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Hodgkin's disease presenting as a cholestatic febrile illness: incidence and main characteristics in a series of 421 patients

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Abstract In order to determine the frequency and characteristics of patients with liver abnormalities as the presenting manifestation of Hodgkin's disease (HD), 421 consecutive HD patients were studied. Six patients in the series (1.4%) presented with liver abnormalities that led to of a liver biopsy and the subsequent diagnosis of HD. All had fever prior to HD diagnosis, four frank jaundice, and one hepatic failure. No patient had pruritus. Moderate hepatomegaly was present in four patients. Cholestasis was observed in all cases; in most patients a moderate increase in the transaminase activity was also seen. Two patients had a mild rise in the serum LDH, four had leukopenia, and one eosinophilia. At liver histologic study, Reed-Sternberg cells were demonstrated in four patients; in the remaining two, the presence of atypical histiocytes, lymphocytes, and eosinophils was highly suggestive of HD, the latter diagnosis being confirmed by subsequent study of bone marrow and/or retroperitoneal lymphadenopathies. In three of the six patients, HD was not demonstrated in sites other than the liver. Three patients older than 60 years died shortly after HD diagnosis. By contrast, three patients younger than 40 years showed a dramatic response to chemotherapy: two of them had a further relapse, and one is considered cured after 14 years of continuous remission. Liver disease constitutes an infrequent form of HD presentation which must be included in the differential diagnosis of any patient with fever of unknown origin.

Key words Hodgkin's diseases · Liver disease · Fever

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Introduction

The frequency of liver involvement is low at presentation of Hodgkin's disease (HD) [1, 8] but increases in the advanced phases of the disease, becoming as high as 60% in autopsy series [8]. At diagnosis, hepatic infiltration by HD is observed in 5–14% of HD patients [1], depending on both the method of liver sampling and the size of the sample [5, 20]. The presence of hepatomegaly and/or abnormalities of the liver enzymes indicate possible liver infiltration by HD [3, 5]. Jaundice is frequent in the terminal phases of HD [2, 3, 13] but exceedingly rare at disease presentation [5]. A few patients have been described with no peripheral adenopathies in whom the presence of liver enlargement, cholestasis, or hepatic failure led to a liver biopsy and the subsequent diagnosis of HD [9, 12, 16, 21–23]. Due to co-existent fever, in most such patients infection was suspected [12, 21–23], whereas in others the possibility of obstructive jaundice or acute liver failure was considered [9, 12, 16, 21]. To date, no information is available on the frequency of the above form of presentation of HD.

The aim of the present study was to determine the frequency of liver disease as the initial manifestation of HD and the clue for its diagnosis, as well as to characterize the clinical, biological, and histological features of such patients.

Patients and methods

Patients. The medical records of 421 patients consecutively diagnosed with HD at the Hospital Clínic of Barcelona between 1972 and 1995 were reviewed. A selection was made of those for whom the HD diagnosis was established based on histologic study of the liver, which had been carried out due to the presence of clinical or biochemical signs of liver dysfunction. These patients are the subject of the present study, and their characteristics are given in the Results section.

Liver biopsy. Liver tissue samples were obtained under peritoneoscopy with a Tru-cut needle (Travenol Laboratories), fixed in

10% formalin and embedded in paraffin. Subsequently, sections of liver stained with hematoxylin and eosin, Masson trichrome, and Wilder's argentic method for reticulin were examined under light microscopy. The existence of liver infiltration by HD was considered following the criteria of Bagley et al. [1].

Staging procedures. In all cases, the main clinical and laboratory data at HD diagnosis were recorded. The presence of enlarged lymph nodes not accessible to physical examination was investigated by X-ray studies and either a lymphangiogram or computed tomography scanning, complemented in some cases by laparotomy study. The staging maneuvers also included a trephine bone marrow biopsy.

Results

Among the 421 patients of the series, six (1.4%) presented with no peripheral adenopathies and had clinical or analytical hepatic abnormalities that led to a liver biopsy and the subsequent diagnosis of HD. Among the remaining 415 patients, in 25 additional cases liver involvement by HD was found in the course of the staging procedures. Thus, the frequency of liver involvement at HD diagnosis was 7.4% in the overall series.

