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Scintigraphic imaging of MHC class II antigen induction in mouse kidney allografts: a new approach to noninvasive detection of early rejection

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Abstract. Mice with kidney transplants were investigated to determine whether early kidney allograft rejection could be detected by radioimmune scintigraphy targeting major histocompatibility complex (MHC) class II antigens induced on donor organ cells. Allografts from C3H/He ($H2^k$) donors were transplanted into BALB/c ($H2^d$) recipients. Each mouse was injected intravenously with 100 μCi of ^{123}I-labeled anti-MHC class II monoclonal antibody (mAb; Y17, anti-IE^k) 16 h before scintigraphy. After imaging, mice were sacrificed for tissue counting and histopathological examination. Radiotracer uptake in the nontreated allografts increased starting on the 3rd day after transplantation, peaked at around the 6th day, and then gradually decreased. Rejecting allografts with only focal perivascular mononuclear cell infiltration could be identified by scintigraphy. However, allografted mice without evidence of rejection and isografted mice did not show an increase in radiotracer uptake. Rejecting BALB/c kidney transplanted into C3H/He mice did not show an increase in Y17 mAb uptake, suggesting that class II antigens induced on donor kidneys are solely responsible for the mAb uptake in positive scintigrams of rejecting allografts. Five allografted mice were treated with anti-CD3 mAb and cyclosporin starting 3–9 days after transplantation. Radiotracer uptake decreased after 4 weeks of treatment and increased 2 weeks after the cessation of immunosuppressive treatment, reflecting suppression and recurrence of rejection, as determined by histological examination. These changes could be followed scintigraphically. We conclude that changes in class II antigen expression can be assessed by the ^{123}I-labeled anti-MHC class II antigen mAb and that it is a sensitive and noninvasive method for detecting kidney allograft rejection.

Key words: MHC class II antigen induction, mouse, kidney – Kidney, mouse, MHC class II antigen induction – Mouse, kidney, MHC class II antigen induction – Rejection, MHC class II antigen, on tubular cells, mouse

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Introduction

Renal allograft rejection is diagnosed largely on the basis of impaired renal function indicating graft damage associated with rejection. However, tests for renal function are not entirely diagnostic for immune rejection and do not necessarily reflect early changes caused by rejection. The definitive standard therefore remains histological examination of tissue taken from the graft. Although many less invasive blood tests have been proposed, none has gained widespread use.

Major histocompatibility complex (MHC) class II antigens are induced on renal tubular cells in human [7] and murine [5, 23] allografted kidneys. With the exception of vascular endothelial cells, hemopoietic cells, and other antigen-presenting cells, normal, nucleated nonlymphoid human cells do not express detectable levels of MHC class II antigens [4, 12, 13, 20]. Therefore, class II antigens induced on the rejecting tubular cells are a possible indicator of rejection.

It has been reported that rejecting mouse [17] and rat [16] cardiac allografts can be visualized before the development of myocyte necrosis by radioimmune scintigraphy using radiolabeled monoclonal antibodies (mAbs), which react with donor-specific or nonspecific class II antigens. In our earlier studies on cardiac allografts, background uptake of ^{111}In anti-MHC class II mAbs in normal kidneys was high and interfered with the application of this scintigraphic technique for the diagnosis of kidney rejection. This problem, however, was solved in the present study by using ^{123}I-labeled mAb instead of ^{111}In as an isotope. Therefore, the primary purpose of this investigation was to show the usefulness of radioimmune scintigraphy using ^{123}I-labeled anti-MHC class II (IE) mAb to detect early kidney allograft rejection in mice. Using this technique,

temporal changes in class II antigen induction in non-treated allografts could be evaluated.

Materials and methods

Animals

BALB/c mice ($H2^d$) and C3H/He mice ($H2^k$) were purchased from Charles River Resources (Boston, Mass.). All animal experiments were approved by the Committee on Research Animal Care Protocol Review and carried out according to Massachusetts General Hospital guidelines.

