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BONE MARROW IS CENTRAL TO THE SEVERITY OF GADOLINIUM-ASSOCIATED SYSTEMIC FIBROSIS

V. Drel[1], Ch. Tan[1], D. Lee[1], J. Barnes[1], Y. Gorin[1], B. Wagner[1, 2]

[1]University of Texas Health Science Center at San Antonio, TX, USA
[2]Medical Service, South Texas Veterans Health Care System
San Antonio, TX, USA
e-mail: drel@uthscsa.edu

Background: Gadolinium-based magnetic resonance imaging contrast induces systemic fibrosis in humans and rodents. Cumulative doses correlate with severity. Bone marrow-derived fibrocytes accumulate in the dermis. Whether target organs liberate chemokines to recruit these cells or if they are stimulated to home to the affected tissue is unknown.

Methods: Transgenic (tagged) donor rats were treated with gadolinium-based contrast. Bone marrow was obtained from the treated animals and age-matched controls. Rats with subtotal nephrectomies were lethally-irradiated followed by salvage transplant with either the contrast-naïve or contrast-exposed bone marrow. Bone marrow recipients were randomized into control or contrast treatment.

Results: Dermal fibrosis was induced by contrast. This was exacerbated in recipients of contrast-exposed marrow. Fibronectin, the C-C chemokine receptors 2 and 7, and oxidative stress were all increased in skin from the contrast-treated animals–all parameters more severe in recipients of contrast-treated animals. The respective ligands, monocyte chemoattractant protein and C-C motif ligand 19, were both elevated in the skin from contrast-treated animals. When a C-C chemokine receptor inhibitor was co-administered with contrast, the severity of skin disease (including dermal cellularity) was reduced. Neutralizing antibody to monocyte chemoattractant protein 1 suppressed myeloid infiltration (using an *in situ* skin punch biopsy/labeled bone marrow co-culture assay).

Conclusions: These data demonstrate that the dermal liberation of specific chemokines recruits circulating myeloid cells. The systemic fibrosis is augmented by bone marrow exposure to contrast. This explains why multiple exposures correlate with severity. Furthermore, bone marrow has a memory of gadolinium exposure; these findings have serious clinical ramifications.