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0014-4754/85/020209-07$1.50 + 0.20/0

The role of the spleen in leukemias and lymphomas including Hodgkin's disease

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Key words. Spleen; leukemia; lymphoma; Hodgkin's disease; non-Hodgkin's lymphoma; malignant histiocytosis.

1. Introduction

The spleen as the largest single lymphoid organ in the body is of interest for clinical medicine and pathology, not only because it may serve as a 'showcase' for the hematopoietic and lymphoid tissue, but also because in cases of lymphoma and leukemia it gets involved sooner or later in the majority of patients. In some it may even be the site of the first or only clinical manifestation of hematopoietic neoplasia.

For obvious reasons, it will not be possible in this chapter to treat all the possible clinical, morphological and functional aspects of splenic involvement in hematopoietic neoplasias.

In classical myeloid or lymphoid leukemia the diagnosis is usually established by the examination of peripheral blood and bone marrow. Involvement of the spleen in these diseases is more in the sense of a 'bystander reaction' although splenomegaly may be one of the earliest symptoms. It has usually no decisive influence on the management of the patient.

In hairy-cell leukemia and malignant histiocytosis, however splenomegaly may be the most important symptom, and not infrequently the diagnosis can only be es-

tablished after pathological examination of the removed spleen. In Hodgkins disease, the demonstration of abdominal and particularly splenic involvement is of critical importance for the definition of the extent of disease which in turn is decisive for the treatment strategy.

In the following, we shall therefore mainly concentrate on topics which are relevant to the diagnosis and management of patients with these neoplasias.

2. Leukemias

2.1. General

Most leukemia patients show involvement of the spleen during the course of their disease, irrespective of the type of leukemia. Splenomegaly is rarely the leading symptom though it may contribute to the anemia and thrombocytopenia through functional hypersplenism. The massively enlarged spleen of chronic myeloid leukemia (CML) or the osteomyelofibrosis syndrome (OMF) may cause symptoms through displacement and oppression of adjacent organs.

Leukemic infiltration of the spleen carries the risk of spontaneous rupture[6] brought about either by capsular infiltration with leukemic blast cells[46] or possibly the ischemic infarctions frequently found in large spleens. That capsular infiltration by blast cells is a potential mechanism for the rupture is supported by the observations in infectious mononucleosis, where this phenomenon is also seen[74]. Since rupture is more common in acute leukemia and infarctions occur more frequently in chronic forms, it may be that infarction is not a major predisposing factor.

Although splenic rupture occurs only in about 1% of leukemia patients[46], leukemia is the single most important cause for this occurrence, accounting for about 40% of reported cases. Rupture occurs most frequently in acute mycloid leukemia (AML) and acute lymphoid leukemia (ALL) but also in hairy-cell leukemia (HCL)[68,77,88]. Interestingly, in 11 cases of ruptured spleens in AML, the mean splenic weight was only 470 g while in all other hematologic neoplasias leading to splenic rupture, the organ weight[6] was between 1000 and 1600 g, a possible indication for the pathogenetic role of blastic infiltration rather than infarction.

Splenic rupture was the first sign of leukemia in 34% of reported cases of leukemia with splenic rupture[6].

It is important to note that in lymphocytic leukemias, the chronic lymphocytic leukemia of T-cell origin – particularly frequent in Japan but rare in western countries – is associated to a high degree with splenomegaly and cutaneous involvement[41].

Pathologically the leukemias, particularly CML, are the most obvious example of a disease selectively involving the red pulp in the spleen (table 1). They always diffusely infiltrate pulp cords and sinuses and only secondarily obliterate the white pulp so that it becomes barely visible.

2.2. Hairy-cell leukemia (HCL)

Hairy-cell leukemia (leukemic reticuloendotheliosis) is an uncommon type of leukemia, accounting for about 2–5% of all leukemias[13,45]. Neither the nature of the leukemic cell nor its physiologic counterpart have been completely elucidated so far. The consensus is that hairy cells probably represent a hybrid form of B-lymphocyte, also exhibiting some functional properties of monocytes[4].

HCL mostly occurs in males, begins insidiously, runs a chronic course and is characterized clinically by pancytopenia and splenomegaly which is present in up to 93% of cases[13]. Hairy-cells are usually identified and cytochemically classified with the tartrate-resistant-acid phosphatase (TRAP) reaction on blood and bone marrow smears and biopsies. However, it may be necessary to establish the diagnosis on a splenectomy specimen. Therefore, pathologists should be acquainted with the splenic morphology in HCL.

The probable B-lymphocytic origin of HCL identifies it as a malignant lymphoproliferative disorder, perhaps near chronic lymphocytic leukemia. Nevertheless, in the spleen it is the only such process to cause diffuse red-pulp disease.

