Renal Localization of ^{67}Ga-Citrate in Renal Amyloidosis: Case Reports

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In scans taken 72 hr after intravenous administration of 5 mCi of ^{67}Ga-citrate, both kidneys were clearly visible in two cases of histologically proven renal amyloidosis. Neither patient had clinical manifestations or laboratory evidence of concurrent inflammatory disease or tumor involving the kidneys. Increased renal concentration of lysosomal organelles and increased affinity of ^{67}Ga for amyloid material contained in the organelles could explain the renal uptake of ^{67}Ga in amyloidosis.

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Renal localization of ^{67}Ga-citrate has been reported in inflammatory diseases, such as pyelonephritis, and in neoplastic diseases, such as lymphoma, leukemia, and malignant melanoma (*1*). This report describes two cases of histologically proven renal amyloidosis, in which the only abnormal feature of ^{67}Ga scans, performed to rule out occult malignancy or infection, was renal localization of the nuclide 72 hr after intravenous administration. Neither patient had clinical manifestations or laboratory evidence of concurrent inflammatory disease or tumor involving the kidney.

CASE REPORTS

Case No. 1. A 62-year-old man was in good health until 3 weeks before hospitalization, when he noticed swelling of the lower extremities. Three days before admission, he rapidly developed gross anasarca. Physical examination revealed generalized edema, but no other abnormalities were noted. Urinalysis showed yellow clear urine (pH 6.0, sp. gr. 1.011, and protein 4+); no sugar, ketone, blood cells, pus cells, or casts were present. The blood cholesterol level was 640 mg% (normal, 170–280 mg%), and the triglyceride level was 260 mg% (normal, 45–155 mg%).

A ^{67}Ga-citrate scan was requested to disclose a possible occult malignancy. Five millicuries of ^{67}Ga-citrate (Medi-Physics, Emeryville, Calif.) was administered intravenously and scans were obtained 72 hr later. An Ohio-Nuclear rectilinear scanner with dual 5-in. detectors was used. Three independent pulse-height analyzers for each detector permitted simultaneous detection of the 93-, 184-, and 296-keV photon emissions of ^{67}Ga. The medium-energy collimator (38H) had a focal depth of 9 cm. Patient preparation consisted of 60 cm^3 of castor oil given orally on the evening before the scan and a cleansing enema a few hours before scanning. Kidney uptake and bladder activity were the only abnormal features observed in the scan (Fig. 1). An intravenous pyelogram was normal. The clinical findings (anasarca, hypertension) and the laboratory data (proteinuria and elevated cholesterol and triglycerides) were thought to indicate nephrotic syndrome.

Renal biopsy, performed 5 days after the scan, revealed the morphologic characteristics of amyloidosis: a fairly dense fibrillar deposit in the thickened basement membranes and in some of the mesangial areas.

Case No. 2. A 25-year-old woman developed edema, proteinuria, and hypertension during her first pregnancy in 1966. In 1969, her second pregnancy was complicated by anemia, proteinuria, and hypercholesterolemia. A clinical diagnosis of systemic lupus erythematosus was made, and antihypertensive medication was instituted. In October 1973,

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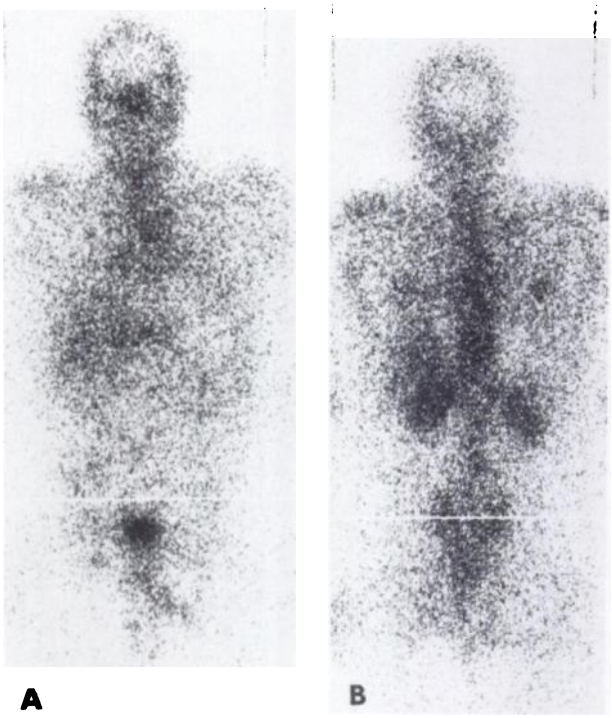

FIG. 1. Anterior (A) and posterior (B) views of ^{67}Ga scan taken 72 hr after injection of 5 mCi of ^{67}Ga-citrate. Anterior view shows activity in urinary bladder. Posterior view shows clear visualization of both kidneys.

