Treatment of delayed radiation necrosis of the brain

A clinical observation

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The authors report two cases of delayed radiation necrosis of the brain. In these cases a dramatic clinical and computerized tomographic improvement was noted after the institution of anticoagulant therapy. Based on a review of the literature, a possible causal mechanism is suggested. It was believed from both the clinical observation and the literature review that the anticoagulant agents had a direct effect upon the improvement in these patients. Laboratory data are needed to determine the role of anticoagulant therapy in the treatment of delayed radiation necrosis of the brain.

KEY WORDS □9 radiation necrosis □9 heparin □9 warfarin □9 brain tumor □9 tumor therapy

There has been a continuing interest in the effect of irradiation on the central nervous system (CNS). The following categories of radiation-induced brain damage have been described: 1) an acute reaction that occurs during the course of radiotherapy; 2) a transient post-radiation effect that occurs a few weeks or months after irradiation and is almost always self-limited and leaves no sequelae; 3) delayed radiation necrosis that presents itself as a mass lesion several months to years after the termination of radiation therapy.

In 1930, Fischer and Holfelder first described a case of delayed radiation necrosis of the brain in man. Since then, many more cases have been documented. It is the major complication of irradiation of the CNS. The literature suggests an increasing incidence of this complication. With conventional fractionation, between 3% and 25% of patients may suffer radiation necrosis after a total of 6000 rads. Although steroids are frequently employed, there is no known effective medical treatment for this complication. We have seen several cases at our institution. We describe two patients with proven radiation necrosis who experienced dramatic improvement, as evidenced clinically and by computerized tomography (CT) scanning, following treatment with anticoagulant agents.

Case Reports

Case 1

This 39-year-old right-handed woman had previously undergone surgery in 1971 for carcinoma of the thyroid. She presented again in 1974 for evaluation of a generalized seizure. She was followed until May 4, 1979, when, because of increasing seizure activity and significant enlargement of a calcified right parietal mass (Fig. 1), she underwent a right parietal craniotomy. A rather large lesion was removed. It was found to be a poorly differentiated follicular thyroid carcinoma similar to the tumor that had been removed from the thyroid 8 years earlier. Her postoperative course was uneventful and she remained neurologically intact. She was given radiation therapy via right and left parallel opposed fields, including the entire intracranial contents. She received a daily midline dose of 180 rads for 28 days until a total midline dose of 5040 rads was delivered. The field was then reduced to cover only the areas of

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Cerebral arteriography revealed an avascular mass in the right parietal region, and a CT scan showed an enhancing lesion in the area of previous surgery, with a right to left shift. She underwent reoperation in November, 1980, and a moderate volume of tissue was removed from the right parietal region. On microscopic examination, the diagnosis was radiation necrosis without evidence of neoplasm. On discharge from the hospital, there was some improvement in the left hemiparesis, and the patient was alert and well oriented. She deteriorated in January, 1981, and a repeat CT scan (Fig. 2 left) showed a considerable shift from right to left due to a large mass in the right parietal area. She again underwent reoperation in January, 1981, with resection of a large mass of tissue which was again diagnosed microscopically as consistent with radiation necrosis. The preoperative dense left hemiplegia did not improve after surgery; however, her mental status did improve. She was discharged in March, 1981, on decreasing doses of steroids. At the time of discharge, she was alert and was able to transfer from a wheelchair. In addition to her hemiplegia she had a partial left homonymous field defect.

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**Fig. 1.** Case 1. Preoperative computerized tomography scan on March 29, 1979, showing a large calcified right parietal mass.

The patient did well until November, 1980, when she was admitted to the hospital because of progressive left hemiparesis and mild alteration in mental status. Six treatments were then given until she had received a total dose of 6120 rads.

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**Fig. 2.** Case 1. Left: Computerized tomography scan on January 21, 1981, showing a large right parietal mass with marked right to left shift. Center and Right: Scans performed on April 22, 1981, after deterioration following the second operation, showing diffuse abnormalities in the right hemisphere.

**Fig. 3.** Case 1. Left and Center: Computerized tomography scans on May 28, 1981, 3 weeks after initiation of treatment. Right: Scan performed on October 26, 1981, showing continued marked improvement.
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The patient was readmitted on April 6, 1981, because of increasing lethargy and confusion. A CT scan on April 22 (Fig. 2 center and right) showed a diffuse abnormality on the right side of the brain, with diffuse contrast enhancement. The patient improved only slightly in response to mannitol therapy and an increased dosage of steroids. Because of the development of deep vein thrombosis, the patient was given a course of heparin on May 6 which was continued until May 15. Warfarin therapy was started on May 8, and she was subsequently discharged on a maintenance dose. Within a few days of initiation of this treatment she became progressively more alert and totally oriented. In addition, there was dramatic improvement in the CT scan performed before discharge on May 28. (Fig. 3 left and center). At that time she had a persistent left hemiplegia and visual field defect, but she was alert and able to walk with a cane. On positron emission tomography (PET), the lesion was hypometabolic, consistent with radiation necrosis.

