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Diffuse Low-density Areas in White Matter on CT Scans After Intracarotid ACNU Infusion —Report of Three Case—
(頸動脈内ACNU注入後におけるCTスキャンでの白質内瀰漫性低吸収領域 3例の報告)

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Diffuse Low-density Areas in White Matter on CT Scans After Intracarotid ACNU Infusion

—Report of Three Cases—

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Abstract

Since 1984, we have treated 11 malignant glioma patients with intracarotid infusion of ACNU [1-(4-amino-2-methyl-5-pyrimidinyl)-methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride] in addition to surgical removal and irradiation. We experienced three patients, who showed clinical manifestation of leukoencephalopathy and computed tomographic (CT) findings of diffuse low-density areas in the white matter on the side of ACNU infusion. Two of the three patients showed an additional CT finding of ring enhancement in the temporo-occipital region. The histological diagnosis of the first case was radiation necrosis, while that of the others was recurrent tumor with coagulation necrosis in the surrounding brain. Our experience suggests that intracarotid ACNU infusion increases the hazard of radiation necrosis, and the optimum dose and effective mode of administration should be evaluated.

Key words: ACNU, glioma, radiation necrosis, chemotherapy, intra-arterial chemotherapy

Introduction

At present, a combination of surgical removal, irradiation, and chemotherapy is thought to be the most effective treatment for malignant gliomas.[15,17] Recently, several clinical reports on the intracarotid infusion of anticancer drugs have indicated favorable results, particularly by using nitrosourea.[7,8,19] On the other hand, the central neurotoxicity of anticancer drugs and delayed radiation necrosis appear as problems with the prolongation of patients' survival time.[1,9,10,12]

Between 1984 and 1987, we performed intracarotid infusion of ACNU [1-(4-amino-2-methyl-5-pyrimidinyl)-methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride] combined with surgical removal and irradiation on 11 patients with malignant gliomas. Among them, three patients showed computed tomographic (CT) findings of diffuse low-density areas in the white matter and suffered memory impairment and disorientation, similar to the symptoms of leukoencephalopathy. We present these cases.

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Case Reports

Case 1: A 58-year-old female was admitted on November 7, 1985, with a 3-month history of headaches and vomiting. The neurological examination on admission revealed bilateral papilledema and mild left hemiparesis. A CT scan showed a heterogeneous low-density area with ring enhancement in the right temporal lobe (Fig. 1A). Six days after admission, the tumor was macroscopically totally removed and histologically diagnosed as a glioblastoma multiforme. Postoperatively, she received whole brain irradiation of 38 Gy in 31 installments followed by focal irradiation of 28 Gy in 24 installments through two opposed fields. Infusion of 100 mg of ACNU dissolved in saline into the right internal carotid artery was performed on November 26, 1985 and January 24, 1986. She was discharged on February 1, 1986, without neurological deficit. A CT scan taken on discharge showed rim enhancement

