PATTERN OF EXTRANODAL INVOLVEMENT IN NON HODGKIN'S LYMPHOMA

Mussavir Hussain Bangash, Iftikhar Hussain, Manzar Zakaria, Mohammad Nadeem Piracha

Combined Military Hospital Rawalpindi

ABSTRACT

Objectives: To study the anatomical and histomorphological pattern of extranodal non Hodgkin`s lymphoma (NHL).

Study Design: Descriptive study

Place and Duration of Study: The study was carried out at Oncology department Combined Military Hospital Rawalpindi during July 2012 to April 2013.

Materials and Methods: All newly diagnosed patients of NHL with extranodal involvement were included in the study. They were categorized as primary extranodal or secondary extranodal lymphomas. Histological pattern and site of involvement were studied.

Results: The male to female ratio was 2.2:1 (Male 31, Female 14), and the mean age was 48.16 years (SD=13.40). Primary extranodal involvement was seen in 55.6% of patients. Secondary extranodal involvement was seen in 44.4% of patients. Diffuse large B- cell lymphoma (DLBCL) was the most common type of NHL observed in both primary and secondary extranodal involvement. Gastrointestinal tract was the most common site for primary extranodal involvement and bone marrow was the most common site for secondary extranodal involvement.

Conclusion: High frequency of primary extranodal involvement was noted in our study. DLBCL was the most common morphological type observed. Gastrointestinal tract and secondary bone marrow involvement were the most common anatomical sites for primary and secondary extranodal involvement respectively.

Keywords: Extranodal lymphoma, Morphological pattern, Non Hodgkin;s Lymphoma.

INTRODUCTION

Non Hodgkin's lymphomas are heterogeneous group of disorders originating in B- lymphocytes, T- lymphocytes or natural killer cells. Non Hodgkin's lymphoma is the seventh leading site of new cancer cases among men and women, accounting for 4% of new cancer cases and 3% of cancer deaths[1]. A substantial number of NHL arise from tissues other than lymph nodes and from sites which normally contain no lymphoid tissue. These forms are referred to as primary extranodal lymphomas. At least one-fourth of the lymphomas are probably of extranodal origin[2]. Lymphomas arising primarily at extranodal sites can be diagnostically challenging due to their morphological variation. There are controversies in literature about definition of extranodal lymphoma, particularly in the presence of both nodal and extranodal disease. Criteria for the diagnosis of extranodal lymphoma, has been proposed by Dawson, 50 years ago[3]. For primary extranodal lymphoma, patients had to present with their main disease manifestation in an extranodal site, have no more than regional lymph node involvement, with no peripheral lymph node involvement and no liver or spleen involvement. Later these criteria were relaxed to allow for contiguous involvement of organs (liver, spleen) and distal nodal disease provided that the extanodal site was the presenting site. Extranodal involvement in the presence of extensive nodal disease represents secondary extranodal involvement.

Extra nodal NHL have been reported to originate from almost every anatomic site of the body such as gastrointestinal tract (most common), head and neck (Waldeyer's ring, nose/ paranasal sinuses/ nasopharynx, salivary glands & etc.), skin, central nervous system (CNS), bone, testis, thyroid, breast, orbit, pancreas, rarely adrenal and the genitourinary tract[4].

Correspondence: Dr Mussavir Hussain Bangash, Department of Oncology, CMH Rawalpindi
Email: mussavir72@yahoo.com
Received: 16 Sep 2013; Accepted: 02 Jan 2014

During the last two decades the incidence of NHL has increased, and that of primary extranodal lymphoma has increased more rapidly than the nodal type. This trend is seen particularly in developing countries, more so in Middle East and Far East[5]. Studies have been published about various aspects of extra-nodal lymphoma, nevertheless there is a dearth of studies about morphological type and pattern of involvement. The aim of this study was to observe the pattern of extranodal NHL in terms of morphological type and site of extranodal involvement at our centre.

MATERIAL AND METHODS

This descriptive study was carried out at department of Oncology Combined Military Hospital (CMH) Rawalpindi from July 2012 to April 2013. All newly diagnosed patients of NHL with extranodal manifestation, treated during this period either as indoor or outdoor cases, were included in this study. The diagnosis was based upon morphological and immunophenotypic criteria according to World Health Organization (WHO) 2008 classification. Computed tomography (CT) scans, bone marrow biopsy, magnetic resonance imaging (MRI) scan (in case of brain, spine or soft tissue involvement) were done for staging. Positron emission tomography (PET) CT scan was not done for staging because of the non availability of the facility at our centre.

Patients were considered to be completely staged when adequate information was available on basis of examination and staging investigations. All those patients who were found to have extranodal involvement after staging investigations were included in the study.

Data was analyzed using SPSS 17. Mean and standard deviation were calculated for age. All relevant information age, sex, histological diagnosis, site and number of extranodal organs involved were noted in the study proforma. Strict criteria proposed by Dawson were used to categorize lymphoma as primary extranodal or secondary extranoda[13].

RESULTS

The study included 45 patients with extranodal NHL. The male to female ratio was 2.2:1 (male 31, female 14), and the mean age was 48.16 ± 13.40 years (range 20 to 70 years). Primary extranodal involvement was seen in 55.6% of patients. Secondary extranodal involvement was observed in 44.4% of patients. Diffuse large B cell lymphoma (DLBCL) constituted 75% of all the patients. Marginal zone lymphoma (MZL) constituted 11.11% (5) of all the patients. Follicular lymphoma and anaplastic large cell lymphoma (ALCL) each constituted 6.6% (3). The types of NHL presenting with primary or secondary extranodal involvement are shown in table.