Macroscopically, the splenic cut surface is homogeneous, red and fleshy, without any nodules. Under light microscopy (fig. 1) the tumor cells are characterized by their bland cytological features with open chromatin, small nucleoli and a virtual lack of mitoses. The nuclei are often indented. The cytoplasm is frequently abundant and clear. In Zenker or B-5 fixed material, cytoplasmic membranes are sharply delineated and the intimate association of the tumor cells sometimes imparts the impression of an epithelial tumor. The hairy-cells diffusely infiltrate cords and sinuses. Intrasinusoidal cells can be seen attaching to each other and to erythrocytes as well as to sinus endothelial lining cells[64]. A unique morphologic feature are the abnormal vascular formations (fig. 2), which have been described by several authors[26, 30, 50] and which were called 'pseudo-sinuses' (fig. 2) by Nanba et al.[61] who first recognized the specificity and the pathogenesis of this lesion. On close observation, one can distinguish two forms[64], namely the true pseudo-sinus and so called 'blood-filled spaces' or 'RBC-pools' which are situated within the cords. Their recognition and distinction may be important

Table 1. Pattern of splenic involvement in hematopoietic neoplasias

Neoplasia	Involves Red pulp diffuse	White pulp nodular
Chronic myeloid leukemia	+	
Myeloid metaplasia		
– agnogenic	+	
– secondary	+	
Hairy-cell leukemia	+	
Chronic lymphocytic leukemia	+ late	+ early
Non-Hodgkins lymphomas		
– lymphocytic well differentiated		+
– lymphocytic plasmocytoid		+
– lymphocytic poorly differentiated		+
– mixed cell type		+
– Burkitt		+
– 'histiocytic'	+ masses	+
Mycosis fungoides	+	+
Hodgkin's disease	+	+
Malignant histiocytosis	+	

Adapted from Burke[16].

when differentiating HCL from similar non-Hodgkins lymphomas involving the spleen.

In abnormal or pseudo-sinuses, hairy-cells are seen lining the lumen. Ultrastructurally they are situated on attenuated endothelial cells or directly on fragmented ring fibers. Where these are lacking, they may interact directly with fixed cord macrophages or other hairy-cells[65]. Hairy-cells attached to the endothelial cells sometimes project cytoplasmic processes between the endothelial cells, which may be virtually surrounded and have a degenerating appearance[65]. Hairy-cells also seem to plug the sinus pores.

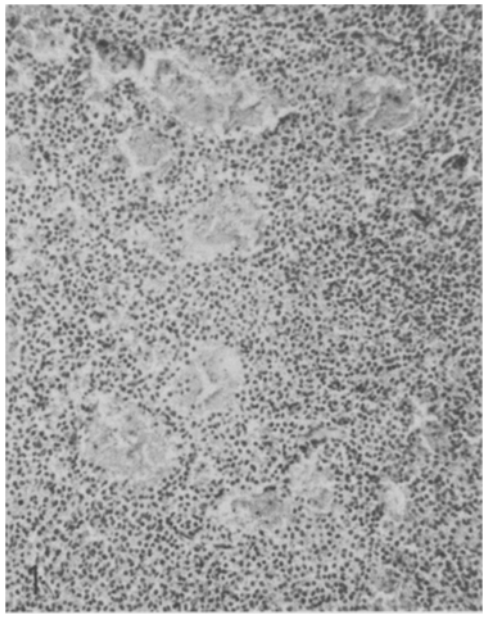

Figure 1. Spleen in hairy-cell leukemia. Diffuse involvement of red pulp cords with many pseudosinuses. HE, × 100.

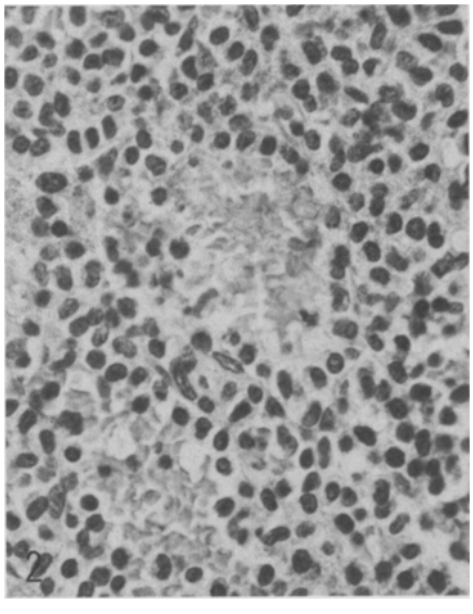

Figure 2. Spleen in hairy-cell leukemia. Tumor cells can be seen lining a pseudosinus (center) and forming an RBC-pool in a cord (right lower half). HE, × 400.

The so called RBC-pools are situated within the cords. They are surrounded by hairy cells and macrophages too but lack endothelial cells and ring fibers and are therefore no sinusoidal structure. Ultrastructurally they contain aggregates of hairy-cells with macrophages and RBCs. The cytoplasmic processes of hairy-cells surround reticulum fibers, RBC and platelets.

