RESEARCH COMMUNICATION

Anaplastic Large Cell Lymphoma: the Most Common T-Cell Lymphoma in Pakistan

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Abstract

    <u>Objective</u>: **To study the prevalence and immunohistochemical profile of the subtypes of anaplastic large cell lymphomas (ALCLs) at a major referral center of Pakistan. <u>Methods</u>: Epidemiological data for all mature T-cell non-Hodgkin's lymphoma (NHL) diagnosed between 1st January 2005 and 30th June 2010 at the Aga Khan University Department of Histopathology were reviewed and analyzed with SPSS v17.0. <u>Results</u>: A total of 178 specimens were diagnosed as mature T- and NK- cell NHL during the period. Of these 100 (56.2%) were diagnosed as systemic ALCL. These tumors were of either T- or null-cell type with consistent (100%) expression of CD30 (Ki-1). Forty three (43%) cases were further classified as ALK positive, fifty (50%) as ALK negative and seven (7%) were not tested for ALK expression. The mean age of the ALK positive group was 26.7 years as compared to the ALK negative of 35.6 years. The gender ratio of ALK positive cases was 2.3:1 (M:F) as compared to the 2.5:1 ratio seen in the ALK negative cases. There were no significant differences in the nodal and extra-nodal involvement patterns between ALK+ and ALK- groups but epithelial membrane antigen was positive more often in the ALK positive group. <u>Conclusion</u>: Compared to other published studies, this proportion of ALCL within the mature T- and NK- cell lymphoma category was found to be alarmingly high and calls for attention. Further studies should be conducted in our region, which in turn would enable clinicians to successfully battle against this neoplastic disease.**

Keywords: Anaplastic large cell lymphoma - CD 30 antigen - ALK protein

Introduction

    Since it was first described by Stein et al in 1985, anaplastic large cell lymphoma (ALCL) has evolved into a fairly well-characterized group of T-cell lymphomas (Stein et al., 1985). On histopathological evaluation, there is malignant proliferation of large lymphoid cells that exhibit strong positivity for CD30 with the "horseshoe" or "wreath" cell being considered to be the cytologic hallmark of this neoplasm (Benharroch et al., 1998). These cells tend to invade lymph node sinuses and are seen to grow cohesively. Based on its morphology, there are several variants of ALCL that include the common type, monomorphic variant, small cell variant, giant cell variant, mixed cell variant, sarcomatoid subtype, Hodgkin-like variant and lymphohistiocytic variant (Stein et al., 2000). Moreover, based on the clinical findings, ALCL can exist as either a widespread systemic syndrome, or as a localized cutaneous disease. Systemic ALCL comprises 2% to 8% of non-Hodgkin lymphomas in adults (Coiffier, 1999)) and 10% of these lymphomas in children (Burkhardt et al., 2005).

    Furthermore, genetic studies have helped elucidate a unique translocation t(2:5) seen in many of the systemic

ALCL cases (Mason et al., 1990). This and other chromosomal abnormalities have been seen to lead to the overexpression of a fusion protein, anaplastic lymphoma kinase (ALK) (Kutok and Aster, 2002). Integrating histopathological and clinical data, many studies have come to show that the expression of this protein is related with clinical characteristics and prognosis. Thus the 2008 WHO classification listed systemic ALCL accordingly, with ALK+ tumors listed as separate from the provisional ALK- tumors which are similar morphologically to the ALK+ cases but do not express the ALK+ protein (Swerdlow et al, 2008)

    As numerous studies have shown, the incidence of many aggressive lymphomas is much higher in South Western Asia, where Pakistan lies, than in Western countries. Therefore with limited studies from our region on the prevalence and characterization of ALCL, this study was undertaken to elucidate the overall proportion of ALCL within the large T-cell non-Hodgkin lymphoma (T-NHL) bracket diagnosed at a major referral center of Pakistan. We also aimed to study the demographic and immunohistochemical characteristics of cases classified according to ALK protein positivity within this tumor population. Our aim was to study whether the features of

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these cases were comparable to our region and worldwide.

