RELATIONSHIP OF HISTOLOGIC FINDING TO CLINICAL STAGES IN HODGKIN'S DISEASE

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INTRODUCTION

The significance of the wide variation in histologic features in Hodgkin's disease has perplexed pathologists since the initial microscopic studies of Greenfield in 1878 and provided the basis for the still existent controversy over the precise nature of the disease. Clinicians have been similary puzzled by the different clinical forms varying from a fulminating febrile form of a few months' duration to a prolonged asymptomatic course of 15 or more years.

A direct relationship between survival and lymphocytic proliferation associated with infrequency of abnormal reticulum cells was reported first by Rosenthal. The description of the paragranuloma type of Hodgkin's disease by Jackson and Parker, however, represented the initial association of histologic features wich localized disease manifestations and slowly progressive disease. This association has been supported by Harrison in a study of prolonged survivors and also by Wright. The distinctive histologic character of this lymphocytic proliferation, however, was sufficient for Smetana and Cohen and Bonenfant to question its relationship to Hodgkin's disease and stimulate Robb-Smith to propose the term "lymphoreticular medullary reticulosis" and Lumb "reticular lymphoma" for this lesion. The sarcomatous type of Jackson and Parker relates a predominant proliferation of neoplastic reticulum cells of the Reed-Sternberg type with rapidly progressive disease. Winterhalter as well as Cro'zat et al, however, were unable to find definite evidence of a relationship between the histologic features and the course of Hodgkin's disease. The widely used classification into paragranuloma, granuloma, and sarcoma proposed by Jackson and Parker appears to have gained only limited support. The infrequency of paragranuloma and sarcoma has resulted in the inclusion of the great majority of all cases in granuloma and limited the prognostic value of the classification.

The application of a clinical staging method by Peters to survival studies in Hodgkin's disease and in the evaluation of the effectiveness of radiation therapy without regard to histologic classification presented a new analytic approach. The extent of involvement when therapy was instituted was

regarded by Dr. Peters as the most important factor in survival. Localized lymphadenopathy, Stage I, was observed with prolonged survival and effective therapy, while generalized involvement, Stage III, was associated with rapidly progressive disease and poor response to therapy. Intensive radiation therapy of the involved lymph nodes and the proximal region was believed to improve the survival rates. The value of clinical staging in survival has been reported by many observers. The subsequent study of Peters and Middlemiss provided further support for the significance of clinical staging and also evidence of the importance of systemic symptoms in staging as a valuable refinement in this approach. A study on the relationship of the histologic changes in involved lymph nodes to the existent clinical stages, however, was never reported until our recent study.

Briefly summarized, our recent investigation in which the significance of the histologic features and clinical stages in survival was evaluated on the basis of 377 U. S. Army cases from World War II (1942-45) appears to have shed some light on the natural history of the disease. The results of this study indicate a relationship between the histologic features, clinical stages, and survival. The histologic types manifested by lymphocytic proliferation were associated with clinical stage I disease and a prolonged median survival; those with lymphocytic depletion were associated with clinical stage III and had a short median survival. An inverse relationship between the frequency of lymphocytes and Reed-Sternberg cells also was noted.

These observations were considered to re-emphasize the importance of the lymphocyte in prognosis in Hodgkin's disease, originally presented by Rosenthal many years ago. They also are believed to be related to the recently described immunologic defect in Hodgkin's disease that is manifested by an inability to develop delayed hypersensitivity and a delay in homograph rejection. The wide variations in the histologic components associated with Reed-Sternberg cells were interpreted as reflections of differences in the state of the host and possibly manifestations of the dramatic interplay in the basic process between the factor(s) involving the Reed-Sternberg cell and the attempted host response. In addition, a new histogic type, nodular sclerosis, emerged with major prognostic significance as a regional expression of Hodgkin's disease in the mediastinum.

In this presentation I will attempt to demonstrate the relationship of the histologic findings and our histologic types, that I have just described, to the clinical stages. This relationship will be interpreted on the basis of our recent study of 377 U. S. Army cases from World War II in a 15 to 18 year follow-up study. Finally, I would like to present a prognostic scheme based on the relationship of clinical stages and histologic types.

This study of 377 U. S. Army cases from 1942-45 is essentially an analysis of Hodgkin's disease in young American males of military age. The group is composed of 370 males (98 per cent) and 7 females (2 per cent). There are 360 Caucasians (95 per cent) and 17 Negroes (5 per cent). The observed ratio of Caucasians to Negroes of 2:1 is based on the 10 per cent Negro incidence in the Army during this period and is similar to that observed by others. The age distribution reflects that of the Army population. There are 282 cases (75 per cent) between the ages of 18 and 30 and only 12 (3 per cent) in the 5th and 6th decades. The distribution of cases according to intervals is the following: 18 to 20 yers, 22 cases (6 per cent); 3rd decade, 260 cases (69 pe rcent); 4th decade, 83 cases (22 per cent); and 12 cases (3 per cent) in the 5th and 6th decades. The median age is 25 years. There is no significant difference in the median age of the patients in the various histologic groups.

