Lung Uptake of Tc-99m Sulfur Colloid in Liver and Spleen Imaging

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Twenty-seven patients with increased lung uptake of technetium-99m sulfur colloid (TcSC) were studied as a group and after classification by the degree of lung uptake (15 patients mild, 6 moderate, and 6 marked) to determine survival rate and the incidence of associated abnormalities. Using life-table data based on all 27 patients, it is estimated that 74% would be alive at 6 mo; this is significantly higher ($p < 0.02$) than the 38% survival estimate at 6 mo for patients reported in the literature. Twenty-two of the 27 patients (81%) had increased splenic uptake of TcSC, 15 (56%) had splenomegaly, 17 (63%) had an abnormal liver image (enlargement or nonhomogeneity), and 9 (33%) had increased bone-marrow uptake. As the degree of lung uptake increased, there was a tendency for the survival rate to decrease and for the incidence of other abnormalities in the liver and spleen images to increase. This tendency was statistically significant ($p < 0.05$) for abnormal liver image, and also for increased bone-marrow uptake and splenomegaly when patients with moderate and marked lung uptake were combined and compared with patients with mild lung uptake. Increased lung uptake of TcSC is strongly associated with other abnormalities in the liver and spleen images, but is not necessarily associated with a poor prognosis, particularly when the degree of increased lung uptake is mild.

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Increased lung uptake of technetium-99m sulfur colloid (TcSC) has been associated with a very poor prognosis (*1–10*). Most reports have dealt with only one or two patients, but one report of 22 patients noted a 50% death rate at 3½ mo after imaging and a strong, although not invariable, association with liver disease (*3*). We studied 27 patients with varying degrees of increased lung uptake of TcSC to determine whether the degree of lung uptake correlates with life expectancy and the prevalence of other abnormalities in the liver and spleen images.

MATERIALS AND METHODS

Patients who showed increased lung uptake of TcSC in liver and spleen images were collected prospectively over a 12 mo period. All patients were injected with 3 mCi of TcSC and imaged in the anterior, posterior, and both lateral projections with either a scintillation camera or a rectilinear scanner. When a scintillation camera was used, images of the left and right sides in the anterior and posterior projections were exposed for equal time to allow comparison of radiotracer concentration in the liver and spleen.

The presence of increased lung uptake of TcSC was evaluated in the anterior and posterior images. With the imaging techniques employed, normal images of the liver and spleen show either no evidence of radiotracer in the lungs or only a barely detectable amount. Rectilinear scans tend to show more evidence of radiotracer in the lungs than do scintillation-camera images, presumably because the lungs are close to the focal plane with the rectilinear scanner.

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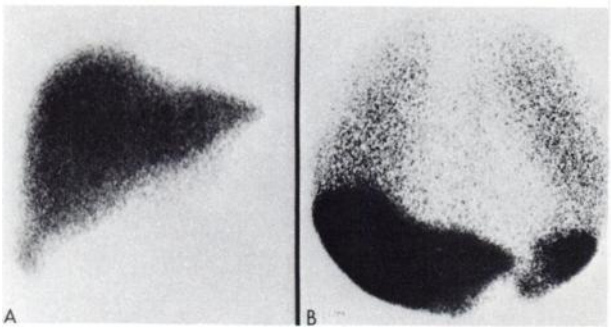

FIG. 1. Normally exposed (A) and overexposed (B) anterior images in patient with normal TcSC study of liver and spleen. Normally exposed image shows no evidence of radiotracer in lungs, whereas overexposed image demonstrates a small amount of radiotracer in lungs.

Even though little or no radiotracer is demonstrated in the lungs with routine imaging techniques, most normal patients can be shown to have some lung uptake of TcSC if the image is overexposed (Fig. 1).

The quality of the radiopharmaceutical and the possibility of in vitro macroaggregation were checked by examining the liver and spleen images of other patients injected with the same preparation of TcSC for the presence of increased lung uptake. An average of five patients were studied with TcSC each day. A patient with increased lung uptake was excluded from the study if either more than two patients, or a majority of the patients examined with the same preparation, showed increased lung uptake on a given day. Patients were also excluded if the degree of radiotracer concentration in the bone marrow, as judged from the lumbar spine in the posterior image, was sufficient to account for the amount of radiotracer in the chest.

