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Delayed Radionecrosis of the Brain

—A case simulating recurrent glioma—

Shin Kwang Khang, M.D., **Jun Ho Song,*** M.D., **Kyu Ho Lee***, M.D.
In Wook Choo,** M.D. and **Je G. Chi,***** M.D.

Department of Pathology, Neurosurgery, Radiology**, Hallym University, and*
Department of Pathology, College of Medicine,
*Seoul National University****

An appreciation of the radiation changes in the brain adjacent to radiated glioma is of considerable importance from both clinical and pathological standpoint because the alteration in the brain parenchyma may result in a picture that mimics recurrence of the neoplasm. A 35 years old woman was admitted because of deterioration of consciousness which has started about 20 days ago. Past history revealed removal of left frontal brain tumor 4 years earlier and the diagnosis was grade II astroma. Postoperative radiation was done at that time. Sice then, she has been doing well. Computerized tomogram showed an ill defined huge low density mass at right frontal and left posterior parietal areas, which was irregularly enhanced in postcontrast study. Unlikely to the usual brain tumors, there was no mass effect on adjacent structures. Histologically acellular necrotic zone was alternating with hypercellular zone and most striking changes were vascular and glial reaction. Most of the vessels showed acellular hyliane thickening of their wall and some vessels were almost completely occluded.

There was marked glial proliferation with considerable cellular and nuclear irregularities. Gemistocytic astrocytes were frequently seen and some were multinucleated.

Key Words: Radiation necrosis, Brain, Astrocytoma

INTRODUCTION

It is well known that radiation therapy to leisions within or around the cranium can lead to brain injury. Historically, adverse effects of irradiation to the brain have been considered according to time apperance[1]. Generally the reactions have been devided into acute, early delayed and late delayed reactions. Acute reaction is widely believed to be due to edema and the main pathology of the early delayed reaction is known to be demyelination, both of which are usually transient and not fatal. The most serious reaction is late delayed reaction which is fatal and morphologically characterized by extensive parenchymal necrosis. This reaction mimics recurrent intracranial or metastatic tumors both on clinical and radiological aspects and histologic diagnosis is required. Recently the incidence of delayed radiation necrosis has been increasing due to several factors[2]: 1) a more aggressive approach by the radiotherapist using higher doses, sometimes concurrent with radiation sensitizers[3] ; 2) more frequent antemortem diagnosis owing to high resolution brain C—T and magnetic resonance imaging ; 3) prolonged survival time after radiation allowing more time for the effects become apparent.

We have seen a case of late delayed radiation necrosis of brain which was histologically proven

and describe clinical and histologic features together with review of literature.

CASE REPORT

A 35 years old woman was admitted because of generalized weakness and deterioration of consciousness. Four years ago, she underwent a left lobe lobectomy because of a brain tumor. Histological diagnosis was astrocytoma grade II. High voltage irradiation was given during 6 weeks' period and the total dose was 5400 rads. She has been doing well since then, but she began to feel generalized weakness from about 1 month ago and her consciousness started to be deteriorated soon after. On neurological examination, she was found to be confused, but well oriented and verbal communication was possible. Motor and sensory funtions were not impaired and deep tendon reflexes were preserved. Pathologic reflex was not observed. Size of the pupil was normal as well as light reflex, but mild papilledema was observed on funduscopic examination. No other abnormal neurologic sign was observed. Analysis of CSF was abandoned for the fear of brain herniation. Results of routine laboratory examination was within normal limits.

Computerized tomography showed huge space occupying lesions with diminished absorption coefficient in right frontal and left posterior parietal areas, which were inhomogeneously enhanced by intravenous injection of contrast material (Fig. 1, 2). The lesion in parietal area crossed the midline. These radiologic features strongly suggests recurrent glioma, but unlikely to the usual brain tumors, mass effect on adjacent structures was minimal compared to its large size. Ventricular contour was well preserved and the falx was only minimally shifted. Marginal edema was not significant, either. Two small biopsies were done at subcortical white-matter in right frontal lesion.

