

## Radiation-Associated Neurotoxicity

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**R**adiation therapy is used to treat a host of different diseases, although the most frequent use revolves around the treatment of cancer. Although effective—sufficient doses are able to effect virtually 100% cellular death of neoplastic cells—the toxicity of such therapy precludes administration of such high amounts to patients. The nervous system is particularly sensitive to radiotherapy and is affected either directly or indirectly during the treatment of cancer. Both central and peripheral nervous system structures can be affected, leading to different syndromes, and may be complicated by involvement of blood vessels and endocrine organs. This review discusses the various effects of radiation on the nervous system, with emphasis on the different areas of nervous system involvement.

### CELLULAR DAMAGE TO THE NERVOUS SYSTEM

The most sensitive structures to radiation within the nervous system are thought to be primarily oligodendroglial and Schwann's cells, with the neurons being less affected because of their postmitotic state.<sup>1</sup> However, any central or nervous system cell can be affected by radiation, depending on several factors, including the dose per fraction, the volume of tissue irradiated, the total dose given, and the energy of the radiation.<sup>2</sup> Host factors are also important in the cellular response to radiation: age<sup>3</sup>, sex,<sup>4</sup> the presence of concurrent diseases,<sup>5</sup> and previous therapy (ie, chemotherapy)<sup>6</sup> are thought to be influential in the nervous system response to radiotherapy. Other factors that are putatively involved in the nervous system response to radiation include the vascular endothelium, which may result in ischemia and necrosis (as addressed later in this discussion), and the immune system, leading to a hypothesized sensitivity reaction.<sup>7</sup> Clearly, the etiology of radiation damage on a cellular basis is multifactorial and most likely represents a combination of factors involving both the radiation itself, which affects different structures within the nervous system, as well as host factors, which either predispose to toxicity or modify response within the nervous system.

### CLINICAL APPROACH TO DIAGNOSIS

The diagnosis of radiation-induced damage of the nervous system may at times be difficult and perhaps require pathologic confirmation. Although formulas exist to calculate the relative energy deposited to nervous system structures, these formulas are at best approximations and do not consider other aspects of the mechanism of cellular injury, including concomitant therapy or host factors.<sup>6</sup> Retrospective reviews have attempted to document the clinical factors that are associated with radiation injury;<sup>8</sup> the patients who appear to be more affected by radiation are male patients,<sup>9</sup> younger patients,<sup>10</sup> and patients who receive higher doses<sup>1</sup> and fractions.<sup>11</sup> However, radiation-induced toxicity should be considered in the differential diagnosis for any patient who has had previous radiotherapy and complains of neurologic symptoms. The physician should be aware as well that a vasculopathy or endocrinopathy caused by radiation injury can also be responsible for neurologic symptoms.<sup>6</sup>

### Classification of Radiation Toxicity

Radiation toxicity can be conveniently classified according to the time of presentation: acute reactions, early delayed reactions, late delayed reactions.<sup>12</sup>

**Acute reactions.** Acute reactions occur during the course of treatment and consist of symptoms of increased intracranial pressure or worsening of existing neurologic symptoms. These symptoms are usually mild and transient and are thought to be caused by radiation-induced edema. Occasionally, the use of corticosteroids or an increase in the dose of corticosteroids is temporarily required.

**Early delayed reactions.** Early delayed reactions occur several weeks to months after finishing radiation treatment. Early delayed reactions may also present with worsening symptoms or manifest by increasing somnolence and fatigue. These symptoms are believed

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to be caused by a temporary inhibition of myelin synthesis. Although this syndrome is typically temporary and mild, some cases of severe reactions requiring intensive medical support have been reported. Careful consideration is necessary to avoid interpreting an early delayed reaction as a treatment failure without enlargement of tumor mass on radiographic imaging.

**Late delayed reactions.** Late delayed reactions may occur months to years after completion of radiation therapy. The major type of late delayed reaction is radiation necrosis, which can mimic tumor recurrence in that the necrosis can be progressive, irreversible, and fatal. This effect may be caused by damage to small and medium arterioles or by a direct effect on glial cells. Radiation necrosis is difficult to diagnose without biopsy. The use of a variety of different imaging modalities, both anatomical (magnetic resonance imaging [MRI], computed tomography [CT]) and functional (positron emission tomography, single photon emission CT), have not reliably differentiated necrosis from tumor recurrence. Treatment of suspected or confirmed radiation necrosis usually consists of surgery; however, only total resection (cf, biopsy) is clinically beneficial. Anecdotal evidence suggests that anticoagulants (heparin and warfarin) may be useful in treatment of radiation necrosis at doses used in stroke management.<sup>13</sup>

## NEUROPATHIES

Perhaps the best described toxicities associated with radiation therapy are related to the neuropathies and plexopathies.

