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Acute Ischemic Stroke Caused by Intracranial Atherosclerosis Associated With Lorlatinib-Induced Dyslipidemia

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Dear Editor,

Lorlatinib is a novel third-generation inhibitor of anaplastic lymphoma kinase (ALK) used to treat non-small cell lung cancer (NSCLC). The most common adverse effect associated with lorlatinib use is dyslipidemia, which occurs in up to 80% of users.[1] Although dyslipidemia is a well-known risk factor for atherosclerosis,[2] the effect of lorlatinib on atherosclerotic stroke is unclear. We report a case of acute ischemic stroke caused by severe intracranial atherosclerosis associated with lorlatinib-induced dyslipidemia.

A 65-year-old male visited the emergency department after 3 days of right hemiparesis. The patient had histories of hypertension and dyslipidemia but no other cardiovascular risk factors. He had ALK-positive NSCLC with multiple brain metastases. The patient had undergone whole-brain radiation therapy 4 years ago and had been taking lorlatinib 100 mg daily. Before commencing lorlatinib treatment, his lipid profile was as follows: total cholesterol, 179 mg/dL; triglycerides, 115 mg/dL; high-density lipoprotein cholesterol (HDL-C), 36 mg/dL; and low-density lipoprotein cholesterol (LDL-C), 139 mg/dL. Significant dyslipidemia developed after 1 month of lorlatinib (total cholesterol, 351 mg/dL; triglyceride, 282 mg/dL; HDL-C, 42 mg/dL; and LDL-C, 290 mg/dL). During 11 months of treatment with rosuvastatin 20 mg doses, LDL-C levels remained above 160 mg/dL. Ezetimibe 10 mg was then additionally prescribed.

After 14 months of lorlatinib treatment, the patient suddenly developed right hemiparesis. A neurological examination revealed mild aphasia and right hemiparesis with Medical Research Council (MRC) grade 2. After hydration, the motor power improved to MRC grade 4. Brain magnetic resonance (MR) imaging revealed an acute cerebral infarction in the left middle cerebral artery (MCA) territory and multiple metastasis (Fig. 1A). There was severe stenosis of the left MCA (Fig. 1B) and delayed cerebral perfusion in the left MCA territory (Fig. 1C). There was no steno-occlusion in the left carotid artery. The lipid levels of total cholesterol, triglycerides, HDL-C, and LDL-C were 183, 174, 30, and 145 mg/dL, respectively. The other laboratory parameters were unremarkable except for slight elevation of D-dimer (0.86 μg/mL). There were no high-risk cardioembolic sources on transthoracic echocardiography and 24-hour Holter ECG monitoring. Therefore, we presumed that the etiology of the stroke was large artery atherosclerosis, and the relevant artery was the left MCA. The patient was treated with aspirin. Because of the high lipid levels despite treatment with high-intensity statin and ezetimibe, subcutaneous evolocumab 140 mg was prescribed.

Four days after admission, right hemiparesis aggravated to MRC grade 2, and left-sided eyeball preference and global aphasia occurred. Follow-up diffusion-weighted imaging did not reveal any new ischemic lesions. However, near occlusion of the left MCA was observed on MR angiography (Fig. 1D). After mechanical thrombectomy and subsequent 24-hour tirofiban infusion, the blood flow in the left MCA improved to mTICI 2b (Fig. 1E and F). Intracranial artery stenting was not performed due to the possibility of bleeding in the brain metastasis. Follow-up MR imaging after 1 day of mechanical thrombectomy revealed a newly