Microscopically, main histologic features were

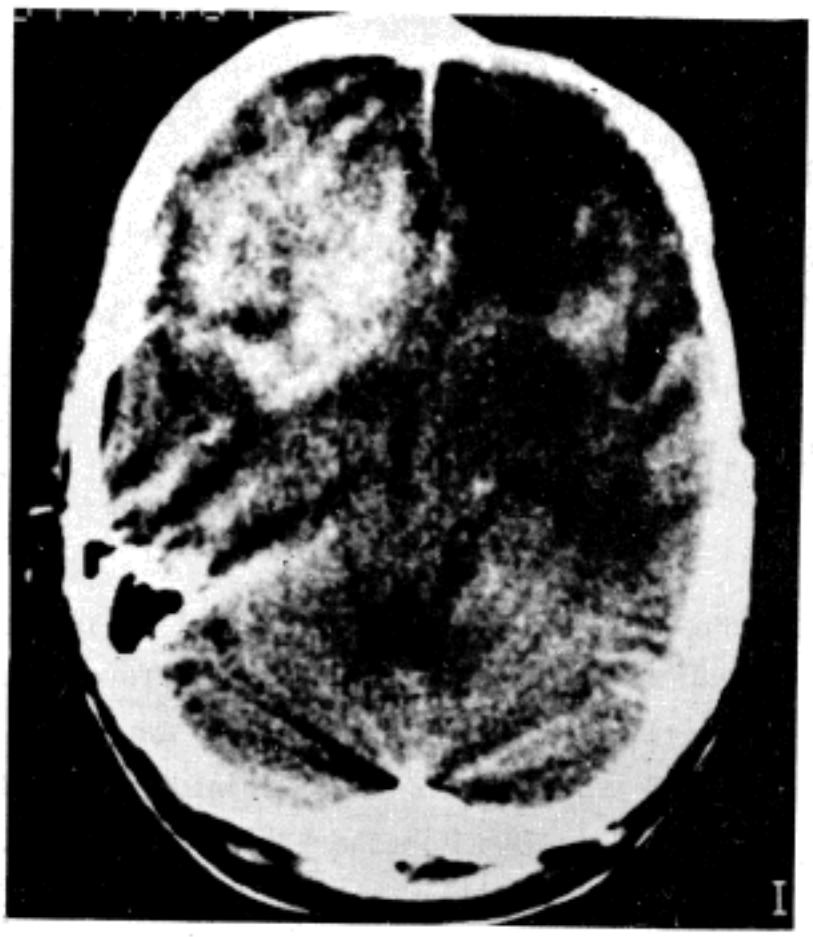

Fig. 1. Huge inhomogeneously enhanced mass in right frontal lobe. Falx is minimally shifted.

