Original Article

Primary extranodal non-Hodgkin's lymphoma: A retrospective analysis of its clinicopathological features and treatment outcomes in a tertiary cancer center of eastern India

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ABSTRACT

Background: Primary extranodal non-Hodgkin's Lymphomas (NHL) is an uncommon entity. It is diverse in its presentation, morphology, histology, and immunophenotyping. No clear-cut consensus exists regarding its management. Indian data is lacking regarding biology and treatment of disease. **Aim:** The aim of this study is to analyze the clinicopathological features and assess treatment modalities utilized and their outcomes in patients with primary extranodal NHL and also the outcome with involved field radiotherapy (IFRT). **Settings and Design:** This is a retrospective observational study from prerecorded hospital data. **Materials and Methods:** Cases of primary extranodal NHL attending the radiotherapy outpatient department of our institute during the last 5 years (July 2007-June 2012) were taken for this study. Hospital recorded data were taken and analyzed regarding the demography, clinical features, histopathological features, and treatment modalities and their outcomes. **Result:** Total 41 patients were identified, out of which six patients did not turn up for any form of treatment. Almost all patients (33 out of 35, 94.28%) received chemotherapy while around 55% (19 out of 35) patients received radiotherapy. During follow-up, around 23% patients had relapsed, that too mostly outside the primary site. **Conclusion:** Immunohistochemistry is essential in all cases to identify the subset which would respond excellently to rituximab (CD20 positive). IFRT has definite role in the management of extranodal NHL in patients having residual disease following chemotherapy.

Key words: Extranodal lymphoma, involved field radiotherapy, treatment outcome

INTRODUCTION

Lymphomas are neoplasms of the lymph reticular system. It has been shown recently that during the last two decades, incidence of lymphomas has increased at a rate of 4% per year.[1] Approximately one-third of non-Hodgkin's lymphomas (NHL) arise in tissues different from the lymph node, they are usually termed extranodal lymphomas. These extranodal presentations are not common and are mostly of non-Hodgkin's variety. It has also been revealed that extranodal lymphomas have increased more rapidly than its nodal counterpart.[2] This trend is seen particularly in developing countries, more so in the Middle East and Far East, with an increase in diffuse histological pattern over nodular, and more aggressive than indolent behavior.[3,4] The study of extranodal lymphomas as a group, regarding etiopathogenesis, biologic features, clinical characteristics, and outcome has been the subject of several publications. Most of those studies include heterogeneous series of patients in which different histological subgroups are merged together. However, there is still a paucity of clinicobiologic studies dealing with primary extranodal NHL in the Indian scenario. Therefore, a retrospective study of treatment modalities utilized and their outcomes in patients with primary extranodal NHL was warranted. We have also focused our efforts to assess the role of involved field radiotherapy in terms of disease control and survival

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advantage in different subsets of extranodal NHL from this retrospective study.

MATERIALS AND METHODS

Patients

Lymphomas that presented in extranodal organs with no or only minor lymph node involvement were considered primary extranodal, whereas lymphomas with lymph node involvement clinically dominant were considered as primary nodal. Waldeyer's ring and spleen were considered nodal sites. Bone marrow was considered an extranodal site. Finally, those lymphomas with extensive disease involving both nodal and extranodal sites were considered nodal.

According to the above mentioned criteria, between July 2007 and June 2012, 41 patients were consecutively diagnosed as primary extranodal NHL from prerecorded hospital data. Six patients did not turn up for treatment; they were considered as dropouts and excluded from the study. Clinical records of 35 patients treated and followed-up in our institution were analyzed in the present study.

Histopathological evaluation

All 35 patients were histopathologically proven as NHL. The diagnosis of NHL and its subtype was based on the criteria established in World Health Organization (WHO) classification for all cases. Immunophenotyping was performed in 30 patients, the panel included CD45, CD20, CD79a, CD3, CD5, CD10, CD23, bcl 2, bcl 6, and ki 67.

Evaluation and staging

Staging procedure included detailed history taking and thorough clinical examination (including Waldeyer's ring area); complete blood counts and serum biochemistry, including serum lactate dehydrogenase (LDH); computed tomography (CT) scan of chest, abdomen, and pelvis; as well as upper gastrointestinal (GI) endoscopy and bone marrow biopsy in selected cases.

