Utility of Gallium Imaging of the Kidneys in Diagnosing Primary Amyloid Nephrotic Syndrome

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We undertook a study to determine the value of gallium imaging of the kidneys in patients who had primary amyloidosis that was manifest clinically by nephrotic syndrome. We studied 28 patients with gallium-67 (^{67}Ga) citrate scans performed 48 hr after injection. Intense (3+ to 4+) uptake was noted in both kidneys in 25 of 28 patients. Renal amyloidosis should be considered in the differential diagnosis when diffuse bilateral renal uptake of [^{67}Ga]citrate is seen in the setting of nephrotic syndrome. Gallium uptake did not differentiate amyloid nephrotic syndrome from other causes of nephrotic syndrome. Renal gallium uptake showed a weak correlation with 24-hr urine protein excretion ($p = 0.06$).

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Three papers have reported a total of 14 patients with systemic amyloidosis (AL) who had gallium-67 (^{67}Ga) citrate scans performed (*1-3*). These papers suggested that gallium imaging has a high sensitivity for the detection of renal AL. We undertook this study to assess the relative value of [^{67}Ga]citrate imaging in the setting of primary renal AL manifest by nephrotic syndrome.

MATERIALS AND METHODS

Patient Selection

All patients included in this study were referred to the Mayo Clinic for diagnostic assessment and treatment of their AL. Scans were performed between October 1987 and March 1989. To be eligible for the study, patients had to have nephrotic-range proteinuria (>3 g protein/day) and normal renal function (creatinine ≤ 160 μmol/l). The requirement for normal renal function was to ensure adequacy of renal blood flow in all scanned patients. All patients had to have biopsy proof of AL; patients with secondary, familial, and dialysis-related AL were not eligible for participation. It is clinical practice when AL is suspected to attempt to establish the diagnosis by the least invasive means possible. At the Mayo Clinic when a patient is seen with nephrotic syndrome, immunoelectrophoresis of the serum and urine is done. If an M component is found in the serum or urine, biopsy of the bone marrow, subcutaneous fat, or rectum will establish the diagnosis in the majority of patients. Only when one strongly suspects AL and less invasive studies are negative will a renal biopsy be performed. The characteristics of these patients are given in Table 1. All patients gave written informed consent prior to gallium injection. Menstruating women all had a negative pregnancy test. This study was approved by the Institutional Review Board of Mayo Foundation.

Scanning Technique

Imaging was obtained 48 hr after i.v. injection of 5 mCi of [^{67}Ga]citrate. Anterior and posterior images (10-min scan) of the kidneys and an anterior image of the heart were obtained. Data were stored in 64-word mode on a computer (MDS A^2, Ann Arbor, MI) for further quantitation. Images were obtained by using a jumbo field of view gamma camera (GE 500A, General Electric Company, Milwaukee, WI) with a medium-energy collimator. Twenty-percent windows were used for each of the three lower photon energies of gallium.

Image Interpretation

The gallium images were coded from 0 to 4+, with the two interpreting physicians blind to the diagnosis. If interobserver disagreements occurred in the interpretation of scans, it was planned to have a third observer resolve disagreements. In this study, which included a small number of scans, no disagreements occurred. Scans from four patients with immune complex nephropathy, diabetes mellitus, minimal change glomerulopathy, and light chain deposition disease, all of whom had nephrotic syndrome and proof by renal biopsy, were randomly included with the 28 amyloid scans to prevent bias in interpretation. The images were coded as 0 uptake = background only; 1+ uptake = minimal uptake just above background; 2+ = definite uptake but less than the lumbar vertebrae, renal outlines well defined; 3+ = uptake equal to the lumbar vertebrae; and 4+ = uptake greater than the lumbar vertebrae. At our institution, a normal gallium scan interpreted at 48 hr will show no uptake in the majority of cases. However, there may occasionally be 1+ activity, which is usually bilateral and uniform. Any uptake in excess of 1+ is considered abnormal. Quantitation of gallium uptake in the

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TABLE 1
Characteristics of 28 Patients with Amyloid Nephrotic Syndrome

	No.	Median	Range
Males	19		
Age, yr		60	40–84
Creatinine, μmol/l		106	53–159
24-hr urine protein loss, g		9.6	3.0–34.9
Echocardiogram demonstrating amyloid	12		
Kidney biopsy positive	16		
Rectal, fat, or bone marrow biopsy positive	11		
Liver	1		

kidneys with background correction and the ratio of kidney to liver counts were obtained with a variable region of interest program. Activity in other organs (heart and liver) also was graded quantitatively. The intensity of uptake was compared in those patients with AL and in nonamyloid nephrotic syndrome patients to determine if the groups could be separated by uptake intensity. All patients with systemic AL had a two-dimensional echocardiogram performed to determine if cardiac AL existed. The purpose was to assess whether cardiac amyloid accumulated [^{67}Ga]citrate. The level of 24-hr urine protein excretion was recorded in all patients and correlated with the intensity of gallium uptake.

