Primary Extra Nodal Non Hodgkin Lymphoma: A 5 Year Retrospective Analysis

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Abstract

Background and Aim: The incidence of extra nodal non Hodgkin lymphoma (ENL) is rising throughout the world. However, data regarding ENL as a group is limited. The aim was to study the epidemiological and histomorphological trends of primary ENL (pENL) in India. Material and Methods: The biopsy materials from sixty eight patients with pENL (45 male, 23 female, M:F= 1.9:1), diagnosed over a five year period (2005-2009), were analysed and pathologically reclassified according to the World Health Organization (WHO) classification, 2008 criteria. Results: Primary extra nodal non Hodgkin lymphomas constituted 22.0% (68/308) of all non Hodgkin lymphomas (NHL). The mean age at presentation for pENL and primary nodal NHL was 43 years and 58 years, respectively with a male predilection (M: F=2:1). Central nervous system (CNS) constituted the most common extranodal site (20/68, 29.5%) followed by gastrointestinal tract (17/68, 25%), and nose/nasopharynx (8/68, 11.8%). Diffuse large B-cell lymphoma (DLBCL, not otherwise specified), extranodal marginal lymphoma of mucosa associated lymphoid tissue (MALT) type, and B cell NHL unclassified (U) were the three most common histological types observed. T-cell phenotype was rarely noted (4%). Follicular lymphomas and anaplastic large cell lymphoma, seen among nodal NHL, were absent at extra nodal sites. Majority (41/68, 60%) of the patients with pENL were immunocompetent and 55% were in stage I-II with favorable prognosis. Conclusion: Central nervous system was the most common site of ENL, followed by gastrointestinal tract. Majority of pENL occurred in immunocompetent hosts with a favorable prognosis.

Keywords: Central nervous system - primary extra nodal lymphoma - immunocompetent

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Introduction

A substantial percentage of non-Hodgkin’s lymphomas (NHL) arise from tissues other than lymph nodes and even from sites which normally contain no lymphoid tissue. These forms are referred to as primary extranodal lymphomas (pENL). At least one-fourth of the lymphomas are probably of extranodal origin (Isaacson, 1994; Zucca et al., 1997; Zucca et al., 1999; Ferry, 2008).

Lymphomas arising primarily in extranodal sites (pENL) can be diagnostically challenging due to their morphological diversities and lack of uniformity in histopathological classification system. For many pENL, there are distinctive clinicopathological features, sometimes associated with an underlying immunodeficiency syndrome (HIV/AIDS, organ transplant), autoimmune disorders [Sjögren syndrome, systemic lupus erythematosus (SLE), scleroderma, inflammatory bowel disease (IBD), dermatomyositis, Hashimoto thyroiditis, rheumatoid arthritis], infection [Helicobacter pylori, Campylobacter jejuni, Borelia burgdorferi, Chlamydia psittaci, Epstein Barr virus (EBV), Human T-lymphotropic virus1 (HTLV-1), Human herpes virus 8 (HHV-8), and Hepatitis C virus (HCV)] or a predilection to affect patients of certain ethnic origin (Bernatsky et al., 2006; Engels 2007; Ferry, 2008). HCV is considered as a virus with triple tissue tropism (hepatotropism, lymphotropism, and sialotropism) and this may explain the higher prevalence of sicca syndrome, cryoglobulinemia, and lymphoproliferative disorder (MALT lymphoma) in patients with chronic HCV infection (Ramos-Casals and Munoz, 2008).

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 sines/nasopharynx, salivary glands, etc.), skin, central nervous system (CNS), bone, testis, thyroid, breast, orbit, and rarely adrenal, pancreas, and the genitourinary tract (Singh et al., 2003;
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 (Dawson et al., 1961; Krol et al., 2003). 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.

It has been observed that during the last two decades the incidence of NHL has increased, and that of pENL increased more rapidly than the nodal type (Jemal et al., 2004). This trend is seen particularly in developing countries, more so in Middle East and Far East, with an increase in diffuse histological pattern over nodular, and more aggressive than indolent behaviour (Yang et al., 2008; 2011; Yaqo et al., 2011). The most dramatic change in trend, in last two decades, has been observed for primary CNS lymphoma (PCNL) which has increased four times as rapidly as other extranodal sites. This is partly due to AIDS pandemic, as well as improved diagnostic modalities, and it continues to rise in immunocompetent hosts of all ages and in both genders as well (Sarkar et al., 2005; Paul et al., 2008; Mahdood et al., 2011).

