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On the angiostructure of lymph nodes in Hodgkin's disease

An immunohistochemical study using the lectin I of *Ulex europaeus* as endothelial marker

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Summary. Using an extended indirect immunoperoxidase method and the lectin I of Ulex europaeus (UEA-I), whose binding sites in lymph nodes are restricted to endothelial cells and erythrocytes, the angioarchitecture of 31 lymph nodes affected by Hodgkin's disease (HD) was demonstrated and analyzed. Compared with the normal state, the lymphocytic predominance type has a low relative vascular density, and venular endothelium is epithelioid throughout. Mixed cellularity types, especially those rich in epithelioid cells, have the lowest relative vascular density; the venular endothelium is often flat. In the sclerosing areas of the nodular sclerosis type structurel differences between capillaries, arterioles and venules vanish. Due to parenchymal atrophy and cellular depletion, relative vascular density is markedly increased in such areas, as is the case in lymphocytic depletion types. Despite all the histomorphological changes occurring in HD, the vascular system of the lymph node, surprisingly, does not undergo profound alteration. There is a positive correlation between the degree of epithelioid transformation of venular endothelium and trans-venular lymphocytic traffic. The conditions are described under which the otherwise non-reactive sinus endothelium expresses the UEA-I receptor.

Key words: Hodgkin's disease – lymph node – angioarchitecture – Ulex europaeus lectin I

Introduction

Despite recent progress in lymph node pathology achieved in a large part by the use of immunhistological methods that have led to the characterization of cellular constituents and data on their distribution the vessels and angioarchitecture of the lymph node and their changes in pathological condi-

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tions have met with only marginal interest (Lott and Davies 1983; Haferkamp et al. 1971). Only some specific conditions with a prominent vascular component – angiofollicular lymphoma, Castleman and lymphogranulomatosis X (including angioimmunoblastic lymphadenopathy) – have been studied in more detail. However, as recent physiological and cytokinetic studies suggest, vessels and sinuses are not merely conductive and distributive but represent an integral part of the microenvironment necessary to create the multiplicity of forms and functions of the elements constituting the immune system (Herman et al. 1972 and 1976; Nightingale and Hurley 1978; Hirschberg et al. 1980; Pober et al. 1982; Chin et al. 1980a and b, 1982; Drayson et al. 1981; Andrews et al. 1982).

Cazal and Lalaurie (1952) described a haemagglutinating property of an extract from Ulex europaeus. Using this extract and an immunofluorescence technique, Kent (1964) demonstrated H-blood-group antigens in epithelial mucins on paraffin and frozen sections. The biochemical purification and characterization of UEA-I and the determination of its sugar specificity (α-L-Fucose) was done by Matsumoto and Osawa (1969). Yonezawa et al. (1982) studied the tissue distribution of UEA-I in colorectal carcinomas and reported on binding at the vascular endothelium. Holthöfer et al. (1982) suggested UEA-I as a marker for human endothelial cells. A distinct, UEA-I accepting, α 1-fucosyl moiety containing glycoprotein has recently been isolated from cultured human endothelial cells (Hormia et al. 1983).

This study aims at the analysis of the vascular system in lymph nodes affected by Hodgkin's disease and is based on paraffin sections of formalin-fixed tissue and an extended indirect immunoperoxidase method using a commercial UEA-I lectin and the corresponding antilectin.

Methods

Twenty-two routinely fixed paraffin-embedded lymph nodes affected by Hodgkin's disease were drawn from the files of the German lymph Node Registry in Kiel. Nine additional cases were taken from the Institute of Pathology in Heidelberg. All cases had apparently good preservation and fixation. Applying the criteria of Lukes and Butler (1966), there were 9 cases of lymphocytic predominance, 11 of nodular sclerosis, 6 of mixed cellularity, and 5 of lymphocytic depletion (additional morphological details are mentioned in 'Results'). For comparison a large series of reactive lymph node lesions and malignant non Hodgkin's lymphomas were stained according to the same procedure (publication in preparation).

Two to four μm thick sections were made, using a special knife holder with disposable blades (Feather, Japan) in order to minimize cutting artifacts. The 4-step indirect immunoperoxidase method for the detection of lectin-binding sites was applied as described elsewhere (Möller 1982). Ulex europaeus I lectin (UEA-I) (Lot no. 0813E) and a rabbit-derived anti-UEA-I (Lot no. 0930D) were purchased from E.Y. Lab. Inc. (San Mateo, CA, USA); pig-anti-rabbit immunoglobulins and a peroxidase-anti-peroxidase complex produced in rabbits were products of Dako (Denmark); 3-3-diamino-benzidine as chromogen was purchased from Fluka, Basel (Switzerland). The UEA-I stock solution, whose protein concentration was indicated as being 1 mg/ml, was diluted in PBS pH 7.6, and so was the anti-UEA-I serum, whose protein concentration was indicated as bein 32 mg/ml. In our hands a dilution of 1:500 of the former and of 1:800 of the latter yielded the best results. Tissue digestion (Pronase 7493; Lot no. 116 825, Merck Chem., Darmstadt, FRG; 1 mg/ml PBS pH 7.6 for 7–10 min at room temperature) prior to lectin application had an intensifying effect on the staining, while the binding spectrum did not change. The specific lectin-binding was considerably reduced but not completely inhib-

