RESEARCH COMMUNICATION

Diffuse Large B Cell Lymphoma (DLBCL) in Pakistan: An Emerging Epidemic?

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Abstract

There has been a recent concern among oncological clinicians and pathologists of our region regarding the disproportionate increase in the number of patients presenting with diffuse large B cell lymphoma (DLBCL). This prompted us to conduct a thorough, hospital-based epidemiological study in a major referral center of Pakistan. A total of 780 specimens were collected over last half decade from cases classified as adult Non Hodgkin's lymphoma (NHL). Out of these 780, 596 (76.4 %) were diagnosed as DLBCLs. The gender ratio was 2.3: 1 (M: F) and the median age was 47.2 years, with an age range of 15-85 years. Nodal-NHLs constituted 42.2 % of all adult NHLs, with the cervical lymph nodes as the most frequent nodal site of presentation. The most frequent extranodal site was the gastro-intestinal tract (GIT), followed by the head and neck. In conclusion, we document an astonishingly high number of DLBCL amounting to an emerging epidemic in Pakistan, with a consideration of probable etiopathogenetic factors.

Key Words: DLBCL - NHL - Pakistani adults

Introduction

The diffuse large B cell lymphoma (DLBCL) is one of the most frequently occurring of all non-Hodgkins lymphomas (NHL) and constitutes a great majority of all aggressive lymphoid neoplasms (Kumar et al, 1999). It is also the largest subtype of NHL, constituting 30 - 40 % of all lymphomas in the West, with frequent extranodal presentation (Moller et al, 2004; Chan et al, 1997). What makes DLBCL so special is the fact that it may be one of the most aggressive lymphomas, yet, it is very chemosensitive with significant absolute and relative cure rates (Coiffier et al, 2005).

Pakistan is a part of the 'lymphoma belt', the geographical boundaries of which extend from south-western Asia to Middle East to northern Africa (Almasri et al, 2004). It is not clear, however, whether the frequency and incidence rates of malignant lymphomas in the included countries are higher than those of the Western countries, since no reliable statistics exist. Our present study, which mainly covers the southern Pakistani population, was therefore conducted in an attempt to analyze the relative prevalence of DLBCL in our country during the past half decade and to compare it with both previous and recent data from other parts of the country as well as with other regions in the 'lymphoma belt' and elsewhere.

Materials and Methods

The histopathology section of the Aga Khan University Hospital (AKUH) is a major referral center of Pakistan where specimens are received from all four provinces of Pakistan through 65 collection points. However, the major proportion of specimens comes from the southern province of Sindh, including Karachi. The specimens are received in 10 % neutral buffered formalin, routinely processed through alcohols and xylene, and embedded in Paraffin. Besides H & E staining, sections are routinely stained with a comprehensive panel of antibodies including LCA, Pan B (CD-20 & CD-79a), Pan T (UCHL1 & CD-3), Ki-1 (CD-30), (CD 15), (CD 43), (CD 10), (Bcl 2), (Bcl 6) and MIB-1 (Ki-67) by Envision system. All the antibodies are obtained from DAKO, Denmark and optimal dilutions are determined in test runs. Positive and negative controls are routinely run with all batches. Quality control for the diagnoses is ensured by participation in international 'epilymph' and CAP surveys. Slides are interpreted by an internationally qualified faculty with a major interest in haematopathology.

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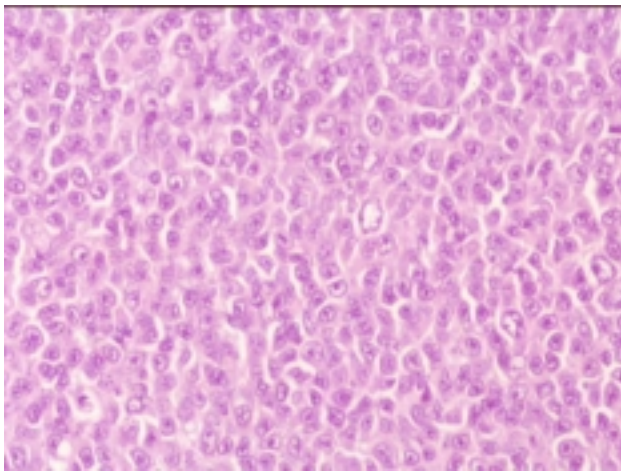
Figure 1. Photomicrograph Showing Typical Morphology of DLBCL. Note marked variability in size and shape of tumor cells with prominent nucleoli. H&E, Mag = 20 X
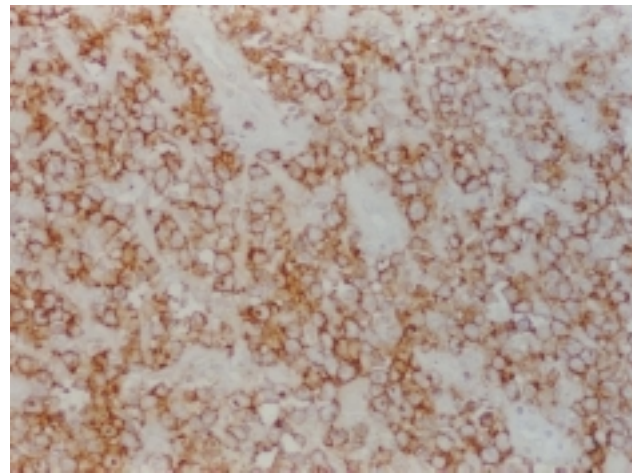

