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Side Effects of Gadolinium Enhanced Magnetic Resonance Imaging in Patients with Renal Failure, a Review.

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Abstract:

Iodinated contrast media in patients with chronic kidney disease induce to loss of residual renal function. So Magnetic resonance imaging with gadolinium has replaced iodinated contrast agents in these patients. Nephrogenic systemic fibrosis is a recently identified disorder seen only in patients with kidney failure, particularly in patients on dialysis. The evidence has implicated gadolinium as the 2 main cause of this disorder Skin involvement occurs in all patients and some have systemic manifestations. It is under-diagnosed by clinicians who are unfamiliar with the condition. Although no Therapy has shown consistent benefit, but prevention in high risk patients should be considered.

Keywords: Nephrogenic systemic fibrosis, Nephrogenic fibrosing dermopathy, Gadolinium.

Introduction:

Iodinated contrast media in patients with renal insufficiency can lead to severe clinical compilcations, including loss of residual renal function and acute pulmonary edema.

Thus, gadolinium (Gd) enhanced magnetic resonance imaging (MRI) has increasingly replaced iodinated contrast agent

examinations in patient with chronic renal disease or end-stage renal disease (ESRD).

Gd contrast media seems to be well tolerated. Adverse effects (AE) such as transient nausea, emesis, headaches, dizziness, anaphylactoid reactions, or acute pancreatitis were reported in only a minority of patients with normal renal function. Contrast nephropathy caused by Gd contrast media seems to be rare. However, recent data conclude that Gd chelates induced contrast nephropathy in patients with severe renal insufficiency in a way similar to iodinated contrast media.[1]

Nephrogenic systemic fibrosis (NSF), previously known as nephrogenic fibrosing dermopathy (because of the characteristic skin findings), to date has been described only in patients with glomerular filtration rate less than 30 ml/min/1.73 m2, patients after liver transplantation, and patients with hepatorenal syndrome.[2]

However, subsequent studies showed that some patients had fibrosis of deeper structures including muscle, fascia, lungs, and heart.[3] Because of the systemic findings nephrogenic systemic fibrosis is preferred to NFD. Among the many complications of chronic kidney disease NSF is highly frustrating.[4]

Background and Epidemiology:

NSF occurs exclusively in patients with kidney failure. The first cases were noted between 1997 and 2000 in hemodialysis patients or patients with failed renal allografts who developed severe skin induration that was initially thought to be scleromyxedema.[5-7]

As of late 2010, totally 600 cases of NSF had been reported globally.[8]

On May 23,2007, FDA requested a black box warning regarding the potential risk of NSF among patients with kidney failure, ever since, there has been a decrease in NSF events ,with no new cases reported over the past 12-18 months.[8]

There is no predilection to NSF by gender, race, or age [3, 9-11], etiology of kidney disease, or duration of renal failure. However, patients undergoing peritoneal dialysis, compared with hemodialysis, may be at a higher risk.[12]

The relationship between time of initiation of dialysis and diagnosis of NSF can vary, ranging from 2 months to 15 years in one series of 12 cases.[13]

Godolinium (Gd) is a non-tissue-specific, nonionic, hyperosmolal contrast agent that is primarily administered for magnetic resonance (MR) imaging or MR angiography studies. Gadolinium chelates are excreted unchanged almost exclusively by the kidney. Its half-life is 1.3 hours in healthy volunteers, 10 hours at an estimated glomerular filtration rate (GFR) of 20-40 ml/min, and 34 hours in patients with end-stage renal disease. For patients with end-stage renal disease, the half-life is reduced dramatically to between 1.9-2.6 hours if hemodialysis follows gadolinium administration.[14-16]

The sixth most commonly used FDA approved godoliniom-chelates differ by biochemical structure and charge (Table1).[17, 18]

There are 2 categories of Gd chelates: linear molecules, such as Gd-diethylene triamine penta-aceticacid (Gd-DTPA) or gododiamide, and macro cyclic molecules, Such as godobutrol. The chelate

binder of the compound influences such characteristic features as molecular weight, thermodynamic stability, and the incidence of in vivo transmetallation.[1] Characteristic features of commercially available Gd contrast agents are listed in table 1.