MAbs

Hybridoma cell line Y17 (anti-$IE^{b,k,r,s,v}$, IgG2b) [21] was purchased from ATCC (Rockville, Md.). Hybridoma cell line YCD3 (anti-CD3) [26] was kindly donated by Dr. Paul S. Russell. Cells were cultured in RPMI 1640 media, supplemented with 10% fetal calf serum and 0.1% gentamycin. Approximately two million hybridoma cells were injected intraperitoneally into pristane-primed BALB/c mice. Resultant ascites was used for purification of mAb. mAb in the ascites was coupled to protein A affinity column (Pharmacia, Piscataway, N.J.) with 10 mM phosphate-buffered saline (pH 7.8) and eluted with 50 mM glycine (pH4). Purified mAb was concentrated using an ultrafiltration concentrator (Amicon, Danvers, Mass.) [15].

Transplantation

Kidney transplantation in mice was performed following the procedure described previously [28]. Donor and recipient mice weighing from 15 to 25 g were anesthetized with chloral hydrate (0.1 ml of a 3.6% solution per 10 g body weight). The left kidney of the donor was mobilized. After injection of cold heparinized saline into the left renal artery, the donor kidney, together with a short segment of aorta, was isolated and stored in iced saline. After ligation of the appropriate lumbar branches of the recipient's aorta and vena cava, ties were placed around the two vessels together and individually, caudad and cephalad to the intended site for the vascular anastomoses, respectively. After occlusion of these vessels by tightening the loops, longitudinal openings were made in each. The side-to-end anastomoses between donor and recipient aortas and between donor renal vein and recipient inferior vena cava were performed in running fashion with 10-0 suture. The recipient's left kidney was removed. In some animals, the connection between donor and recipient bladders was accomplished using 9-0 nylon suture (Ethicon) in running fashion. The ureter was left open in the abdomen in other mice.

Scintigraphy

^{123}I was purchased from Nordion International (Kanata, Canada). Iodination of the mAb was performed using a standard chloramine T method. Approximately 100 μCi of ^{123}I-mAb (10–20 μg of protein) was injected into the tail vein of the recipient mouse 16 h before scintigraphy. Scintigraphy was performed with a gamma camera (Ohio Nuclear 100) equipped with a 3-mm pinhole collimator as described elsewhere [15, 17]. For each scintigram, the intensity of radioactivity in the graft was measured in comparison with that in the native kidney after the renal area had been set by computer planimetry.

Tissue analysis

Mice were sacrificed after scintigraphy. Venous blood was withdrawn and the autologous kidney, transplanted kidney, liver, spleen, heart, and lungs were excised. Both kidneys were washed thoroughly with saline. The biodistribution of radioactivity was determined as previously described [15]. The ratio of percent injected dose per gram of grafted kidney to that of autologous kidney was determined for each mouse.

Animal groups

Twenty-three BALB/c mice were allografted with C3H/He mouse kidneys. Eighteen of the 23 mice were randomly chosen for scintigraphy 1–19 days after transplantation and were injected with radiolabeled mAb and sacrificed thereafter. Another five allografted BALB/c mice were chosen for scintigraphy 3–9 days after transplantation. Immunosuppressive therapy was started the day of the initial scintigraphy in these mice. Fifty microliters of ascites containing approximately 100 μg of YCD3 mAb was intraperitoneally injected daily for 4 days, and cyclosporin (15 mg/kg; Sandoz, Basel, Switzerland) was also subcutaneously injected daily for 2 weeks. Then, the second scintigraphy was performed. The mice were further treated with daily doses of 30 mg/kg of cyclosporin for 2 weeks. The third scintigraphy was obtained. Two mice were sacrificed for tissue analysis after this scintigraphy. In the remaining three animals, the fourth images were taken 2 weeks after the cessation of immunosuppression and they were sacrificed for tissue analysis.

Two C3H/He mice were transplanted with BALB/c kidneys. They were injected with labeled-Y17 mAb at 6 and 8 days after transplantation. Four isografted mice (C3H kidney to C3H recipient), imaged 5, 7, 8, and 21 days after transplantation, served as controls.