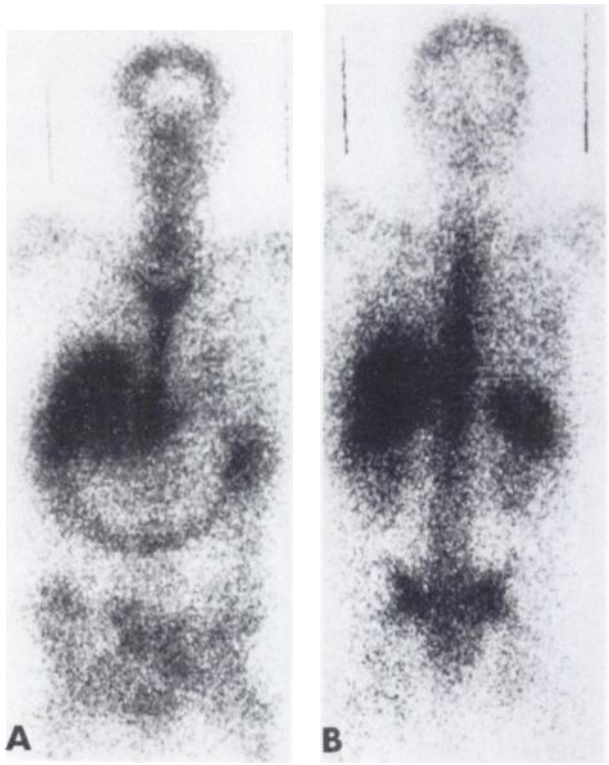

FIG. 2. Anterior (A) and posterior (B) views of ^{67}Ga scan taken 72 hr after injection of 5 mCi of ^{67}Ga-citrate in 25-year-old woman with primary amyloidosis. Bilateral uptake in kidneys is noted in posterior view.

she was hospitalized and, after an extensive workup, systemic lupus erythematosus was ruled out.

In May 1974, the patient was readmitted because of low-grade fever. On this admission, a urine sample, collected over a 24-hr period, revealed marked proteinuria. On several occasions the serum cholesterol level was elevated to 354 mg% (normal, 170–280 mg%), and the albumin levels decreased to 2.0 gm% (normal, 3.2–5 gm%). A ^{67}Ga-citrate scan was performed in search of an occult inflammatory process. The dose, equipment, patient preparation, and technique were as described for Case No. 1. Clear visualization of both kidneys at 72 hr was the only abnormality noted on the scan (Fig. 2). An intravenous pyelogram performed after the scan was normal. A renal biopsy, done 7 days after the ^{67}Ga scan, revealed a pattern typical of amyloidosis. The final clinical impression was that of a nephrotic syndrome secondary to renal amyloidosis.

In both patients, thorough workup revealed no cause for the amyloidosis. Thus, it was concluded that both cases were primary.

DISCUSSION

After ^{67}Ga-citrate is injected intravenously, 30% is bound to plasma proteins, including transferrin and haptoglobin; it also binds loosely to albumin and other globulins. The soluble remainder of the ^{67}Ga-citrate complex diffuses throughout the extracellular space or is excreted by the kidneys. One-third of the injected dose is excreted in the first week: about 25% by the kidneys, predominantly within the first 24 hr, and 10% by the gastrointestinal tract over 7 days. The remaining two-thirds are distributed in the body: 34% in soft tissues; 24% in the skeleton, including the marrow; 5% in the liver; 2% in the kidneys; and 1% in the spleen (*2*). At the time of scanning (72 hr), the normal structures with the highest ^{67}Ga concentrations are the nasopharynx, liver, bone, spleen, lacrimal glands, salivary glands, and the external genitalia (*3*).

The mechanisms by which gallium concentrates in tumors and inflammatory sites are still unknown. Several factors influencing gallium uptake have been proposed: (A) viability or nonviability of the tumor (*4*); (B) a local decrease in pH in the region of the tumor, causing gallium dissociation and binding of the ionic form by tumor proteins (*5*); (C) high tumor vascularity (*6*); (D) hyperpermeability due either to inflammation and neovascularity in tumor-bearing areas or to increased membrane-pore size in tumor cells (*7*); (E) accumulation by histiocytes in the tumor (*8*); (F) poor differentiation of tumor cells (*9*); (G) rapid proliferation of tumor cells (*10*); and (H) exchange of extracellular gallium with the

intracellular calcium pool (*11*). Uptake of ^{67}Ga by lysosomes or lysosome-like organelles has been shown by morphologic and biochemical methods (*12*).

Primary amyloidosis is frequently associated with renal involvement and nephrotic syndrome. Among adults with nephrotic syndrome, amyloidosis is the causative factor in 12%. Amyloidosis may occur as a primary disease process or as a complication of other chronic diseases. Common causes of the secondary form are multiple myeloma, chronic pyogenic infections, chronic granulomatous infections, chronic arthritis, malignancy, and chronic enterocolitis (*13*).

Under the electron microscope, amyloid is seen to consist of rigid nonbranching fibrils. In patients with amyloidosis, these fibrils are reported to be virtually identical to the variable portions of the monoclonal light chain of globulin (Bence–Jones protein) (*14*). The lysosomes of the normal human kidney degrade monoclonal light chains to produce an insoluble polymer. This process could be involved in the formation of renal amyloid fibrils in patients with amyloidosis.

Two mechanisms could explain the renal uptake of ^{67}Ga in amyloidosis. The renal concentration of lysosomal organelles may be increased or the ^{67}Ga may have increased affinity for the amyloid material contained in the organelles. Both mechanisms may operate concurrently. Whatever the specific mechanism, our two cases indicate that amyloidosis should be considered in the differential diagnosis of ^{67}Ga uptake in the kidneys. This diagnosis should definitely be considered if pyelonephritis or tumor involvement are ruled out by ancillary tests.

ACKNOWLEDGMENT

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ERRATUM

Owing to a mechanical error, a line of type dropped out of the article "Carboxyl-Labeled ^{11}C-1-Aminocyclopentanecarboxylic Acid, a Potential Agent for Cancer Detection" (*J Nucl Med* 17:748–751, 1976.) The garbled paragraph (from page 750, Results and Discussion) should read as follows:

In developmental studies before actually producing the ^{11}C-ACPC, carbon, hydrogen, and nitrogen determinations and infrared spectrometry were used to show that the synthesis and purification processes intended for use in the incorporation of ^{11}C into ACPC did indeed yield pure ACPC. Pyrogenicity tests of ^{11}C-ACPC using standard USP techniques gave negative results, and no radiolytic decomposition of ^{11}C-ACPC has appeared in the runs made to date.