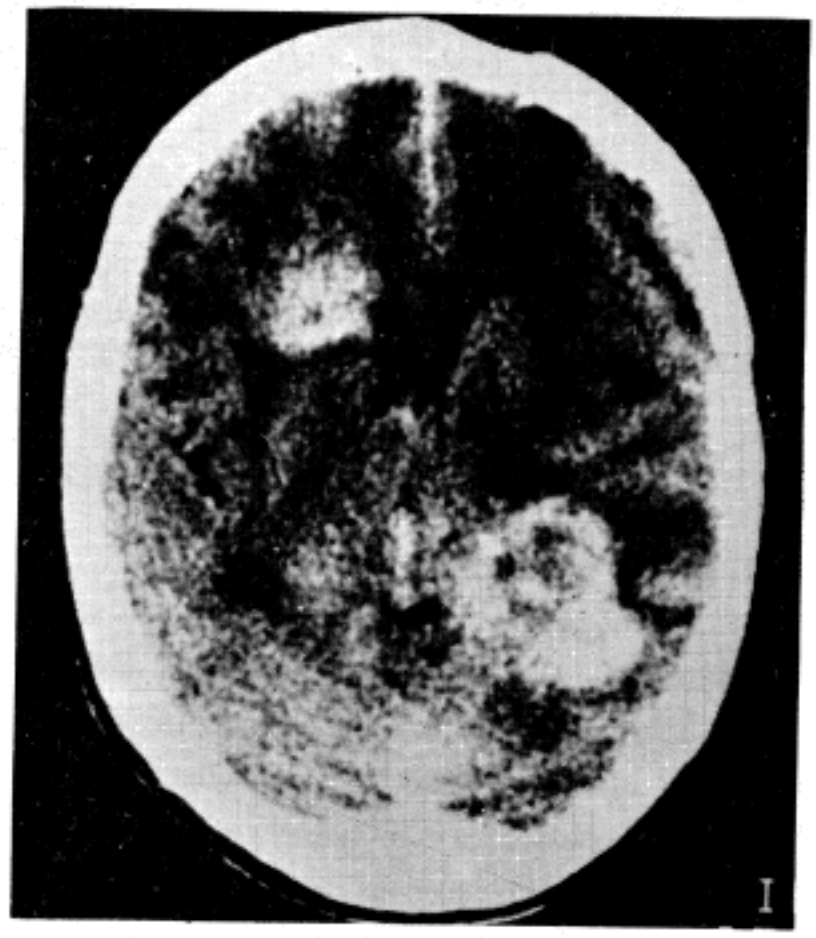

Fig. 2. Another lesion in posterior parietal area crosses the midline.

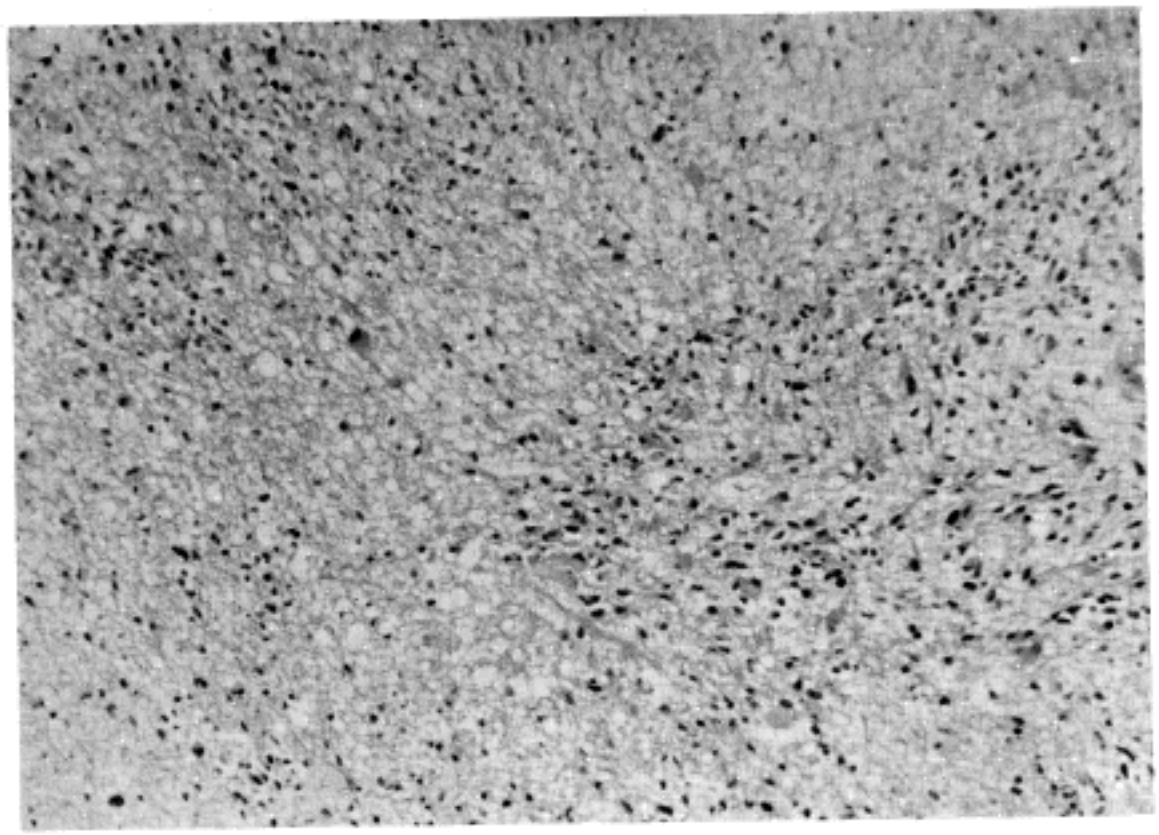

Fig. 3. Acellular necrotic zone is alternating with cellular zone. (H & E, X100).

