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Potential Risk Factors and Prevalence Trend of Diffuse Large Beta Cell Lymphoma in Pakistani population

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Subject: Pharmacology

Abstract

Lymphoma is the most common blood cancer. The two main forms of lymphoma are Hodgkin lymphoma and non-Hodgkin lymphoma (NHL). Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably. Among all types of blood cancers, lymphoma is the most common one. Hodgkin and Non Hodgkin lymphoma are the two major forms of lymphomas. DLBCL is the most frequent type of NHL in which B lymphocytes have potential to grow and proliferate abnormally. Lymph node and outside of the lymphatic system are main arising points for development of DLBCL. Large mass of B cells, B symptoms and extranodal sites are the main features of DLBCL. In Pakistan (2008) DLBCL reaches to an epidemic proportion. WHO had classified the DLBCL according the involvement sites. This study briefly describes the prognostic indicators, possible risk factors and prevalence of DLBCL (NHL) in Pakistan.

Keywords*: DLBCL, NHL, Prevalence, Risk factors, Diagnostic indicators, DLBCL, Hodgkin*

1. Introduction

DLBCL is the most frequent type of lymphoid malignancy[1] and it has found to account for 25-40% of all NHL[2, 3]. Diffuse large beta cell lymphoma is the most common subtype of NHL[4] and is a cancer of B-lymphocytes (essential component of immune system of body)[5]. Characteristically, DLBCL comprises of heterogeneous group of neoplasm in term of morphology, behavior and genetic alterations (table 1)[6]. Large beta cells of this lymphoma have fast proliferation rate[7]. Instead of possessing a single clinical pathological entity, the clinical presentation of this destructive type of lymphoma is variable and is highly reliant on involvement site[8].

1.2. Prevalence of NHL (DLBCL)

Presently, in developed countries like America and Europe, the estimated annual incidence of NHL is found to be 15-20 cases per 100,000[13, 14]. It has been demonstrated in one of the recent studies that developed countries like United States of America, Australia, New Zeeland and Europe has the highest rate of incidence for NHL in comparison with eastern and south central Asia[15]. In USA NHL is ranked 6th among other cancers for both genders. According to American cancer society, total number of 70,800 cases were diagnosed in year 2014 for NHL[16].

One of the studies conducted in Pakistani population has stated that NHL accounts for 73% of all types of lymphomas and amongst them 86% were contributed by B-cell lymphomas. In other words, prevalence of β-cell NHL (DLBCL) moves toward an epidemic proportion in Pakistani community[17, 18]. It has been stated in Punjab cancer registry report of 2012 that NHL is the 2nd and 3rd most commonly diagnosed cancer in males and children respectively. According to the Shoakat khanum cancer registry report, total 2133 cases of NHL (both gender) has been reported from year 2004-2013.In addition, this has been documented that from year 2004-2013, total diagnosed cases for NHL in children were 452(table 2, figure 1).[19]

The main aim of this study is to provide more information to young researchers regarding the DLBCL (causes, diagnostic parameters and it's WHO classification). This study will briefly describe the prevalence pattern of this lymphoma in Pakistan since the last decade.

TABLE 1: Characteristic features of DLBCL

Features	Examples	Reference
Tumor mass of large B-cells	Large B-cells with vesicular nuclei, prominent nucleoli and basophilic cytoplasm.	[9]
Involvement of extranodal sites	gastrointestinal tract, liver, lung, breast, bone marrow, CNS etc	[10, 11]
B symptoms	Weight loss, Fever and drenching night sweats	[8, 12]

TABLE 2: Year wise prevalence of NHL (DLBCL)

	Number of patients diagnosed	
Year	**All age groups and both genders**	**Children(<=18)**
2004	186	30
2005	217	18
2006	238	34
2007	274	39
2008	206	34
2009	116	60
2010	100	61
2011	260	42
2012	305	63
2013	231	71
Total	2133	452

