Delayed effects of acute radiation exposure (DEARE) in a murine model of the hematopoietic acute radiation syndrome: Multiple-organ injury consequent to total body irradiation
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Introduction. Victims of radiation exposure from terrorist activity, radiation accidents or radiologic warfare will face a variety of acute and chronic organ injuries requiring multi-faceted approaches to treatment. The hematopoietic system is the most sensitive tissue to radiation damage, resulting in the hematopoietic acute radiation syndrome (H-ARS) after exposures of 2-10 Gy in mice. If untreated, H-ARS results in death within weeks from opportunistic infection and/or hemorrhage due to loss of neutrophils and platelets, respectively. However, survivors of ARS are plagued months to years later in life by delayed effects of acute radiation exposure (DEARE), a myriad of chronic illnesses affecting multiple organ systems believed to be due to persistent systemic oxidative stress, inflammation, fibrosis and loss of stem cell self-renewal. Fibrosis and collagen deposition disrupt both normal tissue structure and function and are common to organs with late radiation injury including the kidney and heart after radiation doses >15Gy, but have not been shown to exist after doses as low as those used in the H-ARS model (8Gy). The goal of this study was to determine the extent, if any, of heart and kidney DEARE in survivors of H-ARS.

Methods. Mice (male and female C57BL/6) received total body irradiation (TBI; LD50/30 to LD70/30) and kidney and heart were harvested at 9 and 21 months from the H-ARS survivor mice. Tissues were fixed in neutral buffered formalin, paraffin embedded and sectioned, then stained with hematoxylin/eosin (H&E), trichrome, or picrosirius red. Serum was collected at 4.3, 9, and 21 months post-TBI and analyzed for blood urea nitrogen (BUN) as an indicator of kidney function. Total RNA was purified from heart and relative changes in NADPH oxidase 2 (Nox2) mRNA expression were assessed by quantitative real-time PCR.

Results/Significance. Compared to age-matched non-irradiated controls (NI), renal pathology at 9 months post-TBI was manifest primarily as enlargement of Bowman's capsule and glomerosclerosis along with limited interstitial fibrosis. By 21 months there was progression of these pathologies as well as extensive interstitial fibrosis, tubular atrophy, cysts, and atubular glomeruli, all of which were more pronounced in TBI mice compared to NI. Consistent with the renal pathology, BUN in TBI mice was significantly increased at 9 and 21 months post-TBI vs. 4.3 months, but normal in NI mice at all time points. In the heart, pericardial, perivascular and interstitial fibrosis were observed at 9 months with increased severity at 21 months post-TBI compared to NI. The perivascular fibrosis was associated with increased medial layer collagen and apparent loss of vascular smooth muscle cells. Nox2 mRNA in heart was increased at 9 and 21 months post-TBI, indicating an increase in oxidant stress. To our knowledge, such striking heart and kidney damage has not been documented after radiation doses as low as those in our H-ARS model (~8Gy) and indicate that DEARE is a concern for individuals exposed to radiation doses previously thought to not elicit late effects.