### Paresthesias

In the acute setting, paresthesias are the most common manifestation of peripheral nervous system toxicity.<sup>14</sup> These paresthesias typically are not bothersome to patients and are considered benign. No prospective studies have been performed to determine the incidence or prevalence of this toxicity, but paresthesias in the acute setting are not considered to be frequent.<sup>6</sup>

### Brachial Plexopathy

Other early-delayed syndromes occur predominantly in patients who have undergone radiation therapy for Hodgkin's lymphoma<sup>15</sup> and breast carcinoma.<sup>16</sup> Such early-delayed syndromes include brachial plexopathy that is painful at times, is similar to the idiopathic type, and can result in weakness and atrophy.<sup>15,16</sup> This brachial plexopathy may occur during radiotherapy in patients with Hodgkin's lymphoma and several

weeks to months after radiotherapy in patients with breast carcinoma.<sup>15,16</sup> The pathophysiology of this plexopathy is unclear at present but may be associated with acute demyelination.<sup>16</sup> The lumbar plexus may also be affected by this disorder with a relatively short latency (eg, 4 months), although this time frame may be shortened by previous chemotherapy.<sup>6</sup> These early toxicities are usually reversible.

The more common neuropathy/plexopathy associated with radiotherapy is a later, more delayed toxicity from radiation that occurs predominantly in the brachial plexus. Sensory loss is almost always present, with or without weakness.<sup>17</sup> Brachial plexus toxicity from radiation therapy usually occurs months to years after completion of the treatment. Associated signs can include lymphedema and myokymia.<sup>6</sup> The entire plexus is usually affected with either/both sensory and motor findings; however, pain is usually absent.<sup>6</sup> Patients who are younger, have had previous chemotherapy, and have had larger dose fractions have an increased risk for brachial plexus toxicity.<sup>6</sup> Lumbosacral plexopathy secondary to radiation tends to occur earlier (in less than 1 year) but is otherwise similar in nature to the brachial plexopathy.<sup>18</sup> The foot is usually affected initially, and proximal muscle weakness occurs subsequently.<sup>18</sup> Although uncommon, spontaneous resolution has been reported.<sup>19</sup> The main consideration for the differential diagnosis from these lesions is recurrent tumor, which is typically associated with pain, and, in the case of the brachial plexopathy, lower trunk of the brachial plexus involvement.<sup>6</sup> Radiation-induced plexopathy is usually not reversible, although recent studies have shown that these patients may benefit from warfarin administration to doses that increase the pretreatment protime by 1.5 times.<sup>13</sup>

### Cranial Neuropathies

Cranial neuropathies caused by radiation toxicity are uncommon, with the exception of involvement of the olfactory, optic, and facial nerves,<sup>20</sup> although bulbar palsies have been reported as a delayed effect.<sup>21</sup> The olfactory nerve has been noted to be affected in head and neck cancer patients who have undergone radiation therapy, with prominent anosmia. These symptoms may be reversible, which may be related to either dose or concomitant therapy.<sup>20</sup> These effects are not typically disabling. In contrast, radiotherapeutic effects on the visual apparatus can be prominent as a late effect. All aspects of the visual system have been reported to be affected by radiation. Cataracts can develop in the anterior chamber over the lens, and retinopathy has been noted with irradiation in head and neck tumors.<sup>22</sup> The

most disabling delayed radiation effect on the visual system involves the optic nerves, which may be more common than previously recognized.<sup>23</sup> Increases in the incidence of optic neuropathy have been found in patients with concomitant diseases (eg, diabetes) as well as in patients who undergo chemotherapy. When patients receive whole brain irradiation, optic neuropathy occurs between 7 and 26 months after completion of therapy<sup>6</sup> and is typically a painless loss of visual acuity initially, followed by frank visual loss. Whereas the fundoscopic examination may show several different findings, often either no disease is evident or only pale discs are evident.<sup>23</sup> Finally, up to 50% of patients with head and neck cancer treated with 50 to 60 Gy of radiotherapy complain of the loss of ability to taste, a facial nerve function. This loss can be both an acute effect (which is reversible) or a late effect (which is usually irreversible).<sup>24</sup> It is unclear if this loss is a direct effect on the nerve or taste buds or is caused by the loss of smell from effects on the olfactory nerve.

#### **Brain Toxicity**

Acute toxicity of brain in response to radiation can be caused by several pathogenic mechanisms, although edema associated with increases of intracranial pressure is thought to be the most likely mechanism. Patients are more likely to suffer from the acute effects of treatment with larger fraction sizes.<sup>25</sup> In addition, patients may experience pain (headache) and develop additional neurologic symptoms.<sup>25</sup> In most cases, the acute reaction is self-limited and does not require active intervention; however, as noted, occasional cases may require the use of steroids to decrease swelling.