Histological examination

Grafted and autologous kidneys were embedded in paraffin and stained with hematoxylin and eosin. The samples were submitted for blind, histopathological evaluation by two examiners. The extent and severity of lesions were semiquantitatively evaluated on a scale of normal to "+ + +" [25] as follows. The extent of interstitial cellular infiltration and three major structures of the kideny (tubules, vessels, and glomeruli) were analyzed in each. The grade "+" was assigned to mild but definite abnormality, the grade "+ +" to moderate abnormality, and "+ + +" to severe abnormality. In the tubules the following were quantitated: inflammatory cell infiltrate, epithelial damage (attenuation, vacuolation, or frank disruption), or necrosis. In the arteries and arterioles, inflammatory cell infiltrate, fibrinoid change or frank necrosis in the media, changes in endothelial cells, and intimal proliferation or thrombosis were quantitated, and in the glomeruli inflammatory infiltrate, crenation of the basement membrane, collapse of capillary loops and necrosis.

Statistical analysis

A P value less than 0.05 was considered not significant in comparisons among multiple groups of data. All data were expressed as the mean ± standard deviation. Linear regression was computed using the least squares method.

Results

Scintigraphy and histopathology

The graft (G) to native (N) kidney radioactivity (% injected dose/weight) ratio (G/N) measured by tissue counting and that measured by computer planimetry performed in the scintigrams correlated well (G/N scintigraphic image = $0.26 \times$ G/N tissue counting + 0.71, $r = 0.90$, $n = 20$). The G/N ratio obtained from scintigrams also correlated well

with graft/blood radioactivity (% injected dose/weight) ratio measured by tissue counting (G/N scintigraphic image = 2.0 × graft/blood + 1.1, $r = 0.95$, $n = 20$). Therefore, G/N determined from scintigrams by computer planimetry was used as an index of mAb uptake in the grafts in this study.

None of the kidneys developed hydronephrosis. A broad spectrum of histological findings was observed, ranging from nearly normal to severe rejection. Regardless of the time after transplantation, radiotracer uptake reflected histopathological manifestation of rejection. The G/N ratio as compared with degrees of mononuclear cellular infiltration was 1.1 ± 0.2 (normal, $n = 7$), 3.0 ± 1.1 (+, $n = 3$, $P < 0.05$ vs normal), 3.7 ± 1.3 (++, $n = 7$, $P < 0.001$ vs normal), and 4.4 ± 1.5 (+++, $n = 6$, $P < 0.001$ vs normal; Fig. 1). The G/N ratio as compared with degrees of tubular damage was 1.1 ± 0.2 (normal, $n = 6$), 2.5 ± 1.2 (+, $n = 4$), 4.0 ± 1.5 (++, $n = 7$), $P < 0.001$ vs normal), and 4.0 ± 1.4 (+++, $n = 6$, $P < 0.001$ vs normal). The G/N ratio as compared with degrees of glomerular damage was 1.2 ± 0.4 (normal, $n = 8$), 3.9 ± 1.4 (+, $n = 8$, $P < 0.001$ vs normal), 3.7 (++, $n = 1$), and 4.0 ± 1.4 (+++, $n = 6$, $P < 0.001$ vs normal). The G/N ratio as compared with degrees of vascular damage was 1.2 ± 0.4 (normal, $n = 8$), 3.9 ± 1.0 (+, $n = 4$, $P < 0.001$ vs normal), 3.8 ± 1.5 (++, $n = 6$, $P < 0.001$ vs normal), and 4.1 ± 1.6 (+++, $n = 5$, $P < 0.001$ vs normal).

Radiotracer uptake started to increase starting on the 3rd day after transplantation, peaked at 6.76 at around the 6th day, increased, and then declined gradually (Fig. 2). As shown in Fig. 3, increased radiotracer uptake in the graft could be identified scintigraphically. Mild rejection with only interstitial mononuclear cell infiltration but without tubular and glomerular damage on the 3rd and 4th days after transplantation showed an unequivocal accumulation of radiotracer and could be identified by scintigraphy. Isografted mice did not show a significant increase in radiotracer uptake (G/N ranging from 0.94 to 1.16) during the course of observation (Fig. 4 A). C3H recipients allografted with BALB/c kidney did not show an increase in labeled Y17 mAb uptake when compared with isografted mice, although they did show significant histological changes associated with rejection (Fig. 4 B).