These morphologic findings support the following pathogenetic hypothesis for abnormal sinuses and blood-lakes[15, 64, 65]: The plugging of the sinus pores by hairy-cells and their considerable adherence and clumping along the sinus walls obstructs the transsinusoidal blood flow, which results in a rise in the intrasinusoidal pressure. Endothelial cells surrounded by hairy-cells may become deprived of essential nutrients from the blood stream. They degenerate and are unable to synthesize the ring fibers. Progressive replacement of endothelial cells by hairy-cells and loss of ring fibers weakens the sinus wall, which ruptures under the raised blood pressure. The increased intrasinusoidal pressure and additional obstruction of transcordal blood flow by clumping and adherence of hairy-cells to cordal structures may cause the intracordal blood-lakes.

The structural findings also explain the functional hypersplenism in HCL. The blood volume in HCL spleens is about 25% greater then in controls and the splenic red cell pool is disproportionately elevated to 21 ml/100 g as compared to 13–15 ml/100 g in controls[35] reflecting the pooling effect of pseudo-sinuses and blood-lakes. Since cordal macrophages are prominent[15] and erythrophagocytosis by hairy-cells cannot be demonstrated, hypersplenism is probably mainly due to the impediment of transcordal blood flow. The expansion of the cordal space by the leukemic infiltrate, the plugging of pores and the intrasinusoidal and cordal clumping of hairy-cells result in a decreased blood flow, thus leading to an increase of the length of time of exposure of RBC and other formed blood elements to cordal macrophages with resultant increased removal of cells from the circulation and peripheral cytopenia. But even minimally enlarged spleens may already cause significant sequestration[59]. Splenectomy usually corrects the peripheral blood values.

Splenic weight in HCL varies greatly. In published series it is usually between 300 and over 6000 g, the majority being between 1000 and 2000 g (table 2). In a series of 28 patients from our own hospital[68], the mean splenic weight was 1420 g with a range from 300 to 2900 g.

Splenic rupture can occur in HCL as in other leukemias. So far about 10 cases have been reported[68, 77, 88]. The event usually occurs in big spleens with infarctions[88]. It was observed once among 28 patients by

Table 2. Splenic weight in hairy-cell leukemia

Author	Number of cases	Mean weight	Range
Burke et al.[14]	16	1809 g	350–4650 g
Mintz et al.[59]	26	1200 g	250–4450 g
Rhyner[68]	28	1420 g	300–2900 g

Rhyner[68]. The intense vascular changes would seem to enhance the development of splenic rupture. The event might be more frequent if the spleens were not removed early in the course of the disease for therapeutic reasons.

Splenectomy is considered the first treatment in patients with a definite splenomegaly and pancytopenia. The elimination of the sequestering organ usually leads to rapid improvement of peripheral blood counts[45, 59, 68]. Inspite of splenectomy and correction of peripheral blood values, some patients will have progressive disease[44, 59]. The response to splenectomy is usually better in patients with heavier spleens; however, a correlation between splenic weight and survival could not be demonstrated[44]. Overall survival in splenectomized patients seems better than in the non-splenectomized group; but the difference does not exist for patients over 60 years of age with small spleens, minimal cytopenia and long duration of symptoms[45].

A number of cases have been reported, in which a non-Hodgkin lymphoma (NHL) occurred together with HCL in the spleen[1, 34] or in which a NHL closely mimicked HCL[17, 33, 62, 63]. These cases must be distinguished from HCL by the pathologist because of the important therapeutic implications. In our own experience with a similar case (figs 3, 4) the distinction is best achieved by a combination of methods. Macroscopically these cases of NHL regularly show at least partial nodularity of the splenic infiltrate. Pseudo-sinuses are usually absent[62, 63]. The cells are mostly – but not always – negative for TRAP. Ultrastructurally they do not contain ribosomal lamellar complexes, although this lack alone may not preclude HCL because this structure is not strictly specific for HCL and can be demonstrated in a minority of HCL cells only[65]. Thus, meticulous macroscopic and microscopic examination of the spleen by the pathologist is of overriding importance, since HCL never produces a nodular infiltrate.

3. Non-Hodgkin lymphomas (NHL)

Malignant lymphomas presenting in the spleen are rare[16, 29, 78, 81]. In a recent series from the Memorial Sloan Kettering Hospital 2.6% of stage I and IE cases showed location in the spleen[81], while a report from France found splenic presentation in 11.6%[57].

Primary NHL of the spleen may develop after a state of chronic stimulation of unknown etiology, idiopathic splenomegaly, also called 'non-tropical idiopathic splenomegaly'[22, 78].

Involvement of the spleen in the course of NHL presenting in another site is much more frequent and in the order of 35–40%[71, 81]. Nodular lymphomas involve the spleen in about 50–65%, the diffuse types in only about 30%[42, 71]. In patients dying with NHL, splenic tumor is encountered in 50–80% depending on the histologic type involved[69, 81].

Malignant lymphomas typically affect the white pulp of the spleen and therefore always form nodules (figs 5, 6). Since the white pulp is a set of nodules within the red pulp, the subclassification of lymphomas into 'nodular' or 'diffuse' is not appropriate to describe the pattern of splenic lymphomatous involvement. The gross appearance of the cut surface of the spleen allows a reliable distinction between 'small-cell' and 'large-cell' lymphoma types[69]. In the former, small uniform nodules are evenly distributed throughout the cut surface (fig. 5) while in the latter bulky and irregular nodules abound (fig. 6). In cases with transition from small to large cell types, both may coexist in the spleen and can be identified by their gross appearance.