Because of a fractured femur resulting from a fall, the patient was readmitted to the hospital in October, 1981. At this admission she was neurologically unchanged, and a CT scan showed marked improvement (Fig. 3 right). After her hip surgery she was discharged from the hospital, and her course remained stable until September, 1982, when she developed headache and became less alert. A CT scan revealed a subdural hematoma (Fig. 4 left), and, following evacuation of this lesion, the patient returned to her prior clinical status. Warfarin was discontinued immediately prior to this operation. A follow-up CT scan taken in October, 1982, showed no evidence of radiation necrosis (Fig. 4 right).

Case 2

This 35-year-old right-handed man was referred to us because of a 3-year history of increasing left-sided focal seizure activity. A CT scan (Fig. 5) and arteriogram revealed an avascular mass thought to represent a glioma. On January 19, 1979, the patient underwent right frontotemporal craniotomy with subtotal excision of the tumor. On microscopic examination of the specimen, a diagnosis of astrocytoma, Grade II to III, was made. Postoperatively, he was discharged without neurological deficit, and returned to his occupation as an attorney. He underwent a course of radiation therapy consisting of a total dose of 6400 rads in 32 fractions with the 4-MeV linear accelerator; the course was completed on March 16, 1979. All treatments were given at a daily rate of 200 rads per fraction. He received chemotherapy consisting of CCNU (1-{(2-chloroethyl)-3-cyclohexyl-1-nitrosourea}, vincristine, and procarbazine, and he was maintained on anticonvulsant therapy.

The patient did well until November, 1979, when he complained of severe right frontal headache, difficulty with memory, and recurrent focal seizure activity. A CT scan on November 7, showed an enhancing mass in the right frontal region (Fig. 6). On November 9, he underwent reoperation for this right frontal mass and a right prefrontal lobectomy was carried out. The postoperative course was uneventful. The tissue removed was reported to be 80% radiation necrosis and 20% astrocytoma, Grades I to III. Postoperatively, he received additional chemotherapy. He was neurologically intact, and returned to full-time work.
The patient was readmitted to the hospital on July 24, 1981, because of increasing seizure activity, ataxia, and difficulty with concentration. Repeat CT scanning (Fig. 7 left and center) showed an area of encephalomalacia in the right frontal region, with compensatory enlargement of the right lateral ventricle. There were bilateral frontal enhancing lesions associated with white-matter edema and a left to right shift. Cerebral arteriography showed a large left frontal avascular mass. A PET scan revealed this lesion to be hypometabolic and consistent with radiation necrosis. On admission, dexamethasone (16 mg/day) was prescribed, but there was no clinical improvement. On August 14, 1981, the patient was given heparin (24,000 units/day for 8 days) and then warfarin. A repeat CT scan showed less enhancement in the left frontal area, with less mass effect. Shortly after the institution of heparin and warfarin therapy, the patient’s mental status became normal and his ataxia diminished markedly. He was discharged on a course of anticonvulsant medication, decreasing doses of dexamethasone, and warfarin (5 mg every other day). On October 13, 1981, a CT scan showed much less enhancement and improvement in the left to right shift (Fig. 7 right). At the time of this writing, the patient remains functional but has not returned to work. Because of a gastrointestinal hemorrhage, warfarin was discontinued after 10 months.

Discussion

Delayed radiation necrosis of the brain may present as a mass lesion several months to years after radiation therapy. The brain parenchyma is actually replaced by an ill-defined space-occupying lesion. The mass can occur in or near the locus of previous surgery,7 or at a remote site.5 44 “Pure” radiation necrosis of the brain has been studied in patients irradiated for extracranial head and neck pathology.4 35 At present it is virtually impossible to differentiate tumor recurrence from delayed radiation necrosis on a clinical or CT basis.37 44 Positron emission tomography is helpful in establishing the diagnosis of radiation necrosis.41

Aside from clinically apparent mass lesions, there are other more subtle sequelae of irradiation.50 These include CT findings such as ventriculomegaly, cortical atrophy, and white matter attenuation in clinically asymptomatic patients.45 There is autopsy evidence that microscopic changes associated with irradiation of the brain are not an uncommon occurrence.7 These latter studies and others suggest that radiation necrosis of the brain is becoming a more common clinical problem as therapy improves and patient survival times increase.7 45 49 Delayed radiation necrosis of the brain may be a devastating process, but its management is not frequently discussed in the literature. Since there are no studies on the efficacy of different treatment modalities, guidelines for therapy do not exist.