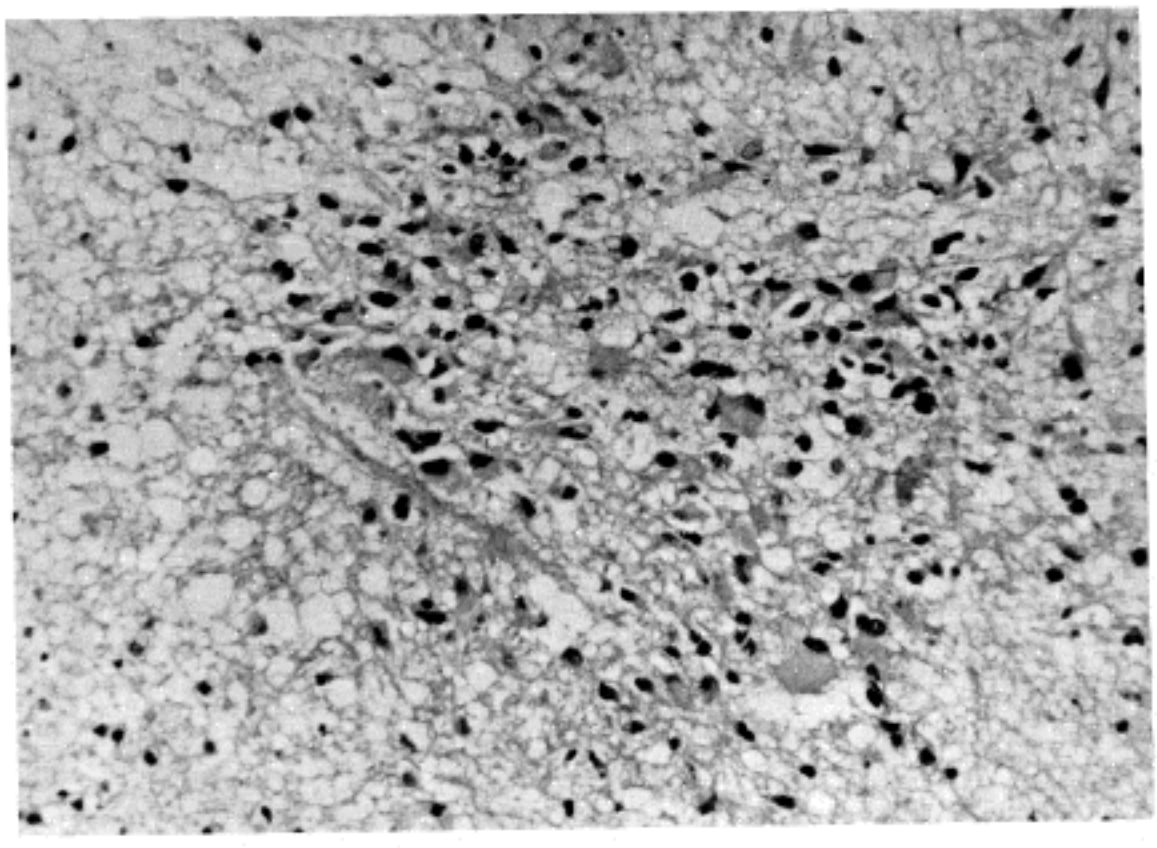

Fig. 4. Proliferation of reactive astrocytes. (H & E, X200).

multifocal necrosis and proliferation of reactive astrocytes. Acellular necrotic zone was alternating with hypercellular zone, the latter of which is mainly composed of reactive astrocytes (Fig. 3). Many of those astrocytes were gemistocytic in appearance and showed considerable unclear irregularities. (Fig. 4) Cells with bizzare giant neclei were occasionally observed. Another prominent finding was vascular changes. Most of the vessels were thick hyalinized with marked narrowing of thier lumens (Fig. 5, 6). Some vessels were totally occluded while others showed infiltration of inflammatory cells within the wall accompanied by focal fibrinoid necrosis. A few vessels showed intraluminal thrombi.