Materials and Methods

The Aga Khan University Hospital (AKUH) is a major tertiary care hospital located in Karachi, the largest metropolis of Pakistan. The section of Histopathology here is the largest center for histopathology in a densely populated country with an estimated population of 170 million. While most of the specimens received at the laboratory are from the southern province in which Karachi is located, overall the laboratory network of Aga Khan University Hospital (AKUH) serves as a referral center for the whole country through its 195 collection points. It is also one of the first laboratories in the region to receive the ISO 9001:2000 certification and the Joint Commission International Accreditation (JCIA). Specimens sent to the laboratory are received in 10% neutral buffered formalin. They are then routinely processed through alcohol and xylene and embedded in Paraffin. Also, besides H & E staining, sections are routinely stained with appropriate antibodies for precise categorization.

Our present study was a retrospective study conducted at the AKUH laboratory by reviewing the laboratory database for all cases of mature T-NHL diagnosed in five and a half years (between January 2005 and June 2010). The data in the laboratory database is classified using the International Classification of Diseases-Oncology (ICD-02) and the cases were retrieved accordingly. Demographics such as age, sex and location were noted along with details of the tumor such as the site, nodal or extranodal status and expression of various immmunohistochemical markers such as Ki-1 (CD30), Leukocyte Common Antigen (LCA), Epithelial Membrane Antigen (EMA), Anaplastic Lymphoma Kinase (ALK), Pan T (CD3) and Pan B (CD20 & CD79a) all from Dako (Denmark) by Envision technique. Positive and Negative controls were run and slides were interpreted by an internationally qualified faculty with a major interest in hematopathology. Cases were further analyzed in SPSS version 17.

Results

This present study included all mature T- and NK-cell neoplasms reported during the past five and a half years i.e. between Jan 2005 and June 2010. During this period, 178 specimens were classified as mature T- and NK-cell neoplasms on the basis of morphology and immunohistochemical staining. Out of these, there were a total of 100 cases that were diagnosed as systemic ALCL constituting an unusually large proportion (56.2%). There were also 3 cases of primary cutaneous ALCL diagnosed during this time constituting about 1.7% of tumors. Further, based on immunohistochemical staining for ALK-protein there were 43 (43%) cases that were classified as ALK-positive, 50 (50%) that were classified as ALK-negative and 7 (7%) that were not tested for ALK-protein.

Overall the mean age at presentation of ALCL in our study group was calculated to be 31.5 years with a strong

**Table 1. Sites of Nodal ALK-positive and ALK-negative Tumors**

Location	ALK+	ALK-
Cervical	6 (27.2%)	8 (29.6%)
Inguinal	5 (22.7%)	4 (14.8%)
Axillary	2 (9.1%)	2 (7.4%)
Mesenteric	3 (13.6%)	3 (11.1%)
Supraclavicular	1 (4.5%)	3 (11.1%)
Para-aortic	0 (0.0%)	1 (3.7%)
Submandibular	3 (13.6%)	0 (0.0%)
Iliac	0 (0.0%)	1 (3.7%)
Not Specified	2 (9.1%)	5 (18.5%)
Total	22 (100%)	27 (100%)