Early delayed toxicity of the brain can manifest as somnolence and the worsening of existing neurologic deficits. Larger volumes of irradiation and the presence of underlying brain disease may increase the incidence of this toxicity.<sup>26</sup> Transient demyelination throughout 4 weeks to 4 months is thought to be responsible for this toxicity, and this effect may even be noted on radiographic imaging (especially MRI). It is especially important not to mistake this type of radiation toxicity to the nervous system as either recurrence of a primary brain neoplasm or brain metastasis. As noted, early delayed toxicity is usually self-limited, and patients recover to baseline status.<sup>27</sup>

Late-delayed toxicity can manifest in several forms: necrosis, atrophy, hemorrhage, infarction, encephalopathy, and neoplastic transformation can occur as a result of the late effects of radiation.<sup>6</sup> The most common manifestations of radiation-induced late effects are necrosis and atrophy/encephalopathy. Brain necrosis

typically occurs 1 to 2 years after the completion of radiation therapy; total dose is related to the incidence of necrosis.<sup>28</sup> Clinically, in patients who have received radiotherapy for primary or metastatic lesions of the brain, symptoms and signs tend to be related to either already present or previously present disease. For the treatment of tumors outside the brain, new focal findings are associated with radiation injury to normal brain structures and are related to those areas that are affected, near the external area irradiated.<sup>29</sup> In cases of suspected radiation necrosis, definitive diagnosis requires biopsy, and treatment typically revolves around removal.<sup>12</sup> Anecdotal reports suggest that steroids and anticoagulation<sup>13</sup> can be used to treat patients suspected of having radiation-induced brain necrosis, with or without surgery.<sup>30</sup>

Cerebral atrophy has been frequently noted after radiotherapy, primarily in patients who have been treated with whole-brain irradiation.<sup>31</sup> Posner<sup>6</sup> reports that these changes occur almost invariably after whole-brain treatment to 3000 cGy (10 fractions) or greater than 5000 cGy (in smaller fractions). Prominent findings on MRI show increases in the ventricular size and periventricular white matter abnormalities, which usually occur after 1 year following radiotherapy. Memory loss, gait abnormalities (resembling an apraxia), and dementia can occur.<sup>32</sup> In contrast to necrosis, no effective therapy has been reported.

#### **Spinal Cord Myelopathy**

A transient myelopathy has been reported to occur with radiation therapy, primarily in the cervical and thoracic region, which is correlated to total dose administered.<sup>1</sup> This early delayed myelopathy is associated with Lhermitte's sign, a shock-like sensation radiating down the spine with neck flexion.<sup>33</sup> The most likely pathogenesis is demyelination of the posterior columns, which is transient; most patients improve during the course of several months to 1 year.<sup>33</sup> It is unknown if the development of the early delayed myelopathy is related to concomitant factors, such as systemic disease or chemotherapy.

Late effects to the spinal cord are less common and more severe. A progressive myelopathy syndrome may develop, manifesting initially as partial cord involvement and progressing to a total transverse myelopathy.<sup>34</sup> The pathogenesis of this disorder is unclear but may be related to a radiation-induced vasculopathy.<sup>34</sup> A relationship may exist between the development of the myelopathic syndrome and total as well as fraction doses of radiotherapy<sup>1,6</sup> and concomitant chemotherapy.<sup>35</sup> The differential diagnosis includes epidural spinal cord compression, intramedullary metastasis, and paraneoplastic necrotic myelopathy.

A less common manifestation of late effect myelopathy associated with radiation is a motor neuron syndrome, first reported by Fossa et al<sup>36</sup> in patients undergoing treatment for testicular cancer. This syndrome is a pure motor syndrome associated with lower motor neuron pattern weakness, atrophy, and fasciculations in both lower extremities.<sup>6</sup> Many patients maintain their ability to ambulate, but prediction of those patients is difficult. Usually, no signs of sensory or autonomic involvement are present. As noted by Posner,<sup>6</sup> this disorder is difficult to differentiate from a pure motor polyneuropathy or isolated motor neuron loss or from paraneoplastic motor neuropathy.

#### SUMMARY

Radiation is an important therapeutic modality, especially in the treatment of diverse types of cancer. However, the effectiveness of this treatment is also associated with the side effects of toxicity, which can be substantial in the nervous system. Any part of the central or peripheral nervous system can be affected, at different times during or after the administration of radiotherapy. Recognition by the astute clinician may result in appropriate management decisions when damage may mimic recurrent tumor, and an understanding of the nature of radiation-induced effects may contribute to the prevention of toxicity altogether. HP

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