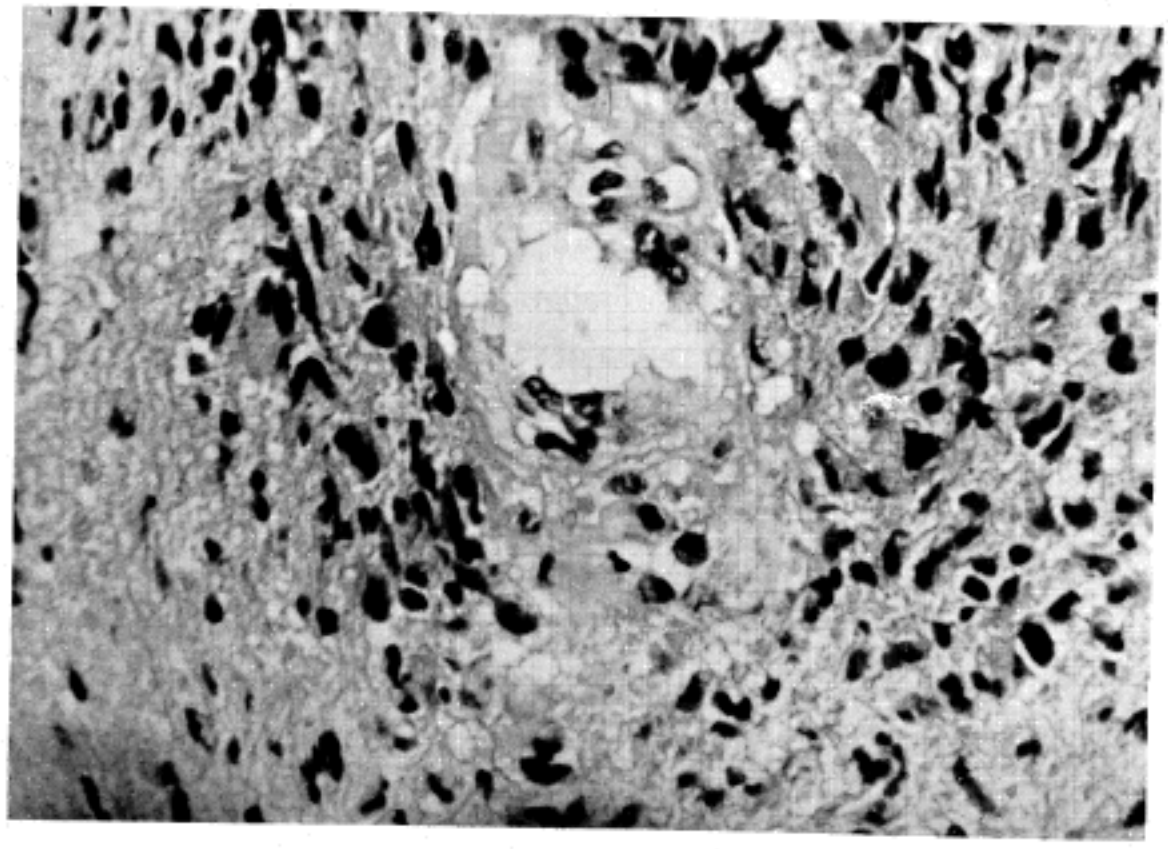

Fig. 5. Vascular endothelial proliferation partially occluding the lumen. (H & E, X400).