The main initial features of the six patients with liver disease as the presenting manifestation of HD are summarized in Table 1. Five patients reported fever and night sweats for 1–6 months prior to HD diagnosis, while the remaining one had fever for 2 days before the liver biopsy was performed. Five patients had experienced malaise and anorexia for the previous 0.5–6 months, and two reported weight loss. No patient had pruritus. At physical examination, moderate hepatomegaly was noted in three patients and two also had a palpable spleen; jaundice was observed in four patients, one of whom also developed hepatic encephalopathy.

Liver function tests were abnormal in all patients (Table 1). Cholestasis was the alteration most frequently observed. Serum gamma-glutamyl-transpeptidase was increased in all patients, alkaline phosphatase in five, and serum bilirubin in four. Increased transaminase activity was found in five patients, and three showed a mild increase in serum LDH. As far as the hematological parameters are concerned, low WBC counts were noted in four patients, moderate anemia in five, and thrombocytopenia in two; only one patient had eosinophilia. The ESR was increased in all cases.

In all patients a diagnosis other than HD was initially made. Thus, due to co-existent fever, infection was suspected in five of the six patients, including tuberculosis, brucellosis, bacterial infection, and severe acute hepatitis. Obstructive jaundice was the initial diagnostic suspicion in the remaining patient. The negativity of the microbiological and other pertinent studies (including serological tests for viral hepatitis, cytomegalovirus and, in some cases, EBV) did not support any of the above diagnoses. With regard to the staging maneuvers, imaging studies disclosed enlarged retroperitoneal lymphadenopathies in two of five patients (one of the four patients in whom computed tomography scanning was carried out and the one submitted to lymphangiography). In these two latter patients a subsequent lymph node biopsy performed at laparotomy yielded the diagnosis of lymphocytic depletion and nodular sclerosing histologic types of HD, respectively. Bone marrow involvement by HD was observed in two of the five patients in whom a marrow biopsy was carried out (excluding one who died 24 h after the liver biopsy). One of the above patients showed simultaneous retroperitoneal lymphadenopathy and bone marrow HD involvement; thus, in three of the six patients HD was not demonstrated in sites other than the liver.

At liver histologic study, massive infiltration of some portal tracts by a mixture of lymphocytes, histiocytes, and eosinophils was observed in all cases. The infiltrates extended widely from the portal connective tissue into the periportal parenchyma. Most histiocytes in the cellular infiltrates were atypical, being large in size and displaying angular nuclei. In four patients Reed-Sternberg cells were seen within the infiltrates (Fig. 1). The unaffected liver parenchyma showed irregularly distributed marked sinusoidal dilatation (Fig. 2) in all cases and bile pigment deposits in three patients. Interlobular bile ducts with normal appearance were present in most unaffected portal tracts but absent in those infiltrated by HD.

The three elderly patients died within 1.5 months of HD diagnosis: one of them developed massive gastrointestinal bleeding shortly after undergoing liver biopsy and died before chemotherapy could be started, another patient died of sepsis during the first C-MOPP/ABV cycle, and the third one died of sepsis in the course of the marrow aplasia period following the sec-

Table 1 Main initial characteristics of patients with liver disease as the presenting manifestation of Hodgkin's disease

Patient no.	age/sex	Duration of symptoms (months)	Liver (cm)[a]	Spleen (cm)[a]	WBC count ($\times 10^9$/l)	Blood eosinophils (%)	ALAT/ASAT (IU/l)	γGT (IU/l)	Alkaline phosphatase (IU/l)	Bilirubin (mg/dl)
1	85/F	3	2	0	3.6	0	41/28	127	1088	0.6
2	30/M	3	0	2	5.3	0	73/66	233	179	0.3
3	68/M	1	4	0	5.2	4	110/97	68	254	13.7
4	21/M	4	0	0	1.9	12	138/92	68	267	10.1
5	40/M	0.5	4	3	2.1	0	422/700	590	1300	21.6
6	77/M	6	0	0	3.4	0	67/37	129	548	10.4

