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Brain Edema in Delayed Radiation Necrosis: Study of Capillary Ultrastructure

—Case Report—

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Abstract

A 42-year-old male was found to have cerebral radiation necrosis 2 years after a split course of radiation therapy following subtotal excision of a left parasagittal meningioma. The surgical specimens were studied by means of conventional ultrathin sectioning and freeze-fracture replication techniques. The electron density of the capillary endothelium was decreased, as was the degree of surface infolding. The width was irregular, and there was an unusually large number of pinocytotic vesicles (37/μm^2). The endothelium was also discontinuous, and the basal laminae were irregular in thickness. The pericapillary space was markedly enlarged, and accumulation of a fibrin-like substance was noted in the extravascular space. The pericapillary zone contained inflammatory cells. However, the tight junctions were preserved and the intercellular junctions were composed of five strands that appeared to consist of continuous particles. The authors conclude that activated pinocytotic vesicles play an important role in increasing vessel permeability in delayed cerebral radiation necrosis and that leakage may occur through interruptions in the endothelium.

Key words: radiation necrosis, cerebral edema, endothelial cell vesicles, glioma

Introduction

It is generally agreed that delayed cerebral radiation necrosis is secondary to fibrinoid degeneration of the vascular walls caused by radiation exposure. However, there are several unanswered questions concerning its pathogenesis. For instance, why do mass effects and severe brain edema persist in the absence of the neoplasm? We previously reported on the pathogenesis of brain edema in glioma from the viewpoint of vascular permeability.[8,9] The radiation necrosis involves degeneration of normal brain vessels following radiation whereas in gliomas the process is proliferation of vessels induced by the tumor.

We examined ultrastructural changes in capillaries in a case of radiation necrosis and compared them with the findings in cases of glioblastoma and astrocytoma. We describe our observations and discuss the pathophysiology of delayed radiation necrosis, giving particular attention to vascular permeability in the etiology of brain edema.

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Case Report

A 42-year-old male had experienced headaches and grand mal seizures from the middle of June, 1983. Postcontrast computed tomography (CT) revealed a homogeneous tumor mass in the left parasagittal region. Under the diagnosis of parasagittal meningioma, the tumor was subtotally removed, the remaining portion being attached to the sagittal sinus. The pathological diagnosis was transitional meningioma. The residual tumor was irradiated with Liniac 40 Gy (using 2 Gy daily and five times a week) in August of the same year. He was followed until May, 1985, when grand mal seizures and headaches recurred. CT demonstrated a large low-density area with thin ring enhancement and marked mass effect in the frontal lobe. The site corresponded to the irradiated region (Fig. 1), and radiation necrosis was diagnosed. The mass was partially removed in January of 1986.

Conventional ultrathin sections and freeze-fracture replicas of the surgical specimens were examined with light and electron microscopy. The degree of capillary changes was variable in and around the center of radiation necrosis in the ultrathin