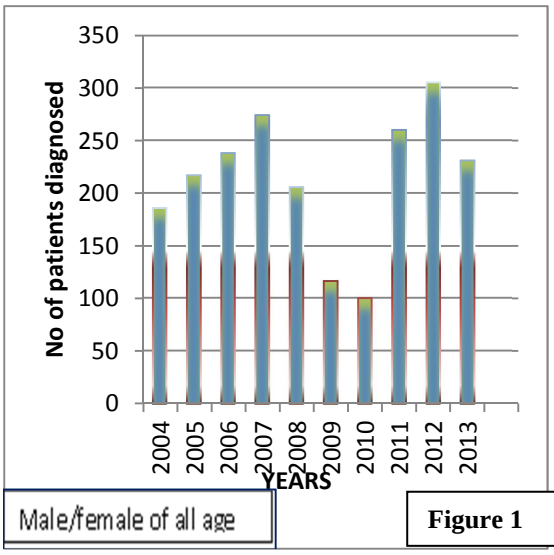

Figure 1

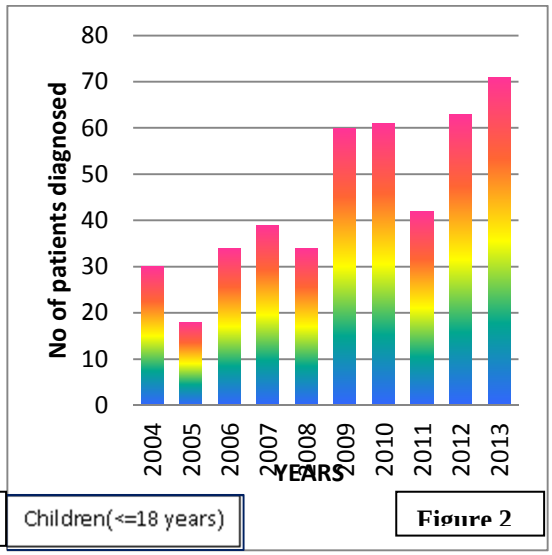

Figure 2

Following table 3 will depict the total number of patients (male/female) diagnosed with NHL and reported in shoakat khanum cancer registry from year 2007-2013[19].Graphical representations were made to represent the number of male and female patients diagnosed with this lymphoma in previous years.

Table 3: Age and gender wise distribution of DLBCL (NHL) patients

Age groups	Number of patients diagnosed from year 2007-2013													
	2007		2008		2009		2010		2011		2012		2013	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
0-4	2	7	1	9	5	8	1	5	1	6	4	7	5	4
5-9	1	10	2	13	6	18	9	23	1	8	5	29	9	18
10-14	4	7	4	5	3	7	4	13	4	11	7	18	4	14
15-19	6	15	2	6	4	9	1	6	2	14	3	14	1	18
20-24	5	17	4	5	2	1	0	4	10	23	12	19	7	22
25-29	9	10	5	9	1	5	1	1	6	32	8	17	7	27
30-34	2	8	3	4	2	3	2	2	11	19	8	21	13	25
35-39	5	21	3	14		1	3	3	3	18	10	15	9	16
40-44	6	10	4	12	2	3	3	4	10	13	12	29	2	6
45-49	8	10	8	15	2	3	2	2	9	26	14	32	4	2
50-54	15	17	6	11	5	1	1	4	6	16	3	5	1	1
55-59	4	15	9	7	3	2	0	0	2	3	4	4	2	1
60-64	11	11	5	9	5	6	0	2	2	1	1	1	2	2
65-69	5	7	3	8	2	1	0	2	0	1	0	2	0	2
70-74	6	5	4	7	1	2	0	2	0	0	0	0	0	2
75-79	3	8	2	2	2	1	0	0	0	0	1	0	2	1
80-84	1	2	0	5	0	0	0	0	1	0	0	1	0	1
85+	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Total	**93**	**181**	**65**	**141**	**45**	**71**	**27**	**73**	**68**	**191**	**92**	**214**	**68**	**163**