Increased lung uptake of TcSC was classified on the basis of the relative concentration of radiotracer in the lungs and liver in the anterior image (*9*). The classification "mild" was used when the concentration of radiotracer in the lungs was clearly visible, but was only a small fraction of that in the liver (Fig. 2). "Moderate" was used when the border between the lungs and liver began to be obscured, and "marked" was used when the radiotracer concentration in the lungs was comparable with that in the liver (Fig. 2).

Liver size was evaluated visually with the aid of a costal-margin marker on one anterior image and knowledge of the patient's height and weight. The presence of nonhomogeneity of radiotracer distribution in the liver, focal decrease in the radiotracer concentration in the liver, and increased radiotracer concentration in the bone marrow were determined subjectively. The spleen was considered enlarged if its longest dimension exceeded 13 cm (*11*) and the concentration of radiotracer in the spleen was considered increased if it clearly exceeded the concentration of radiotracer in the liver in the posterior image (*12,13*).

The medical record of each patient was reviewed to obtain the results of liver-function tests at the time of imaging and the final diagnosis at the time of discharge or last visit. The current status of each patient was determined by contacting either the patient or the patient's physician. The status and survival time of patients with increased lung uptake of TcSC as reported in the literature was compared with the present series using a regression model that allows for the influence of age and sex and generates a continuous curve based on the discontinuous data (*14*). Patients without reported followup information and an unusually large number of patients with the rare disease mucopolysaccharidosis type 11 (*9*) were excluded.

RESULTS

Patient selection. No patient was excluded from this study of increased lung uptake of TcSC among other patients studied on the same day. Relatively few patients were excluded because increased radiotracer concentration in the bone marrow might account for the apparent increased lung uptake.

Survival rate. Of the total group of 27 patients, 20 (74%) were alive an average of 18 mo after the first liver-spleen study that showed increased lung

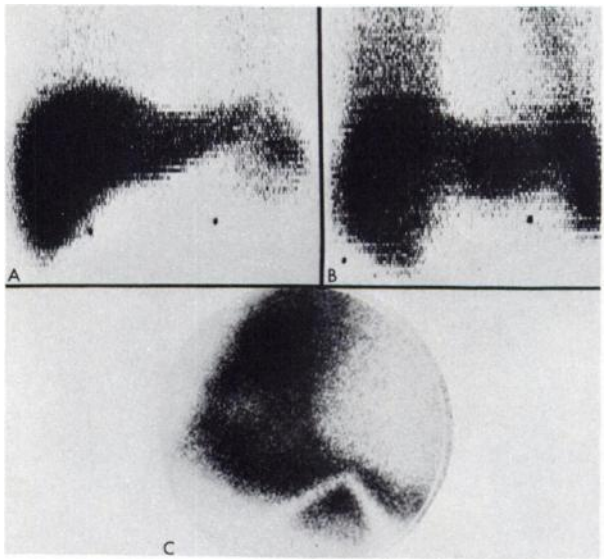

FIG. 2. A, B, and C demonstrate mild, moderate and markedly increased lung uptake of TcSC, respectively, in anterior images of the liver. Increased lung uptake is classified as "mild" when radiotracer concentration in lungs is clearly visible and more than usual, but is only a small fraction of concentration in liver; "moderate" when border between lung and liver begins to be obscured; and "marked" when concentration in lungs appears similar to that in liver.

TABLE 1. IMAGE AND FOLLOWUP FINDINGS IN 27 PATIENTS WITH INCREASED LUNG UPTAKE OF Tc-99m SULFUR COLLOID

Degree of lung uptake	No. of patients	Abnormal liver image (%)*	Increased bone-marrow activity	Increased splenic		Followup status and mean time to followup	
				Size	Activity	Alive	Dead
Mild	15	6 (40)†	2 (13)†	5 (33)†	11 (73)	12 (86) 19 mo	2 (14)‡ 3½ mo
Moderate	6	5 (83)	3 (50)	5 (83)	5 (83)	4 (67) 19 mo	2 (33) ½ mo
Marked	6	6 (100)	4 (67)	5 (83)	6 (100)	4 (67) 13 mo	2 (33) 3 mo
Total	27	17 (63)	9 (33)	5 (56)	22 (81)	20 (74) 18 mo	6 (23) 3 mo

* Indicates significant linear regression ($p < 0.05$) for Mild, Moderate, and Marked categories.
† Indicates significant difference ($p < 0.05$) compared with Moderate and Marked categories combined.
‡ One patient with mild increased lung uptake died during open-heart surgery and is not included.