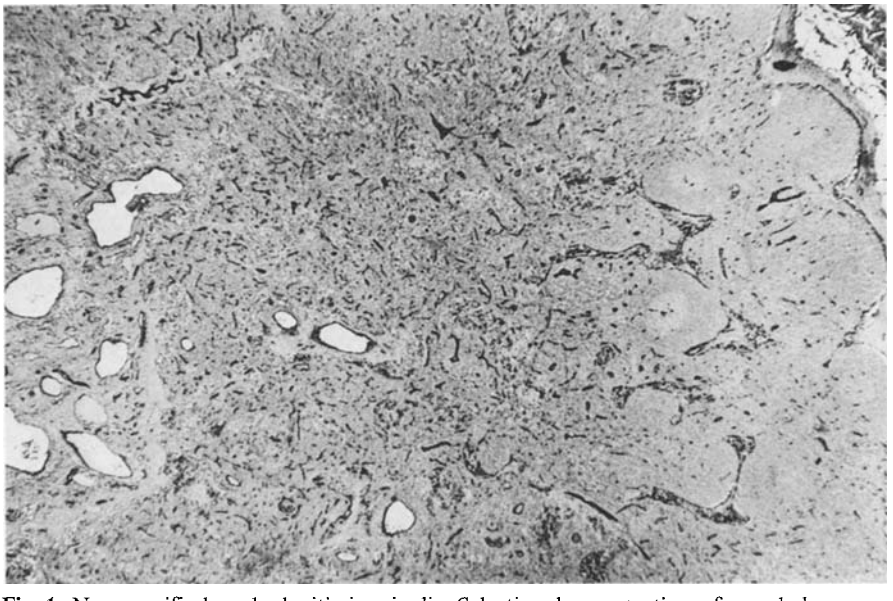


Fig. 1. Non-specific lymphadenitis inguinalis. Selective demonstration of vessels by means of endothelium-specific lectin I of Ulex europaeus (UEA-I). The marginal sinus endothelium (right) is also positive in this case, medullary sinus endothelium is non-reactive. The organic vascular structure reflects the intact lymph node architecture (UEA-I, anti-UEA-I, peroxidase-anti-peroxidase method, diaminobenzidine/haematoxilin – same procedure for Figs. 2–7), (× 33)

ited by adding up to 0.2 M α-L-Fucose (Lot no. 14026-A; E. Y. Lab. Inc) to the lectin solution. Other controls omitting either the lectin or one of the antibodies yielded negative results. The lectin affinity of erythrocytes, which was an inconstant finding in UEA-I staining, turned out to be specific and not due to inappropriate blocking of endogenous peroxidase.

Results

From the technical point of view the UEA-I-staining yielded clear and consistent results: There is hardly any non-specific background. Lectin affinity is restricted to vascular structures and erythrocytes in a group of individual cases. The endothelium of arteries, arterioles, capillaries, venules, and veins reacts equally strongly. The angioarchitecture of the normal unstimulated lymph node is clearly visible in the low power view: arteries entering and veins leaving the lymph node at its hilum (as such discernible by their media structure visible because of the hematoxitine counterstain), the arterial and venous arborisation, the epithelioid venules in the centre of the so-called T-zones, the few capillaries surrounding and entering the follicles. The sinus endothelium has a variable affinity for UEA-I, which is minimal or absent in the intermediate and medullary sinuses and in the vasa efferentia but slightly positive in parts of the marginal sinus (the latter being a regular finding in inguinal lymph nodes) (Fig. 1). All other cells, structures, and fluids are negative, including fibres, basement membranes, hyalin, serum,

