Clinical Case Report

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Fatal contrast medium-induced adverse response to iohexol in carotid artery angioplasty

A case report

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Abstract

Rationale: Adverse drug reactions (ADRs) to iohexol occur infrequently and generally result in good outcomes. This report describes a 51-year-old man suffering from an ADR to iohexol (Omnipaque 300), which proved fatal.

Patient concerns: The patient was admitted to hospital due to intermittent dizziness over 2 years and transient numbness and weakness of the right limbs for 1 week. The patient was investigated using carotid artery angioplasty (CAA), during which the patient suffered a sudden disorder of consciousness and a tonic-clonic seizure leading to status epilepticus. After the CAA, the patient suffered from increasing cerebral edema volume.

Diagnoses: Results of digital subtraction angiography and computed tomography angiography performed at another hospital before the CAA suggested severe stenosis of the left internal carotid artery at the spinal C1 level. In the processes of intraoperative and postoperative CAA, the patient developed severe allergic reactions to the contrast agent including epilepsy, brain tissue edema, and renal failure, which were typical according to the 10th edition of the American College of Radiology Manual on Contrast Media (ACR Manual on Contrast Media, Version 10.3, 2017).

Interventions: The patient was treated with antiepileptic, antianaphylactic therapy, and control of blood pressure. Due to rapid and severe brain edema, a decompressive craniectomy was performed on the left side, but it was unsuccessful in reducing brain edema. Subsequently, the patient was started on continuous renal replacement therapy for progressive renal dysfunction.

Outcomes: Despite the use of a variety of medical and surgical interventions, it was not possible to control the patient's condition, which gradually declined leading to death, 7 days post-CAA.

Lessons: To the authors' knowledge, this represents the 1st case of fatal contrast-induced ADR to iohexol during CAA. Although a variety of preoperative tests for iohexol allergy were performed according to recommendations from the ACR Manual on Contrast Media (Version 10.3, 2017), severe complications related to iodized contrast agent still occurred. If the ADR had been recognized sooner and decompressive craniectomy and continuous renal replacement therapy were applied earlier, it would have improved the patients' prognosis.

Abbreviations: ACR = American College of Radiology, ADRs = adverse drug reactions, AI = arterial injection, CAA = carotid artery angioplasty, CRRT = continuous renal replacement therapy, CT = computed tomography, CTA = computed tomography angiography, DSA= digital subtraction angiography, ICH = intracerebral hemorrhage, IV = intravenously injected, LICA = left internal carotid artery, LVA = left vertebral artery, MRI = magnetic resonance imaging.

Keywords: adverse drug reaction, iodinated nonionic contrast medium, iohexol

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ZY and RL contributed equally to this work.

