Gadolinium and nephrogenic systemic fibrosis: what every physician should know

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Up to some time ago, we radiologists have been using gadolinium in patients affected by renal insufficiency, and this was done very confidently, with assurance that we were utilizing a safe alternative for assessment of these patients.

The Food and Drug Administration (FDA) warning, on June/2006, (http://www.fda.gov/bbs/topics/NEWS/2007/NEW01638.html), concerning nephrogenic systemic fibrosis (NSF)/nephrogenic fibrosing dermopathy obliges us to revise our concepts on safety in the use of gadolinium. After the RSNA 2006, the medical team in our institution started discussing the indication for gadolinium use in patients with renal insufficiency, but up to then strict rules for utilizing gadolinium-based contrast agents in these cases had not been established yet. So, in June/2007, a patient with this disease was admitted to the Hospital das Clínicas of Faculdade de Medicina da Universidade de São Paulo, and I must confess that, seeing for the first time a patient affected by this syndrome associated with gadolinium administration, I have got that old sensation: "this will not happen here". The impact has been so effective that currently in our institution the creatinine clearance is preventively evaluated prior to the administration of gadolinium to patients with moderate or severe renal insufficiency. It might be said that the scenario is critical and that every physician must be aware of the possibility of NSF development.

Until February this year, 200 cases of NSF were described. This disease is systemic, and, just as its name indicates, is characterized by widespread tissue fibrosis. Originally, it was known as nephrogenic fibrosing dermopathy because of its dominant cutaneous findings (http://www.pathmax.com/dermweb).

This condition develops in patients who receive intravenous gadolinium-based contrast agents to enhance the quality of magnetic resonance imaging or angioresonance, angiography or angio-CT, and who present with moderate (stage 4) renal dysfunction (creatinine clearance < 60 ml/min/1.73 m^2) or severe (stage 5) renal dysfunction (< 15 ml/min/1.73 m^2), particularly those requiring dialysis (http://www.massmedboard.org). Also, the development of NFS is reported in patients affected by hepatorenal syndrome[1], and, in these cases, the renal function assessment becomes even more difficult, because the liver fails to produce creatinine, and therefore creatinine blood levels do not reflect the renal picture. The precise cause of NSF in patients with renal disease — usually in those requiring dialysis —, after administration of gadolinium, is still to be known; however, tissue biopsies in cases of NFS detect the presence of gadolinium in the specimens. The effects are dose-dependent and cumulative, so the risk for developing NFS increases with multiple administration of paramagnetic contrast agents. The condition is progressive and develops rapidly (about 2–12 weeks following the gadolinium administration), and sometimes may result in patients becoming confined to a wheelchair because of joints contractures, muscular weakening and arthralgia. The extremities skin hardening and joints contracture leads to immobility. Besides the skin, the involvement of other tissues like lungs, skeletal-muscle system, heart, diaphragm, and esophagus also have been described, although the patients may be asymptomatic. Although the disease may stabilize, there is no report of remission. Up to the present moment, the majority of cases was associated with gadodiamide (Omniscan®; GE Healthcare, Princeton, NJ), however, there are cases associated with gadopentetate dimeglumine (Magnevist®; Berlex Imaging, Montville, NJ) and gadoversetamide (OptiMARK®; Mallinkrodt, St. Louis, MO) or these agents in association, both in doses of 0.1 mmol/kg and more [2].

Therefore, the necessity of gadolinium must be carefully evaluated in the setting of renal disease. Many questions must be answered for a correct indication of

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these so useful contrast agents for imaging diagnosis in these patients: How do renal insufficiency and gadolinium interact for triggering NSF? How do other risk factors (such as electrolytic disorders with increase in calcium, potassium and zinc levels) affect this process? Is metabolic acidosis necessary for NSF to occur? Why did the first reports emerge in 1997, when gadolinium-based contrast agents had already been used in patients with renal insufficiency for several years?

Meanwhile, the FDA suggests the following recommendations:

– Gadolinium, especially at high doses, should only be utilized if undoubtedly necessary in patients with severe renal failure (glomerular filtration rate < 15 ml/min/1.73 m^2). The most prudent course would be to institute dialysis immediately after the gadolinium administration although there is no data to define the utility of this procedure to prevent NSF. In patients with renal insufficiency, the gadolinium excretory rates reach, on average, 78%, 96% and 99% respectively in the first to third hemodialysis sessions. Notwithstanding the development of NSF is associated with only some gadolinium-based contrast agents, the FDA recommends prudence in the use of gadolinium.

There is no report about development of NSF in patients without renal disease and the literature reports that 90% of cases involved dialytic patients, and in the others, patients with stage 4 or 5 chronic kidney disease. Even in patients with severe or end-stage renal disease, the chances to develop NSF seems to be around 3-5%; however, considering the severity of the disease, extreme prudence is recommended[3].

Kuo et al., in a study published in the March/2007 issue of the **Radiology** journal[2], suggest the following steps to be adopted in these cases:

1) Evidence of renal disease absence: creatinine serum levels, creatinine clearance, electrolytes should be checked, besides considering decreased doses for elder, hypertensive and diabetic patients, in the absence of previous data.

2) Discussing with the ordering physician alternative imaging diagnosis methods for these patients. Benefits and risks should be evaluated on an individual bases for each patient.

3) In cases of moderate or severe renal insufficiency where gadolinium is prescribed, a term of informed consent should be signed both by the ordering physician and the patient or his/her legal representative.

4) If administration of gadolinium-based contrast agent is deemed necessary, the lowest dose as possible should be considered.

5) During the MRI examination any non-contrast enhanced sequence that may be helpful should be performed aiming at minimizing the necessity of contrast agent.

6) In patients undergoing hemodialysis, this treatment should be ensured as soon as possible, ideally within three hours after the administration of the gadolinium-based contrast agent. A second dialysis session should be performed within 24 hours, provided it is clinically safe for the patient.

7) In patients undergoing peritoneal dialysis, it is necessary to assure that the patient has no periods with dry abdomen. Additional dialysis cycles are recommended within the 48-hour period following gadolinium administration.

8) Administration of gadolinium is not recommended for patients in whom there may be relatively protected spaces from which gadolinium chelates may not be cleared, such as the amniotic fluid.

9) In patients who have already been diagnosed with NSF, a new gadolinium injection is not recommended.

NSF is a disfiguring and debilitating disease with no effective treatment or preventive regimen[1]. The severity of this disease leads us to remember the hippocratic precept — *primum non nocere* — and in patients with moderate to severe renal insufficiency gadolinium may be associated with severe consequences.

References

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