ORIGINAL ARTICLE

FREQUENCY OF DOUBLE EXPRESSOR LYMPHOMA IN A TERTIARY CARE HOSPITAL

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Background: Accounting for 30% cases of all lymphoid neoplasms, Diffuse large B cell lymphoma (DLBCL) is the commonest lymphoma worldwide. It occurs over a wide age range and has diverse morphology, immunophenotype and clinical outcome. Objectives of the study were to determine the frequency of Double expressor lymphoma (DEL) in a tertiary care hospital. **Methods:** This descriptive cross-sectional study was carried out in the Department of Histopathology, Rehman Medical Institute Peshawar from June 1st to December 1st, 2018. A total of 88 newly diagnosed cases of diffuse large B-cell lymphoma (DLBCL); diagnosed on incisional or excisional biopsies were included in the study by non-probability consecutive sampling. Statistical analysis was carried out using SPSS-23. Quantitative variables were calculated as mean±SD. Qualitative variables were computed as frequency and percentages. Post stratification chi-square test was applied keeping p value equal or less than 0.05 as significance. **Results:** In our 88 cases of DLBCL, 56 (63.6%) were males and 32 (36.4%) were females. Age of patients ranged from 15yrs to 84yrs. Mean age was 50.8±15.2SD. Activated B-cell like (ABC) subtype of DLBCL constitute 51 cases (58%) while 37 cases (42%) were of germinal centre B-cell like (GCB) subtype. Nineteen cases (21.6%) were of DEL. Cervical node was the commonest site of involvement (n=17, 19.3%) followed by stomach (n=10, 11.4%) and tonsil (n=6, 6.8%). Out of 19 cases of DEL, 17 cases (89.5%) were of ABC type. DEL was found to have significant correlation with ABC subtype of DLBCL (p=0.002). DEL had no correlation with gender (p=0.6), age (p=0.27), Mib-1 (p=0.36) and tumour site (p=0.42). **Conclusion:** The frequency of DEL in our study was 21.6% which is comparable to other studies who used similar cut-offs for c-Myc and BCL2 and similar criteria of inclusion as in our study. Significant association was found between DEL and ABC subtype of DLBCL.

Keywords: Double protein lymphoma; Double expressor lymphoma; Diffuse large B cell lymphoma; Double hit lymphoma, Frequency

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INTRODUCTION

Accounting for 30% cases of all lymphoid neoplasms, Diffuse large B cell lymphoma (DLBCL) is the commonest lymphoma worldwide.[1] It occurs over a wide age range and has diverse morphology, immunophenotype and clinical outcome.[1] On light microscopy, DLBCL is characterized by sheets of enlarged lymphoid cells with vesicular nuclei, prominent nucleoli and scant cytoplasm, that completely effaces the nodal architecture (Figure-1).[1]

The different response of DLBCL to conventional chemotherapy led to the emergence of its two subtypes, i.e., Germinal centre B-cell-like (GCB) and Activated B-cell-like (ABC), based on three immunohistochemical markers (CD10, BCL6 and MUM1).[1] Among these two subtypes, ABC type is associated with worst prognosis.[2] The introduction of monoclonal anti CD20 antibody (Rituximab) to cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP chemotherapy) results in dramatic response and improvement in survival of patients with DLBCL who were previously treated with CHOP chemotherapy only.[2] However still 40% of patients who were treated with R-CHOP will either relapse or progress to refractory disease and most of them will die of it.[2] Research on such cases resulted in emergence of a new entity in World Health Organization (WHO) 2008 classification, termed as "B cell lymphoma unclassifiable with features intermediate between Burkitt lymphoma (BL) and DLBCL".[3]