Most Gd chelates are eliminated exclusively by kidneys. They accumulate in patients with severe renal failure, opening the possibility of enhanced or specific adverse effects in patients with ESRD.[1]

Free Gd3+ is poorly soluble, highly toxic, and can form precipitates with anions that tend to be elevated in renal failure. This has led to the hypothesis that excess exposure to free Gd3+in patients with kidney disease leads to tissue damage.

Support for the pathogenic role of gadolinium comes from the demonstration of gadolinium deposition in tissue specimens of some patients with NSF.[19-22]

It was suggested that gadolinium had a tissue residence time of 4 to 11 months.

In addition observational studies show a link between NSF and exposure to gadodiamide (omniscan) , a form of gadolinium that is the only approved MR contrast agent in Europe.[23]

In a detailed review of 75 cases of NSF performed by the United States food and Drug Administration (FDA), all had received a gadolinium-based contrast agent for an MR study two days to18 months before disease onset.[24]

Similar findings were noted by the International NSF registry: More than 95 percent of cases reported to the registry had been exposed to gadolinium within two to three months of disease onset.[8]

NSF has been reported after the administration of the six most commonly used FDA approved gadolinium-chelates in the United States. (table1)[25]

The FDA belives that the potential for NSF may be present for all approved agents. As a result, the FDA has added a boxed warning and new warning to the product labeling about the risk of NSF with all gadolinium-based agents.[25]

However, there is some suggestive evidences that the risk may vary with the different preparations.

As an example , in the United States among cases in which the type of gadolinium preparation was reported, gadodiamide causes greater than 80 percent of cases, with the remainder mostly due to gadopentetate.[4]

Risk Factors:

A separate issue is the magnitude of the risk after exposure to gadolinium in patients with end-stage renal disease. The reported risk has ranged between 2.5 and 5 percent in studies of approximately 400 to 500 dialysis patients.[18, 26, 27]

There is some evidence that a dose-response relationship exits.[28]

Initiation of recombinant human erythropoietin (EPO) therapy or an increase in dose may be associated with NSF, but the true nature of the relationship between EPO and NSF remains incompletely understood. EPO has been implicated because it has fibrogenic properties,[29]

it stimulates the bone marrow, and a large number of bone-marrow derived CD34+ fibroblasts infiltrate the dermis in NSF.[30]

Table1: US Food and Drug Administration-Approved Gadolinium-Containing Magnetic Resonance Imaging Contrast Agents

Trade Name	Generic Name	Date of initial Approval	Gadolinium Content(/ml)	Approved Initial Dose
Magnevist (Bayer Healthcare Pharmaceuticals Inc,Wayne NJ)20	Gadopentetate dimeglumine	June 1988	469.01 mg of gadopentetate Dimeglumine (0.5 mmol)	0.2ml/kg(0.1mmol/kg)
MultiHance(Bracco Diagnostics Inc Princeton,NJ)21	Gadobenate dimeglumine	November 2004	529 mg of gadobenate dimeglumine(0.5 mmol)	0.2ml/kg (0.1 mmol/kg)
Omniscan*22	Gadodiamide	January1993	278mg of gadodiaimide(0.5mmol)	0.1-0.2 ml/kg(0.05-0.1mmol/kg)
OptiMARK*23	Gadoversetamide	December1999	330mg of gadoversetamide (0.5mmol)	0.2 ml/kg(0.1mmol/kg)
ProHance(Braco Diagnostics Inc,Princeton,NJ)24	Gadoteridol	November1992	279.3mg of gadoteridol (0.5mmol)	0.2 ml/kg (0.1mmol/kg)
Vasovist	Gadofosveset	-	-	-

Pathology:

A deep biopsy is needed, since the fibrotic lesions may extend into the subcutaneous tissue.[3]

Routine light microscopy varies with disease marked thickening of the dermis with florid proliferation of fibrocytes with long dendritic processes in fully developed cases , often associated with histiocytes and satellite factor XIIIa-positive dermal dendritic cells.[3, 31]

Thick collagen bundles with surrounding clefts are a prominent finding, and a variable increase in dermal mucin and elastic fibers is usually evident with special stains.

