

Case Report/Case Series

Gadolinium-Associated Plaques

A New, Distinctive Clinical Entity

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IMPORTANCE A new condition, gadolinium-associated plaques (GAP), is reported in 2 patients. It is related to a particular type of gadolinium (gadodiamide) used for contrast-enhanced radiologic studies.

OBSERVATIONS Erythematous plaques, 0.5 to 2.5 cm in diameter, were pruritic in one case and asymptomatic in a second case. Findings from the histopathologic examination revealed eosinophilic, collagenous, round or ovoid bodies (sclerotic bodies) in various stages of calcification. Previously, these sclerotic bodies were thought to be pathognomonic for nephrogenic systemic fibrosis (NSF) in the setting of chronic renal disease with associated gadolinium exposure. Neither patient had NSF, while only 1 of these patients had renal disease. The patient who did not have renal disease received high doses of gadolinium.

CONCLUSIONS AND RELEVANCE Physicians should be aware that GAP can occur without NSF or renal disease and is associated with the use of radiologic dyes. Sclerotic bodies have been reported only in association with gadolinium exposure (eg, gadodiamide) either in the sclerotic skin in NSF or in GAP.

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A rare, distinctive histopathologic feature, the sclerotic body, has been linked to gadolinium exposure in patients with chronic renal disease.¹⁻⁵ Sclerotic bodies are generally associated with nephrogenic systemic fibrosis (NSF).² These eosinophilic, round or oval laminated collagen globules contain scattered solitary cells with plump nuclei, as if in lacunae. Focal calcification and surrounding whirled fibroblasts complete the histopathologic features.¹⁻⁵ We describe 2 patients without NSF who developed erythematous plaques that demonstrated sclerotic bodies on histopathologic examination after exposure to gadolinium-based contrast. In addition, 1 of the 2 patients had no evidence of renal disease. We propose the name *gadolinium-associated plaques* (GAP) for this clinical entity.

Report of Cases

Case 1

A man in his 80s presented with an 18-month history of a pruritic, burning rash on both hands. No other skin lesions were present except actinic poikiloderma in sun-exposed areas. The broad areas of hardened skin with fibrotic nodules and joint contractures typical of NSF were not present. Previous treatment with a combination of clotrimazole and betamethasone dipropionate cream (Lotrisone) twice daily for 8 weeks and then clobetasol dipropionate cream, 0.05%, twice daily for 8

weeks failed to resolve the signs or symptoms. The patient's medical history was significant for cervical spine disease, prostate carcinoma, hypothyroidism, varicella, and gallstones. He received multiple magnetic resonance imaging scans and was exposed to 20 mL of gadodiamide contrast dye (OmniScan; GE Healthcare) in August 2008, September 2008, January 2009, February 2010, and January 2011 (total, 100 mL). His medication regimen included aspirin, divalproex sodium, levothyroxine sodium, methocarbamol, a combination of naphazoline hydrochloride and pheniramine maleate, and omeprazole. Six erythematous annular plaques were present on the dorsal hands ranging from 0.5 to 2.0 cm in diameter. Fine papules were noted at the periphery and scaling was absent (Figure 1). The clinical differential diagnosis included granuloma annulare, annular elastolytic granuloma, and cutaneous sarcoidosis. A 6-mm punch biopsy specimen demonstrated discrete round and oval areas of eosinophilic, finely laminated, amorphous material surrounded by spindle fibrocytes, diagnostic of sclerotic bodies (Figure 2, A and B). Solitary cells with plump nuclei were present within the sclerotic bodies, resembling osteocytes within the bone matrix. In some areas, the amorphous material was centrally calcified, and in others it was completely calcified. No osteoma or cartilagenous tissue was identified. No basaloid cells of the type seen in pilomatricoma were present. A Masson trichrome stain revealed blue staining typical of the sclerotic bodies and Verhoeff-van Gieson stain revealed entrapped but intact elastic fibers within the sclerotic

bodies (Figure 2, C). A panel of immunohistochemical stains, including CD34, CD68, factor XIIIa, CD99, vimentin, and S-100 protein, was performed. The spindled fibrocytes surrounding the sclerotic bodies stained positively with CD68 and factor XIIIa. The solitary cells within the sclerotic bodies as well as the variable number of stromal cells were highlighted by vimentin. The CD34 stained the blood vessels and scattered stromal cells. The S-100 protein and CD99 stains were negative in both the solitary cells within sclerotic bodies and the surrounding fibrocytes (Table). Intralesional injection of triamcinolone acetonide, 20 mg/mL (0.5-1.0 mL per plaque), monthly for 3 months led to complete resolution of symptoms and flattening of the GAPs.

