

Chapter 10: Radiation Nephropathy

Amaka Edeani, MBBS,* and Eric P. Cohen, MD[†]

*Kidney Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland; and [†]Nephrology Division, Department of Medicine, University of Maryland School of Medicine, and Baltimore Veterans Affairs Medical Center, Baltimore, Maryland

INTRODUCTION

The occurrence of renal dysfunction as a consequence of ionizing radiation has been known for more than 100 years (1,2). Initial reports termed this condition “radiation nephritis,” but that is a misnomer, because it is not an inflammatory condition. Renal radiation injury may be avoided by the exclusion of an adequate volume of kidney exposure during radiation therapy, but the kidneys’ central location can make this difficult to impossible when tumors of the abdomen or retroperitoneum are treated, or during total body irradiation (TBI) (3).

BACKGROUND/CLINICAL SIGNIFICANCE

Radiation nephropathy is renal injury and loss of function caused by ionizing radiation; this will occur after sufficient irradiation of both kidneys (4). Ionizing radiation of sufficient energy disrupts chemical bonds and knocks electrons out of atoms. It generates oxygen radicals that cause prompt DNA injury within milliseconds of irradiation. This is the desired action of therapeutic irradiation to cause death of cancer cells. It is also the cause of injury to irradiated normal tissues such as the kidney. The doses of diagnostic X-ray are orders of magnitude less than those of therapeutic irradiation; whereas there may be a very small effect of carcinogenesis from a diagnostic X-ray, there is no risk of normal tissue injury.

The kidneys are the dose-limiting organs for radiation therapy for gastrointestinal cancers, gynecologic cancers, lymphomas, and sarcomas of the upper abdomen and during TBI (5). Damage to normal tissues can be reduced by shielding of non-target tissues, shaping radiation beams that focus the high-dose radiation on the cancer and attempting to avoid surrounding normal tissues, and fractionated radiation dosing. Fractionation enables DNA repair in normal cells between dosing.

Classical radiation nephropathy occurred after external beam radiation for treatment of solid cancers such as seminomas (6); the incidence has declined with the advent of more effective chemotherapy. In recent years, radiation nephropathy has occurred due to TBI used as part of chemo-irradiation conditioning just before hematopoietic stem cell transplantation (HSCT) and also from targeted radionuclide therapy used for instance in the treatment of neuroendocrine malignancies. TBI may be myeloablative or nonmyeloablative, with myeloablative regimens using radiation doses of 10–12 Gy to destroy or suppress the recipient’s bone marrow. These doses are given in a single fraction or in nine fractions over 3 days (4). In addition, TBI for bone marrow transplantation (BMT) is preceded or accompanied by cytotoxic chemotherapy, which potentiates the effects of ionizing radiation (7).

CKD after HSCT occurs in 10%–30% of HSCT survivors in pediatric and adult populations (8). CKD following HSCT can have many causes including medication-induced nephrotoxicity and graft-versus-host disease (9); the role of radiation exposure at the time of the HSCT is also well established (4). CKD has significant patient impact by predisposing to hypertension, by altering medication pharmacokinetics, and by predisposing to ESRD.

Threshold dose

Luxton identified 23 Gy as the threshold dose for radiation nephropathy (6), from radiation of both kidneys when given in 20 fractions over 4 weeks. If the total irradiated renal volume is <30% of both kidneys, CKD will not occur from irradiation alone

Correspondence: Amaka Edeani, Kidney Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 10 Center Dr., Rm. 5-5744, Bethesda, Maryland 20892.

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(10), although there may be injury to the small, irradiated volume of kidneys that leads to hypertension. In the case of radiation nephropathy after BMT, a 10-Gy TBI single dose of X-rays can cause radiation nephropathy within a year after irradiation, as may 14 Gy fractionated over 3 days (11).

