Concentration of In-111-Oxine-Labeled Autologous Leukocytes in Noninfected and Nonrejecting Renal Allografts: Concise Communication

B. David Collier, Ali T. Isitman, H. Myron Kaufman, Shyam A. Rao, Janet Knobel, Robert S. Hellman, Jason S. Zielonka, and Lorie Pelc

Medical College of Wisconsin, Froedtert Memorial Lutheran Hospital, Milwaukee, Wisconsin

Autologous leukocytes labeled with In-111 oxine (ILL) concentrated in the renal allografts of eight patients for whom transplant rejection, infection, or acute tubular necrosis (ATN) could be excluded. All patients had good-to-adequate renal function at the time of ILL scintigraphy, and none developed rejection or renal transplant failure during a 1-mo follow-up period. It is concluded that normally functioning renal allografts without evidence of rejection, infection, or ATN often will concentrate ILL. When a baseline study is not available for comparison, this phenomenon limits the value of ILL scintigraphy as a diagnostic test for transplant rejection or infection.

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Previous reports have emphasized localization of autologous leukocytes labeled with In-III oxine (ILL) in renal allografts undergoing rejection (*1–3*). Concentration of ILL in renal allografts also has been noted to occur, although less frequently, in association with cytomegalovirus (CMV) infection but rarely or never in association with acute tubular necrosis (ATN) (*3*).

Whereas ILL scintigraphy has been suggested as a noninvasive method for distinguishing acute rejection or infection from ATN (*1–3*), the scintigraphic appearance of the normally functioning, noninfected, and nonrejecting renal allograft has not been adequately established. To document the appearance of such normal renal allografts, we reviewed the ILL scintigrams of patients with good renal-transplant function for whom acute rejection, ATN, and allograft infection could be excluded.

MATERIALS AND METHODS

During a 12-mo period, eight adult renal allograft recipients with sepsis or fever of unknown origin were examined with total-body and spot view ILL scintigraphy. Because of continued fever, one of the eight was referred for repeat ILL scintigraphy 2 wk after the first examination. Seven patients had received cadaver renal transplants and one had received a kidney from a living related donor. The interval between transplantation and scintigraphy ranged from 2 to 30 mo (mean 11 mo). All patients were receiving low-dose azathioprine and methylprednisone for long-term immunosuppression, and seven of the patients were being treated with antibiotics.

At the time of scintigraphy and during a 1-mo follow-up period, there was no clinical suspicion of transplant rejection or ATN. In addition, renograms, urine cultures, and CMV titers were normal at or near the time of scintigraphy. Previously described standards for normal renograms and renal images were used (4). All patients had good-to-adequate renal function at the time of imaging, with serum creatinine values in the range of 1.0 to 2.7 mg/dl, and creatinine values for seven of eight patients did not rise significantly during the 2 wk following scintigraphy (Fig. 1). One patient developed transplant rejection, confirmed by nephrectomy and histologic examination 4 mo after ILL. Each of the other seven patients has been followed for at least 7 mo: creatinine values have remained below 2.0 mg/dl, and there

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For reprints contact: B. David Collier, MD, Froedtert Memorial Lutheran Hospital, 9200 W. Wisconsin Ave. Milwaukee, WI 53226.

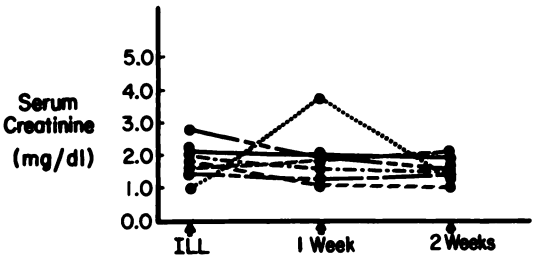

FIG. 1. Serum creatinine values (mg/dl) following ILL scintigraphy in eight renal transplant recipients.

has been no indication of either transplant rejection or infection.

Patients received an average dose of 400 μCi of ILL, which had been prepared using previously described methods (*5,6*). For all patients, gamma camera images were obtained 24 hr later. Two- and 48-hr views also were available for seven of the eight patients, and one patient was imaged up to 96 hr later. When renal allografts were visualized, the intensity of activity was scored as less than (Grade 1), equal to (Grade 2), or greater than (Grade 3) activity originating in the lower lumbar spine. The intensity of renal allograft activity also was compared with cardiac blood-pool activity.

RESULTS

As shown in Table 1, the renal allografts of all eight patients concentrated ILL. For seven of them, activity in the renal transplant at 24 hr was judged to be equal to or greater than activity in the lower spine, and over imaging time of from 2 to 96 hr following injection of ILL, intensity of transplant visualization never varied by more than one grade. For all eight patients, renal transplant activity at 24 hr was more intense than cardiac blood-pool activity. The one patient who underwent repeat ILL scintigraphy had Grade 3 transplant density on both the first and second examinations.