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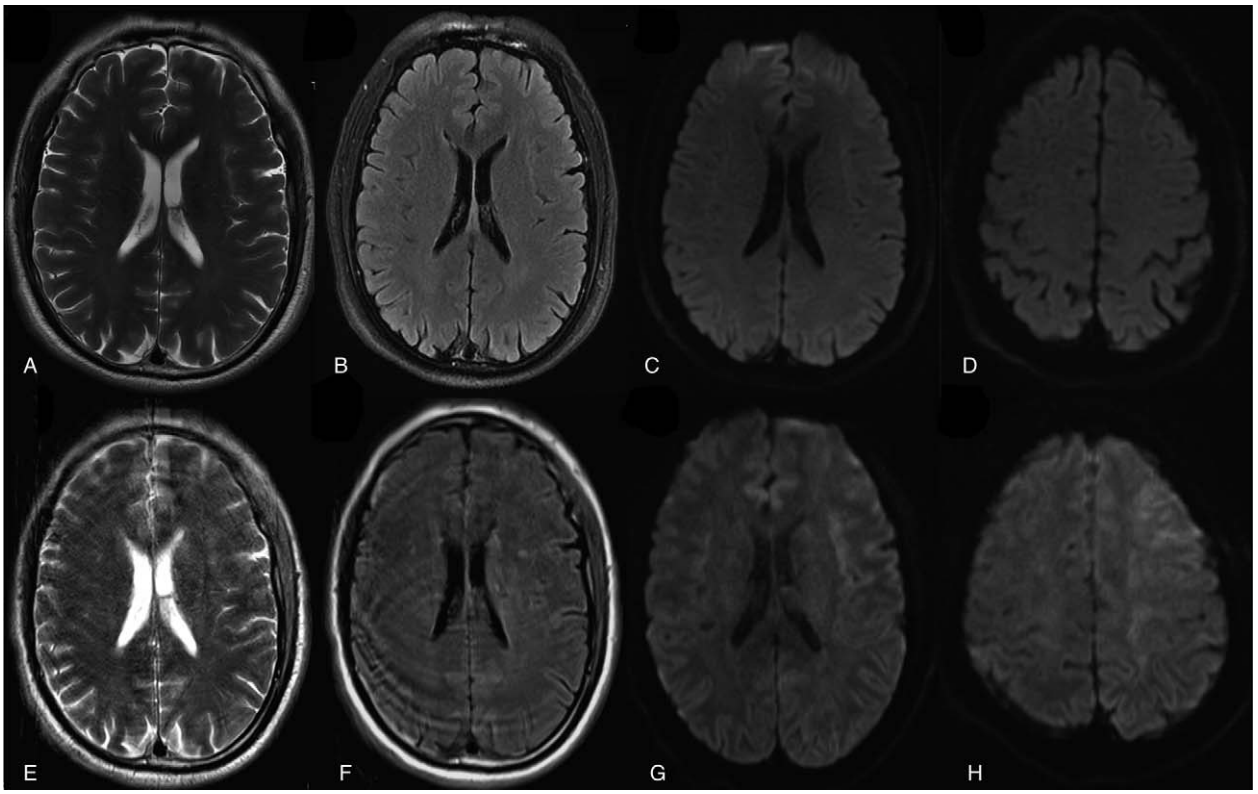

Figure 1. Head magnetic resonance imaging (MRI) before and after operation. (A–D) Inspection of head MRI before the operation showed no obvious abnormity. (E–H) After the operation, MRI showed that fissures, sulci, and gyri have abnormal magnetic memory signals in the regions indicated by arrows.

1. Introduction

Iohexol (Omnipaque 300; GE Healthcare, Princeton, New Jersey) is a water-soluble, nonionic, low-osmolarity contrast agent, which does not inhibit glucose metabolism and is widely used in various vascular interventions. Compared with traditional high-osmolality contrast agents, iohexol exhibits less adverse effects[1] and fewer effects on the blood-brain barrier and neurologic function.[2] Although the safety and efficacy of iohexol administration have been verified by a large amount of clinical trials,[3] the incidence of adverse drug reactions (ADRs) have been reported continually in the literature. ADRs to iohexol fall into 3 categories: allergic-like reactions, physiologic (toxic) reactions, and delayed adverse events. Allergic-like reactions present with urticaria, laryngeal angioedema, arrhythmia, hypotension, anaphylactic shock, and can result in death.[4] Symptoms of physiologic reactions are nausea, flushing, headache, hypertension, arrhythmia, and seizures. Delayed hypersensitivity reactions of iohexol occur from 1 hour to 1 week after administration, and most patients show cutaneous manifestations and renal failure.[5] While serious ADRs to intravenous (IV) iohexol are rare, with an historical rate of approximately 4/10,000 (0.04%),[6] fatal reactions have been reported.[3,7,8] Reports about fatal contrast-induced adverse event to iohexol during digital subtraction angiography (DSA) are rare. This report describes a 51-year-old man suffering from an ADR to iohexol which proved fatal.

2. Case presentation

2.1. History and examination

A 51-year-old man with a history of hypertension, diabetes, and coronary artery disease was admitted to the hospital due to intermittent dizziness over 2 years, and transient numbness and weakness in right limbs for 1 week. Results of nervous system and physical examination were normal. After admission, the patient was subjected to head magnetic resonance imaging (MRI, Fig. 1A–D). Mild stenosis in the V4 segment of the left vertebral artery (LVA) and severe stenosis in the C1 segment of the left internal carotid artery (LICA) were confirmed from computed tomography angiography (CTA; Fig. 2A–C), and DSA which was performed by another hospital 1 year ago (Fig. 2D, E). Our strategy was therefore to expand the LICA stenosis to prevent further transient ischemic attack or stroke.