Lower radiation doses may cause kidney injury after many years of follow-up. Thus, in survivors of the Hiroshima-Nagasaki atomic bombs, estimated single fraction doses of <200 cGy were associated with CKD after many decades (12).

Radiosensitivity

Radiation nephropathy occurs as a late phenomenon, usually presenting months to years after the radiation exposure. This latency is associated with slower cell turnover rates in renal tissue compared to early-responding (rapidly proliferating) tissue such as gastrointestinal epithelium or bone marrow (4). Normal renal tissue has low mitotic rates, which correlate with delayed expression of renal injury after radiation (4). Less than half of subjects exposed to threshold or higher radiation doses will develop radiation nephropathy. The determinants of individual radiosensitivity are not well known.

EXPERIMENTAL MODELS AND PATHOGENESIS

Radiation nephropathy has been reproduced in many animal models, including in mice, rats, dogs, and nonhuman primates. A recent rat model demonstrates injury at similar doses to those relevant in humans, a similar latency period between time of irradiation and manifestations of injury, expression of injury as proteinuria, hypertension, and azotemia, and a similar histopathology (4,13). In this model, suppression of the renin-angiotensin system is beneficial, and angiotensin II infusion exacerbates injury (14). However, in the irradiated rat, there is no evidence of activation of the renin-angiotensin system, which suggests other countervailing mechanisms relevant in pathogenesis. Other notable features in this model include a lack for evidence of chronic oxidative stress (15). Multiple aspects of pathogenesis have been tested for causality in the experimental model of TBI-HSCT in which the major lethal toxicity is renal failure (8). These include oxidative stress, cell proliferation, transforming growth factor- β , glomerular permeability, fibrosis, renin-angiotensin system, and vascular injury. Of these, the roles of the renin-angiotensin system and vascular injury have not been disproven to date; the others are either absent or do not play a causal role (8). Krochak and Baker (16) noted a sequence of events in which the initial reaction to irradiation was an increase in endothelial permeability with an increase of ultrafiltrate extruded from the capillaries in the glomerular tuft, with an escape of increased protein and other high-molecular-weight blood components; these events were transient with normal fluid dynamics restored within a few days, but these permeability changes did appear to contribute to eventual early and late clinical syndromes.

CLINICAL PRESENTATION

The clinical features of radiation nephropathy will vary according to dose and volume of irradiation (17). Presentation can be acute and irreversible or subtle, with a gradual progressive dysfunction over years (5). There is a latent period that is clinically “silent” until a stage is reached when there are clinical manifestations of disease (11). These were well described by Luxton in his observation of 137 men with seminoma who were irradiated with 2250–3250 cGy over 5 weeks (3). The incidence of radiation nephropathy in his cohort was about 20%, with four clinical syndromes as identified in Table 1. One may expect similar presentations after sufficient renal irradiation from any source, external or internal.

Acute radiation nephritis

The onset of acute radiation nephritis is only acute relative to the other variants. Patients present 6–12 months following radiation exposure with fatigue, varying degrees of edema, shortness of breath with exertion and headaches with azotemia, malignant hypertension, and severe anemia disproportionate to degree of renal failure (16,18). Malignant hypertension may present with headaches, encephalopathy, and retinopathy. There may be associated congestive heart failure with anasarca, pleuropericardial effusions, and pulmonary edema. Anemia is normochromic and normocytic with a nonaplastic marrow (17). This has been described as “bone marrow transplant nephropathy” (4,19) when it occurs after HSCT. Some of these cases may present as hemolytic uremic syndrome or thrombotic thrombocytopenic purpura, i.e., as full-blown thrombotic microangiopathies. Proteinuria is generally not severe, with an average of 2 g/g urine creatinine. Prognosis has been variably related to occurrence of malignant hypertension (6) or severity of fluid retention, with oliguria being a terminal event. Patients surviving this acute phase usually are left with progression to CKD.

