Radionuclide Imaging of Primary Renal-Cell Carcinoma by I-131-Labeled Antitumor Antibody

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A goat antibody against human renal-cell carcinoma reacted on immunofluorescence with renal-cell carcinomas from 20 patients, but not with normal adult human tissues, including kidney. After i.v. administration the I-131-linked antibody showed preferential tumor localization in six of seven patients with primary renal carcinoma. Labeled antitumor antibodies may have the specificity for tumor imaging that current radiopharmaceuticals lack.

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Imaging with most currently available tumor-seeking radiopharmaceuticals takes advantage of nonspecific, secondary changes in neoplasms, i.e., altered microvascularity and nonspecific trapping of labels by tumor cells (*1,2*). We have demonstrated that the radionuclide-linked antibodies against mouse-tumor-associated, cell-surface antigens have specificity for tumor imaging (*3,4*). We could also detect tumor metastases in two patients by radionuclide imaging with I-131-labeled xenogeneic antitumor globulin (ATG) against autologous primary tumors (*3,5*). We report here the results of tumor imaging, using an I-131-labeled "polyvalent" antibody to renal cell carcinoma, in seven consecutive patients with histologically proven primary renal-cell carcinoma.

MATERIALS AND METHODS

Renal-cell carcinoma homogenates from two patients were injected repeatedly into two goats (*3,5*). The resulting pooled antisera were absorbed, first with human AB red cells and then with homogenates of a variety of pooled normal human tissues, including kidney. The reactivity and specificity of these sera were established by immunofluorescence as described elsewhere (*3,6*). The absorbed antisera did not react, either with the patients' normal kidney, or with any normal adult human tissue, or with any of several other nonrenal human and murine tumors tested. It reacted only with the immunizing cancers and with sections and smears of all of 20 renal-cell carcinomas obtained from other patients. ATG was prepared from the pooled sera by fractionation with 33% saturated ammonium sulfate, and was bound to carrier and reductant-free I-131 using chloramine T (*6*). After i.v. administration of 100 mg ATG bound to 3.5–4 mCi of I-131, patients were scanned with a rectilinear scanner*, first at 6 hr, then at 24 hr. To prevent uptake of any dissociated I-131 by the thyroid, all patients were given Lugol's iodine in drinking water starting at least 3 days before injection of I-131 ATG. All patients were also scanned with Tc-99m sulfur colloid.

RESULTS

The kidney lesion could be detected by whole-body scanning with I-131 ATG in six of the seven patients with histologically confirmed diagnosis of primary renal-cell carcinoma (Figs. 1A and 2A). Tc-99m sulfur colloid did not show preferential localization in any of the tumors. One patient, whose I-131 ATG scan was normal, had a tumor whose longest diameter was only about 4 cm. On histological examination this tumor did not show any pleomorphism, mitosis, or evidence of invasion and was graded by an independent group as a tumor of low-grade malignancy. There was also no selective lo-

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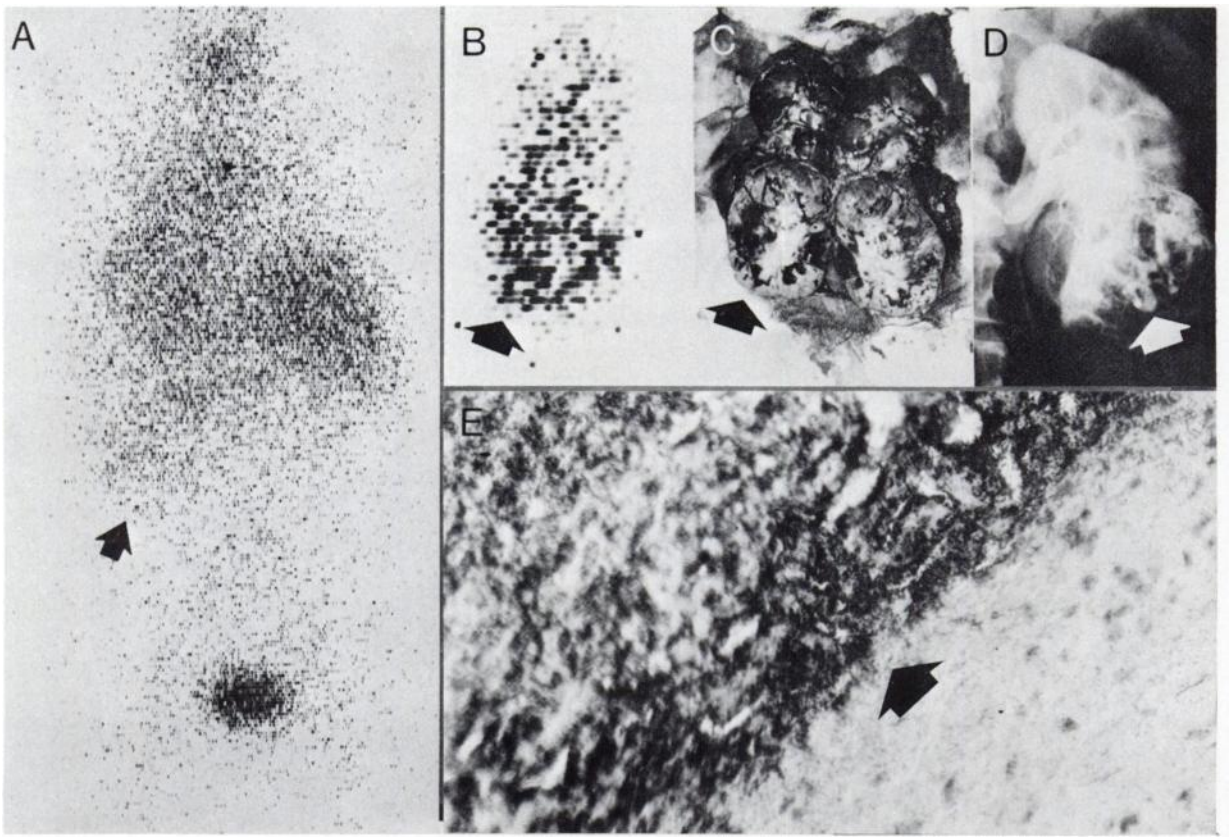