RESULTS

Twenty-eight patients with biopsy-proven systemic AL and nephrotic syndrome were evaluated in this prospective study.

On reviewing the 16 renal biopsies in this study, 15 of the patients underwent biopsy at other institutions and the tissues were reviewed here to establish the diagnosis. Because these tissues were not subsequently available, detailed quantitative morphometric analysis could not be done to correlate the extent of amyloid with the gallium uptake. However, qualitative analysis of amyloid deposits was available, and it established that there was no relationship between the extent of amyloid deposits seen by light microscopy and gallium uptake. There were two patients whose amyloid deposits were limited to either the afferent arterioles or mesangium with complete sparing of the glomeruli. There were three additional patients who had very faint green birefringence on specimens stained with Congo red but extensive amyloid fibrils seen on electron microscopy. In these five patients, all of whom had minimal amyloid deposits seen by light microscopy, the gallium uptake was 4+ in three of the patients and 3+ in the other two. We also separated the patients into those whose diagnosis was established by renal biopsy and those whose amyloid nephrotic syndrome was confirmed by biopsy of extrarenal tissues. Once again, no difference was found in the two groups. Of the 16 renal biopsy patients, 15 had 3+ or 4+ gallium uptake compared to the 12 extrarenal biopsy patients—10 of 12 had 3+ or 4+ uptake, a difference which is not significant.

The results of the scan are given in Figure 1. Thirteen of the twenty-eight patients had 4+ uptake (Fig. 2). Twelve patients had 3+ uptake, and three patients had 1+ or 2+ uptake. Extrarenal uptake was seen in nine of the patients. Grade 1 cardiac uptake of gallium was present in six of the patients, four of whom had echocardiographic evidence of amyloid. There were eight additional patients with echocardiographically demonstrated AL who showed no gallium uptake in the myocardium. One patient had irregular liver uptake on the gallium scan who had biopsy-proven hepatic involvement with amyloid. One patient had uptake in the spleen and one, uptake in both breasts with no demonstrated abnormality on physical examination. Four patients with nephrotic-range proteinuria (3.8–30.8 g per 24 hr) not due to AL were scanned; all had a normal creatinine level (80–124 μmol/l). The uptake in these four patients was as follows: 1+, one patient with light chain nephropathy; 2+, two patients with diabetes and immune complex nephropathy; and 4+, one patient with minimal-change glomerulopathy (Fig. 1). Statistical comparisons of the uptake of gallium and the 24-hr urine protein excretion showed a weak correlation ($p = 0.06$, F test). Because the relationship between urinary protein loss and intensity of gallium uptake is not necessarily linear, $\log_{10}$ urinary protein loss was compared with gallium uptake. The correlation between the variables was statistically significant ($p < 0.05$, $r = 0.35$). Comparison of the quantitative gallium uptake counts with 24-hr urine protein excretion was not significant ($p < 0.10$).

DISCUSSION

It has been proposed that the use of [^{67}Ga]citrate imaging of the kidneys can serve as a marker for both

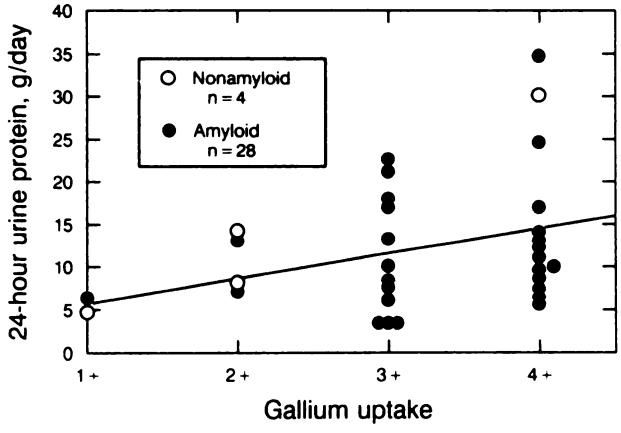

FIGURE 1
Scattergram demonstrating renal uptake of gallium and 24-hr urine protein excretion for 32 patients with nephrotic syndrome.

