THE SIGNIFICANCE OF THE LIVER-SPLEEN UPTAKE RATIO IN LIVER SCANNING

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The use of a simple criterion for assessing the relative uptake of colloid in the liver and spleen was evaluated in a series of patients unselected for type of diagnosis. Categorization of liver scans into groups showing equal, increased, or decreased relative splenic uptake provides useful differential diagnostic information. Increased splenic uptake was seen most commonly in cirrhosis, carcinoma, and diabetes mellitus. Decreased uptake was seen in RES malignancies. No association with anemia alone was found.

Technetium-99m-sulfur colloid is most widely used to image and evaluate hepatic and splenic anatomy. The final image obtained is a function of several factors including the physiological state and distribution of the reticuloendothelial cells among the different organs and the amount of blood flow to these organs. Different disease states may alter one or more of these factors thus changing the relative colloid distribution resulting in an abnormal image. Numerous studies have noted a relative decrease in hepatic uptake of colloid in diseases such as hepatitis (*1,2*) and cirrhosis (*3–6*) which is apparently a reflection of the general impairment of hepatic function seen in these illnesses. However, only a single study to date has come to our attention in which the authors have attempted to analyze the alterations in colloid distribution in a systematic fashion and to determine their clinical significance (*7*).

The latter study was limited to patients with diagnoses of cirrhosis, anemia, systemic proliferative diseases, and hematopoietic tissue neoplasms. As this is not fully representative of the spectrum of diseases seen in most nuclear medicine laboratories, the results are difficult to generalize. The present study was undertaken in an attempt to evaluate the meaning of alterations in the distribution of ^{99m}Tc-sulfur colloid seen on liver images as measured by a simple, easily applied criterion in an unselected group of patients.

METHODS

All ^{99m}Tc-sulfur colloid liver and spleen scans performed at the University of Michigan Medical Center between January 1969 and September 1971 inclusively were reviewed. Only studies performed with a rectilinear scanner were considered. To eliminate the possibility of variations in technical factors affecting the apparent density, only those studies in which both the liver and spleen were visible in a single posterior view were included in the final evaluation. Colloid distribution was assessed by comparison of the area of greatest density in the liver with the area of greatest density in the spleen on the single posterior view. A simple visual estimation of relative density was used and the scans were broken into three groups. Those patients whose scan demonstrated a greater density in the spleen than in the liver (Fig. 1A) were designated Group A. Patients who had greater density over the liver than the spleen (Fig. 1B) were designated as Group B. Equal density in liver and spleen (Fig. 1C) was arbitrarily designated as "normal" and the group of patients showing equal density in both organs was designated as Group C, to serve as controls. All scans were reviewed by both authors. In cases where there was disagreement about the density, the scan was included in Group C. Thus, all patients in Groups A and B had unequivocal differences in the apparent uptake of the liver and spleen.

All scans were performed using ^{99m}Tc-sulfur col-

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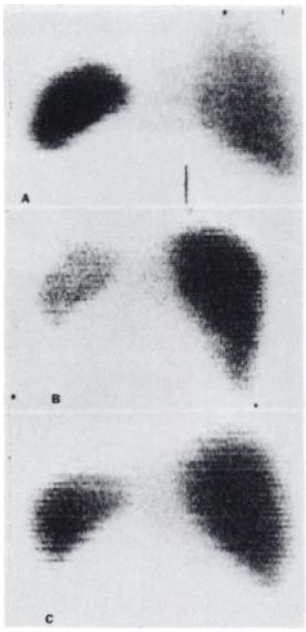

FIG. 1. Posterior scan of Group A patient with increased splenic uptake (A), of Group B patient with decreased splenic uptake (B), and on Group C patient with equal liver-spleen uptake (C).

loid prepared in-house by a technique which has been previously published (*8*). Two millicuries of this preparation were administered to adult patients with proportionate lesser amounts to younger patients included in the series. Clinical and pathological findings were evaluated and correlated for the different groups and evaluated for statistical significance. Patients were evaluated for primary diagnosis, hemoglobin levels, and liver function. Only one diagnosis was recorded for each patient. In patients with a significant secondary diagnosis, the primary diagnosis was considered to be malignancy if present. If the patient had no form of malignancy, liver disease if present was the primary diagnosis. Diabetes mellitus was considered a primary diagnosis only in the absence of malignancy or liver disease.