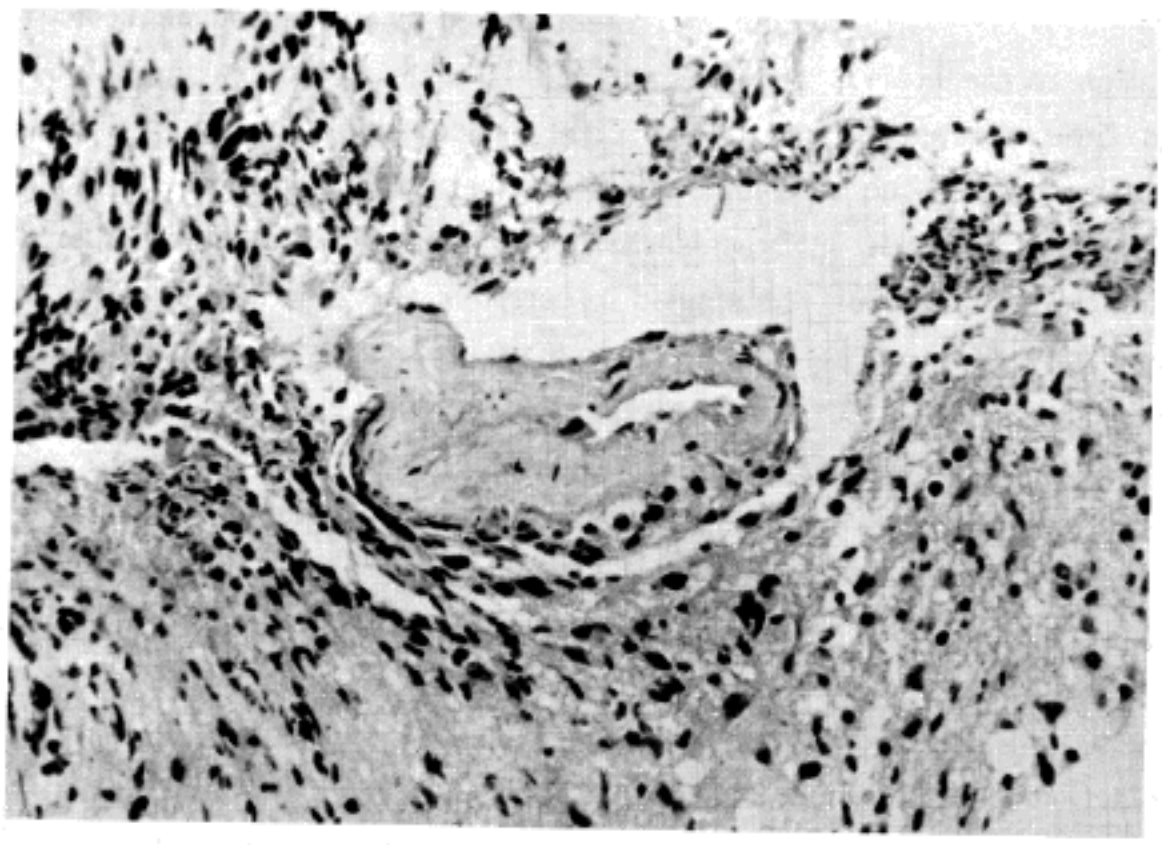

Fig. 6. A hyalinized vessel with marked narrowing of the lumen. Note infiltration of inflammatory cells within the wall. (H & E, X200).

DISCUSSION

Gliomas comprise approximately half of all brain and spinal cord tumors. Since many of these neoplasms cannot be adequately resected because of their intimacy to vital centers and pathway, radiotherapy has been an important mode of treatment. But irradiation also induces radiation necrosis of the brain[4~8]. This complication has been reported not only after irradiation to intracranial neoplasms but also to extracranial neoplasms around the head and neck region such as nasopharygeal carcinoma[9], parotid gland carcinomas[10] and basal cell carcinomas of the face and scalp[11].

The clinical and radiological features of the radiation necrosis resembles recurrent neoplasms in many aspects, so its possibility should be included in the differential diagnosis of any nerological deficit that develops after therapeutic irradiation of the brain[9,10]. It often cannot be differentiated from recurrent neoplasm without biopsy especially if the original tumor was a glimoa or other intracranial aggressive neoplasm that usually recurs.

Since the early description by Fisher and Holfelder, more than one hundred cases of delayed necrosis has been reportd by 1980[1]. Although its precise incidence cannot be clearly estimated, about 15 to 20 per cents of patients who were treated wth 6000 rads or more developed signs of radiation necrosis[1,7].

