Incidental Finding of a Hepatic Lesion: Differential Diagnostic Problems for Fibrolamellar Hepatic Carcinoma

Peter Reuland, Klaus Peter Aicher, Hans-Jürgen Brambs, Gerd Enderle, Ulrich Feine, Hermine-Valerie Gärtner and Paul Weber

Weyer Institute for Nuclear Medicine Diagnostic, Freiburg; and Department of Radiology, Institute for Pathology, Department for Nuclear Medicine, Medical Clinic, University of Tübingen, Germany

We report the case of a 39-yr-old female with a liver lesion that was incidentally detected by ultrasound. Examination of biopsy specimens revealed focal nodular hyperplasia. A metastatic tumor in the right os ileum developed in the following weeks and showed specific uptake of ^{99m}Tc-hepatic 2,6-dimethyliminodiacetic acid (HIDA), suggesting metastasis from a differentiated hepatocellular carcinoma. The final pathologic diagnosis was multifocal, solid and glandular hepatocellular carcinoma, partly differentiated as fibrolamellar carcinoma, and an osseous metastasis from the differentiated hepatocellular carcinoma.

Key Words: hepatocellular carcinoma; technetium-99m-HIDA; bone metastases

J Nucl Med 1994; 35:1342–1346

The diagnostic tests for liver lesions detected by ultrasound include CT and scintigraphy using hepatobiliary agents, as well as ultrasound- or CT-guided biopsy and histologic assessment. The case presented here is especially interesting because histologic evaluation of the primary tumor in the liver revealed focal nodular hyperplasia, but the imaging characteristics (dynamic CT and scintigraphy with ^{99m}Tc–HIDA were not typical for focal nodular hyperplasia. However, specific hepatobiliary tracer uptake in osseous and lymph node metastases provided indirect proof of malignancy of the liver lesion (fibrolamellar hepatocellular carcinoma).

CASE REPORT

Patient History

A 39-yr-old female underwent routine diagnostic procedures before becoming a bone marrow donor. Sonography revealed a liver lesion, which led to further diagnostic procedures including a CT-guided biopsy. The histologic diagnosis at that time was focal nodular hyperplasia (Fig. 1). After bone marrow aspiration at the left sacroiliac joint, she had persistent pain in the sacroiliac region for which she was evaluated scintigraphically.

METHODS

With a dual-head camera (body scan, Siemens, Erlangen, Germany), bone scintigraphy was performed 3 hr after injection of 740 MBq of ^{99m}Tc-dicarboxydiphosphonate (DPD). The total count for the anterior and posterior views was 1,560,000 in 10 min.

Liver scintigraphy was performed with 250 MBq of ^{99m}Tc-HIDA. For dynamic perfusion studies (15 sec/frame), imaging was started at the time of injection. Delayed images (2000 counts/cm^2 = 218 sec/frame) in the anterior view were made 15 min, 30 min and 45 min after injection, with the patient in a supine position using a large field-of-view camera (Dyna Digit, Picker Int., Munich).

RESULTS

Bone scintigraphy showed mildly focal increased tracer uptake in the right iliac spine. The site of bone marrow aspiration in the left sacroiliac joint, however, demonstrated no increased turnover rate, thus ruling out a sequela of the aspiration procedure as a cause of the increased uptake. Conventional radiographs revealed no abnormality at that time.

Laboratory studies showed an increased sedimentation rate and leukocytosis. However, the liver parameters including the alpha-fetoprotein level were in the normal range. The focal lesion in the pelvis was suspected to be a metastasis of an unknown primary tumor.

Bone scintigraphy was performed again 12 days later as the search for other sites of metastases demonstrated an increase in lesion size and in activity in the right ilium (Fig. 2). No further bone lesions were detected.

CT demonstrated a lytic lesion with an aggressive appearance in the right iliac spine (Fig. 3) and progression of the liver lesion with inhomogeneous enhancement, indicating malignancy. The hypothesis of an osseous metastasis from a liver carcinoma was raised. To confirm this, a scintigraphic study was conducted using ^{99m}Tc-HIDA.

In the perfusion series of the ^{99m}Tc-HIDA examination, the caudal part of the right liver lobe showed the same kinetic behavior as the bone lesion in the right iliac bone

Received Oct. 28, 1993; revision accepted Apr. 28, 1994.
For correspondence or reprints contact: PD Dr. Peter Reuland, Weyer Institut für Nuklearmedizin, Schwabentorplatz 6, 79098 Freiburg, Germany.

