A critique and case study of nodular sclerosing Hodgkin's disease

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SYNOPSIS  This paper presents a critique of the present concepts of the pathology of nodular sclerosing Hodgkin's disease and particularly of the criteria required for diagnosis of the condition and its separation from other types of Hodgkin's disease. In addition, the natural history and histopathology of the condition have been studied among 104 cases of Hodgkin's disease presenting at The London Hospital, and the significance of the appearance is discussed.

The histological type of Hodgkin's disease showing a nodular sclerotic pattern was first described by Smetana and Cohen (1956). Lukes and Butler (1966), in a re-classification of Hodgkin's disease, described this condition and coined the term 'nodular sclerosis'; in the simpler classification adapted at the Rye conference, this nomenclature was retained. In later publications Lukes (1971) has laid down criteria for the diagnosis of this condition, requiring the formation of birefringent collagen bands in the node, usually with a thickened capsule, and the presence of the so-called 'lacunar' cell; the latter was considered of major importance, although probably an artifact produced in fixation. The prognosis of nodular sclerosing Hodgkin's disease was considered to be superior to that of the classical form (mixed cellularity) but inferior to that of the lymphocyte predominant type of the Rye classification; and the condition was also considered to be identical with those cases previously described as granulomatous thymoma, mediastinal involvement being frequent. The diagnosis of nodular sclerosing Hodgkin's disease as a distinct entity does not seem to have been clearly defined, and the criteria laid down by Lukes (1971) do not correspond with those of Hanson (1964), Franssila et al (1967), and Cross (1968). This study was undertaken to clarify the incidence and natural history of the condition, the criteria required for diagnosis, and, in particular, the nature of early forms of the disease, the significance of the 'lacunar cell', and the final stages of the condition as seen in postmortem material.

Material and methods

The study was based on a series of 104 consecutive cases of Hodgkin's disease presenting at The London Hospital in the period 1954-64. Surgical biopsies were examined from all these patients and in addition postmortem material was available on seven cases classified as showing nodular sclerosis on biopsy. The period 1954-64 used for the investigation implies that the treatment given is not that employed in the most modern studies. This decreases the value of the study as a guide to clinical prognosis but produces a better indication of the basic natural history of the condition, which was of primary interest. A further nine necropsies of this form of the disease from previous years, during which chemotherapy was not employed and radiotherapy was used only to local nodes, were also examined.

Examples of normal and reactive lymph nodes and lymphoid tissue were studied to observe the possible presence of 'lacunar cells' in non-neoplastic tissue.

The total biopsy and postmortem material was analysed for the following features:

1 the distribution of all cases among the four groups of the Rye classification;
2 the stage at presentation and mean survival time of each group;
3 the incidence of 'lacunar cells' in the total material;
4 the extent of fibrosis, necrosis, and lymphocytic and leucocytic infiltration in nodular sclerosing Hodgkin's disease and in the mixed cellularity group; and
5 the histology of the final stages of nodular sclerosing Hodgkin's disease as seen in postmortem material.

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CRITERIA FOR DIAGNOSIS OF NODULAR SCLEROSING HODGKIN'S DISEASES

Lukes and Butler (1966), Lukes et al (1966), and Lukes (1971) have laid down their criteria for this condition. As stated, two histological features were considered essential—formation of collagen bands, usually with a thickened capsule, and the presence of the lacunar variant of the Sternberg-Reed cell. Fibrosis in the early stages might be minimal and consist of only a single band of collagen extending from a thickened capsule.

For reasons to be discussed later, we do not consider this a reliable basis for diagnosis. Therefore nodular sclerosing Hodgkin's disease was diagnosed only in the presence of fibrosis producing single or multiple isolated islands of lymphoid tissue surrounded by fibrous tissue and with or without the presence of lacunar cells (fig 1).

True sclerosis of a node producing an isolated area of lymphoid tissue must be distinguished from the sclerosis not uncommonly produced by the fusion of the thickened capsules of adjacent nodes (fig 2). Such fusion can usually be recognized by the survival of the subcapsular sinus under the fibrous tissue of the capsules.

Results

The table shows the distribution of the 104 biopsy cases, according to histological type, and the associated factors of stage at presentation, mean survival times, and sex and age distribution.

Histological classification gave results which fitted into the groups of the Rye system with a comparable incidence to that observed by other authors, with the exception that the low incidence of nodular sclerosing Hodgkin's disease observed by Cross (1968) was not seen. A group of five cases presented some of the features of nodular sclerosis but were not sufficiently definite to satisfy our criteria and were treated as an unclassified group, although they would probably have fallen into the early focal cellular phase of nodular sclerosis described by Lukes (1971). The most marked feature of these

Fig 1  Typical picture of nodular sclerosing Hodgkin's disease showing separation of islands of lymphoid tissue by fibrous trabeculae.  × 12
results was the relatively poor prognosis of nodular sclerosing disease as defined by us, the mean survival time and survival curve showing no significant variation from the mixed cellularity form of the disease. This is in contrast to the better prognosis of this type observed by other authors; the younger age distribution and more equal sex incidence in this group, however, were in conformity with previous observations. The good prognosis of lymphocyte predominant disease is in conformity with many other published results (Kaplan, 1972). The group of five cases presenting some of the features of nodular sclerosis but not completely satisfying our criteria showed a more prolonged survival than the mixed cellularity or nodular sclerosing forms of the disease; the possible significance of this will be discussed later.

