The morphology of the lymph node in the macroglobulinaemia of Waldenström

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SYNOPSIS In 16 cases of Waldenström's macroglobulinaemia the following findings were sufficiently frequent to justify a provisional diagnosis: a modestly enlarged node with lymphocytic infiltration through the capsule into the adjacent connective tissue, retention of the sinus and medullary reticulin pattern, few or no peripheral follicles, sinuses marked out by pale histiocytes, scanty mitoses, numerous plasma cells, and dark staining of plasma in blood vessels. Mast cells were not more frequent than in reactive nodes, but were more frequent than in lymphomas. Periodic acid-Schiff-positive inclusions were found in every case, but were usually very scanty. Similar inclusions can rarely be found in other cases.

Since Waldenström described essential macroglobulinaemia in 1944 there have been descriptions of the morphology of the lymph nodes by the following authors: Dalgaard (1950), one case; Dutcher and Fahey (1959), three cases; Kappeler, Krebs, and Riva (1958), two cases; Kok, Whitmore, and Ainsworth (1963), four cases; Kuhn (1967), one case; Lamm (1961), two cases; Lennert (1964), not stated; McCallister, Bayrd, Harrison, and McGuckin (1967), nine cases; Samaracq (1960), three cases; Woodliff, Dougan, Onesti, Lynch, and Finlay-Jones (1968), five cases; and Zollinger (1958), eight cases.

Many workers mention the difficulty of recognizing the disease from the lymph nodes and McCallister *et al* specifically state that in none of their nine cases was the diagnosis made on the lymph node biopsy. Certain features are mentioned repeatedly in the published reports. The loss of follicles and apparent loss of structure, the infiltration into the surrounding fat, the presence of plasma cells and mast cells, the likeness to lymphosarcoma, and, finally, if sought for, the presence of PAS-positive inclusions in the nuclei of lymphocytes or plasma cells. The latter finding is generally regarded as virtually diagnostic. These inclusions are, however, infrequent and it is hardly feasible to search every doubtful lymph node for them. The purpose of the present paper is to draw attention to those features that are sufficiently reliable to justify a provisional diagnosis that would enable one to search for the inclusions and look for serum macroglobulins.

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Material

Thanks largely to Professor Hobbs' interest in the subject, we have been fortunate in having tissue sections from 26 cases of macroglobulinaemia as defined by their serum proteins. Ten of these were unsuitable for the present purpose, in three no lymph node was available, in three the tissues were from necropsies and too autolysed, in three the macroglobulinaemia was due to a frank malignant lymphoma, and in one the lymph node taken for biopsy was almost entirely replaced by amyloid. This left 16 cases with lymph nodes suitable for study, 12 males and four females with a mean age of 63.8 years (median 58 years). Sections were stained by haematoxylin and eosin, by Gordon and Sweet's method for reticulin, by periodic acid-Schiff for inclusions, by polychrome methylene blue for mast cells, and by methyl green pyronin for plasma cells.

Findings

The nodes were only moderately enlarged, the average size being about 13×9 mm with a range of 7×3 mm to 20×18 mm. There was cellular infiltration through the capsule to the adjacent connective tissue in all 16 cases (Figs. 1 and 2). This was usually restricted to the immediate neighbourhood, but occasionally reached a width of 0.5 mm. In nine cases the sections included the connective tissue hilum of the node and in every case this, too, was infiltrated (Fig. 3). The fibrous trabeculae within the

Fig. 1 Periphery of a node with pericapsular tissue containing afferent lymphatics at the top. Arrows mark the capsule and the intact peripheral sinus (silver reticulin $\times 45$).

Fig. 2 Adjacent section to Figure 1. The original capsule (arrows) is difficult to define. Note the heavy staining of the lymph (H & E. $\times 45$).

Fig. 3 Infiltration of the fatty hilum leaving only isolated adipose cells. Note dark staining lymph in efferent lymphatics at top left (H & E. $\times 72$).

Fig. 4 Four fibrous trabeculae (arrows) are distended and loosened by being infiltrated with cells (silver reticulin $\times 41$).

Fig. 5 Adjacent section to Figure 4. The trabeculae are not recognizable as fibrous bodies but are outlined by the pale histiocytes that fill the peritrabecular sinuses (H & E. $\times 41$).

node were similarly infiltrated. In reticulin preparations they were recognizable but instead of being compact the fibres were separated and the whole trabeculae appeared loose. In ordinary preparations they were so packed with cells that they could not be recognized as fibrous bands, but they could often be identified by the pale staining of the sinus cells that outlined them (Figs. 4 and 5).

