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Unexpected Complications of Gadolinium-Based Contrast Agents: Nanoparticles Formation and Profound Perturbation of Metabolism

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Abstract

Gadolinium-induced systemic fibrosis was initially recognized in patients with end stage renal disease (with functioning renal transplants or on chronic hemodialysis) and acute kidney injury. Despite a 'black box' warning against the use of all gadolinium-based agents in anyone with renal insufficiency, such patients are still subjected to gadolinium contrast-enhanced imaging when the diagnostic information is thought to outweigh the risks. The odds ratio for patients with end-stage renal disease contracting gadolinium induced systemic fibrosis after an exposure to gadolinium-based contrast ranges from 20.6 to 41.3. The mechanism of how gadolinium induces systemic fibrosis is central to this review. Our research validates the finding that gadolinium-based contrast agents have effects on renal histology and kidney function. Using lethally-irradiated rats salvaged with tagged bone marrow, we provided experimental evidence that over 40% of the cellularity of gadolinium-induced fibrotic lesions originated from circulating fibrocytes. Through this model we demonstrated that gadolinium-based contrast treatment leads to gadolinium deposition in the skin, histologic features of fibrosis, an increase in dermal cellularity (predominantly of the spindle-type cells similar to what has been described in patients with gadolinium-induced systemic fibrosis), and measurable markers of fibrosis. In a mouse model, we discovered that gadolinium-based contrast agent treatment led to amorphous mesh-like nanowire structures found in multinucleated giant cells of the skin and the renal proximal tubules. Our data indicate gadolinium concentrates in the kidney and induces glomerular pathology. Progression on identifying triggering mechanisms of gadolinium-induced systemic fibrosis will assist in unraveling the process of disease initiation and guide rational approaches for prophylaxis and treatment.

Keywords: Nephrogenic systemic fibrosis; Gadolinium; Nanoparticles; Metabolism

Introduction

Magnetic resonance imaging has revolutionized diagnostic medicine. Six million doses of gadolinium-based contrast are administered annually [1,2]. Approximately 50,000 MRI examinations are conducted world-wide every day, tallying more than 40 million procedures annually. In 1997, a painful and severely debilitating disease was recognized in patients with end-stage renal disease (with functioning renal transplants or on chronic hemodialysis) and acute kidney injury. In 2006, it was realized that this syndrome, misnamed 'nephrogenic' systemic fibrosis1, was caused by gadolinium-based contrast agents. Gadolinium-induced systemic fibrosis is a ghastly disorder. The odds ratio for patients with end-stage renal disease contracting it after an exposure to gadolinium based contrast ranges from 20.6 to 41.3 [1]. Patients with chronic and end-stage renal disease still are at risk for exposure to high-risk gadolinium-based contrast agents (despite the FDA "black box" warning) [3]. Despite a 'black box' warning against the use of all gadolinium-based agents in anyone with renal insufficiency, such patients are still subjected to gadolinium contrast enhanced imaging when the diagnostic information is thought to outweigh the risks. Thousands of hemodialysis patients, 405 peritoneal dialysis patients, and over 1000 severe chronic kidney disease patients were exposed to MultiHance, (a gadolinium-based contrast agent) at the University of Arizona College of Medicine, Banner University

Medical Center in Tucson despite the United States Food & Drug Administration boxed warning about these high-risk populations. This paper was rapidly withdrawn by the authors, citing "the study was not conducted in full accordance with the relevant institutional IRB protocol." The United States Food & Drug Administration Adverse Events Reporting System (FAERS) Public Dashboard lists 574 cases of gadolinium-induced systemic fibrosis under "MultiHance" alone as of this writing and over 3,000 cases when all gadolinium-based contrast agents are included in the search. Gadolinium-based contrast remains a mainstay of diagnostic imaging and alternatives are lacking. Even in academic centers (such as the University of Arizona) thousands of high-risk patients with chronic or acute kidney impairment continue to be exposed to gadolinium-based

contrast agents despite the lack of prospective, randomized, and double-blinded studies demonstrating safety. There is mounting evidence that systemic fibrosis, one among a constellation of gadolinium-based contrast agent-induced disorders, is not limited to patients with kidney impairment [4]. At the September 8th, 2017 United States Food & Drug Administration Medical Imaging Drugs Advisory Committee meeting, the officers, representatives of the pharmaceutical industry, and the National Institutes of Health representative each mentioned that gadolinium-induced systemic fibrosis was part of the same continuum of symptoms exhibited by patients with normal renal function and gadolinium retention.