Scintigraphy correctly identified sources of infection in three septic patients, and in two instances a site of infection showed less intense activity than the patient's renal allograft.

TABLE 2. ACTIVITY OF IN-111-OXINE-LABELED LEUKOCYTES IN RENAL ALLOGRAFTS

Patient	2 hr	24 hr	48 hr	72 hr	96 hr
1	+1*	+2	+1	NI	NI
2	+2†	+2	NI	NI	NI
3	+1	+2	+1	NI	NI
4	+2	+1	+1	+1	NI
5	+1	+2	+2	NI	NI
6	+2	+2	+2	NI	NI
7	+1	+2	+1	NI	NI
8	NI	+3‡	+3	+3	+3
8 repeat	NI	+3	+3	NI	NI

0, Equal to background.
* +1, Greater than background, less than lower lumbar spine.
† +2, Equal to lower lumbar spine.
‡ +3, Greater than lower lumbar spine.
§ NI, No image obtained.

Fig. 2 shows a renal transplant in the right iliac fossa with a concentration of ILL activity approaching that seen in the adjacent lower lumbar spine at both 2 and 24 hr. The medial border of the kidney is over the right sacroiliac joint, with the bulk of the transplant lying in the right iliac fossa anterior to the right iliac wing. As is marked with arrows in the illustrations, increased ILL activity is associated with the renal transplant. This patient (F, age 33), who had received a renal transplant from a living related donor 21 mo previously, underwent ILL scintigraphy for possible meningitis. At the time of scintigraphy, her creatinine was 1.5 mg/dl, BUN 17.0 mg/dl, and CMV titer 1:8. Urine cultures were negative and both the I-131-orthoiodohippurate renogram and Tc-99m DTPA renal image (Fig. 2, left) were normal.

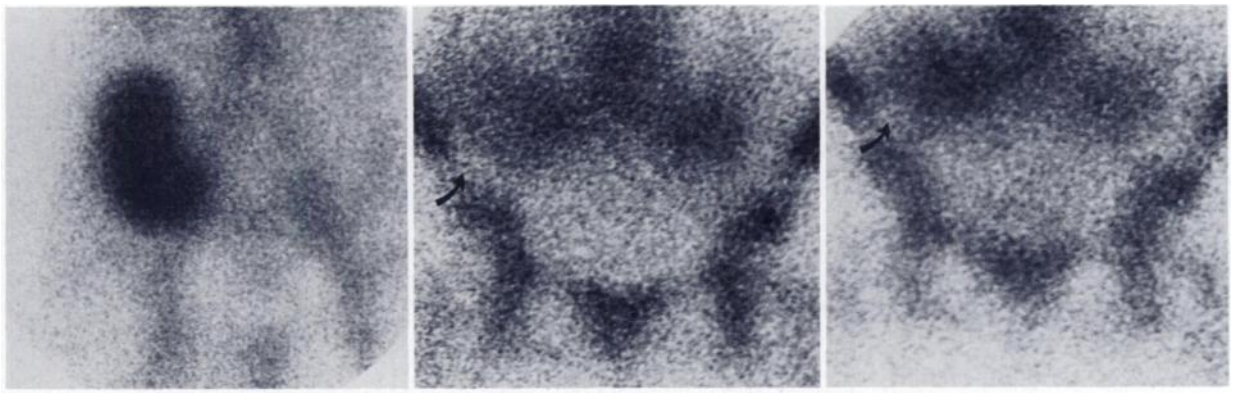

FIG. 2. Tc-99m DTPA 1-min scintigram (left). Prompt clearance of radiopharmaceutical indicates good renal function. Two-hour (center) and 24-(right) ILL scintigrams show renal allograft activity (arrows) approaching that seen in adjacent lumbar spine. Contralateral iliac fossa shown only minimal ILL activity.

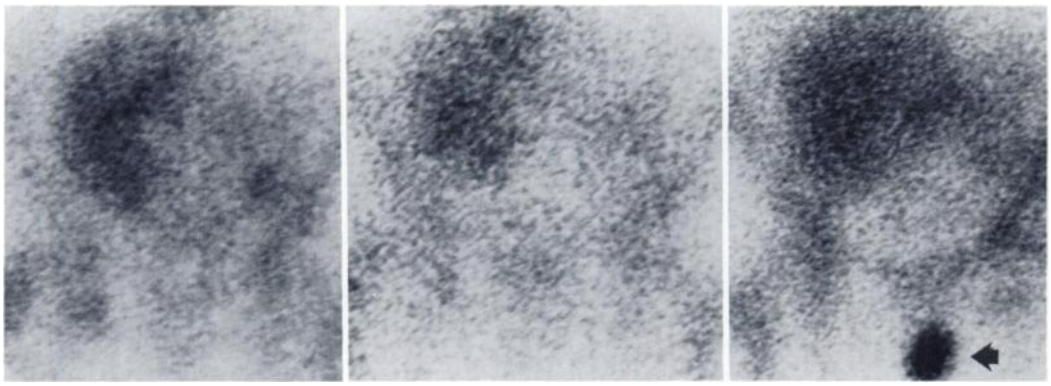

FIG. 3. Initial ILL scintigram at 72 hr (left) shows renal allograft activity surpassing that in adjacent lumbar spine. Initial ILL scintigram at 96 hr (center). Repeat ILL scintigram 2 wk later (right) identifies very intense activity in vaginal abscess (arrow). Renal allograft activity is unchanged.