Although numerous papers dealing with pENL originating in almost every organ in the body have been published, the literature on pENL as a group is limited. Therefore, the present retrospective study, from a single institute in South India, aims to bring about the various aspects of pENL, from epidemiology to morphology, with a brief review of literature.

**Materials and Methods**

Included in the study were all newly diagnosed patients of NHL (n=308) from January 2005 to December 2009 at our hospital. Paraffin embedded Haematoxylin and eosin (H and E) stained tissue sections were analysed by a group of histopathologist to reach at a morphological diagnosis. Immunohistochemical (IHC) analyses were performed manually on the paraffin embedded tissue sections by using a panel of monoclonal antibodies (Peroxidase-antiperoxidase method). Antigen retrieval was done by pre-treatment of paraffin sections by heating in a Pascal pressure cooker in 0.01 M citrate buffer (pH 6.0). The panel of antibodies used for IHC, based upon morphological analyses and anatomic sites, included pan cytokeratin (prediluted, PD), leukocyte common antigen (LCA, 1:75), CD3 (PD), CD20 (PD), CD5 (1:20), CD15 (PD), CD30 (PD), CD99 (PD), Bcl2 (1:200), anaplastic large cell lymphoma kinase-1 (ALK, PD), Cyclin D1(1:20), epithelial membrane antigen (EMA, 1:75), neuron specific enolase (NSE, 1:200), glial fibrillary acidic protein (GFAP, 1:150); all from Biogenex, and terminal deoxytransferase (TdT, PD, DAKO).

All cases were reviewed by minimum of two pathologists and reclassified based upon morphologic and immunophenotypic criteria according to World Health Organization 2008 classification (Swerdlow et al., 2008). Advanced diagnostic techniques such as cytogenetics/fluorescence in-situ hybridisation (FISH) were not performed in any of the cases due to lack of facilities and financial constraints.

Data pertaining to patients’ demography, ethnicity, occupation, clinical presentation, prior drug history, immune status, routine complete blood count (CBC), microbiological (HIV, HCV, and Hepatitis B) status and biochemical parameters [serum total protein, serum albumin, lactate dehydrogenase (LDH), serum urea, creatinin, uric acid, bilirubin and liver enzymes] were obtained from the medical records. Clinical stage was defined according to the Ann Arbor classification (Carbone et al., 1971). Involvement of lymph nodes and Waldeyer’s ring were defined as nodal localisations, and the involvement of other organs was defined as extranodal (Zucca et al., 1997). Patients were considered to be completely staged when adequate information was available on history, status of peripheral lymph nodes (physical examination), Waldeyer’s ring (examination by an ENT specialist), mediastinal lymph nodes (chest X-ray), abdominal lymph nodes, liver and spleen [abdominal Computerized Tomogram (CT) scan] as well on peripheral blood and bone marrow (aspiration and trephine biopsy). The International Prognostic Index (IPI) was calculated according to the description by the International Non-Hodgkin’s Prognostic Factors Project for patients with all required parameters present. Strict criteria proposed by Dawson et al were used to categorize the lymphoma as primary extranodal. Primary nodal NHL with secondary extranodal involvement and plasmacytomas were also excluded from the study. The clinico pathological profiles and pathology of pENL were compared with primary nodal NHL studied during the same study period (2005-2009).

All lymphomas, except PCNL, were managed with surgery and six cycles of chemotherapy [Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone (CHOP) +/- Rituximab (R)], with or without radiotherapy. Primary CNS lymphomas were managed with stereotactic biopsy and Methotrexate based chemotherapy, steroids, with or without radiotherapy.