RESULTS

A total of 1,300 rectilinear liver and spleen scans were reviewed. This included scans from 1,119 patients. Five hundred sixty-three patients had posterior view scans in which there was sufficient liver and spleen demonstrated to determine the relative colloid uptake. Two-hundred-ninety patients were classified as Group A. There were 122 males and 168 females. The average age was 50.5 years. Fifty-eight patients were placed in Group B. This group included 24 males and 34 females with an average age of 51.7 years. Group C consisted of 215 patients; 130 males and 85 females with an average age of 53 years. Overall ages ranged from 1 to 88 years.

The primary diagnoses by major systems are given in Table 1. The types of malignancy are further broken down in Table 2. In both tables the presence of a figure in the column P signifies that there is a statistically significant difference for that category between the adjacent groups as determined by the Chi-square test. If no figure is given, the difference was not significant at the 0.05 level or greater.

Included under miscellaneous liver disease in Table 1 in Group A was one patient each with status post-right hepatectomy for trauma, hepatic abscess, hematoma of the liver after trauma, fasciola hepatica

TABLE 1. PATIENT PRIMARY DIAGNOSIS BY CATEGORY

Diagnosis	Group A (No.) (%)	P	Group B (No.) (%)	P	Group C (No.) (%)	P	Group A (No.) (%)
Malignancy (see Table 2)	139–48		34–59		110–51.2		139–48
Liver disease							
cirrhosis	39–13.4	<0.025	1–1.7		7–3.3	<0.005	39–13.4
hepatitis	22–7.6	<0.25	1–1.7		9–4.2		22–7.6
fatty infiltration of the liver	3–1.0		—		1–0.5		3–1.0
miscellaneous	7–2.4		1–1.7		5–2.3		7–2.4
Diabetes mellitus	30–10.7		4–7.0		7–3.3	<0.005	30–10.7
Alcoholism	6–2.1		—		—	<0.05	6–2.1
Pulmonary disease	6–2.1		2–3.5		9–4.2		6–2.1
Gastrointestinal disease other than liver	11–3.8		5–8.6		8–3.7		11–3.8
Infection	5–1.7		3–5.2		18–8.4	<0.005	5–1.7
Genitourinary	3–1.0		2–3.5		1–0.5		3–1.0
Endocrine disease	1–0.3		1–1.7		5–2.3	<0.05	1–0.3
Cardiovascular disease	5–1.7		—		8–3.7		5–1.7
Nervous system disease	3–1.0		1–1.7		4–1.8		3–1.0
Collagen disease and arthritis	4–1.4		2–3.5		13–6.1	<0.005	4–1.4
Miscellaneous	6–2.1		1–1.7		10–4.6		6–2.1
Total patients	290		58		215		290

TABLE 2. TYPES OF MALIGNANCY

Malignancy type	Group A (No.) (%)	P	Group B (No.) (%)	P	Group C (No.) (%)	P	Group A (No.)
Carcinoma total	100–72	<0.001	16–47	<0.0005	85–77		100
adenocarcinoma							
GI tract	44	<0.01	6		22	<0.05	44
Other	23		2		19		23
squamous cell carcinoma	20		5		28	<0.05	20
other carcinoma	13		3		16		13
Sarcoma	7–5		2–6		11–10		7
Melanoma	14–10		2–6		10–9		14
Hodgkin's disease	11–8	<0.005	9–26	<0.0005	2–2	<0.05	11
Leukemia	5–4		2–6		1–1		5
Multiple myeloma	—	<0.0005	3–9	<0.005	—		—
Miscellaneous	2–1		—		1–1		2