Table 2. Sites of Extra-Nodal ALK-positive and ALK-negative tumors

Location	ALK+	ALK-
GIT	3 (18.8%)	5 (26.3%)
Head & Neck	2 (12.5%)	4 (21.1%)
Reproductive Organs	1 (6.3%)	0 (0.0%)
Thorax	3 (18.8%)	1 (5.3%)
Breast	2 (12.5%)	1 (5.3%)
Skin	3 (18.8%)	0 (0.0%)
CNS	0 (0.0%)	2 (10.5%)
Axilla	0 (0.0%)	2 (10.5%)
Miscellaneous	2 (12.5%)	4 (21.1%)
Total	16 (100%)	19 (100%)
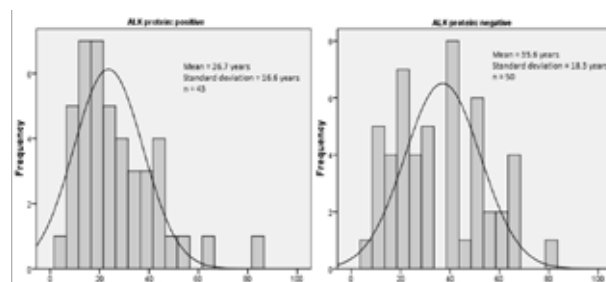
Figure 1. Comparison of age patterns seen in ALK+ ALCL and ALK- ALCL
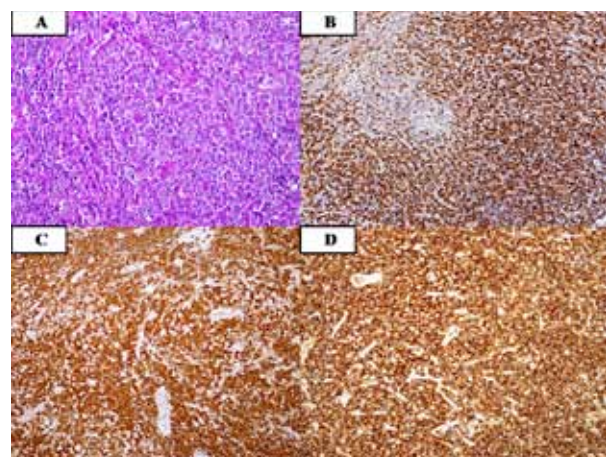
Figure 2. Morphology and Immunophenotype of Anaplastic Large Cell Lymphomas. (A) ALCL in a paraffin section (hematoxylin and eosin), (B) CD30 immunoreactivity of ALCL, (C) Immunoreactivity of an ALCL for the anaplastic lymphoma kinase protein (ALK protein) & (D) Immunoreactivity of an ALCL for Epithelial Membrane Antigen (EMA)

Table 3. Expression of Immunohistochemical Markers in ALK-positive and ALK-negative Tumors

	Ki-1 (CD 30)	LCA	EMA
ALCL ALK-Positive	100%	65.1%	95.3%
ALCL ALK-Negative	100%	58.0%	70.0%

male preponderance in ALCL with a ratio of 2.45:1. On further analysis based on expression of ALK-protein, the mean age for the ALK+ cases was 26.7 years with an age distribution shown in (see Figure 1). Also, these neoplasms had a gender ratio (M:F) of 2.3:1. As compared to these cases, the mean age for ALK- cases was 35.6 with an age distribution also shown in (see Figure 1). These neoplasms also had a higher gender ratio (M:F) of 2.5:1. Overall with regards to the sites of involvement; we found that in the ALK+ group, there were 22 (51.2%) nodal tumors, 16 (37.2%) extranodal tumors with the location of 5 (11.6%) tumors being unspecified. In comparison, in the ALK- group, there were 27 (54.0%) nodal tumors, 19 (38.0%) extranodal tumors and 4 (8.0%) tumors without a site specified. Further, sites of these two tumors were noted based on nodal and extra-nodal status (see Tables 1 and 2). Lastly, the frequencies of the expression of immunohistochemical markers like LCA, EMA and CD30 were recorded (see Table 3). We found that all the tumors, regardless of ALK protein expression, consistently expressed Ki-1 (CD30). However, both LCA and EMA expression was higher in the ALK positive group. According to our study there was 65.1% expression of LCA and 95.3% expression of EMA seen in this set as compared to that of 58% and 70% in the ALK- group. All these tumors were found to be T- or null-cell type.

Discussion

Non-Hodgkin's lymphoma (NHL) is a broad category encompassing a diverse array of B- cell and T-cell tumors. The latter sub-type is relatively uncommon, with an incidence of nearly 12% of all lymphomas (Jaffe et al., 1996; NHL Classification Project, 1997). Anaplastic large cell lymphoma (ALCL) is a CD30 (Ki-1 antigen) positive NHL of T-cell or null-cell pedigree, with trademark pathologic features of pleomorphic large neoplastic lymphoid cells. They usually grow in a cohesive pattern and have a predilection for intrasinusoidal dissemination within the lymph nodes (Stein et al., 2000).