2.2. Carotid artery angioplasty

The patient received oral aspirin (100 mg/d) and clopidogrel (75 mg/d) for 5 days, after which a left CAA was performed under local anesthesia. The patient was injected intravenously with dexamethasone (10 mg) and intramuscularly with phenobarbital (100 mg) half an hour before the CAA. A total of 5000 IU of IV heparin was administered to achieve a periprocedural activated clotting time of 300 seconds. Thereafter, an 8-Fr guiding sheath was advanced into the left common carotid artery and the stenosis was crossed with a 5-mm Emboshield NAV6 Embolic Protection System (Abbott Vascular, Santa Clara, CA). Subsequently, because of plaque elastic retraction, the stenosis was predilated twice with a 5×30-mm rapid-exchange balloon catheter (Abbott Vascular) at a pressure of 8 and 12 atm (Fig. 3A–D). Vital signs were stable during the dilatation (blood pressure, 124/75 mm Hg; pulse rate, 62 beats/min; respiratory rate, 12 breaths/min; O_2 saturation, 95% in room air).

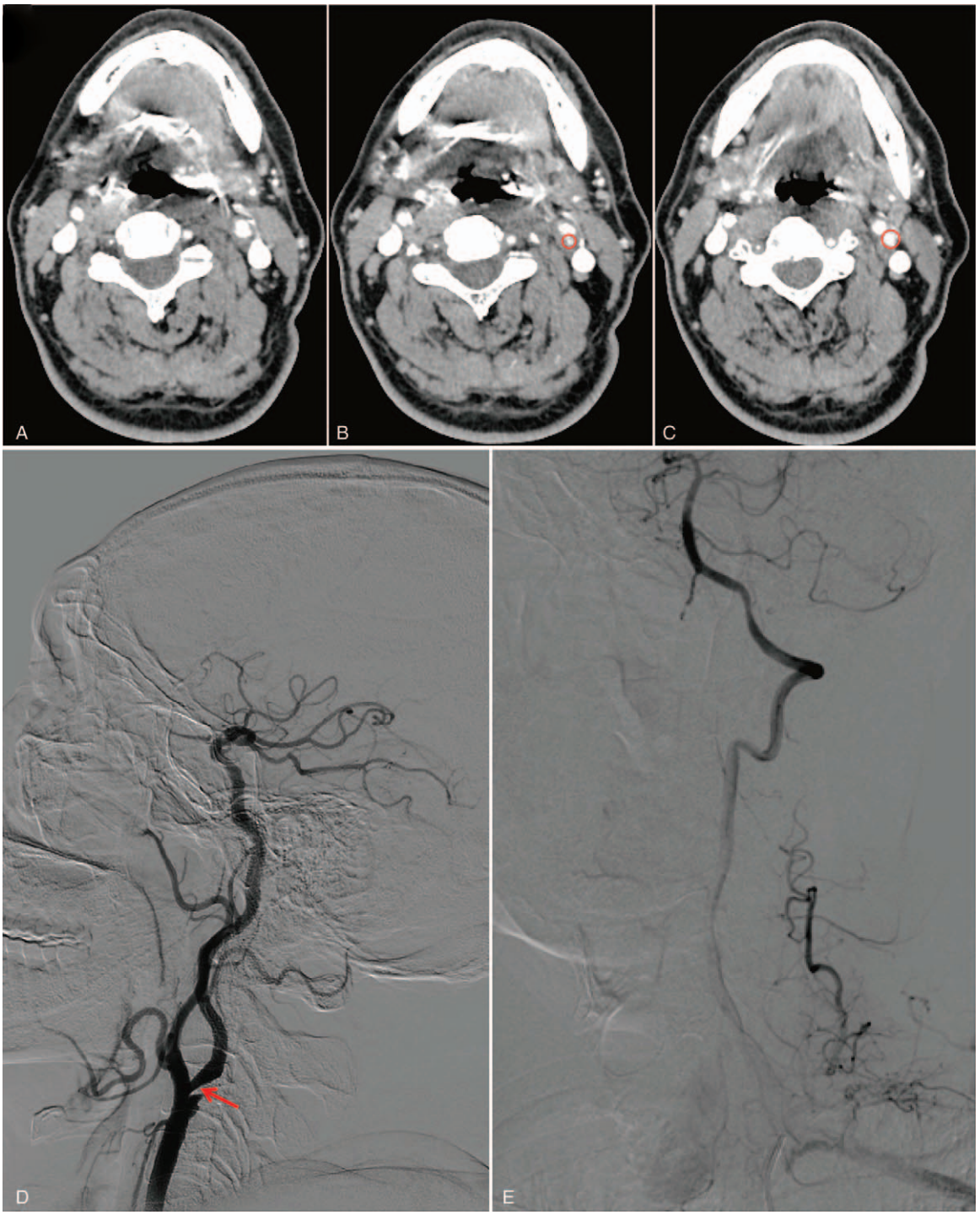

Figure 2. Total cerebral artery imaging. (A–C) Computed tomography angiograph showing cross-sectional image of the left internal carotid artery at cervical level 1. Circled regions indicate severe stenosis. Digital subtraction angiography of the left internal carotid artery (D) showed moderate to severe stenosis, and of the V4 segment of the left vertebral artery (E) showed mild stenosis.

During these procedures, <50 mL of iohexol (Omnipaque 300; GE Healthcare) was used (5–8 mL/injection ×6 times). Five minutes after the balloon dilatation, the patient started to suffer from tonic-clonic seizure, unconsciousness, and before the stent was inserted, the eyes were staring to the right side. Pupils' diameters were 4 mm bilaterally with light reflex bluntness. Electrocardiography was normal. To stop the seizure, IV diazepam was administered at a dose of 20 mg, after which an arteriogram was performed. There was no vasospasm, embolism, or contrast agent extravasation in LICA or LVA compared to images taken before dilatation (Fig. 3E–I). The head CT showed no cerebral or subarachnoid hemorrhage. One hour later, the patient showed impaired consciousness, with a Glasgow Coma scale score of 7 (eye opening: 2, best verbal response: 1, and best

