RADIATION NEPHRITIS

Clinical Manifestations and Pathophysiologic Mechanisms

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Radiation nephritis is an uncommon but potentially devastating complication of irradiation treatment. Confusion exists among physicians not involved in this field because of misleading terminology regarding the time of onset after completion of irradiation and the different syndromes that may result.

It is the purpose of this article to review these clinical aspects and correlate them with the presumed pathophysiologic basis for the damage seen.

Clinical Syndromes

Because radiation nephritis is uncommon, few large series are reported. The largest is that of Luxton and co-workers. They first reported in 1952 on a cohort of patients who received in excess of 2,500 R to both kidneys. This resulted from improved radiation techniques which gave better homogeneity throughout the volume treated at a time when renal sensitivity to ionizing irradiation was not fully appreciated. From this cohort of patients and subsequent clinical experience, we now accept renal tolerance (TD 5/5) to be 2,000cGy. It is also believed that if one third to one half of the renal parenchyma is outside of the high dose volume, unacceptable late renal consequences will not occur. This is only an approximation and has not been substantiated by clinical trials; therefore, it should be applied only after careful review of the clinical situation.

From the 54 patients with radiation nephritis reported by Luxton and Kunkler, four clinical syndromes were identified (Table I). Subsequent further clinical experience substantiates Luxton and Kunkler's initial observations.

It is important to emphasize that there is no true acute syndrome occurring during or immediately after radiation treatment. In this context, the term acute refers to such expressions of radiation injury as radiation nephritis that develop abruptly after a latent period of six months to a year. Unfortunately, little data exist on what may be seen during this latent period.

Avioli et al. followed 10 patients prospectively using glomerular filtration rate, renal plasma flow, and tubular excretory capacity as well as urinalysis, blood urea nitrogen (BUN), and urinary concentrating capacity after irradiation. At no time during therapy or in subsequent follow-up were abnormalities noted in urinalysis or BUN. This was substantiated in an EORTC study in which 74 patients had partial irradiation of the left kidney (30–80% of left kidney to a dose of 4,000cGy). Patients were followed prospectively at six weeks, six months, and yearly after treatment. Proteinuria developed in only 3 patients, and microscopic pyuria

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Onset</th>
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<tr>
<td>Acute radiation nephritis</td>
<td>6–12 mo.</td>
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<tr>
<td>Chronic radiation nephritis</td>
<td>12 mo.</td>
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<tr>
<td>Malignant hypertension</td>
<td>18 mo.</td>
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<tr>
<td>Benign hypertension</td>
<td>18 mo.</td>
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From the 54 patients with radiation nephritis

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The maximum dose that can be given to normal tissues in the irradiated volume without exceeding a 5 per cent incidence of serious complications in the first five years after irradiation.

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or hematuria in 7 patients; this was only detected about eight months after treatment. In all patients the signs subsequently resolved.

The so-called acute radiation nephritis syndrome can onset anywhere from six to twelve months post-treatment. Patients usually present quite dramatically with all of the manifestations of renal failure with no apparent prodrome. Patients may complain of lassitude, shortness of breath, headaches, and edema. Evidence of fluid retention may be manifested by dependent edema, effusions, hypertension, and heart failure. As an early finding, retinopathy is uncommon. Profound anemia associated with elevated creatinine and BUN were evident in Luxton’s series. Urinalysis documented frequent microscopic hematuria and pyuria and symptoms of renal failure with no apparent pro-drome. Patients may complain of lassitude, shortness of breath, headaches, and edema. Evidence of fluid retention may be manifested by dependent edema, effusions, hypertension, and heart failure. As an early finding, retinopathy is uncommon. Profound anemia associated with elevated creatinine and BUN were evident in Luxton’s series. Urinalysis documented frequent microscopic hematuria and pyuria and an inability to concentrate adequately. Gross hematuria was never seen. Proteinuria as well as granular and hyaline casts were evident in the urine from most patients.