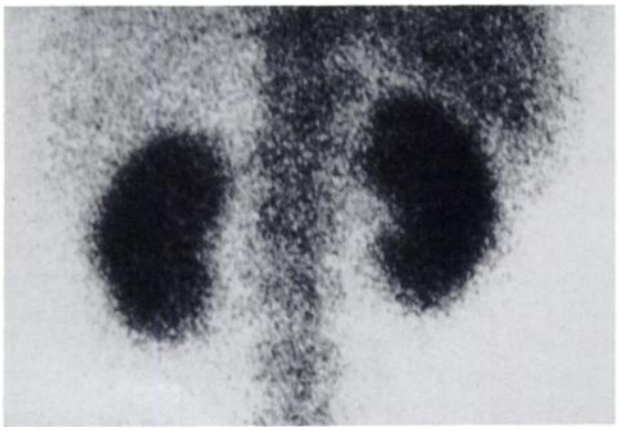

FIGURE 2
A [^{67}Ga]citrate scan demonstrating diffuse bilateral 4+ uptake in both kidneys.

the diagnosis and evaluation of the progress of AL. The mechanism by which gallium binds to amyloid deposits is not known. However, it is known that all amyloid deposits contain glycoprotein amyloid P component. Amyloid P component is known to avidly bind calcium, and this has been the proposed mechanism by which technetium pyrophosphate is thought to bind amyloid deposits. Because gallium is a divalent cation, it would theoretically be capable of binding selectively to the amyloid P component and could account for the mechanism by which gallium accumulates (*4*). After the first 24 hr, the normal kidney has little, if any, uptake of gallium (*5*). Lee et al. (*3*) reported 2+ to 4+ gallium uptake in the kidneys in each of 11 patients with AL. This degree of uptake was seen in 27 of the 28 patients studied here. Gallium uptake was extremely sensitive in its ability to recognize amyloid nephrotic syndrome. Gallium uptake correlates with urinary protein excretion, and we believe the gallium scan added little information diagnostically or clinically to that obtained by measuring the 24-hr urine protein loss. Renal uptake of gallium is not sufficiently specific to consider its introduction as a diagnostic test for AL. We scanned four patients with nephrotic syndrome from causes other than AL and found 2+ to 4+ uptake in three of the four patients. With only four non-AL patients in this study, firm conclusions cannot be drawn with regard to the specificity of the technique and its ability to differentiate between amyloid and nonamyloid nephrotic syndrome. Gallium uptake has been reported bilaterally in pyelonephritis, vasculitis, Wegener's granulomatosis, and acute tubular necrosis (*6,7*). Bilateral intense diffuse renal gallium uptake has also been reported in acute interstitial nephritis and minimal change nephrotic syndrome (*8–12*). Diffuse bilateral renal accumulation has been reported in hemochromatosis, hematologic malignancies, and congestive heart failure, which limits gallium's value as a diagnostic aid (*9,13–16*). Bilaterally symmetric increased uptake of gallium has been reported in patients with advanced hepatocellular disease who had no evidence of renal pathology (*17,18*). Weak gallium uptake (0 to 2+) in the kidneys also has been reported in patients without detectable renal disease (*19*). Lin et al. *10*) reviewed 500 ^{67}Ga scans and found 2+ or greater uptake in the kidneys in 6%. Amyloidosis was not the cause of the uptake in these patients. Gallium uptake in the kidneys would not be useful in screening patients with nephrotic syndrome to find those who have AL.

We found ^{67}Ga uptake in the myocardium of patients with AL demonstrable by echocardiogram. Although the majority of patients with myocardial uptake of gallium did, indeed, have echocardiographic evidence of AL, only half of the patients with AL by echocardiogram showed gallium uptake. We feel myocardial gallium uptake is not as sensitive a technique as the echocardiogram for demonstrating myocardial amyloid deposits. The scintigraphic finding of extrarenal uptake may prove to be more valuable in recognizing amyloid than the intensity of renal gallium uptake alone. Although less sensitive than echocardiography, extrarenal uptake can improve the specificity with which extrarenal amyloid deposits are recognized.

In conclusion, it appears that AL is associated with intense bilateral diffuse gallium uptake in the kidneys. It is possible that gallium actually binds to the amyloid deposits specifically as has been proposed for technetium pyrophosphate (*20,21*). When diffuse bilateral renal gallium accumulation is seen, the diagnosis of AL should be entertained. However, we cannot recommend this test for screening patients with known AL or in patients with known nephrotic syndrome to assist in the differential diagnosis and recognition of amyloid as its cause. Finally, we do not believe that gallium uptake provides greater information than that obtained with a 24-hr urine total protein measure at a substantially lower cost.