FIG. 1. (A) Posterior whole-body scan of patient A.L.M. 24 hr after i.v. injection of 4 mCi of I-131 bound to 100 mg of antitumor globulin. Note localization of radioactivity in neoplastic left kidney (arrow). There is also considerable radioactivity in liver, lungs, spleen, and bladder urine. (B) Scan of kidney excised 65 hr after I-131 ATG injection. There is localization of radioactivity in neoplastic area (arrow). (C) Kidney cut open to demonstrate tumor, and (D) tumor demonstrated by angiography. Arrows indicate location of tumor. (E) Autoradiograph of a section of kidney showing concentration of radioactivity in neoplastic area (arrow) but not in tumor-free area (×190).

calization of Ga-67 in this tumor. Dissociated cells from this tumor did not react with the ATG.

Four neoplastic kidneys showing localization of I-131 ATG on whole-body scanning were also scanned after excision. All showed preferential localization of radioactivity in lesions but not in contiguous normal renal tissue (Figs. 1B and 2B). Autoradiography and immunofluorescence of sections and dissociated cells revealed preferential localization of goat globulin and radioactivity in tumors compared with contiguous normal renal tissue (Figs. 1E and 2D). Washing the dissociated tumor cells with acid citrate buffer (pH 3.2), but not with 0.01 M phosphate-buffered saline (PBS, pH 7.1), could remove both goat globulin and radioactivity from tumor cells. Neither goat globulin nor radioactivity was detected in PBS-washed dissociated cells from those parts of the kidney not invaded by tumor. The lesion from the patient who had not shown I-131 ATG localization on whole-body scanning also failed to show preferential tumor localization of I-131 ATG after scanning of the excised kidney.

DISCUSSION

Using syngeneic mouse tumors, we have demonstrated that radioiodinated antitumor antibodies show progressive preferential tumor localization in vivo, and clear faster than normal xenoglobulins from non-neoplastic tissues (*5*). Ethical considerations do not permit a similar study on the localization of I-131-labeled normal goat globulin in these patients for assessment of the role of possible permeability changes in tumor vasculature in localizing I-131 ATG (*1,2*). We note, however, that there was no localization of I-131 ATG, either in renal cysts found in three of these patients or in a BCG-induced abscess in a fourth patient. There was also no preferential tumor localization of Tc-99m sulfur colloid in any of these patients. Further, the only tumor that did not react with the ATG also failed to concentrate I-131 ATG. These suggest immunological specificity of ATG localization in these tumors, as was demonstrated in mouse tumors (*5*) and in xenografts of human colon cancer (*7*).

