AN EVALUATION OF LUNG UPTAKE OF COLLOID DURING LIVER IMAGING

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A marked increase in lung accumulation of activity was visualized on routine liver scanning in a group of 22 patients selected to eliminate colloid variations, bone marrow uptake, and blood pool activity as contributing factors. The only common findings in the group were the presence of some type of liver disease and a poor prognosis. Clinical and laboratory evidence point to either an alteration in the pattern of RES activity or rapid in vivo clumping and secondary pulmonary microembolization. The present study was inadequate to rule out either of these possibilities. The findings support the concept of significant alterations in the physiology of intravascular colloids in certain severe illnesses and suggest that the liver scan may have a role in the evaluation of such illnesses.

The infrequent occurrence of marked lung uptake of ^{99m}Tc-sulfur colloid during routine liver imaging in our clinical laboratory in addition to casual reports that others were experiencing a similar phenomenon led us to investigate the etiology and significance of this dramatic finding (Fig. 1). Although it is easy to attribute the occurrence of lung uptake to poor colloid preparation (*1*), clinical and laboratory observations strongly suggested that factors intrinsic to the patient might be in part responsible for this finding. This paper relates these observations and discusses their possible etiology and significance.

METHODS

All liver scans performed at the University of Michigan Medical Center between January 1, 1969 and September 30, 1971 were reviewed by two of the authors (GAW and JWK) for significant lung uptake by the following "uptake criteria" (Fig. 1):

1. There was sufficient lung activity to make the demarcation between liver and lung unclear.
2. The heart was clearly outlined as a *cold* area.
3. There was no evidence of technetium in the stomach.
4. There was minimal or no bone marrow uptake as evidenced by no visualization of the sternum anteriorly or the spine posteriorly.

Criteria 2 and 3 were to rule out any contribution to apparent lung activity from free technetium or unphagocytized particulate activity in the blood. Criterion 4 was to eliminate the possibility of marrow uptake in the ribs contributing to the impression of lung uptake.

All scans in this series were done with ^{99m}Tc-sulfur colloid prepared by the following in-house method. Technetium in a volume of 6.5 ml of saline was mixed with 1 ml of 1 *N* HCl and 0.5 ml of 0.8% sodium thiosulfate solution and shaken in boiling water for 5 min. One and five-tenths milliliters of a phosphate buffer was then added, the suspension cooled on ice, and 2.0 ml of 25% sorbitol added for stabilization. Pertechnetate derived from a generator was passed through an ion exchange column to eliminate aluminum contamination before colloid preparation. More recently technetium derived from a liquid-liquid extraction system has been used which eliminates the need for this step.

A knowledge of the exact particle size distribution would be of great importance in evaluating the etiology of lung uptake. Although this is not accurately known for our preparation, it was felt that factors intrinsic to the colloid, such as large particules, could be effectively ruled out by other means.

A set of "quality criteria" was established to evaluate the intrinsic characteristics of the colloid used in

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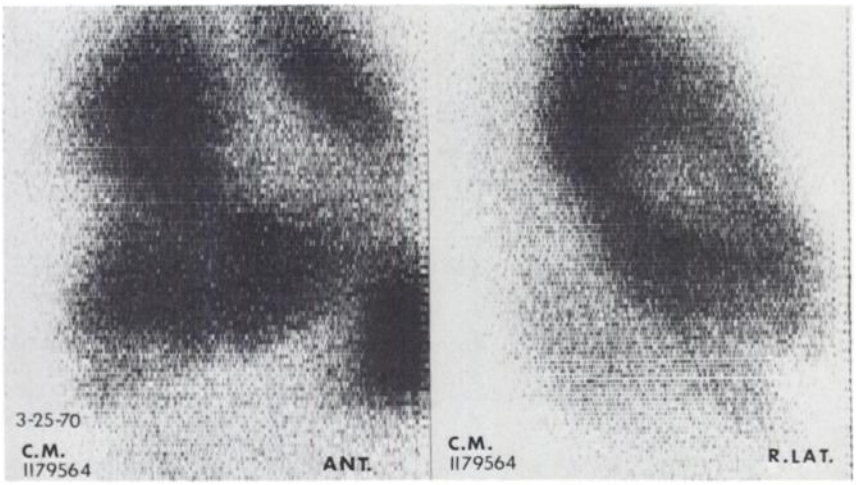

FIG. 1. Lung uptake of ^{99m}Tc-sulfur colloid. Note anterolateral subphrenic abscess (Case CM).

each patient whose scan fulfilled the "uptake criteria".

