Original article:

Extra nodal lymphomas – An Experience in Tertiary Care Hospital

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Abstract

Introduction: Lymphomas are all cancers that affect the lymphocytes. There are many different types and subtypes of lymphoma. The two main categories are Hodgkin's lymphoma, or HL, and Non-Hodgkin's lymphoma, or NHL. Primary extranodal lymphomas (ENL) are much more common in NHL than in Hodgkin's lymphoma. The most frequent site of primary extranodal lymphoma is in the gastrointestinal tract, and almost all of these are NHL. The next most frequent site after the GI tract is the skin. Extra nodal lymphomas can also involve very unusual sites like conjunctiva, lungs, urinary bladder, bones etc.Aim: Aim of the study is to see the response of ENL to regular chemotherapy and monoclonal antibody (Rituximab) and/ or local radiotherapy in some cases.

Methods& Materials: Our study was a retrospective analysis of patient's records (2006-2016) who attended our hospital and received chemotherapy with or withoutRituximab. The local treatment modalities like surgery and radiotherapy was offered to some of the sub-sites.

Results: Patients with primary extranodal NHL received standard chemotherapy and Rituximab. The OS of primary extranodal patients compared to patients with extensive involvement had inferior OS (P<0.001). The DFS of primary extranodal NHL patients was superior to patients those with extensive involvement (P<0.001).

Conclusion: Extra nodal lymphomas are seen in Stomach, Skin, Brain, Breast, Parotid gland , Eye , lungs, urinary bladder, bones etc. Definitely most of the ENLs require local as well as systemic therapy that's where these cases differ from normal lymphoma cases.

Keywords - Lymphoma, Extranodal lymphoma.

Introduction

Lymphomas constitute a group of disorders originating from the malignant transformation of lymphocytes. There are many different types and subtypes of lymphoma. The two main categories are Hodgkin's lymphoma, or HL, and non-Hodgkin's lymphoma, or NHL. The majority of both NHL and HL originate in the lymph nodes and lymphoid organs. It is possible, however, for lymphomas to arise almost anywhere. When lymphoma is believed to have originated outside the lymph nodes and lymphoid organs, it's called extranodal lymphoma, or more precisely, primary extranodal lymphoma. At times, it can be difficult to point out where in the body a lymphoma began. In these cases, it is required to follow a more approximate definition: If the lymphoma at one time had its major tumor mass, its most obvious bulk, in an extranodal site, then it may be considered an extranodal lymphoma. The definition of extranodal lymphoma, particularly in the presence of both nodal and extranodal disease, remains a controversial issue. Different criteria have been proposed by various authors in the past, to categorize these entities[1-2]. As per Dawson

criteria, lymphoma is said to be primarily extranodal if 1) absence of palpable superficial lymph nodes on first physical examination; 2) absence of mediastinal lymphadenopathy detected on plain Chest X-ray; 3) dominant lesion at extranodal sites; 4) involvement of lymph nodes in the vicinity of the primary lesion; and 5) white blood cell (WBC) count within normal range. Primary extranodal lymphomas (ENL) are much more common in NHL than in Hodgkin's lymphoma. Up to 33 percent of all NHL is considered primary extranodal lymphoma, while in HL, primary extranodal disease is thought rare. Extra nodal NHLs 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 sinses/nasopharynx, salivary glands, etc.), skin, central nervous system (CNS), bone, testis, thyroid, breast, orbit, and rarely adrenal, pancreas, and the genitourinary tract[3].The most frequent site of primary extranodal lymphoma is in thegastrointestinal tract, and almost all of these are NHL. The next most frequent site after the GI tract is the skin.

There are great differences in the incidence of extranodal lymphomas among countries: USA 24%, Canada 27%, Israel 36%, Lebanon 44%, Denmark 37%, the Netherlands 41%, Italy 48%, and Hong Kong 29%[4]. There is difference in incidence with in India ranging from 22-44% seen in different studies from different regions[5].The outcome can be different in the disparate specific sites of primary extranodal lymphomas. This is partially due to differences in natural history, but mainly to differences in management strategy which are related to organ-specific problems.