Treatment

Patients were treated with six cycles of primary systemic chemotherapy either with CHOP regimen which consisted of intravenous inj. cyclophosphamide (750 mg/m^2), inj. doxorubicin (50 mg/m^2), inj. vincristine (1.4mg/m^2, maximum daily dose of 2 mg), and per oral tab. prednisolone (100 mg D_1 to D_5) for intermediate and high grade lymphomas or with CVP regimen which consisted of intravenous inj. cyclophosphamide (750 mg/m^2), inj. vincristine (1.4 mg/m^2, maximum daily dose of 2 mg), and per oral tab. prednisolone (100 mg D_1 to D_5) for low grade diseases. Patients who had bulky disease at presentation, partial response, or stable disease after chemotherapy were treated by involved field radiotherapy at dose of 40 Gy in 20 fractions in conventional fractionation over 4 weeks after completion of chemotherapy. Patients with localized disease like orbital NHL were treated by involved field radiotherapy alone at dose of 44 Gy in 22 fractions in conventional fractionation over 4.5 weeks. Patients with CD20 + diffuse large B cell lymphoma (DLBCL) received CHOP plus rituximab at dose of 375 mg/m^2.

The radiation treatment was done using telecobalt unit THERATRON 780C (Theratronics), CT-simulation, and ASHA 3D Planning System (TPS).

Follow-up

Post therapy evaluation consisted of clinical examination in all visits and blood tests and imaging every 6 months. Response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria version. Patients were followed-up on a monthly basis for 1 year and then they were followed-up after every 3 months.

RESULTS

Primary extranodal NHL constituted 22% (41 out of 186) of all the NHL patients studied during this period. Median age of the patients was 60 years (range: 14–84 years) and the male: female distribution was 3:4, 27 out of 41 patients (65.8%) had 'B-symptoms' (significant fever > 38°C (100.4°F), drenching night sweats, and unexplained weight loss exceeding 10% of normal body weight within the previous 6 months], and 22 out of 41 patients (53.7%) had elevated serum LDH levels (>450 U/L) at presentation.

Distribution of patients according to the primary site was as shown in Table 1. Among the studied patients, stomach was the most common primary site (32%) and orbit was the second (19.5%), closely followed by thyroid (14.6%) and skin (12.2%). The rest were of rectum, testis, nasopharynx, breast, liver, and parotid.

Immunohistochemistry report was available for 30 patients out of 35 (due to logistic reasons, rest of the patients could not afford to do it), the rest were diagnosed only by histopathology. Distribution of the patients according to histopathologic subtypes was as shown in Table 2. Diffuse large B cell variety was the most frequently found subtype (60%) followed by follicular lymphoma (17.1%).

Immunohistochemistry reports showed that out of 30 patients, 18 were CD 20+ve, all of them were histopathologically DLBCL.

Patients were also categorized according to international prognostic index (IPI) for aggressive NHL and follicular

lymphoma international prognostic index (FLIPI) for patients with follicular lymphoma according to the description by the International Non-Hodgkin's Prognostic Factors Project for patients with all required parameters present [Tables 3 and 4]. In IPI, one point is given for each of following characteristics: Age > 60 years, elevated serum LDH level, Eastern Co-operative Oncology Group (ECOG) performance status 2 or worse, Ann Arbor stage III or IV, and more than two extranodal sites. For FLIPI, one point is given for presence of each of the following characteristics: Age > 60 years, elevated serum LDH level, hemoglobin level < 12 g/dl, Ann Arbor stage III or IV, and number of involved nodal areas > 4.

Treatment

Chemotherapy was the mainstay of treatment. Out of 35 patients, 33 received chemotherapy. Twenty-three patients received chemotherapy with CHOP regimen and 4 patients received CVP regimen. R-CHOP regimen (rituximab with CHOP regime) was given to six patients. In total, 19 out of 35 patients (54.28%) of primary extranodal NHL required involved field radiotherapy (IFRT). Two patients with orbital follicular lymphoma were treated with IFRT alone and in the remaining 17 patients IFRT was added to chemotherapy [Table 5].

