Changes in Diagnosis of Non-Hodgkin's Lymphomas over Time

Peter M. Banks

Cancer Res 1992;52:5453s-5455s. Published online October 1, 1992.

[CANCER RESEARCH (SUPPL.) 52, 5453s–5455s, October 1, 1992]

Changes in Diagnosis of Non-Hodgkin's Lymphomas over Time[1]

Peter M. Banks

Department of Pathology, University of Texas Health Science Center at San Antonio, San Antonio, Texas 78284-7750

Abstract

The question is raised as to whether changes in criteria for the diagnosis of non-Hodgkin's lymphomas, both clinical and pathological, have changed over the past four decades in sufficient scale to create a spurious increase in the apparent incidence of this grouping of disease. In the decade of the 1970s refinement in histomorphological criteria for the diagnosis of Hodgkin's disease resulted in as many as 10–15% of cases which previously would have been diagnosed as Hodgkin's disease being diagnosed instead as non-Hodgkin's lymphoma. Other considerations, including distinction of non-Hodgkin's lymphomas from leukemias and plasma cell myelomas, and recent recognition of angioimmunoblastic lymphadenopathy and extranodal "pseudolymphomas" as variant forms of non-Hodgkin's lymphoma, appear to have added only marginally to the total of reported cases. It is concluded that the increase in reported incidence of non-Hodgkin's lymphoma cannot be explained on the basis of changes in diagnostic criteria.

Introduction

One important consideration in judging the validity of reported increase in incidence of non-Hodgkin's lymphomas pertains to the criteria used for diagnosing this grouping of disease. If criteria, clinical and pathological, have changed during the time period, then the apparent change in incidence could be spurious. Because our understanding and classification of the non-Hodgkin's lymphomas have been revolutionized by applications of new concepts and methods of immunology over the past two decades, a detailed review of this issue is warranted.

Closely Related Malignancies

In the case of some lymphoid malignancies, their designation as malignant lymphoma depends primarily on the topographic distribution of disease. Modern immunophenotyping studies have confirmed the unity of processes which can be considered either leukemia or lymphoma, according to whether the process is widely dispersed (leukemic) or localized as tumor-forming masses (lymphoma) (1). Common examples include low-grade small lymphocytic lymphoma and chronic lymphocytic leukemia (2), and lymphoblastic lymphoma and acute lymphoblastic leukemia (3). Similarly, immunosecretory neoplasms of either low or high grade can be considered plasmacytic lymphoma or plasmacytoma (myeloma in bony tissues). The distinction is generally straightforward on the basis of clinical findings, in particular the anatomy of the disease process; however, in a small minority of cases there are overlapping features (4).

Confusion has occurred when different terminologies are applied by various pathologists to entities in these paired groups. For example, in Europe the term "B-chronic lymphocytic leukemia" of the Kiel classification is used for all low-grade neoplasms of small lymphocytic composition lacking immunosecretory differentiation, even when neither bone marrow nor peripheral blood is involved (5).

For the purposes of this Workshop, the question to be asked is whether over the past four decades there has been any trend among clinicians, as well as pathologists, toward considering these malignancies lymphomas rather than leukemias (or plasma cell neoplasms). The answer is definitely no. Indeed, to the contrary, with advancement in our understanding of the pathobiology of these processes, pathologists, oncologists, and hematologists together have learned the importance of staging evaluation early in the evaluation of patients suffering such diseases. In current practice patients will often undergo initial peripheral blood and bone marrow analysis prior to resection or biopsy of lymph nodal or mediastinal tumor, on the basis of clinical suspicion that the process may have a leukemic (or myelomatous) component which would avoid the need for surgery. Therefore, trends in clinical practice should be working to reduce rather than increase the reporting of this grouping as lymphoma (6).