For each scan meeting the "uptake criteria" it was determined that:

1. There had been at least one other scan done with the same batch of colloid which did not show lung uptake (a "control" scan).
2. No more than one scan from any batch of colloid showed lung uptake.

All scans which did not also fulfill the "quality criteria" were eliminated from further consideration. The second "quality criterion" may have led to the elimination of a few scans when a "control" scan was available. This is not known as such cases were not screened for "control" scans. This criterion was included because the occurrence of significant lung uptake by our criteria was so unusual that the finding of two patients demonstrating the phenomenon on the same day was taken as prima facie evidence of poor colloid.

In addition to the "quality criteria", all scans were eliminated which had not been begun within 5 hr of the preparation of the colloid which is the minimum useful shelf-life of our colloid preparation. The time of colloid preparation and patient injection were determined from laboratory records. In cases where the time interval was uncertain, this scan was also eliminated.

Scans were performed using 2 mCi of the colloid preparation. Most studies were performed on a dual-head, 5-in. scanner although some were done with an Anger camera. All rectilinear scans included four views comprising anterior, posterior, right, and left laterals. Camera studies generally included six views, the extra views being necessary to include the left portion of the liver and the spleen in the anterior and posterior views.

RESULTS

A total of 1,499 scans obtained on 1,205 patients were reviewed. Fifty-five patients had scans which met the "uptake criteria" but 33 were eliminated because they failed to meet the "quality criteria". Twenty-four scans performed on 22 patients met all criteria giving an incidence of 1.6%. Three additional scans on these patients did not show lung uptake. Table 1 summarizes the clinical findings associated with the acceptable cases. Ages ranged from 2 to 77 with a mean age of 41 years. There are 14 men and 8 women in the group.

The column headed "Diagnosis" lists the major diseases of each patient at the time of the scan. The commonest is some form of malignancy, diagnosed in 11 patients. Cirrhosis was present in four patients and intra-abdominal abscess in three. One patient (JB) with a left hilar mass showed no change after 6 months, and no definite diagnosis was established. Two patients had anemia. This was due to myelofibrosis in one but remained obscure in the second after extensive studies over several years.

Eighteen patients showed evidence of liver abnormality by tissue examination and/or laboratory studies. Even massive lung accumulation of activity did not obscure changes in liver uptake and all but one patient had a liver scan which showed an abnormality in addition to the lung uptake. This included the four patients without other evidence of liver disease. Scan abnormalities included definite areas of decreased uptake in ten patients, hepatomegaly in six patients, splenomegaly in seven patients, and patchy uptake in six. The spleen showed more activity than liver in the posterior view in six patients and less in two (*2*). Multiple abnormalities were present in several patients.

Five patients had two scans done during the course of their illness. In one, increased lung uptake was

TABLE 1. SUMMARY OF CLINICAL FINDINGS

Patient	Age	Sex	Diagnosis	Evidence of liver disease*	Current status of patient†
EK	51	M	Adenocarcinoma of colon with metastasis	Yes	Death 2½ mo.
JB	50	M	Left hilar mass	No	Alive 6 months
JE	41	F	Cirrhosis of liver	Yes	Alive 3 months
SR	57	M	Adenocarcinoma of ampulla of Vater, diabetes mellitus	Yes	Death 1 week
CF	56	F	Cirrhosis of the liver	Yes	Death 3 weeks
AH	40	F	Carcinoma of breast with metastasis	Yes	Death 2½ mo.
RJ	40	M	Lymphoma, IV-B	Yes	Death 1 month
FH	41	F	Multiple hepatic abscesses, subphrenic abscess, hepatic coma, Ca of bile duct, diabetes mellitus	Yes	Death 2 weeks
BR	3	M	Hemophilia A, Subcapsular hematoma of liver	Yes	Unknown
EO	57	M	Cirrhosis of liver	Yes	Death 2 weeks
SB‡	17	M	Acute stem cell leukemia	Yes	Death 2 days
NP	55	M	Anemia, etiology undetermined	Yes	Unknown
RW	12	M	Embryonal cell sarcoma with hepatic metastasis	Yes	Death 3½ mo.
CM‖	17	F	Chronic purulent inflammation of the gallbladder, multiple liver abscesses	Yes	Alive 1 year
KM‡	18	F	Crohn's Disease, malnutrition, abscess right lower abdomen	No	Alive 3 months
RB	31	M	Membranous glomerulonephritis	No	Alive 6 months
VW‡	56	M	Exfoliative dermatitis with lymphoma or leukemia	Yes	Death 2½ mo.
SH	2	M	Metastatic neuroblastoma	Yes	Death 2 months
MS	55	F	Virilizing adrenal cortical carcinoma	Yes	Alive 3 months
RG	77	M	Adenocarcinoma of colon	No	Alive 6 months
DC	66	M	Myelofibrosis	Yes	Alive 4 months
NC	61	F	Biliary cirrhosis	Yes	Alive 4 months

