Gadolinium-Induced Nephrogenic Systemic Fibrosis

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Nephrogenic systemic fibrosis (NSF) is a clinicopathologic syndrome that has been associated with the use of gadolinium-based contrast agents (GBCAs).[1] First discovered in 1997, NSF was initially termed nephrogenic fibrosing dermopathy due to its notable skin findings in 15 dialysis patients.[1] Since that time, hundreds of cases have been reported with the use of gadolinium-based contrast agents (e.g., gadopentetate dimeglumine, gadodiamide, and gadoversetamide).[1,2]
This systemic disorder is not only characterized by skin manifestations but can also lead to multiorgan failure and death.[3] Its prevalence increased after the FDA approved the use of noniodinated contrast agents for magnetic resonance imaging studies in the late 1980s and early 1990s.[3] Unaware of the possible dire consequences, physicians initially embraced the use of these newer contrast agents since they afforded a contrast-enhanced study that would circumvent iodine nephropathy, and GBCAs were considered safe for use in renal patients. However, recent studies have found a causal relationship between NSF and GBCA exposure.[3] The following are 10 points to remember about nephrogenic systemic fibrosis and its link to GBCAs.

1. Nephrogenic systemic fibrosis has no predilection for age, sex, or race. It has been reported in children and adults around the world.[1]
2. Patients at increased risk for NSF include those with acute renal failure or chronic kidney disease (CKD) stages 4 or 5 with eGFR < 30 mL/min/1.73 m^2; however, it has also been documented in patients with CKD stage 3. Higher-than-recommended doses of gadolinium contrast or repeated doses increases the risk of NSF. Patients on peritoneal dialysis have a higher incidence of NSF than those on hemodialysis, possibly because the peritoneum is less effective in clearing the contrast.[4]
3. In those with renal dysfunction and GBCA exposure, the NSF risk increases in the presence of a proinflammatory state; this includes infection, ischemia, malignancy, recent surgery, thrombosis, or major trauma or injury.[4]
4. A multicenter retrospective study of renal-insufficient patients found that gadodiamide exposure had an odds ratio of NSF development that was 13 times higher than gadopentetate exposure. This is because gadodiamide is less stable compared to the other gadolinium agents. With decreased stability, gadodiamide dissociates from its chelate and becomes Gd^{3+}. This cation stimulates production of profibrotic cytokines, chemokines, and collagen formation, resulting in tissue fibrosis. In patients with nondialysis-dependent CKD stage 5, the half-life of gadodiamide is 34.3 hours compared to 70 minutes in those with intact renal function. Therefore, the toxic effects of exposure increase with decreased clearance of gadolinium.[3,5]
5. Clinical manifestations of NSF can occur days to years after GBCA exposure. The early clinical signs of NSF include weakness, burning pain, pruritus, and cutaneous papules and plaques accompanied by edema. As the disease progresses, the skin becomes thickened, hyperpigmented, and "peau d'orange." The involvement of joint tissue often results in contractures. The disease can progress from distal to proximal extremities and can involve both the upper and lower extremities, sparing the face. The fibrosis eventually may involve the lungs, renal tubules, rete testes, dura mater, ocular sclerae, and cardiac and skeletal muscle. Mortality increases with respiratory involvement, particularly with diaphragm involvement. Infections also lead to higher mortality rates in these patients.[3]
6. Diagnosis is made with a history, physical exam, and exclusion of other likely diagnoses. No laboratory studies support the diagnosis of NSF, and imaging may only show nonspecific enhancement in involved areas. A biopsy of any affected organ, including the skin, may reveal supportive findings.[3]
7. Biopsy findings illustrate systemic fibrosis with thickened bundles of dermal collagen and increased dermal

mucin. Late in the disease, histology reveals dystrophic calcifications, calcified sclerosis, and osseous metaplasia.[3]

8. Since there are no tests for diagnosing NSF, other possible diagnoses must be excluded. B2-microglobulin amyloidosis is the only other condition with fibrosis in patients with advanced CKD. A few other differentials include scleromyxedema, scleroderma, and lipodermatosclerosis.[3]
9. There is no known cure for NSF, although case reports have found clinical improvement with pentoxifylline, sodium thiosulfate, ultraviolet phototherapy, extracorporeal photopheresis, and intravenous immunoglobulin. Imatinib mesylate, a tyrosine kinase inhibitor, has been shown to reduce collagen formation in some patients. Other supportive measures include physical and occupational therapy as well as analgesia for painful joint contractures. Although hemodialysis after contrast exposure does increase contrast clearance, there is no evidence that it reduces the risk of NSF development. However, treatment at the earliest onset of symptoms appears to improve the disease course.[1,3,4]
10. The increased risks of gadolinium- and iodine-based contrast agents in those with renal disease has prompted investigation of alternative agents. One possibility is ferumoxytol, which is currently indicated for iron deficiency anemia in patients with CKD. It is being used in magnetic resonance imaging as an off-label alternative contrast agent for renal insufficient patients in some institutions. Hopefully with time, safer contrast agents will be developed for those with renal dysfunction.[6]

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