Our previous study in cancer patients involved the

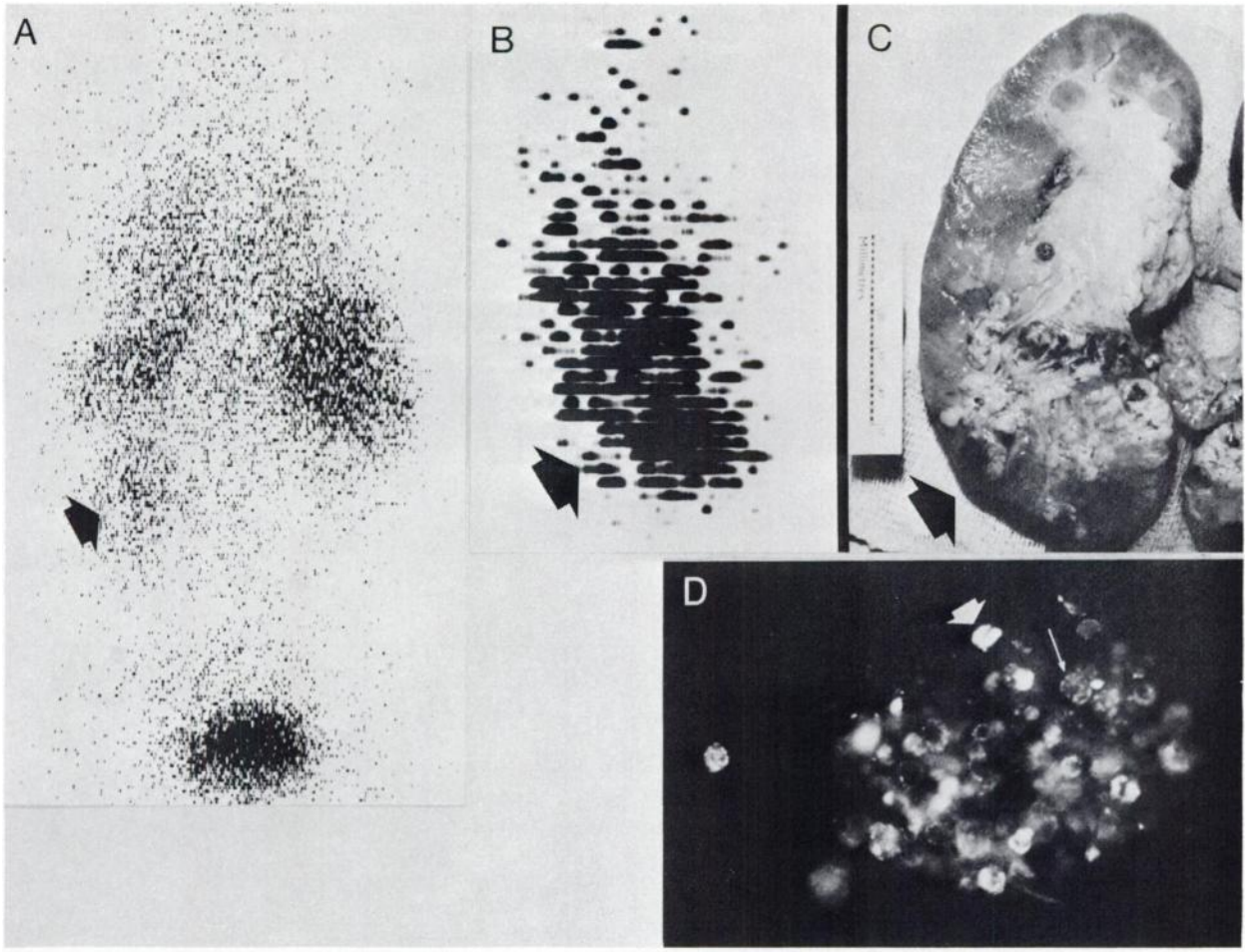

FIG. 2. (A) Posterior whole-body scan of patient G.H. 48 hr after i.v. injection of 4 mCi of I-131 bound to 100 mg of antitumor globulin. Note localization of radioactivity in neoplastic left kidney (arrow). (B & C) Scan and gross view of same patient's kidney excised 144 hr after injection of I-131 ATG. Arrows indicate location of tumor. (D) Fluorescence photomicrograph of patient's dissociated tumor cells treated with fluoresceinated rabbit antigoat immune globulin showing localization of goat globulin on tumor cells. Dead cells (large arrows) show diffuse fluorescence whereas viable cells (thin arrow) show discrete "membrane staining."

production of xenogeneic ATG against the primary tumor, and the use of the resulting I-131 labeled ATG for the detection of metastases (*3,4*). The availability of "polyvalent" ATG preparations that cross-react with renal-cell carcinoma from different patients has now eliminated the necessity for the production of ATG against individual tumors. However, whether these ATG preparations will react with all human renal adenocarcinomas remains to be determined.

Nonspecific trapping of xenogeneic ATG by reticuloendothelial cells in liver, spleen, and lungs limits the usefulness of tumor detection by radiolabeled ATG. However, the ATG preparations used in these experiments did not contain more than 1% specific antitumor antibody (*4*) and purer preparations of antitumor globulins or their F(ab)2 fragments might eliminate at least part of the incorrect homing (*3*).

Further studies of this noninvasive method for detection of primary renal-cell carcinomas and their metastases are in progress to determine the limits of sensitivity (i.e., smallest tumor mass detectable) and specificity (i.e., concentration of radiolabeled ATG in areas of necrosis and inflammation). These studies include quantitative determination of the amount of I-131 activity in the neoplasms themselves, in adjacent nonneoplastic renal tissues, and in serum, after i.v. administration of I-131 ATG in patients with renal-cell carcinoma. Comparison with other tumor-localizing radiopharmaceuticals (*6*) and conventional radiographic methods will be required for evaluation of the clinical potential of this technique.

FOOTNOTE

* Ohio Nuclear DPRS, Solon, OH.

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