Testis and thyroid lymphomas are more often seen in elderly patients, while a significantly higher incidence of hepatic and intestinal lymphomas is related to younger age. Salivary gland and thyroid lymphomas are significantly more common in females, while intestinal and pulmonary lymphomas are more often found in males. NHL of the stomach, salivary glands and thyroid are more frequently localised, whereas extranodal lymphomas of the lungs, liver, bones and testes are often widespread. With respect to histological classification, aggressive subtypes (usually diffuse large B-cell lymphomas) are predominant in NHL of CNS, testes, bone, liver, and to some extent the stomach. Certain extranodal sites have characteristic patterns of either B-cell (e.g. gastric marginal zone lymphoma, MALT type) or T-cell disease (e.g., cutaneous lymphoma clearly comprises a wide range of lymphomas of T-cell origin, even though a subset of B-cell cutaneous lymphomas does exist).

Aims and Objectives: Aim of the study is to see the prevalence of ENL in tertiary care hospital Visakhapatnam and also measure the response of ENL to regular chemotherapy and monoclonal antibody (Rituximab).

Materials and Methods

We have done retrospective analysis of patient's records from year 2006 to 2016 with diagnosis of lymphoma. We have includedonly the patients withHisto-pathological confirmation report (Fig1). These patient records were further studied with various subsites that are involved with ENL.These patients had other confirmatory test like immuno-histochemistrywith CD45, CD20, CD3, CD5, CD30andCD15 (Fig 2,3). CTscan of chest, abdomen ,bone marrow aspiration and biopsy were thediagnostic procedures for staging of the disease. Patients were informed about the nature of disease and stage. Chemotherapy was initiated after obtaining the consent. These patients were given the standard regimens include CHOP and RCHOP in patients with NHL and ABVD in patients with

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HD. The local treatment methods like surgery and radiotherapy was also offered to some of the sub-sites.

Observations and Results

Staging results of all 76 patients included in the database are presented in Table 1. Patients who presented with extranodal NHL had localisations in a wide variety of organs; the digestive tract and bone marrow were the sites most frequently involved (Table 2). The involvement of extranodal sites revealed by staging investigations is also presented in Table 1. The REAL classification of all lymphomas, also subdivided primary extranodal or extensive involvement, is presented in Table 3. Patients with primary extranodal NHL received regional treatment in the form of Surgery or Radiotherapy. The OS of primary extranodal patients defined that patients with extensive involvement had inferior OS ($P < 0.001$) .

Discussion

The definition of primary extranodal NHL is a controversial issue. In the Ann Arbor classification[4], no distinction is made between primary nodal and primary extranodal lymphomas, clearly because primary extranodal involvement is extremely rare in patients with Hodgkin's disease, for whom this classification was originally designed. The limited validity of the Ann Arbor classification for NHL patients, as established by Rosenberg[6], and the observation by Musshoff and others that primary extranodal NHL constitutes a separate clinical entity with a relatively favourable prognosis was reason to propose a modification of the Ann Arbor classification to be used for NHL[7], in which primary nodal and extranodal NHL were classified separately. However, this proposal has never been widely accepted.

Following review of the literature it can be concluded that some authors use strict criteria to define primary extranodal NHL, whereas others use a more liberal definition. Strict criteria were proposed in 1961 by Dawson[8], reporting on a series of primary intestinal lymphomas. Patients were only included in this study if no palpable superficial lymphadenopathy was found at first examination, chest X-ray showed no obvious enlargement of mediastinal lymph nodes and the white blood cell counts were within normal limits.

Other investigators used more liberal criteria in their reports on primary extranodal lymphomas. Lewin et al[9], describing a series of gastrointestinal tract lymphomas treated at Stanford University Medical Centre, included gastrointestinal lymphoma patients who presented with gastrointestinal symptoms, and also those who appeared to have disseminated disease upon staging.The favourable response rate and OS found for extranodal NHL patients defined in this strict way is, as we showed, the result of selection.

