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Invited Review

Histopathology of the spleen in non-Hodgkin's lymphoma

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Summary. The human spleen has several different lymphoid compartments, which may be preferentially involved by non-Hodgkin's lymphomas. Low grade B-cell lymphomas tend to involve the compartments of the spleen where their normal physiological counterparts are found. High grade B-cell lymphomas grow more destructively without respecting lymphoid compartments. T-cell lymphomas involve mainly the T-cell areas, but may also involve follicles and the red pulp. Since non-Hodgkin's lymphomas can be regarded as clonal proliferations of lymphocytes frozen at a stage in differentiation, one possible conclusion is that low grade lymphomas are governed by normal homing mechanisms. High grade lymphomas may have lost their homing properties.

Key words: Spleen, non-Hodgkin's lymphoma

Introduction

There is hardly any topic in pathology, where developments in immunohistochemistry and molecular biology have led to such a marked increase in understanding of the pathogenesis, as in the field of malignant lymphomas (Harris, 1987; Mason, 1987; Picker et al., 1987; Williams et al., 1987; Cossman et al., 1988; Van der Valk and Meijer, 1988; de Jong et al., 1989a,b; Jaffe, 1990). However, diagnostic nomenclature is clearly underdeveloped in this area and the numerous classification schemes that exist further add to the confusion. As a result, many pathologists are uncomfortable with surgical hematopathology and leave the diagnosis, and particularly the subclassification, of malignant lymphomas to the so-called «lymphomaniacs».

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The human spleen remains an organ with which many pathologists feel most uncomfortable (Crosby, 1980). In addition to the complexity of hematopathology most pathologists rarely look at the organ except at the time of autopsy. Due to the large number of splenic macrophages with their proteolytic enzymes, rapid autolysis is inevitable, making histologic sections difficult to analyze (Wolf and Neiman, 1989). Only rapidly fixed and well processed tissue sections allow evaluation of all the delicate structures of the human spleen (van Krieken et al., 1985b).

Since the human spleen contains abundant lymphoid tissue, it is not surprising that non-Hodgkin's lymphomas may originate in and often spread to the spleen. In some types of lymphoma the spleen contains the main tumour load; in others there is no involvement or only a minor one (Stutte, 1984; Burke, 1985; Van Krieken et al., 1989b; Wolf and Neiman, 1989).

This review describes the histopathology of non-Hodgkin lymphomas in the spleen, in particular those of B-cell origin, and relates the pattern of lymphoma involvement to the structure of the normal spleen. Use is made of the Kiel-classification, as it recognizes clinicopathologic entities which are immunologically defined and related to physiological-occurring lymphocyte subsets (Lennert, 1981).

Architecture of the lymphoid tissue in the spleen

The lymphoid tissue in the human spleen is organized in several compartments, each with a specific cell population (Van Krieken and te Velde, 1988; Figs. 1, 2). These lymphoid compartments form the macroscopically discernible white pulp, but are also a major component of the red pulp. The white pulp consists of T-cell areas and follicles (Fig. 3). The T-cell areas surround central arteries and consist of concentric reticulum fibres filled with aggregates of CD4 (helper/inducer)-positive lymphocytes, intermingled with some CD8 (suppressor/cytotoxic)-positive lymphocytes and interdigitating

reticulum cells (Timens and Poppema, 1985; Van Krieken and te Velde, 1986). In a H & E stained section, these T-cell areas can be recognized as irregular groups of small lymphocytes without a surrounding marginal zone (see below). The nuclei of the lymphocytes have slightly irregular contours.

The B-cell areas represent follicles, part of which are contiguous with the T-cell areas and which may or may not contain a germinal centre. The follicle mantle zone (if a germinal centre is present) and the primary follicles are round, consisting of small and regular IgD-positive lymphocytes, with round nuclei. Invariably the follicles are surrounded by a marginal zone, which can vary greatly in width. The marginal zone consists of intermediately-sized lymphocytes, larger than the mantle zone cells, that lack IgD (Van Krieken et al., 1989a). We consider the marginal zone to be a part of the follicle. T-lymphocytes are also admixed in the marginal zone, in small numbers.

Between the white pulp (T-cell areas and B-cell follicles) and the red pulp a transitional area is present, which consists of incomplete sinusoidal structures and contains a cell population which is similar to that of the peripheral blood. We call this area the perifollicular zone (Fig. 3). Another compartment not clearly part of either the red or white pulp is a small rim of cells which closely follows the central arteries of the T-cell areas as well as its branches to the red pulp extending to the capillaries. This rim is comprised of mature lymphoplasmacytoid lymphocytes and plasma cells and CD8 positive lymphocytes. The CD 8 positive lymphocytes gradually increase in number towards the capillary endings (Van Krieken et al., 1986, 1989b).

The red pulp is a tissue (cords of Billroth) with many interconnecting sinuses. In the red pulp, areas devoid of capillaries and surrounded by sinuses contain B- and T-lymphocytes (more CD8 than CD4) and mononuclear phagocytes. We have called these regions non-filtering areas (Van Krieken et al., 1985 a, Fig. 4), in contrast to the major part of the red pulp that contains vessels and which represents the filtering regions of the spleen.

White pulp vs nodular involvement

Involvement of the white pulp is generally accepted as the growth pattern of non-Hodgkin's lymphomas in the spleen (Stutte, 1984; Burke, 1985; Wolf and Neiman, 1989). However, B-cell follicles do not have their own architectural framework, consisting of relatively persistent reticulum fibres, such as is the case within the T-cell areas. Therefore, after a follicle has disappeared, no remnants can be observed, which makes it impossible to prove that a follicle is involved completely by tumour. In contrast, T-cell areas do have a framework of parallel running reticulum fibres (Van Krieken and te Velde, 1988). This can be seen especially in spleens of patients treated by severe immune suppression. One sees «empty» T-cell areas, but follicles are absent.

Because lymphoid aggregates in normal spleens are called white pulp, nodular involvement of the spleen by lymphoma is often regarded as involvement of the white pulp. However, an examination in many cases has revealed preexisting atrophic white pulp, which can be discerned apart from the tumour, whereas partly involved follicles have not been detected, nor described in the literature. In addition, small tumour nodules are often located in the red pulp, especially in its lymphoid compartment, and the non-filtering areas (Van Krieken et al., 1989b). Furthermore, in many involved spleens the number of tumour nodules greatly exceeds the number of white pulp follicles and T-cell areas one finds in normal spleens. Therefore, we have previously suggested that malignant lymphoma involving the spleen often originates in the red pulp and mimicks white pulp involvement.

B-cell lymphomas

The cells of B-cell lymphomas and leukemias, like most malignant cells, have retained many properties (morphological, phenotypical, functional) of the cell from which they are derived. In most B-cell malignancies it is possible to relate the malignant cell to a physiological counterpart on morphological and immunophenotypical grounds (Salmon and Seligman, 1974; Lennert, 1981). For instance, follicle centre cell lymphomas (CBCC) are related to germinal centre cells; immunocytoma to the plasma cell differentiation pathway; CLL to the pool of circulating B-lymphocytes; etc.

