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Anaphylaxis after Idarucizumab Infusion

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Dear Editor,

Dabigatran etexilate is commonly used for the prevention of stroke in patients with nonvalvular atrial fibrillation, and is as effective as and safer than warfarin.[1] However, there is no reversal agent despite serious outcomes of bleeding complication,[2] with hemodialysis being the only reliable option. Idarucizumab has recently been developed as a genuine reversal agent of dabigatran, with demonstrated efficacy in clinical trials.[3] The reported adverse events of idarucizumab are only mild, and are considered acceptable without requiring discontinuation.[3] Here, we present the first report of an anaphylactic reaction after the infusion of idarucizumab.

A 77-year-old woman was brought to the emergency room. She had history of stroke but recovered well before this presentation, which was with left-side weakness, drowsiness, and loss of verbal fluency. She exhibited atrial fibrillation and was taking dabigatran at 110 mg twice daily. She had no history of atopic disease or drug allergy. At the emergency room, her initial blood pressure was 142/80 mm Hg and pulse rate was 79 beats/min. The laboratory findings for her coagulation status were also normal. Brain CT showed a hemorrhage with multiple fluid levels in the right temporoparietal area (Fig. 1A). A mild midline-shift was observed in the supratentorial area (Fig. 1B), but, there was no evidence of brainstem compression.

Mannitol was immediately administered at a dose of 1 g/kg. She was enrolled in a clinical trial[4] in which a 50-mL bolus containing 2.5 g of idarucizumab was infused. Four minutes after administering idarucizumab, her consciousness decreased with vomiting and skin rash (Fig. 1C and D) and her oxygen saturation dropped below 80% despite oxygen being supplied via a face mask at 15 L/hour. Her blood pressure dropped to 77/40 mm Hg and her pulse rate increased to 110 beats/min. We immediately stopped the administration of idarucizumab, and epinephrine and norephinephrine were administered with full drips of normal saline. The blood pressure and oxygen saturation normalized at about 6 hours after administering idarucizumab. The size of the hemorrhage did not change, and there was no perilesional edema in follow-up brain CT. The findings of an electrocardiogram, echocardiography, chest X-ray, blood culture, and blood tests for inflammatory markers were also normal. There was no seizure-like activity during hospitalization and no evidence of seizure on electroencephalography. She was restored to her initial neurological status without further deficits.

Idarucizumab is a kind of monoclonal antibody that may provoke severe infusion reactions, including anaphylaxis.[5] To the best of our knowledge, this is the first report of anaphylaxis potentially related to idarucizumab. There was no direct laboratory evidence to support anaphylaxis, but the patient met all the clinical criteria for an anaphylaxis diagnosis,[6] and other possible causes of hypotension and desaturation were excluded mostly based on clinical and laboratory findings (e.g., seizure, septic or cardiogenic shock, and hypotension caused by brain lesions). The cerebral hemorrhage responsible for the patient being hospitalized did not lead to this event and follow-up brain CT did not detect any changes. Additionally, the possibility of hypotension resulting from the progression of brain lesions was excluded by the im-