The scintigrams in Fig. 3 are from a 40-yr-old man who was febrile; allograft intensities at 72 and 96 hr exceed that in the adjacent lumbar spine. Two weeks later (fever still present) a vaginal abscess was revealed by a repeat scintigram (Fig. 3, left). Six months later the patients in Figs. 2 and 3 showed no evidence of transplant rejection or infection.

DISCUSSION

When ILL were prepared using previously described methods (*5,6*) eight renal allografts not affected by rejection, infection, or ATN were visualized. It is known that normally functioning native kidneys that are free of infection do not concentrate ILL, and limited experience with canine autografts suggests that renal autografts do not concentrate ILL (*2,7*). Thus it appears that while visualization on ILL scintigraphy might suggest infection of native kidneys or renal autografts, this same finding should be considered "normal" for renal allografts. Furthermore, in this series there was no evidence of renal allograft rejection for seven out of eight ILL-visualized transplants that were followed for more than 6 mo. This suggests that the concentration of ILL in a renal allograft does not signify early or impending rejection.

Visualization of all eight normally functioning renal allografts cannot be explained by incidental In-111 oxine labeling of platelets and/or erythrocytes. When using the In-111 oxine technique, preferential labeling of leukocytes requires separation from other cells in the peripheral blood followed by in vitro incubation with the tracer. It must be admitted that, typically, complete separation of leukocytes from erythrocytes and platelets is not achieved. Using the same techniques as in the current study to separate leukocytes from the whole blood of normal human donors, Clay et al. found that, on average, 72% of activity was associated with leukocytes, 8% with platelets, 8% with erythrocytes, and 12% with the discarded supernatant (*6*). Because of the leukocytosis and elevated erythrocyte sedimentation rate of the eight febrile patients in this report, preferential labeling of leukocytes equal or superior to the results reported by Clay was obtained for all eight in this series. These results were confirmed by routine light microscopy of a sample of the ILL preparation. However, the eight renal allograft examinations in this report are not typical of either In-111 platelet or In-111 erythrocyte scintigraphy. Significant In-111 oxine labeling of erythrocytes or platelets would have produced a blood-pool agent with scintigraphic visualization of the renal allograft, major vessels, and cardiac blood pool (*8–10*). However, in all eight patients examined with ILL, activity over the renal allograft at 24 hr was significantly greater than activity in the cardiac blood pool. In addition, In-111 oxine labeling of substantial numbers of platelets with subsequent platelet localization in the renal allograft is an unacceptable explanation for the current results. Several authors have reported that platelets labeled with In-111 oxine will concentrate in a rejecting kidney but fail to visualize a normal renal allograft (*11–16*). It is reasonable to conclude that accumulation of ILL in normally functioning renal allografts accounts for the observed uptake, rather than pitfalls in the In-111 oxine labeling technique.

Previous reports focused on the ILL scintigraphy of the rejecting renal transplant rather than the appearance of the normally functioning transplant. Forstrom and co-authors found increased renal allograft uptake in 11 out of 15 rejecting kidneys and two out of 11 kidneys with CMV infection. In their experience with a total of 53 patients, only one showed unexplained abnormal uptake in the transplanted kidney (*3*). The techniques for ILL preparation and scintigraphy used by Forstrom et al. were similar to those in this study. Differences in patient selection—including time since transplantation, degree of immunosuppression, antibiotic therapy, and renal function—may account for the accumulation of ILL by all renal allografts included in our series. Unfortunately, these patient characteristics are not reported

by Forstrom and his co-authors. Working with mongrel dogs in a controlled laboratory experiment, Pontes et al. found ILL scintigraphy visualization of a renal allograph to be both sensitive and specific for rejection (*2*). However, the claim for diagnostic specificity is based on failure to visualize ILL accumulations either in renal autografts or in allografts imaged within the first 72 hr after transplantation. The scintigraphic appearance of the normally functioning renal allograft months to years after transplantation was not described in the reports cited.

Based on this report of eight renal transplant recipients, all of whom were beyond the immediate postoperative period, we conclude that normally functioning renal allografts without evidence of rejection, infection, or ATN often will concentrate ILL. When a baseline study is not available for comparison, this phenomenon limits the value of ILL scintigraphy as a diagnostic test for transplant rejection or infection.

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