Circulation and homing to specific tissues or tissue compartments are properties of many B-cells and their related malignancies (Picker et al., 1988; Pals et al., 1989). For instance, gastrointestinal lymphomas often remain localized, which might be due to such homing mechanisms (Isaacson and Spencer, 1987). Until now no specific homing receptors have been described for one of the splenic lymphoid compartments.

Because of their retained homing properties, one might expect malignant B lymphocytes to involve the tissues or tissue compartments where one normally finds the benign and normal physiological counterparts of these malignant cells. In our survey of non-Hodgkin's lymphoma involving the lymphoid compartments of the human spleen such was the case for low grade (according to the Kiel-classification) lymphomas (Van Krieken et al., 1989b).

B-cell chronic lymphocytic leukemia (B-CLL)

The spleen is involved in most cases of B-CLL and splenomegaly is a common clinical sign. Splenectomy is usually performed only on patients suffering from severe hypersplenism or local discomfort. More often spleens are removed when there is tumour progression, leading to more rapid growth (Wolf and Neiman, 1989). Histologically, numerous small (monoclonal) B-lymphocytes are found throughout the red pulp, both in the pulp cords as well as in the sinuses (Fig. 5), reflecting peripheral blood in involvement rather than splenic involvement, because blood cells that circulate through

the spleen are found mainly in the red pulp. Except for some extensively involved cases, the red pulp structure remains intact (Kraemer et al., 1984). In some cases, in which there is a marked pseudofollicular growth pattern in the lymph node, the same pseudonodules can be found, especially in the red pulp.

The white pulp is completely abnormal (Kraemer et al., 1984). Normal follicles are not present (as occurs in the lymph node in most cases) and only remnants of the T-cell areas are present at the periphery of tumour nodules. These findings suggest growth from the periarteriolar rim within the T-cell areas (Van Krieken et al., 1989b). The tumour nodules vary in diameter and are mostly round. They are composed of small lymphocytes (monoclonal B-CLL cells) with occasional paraimmunoblasts. Prolymphocytic leukemia has a red pulp distribution similar to CLL, but nodular growth is found in the perifollicular zone of the T-cell areas (Lampert et al., 1980). Furthermore they may show subendothelial growth in veins.

Immunocytoma

Immunocytomas are derived from B-lymphocytes maturating along the plasma cell pathway. Splenomegaly and leukemia are common features, but less prominent than that seen in CLL. Splenectomy is not often performed.

In most cases normal B-cell follicles and T-cell areas are found in the spleen. The tumour cells tend to grow in nodules (Fig. 6) that are present in the perivascular rim, both in the T-cell areas of the white pulp and along capillaries of the red pulp. The nodules are most prominent in the lymphoplasmacytic subtype. The lymphoplasmacytoid variant tends to grow more diffusely in the T-cell areas and in the non-filtering areas of the red pulp (Van Krieken et al., 1989b). Especially in leukemic cases diffuse involvement of the red pulp is found (Audouin et al., 1988). In fact, one can find immunocytoma in all the lymphoid compartments, but the distribution of the tumour cells is closely related to the stage of maturation. Physiologically, during the plasmacell differentiation small round lymphocytes get more cytoplasm and more distinct nuclei. Mature plasma cells are generally present along the periarteriolar rim, so the more mature immunocytomas are indeed present in the compartment of the more mature counterparts.

Centroblastic-centrocytic lymphoma (CBCC)

Most patients with follicle centre cell lymphoma present with disseminated disease including spleen involvement. In lymph nodes, a nodular growth pattern is often one of the hallmarks of the disease. However, in the spleen the growth pattern of the lymphoma is more difficult to assess (Wolf and Neiman, 1989). Because the white pulp is nodular by nature, one cannot say that tumour nodules in the spleen mean nodular growth (Fig. 7). In contrast with lymph nodes, the spleen in most cases is not completely involved and its red pulp architecture is retained (Kraemer et al., 1984).

In some cases it may be difficult to differentiate reactive from malignant follicles, as tumour nodules may mimic the marginal zone (Diebold et al., 1987). In these cases, immunophenotypic analysis may be necessary to differentiate neoplastic cells from reactive cells. Generally, normal follicles are not present and, even in minimal involved spleens, partial involvement of a follicle is never seen (Diebold et al., 1987). T-cell areas are present, but they may have an altered appearance due to tumour growth within the perivascular rim (Fig. 8). Small tumour nodules are often present in the red pulp, mainly in the non-filtering areas. If one imagines growth of these small nodules, one might expect disruption of the surrounding red pulp with stretching of the sinuses, leading to a picture of larger nodules surrounded by a perifollicular zone; exactly the structure that mimics involved follicles. This is the reason why we have postulated that, especially in follicle centre cell lymphoma the spleen is not involved through the white pulp follicles, but by lymphoma originating in the red pulp lymphoid tissue, especially the non-filtering areas (Van Krieken et al., 1989b).

Centrocytic lymphoma

At the time of the introduction of the Kiel-classification lymphoma was regarded as related to follicle centre cells (Lennert, 1981). However, the presence of the CD5 antigen and the absence of the bcl2 translocation suggest that centrocytic lymphoma is not a follicle centre cell lymphoma, but rather a separate entity (Jaffe et al., 1987). The derivation of centrocytic lymphoma is not completely clear at the moment, although immunohistochemical studies point to a derivation from mantle zone lymphocytes. In cases of centrocytic lymphoma no normal follicles are present similar to the lymph nodes of these patients. Centrocytic lymphoma grows in nodule, mainly in the perifollicular zone of the T-cell areas, and to a lesser extent in the perivascular rim (Narang et al., 1985). Red pulp involvement is seen only rarely. This distribution pattern is similar to that of immunocytoma, with the difference that immunocytoma is seen more often in the perivascular rim, whereas centrocytic lymphoma is more related to the perifollicular zone (Van Krieken et al., 1989b). These data are not strong enough to support a hypothesis of centrocytic lymphoma or mantle zone lymphocytes being intermediate between follicle centre cell lymphoma or cells and immunocytoma or plasma cell differentiation (Van Krieken et al., 1989a).

Hairy cell leukemia

Hairy cell leukemia is a peculiar B-cell neoplasia. The malignant cells have a specific morphology and phenotype, that is not clearly related to a normal physiological counterpart lymphocyte (Burke et al., 1974; Jansen et al., 1982; Hsu et al., 1983). It is clear that it is a B-cell neoplasia, due to its expression of monoclonal immunoglobulin and rearrangement of the immunoglobulin