**Results**

Primary extranodal NHL constituted 22% (68/308) of all NHL studied during this period. These included 45 males and 23 females (M: F=2:1) and peak incidence was during the 4th to 5th decade of life (age range 6-75 years, mean 43 years) (Figure 1a). Majority of patients (41/68, 60%) had no detectable underlying co-morbidities, whereas autoimmune disorders such as rheumatoid arthritis, Sjogren syndrome, and psoriasis, were present in 6%, 4% and 3% of patients respectively. Ten percent (10%) of gastric MALT (mucosa associated lymphoid tissue) lymphomas had a prior history of *H. pylori*.
associated gastritis detected in gastric biopsies on routine Giemsa staining. Seropositivity for HIV was present in 4% (3/68) of patients whereas association with HBV and HCV were seen in 2% of patients each. Nine percent of the patients were diabetic (type 2) (Figure 1b).

Central nervous system constituted the most common site of pENL (20/68, 29.5%), followed by gastrointestinal tract (17/68, 25%) (10 stomach, 2 duodenum/jejunum, and 5 colon), nose/nasopharynx (8/68, 11.8%), parotid, maxilla [4 patients (6%) each], and skin (3/68, 4.5%). Long bones (femur), oral cavity, testis, spleen (2 patients each), lacrimal gland, vulva, kidney, and pleural cavity (1 patient each) were the rare anatomic sites of pENLs observed (Figure 2).

On IHC, 65/68 (96%) of pENL had B immunophenotype whereas T cell phenotype was observed in only 3 patients (4%). Diffuse large B-cell lymphoma, not otherwise specified (DLBCL) was the most common histological type observed in 69% (47/68), followed by extranodal marginal zone lymphoma of MALT type (9/68, 13.2%). B-NHL unclassifiable (U) (morphologically in between DLBCL and Burkitt lymphoma), peripheral T cell lymphoma, not otherwise specified (PTL-NOS) were seen in 5 and 2 patents respectively whereas T-cell rich B-cell lymphoma, mycosis fungoides (MF), and AIDS associated primary effusion lymphoma (PEL) involving pleural cavity were observed in one patient each (Figures 3a-c, 4a-c, 5).

Thirty-seven of 68 (54.5%) patients were in stage I/II, 23/68 (34%) in stage III, whereas 8/68 (12%) were in stage IV. On follow-up (30/68, duration 3 months to 5 years), 16 had complete remission, 6 had progressive disease (4 lost to subsequent follow-up), 3 with relapse with high grade morphology with increased proliferation index, and 5 died due to complication of chemo radiotherapy.

Figure 1. a) Age and Sex Distribution in Primary Extranodal Non-Hodgkin Lymphomas (n=68), b) Immunological Status, Co-Morbid Illness, Infection Associated with Primary Extranodal Non-Hodgkin Lymphomas (n=68)

Figure 2. Anatomic Distributions in Primary Extranodal Non-Hodgkin Lymphomas (n=68)

Figure 3. Primary Diffuse Large B Cell Lymphoma of Brain. (a) showing diffuse sheets of medium to large lymphoid cells infiltrating the brain parenchyma (Haematoxylin eosin, 200X), These cells showed prominent angiocentricity, better demonstrated by silver reticulin stain, (b) (Gomori Methenamine Silver, 400X). The tumor cells showed intense membranous positivity for CD20 and negativity for Glial Fibrillary Acidic Protein (GFAP), (c) (Peroxidase-antiperoxidase, 200X)

Figure 4. Coronal Post Contrast Computerized Tomogram Image. a) showing a homogenously enhancing soft tissue mass involving the right lacrimal gland in an elderly male causing inferomedial displacement of right eye. Low (b, 200X) and high (c, 400X) power photomicrograph of the mass lesion showed centrocyte like cells infiltrating glandular epithelial cells (lymphoepithelial lesion) (thick arrow) (Haematoxylin eosin). The immunohistochemical characteristics were that of a low grade marginal zone lymphoma of MALT type