Clinical stages to survival: The distribuition of cases into clinical stages according to the original method of Peters is recorded in this table in comparison with the distribution of cases by a modification of the method of Peters and Middlemiss in which stages II and III are subdivided according to the presence or absence of systemic symptoms. There are 142 cases (38 per cent) in stage I, 127 cases (34 per cent) in stage II and 108 cases (28 per cent) in stage III. Since the staging was accom-

plished retrospectively from clinical records without the advantage of lymphangiography, the proportion of cases in stage I is unquestionably larger than if based on a present-day prospective evaluation. The influence of systemic symptoms in staging the same case population results in a meaningful subdivision, particularly when viewed in terms of 5-, 10-, and 15-year survivals.

The influence of clinical stages on survival is summarized in this table. It is readily apparent that there is a definite relationship between clinical stage and survival. The prolonged medial survival of 9.1 years in stage I is in marked contrast with 3.2 and 1.3 years for stages II and III, respectively. From this observation it appears that, in a large number of patients with localized manifestations, the disease remains quiescent for many years. It also indicates, as does the presence of 51 of the 56 survivors at 15 years in Stage I, that, in general, stage I represents a quiescent form of Hodgkin's disease and stages II and III represent progressive disease.

The distribution of survivors at 5, 10, and 15 years according to the initial clinical stages of Peters also is recorded in this table. There is a marked contrast in the incidence of survivors in stage I with those in stages II and III disease survived 10 years and only 4 per cent of stage II and none of stage III survived for 15 years. The incidence of survival for the entire group at 5 years (40 per cent) is the same as that reported by Peters and Middlemiss for the males in their group for the same period.

Further comparison of the incidence at 10 years reveals almost identical results with 22 per cent in our series and 24 per cent for the males in their group. The 2 groups are fairly comparable with the possible exception of age, since our series is composed of 98 per cent males.

Histologic types to clinical stages of Peters: The distribuition of cases in the histologic types according to clinical stages of Dr. Peters, based on her initial method of staging, is presented graphically in this figure. Several significant associations are readily apparent. The cases of the L & H types associated with lymphocytic proliferation are observed primarily in stage I and include 78 per cent of the nodular type and 65 per cent of the diffuse type. By contrast, the histologic types with lymphocytic depletion, diffuse fibrosis (62 per cent) and reticular (43 per cent) types, are observed most commonly in stage III. In addition, over 80 per cent of both types occur with stage II and III disease. Nodular sclerosis and the mixed types are observed with almost equal frequency in the 3 stages, with slight predominance in stages I and II.

It appears from this data that the histologic types associed with lymphocytic and histiologic proliferation and few Reed-Sternberg cells primarily are expressed clinically by localized manifestation or stage I. The histologic types with depletion of lymphocytes and Reed-Sternberg cell proliferation or disorderly fibrosis are associated with disseminated disease, either stage II or III. It appears that nodular sclerosis represents a regional expression of Hodgkin's disease. The observation of nodular sclerosis with almost equal distribution in the 3 stages is interpreted as an indication that nodular sclerosis may be observed in any clinical stage as the disease process generalizes. The mixed type is found also in all stages with almost equal frequency and seems to represent an expression of changing disease since it occupies an intermediate position between lymphocytic proliferation represented by the L & H types and lyphocytic depletion manifested by the diffuse fibrosis and reitcular types.

Histologic types to clinical stages and survival: The distribution of cases accoording to histologic types and clinical stages is summarized in this table along with the median survival. The L & H types, which occur predominantly in stage I, have prolonged survivals of 16 years for the nodular type and 9.5 years for the diffuse. Diffuse fibrosis and reticular, the lymphocytic depletion types that are observed most commonly in stage III, have remarkably beief median survivals of 0.4 and 0.6 years in this stage. In stage II and III the L & H types have prolonged median survivals in comparison to other types in these stages, but the groups are too small for statistical significance.

Nodular sclerosis in stage I is of major prognostic significance, with a median survival of 11 years, since it is by far the most common lesion observer in stage I with 53 cases. By contrast the next most common type in stage I, the mixed type with 36 cases, has a median survival of 4.8 years. Nodular sclerosis and mixed types in stages II and III have fairly similar median survivals that range from 1.2 to 3.2 years, indicative of progressive disease. The median survival in the reticular type in stage I is surprisingly long (5.7 years) but the number of cases is small.