There is a dearth of epidemiological studies conducted on NHL in developing countries. Studies done in this region on the prevalence of ALCL reported figures ranging from 1.5%, 2.3% and 4.3% in Japan (WHO, 2000), China (Chou et al., 1996) and India (Naresh et al., 2000) respectively. The proportion of ALCL cases in total NHL patient group was also found to be similar in western studies with figures from large studies of about 2.4% (NHL Classification Project, 1997).

Very few studies have calculated the percentage of ALCL cases within the mature T-cell or NK/T-cell lymphoma group. A recent study presented 198 cases of ALCL that constituted 20.6% of all patients in the category of mature T- or NK-cell lymphoma (Liang et al, 2010). Our results therefore showed an unusually high

proportion, with 56.2% of all diagnosed cases of mature T- or NK-cell lymphoma diagnosed as ALCL. To the best of our knowledge, this is the highest proportion of ALCLs ever reported. This suggests that ALCLs are a growing menace for the developing world. More epidemiologic studies on mature T- or NK-cell lymphomas should be done in our region to further validate these results showing astoundingly high proportion of ALCL cases.

In this study the mean age at presentation of ALCL in our study group was calculated to be 31.5 years. This was similar to other published studies in literature, with Park (Park et al., 2008), Greer (Greer et al., 1991) and Noorali (Noorali et al., 2004) reporting median ages in their results to be 39, 35 and 45 years respectively. Park and his group (Park et al., 2008) studied 36 cases of ALCL in which the male to female (M:F) ratio was 4.2:1. Gascoyne and his group (Gascoyne et al., 1999) examined 70 patients with systemic ALCL with a M:F ratio of 1.7:1. A previous study from our institution in 2004 by Noorali et al (Noorali et al., 2004) reported a M:F ratio of 3.4:1. We further confirm these findings of strong male preponderance in ALCL with a ratio of 2.45:1 in our results.

Initial efforts to achieve an international agreement on the classification of lymphoid diseases were based on "The Working Formulation". However, these results were published prior to Stein et al's description of ALCL in 1985. Further progress for International consensus was accomplished though publication of Revised European-American Classification of Lymphoid Neoplasms (REAL). ALCL was included under the category of 'Peripheral T-cell and NK-cell Neoplasms' and its description here took account of its clinical, histopathological and immunophenotypic features, along with cytogenetics (Harris et al., 1994). Soon after this classification, the t(2;5) mutation rearrangement which caused fusion of the nucleophosmin (NPM) gene on chromosome 5q35 with a protein tyrosine kinase gene ALK on chromosome 2p23 was discovered. Finally in 2008, the World Health Organization (WHO) classification of lymphomas included the complete profile of ALCL, including its clinical, histopathological, immunophenotypical, cytogenetic and molecular features. According to this classification, ALCL was divided into cutaneous and systemic clinical subtypes, the latter being further divided into ALK-positive and ALK-negative ALCL neoplasms (Swerdlow et al 2008). ALK expression is highly specific for primary ALCL and is not found in Hodgkin's lymphoma (Pulford et al.,1997).

ALK positivity in studies may be influenced by the median age of the population studied and the pathologic criteria used for diagnosis. We studied 100 patients with ALCL, of which 43% were found to be ALK positive and 50% as ALK negative. The frequency of ALK expression reported in other studies has been 51% (Gascoyne et al., 1999), 34% (Agarwal et al., 2002), 43% (Park et al., 2008) and 45% (Savage et al., 2008), which is quite comparable to our results. However, Benharroch et al (1998) studied 123 cases of ALK+ ALCL out of their cases of ALCL and found the frequency of ALK positivity to be as high as 85%.

As depicted in this study, ALK+ patients in our study were more likely to be younger as compared to the ALK-

cases (mean age 26.7 vs 35.6 years). This is in agreement with the results of previous studies (Park et al., 2008); (Savage et al., 2008). Furthermore, we showed that ALK+ patients were more likely to test positive for EMA (95.3% vs 70.0%), a finding also observed by Savage and his group (Savage et al., 2008) in 2008. Conversely, the frequency of Leukocyte Common Antigen expression was the same in both ALK+ and ALK- groups.