Mechanisms

It is known that gadolinium-based contrast agent administration stimulates the infiltration of bone marrow-derived fibrocytes into target lesions and that this is accompanied by the generation of reactive oxygen species from NADPH oxidase homolog type 4 (Nox4) [5]. Gadolinium from magnetic resonance contrast agent treatment whether open-chained or macrocyclic is retained in every organ tested [6]. Myeloid cells retain a 'memory' of prior gadolinium exposure [7]. The monocyte chemoattractant protein 1/C-C chemokine receptor 2 pathway is requisite for gadolinium-induced systemic fibrosis [7]. Gadolinium-based contrast agents aggregate in the lysosomes of the renal proximal tubule and ravage the cortex with subsequent alteration of renal metabolism [7], Cases of gadolinium-induced systemic fibrosis-like symptoms and signs have been reported in patients with normal renal function subjected to one or more gadolinium enhanced scans [8]. In one of the cases, gadolinium was detected in a skin biopsy four years after a Food & Drug Administration recommended label dose of gadolinium-based contrast agent for a cardiac magnetic resonance imaging scan. Symptoms and signs of extremity fibrosis persisted for at least seven years. Gadolinium may cause histologically-similar dermal plaques in the absence of renal insufficiency [9]. A patient with normal renal function who received numerous gadolinium-enhanced scans over an 11-year period (all stemming from the diagnosis, resection, and complications of a left temporal cerebral glioblastoma) was found to have very high levels of gadolinium deposited in his skin [4]. Many of the criteria for gadolinium-induced systemic fibrosis were met, including skin CD34 positivity "indicating inflammation and/or tissue injury," and joint contractures.

In a retrospective study of pregnant women (2003-2015), gadolinium-enhanced magnetic resonance imaging was associated with increased risks for stillbirth and neonatal death [10]. Furthermore, gadolinium exposure correlated with rheumatological, inflammatory, and infiltrative skin diagnoses (by ICD-9 codes) in the children from birth to 4 years of age. Until the pathologic effects are discerned, it was concluded that gadolinium should be avoided during pregnancy. Gadolinium-based contrast for the enhancement of nuclear magnetic resonance images is widely used throughout the United States. The discovery that gadolinium induced systemic fibrosis was caused by gadolinium-based contrast media dramatically altered clinical practice. Recently new conditions have been proposed, 'gadolinium storage condition' and 'gadolinium deposition disease, describing gadolinium-based contrast induced chronic adverse events that occur in patients with normal renal function. The risk of gadolinium-based contrast agent-induced adverse events (not limited to systemic fibrosis) likely follows a curvilinear function with decreasing glomerular filtration rate **(Figure 1).** Patients suffering from renal disease have a tendency to be burdened with cutaneous afflictions that are not well-understood [11]. Gadolinium-induced systemic fibrosis is a ghastly condition that is characterized by generally permanent skin sclerosis, muscle fibrosis, joint contractures, and the involvement of several organs [3]. The symptoms and signs of gadolinium-induced systemic fibrosis are similar to many sclerotic disorders, but the distribution of findings and histology are unique. In scleredema diabeticorum (diabetic thick skin), much of the dermal histology resembles what has been described in gadolinium-associated dermal fibrosis, i.e., large and disorganized collagen bundles, mucopolysaccharides, and active fibroblasts [12]. Much like gadolinium-induced systemic fibrosis, there is no definitive treatment for scleredema. Not all chronic kidney disease patients, including those with end-stage renal disease, succumb to gadolinium-induced systemic fibrosis even after multiple exposures. Therefore, there have to be other risk factors other than renal insufficiency and contrast exposure. Diabetes was the only predictor of early mortality in patients with cutaneous changes resembling gadolinium-induced systemic fibrosis in a cohort study involving 216 end-stage renal disease patients [13]. Perhaps the pro-fibrotic milieu of metabolic derangement shares elements with what is triggered by gadolinium.