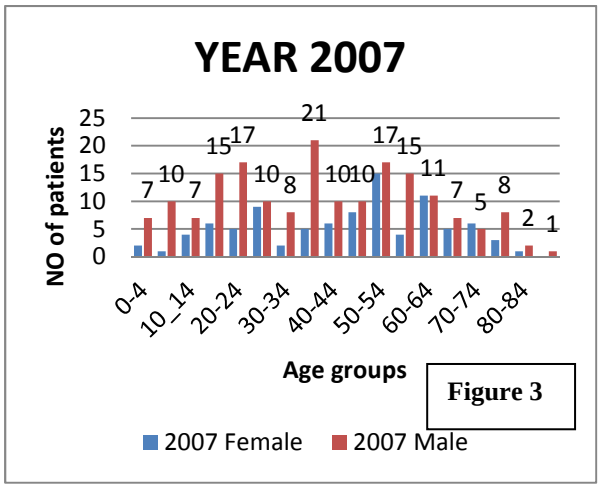

Figure 3

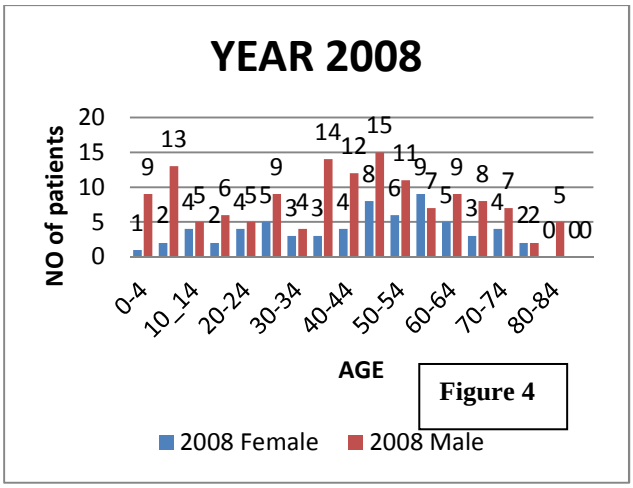

Figure 4

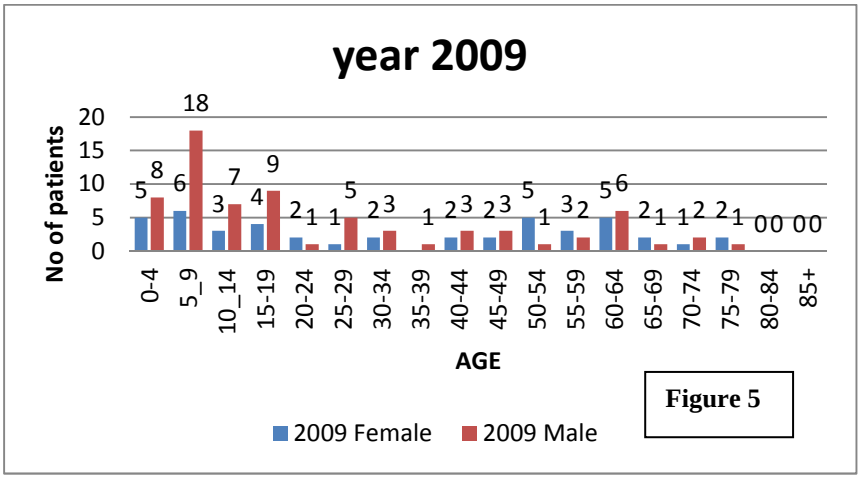

Figure 5

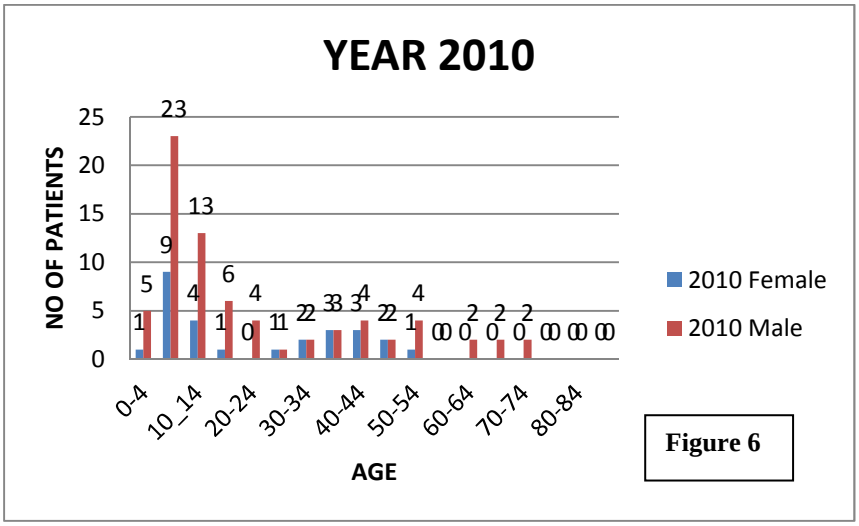

Figure 6

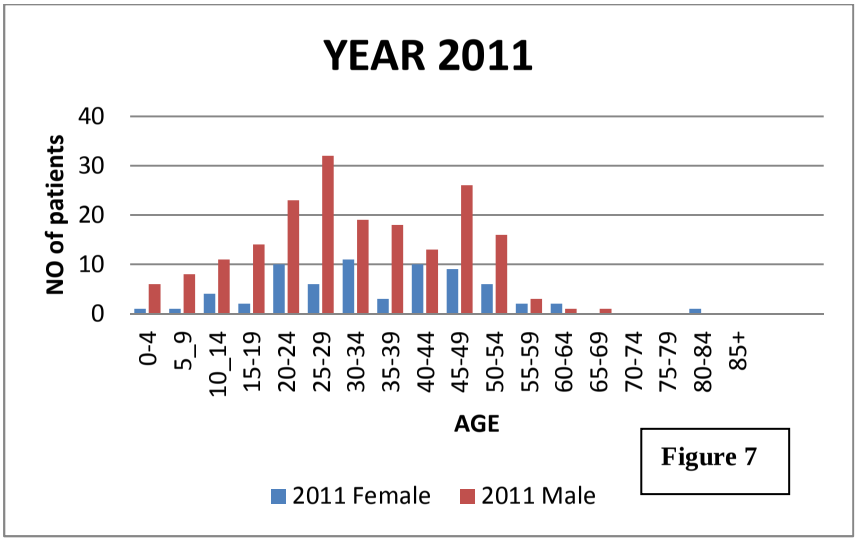

Figure 7

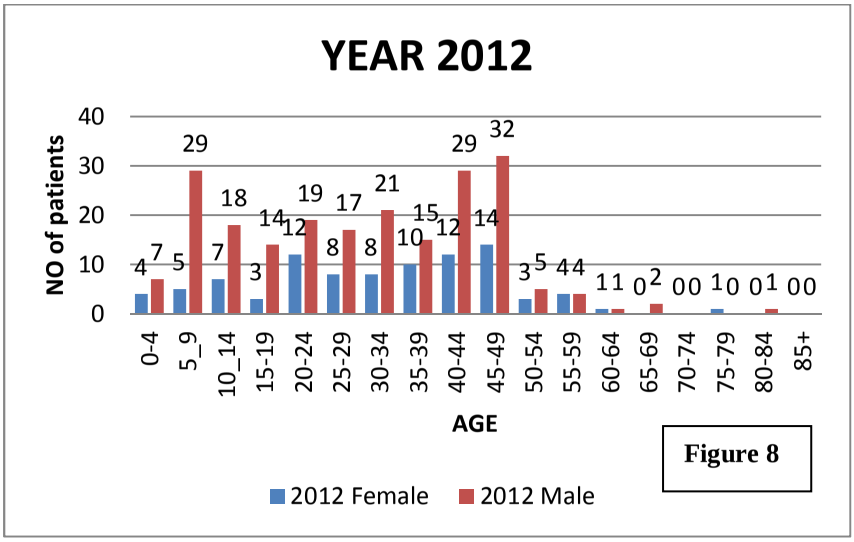

Figure 8

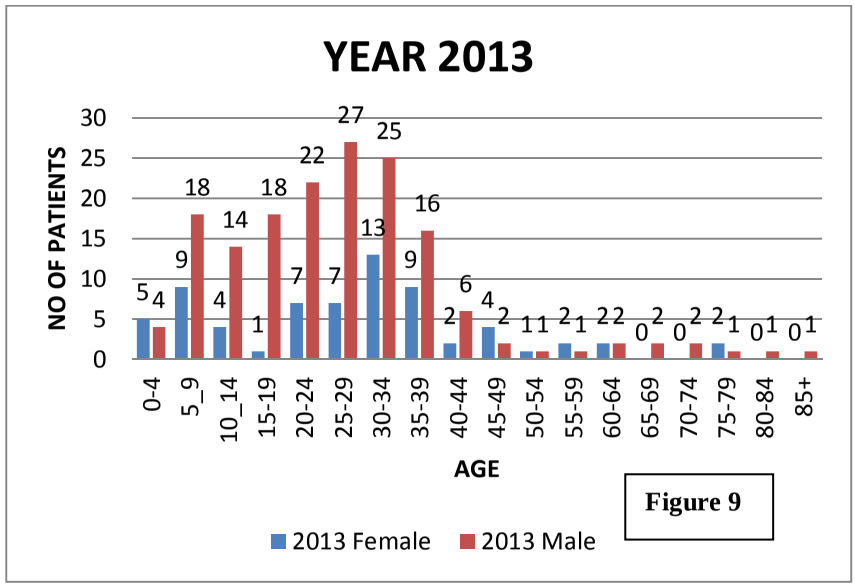

Figure 9

2. Prognostic indicators for DLBCL

In general, the places of origin from which this lymphoma usually develops are lymph node in neck and abdomen with wide spreading capacity[20]. Basically, these lymphoma originates from mature B-lymphocytes[21] that are distinguished from other B-cells by having B-cell antigens on immunohistochemistry like CD19, CD20, CD22, and CD79a in addition to CD45 on tumor cells[22-25]. The most important indicators for diagnosis of DLBCL are International Prognostic Index (IPI) that gives estimation about patient's survival[26].

Table 4: Prognostic groups and contributive factors for international prognostic index

Possible indicators	Description	Reference
Contributive factors for IPI	Factor 1:Age greater than 60 years Factor 2: Serum lactate dehydrogenase Factor 3: ECOG performance status greater than 2 Factor 4: Extranodal sites>1 Factor 5: Disease stage (III and IV)	**[4, 27]**
Prognostic groups by utilizing IPI factors	Group I:low-risk group (LR) with 0-1 prognostic factors Group II: low intermediate risk group (LIR) with 2 prognostic factors, Group III: high intermediate risk group (HIR) with 3 factors. Group IV: high risk group (HR) with 4-5 factors	
% of 5 year survival	73% for group I 51% for group II 43% for group III 26% for group IV	

3. Risk factors/ Aetiological causes of DLBCL

Worldwide and in Pakistan there are many risk factors that have enough contribution to cause Diffuse Large Beta Cell Lymphoma (table 5).

