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EDITORIAL

The need for radiologists' awareness of nephrogenic systemic fibrosis

Üstün Aydıngöz

Editor *(uaydingo@hacettepe.edu.tr)*, Diagnostic and Interventional Radiology, Hoşdere Cad., Güzelkent Sok., Çankaya Evleri F/2, 06540 Ankara, Turkey.

We as radiologists generally take for granted the relative safety of gadolinium agents in terms of their adverse effects. Millions of MR imaging studies are performed each year with the use of these expensive but apparently safe contrast agents and minimal, if any, adverse effects are seen in only a fraction of cases. Therefore, recent news of a possible link between the use of gadolinium contrast agents and the development of the so-called "nephrogenic systemic fibrosis" (NSF) in patients with renal failure came quite as a surprise for the radiology community, effectively blindsiding us.

The first case of NSF was identified in March 1997 and the condition in 15 cases was published in the medical literature as "scleromyxoedema-like cutaneous disease" in September 2000 (1). The entity was later renamed "nephrogenic fibrosing dermopathy" (NFD) (2). A more widespread variant of this fibrosing skin disease with involvement of other organs (e.g., lungs, liver, muscles and the heart) was described as NSF (3-5). An international registry of NSF/NFD cases was created in the internet (5). As of October 2006, approximately 70 scientific articles have been published about this condition and several recent articles implicate gadolinium based contrast media as a potential risk factor (6-8). No other exposure/event than gadodiamide (Omniscan™; GE Healthcare; Oslo, Norway; Princeton, New Jersey, USA) could be identified as common to more than a minority of the patients (8). As of September 2006, it is estimated that about 5 million patients are administered Omniscan™ each year, and that a total of about 30 million patients have been administered Omniscan™ since its introduction to the market (9). In June 2006, the U.S. Food and Drug Administration issued an alert for healthcare professionals regarding the "development of serious and sometimes fatal NSF/NFD" in patients with advanced renal failure (those currently requiring dialysis or with a glomerular filtration rate [GFR] ≤15 ml/min) undergoing contrast-enhanced MR imaging (10). Physicians were advised in this alert to "administer the minimal needed dose of contrast agent if MR [imaging] with contrast is necessary".

The precise mechanism of NSF is not yet known. According to a promising speculation, "circulating fibrocytes of bone marrow origin are aberrantly recruited to" various body sites including the skin "by a process likely triggered or exacerbated by endothelial damage" (11).

In the U.S., an estimated 40 million doses of gadolinium agents have been used since 2000 and there are 215 registered NSF cases (with 3 deaths) as of October 2006 (6). (A similar total number of NSF cases is estimated for Europe.) What should these facts tell us? Are we seeing only the tip of the iceberg now? Or, is this pretty much the "actual" NSF adverse effect frequency? These questions remain unanswered. However, it is prudent for radiologists to be extra careful in using gadolinium agents especially

in kidney disease patients bearing in mind the possibility of this condition. Special emphasis should be made here for contrast-enhanced MR angiography, where double-dose of gadolinium containing contrast is widely used, in patients with borderline renal function or frank renal failure. Although an overwhelming majority of NSF cases has an apparent link to gadodiamide as a causative agent, implications for the role of other gadolinium agents are also made—without definite proof for their link, however—and no gadolinium agent yet appears completely acquitted. Strict observance of serum creatinine levels for the use/non-use of iodinated contrast materials (a threshold of 1.5 mg/dl in many centers) may well be the way to go for gadolinium agents. Glomerular filtration rate (a threshold of 15 ml/min for end-stage renal disease) is a more reliable—although apparently less practical—parameter to observe in the administration of contrast materials in patients suspected to have renal failure. Prompt hemodialysis within the first several hours after MR imaging may be recommended for quick removal of the gadolinium agent from the blood circulation. We radiologists should also collaborate with our colleagues from other medical specialties (dermatologists, in particular) in a search for identifying patients with NSF to add to the limited existing database.

In conclusion, we now have a compelling reason to question the safety of gadolinium agents in conditions where they were rather indiscreetly used before. Gone are the days when many of us thought that at last we had a modality where contrast agents were widely used nearly risk-free.

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