uptake of TcSC; six patients (23%) were dead an average of 3 mo after the TcSC study (Table 1). One patient with mildly increased lung uptake died during open-heart surgery and was excluded from survival analysis. Twenty-seven patients with increased lung uptake and adequate followup information were reported in the literature (Table 2). Eleven of these (41%) were alive an average of 5 mo after the TcSC liver-spleen study, whereas 16 (59%) were dead an average of 1 mo after the TcSC study. There were no deaths in either the present or the literature series of patients beyond 6 mo after the TcSC study. Life-table estimates (*14*) for a 6-mo followup time give an estimated survival rate in the present series of 74%. This is significantly higher ($p < 0.02$) than the 38% estimated 6-mo survival rate for patients reported in the literature. The survival rate for the literature group at 6 mo is lower than the raw survival rate for this group because some of the surviving patients were followed for less than 6 mo.

Patients with mild lung uptake had the best survival rate (86% at 19 mo). This is significantly better ($p < 0.01$) than the average survival rate reported in the literature, but is not significantly better than the 67% survival rate for moderate and marked lung uptake combined.

TABLE 2. FOLLOWUP STATUS OF PATIENTS WITH INCREASED LUNG UPTAKE OF Tc-99m SULFUR COLLOID AS REPORTED IN THE LITERATURE

Reference No.	Number of patients	Followup status	
		Alive	Dead
3	20	9	11
7	2	1	1
2	2	1	1
5	1	0	1
4	1	0	1
10	1	0	1
Total	27	11 (41%)	16 (59%)

Associated abnormalities of RES function. Increased lung uptake of TcSC was frequently associated with other abnormalities in the liver and spleen images; only four patients (15%) had no associated abnormalities. Seventeen patients (63%) had abnormal liver images (usually enlargement or nonhomogeneity, but focal defects in two cases); 15 (56%) had splenomegaly; 22 (81%) had increased radiotracer concentration in the spleen (including five without evidence of liver disease clinically or by imaging); and nine (33%) had increased radiotracer concentration in the bone marrow. In the case of these last nine, the radiotracer concentration in the chest was always significantly greater than that in the bone marrow; it never had the linear pattern of ribs, and it always had the shape of lungs with decreased radiotracer concentration corresponding to the mediastinum and heart (Fig. 3).

Analysis of patient subgroups with a chi-squared test for trend (*15*) showed a significant relationship ($p < 0.05$) between increasing amounts of lung uptake of TcSC from mild to moderate to marked, and the incidence of abnormal liver images. With the traditional chi-squared test, there was no significant difference between patients with moderate and markedly increased lung uptake for any of the findings. When the moderate and marked groups were combined, they had a significantly higher incidence ($p < 0.05$) of abnormal liver images, increased bone-marrow radiotracer, and splenomegaly compared with patients with mild lung uptake (Table 1). The 73% incidence of increased radiotracer concentration in the spleen in patients with mild lung uptake

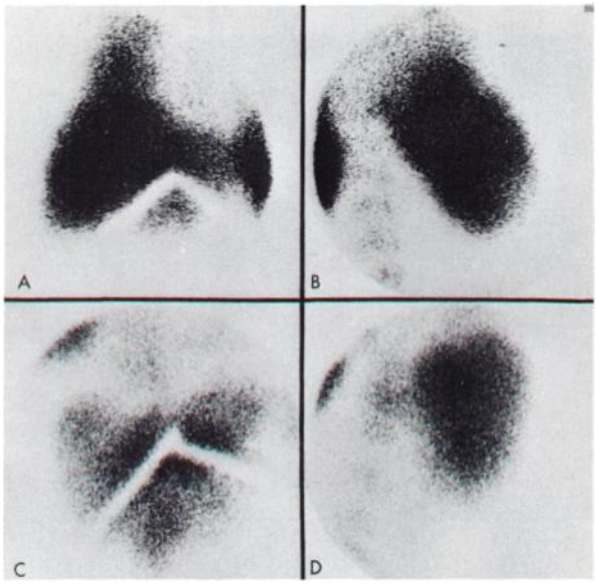

FIG. 3. Anterior and posterior images of TcSC studies in two patients, A, B, and C, D, demonstrate increased lung uptake in presence of increased radiotracer concentration in bone marrow, as determined from posterior image of lumbar spine, is insufficient to account for amount of radiotracer in chest. Second patient has ascites causing separation between right lung and liver (C).

was not significantly lower than the combined 92% incidence in patients with moderate and marked lung uptake.