**Lacunar Cells**

These cells were defined, according to the criteria of Lukes (1971), as showing, first, abundant pale to water clear cytoplasm with a sharply demarcated peripheral margin, and, secondly, hyperlobation with small nuclei, which however was not found in all cells. The cytoplasmic lacunar change was admitted to be largely an artifact of formalin fixation but was considered to be the most distinctive feature of the cell, as will be seen later. However, this change occurs also in reactive lymph nodes and is not peculiar to Hodgkin’s disease.

Figure 3 shows the incidence of lacunar cells in nodular sclerosing Hodgkin’s disease compared with the mixed cellularity type of the disease, the criteria for identification of the lacunar cell being those of Lukes (1971). These results suggest that,
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Incidence of lacunar cells in nodular sclerosing (NS) Hodgkin's disease compared with lesions of the mixed cellularity (MC) type.

Although a raised incidence of lacunar cells occurs in nodular sclerosing lymph nodes, especially where large areas of lymphoid tissue have survived, some 75% of cases of Hodgkin's disease of the mixed cellularity type may contain smaller numbers of lacunar cells.

Incidence of fibrosis and necrosis

Figure 4 shows the degree of fibrosis in nodular sclerosing Hodgkin's disease.

Fibrosis in nodular sclerosing disease shows a marked increase over that in the mixed cellularity group, and both minor and severe degrees of necrosis are less marked.

Leucocytic infiltration in lymph nodes

The degree of infiltration with neutrophil and eosinophil leucocytes in nodular sclerosing and mixed cellularity Hodgkin's disease is shown in figure 5. These showed opposed pictures in that neutrophil infiltration appeared less in nodular sclerosing disease and eosinophil infiltration more marked than in the mixed cellularity group although this increase is not sufficiently gross to be of diagnostic value. Figure 6 shows the degree of lymphocytic infiltration in relation to the survival time of the patients and demonstrates the positive relationship between a high degree of lymphocytic infiltration and an improved prognosis. The possible significance of this is discussed later.

Pathology of postmortem cases of nodular sclerosing Hodgkin's disease

These 16 cases showed features which were not as prominent in biopsy material and which do not appear to have attracted attention from other authors.

The predominant feature was the occurrence of lymph node changes which were taken to represent the final evolution of the process in an individual node. Such nodes showed

1. extreme sclerosis of the node, only scattered islands of lymphoid tissue remaining (fig 7);
2. absence of Sternberg-Reed cells in some individual lymph nodes;
3. frequent absence of lacunar cells (12 of 16 cases);

Figure 6 shows the degree of lymphocytic infiltration in nodular sclerosing disease and in disease of the mixed cellularity type.
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4 presence of sarcomatous change with invasion of neighbouring structures (fig 8) (five of 16 cases).

Extreme sclerosis of nodes was seen in the greater part of all postmortem specimens, but more cellular nodes were always present in some areas of the body (fig 9).

Presence of lacunar cells in lymph node reactions other than nodular sclerosing Hodgkin's disease

Apart from the occurrence of these cells in Hodgkin's disease, cells showing the characteristic vacuolated appearance of the cytoplasm were observed in reactive lymph nodes and in the lymphoid tissue of the normal appendix (fig 10). Such cells did not, of course, have the nuclear abnormality of the Sternberg-Reed cell but the remainder of the change appeared identical with that in Hodgkin's disease, although these cells are normal macrophages.

Discussion

Numerous attempts have been made to separate nodular sclerosing Hodgkin's disease as a distinct entity, and it should be considered what success and what value such efforts have achieved.

The separation of the condition from other forms of Hodgkin's disease appears to have been established beyond doubt. The characteristic histology, the age and sex distribution, the distribution of affected nodes, and, to a less extent, ether prognosis appear as distinguishing features; in addition, some variation in HL-A antigen specificity appears to exist in these patients as compared with other forms of Hodgkin's disease (Festenstein et al, 1972). A further factor described by us in postmortem material is the presence of sarcomatous invasion of neighbouring tissues which did not occur in 75 necropsy cases of disease of the mixed cellularity or lymphocyte predominant types studied by us. The value of classifying this subdivision of the Hodgkin group is less certain. The prognosis of nodular sclerosing disease varies greatly in the results of different

Fig 6 Variation in lymphocyte content of nodes in nodular sclerosing Hodgkin's disease in relation to mean survival.

