Acta Oncologica Vol. 30 No. 5 1991

FROM THE CLINICAL CYTOLOGY LABORATORY, THE DEPARTMENTS OF PATHOLOGY AND ONCOLOGY, AND THE CENTRE OF ONCOLOGY, UNIVERSITY HOSPITAL, UMEÅ, SWEDEN.

HODGKIN'S DISEASE IN NORTHERN SWEDEN 1971–1981

I. A histopathological reevaluation of 223 cases

U. DIGE, H. JOHANSSON, P. LENNER, B. NORBERG and G. ROOS

Abstract

A histopathological reexamination was made of diagnostic material in 223 patients with Hodgkin's disease (HD) collected between 1971 and 1981. The diagnosis of HD was considered to be incorrect in 90 cases (40%). Change of diagnosis to non-Hodgkin's lymphoma was made in 56 cases, of which 23 were high-grade and 26 were low-grade lymphomas (7 not determined), and to angioimmunoblastic lymphadenopathy in 10 cases. These discrepancies were considered to be due mainly to progress in the understanding and classification of malignant lymphomas, which stresses the importance of review of histologic material in retrospective studies on Hodgkin's disease.

Key words: Hodgkin's disease, histopathology, reevaluation.

The classification of malignant lymphomas has improved significantly during the last two decades. This is particularly true for non-Hodgkin's lymphomas (NHL) mainly due to advances in immunophenotyping, cytogenetics and molecular biology (1, 2). Modern classifications, e.g. the Kiel classification (3), which are based on a modern view on the origin of lymphoma cells, have defined new entities of non-Hodgkin's lymphomas. Besides, different types of Hodgkin-like T-cell disorders like angioimmunoblastic lymphadenopathy (AILD) have been better characterized. The improved classification of these disorders has made the borderline sharper towards Hodgkin's disease (HD) and thus diminished the differential diagnostic problems.

Although the diagnostic improvements for non-Hodgkin's lymphomas have been of importance for clarifying the borderline towards HD, the diagnostic criteria for this disease are still based on the system proposed in 1966 by Lukes and Butler and later modified at the Rye Conference (4, 5).

With this background we made a histopathological reexamination of 223 cases of HD diagnosed 1971–1981. This reevaluation was the initial part of a clinical retrospective study of HD presented in two following papers (6, 7).

Material and Methods

During the period 1971–1981, 223 patients with a diagnosis of HD were admitted to the Department of Oncology, Umeå, for staging and treatment. Follow-up data for these patients were collected from the clinical records. Survival curves were generated by the life-table method (8).

For 214 of the 223 patients the HD diagnosis was based on paraffin-embedded biopsy material and for 9 patients on fine-needle aspiration smears only. All relevant material was independently reexamined by two of us (UD, GR).

Due to technical reasons material from several patients was resectioned and stained with hematoxylin-eosin, Giemsa and periodic acid-Schiff. In selected cases immunohistochemical stainings were applied using peroxidase-anti-peroxidase technique. Antibodies used were directed against kappa and lambda light chains, lysozyme and alpha-1-antitrypsin (Dakopatts A/S, Denmark). The Leu-M1 antibody (Becton/Dickinson AB, Stockholm, Sweden), which has been claimed to be useful in establishing a diagnosis of HD (9), was tested in selected cases. The classification of HD proposed at the Rye Conference (5) was used. Lesions judged as non-Hodgkin's lymphomas were classified according to the Kiel classification (3).

Submitted 27 June 1989.
Accepted for publication 31 August 1990.