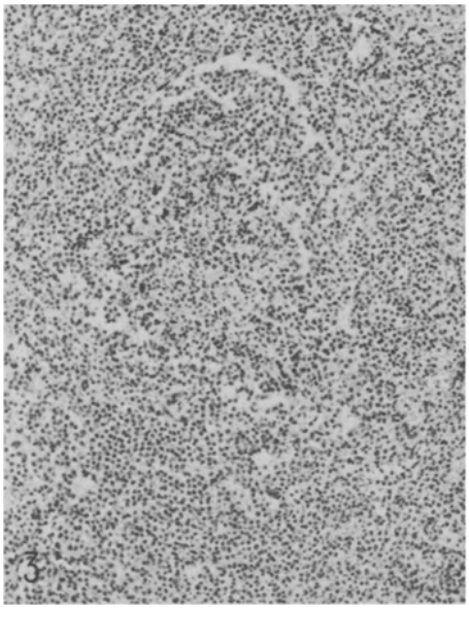

Figure 3. Hairy-cell like malignant non-Hodgkin-lymphoma (of B-cell type according marker studies) involving spleen. Note vaguely nodular pattern (center). HE, × 80.

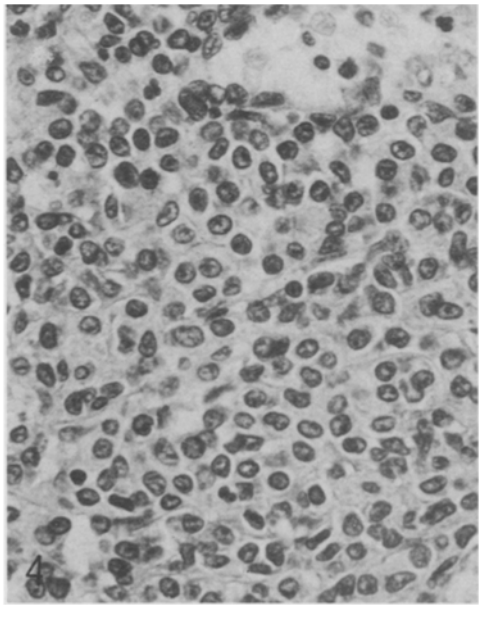

Figure 4. Same case as figure 3. Note close resemblance of tumor cells to hairy-cells and cohesive infiltration of pulp cords. Dilated sinus with partially destroyed endothelial lining (left upper corner). HE, × 400.

The size of the spleen correlates with involvement; however, as in Hodgkin's disease, splenic weight is not a reliable indicator of involvement. In an autopsy series from Stanford[69] involved spleens had a mean weight of 250 g (75–1400 g) while uninvolved ones weighed 150 g (31–950 g), thus demonstrating considerable overlap. Although there is evidence that spleens of more than 400 g are involved in NHL[71] this is no proof. As in Hodgkin's disease (see section 4), modern non-invasive techniques cannot reliably document splenic involvement with nodules less than 2 cm in diameter[21]. The question of staging laparotomy therefore comes up and must be answered in view of the therapeutic and prognostic significance of splenic involvement in NHL.

There is a consensus of opinion today that the documentation of disease in the spleen is of less importance in patients with NHL than in Hodgkin's disease, since a greater proportion presents with generalized disease and the recognition of splenic involvement is less likely to alter the treatment plan.

Up to 60% of patients with NHL are at stage IV after sequential clinical staging because of organ or bone marrow infiltration[20]. In patients with the frequent nodular, poorly differentiated lymphocytic type of NHL, this rate may even go up to 75%[54]. Patients with this type of lymphoma and clinical stage III would not be managed differently if laparotomy demonstrated splenic or hepatic involvement, advancing the patient to stage IV. Laparotomy to demonstrate splenic involvement is therefore unnecessary in these patients.

On the other hand, in series of patients undergoing staging laparotomy it has been shown that NHL of diffuse 'histiocytic' type involve the spleen much less frequently[38, 42]. It is also known that diffuse 'histiocytic' lymphomas present in stages I and II in a much higher percentage than nodular lymphomas[71]. It was originally felt, that these localised forms could be treated by local radiotherapy alone. However, it has now been shown, that only patients with stage I disease after extensive staging can successfully be controlled with radiotherapy, and that higher stages should receive aggressive systemic chemotherapy, which indeed has considerably altered the previously poor prognosis of these patients[31, 52, 58, 76]. Thus, for a patient with diffuse 'histiocytic' NHL in stage I after sequential clinical staging[20], the demonstration or exclusion of abdominal and/or splenic involvement is crucial. Presently, the consensus seems to be that staging laparotomy in NHL should be reserved for this minority of patients, who are candidates for local radiotherapy[20, 42, 54], because non-invasive methods like ultrasound and computed tomography cannot yet replace laparotomy and pathological examination for the demonstration of splenic disease[21, 43] (see also section 4).