Figure 2. Photomicrograph of DLBCL Stained with a Monoclonal Antibody against CD 20. Note Diffuse membrane staining. Mag = 20 X

Results

The present study included all adult (age > 15 years) NHLs reported during the past half decade i.e. between Jan 1998 and Jun 2003. During this time period, 780 specimens were classified as adult NHLs on the basis of morphology and immunohistochemical staining (Figures 1 & 2). Out of these, 596 (76.4%) of all adult NHLs were classified as DLBCLs, constituting a surprisingly high (76.4%) proportion . The gender ratio (M: F) was 2.3: 1 and the median age was 47.2 years, although the age range was broad (15-85).

Recent molecular studies have provided adequate aetiological and genetic data which suggest that the distinction between nodal and extranodal DLBCLs is not only pathogenetically but also clinically important. In this regard, we also calculated the nodal and extranodal proportions and the most frequent sites in each group. In our study, extranodal NHLs outnumbered nodal NHLs with the former group constituting 58.8 % and the latter 42.2 % of all adult NHLs. The most frequent sites of extranodal lymphomas are listed Table 1. The predominant lymph node groups of primary nodal NHLs are similarly summarized in Table 2.

Discussion

In this retrospective study, DLBCLs accounted for an impressive 76.4% of all adult NHLs. This finding is not in agreement with observations made in the past from other neighboring countries both in the lymphoma belt and elsewhere but quite similar when compared with studies from other regions of Pakistan (Khalil, 1992; Khan et al, 1995;Muzaffar et al, 1997). In the middle eastern countries like Jordan, DLBCLs were found to account for 53 % of all NHL cases (Almasri et al, 2004), and similar observations have been made in other countries of the region including the Kingdom of Saudi Arabia (Thomas et al, 1995), and Oman (Bamanikar et al, 1995). In the other Asian countries including the Far East, Hong Kong has demonstrated the highest percentage of B cell lesions out of diffuse NHLs, as evident in two different studies giving figures of 66.3 % (Shih et al, 1991) and 63.8 % (Ng et al, 1986). However, only 24.4 % of all NHLs exhibited diffuse large cell histology. In Korea, nearly half of the NHLs were found to be of B cell phenotype with a diffuse large cell pattern (Chi et al, 1985). China (Ng et al, 1988), Taiwan (Chang et al,

Table 1. Extranodal NHLs

Extranodal Sites	Frequency	% Extranodal NHLs
GIT	172	37.5%
Head & Neck	68	14.8%
Bone	52	11.3%
CNS	42	9.2%
Tonsil	26	5.7%
Reproductive Organs	17	3.7%
Thorax	16	3.5%
Retroperitoneal	12	2.6%
Miscellaneous	9	2.0%
No site stated	45	9.8%
TOTAL	459	58.9%

Table 2. Nodal NHLs

Nodal Sites	Frequency	% of Nodal NHLs
Cervical LNs	122	38.0%
Inguinal LNs	52	16.2%
Axillary LNs	48	15.0%
Mesenteric LNs	17	5.3%
Supraclavicular LNs	8	2.5%
Para-aortic LNs	3	0.9%
Submandibular LNs	2	0.6%
Retroperitoneal LNs	2	0.6%
Paratracheal LNs	2	0.6%
Infraclavicular LNs	1	0.3%
Submental LNs	1	0.3%
Miscellaneous LNs	63	19.6%
TOTAL	321	42.2%

1989), Taipei (Su et al, 1985), and Thailand (Piankijagum et al, 1980) also had similar results, whereas, Japan (Aozasa et al, 1985), Malaysia, Indonesia, and Singapore had comparatively low prevalences of DLBCLs (Shih et al, 1991). The European region has remained fairly stable in this regard during the past decade. Epidemiological studies from Denmark have revealed DLBCLs to comprise 33 % of all NHLs (Moller et al, 2004). Turkey and Italy also have similar observations with 28.2 % (Isikdogan et al, 2004), and Italy slightly higher (Di Leonardo et al, 2000), respectively. The United States National Cancer Institute's SEER (Surveillance, Epidemiology, and End Result) data also predict a transition of predominance from follicular to diffuse pattern (Newell et al, 1987), with DLBCLs as the most frequently occurring of all NHLs (except in children less than 15 years of age) (Greiner et al, 1995).