Table 1

Morphologic diagnoses after reexamination of 223 Hodgkin's disease cases

Diagnosis	n	%
Hodgkin's disease	133	60
Non-Hodgkin's lymphoma	56	25
Angioimmunoblastic lymphadenopathy	10	4
Malignancy NUD	6	3
Benign lymphadenopathy	7	3
Unsatisfactory material	11	5
Total	223	100

Results

In 133 of the initial 223 patients (60%) the diagnosis of HD was accepted upon review. This figure changed the frequency of HD among all lymphomas to approximately 15% during the studied period. Most diagnostic discrepancies were considered to represent non-Hodgkin's lymphomas, although a significant number of patients with AILD was also found (Table 1). A benign diagnosis was made in 7 cases. Available material was considered as unsatisfactory and not useful for diagnostic purposes in 11 cases. Among the non-Hodgkin's lymphomas, 26 were classified as low-grade and 23 as high-grade, whereas the material was considered inadequate for such subdivision in 7 cases.

In cases accepted as HD the best agreement was achieved for the nodular sclerosis (NS) type. Altered HD diagnoses were mainly found among cases initially diagnosed as lymphocytic predominance (LP) or lymphocytic depletion (LD) subtypes (Table 2). Most low-grade non-Hodgkin's lymphomas were found in the LP group and most high-grade lymphomas in the LD group. HD diagnoses considered incorrect were more often found in elderly patients than in the younger age group (Fig. 1). The Leu-M1 antibody was not found to be a reliable HD-marker, since many morphologically typical HD lesions

Table 2

Hodgkin's disease subtypes before and after reexamination

Subtype	Before		After	
	n	%	n	%
Lymphocytic predominance	44	20	19	15
Nodular sclerosis	29	14	30	23
Mixed cellularity	107	50	71	56
Lymphocytic depletion	33	16	8	6
Total	214	100	128	100
Subtype not established (cytological material)	9		5	

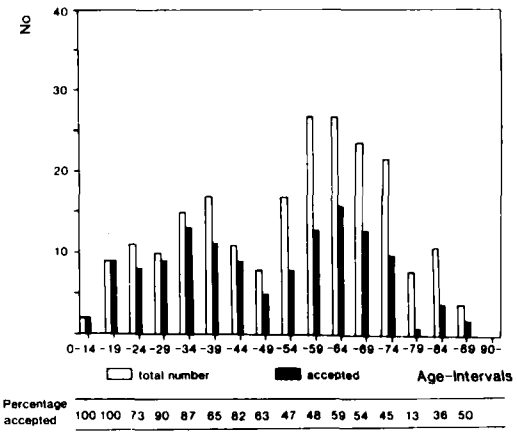

Fig. 1. Age distribution for the total number of patients before histo-pathological reexamination (n = 223) and for the accepted HD-cases (n = 133). The percentage of accepted diagnoses in different age-intervals are given below.

were negative for this marker. Also, a positive reaction could sometimes be found in cells not considered as Hodgkin- or Reed-Sternberg cells.

Clinical follow-up revealed a slightly better prognosis for patients with accepted HD diagnosis after review compared to the initial patient group (Fig. 2). Up to 7 years observation of the reclassified material showed unfavourable survival curves for patients with AILD and high-grade non-Hodgkin's lymphomas, whereas HD and low-grade lymphomas had clearly better prognosis (Fig. 3).

Discussion

In the present reclassification it was demonstrated that previous HD diagnosis could not be accepted in 40% of cases, which must be considered as a high figure. Other studies have reported a change of HD diagnosis in 6–47%

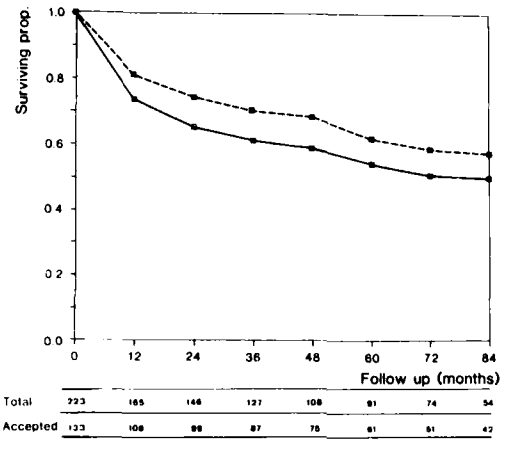

Fig. 2. Life-table survival for the total number of patients before histo-pathological reexamination and for the accepted HD-cases. —□— = total material; —■— accepted as HD.

