Are Gadolinium-Based Contrast Media Nephrotoxic?
A Renal Biopsy Study

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Gadolinium-based contrast media were originally introduced as alternatives to iodinated media for magnetic resonance imaging. Although originally thought to be non-nephrotoxic, gadolinium-based contrast media have recently been reported to be associated with acute renal failure; the mechanism and the underlying renal injury are not completely understood. We report what is, to our knowledge, the first renal biopsy in this context. A 56-year-old patient underwent 2 consecutive vascular imaging procedures in conjunction with gadolinium-based contrast medium administration. A few days later, the patient developed acute renal failure. A renal biopsy showed acute tubular cell injury including patchy tubular cell necrosis, tubular cell degeneration, and marked proliferation of tubular cells, together with mild interstitial edema and interstitial inflammation, but without significant glomerular or vascular changes. During supportive therapy, renal function was partially regained. This case emphasizes the potential nephrotoxicity of gadolinium-based contrast media and suggests that the nephrotoxicity is related to potentially reversible acute tubular cell injury.

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With the increased utilization of diagnostic and interventional angiographic procedures,1,2 nephrotoxicity due to iodinated contrast media has become the third most common cause of acute renal failure. Iodinated contrast medium-induced nephropathy has been reported in up to 20% of patients subjected to these procedures, and in those with preexisting renal insufficiency, the incidence may be as high as 50%.3,4

Among maneuvers to obviate contrast medium-induced nephropathy, replacement of iodinated contrast media by those based on gadolinium has received much attention.1,3,4 Gadolinium is a member of the lanthanide series of transition metals that has strong hydrogen-proton spin-lattice relaxation effects, which can be exploited to provide enhanced contrast between healthy and diseased tissue.5,6

Four gadolinium-based contrast media are available in the United States—gadopentetate dimeglumine, gadodiamide, gadoteridol, and gadoversetamide—in each of which gadolinium ion is chelated to various anion groups to form gadolinium salts.7 Since gadolinium-based contrast media were initially thought to be nonnephrotoxic, they have become increasingly popular, especially for vascular imaging with magnetic resonance angiography or digital subtraction angiography.8 A few recent studies have described their renal side effects, but the actual risk and the underlying mechanism are not completely known. This limited understanding is multifactorial but in no small part due to a lack of knowledge of the nature of the renal tissue injury, especially in humans.

We report herein the first renal biopsy from a patient with acute renal failure associated with gadolinium-based contrast media to emphasize their potential nephrotoxicity and to discuss the possible mechanism of this condition in the context of the renal biopsy findings.

REPORT OF A CASE

A 56-year-old woman was admitted with a hypertensive crisis (blood pressure, 250/120 mm Hg), for which she was treated withvalsartan (160 mg/d) and hydrochlorothiazide (12.5 mg/d). The serum creatinine 2 months previously was 1 mg/dL and the urine protein-creatinine ratio was 0.02. Four days after the hypertensive crisis, her serum creatinine was 1.0 mg/dL. Because of persistent headache, magnetic resonance imaging of the head with intravenous injection of 17 mL (8.5 mM, 0.10 mM/kg body weight) gadolinium-diethylenetriaminepentaacetic acid (DTPA) (Magnevist, Berlex Laboratories, Wayne NJ) was performed; it showed a tumor consistent with a meningioma. For the workup of the hypertensive crisis, magnetic resonance imaging of the abdomen was also performed the next day with a bolus intravenous injection of 30 mL (15 mM, 0.19 mM/kg body weight) gadolinium–DTPA-BMA (Omniscan, Sanofi-Winthrop, New York, NY), but a vascular lesion was not found. Her serum creatinine started to increase and 6, 7, and 9 days after the last magnetic resonance imaging reached levels of 1.5, 2.8, and 3.4 mg/dL, respectively. The patient had Type 2 diabetes for the preceding 10 years that was being treated with glimepiride and metformin hydrochloride, and also hypertension of unknown duration that was being treated with amlodipine besylate and valsartan. Physical examination was unremarkable. Laboratory tests showed a white blood cell count of 9.55 × 10^9/mm^3 (differential: 65% neutrophils, 23% lymphocytes, 6% monocytes, 6% eosinophils); hemoglobin, 13.5 g/dL; hematocrit, 39.4%; platelet, 247 000/mm^3; prothrombin time, 14.1 seconds; partial thromboplastin time, 34.3 seconds; serum Na, 137 mEq/dL; K, 4.0 mEq/dL; Cl, 100 mEq/dL; blood urea nitrogen, 60 mg/dL; creatinine, 3.4 mg/dL; glucose, 112 mg/dL; calcium, 10.2 mg/dL; total serum protein, 8.1 g/dL; serum albumin, 4.9 g/dL; uric acid, 9.2 mg/dL; phosphate, 4.0 mg/...
Figure 1. The glomerulus shows mild mesangial sclerosis. The tubules show focal flattening of tubular epithelial cells, degenerated cells in tubular lumens (thick arrows), or detachment of tubular epithelial cells from the underlying basement membrane (thin arrows). There is interstitial edema and fibrosis (toluidine blue, original magnification ×400).

