Non-Hodgkin's Lymphomas in Pakistan: Does Late Diagnosis Fully Explain Transformation into Diffuse Aggressive Lesions?

Pages with reference to book, From 102 To 102

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Non-Hodgkin's lymphomas (NHL) are the most frequent tumours occurring in patients between the ages of 20-40 and include several distinct clinico-pathologic sub-types, among which diffuse lymphoma is the most clinically relevant in terms of morbidity and mortality[1]. Diffuse large cell lymphomas include intermediate grade lymphomas with pure diffuse large or mixed small and large histology, as well as high grade inimunoblastic lymphomas[2]. In essence, diffuse large cell lymphomas represent a heterogenous group of neoplasms that are treated homogenously.

In contrast to diffuse B NHLs, follicularlymphomas are exceptionally rare in our setting. In a recent study by us in which 103 consecutive lymphomas were classified and immunophenotyped, only two were follicular[3]. Similar results are reported from AFIP, Rawalpindi[4]. In a sharp contrast to this, for instance, in USA 40% of adults NHL are follicular[2]. A question then arises and is frequently addressed that whether it is the late diagnosis which allows most follicular lymphomas to transformto diffuse lymphomas before they are picked. However, we must remember that the natural history of these two entities is quite different. A great majority of follicular lymphornas (approx. 80-90%) on presentation are already stage Ill-IV disease with bone marrow involvement and multiple lymph node enlargements. In comparison, most diffuse large cell NHL present as a single lymph node enlargement while approximately 50% are stage I or II at the time of diagnosis[2]. Therefore, this cannot be presumed that all diffuse B cell lymphomas were originally follicular neoplasms.

Otherevidence comes from genetic differences between follicular versus diffuse B cell lymphomas. Translocation (14:18) involving rearrangement of the bcl-2 gene with resultant bcl-2 protein expression is present in 70% to 95% of follicularlymphoma cases[5], while only about 20% of diffuse B cell NHL show this translocation6. Because of these clinical and genetic differences, itcanbe concluded that large majority of diffuse B cell NHLs originate 'de novo' while less than 1/4th probably result from transformation of follicular lymphomas. Recently, it was shown that among heterogenous diffuse large B cell spectrum translocation (3:22) i.e., bcl-6 rearrangements were significantly more frequent in tumours displaying a pure diffuse large cell histology, all of which lacked bcl-2 rearrangements. Considering that diffuse large cell lymphomas[6] can originate both 'de novo' and from the transformation of follicular lymphoma and that the latter typically carries bcl-2 rearrangements, it suggests that bcl-6 rearrangements may be specifically involved in the pathogenesis of 'de novo' diffuse large B cell lymphomas[7]. In a recent study by us, it was shown that a significant proportion of diffuse NHL (39%) were of T cell phenotype[3]. This is again much unusual as in most European and US studies, these tumours comprise less than 15% of lymphomas. It is well known that T cell neoplasms tend to do worse than B cell neoplasms with more chances of recurrence. This may partly add to the aggressive nature of our NHL. However, this question needs to be further addressed and investigated with the help of gene rearrangement studies.

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