4. Hodgkin's disease (HD)

In contrast to NHL, HD is a neoplastic process which usually begins confined to one site and frequently spreads slowly. Most important, the spread follows an orderly path from one lymph node chain to another, with which direct lymphatic channel communications exist[47, 48]. The concept of spread 'by contiguity'[70], has been refined by experience with large numbers of cases examined meticulously[47]. In a patient with a given site of presentation it allows the prediction of the pattern of subsequent involvement within and beyond the lymphatic system with a high degree of probability. One can predict, for example, that involvement of para-aortic and/or celiac nodes is associated with a high probability of splenic disease; spleen involvement on the other hand is the basis for spread to liver and bone marrow, since involvement of these organs is invariably associated with splenic disease. Its slow, predictable spread and the high proportion of patients with localized disease make HD suitable for localized radiotherapy. The precise demonstration of the anatomical extent of disease is therefore crucial. Proof of the presence or absence of HD in the spleen is therefore important and the reason for staging laparotomy and splenectomy.

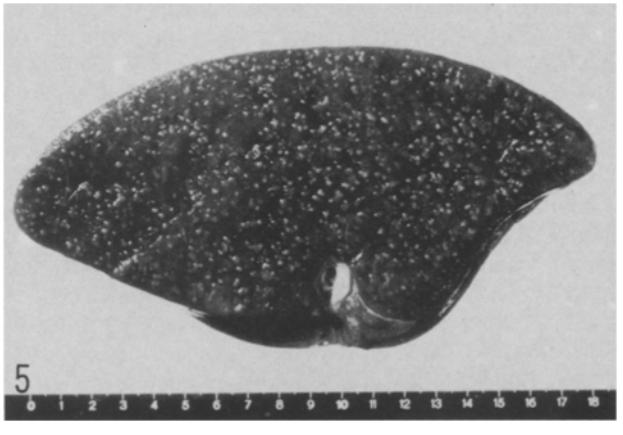

Figure 5. Finely nodular involvement of spleen in non-Hodgkin-lymphoma of diffuse 'lymphocytic' type.

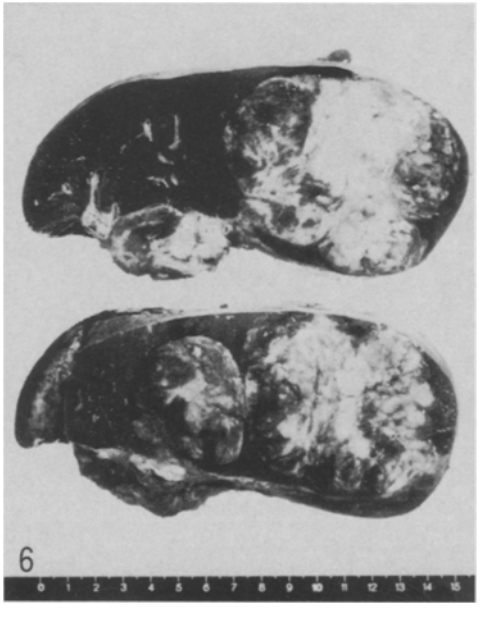

Figure 6. Coarsely nodular splenic tumor involvement in non-Hodgkin-lymphoma of diffuse 'histiocytic' type.

Morphologically, HD involves the spleen in a nodular fashion, the earliest focal lesions occurring in the marginal zone of the follicles[16]. In advanced cases, the spleen contains scattered tumor nodules of various size and number. Spleens removed at staging laparotomy may contain only a solitary tumor nodule between one and a few millimeters in diameter – a fact with which every pathologist examining such spleens must be familiar. Consequently, gross examination of a HD spleen is only adequate if the whole organ has been sectioned into slices of less than 5 mm thickness and if all suspicious nodular formations have been excised for careful histologic examination. The importance of this approach has been underscored again by a study of Diebold et al.[27] who did not find any microscopic disease in 147 spleens juged normal on gross inspection while a single small lesion was present in 9% of their 103 cases where the spleen contained Hodgkin's disease. Inadequate sectioning of these spleens could have given false negative results.

These findings would also seem to discourage partial splenectomy, recently proposed as a staging procedure in HD in order to lessen the negative effects of splenectomy, particularly in children[17, 23, 49, 72].

Histologic diagnosis of HD in the spleen depends on the same criteria as for the lymph nodes[55], namely the demonstration of diagnostic Reed-Sternberg cells in an appropriate cellular background. The adherence to strict criteria is important, so as not to overdiagnose organ involvement, particularly in view of the occurrence of epithelioid granulomas in the spleen of HD patients. They are found in approximately 9% of cases, may occur in the absence of splenic involvement by HD and seem to be a favorable prognostic sign[75]. Histologic subclassification of Hodgkin's disease in the spleen is not mandatory, since it is frequently impossible to distinguish reliably between nodular sclerosis and mixed cell type in the spleen[16].