Other findings. Liver-function tests were available in 22 of the 27 patients in our series. They were abnormal in four of twelve patients (33%) with mild lung uptake; in three of five patients (60%) with moderate lung uptake; and in four of five patients (80%) with marked lung uptake. This apparent relationship of an increasing frequency of abnormal liver-function tests with an increasing amount of lung uptake was not statistically significant ($p = 0.08$).

The primary diagnoses were cancer in 12 patients (eight of these had metastatic breast carcinoma), collagen-vascular disease in six, Laennec's cirrhosis in four, infection in three, and hematologic disease in two. All four patients with cirrhosis had markedly increased lung uptake, but this may reflect the exclusion of cirrhotic patients with mild or moderately increased lung uptake because the amount of radiotracer in the ribs made it difficult to ascertain that lung uptake was present in addition. The distribution of the other disease categories among the various degrees of lung uptake did not deviate from the distribution expected by chance. The diagnoses in the six patients who died were cancer in four, cirrhosis in one, and cirrhosis complicated by hepatoma in one.

There was a strong tendency for repeat liver-spleen studies to remain positive for increased lung uptake of TcSC. In six patients with multiple studies, 13 of 15 studies were positive. The negative studies were in two patients who each had two of three studies positive; in one patient the middle study was negative and in the other patient the last study was negative. Four of the six patients who had increased lung uptake on more than one study had nonprogressive, relatively asymptomatic, metastatic breast carcinoma. The average time from the first positive study to followup in these four patients was 23 mo. The other two patients had systemic lupus and a viral infection complicated by thrombocytopenia. All of these patients had mild or moderately increased lung uptake.

DISCUSSION

Increased lung uptake of TcSC is an abnormal finding that is most often caused by pathophysiologic changes rather than technical factors. It is often, but not invariably, associated with other abnormalities in the biodistribution of TcSC, and indicates the terminal stage of disease in some, but not all, patients. A small amount of lung uptake of TcSC is normal, but it is usually not sufficient to be apparent in routine liver and spleen imaging (Fig. 1). The conclusion that increased uptake is abnormal rests on the findings that the concentration of TcSC in lungs of large numbers of normal animals is low and varies over a relatively narrow range (*16,17*); that it is seen in only a small percentage of patients (*3,9*); that it is often associated with other abnormalities of TcSC distribution; and that in some studies it has correlated with a very poor prognosis (*3*).

The significantly better survival rate among the patients in the present study, compared with those reported in the literature, may reflect a tendency to exclude patients with mildly increased lung uptake in earlier studies (*3*). In the present study patients with mildly increased lung uptake apparently had a better survival rate than those with moderate and marked lung uptake, but this difference was not statistically significant. Previous studies have shown that in progressive diseases—such as metastatic cancer and mucopolysaccharidosis type II—the degree of lung uptake tends to increase as the severity of the disease increases (*3,9*). Whereas patients with marked lung uptake have had a poor prognosis in most studies (*2–5,7,10*) the patients with metastatic breast carcinoma in the present study, and the patients with mucopolysaccharidoses reported previously (*9*), demonstrate that the disease process may remain stable or progress only slowly over two or more years in the presence of mild to moderately increased lung uptake of TcSC.

The present study confirms the high incidence of other abnormalities in liver and spleen images in association with increased lung uptake of TcSC (*3*) and indicates a strong tendency for the incidence of other abnormalities to increase with increasing lung uptake. The strongest association for all degrees of increased lung uptake was with increased splenic uptake of TcSC (83%); this association has not been reported previously. Five of the 22 patients with increased radiotracer concentration in the spleen had no other evidence of liver disease and, therefore, this finding may not be due to decreased hepatic clearance of TcSC or to portal hypertension.

The pathophysiology of increased lung uptake of TcSC is poorly understood. In general, evidence from patient and animal studies does not support the hypothesis that in-vivo macroaggregation results in the formation of TcSC microemboli that are trapped in the lung (*1,2,8,17*). The evidence does support—or at least does not exclude—the possibilities of increased phagocytic activity in the pulmonary capillary bed (*2,18*) or adherence of TcSC to altered endothelium in the pulmonary capillaries (*19*). The 83% incidence of increased TcSC in the spleen in the present study, and the absence of liver disease in five of the patients with this finding, raise the possibility that the mechanism of increased lung uptake is associated with an altered immunologic state. Increased clearance of TcSC by the spleen and mild splenomegaly have previously been associated with a stimulated immunologic state (*20–22*). However, diffuse liver disease and decreased hepatic clearance of TcSC in the presence of normal liver images, bone marrow uptake, and liver-function tests cannot be completely excluded.

