Gadolinium Induced Acute Kidney Injury and Nephrogenic Systemic Fibrosis

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ABSTRACT

Use of contrast agents like gadolinium in MR imaging studies has considerably increased. Although safe in patients with normal kidney function, administration of these agents in people with renal dysfunction can result in many clinical problems that the nephrologists should be familiar with. This brief review discusses these iatrogenic problems that can be induced by contrast agents like gadolinium. JMS 2012;15(2):166-69

Key words: Gadolinium, MRI, contrast agents, renal function test, nephrotoxicity

Magnetic resonance imaging (MRI) scans are significantly enhanced by use of gadolinium based contrast (GBC) agents.¹ Until recently the use of gadolinium was thought to be risk-free compared with alternative contrast agents.^{2,3} Recent studies, however, had raised serious concerns regarding the safety of gadolinium chelates.⁴ Although safe in patients with normal kidney function, administration of these agents in people with renal dysfunction can result in up to three clinical problems that the nephrologists should be familiar with.^{5,8}

First is GBC associated nephrotoxicity (acute kidney injury) particularly in patients with underlying kidney disease.^{9,10} Second and more concerning was the development of nephrogenic systemic fibrosis in patients with advanced kidney failure.¹¹⁻¹³ Of less significance is a labora-

tory artifact of pseudohypocalcemia. This review with discuss the rise and fall of these iatrogenic complications.

Gadolinium Based Contrast agents (GBC's)

Gadolinium (GD) is a lanthanide metal with paramagnetic properties.¹ It is used as intravenous or intra-arterial contrast agent while performing MRI scan. GD in its ionic form is highly toxic; this can be avoided by having GD in chelate form. Chelates are organic molecules which form stable, non-toxic and bio-chemically inert complexes with GD.^{1,5} Gadodiamide (Omniscan), Gadopentetate dimeglumine (Magnevist), Gadobenate dimeglumine (MultiHance) and Gadoteridol (ProHance) are some GD containing chelates commonly used.¹ Macrocyclic chelates are less toxic as they bind GD more tightly and are less likely to liberate free GD. They are eliminated unchanged by the kidneys with a mean terminal half-life ($t_{1/2}$) of 1.3 hours. The $t_{1/2}$ is prolonged to 5.6 hours in patients with moderate renal failure and up to 30 hours in patients with GFR of $<5\text{ml/min}$.^{1,3,4}

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Nephrotoxicity (Acute Kidney Injury)

Since GBC agents have significantly lower viscosity compared to iodinated radio contrast agents and the volume used is 4-11 times less, the nephrotoxicity due to GD was thought to be significantly less.^{2,3} Nephrotoxicity of GBC agents has been studied in experimental animals and minimal elevation of serum creatinine was reported when high doses (>1.0 mmol/kg) were used.⁴ Nephrotoxicity of GBC agents has been studied in healthy individuals and in patients with mild to moderate kidney disease.^{6,7,8,9} Several of these studies demonstrated that GBC agents lack significant nephrotoxicity particularly in patients who have normal or minimally elevated (<2.5mg/dl) serum creatinine.^{7,8} In these studies GBC associated nephrotoxicity developed in 0-5% of patients which was less than iodinated contrast (17-40%).

In contrast to these favorable studies, a number of other studies suggest that GBC's exhibit variable degrees of nephrotoxicity.^{9,10} GD based contrast agents are reported to induce acute kidney injury (AKI) in a high-risk population group at the usual dose for MRI and MRA examinations.⁹ This was noted more frequently in patients with elevated baseline creatinine ≥ 3 mg/dl and in patients with hypertension, diabetes mellitus and sepsis.¹⁰ In these studies nephrotoxicity developed in 5-50% of patients which was equal to or greater than that seen with iodinated radio contrast agents. In conclusion majority of studies suggest renal safety but GBC induced nephrotoxicity can develop. Factors which increase the risk of GBC associated nephrotoxicity are advanced CKD, higher doses, and arterial injection.⁹

Nephrogenic Systemic Fibrosis (NSF)

NSF is a rare syndrome characterized by fibrotic skin, muscle contractures, decreased range of joint motion and organ fibrosis.^{14,15} The first case of NSF was reported in 1997, since then many cases and small cases series have been reported.¹²⁻¹⁸ The largest series from India consists of seven patients of NSF reported from Kolkata.¹⁹ It was initially recognized as a novel, idiopathic, progressive, scleromyxedema like fibrosing disorder of the skin but soon it was recognized that fibrosing process is not limited to skin but occurs as a systemic condition.¹⁵ Over last decade multiple reports have revealed an associated between NSF and prior exposure to GBC agents in patient with advanced renal failure.¹⁵ However no new case of NSF has been reported from USA after 2009. Patient, physician, hospital, product, regulatory and country considerations account for the emergence and disappearance of NSF.