Table 5: possible Risk factors for DLBCL

Risk factors	Reference
Chemical substances for example, benzene, polychlorinated biphenyls, dioxins, furans, organochlorine pesticides and fertilizers.	[28]
Concomitant use of alkylating agents and ionizing radiation.	[26]
Inherited immunologic disorders/immunologic deficiency diseases (e.g. ataxia-telengectasia, Wiskott–Aldrich syndrome, severe combine immunodeficiency, X-linked lymphoproliferative disorder, Nijmegen breakage syndrome, autoimmune lymphoproliferative syndrome, hyper-IgM syndrome, Sjögren's syndrome, Swiss-type agammaglobulinemia, acquired hypogammaglobulinemia, and acquired immunodeficiency syndrome)	[2, 29, 30]
Immunosuppressive drugs in organ transplantation	[31, 32]
Epstein barr virus	[32, 33]
hepatitis-C virus (HCV)	[34]
Human immunodeficiency virus (HIV)-infection	[33, 35]
Human herpes virus 8 (HHV8)	[23]
Castleman disease (CD)	[36]
Obesity	[37]
Physical inactivity	[38]
Inadequate intake of cruciferous vegetables	[39, 40]
Avoidance to sun exposure	[41]

Table 6: WHO classification of DLBCL

Types	Morphological features and phenotype	References
1. DLBCL, not otherwise specified		**[26, 42-45]**
	Centroblasts/ immunoblasts Variable histiocytes Globally high number of mitotic figure DLBCL with myxoid or fibrillary features multi-lobated and anaplastic large cell Cells of DLBCL (NOS) express B cell related antigens such as CD19,CD20, CD22, CD79a and CD45+ and PAX5+ Additional useful markers for DLBCL are BCL-2, p53, KI-67, NF-*k*B components.	
	A. Histiocyte/T-cell-rich large B-cell lymphoma (H/TCRBCL) Dispersed large B-cells immersed in a T-cell rich back-ground(CD3+/CD4+ T cells). Presence of histiocytes (CD68+). Express mature B-cell markers (commonly BCL-2, EMA). Be deficient of CD30, CD15, and CD138. Usually presented as disseminated disease involving lymph nodes, spleen, liver and bone marrow.	**[12, 46]**
	B. EBV+ DLBCL of the "elderly" Patients with age above 50 are more susceptible to EBV+ DLBCL Presented with extra nodal disease Show contentious behaviour with approx. 2 years of survival Generally express CD20, CD79a and IRF4 Show negative results for CD10, CD15 and Bcl-6.	**[46]**
2. DLBCL with a predominant extranodal location	**A. Primary mediastinal (thymic) large B-cell lymphoma (PMBL)** Originate from B cell of thymus Morphologically, this lymphoma is diverse in nature, predominately compose of giant cells possessing ovoid nucleus and clear cytoplasm Infrequent present of Reed–Sternberg like cells Fibrosis is certainly present Express mature B cell markers and Ig transcription factors Give positive results for CD30 but show negative for CD15. Gene expression signature for PMBL is typically closer to CHL	**[47, 48]**
	B. Intravascular large B-cell lymphoma (IVLBCL) Selectively, this lymphoma is distinguished by discriminative growth of large B cells inside the lumina of capillaries and vessels (small to medium sized). Extensively express CD5 (protein) on B-cells. More frequently diagnosed in eastern population as compared to western countries.	**[49]**
	C. Primary cutaneous DLBCL, leg type (PCLBCL, leg type) Most commonly appear from the skin of lower extremities (particularly leg) B-cells of this lymphoma possess prominent nucleoli Expresses positive results for interferon regulatory factor4(IRF4) Give negative results for CD10. 50% cases of this primary cutaneous lymphoma of B cells have 5 years survival Have genetic resemblance to DLBCL of NOS(ABC type)	**[50]**

