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European Journal of Radiology 66 (2008) 230–234

EJR
EUROPEAN JOURNAL OF RADIOLOGY

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Nephrogenic systemic fibrosis associated with gadolinium based contrast agents: A summary of the medical literature reporting

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Received 4 February 2008; received in revised form 4 February 2008; accepted 4 February 2008

Abstract

Nephrogenic systemic fibrosis (NSF) is a systemic fibrosing disorder that principally affects the skin, but can involve virtually any tissue in the human body and result in significant disability and even death. Since 2006 numerous retrospective case reports and case series have reported a very strong association of this disease with exposure to gadolinium-based contrast agents (Gd-CA) for MR imaging in the setting of severe or end-stage renal disease. The purpose of this report is to summarize the medical literature reporting of biopsy-proven NSF cases in which the authors specifically investigated patient exposure to Gd-CA. A Pub Med MEDLINE search was performed using the key words—nephrogenic systemic fibrosis and nephrogenic fibrosing dermopathy. All case reports and case series of NSF were reviewed to determine if patients had a preceding exposure to Gd-CA and which specific Gd-CA was involved. If the original reports did not clarify the specific Gd-CA, I reviewed follow-up letters to the editors or contacted the authors to clarify which specific Gd-CA were linked to the NSF cases. If several reports originated from the same institution, clarification was also obtained to avoid redundant reporting. As of February 1, 2008 there have been 190 biopsy-proven cases of NSF published in the peer-reviewed literature with the following associations: 157 gadodiamide (Omniscan, GE Healthcare), 8 gadopentetate (Magnevist, Bayer Healthcare), 3 gadoversetamide (OptiMARK, Covidien), and 18 unspecified Gd-CA, and 4 confounded cases with more than one Gd-CA. Five cases of NSF were unassociated with Gd-CA.

Keywords: Renal failure; Nephrogenic systemic fibrosis; Nephrogenic fibrosing dermopathy; Gadolinium; MR imaging

1. Introduction

In 2000 Cowper first described a new scleromyxedema-like cutaneous disorder that developed in 15 dialysis patients and was subsequently called nephrogenic fibrosing dermopathy [1]. This condition has been shown to result in persistent skin induration, thickening and hyperpigmentation involving the extremities and trunk with facial sparing. Numerous case reports and autopsy series have documented multi-systemic involvement of this disorder such that it was later renamed nephrogenic systemic fibrosis (NSF). In 2006 Grobner first proposed that Gadolinium-based contrast agents (Gd-CA) may trigger the development of NSF in dialysis patients with underlying metabolic acidosis [2]. Prior to that report, the only condition consistently associated with NSF was underlying severe or end-stage kidney disease. Since Grobner's article, the vast majority of published case reports have found a very strong association of NSF with Gd-CA exposure when a meticulous chart review was performed. These latter case reports with historical information regarding Gd-CA exposure serve as the basis for our analysis and summary of the medical literature.

2. Methods

A Pub Med MEDLINE search was performed at the U.S. National Library of Medicine using the key words—nephrogenic systemic fibrosis and nephrogenic fibrosing dermopathy. All case reports and case series of NSF reported in the peer-reviewed literature (including those published online before print) before February 1, 2008 were reviewed to determine if patients had a preceding exposure to Gd-CA and which specific Gd-CA was involved. If the original report did not clarify the specific Gd-CA, I reviewed follow-up letters to the editors or contacted the authors to clarify which specific Gd-CA were linked to the NSF cases. If several reports originated from the same institution, clarification was obtained as to the exact num-

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doi:10.1016/j.ejrad.2008.02.011

ber of unique cases from their institution to avoid redundant counting of their NSF cases. The NSF cases were categorized and tabulated based on their association with a specific Gd-CA, an unspecified Gd-CA, confounded administration of several Gd-CA or lack of association with Gd-CA. Only NSF cases confirmed with skin biopsy were included in the final summary, although additional remarks were included regarding the unproven cases.

