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The Liver in Hodgkin's Disease—II. Histopathologic Findings

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Abstract—*Histopathologic findings in 459 liver biopsies performed in 308 patients with Hodgkin's disease were reviewed. Typical Hodgkin infiltrates were found in only 11/459 biopsies (2.4%) and infiltrates suspect for Hodgkin's disease in only 8/459 (1.7%), whereas unspecific changes were more common. Lymphocytic infiltration was seen in 47% of the biopsies and focal necrosis in 19%. No correlation could be demonstrated between unspecific changes and clinical characteristics, including prognosis.*

INTRODUCTION

IN A PREVIOUS study we described the clinical characteristics of a consecutive series of patients with Hodgkin's disease, with particular reference to the liver findings. As in other series published, biopsy-proven Hodgkin's disease in the liver was an infrequent *in vivo* finding, but on the other hand apparently non-specific liver infiltrates were very common. The present study gives a more detailed account of the same patient group with regard to the histological findings and the prognostic relevance of the various types of infiltrates.

MATERIALS AND METHODS

The patient material, the methodology and the histological criteria are as described in the preceding study[1].

A total of 472 liver biopsies were made during the period of the investigation, each patient undergoing from one to four biopsies. A total of 13 biopsies could not be evaluated histologically. Seventy-seven percent of the 459 suitable biopsies were primary percutaneous biopsies or surgical wedge biopsies made in connection with the clinical staging, while 21% were made later in the course of the disease on the grounds of a suspected relapse.

RESULTS

In 10 patients, represented by 11 out of the 459 (2.4%) liver biopsies, infiltrates were demonstrated consisting of Sternberg–Reed cells and abnormal histiocytic cells against the characteristic background of lymphocytes together with neutrophilic and eosinophilic granulocytes. These definite infiltrates of Hodgkin's disease were found in 6 primary percutaneous biopsies and one primary wedge biopsy (where a prior percutaneous biopsy had not been made), in three percutaneous re-biopsies later in the course of the disease, the primary percutaneous biopsy in these three cases having been negative, and in one percutaneous re-biopsy, where the primary percutaneous biopsy had also been positive.

None of the six patients with a positive percutaneous biopsy proceeded to surgical biopsy. Among the 281 patients with negative primary percutaneous biopsies, 55 proceeded to surgical wedge biopsy, which in all cases was also negative. In 20 patients only surgical wedge biopsy was done, and infiltrates of Hodgkin's disease were found in one of them.

In 10 of the 11 positive liver biopsies, infiltrates of Hodgkin's disease (usually 100–200 μm in size) could be identified in all sections of the biopsy. In one case there was only a minor infiltrate, which was found in 4 out of 28 sections.

The accompanying clinical finding in these patients have already been described in detail[1].

In a further 8 patients, infiltrates were found which had all the characteristics of Hodgkin's disease except for Sternberg–Reed cells. They were designated as infiltrates suspect for

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Hodgkin's disease. Two of the biopsies originated from the primary percutaneous biopsy procedure, while six were re-biopsies done later on in the course of the disease.

Since the 8 patients subsequently received systemic treatment (chemotherapy), it is difficult to evaluate from their course whether the Hodgkin-suspect infiltrates represented true cases of Hodgkin's disease in the liver or not. However, in one out of three repeated re-biopsies made later, regular infiltrates of Hodgkin's disease were found, and three out of the five patients who died and came to autopsy showed infiltrates of Hodgkin's disease in the liver.

The most frequent biopsy finding (in 173/308 patients, 56%) was lymphocytic infiltration in the portobiliary space, consisting mainly of mature lymphocytes without the presence of abnormal histiocytic cells. An arbitrary grading into slight, moderate and severe degrees of infiltration grouped the patients into 79, 20 and 1% respectively. In 1/4 of these cases the boundary between the infiltration and the surrounding liver parenchyma was blurred and the parenchyma showed necrosis of individual liver cells (piecemeal necrosis).