FIGURE 1. Broad, partly hyalinized bundles of collagen and proliferation of bile ducts without the typical acinous structure. Hepatocytes show a pseudolobular pattern (H&E). Diagnosis: focal nodular hyperplasia.

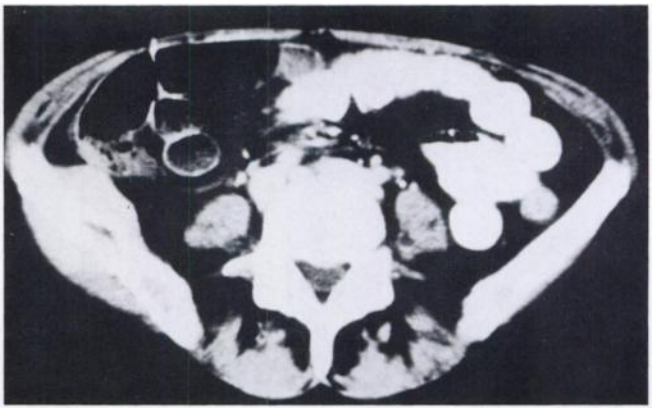

FIGURE 3. CT of the pelvis showing a destructive lesion in the right iliac bone. Note the pronounced enhancement after contrast administration.

(Fig. 4A). Static planar scintigrams revealed tracer uptake in a parailiac lymph node near the aortic bifurcation and in another pelvic lymph node (Fig. 4B). The center of the primary tumor showed no specific tracer uptake (cold lesion) but the surrounding liver tissue showed very inhomogeneous uptake (Fig. 4C).

At surgery the pelvic tumor was partially resected. Histologic examination confirmed the diagnosis of metastasis from a highly differentiated hepatocellular tumor (Fig. 5A). Examination of biopsied specimens of the primary tumor in the liver showed the development of parallel bands and lamellae of stroma in combination with polygonal tumor cells with one nucleolus and only few mitoses and little pleomorphism (Fig. 5B).

The tumor cells were negative for carcinoembryonic antigen (CEA) and demonstrated no expression of alpha-fetoprotein (Fig. 5C). These findings are typical for the fibrolamellar subtype of a hepatocellular carcinoma.

The patient was locally treated with repeated chemoembolization of the liver tumor and systematically with tamoxifen. Nevertheless the tumor progressed. Satellite tumors in the liver (Fig. 6) and lung metastases developed. The patient died 20 mo after the first diagnosis of the liver lesion, by liver failure–induced coma and tumor cachexia. Autopsy showed that most parts of the primary tumor were the fibrolamellar subtype of a hepatocellular carcinoma but some parts were the common solid and glandular type. The metastases, however, demonstrated signs of a highly differentiated carcinoma, without the typical findings for the fibrolamellar type.

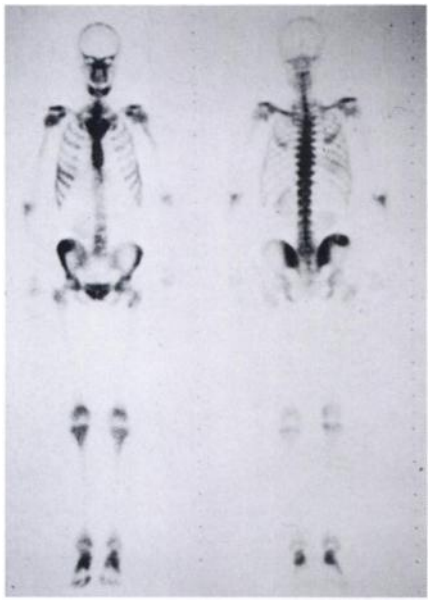

FIGURE 2. Increased tracer uptake in the lateral part of the right iliac bone, visible on anterior and posterior views (^{99m}Tc-DPD, 3 hr after injection).