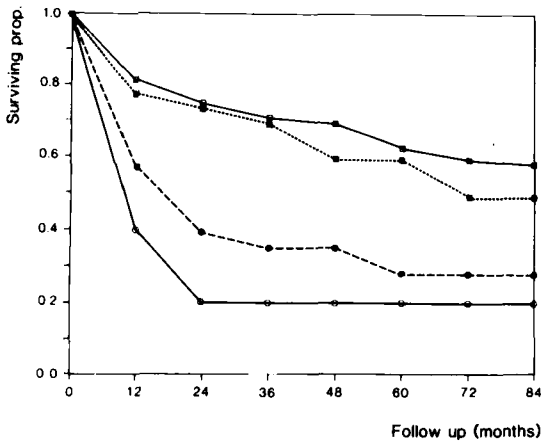

Fig. 3. Life-table survival for the different diagnoses established by histo-pathological reexamination: □— HD (n = 133); ■- - - - non-Hodgkin lymphomas low-grade (n = 26); ●- - - non-Hodgkin lymphomas—high grade (n = 23); ○— angio-immunoblastic lymphadenopathy—AILD (n = 10).

of cases (10–14). We believe that modern classifications of non-Hodgkin's lymphoma, like the Kiel classification, have facilitated the discrimination between HD and non-Hodgkin's lymphomas. As a consequence, the higher incidence of HD in our region before 1981 than after can mainly be attributed to altered diagnostic criteria.

In HD the morphologic features of the subtypes NS and mixed cellularity (MC) are easiest to recognize. Thus, most diagnostic failures were found in the LP and LD subgroups. It is not surprising that relatively recently characterized disorders such as AILD and Lennert's lymphoma were diagnosed as HD before these conditions were recognized.

For fresh samples and frozen sections the Ki-1 antibody may be useful in establishing a diagnosis of HD (15). The Ki-1 antibody is, however, not specific for Hodgkin- or Reed-Sternberg cells. Moreover, it cannot be applied on paraffin-embedded material (16). The Leu-M1 antibody has been claimed to be a marker of HD in paraffin sections. This contention could, in agreement with the findings of others (17), not be verified in the present study. Thus, no reliable immunohistochemical markers for HD are at present available for retrospective studies. However, a helpful criterion for establishing a diagnosis of non-Hodgkin's lymphoma is for example the presence of monoclonal cytoplasmic Ig.

It is of course not possible in every case to prove that the altered diagnosis is more accurate than the original one. However, the clinical course for the main morphologic groups gives some justification for the results of the reclassification. Two groups with a poor prognosis were found, namely AILD and high-grade non-Hodgkin's lymphomas. Since we do not know what the results would have been with other treatment for the AILD patients, we cannot state precisely whether standard treatment for stage IV HD was accurate or not. The observed survival curve for high-grade non-Hodgkin's lymphomas is quite characteristic for these disorders with a high death rate during the first two years. The fraction of these patients showing long-term survival is comparable to that found in other patient material treated by protocols designed for non-Hodgkin's lymphomas (18–20). The survival curve for low-grade lymphomas was similar to that for HD and comparable to those found in other studies (18, 20).

In conclusion, a high fraction of HD diagnoses was retrospectively considered to be wrong. It must be stressed that in retrospective clinical studies of malignant lymphomas, morphologic reexamination of the diagnostic material is necessary in order to achieve a solid base for evaluation of clinical results.

ACKNOWLEDGEMENTS

This study was supported by the Swedish Cancer Society and Lions Cancer Research Foundation, Umeå, Sweden.

Corresponding author: Dr Bengt Norberg, Department of Oncology, Central Hospital, S-551 88 Jönköping, Sweden.