* Other than scan.

† Time measured from date of scan.

‡ These patients showed increasing lung uptake on sequential scans associated with worsening of the clinical picture.

‖ This patient showed decreased lung uptake on sequential scans associated with clinical improvement.

present on both studies. In the others, there was an apparent tendency for pulmonary accumulation to parallel the severity of the underlying illness. Three patients showed a change from no lung uptake to definite lung uptake in relatively short periods of time. In each case the appearance of lung uptake was associated with worsening of the patient's clinical condition (Fig. 2). One patient who eventually recovered showed a decrease in the amount of lung accumulation with the passage of time. A most striking finding was the high mortality rate of those patients included in the study. Eleven of the 22 patients died within 3½ months and 10 within 2½ months after scanning.

DISCUSSION

Significant localization of ^{99m}Tc-sulfur colloid within the lung may have diverse causes. Available biologic distribution data suggest that 1–2% of an administered dose will appear in the lungs (*3,4*). This figure depends upon the colloid formulation used and in our personal experience certain preparations, notably some commercial kits, show lung accumulation regularly although it is generally quite faint. These variations in lung uptake are presumably due to physical and/or chemical variations in individual colloids although accurate characterizations of individual colloid formulations are not available.

The lack of adequate data to characterize colloid led us to select a set of "quality criteria" to evaluate the in vivo performance of our colloid preparation on an individual batch basis. Qualitative variations in any individual batch of colloid which would lead to lung accumulation should cause increased lung uptake in all patients receiving colloid from that batch. Thus all patients studied with colloid from the same batch form a set of "controls" for that batch. If lung uptake is seen only in one patient out of several receiving colloid from the same preparation, it would suggest that some factor, or factors, within the patient is responsible.

The use of batch "controls" in this way has the advantage that the colloid does not need to be completely characterized to draw meaningful conclusions about its quality and behavior within the body. It also means that once a norm for lung uptake has been established in an individual laboratory, the significance of variations from this norm can be evaluated independently of exact characterization of

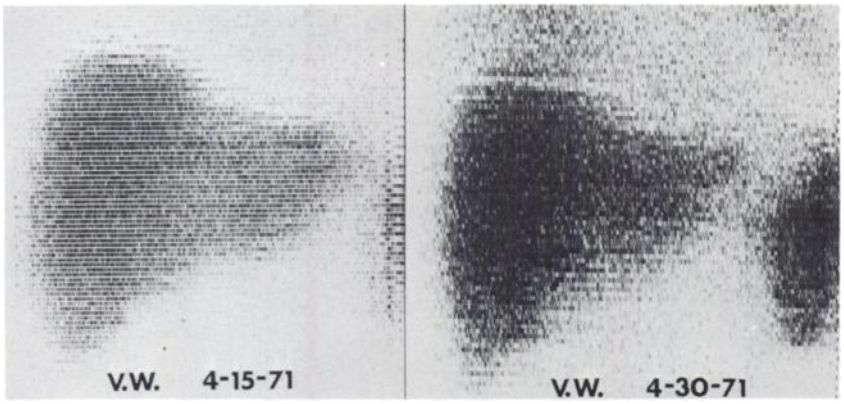

FIG. 2. Progressively increasing uptake of colloid by lung associated with clinical deterioration in 56-year-old male with lymphoma (Case VW).

the colloid used. Thus other investigators should be able to evaluate our findings in terms of their own individual experience.

In the group of patients evaluated in this study, it appears that there has been a major alteration in the physiologic pattern of intravascular foreign colloid clearance. Clarification of the nature of this alteration may offer considerable insight into the physiology of severe or terminal illness.