An interesting finding in our study was the superior DFS found for patients with primary extranodal NHL. It is possible that differences in biological behaviour of NHL originating in nodal and certain extranodal sites account for this observed difference in DFS. Patients with lymphomas originating in the gut-associated lymphatic tissue (GALT) were found to have a significantly lower distant relapse rate than patients with nodal lymphomas and patients with extranodal lymphomas from other sites than the GALT.

ENL BONE:

Primary non-Hodgkin lymphoma of bone (PLB) presents as solitary or multiple, destructive bone lesions. Primary lymphoma of bone (PLB) is a rare disease that accounts for less than 2 percent of all lymphomas in adults [7]. It is estimated that PLB accounts for 3 to 7 percent of primary bone tumors [8, 9] and 3 to 5 percent of all extranodal non-Hodgkin lymphomas[10]. Men are diagnosed slightly more frequently than women with a male:

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female ratio ranging from 1.2 to 1.8 [11-14]. The vast majority of patients present over the age of 30 years (92 percent) with the largest cohort consisting of those over age 60 (56 percent)[11,13]. The majority of patients present with bone pain not relieved by rest. A palpable mass due to soft tissue extension of the bony disease is seen[12](Fig4) Swelling, pathologic fracture, cord compression and systemic "B" symptoms (i.e., fever, weight loss, night sweats) may also be present at the time of diagnosis [14]. Even today the diagnosis of PLB can be difficult due to the relatively non-specific radiographic appearance and the sometimes profound proliferation of reactive fibroblasts at the histological level[15]. Several studies suggest that the combination of chemotherapy and radiotherapy is the best treatment, as a consequence of which resection or amputation can be prevented[7,16]. PLB patients seem to have a better survival than other NHL patients (Fig 5).

ENL HEAD AND NECK:

Tonsil was the most common site in the head and neck region. Pharyngeal lymphomas often present in Waldeyer's ring. The most common presentation is tonsillar DLBCL [17].It is usually unilateral and may involve ipsilateral regional lymph nodes (stage II). The lymphoid tissues of Waldeyer'sring have many immune pathologic characteristics of mucosa-associated lymphoid tissue (MALT), but interestingly, MALT lymphoma is not common in thissite.

The standard treatment for indolent localized lymphomas is ISRT. As far as Lymphomas of the Nasal Cavity and Paranasal Sinuses are concerned, extranodal NK/T-cell lymphomas of the nasal type are common in certain parts of the world, notably eastern Asia and South America. In Western countries, when this location is involved, DLBCL is the most common histology and the standard treatment is rituximab, cyclophosphamide, hydroxydaunomycin,oncovin (vincristine), and prednisone (R-CHOP) with additional therapy for CNS prophylaxis for some cases, followed by RT[18].

ENL ORBIT and Orbital Adnexa:

Lymphomas of the Orbital and ocular Adnexa are heterogeneous group of malignancies, accounting for approximately 1% to 2% of NonHodgkin lymphomas (NHLs) and 8% of extranodal lymphoma[19](Fig6). The majority of orbital and ocular adnexal lymphomas (OALs) are primary extranodal neoplasms; however, 10% to 32% are secondary tumors in patients with disseminated lymphoma[20] More than 95% are of B-cell origin, and 80% are low-grade lymphomas. The most common subtype of primary orbital and OALs (accounting for 35% to 80% of cases) areextranodular marginal zone lymphoma (ENMZL) of mucosa-associated lymphoid tissue (MALT) type, followed by follicular lymphoma (20%), diffuse large B-cell lymphoma (8%), and less commonly mantle cell lymphoma, small lymphocytic lymphoma, and lymphoplasmacytic lymphoma[20]. Few cases of primary T-cell lymphoma and Hodgkin lymphoma of the ocular adnexa have been reported[21].OAMLs are mostly seen in the 5th to 7th decade of life (median age, 65 years), with female predominance (male/female 1:1.5/ 2). Most frequent site of origin is the orbit (40%), followed by conjunctiva (35%-40%), lacrimal gland (10%-15%), and eyelid (10%). Majority (85%-90%) of patients with OAML present with localized disease (stage I)(Fig7) Nodal involvement is reported in approximately 5% of patients. In various case series, 10% to 15% of patients have disseminated disease (stage IV) at initial presentation, including bone marrow involvement in approximately 5%. Numerous reports confirm the efficacy of conventional treatment strategies such as surgery, radiotherapy