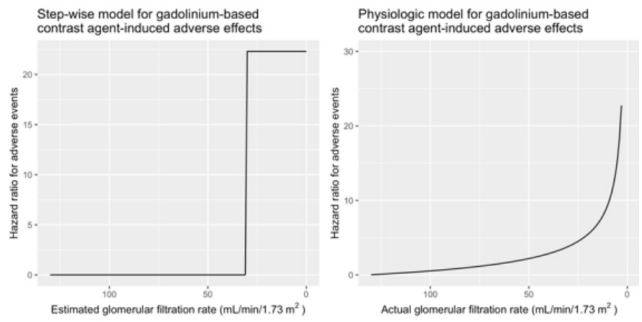

Figure 1 Competing risk models for adverse events from gadolinium-based contrast agents. (Left) American College of Radiology step-wise model of systemic fibrosis risk and estimated (i.e., not actual) glomerular filtration rate. (Rarely are natural phenomena so capricious.) (Right) Physiologic model of systemic fibrosis risk with actual glomerular filtration rate. as with essentially every risk and co-morbidity in patients with kidney disease, the risk for adverse events universally increases with worsening kidney function.

The Mechanisms of Gadolinium-Induced Systemic Fibrosis

There are very few laboratories conducting mechanistic research concerning gadolinium toxicity, and even fewer with mouse models. Dr. Mandip Panesar (Erie County Medical Center, State University of New York at Buffalo) has studied the effect of gadolinium-based contrast (3 mmol/kg once per week for 2-6 doses) in wild-type and in renin-secreting transgenic mice. With this relatively small amount of gadolinium, there was an impressive increase in mesangial cellularity and renal interstitial fibrosis. This supports what our laboratory has discovered in gadolinium-treated mice with tagged marrow, i.e., there is an increase in bone marrow-derived cells to the kidney. The work of Dr. Peter Rowe et al. [11] (University of Kansas Medical center) suggest that there are many more patients at risk for gadolinium-induced systemic fibrosis than just a subset of those afflicted with severe kidney insufficiency [11].

Establishment of a Mouse Model of Gadolinium-Induced Systemic Fibrosis

Using lethally-irradiated rodents salvaged with tagged bone marrow, we have repeatedly provided experimental evidence of gadolinium-induced systemic fibrotic lesions [1,5-7]. Through these models we demonstrated gadolinium deposition in every vital organ, histologic features of skin fibrosis, an increase in dermal cellularity, and amorphous mesh-like nanowire structures found in multinucleated giant cells of the skin and the renal proximal tubules [6]. Over 40% of the dermal cellularity of gadolinium-induced fibrotic lesions originated from circulating fibrocytes [5]. Although there are great advantages in leveraging the numerous genetic manipulations in mice, there are few murine models of gadolinium-induced systemic fibrosis. Our research team published the first chimeric rat and mouse model of gadolinium-induced systemic fibrosis [5,6].

Gadolinium Contrast Induces Systemic Fibrosis in Mice

Gadolinium has been found in affected skin biopsies and has been measured in the skin 41 to 331 days after exposure [14-16]. Mice with 5/6 nephrectomies (to model chronic kidney disease) were lethally-irradiated (two doses of 450 rad separated by 3 hours, Gammacell 40 cesium-source irradiator) then salvaged with marrow obtained from green fluorescent protein-expressing donors. After several weeks to allow for engraftment the animals were weight-matched and randomized to control or contrast treatment (gadodiamide, 2.5 mmol/kg intraperitoneally, 20 doses over 4 weeks).

Gadolinium (as measured by inductively coupled plasma mass spectroscopy) was detectable in the skin from the contrast treated animals. Hematoxylin and eosin-stained sections of paraffin-embedded fixed tissue demonstrated disorganized extracellular matrix, thickened collagen bundles, and numerous spindle-shaped cells in the dermis of the contrast-treated animals **(Figure 2A).** Three random sections of dermis were photographed on high power and nuclei were quantified; similar to our previous findings in contrast-treated rats [5,6], there was an increase in dermal cellularity in the gadolinium-treated mice. Fibronectin expression was diffusely increased in the dermis of the gadolinium-treated mice. Protein from homogenized skin demonstrated increased levels of fibronectin and collagen type I, quantifiable markers of fibrosis. This experiment demonstrated that magnetic resonance imaging contrast treatment leads to gadolinium deposition in the skin, histologic features of fibrosis, an increase in dermal cellularity (predominantly of the spindle-type cells similar to what has been described in patients with gadolinium-induced systemic fibrosis), and measurable markers of fibrosis. This validated a mouse model of gadolinium-induced fibrosis.

