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Multiple Cerebral Hemorrhages in a Patient Receiving Lecanemab and Treated with t-PA for Stroke

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TO THE EDITOR:

The results of the phase 3 trial of the anti–amyloid-β drug lecanemab for the treatment of early Alzheimer's disease, reported in the *Journal* by van Dyck et al.,[1] have suggested a beneficial effect on cognition scores and daily activities over a period of 18 months. An extension phase of the trial is ongoing. We report a case of numerous acute intracerebral hemorrhages that developed after treatment with intravenous tissue plasminogen activator (t-PA) for acute ischemic stroke syndrome in a patient who received three doses of intravenous lecanemab.

A 65-year-old patient who was homozygous for the *APOE* ε4 allele and was in the early stages of cognitive decline presented to an emergency department 30 minutes after the acute onset of aphasia and left gaze preference due to an ischemic stroke. The patient had participated in the randomized phase of the trial of lecanemab, during which the treatment assignment is not known, followed by participation in the open-label phase, in which three intravenous lecanemab infusions were received (one infusion every 2 weeks), with the latest infusion administered 4 days before the stroke. Magnetic resonance imaging (MRI) of the head that had been performed 81 days before the stroke showed mild small-vessel disease, with no microhemorrhages, edema, or amyloid-related imaging abnormalities (Figs.

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S1 and S2 in the Supplementary Appendix, available with the full text of this letter at NEJM.org), and computed tomography (CT) performed just before t-PA administration showed hypodensities in the left temporal–parietal regions and a distal left middle cerebral artery branch occlusion but no hemorrhage. (Further clinical information is provided in the Supplementary Appendix.)

The patient had no contraindications to thrombolysis (blood pressure, 163/84 mm Hg; platelet count, 256×10^3 per microliter; international normalized ratio, 1.0; fibrinogen level, 304 milligrams per deciliter) and was within the conventional time window for thrombolysis. After intravenous administration of an 8-mg t-PA bolus and 50 minutes into the t-PA infusion (when 65.7 mg of the total dose of 76 mg had been administered), hypertension suddenly developed (blood pressure, 250/111 mm Hg) and the t-PA infusion was stopped. A CT scan showed extensive, multifocal intraparenchymal hemorrhages. There was no systemic bleeding. Cryoprecipitate and tranexamic acid were administered. The patient had global aphasia and severe agitation; frequent, nonconvulsive seizures seen on electroencephalography were treated successfully with multiple antiseizure medications. Three days after presentation for the stroke, the patient underwent endotracheal intubation. MRI of the head showed acute right thalamocapsular infarction and innumerable multifocal cortical and subcortical hemorrhages with surrounding edema (Fig. 1A and 1B). The patient was treated with comfort measures at the request of the family and subsequently died. The autopsy showed extensive multifocal intraparenchymal hemorrhages, cerebral amyloid angiopathy, “high” Alzheimer’s disease neuropathologic changes,[2] and diffuse histiocytic vasculitis with necrotizing vasculopathy involving amyloid deposition within (but not outside) the blood-vessel walls (Fig. 1C, 1D, and 1E).

The extensive number and variation in sizes of the cerebral hemorrhages in this patient would be unusual as a complication of t-PA solely related to cerebrovascular amyloid. The findings raise the possibility of cerebral hemorrhages and necrotizing vasculopathy associated with t-PA infusion in a patient with cerebrovascular amyloid who had received lecanemab.