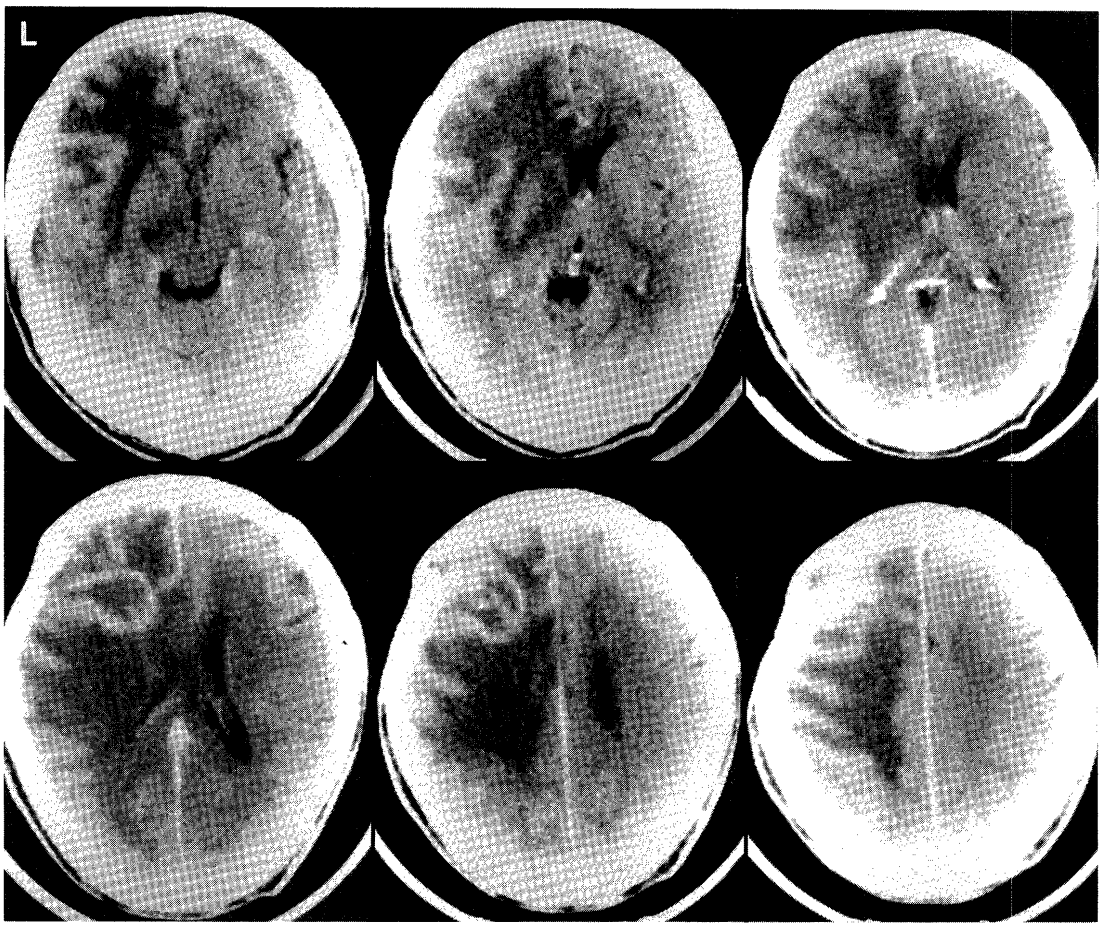

Fig. 1 Postcontrast CT scan obtained 2 years after radiation therapy, showing a heterogeneous mass with ring enhancement surrounded by a low-density lesion in the left frontal region.

specimens, but the changes were essentially the same throughout. The electron density of the capillary endothelium was markedly attenuated and surface infolding was indistinct. There were also irregular hypertrophy and thinning, increased numbers of pinocytotic vesicles and vacuoles, and irregular hypertrophy of the basal laminae. However, the tight junctions were normal. The pericapillary space was markedly enlarged, and a fibrin-like substance and infiltration by inflammatory cells were observed (Fig. 2).

Under high magnification, the electron density of endothelial cells was attenuated and numerous pinocytotic vesicles and a few vacuoles were found (Fig. 3 *left*). In 10 replica samples, the average number of pinocytotic vesicles was $37/\mu m^2$ of capillary endothelium, a significant increase (Fig. 3 *right*). Some parts of the endothelial cells had thinned and appeared membranous (Fig. 4 *left*), and were also found in some discontinued endothelial cells (Fig. 4 *right*). The intercellular junctions were normal and the tight junctions of the replica specimens

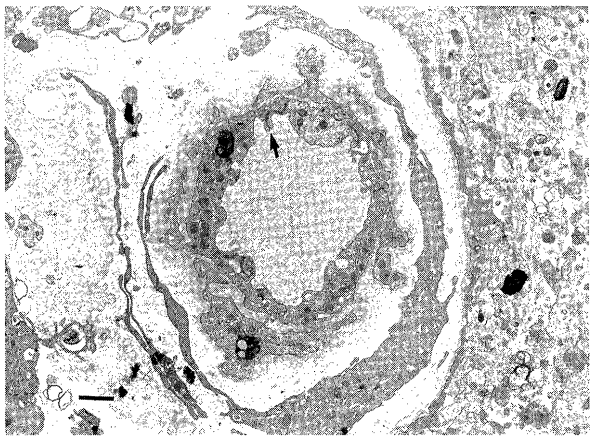

Fig. 2 Ultrathin section of a capillary from the necrotic region, showing attenuation of its electron density, a lesser degree of surface infolding, variable width, tight junctions (*arrow*), irregular basal laminae, and an enlarged perivascular space. Bar = 1 μm.

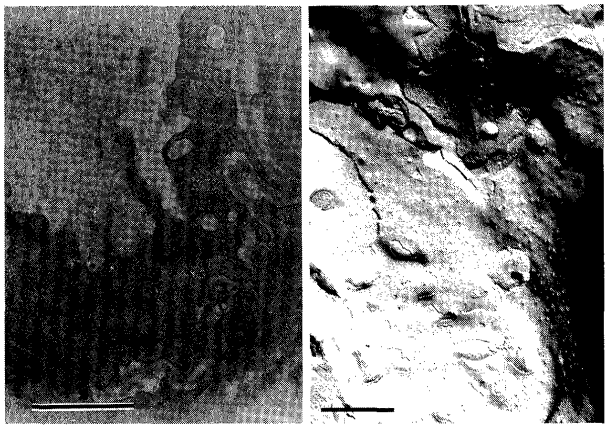

Fig. 3 At higher magnification, a specimen of radiation necrosis exhibits an increased number of pinocytotic vesicles (*left*), which were calculated to be $37/\mu m^2$ in a replica specimen (*right*). Bar = 1 μm.