Epidemiology

NSF has been exclusively reported in patients with renal disease with a glomerular filtration rate (GFR) <60 ml/min/1.73m². NSF has been reported in the setting of acute or chronic kidney disease, as well as in either haemo or

peritoneal dialysis therapy.¹⁶ Approximately 90% of cases have been reported in dialysis patients and 10% of cases in patients with stage 3 or 4 CKD.¹² NSF is an indolent disease with several weeks to months of symptoms prior to diagnosis but can present as rapidly progressive disease often with systemic involvement.¹⁶ NSF occurs in patients regardless of age, gender or race and has been reported in pediatric patients as young as 8 years old.^{17,18} Fibrosis affecting skin and or systemic organs dominates the clinical picture.²⁰

Cutaneous Involvement

NSF first affects the skin as dermal hardening with tethering to deep dermal tissue, giving a characteristic woody feel.²⁰ Additional skin findings are brownish hyper pigmented plaques, brawny indurations, waxy erythematous papules, and subcutaneous nodules. Extremities as well as trunk may be affected but NSF typically presents in lower extremities at calves in a symmetrical fashion. Involvement of upper extremities follows the development of disease in lower extremities. Trunk is involved late in the severe form of the disease whereas face is usually spared.^{15,20}

Systemic Involvement

Systemic fibrosis is an important and a well recognized feature of NSF and can involve skeletal muscles, bones, lungs, pleura, pericardium, myocardium, renal tubules, testes and duramater.^{15,21} NSF can lead to joint contractures due to fibrosis of periarticular structures involvement of shoulders, elbows, wrists and hands causes significant functional disability. Joint contractures of hips, knees and ankles can predispose to falls and fractures. Lung involvement leading to fibrosis and diffuse diaphragmatic infiltration leading to respiratory failure is known in NSF.

Etiology

No definite correlation is yet established but a possible connection with severity of renal failure, history of hyperthyroidism, thrombotic episodes, dependent edema, and vascular procedures has been reported. Many drugs including high dose erythropoietin therapy, past angiotensin converting enzyme inhibitor and sevelamer therapy, has been implicated but not statistically proved.^{22,23} An Austrian study correlated NSF with Gadolinium exposure, renal insufficiency and concurrent acidosis whereas a Danish study calculated a strong link between GD exposure and subsequent onset of NSF in renal insufficiency patients with or without acidosis.¹⁴

Diagnosis

Often physical examination and laboratory analysis are adequate to make the diagnosis of NSF in appropriate clinical setting. Non-Gadolinium enhanced MRI may reveal skin thickening and elevated T2 signals in muscles. Skin biopsy is needed in some cases to confirm diagnosis.²⁰

Histopathology of NSF

Well described pathological features of NSF include dermal thickness, increased collagen bundles, increased mucin, fibroblast proliferation and spindle shaped fibroblast. Fibrosis can extend into subcutaneous tissue, fascia and even skeletal muscles. Immunolabelling for CD 34 and procollagen I in the spindle cells of NSF may provide a sensitive and specific method of diagnosis. Scanning electron microscopy and inductively coupled mass spectrometry identified GD in biopsies from NSF patients.^{15,16}

Differential Diagnosis

The closest differential diagnosis of NSF is scleromyderma in which skin thickness occur over head, neck, arms and upper trunk while as in NSF characteristic lesional distribution (acral and truncal preferences, facial sparing), raised ESR and CRP lack of inflammatory cells on histology, lack of paraproteinemia and characteristic immunohistochemistry with CD 34 and procollagen I favors the diagnosis of NSF. Systemic sclerosis may be considered as second most important differential diagnosis but serologic finding and histopathology provides the clue. Eosinophilic fasciitis is characterized by peripheral eosinophilia, hypergammaglobinemia and dermal inflammation on skin biopsy and thus differentiating it from NSF.¹⁹

Treatment

Physiotherapy is advised to maintain joint mobility. Many pharmacological agents have been tried to improve skin and systemic fibrosis including corticosteroids, thalidomide, cyclophosphamide, mycophenolate mofetil, intravenous immunoglobulin with variable results. Plasma exchange and plasmapheresis has been reported to improve skin fibrosis. Extracorporeal photopheresis has been shown to be more effective than others in improving fibrosis but is very expensive.²⁴⁻²⁶

To conclude it is important that the clinicians should be cognizant of GBCA's risk and benefits. NSF fears should not lead to denial of enhanced MR imaging examinations with lower risk stable GBCA's, when clinically appropriate. It is important to identify high-risk patients and closely monitor renal function after administration of GD.

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