Liver Involvement in Lymphoma: Role of Gallium-67 Scintigraphy

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CASE HISTORY

A 41-yr-old female was admitted with an 8-kg weight loss and abdominal pain increasing in severity for 1 mo prior to her admission. Physical examination revealed pallor and a large right abdominal mass, but was otherwise normal. Abdominal ultrasonography showed a solid mass, 15 cm in diameter, in the right hepatic lobe. A liver-spleen scan showed hepatomegaly (liver span in the midclavicular line was 25 cm) with a large photopenic region in the inferior aspect of the right lobe (Fig. 1A). The spleen was normal.

Perfusion and blood pool were normal in the area of the mass on a ^{99m}Tc-labeled red blood cell scan. Abdominal CT demonstrated a 10 × 10 × 14-cm mass with necrotic areas, involving most of the enlarged right hepatic lobe. Chest CT showed a 5 × 5 × 4-cm mass in the right anterior mediastinum at the level of the right hilum. Since lymphoma was considered in the differential diagnosis, ^{67}Ga scintigraphy was performed. Abnormal, increased, nonuniform activity of ^{67}Ga was seen in the region of the photopenic liver-spleen scan abnormality. Abnormal ^{67}Ga activity in the right mediastinum was also observed (Fig. 1B).

The patient underwent explorative laparotomy with excisional biopsy of the liver lesion, and high-grade lymphoma was diagnosed. Chemotherapy with cyclophosphamide, adriamycin, vincristine, prednisone and bleomycin was initiated and the patient was re-evaluated after three chemotherapeutic courses. A liver-spleen scan showed a decrease in liver size (liver span was 19 cm) and in the size of the photopenic abnormality (Fig. 1C). Gallium-67 whole-body scintigraphy was normal (Fig. 1D). After six chemotherapeutic courses, hepatomegaly was still present on physical examination. After nine chemotherapy courses, liver size was normal on physical examination. Liver scintigraphy showed further decrease in liver size (liver span = 16 cm) and in the size of the photopenic abnormality. CT showed a normal liver and a residual mediastinal mass. The patient has been free of disease 6 yr after completing chemotherapy.

DISCUSSION

Lymphoma of the liver can be primary or secondary to disease involvement of other sites. Primary lymphoma of the liver is often focal, presenting as a large, multilobulated mass, which is easily identified (*1–3*). Secondary involvement of the liver is most commonly diffusely infiltrating. Primary lymphoma of the liver is rare (only 54 cases have been reported) (*4,5*) and is confined to the liver at initial presentation. Liver involvement in Hodgkin's disease (HD) usually occurs as diffusely infiltrative involvement, or sometimes as miliary lesions. Discrete nodular lesions are uncommon. Initially there is involvement of the portal areas, progressing to small nodules. It is almost invariably associated with disease involving the spleen, and both are likely to be involved in the course of hematogenous spread (*6*). In autopsy studies, liver involvement has been detected in about 60% of patients with HD (*1,7*). Other investigators have found liver involvement in 23% of untreated HD patients at presentation (*6,8*). In non-Hodgkin's lymphoma (NHL), as in HD, the portal areas are also initially involved. Discrete nodular lesions in the liver occur in about half of the patients. The lymphocytic form in the liver tends to be miliary and the histiocytic type is nodular or tumoral (*9*). In autopsy series, liver involvement has been detected in more than half of the patients with NHL (*1,10*). In untreated NHL, liver involvement was found in 16% of patients at presentation (*11*).

Ultrasonographic diagnosis of liver involvement by lymphoma is based only on the presence of focal lesions. Hepatomegaly alone is not considered a positive finding (*12*). The focal hepatic lesions show relatively uniform,