Effects of immunosuppressive therapy

Five allografted mice imaged at 3, 4, 6, 6 and 9 days after the operation showed an increase in the G/N ratio (5.0 ± 1.3). After 2 weeks of anti-CD3 and cyclosporin therapy, the G/N ratio was significantly reduced (2.9 ± 0.6, $P < 0.05$ vs before treatment). After another 2 weeks of cyclosporin treatment, the ratio decreased further (1.9 ± 0.5, $P < 0.01$ vs 2 weeks). Two mice sacrificed after this scintigraphy showed substantial cell infiltration, but tubular and glomerular changes were not severe (grade 0 or +). Two weeks after the cessation of treatment, the ratio increased (3.1 ± 1.2, $n = 3$, $P < 0.05$ vs 4 weeks; Fig. 5). These grafts showed profound changes in tubules and glomerulus, suggesting recurrence of rejection. These changes in radiotracer uptake could be assessed by the scintigraphic images (Fig. 6).

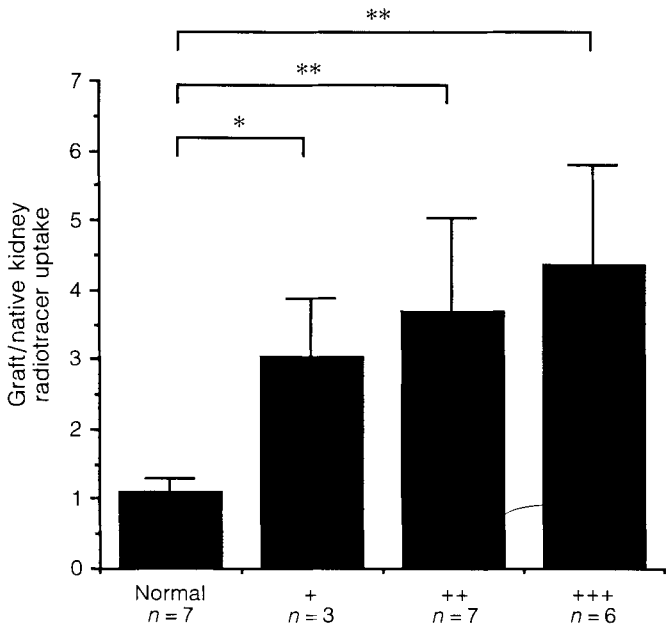

Fig. 1. The graft/native kidney radiotracer uptake ratio determined from scintigrams by computer planimetry compared with degrees of mononuclear cellular infiltration by histological examination. * $P < 0.05$, ** $P < 0.001$

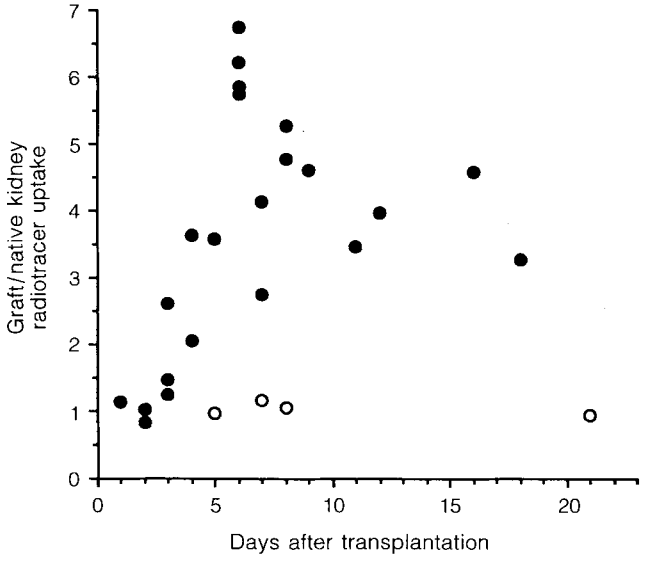

Fig. 2. Time course of Y17 mAb uptake in allografted (●) and isografted (○) kidneys without treatment. Graft/native kidney uptake ratio was determined from scintigrams by computer planimetry

Discussion

The results of this study demonstrate that anti-MHC class II mAb scintigraphy is a sensitive technique for the detection of early kidney allograft rejection. Although determination of serum creatinine level is clinically useful for detecting kidney rejection, elevation of serum creatinine simply reflects a decline in graft function that may be caused by several factors other than rejection. Therefore, a noninvasive technique to detect early rejection in