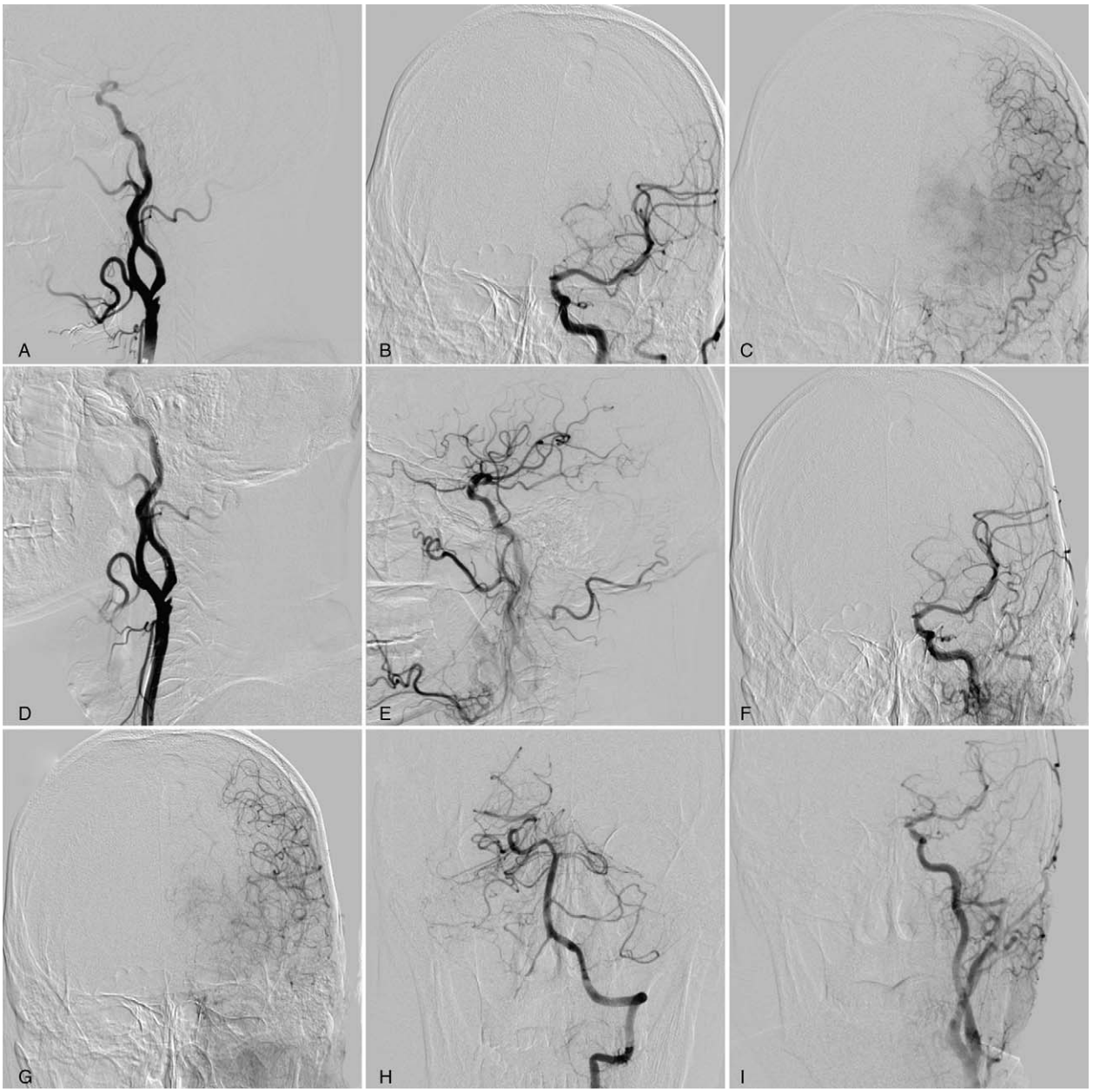

Figure 3. Cerebral angiography. (A–C) Angiography of the left internal carotid artery preoperation and (D–I) digital subtraction angiography after balloon dilation.

motor response: 4). The neurologic examination revealed right hemiplegia with manual muscle power grade 0, and intermittent clonic seizures of the left limb.

2.3. Operation

Under sedation, the patient was subjected to head MRI using a T2 DWI-FLAIR sequence. This showed multiple patchy high signals in the left frontal lobe, the area surrounding the lateral ventricle, bilaterally in the parietal lobe and in the white matter (Fig. 1E–H). To avoid epileptic convulsions, midazolam was administered continuously. Reduced glutathione, esomeprazole sodium, and 20% mannitol were administered intravenously as well as the phenobarbital sodium, diazepam, and methyl prednisolone hormone. Sodium nitroprusside was continuously pumped to try to reduce the blood pressure below 140/90 mm Hg. After the operation, vital signs remained stable (body temperature, 36.6°C; pulse, 90/min; breathing, 18/min; blood pressure, 114/82 mm Hg).

However, 19 hours after CAA, the left pupil size became 5 mm, light reflex disappeared, and computed tomography (CT) of the head implied brain tissue edema, midline shift and the formation of cerebral hernia (Fig. 4A–C). Decompressive craniectomy was immediately performed on the left side of the skull. After the operation, a head CT scan was reexamined. The cerebral edema was still increasing seriously (Fig. 4D–F). Diameters of both pupils were 5 mm, with no light pupillary reflex or spontaneous breathing, accompanied by uric acid 463.0 μmol/L, creatinine 252.0 μmol/L, white blood cell count 22.53×10^9/L, neutrophil count 21×10^9/L, blood sugar 43.40 mmol/L. As a result of progressive renal dysfunction, we treated the patient with