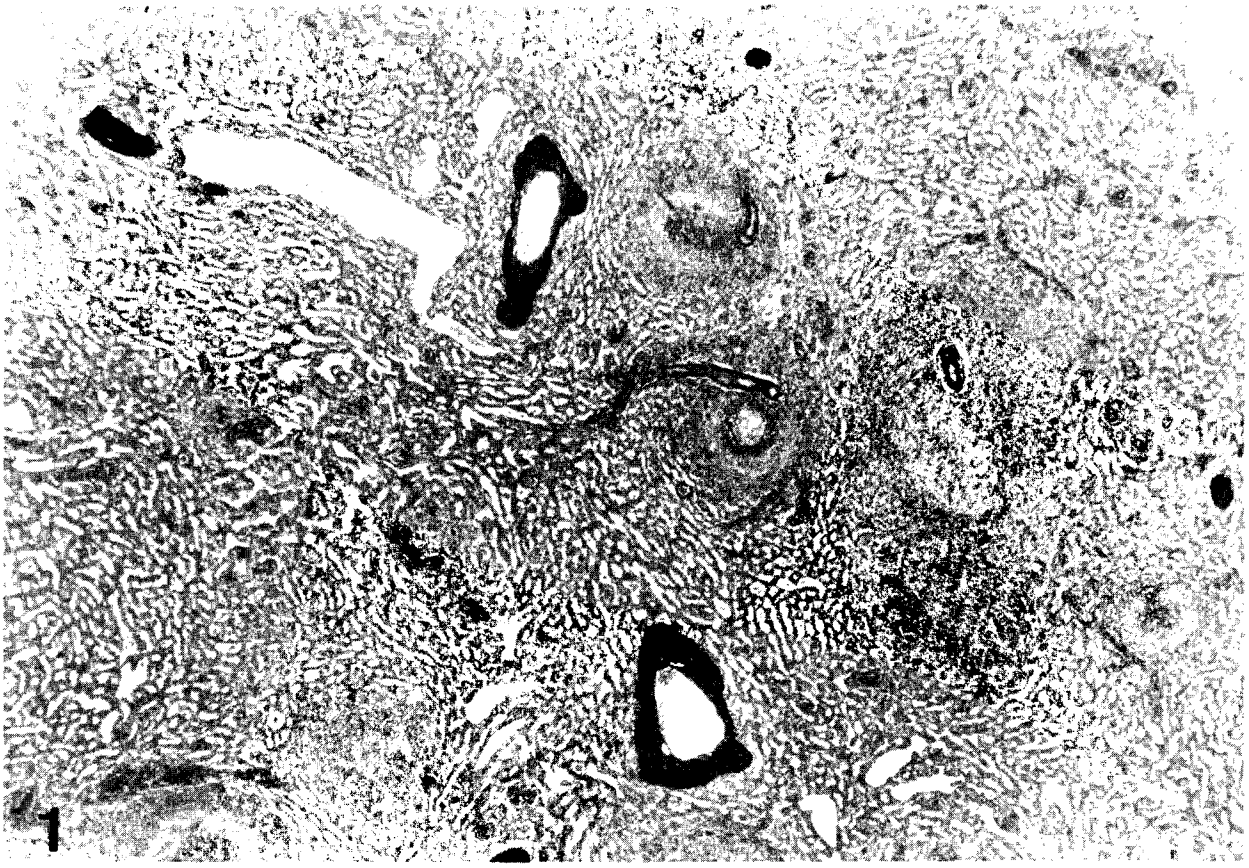


Fig. 1. Low power view of representative part of «normal» spleen (all figures: methenamine-silver/H&E, methylmethacrylate embedding). Several follicles, some with a germinal centre are present. Note the zoning of the follicles: germinal centre = light; mantle zone = dark; marginal zone = light; perifollicular zone = dark. Compare with figure 2 for dimensions.

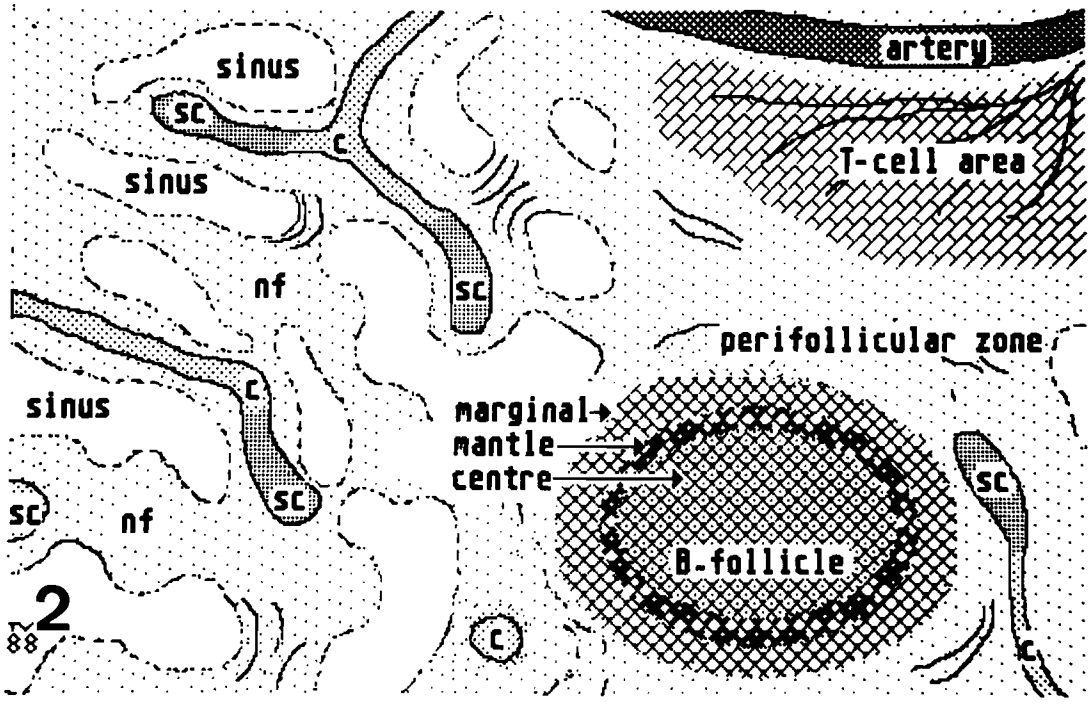
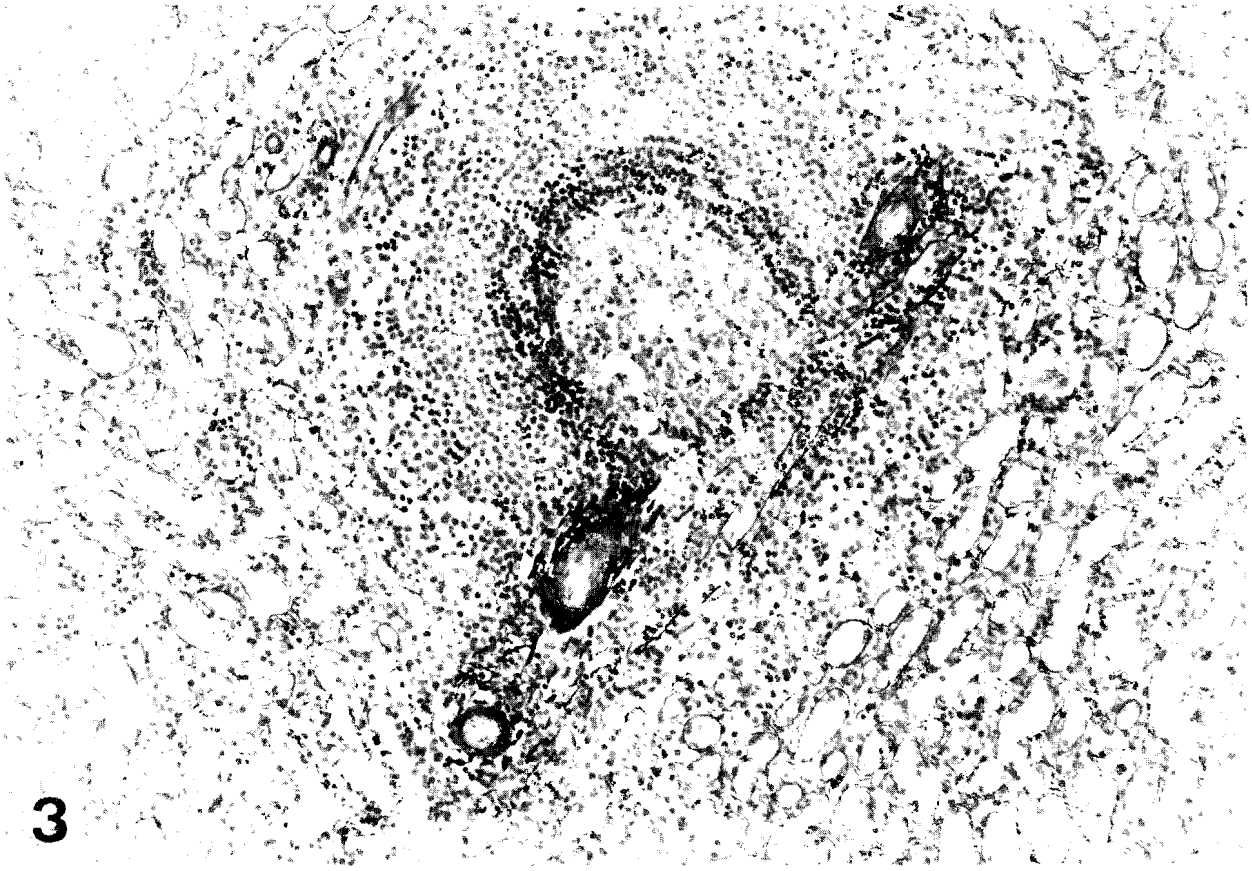