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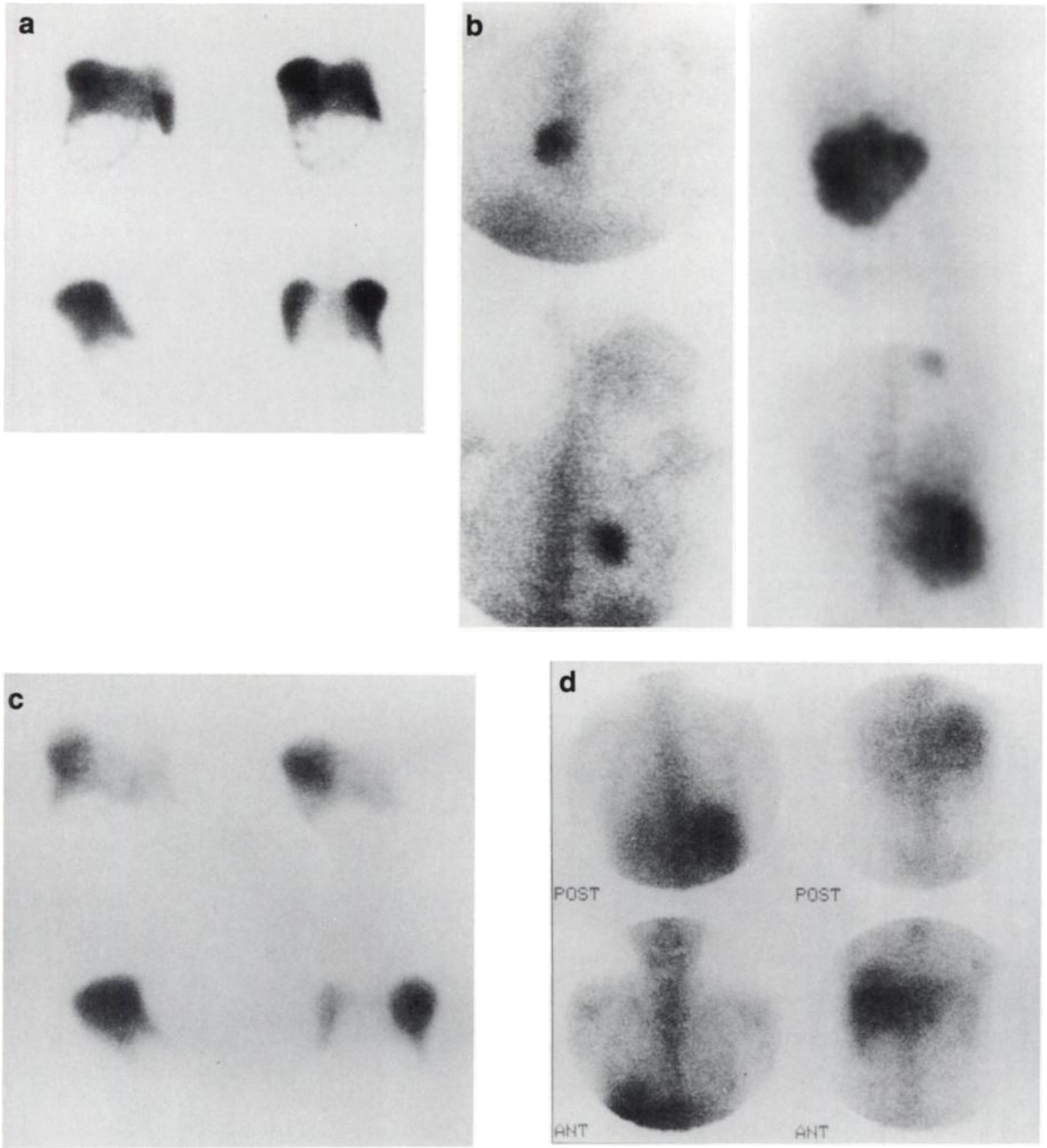

FIGURE 1. A 41-yr-old female with NHL with liver and mediastinal involvement. (a) Liver-spleen scintigraphy shows hepatomegaly with a large photopenic defect in the inferior aspect of the right liver lobe. (b) Anterior (top) and posterior (bottom) ^{67}Ga images of the mediastinum (left) and the abdomen (right) show abnormal increased activity in the inferior aspect of the right lobe of the liver and abnormal activity in the right mediastinum. (c) Liver-spleen scintigraphy after three chemotherapeutic courses shows a decrease in liver size and in the size of the photopenic abnormality and (d) ^{67}Ga scintigraphy is normal. The patient achieved complete response and has been free of disease for 6 yr after completing chemotherapy.

hypoechoic, irregularly marginated masses on sonography. In addition, echogenic foci surrounded by a hypoechoic rim ("target" lesions) or, rarely, extensive hypoechoic liver infiltrates ("geographical" infiltration) may be seen (*13*).