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REFERENCES

1. Banzo-Marraco J, Nerin-Mora E, Abos-Olivares MD, et al. renal uptake of ^{67}Ga-citrate in renal amyloidosis due to familiar Mediterranean fever. *Eur J Nucl Med* 1981; 6:277–280.
2. Bekerman C, Vyas MI. Renal localization of ^{67}Ga-citrate in renal amyloidosis: case reports. *J Nucl Med* 1976; 17:899–901.
3. Lee VW, Skinner M, Cohen AS, Ngai S, Peng TT. Renal amyloidosis. Evaluation by gallium imaging. *Clin Nucl Med* 1986; 11:642–646.
4. Yood RA, Skinner M, Cohen AS, Lee VW. Soft tissue uptake of bone seeking radionuclide in amyloidosis. *J Rheumatol*

1981; 8:760–766.
5. Wood BC, Sharma JN, Germann DR, Wood WG, Crouch TT. Gallium citrate Ga-67 imaging in noninfectious interstitial nephritis. *Arch Intern Med* 1978; 138:1665–1666.
6. Kumar B, Coleman RE. Significance of delayed ^{67}Ga localization in the kidneys. *J Nucl Med* 1976; 17:872–875.
7. Long SE, Sonnemaker RE, Burdine JA. Renal accumulation of ^{67}Ga-citrate. *Semin Nucl Med* 1984; 14:52–54.
8. Bakir AA, Lopez-Majano V, Hryhorczuk DO, Rhee HL, Dunea G. Appraisal of lupus nephritis by renal imaging with gallium-67. *Am J Med* 1985; 79:175–182.
9. Frankel RS, Richman SD, Levenson SM, Johnston GS. Renal localization of gallium-67 citrate. *Radiology* 1975; 114:393–397.
10. Lin DS, Sanders JA, Patel BR. Delayed renal localization of Ga-67: concise communication. *J Nucl Med* 1983; 24:894–897.
11. Linton AL, Clark WF, Driedger AA, Turnbull I, Lindsay RM. Acute interstitial nephritis due to drugs. *Ann Intern Med* 1980; 93:735–741.
12. Sherman RA, Byun KJ. Nuclear medicine in acute and chronic renal failure. *Semin Nucl Med* 1982; 12:265–279.
13. Engelstad B, Luk SS, Hattner RS. Altered ^{67}Ga citrate distribution in patients with multiple red blood cell transfusions. *Am J Roentgenol* 1982; 139:755–759.
14. Higgins CB, Taketa RM, Taylor A, Halpern SE, Ashburn WL. Renal uptake of ^{99m}Tc-sulfur colloid. *J Nucl Med* 1974; 15:564–566.
15. Linton AL, Richmond JM, Clark WF, Lindsay RM, Driedger AA, Lamki LM. Gallium^{67} scintigraphy in the diagnosis of acute renal disease. *Clin Nephrol* 1985; 24:84–87.
16. Larson SM, Milder MS, Johnston GS. Interpretation of the ^{67}Ga photoscan. *J Nucl Med* 1973; 14:208–213.
17. Sterkel BB, Alazraki NP, Taylor A. Persistent renal uptake of gallium in the absence of renal pathology in patients with severe hepatocellular disease [Abstract]. *J Nucl Med* 1980; 21:67–68.
18. Alazraki N, Sterkel B, Taylor A Jr. Renal gallium accumulation in the absence of renal pathology in patients with severe hepatocellular disease. *Clin Nucl Med* 1983; 8:200–204.
19. Garcia JE, Van Nostrand D, Howard WH III, Kyle RW. The spectrum of gallium-67 renal activity in patients with no evidence of renal disease. *J Nucl Med* 1984; 25:575–580.
20. Lee VW, Caldarone AG, Falk RH, Rubinow A, Cohen AS. Amyloidosis of heart and liver: comparison of Tc-99m pyrophosphate and Tc-99m methylene diphosphonate for detection. *Radiology* 1983; 148:239–242.
21. Gertz MA, Brown ML, Hauser MF, Kyle RA. Utility of technetium Tc-99m pyrophosphate bone scanning in cardiac amyloidosis. *Arch Intern Med* 1987; 147:1039–1044.