Lymphocytic infiltration was demonstrated in 131 primary percutaneous biopsies. Of these patients, 26 also underwent surgical wedge biopsy, and 81% of them were found to have the same type of infiltration. One hundred and fifty-six primary percutaneous biopsies contained no lymphocytic infiltration. In 49 of these patients a surgical wedge biopsy was subsequently performed, and here the original negative finding was confirmed in only a little more than half, while 45% were now found to have lymphocytic infiltration. At re-biopsy later in the course of the disease, varying types of treatment having been given in the intervening period, the percentage of lymphocytic infiltration among the initially negative cases was 27% and among the initially positive cases, 50%.

Focal necrosis was the most common finding after lymphocytic infiltration, occurring in 73 out of 308 patients (24%). Twenty-four patients with focal necrosis in the primary biopsy underwent re-biopsy or surgical wedge biopsy, with the result that focal necrosis could be identified again in only nine patients.

Pleomorphic cell infiltrates and epithelioid cell granulomas were recorded in only eleven patients (4%) and five patients (2%) respectively. Only one of these patients underwent the re-biopsy. On explorative laparotomy, epithelioid cell granulomas were found in two liver biopsies and in nine spleens; in one case both liver and spleen were affected. None of the patients with granulomas in the liver or spleen showed clinical signs of sarcoidosis, just as staining for specific infections was negative.

In only 93 out of 308 patients (30%) the liver biopsy contained none of the above pathological or non-specific lesions and they were therefore designated as 'normal'.

Apart from the abnormal histological findings already mentioned, Kupfer cell hyperplasia occurred in 52% of the primary liver biopsies, a slightly increased deposit of iron in 23% and steatosis of moderate and severe degree in 20%. These findings were recorded with the same frequency in untreated and previously treated patients. Amyloidosis was demonstrated in 3 patients, all previously treated and with a prolonged course of the disease prior to staging (from 73 to 228 months). Finally, one patient who was previously untreated showed cirrhosis in the primary biopsy.

The occurrence of specific and non-specific types of changes in each category of liver biopsy is shown in Table 1. In a number of cases, the same biopsy showed several different types of infiltrate. The surgical wedge biopsies were distinguished from the percutaneous needle biopsies by fewer cases of normal histology ($P < 0.01$) and a greater incidence of lymphocytic infiltration ($P < 0.001$) and focal necrosis ($P < 0.01$), while the other non-characteristic infiltrates occurred with the same incidence. This is all the more remarkable since almost all the surgical wedge biopsies originated from selected patients with early stages of the disease (I, II and III A), while the primary percutaneous biopsies were from patients in all stages of the disease.

Table 2 shows the distribution of the respective types of infiltrate in the 459 suitable liver biopsies. The number of coincidences between two types of infiltrates is compared to the statistically expected coincidence to elucidate a possible common mechanism for the various types of infiltrates. The combination of lymphocytic infiltration and focal necrosis was recorded more frequently than expected ($P < 0.001$). None of the other combinations occurred more frequently than would be expected by chance, and in particular there appears to be no relationship between any of the non-specific types of infiltrates and infiltrates of Hodgkin's disease.

Forty-three percent of the patients had received some form of treatment prior to the primary percutaneous liver biopsy: radiation treatment alone, 29%; radiation plus chemo-

Table 1. Histological findings in primary percutaneous biopsies and surgical liver biopsies

Liver biopsies	No.	Percentage occurrence of liver infiltrates							
		Normal	Hodgkin's disease	Suspect for Hodgkin's disease	Lympho-cytic	Piece-meal	Focal	Pleo-morphic	Epi-thelioid
Primary percutaneous	287	44	2	1	46	10	19	3	1
Surgical wedge biopsy	75	27	1	1	65	17	20	1	3

Table 2. Distribution of abnormal histological findings in 459 liver biopsies (percutaneous and surgical)