Gadolinium Induces Renal Fibrosis and Albuminuria in a Mouse Model

Gadolinium-associated fibrosis involves numerous organs (hence the term 'systemic'), including the kidney [17]. Mice with intact renal function were treated with gadolinium-based contrast (2.5 mmol/kg intraperitoneally, 20 doses over 4 weeks). Glomeruli from the contrast-treated animals demonstrated more mesangial matrix by periodic acid-Schiff (PAS) staining **(Figure 2B)**, increased glomerular fibronectin, and increased glomerular collagen type IV **(Figure 2C).** Furthermore, there was greater staining for the C-C chemokine receptor 2. Gadolinium was undetectable in the kidneys of control animals and elevated in the contrast-treated group. Prior to the endpoint, 24 hour urine collections were obtained for each group.

Gadolinium treatment induced a three-fold increase in urinary albumin. Therefore, the renal tissue was examined for the podocyte markers p57 and synaptopodin. Each of these was diminished by gadolinium contrast treatment. In summary, these data indicate that gadolinium concentrates in the kidney and induces glomerular pathology. Metabolomics from the kidney tissue demonstrated that gadolinium-based contrast agent treatment induced the Warburg effect, i.e., there was a reduction in the tricarboxylic acid cycle, and increase in glycolysis with an elevation in pyruvate conversion to lactate similar to the metabolic switching that occurs in cancerous cells and in the proximal tubular cells during acute kidney injury (Geng et al.).

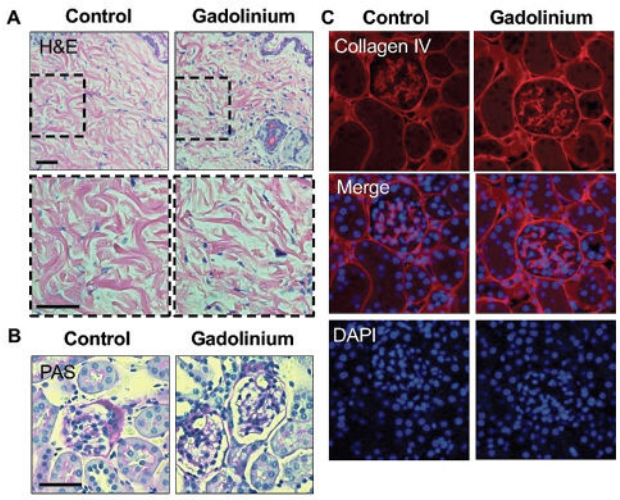

Figure 2 A. The systemic impact of gadolinium-based contrast agent toxicity in mice. Gadolinium-based contrast agent treatment induced skin fibrosis and dermal hypercellularity in mice. H&E, calibration bar=0.05 mm. B. In gadolinium-based contrast agent-treated mice, glomeruli demonstrated increased mesangial cellularity, matrix expansion, and tubular vacuolization. Periodic acid-Schiff, calibration bar=0.05 mm. C. Increased interstitial and mesangial collagen type IV in gadolinium-based contrast agent-treated mice. Immunofluorescence, 400.

Gadolinium-Rich Amorphous Mesh-Like Nanostructures Form in Multiple Organs *In Vivo*

We have previously detected macrophages and alternatively-activated macrophages in the affected tissues of his gadolinium-induced fibrosis model. Macrophages are participant cells in the innate immune system and propagate fibrosis by activating myofibroblasts with cytokines such as interleukin 1β and interleukin 18. Monocyte chemoattractant protein 1 was found to be elevated in affected organs and a mediator of cell recruitment via the C-C chemokine receptor 2 (CCR2) in rats and mice. The kidney is among the largest reservoirs for gadolinium retention. Furthermore, gadolinium-based contrast agent treatment led to amorphous mesh-like nanowire structures found in multinucleated giant cells of the skin and the renal proximal tubules **(Figure 3)**. These sea urchin-shaped anomalies resemble how rare earth elements leach phosphates out of bacterial membranes (Dr. Kimberly Bulter, Ph.D., Sandia National Laboratories, Personal Communication).