Outcome

Eleven out of 23 (47.82%) patients receiving first-line CHOP achieved complete response (CR) clinically and radiologically. Remaining ten patients, who achieved partial response (PR) and two patients, who achieved stable disease (SD) were treated with IFRT. Seven patients achieved CR after IFRT, four patients had partial response, and one patient died of hemorrhagic stroke while on treatment. Four patients were treated with primary systemic chemotherapy with CVP regimen; one of them achieved CR while three required IFRT. All three patients receiving IFRT following CVP achieved CR. Two patients with orbital follicular lymphoma treated with IFRT alone achieved CR.

Three patients of CD20+ve gastric DLBCL and three patients of CD20+ve DLBCL of orbit received six cycles of primary systemic treatment with R-CHOP. All three patients of gastric DLBCL who were treated with six cycles of R-CHOP and one out of three patients of DLBCL of orbit achieved complete response, proven by endoscopy and biopsy in the gastric cases and with positron emission tomography (PET)-CT scan in the case of DLBCL of orbit. However, two patients of DLBCL of orbit achieved partial response and required IFRT. Both of them achieved CR after IFRT. Table 6 shows the summary of outcomes of treatment modalities.

Median follow-up: 37 months.

Patterns of failure

During follow-up, 8 out of 30 patients (26.67%) who achieved CR relapsed, one of them was a follicular

Table 1: Distribution of patients according to primary site

Primary site	No. of patients
Stomach	13
Orbit	8
Thyroid	6
Skin	5
Rectum	2
Testis	2
Nasopharynx	2
Breast	1
Liver	1
Parotid	1

Table 2: Distribution of the patients according to histopathologic subtypes

Histopathologic subtype	No. of patients	Percentage
Diffuse large B cell lymphoma	21	60
Follicular lymphoma	6	17.1
Anaplastic large cell lymphoma	4	11.4
Extranodal natural killer (NK)/T cell lymphoma, nasal type	2	5.7
Hepatosplenic T cell lymphoma	1	2.85
Extranodal marginal zone lymphoma	1	2.85

NK: Natural killer

Table 3: Distribution according to IPI for aggressive non-Hodgkin's lymphoma

Risk category	IPI score	No. of patients
Low	0 or 1	19
Low-intermediate	2	6
High-intermediate	3	2
High	4 or 5	2

IPI: International prognostic index

Table 4: Distribution according to FLIPI for six patients with follicular lymphoma

Risk category	FLIPI score	No. of patients
Low	0 or 1	3
Intermediate	2	2
High	3 or more	1

FLIPI: Follicular lymphoma international prognostic index

Table 5: Treatment received by patients

Treatment modality	No. of patients
CHOP alone	11
CVP alone	1
IFRT alone	2
CHOP+IFRT	12
CVP+IFRT	3
CHOP+Rituximab+IFRT	2
CHOP+Rituximab	4

CHOP: Inj. cyclophosphamide (750 mg/m^2), inj. doxorubicin (50 mg/m^2), inj. vincristine (1.4 mg/m^2, maximum daily dose of 2 mg), and per oral tab. prednisolone (100 mg D1 to D5), CVP: Inj. cyclophosphamide (750 mg/m^2), inj. vincristine (1.4 mg/m^2, maximum daily dose of 2 mg), and per oral tab. prednisolone (100 mg D1 to D5), IFRT: involved field radiotherapy

Table 6: Outcome of patients received treatment (*n*=35)

Treatment received	CR	PR	SD	Death
CHOP (*n*=23)	11	10	2	-
CVP (*n*=4)	1	2	1	-
R-CHOP (*n*=6)	4	1		-
IFRT (*n*=19)	14	4	-	1

CHOP: Inj. cyclophosphamide (750 mg/m^2), inj. doxorubicin (50 mg/m^2), inj. vincristine (1.4 mg/m^2, maximum daily dose of 2 mg), and per oral tab. prednisolone (100 mg D1 to D5), CVP: Inj. cyclophosphamide (750 mg/m^2), inj. vincristine (1.4 mg/m^2, maximum daily dose of 2 mg), and per oral tab. prednisolone (100 mg D1 to D5), R-CHOP: Rituximab with CHOP regime, IFRT: Involved field radiotherapy

lymphoma of orbit which recurred in the same site, one of them had bone marrow failure, and six others recurred in lymph nodes other than the region of primary site. Half of the total relapses (four out of eight) occurred in patients of follicular lymphoma, one of them at involved site of primary origin, and three others relapsed in lymph nodes other than the site of primary involvement. Two of the DLBCL patients also relapsed, one of them had bone marrow failure. All the relapses were treated with salvage chemotherapy.