This lymphoma has some morphologic and molecular overlapping features with that of DLBCL and BL and is now called as Double Hit Lymphoma (DHL). It has c-MYC (myelocytomatosis gene) rearrangement in combination with either BCL2 (B-Cell Lymphoma 2), rarely BCL6 (B-cell lymphoma 6) or very rarely other oncogene rearrangement.[3–5] DHL having MYC & BCL2 rearrangement have poor

prognosis with a mean survival of 8 months.[5] Mostly, these tumours arise in GCB type of DLBCL.[5] The term "Double protein lymphoma (DPL) / Double expressor lymphoma (DEL) / Immunohistochemical Double Hit diffuse large B-cell lymphoma (IDHL)" is used for those cases of DLBCL which co-expresses c-MYC and BCL2 on immunohistochemistry (Figure-1).[5,6] It accounts for 17.6% of DLBCL.[5,6] This lymphoma has similar clinical course and worse prognosis as that of DHL.[7] DEL is more common in ABC type of DLBCL (in contrast to DHL) and has poor outcome than the DLBCL cases expressing either no or only one protein.[2] In 2016 WHO classification of haematolymphoid neoplasms, DEL remains in the category of DLBCL-not otherwise specified.[8]

Although half of DLBCL cases express MYC protein, but the prognostic value of MYC depends on percentage of cells expressing MYC protein.[7] More than 40% expression by tumour cells is considered to be the cut-off point for defining MYC overexpression; as using this cut-off on IHC have shown to be associated with gene rearrangement by FISH.[7,9] As the facility of FISH is not available in every setup and is not affordable to all patients, so it is important to apply MYC immunohistochemical marker on DLBCL to identify DEL.[10] A Chinese study on 336 patients of DLBCL also concludes that expression of MYC and BCL2 detected by immunohistochemistry (i.e., DEL) correlates well (>90% specificity) with rearrangements of MYC and BCL2 detected by Fluorescent in situ hybridization (FISH) i.e., DHL.[11]

Because the expression of MYC and BCL2 on IHC correlates well with their translocation/rearrangement on FISH, and as IHC is relatively cheap and readily available in most centres as compared to fluorescent in situ hybridization (FISH), early diagnoses of such patients (DEL) on immunohistochemistry will probably help in early prognostication of disease and personalization of chemotherapy for DEL.

To the best of our knowledge, no data is available about DEL in our region (Khyber Pakhtunkhwa); rather in any region of Pakistan, determining its frequency in our hospital setup will highlight its burden in our area and will alert the researchers/scientists to do further genetic workup and introduce new treatment modalities in treating this aggressive lymphoma.

MATERIAL AND METHODS

This cross-sectional study was carried out at Rehman Medical Institute (RMI) Peshawar after approval by institutional review board and ethical committee of RMI. The newly diagnosed cases of DLBCL presented to our laboratory from June 1st to December 1st 2018 and meeting the inclusion criteria were included in the study.

The slides were examined under light microscope (Nikon E100) and diagnosis of DLBCL was made using initial panel of CD3 (DAKO: Polyclonal rabbit antihuman CD3), CD20 (DAKO: Monoclonal mouse antihuman CD20cy, Clone L26) and Mib-1 (DAKO: Monoclonal mouse antihuman Ki-67 antigen, Clone MIB-1). CD10 (DAKO: Monoclonal mouse antihuman CD10, Clone 56C6), BCL6 (DAKO: Monoclonal mouse antihuman BCL6 protein, Clone PG-B6p) and MUM1 (DAKO: Monoclonal mouse antihuman MUM1 protein, Clone MUM1p) were then applied for subtyping of DLBCL into GCB and ABC subtypes. Afterwards c-MYC (Cell marque; Rabbit monoclonal, clone EP121) and BCL2 (DAKO: Monoclonal mouse antihuman BCL2 oncoprotein, Clone 124) were applied to detect DEL.

Any of the immunohistochemical marker was considered positive if it is expressed in following percentages of tumour cells: CD10 (≥30% of tumour cells), MUM1 (≥30% of tumour cells), BCL6 (≥30% of tumour cells).[12,13] These three markers were used to classify DLBCL into GCB and ABC subtype. MYC (40% of tumour cells) and BCL2 (50% of tumour cells) were used to identify DEL.[14–16]

The site of positivity of IHC markers will be different depending on the location of antigen in a cell. Staining at the following sites for each antibody was considered positive: Nuclear positivity for Mib-1, c-MYC, BCL6 and MUM1, cytoplasmic positivity for BCL2, membranous positivity for CD10 and CD20, and both membranous and cytoplasmic positivity for CD3.