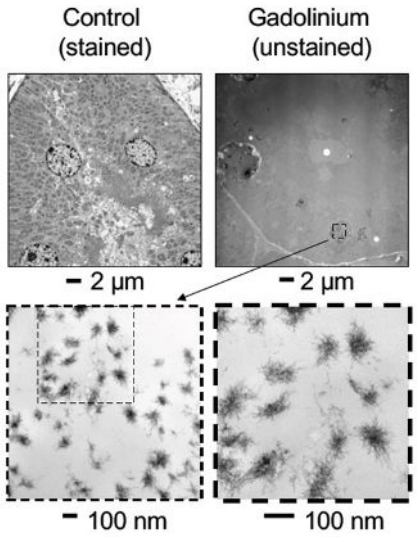

Figure 3 Gadolinium-based contrast agent treatment leads to the formation of amorphous, mesh-like, nanowire "sea urchin" structures in the proximal tubule. Depicted are sections of renal cortex, stained from an untreated mouse and unstained from a gadolinium-treated mouse to demonstrate gadolinium-rich electron densities.

Gadolinium-Based Contrast Agent Treatment Induces the Recruitment of Bone Marrow-Derived Cells to Affected Areas in Mice

Many organs are involved in gadolinium-induced systemic fibrosis. Therefore, renal tissue was examined in these mice. The cortex from gadolinium-treated animals demonstrated vacuolization of the proximal tubules. The PAS-stained sections demonstrated increased glomerular mesangial matrix relative to the controls. Gadolinium-treated animals invariably demonstrated proximal tubule vacuolization and often severe peri-glomerular fibrosis. Furthermore, glomerular fibronectin was increased by immunofluorescence and immunoblot of the renal cortex.

These mice were lethally-irradiated and salvaged with 'tagged' bone marrow in order to trace the myeloid lineage of infiltrating cells. The myeloid marker, green fluorescent protein, was increased in the renal cortex of the gadolinium-treated animals. CD45RO is a marker thought to be specific for fibrocytes [14] and proposed to be among the diagnostic criteria for gadolinium-induced systemic fibrosis. Immunofluorescent-stained microscopy for green fluorescent protein and the fibrocyte marker CD45RO demonstrated marked myeloid infiltration of the renal glomeruli and interstitium of the gadolinium-treated animals. This was the first discovery that gadolinium-based contrast induced renal pathology and promoted the infiltration of bone marrow-derived cells into the renal glomeruli and interstitium [6]. This is entirely consistent with what has been demonstrated in rats [5].

Gadolinium-Based Contrast Agents are Major Metabolic Disruptors

It has been demonstrated that $GdCl_3$ decreases mitochondrial metabolic activity in a dose-dependent manner [15]. Mitochondrial generation of reactive oxygen species has been implicated in diabetic nephropathy [18], and we were the first to detect NADPH oxidase homolog 4 (Nox4) as the source of reactive oxygen species in gadolinium-based contrast agent-induced systemic fibrosis. Given the profound impact of gadolinium-based contrast agent-induced manifestations, and incorporation of gadolinium into mitochondria *in vivo*. the global metabolic profiles were obtained using the flash-frozen kidney cortices from control and gadolinium-based contrast agent-treated mice. There were major alterations in glycolysis, the tricarboxylic acid (TCA) cycle and mitochondrial oxidative phosphorylation **(Figure 4).** Far from being an inert substance, gadolinium-based contrast agents cause substantial energetic perturbations.

Conclusions

Because little is understood regarding the etiology of gadolinium-based contrast agent-induced systemic fibrosis, current clinical recommendations are entirely anecdotal. These include 1) avoid gadolinium-based contrast in those with renal failure, 2) if necessary use “higher stability” gadolinium chelates at low doses, and 3) consider hemodialysis soon after contrast administration. There are no experimental studies to support the latter two among the 10 highest-income countries, the United States has the second highest number of magnetic resonance imaging units per capita, and the second highest rate of magnetic resonance imaging examinations per 1000 population. Provided the aging population, with the numerous hazardous exposures and concomitant co-morbidities found in the United States veteran population, there is going to be an associated increased likelihood of magnetic resonance imaging use and exposure to gadolinium based contrast agents. Because prominent experts are endorsing specific classes of gadolinium-based contrast, an understanding of how this metal induces such drastic, irreversible and untreatable effects needs to be sought. Gadolinium-based contrast agents are used to make critical medical decisions. However, gadolinium is conditionally-toxic. Renal impairment is one factor, but it is clearly not the only factor as numerous end-stage renal disease patients have been exposed to gadolinium and have yet to develop systemic fibrosis. And now systemic fibrosis is being increasingly recognized in patients with normal renal function.