[a] Below costal margin

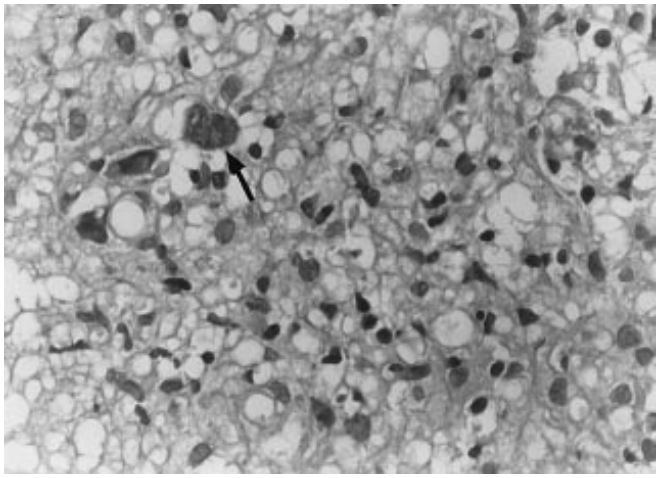

Fig. 1 Pleomorphic cellular infiltrate containing one Reed-Sternberg cell (*arrow*) at the edge of a portal tract. (H&E × 400)

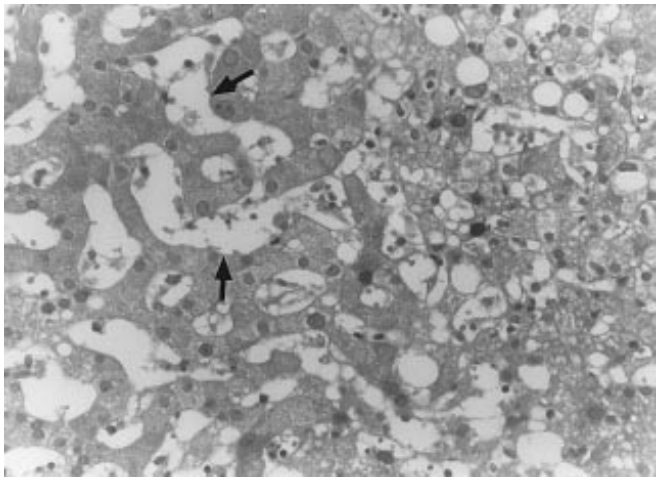

Fig. 2 Sinusoidal dilatation (*arrows*) of irregular distribution and fat vacuoles in some hepatocytes. (H&E × 220)

ond C-MOPP cycle. In contrast, the three younger patients showed a dramatic response to chemotherapy and attained remission. One of the latter patients remains in remission 14 years after HD diagnosis and is considered cured; another had a hepatic relapse of HD 2 years after the initial response to MOPP/ABVD alternating chemotherapy, achieved a further response to MOPP/ABV combination chemotherapy, and remains in remission 2 years latter; the third one relapsed 2 years after the initial response to C-MOPP and had a favorable response to ABVD chemotherapy but died of secondary acute myeloblastic leukemia 5.5 years after HD diagnosis.

Discussion

A small proportion of HD patients show hepatic abnormalities at disease presentation, with tumoral liver infiltration being the most common underlying mechanism [1, 8]. The finding of liver involvement by HD varies depending on the method by which the liver specimen is obtained and its size. Thus, only 5% of samples taken by percutaneous liver biopsy display histologic changes consistent with tumor involvement, but a twofold frequency is registered when peritoneoscopy-guided biopsy is performed, especially if gross abnormalities are observed on the liver surface [1, 8, 11, 20]. In the present series, initial liver involvement by HD was demonstrated in 7.4% of the patients. Liver infiltration is more common in the aggressive lymphocytic depletion and mixed cellularity histologic types of HD [11].