Increased uptake within the lung could be due to enhanced phagocytic activity by RES cells in the lung. Increased RES phagocytic activity has been demonstrated in patients with both neoplasia and infection (*6–8*) which would include most of our patients. One of us (JDQ) has demonstrated that in rats, the prior injection of a known RES stimulator, endotoxin, causes a twenty-fold increase in the deposition of technetium-sulfur colloid in the lungs relative to liver. Bone marrow deposition is also enhanced. This deposition was demonstrated to be intracellular by radioautography (*9*).

The fact that lung uptake did not obscure changes within the liver is consistent with the hypothesis that the phenomenon is due to a regional variation in RES response rather than to a basic change in the in vivo handling of the colloid. If the changed pattern of colloid deposition were due to a mechanism other than RES uptake, an altered pattern of liver deposition (e.g., no significant liver accumulation) might be anticipated.

Why enhanced RES activity should be manifest as increased relative lung uptake is not clear. Perhaps the fact that the lungs represent the first site of RES activity encountered following intravenous injection of the colloid is responsible for this apparent nonuniform enhancement.

Variations in the white blood cell phagocytic activity might be anticipated in association with enhanced RES activity. Harper, et al (*5*) have reported an increased concentration of radioactivity in the buffy coat following the injection of ^{99m}Tc-sulfur colloid into a patient with extensive liver destruction. White blood cell counts in our patients showed no consistent pattern, but we did not test for functional changes.

The mechanism of RES enhancement in neoplastic disease is unclear. It may be due to qualitative or quantitative variations in the family of proteins known as opsonins (*8*). This is a tempting explanation in our cases because of the common association of alterations in plasma proteins with liver disease. Fifteen of our patients had serum protein electrophoresis determinations. No consistent pattern of variation was evident and several patients had entirely normal patterns. As electrophoresis is relatively insensitive to small variations in protein subgroups, this possibility still appears plausible.

There is also evidence to suggest that lung uptake may be due to the rapid intravascular clumping of the injected colloid particles with subsequent entrapment in the pulmonary capillary bed. Fischer (*10,11*) has noted that in mice injected with a gelatin-stabilized colloidal suspension of stannic oxide, deposition is normally in the liver and spleen just as with ^{99m}Tc-sulfur colloid. If the animal is pretreated with heparin, the predominant site of uptake becomes the lung. As heparin is also an RES stimulator (*8,12*), this lung uptake might also be assumed to be due to enhanced phagocytic activity in the lungs. These animals, however, become sick and die quickly suggesting the development of multiple pulmonary microemboli. Fischer (*12*) also discusses the intravascular clumping which can occur following the injection of "unprotected" particles. Fischer's work did not document the actual site of deposition of particles in the lung, and the development of intravascular clumps with subsequent microembolism is only presumptive. It is noteworthy that 4 of the 22 patients in our present series were receiving heparin.

There is other indirect evidence against a variation in RES activity being the sole cause of increased

lung accumulation. It is quite common for patients with advanced liver disease, particularly cirrhosis, to manifest markedly increased bone marrow uptake. This phenomenon of increased relative phagocytic activity could be considered analogous to the enhancement seen with RES stimulators such as endotoxin. If this were so, enhanced marrow uptake should be associated with increased lung uptake in most patients with impaired hepatic phagocytosis. We have not found this to be true in our laboratory, and the elimination of the "uptake criterion" regarding bone marrow uptake would not have markedly increased the number of patients in the present series.

Also if enhanced lung uptake were due to generalized RES stimulation, it should be associated with increased bone marrow uptake relative to liver in accordance with Quinones' findings in mice following endotoxin (*9*). As the present series specifically excluded patients with bone marrow uptake, this would argue against generalized, increased RES activity in this group of patients.

There is insufficient evidence at the present time to determine the role of either altered RES function or clumping and embolization in the etiology of lung accumulation of radiocolloid. In view of the apparent correlation of this scintigraphic finding with both the severity and the course of the patient's illness, this phenomenon appears to represent an alteration in colloid physiology due to the presence of disease. Further investigation may lead to new insight into the physiologic changes associated with terminal illness and offer new applications of liver scanning to the evaluation of the seriously ill.

Our findings do indicate the occurrence of some type of liver disease in all patients in this series. In this respect the appearance of lung uptake can be considered an indicator of liver disease, albeit a highly nonspecific one, if colloid variations can be ruled out.

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