There is a considerable diagnostic error associated with the assessment of splenic involvement based on clinical or radiologic enlargement of the organ. The error is about 35–40% false positive results for enlarged spleens and 25–35% false negative assessments for normal sized spleens[48]. This is reflected in the fact that splenic weight is not a reliable indicator for involvement. The spleen may be considerably enlarged due to reactive hyperplasia in the absence of HD. A normal weight on the other hand does not exclude involvement. Thus Colby[19] found a mean weight of 170 g (40–1400) in 336 uninvolved spleens while those 92 patients with 1+ and 2+ involvement had mean weights of 180 and 170 g respectively with a range between 65 and 450 g. Broad overlapping of splenic weight between involved and uninvolved organs has also been noted by others[3, 27]. In a series from our own institution, 4 out of 17 spleens weighing less than 150 g were involved[39].

Finally, the spleen is not visualized by lymphangiography. For all these reasons, surgical staging with splenectomy has been established as a routine procedure over the last years for most patients who were not proven to be stage IV by sequential clinical staging.

The surgical procedure with pathologic examination of removed lymphnodes, spleen and liver tissue results in a change of stage in a considerable proportion of cases, as was confirmed by many controlled studies from different institutions. The change of stage mostly involves a switch from stage II to stage III, with potentially crucial therapeutic consequences. In the Stanford series there was a change of stage in 31% of patients. In the series of Gill et al.[36] as many as 43% changed stage and 18% of patients were treated with chemotherapy instead of radiotherapy as a result of the staging findings. Sterchi et al.[80] noted a change of stage in 38% of patients; 23% were upstaged, 15% downstaged. A change of therapy resulted in all 38%. According to the experience of the Royal Marsden Hospital with 310 patients[37], 30% had their staging altered by laparotomy. In Worthy's series[87] 22% of patients changed from stages II to III and 1.5% from stages II to IV due to liver involvement.

It was hoped that the advent of more sophisticated non-invasive diagnostic procedures such as computed tomography and ultrasound might replace staging laparotomy – which is a purely diagnostic procedure with a morbidity and mortality, albeit a low one – for the detection of splenic involvement in HD. Experience so far has demonstrated that these procedures can detect enlargement of the spleen, and sometimes also nodules within the organ with a diameter greater than 2 cm. However, at present these methods are not capable of detecting the small nodules of a few millimetres in diameter which are so essential in HD of the spleen.

We studied 25 patients who were staged with computed tomography and ultrasound and then by laparotomy and splenectomy. We found that the assessment of the spleen was false negative in 13% for the ultrasound and in 18% for the computed tomography. Astonishingly, there was a 50% false positive rate for both procedures[43]. We therefore concur with others[21] who state that at present neither ultrasound nor computed tomography can detect splenic involvement in HD with sufficient accuracy reliably to replace laparotomy for the staging of those patients with HD for whom demonstration of splenic disease involves essential therapeutic decisions. However, this group may now become smaller and mostly comprise patients in clinical stages I and IIA, since in higher stages the application of chemotherapy has become more frequent and is also more promising than the application of radiotherapy alone[25].

The frequency of splenic involvement in HD at staging laparotomy is rather constant and lies in the order of 40%. Even at autopsy, patients who did not undergo splenectomy have a rate of involvement of 36%, although this rate rises to 67% in the presence of residual disease[18]. The probability of splenic involvement is strongly dependent on the histologic subtype of HD involved. According to the Stanford experience, the spleen was involved in 16% of lymphocyte predominance cases, in 35% of nodular sclerosis, in 59% of mixed cellularity and 83% of lymphocyte depletion cases. As a consequence, the likelihood of a change of stage through laparotomy also depends on the histologic type and was 13.3% for LP, 19.2% for NS and 36.8% for mixed cell types[47, 48].

Paraaortic or splenic hilar lymph nodes are only involved singly or together in 48% of patients with positive spleens and in 6.5% of patients with negative

spleens. There remains a considerable proportion of patients in whom the spleen may be the only intraabdominal site of disease[48]. This raises the question of the route of involvement of the spleen. If spread to the spleen were a sign of hematogeneous dissemination, one would expect recurrent disease outside the radiation fields in organs like lung, bone marrow or liver of patients with splenic disease and local radiation treatment only. The high proportion of disease-free survival in these patients contradicts this assumption. The available evidence appears most consistent with the 'contiguity' theory of involvement[47]. The possibility has to be considered that a reversal of the lymph flow in the thoracic duct induced by the upright position of men and mechanical occlusion of the duct by enlarged lymph nodes near its insertion into the subclavian vein may play a causal role. This would be consistent with the observation that left-sided cervical lymphadenopathy is more frequently associated with splenic involvement.

HD patients, even with localized disease, suffer from a selective and often subtle impairement of cell-mediated immunity, which makes them susceptible to various kinds of infections. It appears to be due to functional alterations of T-lymphocytes rather than quantitative depletion of B or T cells; serum inhibitory factors and suppressor cell effects may also be involved[47].

To what extent the spleen contributes to this defect has been examined by numerous workers over the past few years. Though not entirely conclusive and free of contradictions, the results seem to be consistent with the idea of a functional disturbance of cell-mediated immunity.