Figure 5. Primary Splenic DLBCL Presenting as a Multiple, Large, Fleshy, Greyish White, Nodular Masses
Table 1. Comparison between Present Series of Primary Extranodal non Hodgkin Lymphoma with Published Series in Regard to Epidemiology, Pathology, and Biologic Behaviour

| Author, Year, Place | NHLs (n) | Study period (Years) | Anatomic sites | Histopathology | Remark/risk factor |
|---------------------|----------|----------------------|----------------|----------------|--------------------|
| Yang et al., 2011, China | 5549 | 9 | 2968 (53.5) | WR, GIT, NPNS Skin | DLBCL, MALT | High frequency of ENKTL of nasal type, EBV, pesticides, chemical solvents |
| Yaqo et al., 2011, Iraq | 205 | 7 | 99 (48.3) | Intestine WR, Nose Stomach Skin | DLBCL, MALT | Pediatric age group |
| Yun et al., 2010, Korea | 48 | 11 | 48 (100) | Adrenal, Ovary, Esophagus, Prostate Pancreas, Uterus | DLBCL (MC) | Bad prognosis |
| Chen et al., 2010, Taiwan | 278 | 12 | 125 (45) | GIT (MC) | DLBCL (MC) PTCL (10.6%) | Worse prognosis for ENL |
| Nagi et al., 2010, Pak & KSA | 5 | 147 | GIT, NPNS Salivary gland-Bone | Liver, Lungs, Cervix, Bronchous CNS | DLBCL, MALT FL, BL | Male:Female=1:1 |
| Fujita et al., 2009, Japan | 847 | 7 | 395 (46.6) | GIT WR Orbit | Bone, Thyroid, Skin, Prostate, Testis, CNS, Breast, Uterus | DLBCL, MALT FL, BL | HTLV-1 non endemic zone |
| Lal et al., 2008, Pakistan | 557 | 16 | 235 (42) | GIT Aerodigestive | Bone, Breast Testis, CNS Skin | All cases DLBCL | ENL at early stage, favorable |
| Temmim et al., 2004, Kuwait | 16 | 106 (41) | Stomach, Skin-adults Intestine-Pedicatric | DLBCL-Adults BL-Pediatric | Adult: Favorable, Pediatric-Bad |
| Singh et al., 2003, India | 241 | 3 | 106 (44) | Head and neck (tonsil) GIT (stomach) | Brain, Skin Bone, Testis, UB | Diffuse large cell lymphoma (Intermediate grade) (Working formulation) | Poor oro-dental hygiene, tobacco chewing |
| Present study, 2012, South India | 308 | 5 | 68 (22) | Brain GIT NPNS | Bone, Testes Spleen, vulva, Lacrimal gland, Kidney | DLBCL, MALT B-NHL (U), IPSID, PEL, MF | Immunocompetent, early stage |

*NHLS: non Hodgkin lymphoma, ENL: extra nodal non Hodgkin lymphoma, n: number of patients studied, WR: Waldeyer’s ring, GIT: gastrointestinal tract including stomach, small and large intestine, NPNS: nose, nasopharynx, and paranasal sinus, CNS: central nervous system including brain and spinal cord, MC: most common, UB: urinary bladder, DLBCL: diffuse large B cell lymphoma, FL: follicular lymphoma, SLL: small lymphocytic lymphoma, ENKTL: extranodal natural killer/T cell lymphoma of nasal type, MALT: extranodal marginal zone lymphoma of mucosa associated lymphoid tissue type, PTCL: peripheral T cell lymphoma, BL: Burkitt lymphoma, ATLL: adult T cell lymphoma/leukemia, B-NHL: B cell non Hodgkin lymphoma morphologically intermediate between Burkitt lymphoma and DLBCL, IPSID: Immunoproliferative small intestinal disease, PEL: primary effusion lymphoma involving pleural cavity, MF: mycosis fungoides, EBV: Epstein Barr virus, HTLV: Human T-lymphotropic virus1, CT: chemotherapy, RT: radiotherapy, Pak & KSA: Pakistan and Kingdom of Saudi Arabia