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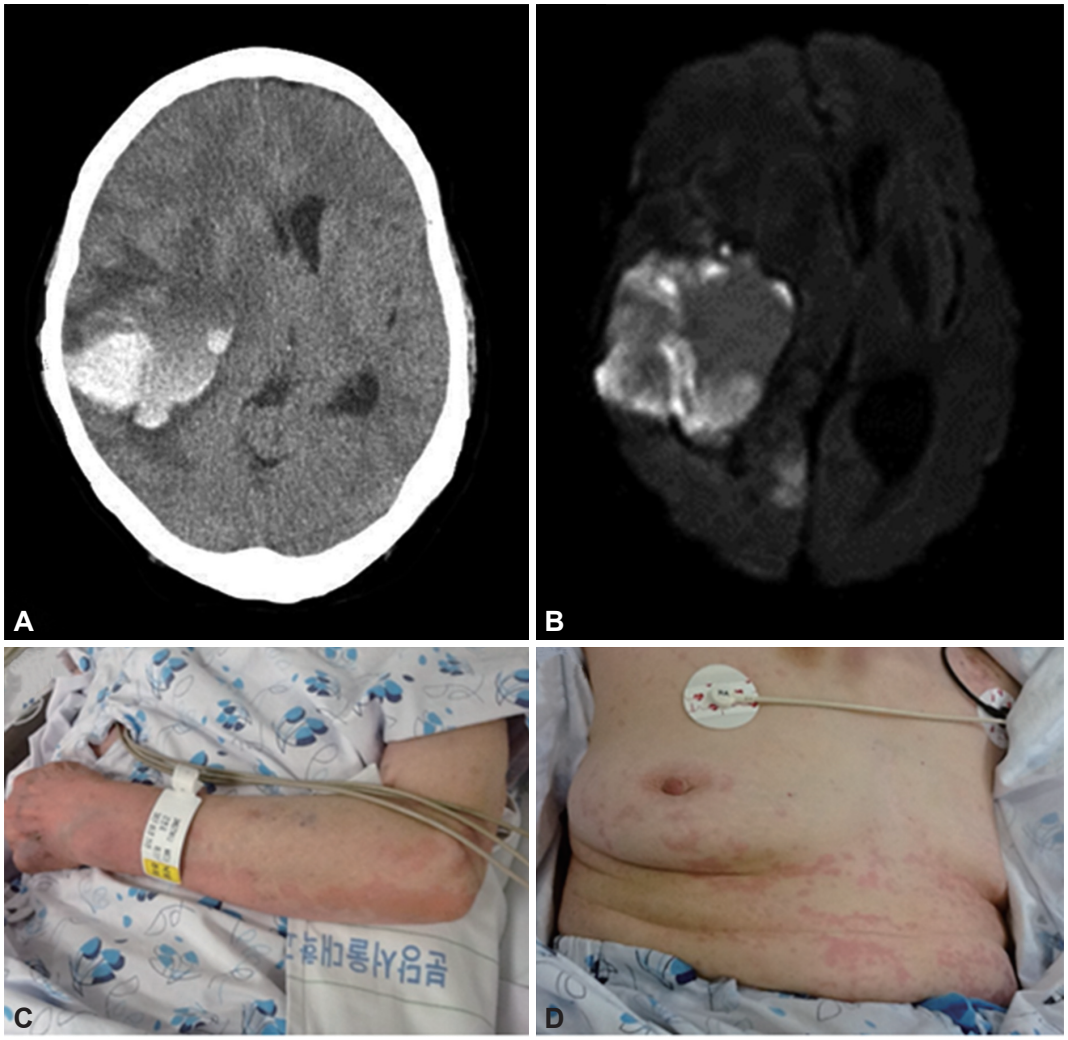

Fig. 1. Brain and skin lesions after the anaphylactic event. A: Initial brain CT. B: Diffusion weighted imaging showed a hemorrhage with multiple fluid levels in the right temporo-parietal area. C and D: A skin rash developed on the trunk and both upper limbs immediately after the infusion of idarucizumab.

mediate restoration of her neurological status. It therefore seems reasonable to attribute the hypotensive episode to anaphylaxis.

In conclusion, we have reported the first case of anaphylaxis after using idarucizumab. Careful monitoring when infusing idarucizumab is recommended.

Conflicts of Interest

H.-J.B. is involved as the principal investigator, a member of the steering committee, and site investigator of multicenter clinical trials and clinical studies sponsored by Otsuka Korea, Bayer Korea, Boehringer Ingelheim Korea, Handok Pharmaceutical Company, SK Chemicals, Pfizer, ESAI-Korea, Daewoong Pharmaceutical, Daichi Sankyo, AstraZeneca Korea, Dong-A Pharmaceutical, and Yuhan Corporation. H.-J.B. has served on the scientific advisory boards for Bayer Korea, Boehringer Ingelheim Korea, BMS Korea, and Pfizer Korea; served as a consultant for YuYu Pharmaceutical, Daewoong Pharmaceutical and Korean Drug and received modest lecture honoraria from AstraZeneca Korea, Bayer Korea, BMS Korea, Coviden Korea, Esai Korea, Daichi Sankyo Korea, and Sanofi-Aventis Korea.

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Boehringer Ingelheim is the sponsor of the RE-VERSE AD study and has reported this event to health authorities worldwide and informed all known related investigators. Other possible explanations of this event are being considered.

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