Interest in Heavy Metal Puts Young Researcher on Gadolinium's Trail

BY ERIK L. GOLDMAN
Contributing Writer

NEW YORK — Dr. Whitney A. High is into heavy metal and skin, but if you think he's a biker with a leather vest and a Black Sabbath tattoo, you've got it wrong.

Dr. High, of the University of Colorado, Denver, is a clean-cut young dermatopathologist with a soft spot for geology and physics, and his interests in heavy metal involve titanium and vanadium, not Metallica and Megadeath.

His unique set of interests—skin disease, metals, and physics—has landed him in the center of the growing controversy around gadolinium contrast agents and their role in nephrogenic systemic fibrosis.

Dr. High is part of an elite team of investigators trying to determine whether the gadolinium agents in MRI contrast media play a causative role in this devastating, largely untreatable skin disorder. Their answer could have major medicolegal and clinical implications.

Nephrogenic systemic fibrosis (NSF) is characterized by excessive fibrosis in the skin and other soft tissues that leads to disfigurement, tissue constriction, and in some cases, respiratory failure, ocular damage, and cardiac problems. It was first reported as "scleromyxedema-like disease" in renal dialysis patients in 1997. In the last decade, hundreds of cases have emerged worldwide, primarily, if not exclusively in people with end-stage renal disease (ESRD). Other than that, there were few clues as to what caused the distinctive skin and soft tissue changes.

"For a long time, we could not figure out what was going on," Dr. High said at the American Academy of Dermatology's Summer Academy 2007. The first break came in January 2006, when Austrian researchers described nine patients with ESRD, five of whom had developed NSF, with all five having undergone imaging procedures with gadolinium contrast agents. These five patients developed signs and symptoms consistent with the disorder within about 4 weeks of exposure to gadolinium-based contrast used in magnetic angiography.

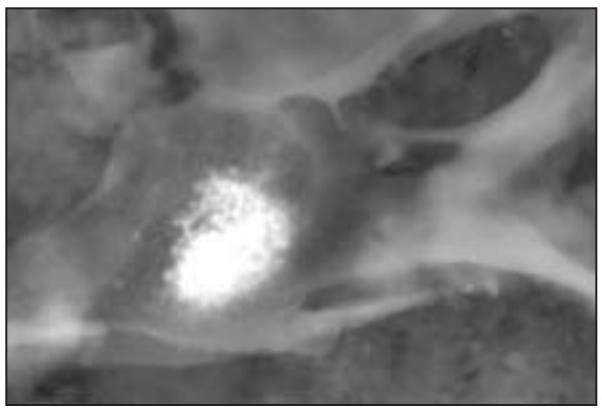
Further damning evidence emerged late last summer, when Danish investigators reported that 13 of 13 ESRD patients with NSF had received gadodiamide, a commonly used gadolinium contrast agent. There were no other shared risk factors among the 13 cases.

Is there a gadolinium smoking gun in the tissues of NSF patients? That's the question Dr. High is seeking to answer.

"I had previously reported on a granulomatous reaction to titanium alloy in a patient with ear piercings. That's how people knew I was interested in metals and skin disorders, and that's why I got called in on this gadolinium issue," he said.

There are five gadolinium contrast agents currently in use around the world. The two most common are Magnevist (gadopentetate) and Omniscan (gadodiamide). Manufacturers of the products, already reeling from the Food and Drug Administration's recent issuance of a black box warning about the potential risk of NSF, are hoping that gadolinium will be judged an innocent victim of circumstance.

Malpractice lawyers, of course, hope for the opposite.



COURTESY DR. WHITNEY A. HIGH

Gadolinium conglomerations in a fibrohistiocytic cell from the skin of an NSF patient are shown above.

So far, the findings seem to be favoring the lawyers. Using a technique called energy dispersive spectroscopy (EDS), investigators are able to detect metals such as titanium, vanadium, and gadolinium in human tissues, said Dr. High. He has detected gadolinium in the skin of four of seven NSF patients he has studied (J. Am. Acad. Dermatol. 2007;56:21-6).

He stressed, however, that EDS is "a semiquantitative technique, not a mass-based technique, and it should not be used as such." EDS can tell whether certain metals are present in the tissue, but it cannot be used to determine how much is present, except in a relative type of way.

That type of determination requires a technique like mass spectrometry. This method, too, showed significantly elevated levels of gadolinium in all NSF patients of Dr. High's original series.

Dr. High and his colleagues have used mass spectrometry to analyze a range of different tissues. Infant foreskin samples, predictably, show no gadolinium. Multiple sclerosis patients without renal problems who had undergone semiannual MRIs showed no gadolinium. Tissue samples from Mohs surgery for skin cancer? Also clear, as were skin samples from ESRD patients who have not had gadolinium-based scans. ESRD patients who had undergone imaging with gadolinium contrast, however, did show traces of the metal albeit at much lower levels than the patients with NSF.