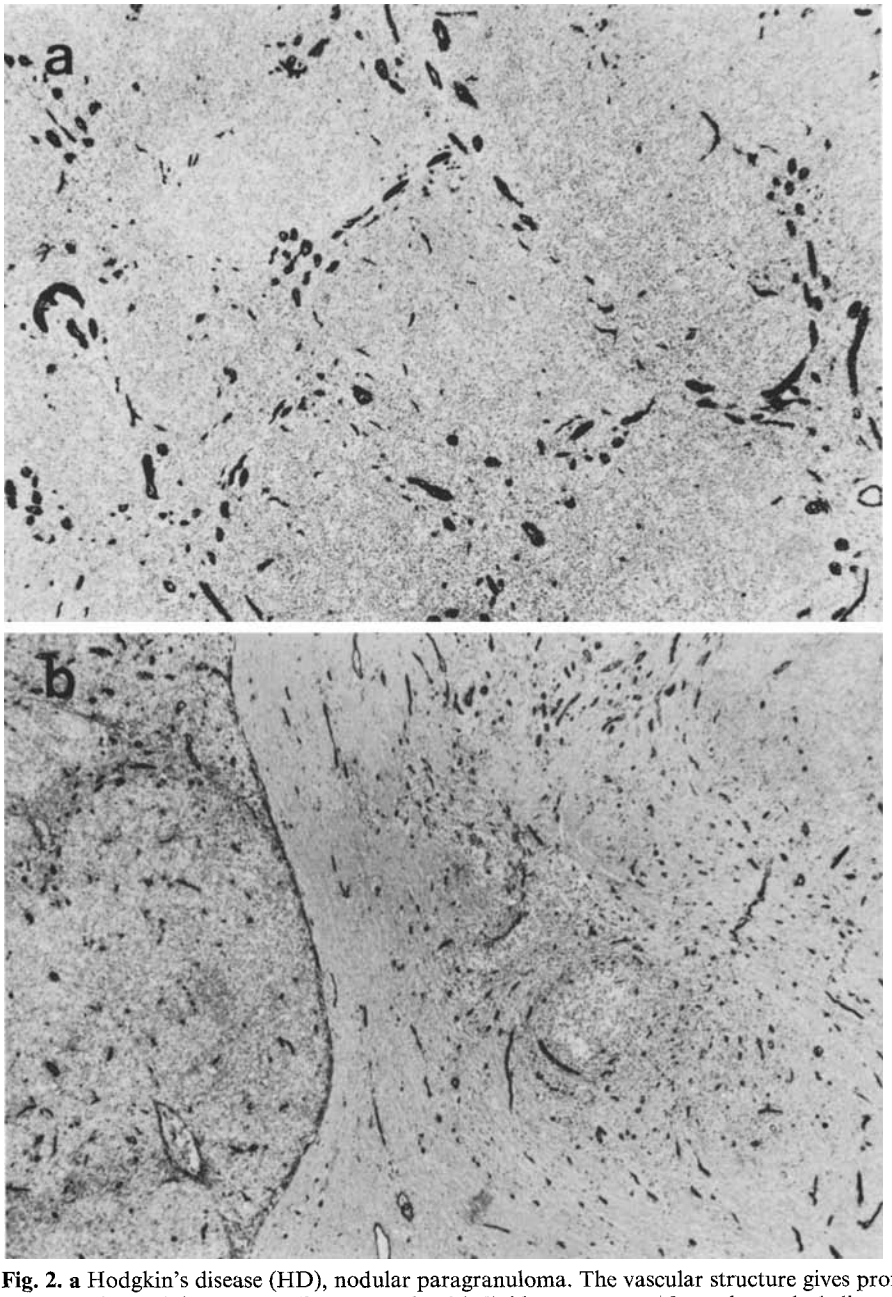
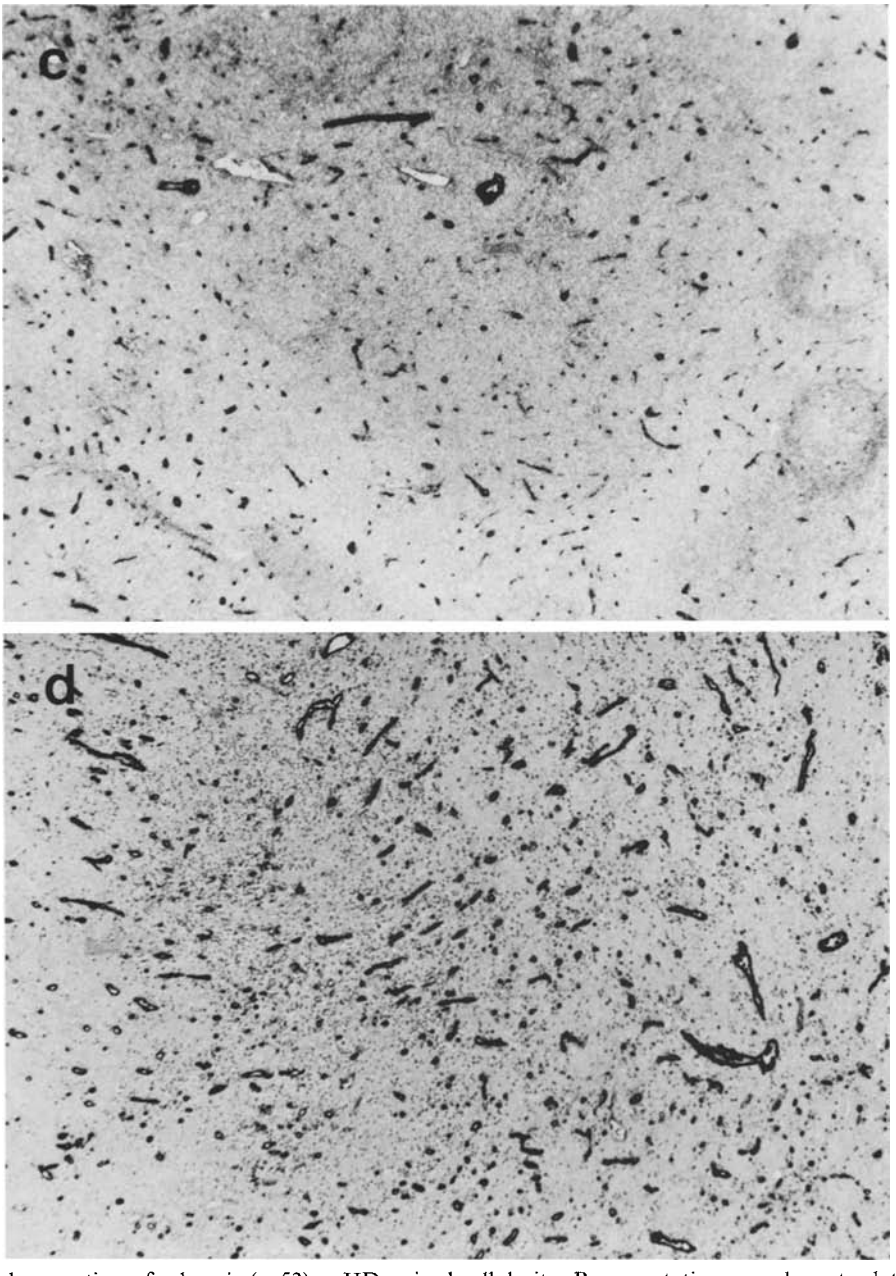


