Vasculopathy of the Anterior Choroidal Artery Following Intra-arterial Chemotherapy
—Case Report—

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Abstract

A 40-year-old male, treated with radiotherapy and supraophthalmic intracarotid artery (ICA) ACNU infusion for glioblastoma in the right occipital lobe, developed cerebral infarction secondary to vasculopathy manifesting as hemiparesis 3 months after a second ICA injection. The initial diagnosis was focal neurotoxicity, but angiography revealed severe vasospasm of the anterior choroidal artery. The symptoms improved gradually with therapy for the vasospasm. Angiography is required to discriminate vasospasm and focal neurotoxicity as a complication of ICA injection of antineoplastic agents.

Key words: vasculopathy, intra-arterial infusion, ACNU

Introduction

The pharmacokinetic advantage of intra-arterial drug administration is firmly established, and many centers are using intracarotid artery (ICA) infusion of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) or 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3-nitrosourea (ACNU) and/or cisplatin to treat patients with malignant glioma. The uptake and binding of BCNU in brain tissue given by ICA infusion is two to five times greater than that achieved by intravenous administration, indicating that ICA administration would be particularly effective in patients with malignant brain tumor in a region of the brain supplied by a major intracranial artery. This advantage of ICA infusion is thought to outweigh the risk of morbidity due to selective arterial catheterization and short-term infusion, and is more effective and associated with fewer complications than intravenous administration. However, various complications have occurred, including ocular toxicity with visual loss, brain necrosis, and brain edema. The risk of ocular toxicity can be reduced by administration through a catheter placed distal to the origin of the ophthalmic artery.

We describe here a patient with malignant glioma who developed cerebral infarction due to vasculopathy of the anterior choroidal artery following supraophthalmic ICA infusion of ACNU.

Case Report

A 40-year-old male consulted a local hospital because of headache. Computed tomography (CT) showed abnormal findings, so he was referred to our clinic. Physical and neurological examination on admission revealed no abnormalities. CT of the brain revealed a round cystic neoplasm with diffuse enhancement involving the right occipital region, abnormal calcification in the left occipital region, and midline shift to the left (Fig. 1). Angiography showed a tumor stain of the right occipital tumor fed by the middle cerebral artery and anterior cerebral artery. The right occipital tumor was totally removed at the first operation. Histological examination of the surgical specimen demonstrated fibrillary glioma. One month...
later, the left occipital abnormal calcification was removed. Histological examination showed this was a cavernous angioma. The postoperative course was uneventful, and he was discharged without adjuvant therapy.

One year after discharge he had no symptoms, but follow-up CT revealed recurrence of the right occipital tumor. Reoperation was performed. Histological examination found malignant changes consistent with glioblastoma. He was then treated with chemoradiotherapy. Selective catheterization was carried out with a Tracker-18 catheter (Target Therapeutics, San Jose, Cal., U.S.A.). ACNU, 50 mg dissolved in 20 ml of saline, was administered through a catheter placed distal to the origin of the ophthalmic artery, using a syringe driven by an infusion pump (Terumo, Inc., Tokyo). Subsequently, he received radiation therapy (total dosage 50 Gy; 30 Gy whole brain and 20 Gy local irradiation) and interferon-beta administered intravenously. Two months after the first ICA injection of ACNU, he received a second injection in the same way. Subsequently, angiography showed a non-spastic, i.e. normal, anterior choroidal artery (Fig. 2 left). He was discharged with no neurological deficit.

Three months after the second ICA injection, he was readmitted with left hemiparesis. CT revealed a low-density area in the right internal capsule to the corona radiata, but no tumor recurrence (Fig. 3). The diagnosis was focal neurotoxicity, but angiography showed severe vasospasm of the anterior choroidal artery (Fig. 2 right). He was treated with low-molecular-weight dextran, hyperbaric oxygen therapy, sodium ozagrel, glycerin, and steroid. The symptoms improved gradually, and he was discharged with left mild hemiparesis after a

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**Fig. 1** CT scans on the first admission showing a round tumor with diffuse enhancement surrounded by a cyst in the right occipital region, abnormal calcification in the left occipital region, and slight midline shift to the left.