3. Results

Presented in Table 1 is a summary of the peer-reviewed medical literature reporting of biopsy-proven NSF cases for which Gd-CA exposure was investigated. As of February 1, 2008 there have been 190 biopsy-proven cases of NSF published in the peer-reviewed literature associated with Gd-CA and 5 cases unassociated with Gd-CA [3–43]. Of the 190 NSF cases asso-

Table 1
Medical Literature report of NSF as of February 1, 2008

Author	Reference	Year	Omniscan cases	Magnevist cases	OptiMARK cases	Unspecified Gd-CA	Confounding cases	Definitively not exposed to Gd-CA	Other remarks
Evenepoel	[2]	2004	2						
Jain	[4,5]	2004	2						
Grobner	[2]	2006	5						
Marckmann	[6]	2006	13						
Nowack	[7]	2006	1						
Maloo	[8]	2006	1						
Boyd	[9]	2007	2			2			
High	[10]	2007				7			
Broome	[11]	2007	12						
Khurana	[12]	2007	6						
Sadowski	[13]	2007	12				1		Omniscan/MultiHance
Cheng	[14]	2007	15		3		1	1	Omniscan/OptiMARK
Pryor	[15]	2007	6						Includes 2 case reported by Maloo
Richmond	[16]	2007	7						
Yerram	[17]	2007	1						
Thakral	[18]	2007		1					
Moreno-Romero	[19]	2007	3						
Marckmann	[20]	2007	6						13 previously reported
Lim	[21]	2007	2						
Swaminathan	[22]	2007	12						
Deo	[23]	2007	2	1					
Wahba	[24]	2007						2	
Collidge	[25]	2007	11					1	2 other NSFcases with Omniscan Without skin biopsy
Introcaso	[26]	2007				9			
Plamondon	[27]	2007	1						
Othersen	[28]	2007	4						
Todd	[29]	2007		5					20 other suspected NSF cases with Magnevist without skin bx
Cheung	[30]	2007	1						
Lauenstein	[31]	2007	9						
Clorius	[32]	2007	1						
Saussereau	[33]	2007					1		Omniscan/Dotarem
Tsai	[34]	2007	1						
Krous	[35]	2007					1		Omniscan/Magnevist/ Optimark
Kintossou	[36]	2007	1						
Rydahl	[37]	2008	8						19 previously reported
Caccetta	[38]	2008	1						
Anavekar	[38]	2008						1	
Naylor	[40]	2008	1						
Kalb	[41]	2008	1						
Wiginton	[42]	2008	6						1Omniscan case without bx
Weigle	[43]	2008	1	1					1 case previously reported
Total			157	8	3	18	4	5	

ciated with Gd-CA, there were four cases with confounded association with more than one Gd-CA and 18 cases with an unspecified Gd-CA (which could not be verified by authors of the case reports). The remaining 168 NSF cases could be linked to a specific Gd-CA with the following associations—157 gadodiamide (Omniscan, GE Healthcare, Chalfont St.- Giles, United Kingdom), 8 gadopentetate (Magnevist, Bayer Schering Pharma AG, Berlin, Germany), and 3 gadoversetamide (OptiMARK, Covidien, St. Louis, USA).

4. Discussion

NSF is a multi-systemic fibrosing disorder that has a wide distribution of patient age, but no sex or ethnic predilection. The early clinical manifestations of NSF include pain, swelling, skin erythema, pruritus, transient alopecia as well as gastrointestinal symptoms of nausea, vomiting, diarrhea and abdominal pain. Chronically the skin develops nodules, patches or confluent regions of hyperpigmentation with associated skin thickening and brawny induration. The skin changes usually start in the distal extremities, then spread proximally and may involve the trunk. Progressively, patients may develop stiffness of the joints, myalgia, deep bone pain, muscle weakness, joint contractures and leg restlessness. Yellowish scleral plaques have also been described.