Thus, Bieber et al.[7] were able to demonstrate an E-rosette-inhibiting factor in extracts of spleens involved with HD. The factor could later be identified as a glycolipid[8]. A complement-dependent, cold-reactive lymphocytotoxic factor was noted in the sera of about 30% of HD patients by Björkholm[11]. This factor was more frequent and more concentrated in patients with large tumor-involved spleens. The activity seems to persist after successful treatment and may be responsible for a long-standing functional defect in blood T-lymphocytes.

The number and distribution of splenic lymphocytes were investigated by several groups. A reduction in splenic T cells was reported by Han et al.[40] while Baroni et al.[5] found elevated numbers in spleens involved with disease. Both studies used E-rosette formation as a T-cell indicator. Two studies using a set of monoclonal antibodies also provided contradictory evidence. While Dorreen et al.[28] found the total T cell number reduced, probably due to reduction of T-inducer cells, Posner et al.[66] reported an equal increase of T cells in involved and uninvolved spleens of HD patients. Evidence was further provided for the assumption that the observed immunodeficiency might be due to a lack of monocyte-macrophage cells interacting with the lymphocytes, or due to the presence of an 'immature subset' of T cells in the spleen[66].

Morphometric analysis of spleens in HD patients showed a reduced T-cell area[86].

On a functional level, Ruco et al.[73] observed significantly elevated natural killer cell activity in involved spleens and lymph nodes while Björkholm et al.[10] found an inverse correlation between splenic weight and blood lymphocyte mitogen-induced DNA-synthesis.

In the peripheral blood of patients with large involved spleens (over 500 g) one may find lower total lymphocyte counts and a lowering of IgG and IgM levels[86]. Others[9, 66] noted no specific alterations in the Ig levels nor the blood lymphocyte function attributable to splenectomy. Splenectomy seemed to prevent blood lymphocytopenia due to therapy[9].

An indication of a splenic influence on polymorphonuclear cell function in lymphoma patients, which might partly explain the frequent bacterial infection in this group, was noted by v. Fliedner[32]. After splenectomy, PMN adherence was elevated, and the nitroblue-tetrazolium reduction capacity lowered.

Apart from immediate post-operative morbidity, the question of long term morbidity and mortality due to post-splenectomy sepsis must be addressed. Splenectomised patients are at an increased risk for potentially fatal pneumococcal sepsis and meningitis, particularly if treated with combined radio- and chemotherapy. It is felt that these complications, which occur mostly in children, can be prevented by the use of pneumococcal vaccine and constitute no contraindication for staging laparotomy[48, 54].

5. *Malignant histiocytosis (MH)*

MH is a systemic neoplasia of histiocytes[67] with splenomegaly as leading symptom[85].

In the spleen, the malignant histiocytes diffusely infiltrate the red pulp (table 1) cords and sinuses as non-cohesive cell masses (fig. 7), which may encroach upon the follicles of the white pulp[15]. The malignant histiocytes usually show marked nuclear pleomorphism (fig. 8), although in our experience there is nearly always a tumor cell population present with bland cytological features. Erythrophagocytosis, which is usually readily apparent

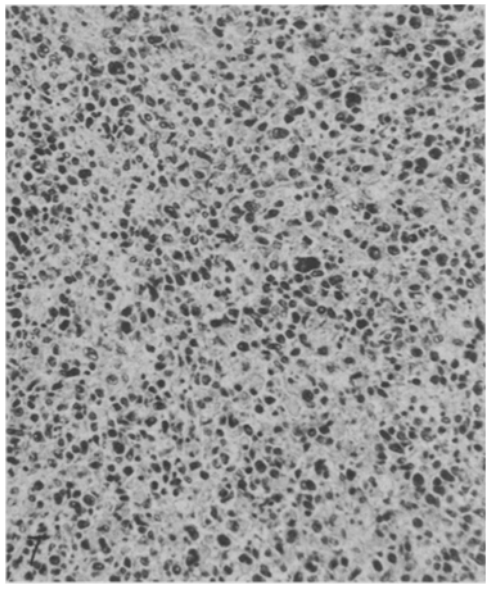

Figure 7. Diffuse involvement of splenic red pulp by malignant histiocytosis. Note spectre of cells ranging from bland round cells to highly atypical large tumor cells. HE, × 125.

within tumor cells, is most prominent in these bland forms and may be completely lacking in the more undifferentiated cells. The immunohistochemical demonstration of lysozyme (muramidase) and chymotrypsin within the tumor cells[82] is a useful tool for the diagnosis, particularly in cases where phagocytosis is not a prominent feature. The degree of lysozyme activity in the cytoplasm seems to be dependent on the degree of differentiation, since cells with considerable atypia usually do not stain for lysozyme[56].

Fever, hepato-splenomegaly and pancytopenia due to removal of formed blood elements in the spleen are typical clinical symptoms of MH and the diagnosis can be readily made on a bone marrow film. While this is true for classical cases with rapid course, there are patients who clinically and morphologically show less pronounced signs of disease and who may represent a less aggressive variant of the entity. In some[2,24,84] splenomegaly may even be the only symptom. Among the 4 cases of Vardimann et al.[84] 3 developed systemic disease between 3 and 10 months after diagnosis while one remained asymptomatic after splenectomy alone. The same observation was made by Artusi et al.[2], whose patient was free of disease 15 months after splenectomy alone. These observations show that MH may run a protracted course. Interestingly, all the cases described by Vardimann[84] showed excessively large spleens with weights between 2200 and 5400 g while the average weight of the spleen in reported cases was 950 g. One is therefore tempted to speculate that massive splenomegaly might be a sign of slow tumor growth.