DISCUSSION

Liver lesions are frequent incidental findings (*1–3*) as in this middle-aged female who was examined prior to donating bone marrow. The patient was referred to our hospital with the diagnosis of focal nodular hyperplasia, based on findings by CT and scintigraphy with ^{99m}Tc-HIDA (*4–11*). However, because this diagnosis was not convincing, the diagnostic procedures including CT and CT-guided biopsy were repeated. The diagnosis was again focal nodular hyperplasia, based on histologic findings in a specimen obtained from the border of the lesion. These findings, however, did not rule out a fibrolamellar type of hepatocellular carcinoma, as tissue characteristics similar to those of focal nodular hyperplasia can occur in the periphery of fibrolamellar hepatocellular carcinoma (*12–14*) or in liver tissue adjacent to these tumors (*15*). The theory that focal nodular hyperplasia undergoes transition to fibrolamellar carcinoma is generally unaccepted (*12*), but sometimes fibrolamellar carcinoma is called the malignant counterpart of focal nodular hyperplasia (*16*).

In our patient, scintigraphy with ^{99m}Tc-HIDA was not diagnostic for the primary tumor, but the central cold lesion and irregular uptake in the surrounding tissue were indicative of malignancy. Dynamic CT demonstrated

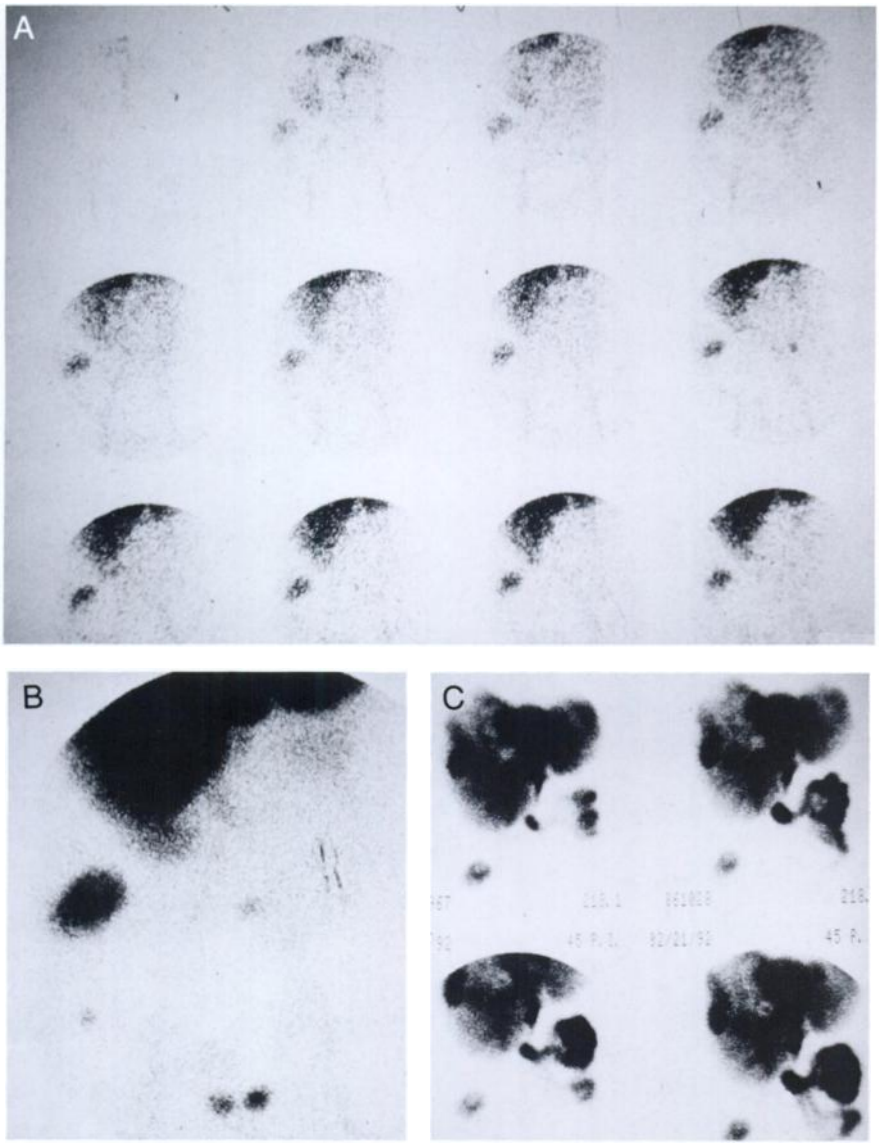

FIGURE 4. (A) Increased arterial blood supply to the caudal part of the right liver lobe and good demarcation of the pelvic lesion in the perfusion series (^{99m}Tc-HIDA). (B) After 20 min, tracer uptake is visualized in the pelvic lesion and a parailiac and right lateral pelvic lymph node. The urinary bladder starts filling and imitates two other lesions. (C) The right liver lobe shows an irregular pattern with partly delayed tracer discharge. The area of the early diagnosed lesion is predominantly cold. (^{99m}Tc-HIDA: upper left, 15 min; upper right, 30 min; lower row, 45 min after injection).