	D. Primary DLCBL of the central nervous system(CNS DLBCL) DLBCL of central nervous system exhibit a confined homing to the major immune sanctuaries ((brain, eyes and testis) that have association with diminished or absent expression of human leukocyte antigen (HLA) which prevent tumor cells from further immune attack. Site of presence for tumor cells is perivascular space. B cell markers for this lymphoma are CD20, CD22 or CD79a, CD10, BCL6 and IRF4/MUM1	**[51-54]**
	E. Lymphomatoid granulomatosis This lymphoproliferative disorder appears as aggressive disease. Usually characterized by presenting nodules in the lung, brain, kidney, liver, and skin Mostly diagnosed in patients with immunodeficiency either by congenital or acquired (by HIV infection/immune-suppression).	**[55-57]**
3.Large-cell lymphomas of terminally differentiated B-cells	These cells are differentiated by the entirely absence or alterable expression of CD20. CD79a is Less frequently expressed in terminally differentiated B cells. Most commonly expressed antigens are CD38, CD138, hTPD52. Viruses such as EBV and HHV8 are mostly positive for these lymphomas .	**[26]**
	A.ALK-positive large B-cell lymphoma Marked by rapid proliferation of immunoblast like B-cells Sometime expressing plasmablastic differentiation. These lymphoma cells are positive for ALK protein due to chromosomal translocation(t2;17 and t2;5) Show positive expression for CD30 antigen. Express negative results for EBV Immunocompromised male(specially with lymphadenopathy) are more susceptible to this lymphoma	**[58]**
	B. Plasmablastic lymphoma (PBL) This aggressive form of lymphoma is characterized by neoplasm of large B cells with immunoblastic morphology and contains immunophenotype plasma cells Most commonly diagnosed in immunosuppressed patients. Mainly presented with involvement of extranodal sites(GIT and buccal mucosa) Plasmablastic lymphomas are positive for EBV.	[59, 60]
	C. Primary effusion lymphoma (PEL) Usually observed in Immunocompromised patients Generally presented as serous effusions from lymphoma cells that are plasmablastic or pleomorphic B-cells. Rarely show involvement of extranodal sites Show positive expression for CD30 and plasma cell related antigens Deficient of B cell markers and immune globulin This lymphoma is positive for HHV8 and EBV	[61]
	D. **Pyothorax-associated lymphoma (PAL)** This lymphoma is emerged as an aggressive disease that is associated with chronic inflammation. Have dismal prognosis and is marked by plasmablastic differentiation Express immunoreactivity for CD45, Bcl-2 protein, Ki-67 marking and B cell markers CD138, IRF4 and CD30 are variably expressed in PAL Show positivity toward EBV PAL is negative for HHV8 infection	**[62-64]**

4.B-cell neoplasms with features intermediated between DLBCL and other lymphoid tumours	**A. B-cell neoplasm with features intermediate between DLBCL and Burkitt lymphoma** These type of neoplasms are more frequently diagnosed in adults With intermediate characteristics these lymphomas have rapid proliferation rate and are aggressive in nature. Show marked germinal center B cell phenotype(CD20+, CD10+, BCL6+) Express rearrangement of *MYC* gene (regulator gene). Morphologically, these lymphomas have very close resemblance with Burkitt lymphoma but their phenotype is atypical in nature due to over expression of Bcl-2 gene.	**[65, 66]**
	B. B-cell neoplasm with features intermediated between DLBCL and CHL Morphological, clinical and phenotypic characteristics for this category of lymphomas are superimposed on each other. Particular example is lymphoma having intermediate features between Primary Mediastinal Large B-Cell Lymphoma and classical Hodgkin lymphoma Morphologically these lymphomas are characterized by larege sheets of pleomorphic cells in fibrotic stroma High expression of CD20, CD79a, BOB-1, OCT2 and PAX-5 in combination with CD30 and CD15 are Characteristic features of these neoplasm.	**[67]**

5. Conclusion

Diffuse large cell lymphoma is the most common lymphoma, representing 31% of the non-Hodgkin lymphomas (NHLs), and it is rapidly fatal if untreated. This brief study elucidates the characteristic features, diagnostic indicators, potential risk factors and WHO classification of diffuse large beta cell lymphoma. In addition this study also describes the prevalence rate of DLBCL in Pakistan since last seven years. It is depicted from the annual cancer registry report of SKMCH & research center that prevalence rate of DLBCL is increasing tremendously among children since last decade but among male/female of all age groups its maximum prevalence has been recorded in year 2012 as compared to previous years.

"Cite this Article"

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