**Fig. 2** left: Right carotid angiogram at the second ICA injection of ACNU showing a non-spastic anterior choroidal artery (arrows). right: Right carotid angiogram on the third admission demonstrating severe vasospasm of the anterior choroidal artery (arrows).

**Fig. 3** CT scans on the third admission revealing a low-density area in the right internal capsule to the corona radiata.

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hospital stay of 2 months. Follow-up angiography 1 year after the second ICA injection demonstrated slight improvement in the severe vasospasm of the anterior choroidal artery. His left mild hemiparesis had improved.

Discussion

Di Chiro et al.\(^2\) reported four cases of cerebral necrosis after supraophthalmic ICA chemotherapy (BCNU), in two of which the necrotic area most profoundly affected obviously corresponded to the distribution territory of the lenticulostriate artery. Kapp and Sanford\(^4\) reported that three of 24 patients with malignant gliomas treated with ICA infusion of cisplatin and BCNU developed permanent neurological deficits after infusion, which were attributed to focal toxicity, but vasospasm could not be excluded.

In our patient, left hemiparesis appeared 3 months after the second ICA injection and CT revealed a low-density area in the right internal capsule to the corona radiata. We thought focal neurotoxicity had occurred due to ICA chemotherapy as in many previous reports, because the lesion was separate from the tumor and corresponded with the location of ICA injection. However, angiography demonstrated severe vasospasm of the anterior choroidal artery, and therapy for cerebral ischemia was effective in relieving the symptoms. Follow-up angiography also demonstrated a slight improvement of severe vasospasm. Therefore, the deficits in our case were thought to be due to vasospasm, resulting from vasculopathy.

A possible cause of these complications is non-uniform drug delivery due to intravascular drug streaming. Experiments with intra-arterial drug administration at infusion rates similar to those currently used clinically resulted in drug streaming with markedly heterogeneous drug deposition in the perfused hemisphere. This streaming phenomenon occurred in all selected anatomic areas after slow and medium rates of intra-arterial infusion.\(^9\) One consequence is that supraophthalmic drug infusion is more toxic to brain tissue than infusion into the cervical portion of the ICA.\(^7\) Blacklock et al.\(^1\) examined the distribution of ICA drug administration in theses monkeys. There was striking non-uniformity of drug delivery in the slow intra-arterial infusion group, with differences as large as 13-fold in anatomically contiguous areas. This may result in suboptimal drug levels in tumors and toxic levels at sites within the perfused hemisphere, but can be prevented by techniques that eliminate drug streaming.

Saris et al.\(^7\)\(^-\)\(^9\) found that streaming phenomena occurred in all selected anatomic areas after slow and medium rates of intra-arterial infusion,\(^9\) but that pulsed intra-arterial infusion during diastole provides a technically simple method for improving intravascular drug mixing, resulting in drug delivery to tissue capillaries that is proportional to blood flow. The magnitude of streaming can be substantially reduced or eliminated with diastolic-phased pulsatile infusion (DPPI). Therefore, DPPI should be considered when using intra-arterial infusion to assure uniform drug delivery to the brain. Other methods to improve mixing should be assessed for ICA administration of drugs, including increasing the infusion rates and improving tip design.\(^6\)

Chemotherapy-induced necrosis resembles the more familiar postradiation tissue damage histologically, with white-matter demyelination, focal coagulation necrosis, reactive gliosis, petechial hemorrhage, and prominent vasculopathic change.\(^7\) and may result in permanent neurological deficits.\(^9\) In contrast, vasospasm requires therapy for cerebral ischemia and circulation disturbance. Angiography is necessary to discriminate vasospasm and focal neurotoxicity even when onset of the complication is delayed.

References


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