Distinction from Hodgkin's Disease

Since Hodgkin's disease is the grouping of lymphomas in contradistinction from all others, *i.e.*, the "non-Hodgkin's" lymphomas, and because it is a relatively common lymphomatous malignancy in North America and Europe, this represents an obvious source for recruitment of cases. Have the criteria for distinguishing Hodgkin's from non-Hodgkin's lymphomas changed? The answer is yes, without doubt.

In the simpler, traditional classification of lymphomas which prevailed prior to 1970, some cases considered to be Hodgkin's disease would instead be classified as non-Hodgkin's lymphoma based on more modern concepts (see Fig. 1). While the presence of large Reed-Sternberg tumor giant cells was long emphasized as the essential criterion for establishing the diagnosis of Hodgkin's disease histologically, the Rappaport classification system in 1966 (7), as well as a separate study directed toward this issue itself (8), emphasized the benign-appearing tissue background cellularity surrounding such tumor cells as specific for Hodgkin's disease. This allowed inclusion of cases with large tumor giant cells in the setting of a histologically neoplastic background into the non-Hodgkin's lymphomas. More recent studies utilizing immunophenotyping methods have identified variant forms of T-cell lymphomas (9) and so-called anaplastic large-cell lymphomas (10), which would earlier have been classified as Hodgkin's disease (see Fig. 2). In aggregate, these changes in pathological criteria have resulted in recruitment of about 10–15% of the cases which would have been diagnosed as Hodgkin's disease 30 to 40 years ago into the grouping of non-Hodgkin's lymphomas today. While some small percentage of switchover from Hodgkin's disease is the result of special immunological studies available only in the last decade, most of this change was effected in the early 1970s on the basis of more precise histomorphological criteria and clinical correlation. Therefore, whatever increase in the reporting of non-Hodgkin's lymphomas derives from earlier assignment to Hodgkin's disease is confined, for the most part, to the era from 1950 to 1970 and not in the recent decades.

Newly Recognized Variant Forms of Lymphoma

Although the Working Formulation for classifying non-Hodgkin's lymphomas has proved to be a useful and practical

[1] Presented at the National Cancer Institute Workshop, "The Emerging Epidemic of Non-Hodgkin's Lymphoma: Current Knowledge Regarding Etiological Factors," October 22–23, 1991, Bethesda, MD.

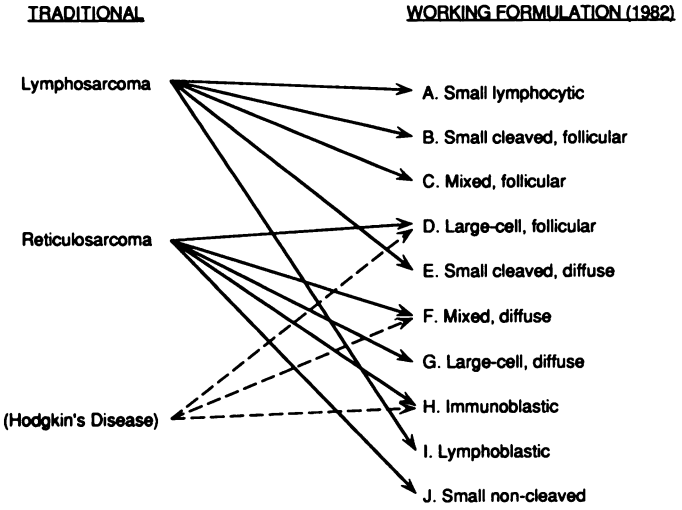

Fig. 1. A comparison of traditional lymphoma classification simplified into three categories with the Working Formulation. As high a portion as 10 or even 15% of cases diagnosed originally as Hodgkin's disease between 1950 and 1970 would now be diagnosed instead as non-Hodgkin's lymphomas in Working Formulation categories D, F, H.