Two theories have been proposed to explain the pathogenesis of delayed radiation necrosis. The first suggests that radiation primarily affects the neurons and glia, and that vascular damage is of minor importance. The second postulates that the primary insult is vascular, and that the chronic changes are secondary to ischemic anoxia.25 28 29 36 Vascular changes are the most striking findings in autopsy studies of these patients. Animal studies strongly implicate the vasculature as the most vulnerable tissue. These structural changes are noted early in the evolution of the lesion.8 22 25 29 36 39 It has been suggested that hypertension in irradiated animals can facilitate the vascular damage.24

While the vascular changes may not be the only process involved, alteration of the capillary structure appears to be sufficient to interfere both with luminal size and with maintenance of capillary wall permeability.10 36 Fibrinoid necrosis of the vessel walls and areas of endothelial proliferation with varying degrees of periventricular fibroblastic proliferation occur. Obliteration of the lumen may result. Thrombotic occlusion of various ages and thickening of the basal lamina are also frequent features.29 40 Some authors have reported diffuse hyperplasia of the capillaries throughout the cortex with atypical endothelial cells, including areas remote from the main lesion.25 29 22 The hyalinized vessel

![Fig. 7. Case 2. Computerized tomography scans 2 weeks before (July 27, 1981, left and center) and 2 months after (October 31, 1981, right) institution of anticoagulant therapy.](image-url)
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...wall appears extremely thickened and smooth-muscle cells are atrophic, being replaced by fibrin deposits. In addition, the presence of perivascular chronic inflammatory cells is a common finding. This report stems from the dramatic improvement of two patients with proven radiation necrosis while on anticoagulant therapy. The possible role of these anticoagulant drugs became apparent after a review of the literature. Endogenous heparin is a very effective anti-inflammatory agent and modifies allergic reactions. It may be useful in treating collagen vascular diseases such as lupus erythematosus and rheumatic fever, and has significantly improved patients with chronic obstructive pulmonary disease. Heparin binds and inactivates histamines in the mast cell. In so doing, it inhibits histamine release in antigen antibody reactions. Heparin also binds and inactivates many substances that may injure vascular endothelium, such as serotonin, lysozymes, angiotsin, bradykinin, complement, and many toxins and drugs. Experimentally, heparin has been shown to decrease the ischemic injury in myocardial infarction, and decrease the extension of thermal burn lesions.

Heparin has been shown to affect dynamic cell processes. It stimulates phagocytosis by hepatic Kupffer cells, and stimulates pinocytosis and motility in murine fibroblasts and macrophages. Mast cell heparin stimulates capillary endothelial cell migration. Arterial smooth-muscle cell proliferation is inhibited by heparin, and this mechanism is proven not to be dependent upon anticoagulation. That is, if the heparin molecule is fractionated chromatographically, the non-anticoagulant component is just as effective as the anticoagulant fraction.

Heparin administered intravenously, intramuscularly, or intrathecally is sequestered in vascular endothelial cells at concentrations much above the blood level. Thus, endothelial cells can act as long-term reservoirs of heparin for release into the circulation. Endothelial cells have endogenous heparin-like compounds on their cell surface. Fibroblasts also take up heparin and subsequently release it unchanged. It is apparent, then, that endogenous heparin activity, is present normally at or very close to the endothelial surface. By virtue of its attachment to and its concentration in endothelial cells, it could minimize the harmful effects of many noxious agents.

Finally, platelets attach and aggregate at the site of endothelial injury. Aggregated platelets release vasoactive agents such as epinephrine, serotonin, lysosomal enzymes, and cationic proteins. Heparin effectively inhibits platelet deposition and agglutination.

Both of the patients presented here were maintained on warfarin after the initial administration of heparin and both continued to improve. Some studies have claimed lower mortality and morbidity rates in cancer patients treated with warfarin. This may be due to a reduction in the incidence of metastases or an actual reduction in the size of the primary tumor. In addition, warfarin has the ability to uncouple oxidized phosphorylation, which might be responsible for decreasing the morbidity associated with malignant cells.

The clinical observation of the dramatic improvement in the two patients presented here may be anecdotal. However, the increasing incidence and poor prognosis of delayed radiation necrosis of the brain makes its further investigation imperative. We believe that the improvement observed during anticoagulant therapy was not coincidental. In fact, there have been reports that heparin may have some radioprotective properties in the experimental animal.

References


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