Out of 25 patients with primary extranodal lymphoma 32% (8 patients) had gastrointestinal tract involvement. This made it the most common site. It was followed by bone involvement observed in 24% (6 patients). Primary bone marrow involvement and primary involvement of head and neck was seen in 12% (3 patients each). Other less frequently involved primary extranodal anatomic sites were lung 8% (2 patients), kidney and breast 4% (1 patient each).

The most common site for secondary extranodal involvement was bone marrow 55% (11 patients), followed by secondary CNS involvement 15% (3 patients), testis, lung and pleura 10% (2 patients each).

DISCUSSION

Extra nodal NHL is a heterogeneous disease with geographical, ethnic, anatomic, etiological, and morphological variations[6]. The frequency of extranodal NHL varies in different parts of the world. Countries with high incidence of lymphoma also tend to have increase incidence of extranodal involvement[7]. Epidemiological studies have shown that Pakistan is a part of the 'lymphoma belt', the geographical boundaries of which extend from south-western Asia to Middle East to northern Africa[8].

Our study explored the pattern of extranodal involvement in NHL. Studies from western

countries have reported the occurrence of extranodal NHL as 24-48% of all NHLs[9]. In the lymphoma belt, including Pakistan and Saudi Arabia the incidence of primary extranodal lymphoma has shown to be very high (up to 50%)[10,11]. In our study high incidence of primary extranodal involvement was seen (55.6%).

Table-: Types of NHL with extranodal involvement.

Type	Primary extranodal (n= 25)	Secondary extranodal (n= 20)
	No. of patients	No. of patients
DLBCL	17	17
Follicular	1	2
ALCL	2	1
MZL	5	-

DLBCL (Diffuse Large B Cell Lymphoma), ALCL (Anaplastic Large Cell Lymphoma), MZL (Marginal Zone Lymphoma)

Diffuse large B cell lymphoma is the largest subtype of NHL accounting for 30 – 40 % of all lymphoma[12]. Incidence of DLBCL is markedly high in Pakistan and other countries included in the lymphoma belt as compared to the western studies[4,11]. In these studies DLBCL was also noted to be the predominant phenotype with extranodal involvement[10,11,13]. The higher incidence observed in our study is in accordance with these studies[4,11]. There is no definite explanation but several factors are thought to be the cause of this high incidence including consanguineous marriages resulting in sustained acquisition of the genetic lesions and environmental factors[4]. Marginal zone lymphoma (MZL) was the other common histological subtype observed and all these cases had gastric involvement. Other studies in the region have also reported MZL as the second most common histological subtype after DLBCL presenting as primary extranodal lymphoma[4,10]. Helicobacter pylori infection contributes to the pathogenesis of primary gastric MZL[14]. Several studies have reported high prevalence of H.pylori infection in Pakistan (58%) and despite this high prevalence the number of cases of gastric MZL were not found to be very high in Pakistan[15,16,17]. The other phenotypes presenting with primary extranodal involvement are follicular lymphoma and ALCL whereas these phenotypes were found to be distinctly absent at extranodal site in other studies in Asia[4,13]. As suggested by Yang et al and Baigi et al, geographic variation in molecular expression profiling in follicular lymphomas could be the reason for complete absence of this entity in other studies[13,18].

In terms of site of involvement gastrointestinal tract was the commonest site involved by primary extranodal NHL followed by head and neck, bone. Gastrointestinal tract is reported as the most commonly involved site in primary extranodal NHL in other regional studies whereas head and neck was the predominant site of involvement in studies from China[10,11,13,19]. Primary extranoodal involvement of other sites (bone, lung, muscle, kidney , breast and bone marrow) are observed less frequently[4,13]. Importantly primary CNS lymphoma involvement was not seen in our study although primary CNS involvement is reported to be rising in some studies from India[4].

As noted in the primary extranodal lymphomas, DLBCL was also the most common morphological type observed in secondary extranodal involvement followed by follicular lymphoma and ALCL. In terms of site of involvement bone marrow infiltrates were seen in 11 out of 20 (55%) patients with secondary extranodal involvement. Secondary bone marrow involvement is more common than primary bone involvement as shown by Conlan et al[20], but the frequency observed in our study is quiet high as compared to other studies in the region[4,21].

Extranodal lymphoma are associated with underlying conditions such as immunodeficiency syndrome (HIV/AIDS, organ transplant),

autoimmune disorders, infections like helicobacter pylori, campylobacter jejuni, epstein barr virus (EBV), human T-lymphotropic virus 1 (HTLV- 1), hepatitis C virus (HCV) and this could be the reason for their predilection to affect patients of certain ethnic origins[22,23,24]. However this aspect was not studied by us.

CONCLUSION

To conclude the overall pattern of extranodal involvement especially the high frequency of primary extranodal lymphoma observed in our study is in accordance with other regional studies except that primary CNS involvement was not observed and the frequency of secondary bone marrow involvement was quiet high. The dominance of specific morphological subtypes of NHL (DLBCL), as extranodal lymphoma, and involvement of specific anatomical sites (GIT) needs further investigation to ascertain the relationship of extranodal involvement with different etiological factors. Larger scale and multicenter studies are required for this purpose.

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