equivocal findings with inhomogeneous enhancement after administration of contrast medium. These signs can occur with focal nodular hyperplasia, whereas typical findings like a star phenomenon or fast and strong transient enhancement are less frequent (*5, 7*) and are not prerequisites for the diagnosis. Thus, a rather low specificity of noninvasive imaging modalities has been confirmed here (*3, 6, 17*).

The bone lesion was considered highly suspicious for metastatic disease, by both bone scintigraphy and CT of

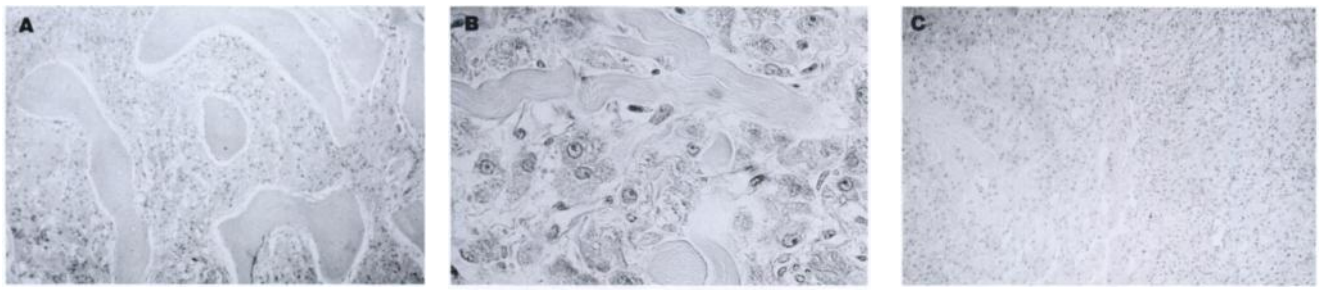

FIGURE 5. (A) Biopsy specimen of the right pelvis showing a destroyed spongiosa structure and proliferation of atypical hepatocytes lying in a trabecular pattern, and polymorphic nuclei. There are no lamellar collagen structures as in the primary tumor. (B) Biopsy specimens of the primary tumor show parallel bands and lamellae of stroma in combination with polygonal tumor cells with one nucleolus, only a few mitoses and little pleomorphism. (C) Immunostaining with anti-alpha-fetoprotein shows no specific binding.

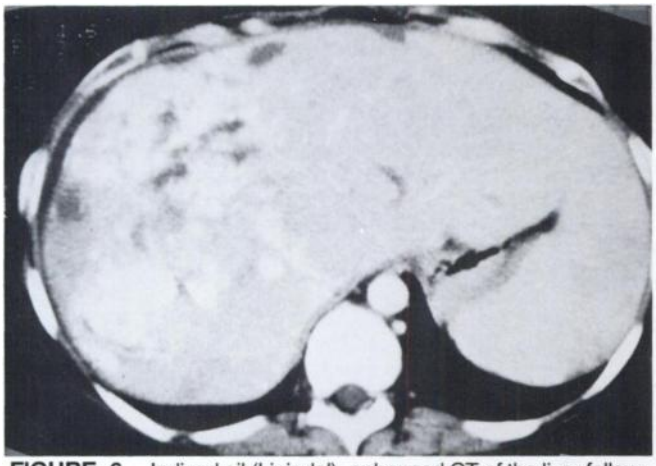

FIGURE 6. Iodized oil (Lipiodol)–enhanced CT of the liver following chemoembolization demonstrating multiple foci in the right liver lobe, indicating progression of the disease.

the pelvis. However, the specific uptake of ^{99m}Tc-HIDA (*18*) corroborated by the histologic findings of highly differentiated tumorous liver tissue in the metastases provided evidence that the liver lesion was the origin of the metastatic bone tumor.