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or chemotherapy, alone or in combination, with no significant survival difference[22]. Surgery as the only treatment modality should not be administered, because there is obviously a high likelihood of local relapse after surgery according to previous reports[23]. The difficulty of complete resection with preservation of function in the orbit may explain the high relapse rate. Radiation therapy as the initial treatment has been reported to be very effective in MALT lymphoma of the orbit[24](Fig8) Radiotherapy with a dose range of 25 to 35 Gy seems to be a standard approach because it provides local control and cure for localized orbital lymphoma[24]. Current National Cancer Center Network guidelines recommend radiotherapy of 20 to 30 Gy for initial treatment of earlystagenon-gastric ENMZL of all sites and reirradiation for locally recurrent disease.

ENL SKIN:

Primary cutaneous lymphomas can be defined as the presence of cutaneous localisations alone, with no nodal or systemic disease. They represent a very peculiar group of extranodal lymphomas, accounting for approximately 10% of cases.Moreover, the skin is a relatively common site of dissemination of many nodal NHLs, especially those of T-cell phenotype. However, the clinical behaviour of primary cutaneous lymphomas is usually different from that of primary nodal lymphomas of similar histology involving the skin secondarily. It is difficult to define properly the primary cutaneous lymphoma on morphologic grounds alone: several types of primary lymphoma of the skin classified as high grade according to the Kiel classification or the Working Formulation very often show an indolent clinical behaviour. Therefore, only a combination of histologic, immunologic and clinical data can adequately define the primary cutaneous lymphoma entities. On this basis, a new classification scheme has recently been proposed by the EORTC cutaneous lymphoma study group[25].

Lymphomas of the skin are more often of T-cell type, with mycosis fungoides and Sezary syndrome constituting around 65% of the cases. The other types of primary cutaneous T-cell lymphomas (CTCL) are less frequent and may be further characterised according to the specific expression of cell surface antigens such as CD30. They differ from mycosis fungoides in that the epidermotropism is usually absent (i.e.,the neoplastic T-cells usually infiltrate the dermis and subcutaneous tissue but not the epidermis[25](Fig:9,10)

Classification of primary cutaneous B-cell lymphomas is particularly controversial[4]. The subtypes, follicle-centre lymphoma of the head and trunk and immunocytoma of the EORTC classification, constitute over 90% of primary cutaneous B-cell lymphomas[25]. This group includes a large percentage of diffuse large-cell lymphomas which, in the scalp and in the trunk, despite their cytologically and histologically aggressive features, spread only very rarely beyond the skin and have a clinically indolent course. More aggressive is the clinical course of primary cutaneous large B-cell lymphoma of the leg. Moreover, cutaneous follicle-centre lymphoma appears to be distinctly different from the nodal counterpart both immunophenotypically and genotypically, lacking the chromosomal translocation t(14;18) and the expression of the common leukocyte antigen (CD 10). Extranodal marginal zone lymphomas (MALT type) of the skin have been described and the cutaneous immunocytoma may also be interpreted as a low-grade B-cell lymphoma of MALT type[4,25]. Since skin-associated lymphoid tissue (SALT) is usually devoid of B-cells, in analogy to the MALT concept in the stomach, an acquired SALT could represent

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the background for the development of the lymphoma[26]. Furthermore, the association of cutaneous B-cell lymphoma with acrodermatitischronicatrophicans suggests that Borreliaburgdorferimight have a role similar to that of H.pylori in the stomach[27].Other rare ENLs that we treated are Hodgkins lymphoma of Spine and Lung(13,14) and NHL Urinary Bladder. The treatment consisted of chemotherapy and or Radiotherapy.

CONCLUSION:

Primary extranodal lymphomas constitute a diverse group ofhematolymphoid malignancies. The incidence of ENL is lowin India compared to data from other parts of the world. Thediagnosis is a frequent challenge to the pathologists, due totheir morphological mimics, and varied clinical presentations. Therefore, the possibility of ENL should be kept in mind eventhough it arises in an extranodal site. Extra nodal lymphomas can affect very unusual sites like conjunctiva, lungs(11,12), urinary bladder, bones etc. As most of the patients express CD20, Rituximab is very effective in controlling disease and also for maintenance in some cases. Definitely most of the ENLs require local as well as systemic therapy that's where these cases differ from normal lymphoma cases.