Abnormal findings in liver biopsies	No. of biopsies with abnormal findings*		Number of biopsies with coincidence of two abnormal findings†							
			Lymphocytic infiltrates		Focal necrosis		Pleomorphic infiltrates		Epithelioid granulomas	
Infiltrates of Hodgkin's disease	11	(7)	3	(5)	2	(2)	0	(0)	0	(0)
Infiltrates suspect for Hodgkin's disease	8	(6)	2	(3)	0	(1)	0	(0)	0	(0)
Lymphocytic infiltrates	216	(149)			56	(40)	5	(5)	3	(2)
Focal necrosis	85	(26)					2	(2)	1	(1)
Pleomorphic infiltrates	11	(4)							0	(0)
Epithelioid granulomas	5	(2)								

*The number of liver biopsies where the abnormal finding in question occurred isolated are in parentheses.
†The number anticipated by chance are in parentheses.

therapy, 11%; chemotherapy alone, 3%. The incidence of non-specific infiltrates taken as a whole in untreated patients was 60%, compared to 50% in patients who had received treatment previously. Apart from lymphocytic infiltration, which occurred with a significantly greater incidence in the untreated group ($P < 0.01$), there was no difference in the occurrence of the respective types of infiltrate in the two groups.

The histological pattern in the primary liver biopsy was examined in relation to a number of other findings. No statistically significant difference in the distribution of the respective types of liver infiltrate could be demonstrated with respect to histologic type of the original lymph node biopsy, clinical stage or other clinical findings (Table 3).

In those patients who underwent exploratory laparotomy, the histological findings from wedge biopsy were compared with spleen weight and the occurrence of Hodgkin's disease in the spleen (Table 4). A normal wedge biopsy was accompanied by normal spleen weight and rarely by the occurrence of Hodgkin's disease in the spleen. On the other hand, lymphocytic infiltration, piecemeal necrosis and focal necrosis in the wedge biopsy were accompanied relatively often by abnormal spleen weight and infiltrates of Hodgkin's disease in the spleen.

Survival was calculated by the actuarial method, both for the total material and for those patients whose liver biopsy showed normal liver histology, lymphocytic infiltration, focal necrosis, infiltrates of pleomorphic cells, epithelioid cell granulomas of Hodgkin's disease (Fig. 1). Patients with infiltrates of Hodgkin's disease and patients with infiltrates of pleomorphic cells appeared to have a reduced survival, but these groups were too small for a statistical difference to be demonstrated. Nor could any significant difference in survival be demonstrated between the other groups and the group with normal histology.

In order to evaluate the pattern in the development of the various liver findings, the occurrence of infiltrates of Hodgkin's disease in the liver was examined at autopsy. Table 5 shows that Hodgkin's disease was present in the liver at autopsy, with about the same incidence in patients whose liver biopsy showed normal histological findings in life as in patients who had lymphocytic infiltration or focal necrosis in life.

DISCUSSION

An evaluation of 459 suitable liver biopsies in

patients with Hodgkin's disease revealed abnormal histological changes in more than half of the biopsies (58%), almost exclusively in the form of non-specific infiltrates, while infiltrates of Hodgkin's disease were recorded only rarely.

Malignant involvement of the liver was found in about 2% of the patients in our non-selected material, which is somewhat lower that the figure in most corresponding series[2–7]. The lower incidence in our study may be due to a higher incidence of patients who were in the early stages of the disease, where involvement of the liver is unusual, but it is also of significance that the studies mentioned are mainly laparotomy series since involvement of the liver is diagnosed almost twice as frequently with this procedure as with percutaneous needle biopsy[8]. In the present study, exploratory laparotomy was done only in patients in the earlier stages (I, II and IIIA), while patients in the more advanced stages underwent percutaneous liver biopsy exclusively. In most cases of infiltrates of Hodgkin's disease in the liver there was no great difficulty in making the histological diagnosis, as the infiltrates were relatively large and could be identified in most sections. In one case, however, only one small infiltrate was found in 4 out of 28 sections, which emphasises the significance of serial sections in studies of liver biopsies.

