

Multiple Hepatic Lesions During Acute Leukemia Remissions

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ABSTRACT

The US and CT manifestations of multiple small hepatic lesions of 15 patients during their remissions following chemotherapy for acute leukemia were reviewed. Liver biopsies established the diagnoses in 5 of the 15 patients. Despite their remissions, two cases had leukemic involvement. Others had microabscesses, 2 due to candida and 1 due to peptostreptococcus.

Ultrasonographically, the microabscesses and leukemic involvement in the liver consisted of multiple round hypoechoic and target-like masses. With CT, these appeared as multiple zones of diminished attenuation. Only distal acoustic enhancement with US could differentiate these disease processes.

Intensive chemotherapy improved the prognoses of acute leukemia patients, but the incidence of secondary fungal infection and tumor-forming leukemias has been increasing^{9,15,18}. The mortality of acute leukemia patients with fungal infections is about 70% within one year, posing a serious problem⁷. Since the advent of ultrasound (US) and computed tomography (CT) as diagnostic tools, fungal infections of the liver have been reported^{1-3,6,16}.

Recently we encountered patients with multiple small hepatic lesions after chemotherapy for acute leukemia. In spite of their remissions, there was subsequent leukemic involvement, and differentiating leukemic involvement from microabscesses was difficult. This report describes our experiences with microabscesses and leukemic involvement of the liver.

SUBJECT AND METHODS

From March 1982 to September 1984 at Hiroshima University Hospital, 15 patients with acute leukemia (ALL:6, ANLL:9) who were

evaluated by US and CT had multiple small hepatic lesions. Results of their diagnostic studies are reviewed here. These patients complained of continuous fever and, except for case 5, hypochondralgia. Usually their fevers resolved when the patients recovered from bone marrow suppression following first and second induction chemotherapy and maintenance chemotherapy. Diagnoses were established for 8 patients by ultrasound-guided liver biopsies. Hematologically, all eight patients were in complete remission when the liver biopsies were performed. There were no blast cells in the peripheral blood, and less than 5% in the bone marrow.

The ultrasonograms were reviewed with special attention to the size, shape, echogenicity, distal acoustic enhancement, halo and echogenic walls of the lesions^{4,17}. The CT findings were reviewed with attention to the appearance of margins, alterations of margins with contrast enhancement, and alterations of lesions following chemotherapy¹⁹. US was performed using a 3.5MHz transducer with a real-time scanner

(Aloka, SSD 250), and CT was performed with slices at 1cm intervals and 9.6 sec. scan times, using a GE CT/T 8800 scanner with and without intravenous contrast medium.

RESULTS

By US, the hepatic lesions of the 15 patients appeared as multiple round or ovoid hypoechoic masses with target appearances and ranged from 0.5cm to 2.5cm in diameter. Target lesions less than 1cm in diameter included parallel-line or lobulated echodense appearances (Fig. 3). The echogenicity of larger lesions with target appearances varied and included isoechoic, low echoic or hyperechoic centers (Fig. 1). Hypoechoic centers were most frequent, followed by isoechoic and hyperechoic centers. There seemed to be no definite correlations between these target appearances and onsets, these target-like appearances coexisted in the same patient, but the margins of the targets were irregular in the early stages. Distal acoustic enhancement was seen in 4 cases. Echogenic walls were observed about 3 weeks after onset in 6 cases, and peripheral halos with echogenic walls were observed in 5 cases about 3 weeks after onset.

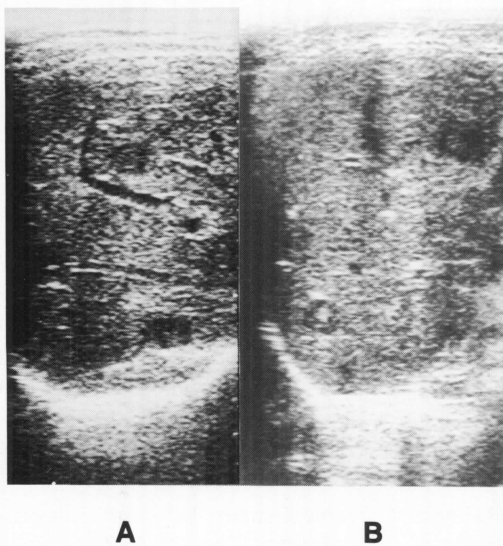


Fig. 1. Target appearance with US.
A. Multiple target-like lesions larger than 1cm with hypoechoic centers are shown.
B. A hyperechoic center was seen near the diaphragm.