The adverse effects of irradiation to the brain has been devided according to time of appearance[1,2]. Acute reaction, occuring during the course of irradiation, is transient and of little importance. It is widely believed to be due to brain edema and corticosteroid therapy may be useful for symptomatic relief. Early delayed reaction usulally appears within 3 months after irradiation and the main pathologic change is demyelination often forming demyelinated plaques resembling those observed in acute multiple sclerosis. This reaction is also transient and almost always non—lethal with a few exceptions[5]. Late delayed reaction is the most serious reaction, which is progressive and lethal. It occurs months to years after irradiation and is histologically characterized by extensive parenchymal necrosis and characteristic vascular changes. This reaction selectively involves white matter and the cortex is usually spared. Pathologic appearances are extensive coagulation necrosis accompanied by proliferation of reactive astrocytes, the nuclei of which often show considerable irregularities and hyperchromatism with occasional bizzare multinucleated giant cells. Inflammatory cellular reaction is usually mild or absent. Vascular changes are among the most striking and repeatedly emphasized. Alteration consists of fibrinoid necrosis of the vessel walls, which may be partial or complete, thrombotic occlusions of various ages, proliferation of vascular endothelium with ultimate obliteration of the lumen, periadventitial fibroblastic proliferation and fibrous acellular hyaline thickening in late stage[4~7,12]. These vascular changes are quite smilar to those that can be observed in irradiated gliomas and regarded as characteristic reaction to irradiation[7].

The pathogenesis of delayed radiation necrosis remains speculative. Some investigators suggested immunologic mechanism[6]. They thought that cellular protein altered by irradiation might act as an allergen and be able to induce immunologic reaction. Their speculation was based on histologic smilarities between radiation necrosis and hypersensitivity reaction. This speculation might be applied to early delayed reaction, in which the main pathology is demyelination and agent that has demyelinating activity on tissue culture was stated. But this view has not been widely accepted and others contended that vascular mechanism plays the principal role[4,5,13]. The postulated sequences of event is that initial endothelial damage by irradiation causes increased vascular permeability with subsequent insudation of plasma proteins into vessel walls. This plasma insudation leads to fibrinoid necrosis and hyalinization of the wall followed by ischemic necrosis of the parenchyma. We favor vascular theory because similar changes are observed in irradiated tumors[7], the necrosis of which cannot be explained by immunologic reaction. Another fact favoring the vascular mechanism is good response to anicoagulant therapy[2]. Furthermore, We think that direct injury to parenchymal cells may play a role.

As we described at the beginning of this discus-

sion, diagnostic studies other than biopsy is rarely decisive because both radiation necrosis and recurrent glioma may apper on computerized tomography as an area with diminished absorption coefficient that may not be enhanced on injection of contrast material. Our case also appears as a low density mass on computerized tomography which is inhomogeneously enhanced. But relatively mild compressing sign on adjacent structures is supposed to be a finding unusual for a glioma together with multiple lesions.

Possibility of recurrent glioma might be remained, because only two small pieces of tissue were biopsied. But vascular changes of our case are consistent with those of radiation injury and it is not logical that radiation vascular changes are present in recurrent tumor, the vasculatures of which are newly formed. Another evidence against to recurrent astrocytoma is relationship between necrosis and cellular atypia. Necrosis has been regarded as one of the histologic hallmarks for malignancy in gliomas and usually accompanied by marked cellular atypia. In this case, the necrosis is extensive while cellular atypia is minimal. In korea, where megavoltage irradiation is widely being practiced, only one case has been reported recently without detailed description for histology[14]. The importance of histologic confirmation cannot be emphasized too much.

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＝국문초록＝

지연성 방사선 뇌괴사
—1예 보고—

한림대학 병리학교실, 신경외과학교실* 및
방사선과학교실*

강신광 · 송준호* · 이규호* · 주인욱**

서울대학교 의과대학 병리학교실

지　　제　　근

뇌종양의 방사선 치료후 발생한 지연성 방사선 뇌괴사 1예를 경험하여 문헌 고찰과 함께 보고한다. 환자는 35세 여자로 4년전 좌측 전두엽에 발생한 뇌종양

을 제거한 후 약 6주 동안 총 5400 rads의 방사선 치료를 받았다. 당시의 병리학적 진단은 grade II성상교종 이었다.

환자는 그후 건강히 지내다 입원 20일 전부터 의식상태가 혼미해지기 시작하였다. 전산화 단층 촬영상 우측 전두엽 및 좌측 두정엽에서 저음영의 커다란 종괴가 관찰되어 재발성 성상교정이 의심 되었으나 생검 결과 특징적인 혈관 변화와 신경 교증을 동반하는 뇌조직의 괴사가 관찰되어 방사선 조사에 의한 지연성 뇌괴사임이 확인되었다.