Extralymphatic Disease Is an Independent Prognostic Factor in Hodgkin Lymphoma

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Abstract

A retrospective study was performed of 341 cases of extralymphatic Hodgkin lymphoma (HL) to identify its characteristics and outcomes. Sites were lung in 29 patients (44%), bone in 22 (33%), and liver in 5 (18%). Extralymphatic HL is a rare occurrence (16%) associated with poor clinical outcome.

Purpose: To identify the characteristics and outcomes of patients with extralymphatic Hodgkin lymphoma. **Patients and Methods:** We performed a retrospective single-institution study of 341 cases comprising 207 male (61%) and 134 female (39%) subjects with a median follow-up of 44 months. **Results:** Fifty-five patients (16%) had extralymphatic disease. The sites were lung in 29 patients (44%), bone in 22 (33%), liver in 12 (18%), and kidney in 3 (5%). In 46 patients (86%) only one organ was involved, while in 7 patients (13%) extralymphatic disease was present in 2 sites and in 2 patients (3%) in 3 sites. The extralymphatic disease group had a poorer prognosis than the lymphatic disease group. Complete remission rates in the extralymphatic and lymphatic patient subsets were 65% and 82% ($P = .043$), respectively. **Conclusion:** Extralymphatic disease in patients with Hodgkin lymphoma is a rare occurrence (16%) associated with poor clinical outcome.

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Introduction

Hodgkin lymphoma (HL) accounts for 10% to 15% of lymphoma cases.[1] With current therapy, more than 75% of patients will survive free of disease for more than 5 years; most of these will be cured.[2,3] These results have been obtained thanks to the judicious use of progressively improved staging methodologies over time, as well as of a stage-adapted treatment strategy.[4,5]

At presentation, HL is usually supradiaphragmatic, contiguous spread often occurring predictably from one nodal group to the next along the lymphatic pathways. HL is usually almost entirely confined to the lymph nodes. To define a certain anatomical area, the term "Waldeyer ring" is used to include the lymphoid tissues of the faucial tonsils, nasopharynx, base of the tongue, and oropharynx; this is therefore considered an extranodal but not an extralymphatic site. HL cases arising from this tissue, although uncommon, are well characterized. Therefore, the terms extranodal and extralymphatic lymphoma have been used to describe the uncommon forms of lymphoid malignancy in which there is neoplastic proliferation at sites other than the expected native lymph nodes and lymphoid tissue. Because of the difficulty in defining such cases, the frequency of this type of variation is not well established; nevertheless, if sites rich in primary lymphoid tissue such as Waldeyer ring and spleen were to be considered as extranodal, then extranodal lymphomas would account for 25% to 50% of all non-HLs and only 2% to 5% of HL. Initial staging is crucial to demonstrate the presence of extralymphatic involvement, which will affect therapeutic decision making.[6,7]

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To further assess the presenting features and the prognostic significance of extralymphatic disease in HL, we performed a retrospective single-institution study.

Patients and Methods

This retrospective study analyzed data of 341 patients with newly diagnosed classic HL treated at Bari University Hospital (Italy) between 2006 and 2016. Histologic diagnoses were established according to the World Health Organization classification.[8]

Patients diagnosed with nodular lymphocyte-predominant HL, HIV-positive patients, and patients treated only with radiation or palliative care were excluded.

No patient refused authorization to use their medical records for research. No patients were lost to follow-up.

Clinical characteristics at diagnosis are listed in Table 1; 207 subjects (61%) were male and 134 (39%) female. Median age at diagnosis was 36 years (range, 15-83 years), 106 patients (31%) had advanced stage disease (III-IV), 128 (38%) had bulky disease, 161 (47%) presented B symptoms, 92 (27%) had spleen involvement, and 55 (16%) had extralymphatic disease. The histology was nodular sclerosis in 287 (84%).

The treatment policy differed during the course of the study period according to Ann Arbor clinical stage. All patients were treated with the doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) regimen; 235 patients (69%) received radiotherapy of the involved field. A total of 188 had early stage and 47 advanced stage disease. Median follow-up was 44 months. The baseline characteristics recorded for each patient are listed in Table 2.

Two patients died of causes not related to lymphoma, and 6 patients died of lymphoma progression.

Staging and Routine Laboratory Evaluations

The disease of all patients was clinically staged according to the Ann Arbor system. Data were gathered including medical history; complete physical examination; blood counts; biochemical profile; chest X-ray films; computed tomography (CT) of the chest, abdomen, and pelvis; fluorodeoxyglucose positron emission tomography with CT (PET/CT) of the total body; and unilateral bone marrow biopsy. Hemoglobin concentrations, white blood cell counts and differential, erythrocyte sedimentation rate, serum albumin, and serum lactate dehydrogenase levels were measured by standard assays. Anemia was defined as the presence of hemoglobin levels < 13 g/dL for male subjects and < 11.5 g/dL for female subjects. Serum albumin was analyzed with a cutoff of 3.5 g/dL, which is the normal lower limit at our laboratory. Serum β2-microglobulin was measured by radioimmunoassay (normal values, 1.0-2.4 mg/L).

Response Evaluation

Tumor responses were assessed at the end of the treatment and were classified as complete response, partial response, stable disease, or progressive disease according to the International Workshop Criteria.[9]

Statistical Analysis

Definitions of response criteria and progression-free survival (PFS) were based on the International Harmonization Project Lymphoma guidelines.[9] PFS was defined as the time from HL diagnosis to the time to progression, relapse from complete response, death as a result of any cause, or last follow-up.

Table 1 Patient Characteristics

Characteristic	Lymphatic Disease		Extralymphatic Disease		*P*
	N	%	N	%	
Patients	286	84	55	16	
Sex					
Male	176	62	31	56	
Female	110	38	24	44	
Age ≥ 60 years	51	18	8	15	
Histologic Type					
Lymphocyte predominant	15	5	1	2	
Nodular sclerosis	240	84	47	85	
Mixed cellularity	31	11	7	13	
Clinical Disease Stage					
I-II	228	80	7	13	
III-IV	58	20	48	87	<.001
B symptoms	125	44	36	65	.003
Bulky disease	100	35	28	51	.025
Abnormal LDH	71	25	20	36	
Abnormal β2-microglobulin	86	30	26	47	.012
Spleen involvement	62	22	30	55	<.001
IPS 3-5	31	11	21	38	<.001

Abbreviations: IPS = International Prognostic Score; LDH = lactate dehydrogenase.