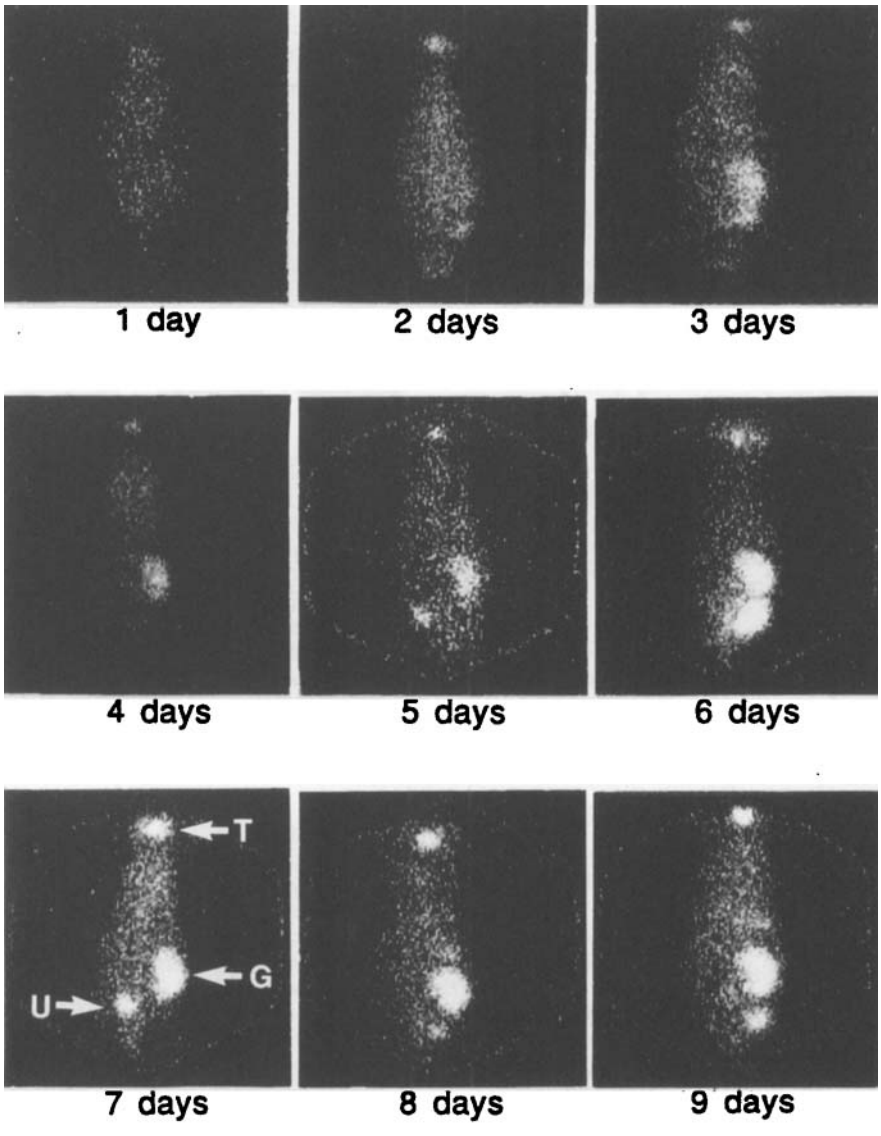

Fig. 3. Temporal changes in scintigrams in nontreated BALB/c mice transplanted with C3H/He mouse kidneys. Each panel is taken from a different animal. An increase in radiotracer uptake can be identified starting on the 3rd day after transplantation. *G*, Grafted kidney; *T*, thyroid gland; *U*, urine