In spite of the malignant-looking invasion outside the capsule the normal reticulin architecture was surprisingly well preserved. In all 16 cases it was possible to identify the peripheral sinus and at least some of the medullary sinuses. The normal regular network of the medullary reticulin was generally well preserved, though in 10 of the 16 cases the fibres were a little denser or coarser than normal. In no case was the reticulin pattern wholly destroyed. Lymphoid follicles could be recognized in some cases as rounded foci with very scanty reticulin fibres. These were seen in about normal numbers in three cases, there were eight in one case, two in another, and one in each of

three other cases. In the other eight cases follicles could not be recognized in reticulin preparations.

With ordinary stains follicles were easily seen in the three cases with normal numbers, but in the other 13 cases with scanty follicles they could not be identified with certainty. In almost all cases the sinuses could easily be recognized and in 12 cases the sinus histiocytes were prominent enough for the sinuses to stand out as pale strands against the dark background of lymphocytes (Fig. 5). In one case all the sinuses were enormously distended by lymph so that they formed the greater part of the node and the lymphoid component was reduced to strands between them (Fig. 6).

At first sight the monotonously uniform background of small dark cells, taken with the absence of lymphoid follicles, and the invasion of the capsule, strongly suggested a lymphosarcoma. In fact, this diagnosis seems frequently to have been made in published cases. On more careful study there are two obvious discrepancies: mitoses are often surprisingly

Fig. 6 Sinuses greatly distended by deep staining lymph. Pericapsular infiltration at the top and surviving follicle at top right (H & E. $\times 55$).

infrequent, and the cell population is not uniformly lymphocytic, nor is it anaplastic. Mitoses were counted in 100 oil immersion fields ($= 2.4 \text{ sq mm}$) in each of the 15 surgically excised cases. The results were: four cases with 0, two with one, three with two, two with three, one with six, one with 26, one with 32, and one with 50. The corresponding figures for 15 cases of lymphosarcoma averaged 104 mitoses per 100 oil immersion fields with a range of 18 to 330. The cell population usually contains a considerable number of plasma cells. This was seen in 14 out of 16 cases. Plasma cells were too scanty to be a noticeable feature in the other two. Another finding that is frequent enough to give a clue to the diagnosis is the dark staining of the plasma in the blood vessels. This was seen in 14 out of the 16 cases.

On these findings, and using only the conventional haematoxylin and eosin and reticulin stains, one is faced with a node that is of normal size or only modestly enlarged, that shows capsular, hilar, and trabecular invasion yet retains a surprisingly

normal reticulin pattern, that has probably no follicles but may show sinuses marked by their content of pale staining histiocytes, that has scanty mitoses and quite numerous plasma cells, and has dark staining plasma in the blood vessels. This combination is sufficient to suggest a diagnosis of Waldenström's macroglobulinaemia. The two remaining criteria given in published descriptions are the presence of numerous mast cells and the presence

Fig. 7 Four examples of PAS-positive intranuclear inclusions. The depth of PAS staining varies (PAS $\times 1350$).

of PAS-positive intranuclear inclusions (Fig. 7). The question naturally arises, are these two findings constant and are they specific.

Mast cells and intranuclear inclusions were counted in 100 oil immersion fields in each case. Mast cells were found in every case but their frequency varied from seven to 185 with a mean of 63.3 and a median of 46. As controls similar counts were made on 30 normal or inflammatory nodes. Here the mean count was 21.2 per 100 fields and the range 0-65. It is apparent from these figures that the presence or number of mast cells is of no diagnostic value in distinguishing macroglobulinaemia cases from reactive ones. Similar counts were made on 25 malignant lymphomas, 10 Hodgkin nodes, 10 lympho- or reticulosarcomas, and five follicular lymphomas. These had a mean count of 4.7 per 100 fields with a range of 0 to 18 and a median of 2. These figures have a certain value because although there is some overlap, mast cells are likely to be scanty in malignant lymphomas and frequent in cases of macroglobulinaemia.

The number of PAS-positive, intranuclear inclusions was counted at the same time as the mast cells. The actual figures were: 1, 1, 2, 3, 3, 3, 3, 4, 4, 5, 8, 15, 16, 26, 35, 82. In no case did we fail to find an inclusion but it could well happen that more than 100 fields might need to be examined before finding one. Since this is stated to be the specific finding on which the diagnosis depends, it is important to be sure that PAS-positive inclusions in lymphocytes or plasma cells cannot be found in other cases. A search was made in the same control cases as were used for mast cells, that is, 30 normal or reactive and 25 lymphoma cases. In fact, four intranuclear inclusions not morphologically distinguishable from those of macroglobulinaemia were found. One was in a normal node, one in a mesenteric node draining a loop of inflamed intestine, one in a scalene node removed for evidence of tuberculosis and showing only mild reactive changes, and finally, one slightly

atypical inclusion in a node with Hodgkin's disease. Regrettably, it appears that even this criterion is not quite diagnostic. This is perhaps all the more reason for putting more stress on the other criteria listed above, and in any case the inclusions in established cases of Waldenström's macroglobulinaemia are so scanty in the majority of cases that they cannot do more than add confirmation to a provisional diagnosis already made.

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