Metastases of hepatocellular carcinomas can occur in many different organs but the occurrence rate in bone is rather low (*19,20*). Bone metastases, however, can occur at an early stage of the disease, as in our patient (*20*). Uptake of imino acids in hepatocellular metastases is rather variable, possibly depending on the grade of tumor differentiation (*21–23*).

Pons et al. (*24*) were the first to report the uptake of ^{99m}Tc-DISIDA in a bone metastasis from a hepatocellular carcinoma, and we found no other reports in the literature available to us. Therefore, the present case is another rare example of a ^{99m}Tc-HIDA–positive bone metastasis from hepatocellular carcinoma. We believe the uptake of the tracer is specific due to bile production, as confirmed in other patients with metastases and uptake of imino acids (*22*).

Strashun and Goldsmith (*25*) reported the imino acid concentration in a liver metastasis from a breast tumor as an unspecific accumulation, but without strong evidence that there was really intracellular uptake. To our knowledge no unspecific accumulation of imino acids in metastases of primary liver tumors has been reported. So in our patient the uptake of ^{99m}Tc-HIDA in the bone lesion raised strong suspicion for metastasis from the progressive tumor in the liver.

The histologic findings of the primary tumor included parallel bands and lamellae of stroma in combination with polygonal tumor cells with one nucleolus, only a few mitoses and little pleomorphism. The tumor cells were CEA negative and showed no expression of alpha-fetoprotein. These findings are typical for fibrolamellar hepatocellular carcinoma, a subtype of hepatocellular carcinoma (*12,15*).

Fibrolamellar hepatocellular carcinoma is a distinct clinical entity. The mean age of patients at the time of detection is 23 yr, and less than 10% occur in patients over 35 yr old. Males and females are affected almost equally. Compared to the solid glandular type, fibrolamellar hepatocellular carcinoma is characterized by a better prognosis due to the absence of underlying cirrhosis (*12,14,15,26*). Autopsy demonstrates that considerable parts of tumorous tissue lack the typical histologic features of a fibrolamellar carcinoma (*12,13,15*). It is unknown whether the solid glandular parts of the multifocal carcinoma are responsible for the development of metastases in bone, lymph nodes and lungs, which in our patient showed only the histologic features of the common hepatocellular carcinoma without fibrolamellar structures.

The local aggressiveness of the liver carcinoma, however, was not caused by the common solid, glandular part of the tumor. The dominant part of the liver tumor at autopsy was fibrolamellar, which led to liver failure–induced coma and death despite treatment with chemoembolization and systemic chemotherapy. The survival time for our patient was 20 mo, considerably lower than the average survival time of 32 (*12*)–68 months (*15*).

The case reported here is especially interesting because of the problem of correct diagnosis of the primary tumor, a fibrolamellar hepatocellular carcinoma and the indirect proof of metastatic liver malignancy by specific tracer uptake in highly differentiated metastases in bone and lymph nodes.