The CT appearance is not specific for hepatic lymphoma. The diffuse distribution throughout the hepatic parenchyma leads to hepatomegaly, which is nonspecific. Hepatomegaly was found in 46% of 1229 patients with NHL, but histological examination was positive in only 15% (*10,14*). On the other hand, lymphomatous infiltration can be present in a normal-sized liver (*7*). Nodular size is usually small, under 0.5 cm, and therefore beyond the resolution of CT (*15,16*). Zoronza et al. (*14*) reported that CT revealed definite hepatic involvement in 4% of lymphoma patients. These authors reported a sensitivity of 64% and specificity of 88% for CT in the detection of hepatic lymphoma. Sanders et al. (*16*) describe the CT

TABLE 1
Hepatic Imaging Findings in 14 Patients with Liver Involvement in Lymphoma

	Imaging at presentation			Imaging after treatment			
	CT	L-S	Ga-67	CT	L-S	Ga-67	Outcome
HD (n = 3)							
	Single mass (n = 1)	Photopenic defect (n = 1)	Focal increased uptake (n = 1)	Residual mass (n = 1)	Normal (n = 1)	Normal (n = 2)	CR (n = 2)
	Two masses (n = 1)	ND (n = 1)	Two foci of increased uptake (n = 1)	No change (n = 1)	ND (n = 1)	No change (n = 1)	NR (n = 1)
	Multiple masses (n = 1)	Multiple photopenic defects (n = 1)	Uniform uptake (n = 1)	Normal (n = 1)	Nonuniform uptake (n = 1)		
NHL (n = 11)							
	Single mass (n = 7)	Photopenic defect (n = 4)	Focal increased uptake (n = 5)	Residual mass (n = 3)	Decreased size of photopenic defect (n = 1)	Normal (n = 6)	CR (n = 6)
	Multiple masses (n = 2)	Multiple photopenic defects (n = 2)	Focal increased uptake, centrally photopenic (n = 1)	No change (n = 1)	ND (n = 10)	No change (n = 1)	NR (n = 1)
	Diffuse involvement (n = 2)	ND (n = 5)	Nonuniform uptake (n = 1)	Normal (n = 3)		ND (n = 4)	No follow-up (n = 2)†
			Uniform uptake (n = 3)*	ND (n = 4)			Died (n = 2)‡

L-S = Liver-spleen scintigraphy; CR = complete response; NR = no response.
*Uniform ^{67}Ga liver uptake was seen in one patient with a focal liver lesion and in two patients with diffuse liver involvement.
†Two patients were newly diagnosed and do not yet have followup studies performed.
‡Two patients died (one of lymphoma, one of coronary artery disease).

findings in six patients with primary lymphoma of the liver. All had solitary large liver masses which were hypodense compared with the normal liver parenchyma. Follow-up CT scans in four patients who achieved complete response showed continuous resolution of the mass, and two patients subsequently developed several low-density hepatic masses, indicating disease progression. Focal areas of lymphoma are seen as large, multilobular masses of decreased attenuation (*14*). Variable patterns, such as necrosis and calcifications, different patterns of enhancement after contrast media administration, as well as satellite masses may be seen on CT. The same CT characteristics can be seen in primary hepatocellular carcinoma, metabolic diseases and in many benign lesions, such as cavernous hemangioma, focal nodular hyperplasia and adenoma (*17*).

MRI parameters are not significantly different in normal liver and diffuse liver infiltration by lymphoma (*18,19*). Only focal lesions are detected by MRI (*20*). The signal intensity of lymphomatous masses—hypointense or isointense on T1-weighted images and hyperintense on T2-weighted images—is similar to that of hepatocellular carcinoma and these two tumors cannot be differentiated by current MRI techniques. Thus, MRI, despite its superior contrast resolution, is not better than CT for the evaluation of lymphoma involvement of the liver (*5,18–20*). Ultrasonography, CT and MRI are therefore unsatisfactory in the detection of liver involvement in lymphoma.

Nuclear medicine techniques also have not played a major role in the assessment of lymphoma involvement of the liver. Liver-spleen scans are somewhat less accurate compared to other imaging modalities in the diagnosis of liver lymphoma (*14,21*). In 65 lymphoma patients (7 with lymphoma involvement of the liver and 58 with no disease involvement), five of seven cases were identified by liver-spleen colloid scintigraphy (sensitivity = 71%) and there were 11 false-positive liver-spleen colloid scans (specificity = 81%) (*14*).

Since ^{67}Ga scintigraphy has an important role in monitoring response to treatment and in early detection of recurrent lymphoma (*22,23*), it's role in the evaluation of liver lymphoma should now be reassessed. Gallium-67 is taken up both by lymphoma tissue and by the normal liver tissue and therefore may not be useful in certain lymphoma patients. Gallium-67 uptake in a photopenic liver-spleen scan lesion showing higher uptake than that of the normal liver has been described in liver abscesses, amebic or pyogenic (*24,25*), in hepatoma (*26–30*), malignant melanoma (*29*), or rarely in actinomycosis, hepatic angiosarcoma (*31*), hepatic adenoma (*32*) and lymphoma (*14*). The diagnosis should be made by liver biopsy. In the case presented here, involvement of both the liver and the upper mediastinum was suggestive of lymphoma and was confirmed by a liver biopsy.