Fig. 2. a Hodgkin's disease (HD), nodular paragranuloma. The vascular structure gives prominence to the nodular pattern. Pronounced epithelioid appearance of venular endothelium between the nodules. Note the low capillary density within the nodules (× 53). **b** HD, nodular sclerosis, Representative area: low relative vascular density within cellular nodules, increased density in sclerotic parts of the lesion. Note as an inconstant feature the UEA-I-positive



demarcation of sclerosis (× 53). **c** HD, mixed cellularity. Representative area: lowest relative vascular density of all Hodgkin types. Effacement of the organic vascular structure. Venular endothelium tends to be flat (× 53). **d** HD, lymphocytic depletion. Representative area: highest relative vascular density of all Hodgkin types. Flat venular endothelium; capillaries, venules, arterioles hardly distinguishable: 'degenerative dedifferentiation' (× 53)

and lymph. This was confirmed in a large number of reactive lymph node lesions and non-Hodgkin's lymphomas (unpublished observations).

The vascular patterns of the subtypes of HD are described separately, mentioning specifical details of individual cases.

Lymphocytic predominance

Among the 9 cases described there are 2 classical nodular paragranulomas with progressively transformed germinal centres; 2 are diffuse, in 6 there are areas with nodular structures, 2 of which contain foci of mixed cellularity and 2 others, some sclerotic bands. Compared with the normal state and with the other Hodgkin types, the ratio between the cellular and the vascular volume is increased, i.e. the relative vascular density is low (Fig. 2a). The endothelial cells of the venules, however, show a marked epithelioid appearance (Fig. 3b, c, e).If there is a nodular pattern, epithelioid venules surround the nodules which only contain very few capillaries themselves; a close approximation of Hodgkin cells to the venules is the exception, while many lymphocytes are stuck between endothelial cells or between the endothelial layer and the basement membrane, thus illustrating the transvenular lymphocyte traffic (Fig. 3b). In sclerosing areas, the venular endothelium is flattened. The predominantly unstained sinuses only express UEA-I receptors on a loose meshwork of endothelial cells in the neighbourhood of sclerotic ribbons.

Nodular sclerosis

Among the 11 cases examined, 4 are typical, within the nodules 3 show a polymorphic cellularlity and 2 a lymphocytic predominance picture, whereas one case is partially depleted of cells while sowing a diffuse fibrosis; a further case contains areas of atypical Hodgkin cells with partial necrosis, thus showing some characteristics of Hodgkin's sarcoma.

The venular density of this type is comparable to that of the normal lymph node, the angioarchitecutre, however, is changed according to the extent of the sclerosis (Fig. 2b). Regardless of their character, the vessels within the sclerotic ribbons have a flat endothelium.

In the cellular parts, the epithelioid appearance of the venular endothelium is exceptional and restricted to areas rich in lymphocytes. In one case the venules are surrounded by Hodgkin cells (Fig. 3a). The cells of the sinus wall within the nodules are UEA-I negative or very faintly positive, respectively. Perisclerotic sinuses are inconsistently detectable and their endothelial cells are strongly reactive (Figs. 2b, 6a). This loose endothelial meshwork is no barrier to small lymphocytes (Fig. 6b). One case has foci of lymphangiosis lymphogranulomatotica; here the strongly reactive sinus endothelium forms a plexiform reticulum as in areas of 'immature sinus histiocytosis' (Fig. 5) (see below).