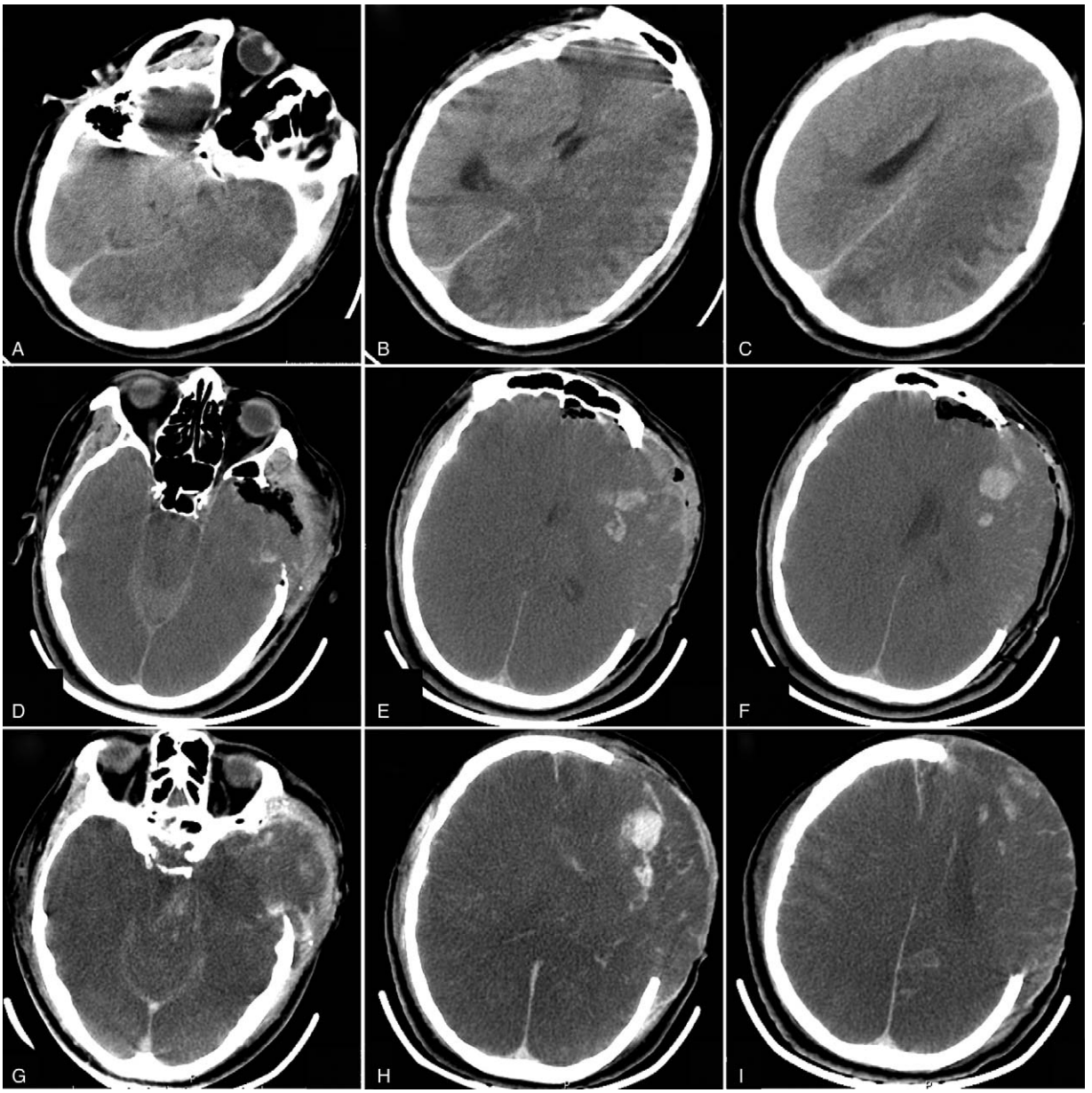

Figure 4. Computed tomography scan after carotid artery angiography. (A–C) Nineteen hours after the balloon dilatation, the left frontal, temporal, and parietal lobes showed low-density shadows and brain sulci and gyri become shallow. (D–F) Twenty-six hours after the balloon dilatation, computed tomography scans showed a low-density shadow on the left hemisphere, where sulci and gyri of the brain disappear and the midline shifts. (G–I) On the 6th day postoperation, acute diffuse brain swelling, subarachnoid hemorrhage, and cerebral hemorrhage appear in the left frontal and temporal lobes.

continuous renal replacement therapy. Five days after the decompressive craniectomy, the head CT scan revealed that the trend of diffuse edema in brain tissue remained uncontrollable, associated with subarachnoid hemorrhage and intracerebral hemorrhage (ICH) (Fig. 4G–I). Finally, 7 days postoperation, the patient died.

