival though the prognosis was not different according to the involved extranodal sites. Relapse was observed in 3 patients (13.6%), 2 of which lacked a combined treatment because of an old age and advanced stage. All patients with relapse received ABVD regimen. In the patients with relapse, the involved extranodal sites were the liver and bone before treatment. Advanced stage, extranodal site, or treatment might have contributed to relapse, but we could not find a significant association owing to too few cases in this study.

In conclusion, although HL with extranodal involvement is not common, it should be considered a unique form of HL. IPS seems unsuitable for evaluating the prognosis of HL patients with extranodal involvement. Moreover, patients with HL involving the liver at diagnosis might need a more intensive therapeutic strategy. Further studies are warranted to analyze this distinctive HL.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (No. 81071950), Fundamental Research Funds for the Central Universities (No. 10ykpy36), National Eleventh Five-year Technology Major Project (No. 2008ZX09312-002, 2012ZX09301), and Research Award Funds for Outstanding Young Researchers in Sun Yat-sen Cancer Center.

Received: 2012-01-09; revised: 2012-03-18; accepted: 2012-03-31.

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