The CT patterns of multiple hepatic lesions were classified as low attenuation, with target appearances, and low attenuation with intermediate zones (Fig. 2). With contrast enhancement, the lesions did not change and were unenhanced, or their patterns were changed or disappeared, had well defined margins with or without decreasing size, or disappearance of intermediate zones. Most of these changing patterns coexisted with hypergenic rims after contrast enhancement. Hyperdense rims with contrast enhancement were seen in 7 cases 4 days after onset in the earliest case. These hepatic lesions were more readily detected with plain CT than with contrast enhancement. But CT did not visualize lesions in one case which with US appeared as hypoechoic and had a target-like appearance. A lesion with a target-like appearance by US appeared as a target or as an intermediate zone with CT (Fig. 3).

Liver biopsies were examined in eight cases (11 times) to establish the diagnoses, but the diagnoses of only five cases were confirmed. Two had leukemic involvement; others had microabscesses, 2 due to candida, and 1 due to peptostreptococcus (Table 1,2,3). Differentiating leukemic involvement from microabscesses due to fungus or bacteria was difficult. Only distal acoustic enhancement with US differentiated the abscesses from leukemic involvement.



Fig. 2. CT manifestations of hepatic lesions in acute leukemia.
Plain CT shows a target-like appearance and a transitional zone with intermediate attenuation.

Table 1. The US findings in eight patients with multiple hepatic lesions during acute leukemia remission

Case	Age	Sex	Diagnosis	days after onset	size (cm)	shape	echogenicity	distal acoustic enhancement	halo	echogenic wall
1.	21	M	ALL	20	.5-1	round	hypo target	+	-	-
				14 (95)	.8-1.5	irregular round	target	+	+	+
2.	23	F	ALL	40	.8-2	oval	hypo target	+	+	+
3.	42	M	ALL	40	1-1.5	irregular round	hypo	-	-	-
				7	1-2	round	hypo target	+	-	-
4.	57	M	ALL	10	1-1.5	irregular	hypo	-	-	-
				70	1	irregular	target	-	+	+
5.	35	M	AML	?	1-2.5	irregular	hypo target	-	+	-
6.	19	F	AML	30	.7	oval	target	-	-	-
7.	59	M	AML	3	.5-.8	irregular	target	-	-	-
8.	42	F	AML	20	.5-1.5	round	target	biopsy(+)		
								-	+	+

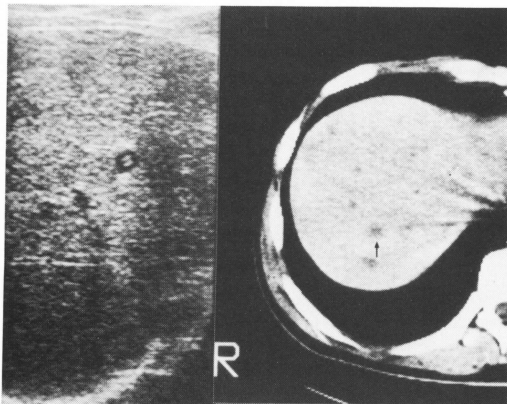


Fig. 3. A target-like appearance with US, that shows a transitional zone with intermediate attenuation.

A central echo-dense structure gives a parallel-line appearance measuring less than 1cm in diameter.

With serial US and CT examinations, decreases in the numbers and definition of the margins of the lesions were noted with effective therapy, but increases in the numbers, sizes and ill-defined margins during treatment indicated

progression of lesions. The distribution of the lesions was not fixed, but the more frequent sites were under the dome of the diaphragm and these lesions showed resistance to treatment and were of prolonged duration.

Ancillary findings included three cases with associated pleural effusions and five with associated pulmonary consolidations. Splenic lesions resembling the hepatic ones were observed in 10 cases (Fig. 4). Three had associated CNS involvement.