Immunohistochemical staining reveals abundant CD34+ dermal cells, with the dendritic processes begin aligned with elastic fibers and around collagen bundles in a dense network.[3, 31]

It has been suggested that the CCD34+ cells are circulating fibrocytes that have been recruited to the dermis.[3, 10]

There is also an increased number of CD68+ and factor XIII-positive dendritic cells, some of which are positive for both markers.[14, 32]

As mentioned earlier, special testing may reveal gadolinium in tissue specimens from some patients who have been exposed to gadolinium.[19, 20, 22]

Pathogenesis:

The pathogenesis of NSF is not well understood.

The resemblance between NSF and a tissue injury reaction and the presence of myofibroblasts in the tissue specimens suggest that fibrogenic cytokines may be important, possibly resulting in a cascade of events similar to wound healing.[33, 34]

Two proposed contributors to the exaggerated tissue fibrosis are:

• Activation of the transforming growth factor (TGF)-beta-I pathway.

• An increase in circulating fibrocytes.[10, 13, 31-33]

Role of Free gadolinium:

With either theory, the inciting event may be the tissue deposition of an initiating toxin, such as gadolinium.[33]

Free gadolinium (Gd3+) is poorly soluble, highly toxic and can form precipitates with anion that tends to be a large or-

ganic molecule (Called a chelate) which prevents its dissociation.

Free Gd3+ may dissociate from the chelate with prolonged exposure to gadolinium in those

With kidney failure who do not undergo dialysis. Iron mobilization may also induce the dissociation of gadolinium.[34, 35]

Free Gd3+ has several deleterious effects in vivo, It precipitates in tissues, disrupts calcium ion passage in nerve and muscle cells, and interferes with intracellular enzymes and cell membranes through a process of transmetallation, where in Gd3+ replaces endogenous metals such as zinc, copper and iron.[1, 36]

Anions, such as phosphate, which tend to be elevated in renal failure, may be a cofactor in development of NSF by precipitating with free Gd3+.[33]

Clinical Manifestations;

NSF is characterized by skin involvement in all patients and systemic involvement in some.[3] Among patients, with gadolinium exposure the latent period between exposure and disease onset is usually two to four weeks.[23, 37] However, the reported range is as short as two days and as long as 18 months.[24]

Skin involvement:

Skin disease in NSF typically presents as symmetrical, bilateral fibrotic indurate papules plaques or subcutaneous nodules that may or may not be erythematous.[3, 31, 38]

In the majority of cases, the lesions first develop on ankles, lower legs, feet, and hands and move proximally to involve thighs, forearms and less often the trunk or buttocks. Common distribution patterns have been reported involving the skin overlying the mid [39], and lower abdomen.[13, 14] Head is spared.[13, 40]

The lesions are often preceded by edema and may initially be misdiagnosed as cellulitis. Edema usually resolves and the involved skin retains a thickened and firm texture.[3] The skin may have a cobblestone [41], woody, [13, 32, 42], or peau d'orange appearance.(40, 42) The lesions may be pruritic and accompanied by sharp pain or a burning sensation.[4, 32, 42]

Movement of the joints may be so limited by the fibrosis that flexibility is lost. (Picture 1)

There may be sclerodactyly or loss of skin appendages of the dersum of the hands and lower extremities.[4, 32] Unlike autoimmune sclerosing conditions, livedo reticularis is not a feature of NSF.

Systemic involvement:

The prevalence of systemic involvement is unknown, but a number of different orange system manifestations have been described:

- Muscle induration may be seen,[3, 43, 44]
- Joint contractures are common with advanced disease.[13, 32, 43]
- Muscle fibrosis is also seen on histologic examination.[43]
- Fibrosis has also been identified in a variety of internal organs, including lungs (with reduced diffusing capacity for carbon monoxide) [32], and diaphragm (with respiratory failure [3], myocardium [3, 32, 45], pericardium and pleura [3], and dura mater[45], yellow asymptomatic scleral plaques are common [10, 42]

Diagnosis:

The diagnosis of NSF is based on histhologic examination of a biopsy of an involved site.