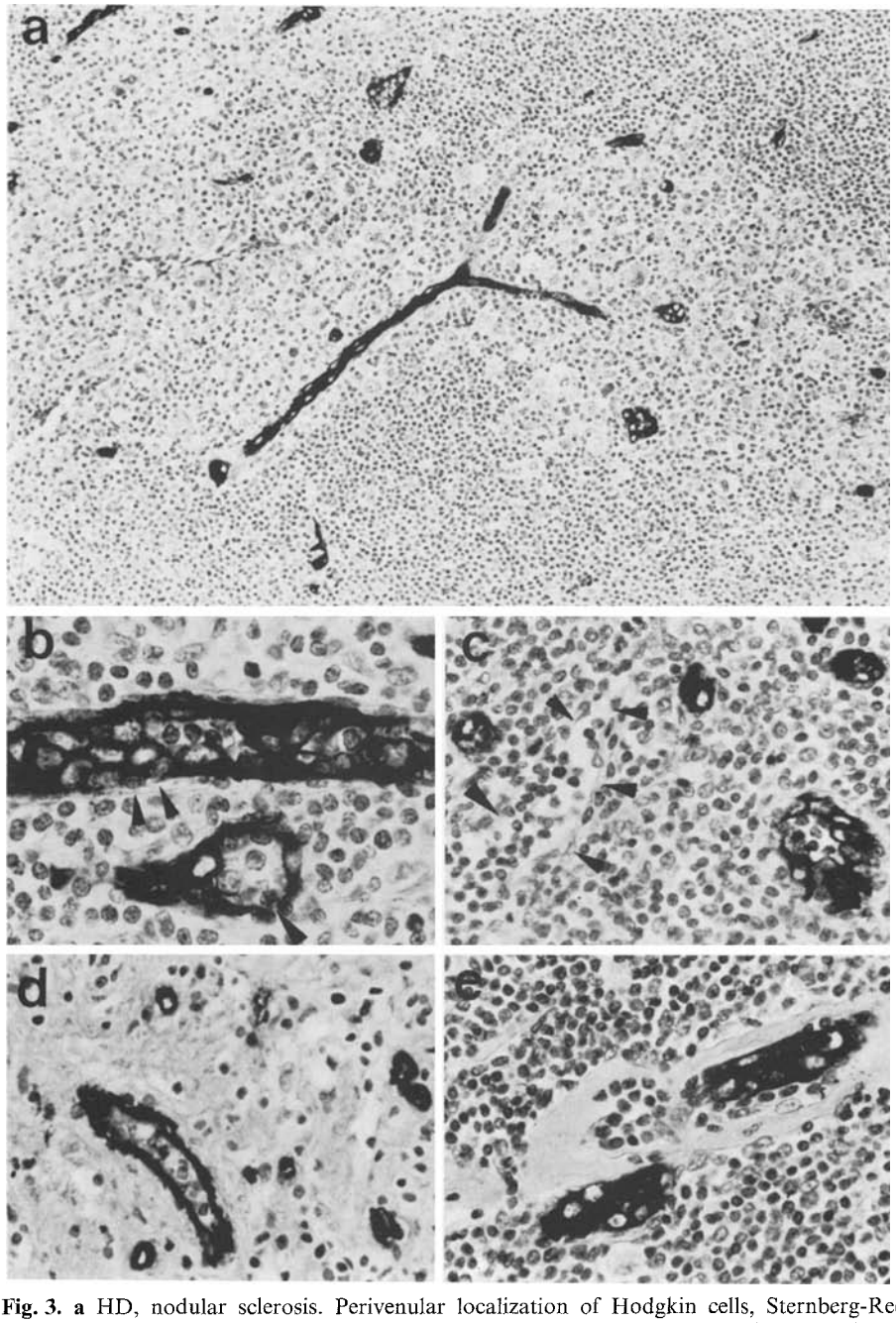


Fig. 3. **a** HD, nodular sclerosis. Perivenular localization of Hodgkin cells, Sternberg-Reed cells and some lacunar cells: an infrequent phenomenon (in the cellular phase venules are normally surrounded by lymphocytes) (×133). **b** HD, lymphocytic predominance, nodular paragranuloma.Venules with epithelioid transformation of endothelium. Numerous lymphocytes passing through the vessels wall (*arrow heads*) (×418). **c** HD, lymphocytic predominance. In the normal, resting sinuses endothelial cells do not express the UEA-I receptor (*arrow heads*) (×285). **d** HD, lymphocytic depletion. 'Degenerative dedifferentiation' of venules: flattening of venular endothelium, perivascular fibro-hyalinosis, thickening of vascular basement membranes (vd. Möller et al. 1983), no visible transvascular lymphocytic traffic (×266). **e** HD, nodular paragranuloma, detail; two epithelioid venules, one showing lymphocytic transit in spite of perivascular hyalinosis (×178)