Sinusoidal dilatation is frequently observed in liver specimens from HD patients. Although considered a nonspecific manifestation of the disease, it can result in mild increases in serum alkaline phosphatase and gamma-glutamyl-transpeptidase [4]. On the other hand, some patients show marked cholestasis without histologic evidence of liver infiltration, this constituting the so-called idiopathic cholestasis associated with HD [2, 4, 14, 18], a syndrome poorly understood and often considered paraneoplastic [19]. Extrahepatic obstruction due to infiltration or tumor compression of the biliary tract is an infrequent cause of jaundice in HD patients [16]. Finally, the vanishing bile duct syndrome has recently been added to the list of possible mechanisms for intrahepatic cholestasis in HD [10]. Vanishing interlobular bile ducts may be due to invasion by neoplastic cells, this being the most likely cause of jaundice in our patients.

For a diagnosis of hepatic infiltration by HD it is mandatory to observe Reed-Sternberg cells, which are usually found in a characteristic environment of lymphocytes, histiocytes, eosinophils, and plasma cells [15]. In addition, as it occurred in two of the patients of the present series, the finding of atypical histiocytes without Reed-Sternberg cells in the infiltrate is highly suggestive of hepatic involvement by HD [7]. Other features, although nonspecific, may suggest HD hepatic infiltration, but only in the setting of known or suspected HD [6]. This is the case with non-necrotizing epithelioid granulomas [17], nonspecific triaditis, a high frequency of portal infiltrates larger than 1 mm in diameter, acute cholangitis, portal edema, and portal infiltrates with a predominance of atypical lymphocytes [6].

The presence of hepatic abnormalities due to tumor infiltration as the initial manifestation of HD, as in patients without peripheral adenopathies or other features allowing the diagnosis of the disease, is extremely infrequent. Indeed, only 11 patients have been reported in whom cholestasis and/or hepatic failure constituted the most prominent manifestations of HD presentation, which led to taking a liver biopsy that allowed for HD diagnosis [9, 12, 16, 21–23]. Due to the presence of fever, as was the case in the present series, in most such patients bacterial infection was initially suspected, including cholangitis, hepatic location of a bacterial infec-

tion, and liver or subphrenic abscesses [21–23]. In other cases, as in one of our patients, the clinical picture rather mimicked severe acute hepatitis, acute liver failure, or obstructive jaundice [9, 12, 16, 21]. Except for one study including a group of patients referred to a liver unit because of jaundice and liver failure [21], all previous publications on the subject have reported isolated patients [9, 12, 16, 22, 23]. Because of this, no information was available on the proportion of the overall HD population that these patients represent. In this sense, the six patients herein reported constituted less than 1.5% of a large series of HD, which included all individuals diagnosed with this disease in a university hospital during a 22-year period. It is also of note that in three of the six patients HD was apparently limited to the liver.

Cholestasis was the hepatic abnormality most consistently found in the patients of the present series, with frank jaundice being noted in four of the six patients. The absence of pruritus was noteworthy, however. In addition, a moderate increase in serum transaminase activity was almost the rule, whereas a slight raise in serum LDH was registered in half of the cases. With regard to hepatomegaly, when present, it was moderate and often accompanied by a slight splenomegaly. On the other hand, the existence of leukopenia in most patients of the present series is also noteworthy, since this would be an unexpected finding in the setting of infection. By contrast, eosinophilia, a feature considered to be typical of HD, was present in only one patient.

Overall, the prognosis for patients with liver disease as the initial manifestation of HD is poor [9, 12, 16, 21–23]. Thus, in three of the reported patients HD diagnosis was established only by post-mortem examination [12, 21], whereas in two others the disease had a rapidly fatal course, not even allowing initiation of chemotherapy [9, 21]. Moreover, two additional patients died of disease progression or infectious complications during the first chemotherapy course [21]. Such a fatal course is not the rule, however, since three of the published patients showed a favorable response to chemotherapy and did not relapse [9, 16, 23]. In the present series, the three elderly patients died shortly after HD diagnosis. By contrast, a favorable therapeutic response was observed in the three younger patients, one of whom is considered cured after a 14-year follow-up.

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