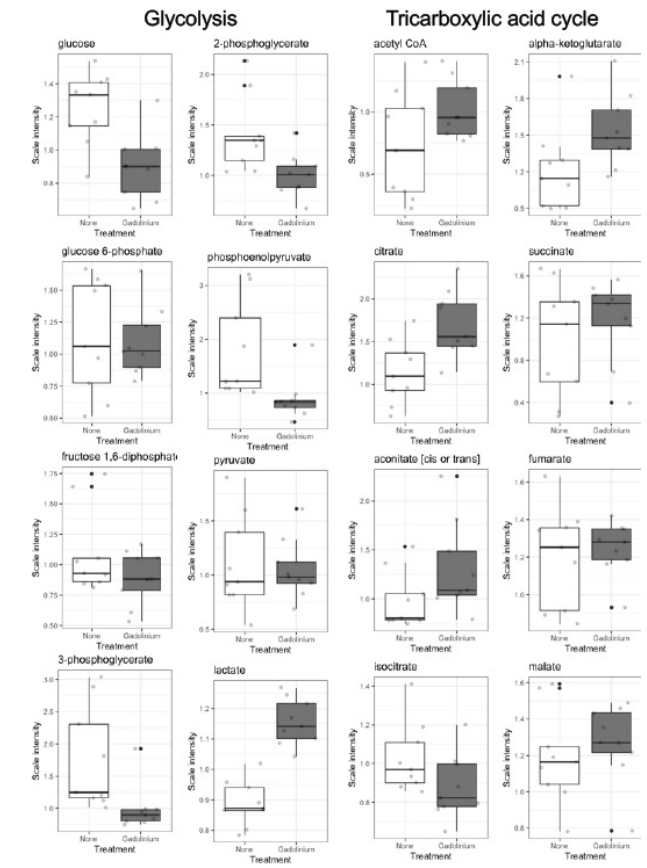

Figure 4 Gadolinium-based contrast agents induce glycolytic switching the Warburg effect in the kidney cortex. Flash-frozen tissue was used for metabolomic analysis. The boxes depict the upper and lower quartile limits, median, and the whiskers the maximum and medium of the distribution.

The risk of gadolinium based contrast agent-induced adverse events (not limited to systemic fibrosis) likely follows a curvilinear function with decreasing glomerular filtration rate. Renal toxicity is irrefutable; The damaging effects of multiple gadolinium-based contrast agents on the kidney, including interstitial fibrosis, amyloid deposits, and cellular infiltrates, in a rodent model have been recently replicated. Gadolinium based contrast-induced nephrotoxicity has been described in patients and in animal models, and gadolinium-based contrast has been reported to be nephrotoxic in humans. At present, there is no evidence that prophylactic measures (such as prompt dialysis after gadolinium exposure) or treatments are uniformly efficacious. Aside from just two risk factors (renal insufficiency and gadolinium) the pathophysiology of systemic fibrosis is largely unknown. Most of the medical literature on this subject is comprised of case reports and narrative reviews. A good portion of the remaining *in vivo* publications have been conducted by pharmaceutical companies that market competing magnetic resonance imaging contrast agents. This has led to a largely conjectural model of gadolinium-induced systemic fibrosis. There are very few researchers using transgenic animals in the exploration of gadolinium-associated systemic fibrosis,

and ours is the only model that tracks and manipulates bone marrow derived fibroblasts.