CASE REPORTS

Case 1: This 20-year-old man was admitted for relapse of his ALL (FAB grade L2). There were 95% blast cells in his bone marrow. During induction chemotherapy, temperature elevations appeared. Pulmonary aspergillosis was suspected by chest radiography (Fig. 5A). He was treated with an antimycotic drug, but his fever continued and he developed right side abdominal pain. US disclosed multiple, small (0.5-1cm diameter) hypochoic lesions in the liver with distal acoustic enhancement and target lesions (Fig. 5B). CT showed multiple low attenuation

Table 2. The CT manifestations and ancillary findings

Case	days after onset	pattern		hypergenic rim	detectability		ancillary findings
		plain-CT	CE-CT		plain-CT	CE-CT	
1.	36	target	target	—	+	+	Aspergillosis, pl. effusion spleen
	31 (114)	low	well defined margin	+	+	++	same above
2.	35	target			+		CNS involvement pl. effusion, spleen
3.	30	target, low	disappeared	—	++	+	pulm. consolidation, spleen
	10	intermediate	disappear of intermediate zone	—	++	+	spleen kidney
4.	6		target	—		+	spleen
	40	target		—	+		Aspergillosis, spleen
5.	?	intermediate	well defined margin	+	+	+	spleen
6.	30	target	well defined margin	+	++	+	
7.	4	low intermediate	well defined margin intermediate	+	++	+	
8.	20	intermediate target	intermediate target	—	++	+	spleen, gall bladder ascites

Table 3. The causative organism and outcome in eight patients

Biopsy				
Case	days after onset	causative organism	duration of antifungal Tx.	Outcome
1.	72 30 (97)	Peptostreptococcus negative	after onset +	death after 4 mos. relapse.
2.	40	Candida tropicalis	—	death after 2 mos relapse
3.	43 18	unknown s/o abscess	after onset —	death after 2 mos relapse.
4.	24 70	unknown Mbl	— 2W	recovered
5.	?	Mbl	—	recovered
6.	37	unknown	12d	recovered
7.	10	Candida	4d	recovered
8.	21	unknown	after onset	recovered

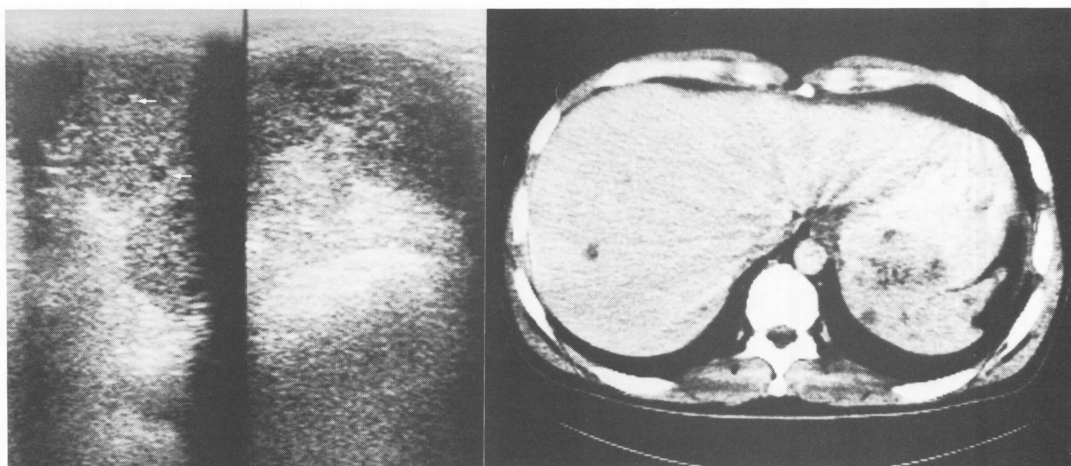


Fig. 4. Multiple small target-like lesions in the spleen. The same case as Fig. 3. The causative organism was not established.

lesions with target appearances in the liver. These appeared to decrease in size with contrast enhancement (Fig. 5C). Under the guidance of real-time ultrasonography, two such lesions were biopsied by aspiration, and cultures of the aspirate revealed peptostreptococcus. Antibiotics intravenously resulted in decreases in numbers of lesions. However he died of a relapse of ALL within 4 months.

Case 4: This 57-year-old man was admitted for relapse of his AML (FAB grade M2). A complete remission was accomplished in 1 month by treatment with induction and maintenance chemotherapy, including B-DOMP. Fever and liver function abnormalities reappeared. CT revealed numerous small hepatic lesions in the liver (Fig. 6A). Aspiration biopsy was performed, but the culture was negative. Six months later, after consolidation chemotherapy, fever and general malaise appeared. US and CT were performed (Fig. 6B,C). Blast cells were shown in the aspirate (Fig. 6D). Reinduction chemotherapy was administered, but the hepatic lesions retained their target appearances.