Mediastinal involvement: The incidence of mediastinal involvement in nodular sclerosis is compared in this figure with all other histologic types combined. Nodular sclerosis accounts for 88 of the 149 cases (59 per cent) presenting with mediastinal involvement. The difference in mediastinal involvement is most marked in stage I, where the frequency in nodular sclerosis (45 per cent) is 15 times that in all other stages combined. In stages II and III the frequency of mediastinal involvement in nodular sclerosis is approximately twice that of all other types combined and it is also numerically greater.

These data demonstrate the striking relationship between nodular sclerosis and mediastinal involvement in all stages of the disease. Thus, mediastinal involvement has no particular prognostic connotation in nodular sclerosis but in all other histologic types it is restricted almost exclusively to stages II and III and is associated, therefore, with a less favorable prognosis. The lesion of nodular sclerosis has been observed almost exclusively in the experience of the authors during the past few years in lymph nodes and masses from the mediastinum, particularly the anterior superior mediastinum, and the adjacent scalene, supraclavicular and lower cervical region. This observation on distribution plus the high incidence of initial mediastinal involvement are believed to indicate that nodular sclerosis is a regional expression of Hodgkin's disease.

Nodular sclerosis as a regional expression of Hodgkin's disease in the mediastinum may be seen with any form of Hodgkin's disease. Although it has not been possible thus far to relate the variations in cellular components in nodular sclerosis to the clinical stage, the sclerosis appears to be predominantly lymphocytic in quiescent disease and composed predominantly of Reed-Sternberg cells in progressive disease. The emergence of nodular sclerosis as a lesion of major prognostic significance is evident from this study and has been supported by the observations of Hanson.

The prognostic importance of nodular sclerosis also was dramatically demnostrated in a comparative study of the prolonged survival cases collected from many of the major radiotherapy groups and reviewed histologically by Lukes, Nezelof and Gompel at the Paris meeting on Hodgkin's disease in February 1965. The majority of the 155 validated cases of Hodgkin's disease surviving more than 10 years exhibited the features of nodular sclerosis. Achievement of cure in Hodgkin's disease now appears to be established as a result of this histologic validation.

The high incidence of nodular sclerosis among those proposed cures raises the possibility that the cure of Hodgkin's disease may be accomplished only in a susceptible condition and usually with nodular sclerosis. Futhermore, consideration of the significance of the histologic types, as expressions of the host's responsiveness and their relationship to the clinical stages, suggests that the effectiveness of therapy to a large extent is dependent upon the state of the host. From these observations and the prognostic schema it now appears that achievement of cure in the course of the natural history of the disease may be accomplished only when it is a quiescent state that is expressed histologically by the L & H types or nodular sclerosis and clinically by stage I disease.

The distribution of the histologic types of Jackson and Parker according to the clinical stages of Peters is recorded in this figure. The occurence of 91 per cent of the cases in the heterogeneous granuloma group, almost equally distributed in the stages, essentially obscures any relationship of these histologic types to clinical stages. Paragranuloma occurs principally in stage I, but the group is mall. The general ineffectiveness of the Jackson and Parker

types is dramatically demonstrated in this figure in a comparison of the incidence of survivors at 15 years with clinical stages. The incidence of survivors in the 30 cases of paragranuloma (40 per cent) is remarkably similar to the 142 cases in stage I (36 per cent) but the number of cases in each group is strikingly different.

Further proof of the ineffectiveness of both granuloma and paragranuloma was provided by the histologie evaluation of the prolonged survival cases in the major radiotherapy groups reported at the Paris Meeting on Hodgkin's disease by Lukes, Gompel and Nezelof, where only 7 per cent the cases with 10 years or more survival were paragranuloma and the remainder exhibited the features of granuloma. In a comparative classification study of the same cases by Lukes, Nezelof and Gompel the majority of cases classified as granuloma according to the Jackson and Parker criteria were classified as nodular sclerosis according to the histologic types of the authors. The ineffectiveness of the histologic types of Jackson and Parker in prognosis now seems to be established definitely from these observations.

EVOLUTION OF TH HISTOLOGIC PROCESS

From the observation on the relationship of the histologic features to clniical stages and survival it now appears possible to propose the evolution of the histologic process as summarized in the Table as an expression of the natural history of the disease. In this proposal nodular sclerosis is considered separately since it has been impossible at this time to establish the sequence of events in this lesion. It appears, however, that there is a parallel between the nodular sclerosing process and the evolution of the process involving the remaining types, possibly because nodular sclerosis seems to represent a regional expression of Hodgkin's disease.

Initially in Hodgkin's disease there appears to be a predominant lymphocytic proliferation with a variable histiocytic component that is associated with clinical stage I disease. When the lesion is nodular it is more likely to remain limited in its manifestations whereas the diffuse type at times may also be found in stage II. The addition of other cellular elements such as eosinophils, plasma cells and mature neutrophils and the early development of disordely fibrosis is indicative of the mixed type and heralds the onset of changing disease that is associated with the appearance of stage II and III disease. Subsequently the depletion of cellular components, except for Reed-Sternberg cells, represented by the diffuse fibrosis and reticular types provides evidence of systemic progressive disease of brief duration, or stages III and IV.