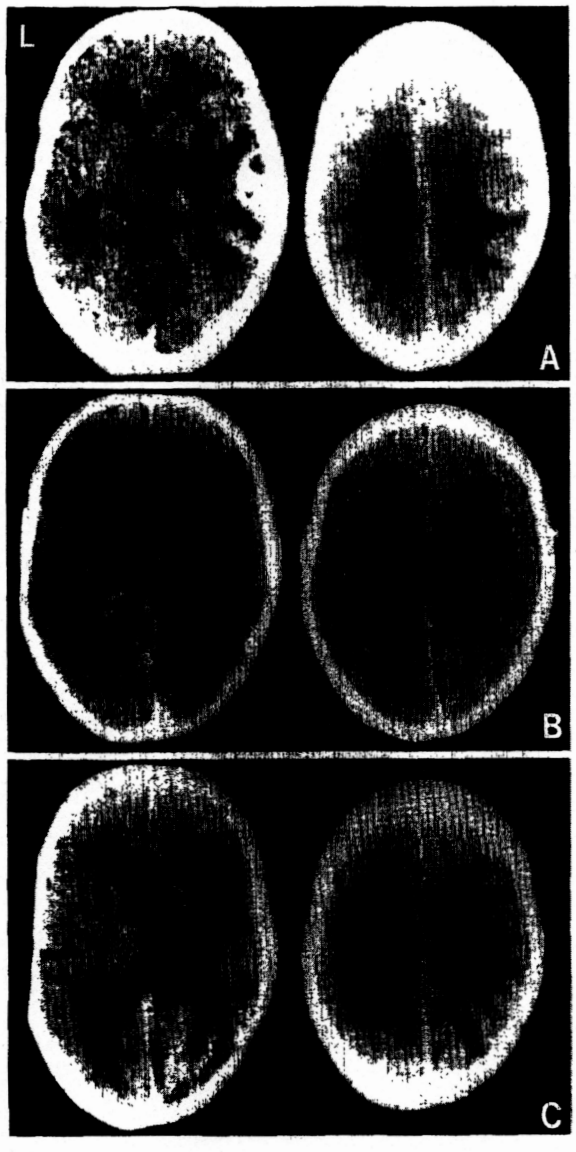

Fig. 1 Sequential postcontrast CT scans in Case 1. A: On admission, an enhanced mass in the right temporal region is seen. B: At discharge, a rim of contrast enhancement is noted. C: At readmission, a diffuse low-density area with contrast enhancement and mass effect in the right white matter are shown.

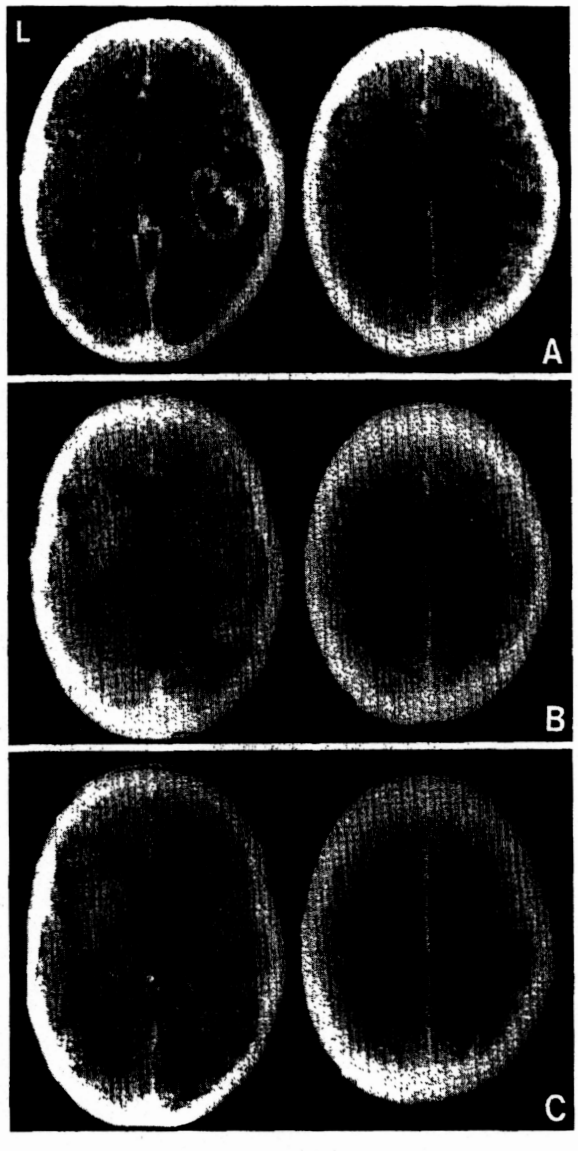

Fig. 2 Sequential postcontrast CT scans in Case 2. A: On admission, an enhanced mass in the right temporal lobe and surrounding brain edema are seen. B: Six months after the second operation, the right temporo-occipital region is heterogeneously enhanced without mass effect. A diffuse low-density area in the white matter is also seen. C: Five months later, the enhanced areas are changed.

in the operation area (Fig. 1B), but we could not determine it to be residual tumor or gliosis.

In September, 1986, she was readmitted due to memory disturbance, disorientation, and unsteady gait. A CT scan revealed a low-density area in the right temporoparietal lobe and minimum enhancement in the white matter of the occipital lobe. A low-density area in the centrum semiovale and gyral enhancement in the parietal lobe were also seen (Fig. 1C). Angiograms disclosed an avascular mass, partially containing fine neovascularization, in the right temporo-occipital region. A right temporo-occipital lobectomy was performed. The histological examination showed coagulation necrosis and hyalinized blood vessels, without tumor cells. After the second operation, her mental condition gradually deteriorated to the vegetative state and she died on December 17, 1987.