Case 5: This 35-year-old man was admitted for petechiae and purpura. A diagnosis of AML (FAB grade M2) was made. He underwent successful induction chemotherapy with B-DOMP.

Six months later, he was readmitted for consolidation chemotherapy when multiple filling defects were observed by hepatic scintigraphy (Fig. 7). To rule out neoplastic disease, CT, US and celiac angiography were performed. Blast cells were demonstrated in the aspirate.

Case 7: This 59-year-old man was admitted for relapse of his AML (FAB grade M5). After reinduction chemotherapy, fever appeared. His clinical course after admission is shown in Fig. 8A. Cultures confirmed candida (Fig. 8B).

DISCUSSION

Fungal infections in acute leukemia have been increasing as a result of altered host resistance secondary to multiple chemotherapeutic agents¹². Fungal abscesses in the liver and spleen are not unusual, but they may be obscured by the primary disorder and other concomitant infections, so the antemortem diagnosis of fungal infection is rare and carries a high mortality^{5,20}.

Ultrasonographically, intrahepatic abscesses have indistinct or sharp echogenic walls with peripheral halos inside or adjacent to the echogenic wall, related to the age of the abscess^{8,13,17}. With lowered resistance to infection in immunocompromised patients, there may be no capsule formation and the lesions may

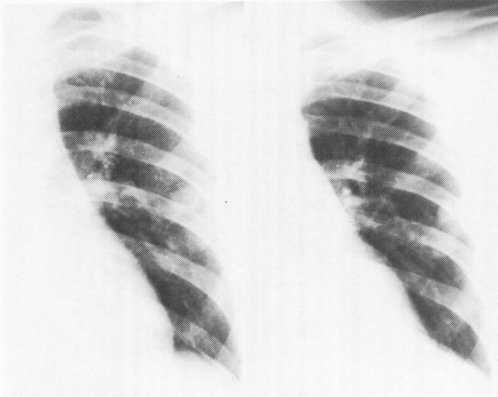
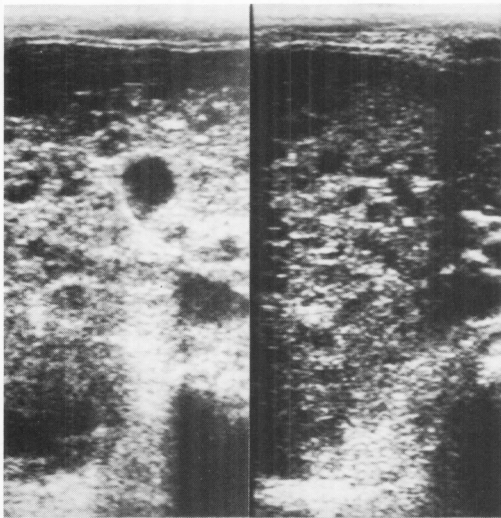
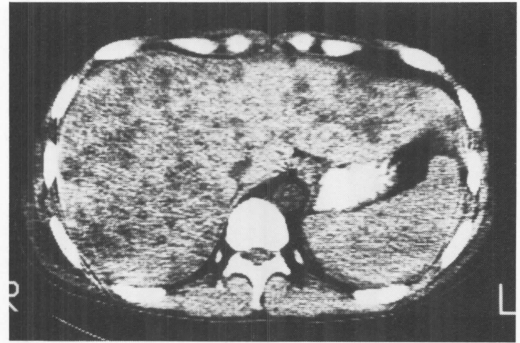


Fig. 5. Case 1, male, 20 years of age with ALL. A. Posteroanterior chest radiograph demonstrates pulmonary aspergillosis in the mid lung field. Treatment with an antimycotic drug transformed the consolidation into a characteristic fungus mass with a cavity.

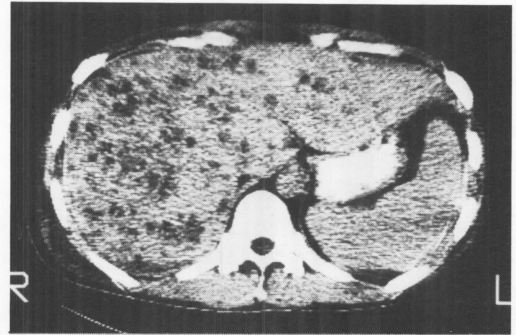


C. With US numerous hypoechoic and target-like lesions with distal acoustic enhancement were demonstrated.

A strain of peptostreptococcus, rather than candida, was cultured from biopsy material.



plain CT



enhanced CT

B. Plain CT shows multiple low density lesions in the liver and spleen with target-like appearances. With contrast enhancement, these lesions were definitely imaged, and they decreased in size.