After Grobner's 2006 seminal article, numerous published case series have confirmed a very strong association of NSF with exposure to Gd-CA. Nearly all of the NSF cases reported in the peer-reviewed literature after Grobner's report have been linked to exposure to Gd-CA [3–23,25–38,40–43]. Several reports published prior to this report have been updated to indicate their association with Gd-CA [3,4,5,8]. Four confounded cases have been reported in which the patients were exposed to more than one Gd-CA within a short period of time before onset of NSF [13,14,33,35]. These patients were exposed to gadodiamide (Omniscan) and one or more other GBCM including gadoversetamide (OptiMARK), gadobenate (MultiHance, Bracco Diagnostics, Milan, Italy), gadopentetate (Magnevist), gadoterate meglumine (Dotarem, Guerbet, Paris, France). No cases of NSF have been reported in the peer-reviewed medical literature to be associated with gadoteridol (ProHance, Bracco Diagnostics, Milan, Italy). There have been 18 additional cases that have been linked to an unspecified Gd-CA [9,10,26]. Only five cases of NSF have been published that have no reliable Gd-CA exposure [14,24,25,39]. In summary, 93% of the unconfounded biopsy-proven NSF cases linked to a specific Gd-CA have been associated with gadodiamide (Omniscan). These finding are similar to the findings of the International Center for Nephrogenic Fibrosing Dermopathy Research (ICNFDR), a registry of over 250 well-documented NSF cases maintained by Shawn Cowper of Yale University, which has linked 85% of its cases to gadodiamide (Omniscan) [44,45]. Smaller percentages of NSF cases in the medical literature have been directly linked to gadopentetate dimeglumine (Magnevist), gadoversetamide (OptiMARK). One confounded cases was associated with gadobenate (MultiHance) [13]. The US Food and Drug Administration MedWatch program and the UK Commission on Human Medicines together with the European Pharmacovigilance Working Party have also reported a disproportion number of NSF cases associated gadodiamide (Omniscan) compared to the other Gd-CA. However, NSF reporting to these regulatory agencies is voluntary, prone to redundant reporting, less substantiated, and less verifiable when compared to the peer-reviewed medical literature.

Deep skin biopsy is considered essential for definitive diagnosis of NSF because other clinical condition can mimic NSF, such as scleromyedema, scleroderma, morphea, eosinophilic fasciitis, eosinophilia–myalgia syndrome, toxic oil syndrome, and calciphylaxis [1]. The skin biopsy should include the entire dermis and subcutaneous fat to the level of the fascia, if possible [44]. Histology shows extensive dermal fibrosis with an altered pattern of collagen bundles with surrounding clefts and increased number of spindle cells, which typically stain positive for CD34 and Procollagen-1 surface markers [1,44]. The spindle cells stain identical to circulating fibrocytes which are known to be associated with scar formation and wound healing [46,47]. Frequently there is increased mucin deposition in the dermis. Additionally, the histology does not show inflammatory changes with significant leukocyte infiltration. In the peer-reviewed medical literature there have been several published NSF cases which did not have a confirmatory skin biopsy. These include 20 NSF cases associated with gadopentetate (Magnevist) [29] and three cases associated with gadodiamide (Omniscan) [25,42]. These cases were not included in our total count of NSF cases, but were mentioned in our remarks section of Table 1. However, if the 23 published NSF cases without biopsy confirmation were included, 84% of the unconfounded NSF cases would be linked to gadodiamide (Omniscan).