Some patients on maintenance hemodialysis have been repeatedly exposed to magnetic resonance imaging contrast and have yet to acquire the disease whereas there are patients with acute or chronic kidney disease who succumb to irreversible fibrosis after just one dose. Now it is recognized that gadolinium-induced systemic fibrosis represents a continuum of disorders spanning any glomerular filtration rate. This entails other risk factors that will not be elucidated from human studies because of ethical considerations and the rarity of the condition. Our discoveries demonstrate that gadolinium contrast treatment can induce renal injury in animals with normal clearance. Sleep of reason brought forth the monster of this man-made disease, gadolinium induced systemic fibrosis (Poltroonery prevents some clinicians from advocating for their patients. To expose patients with renal impairment to gadolinium-based contrast agents regardless of the chemical structure is a very risky gamble, and often considered in non-life saving scenarios. Nonetheless, with footing entirely in the absence of evidence, many servile to pharmaceutical companies rather than to their patients-are pushing the notion that newer gadolinium-based chemicals are risk free in renal insufficiency). Patients with chronic kidney disease denied contrast enhanced magnetic resonance scans are hostages to fortune; a potentially valuable diagnostic technique is being withheld because of a real risk of triggering a horrific, incurable, disease. In lieu, patients are often exposed to iodinated contrast. Research in this area has greatly expanded the overall knowledge of how gadolinium induced systemic fibrosis occurs and the biologic impact of gadolinium retention. The resultant discoveries will help design rational clinical prophylaxis and treatments. Furthermore, progression on the identification of candidate mechanisms that trigger gadolinium induced systemic fibrosis will assist in unraveling the process of disease initiation and guide rational approaches for prophylaxis and treatment.

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Disclosures

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References

1. Wagner B, Drel VR, Gorin Y (2016) Pathophysiology of gadolinium-associated systemic fibrosis. Am J Physiol Renal Physiol 311: F1-F11.
2. Idee JM (2006) Clinical and biological consequences of transmetallation induced by contrast agents for magnetic resonance imaging: a review. Fundam Clin Pharmacol 20: 563-576.
3. Leyba K, Wagner B (2018) Gadolinium-based contrast agents: why nephrologists need to be concerned. Curr Opin Nephrol Hypertens.
4. Roberts DR (2016) High Levels of Gadolinium Deposition in the Skin of a Patient With Normal Renal Function. Invest Radiol 51: 280-289.
5. Wagner B (2012) Gadolinium-induced systemic fibrosis: Evidence for bone marrow-derived fibrocytes in skin, liver, and heart lesions using a 5/6 nephrectomy rodent model. Am J Pathol 181: 1941-1952.
6. Do C (2014) Type of MRI contrast, tissue gadolinium, and fibrosis. Am J Physiol Renal Physiol 307: F844-F855.
7. Drel VR (2016) Centrality of bone marrow in the severity of gadolinium-based contrast-induced systemic fibrosis. FASEB J 30: 3026-3038.
8. Semelka RC (2016) Presumed Gadolinium Toxicity in Subjects With Normal Renal Function: A Report of 4 Cases. Invest Radiol 51: 661-665.
9. Gathings RM (2015) Gadolinium-associated plaques: a new, distinctive clinical entity. JAMA Dermatol 151: 316-319.
10. Ray JG (2016) Association Between MRI Exposure During Pregnancy and Fetal and Childhood Outcomes. JAMA 316: 952-961.
11. Gilchrest BA, Rowe JW, Mihm MC (1980) Clinical and histological skin changes in chronic renal failure: evidence for a dialysis-resistant, transplant-responsive microangiopathy. Lancet 2: 1271-1275.
12. Hanna W (1987) Pathologic features of diabetic thick skin. J Am Acad Dermatol 16: 546-553.
13. Todd DJ (2007) Cutaneous changes of gadolinium-induced systemic fibrosis: predictor of early mortality and association with gadolinium exposure. Arthritis Rheum 56: 3433-3441.
14. Pilling D (2009) Identification of markers that distinguish monocyte-derived fibrocytes from monocytes, macrophages, and fibroblasts. PLoS ONE 4: e7475.
15. Feng X (2010) Impaired mitochondrial function and oxidative stress in rat cortical neurons: implications for gadolinium-induced neurotoxicity. Neurotoxicology 31: 391-398.
16. Khurana A, Greene JF (2008) High, Quantification of gadolinium in gadolinium-induced systemic fibrosis: re-examination of a reported cohort with analysis of clinical factors. J Am Acad Dermatol 59: 218-224.
17. Girardi M (2011) Gadolinium-induced systemic fibrosis: clinicopathological definition and workup recommendations. J Am Acad Dermatol 65: 1095-1106.
18. Forbes JM, Coughlan MT, Cooper ME (2008) Oxidative stress as a major culprit in kidney disease in diabetes. Diabetes 57: 1446-1454.