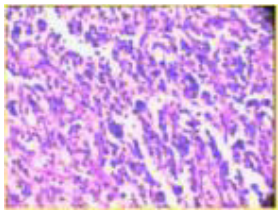

Figure 1: Histopathology picture

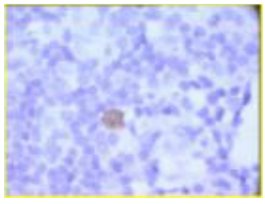

Figure 2: LCA Staining

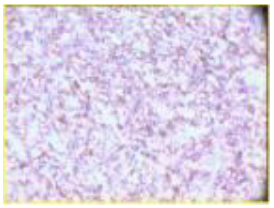

Figure 3: CD 30 Staining

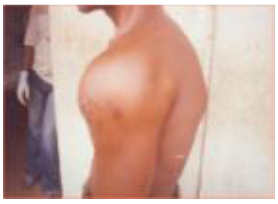

Figure 4: A case of primary ENL of bone with right region of left head of humerus

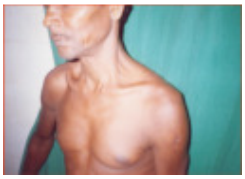

Figure 5: Response after treatment

Figure 6: A case of primary ENL of ocular Adnexa

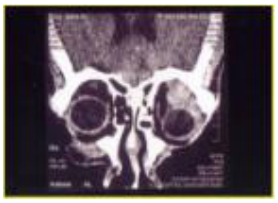

Figure 7: CT Scan showing primary ENL of Ocular Adnexa

Figure 8: Post treatment response

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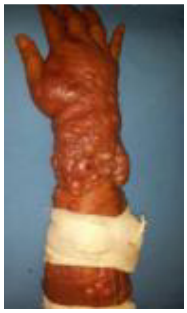

Figure 9: A case of skin ENL of right upper limb

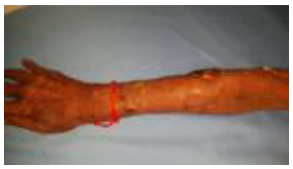

Figure 10: Post treatment response of skin ENL of right upper limb

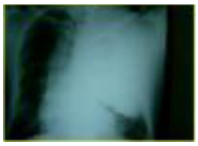

Figure 11: Case of primary ENL (NHL) of left lung

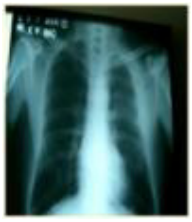

Figure 12: Post treatment of left lung

Table 1: Patient characteristics (*n*=76) extra-nodal lymphoma

Female Gender	12
Age>60 Years	16
Performance (KI) <80%	12
LDH greater than normal	39
Ann Arbor stage III+IV	11
> 1 EN localizations	4

KI- Karnofsky Index; EN- Extra-Nodal, LDH-Lactate dehydrogenase

Table 2: Involved sites for all patients

Presenting site	**No of Patients (*n*)**
Salivary glands	6
Oral cavity	2
Stomach	8
Small Intestine	4
Colon	4
Lung	3
Pleura	1
Bone	4
Soft tissue	4

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Skin	13
Female Breast	4
Testis	5
Urinary bladder	1
Eye and lacrimal gland	4
Brain	6
Spinal cord	4
Thyroid gland	3

Table 3: Histological classification

B-cell chronic lymphocytic leukemia/lymphoma	4
Lymphoplasmacytoid	2
Follicular center lymphoma, follicular grade 1-2	3
Follicular center lymphoma, follicular grade 3	1
Follicular center lymphoma, diffuse, small cell	2
Marginal zone extra-nodal (Malt- low grade)	8
Mantle cell lymphoma	2
Diffuse large B-cell lymphoma	48
Anaplastic large T-cell	6

REAL- Real European-American Lymphoma Classification

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