REFERENCES

1. Friedman AC, Fishman EK, Radecki PD, et al. *Focal disease Radiology of the liver, biliary tract, pancreas and spleen*. Baltimore: Williams and Wilkins; 1985.
2. Saini S. Editorial: diagnostic imaging of the liver. *J Nucl Med* 1992;33:1344–1345.
3. Rubin RA, Lichtenstein GR. Hepatic scintigraphy in the evaluation of solitary solid liver masses. *J Nucl Med* 1993;34:697–705.
4. Biersack HJ, Thelen M, Torres JF, et al. Focal nodular hyperplasia of the liver established by ^{99m}Tc-sulfur colloid and HIDA scintigraphy. *Radiology* 1980;137:187.
5. Drane WE, Krasicky GA, Johnson DA. Radionuclide imaging of primary tumors and tumor-like conditions of the liver. *Clin Nucl Med* 1987;12:569–582.
6. Calvet X, Pons F, Bruix J, et al. Technetium-99m-DISHIDA hepatobiliary agent in diagnosis of hepatocellular carcinoma: relationship between detectability and tumor differentiation. *J Nucl Med* 1988;29:1916–1920.
7. Reuland P, Kurtz B, Müller Schauenburg W, Feine U. Comparison of computer tomography and scintigraphic methods in the diagnosis of focal liver disease. *Nucl Med* 1991;30:43–54.
8. Yeh SH, Wang SJ, Chu LS. Sensitivity of technetium-99m-HIDA liver scintigraphy for diagnosing hepatoma [Abstract]. *J Nucl Med* 1981;6:P86.
9. Vincent LM, Renner JB. Uptake of hepatobiliary agents by hepatocellular carcinoma (1). *Am J Radiol* 1984;143:1119–1120.
10. Rogers JV, Mack LA, Freeny PC, Johnson ML, Sones PJ. Hepatic focal nodular hyperplasia: angiography, CT, sonography, and scintigraphy. *Am J Radiol* 1981;137:983–990.
11. Welch TJ, Sheedy II PF, Johnson CM, et al. Focal nodular hyperplasia and hepatic adenoma: Comparison of angiography, CT, US, and scintigraphy. *Radiology* 1985;156:593–595.
12. Craig JR, Peters RL, Edmondson HA, et al. Fibrolamellar carcinoma of the liver: a tumor of adolescents and young adults with distinctive clinicopathologic features. *Cancer* 1980;46:372–379.
13. Slavutin LJ and Diamond N. Case report. Hepatocellular carcinoma with lamellar fibrosis: an important histological variant. *Pathology* 1981;13:775–781.

14. Nagorney DM, Adson MA, Weiland LH, et al. Fibrolamellar hepatoma. *Am J Surg* 1985;149:113–119.
15. Berman MM, Libbey PN, Foster JH. Hepatocellular carcinoma. Polygonal cell type with fibrous stroma-an atypical variant with a favorable prognosis. *Cancer* 1980;46:1448–1455.
16. Vecchio FM, Fabiano A, Ghirlanda G, et al. Fibrolamellar carcinoma of the liver: the malignant counterpart of focal nodular hyperplasia with oncocytic change. *Am J Clin Pathol* 1984;81:521–526.
17. Titelbaum DS, Burke DR, Meranze SG, et al. Fibrolamellar hepatocellular carcinoma: pitfalls in nonoperative diagnosis. *Radiology* 1988;167:25–30.
18. Lee VW, O'Brien MJ, Devereux DF, Morris PM, Shapiro JH. Hepatocellular carcinoma: uptake of ^{99m}Tc-HIDA in primary tumor and metastases. *Am J Radiol* 1984;143:57–61.
19. Lei MH, Ko YL, Kuan P, Lien WP, Chen DS. Metastasis of hepatocellular carcinoma to the heart: unusual patterns in three cases with antemortem diagnosis. *J Formos Med Assoc* 1992;91:457–461.
20. Gambari PI, Ricci S, Castaldini L, Rossi G, Roversi R. Metastasi ossee da carcinoma epatocellulare: osservazioni nei pazienti trattati con chemioembolizzazione arteriosa transcatetere. *Radiol Med Torino* 1993;85:450–454.
21. Wang PW, Tai DI, Chen HY. Technetium-99m-HIDA hepatobiliary agent in the diagnosis of pulmonary metastasis from hepatocellular carcinoma. *Clin Nucl Med* 1991;16:120–123.
22. Lee VW, O'Brian MJ, Devereux DF, Morris PM, Shapiro JH. Hepatocellular carcinoma: uptake of ^{99m}Tc-IDA in primary tumor and metastasis. *AJR* 1984;143:57–61.
23. Calvet X, Pons F, Bruix J, et al. Technetium-99m-DISIDA hepatobiliary agent in diagnosis of hepatocellular carcinoma: relationship between detectability and tumor differentiation. *J Nucl Med* 1988;29:1916–1920.
24. Pons F, Lomena F, Calvet X, et al. Uptake of technetium-99m-DISIDA by bone metastasis from a hepatoma. *Clin Nucl Med* 1988;13:280–282.
25. Strashun A, Goldsmith S. Increased focal uptake of ^{99m}Tc-IDA hepatobiliary agent by a liver metastasis. *Clin Nucl Med* 1981;6:295–296.
26. Soreide O, Czerniak A, Bradpiece H, et al. Characteristics of fibrolamellar hepatocellular carcinoma. A study of nine cases and a review of the literature. *Am J Surg* 1986;151:518–523.