Between 1985 and 1993, 14 patients at our center had lymphoma involvement of the liver at presentation (8 patients) or at recurrence (6 patients). There were 12 females and two males, aged 17–87 yr. Three patients had HD and 11 had NHL. Diagnosis was made by liver biopsy (5 patients) or

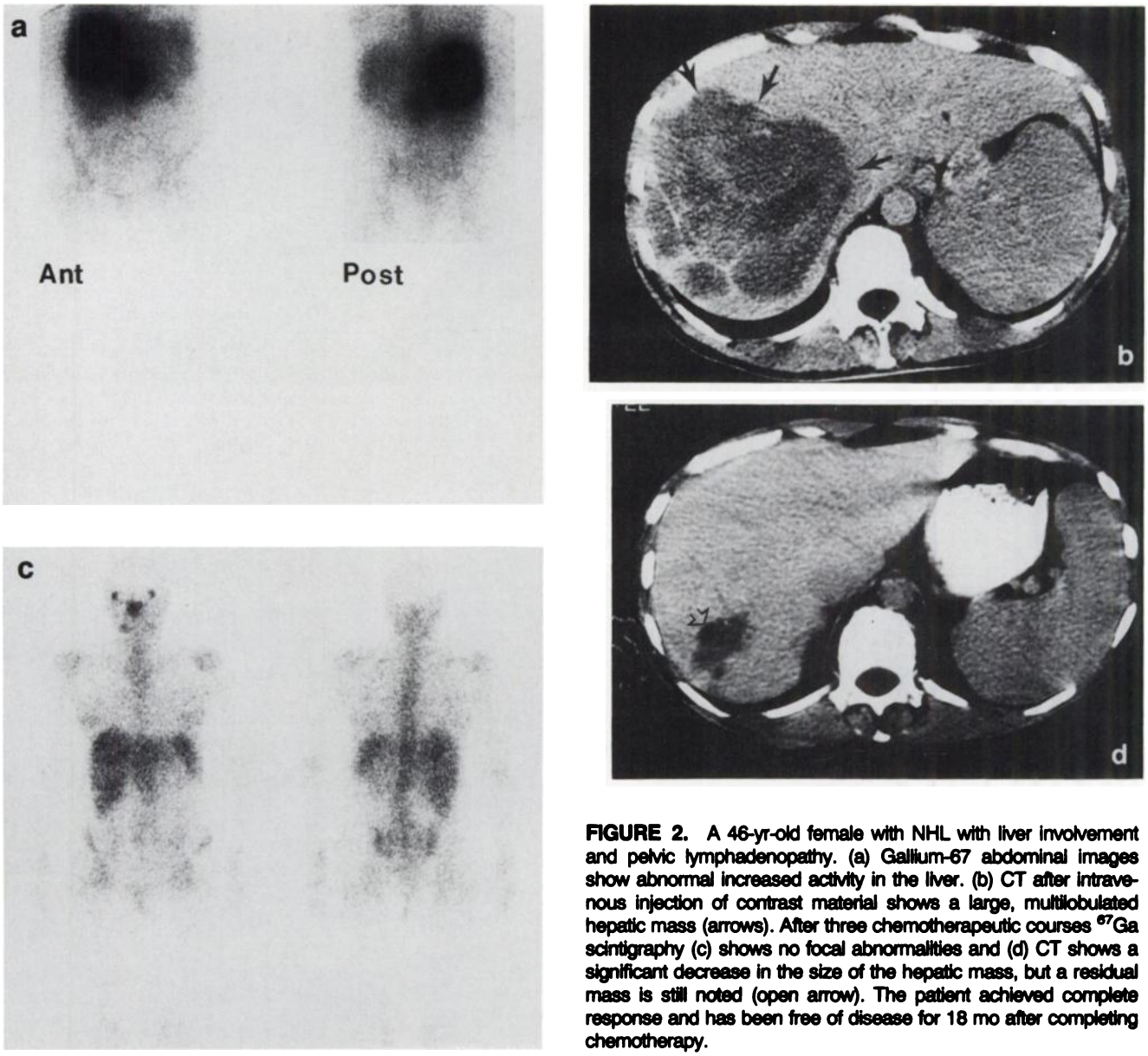

FIGURE 2. A 46-yr-old female with NHL with liver involvement and pelvic lymphadenopathy. (a) Gallium-67 abdominal images show abnormal increased activity in the liver. (b) CT after intravenous injection of contrast material shows a large, multilobulated hepatic mass (arrows). After three chemotherapeutic courses ^{67}Ga scintigraphy (c) shows no focal abnormalities and (d) CT shows a significant decrease in the size of the hepatic mass, but a residual mass is still noted (open arrow). The patient achieved complete response and has been free of disease for 18 mo after completing chemotherapy.