Case 2: A 50-year-old female was admitted on March 5, 1985, with a 1-month history of headaches and vomiting. The neurological examination on admission revealed mild left hemiparesis. A CT scan showed a low-density area with ring enhancement in the right temporal lobe (Fig. 2A). On March 13, 1985, macroscopic total removal of the tumor and an anterior temporal lobectomy were performed. The histological examination revealed necrosis, pseudopalisading, endothelial proliferation, and in places, mitoses. The diagnosis was glioblastoma multiforme. She received focal irradiation of 60 Gy in 30 installments in a field of 11 × 10 cm from April 1 to May 14. Infusion of 100 mg of ACNU into the right internal carotid artery was performed on March 26 and May 24. She was discharged on May 28, 1985, without neurological deficit.

Six months after surgery, a CT scan showed an equivocal enhanced region in the surrounding area of operative deficit. A third intracarotid infusion of ACNU was performed on September 26, 1985. A CT scan obtained on November 14 revealed enhancement in the medial temporal lobe. Although she had no neurological signs or symptoms, she underwent excision of the medial and posterior temporal lobe on December 2. Histological examination showed coagulation necrosis and hyalinized vessel walls, without tumor cells.

Six months after the second operation, a CT scan revealed an enhanced lesion in the right temporal lobe and a low-density area in the right centrum semiovale (Fig. 2B). A repeat CT scan showed the enhanced areas changing from time to time (Fig. 2C). In May, 1987, 17 months after the second operation, she experienced memory loss, disorientation, and dyscalculia. A CT scan showed ventricular enlargement, and a metrizamide CT scan revealed ventricular reflux and delayed clearance of contrast medium. The cerebrospinal fluid protein level was 118 mg/dl. She underwent ventriculoperitoneal shunting, but no clinical improvement was obtained. She deteriorated in October, 1987, and a repeat CT scan showed an enhanced lesion in the corpus callosum and diffuse low-density areas in the bilateral white matter. She underwent resection of the enhanced lesion in the right temporo-occipital lobe. The tissue removed was histologically diagnosed as recurrent glioblastoma multiforme. However, coagulation necrosis and hyalinized blood vessel walls were seen in the surrounding white matter. Neurologically, she remained unchanged and is still in hospital.

Case 3: A 63-year-old female was admitted on September 28, 1984, because of a 3-month history of left hemiparesis. She had experienced tremor in the left hand from the beginning of 1984. Neurological examination on admission revealed mild consciousness disturbance (slight drowsiness) and left hemiparesis. A CT scan showed a round low-density area, without contrast enhancement, extending from the right basal ganglia to the thalamus. The central area of this lesion showed intense low density, suggesting necrosis (Fig. 3A). A needle biopsy was per-