Chronic radiation nephritis

There are two variants of chronic nephritis (6): 1) primary chronic radiation nephritis—initial presentation up to 2 years or longer following irradiation with proteinuria and other evidence of chronic nephritis; and 2) secondary chronic radiation nephritis—seen in patients who survived acute radiation nephritis and continued with signs of chronic renal damage.

Signs and symptoms are indistinguishable from renal failure from any other cause, with hypertension, albuminuria, anemia, azotemia, and small atrophic kidneys on imaging.

Table 1. Clinical syndromes following renal irradiation (3)

Type	Latent period
Acute radiation nephritis (nephropathy)	6–12 months
Chronic radiation nephritis	≥18 months
Malignant hypertension	12–18 months
Benign hypertension	≥18 months

Malignant hypertension

In Luxton's series of patients, malignant hypertension developed either during the acute phase or later, 12–18 months following irradiation (6,20), with some presenting many years after exposure. Clinical features included hypertensive encephalopathy, retinopathy, and seizures. Renal size is variable.

Benign hypertension

Luxton showed that hypertension may occur as a manifestation of renal radiation injury in the absence of renal failure, with variable degrees of proteinuria. However, other studies have shown close correlation between degree of azotemia and prevalence of hypertension (1). This is also valid for the hypertensive CKD that occurs after HSCT (4,21).

Hypertension following unilateral renal irradiation

Hypertension alone may be the presenting feature if only a single kidney is irradiated. This may occur because the irradiated kidney shrinks and creates renin-dependent hypertension in the manner of a Page kidney (22). Such cases have been successfully treated by unilateral nephrectomy (23–25).

Histopathology

There are early and late changes following renal irradiation (3,26). Early changes include endothelial microvascular injury with cell swelling, subendothelial expansion, and capillary loop occlusion (Figure 1). There is often mesangiolysis and variable tubular injury. Ultrastructural examination shows amorphous material within the subendothelial space, which appears to extend the lamina rara interna (Figure 2). Late changes include sclerosis of interlobular and arcuate arteries, with residual parenchymal damage with increased mesangial matrix, glomerular scarring, tubular atrophy, and renal mass reduction. Fibrosis may be extensive.

TREATMENT

Because it is uncommon, there are no controlled trials to guide the management of radiation nephropathy. Thus, treatment of radiation nephropathy is guided by the same principles of treatment of any hypertensive kidney disease, including blood pressure control and correction of metabolic acidosis. Standard management of anemia, secondary hyperparathyroidism, and electrolyte disturbances may be useful. Experimental data show that angiotensin converting enzyme inhibitors or angiotensin receptor blockers are preferentially beneficial in radiation nephropathy (14). Supportive measures are beneficial including treatment of peripheral and pulmonary edema and treatment of anemia with blood transfusions and/or erythropoietin stimulating agents.

Prevention may be better than treatment. There are favorable trends for the benefit of captopril to mitigate the late occurrence of CKD after TBI-based HSCT (28). This clinical

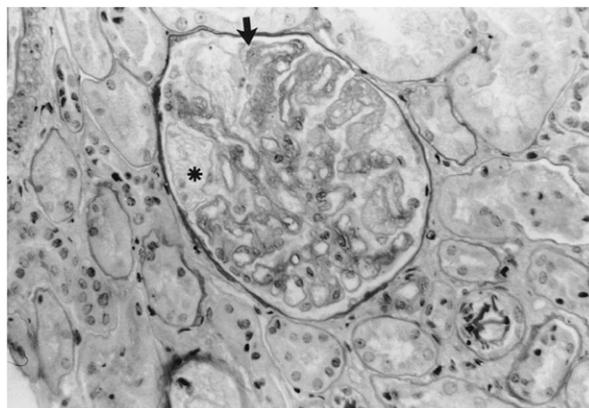


Figure 1. Photomicrograph by light microscopy of a renal biopsy specimen in case of BMT nephropathy (4). There is mesangiolysis (*) and extreme widening of the space between endothelium and glomerular basement membrane (arrow). The tubular epithelium is intact, but the tubules are separated by an expanded interstitium. periodic acid-Schiff stain; magnification, 250 \times . Reproduced with permission from reference 4.

trial was based on the hypothesis of mitigation: when a subject has received sufficient irradiation to kidneys, use of an angiotensin-converting enzyme inhibitor after exposure but before expression of injury may be beneficial in mitigating the later injury.