Fig. 2. Schematic representation of red (left) and white (right) pulp of the human spleen. Compare with figures 1, 3 and 4 for dimensions. SC = sheathed capillary; NF = non-filtering area.



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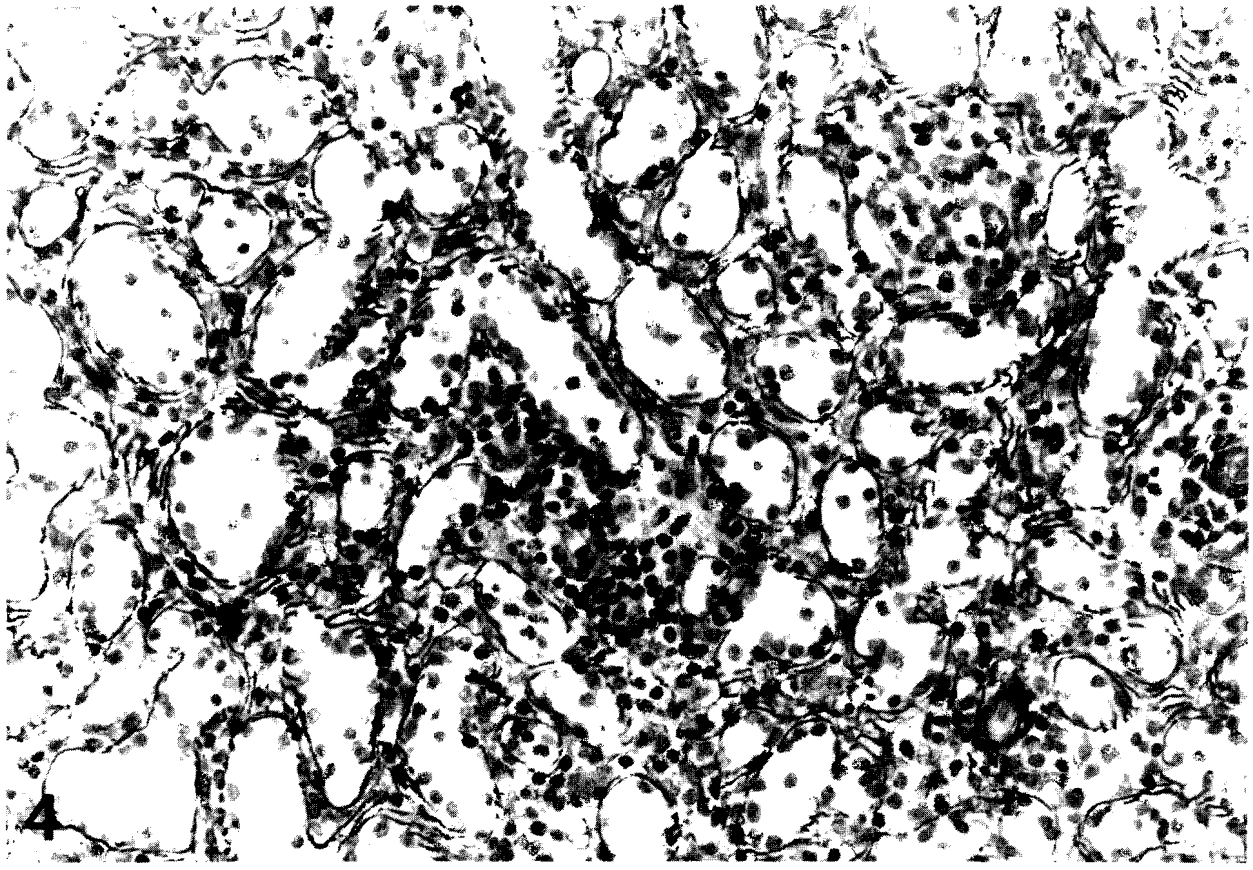

