ARTÍCULO DE REVISIÓN

Gadolinium nephrogenic systemic fibrosis

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Resumen

La fibrosis sistémica nefrogénica (FSN) fue descrita en 1997. Es una enfermedad secundaria al uso de medios de contraste que contienen gadolinio. Es una enfermedad debilitante y progresiva que se caracteriza por la presencia de fibrosis. Se desarrolla especialmente en enfermos con insuficiencia renal que son expuestos a gadolinio. Se manifiesta clínicamente por induración e hiperpigmentación cutánea y contracturas articulares. El proceso fibroso se puede extender a músculo esquelético, hígado, pulmón y corazón. La mortalidad puede llegar a ser de 31%. Los tratamientos desarrollados para esta enfermedad son de utilidad limitada, por lo que se recomienda que los médicos que indiquen un estudio con gadolinio evalúen la función renal con base en la depuración de creatinina y en caso necesario se utilicen otras alternativas diagnósticas.

Palabras clave. Dermopatía fibrosante nefrogénica. Gadolinio. Insuficiencia renal.

Abstract

Nephrogenic systemic fibrosis (NSF) was described in 1997. Is a disease linked to the use of gadolinium based contrast agents. NSF is a debilitating fibrosing disorder that develops in patients with underlying kidney disease exposed to gadolinium. Clinical manifestations are cutaneous hyperpigmentation and induration and joint contractures. Fibrosis may also develop in other organs like skeletal muscle, liver, lung and heart. The mortality can reach 31%. Current management is disappointing. In all patients with elevated serum creatinine physicians should estimate his kidney function in order to ensure the safety of magnetic resonance imaging. Prevention with hemodialysis immediately following gadolinium-based contrast agents has been recommended. Physicians should use alternative imaging modalities for patients who are at risk.

Key words. Nephrogenic fibrosing dermopathy. Gadolinium. Kidney failure.

INTRODUCTION

Nephrogenic systemic fibrosis (NSF) is a fibrosing disease, primarily identified in the skin and subcutaneous tissues but also known to involve other organs. Symptoms and signs may develop and progress rapidly. Death may result in some patients as a result of visceral organ involvement. NSF occurs in patients with renal failure, acute renal insufficiency related to the hepatorenal syndrome or perioperative liver transplantation and patients with a proinflammatory state (like recent surgery, sepsis or endovascular damage) exposed to gadolinium based contrast media or in patients under treatment with immunosuppressants drugs. The first cases where reported between 1997 and 2000, in patients with hemodyalisis, peritoneal dialysis, acute renal failure, chronic renal failure and in patients with renal transplantation.[1] In late 2008, two hundred cases of NSF where reported internationally, the majority where reported in adults and some of them in children.[2] The aim of this paper is review current concepts of NSF.

ETIOLOGY

NSF is a recently discovered disease, secondary to the exposition of drugs, infectious agents or toxins, in patients with renal failure. Gadolinium contrast agents used in magnetic imaging resonance (MIR) have been implied like the principal cause of NSF.[3]

Gadolinium is a very useful marker for MIR because of the density of unpaired electrons; free Gadolinium is extremely toxic because it's a potent inhibitor of calcium channels and forms insoluble hydroxides and phosphates at physiologic pH. To avoid toxicity, Gadolinium is given as organic complexes like gadodiamide, gadopentetate dimeglumide and gadoteridol (Figure 1).[4]

Gadolinium complex are excreted by the kidney, they have a $t_{1/2}$ of 1.3 h in patients with normal renal function, but 30-120 h with advanced renal failure.[3] Cleared well by hemodialysis, with 80% removed after a 4 h session; peritoneal dialysis is not as effective as hemodialysis.[5]

These complexes are very stable with finite dissociation constants, Gadolinium may be displaced by other metal

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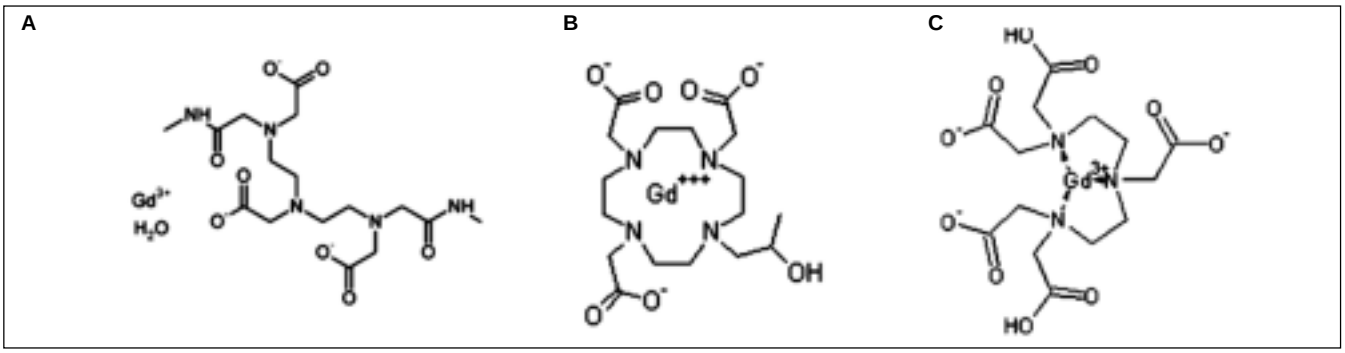