Despite treatment, patients with radiation nephropathy may evolve to ESRD and require chronic dialysis therapy or undergo kidney transplant. When this occurs after HSCT, survival on dialysis is poor (29). Such patients may be eligible for kidney transplantation and could avoid the need for immunosuppression if the transplanted kidney was from the same donor as gave them their hematopoietic stem cells (30,31).

RISK OF CANCER FROM IMAGING

High-dose ionizing radiation can cause cancer. The threshold dose at which there is increased excess risk after a single exposure is 34 mSv (32). For reference, an absorbed dose of 1 mGy is equivalent to an effective dose of 1 mSv, the body radiation dose of a chest X-ray is <0.1 mSv, and that of a body computed tomography (CT) scan is approximately 10 mSv. Recent reports express concern about the possible cancer risks of radiologic imaging in patients with kidney disease. Kinsella *et al.* (33) reported estimated X-ray doses received by dialysis patients, and Nguyen (34) reported X-ray exposure in subjects undergoing workup for kidney transplantation. However, rather than create real worry, these reports actually underline the lack of risk, and neither one reports cancers caused by radiation. The median cumulative doses were 22 and 29 mSv in each report, respectively. The single fraction equivalent doses are about half of those values, well below the single fraction dose at which there is significant excess cancer risk. Furthermore, because radiation-induced cancer takes

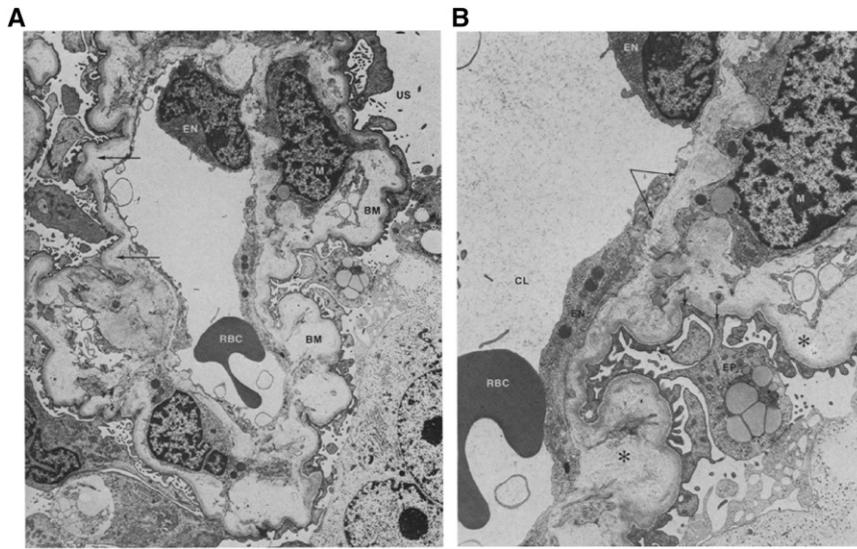


Figure 2. Electron micrographs of glomerular capillary loop in a case of radiation nephropathy (27). (A) Wrinkled capillary basement membrane (BM) with variable widening of lamina rara interna (arrows). Capillary lumen (CL) contains circulating red blood cells (RBCs) and has intact endothelial cell lining. Endothelial cells (ENs) are occasionally swollen and contain prominent organelles. Original magnification, 6,300 \times ; reduced by 31%. (B) Higher magnification of A reveals variable widening of lamina rara interna and deposits of fluffy material (*) resembling that within the capillary lumen. Newly formed basement membrane material is also evident adjacent to the lining endothelium (long arrows). Original magnification, 13,500 \times ; reduced by 31%. M, mesangial cells; EP, epithelial cells; US, urinary space. Reproduced with permission from reference 27.

