Discussion on: The Pathology and Nomenclature of Hodgkin's Disease

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The correlation of the histologic features of Hodgkin's disease with its clinical progress and its response to therapy presents a challenge to pathologists as well as to therapists. Dr. Lukes' very interesting data tend to indicate that within each clinical stage certain histologic types are indicative of a better prognosis than others. Based on this premise a subclassification has been proposed that adds to the complexity of the problem but at the same time emphasizes certain observations, some of them previously reported (1, 5, 7), that are of great interest: (a) that abundance of mature, well-differentiated lymphocytes in tissue sections is of favorable prognostic significance; (b) that, in general, lymphocytic depletion, whether associated with diffuse fibrosis or marked proliferation of Sternberg-Reed cells and other malignant histiocytes, indicates a bad prognosis; (c) that 1 form of fibrosis that has been designated as nodular sclerosis is often associated with long patient survival (2, 6, 8) even though there is lymphocytic depletion.

In the discussion of the pathology of Hodgkin's, 3 major problems arise: (a) Why do we regard Hodgkin's disease as a neoplasm? (b) What is the possible biologic significance of the great variations in the histologic appearance of Hodgkin's disease? (c) What are the histologic criteria that enable us to diagnose Hodgkin's disease as a progressive neoplastic disorder?

Even though Dr. Lukes is not fully convinced that every variant or type of Hodgkin's disease is necessarily a neoplasm, a common denominator does exist in all types of Hodgkin's disease in the form of atypical reticulum cells that appear to be neoplastic cells by generally accepted cytologic criteria. Some or many of them are the diagnostic Sternberg-Reed cells with multiple or multilobed nuclei; others are mononuclear cells with similar nuclear chromatin structures. Almost invariably this neoplastic cellular proliferation is associated with a presumably reactive process that is composed of differentiated lymphocytes, plasma cells, eosinophilic and neutrophilic segmented granulocytes, histiocytes, and fibroblasts. The relative numerical proportions of these cell types vary and so do the ratios of neoplastic and inflammatory elements. When the reactive cellular proliferation is purely or almost purely lymphocytic, the term "paragranuloma" has been employed. When inflammatory elements are scant or lacking, the term "Hodgkin's sarcoma" is applicable. All other variants of Hodgkin's disease have been grouped together under the term "Hodgkin's granuloma," representing roughly 90% of all instances of Hodgkin's disease. Dr. Lukes has shown that between the 2 extremes—namely, Hodgkin's paragranuloma, on one end of the spectrum, and Hodgkin's sarcoma on the other—a considerable morphologic heterogeneity exists, with a particularly wide range in the ratio of lymphocytes to neoplastic histiocytes. Of great interest is the abundance of mature lymphocytes in 1 form of Hodgkin's disease and the possible significance of this feature. It has been shown by several groups of observers that not only Hodgkin's paragranuloma but also Hodgkin's granuloma, in which lymphocytes predominate to the extent of roughly 80% or more of the inflammatory cells (1), is indicative of long patient survival. The terms "benign Hodgkin's disease" (3), "Hodgkin's disease, Grade I" (4), and "indolent Hodgkin's disease" (9) have been applied to Hodgkin's paragranuloma as well as to Hodgkin's granuloma with great abundance of lymphocytes. It has been suggested that this lymphocytic response represents a host reaction (8) that may serve a useful purpose. If it does, the question could be raised as to whether the use of lymphocytolytic agents in the treatment of Hodgkin's disease may not affect this reaction in an adverse manner.

I can add little to what Dr. Lukes said about that form of Hodgkin's granuloma that was designated as nodular sclerosing type. We really have no adequate explanation why patients with this form of Hodgkin's disease have a considerably longer life expectancy than patients who lack this feature except the suggestion that this very pronounced fibrosis may represent a peculiar type of defensive host reaction that limits the progression of the neoplastic process for protracted periods of time.

It has been established beyond any reasonable doubt that the factor of greatest prognostic significance is the confinement of Hodgkin's disease to a single lymph node or lymph node group. A correlation between histologic types of Hodgkin's disease and patient survival can only be made within each clinical stage. Recently, the accuracy of clinical staging has been greatly improved by lymphangiography. Dr. Lukes' patients have been studied clinically at a time when lymphangiography was not available and although his data do show important trends, their confirmation based upon more accurate staging would be highly desirable.

One aspect of Hodgkin's disease is of particular concern to clinicians, radiotherapists, and pathologists—namely, the difficulty of making an unequivocal histologic diagnosis in some instances. Because of the fact that the inflammatory components of Hodgkin's disease predominate so often, differentiation from other inflammatory diseases may present a problem and misinterpretation of such lesions as Hodgkin's disease is not at all unusual. It is for this reason that the prudent and cautious pathologist insists on demonstrating Sternberg-Reed cells with multiple or multilobed nuclei before making an unequivocal diagnosis. This is particularly vexing to clinicians when they have cases which clinically appear to be Hodgkin's disease but in which the pathologist is unwilling to commit himself. The difficulty is almost always attributable to a scarcity of diagnostic Sternberg-Reed cells; this may result in their absence at a given
level. I usually recommend that multiple additional sections be cut through the blocks and, if this is still without positive result, that additional lymph node biopsies be obtained. On occasion, the pathologist can do no more than state that the sections are consistent with Hodgkin's disease. In such instances, clinical judgment will have to prevail in deciding whether or not to treat the patient. The difficulty of diagnosing Hodgkin's disease with consistent accuracy was reemphasized in the recent meeting on Hodgkin's disease that was held in Paris. I was told that 3 competent pathologists could not agree on the diagnosis in 5% of the cases. While this figure appears high to me, we must accept the fact that there is a small percentage of cases in which a histologic diagnosis of Hodgkin's disease cannot be made with certainty on the basis of the available biopsy material.

References

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