REFERENCES

1. Habeshaw JA. Specialized laboratory methods. In: Stansfeld AG, ed. Lymph node biopsy interpretations. London: Churchill Livingstone, 1985; 44–46.
2. Goldman JM, Marnden DG, eds. Genetic rearrangements in leukemia and lymphoma. Leukemia and lymphoma research 2. London: Churchill Livingstone, 1986.
3. Lennert K. Classification of non-Hodgkin's lymphomas. In: Lennert K, Mohri N, Stein H, Kaiserling E, Muller-Hermeling HK, eds. Malignant lymphomas other than Hodgkin's disease. Histology, cytology, ultrastructure, immunology. Berlin: Springer-Verlag 1987: 83–110.
4. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the committee of Hodgkin's disease staging classification. Cancer Res 1971; 31: 1860–1.
5. Lukes RJ, Carver LF, Hall TC. Report of the nomenclature committee. Cancer Res 1966; 26: 1311.
6. Norberg G, Dige U, Roos G, Johansson H, Lenner P. Hodgkin's disease in Northern Sweden 1971–1981. II. A retrospective analysis of prognostic factors. Acta Oncol 1991; 30: 597–601.
7. Norberg B, Dige U, Roos G, Johansson H, Lenner P. Hodgkin's disease in Northern Sweden 1971–1981. III. The clinical and prognostic impact of age. Acta Oncol 1991; 30. (Accepted for publication).
8. Lee ET. Statistical methods for survival data analysis. Belmont Lifetime Learning Publ 1980; 75–156.
9. Pinkus GS, Thomas P, Said JW. Leu-M1—A marker for Reed-Sternberg cells in Hodgkin's disease. An immunoperoxidase study of paraffin-embedded tissues. Am J Pathol 1985; 119: 244–52.
10. Symers W. Survey of the eventual diagnosis in 600 cases referred for second histologic opinion. J Clin Pathol 1968; 21: 650–3.
11. Hancock BW, Aitken M, Martin JF, et al. Hodgkin's disease in Sheffield (1971–76) (with computer analysis of variables). Clin Oncol 1979; 5: 283–97.

12. Miller TP, Byrne GE, Jones SE. Mistaken clinical and pathological diagnoses of Hodgkin's disease: A Southwest Oncology Group study. Cancer Treat Rep 1982; 66: 645–51.
13. Nordentoft AM, Pedersen-Bjergaard J, Brincler H, et al. Hodgkin's disease in Denmark. A national clinical study in the Danish Hodgkin study group. LYGRA. Scand J Haematol 1980; 24: 321–34.
14. Franssila KO, Heiskala MK, Heiskala HJ. Epidemiology and histopathology of Hodgkin's disease in Finland. Cancer 1977; 39: 1280–8.
15. Stein H, Gerdes J, Schwab U, et al. Identification of Hodgkin and Reed-Sternberg cells as a unique cell type derived from a newly detected small-cell population. Int J Cancer 1982; 30: 445–59.
16. Schwab U, Stein H, Gerdes J, et al. Production of a monoclonal antibody specific for Hodgkin and Reed-Sternberg cells of Hodgkin's disease and a subset of normal lymphoid cells. Nature 1982; 299: 65–7.
17. Sheibani KS, Battifora H, Burke JS, Rappaport H. Leu-M1 antigen in human neoplasms. An immunohistologic study of 400 cases. Am J Surg Pathol 1986; 10: 227–36.
18. Rosenberg SA. Current concepts in cancer: Non-Hodgkin's lymphomas—selection of treatment on the basis of histologic type. N Engl J Med 1979; 301: 924–8.
19. DeVita VT, Canellos CP, Chabner B, Schein P, Hubbard SP, Young RC. Advanced diffuse histiocytic lymphoma, a potentially curable disease. Results with combination chemotherapy. Lancet 1975; 1: 248–50.
20. Brittinger B, Bartels H, Common H, et al. Clinical and prognostic relevance of the Kiel classification of non-Hodgkin lymphomas—results of a prospective multicenter study by the Kiel lymphoma study group. Hematol Oncol 1984; 2: 269–306.