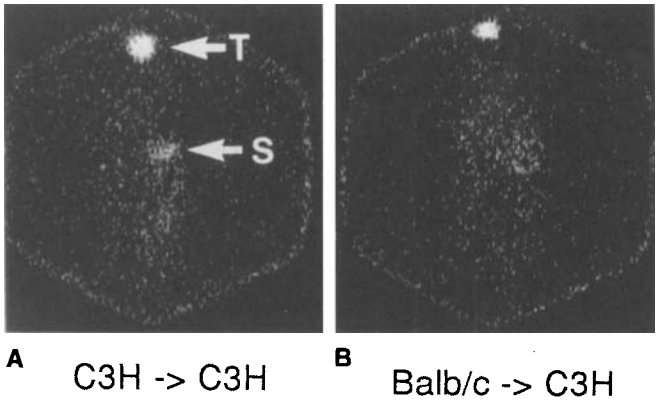

Fig. 4. **A** A scintigram taken from isografted mouse 5 days after transplantation. Faint uptake in the spleen *(S)* is noted. **B** A scintigram taken from C3H/He mouse allografted with BALB/c kidney 7 days after transplantation. Rejecting BALB/c ($H2^d$) kidney transplanted into C3H/He ($H2^k$) is not visualized by Y17 mAb, which binds with IE^k but not with IE^d

association with immunological processes would be desirable for the improved management of patients.

MHC class I and class II molecules play an essential role in the pathogenesis of rejection [11, 19, 20]. The expression of class II antigens in the kidney is limited to parenchymal cells [12, 23]. The expression on vascular endothelial cells is found in normal humans but not in rodents [6]. However, class II antigens are induced in association with organ rejection [2, 18, 22, 27]. Massive induction of class II antigens, primarily on tubular cells, is reported in allografted kidney in mice [5], rats [23], and humans [7]. Once initiated, the cellular infiltrate of the rejection response will release a wide variety of lymphokines. Among these lymphokines, gamma interferon acts on the cells in the vicinity to induce MHC class I and class II antigens [8]. These observations, obtained by tissue staining, suggested a rationale for utilizing induced class II antigens as a target for the detection of rejection.

One of two mouse MHC class II molecules (IE) was selected as a target for the radioimmune imaging in this study. This mAb reacts with C3H/He ($H2^k$) mouse IE

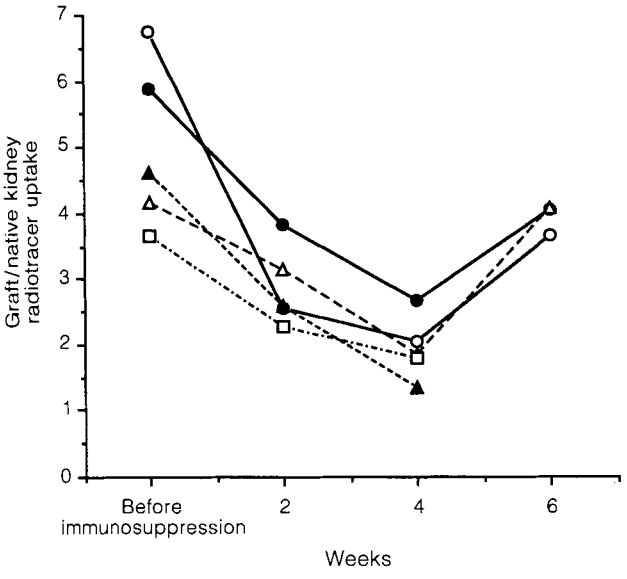

Fig. 5. Serial changes in radiotracer uptake in BALB/c mice transplanted with C3H/He allografts before, during, and after immunosuppression. The first scintigraphy was performed 3–9 days after transplantation. Scintigraphy was repeated every 2 weeks. Animals were treated with a 4-day course of anti-CD3 antibody (approximately 100 μg/day) and 4 weeks of cyclosporin starting after the initial scintigraphy. After the third scintigraphy two mice were sacrificed for histological analysis. The fourth scintigraphy was obtained in three animals 2 weeks after cessation of the treatment, after which they were killed. ○, ●, ▲, △, □. Each symbol denotes a different animal

antigen but not with BALB/c ($H2^d$). Isografted C3H mice did not show any specific uptake of radiotracer. In the allografted mice, the uptake of labeled Y17 mAb began on the 3rd day after transplantation and increased progressively until the 6th day. This increase in mAb uptake was clearly visualized by gamma scintigraphy.