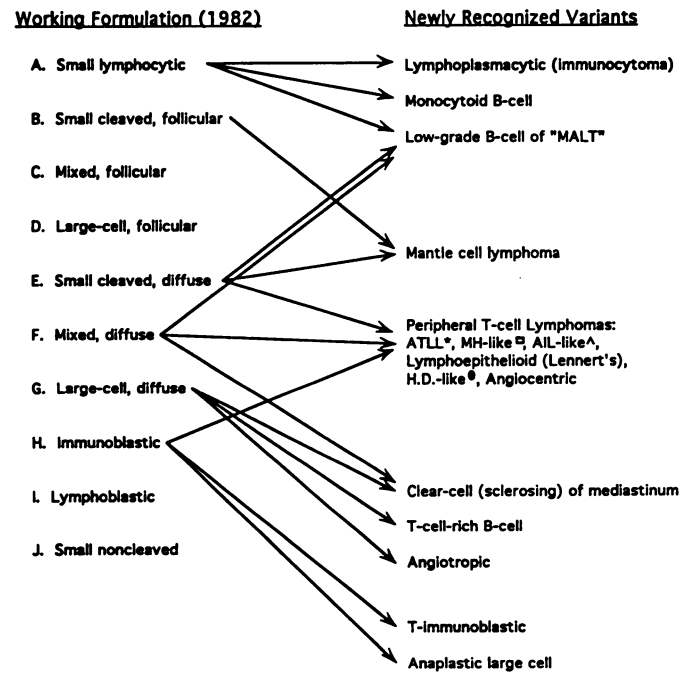

Fig. 2. Newly recognized distinct variants of non-Hodgkin's lymphomas are related to categories in the Working Formulation. ATLL, adult T-cell leukemia/lymphoma; MH, malignant histiocytosis; AIL, angioimmunoblastic lymphadenopathy; H.D.-like, Hodgkin's disease-like.

system, it is necessarily limited by its dependence upon conventional histomorphological information only (11). Since the publication of the Working Formulation in 1982, considerable resolution of distinct variants of non-Hodgkin's lymphomas has been achieved through the correlation of detailed immunophenotyping with histological and clinical parameters (12) (Fig. 2). Of course, in general this is of no consequence in regard to the overall occurrence of non-Hodgkin's lymphomas. However, in respect to two entities there is recruitment of cases from what previously were considered benign lymphoid disorders.

First, the disease process originally described as angioimmunoblastic lymphadenopathy has been shown to share many features of non-Hodgkin's lymphoma, such that, in the larger proportion of cases these are now considered (angioimmunoblastic lymphadenopathy-like) T-cell lymphomas (13).

Second, Isaacson and Wright (14) have called attention to a favorable variant of lymphoma which arises in, and often long remains confined to, extranodal mucosal tissues. They have called these low-grade B-cell lymphomas of mucosa-associated lymphoid tissues. Recent studies have documented the presence of such tumors in a large diversity of extranodal organ sites (15). Although advanced cases of this disease process were doubtless recognized even in the past as lymphomas, many were considered so-called pseudolymphomas (16).

Can the newly gained recognition of these two variant forms of lymphoma account for the reported increase in non-Hodgkin's lymphomas over the past decade? Both variant forms are relatively rare, together contributing less than 3% of non-Hodgkin's lymphomas in the massive German lymphoma registry in Kiel (17, 18). Therefore, although the addition of these variants has added to the identification of cases as non-Hodgkin's lymphomas in recent years, there seems to be only a very small increment.

Summary

While there has been considerable progress in understanding the biology of non-Hodgkin's lymphomas, with resultant change in classification over the past two decades, the only impact in relation to reported incidence derives from changes in criteria for the distinction of Hodgkin's disease *versus* non-Hodgkin's lymphoma. In testing whether such a change in pathological diagnosis could account for observed incidence changes, the periods for differing criteria correspond approximately to before and after 1970.

Acknowledgments

The author is grateful to Linda Streckfus for the preparation of this manuscript.