Case 2

A woman in her 70s presented with a 2-year history of a slowly enlarging, asymptomatic tan-brown plaque on the right anterior lower leg after exposure to an unknown dose of gadolinium for several contrast-enhanced radiologic procedures. The broad areas of hardened skin and contractures indicative of NSF were not present. Her medical history was significant for parathyroidectomy and she had chronic renal insuffi-

ciency that was managed with regular hemodialysis. A firm, 2.5 × 2.0-cm, irregular tan-brown lesion was present on the right anterior lower leg. An initial biopsy specimen revealed sclerotic bodies with focal calcification throughout the superficial reticular and midreticular dermis, with surrounding dermal fibrosis (Figure 3). An increased number of CD34-positive stromal cells were present. Large amounts of hemosiderin pigment, confirmed by iron stain, correlated with the brownish coloration of the plaque. An increased number of small-caliber vessels and subtle mucin deposition between collagen bundles were also noted (Table).

Discussion

The combined clinical and histopathologic features of these 2 cases are unique in the literature, to our knowledge. The distinctive dermal sclerotic bodies have been previously described only in patients with renal disease, usually in association with NSF.¹⁻⁵ Sclerotic bodies are well-defined, pink, finely laminated eosinophilic globules that are similar in character to osteoid and may calcify. This material is distinguished from bone by the absence of Haversian channels. The sclerotic bodies are surrounded by concentrically arranged spindled cells with loose fibrotic stroma and preserved elastic fibers.¹⁻⁵

The single case of sclerotic bodies in a patient without NSF was associated with significant gadolinium exposure and supports our contention that this finding is not pathognomonic for NSF.² In fact, we provide evidence that gadolinium in high doses can produce sclerotic bodies within GAPs, even in the absence of renal disease (case 1).

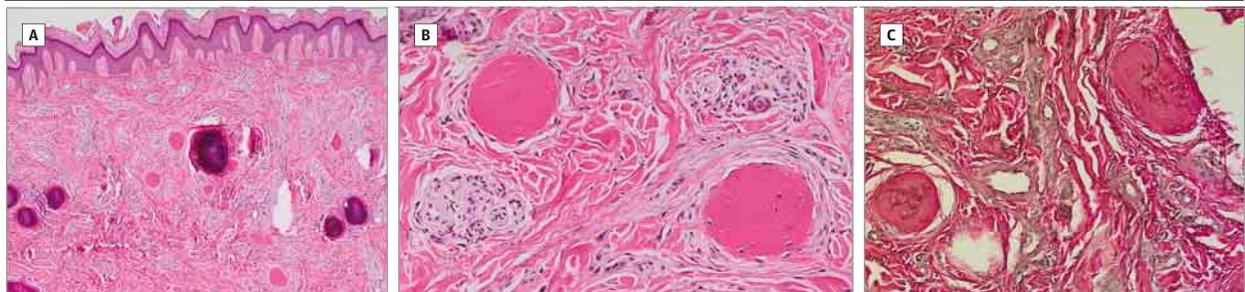
Gadolinium-associated plaques are characterized clinically by variably sized, erythematous annular plaques. In case 1, itching and burning were present, while the plaques in case 2 were asymptomatic. The plaques resemble dermal infiltrative processes such as granuloma annulare or cutaneous sarcoidosis. Eosinophilic, collagenous, round, or ovoid sclerotic bodies are the pathognomonic histopathologic feature of GAP. These structures contain scattered cells and focal calcifications. These collagenous plaques, which stain blue on Masson trichrome, are not to be confused with the osseous metapla-

Figure 1. Gadolinium-Associated Plaques, Case 1



Three pruritic, burning, firm erythematous plaques measuring 0.5 to 1 cm are present over the dorsal aspect of the right hand.