In 2% of our patients, morphological changes were found in the liver which were typical but not pathognomonic of Hodgkin's disease, since demonstrable Sternberg-Reed cells were missing. The diagnostic problem is

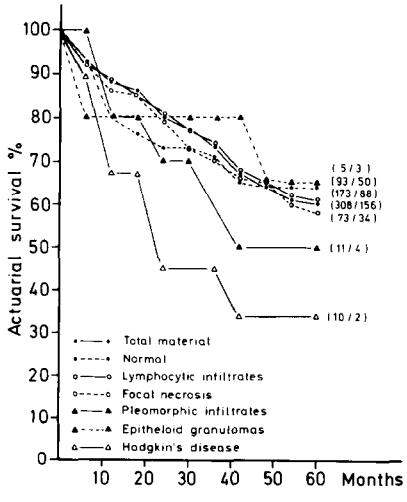

Fig. 1. Actuarial survival of 308 patients with Hodgkin's disease according to type of histologic liver infiltrate. Numbers in parentheses indicate number of patients in subset at onset/number of patients alive at 60 months.

Table 3. Relationship of the histological findings in primary liver biopsy with the lymph node histology, as well as with the clinical data

Histological findings in the primary liver biopsy†		Percentage occurrence*												
		Lymph node histology				Clinical stage			B-symptoms	Positive lymphography	Clinically enlarged spleen	Clinically enlarged liver	Elevated emzymes
		LP	NS	MC	LD	I–II	III	IV					
Normal	(126)	10	48	36	4	48	26	25	54	42	6	10	21
Lymphocytic infiltrates	(131)	12	48	34	6	46	29	25	57	47	9	15	29
Piecemean necrosis	(28)	11	46	36	7	54	32	14	54	50	14	14	18
Focal necrosis	(54)	11	48	35	4	50	30	20	57	42	7	7	30
Pleomorphic infiltrates	(9)	1/9	2/9	6/9	0/9	4/9	1/9	4/9	4/9	3/7	0/9	0/9	2/9
Epithelioid granulomas	(3)	0/3	3/3	0/3	0/3	2/3	0/3	1/3	1/3	1/3	1/3	0/3	1/3
Total material	(287)	12	47	35	5	48	27	25	53	44	7	11	27

*Absolute numbers are given for pleomorphic infiltrates and epitheliod granulomas.
†The total number of patients with the respective types of infiltrates in the primary biopsy are in parentheses.

Table 4. Relationship between the histological findings in the surgical wedge biopsy and spleen weight and occurrence of Hodgkin's disease in the spleen

Histological findings in the wedge biopsies	No. of wedge biopsies	Weight of spleen*		No. of wedge biopsies	Hodgkin's disease in the spleen
		< 250 g	> 250 g		
Hodgkin's disease	1	1	0	1	1
Susp. for Hodgkin's dis.	0	0	0	0	0
Normal	17	15	2	19	1
Lymphocytic infiltrates	41	26	15	48	12
Piecemeal necrosis	12	6	6	12	3
Focal necrosis	12	4	8	14	2
Pleomorphic infiltrates	1	1	0	1	0
Epithelioid granulomas	1	1	0	2	

*The information on spleen weight was not available for all spleens removed, while the histological study was made in all cases.

Table 5. Autopsy findings in the liver in 111 patients in relation to infiltrates in the liver in life

Liver histology	No. of patients dead/ No. with histologic finding		Hodgkin's disease in liver at autopsy/number of autopsies	
Hodgkin's disease	6/10		4/6	
Suspect for Hodgkin's disease	6/8		3/5	
Normal	44/93	(47%)	13/34	(38%)
Lymphocytic infiltrates	80/173	(46%)	22/50	(44%)
Focal necrosis	37/73	(51%)	7/25	(28%)
Pleomorphic infiltrates	6611		0/4	
Epithelioid granulomas	2/5		1/1	
Total material	151/308	(49%)	45/111	(41%)

well-known, and the suspected lesions can usually be regarded as expressing a malignant involvement. The subsequent course of the disease will often confirm the suspected diagnosis.