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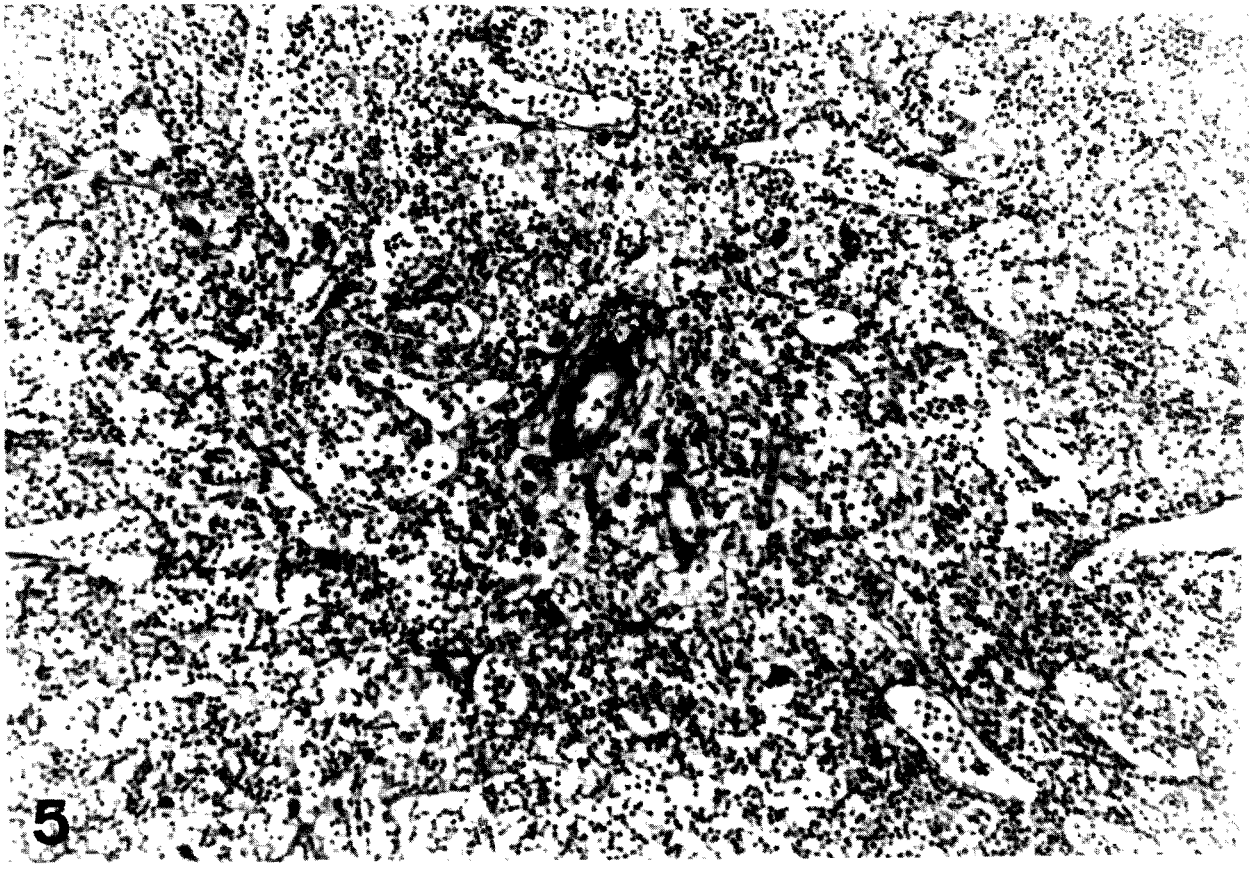

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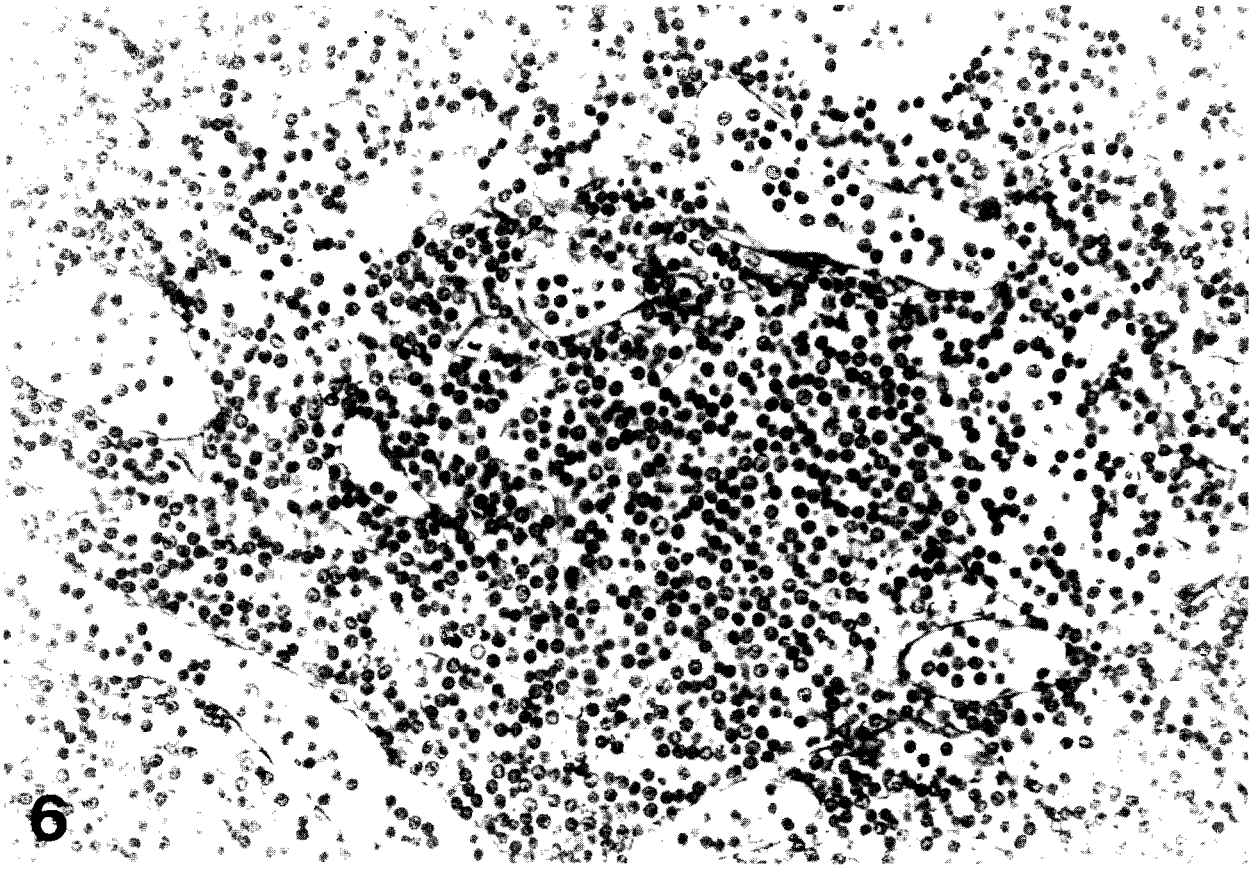