Results of every case was compiled under the heading of Patient Personal Information (including MR number, age, sex, site of biopsy, date of admission) and Immunohistochemical markers (Positive / Negative for each antibody).

RESULTS

In our 88 cases of DLBCL 56 (63.6%) were males and 32 (36.4%) were females. Age of patients ranged from 15–84 years. Mean age was 50.8±15.2SD. Among all 88 cases, 28 patients (31.8%) were >60 years of age while 60 patients (68.2%) were of ≤60 years of age. Activated B-cell like subtype of DLBCL constitute 51 cases (58%) while 37 cases (42%) were of germinal centre B-cell like subtype.

Of the total 88 cases of DLBCL, 19 cases (21.6%) were of DEL. Seven cases (8%) have only c-MYC expression, 40 cases (45.5%) have only

BCL2 expression while 22 cases (25%) have no expression of either c-MYC or BCL2.

Cervical node was the commonest site of involvement (n=17, 19.3%) followed by stomach (n=10, 11.4%) and tonsil (n=6, 6.8%). Other anatomical sites of involvement include testis (n=5), maxilla and ileum (n=4 each), colon, pelvis and nasopharynx (n=3 each), axillary node, inguinal node, para-aortic node, GE junction, cecum, duodenum, mandible, oropharynx, palate and parapharyngeal area (n=2 each), abdominal node, brain posterior fossa, breast, bronchus, epigastrium, hilar node, iliac fossa, iliac node, jejunum, knee joint, lung, nostril and pancreas (n=1 each).

Mib-1 was 80–85% in 25 cases (28.4%) followed by 86-90% in 17 cases (19.3%). The lowest Mib-1 was 50–55% in 4 cases (4.5%) while highest Mib-1 positivity of 95–98% was seen in 7 cases (8%). CD10 was positive in 25 cases (28.4%), BCL6 in 38 cases (43.2%), while MUM1 was positive in 51 cases (58%). Fifteen (79%) out of 19 cases of DEL have > 80% Mib-1 proliferative index.

Out of 19 cases of DEL, 17 cases (89.5%) were of ABC type (Table-1). DEL was found to have significant correlation with ABC subtype of DLBCL (p=0.002). No correlation was seen between DEL with gender (p=0.6), age (p=0.27), Mib-1 (p=0.36) and tumour site (p=0.42).

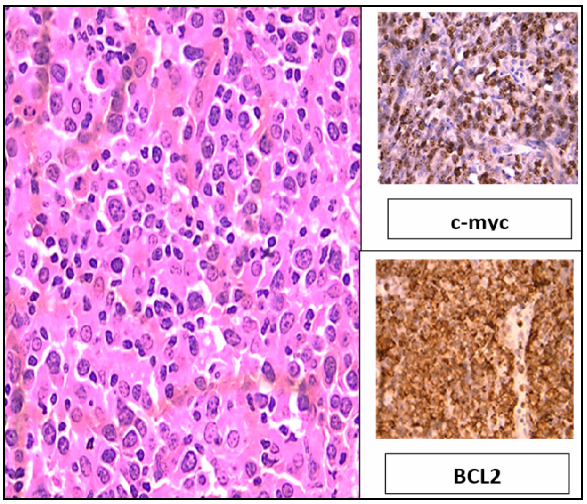

Figure 1: H/E section at 40x magnification showing sheets of tumour cells with enlarged nuclei, prominent nucleoli and high N/C ratio. Scattered mature lymphocytes and mitotic figures are also noted. Inset shows immunohistochemical staining for c-myc and bcl2

Table-1: Stratification of DEL with subtype of DLBCL (p=0.002)

	ABC subtype (n)	GCB subtype (n)	Total (n)
Dual expression	17	2	19
Single / No expression	34	35	69
Total	51	37	88

Table-2: Comparison of our study with others conducted in various geographic zones