While splenomegaly is present in up to 70% of adult cases[85] it seems to be less prominent in children[89].

In cases with isolated splenomegaly, the diagnosis will have to be made by the pathologist on the splenectomy specimen. Recognition of the disease poses no great problem in typical cases. Application of immunohistochemistry will be helpful in cases where the histiocytic nature of the tumor cells is not readily apparent.

Differential diagnoses to be considered are HCL and diffuse 'histiocytic' NHL as well as Hodgkin's disease. HCL also involves the splenic red pulp but can be distinguished by the very different cytology (see section 2). Diffuse 'histiocytic' NHL is an important differential diagnosis. In contrast to MH, diffuse 'histiocytic' NHL produces tumor masses with cohesive cell clusters and exhibits no phagocytosis. The demonstration of monoclonal Ig or T cell markers on the tumor cells by immunohistochemical methods[79,82] will prove the lymphocytic origin of the tumor cells.

Due to the sometimes considerable polymorphism of cells in MH, Hodgkins disease must be excluded also. Again, HD involves the spleen in an nodular fashion. Adherence to the precise morphological criteria[55] for a diagnosis of HD is important. Immunocytochemistry with application of one of the new monoclonal antibodies directed against RS-cells may be of help[79]. Splenic imprints are valuable for cytochemical stains for nonspecific esterase to demonstrate the histiocytic nature of the tumor cells.

Table 3. Frequency of splenic involvement detected at staging laparotomy for Hodgkin's disease

Author	Number of patients	Positive spleen (%)
Kaplan[48]	814	38
Colby[19]	591	36
Glees[37]	310	44
Diebold[27]	250	41
Sterchi[80]	123	42
Lee[53]	50	38
Häggi[39]	39	40

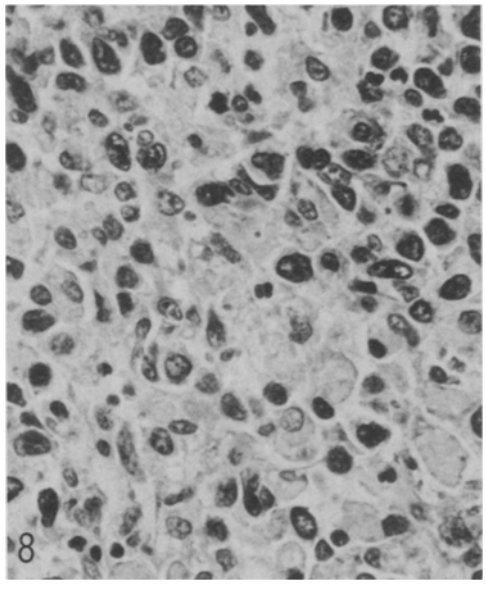

Figure 8. Malignant histiocytosis in spleen. Note abundant erythrophagocytosis, particularly in cells of less conspicious atypia. HE, × 400.

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0014-4754/85/020215-10$1.50 + 0.20/0

Pathology of the splenic artery

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Key words. Spleen; artery, splenic, pathology of.

The human splenic artery has been attracting the interest of pathologists for a long time, because of the frequent occurrence of an increase in length and tortuosity. Although a number of macroscopical descriptions exist[4], the information concerning morphology, ultrastructure and pathophysiology available so far is limited. In reviewing data obtained from the examination of about 1500 splenic arteries derived from various species during the last 10 years, using a variety of techniques, we will try to summarize the available knowledge about the extrasplenic part of the splenic artery.

Length and diameter

As early as 1935, Thiersch[32] described a splenic artery (SA) with an absolute length which was 3.5 times the direct distance between its origin and the spleen. Springorum[27] was the first to introduce an 'index' $\left(I = \frac{100 \times L}{D}\right)$ for the relation between the length of the artery (L) and the direct distance (D). He saw an autopsy case with an I of 363. Later on values of 390[30] and 505[1] were reported. Carmel[2] observed that in ⅕ of cases the SA follows an extremely tortuous course. In 1973 Tischendorf[31] reported an I-value of 659, the highest yet found.

The direct distance between origin and spleen in man is about 10.5 cm (table). The true length of the SA is about twice that, being significantly greater in males than in females ($p < 0.05$). The total index for males was found to be 192, for females 162. Dividing the direct distance between origin and spleen into quarters and examining the length of the SA, one can observe a continuous decrease from proximal to distal (table). The absolute I-values are always higher in males than in females, but the difference is significant only for the proximal quarter ($p < 0.05$) of the course of the SA. If the material taken from autopsies is grouped according to age (greater or less than 50 years), a longer artery can be seen in the older age group. In studying a larger