Circumstantial? Unlikely. "If you have gadolinium in your tissues, you got it from somewhere. There is no regularly encountered source of gadolinium in this form in nature. So unless you happen to be a gadolinium miner, you got it from a doctor," said Dr. High.

But Dr. High seems reluctant to pin blame for NSF exclusively on gadolinium contrast agents. Bear in mind that nearly all NSF patients have ESRD, meaning that their ability to filter and eliminate toxins such as metals is sorely impaired. "Renal failure patients are a toxic soup of metals—calcium, iron, zinc, copper, aluminum—all sorts of metals," Dr. High said, adding that he believes NSF results from "a collusion of coconspirators. Gadolinium alone may not be the only prerequisite exposure, and other metals may be involved in its deposition or in disease evolution." Only time will tell.

Case in point, the prevailing model for how gadolinium ends up in the skin involves a hypothetical process called "transmetallation," in which other metals, such as iron or calcium present in the tissue, knock the gadolinium off the chelator to which it is normally bound.

"Transmetallation is just a theory at this point. It hasn't yet been irrefutably proven to occur in the body. Electron microscopy cannot detect what a metal is bound to, but a special kind of subatomic particle accelerator can."

To that end, Dr. High will soon be the first dermatopathologist to gain access to such an instrument. By the time this article is published, he will have been engaged in particle accelerator experiments designed to prove whether gadolinium in tissue is no longer bound to its chelators, as the transmetallation theory suggests. "There will likely be other information coming out to show that other metals may contribute to gadolinium deposition and perhaps to NSF itself," he said.

Even if gadolinium is not the only cause of NSF, it certainly appears a strong trigger in susceptible individuals. Estimates indicate that 3%-5% of patients with ESRD may be at risk for NSF. It appears that, in addition to ESRD, predisposition to thrombosis and inflammation may be involved. The risk is also likely proportional to the number of scans a person receives during renal failure.

For those who develop the disorder, there's little physicians can do. "I see about 10-12 patients with NSF at the University of Colorado. We've tried everything—photopheresis, plasmapheresis, renal transplant. No single treatment works uniformly well for all patients. And there are no formal studies comparing modalities."

Dr. High predicted that the current controversy about gadolinium will prompt a surge of interest in "medical geology" and the study of how elemental metals affect human health. Currently, Dr. High is working on a rapid, noninvasive screening device to detect metals such as gadolinium in human tissue. ■

Gadodiamide, NSF: Direct Link Identified

BY HANNAH BROWN
Contributing Writer

BIRMINGHAM, ENGLAND — A direct relationship between gadodiamide—a chelate used regularly to identify renal artery stenosis in patients who are potential transplant recipients—and the activation of fibroblasts in nephrogenic systemic fibrosis has been identified, Dr. Susie Mukherjee reported at the annual meeting of the British Association of Dermatologists.

The origin of nephrogenic systemic fibrosis (NSF) has long intrigued the radiologic, renal, and dermatologic worlds because of the paucity of cases, said Dr. Mukherjee. Although NSF was initially thought to be a cutaneous condition, two recent case reports have indicated that it is in fact systemic.

Dr. Mukherjee, a dermatologist at Glasgow University, and her colleagues examined the levels of hyaluronan and collagen—both key components of the extracellular matrix—of six female patients with end-stage renal failure and biopsy proven NSF. Their median duration of dialysis was 4.8 years and the mean time to developing NSF symptoms after receiving gadodiamide was 1 month.

The investigators obtained 20 mL of blood from the patients and compared the blood with that of controls. Punch biopsies were used to establish fibroblast activity.

Serum samples from the NSF patients stimulated up to a 7-fold increase in hyaluronan synthesis and a 3.3-fold increase in collagen; both increases were statistically significant when compared with control patient samples, she said. Histology samples showed thickened collagen bundles signified by strong alcian blue staining on slides, she said.

Dr. Mukherjee also found that it only takes tiny concentrations of gadolinium to stimulate hyaluronan synthesis by fibroblasts. Both 10-mmol/L and 1-mmol/L concentrations of gadolinium caused a 2.3-fold increase in hyaluronan synthesis, "which is still quite a small level compared to what patients are exposed to," she said. "So really from these simple in vitro experiments we can suggest that NSF lesional fibroblasts synthesize excess hyaluronan and collagen, which increases after prolonged exposure to gadodiamide," explained Dr. Mukherjee. "These are the first experiments to demonstrate a direct relation between gadodiamide and activation of fibroblasts."

Evidence for a link between NSF and gadolinium was first described in a case series of 13 patients, all of whom developed NSF after being exposed to gadolinium (J. Am. Soc. Nephrol. 2006;17:2359-62).

Early symptoms of NSF include swelling, pruritus, and muscle pain of the limbs. Later changes include flexion contractures and grossly thickened indurated skin.

Further work should assess the effect of gadolinium on circulating fibrocytes and their ability to migrate into skin, according to Dr. Mukherjee. ■