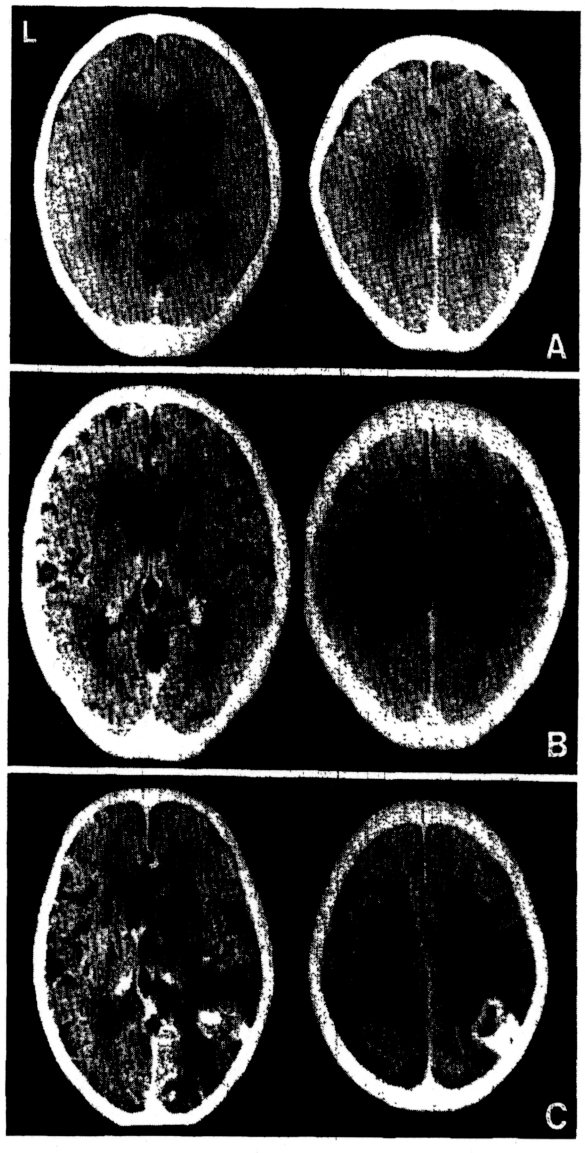

Fig. 3 Sequential postcontrast CT scans in Case 3. A: On admission, a round low-density area without contrast enhancement in the right basal ganglia and thalamus is shown. B: One year prior to readmission, no recurrence of tumor is seen. C: At readmission, ring enhancement in the right parieto-occipital region and a diffuse low-density area in the white matter are seen.

formed on October 17, 1984. Histological examination revealed the tumor consisting of astrocytes with anaplastic nuclei and mitoses. No necrosis or endothelial proliferation was found. The diagnosis was astrocytoma, grade 3. From October 22, she received focal irradiation of 60 Gy in 30 installments in a field of 11 × 8.5 cm. Intracarotid infusion of 100 mg of ACNU was performed on December 21, 1984 and January 8, 1985. Her condition improved and she was discharged on February 1, 1985, without neurological deficit.

She did well until March, 1987, when she complained of memory difficulty. She was readmitted on August 11, 1987, because of progressive incontinence, left hemiparesis, and left homonymous hemianopia. One year prior to readmission, a CT scan had shown no recurrence of tumor (Fig. 3B). However, a CT scan taken on readmission disclosed a low-density mass in the right basal ganglia with compression of the anterior horn of the lateral ventricle. Ring enhancement in the right parieto-occipital region and a diffuse low-density area in the ipsilateral white matter were also seen (Fig. 3C). A right occipital lobectomy was performed on December 7. The majority of the tissue removed was histologically diagnosed as glioblastoma multiforme. Coagulation necrosis in the surrounding white matter and thickened, hyalinized vessel walls were also seen. There was no neurological improvement after surgery.

Discussion

The histological diagnosis of Case 1 was radiation necrosis, while that of Cases 2 and 3 was recurrent tumor with radiation necrosis in the surrounding brain. All three cases had clinical symptoms similar to leukoencephalopathy and CT findings of diffuse low-density areas in the white matter. These clinical and radiological characteristics differed from the typical features of mere recurrent glioma. Even in our two cases with recurrent tumors, the surrounding brain showed coagulation necrosis and thickened, hyalinized blood vessels, a typical feature of radiation necrosis (Fig. 4). Considering the spongy degeneration of the white matter, it was difficult to differentiate the radiation necrosis and brain edema. However, thickened, hyalinized vessel walls suggested radiation necrosis.

Rubinstein[14] stated that the appreciation of radiation-induced changes in the brain adjacent to irradiated glioma is of considerable importance from both the clinical and pathological standpoints. It is difficult to determine a relationship of the tumor recurrence and radiation necrosis to the clinical manifestation of symptoms. However, the clinical courses of Cases 2 and 3 were relatively stable and long, and this suggests the considerable contribution of radiation necrosis.