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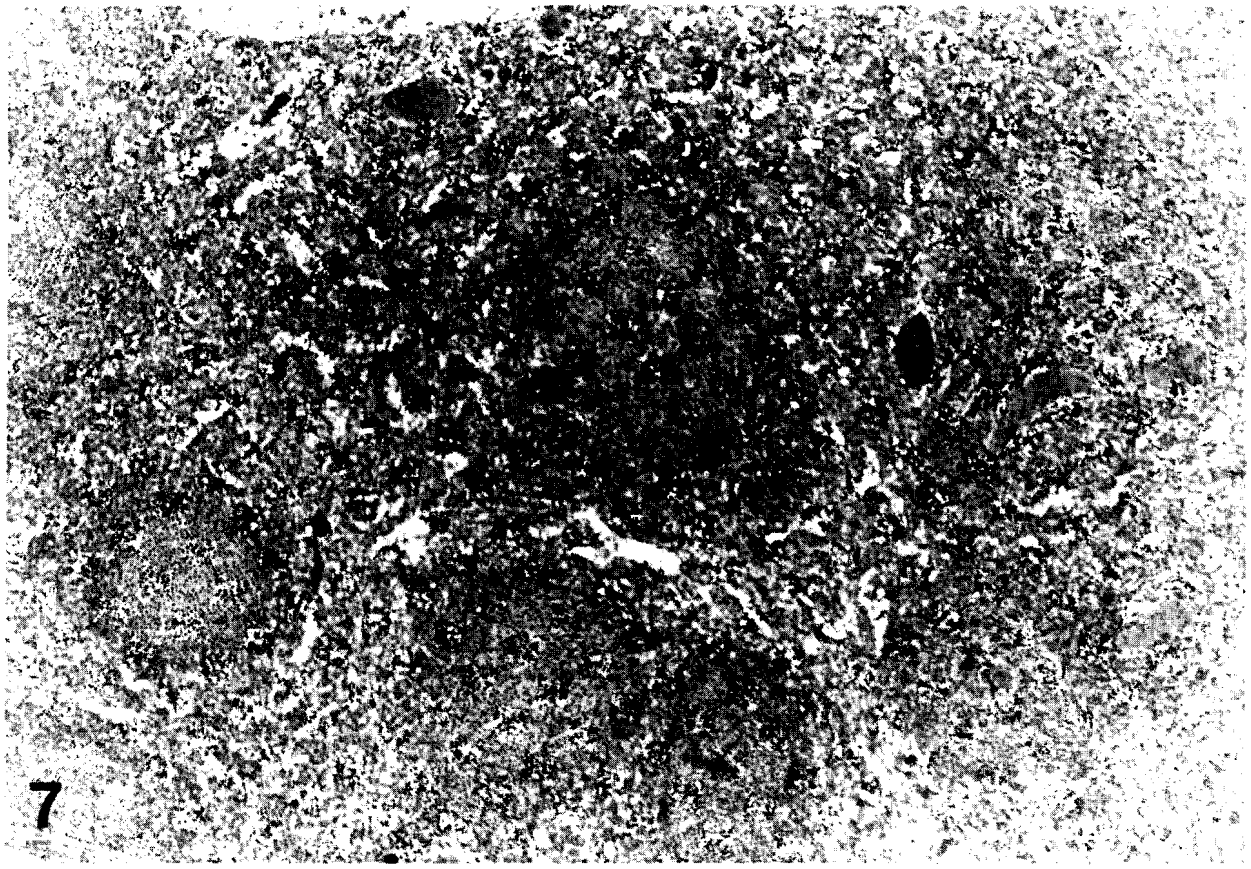

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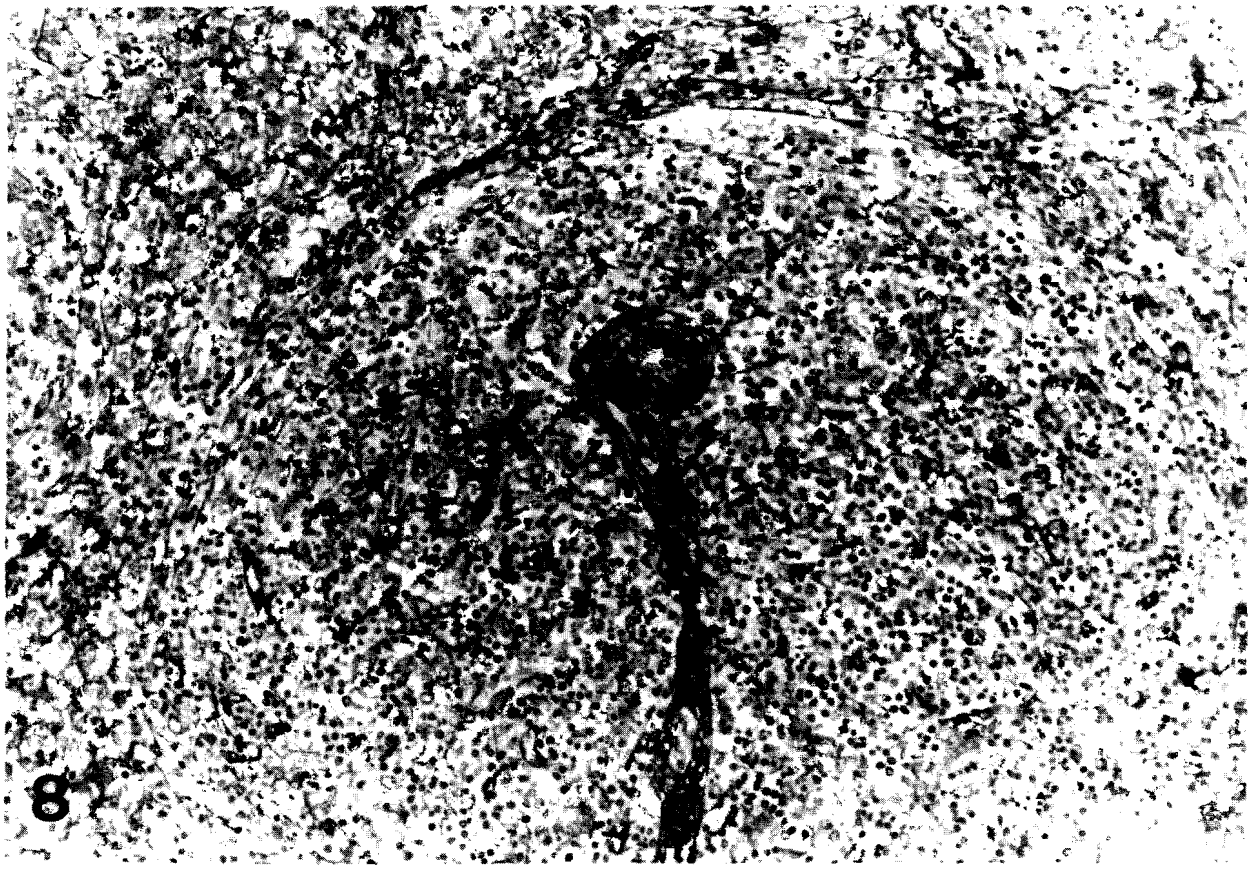

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Fig. 3. White pulp of the human spleen. T-cell area with reticulum fibres around central artery, bordered by a well developed follicle. Note the transition of a capillary into a sheathed capillary in the perifollicular zone (left upper part).

Fig. 4. Red pulp of the human spleen. Note the non-filtering area in the centre, the sheathed capillary in the right upper and the (unsheathed) capillary in the right lower part.

Fig. 5. Case of B-CLL. Large numbers of tumour cells in the red pulp cord tissue and sinuses. In the centre there is a severely depleted T-cell area and the few T-cells can be detected only by using immunohistochemistry.

Fig. 6. Case of lymphoplasmacytic immunocytoma with tumour nodule in the non-filtering area of the red pulp. The patient was leukemic, reflected by the high number of tumour cells in the cord tissue and the sinuses.

Fig. 7. Case of CBCC with several tumour nodules, reminiscent of normal follicular white pulp. The small nodule to the left has probably arisen in a non-filtering area.

Fig. 8. Case of CBCC with tumour nodule in the perivascular rim. The remnants of the T-cell area are stretched around the tumour nodule which is discernible by the reticulum fibres.

heavy and light chain genes. Splenomegaly is a prominent clinical feature, and before the introduction of interferon therapy splenectomy was often performed.