Median time to progression was 23 months.

DISCUSSION

Extranodal NHL is surprisingly diverse in its clinical presentation, morphology, and immunophenotyping characteristics. The diagnosis was often late and difficult owing to the paucity of clinical symptoms.

The etiology of NHL is poorly understood and possible risk factors such as suppression of immune system, diet, exposure to pesticides, petrochemicals, solvents, or exposure to sunlight have been reviewed.[5] Given the diversity of sites and subtypes involved in primary extranodal NHL, it may be more important to identify specific local factors, for example the association of *Helicobacter pylori* infection with gastric lymphomas,[6] or Hashimoto's thyroiditis in case of thyroid lymphomas.

According to western data, the most common sites were skin, stomach, and small intestine and high-grade lymphomas were predominant.[7] An excess in male incidence was observed for extranodal NHL overall, at all ages, and for most sites.[7] In our study, stomach was the most common site followed by orbit, thyroid, and skin in decreasing order of frequency. However, we found a slight female predominance in our study (male:female = 3:4).

Blacks and Asians/Pacific Islanders (APIs) experienced incidence rates about the same as or lower than whites' for B cell extranodal NHL as a whole and most of its histologic subtypes.[8] In harmony with western statistics, we found DLBCL to be the most frequent subtype affecting our population suffering from primary extranodal NHL, and follicular lymphoma to be the second most common subtype.

Primary modality of treatment in almost all cases except localized indolent lymphoma without systemic symptoms consists of systemic chemotherapy. A little less than half (45.7%) of the total patients studied achieved complete response with primary systemic chemotherapy alone.

The biological behavior of primary ENL has been complex in different studies. Worse therapeutic outcome was seen for patients with lymphoma involving rare sites,[9] those with T-cell phenotype,[10] and among pediatric age group.[11] Lal *et al*.,[12] reported that age, performance status, stage of disease, and serum LDH level were independent prognostic variables, whereas nodal or extranodal site did not have any prognostic significance. However, it was shown by Krol *et al*.,[13] that extranodal lymphoma has better outcome.

In our study, the following variables predicted for CR achievement: Age younger than 60 years; ambulatory performance status (ECOG score < 2); absence of B symptoms; absence of bulky disease; early Ann Arbor stage; no bone marrow involvement; normal hemoglobin, platelet count, serum albumin, LDH levels; as well as the IPI. No single antigen expression or differentiation predicted for CR.

Though our experience with rituximab and CHOP combination in primary extranodal lymphoma is limited due to prohibitive cost of rituximab itself, response rates were however, remarkably higher in patients of CD20+DLBCL who could afford first-line therapy with R-CHOP, compared to those patients who got CHOP alone. This is in contrast to earlier studies by Gutiérrez-García *et al*.,[14] and Jang *et al*.,[15] who found that primary extranodal DLBCL derives much less benefit from addition of rituximab to CHOP based chemotherapy than their nodal counterparts.

IFRT was found to be efficacious for primary extranodal NHL, especially so in extranodal natural killer (NK)/T cell lymphoma, nasal type of nasopharnyx, and follicular lymphoma arising from orbit. It was found to be extremely useful and cost-effective in clinical situations where patients failed to achieve CR with six cycles of first-line systemic chemotherapy. Fourteen out of 19 (73.68%) patients treated with IFRT achieved complete response (CR). There is a dearth of Indian as well as western data regarding the role of IFRT in first-line treatment of primary extranodal NHL.

Majority of relapses were noted to be outside the primary site in our study and half of the total relapses (four out of eight) occurred in patients of follicular lymphoma. Rudders *et al*.,[16] reported that 33% of relapses occur as solitary

extranodal "skip" recurrences responsive to radical local treatment resulting in long disease-free survival. However, nodal relapses distal to the primary site predominated in our study (six out of eight relapses) and required salvage chemotherapy. From the patterns of failure, it was evident that low grade lymphomas run an indolent course with remissions and relapses, while high grade lymphomas, though clinically more aggressive, are more amenable to curative.