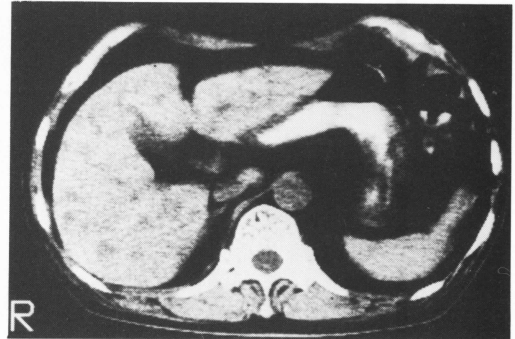
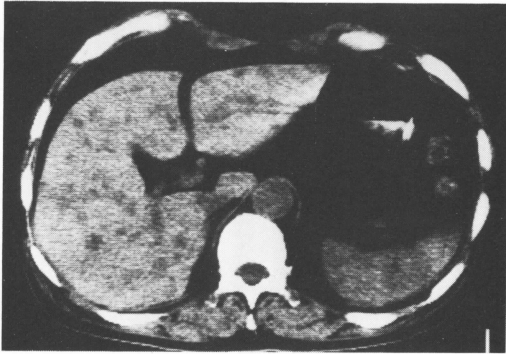
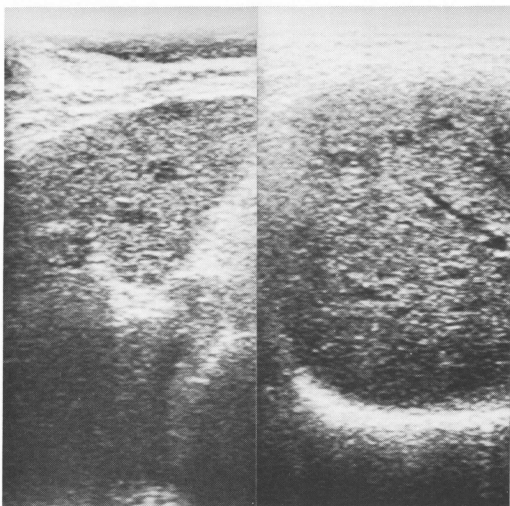
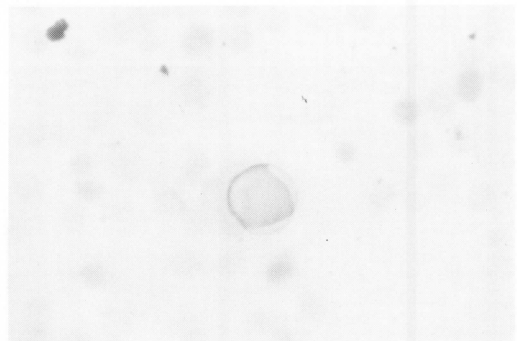


Fig. 6. Case 4, A 57 year-old-man with AML.
A. Initial unenhanced CT demonstrates multiple lesions in the liver and spleen.

B. Unenhanced scan 6 months later shows multiple focal lesions. The patient had fever and general malaise.



C. US shows target-like and low echoic lesions.



D. MG stain ($\times 1000$) with US guided liver biopsy shows blast cell.

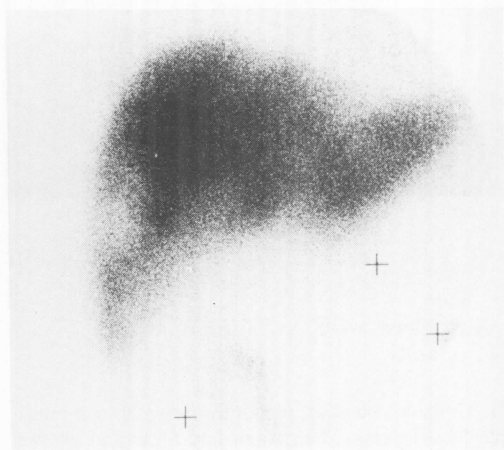
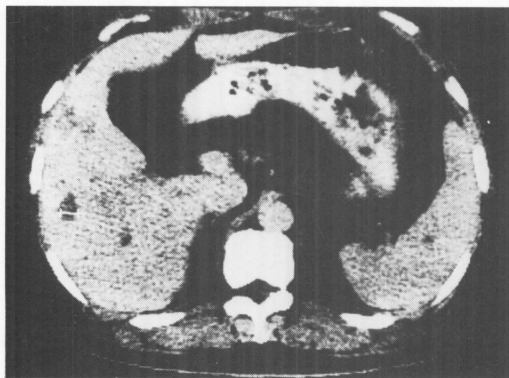