Figure 2. Gadolinium-Associated Plaque Staining, Case 1



A, Round or ovoid calcified sclerotic bodies with smooth outlines and peripheral paucicellular hyalinized collagenous zone, surrounded by spindled pericytes, seen in the superficial reticular and midreticular dermis. Scattered in between are smaller, noncalcified sclerotic bodies (hematoxylin-eosin, original magnification ×100). B, Smaller early sclerotic bodies without calcifications.

Solitary cells, resembling osteocytes in the lacunae are seen within these eosinophilic, paucicellular globules (hematoxylin-eosin, original magnification ×400). C, Elastic fibers staining black are intact and entrapped within the sclerotic bodies (hematoxylin-eosin, original magnification ×400).

Table. Summary of Findings in Patients With Gadolinium-Associated Plaques

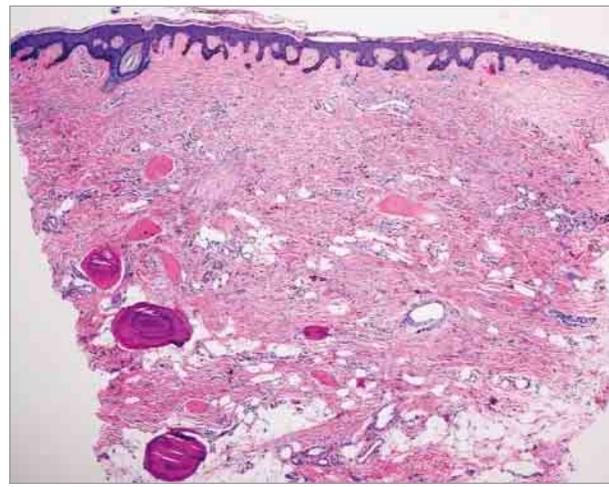
Characteristic	Case	
	1	2
Size of lesion(s)	Multiple, 0.5-2.0 cm in diameter	2.5 × 2.0 cm
Location	Bilateral dorsal hands	Right lower leg
Physical appearance	Erythematous plaques, some annular	Irregular, 2-colored, mottled pigmentation
Duration	18 mo	2 y
History of underlying renal insufficiency	No	Yes
History of gadolinium exposure	Yes, 5 × 20 mL OmniScan; 100 mL total	Yes (multiple procedures with gadolinium, unknown type and amount)
History of nephrogenic systemic fibrosis	No	No
Clinical features		
Patterned plaques	No	No
Joint contractures	No	No
“Cobblestoning”	No	No
Marked induration, “peau d’orange”	No	No
Puckering/linear banding	No	No
Histopathologic features		
Osseous metaplasia	Yes	Yes
Solitary cells with plump nuclei resembling osteocytes in bone	Yes	Yes (partial)
Calcification	Yes (partial and complete in few sclerotic bodies)	Yes
Entrapped elastic fibers	Yes	Yes
Special stains	1. CD34: positive for blood vessels, scattered stromal cells 2. CD68: positive for spindled fibrocytes surrounding the sclerotic bodies 3. Factor XIIIa: positive 4. Vimentin: positive for solitary cells within sclerotic bodies, scattered stromal cells 5. Masson trichrome: sclerotic bodies stain blue similar to collagen 6. Elastic: elastic fibers staining black are intact and entrapped within the sclerotic bodies 7. S-100 protein: negative 8. CD99: negative	1. Melan-A: negative 2. Mucin: positive for slight mucinosis 3. Iron: abundant dermal hemosiderin deposits

sia sometimes seen in NSF, which may represent a further evolution of sclerotic bodies not seen in these cases.^{3,4}

Sclerotic bodies and associated GAPs are specifically associated with gadolinium exposure. This is supported by the following data:

1. Sclerotic bodies are pathognomonic of gadolinium exposure.¹⁻⁵ In fact, each patient with sclerotic bodies, including one of our cases in which this could be ascertained, received the same type of gadolinium (gadodiamide contrast dye; OmniScan; GE Healthcare)^{2,4,5} Interestingly, Omniscan

Figure 3. Gadolinium-Associated Plaque Staining, Case 2



Both calcified and noncalcified sclerotic bodies throughout the dermis with smooth outlines with a peripheral, paucicellular, hyalinized collagenous zone are surrounded by spindled pericytes.

is a linear gadolinium chelator. Linear chelators hold gadolinium less well than cyclical chelators, which could theoretically result in increased tissue deposition.