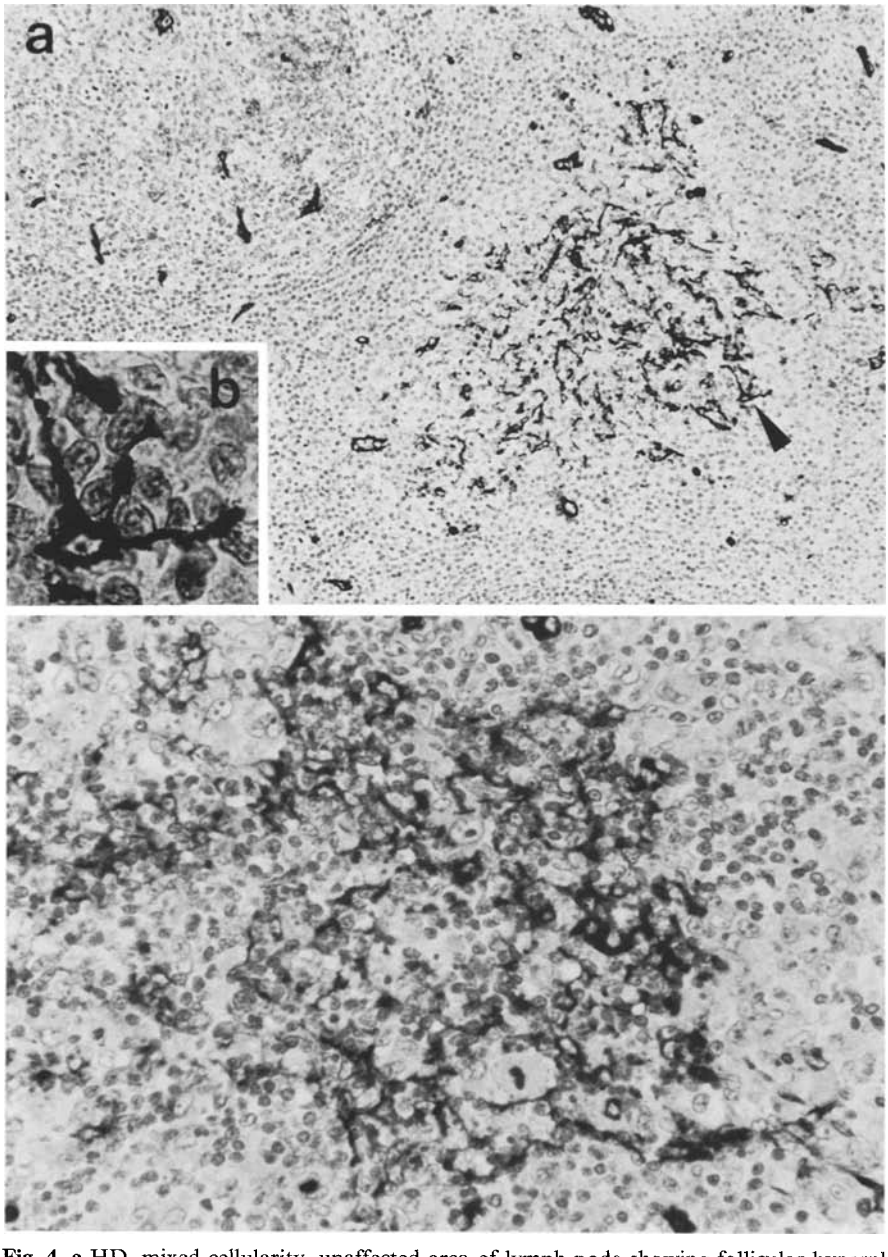


Fig. 4. **a** HD, mixed cellularity, unaffected area of lymph node showing follicular hyperplasia (*top left*) and 'immature sinus histiocytosis' conspicuous due to a cribriform splitting of the sinus and strongly UEA-I-positive arachnoid-shaped endothelial cells (×133). **b** Endothelial cell (marked by an arrow head in **a**) with strong cytoplasmic affinity to UEA-I, long cytoplasmic processes, between 'immature sinus histiocytes' (×700)

Fig. 5. HD, nodular sclerosis with areas of lymphocytic depletion and spreading of Hodgkin cells. Sinus endothelium forming a loose network and expressing UEA-I receptors as in 'immature sinus histiocytosis' (×333)