3. Discussion

The incidence of ADRs to nonionic iodinated contrast media is rare. Mortelé et al[3] and Cochran et al[7] have reported rates in adults of 0.7% and 0.3%, respectively. Similarly, Wang et al[9] reported 0.6%, with 2% of these resulting in severe events. While severe and moderate complications related to iohexol have been reported,[9] to the best of our knowledge, fatal reactions during CAA have not been reported up to now. Before the CAA, both DSA and CTA were completed by another hospital, and the patient denied any history of allergy to contrast media. During the CAA, we speculated as to whether the vasospasm, embolism, and hemorrhage had occurred at the beginning of the procedure. However, cerebral vascular obstruction was not found in the results of the DSA. Additionally, we excluded cerebral blood flow hyperperfusion after examining the head MRI and CT scan. These examinations could not explain the total cerebral diffuse edema, acute renal failure, and especially the right hemisphere edema. We then inquired as to whether ADRs to iohexol bring about allergic-like reactions, physiologic (toxic) reactions, or delayed adverse events.

Similar ADRs such as total diffuse edema and ICH have been reported in animal experiments.[10] In individual cases, manifestations include tonic-clonic seizures, coma, total cerebral edema, acute renal failure, and similar head MRI images to those reported by Gollol Raju et al.[11] We highly suspected iohexol-induced neurotoxic hypersensitivity.[5] This is supported by the fact that when iohexol was injected into the patient's LICA, the patient showed signs of seizure with the eyes staring to the right, suggesting left hemisphere involvement. This could have resulted from neurotoxic damage to the cortex induced by iohexol.[12] Physiologically, the osmotic pressure of iohexol is lower than that of 1st-generation contrast agents, which have an osmolality of around 500 to 700 mOsm/kg. This is twice the plasma osmotic pressure, and therefore increases the risk of high vascular pressure and tissue edema. It has been reported that there are higher ADR rates when iohexol is administered intravenously compared to arterial injection (AI). However, whether this conclusion applies to all 2nd generation-iodinated nonionic contrast media still needs to be clarified.

We searched PubMed from 1982 to 2018 for clinical trials on ADRs to iodinated nonionic contrast medium. Firstly, we searched ([iodinated nonionic contrast medium] OR iomeprol OR iopamidol OR iohexol OR iopromide OR ioversol) AND (adverse reactions) as the retrieval type, and a total of the 171 papers were returned. Secondly, we excluded nonspecific contrast agents, vague injection methods, samples of <100, not adult, non-English literature, or inexact ADRs. Finally, 38 papers about IV-related ADRs and 18 papers about AI-related ADRs were selected, and we analyzed the incidence of ADRs between IV and AI using a *t* test. There was a significant difference in the incidence of ADRs between the 2 groups ($P=.012$) (Supplementary Tables S1 and S2, http://links.lww.com/MD/D161). The results suggested a higher risk of using AI to administer iodinated nonionic contrast medium. This may have been one of the risk factors that caused adverse reactions in this patient.

This study lacks pathologic results and is only a case report. At present, there are few studies published about death caused by iohexol during CAA, the pathogenesis and mechanisms of which are still unclear. Further research is needed to investigate this phenomenon.

4. Conclusion

Adverse reactions to iohexol are rare, among which, few are moderate or severe. Even with sufficient nursing measures such as intensive blood pressure control, antiplatelet drugs and testing for allergies of iohexol, the occurrence of adverse reactions was still not predicted. Furthermore, we conclude that the risk of ADRs from AI is higher than that from IV. Given the potential adverse reactions to iohexol, further consideration of the risk of malignant cerebral edema is required during DSA.

Author contributions

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Funding acquisition: Rong Yin.
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