Author	Year	Country	Sample size	Study population	c-Myc and BCL2 cut offs	Frequency
Johnson *et al.*	2012	Multicentric	167	de novo DLBCL	40% and 50%	21%
Ye *et al.*	2015	Multicentric	898	de novo DLBCL	70% for both	17.6%
Hu *et al*	2013	USA	893	de novo DLBCL	40% and 70%	34%
Green *et al*	2012	Denmark	185	de novo DLBCL	40% and 70%	29%
Harrera *et al*	2016	USA	117	Relapsed / refractory DLBCL	40% and 50%	44%
Miura *et al*	2015	Japan	38	Relapsed / refractory DLBCL	40% and 50%	45%
Kawashima *et al.*	2017	Japan	60	Relapsed / refractory DLBCL and transformed DLBCL cases from follicular lymphoma	40% and 50%	62%
Allen *et al.*	2018	USA	167	Relapsed / refractory DLBCL	40% and 50%	16%
Lu *et al*	2015	China	246	de novo DLBCL	40% and 50%	26%
Takahashi *et al*	2016	Japan	40	de novo DLBCL	40% and 50%	25%
Kawamoto	2016	Japan	61	de novo DLBCL	30% for both. 30% and 1%	Different frequency for different cutoffs. 39% and 36%
Raess *et al*	2017	USA	145	de novo DLBCL	40% and 50%	33%
Sawage *et al*	2016	Canada	428	de novo DLBCL	40% and 50%	30%
Petrella *et al*	2017	Multicentric (Canada and France)	285	de novo DLBCL	40% and 50%, 40% and 70%	26% and 24.9% with two different cutoffs
Our study	2018	Pakistan	88	de novo DLBCL	40% and 50%	21.6%

DISCUSSION

As the DEL is a relatively new entity with poor outcome, is resistant to most conventional treatments of DLBCL, and no study is done on it till now in Pakistan, the primary aim of our study was to determine its frequency in our set up. DEL is more common than DHL and accounts for 18–44% cases of DLBCL.[5] In our study, 88 cases of DLBCL of different anatomical sites were included and the dual expression of c-MYC and BCL2 (DEL) was found in 21.6% of cases. In a study by

Johnson NA *et al*., 167 patients of DLBCL were included, and using the same cut-offs for c-MYC and BCL2 (40% and 50%), concurrent expression of c-MYC and BCL2 was found in 21% of cases, which is similar to our study.[15] In a large study of Ye Q *et al*., 898 cases of DLBCL were included and found 17.6% of cases to be DEL.[5] This slightly lower frequency of DEL as compared to our study may be attributed to the high cut-offs for c-MYC and BCL2 (≥70% for both), while we used the cut-offs (MYC 40% and BCL2 50%) as recommended by World Health Organization WHO.[8,14]

In a large cohort of 893 cases of DLBCL treated with R-CHOP, DEL was found in 34% of cases, using the cut-offs 40% and 70% for c-MYC and BCL2.[17] Using similar cut-offs, Green *et al.* found DEL in 29% (54 out of 185 cases) of cases.[18] This difference in frequencies of DEL are partly due to different cut-offs used for c-MYC and BCL2. Other factors that may contribute include different antibodies used, fixation methods and regional differences.[18] In a study of 117 cases of relapsed / refractory DLBCL by Herrera AF *et al*., 44% of cases had DEL.[19] Although they used similar cut-offs for c-MYC and BCL2, but this quite high frequency was due to the fact that only relapsed / refractory cases of DLBCL, who underwent autologous stem cell transplantation (ASCT), were included in the study. Such resistant/relapsed cases are by default aggressive and are more likely suspected of having c-MYC and BCL2 expression. This fact is also supported by another study by Miura K *et al*., in which 38 patients of relapsed / refractory DLBCL were included and frequency of DEL was found to be 45%.[20] Similarly, another study by Kawashima I *et al*. also supports this view, in which 60 patients were included who underwent Allogeneic Hematopoietic Cell transplantation (HCT).[21] Sixty two percent (62%) were having DEL. This quite high frequency is due to two factors. First patients undergoing stem cell transplantation have already aggressive disease and, secondly, their study population also included those DLBCL cases which transformed from follicular lymphoma. Hence, both these factors are more likely to be associated with poor prognosis and are more likely of having double expressor phenotype. In contrast, Allen J et al. using similar cut offs in relapsed / refractory DLBCL found 16% patients having DEL.[22] Several other factors may be responsible for this. Firstly, they used different IHC clones for c-MYC (Clone Y69 Abcam Epitomics 1:50 dilution) and BCL2 (Clone 214 Cell Marque). Secondly, the patients were treated with different chemotherapy (R-ICE (rituximab, ifosfamide, carboplatin and etoposide)), which might affect protein expression. Lastly, different fixation methods may be responsible for it.