References

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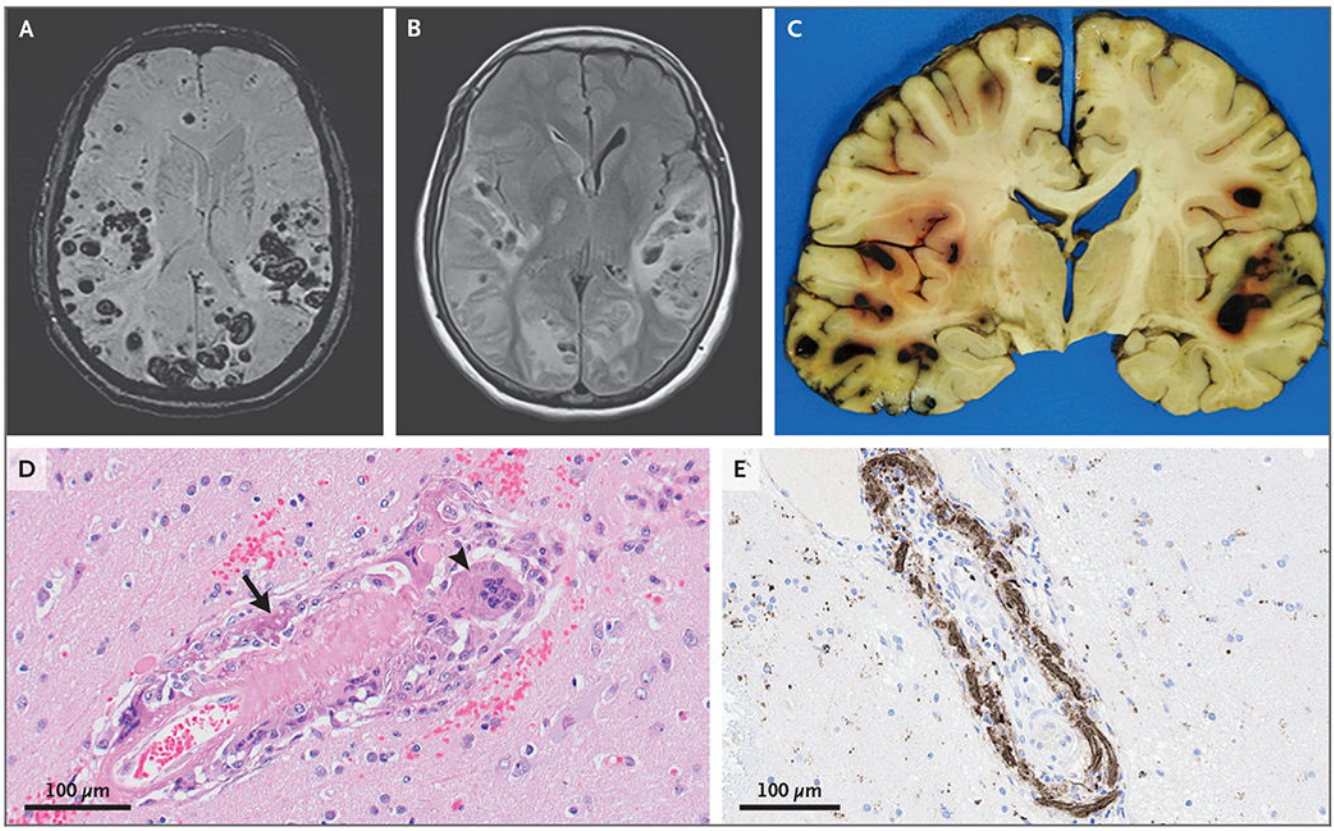

Figure 1. MRI and Neuropathological Findings.

Panel A shows a magnetic resonance imaging (MRI) susceptibility-weighted sequence in which extensive multifocal cortical intraparenchymal hemorrhages are visible. Panel B shows an MRI T2 fluid-attenuated inversion recovery (FLAIR) sequence in which extensive cerebral cortical and subcortical edema is seen in association with multifocal hemorrhages, as well as a right thalamocapsular acute ischemic infarct. Panel C shows a coronal section of the formalin-fixed cerebral hemispheres in which numerous cortical intracerebral hemorrhages are present. Panel D shows a representative hematoxylin and eosin–stained section of the left parietal cortex, in which a blood vessel with probable amyloid angiopathy and histiocytic infiltration of the blood-vessel wall is visible. Multinucleated histiocytes (arrowhead) and focal fibrinoid degeneration (arrow) are present. Panel E shows amyloid-β immunohistochemical staining of a cortical blood vessel affected by cerebral amyloid angiopathy. The vascular amyloid is fragmented, and the blood-vessel wall shows infiltration by lymphocytes and histiocytes.