Fig 7 Extreme sclerosis of node with only scattered lymphoid cells and no Sternberg-Reed cells. Taken at necropsy from an untreated case. × 360
workers; in our cases, it showed little advantage over that of the mixed cellularity type, and Cross (1968) considered that prognosis was variable and related to the degree of differentiation and number of reticulum cells in the lesions rather than to the presence of nodular sclerosis. Variations of this type would make the assessment of prognosis from the histology highly subjective; and the diagnosis of nodular sclerosis probably indicated only a moderate improvement in prognosis compared with disease of the mixed cellularity type. The main significance of the separate recognition of nodular sclerosis may lie in suggesting variations in nature of Hodgkin's disease. Such a variation has been suggested by
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Smithers (1970), who regarded nodular sclerosing Hodgkin's disease as being a form in which host resistance was high, as manifested by the fibrosis in glands, the improved prognosis, and the occurrence in younger age groups and in a higher proportion of females. This suggestion involves some very uncertain assumptions on the significance of fibrosis in tumour resistance and of variations in age distribution or of sex differences in immunity. The nature of the variation in nodular sclerosis is unknown and might be due either to a difference in aetiology or to the type of functional activity of the cells involved. The criteria for the diagnosis of nodular sclerosing Hodgkin's disease as laid down by Lukes (1971) require criticism on two points. The diagnosis of the disease in the virtual absence of fibrosis, as in the 'focal cellular phase' of Lukes, invites confusion with nodes which are examples of lymphocyte predominant Hodgkin's disease and may account for the different incidences of the disease reported by different authors; Lukes admits the impossibility of relating such variants to survival and prognosis. This is not to discredit the studies of Kadin et al. (1971) or Strum and Rappaport (1971), who have demonstrated cellular phase lesions and nodular sclerosing lesions in the same patient, but to provide an unequivocal basis for diagnosis which in practice cannot be mistaken. A further criticism involves the significance of the lacunar cell. This cell occurs in other variants of Hodgkin's disease, and we have shown the production of its characteristic cytoplasmic change in normal lymphoid tissue. The cell is probably an artifact, produced by formalin fixation, and its scarcity in postmortem specimens of the disease renders its diagnostic value doubtful. The occurrence of the cytoplasmic changes in normal lymphoid tissue further demonstrates its lack of specificity. We would suggest, therefore, that the only reliable diagnostic criterion of nodular sclerosing Hodgkin's disease is nodular sclerosis—the presence of islands of lymphoid tissue separated by fibrous tissue septa.

The absence of Sternberg-Reed cells from some lymph nodes in necropsy examples of this condition raised a fundamental question in the diagnosis of Hodgkin's disease. The majority of authors are convinced that the presence of Sternberg-Reed cells is essential for diagnosis; this cannot be accepted if involved nodes from proved cases of Hodgkin's disease do not contain them. There is clearly a risk in making such a diagnosis in their absence, but no other condition of lymphoid tissue exists which could mimic the complete appearance of nodular sclerosing disease even in their absence;

Fig 10 Normal appendix showing cell with cytoplasmic changes of lacunar cell but with normal nucleus. × 1500
in addition, postmortem tissues usually contain the large reticulum cell also seen in Hodgkin's disease, with a prominent nucleolus but a nucleus of normal morphology, and which may provide a helpful diagnostic feature in the absence of classical Sternberg-Reed cells.

A final point concerns the aetiology of the fibrosis seen in nodular sclerosis, the significance of the eosinophil and neutrophil infiltration which is a marked feature of the cellular reaction and of the lymphocytic proliferation. Hanson (1964) has suggested that the focal areas of necrosis frequently seen in the nodes may precede many of the areas of fibrosis; while some fibrosis may originate in previous areas of necrosis, the widespread interlacing bundles of collagen seen in the fully developed form of the disease could not be explained in this way, and the areas of necrosis in Hodgkin's disease of the mixed cellularity type do not result in a fibrotic pattern. The nature of the eosinophil infiltration is rendered complex by the difficulty of deciding the relative partition in Hodgkin's disease between neoplastic and reactive cellular elements. It is commonly assumed that the only neoplastic elements in Hodgkin's disease are the reticulum cell and the Sternberg-Reed variant, the leucocytic, lymphocytic, and plasma cell elements being of reactive origin. Pullinger (1932) claimed that the eosinophil and neutrophil leucocytes commonly present were derived from reticulum cells and cannot therefore be regarded as reactive elements but are analogous to the excess leucocytes produced in chronic myeloid leukaemia. There has been little confirmatory evidence for this view, but a different situation exists with regard to the lymphocytic elements in the disease. Several authors (Sinks and Clein, 1966; Tindle et al., 1972; Taylor, 1974) have produced evidence suggesting that the Sternberg-Reed cell is derived from the lymphocytes of the node; in this event the lymphocytic proliferation is possibly not reactive in nature but is part of the neoplastic process. The recent attempts to interpret much of the histology of Hodgkin's disease on the basis of cellular immunology carries the risk of ignoring the basic neoplastic nature of the condition.

Similarly, the improved prognosis in Hodgkin's disease associated with predominance of lymphocytes may not represent a host immune response but a tumour with fewer anaplastic and undifferentiated elements.

References