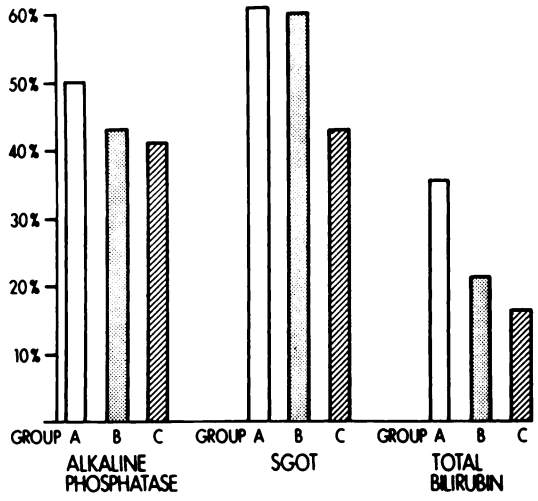

FIG. 2. Percent of each group with elevated alkaline phosphatase, SGOT, and total bilirubin level.

infestation, alcoholic liver disease, glycogen storage disease, multicystic renal and liver disease, and one with undiagnosed hepatomegaly and elevated liver enzymes. In Group B the patient with miscellaneous liver disease had a laceration of the liver secondary to trauma. In Group C the miscellaneous group included two patients with cholecystitis with cholelithiasis, one with a hemangioma of the liver, one with acute liver injury due to drugs, and one patient with abnormal liver function studies but in whom no specific liver disease could be demonstrated after extensive evaluation.

Miscellaneous malignancy in Table 2 includes one patient with seminoma and one patient with a beta cell tumor of the pancreas in Group A, and in Group C one patient had a malignant mesothelioma.

Patients in Group A had an average hemoglobin of 12.04 gm; males 12.7 gm and females 11.9 gm. In Group B the average level of hemoglobin was 11.6 gm; males 12.1 gm and females 11.4 gm. Group C average hemoglobin level was 12.8 gm; males 13.1 gm and females 12.3 gm.

Abnormally elevated alkaline phosphatase levels (Fig. 2) were present in 50% of Group A patients, in 43% of Group B patients, and in 41% of Group C patients. Serum glutamic oxaloacetic transaminase levels were elevated in 61% of Group A patients, in 60% of Group B patients, and in 43% of Group C patients. Serum bilirubin levels greater than 1 mg% were present in 35% of Group A patients, 21% of Group B patients, and in 16% of Group C patients.

DISCUSSION

Malignancy was the most frequent primary disease in all three groups and is probably a reflection of the frequent use of the liver scan to detect possible metastases in patients with known malignancy. The incidence of the different types of malignancy, however, varied between the groups. Some form of carcinoma was present in about three-quarters of all types of malignancy in Groups A and C whereas carcinoma accounted for less than half the malignancy in Group B. The type of carcinoma also influenced the liver–spleen colloid distribution but to a lesser degree than did the presence of carcinoma. The incidence of adenocarcinoma in Group A patients with malignancy was higher than in Group C. This phenomenon may be explained in part by the predilection of adenocarcinoma to metastasize to the liver (*9*). The presence of metastases in the liver displacing liver tissue could interfere with colloid uptake and result in a decreased liver–spleen ratio.

The presence of a decreased hepatic uptake, however, does not necessarily signal the presence of metastasis. Five of the patients in Group A with known malignancy did not have any evidence of liver metastasis when the liver was examined at laparotomy or at autopsy. There are numerous changes which occur in hepatic enzyme systems in

the presence of remote malignancy (*10,11*). Similar effects on hepatic RES function may explain in part the decrease in hepatic colloid uptake seen in patients who do not have actual invasion of the liver by tumor.

Of the 34 patients with malignancy in Group B, 12 had a form of Hodgkin's disease or multiple myeloma. This fourfold increase in incidence in Group B patients compared with Group A or C patients is quite significant and when malignancy is suspected, the presence of decreased colloid uptake by the spleen should alert one to consider Hodgkin's disease or multiple myeloma. There were three cases of multiple myeloma in the entire study of 563 patients and all three were in Group B. No significant difference was observed in the incidence of leukemia in the three groups.

Primary liver disease was the second most frequent diagnosis in Groups A and C and accounts for 24% of Group A patients, 10% of Group C patients, and 5% of Group B patients.