None of the five allografted mice that were deemed to be without cellular infiltrate showed an increase in mAb uptake, nor did the four isografted mice. In contrast, all of the allografted mice with mononuclear cellular infiltrate had an elevated G/N ratio. Mice with relatively advanced rejection (tubular necrosis and glomerular damage) showed an increased uptake of radiotracer without exception. Two allografts with only perivascular cellular infiltration and without tubular or glomerular changes showed an increase in the G/N ratio and were unequivocally identified by the scintigraphic images. Therefore, MHC class II scintigraphy was shown to provide a sensitive method of detecting kidney allograft rejection.

The mAb uptake tended to decrease beginning 1 week after allografting. There are several possible reasons for this relative reduction in mAb uptake. Allografted kidneys developed tubular necrosis to a varying extent about 1 week after transplantation and the necrotic area increased progressively. Therefore, one of the reasons for a reduction in mAb uptake is likely to be a loss of donor tubular cells that can express class II antigens.

Four allografted mice that were sacrificed 1–4 days after the operation showed scattered areas of necrosis and

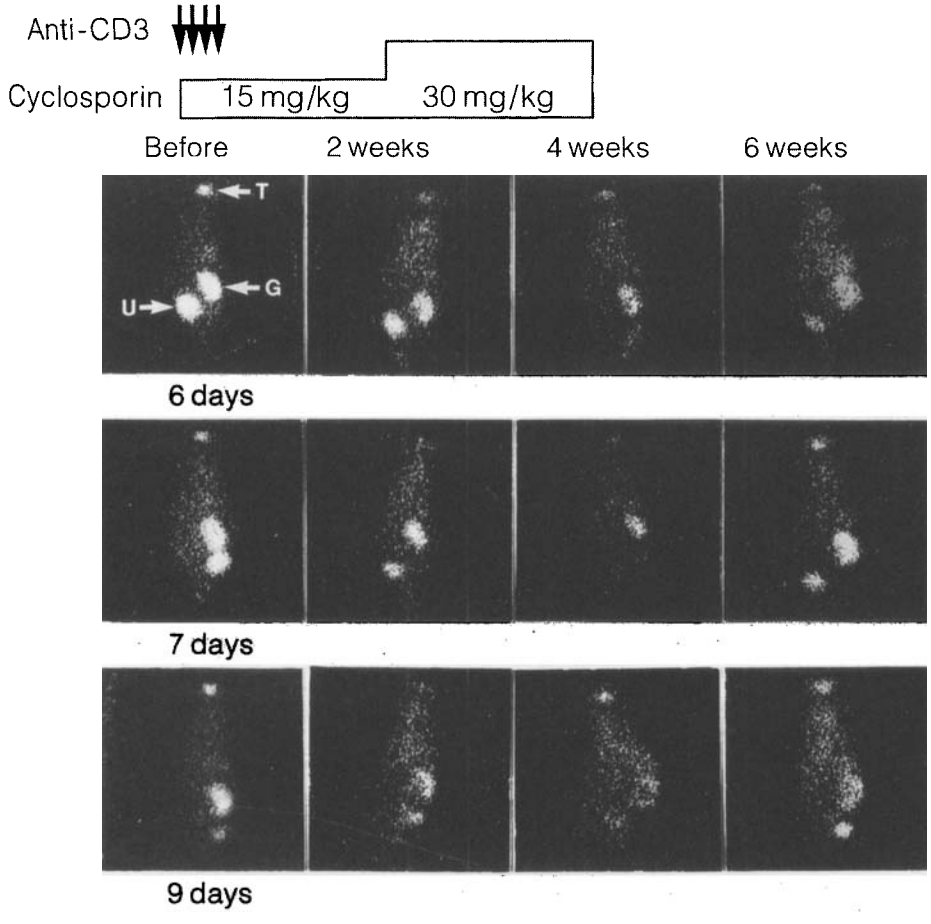

Fig. 6. Serial scintigrams from three allografted mice before, during, and after immunosuppression. *G*, Grafted kidney; *T*, thyroid gland; *U*, urine

hemorrhage, probably due to perioperative ischemic injury. One of these mice with histological evidence of rejection was positive for the scan, whereas others without rejection did not show an increase in the mAb uptake. These findings show that cell necrosis caused by ischemia does not cause the increased uptake of mAbs to MHC class II antigens.