The splenic red pulp is heavily infiltrated by the hairy cells. The white pulp, although often atrophic, is clearly spared. A peculiar phenomenon of the hairy cells is the formation of so-called blood lakes, lined by hairy cells (Nanba et al., 1977). A few reports describe early involvement of the spleen by hairy cell leukemia. It is not clear whether or not these cases are indeed classical hairy cell leukemia, or might better fit into other entities such as atypical hairy cell leukemia, monocytoid B-cell lymphoma, or small lymphocytic lymphoma resembling hairy cell leukemia (Neiman et al., 1979; Sheibani et al., 1986; Melo et al., 1987; Piris et al., 1988; Traweek et al., 1989).

Primary splenic lymphoma

There is no agreement regarding the existence of primary splenic lymphomas. In part this disagreement is definitional (Gupta et al., 1965; Ahman et al., 1966; Hara et al., 1985; Narang et al., 1985; Diebold et al., 1987; Audouin et al., 1988). For example, some authors exclude from this group all cases with lymph node, peripheral blood or bone marrow involvement. In contrast, others include patients with extensive splenic lymphoma with only subclinical dissemination. In any case, although most of the so-called primary splenic lymphomas fit into one of the categories of the Kiel-classification (immunocytoma, CBCC, etc), there are reports of specific morphology or immunophenotypic findings (Melo et al., 1987; Palutke et al., 1988). As a rule these are low grade lymphomas, which have a remarkably good prognosis (Kraemer et al., 1984; Narang et al., 1985).

High grade (Kiel) lymphomas

High grade B-cell lymphomas (centroblastic, immunoblastic, lymphoblastic) are disseminated at presentation less often than low grade lymphomas, and therefore splenic involvement is less frequent. They grow as tumour nodules that destroy the preexistent splenic structure (Ahmann et al., 1966; Kim and Dorfman, 1974; Kraemer et al., 1984; Burke, 1981; Harris et al., 1984) and show no preference for certain splenic compartments. In most cases the diagnosis is not difficult.

T-cell lymphomas

At the moment there is no classification of T-cell neoplasia which correlates clinicopathological syndromes with physiological counterpart lymphocytes as is the case for B-cell lymphomas. The best approaches are the grouping of T-cell neoplasia into syndromes: prethymic or immature T-cell neoplasia (mainly T-ALL), cutaneous T-cell lymphoma (mainly Mycosis Fungoides), and other peripheral T-cell lymphomas. In the latter group there is a subdivision of low and high grade cases based on histopathological findings, the latter containing mainly large cells. This subdivision is, however, not well correlated with clinical features. The description of splenic involvement by T-cell lymphomas is therefore not as logical and understandable as that of B-cell lymphoma. Furthermore, T-cell lymphomas are less common than B-cell lymphomas, and splenic involvement is correspondingly less frequent.

In most described cases of splenic involvement by T-cell lymphoma the lymphoma infiltrates the T-cell areas. In leukemic cases (T-CLL) large numbers of leukemic cells are present in the red pulp cord tissue and sinuses. As in B-CLL it is debatable whether or not to call this involvement. B-cell follicles are normally preserved, although infiltration of follicles has been noted also.

Conclusions

The number of spleens with non-Hodgkin's lymphoma submitted for pathologic examination has decreased, since treatment is often not influenced by the results of staging laparotomy. Still, pathologists will encounter splenectomy specimens which show non-Hodgkin's lymphoma, for instance, in cases of splenomegaly with unknown cause, so-called primary splenic lymphoma, or unexpectedly in cases of traumatic rupture of idiopathic thrombocytopenic purpura. This review has been written to give some guidance to the detection and classification non-Hodgkin's lymphoma in the spleen.

Cornerstones of the Kiel-classification are the cytology and the immunophenotye of the tumour cells. These criteria are applicable in most cases of splenic B-cell lymphoma. They are well described in the literature and therefore these descriptions are not included in this review. Architectural features of lymphomas in the spleen are different from lymph node-based lymphomas.

and can cause problems in the diagnosis and classification of lymphoma. For instance, effacement of the lymph node architecture is of great help in diagnosing CLL or CBCC in a lymph node, but this is less often the case in the spleen.

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References

Ahmann D.L., Kiely J.M., Harrison E.G. and Payne W.S. (1966). Malignant lymphoma of the spleen. Cancer 19, 461-489.

Audouin J., Diebold J., Schvartz H., Le Tourneau A., Bernadou A. and Zittoun R. (1988). Malignant lymphoplasmacytic lymphoma with prominent splenomegaly (primary lymphoma of the spleen). J. Pathol. 155, 17-33.

Burke J.S., Byrne G.E. and Rappaport H. (1974). Hairy cell leukemia (leukemic reticuloendotheliosis). I. A clinicopathologic study of 21 patients. Cancer 33, 1399.

Burke J.S. (1981). Surgical pathology of the spleen: an approach to the differential diagnosis of splenic lymphomas and leukemias: part 1. Diseases of the white pulp. Am. J. Surg. Pathol. 5, 681-694.

Burke J.S. (1985). The diagnosis of lymphoma and lymphoid proliferations in the spleen. In: Surgical pathology of the lymph nodes and related organs. Jaffe E.S. (ed). W.B. Saunders. Philadelphia. pp 249-281.

Cossman J., Uppenkamp M., Sundeen J., Coupland R. and Raffeld M. (1988). Molecular genetics and diagnosis of lymphoma. Arch. Pathol. Lab. Med. 112, 117-127.

Crosby W.H. (1980). The spleen. In: Blood. pure and eloquent. Wintrobe M.M. (ed). Mc Graw-Hill. pp 96-138.

Diebold J., Kanavaros P., Audouin J., Bernadou A. and Zittoun R. (1987). Les lymphomes malins centroblastiques centrocytiques et centroblastiques a predominance splenique (ou primitifs de la rate). Etude anatomo-clinique de 17 cas. Bull. Cancer 74, 437-453.

Gupta T.B., Coombes B.C. and Brasfield R.D. (1965). Primary malignant neoplasms of the spleen. Surg. Gyn. Obstet. 120, 947-960.

Hara K., Ito M., Shimizu K., Matsumoto T., Suchi T., Iijima S., (1985). Three cases of primary splenic lymphoma. Case report and review of the Japanese literature. Acta Pathol. Jpn. 35, 419-435.

Harris N.L., Aisenberg A.C., Meyer J.E., Ellman L. and Elman A. (1984). Diffuse large cell lymphoma of the spleen. Clinical and pathologic characteristics of ten cases. Cancer 54, 2460-2467.

Harris N. (1988). Lymphoma 1987; an interim approach to diagnosis and classification. In: Pathology Annual. Rosen P.P. and Fechner R.E. (eds). Apleton and Lange. Connecticut. pp 1-67.

Hsu S.M., Yang K. and Jaffe E.S. (1983). Hairy cell leukemia: A B-cell neoplasm with a unique antigenic profile. Am. J. Clin. Pathol. 80, 421.