**Discussion**

Extra nodal non Hodgkin lymphoma (ENL) is a heterogeneous disease in regard to geographical, ethnic, anatomic, etiological, and morphological diversities (Anderson et al., 1998). The frequency of extranodal NHL varies in different parts of the world. In countries where total lymphoma incidence is high the incidence of lymphomas at each extranodal site also tends to be high (Newton et al., 1997). Studies from Western countries have reported the occurrence of extranodal NHL as 24-48% of all NHLs (Morton et al., 2006). A previous pioneer study from North India has shown the incidence to be 44% (106 of 241 cases of NHLs over a 3 year period) (Singh et al., 2003). However, the incidence of ENL has been shown to be very high in neighbouring Pakistan and Saudi Arabia (up to 50%) (Nagi et al., 2011), Kuwait (45%) (Temmim et al., 2004), Northern Iraq (48.3%) (Yaqo et al., 2011, Taiwan) (47.2%) (Chen et al., 2010), Japan (46.6%) (Fujita et al., 2009), Korea (55%) (Yoon et al., 2010), Thailand (58.7%), and China (44.9%-61.4%) (Yang et al., 2011). Compared to these epidemiological data, the incidence in our series is relatively low (22%). This may be explained by i) overall less number of NHL during the study period (308 in 5 years); ii) strict inclusion criteria, and iii) small duration of study period. Tonsil and Waldeyer’s ring, sites historically considered as extranodal despite histological similarity with that of peripheral lymph node, were excluded from our series.

In the present study, compared to patients with primary nodal NHL (during the same study period, n=240), patients with pENL were younger (mean: 58 years vs. 43 years, respectively) with lesser B symptoms [133/240 (55%) vs 29/68 (43%), respectively] though the gender predilection was similar (2.8:1 vs 2:1, respectively). Majority of patients in both groups were immunocompetent (44% vs. 60%, respectively). Therefore, it can be postulated that host genetic makeup, lifestyle, environmental factors; rather than infections and immunological dysregulation might have some pathogenetic role in these malignancies.

In accordance with the literature, DLBCL was the most common histological subtype observed, both at nodal and
extra nodal sites. DLBCL, follicular lymphoma, anaplastic large cell lymphoma (ALCL; ALK positive), and nodal marginal zone lymphoma were the four most common phenotype at nodal site; whereas DLBCL, extranodal marginal zone lymphoma of MALT type, B-NHL (U) (morphologically between Burkitt and DLBCL), and MF/PTL-NOS were most common at extranodal sites. Follicular lymphoma and ALCL were distinctly absent at extranodal site. As suggested by Biagi and Seymour (2002); and Yang et al. (2011), geographic variation in molecular expression profiling in follicular lymphomas as well as between nodal and extra nodal sites may be the possible explanations for complete absence of this entity in our series. Furthermore, high grade transformation of pre-existent low grade MALT or follicular lymphoma into DLBCL at extra nodal sites might also be another explanation for this observation.

A comparative review of literature of ENLs in regard to epidemiology, clinicopathological features, and biologic behaviour is presented in Table 1. Gastrointestinal tract is reported to be the most common site of involvement in extra nodal lymphomas and its incidence is rising throughout the world (Arora et al., 2011). But, head and neck region including Waldeyer’s ring, nose and paranasal sinuses, have been reported to be the most common sites of origin of pENL in various studies from different parts of China (Yang et al., 2011), India (Singh et al., 2003), Japan (Fujita et al., 2009), Taiwan (Chen et al., 2010). It was reported to be the second most common site among Iraqis (Yaqo et al., 2011). Epstein Barr Virus, agricultural pesticides, environmental pollutants (Chen et al., 2011), poor oro-dental hygiene/toothbacco chewing (Sing et al., 2003), more predilection of NK/T cell lymphoma phenotypes for head and neck region (Vose et al., 2008; Ko et al., 2009) were reported to be the possible explanation for this difference. Besides this, compared to the western and Middle East countries, low incidence of DLBCL among Asians and high incidence of NK/T cell lymphomas at head neck region possibly explains these diversities (Yaqo et al., 2011).