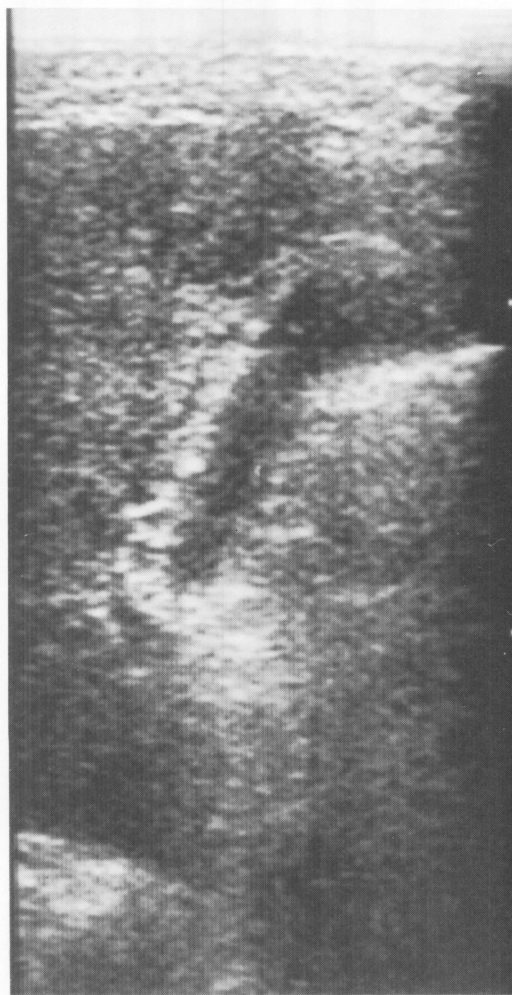
Fig. 7. Case 5, 35 year-old-man with AML.
 A. A liver and spleen scan using ^{99m}Tc -sulphur colloid shows multiple defects in the liver.



C. Enhanced CT demonstrates irregular hepatic lesions with hypergenic rims near the gall bladder. Low attenuation masses are seen in the liver and spleen.



B. Angiography with a common hepatic injection shows an avascular mass within a heterogeneous stain in the right anterior segment.



D. The liver margin bulges with an isoechoic mass near the gall bladder.

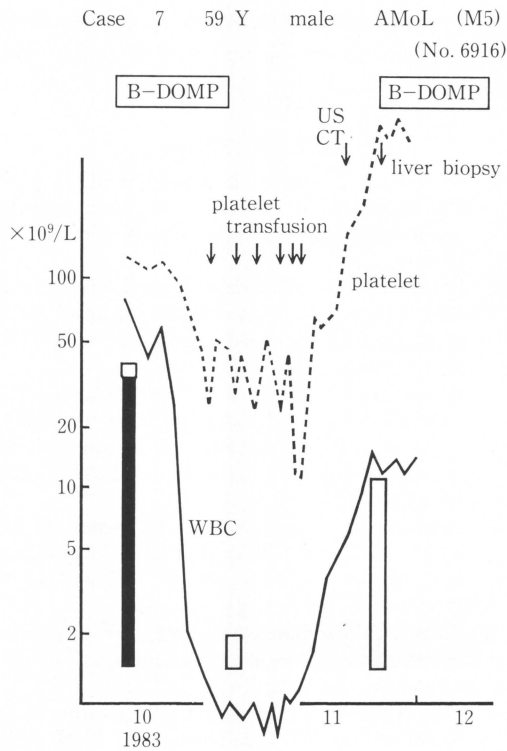
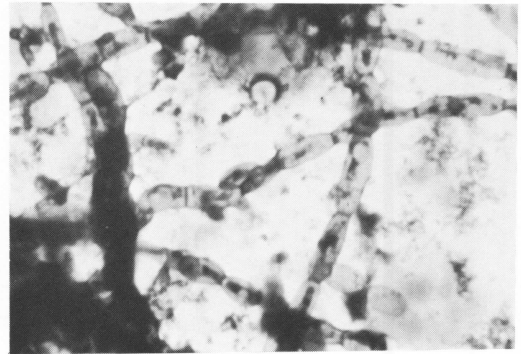