The present study supports the concepts that the incidence of other abnormalities in the liver and spleen images tends to increase with the degree of increased lung uptake, and that mild to moderately increased lung uptake is compatible with several years of relatively asymptomatic life. However, more needs to be learned about the factors that determine the degree of lung uptake of TcSC before this finding can be used optimally in the interpretation of liver and spleen images.

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REFERENCES

1. STEINBACH HL: Pulmonary accumulation of ^{99m}technetium sulfur colloid during liver scanning. *Tex Med* 68: 137–138, 1972

2. KLINGENSMITH WC, RYERSON TW: Lung uptake of ^{99m}Tc-sulfur colloid. *J Nucl Med* 14: 201–204, 1973

3. KEYES JW, WILSON GA, QUINONES JD: An evaluation of lung uptake of colloid during liver imaging. *J Nucl Med* 14: 687–691, 1973

4. GILLESPIE PJ, ALEXANDER JL, EDELSTYN GA: High concentration of ^{99m}Tc-sulfur colloid found during routine liver scan in lungs of patient with advanced breast cancer. *J Nucl Med* 14: 711–712, 1973

5. TURNER JW, SYED IB, HANC RP: Lung uptake of ^{99m}Tc-sulfur colloid during liver scanning. *J Nucl Med* 15: 460–462, 1974

6. BOBINET DD, SEVRIN R, ZURBRIGGEN MT, et al: Lung uptake of ^{99m}Tc-sulfur colloid in patient exhibiting presence of Al^{3+} in plasma. *J Nucl Med* 1220–1222, 1974

7. IMARISIO JJ: Liver scan showing intense lung uptake in neoplasia and infection. *J Nucl Med* 16: 188–190, 1975

8. BOWEN BM, COATES G, GARNETT ES: Technetium-99m-sulfur colloid lung scan in patients with histiocytosis X. *J Nucl Med* 16: 332, 1975

9. KLINGENSMITH WC, EIKMAN EA, MAUMENEE I, et al: Widespread abnormalities of radiocolloid distribution in patients with mucopolysaccharidoses. *J Nucl Med* 16: 1002–1006, 1975

10. Case records of the Massachusetts General Hospital. *N Engl J Med* 290: 1474–1481, 1974

11. LARSON SM, TUERELL SH, MOORES KD, et al: Dimensions of the normal adult spleen scan and prediction of spleen weight. *J Nucl Med* 12: 123–126, 1971

12. BEKERMAN C, GOTTSCHALK A: Diagnostic significance of the relative uptake of liver compared with spleen in ^{99m}Tc-sulfur colloid scintiphotography. *J Nucl Med* 12: 237–240, 1971

13. WILSON GA, KEYES JW: The significance of the liver-spleen uptake ratio in liver scanning. *J Nucl Med* 15: 593–597, 1974

14. COX DR: Regression models and life tables. *J R Statist Soc B* 34: 187–220, 1972

15. COCHRAN WG: Some methods for strengthening the common χ^2 tests. *Biometrics* 10: 417–451, 1954

16. KLINGENSMITH WC, LOVETT VJ: Lung uptake of ^{99m}Tc-sulfur colloid secondary to intraperitoneal endotoxin. *J Nucl Med* 15: 1028–1031, 1974

17. KLINGENSMITH WC, TSAN MF, WAGNER HN: Factors affecting the uptake of ^{99m}Tc-sulfur colloid by the lung and kidney. *J Nucl Med* 17: 681–684, 1976

18. QUINONES JD: Localization of technetium-sulfur colloid after RES stimulation. *J Nucl Med* 14: 443–444, 1973 (Abst)

19. ZWEIFACH BW: An analysis of the inflammatory reaction through the response of the terminal vascular bed in micro-trauma. *Rev Canad Biologie* 12: 179–188, 1953

20. DELAND FH: The value of determining splenic weight in radionuclide imaging. *J Nucl Med* 14: 390, 1973 (Abst)

21. GOLDMAN AB, BRAUNSTEIN P, SONG C: Augmented splenic uptake of ^{99m}Tc-sulfur colloid in patients with malignant melanoma. *Radiology* 112: 631–634, 1974

22. KLINGENSMITH WC: Resolution of increased splenic size and uptake of ^{99m}Tc-sulfur colloid following removal of a malignant melanoma. *J Nucl Med* 15: 1203–1204, 1974