One of the most striking outcomes of the present study was the central nervous system forming the most common extra nodal site of pENL (20/68, 29.5%), surpassing GIT (17/68, 25%). Primary central nervous system lymphoma (PCNL) is defined as lymphoma arising in and confined to the cranial-spinal axis (brain, eye, leptomeninges and spinal cord). Formerly a rare tumour, PCNL has shown increased incidence both in immunocompromised (congenital, acquired or iatrogenic) high-risk groups and in the general population (Zucca et al., 1997). Various multi institutional studies from India in recent past, have addressed the changing trends of PCNL in regard to incidence, risk factors, and pathophysiology (Sarkar et al., 2005; Paul et al., 2008; Mahdhoomi et al., 2011). Compared to western data, the incidence of PCNL in India, in last decade, has been fairly constant, and is unrelated to HIV or other immunodeficiency states. As pointed out by Paul et al. (2008), occurrence of PCNL in an immunologically protected site such as CNS, that to in an immunocompetent host (none of 20 patients in our series were HIV positive), is multifactorial, with a complex interplay between infectious agents (EBV), host immunity, and possibly some adhesion molecules as well. Inspite of alarming increase in incidence of PCNL in the West (because of HIV/AIDS), the incidence is fairly low or at least, stable in the Middle East and Asian countries, including India. As suggested by Sarkar et al. (2005), early infection related deaths among Indian HIV patients might be an explanation for this trend in South East Asia. Moreover, the increased number of PCNL in our series is possibly explained because of improved neuroimaging techniques and stereotactic brain biopsies studied rather than anything else. This is because, tests, another immunologically protected anatomic site, have not shown similar trend like PCNL in the last decade, as was evidenced by only two cases in our series.

The pattern of primary gastrointestinal lymphoma in our patients was similar to the western population as well as from India (Zucca et al., 1997; Arora et al., 2011). Stomach was the most common site of involvement, followed in frequency, by large intestine and duodenum/jejunum. Ten percent of gastric MALT lymphomas had history of H. pylori gastritis demonstrated by routine Giemsa staining. Studies from Middle East countries like Iraq (Yaqo et al., 2011) and Kuwait (Temimm et al., 2004) have reported higher incidence of intestinal localization of lymphomas, as these studies have reported more number of Burkitt lymphomas among pediatric patients which tend to occur more at these sites. Immunoproliferative small intestinal disease (IPSID), more commonly reported from the Middle East countries was observed in two young males (26 years, 34 years) with history of loose motion, and malabsorption. In both cases, the pathology was confined to the duodenum and upper jejunum with dense lymphoplasmacytic infiltrate involving lamina propria associated with blunting of villi.

A recent large international retrospective study validated the geographic variations and showed the high frequency of ALK-positive, ALCL in North America, ATLL (angioimmunoblastic T cell lymphoma) and ETCL (enteropathy associated T cell lymphoma) in Europe, ATLL (adult T cell lymphoma/leukemia) in Japan, and ENKTCL in Asian countries other than Japan (Vose et al., 2008). In fact, the geographic variations also could be found across China; ENKTCL is the most common subtype of PTCL in Hong Kong, whereas PTCL, NOS (peripheral T cell lymphoma, not otherwise specified) in all other parts (Yang et al., 2011). The incidence of T cell lymphoma in Indian subcontinent is low as was seen in our series, being confined to skin only (n=3).

The biological behaviour of ENL has been complex in different studies (Table 1). Worse therapeutic outcome was seen for patients with lymphoma involving rare sites (Yun et al., 2010), those with T- cell phenotype (Ko et al., 2009), and among pediatric age group (Temimm et al., 2004). In another study, age, performance status, stage of disease, and serum LDH level were independent prognostic variables, whereas nodal or extra nodal site did not have any prognostic significance (Lal et al., 2008). In the present series, patients with pENL were younger at presentation, had lesser B symptoms, lower serum LDH level, low mean proliferation index, and lesser percentage
of marrow involvement. This probably explained the favorable prognosis in our cohort of patients. However, the number of cases with rare extra nodal site of involvement is negligible to make any comparison with other studies.

To conclude, the incidence of pENL in Indian subcontinent is low compared to data from other parts of the world. Central nervous system and gastrointestinal tract were the two most common extra nodal sites observed. Compared to published series, no difference was noted in regard to gender predilection and morphology; though T cell/NK cell immunophenotype was distinctly rare. Majority of our patients were immunocompetent, presented at younger age, and earlier stages. Being mostly an epidemiological and morphological study, data pertaining to the detail therapeutic outcome are lacking. Lack of comparison with pediatric group (due to very less number) was another drawback of our study. However, we do believe that more in depth studies of similar kind, highlighting the genetic profile of lymphomas, should be carried out from time to time in order to understand the biology of this group of tumors.

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