Figure 2. A, Focal acute tubulointerstitial changes including tubular epithelial flattening (arrows), interstitial edema, and early interstitial fibrosis. Pale blue material admixed with calcium phosphate (asterisk) is noted in the lumens of the tubules with acute injury (hematoxylin-eosin, original magnification ×400). B, The tubules with acute injury in the tissue section consecutive to that in A show several tubular cell nuclei stained positive for MIB-1 (arrows), a cell proliferation marker (immunostain, original magnification ×200).

Figure 3. The glomerular capillaries and mesangium are normal by electron microscopy (original magnification ×2000).

dL; Mg, 2.0 mg/dL; cholesterol, 197 mg/dL. Results of the liver function tests were normal. The serum levels of metanephrine and normetanephrine were normal. Serologic testing for antinuclear antibody, antineutrophil cytoplasmic antibody, and anti-glo- merular basement membrane antibodies were negative. Ura- nalysis showed no protein, glucose, ketones, or bilirubin. The urine and serum electrophoreses showed no monoclonal spike. A renal biopsy, performed 10 days after the last magnetic resonance imaging, showed features of acute tubular necrosis consistent with gadolinium nephrotoxicity (see “Renal Biopsy Findings”). The absence of renal artery stenosis was confirmed by CO2 angiography. During supportive therapy, renal function improved gradually, and the serum creatinine was 3, 2.7, 2.3, and 1.6 mg/dL on days 6, 12, 18, and 65, respectively, after the renal biopsy, during which time the blood pressure was well controlled. Sixty-five days after the renal biopsy, the meningioma was successfully excised.

RENAL BIOPSY FINDINGS

The renal biopsy showed both cortical and medullary tissue, with up to 10 glomeruli present in each represen- 

tative tissue section. Two of the glomeruli showed global sclerosis with subcapsular fibrosis. The other glomeruli were opened but displayed focal segmental, mild mesangial sclerosis, and hypercellularity (Figure 1). There was focal chronic tubulo-interstitial injury characterized by tubular atrophy and interstitial fibrosis, which involved about 20% of the cortical surface area. In addition, there were also multifocal acute tubulo-interstitial changes including interstitial edema and mild mononuclear inflammatory cell interstitial infiltrate. Several tubular cross sections showed acute tubular cell injury characterized by flattening of the tubular epithelium, areas of denuded tubular basement membrane, and degenerated or necrotic tubular epithelial cells in tubular lumens (Figure 2, A). Immunostain for MIB-1, a cell proliferation marker, showed several positive tubular cell nuclei (Figure 2, B). The tubules with acute injury were focally associated with luminal deposits consistent with calcium phosphate. Both
the small arteries and arterioles showed mild-to-moderate fibrous intimal thickening, but without hyalinosis. Glomeruli were not seen in the tissue submitted for immunofluorescent studies. The tissue portion submitted to electron microscopy showed cortical and medullary tissue, including 5 open glomeruli, and displayed features as seen in the light microscopic portion. Ultrastructural examination showed focal segmental mild thickening and wrinkling of the glomerular basement membrane and mild mesangial sclerosis (Figure 3). Immune-type, electron-dense deposits were not identified. Renal changes of malignant hypertension, including thrombosis or fibrinoid necrosis of glomerular capillaries or arterial blood vessels or fibromyxoid vascular intimal thickening, were not seen, nor were features of advanced diabetic nephropathy or acute drug-induced interstitial nephritis detected. The final diagnosis was acute tubulointerstitial injury associated with gadolinium-based contrast exposure, developing against the background of mild hypertensive nephrosclerosis.

**COMMENT**

Contrast medium nephrotoxicity is defined as an increase in serum creatinine of more than 25% or of 0.5 mg/dL occurring within 3 days following the intravascular administration of contrast medium, in the absence of an alternative etiology. Gadolinium-based contrast media were originally introduced as an alternative to the iodinated media for magnetic resonance imaging studies. Some early studies suggested that gadolinium-based contrast media are not nephrotoxic, even in patients with preexisting renal insufficiency. Following a few anecdotal reports that gadopentate dimeglumine was successfully used for vascular imaging in patients whose baseline serum creatinine was as high as 4.8 mg/dL, Prince et al in 1996 studied 64 azotemic patients who received both a gadolinium-based contrast medium for magnetic resonance angiography and an iodinated contrast medium for computed tomographic scan on different occasions. They found that renal failure was noted in 5 instances in the latter group but in none in the former one. This difference may be attributed, however, to a very high dose of iodinated contrast material injected intra-arterially, with direct exposure to the renal vasculature, in several patients. More recently, Rieger and coworkers reported only 1 episode of acute renal failure out of 39 gadopentate dimeglumine-based angiographic imaging procedures in 29 patients with renal insufficiency (serum creatinine 1.7–7 mg/dL, mean 3.6 mg/dL), 59% of whom were diabetic.