Fig. 8. Case 7, A 59 year-old-man with AML. A. His clinical course during his admission is shown.

contain little debris²). In our cases, the microabscesses also had echogenic walls and hypergenic rims with contrast CT. Changing patterns with contrast enhancement suggest the presence of an abscess wall¹⁹. Although not histologically confirmed, these were thought due to delays in repair so there may have been abscess walls. In fungal abscesses, a so-called bulls-eye target lesion and a round or oval anechoic mass have been described^{2,3}, but none of the liver microabscesses observed in this study had anechoic lesions. Echoic centers were located concentrically or eccentrically and these are reported to represent growing fungi¹¹. In our experience, these can also represent other organic infections and leukemic involvement. The target appearance was rather nonspecific. Variable sonographic appearances are entirely dependent on the morphology of a lesion^{10,17}. In abscesses, the target appearance is a manifestation of a phase of early abscess formation. Sur-



B. Candida. Wright stain.

rounding the echoic center, there is a peripheral halo which was reported in the early stage of abscess formation and the pattern of the center was changing with diminished amplitude of echoes⁴.

But there were no definite correlations between these target appearances and onsets of lesions, because onset could not clearly be determined, and they may actually be recurrent infections in the liver. Serial US or CT examinations proved useful in demonstrating responses to therapy^{1,5,10,14}. Decreases in numbers of lesions and increases in attenuation levels occurred with the eradication of lesions (Fig. 9). Leukemic involvement or tumor formations in leukemia of the liver are seen with hematological evidence of remission. But reports of abdominal lesions in leukemia are few, due to difficulties in diagnosing these lesions⁵. During hematologically active disease, enlargement or reduction in organ size and/or alteration of tissue texture according to US during chemotherapy have been reported⁵. Our cases showed multiple liver and spleen abnormalities. Case 5 resembled metastasis and case 4 resembled a fungal infection which may have been superimposed on leukemic involvement.

CNS involvement was observed in three cases, and 1 of 3 patients with CNS involvement who died from a tumor form of leukemia. However, liver biopsy was not performed, so an antemortem diagnosis of fungal infection or leukemic involvement was not established. Candida and streptococcus were found in the sputum, urine and by stool cultures at the time CT and US were performed 3.5 months antemortem. US

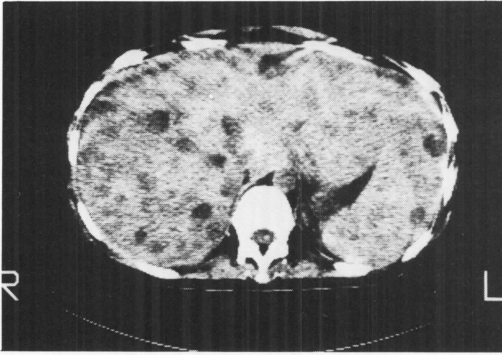
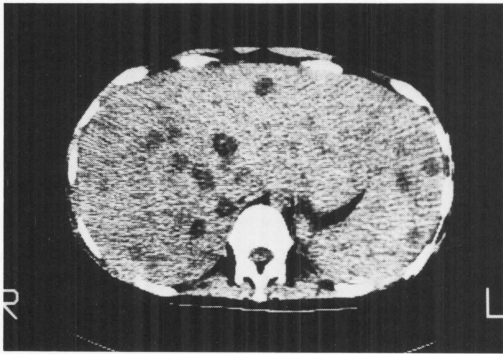


Fig. 9. Case 2, A 23-year-old woman with ALL. A. Initial unenhanced CT demonstrates multiple lesions with decreased attenuation in the liver and spleen.



B. Unenhanced CT after 1 month of antifungal therapy. Lesions in the liver and spleen have decreased in number.

was useful in evaluating the hepatic lesions of immunosuppressed patients, but information provided by CT was valuable for evaluating splenic lesions and other ancillary findings. US-guided liver biopsies are mandatory when the patients' clinical conditions permit, and biopsies must be performed before, or as early as possible after, prescribing antimycotic and antibiotics agents.