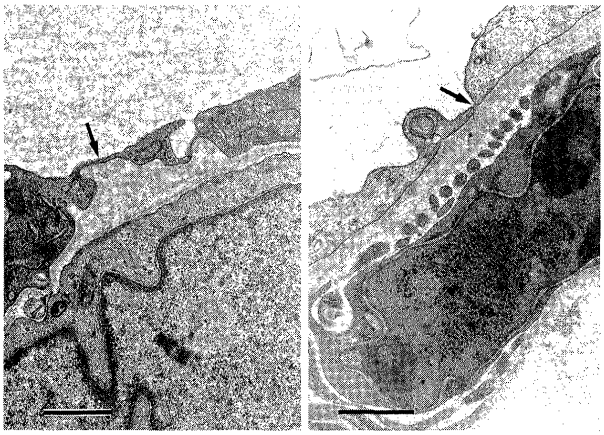

Fig. 4 Capillary endothelium showing a membrane like structure (*left*) and discontinuity (*right*) (*arrow*). Bar = 1 μm.

consisted of five strands (Fig. 5).

Discussion

The basic morphological changes in radiation necrosis and glioma appear similar. Both diseases entail marked brain edema, as evidenced by CT, and both are accompanied by increased intracranial pressure.

The specific features of the vascular endothelium in radiation necrosis are thinning, decreased electron density, an increase in the number of pinocytotic vesicles, and discontinuity of the endothelial cells (Table 1).[1,3,4,6,7,12] Therefore, it is assumed that edema occurs because the numerous vesicles absorb serum components and transport them out of the

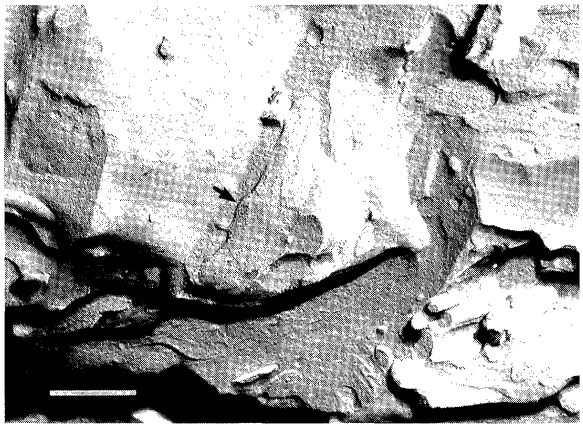

Fig. 5 Intercellular junction. The tight junction is composed of five strands (*arrow*). Bar = 0.5 μm.

vessels; the situation is aggravated by leakage from the discontinued endothelium. The marked dilation of the perivascular space also enhances retention of edema fluid.

Brain edema is severe in glioblastoma and mild in astrocytoma. In ultrathin sections of glioblastoma, one can clearly see such changes as endothelial cell hyperplasia with surface infolding or finger-like projections, vacuoles of varying size, short or elongated junctions, irregular basal laminae, and an enlarged perivascular space. These abnormalities are less distinct in astrocytoma. In replica specimens of both types of glioma, pinocytotic vesicles are increased; however, the intracellular junctions of glioblastoma contain fewer strands than those of astrocytoma (Table 1). Thus, the edema of glioblastoma involves leakage from the immature junctions as well as vesicular transport of serum components. Irregular basal laminae and the enlarged perivascular space also contribute to edema.[8,9]

Fenestration has only rarely been observed with radiation necrosis and glioblastoma.[2,5,10,11] It is entirely possible that fenestration would be found in the vessels of a glioblastoma or necrotic lesion if the necrosis or tumor has invaded the arachnoid membrane at the brain surface, since normal arachnoid membrane has fenestrated capillaries. As we reported previously,[9] however, glial tumors, such as astrocytoma, glioblastoma, ependymoma, and medulloblastoma, have nonfenestrated capillaries, as do normal cerebral arteries. In radiation necrosis, the cerebral vessels are damaged by radiation but remain nonfenestrated. This differentiates glial tumors and radiation necrosis from such nonglial tumors as meningioma, hemangioblastoma, pituitary adenoma, and acoustic tumor and from such metastatic tumors

Table 1 Ultrastructural characteristics of capillary endothelium in delayed radiation necrosis and glioma

Diagnosis	No. of cases	Ultrathin section								Replica		
		EW	D	SI	PV	F	IJ	BL	PS	F (/μm^2)	PV (/μm^2)	IJ (No. of strands)
Radiation necrosis	1	irregular	attenuated	moderate	+++	−	uniform	thick	markedly enlarged	0	37	5-6
Glioblastoma	5	thick	increased	marked	++	−	short and elongated	irregular	enlarged	0	23	2-6
Astrocytoma	6	uniform	increased	moderate	+	−	uniform	uniform	normal	0	20	5-6

EW: endothelial width, D: density, SI: surface infolding, PV: pinocytotic vesicles, F: fenestration, IJ: intercellular junction, BL: basal lamina, PS: perivascular space.

as breast and lung cancers, which have fenestrated vessels.[9]

In summary, in both gliomas and delayed radiation necrosis, vesicular transport plays the main role in the development of brain edema. However, in radiation necrosis, discontinuity of the endothelium appears to accelerate edema, whereas in the case of gliomas, edema is enhanced by paracellular transport through immature junctions between endothelial cells. While the etiology of edema differs somewhat in the two groups of edema, the basic morphological changes are the same.

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