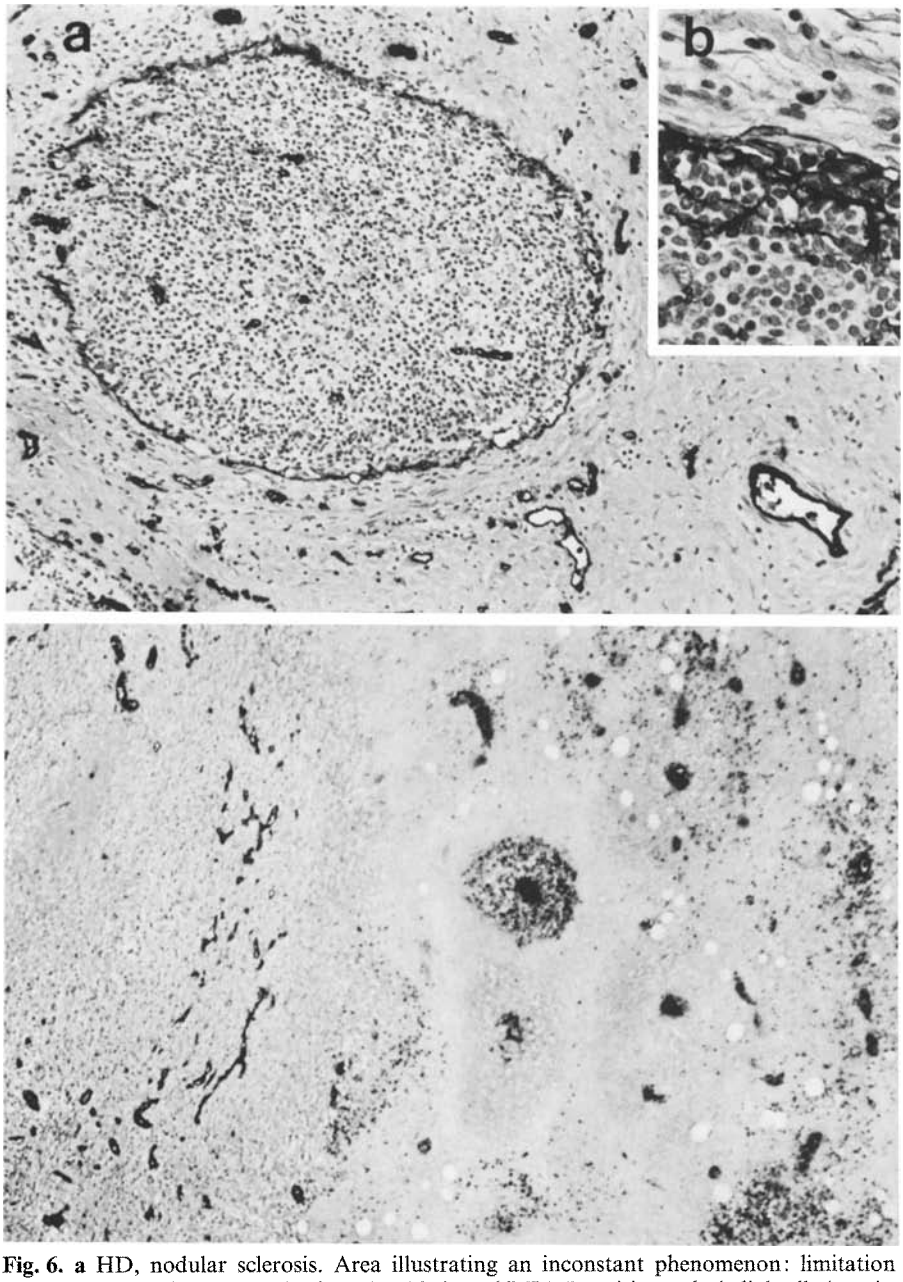


Fig. 6. a HD, nodular sclerosis. Area illustrating an inconstant phenomenon: limitation of a cellular nodule by a network of arachnoid-shaped UEA-I-positive endothelial cells (neosinus? vascular sinus transformation?) (× 133). **b** Detail from **a**: network of UEA-I-positive endothelial cells at the nodular border (× 285)

Fig. 7. HD, lymphocytic depletion. Area of necrosis. Vessels passing through or entering the necrosis still show UEA-I affinity and are surrounded by globular haemorrhages. Erythrocytes of this case are UEA-I-positive (× 53)

Mixed cellularity

Among the 6 cases examined there is one rich in epithelioid cells. In low magnification, the angioarchitecture appears to be effaced, densified in some parts, and blown up in others (Fig. 2c), especially in the case rich in epithelioid cells which exhibits the lowest relative vascular density of all cases examined. The most striking feature is the complete absence of epithelioid endothelium in venules in 3 cases. Transvenular lymphocyte traffic is reduced and seems to be completely lacking in the case rich in epithelioid cells. A relationship of Hodgkin and Sternberg-Reed cells to vessels is not conspicuous. The majority of the sinuses are not marked by the lectin; the case rich in epithelioid cells shows UEA-I-positive marginal and intermediate sinuses, and another lymph node contains foci of 'immature sinus histiocytosis'. These areas are very prominent in this stain because of the splitting-up of the sinus and a cribriform arrangement of strongly reactive arachnoid-shaped endothelial cells (Fig. 4a). Among these cells the medium sized lymphoid cells typical of this specific lesion are accumulated (Fig. 4b).

Lymphocytic depletion

Among the 5 cases of this type one exhibits geographical necroses, one other sarcomatous areas. Reticular fibrosis becomes conspicuous by an increase of the relative vessel density, while the vascular lumina are small and capillaries, arterioles and venules are hardly discernible; endothelium is generally flattened (Fig. 2d). There is no lymphocyte traffic (Fig. 3d). There are vessels entering the necrosis, being themselves partially necrotic and the centre of globular haemorrhages (Fig. 7). The marginal sinuses are weakly stained. One case presenting a sinusoidal lymph oedema contains a fine granular UEA-I affinity of single sinusoidal endothelial cells.

Discussion

Epithelioid venules

There is a considerable amount of data concerning these structures in lymph nodes. The group of Woodruff presented experimental data suggesting that lymphocytes leave the blood stream only via this vascular sector (Stamper and Woodruff 1976). Basically there seems to be a specific recognition system on the surface of B and T cells, that is, a neuraminidase-resistant, trypsin-sensitive glycoprotein at the top of microvilli. Its expression is energy- and potassium-dependent. These atuhors suggest that the venular endothelium, by contrast, plays a more passive part, as even glutaraldehyde-fixed endothelial cells are recognized as such by vital lymphocytes (Stamper and Woodruff 1977; Chin et al. 1980 and 1982). Working on the venular aspect, Ford and his collaborators found in animal systems that the venular lymphocyte transit can be 'frozen' by the administration of prednisolone (Cox and Ford 1982). They succeeded in isolating a sulphur-containing secretion product of these special endothelial cells, whose rate of synthesis

seems to increase 4 days after antigenic challenge (Drayson et al. 1981). The epithelioid transformation of the venular endothelium is regarded as a dynamic and transitory expression of functional activation (Baldwin 1982).