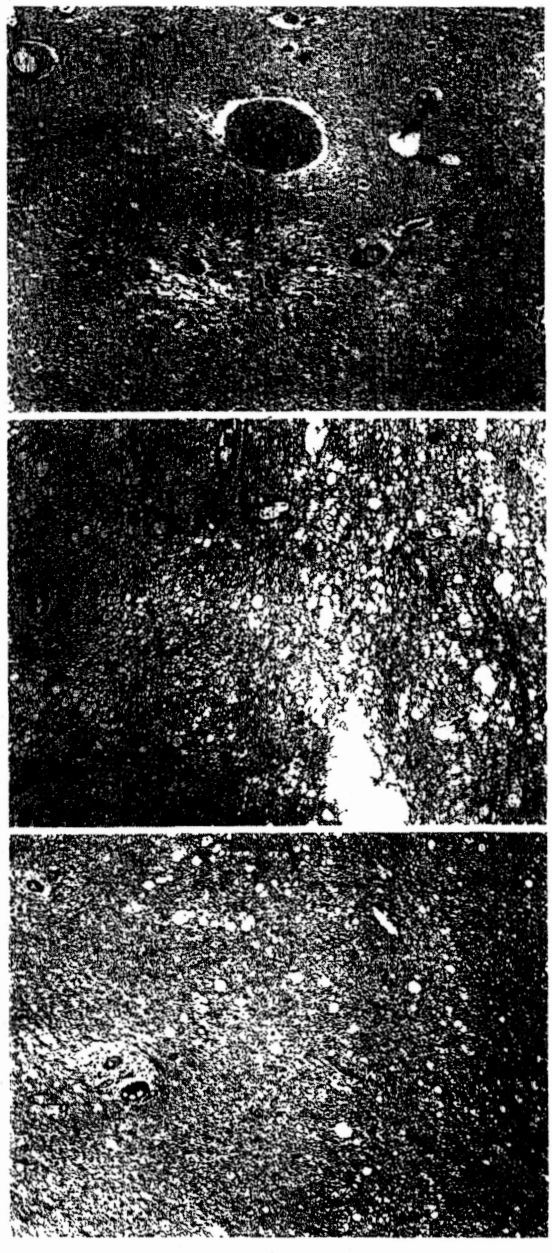

Fig. 4 Photomicrographs in Cases 1 (A), 2 (B), and 3 (C), showing coagulation necrosis and thickened, hyalinized vessels. HE stain, ×100.

Distinguishing between radiation necrosis and recurrent tumors in cases of glioma has been reported to be difficult.[2,5] In the present cases, CT and angiography did not provide helpful information for this purpose. Several investigators[4,13] reported the usefulness of the measurement of glucose metabolism by positron emission tomography (PET) in dis-

tinguishing radiation necrosis from tumor recurrence, but unfortunately this diagnostic tool is not readily available.

It is unclear whether or not the intracarotid ACNU infusion is responsible for occurrence of radiation necrosis. Lee *et al.*[10] reported a high incidence of leukoencephalopathy in patients receiving intracarotid infusion of cisplatin with or without BCNU [1,3-bis(2-chloroethyl)nitrosourea]. Mahaley *et al.*[12] observed that coagulation necrosis in the white matter occurred in five of 16 patients with anaplastic gliomas who received intra-arterial BCNU infusion and irradiation. Kleinschmidt-DeMasters[9] reported a patient with a grade 4 astrocytoma who had severe necrosis, predominantly in the white matter, confined to the territory of BCNU-infused artery. This case had received no other chemotherapy or irradiation, but microscopic examination at autopsy revealed coagulation necrosis and fibrinoid vascular necrosis, which were very similar to delayed radiation damage. Van der Kogel and Sissingh[16] have reported that anticancer drugs enhance the delayed vascular damage induced by irradiation. The central neurotoxicity of nitrosoureas has also been found in animal experiments by many investigators.[6] It should be noted that the dose of irradiation given to the malignant glioma patients in our hospital was between 60 and 66 Gy, but radiation necrosis was induced in three of 11 patients receiving intracarotid ACNU infusion. Moreover, the diffuse low-density areas in the white matter on CT scans were observed only on the infused side. These facts suggest that intracarotid ACNU infusion seems to modify the incidence of radiation necrosis.

The age of three patients described here were all over 50 years. There has been no discussion of the relationship between radiation necrosis and age. However, if we consider the main cause of delayed radiation necrosis to be vascular damage, we should more carefully perform a combination therapy with irradiation and intracarotid chemotherapy in aged patients.

Myelosuppression is a common side effect of ACNU, but was not observed in the present study. This is reasonable because ACNU is absorbed by the brain tissue in the first circulation and the effect on the whole body can be reduced. In contrast, central neurotoxicity could become a problem in the future with respect to the prolongation of patients' survival time.

Levin *et al.*[11] reported that the concentration of ACNU after intracarotid infusion was 2.8 times higher than that after intravenous infusion. We have also reported,[3,18] using PET, that the distribution of ^{11}C-labeled BCNU depends on the cerebral blood flow. Thus, the delivery of drugs is altered by the mode of administration and cerebral blood flow, especially in the tumor. Therefore, investigation of the optimum dose of ACNU and interval of intracarotid infusion in relation to cerebral blood flow is imperative to reduce the central neurotoxicity.

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