Extranodal lymphoma: An Experience from a tertiary care centre in North-east India

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ABSTRACT

Background - Amongst the various definitions, lymphomas are considered as primarily extranodal when, after routine staging procedures, there is either no or only 'minor' nodal involvement along with a clinically 'dominant' extranodal component, to which primary treatment must often be directed. Objective: To explore the prevalence of various sites, subtypes, clinicopathological characteristics, effect of different modality of treatment along with long term outcome of various extranodal lymphomas in our institute, a regional cancer centre of North-east India.

Materials and method: The study was a retrospective analysis of all IHC proven lymphoma cases presented with dominant extranodal component diagnosed between 1st January 2011 to 31st December 2015.

Results: Of 257 total NHL cases 80 were extranodal. The median age at presentation was 56 year with slight male preponderance. The most common sites were found to be head and neck (tonsils > oropharynx > nasopharynx) followed by stomach and orbit. Most common subtypes were DLBCL followed by PTCL and FL.

Conclusion: Its always interesting to know the pattern of disease and the outcomes amongst different population. The present study findings were comparable to most of the studies in India and Asia. Further research regarding etiology, course and pattern of each specific site using population based studies is warranted to achieve conclusive results.

Key words: extra, nodal, survival, north-east, population

Background

In general, primary extranodal lymphomas are considered as lymphoma arising from tissue other than lymph nodes and even from sites which normally do not contain lymphoid tissue. This will be confusing especially in patients where both nodal and extranodal sites are involved as, both nodal and extra nodal lymphomas have the capability to disseminate. Although there is no proper guidelines for the treatment of extranodal lymphoma, literature review says that extranodal lymphomas have got better prognosis and disease free survival.

As of now from the available literature, we considered lymphomas as primarily extranodal when, after routine staging procedures, there is either no or only 'minor' nodal involvement along with a clinically 'dominant' extranodal component, to which primary treatment must often be directed. The reported incidence of Non Hodgkin Lymphoma (NHL) arising from different extranodal site is around 25-40%, but the literature on primary extranodal lymphoma as a separate group is very limited.

With this background a study was undertaken with the objective of exploring the prevalence of various sites, sub entity, clinicopathological characteristics, effect of different modality of treatment along with long term outcome of various extranodal lymphomas in our institute, a regional cancer centre of North-east India.
Materials and method:

The study was a retrospective analysis of all lymphoma cases presented with dominant extranodal component diagnosed between 1st January 2011 to 31st December 2015. All cases were diagnosed on the basis of morphology and immunohistochemistry. The panel of antibodies used for IHC includes pancytokeratin, leukocyte common antigen, CD3, CD4, CD5, CD8, CD19, CD20, CD23, CD10, CD15, CD30, CD99, Bcl2, Bcl6, Tdt, anaplastic lymphoma kinase-1 (ALK-1), cyclinD1, Ki67 and epithelial membrane antigen (EMA). Molecular diagnostic tests were not performed due to lack of facilities. A detailed history of patients characteristics, clinical features, accompanying disease including immune status in few, treatment modalities, clinical course, long term outcomes and its determinants were analysed using Hospital Based Cancer Registry-database at our institute, for the calendar year 2011 and followed up to December 2016. All the patients in the study group had undergone staging computerized tomography (CT) and bone marrow evaluation. For clinical staging Ann-Arbor system was used. An analysis of multiple potential prognostic factors such as age, sex, stage, adjuvant treatment and histology was done. Nodal lymphoma with secondary involvement of extranodal sites, granulocytic sarcoma, histiocytic neoplasms and plasma cell neoplasms were excluded from the study. The tonsil and Waldeyer’s ring (WR) are considered as extranodal, as they have historically been included among the extranodal sites.

Results

Of 257 total NHL cases, 177 cases were nodal and 80 cases were extranodal, which constitute around one third of all NHL cases. After the initial diagnosis, only 47 cases have been found to complete their treatment and followed up till December 2016 as many of them have discontinued the treatment and follow up. So these 47 patients were analysed for various statistical parameters and tests using software SPSS 17. The Kaplan-Meier test was used for calculating survival time, and the differences between the groups were evaluated by log-rank test. Cox regression analysis was used to evaluate Hazard ratio among different groups. Statistical significance was defined as \( P \leq 0.05 \) at 95% Confidence interval.

Age and sex distribution

Age of the patients ranged 8-82 years and the median age at presentation being 56 years. Slight male predominance is seen with male to female ratio of 1.3:1, and the median and mean age were 54 and 51.9 years respectively.