There have been previous reports on the finding of a decreased liver–spleen uptake ratio in patients with cirrhosis and hepatitis. Our findings substantiate these reports in the case of cirrhosis but not for hepatitis. Whereas the incidence of cirrhosis in Group A patients of 13.4% compared with an incidence in control Group C patients of 3.3% is highly significant, the incidence of hepatitis of 7.6% in Group A and 4.2% in Group C is not. This may possibly be a result of the duration of these diseases. The gradual onset and development of cirrhosis may allow time for a shift of the distribution of the reticuloendothelial elements or the development of an impaired hepatic circulation affecting RES function. The development of hepatitis being more acute, there may be insufficient time for detectable changes to take place.

A surprising finding was the highly significant incidence of diabetes mellitus in patients with a liver-spleen uptake ratio of less than one. In 10.7% of Group A patients compared with 3.3% of Group C patients there was a primary diagnosis of diabetes mellitus which was not associated with any known liver or malignant disease. When patients with a secondary diagnosis of diabetes were included, the incidence was 18% in Group A compared with 7% in Group B and 6% in Group C. A p value of less than 0.05 was obtained by comparing Group A with Group B and p of less than 0.005 by comparing Group A with Group C.

It is interesting to note that all six patients in the study with a primary diagnosis of alcoholism, a condition commonly associated with liver disease and frequently with fatty infiltration of the liver, and three of the four patients with fatty infiltration of the liver were in Group A. Part of the apparent decrease in the liver density may be the result of mechanical factors. With the increased fat content in the liver the reticuloendothelial cells may not be in as close approximation to one another as in the normal liver. These same factors may explain the relative decrease in hepatic uptake in some patients with diabetes, a condition frequently associated with fatty infiltration of the liver. However, not all patients with diabetes have a sufficient increase in hepatic fat content to explain the image on this basis. The present data suggests that functional changes in the hepatic reticuloendothelial cells may occur in diabetes.

The relative colloid uptake in the liver and spleen was also correlated with other liver function tests, specifically the alkaline phosphatase, serum glutamic oxaloacetic transaminase, and serum bilirubin (Fig. 2). There were no significant differences in the incidence of abnormal tests between Groups A and B. Whereas only the incidence of an abnormal SGOT was significant ($p < 0.05$) between Group B and Group C, there was a significant difference between Group A and Group C in the incidence of all abnormal liver function tests (alkaline phosphatase $p < 0.05$, SGOT < 0.005, serum bilirubin $p < 0.005$).

A previous report (*7*) suggested that there is a relation between splenic uptake, particularly increased uptake, and primary anemia. In the present study we found no case in which there was a primary diagnosis of anemia unassociated with liver disease or malignancy. The present results support the concept that altered relative splenic uptake is not due to the anemia itself but to the presence of other diseases frequently associated with anemia such as cirrhosis or malignancy.

In the present study only rectilinear scans were evaluated for the reasons given above. There appears to be no reason why our findings should not be equally applicable to studies performed with the gamma camera provided suitable precautions are taken to assure identical exposure factors for both the liver and spleen as has been stressed elsewhere (*7*). Although only one colloid preparation was used in this study, there is no reason to believe other colloid preparations would not behave in a similar manner.

The simple visual categorization of relative uptake of colloid by the liver and spleen in the posterior projection into groups showing equal, increased splenic or decreased splenic uptake seems to offer a useful diagnostic criterion with some differential diagnostic significance.

The presence of increased relative splenic uptake is more common in cirrhosis. In the absence of cirrhosis or malignancy increased splenic uptake should alert the observer to the possibility of diabetes mellitus. This finding may also be used as a nonspecific indicator of liver disease in the same fashion as an elevated alkaline phosphatase or serum bilirubin level.

In the presence of known or suspected malignancy, increased splenic uptake suggests carcinoma rather than other types of malignancy. Conversely, decreased splenic uptake suggests Hodgkin's disease [and probably other lymphomas (7)] or multiple myeloma.

The presence of an unequal liver/spleen ratio suggests a chronic rather than an acute process.

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