Current data on gene expression and comparative genomic hybridization have confirmed ALK+ ALCL to be a distinct entity from ALK- ALCL at a molecular and genetic level (Lamant et al., 2007); (Salaverria et al., 2008). In addition, several studies have proved ALK+ALCL to have a comparatively better prognosis than ALK- disease (Gascoyne et al., 1999); (Falini et al., 1999); (ten Berge et al., 2000). This suggests that it is very important to distinguish between the two subsets of the ALCL.

According to the WHO classification, ALK- ALCL is defined as a 'lymphoma that is morphologically within the spectrum of ALK+ ALCL, with strong and uniform expression of CD30, but lacking ALK protein expression' (Medeiros and Elenitoba-Johnson, 2007). The prognosis of ALK- disease was found to be very similar to that of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) (ten Berge et al., 2003a). It has thus been speculated if ALK- is actually a variant of PTCL-NOS (Medeiros and Elenitoba-Johnson, 2007) (ten Berge et al., 2003b). However, a number of clinical and pathologic differences between the two entities have made this association unlikely. Patients with ALK- ALCL were less likely to have splenic or bone marrow involvement and thrombocytopenia compared to PTCL-NOS. They had a much improved performance status and fewer B symptoms as well. Pathological assessment also revealed differences between the two entities, with ALK- ALCL being ubiquitously CD30 positive, and comparatively more likely to express cytotoxic marker and EMA. ALK- ALCL was also less likely to be positive for several T-cell markers, such as CD2, CD3, CD4 and CD43, when compared to PTCL(Savage et al., 2008).

Generally speaking, lymphomas with clinically significant lymph node involvement are regarded as primary nodal lymphomas. Conversely, those that present as a disseminated disease or with minimal nodal involvement are considered primary extranodal lymphomas. We studied the nodal and extra-nodal sites harbored by both ALK+ ALCL and ALK- ALCL tumors. Within the ALK+ group, 51.7% of the cases had a nodal disease while 37.2% had significant extra-nodal involvement. This was similar to findings in the ALK- cluster with 54.0% and 38.0% for nodal and extra-nodal involvement, respectively. The location of small minority of the cases in both groups was not specified. Furthermore, we also looked at the specific sites that were involved in both the groups. Cervical and Inguinal nodes were mostly commonly reported sites for nodal disease in both ALK+ and ALK- groups. For extra-nodal involvement, ALK+ population showed gastrointestinal tract, thorax and skin to be the predominant locations. Although ALK- cluster also demonstrated GIT to be the most commonly

involved extra-nodal site, the involvement of thorax and skin was almost non-existent. Savage and his group (Savage et al., 2008) collected data from 22 organizations encompassing Asia, Europe and North America and found differing patterns between the two subsets of ALCL with respect to the extra-nodal sites harbored by these tumors. Spleen, bone marrow and subcutaneous tissues were more commonly involved areas for ALK+ ALCL while skin, liver and GIT were more likely to be involved in ALK- ALCL. Thus our findings need further validation by more studies to further clarify the clinical differences between these tumors in our population. It is through this process that we will be able to stratify our patients and treat them accordingly.

Thus, in conclusion, ALCL is a growing menace in the developing world, constituting an unusually large fraction of the mature T- or NK-cell lymphoma group. The disease commonly affects the adult male population, and ALK positivity correlates inversely with the mean age on presentation. ALK expression may also be directly linked to EMA positivity. We did not find any notable differences in the nodal and extra-nodal involvement patterns between ALK+ and ALK- disease subtypes. ALK+ ALCL has proven to have a better overall survival compared to the ALK- variants. Previous studies have demonstrated a less favorable prognosis of ALCL in Asia when compared with the data from western countries (Ko et al., 2009). The unusually large proportion of ALCL cases as seen in our results is thus a matter of great concern for practicing physicians and effective therapeutic and preventive steps are mandated to curtail this epidemic in the years to come.

Acknowledgements

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