Isaacson P.G. and Spencer J. (1987). Malignant lymphomas of mucosa-associated lymphoid tissue. Histopathology 11, 445-462.

Jaffe E.S., Bookman M.A. and Longo D.L. (1987). Lymphocytic lymphoma of intermediate differentiation: mantle zone lymphoma - a distinct subtype of B-cell lymphoma. Hum. Pathol. 18, 877-880.

Jaffe E.S. (1990). The role of immunophenotypic markers in the classification of non-Hodgkin's lymphomas. Sem. Hematol. (in press).

Jansen J., LeBien T.W. and Kersey J.H. (1982). The phenotype of the neoplastic cells of hairy cell leukemia studied with monoclonal antibodies. Blood 59, 609.

Jong D. de, Voetdijk B.H.M., Ommen G.J.B. van, Kluin-Nelemans J.C., Beverstock G.C. and Kluin Ph.M. (1989a). Translocation t (14;18) in B cell lymphomas as a cause for defective immunoglobulin production. J. Exp. Med. 169, 613-624.

Jong D. de, Voetdijk B.M.H., Ommen G.J.B. van and Kluin Ph.M. (1989b). Alterations in immunoglobulin genes reveal the origin and evolution of monotypic and bitypic B cell lymphomas. Am. J. Pathol. 134, 1233-1242.

Kim H. and Dorfman R.F. (1974). Morphological studies of 84 untreated patients subjected for laparatomy for the staining of non-Hodgkin's lymphoma. Cancer 33, 657-674.

Kraemer B.B., Osborne B.M. and Butler J.J. (1984). Primary splenic presentation of malignant lymphoma and related disorders; a study of 49 cases. Cancer 54, 1606-1619.

Lampert I., Catovsky D., Marsch G.W., Child J.A. and Galton D.A.G. (1980). The histopathology of prolymphocytic leukaemia with particular reference to the spleen: a comparison with chronic lymphocytic leukaemia. Histopathology 4, 3-19.

Lennert K. (1981). Histopathology of non-Hodgkin's lymphoma. Springer Verlag. Berlin.

Mason D.Y. (1987). A new look at lymphoma immunohistology. Am. J. Pathol. 128, 1-4.

Melo J.V., Hedge U., Parreire A., Thompson I., Lampert I.A. and Catovsky D. (1987). Splenic B cell lymphoma with circulating villous lymphocytes: differential diagnosis of B cell leukaemias with large spleens. J. Clin. Pathol. 40, 642-651.

Nanba K., Soban E.J., Bowling M.C. and Berard C.W. (1977). Splenic pseudosinuses and hepatic angiomatous lesions. Distinctive features of hairy cell leukemia. Am. J. Clin. Pathol. 67, 415.

Narang S., Wolf B.C. and Neiman R.S. (1985). Malignant lymphoma presenting with prominent splenomegaly. A clinicopathologic study with special reference to intermediate cell lymphoma. Cancer 55, 1948-1957.

Neiman R.S., Sullivan A.L. and Jaffe R. (1979). Malignant lymphoid simulating leukemic reticuloendotheliosis: a clinicopathologic study of ten cases. Cancer 43, 329-342.

Pals S.T., Horst E., Ossekoppele G.J., Figdor C.G., Scheper R.J. and Meijer C.J.L.M. (1989). Expression of lymphocyte homing receptor as a mechanism of dissemination in non-Hodgkin's lymphoma. Blood 73, 885-888.

Palutke M., Eisenberg L., Narang S., Han L.L., Peeples T.C., Kukuruga D.L. and Tabaczka P.M. (1988). B lymphocytic lymphoma (large cell) of possible splenic marginal zone origin presenting with prominent splenomegaly and unusual cordal red pulp distribution. Cancer 62, 593-600.

Picker L.J., Weiss L.M., Medeiros L.J., Wood G.S. and Warnke R.A. (1987). Immunophenotypic criteria for the diagnosis of non-Hodgkin's lymphoma. Am. J. Pathol. 128, 181-201.

Picker L.J., Medeiros L.J., Weiss L.M., Warnke R.A. and Butcher E.C. (1988). Expression of lymphocyte horming receptor

antigens in non-Hodgkin's lymphoma. Am. J. Pathol. 130, 496-504.

Piris M.A., Rivas C., Morente M., Cruz M.A., Rubio C. and Oliva H. (1988). Monocytoid B-cell lymphoma, a tumour related to the marginal zone. Histopathology 12, 383-392.

Salmon S.E. and Seligman M. (1974). B-cell neoplasia in man. Lancet 2, 1230.

Sheibani K., Sohn C.C., Burke J.S., Winberg C.D., Wu A.M. and Rappaport H. (1986). Monocytoid B-cell lymphoma. A novel B-cell neoplasm. Am. J. Pathol. 124, 310-318.

Stutte H.J. (1984). Die Milz. In: Pathologie. Springer-Verlag, Berlin.

Timens W. and Poppema S. (1985). Lymphocyte compartments in human spleen. An immunohistologic study in normal spleens and non-involved spleens in Hodgkin's disease. Am. J. Pathol. 120, 443-454.

Traweeks S.T., Sheibani K., Winberg C.D., Mena R.R., Wu A.M. and Rappaport H. (1989). Monocytoid B-cell lymphoma: its evolution and relationship to other low-grade B-cell neoplasms. Blood 73, 573-578.

Van der Valk P. and Meijer C.J.L.M. (1988). The non-Hodgkin's lymphomas: old and new thinking. Histopathology. 13, 367.

Van Krieken J.H.J.M, Velde J. te, Hermans J. and Welvaart K. (1985a). The splenic red pulp: a histomorphometrical study in splenectomy specimens embedded in methylmethacrylate. Histopathology 9, 401-406.

Van Krieken J.H.J.M, Velde J. te, Kleiverda K., Leenheers-Binnendijk L. and Velde C.J.H. vd. (1985b). The human spleen: a histological study in splenectomy specimens embedded in methylmethacrylate. Histopathology 9, 571-585.

Van Krieken J.H.J.M and Velde J. te (1986). Immunohistology of the human spleen: an inventory of the localization of lymphocyte subpopulations. Histopathology 10, 285-294.

Van Krieken J.H.J.M and Velde J. te (1988). Normal histology of the human spleen. Am. J. Surg. Pathol. 12, 777-785.

Van Krieken J.H.J.M., Schilling C. von, Kluin Ph.M. and Lennert K. (1989a). Splenic marginal zone lymphocytes and related cells in the lymph node: a morphologic and immunohistochemical study. Hum. Pathol. 20, 320-325.

Van Krieken J.H.J.M., Feller A.C. and Velde J. te (1989b). The distribution of non-Hodgkin's lymphoma in the lymphoid compartments of the spleen. Am. J. Surg. Pathol. 13, 757-765.

Williams M.E., Innes M.E., Borrowitz M.J., Lovell M.A., Swerdlow S.H., Hurtubise P.E., Brynes R.K., Chan W.C., Bryne G.E., Whitcomb C.C. and Thomas C.Y. (1987). Immunoglobulin and T cell receptor gene rearrangements in human lymphoma and leukemia. Blood 69, 79.