The frequency of primary extranodal NHL in our study is 58.8 % which is nearly similar (or slightly greater) to other regions of Pakistan, but significantly greater than the U.S. (Chiu et al, 2003), Europe (Denmark: 40% (Moller et al, 2004), Turkey: 44.5% (Isikdogan et al, 2004), and Italy: 50% (Di Leonardo et al, 2000) and other countries located in the lymphoma belt (Jordan: 43% (Almasri et al, 2004)) where nodal NHL predominate. The most common site of origin of extranodal NHL in our study is the GIT, constituting 37.5% of all extranodal NHL, whereas the most common nodal site are the cervical lymph nodes, comprising of 37.1% of all nodal NHL. This observation is consistent with other regions in the lymphoma belt. For instance, in Jordan, primary GIT lymphomas account for 40.4 % of all extranodal NHL (Almasri et al, 2004). Similar results are reported by Algeria (Ladjadj et al, 1984); whereas, it is slightly lower than the West (Isikdogan et al, 2004).

It is clearly evident from our study that DLBCL is more common in males as compared to females with a male-to-female ratio of 2.3: 1 and the median age of about 47.2 years. However, the age range is wide (15-85) with DLBCL still constituting a considerable proportion of early adulthood lymphomas. This ratio has been reported to be 1.4: 1 in the U.S. SEER program data (Greiner et al, 1995). Similar male-to-female ratios have been reported by the Middle Eastern countries including Jordan with 1.4 : 1 (Almasri et al, 2004) and European countries including Turkey with a ratio of 1.78 :1 (Isikdogan et al, 2004). Since DLBCL is predominantly an adult lymphoma, the median age (47.2 years) of our study has come out to be comparable to the other regions of the lymphoma belt and slightly lower as compared to the West. For example, the median age in Jordan is 44 years (Almasri et al, 2004), and this observation is also in agreement with the other Middle Eastern countries (Ladjadj et al, 1984; Almasri et al, 1997). In the West, the median age lies in the sixth decade (Harris et al, 1994), and the age-specific incidence rates increase with age (Greiner et al, 1995). Furthermore, more that 50 % of NHL in the elderly (people greater than 65 years) are DLBCL (Greiner et al, 1995).

It is evident from the above discussion that DLBCL, in its growth, has surely outpaced all other entities of NHL globally. But the increment in its incidence has particularly been marked in the 'lymphoma belt', specially in the Middle East and the western Asian region including Pakistan. What makes DLBCL an 'emerging epidemic' remains to be unveiled, but at least several major factors, along with their interplay, are thought to be the culprits.

Recent transition from morphology-based classification to modern immunohistochemistry & genetics-based classification techniques of lymphomas in this part of the world could be the first contributory factor towards increased diagnosis of DLBCL. This fact is also supported by the obvious decrease in the relative frequency of lymphomas in the unspecified category of the miscellaneous NHLs with simultaneous reclassification of pseudolymphomas as monoclonal B-cell neoplasms (Greiner et al, 1995).

Secondly, certain biologically incompatible tribal trends and social customs, like consanguineous marriages have still, very much, prevailed in our society with resultant 'sustained acquisitions of genetic lesions. However, this essential aspect of lymphomagenesis needs to be further addressed and investigated.

Environmental agents contribute significantly towards tumorigenesis and many new environmental mutagens have also been shown to increase the risk of various entities of NHL including DLBCL. These agents mainly include herbicides, pesticides, and hair coloring dyes (Greiner et al, 1995). Since Pakistan is an agricultural country and much of its economy depends on agro-based products, extensive use of herbicides and pesticides is nearly inevitable. More specifically, a particular ingredient of common herbicides, 2, 4-dichlorophenoxyacetic acid (2, 4-D), has been shown to increase the risk of DLBCL [Zahm et al, 1990]. In addition, an urge for rejuvenation in the general population in this part of the globe has led to an accelerated consumption of hair coloring dyes, which has also been shown to increase the risk of various subtypes of NHL (Zahm et al, 1992).

Last, but not the least, reason for the increased proportion of DLBCL cases observed in this part of the world could be due to increase in the congenital and acquired immunodeficiency states. This observation is similar to the one seen in the U.S. in 1980s with increased incidence rates of Diffuse NHL which were also attributable largely to Acquired Immunodeficiency Syndrome (AIDS) epidemic (Greiner et al, 1995), (Freter et al, 1990). Epstein Barr Virus (EBV) is implicated in the pathogenesis of DLBCL that arise in the setting of acquired immunodeficiency states and iatrogenic immunosuppression (for example in post-transplant patients). In some recent studies from our institution, EBV has also been shown to be associated with a high percentage of T-cell NHL (Noorali et al, 2003). Unsafe health practices have surely increased the incidence of AIDS in this part of the world as well with resultant corresponding increase in DLBCL.

In conclusion, it is disappointing to see such an aggressive tumor proliferating at knots, but we can still achieve effective prevention against the causative factors prophylactically and aggressive management therapeutically.

Before we take on this task, further immunohistochemistry based epidemiological studies with strict quality controls are mandatory from various regions of this part of the globe for analysis of the pattern of distribution of DLBCL here. The element of hope lies in the fact that DLBCL is like a two-edged sword : an aggressive tumor that is rapidly fatal if untreated but potentially curable with intensive, combination chemotherapy.

Acknowledgement

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