The proposed trigger for NSF is transmetallation of the gadolinium chelate whereby free gadolinium ion is released from the chelate in exchange for endogenous metals (such as zinc, copper and calcium) with subsequent binding to human tissue [2,6]. Patients with severe or end-stage renal disease are more likely to undergo in vivo transmetallation because of markedly prolonged clearance of Gd-CA. This theory has been substantiated by detection of gadolinium within tissue months after Gd-CA exposure [9,10,33]. The likelihood of in vivo transmetallation of linear gadolinium chelates appears to be related to difference on the conditional thermodynamic stability constant values, which vary from 100 to 1000 fold [48]. Linear nonionic chelates such as gadodiamide (Omniscan) and gadoversetamide (OptiMARK) would seem to be at higher risk for transmetallation than the linear ionic chelates such as gadopentetate dimeglumine (Magnevist) and gadobenate dimeglumine (MultiHance) [48]. The macrocyclic gadolinium chelates such as gadoteridol (ProHance), gadobutrol (Gadovist, Bayer Schering Healthcare, Berlin, Germany) and gadoterate meglumine (Dotarem) would seem to carry the lowest risk because of a stronger inherent binding and chemical stability under physiologic conditions [48]. The exact pathogenesis is unclear, but it likely involves the migration of CD34 and procollagen-1 positive circulating fibrocytes from the blood to the involved tissue as proposed by Cowper [44,46,47]. These fibrocytes likely activate a fibrotic response through cytokine production and T-cell acti-

vation [46,47]. Several reports have shown increased expression of transforming growth factor β1 and CD68-Factor XIIIa within the affected skin and skeletal muscle which are also important markers associated with wound healing and fibrosis [49]. In addition, gadodiamide has been shown to stimulate a dose-dependent fibroblast growth in cell cultures as well as increased matrix synthesis and differentiation into myofibroblasts [50]. Additional evidence of in vivo transmetallation has been provide by a preclinical trial in which rats exposed to repeated high-dose Gd-CA injection developed a NSF-like skin lesion consisting of epidermal ulceration, acanthosis, dermal fibrosis and CD34 fibrocytic infiltration with high concentrations of gadolinium in the skin. These findings were more severe with gadodiamide (Omniscan) compared to gadopentetate (Magnevist) [51]. The differences in conditional thermodynamic stability constants and stimulatory response of gadodiamide on fibroblasts may explain the higher incidence of NSF with gadodiamide (Omniscan). The medical literature reporting of NSF and this additional evidence would seem to indicate a stratified risk within the class of Gd-CA [45].

There are certain limitations to consider when interpreting the medical literature reporting of NSF cases associated with specific Gd-CA. The first consideration is that market shares of Gd-CA vary from country to country and continent to continent. What is more important to consider is the total number administrations of each Gd-CA. As of 2007 the worldwide estimated total number of administration of each Gd-CA approved in the US was: Magnevist 79.7 million, Omniscan 36.5 million, ProHance 12.5 million, MultiHance 2.1 million, and OptiMARK 1.5 million [52]. To these figures one must add the administration of agents approved outside the US: Dotarem, Gadovist, Vasovist and Primovist. It is estimated that they have been given to more than >15 million patients (HS Thomsen, personal communication). Secondly, report of NSF in the medical literature will likely be biased toward reporting from academic centers, which may have a greater usage of one or two Gd-CA over the remaining agents. However, these same institutions are more likely to be perform MR angiography or MR imaging on dialysis patients or patients with severe kidney disease. Thirdly, it is difficult to be certain that all the cited NSF cases in Table 1 are unique cases, with no overlap or duplicate reporting of cases. When reports originated from the same institution, I made efforts to contact the authors to verify that there was no redundancy of reporting. However, there may have been case material (particularly pathology material) that was shared between institutions, possibly resulting in redundant reporting of a few cases.

In summary, since 2006 a number of case reports and case series have reported a very strong association of Gd-CA with the development of NSF. Although the medical literature reporting of this condition is still in flux, it has certainly grown beyond its infancy. Even accounting for differences in market shares and total number of contrast administration, gadodiamide continues to be the Gd-CA most strongly associated with NSF. With continued reporting of NSF, the medical literature will continue provide additional information expanding our knowledge and understanding of NSF in regard to its etiology, pathogenesis, associations, prognosis and management.

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