CONCLUSION

The present study involved a relatively small number of patients, as primary extranodal lymphoma is by itself an uncommon disease; and owing to lack of infrastructure, many patients succumb to their disease before they reach tertiary oncology care. Immunophenotyping could not be done in all patients due to logistic reasons and affordability concerns. Further studies involving larger number of patients and institutions are necessary to chalk out appropriate management for these patients, which continue to evolve as our armamentarium against lymphoma expanding over time.

REFERENCES

1. Harrison's Principles of Internal Medicine. In: Lango DL, editor. 18th ed. New York City: Publisher Mc Graw Hill; 2012. p. 919-35.
2. Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, Ward E, *et al*. Cancer statistics, 2004. CA Cancer J Clin 2004;54:8-29.
3. Yaqo RT, Hughson MD, Sulayvani FK, Al-Allwai NA. Malignant lymphoma in Northern Iraq: A retrospective analysis of 270 cases according to the World Health Organization classification. Indian J Cancer 2011;48:446-51.
4. Yang QP, Zhang WY, Yu JB, Zhao S, Xu H, Wang WY, *et al*. Subtype distribution of lymphomas in Southwest China: Analysis of 6,382 cases using WHO classification in a single institution. Diagn Pathol 2011;6:77.
5. Cartwright RA, McNally RJ. Epidemiology of non-Hodgkin's lymphoma. In: Burnett A, Armitage J, New-land A, Keating A, editors. Cambridge Medical Reviews: Haematological Oncology. vol 3. Cambridge: Cambridge University Press; 1994. p. 1-34.
6. Parsonnet J, Hansen S, Rodriguez L, Gelb AB, Warnke RA, Jellum E, *et al*. *Helicobacter pylori* infection and gastric lymphoma. New Engl J Med 1994;330:1267-71.
7. Gurney KA, Cartwright RA. Increasing incidence and descriptive epidemiology of extranodal non-Hodgkin lymphoma in parts of England and Wales. Hematol J 2002;3:95-104.
8. Wu XC, Andrews P, Chen VW, Groves FD. Incidence of extranodal non-Hodgkin lymphomas among whites, blacks, and Asians/Pacific Islanders in the United States: Anatomic site and histology differences. Cancer Epidemiol 2009;33:337-46.
9. Yun J, Kim SJ, Kim JA, Kong JH, Lee SH, Kim K, *et al*. Clinical features and treatment outcomes of non-Hodgkin's lymphomas involving rare extranodal sites: A single-center experience. Acta Haematol 2010;123:48-54.
10. Ko OB, Lee DH, Kim SW, Lee JS, Kim S, Huh J, *et al*. Clinicopathologic characteristics of T-cell non-Hodgkin's lymphoma: A single institution experience. Korean J Intern Med 2009;24:128-34.
11. Temmim L, Baker H, Amanguno H, Madda JP, Sinowatz F. Clinicopathological features of extranodal lymphomas: Kuwait experience. Oncology 2004;67:382-9.
12. Lal A, Bhurgri Y, Vaziri I, Rizvi NB, Sadaf A, Sartajuddin S, *et al*. Extranodal non-Hodgkin's lymphomas--a retrospective review of clinico-pathologic features and outcomes in comparison with nodal non-Hodgkin's lymphomas. Asian Pac J Cancer Prev 2008;9:453-8.
13. Krol AD, le Cessie S, Snijder S, Kluin-Nelemans JC, Kluin PM, Noordijk EM. Primary extranodal non-Hodgkin's lymphoma (NHL): The impact of alternative definitions tested in the Comprehensive Cancer Centre West population-based NHL registry. Ann Oncol 2003;14:131-9.
14. Gutiérrez-García G, Colomo L, Villamor N, Arenillas L, Martínez A, Cardesa T, *et al*. Clinico-biological characterization and outcome of primary nodal and extranodal diffuse large B-cell lymphoma in the rituximab era. Leuk Lymphoma 2010;51:1225-32.
15. Jang G, Yoon DH, Kim S, Lee DH, Lee SW, Huh J, *et al*. Addition of rituximab to the CHOP regimen has no benefit in patients with primary extranodal diffuse large B-cell lymphoma. Korean J Hematol 2011;46:103-10.
16. Rudders RA, Ross ME, DeLellis RA. Primary extranodal lymphoma: Response to treatment and factors influencing prognosis. Cancer 1978;42:406-16.

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