Figure 1. Molecular structure of Omniscan (A), Magnevist (B) and Prohance (C).

ions like iron, zinc and lanthanum. Initially Gadolinium was thought to be "*safe*" in renal disease and widely used, but over the past decade, an unusual skin problem appeared in patients with end stage renal disease. Initially called nephrogenic fibrosing dermopathy, later renamed NFS.[6]

In the international NSF registry more than 95% of cases reported where exposed to Gadolinium in the last 2 to 3 months prior to the start of the symptoms.[4] The risk reported between chronic renal failure and NSF is 2.5-5% in studies with 500 patients.[5] A retrospective study, demonstrates that the presence of an infection in the moment of exposition to Gadolinium, increases the risk of NSF in patients under dyalisis.[6] Study of cases reported two patients with NSF without previous exposure to Gadolinium. The authors postulate that vascular manipulations or endothelial lesion might cause NSF. [7]

Many of the published series have suggested that renal failure patients are at highest risk when they are exposed to high doses or multiple doses of gadolinium. Nonetheless, there are clearly reported instances of NSF occurring in patients who have been exposed to standard single doses of Gadolinium base contrast media.[8]

PHYSIOPATHOLOGY

Gadolinium dissociates from its chelate in patients with significantly diminished renal function due to the prolonged clearance times. This dissociation occurs by a process known as transmetallation, whereby other cations replace the gadolinium associated with the chelate. Suspected cations include (in acidic environments), calcium, iron, zinc, copper, lanthanum carbonate, and rare metals. Gadolinium forms a stable salt with other anions (such as phosphate or bicarbonate) and results an insoluble precipitate which is deposited in the skin and subcutaneous tissues as well as another locations via a process that is still poorly understood. A fibrotic reaction ensues, involving the activation of circulating fibrocytes and cytokines. The fibrogenic cytokines produce a cascade of inflammatory events, which generates an exaggerated tissular fibrosis. Dendritic cells/CD68/factors XIIIa are activated by a harmful stimulus, causing the synthesis of transforming growth factor beta-1, which regulates the maturation and activation of these cells, producing fibrosis. Another theory, propose that a toxin stimulates the bone marrow, for production of CD34 fibrocytes. *In vitro* studies, demonstrate the increase in the IL-13, IL-4, IL-6 levels synthesized by peripheral monocytes in response to Gadolinium chelants.[9]

Free Gadolinium has many tissular effects *in vivo*, it alters the calcium flux though nerves and myocytes and also interferes with intracellular enzymes and cellular membranes. Anions like phosphate tend to be higher in patients with chronic renal failure and could be a cofactor for the development of NSF.[10] There is a direct relationship between total cumulative dose and the severity and likelihood of NSF.

CLINICAL MANIFESTATIONS

The period between exposition to gadolinium and beginning of symptoms ranges between two days to 18 months. Skin affections in NSF are characterized by symmetric bilateral indured fibrotic papules, plaques or subcutaneous nodules, with or without eritema.[11] In the majority of cases, the primary lesion begins in the ankles, thighs, feet and hands. Later these lesions appear in forearms and less frequently in trunk, most of times with edema which can be confused with cellulitis.[8] When edema resolves, the affected skin get indurated with firm texture and oran-

