Ocular Pathologic Features and Gadolinium Deposition in Nephrogenic Systemic Fibrosis

Nephrogenic systemic fibrosis (NSF), first described in 2000 in a 15-patient case series, is an extremely debilitating, multisystemic fibrosing disorder. Since that initial report, more than 300 cases have been recognized, and their histopathologic features have been categorized. Two known associations with NSF are renal dysfunction and exposure to gadolinium (Gd)—containing magnetic resonance contrast agents (GCCAs), as first suggested by Grobner in 2006. Multiple reports have also demonstrated the deposition of insoluble Gd phosphates in tissues of patients with NSF, further confirming the importance of toxic Gd release from the chelated compounds occurring in some patients with renal failure.

Ophthalmic interest in NSF stems from many reports of scleral plaques seen clinically in young patients with NSF and the appearance of “chronic scleral injection” in all cases reported by Levine et al.

Our study evaluated the previously unreported ophthalmic pathologic features of 2 autopsy cases of NSF, including scanning electron microscopy with energy-dispersive x-ray spectroscopy (SEM-EDS) analysis for Gd and also for the composition of the scleral plaques.

Report of Cases. Case 1. A 24-year-old white man with renal dysplasia who received hemodialysis for 10 years had received GCCAs for magnetic resonance imaging studies; he had biopsy-confirmed NSF with skin and joint involvement. Significant pathologic features on autopsy results included terminal aspiration pneumonia; parathyroid hyperplasia; end-stage renal parenchyma with calcification, fibrosis, and cysts; and NSF involving dura mater and heart. Extensive pannus with contraction of the shoulders, elbows, wrists, hips, knees, and ankles.

Significant ocular histopathologic findings included 2 large scleral plaques anterior to the medial and lateral rectus muscles, a posterior scleral deposit near the macula, and a large episcleral bony plaque. Significant ocular histopathologic findings included 2 large scleral plaques anterior to the medial and lateral rectus muscles, a posterior scleral deposit near the macula, and a large episcleral bony plaque. (Figure 1A and B). Limbal-corneal and conjunctival calcification was noted (Figure 1C), as well as focal rectus muscle degenerate fibers. The scleral plaques had many osteoclast-like giant cells and histiocytes positive for CD68 but not CD34 among the fragmented scleral lamellae (Figure 2). Gadolinium was detected in and around blood vessels of the choriocapillaris but not in the scleral plaques, which SEM-EDS showed to be composed entirely of calcium phosphate (Figure 3).

Case 2. A 63-year-old man had end-stage renal disease secondary to IgA nephropathy. He had been receiving hemodialysis since 2003 and underwent Gd-enhanced magnetic resonance imaging of the abdomen in June 2005. In March 2009, NSF was diagnosed from skin biopsy results, and he died that September. Conjunctival plaques in the eye were seen clinically (Figure 4), and SEM-EDS demonstrated calcium phosphate content. As in case 1, these plaques showed no detectable Gd. However, the plaques in case 2 did not show the cellularity evident in case 1. No Gd was detectable in the choriocapillaris.

Comment. The deposition of calcium salts is seen in a variety of patients, including those with chronic renal failure, hyperparathyroidism, sarcoidosis, and calciphylaxis, as well as in elderly patients. Our autopsy findings demonstrate that the deposition of calcium phosphate also causes the scleral plaques seen in NSF. This finding is not entirely surprising, since calcification has been described in some cases as a feature of NSF and because all deposits of Gd in tissues have been with calcium and phosphorus.

It is difficult to separate the calcification noted in NSF from that often seen in patients with renal failure because high calcium and
phosphate levels can be common to both diseases. In the report by Levine et al,4 the only metabolic abnormality uniformly observed in their patients with NSF was high levels of calcium and phosphate. The inability of SEM-EDS to demonstrate detectable Gd in the scleral plaques in our cases does not exclude the presence of Gd in those plaques at concentrations too low to detect with this method but further supports the idea that the scleral plaques observed in NSF may be related more to altered calcium and phosphorous metabolism disturbances in chronic renal failure and hyperparathyroidism than to specific Gd toxicity. Recent research5 demonstrates that gadolinium chloride promotes the precipitation of calcium phosphate in vitro. This finding suggests that the release of Gd3+ from the chelated Gd may accelerate the calcification seen in chronic renal failure.

The NSF scleral plaques differ from the typical Cogan plaques of aging (usually seen in patients older than 70 years) that are calcium phosphate deposits in the sclera surrounded by acellular collagen without an inflammatory response.6 Our first case revealed plaques associated with an inflammatory response (not seen in Cogan plaques), including osteoclast-like giant cells, which are similarly observed in dermal biopsy specimens from patients with NSF. In addition, the ocular manifestations in case 1 included limbal-corneal and conjunctival calcification.

Case 2 did not show the cellularity associated with the plaque seen in case 1, nor was any Gd detectable in the choriocapillaris. Klaassen-Broekema and van Bijsterveld7 suggest that a minor tissue injury of the limbal-corneal and conjunctival epithelium—referred to as a “local challenger”—is more likely than systemic factors to determine the degree of ocular calcification in patients undergoing dialysis. The pattern of cellularity seen in case 1 may be directly linked to the injury caused by

Figure 2. Histopathologic features of scleral plaques. A, Staining of a scleral plaque (hematoxylin-eosin, original magnification ×50). B, Staining of a scleral plaque showing cellularity and osteoclast-like giant cells (arrows) (hematoxylin-eosin, original magnification ×400). C, Positive staining of a giant cell (CD68, original magnification ×400). D, Negative staining of a giant cell. The internal control (endothelium) is positive (CD34, original magnification ×400).

Figure 3. Light microscopic and scanning electron microscopy with energy-dispersive x-ray spectroscopy (SEM-EDS) features from case 1. A, Posterior scleral plaque (bracket). Retina and choroid are seen above the bracket (hematoxylin-eosin, original magnification ×400). B, Vascular choroid. Arrows indicate choriocapillaris (hematoxylin-eosin, original magnification ×400). C, SEM-EDS. Top: backscattered electron images (negative mode; features with a higher atomic number are darker). Choroid shown in the top photos are seen in low (left) and high (right) magnification. A detail of the area in the box in the top left image is shown at higher magnification in the top right image. The plus sign indicates the deposit with a high atomic number from which the EDS spectrum in the bottom panel was collected. The bottom panel shows the gadolinium detected in the deposit. Larger peaks of phosphorus, calcium, and sodium are present but are off the scale. D, These SEM-EDS images of anterior scleral plaque confirm the presence of calcium and phosphorus with no detectable gadolinium. The layout used in C was also used for D.

Figure 4. Clinical photograph of case 2 shows plaque-like calcification in the conjunctiva and episclera.
Gd\textsuperscript{3+} deposition in blood vessels, evident in case 1, is commonly seen in NSF tissues\textsuperscript{3} and is associated with vascular calcification common in NSF and in chronic renal failure.

In conclusion, we have shown seemingly unique histopathologic features associated with the scleral plaques in NSF and have demonstrated insoluble Gd deposits in the eye in patients with NSF. It remains unknown whether Gd accelerates the calcification seen in chronic renal failure and whether the presence of Gd in the eye leads to the inflammatory pattern that was noted in case 1. The long-term visual significance of this process remains to be determined.

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