Prognosis in the past was related to the severity of the hypertensive component. Whether this can be more adequately managed at the present time has not been proved, although one would expect with the advent of aggressive medical regimens associated with dialysis, if necessary, that this phase is potentially more manageable today. Those patients who survive the acute phase will be left with some degree of chronic renal failure requiring ongoing care.

Chronic irradiation nephritis on the other hand may have its onset as a direct extension of the acute phase or it may be more indolent in its presentation, presenting as late as fourteen years after treatment. The signs and symptoms are no different than renal failure from other causes. Assessment of renal size will usually disclose small atrophic kidneys. This chronic phase is compatible with many years of life depending on the severity of the renal failure.

In Luxton’s series of patients, malignant hypertension developed in 28 per cent either during the acute phase or remotely. This remote presentation may occur eighteen months to many years after therapy. Hypertensive encephalopathy, retinopathy, and seizures can be presenting symptoms. Renal failure was not usually a major component in this presentation but was often noted preterminally. Renal size can be variable, but it is imperative to rule out a unilateral small kidney resulting in a Goldblatt effect. This latter circumstance has been adequately treated with unilateral nephrectomy in some instances.

Finally, benign hypertension has been attributed to radiation treatment. Of the 6 patients in Luxton’s group, 2 patients went on to develop congestive heart failure and in another patient, malignant hypertension developed eleven years later. The relationship of irradiation to benign hypertension is unclear, but hypertension attributed to irradiation treatment requires close follow up for life, as does so-called benign hyper-tension in the unexposed.

Proteinuria has been observed without other alteration in renal function. This was often intermittent and of no clinical consequence. It is possible that this may represent latent nephritis indicating poor renal reserve, but has not been clearly documented.

Little practical experience exists in the use of concurrent chemotherapy and radiation treatment. Nevertheless, there is the suggestion that combination treatment with actinomycin D in the pediatric age group may result in treatment-related nephritis at doses between 1,500-2,000 cGy even when fractionated 100 cGy per day or less. Thus if both kidneys are to be treated in this fashion, one must be aware of the potential toxicity.

Pathophysiology

To understand the radiobiologic basis of radiation-induced nephritis, some features of renal physiology need to be recognized. The kidney is highly vascular. One fifth of the blood volume passes through the kidney each minute. As an organ, the kidney has a 30 per cent greater oxygen requirement than brain, heart or liver. An intact vasculature is necessary for kidney function. Successive branches of the renal artery give rise to the interlobular arteries from which arise the glomerular arterioles (afferent arterioles). In the glomeruli, these break up into a compact collection of capillaries which then anastomose to form the efferent arteriole which also is the vascular supply to the tubules. The renal arterioles are end arteriole in the sense that they are usually the only blood supply to the local tissue.

In common with the microvasculature of other sites, the capillaries consist of a single layer of endothelial cells on a basement membrane. A minor difference should be noted. The capillaries are close together, tangled, convoluted, and the capillary blood pressure is generally higher than for capillaries at other anatomic sites. The capillary endothelial cells, like the tubular epithelium, are conditional cell renewal...
Proliferation of the epithelial cells from other tissues is radiosensitive than epithelial cells from other tissues. However, the renal parenchyma may be shielded.

The depression of erythropoietin production by the kidneys after radiation doses (of 20 Gy) is believed to be a contributing factor to the anemia. Whether this is direct suppression of erythropoietin production by irradiation or just another manifestation of renal failure is not known.

Hypertension is a common late expression of radiation injury to the kidney. The radiobiologic basis for the hypertension is not well understood. With experimental animals a radiation dose to both kidneys as low as 300 rad will result in a slowly developing hypertension after a time interval corresponding to about one third of the animal's normal life expectancy. In rodents, hypertension can be induced following total body irradiation with the kidneys shielded. The increased blood pressure takes longer to develop but eventually approximates the same degree of hypertension as when the kidneys were included in the radiation field.

The studies of Wachholz and Casarett have led the authors to conclude that minimum