In a Japanese study of 40 patients of de novo DLBCL, Takahashi H *et al*. found co-expression of c-MYC and BCL2 in 25% of cases.[23] Although using similar cut-offs as our study for c-MYC and BCL2, this difference may be attributed to the fact that their study only included those patients who were high risk according to the age-adjusted International Prognostic Index (aaIPI) and such high-risk patients are more likely of having dual expressor phenotype.

In a Japanese study of 61 patients of DLBCL, Kawamoto K *et al*. found frequency of DEL to be 39% when cut-off was 30% for both c-MYC and BCL2, while frequency was 36% when cut-off for c-MYC was 30% and that of BCL2 was 1%.[24] This high frequency of DEL is clearly attributed to the lower cut-offs used for c-MYC and BCL2. Raess PW *et al.* evaluated 187 cases of aggressive B-cell lymphoma. Of these, DLBCL cases were 145, of which 48 cases (33%) expressed both c-MYC and BCL2.[10] In the phase 3 LNH03-6B trial, frequency of DEL comes out to be 26% when cut-off for c-MYC and BCL2 was similar to our study (40% and 50% respectively) and 24.9% when cut-off for BCL2 was increased to 70%.[25] Similarly in a study by Savage KJ *et al*., which was to find out the impact of dual expression on CNS relapse, 30% of patients had DEL.[26] In all these three studies, cut-offs for c-MYC and BCL2 were similar to our study suggesting that this 3–8% difference in frequency of DEL may be due to different antibodies used, different fixation methods or regional differences in the biology of DEL. Comparison of our study with other studies in various geographic zones is tabulated in table-2. Lastly, we found significant association (p=0.002) between DEL and ABC subtype of DLBCL which is also supported by Ye Q *et al.* (p=0.0079), Johnson NA *et al.* (p<0.001), Savage KJ *et al*. (p=0.0001) and Hu S *et al.* (p=0.03) [5,15,17,26] There was marginal association (p=0.09) in a study by Petrella T *et al.*[25]

Limitations and recommendations:

No cytogenetic study (FISH etc.) was done to find out the frequency DHL and its association with DEL due to non-availability of FISH facility and financial aspects. No follow up of the patients was done to find the impact of dual expression of c-MYC and BCL2 on overall survival (OS) and progression free survival (PFS). DEL was found to be strongly associated with ABC sub type of DLBCL, so any DLBCL case having ABC phenotype on immunohistochemistry should be tested for c-MYC and BCL2 protein overexpression to early diagnose and treat DEL.

CONCLUSION

The frequency of DEL in our study was 21.6% which is comparable to other studies using similar cut-offs for c-MYC and BCL2 and similar criteria of inclusion. The studies which show slightly or markedly high frequency was attributed to different cut-offs for c-Myc and BCL2, inclusion of relapsed or refractory cases or other lymphomas that transformed to DLBCL. We used newly diagnosed cases of DLBCL. Secondly significant

association was found between DEL and ABC subtype of DLBCL. This study will not only give as estimate of burden of this aggressive entity but will also encourage other prognostic studies and therapeutic trials on such aggressive entity in our setup.

AUTHORS' CONTRIBUTION

MH, MTK: Concept and design. SJ, SUS: Data collection. MH: Data analysis and interpretation. SJ, MTK: Introduction and conclusion. MH, MAQ, SUS: Discussion and methodology. MH: Drafting and revision:

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