The occurrence on non-specific liver infiltrates in Hodgkin's disease has been described in several earlier studies, but both the type of the abnormal findings and the frequency with which they are recorded varies somewhat in the individual series[3, 8–11]. Lymphocytic infiltration in the portal space and focal necrosis of the liver parenchyma nevertheless appear to be the most constant abnormal findings, with a mean incidence of 21–29% and 50% respectively[3, 10–12]. In the present material, lymphocytic infiltration was observed in 56% of the patients and focal necrosis in 24%. Pleomorphic infiltrates in the liver in Hodgkin's disease have only been described in a few studies. Høst *et al.*[11] found an incidence of 15% compared to our value of 2%. Epithelioid cell granulomas in the liver occurred very rarely in our material (2%), considerably lower than the 5–14% of other reports[3, 11, 13–15]. Finally, like others we have noted Kupfer cell hyperplasia[10], steatosis[3, 8–11] and haemosiderosis[3, 9] as frequent findings.

There is no obvious explanation as to why the incidence of the various non-characteristic findings varies so much in the individual series. It can hardly be explained as being due to a difference in the composition of the patient material as there does not appear to be any relationship between non-specific changes in the liver on the one hand and the duration of the disease, the stage of the disease or the subclassification of the lymph node histology on the other. Part of the explanation could be differences in definition with respect to delimitation of a pathological finding. For example, Høst *et al.* [11] also allow abnormal histiocytic cells in pleomorphic cell infiltrates, i.e. a morphology which in the present study would be classified as an infiltrate suspect for Hodgkin's disease.

On comparing the histological findings in needle biopsies and wedge biopsies, lymphocytic infiltration was observed to be about twice as frequent in the wedge biopsies as in the needle biopsies. This finding could be due to

differences in the size of the biopsy material or in the site of the biopsy. Against this is the observation that the other non-specific changes occur with equal frequency in both types of biopsy.

More than one type of infiltrate was recorded relatively often in the individual liver biopsy, but only the combination of lymphocytic infiltration and focal necrosis occurred more frequently than expected ($P < 0.001$), possibly expressing a common initiating mechanism. We did not find any other unexpected interrelations between the non-specific infiltrates, or between these and infiltrates of Hodgkin's disease, a finding which is in agreement with other published data[3, 8]. Thus occurrence of lymphocytic infiltration, focal necrosis, pleomorphic cell infiltrates and epithelioid cell granulomas does not appear to provide any evidence for malignancy in the liver, just as there is no relationship with Hodgkin's disease in the spleen.

The significance of the non-malignant liver findings has been discussed in only a few previous studies. Oehlert *et al.*[10] correlated mesenchymal reactions and parenchymal damage to age, duration of disease, stage of disease, laboratory findings and prognosis. However, they only found a possible relationship to the B-symptom of fever, as well as to blood eosinophilia. Their classification of the non-specific liver findings was not fully identical with the classification in our study. In a similar study on lymphocytic infiltration in the portal space, Bagley *et al.*[8] found no positive correlations, especially not to fever or blood eosinophilia. Our data provide no evidence for correlation between non-specific liver findings and aspects of the clinical or biochemical studies. The groups with the respective types of infiltrate showed the same distribution into disease stages and Luke's subclassification of lymph node histology, and there was an equal incidence of B-symptoms, hepatomegaly, splenomegaly, positive lymphography, elevated alkaline phosphatase and/or S-GOT.

The poor prognosis in malignant involvement of the liver is well-established[16, 17], and it also appears from the present study. The demonstration of the presence of non-specific liver infiltration does not seem to have affected the prognosis, as survival in patients with the respective types of infiltrates did not differ from that in patients without liver infiltrates.

The study has thus demonstrated that the liver in Hodgkin's disease is only rarely the site of malignant involvement early in the course of the disease. On the other hand, it is frequently the site of non-specific changes which are not indicators of liver malignancy and which do not appear to have any significance for the course of the disease.

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