In conclusion, microabscesses became evident both after patients recovered from neutropenia and were in remission, and leukemic involvement was also in remission. Ultrasonographically, both lesions appeared target-like or were hypoechoic structures measuring 0.5-2.5cm in diameter in the liver and spleen. Distal acoustic enhancement

is a reliable indicator seen only in microabscesses. Verification of bacteriologic or neoplastic etiology can be established by US-guided liver biopsy.

REFERENCES

1. Berlow, M.E., Spirt, B.A. and Weil, L. 1984. CT follow-up of hepatic and splenic fungal microabscesses. *J. Comp. Assist. Tomogr.* 8: 42-45.
2. Bondestam, S., Jansson, S.E. and Kivisaari, L. 1981. Liver and spleen candidiasis: imaging and verification by fine-needle aspiration biopsy. *Br. Med. J.* 282: 1514-1515.
3. Callen, P.W., Filly, R.A. and Marcus, F.S. 1980. Ultrasonography and computed tomography in the evaluation of hepatic microabscesses in the immunosuppressed patient. *Radiology* 136: 433-434.
4. Dewbury, K.C., Joseph, A.E.A., Sadler, M. and Birch, S.J. 1980. Ultrasound in the diagnosis of the early liver abscess. *British J. Radiology* 53: 1160-1165.
5. Gore, R.M. and Shkolnic, A. 1982. Abdominal manifestations of pediatric leukemias; sonographic assesment. *Radiology* 143: 207-210.
6. Halvorsen, R.A., Korobkin, M., Foster, W.L., Silverman, P.M. and Thompson, W.M. 1984. The variable CT appearance of hepatic abscesses. *AJR.* 142: 941-946.
7. Kawashima, K., Ueda, R., Takeyama, H. et al 1977. Fungal infection in leukemic patients at autopsy. *Rinshoketsueki* 18: 1128-1136.
8. Kuligowska, E., Connors, S.K. and Shapiro, J.H. 1982. Liver abscess: sonography in diagnosis and treatment. *AJR.* 138: 253-257.
9. Kurita, S. 1982. Tumor forming leukemia *Rinshoketsueki* 23: 433-440.
10. Kurtz, A.B., Dubbins, P.A., Rubin, C.S. et al 1981. Echogenicity: analysis, significance, and masking. *AJR.* 137: 471-476.
11. Laurin, S. and Kaude, J.V. 1984. Diagnosis of liver-spleen abscesses in children with emphasis on ultrasound for the initial and follow-up examinations. *Pediatr. Radiol.* 14: 198-204.
12. Miller, J.H., Greenfield, L.D. and Wald, B.R. 1982. Candidiasis of the liver and spleen in childhood. *Radiology* 142: 375-380.
13. Mirsky, H.S. and Cuttner, J. 1972. Fungal infection in acute leukemia. *Cancer* 30: 348-352.
14. Rubinson, H.A., Isikoff, M.B. and Hill, M.C. 1980. Diagnostic imaging of hepatic abscesses: a retrospective analysis. *AJR.* 135: 735-740.
15. Scheible, W., Gosink, B.B. and Leopold, G.R. 1977. Gray scale echographic patterns of hepatic metastatic disease. *AJR.* 129: 938-987.
16. Singer, C., Kaplan, M.H. and Armstrong, D. 1977. Bacteremia and fungemia complicating neoplastic disease. *Ame. J. Med.* 62: 731-742.

17. **Sty, J.R. and Starshak, R.J.** 1983. Comparative imaging in the evaluation of hepatic abscesses in immunocompromised children. *J. Clin. Ultrasound* **11**: 11-15.
18. **Subramanyam, B.R., Balthazar, E.J., Raghavendra, B.N., Horii, S.C., Hilton, S. and Naidich, D.P.** 1983. Ultrasound analysis of solid-appearing abscesses. *Radiology* **146**: 487-491.
19. **Suzuki, H., Harada, K., Higashi, F., Fujimori, I. and Fukuda, J.** 1979. Detection of liver microabscess due to candida albicans by liver biopsy in a patient with leukemia during complete remission. *Kansenshogaku Zasshi* **53**: 23-28.
20. **Terrier, F., Becker, C.D. and Triller, J.K.** 1983. Morphologic aspects of hepatic abscesses at computed tomography and ultrasound. *Acta Radiologica Diagnosis* **24**: 129-137.
21. **Wald, B.R., Ortega, J.A. Ross, L. et al.** 1981. Candidal splenic abscesses complicating acute leukemia of childhood treated by splenectomy. *Pediatrics* **67**: 296-299.