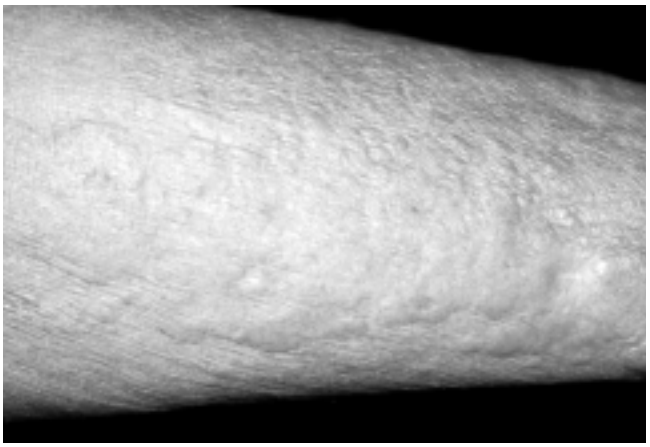

Figure 2. Thickening of skin characteristic of Nefrogenic Systemic Fibrosis. Source: http://img.webmd.com/dtmcms/live/webmd/consumer_assets/site_images/articles/health_tools/what_your_skin_says_about_your_health_slideshow/doj_photo_of_nephogenic_systemic_fibrosis.jpg

ge skin appearance. These lesions could present pruritus and burning sensation[11] (Figure 2).

The movement and flexibility of articulations could be limited by fibrosis. The patients can present sclerodactilia or loss of skin in dorsum of hand and feet. In advanced stages there is hyperpigmentation, loss of hair and skin atrophy.[12]

Prevalence of systemic manifestations is unknown, many organs can be affected, like muscles with limited flexibility, periarticular thickening of the skin, which limits mobility, there is no evidence of arthitis or synovitis. In severely affected patients, computed tomography shows muscular fascia fibrosis, which can be seen on biopsy.[8,13] Other organs affected are the lungs, with a significantly reduced carbon monoxide diffusion capacity, the diaphragm, the myocardium, the pericardium and the dura mater.[14] Patients with systemic affection show high levels of reactive C protein and globular sedimentation rate.[4]

DIAGNOSIS

With the clinical suspicion of NSF, we should ask about previous exposition to Gadolinium. Biopsies of affected areas confirm the diagnosis. The biopsy should be deep, because some changes can extend to the fascia, muscle and subcutaneous tissue. If the first biopsy is not characteristic and there is high clinical suspicion, it has to be repeated. In the majority of cases the biopsy shows marked dermis thickening, fibrocyte proliferation, prominent collagen fibers and increase in mucin production[11]. Immunohistochemistry studies reveal abundant circulant CD34 fibrocytes that are recruited in dermis[12]. Special tests can show Gadolinium in tissues. [13] There is not a specific laboratory test to diagnose NSF, only the chronic inflammation markers mentioned above can be used. Pulmonary function tests show a decrease in total pulmonary capacity, volume and diffusion capacity. Echocardiogram can show ventricular dysfunction.

DIFFERENTIAL DIAGNOSIS

Thickening and hardening of skin, are characteristic of NSF, and should be differentiated of systemic scleroderma, escleromyxedema and eosinophilic fasciitis. Patients with NSF don't manifest neither Raynau's Phenomenon nor presence of antinuclear, anticentromer and anti-DNA topoisomerase antibodies. Eosinophilic fasciitis also involves hand and feet, but shows eosinophils infiltration instead of CD34+ fibrocytes that occurs in NSF.[14,15]

PREVENTION

There are several risk factors associated to develop NSF. These include metabolic acidosis or medications that predispose patients to acidosis, increased iron, calcium, and/or phosphate levels, high-dose erythropoietin therapy, immunosuppression, vasculopathy, an acute proinflammatory event, and infection. The best preventive measure is to avoid the use of Gadolinium in patients with hepatorenal syndrome, renal failure, creatinine clearance below 30 mL/min and other risk factors. If the administration of Gadolinium is essential, hemodyalisis is safe measure for its elimination. In patients with peritoneal dialysis, it's recommended to increase the sessions during the next 48 h after the exposure.[16,17]

TREATMENT

There isn't an adequate treatment for NSF. Extracorporeal photopheresis it's a therapeutic regimen used as an alternative, which consists in the stimulation of peripheral mononuclear cells with activated metoxipsolaren-8, which stimulates the production of tumor necrosis factor alfa, which decrease the collagen production and increases the collagenase activity.[18] One of the most used treatments is the type A ultraviolet phototherapy, which inhibits the procollagen synthesis in

skin.[19] Other treatments like imatinib,[20] pentoxiphiline,[21] high doses of intravenous immunoglobulin,[22] oral prednisone and topical calcipotriene plus betamethasone have been suggested. Renal transplantation is the most recommended therapy in patients with worsening renal failure. To control pain and improve join function are recommended deep tissue massages, physical therapy and low impact exercises. Surgery has no role in the treatment of this disease.

CONCLUSION

NSF is a recently described disease, secondary to MIR Gadolinium based contrast media exposition in patients with end stage renal disease. Characterized by thickening of the skin and sometimes fibrosis of articulations limiting their movement. The diagnosis is purely clinical. There are few treatment options which are not effective nowadays.

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