References

1. Foon, K. A., and Todd, R. F., III. Immunologic classification of leukemia and lymphoma. Blood, *68:* 1–31, 1986.
2. Dick, F. R., and Maca, R. D. The lymph node in chronic lymphocytic leukemia. Cancer (Phila.), *41:* 283–292, 1978.
3. Cossman, J., Chused, T. M., Fisher, R. I., Magrath, I., Bollum, F., and Jaffe, E. S. Diversity of immunological phenotypes of lymphoblastic lymphoma. Cancer Res., *43:* 4486–4490, 1983.
4. Strand, W. R., Banks, P. M., and Kyle, R. A. Anaplastic plasma cell myeloma and immunoblastic lymphoma. Clinical, pathologic, and immunologic comparison. Am. J. Med., *76:* 861–867, 1984.
5. Lennert, K. Chronic lymphocytic leukemia of B-cell type (B-CLL). *In:* Histopathology of Non-Hodgkin's Lymphomas, pp. 26–32. New York: Springer Publishing Co., 1981.
6. Lester, E. P., and Ultmann, J. E. Lymphoma. *In:* W. J. Williams, E. Beatler, A. J. Erslev, and M. A. Lichtman (eds.), Hematology, Ed. 4, p. 1075. New York: McGraw-Hill, 1990.
7. Rappaport, H. Tumors of the hematopoietic system. *In:* Atlas of Tumor Pathology, Sect. III, Fascicle 8. Washington, DC: Armed Forces Institute of Pathology, 1966.
8. Strum, S. B., Park, J. K., and Rappaport, H. Observation of cells resembling Sternberg-Reed cells in condition other than Hodgkin's disease. Cancer (Phila.), *26:* 176–184, 1970.
9. Weiss, J. W., Winter, M. W., Phyliky, R. L., and Banks, P. M. Peripheral T-cell lymphomas: histologic, immunohistologic, and clinical characterization. Mayo Clin. Proc., *61:* 411–426, 1986.
10. Rosso, R., Paulli, M., Magrini, U., *et al.* Anaplastic large cell lymphoma, CD30/Ki-1 positive, expressing the CD15/Leu-M1 antigen. Immunohistochemical and morphological relationships to Hodgkin's disease. Virchows Arch. A Pathol. Anat. Histopathol., *416:* 229–235, 1990.
11. The Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas. Summary and description of a working formulation for clinical usage. Cancer (Phila.), *49:* 2112–2135, 1982.

12. Banks, P. M. Newly recognized variant forms of non-Hodgkin's lymphomas. Hematol. Oncol. Clin. N. Am., *5:* 935–952, 1991.
13. Feller, A. C., Griesser, H., Schilling C. V., *et al.* Clonal gene rearrangement patterns correlate with immunophenotype and clinical parameters in patients with angioimmunoblastic lymphadenopathy. Am. J. Pathol., *133:* 549–556, 1988.
14. Isaacson, P., and Wright, D. H. Extranodal malignant lymphoma arising from mucosa-associated lymphoid tissue. Cancer (Phila.), *53:* 2515–2524, 1984.
15. Pelstring, R. J., Essell, J. H., Kurtin, P. J., Cohen, A. R., and Banks, P. M. Diversity of organ site involvement among malignant lymphomas of mucosa-associated tissues. Am. J. Clin. Pathol., *96:* 738–745, 1991.
16. Saltzstein, S. L. Pulmonary malignant lymphomas and pseudolymphomas: classification, therapy, and prognosis. Cancer (Phila.), *16:* 928–955, 1963.
17. Lennert, K., and Feller, A. C. Seltene B-Zellenlymphome. *In:* Histopathologie der Non-Hodgkin-Lymphome (nach der aktualisierten Kiel-Klassifikation), p. 141. Berlin: Springer-Verlag, 1990.
18. Lennert, K., and Feller, A. C. T-Zellenlymphome vom AILD (Lgrx)-Typ. *In:* Histopathologie der Non-Hodgkin-Lymphome (nach der aktualisierten Kiel-Klassifikation), p. 186. Berlin: Springer-Verlag, 1990.