On the basis of inflammation experiments, Nightingale and Hurley have set up the theory that the high endothelium is the consequence of increased lymphocytic transit in the context of immune response; lymphokinetic data given by Drayson et al. (1981) support this view.

Our results only illustrate the positive correlation between lymphocytic passage and the degree of endothelial swelling (Figs. 3b, d). In areas with perivascular fibrosis of sclerosis, migrating lymphocytes cannot be detected, whereas a perivascular hyalinosis does not seem to be more of a obstacle than basement membranes are (v. Claesson et al. 1971) (Fig. 3e).

Behaviour of sinuses with regard to UEA-I affinity

An unexpected phenomenon was the different affinity of the sinus endothelium to UEA-I-lectin. In normal cervical lymph nodes sinuses are negative, which is the case in the lymphocytic predominance type of HD (Fig. 3c). The mixed cellularity type, however, has some positive sinuses, with a loose network of stained endothelial cells communicating by thin cytoplasmic processes. A constant feature is the plexiform pattern of arachnoid sinus cells in areas of 'immature sinus histiocytosis' (Fig. 4a, b), this by itself being rather typical of Piringer's lymphadenitis. Such foci are very scarce and can mostly be found in reactive parts of incompletely infiltrated lymph nodes and sometimes in lymphogranulomatous areas. The significance of this arrangement is still obscure. In cases of capsular or nodular sclerosis, marginal sinuses also show the network of cells expressing the UEA-I receptor. In addition, a UEA-I-positive endothelial demarcation is realized, however not constantly. It looks as if a 'seeping trail' were established, which contains some erythrocytes (Fig. 6a). Whether these are neo-sinuses or pseudo-vessels, cannot be determined. The 'vascular sinus transformation' concept of Lennert (Haferkamp et al. 1971) as found in chronic lymphatic obstruction (see Wolfe et al. 1983) can be applied to this structural change, so readily visible in this lectin stain.

Vascular structure of lymphogranulomatosis

There are distinctive vascular patterns within the lymph node reflecting the main subtypes of HD defined by Lukes and Butler (1966) (Fig. 2). The lymphocytic predominance type shows an expansion of the vascular tree due to lymphocytic accumulation around the scattered Hodgkin cells. The marked epithelioid appearance of the venular endothelium, paralleled by an increase of inter- and subendothelial lymphocytes, is characteristic of this type. Relative vascular density is low. It is lowest in the mixed cellularity type which is rich in epithelioid cells, also because of the accumulation of these voluminous cells. Just as in other variations of the mixed cellularity type, the vessels are displaced by a comparatively angiocentric

polymorphous cellular population. Furthermore, the venules are far less obvious, due to the incomplete epithelioid change of the endothelium. Thus, the organic structure of the vascular tree is no longer evident and seems to be effaced. The vessels in sclerotic or fibrotic areas do not show a striking change in their arborisation pattern; however, differences in calibration, endothelial equipment, and mediastructure of arterioles, capillaries, and venules are equalized. This is a situation that invokes the idea of a "degenerative dedifferentiation" of the vascular tree (Fig. 3d). No lymphocytic transit can be observed in such areas. The relative vascular density whithin sclerosis or fibrosis is high, the maximum density can be found in the lymphocytic depletion type with diffuse fibrosis. This might be explained by contraction and scarring of the area depleted of cells while vessels persist.

In conclusion it can be said that in all types of Hodgkin's disease the 'primary structure' of the vascular tree within the lymph nodes seems preserved, while variations in the 'secondary structure' exist: There is an expansion in the course of cellular accumulation and proliferation, and condensation in the course of devastation, which is itself accompanied by a degenerative dedifferentiation of the vascular system. Vascular proliferation cannot be visualized by the method applied. Whether it exists in lymph nodes during granulomatous processes (Hodgkin's disease included), as it is described in healing wounds (Clark et al. 1982), remains undecided. At present there are only indirect data supporting this view: Prostaglandin E_2, synthetized by stimulated 'suppressor' macrophages (Gemsa et al. 1982) was found in increased amounts in the serum of patients suffering from HD (Goodwin et al. 1977; Passwell et al. 1983). Recently, a vasoproliferative effect of this prostaglandin was described (Form and Auerbach 1983). Herman and coworkers (Herman et al. 1979) used microspheres and microangiography in an experimental setting in order to study changes of vascularization in lymph nodes after antigenic challenge. They were actually able to show the appearance and disappearance of 'hypervascularization' in the course of granuloma formation. The authors, however, interpreted their data as an effect of transitory opening of collapsed capillaries and arteriovenous shunts and characterized the angioarchitecture of the lymph node as 'surprisingly constant'.

To date, the question of whether necroses, so frequently observed in the nodular sclerosis type of HD, are toxic or ischaemic in nature (Möller et al. 1983), remains unsolved; in our view the presence of vessels reaching areas of necroses and surrounded by globular bleedings as mentioned above (Fig. 7) is not unequivocal evidence of an inadequate blood supply.

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