A wide variation in the number and character of Reed-Sternberg cells is associated with the histologic types and the evolving histologic process in Hodgkin's disease. Reed-Sternberg cells are infrequent or rare with the lymphocytic proliferation of the L & H types and numerous and even pleomorphic with the lymphocytic depletion types, diffuse fibrosis and reticular. In addition, the peculiar polyploid variants of Reed-Sternberg cells that may be fairly numerous with lymphocytic proliferation and nodular sclerosis but lack the characteristic huge nucleoli, seem to represent partially developed Reed-Sternber cells. These observations on the frequency and character of Reed-Sternberg cells and the general evolution of the process in relationship to the clinical stages, provide the basis for a proposal that the Hodgkin's disease process may represent the attempted induction of neoplasia. The variation in the histologic findings in this situation would represent varying degrees in the effectiveness of the host's attempt to resist neoplastic induction.

Although it is the contention of some observers that the Reed-Sternberg cells from their morphologic character are neoplastic, it is the belief of the authors that only the pleomorphic type may be neoplastic. This view also conflicts with that the Hodgkin's disease process is a mixed lymphoma. From these brief comments on the possible evolution of the Hodgkin's disease process, particularly the relationship of the histologic types to clinical stages, it appears that the possibility of

cure may be largely dependent on the susceptibility of the process to therapy which is reflected by the histologic type.

CONCLUSION

The effectiveness of the proposed histologic classification in prognosis will ultimately be determined by the ease of application and the prognostic usefulness for other workers. These histologic classifications have proven even more effective in our hands as a basis for evaluating the state of the disease and in estimating prognosis during the past few years than in our reported study because of more ideal control over the quality and selection of biopsies. The commonly emphasized variability of the histologic findings in different sites in Hodgkin's disease that has caused considerable debate now can be answered on the basis of the histologic observations of the authors when considered in relationship to the clinical states. Differences in the histologic findings in 2 sites are believed to reflect changing disease which is related to the existence of lymphadenopathy in more than one area, e.g., stage II or stage III disease. Differences in the findings in a snigle lymphnode in stage I also may indicate that the rate of progression and the state of the host are changing. Our experience with biopsies of recurrent lymphadenopathy in a single region in patients with prolonged survival, however, demonstrates a maintenance of histologic types, one case exhibiting the same L & H nodular process in 5 biopsies over a period of 10 years.

The relationship of the histologic findings to the clinical stages re-emphasizes the importance of staging and provides evidence that the clinical stages are dependent on the state of the host, which is reflected by the histologic findings. A question has been raised whether the correlation in our case material between the histologic type and prognosis is not attributable to the correlation of the histologic type and anatomic extent and that therefore the prognosis is related to the anatomic extent. This consideration, in fact, is the crux of our proposal, but with an important basic difference in the interpretation. The histologic changes do appear to be related to the anatomic extent of the disease. It seems to the authors, however, that the anatomic extent and the rate of progression are related to the state of the host, which is reflected by the histologic type. It therefore appears that the anatomic extent or clinical stage is the result of the state of the host and the histologic type rather than the reverse.

Together the histologic types and the clinical stages provides an effective basis for prognosis as demonstrated in the prognostic schema, from the authors' study, particularly when systemic symptoms are used as criteria to modify staging. From this summary it appears that Hodgkin's disease occurs essentially in 2 forms, quiescent and progressive, with intermediate changing disease. Quiescent disease is associated with the histologic expressions of the L & H and nodular sclerosis types with clinical Stage I. Progressive disease is associated with the lymphocytic depletion types, diffuse fibrosis and reitcular, and with Stages II and III and systemic symptoms. Nodular sclerosis may be found in any form as a regional expression of Hodgkin's disease, but it has emerged as a lesion of major prognostic importance in stage I, where it is the most frequent histologic type and has a median survival similar to the L & H types. Consideration of the histologic types as expression of the state of the host and their relationship to the clinical stages provides a basis for suggesting that the effectiveness of threapy and the possibility of cure, therapeutic or spontaneous, may be largely dependent on the state of the host. Undoubtedly the accuracy of prognosis and the evaluation of the status of individual patients will be greatly enhanced by the addition of immunologic studies as another parameter of the prognostic schema. The importance of the lymphocyte in the histologic process of Hodgkin's disease, the recently demonstrated immunologic defect involving the lymphocyte, and the initial observations of defective lymphocyte transformation with phytohemagglutinin emphasize the key role of the lymphocyte in the Hodgkin's disease process and the need for intensive investigation to elucidate the precise nature of the lymphocyte abnormality.