5–10 years to develop, for the average dialysis patient, i.e., those starting dialysis at age 65 or more, radiation-induced excess risk of cancer cannot be a major risk because the expected remaining lifetime is 4 years or less for a 65 year old starting dialysis (35).

Although cancer after kidney transplant is a genuine concern, one would expect a surfeit of leukemias if pretransplant radiation exposure was the culprit, and leukemia after kidney transplant is rare. An unjustified fear of cancer should not get in the way of essential radiologic imaging. However, prevalent kidney transplant patients received cumulative median doses of 17 mSv in another report, and 12% of that cohort had cumulative exposures of 100 mSv (36). Thus, there may be reason for concern in individual patients, perhaps especially in younger people with longer expected lifetimes and therefore more possibility of late radiation-induced cancers. Finally, the concern about exposure to ionizing radiation has affected practice in surveillance for nephrolithiasis; ultrasound, rather than CT may be preferable for serial imaging.

FUTURE CONCERNS

The apparent excess of CKD in some Hiroshima-Nagasaki survivors emphasizes that wartime or terrorist radionuclear events could cause significant renal injury in those exposed to acutely survivable irradiation. Space exploration is another potential risk for both cardiovascular and renal disease.

TAKE HOME POINTS

- Radiation nephropathy can result from external or internal radiation exposures.
- Radiation nephropathy will not occur after diagnostic X-ray exposures.
- Accidental or belligerent radiation exposures may result in renal radiation injury.
- Radiation nephropathy is associated with mesangiolytic and glomerular capillary thrombosis on renal biopsy; it can lead to a full blown thrombotic microangiopathy.
- Mitigation of radiation nephropathy may be possible with angiotensin converting enzyme inhibitors.

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DISCLOSURES

None.

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REVIEW QUESTIONS

1. Which of the following statements is false?
 - a. Radiation nephropathy may result from radionuclide therapy
 - b. Acute radiation nephritis may be associated with thrombotic thrombocytopenic purpura
 - c. A single dose of 10 Gy of X-rays can lead to radiation nephropathy
 - d. CKD has been associated solely with myeloablative total body irradiation regimens
 - e. Cytotoxic chemotherapy can potentiate the effects of ionizing radiation.

Answer: d is correct. CKD can complicate both myeloablative and nonmyeloablative regimens. The other statements are correct.

2. The pathologic features of radiation nephropathy include the following except:
 - a. Subendothelial expansion with amorphous material
 - b. Mesangiolysis
 - c. Neutrophilic infiltration of the mesangium
 - d. Arteriolar sclerosis
 - e. Varying degrees of tubular atrophy and interstitial fibrosis

- f. Endothelial cell swelling

Answer: c is correct. Pathologic features of radiation nephropathy include endothelial cell swelling with subendothelial expansion with amorphous material and mesangiolysis, and late changes include arteriolar sclerosis and varying degrees of tubular atrophy and interstitial fibrosis; there is no evidence of glomerular leucocytic infiltration.

3. Which of the following statements is false regarding hypertension associated with radiation nephropathy:
 - a. Hypertension following unilateral radiation may be treated with nephrectomy of the affected kidney
 - b. Acute radiation nephritis is not associated with malignant hypertension
 - c. Hypertension may occur in the absence of renal failure
 - d. ACE inhibitors and/or angiotensin receptor blockers have been shown to be beneficial in management of hypertension

Answer: b is correct. Malignant hypertension in the setting of radiation nephropathy may occur as part of the acute radiation nephritis complex, and it may also occur as an initial presentation, 12–18 months after irradiation. The other statements are correct.