Site of origin

The most common sites of extranodal lymphoma were found to be from head and neck (tonsils > oropharynx > nasopharynx) followed by stomach and orbit. (Table 1)

Histological subtypes

Most cases were found to have DLBCL followed by PTCL and FL. (Table 2)

Clinical (Ann –arbor) staging

Most cases were diagnosed at stage II with B symptoms amongst the 64 cases, evaluated for staging. (Table 3)

Management

Out of 80 patients, 58 have been initiated with the treatment, but 11 discontinued. (Table 4)

Outcome

Of 47 patients with complete followed up till 31st December 2016, 24 died during treatment and just after completion of the treatment. The cause of death were not been able to evaluate. There were 3 relapse amongst 23 survivors. (Table 5)

Discussion

Our 5 year retrospective analysis revealed that around one third of the total NHL were extranodal lymphoma. The occurrence rate is different amongst different regions, in western countries like USA (24%), Canada (27%), Israel (36%), Lebanon (44%), Denmark (37%), Netherlands (1%), Italy (48%), and Hong Kong (29%) ranges from 1%-48% \(^{1,8,9,10}\) while studies from Asian countries like Pakistan \(^{42}\), Kuwait \(^{45}\), Japan \(^{46.6%}\), Korea \(^{55}\%), Thailand \(^{58.7}\%), and China \(^{44.9-61.4}\%\) show a relatively comparable occurrence. \(^{11-15}\) The exact incidence is not known in India as such, but the studies from southern India showed extranodal lymphomas constitute around 22.6% \(^{16,3}\) in contrast to 44% of occurrence in northern part \(^{17}\) and 54.7% in western part. \(^{19}\) Add on to that, our study which is a first ever study from the entire north-east India revealed the occurrence rate of extranodal lymphoma is 31.1%. These variation in frequency in different countries or different parts of the same country may be attributed to variation in genetic or ethnic factors, environmental factor as well as the diverse definition criteria. In our study the mean age at presentation was 56 year with a male to female ratio was 1.3:1, which is comparable to any other Indian studies but is in contrast to the elderly age group of western and other countries. In the present study the most common site of extranodal NHL was head and neck regions (tonsils with oropharynx and nasopharynx) followed by GIT and orbit which was similar to Mishra et al. from south India and Singh et al. from north India, whereas in north-western India, CNS was the most common site for extranodal lymphoma. \(^{18}\)
According to the literature, an increased incidence of extranodal lymphoma has been reported in central nervous system followed by gastrointestinal tract and skin due to the increased prevalence of immunodeficiency state like AIDS, immunosuppressive treatment, viral infections etc. Similar to the available literature, we also found DLBCL as the most common subtypes followed by PTCL and FL. According to the site wise distribution, DLBCL by far the most common lymphoma encountered in the central nervous system, including the eyes, paranasal sinuses, waldeyer ring, bone, heart, adrenals, and testis. It is the most common type of lymphoma encountered in the gastrointestinal tract and the female genital tract and it also occurs in the salivary glands, thyroid, the mediastinum, the orbit, the oral cavity, and other site. Likewise, DLBCL was the most common subtype involving orbit, nasopharynx, tonsil and palate.

In most extranodal sites, marginal zone lymphoma is much more common low grade lymphoma than follicular lymphoma or mantle cell lymphoma while in our study follicular lymphoma was 31% common subtype involving orbit, nasopharynx, tonsil and palate.

Literature revealed DLBCL differs in prognosis depending on its involved sites; waldeyer’s ring and GIT shows favourable prognosis while other sites show poorer outcomes. This difference was related to different natural histories and hence considering them as separate entities by few authors. Therefore further research using population based studies is warranted to achieve conclusive results.

To evaluate the survival benefit amongst different subtypes, we considered DLBCL as one entity against rest of the subtypes as single entity due to the limited number of cases. At the end of 1 year and 5 year of time interval survival rate was 64% Vs 79% and 44% Vs 59% respectively. That means although DLBCL carried worse prognosis initially, at end of long run both types carried almost similar survival benefit.

The Overall 5 year median survival rate estimated by Kaplan Meir method for extra nodal NHL was found as 50 months. The overall 1, 3 and 5 year survival is 68%, 52% and 48% respectively. (Figure 1)The 1, 2 and 5 year survival rate for <=56 years against >56 years was 69% Vs 65%, 66% Vs 46% and 60% Vs 31% respectively. The median survival rate for those who attained 56 years and more is only 18 months. That means the survival rates for extra-nodal NHL vary widely by age with younger people tending to have better outlook than older people. The difference in survival between the groups is not found as statistically significant p=0.165. Again when compared with the effect of radiation therapy over the principle mode of treatment i.e chemotherapy, showed no much benefit with add on radiotherapy.

**Conclusion**

To conclude, we have presented first ever documented study on the clinicopathological features with statistical evaluation of extranodal Non Hodgkins lymphoma involving various sites in North-eastern Indian population. The findings were comparable to published series from other parts of India, in regard to prevalence, age, gender predilection, site and morphologic variants. But of course there are difference do exist from western studies with respect to the median age, common sites and morphologic variants. Being mostly an epidemiological and morphological study, data pertaining to the detail outcome of individual subtypes and site specific outcome were lacking. Though it presented at different sites, with varied clinical presentation and posed a diagnostic dilemma having different differentials morphologically, IHC was of great help in unveiling the correct diagnosis. Further molecular based studies are required to know the different course and outcome of each subtypes and specific sites.

**References**