A deep incisional or punch biopsy should be performed since the typical changes can extend into the subcutaneous fat, fascia and muscle.[10, 33]

Laboratory tests:

There is no laboratory test that is specific for NSF. Affected patients have finding consistent with chronic inflammation, including elevations in serum c-reactive protein, serum ferritin ,and the erythrocyte sedimentation rate and a reduction in serum albumin.[13] Increasing of serum Iron, total Iron binding capacity, transferrin saturation have also been reported.[46]

Differential Diagnosis:

Thickening and hardening of the skin overlying the extremities and trunk can simulate a variety of other disorders such as systemic sclerosis (scleroderma), scleromyxedema, and eosinophilic fascitis.

The following finding is helpful in the differential diagnosis.

The absence of Reynaud's phenomenon argues strongly against systemic sclerosis. In addition, the absence of antinuclear antibodies and either anticentromere or anti-DNA topoisomerase(SCL-70) antibodies argues against both the limited and diffuse forms of systemic sclerosis.

The skin lesion and histopathologic findings in NSF resemble those in scleromyxedema [47], distinguishing clinical features are sparing of the head in NSF and the association of most scleromyxedema cases with a monoclonal gammopathy usually with an IgG lambda paraprotein[13, 40]

The clinical manifestations in NSF resemble eosinophilic fascitis but are distinguished by frequent involvement of the hands and feet, witch are typically spared in eosinophilic fascitis, and the absence of eosinophilia and eosinophilic tissue infiltration.[38]

Skin tightening and joint stiffness are features of systemic fibrosing disorders. (Table 2)

Chronic kidney disease may develop in patients with scleroderma as a result of scleroderma renal crisis, but it is unusual for scleroderma to develop in patients with preexisting chronic kidney disease. The absence of Raynaud's phenomenon, dysphagia, heart-burn, and facial involvement is in consistent with a diagnosis of scleroderma. Many patients with scleroderma present with circulating antinuclear antibodies, some of which have specificity for topoisomerase I (anti-scl-70 antibodies).

The absence of facial involvement is also inconsistent with a diagnosis of scleromyxedma.

Localized cutaneous fibrosing disorders such as morphea, scleroderma diabeticorum, and lipodermatosclerosis can be ruled out because the apperance and distribution of skin changes typical of these conditions differ from those observed in NSF.[46]

Course:

NSF disease has a chronic and unremitting course in most patients.[48, 49]

In a review of the published literature, 28 percent of patients had no improvement, 20 percent had modest improvement, and 28 percent of patients died.[13] More severe and rapid progression of the skin disease is associated with a poor prognosis and death.

Table2: Fibrosing Disorders

Disorder	Associated Features
Localized idiopathic cutaneous fibrosing disorders	
Morphea(localized scleroderma)	Circumscribed sclerotic plaques
Linear scleroderma(Localized scleroderma)	Circumscribed linear sclerotic plaques
Scleredema diabeticorum	Neck,shoulders,and upper back affected, not the extremities;diabetes mellitus
lipodermatosclerosis	Painful ,brownish tightening of the skin of the iower legs _does not affect the arms chronic venous insufficiency
Systemic idiopathic fibrosing disorders Diffuse systemic sclerosis (scleroderma)	Raynauds phenomenon,dysphagia,heartburn,facial involvement Circulating antinuclear antibodies,including anti_topoisomerasel (anti_Scl-70) antibodies
Scleromyxedema	Facial involvement;circulating monoclonal paraprotein(usually lgG lambda)
Eosinophilic fasciitis	Joint stiffness,peripheral eosinophilia(intermittent)
Fibrosing disorders with identified causes	
Spanish toxic oil syndrome	Caused by olive oil adulterated with rapeseed oil
Eosinophilia-myalgia syndrome	Caused by contamination of L-tryptophan with 1,1-ethylidenebis {L-tryptophan}
Graft-versus-host disease	Previous bone marrow transplantation
Nephrogenic systemic fibrosis	Exposure to gadolinium-containing contrast agents in the setting of chronic kidney disease

Prevention:

The major preventive measure that can be currently recommended to patients with advanced kidney failure is the avoidance of gadolinium.