The risk of gadolinium-induced nephrotoxicity is, however, strongly suggested by more recent experimental and clinical studies. Nephrotoxicity, diagnosed by laboratory parameters including increased serum creatinine, decreased creatinine clearance, or elevated tubular cell enyzymuria, was induced in the mouse, rat, rabbit, dog, and pig by intravascular injection of various gadolinium chelates. The underlying renal lesions were not well defined since renal tissue was not evaluated in most of these studies, except for those by Sekido et al and Spencer et al. In the former, a single dose of gadolinium chelates to dogs caused diffuse vacuolization of renal cortical tubular cells. In the latter, intravenous injection of gadolinium in mice or rats caused mineral deposits in glomeruli and peritubular capillaries at the renal papillae, which contained both gadolinium by x-ray diffraction studies and calcium by a weak alizarin red stain. Prompted by 2 recent case reports of acute renal failure after gadolinium-based angiography, Sam et al comprehensively studied 260 patients (195 with chronic renal insufficiency and 65 without) subjected to gadolinium angiography and found that acute renal failure developed in 7 patients (3.5%) in the chronic renal insufficiency group but was not encountered in the other group. The serum creatinine returned to baseline within 4 to 12 days in 5 patients, but end-stage renal disease developed in 2. The risk of acute renal failure was higher for digital subtraction angiography (4 [9.5%] of 42 procedures) than for magnetic resonance angiography (3 [1.9%] of 153 procedures). The minimum dose associated with nephrotoxicity in normal individuals has not been determined. In most studies the doses ranged from 0.27 to 0.41 mM/kg of body weight. It is recommended that the dose should not be more than 0.3 mM/kg and, in patients with renal insufficiency, even lower doses should be used.

Distinct from, but closely related to, the problem of gadolinium-based contrast nephrotoxicity is the recent introduction of gadolinium chelates as a radiosentitizer for radiotransport therapy. Rosenthal et al reported that 4 of 41 patients who received a single intravenous dose of gadolinium texaphyrin in conjunction with radiation therapy for advanced cancers developed acute renal failure from the background of normal renal function, but the condition was reversible in all within 4 days. Renal biopsy was performed only in 1 case; the biopsy specimen had features of acute tubular necrosis, but the glomeruli were normal. These observations prompted the recommendation by the European Society of Urogenital Radiology against the use of gadolinium-based contrast media for angiographic procedures.

The acute renal failure in the current case is most probably due to gadolinium-based contrast media. The normal baseline renal function, the rapid and marked increase in serum creatinine shortly after administration of the contrast media, the return of renal function during supportive therapy (albeit not to baseline), and the absence of an alternative explanation for the acute renal failure all support this possibility. The acute renal failure was most probably unrelated to the hypertensive crisis for the following reasons:

1. The serum creatinine remained at the baseline of 1 mg/dL at least 5 days after the onset of the hypertensive crisis; in contrast, the acute renal failure only developed 11 days after gadolinium administration.
2. Acute renal failure secondary to malignant hypertension is frequently associated with proteinuria, even reaching the nephrotic range; yet no proteinuria was detected in this patient by repeated urinalysis.
3. The renal biopsy material should show characteristic changes in cases of malignant hypertension–induced acute renal failure, but these changes were not identified in the current renal biopsy material. Furthermore, the current biopsy material showed severe acute tubular cell injury, including a marked proliferation of tubular epithelial cells, which is not a feature of malignant hypertension–induced acute renal failure.

To the best of our knowledge, this is the first time renal biopsy findings have been described for gadolinium–based contrast medium nephrotoxicity. These changes, which point to an acute injury of tubular epithelial cells...
and preservation of renal blood vessels and glomeruli, are similar to those noted in cases of acute renal failure associated with iodinated contrast media. Gadolinium chelates have pharmacokinetics similar to those of iodinated contrast media. They are distributed in the extracellular space and are eliminated almost exclusively by the kidney through glomerular filtration. In patients with normal renal function, about 98% of gadolinium chelates are excreted within 24 hours. Renal failure impairs but maintains effective gadolinium excretion without resorting to a nonrenal route of excretion or toxic degeneration of the chelates. Even in patients with end-stage renal disease, gadolinium was not found in blood several days after intravenous injection. Within the tubular lumens, the chelates are intensely hydrophilic and behave like biologically inert compounds such as mannitol or inulin, without being absorbed by tubular epithelial cells. The nephrotoxic effects of iodinated contrast agents may be multifactorial, including a vasoconstrictive effect leading to hypoxic or ischemic tubular cell injury and a direct tubulotoxicity mediated by the generation of reactive oxygen species. Very little is known about the mechanism of gadolinium nephrotoxicity, and this limitation is at least in part due to meager data on the renal lesions in this condition. Since gadolinium-based and iodinated contrast agents share the same pharmacodynamics and their nephrotoxic effects are clinically similar, they may cause renal damage through the same mechanisms. In this respect, the renal biopsy findings in the current case imply a primary tubular cell injury as a crucial pathway by which gadolinium chelates lead to nephrotoxicity.

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References