by clinical and radiological evidence of liver involvement (9 patients). Liver-spleen scintigraphy was performed in eight patients and ^{67}Ga scintigraphy and CT were performed in all 14 patients. The findings on the imaging studies are summarized in Table 1. Of the HD patients, one patient had a solitary liver mass and two had multiple liver lesions in addition to involvement of other sites. Of the NHL patients, seven had single liver lesions, two had multiple liver lesions and two had diffuse liver disease. One NHL patient with a solitary finding and another patient with multiple liver lesions had primary lymphoma of the liver. Eight patients (two with HD, six with NHL) with single or multiple liver lesions had photopenic defects on liver-spleen scintigraphy. Gallium-67 scintigraphy showed focal increased activity in nine patients (2 with HD, 7 with NHL), nonuniform liver uptake of gallium in one patient with HD and uptake similar to that of normal liver in four patients. Of these, one patient with NHL had a focal lesion on CT and liver-spleen scan; one patient with HD and another with NHL had multiple focal abnormalities on CT and liver-spleen scintigraphy, and one patient with NHL had diffuse liver involvement on CT and no liver-spleen scan was obtained.

Follow-up CT and ^{67}Ga scintigraphy was performed in 10 patients. Of the remaining four patients, two were newly diagnosed and did not yet have follow-up studies, one patient died of the lymphoma before follow-up and another died of ischemic heart disease. Gallium-67 scintigraphy correctly diagnosed response to treatment in six patients (2 with HD, 4 with NHL) with focal disease. Of these, four patients had normal follow-up ^{67}Ga scintigraphy and achieved complete remission (Fig. 2); two patients had unchanged findings on ^{67}Ga scintigraphy and died with active disease. Gallium-67 scintigraphy was not useful in evaluating response to treatment of liver involvement in

four patients who did not have focal abnormalities of increased ^{67}Ga uptake prior to therapy, in two patients with multiple small liver lesions, in one patient with diffuse liver involvement and in another patient with a single liver lesion. In these patients ^{67}Ga uptake was similar to the surrounding normal liver tissue and therefore was not useful in the assessment of response to treatment of the liver involvement. In these ten patients, CT correctly diagnosed response to treatment in five patients with focal disease (three with single and two with multiple liver lesions) and in one patient with diffuse liver involvement. CT showed a residual liver mass in three patients with focal disease who did achieve a complete response. In two of these patients, ^{67}Ga scintigraphy became normal after treatment (Fig. 2) and in one patient ^{67}Ga activity in a photopenic liver-spleen lesion was the same as in the normal liver. CT showed residual disease in other sites in four of the ten patients. Two of them also had abnormalities on ^{67}Ga scintigraphy and did not achieve complete response. The other two patients did achieve complete response and had normal ^{67}Ga scans.

CONCLUSION

Our series demonstrated photopenic defects on colloid liver-spleen scintigraphy in all patients in whom it was performed. Increased ^{67}Ga uptake in focal liver lesions was present in nine of the 14 cases (64%). After treatment, both CT and ^{67}Ga scintigraphy were useful to monitor response to treatment in six of the ten patients (60%). They, however, did not correctly diagnose the same patients. In two patients, ^{67}Ga scintigraphy was correct in diagnosing therapy response, while CT still showed a lesion and the patients had achieved complete response. In three patients with normal ^{67}Ga uptake in the liver lesion compared to the surrounding normal liver, ^{67}Ga scintigraphy could not be used and CT was better able to evaluate response to therapy. Since ^{67}Ga scintigraphy and CT correctly diagnosed different patients, they probably have a complimentary role in liver lymphoma. In cases of large focal liver lesions, a residual mass on CT does not necessarily indicate residual disease. In these cases, ^{67}Ga scintigraphy can more accurately predict the clinical outcome. Gallium-67 whole-body scintigraphy can also be helpful in monitoring response to therapy in other involved sites. As in lymphoma involvement in other sites, ^{67}Ga scintigraphy should be used to monitor response after treatment only when there is clearly evidence of abnormally increased uptake prior to therapy. In patients with ^{67}Ga uptake similar to that of the normal liver, CT may be a better indicator of tumor response.

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