2. Nephrogenic systemic fibrosis has been reported to occur with all 5 types of US Food and Drug Administration-approved gadolinium magnetic resonance imaging contrast dye in the United States.⁶ Ranges of exposure varied from 15 to 90 mL. Patients with NSF have associated renal failure, which would produce relatively high serum levels of gadolinium, even when relatively small doses are given.⁷
3. Evidence in the literature suggests that the pathophysiologic features of sclerotic bodies in NSF are directly related to destabilized gadolinium chelates, which stimulate fibroblast proliferation and collagen synthesis to create a pro-inflammatory environment.^{2,7} In fact, tissue from patients with NSF examined with field emission scanning electron microscope in an electron backscatter mode identified metal confirmed as gadolinium by energy-dispersive spectroscopy.⁷ Renal failure has been proposed to delay the excretion of gadolinium and thus prolong the half-life within the body.⁷ There is no reason to think this pathognomonic sign is caused by anything else in patients with GAP, considering the 100-mL gadodiamide exposure in our patient without renal failure and the presence of renal failure in the second patient.
4. The propensity of sclerotic bodies to calcify is a distinctive feature, although calcification has been reported in just 2% to 5% of patients with NSF.⁸ It has been postulated that secondary hyperparathyroidism associated with chronic renal failure may explain the presence of dystrophic calcium deposition in sclerotic bodies and other tissues. In fact, our second patient had a history of parathyroidectomy. In our first patient, however, focal calcification of sclerotic bodies was present in the absence of renal failure or any evidence of a parathyroid abnormality.^{4,9}

5. These patients experienced the onset of GAP roughly 3½ years after exposure to gadolinium, which is comparable with the 5-year delay in onset seen in the 1 other reported case of sclerotic bodies occurring in the absence of NSF.² While previous authors have suggested that sclerotic bodies may be a delayed finding in NSF, we believe the presence of sclerotic bodies depends on the type of gadolinium and the timing of onset depends on the date of gadolinium exposure, not the date the patients develop NSF.

Clearly our patients do not meet the criteria for NSF. Patient 1 had pruritic, painful, burning erythematous plaques and patient 2 had a solitary asymptomatic plaque. Both demonstrated sclerotic bodies identical to those seen in NSF, but the clinical prerequisite for a diagnosis of this condition (renal disease) was not present in patient 1.¹⁰ Of course, it is possible that the patient could have had transient renal dysfunction at the time of gadodiamide administration. Neither patient presented with the broad areas of induration, joint contractures, discrete plaques on the sclera, and “cobblestoning” that are typical of NSF.¹⁰ Finally, the histopathologic features of NSF correlating with cutaneous induration were not present in these cases. Whereas dendritic fibrocytes throughout the dermis and extending into interlobular fat septate typically stain strongly positive for CD34 and procollagen I in NSF, the CD34 stain in

patient 1 highlighted only a few blood vessels and scattered stromal cells.^{1,11} In some patients with NSF, CD68 and factor XIIIa stains have been strongly positive throughout the dermis.¹ In case 1, only the fibrocytes surrounding the sclerotic bodies stained positively with CD68 and factor XIIIa.

Although calcifying sclerotic bodies could be misdiagnosed as osteomas or calcinosis cutis, this is not a viable consideration because dystrophic calcification produces irregular clumps of calcium of various sizes often present in the fibrous tract of follicular structures that have been destroyed by trauma or infection. These are unlike the distinctive, rather uniform oval and round sclerotic bodies in GAP and NSF. Finally, these calcified structures are clinically unapparent.

Conclusions

In summary, both multiple and solitary plaques in association with the distinctive histopathologic findings of sclerotic bodies with various stages of calcification should lead to a consideration of GAP and prompt questions about gadolinium exposure. This confluence of findings can occur in the absence of renal disease (case 1) and with renal disease (case 2), but in both cases, without evidence of NSF.

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