Avoidance of gadolinium: Based upon the apparent association between NSF and gadolinium in the great majority of cases[23, 37, 50], the United States Food and Drug Administration (FDA) made the following recommendations in patients with advanced kidney failure.[25]

Gadolinium-containing contrast agents, especially at high doses, should be used only if clearly necessary Gadolinium should be avoided in patients with a diagnosis or clinical suspicion of NSF.

Although there are no data that support the following approach, it may be prudent to institute prompt hemodialysis after the imaging study is completed if gadolinium is given.

The FDA defined patients at risk as those with acute or chronic severe renal insufficiency estimated glomerular filtration rate (GFR) less than (30 ml/min)or patients with acute renal failure of any severity due to hepatorenal syndrome or in the perioperative liver transplantation period.

The risk of NSF after gadolinium administration has not been defined in patients who have an estimated GFR between 30 and 60 ml/min.[25]

Among patients with moderate to advanced renal failure who it is felt must receive a gadolinium contrast study, the following approach is suggested:

• The patient should be informed of the benefits, risk and alternatives.

• Given that the great majority of cases of NSF have followed imaging with gadodiamide , giving one of the other gadolinium preparations (such as as gadoteridol).[23, 37]

Treatment:

There is no proven therapy for NSF other than recovery of renal function.[13, 46] Only two cases have been reported in which patients had spontaneous improvement with resolution of acute renal failure,.[46]

Intensive physical therapy is recommended in all patients to prevent or reverse disability related to joint contractures.[40]In addition, the hands should be splinted in a functional position to prevent progressive contractures of the finger joints.[51]

Renal transplantation may offer the best hope of benefit in patients who are candidates for this procedure although efficacy is unproven.[52]

Extracorporeal photophersis (ECP), involves extracorporeal exposure of peripheral blood mononuclear cells to photoactivated 8-methoxypsoralen, followed by reinfusion of the treated cells.ECP induces monocyte-derived tumor necrosis factor-alpha, which in turn suppresses collagen synthesis and enhances collagenase production.[53]

Post imaging dialysis has also been proposed as a way to mitigate the development of NSF in certain high-risk patients by removing circulating gadolinium-based contrast agents (gadolinium-based contrast agents (GBCA) in a timelier manner. Currently, this is recommended only in cases in which the patient is already receiving hemodialysis. For those not being dialyzed, or those on peritoneal dialysis, no specific recommendations exist.[54]

A number of other modalities have been tried in case reports or small series. Possible efficacy has been noted with photodynamic therapy [55], pentoxifylline[46], imatinib [4, 56], intravenous sodium thiosulfate, [57, 58], and high dose intravenous immune globulin.[59]

However, other therapeutic approaches such as topical and oral steroids, immunosuppressive drugs, and plasmapheresis, have failed to improve the skin changes associated with nephrogenic systemic fibrosis.[46]

Summary and Conclusion:

Nephrogenic systemic fibrosis (NSF) is a recently identified fibrosing disorder seen only in patients with moderate to severe kidney failure, particularly patients on dialysis.

• Increasing evidence has implicated gadolinium-containing contrast agents, which are excreted exclusively by the kidney as the cause of NSF.

• Routine light microscopy of a skin biopsy may reveal subtle proliferation of dermal fibrocytes in early lesions or marked thickening of the dermis with severe disease special testing may show gadolinium.

• Skin involvement occurs in all patients, while only some have systemic manifestations. The skin disease presents with plaques, papules, and or nodules, with the affected skin becoming thickened and firm and possibly assuming a peau d'orange appearance .Manifestation of systemic involvement may include muscle induration, joint contracture, and fibrosis of the lungs, pleura, diaphragm, myocardium, pericardium, and dura mater.

• No therapy or combination of therapies has shown consistent benefit in NSF other than recovery of renal function .So prevention is the best option.

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