MHC class II antigens are induced not only on donor cells but also on infiltrating mononuclear cells derived from recipients. It has already been demonstrated that induced donor class II antigens are solely responsible for the increase in radiotracer uptake in a mouse cardiac allograft model [17]. The observations of the present investigation in kidney allografts were consistent with the previous findings. Scintigrams of the two C3H ($H2^k$) mice transplanted with BALB/c ($H2^d$) kidney were negative in spite of the histological signs of severe rejection because Y17 mAb reacts with IE^k but not with IE^d. This finding also rules out the possibility that a nonspecific accumulation of mAb at an inflammatory site caused the positive scan of rejecting kidneys.

In this study, background tracer uptake was significantly reduced by using ^{123}I as an isotope. Our preliminary studies using ^{111}In showed a high uptake of radiotracer in the normal liver and kidney. This high accumulation of ^{111}In in the normal kidney had hampered an application of this scintigraphic technique for the detection of rejecting kidney. However, uptake in the liver and kidney was significantly less when the mAb was labeled with ^{123}I than with ^{111}In. Several differences in the two radioisotopes, such as the stability of the compound, the half-life of the isotope, and the catabolism of radiotracer, may account for the difference in background uptake. However, the mechanism of this difference has yet to be established.

In Figs. 3 and 5, radioactivity in the urine was remarkable in animals sacrificed on the 5th day or later. One of the problems of our mouse kidney transplant model is the reconstruction of urinary tracts. Donor ureter was not connected to the bladder of the recipients in the majority of the animals. Isolated intraperitoneal cavity containing urine was sometimes found at the time of sacrifice in some animals, though none had hydronephrosis. Therefore, radioactive-free iodine in the urine trapped in the cavity could account for the strong urine activity observed in animals sacrificed more than 5 days after transplantation. Investigations using larger animals would solve this problem.

In the previous study, it was demonstrated that mice with cardiac allografts treated with cyclosproin starting at the time of transplantation did not show any significant increase in radiolabeled donor-specific anti-MHC class II mAbs 1 week after the operation, reflecting suppresssion of rejection. In this study, the changes in mAb uptake by immunosuppressive therapy were evaluated. It appears that the reduction in mAb uptake after 4 weeks of immunosuppressive therapy reflects the reduction in MHC class II antigens by immunosuppression, and its increase after the cessation of the treatment reflects the reinduction of class II antigens due to a recurrence of rejection; however, the number of animals was not sufficient to allow a definite conclusion to be drawn. These changes were demonstrated by the scintigraphic images.

In the clinical management of kidney transplantation, differential diagnosis of renal failure due to acute rejection from cyclosporin nephrotoxicity is sometimes crucial but often difficult. Cyclosporin, which is a potent inhibitor of gamma interferon [1], suppresses the induction of class II antigens in vivo [24]. As suggested in the present study, treatment of allografts with cyclosporin and anti-CD3 mAb reduces the radiotracer uptake. This is certainly a reflection of suppressed class II antigen expression by the immunosuppression. Further studies are necessary to show the usefulness of this scintigraphy in the noninvasive differentiation of cyclosporin-induced renal dysfunction from acute rejection.

The usefulness of scintigraphy targeting class II antigen in detecting early kidney allograft rejection in large animals, including humans, should be investigated. One difference in the pattern of MHC class II antigen expression between mice and other large animals, including humans, requires consideration. The pattern of normal expression of MHC class II antigens seems to be species-dependent. Normal human vascular endothelial cells express class II antigens [6], but those in the mouse do not ubiquitously express class II antigens [5]. However, normal tubular cells do not express detectable levels of MHC class II antigens in any of the species reported. Although class II antigens are massively induced in the tubular cells in association with rejection, normal expression of class II antigens in the vascular endothelial cells may affect the sensitivity of the anti-class II antibody scintigraphy. This issue should be investigated in large animals before clinical application.

The induction of MHC class II antigen is reported not only in rejecting organs but also in tissues undergoing autoimmune injury [9, 10, 30], in viral disease [14, 29], and in inflammatory disease [3]. MHC class II antibody scintigraphy could, therefore, also be applied to the detection and localization of these disorders.

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