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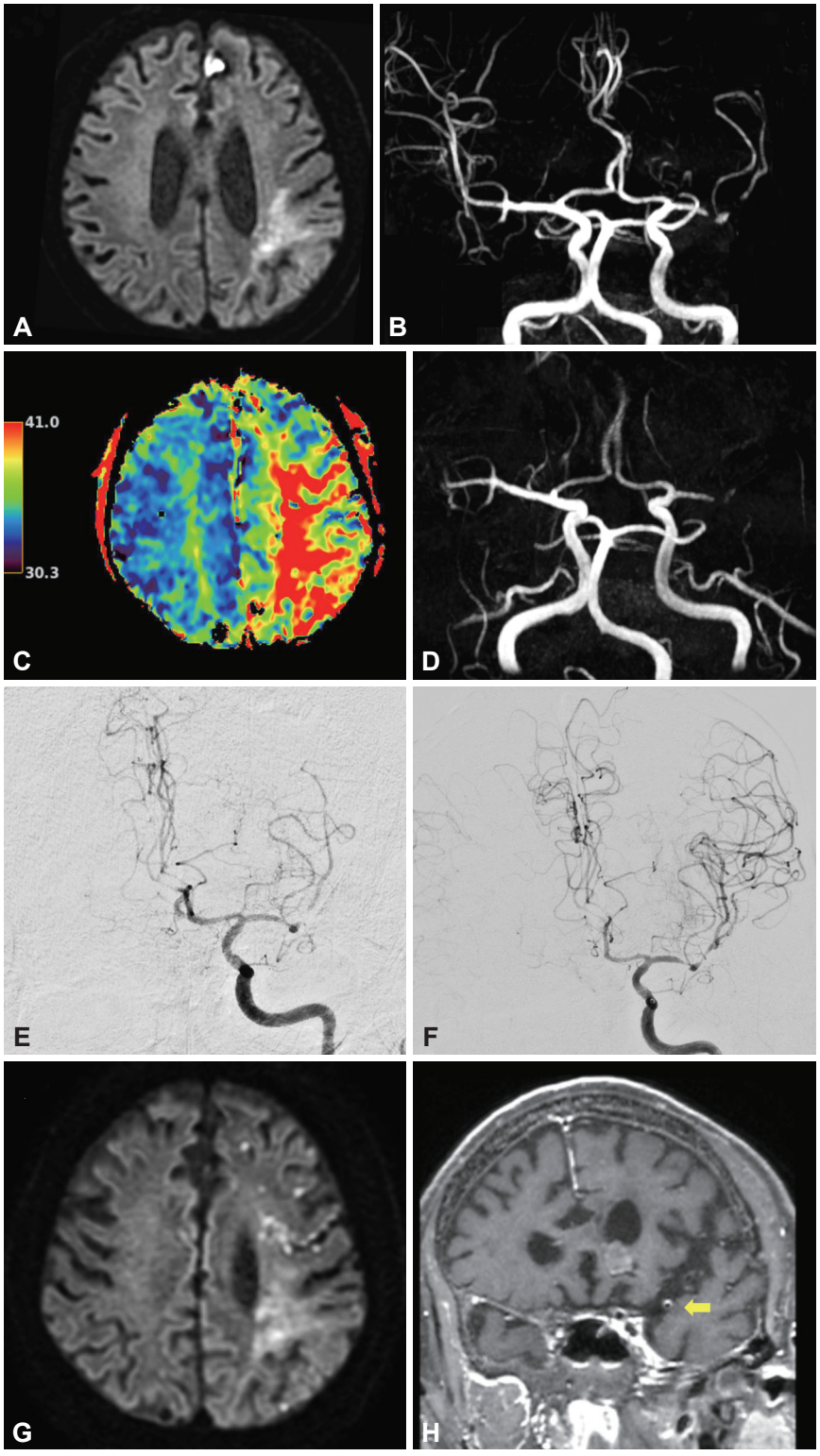

Fig. 1. Brain imaging of a patient with acute ischemic stroke that occurred after long-term lorlatinib use. A: Brain magnetic resonance (MR) imaging indicating acute cerebral infarction in the left middle cerebral artery (MCA) territory and a left frontal metastatic lesion. B: MR angiography revealing severe stenosis in the left MCA. C: Perfusion MR imaging revealing delayed cerebral perfusion in the left MCA territory. D: Follow-up MR angiography after symptom aggravation indicating near occlusion of the left MCA. E: Cerebral angiography demonstrating reduced blood flow in the left MCA territory (mTICI 2a). F: Improvement in blood flow (mTICI 2b) after mechanical thrombectomy. G: Diffusion-weighted image after mechanical thrombectomy revealing newly developed multifocal cerebral infarction in the left MCA territory. H: Atherosclerotic plaque (arrow) of the left MCA on vessel wall MR imaging.

developed multifocal cerebral infarction in the left MCA territory (Fig. 1G). Vessel wall MR imaging revealed multiple atherosclerotic plaques on the left MCA (Fig. 1H). Although mild aphasia persisted, the motor power of the right extremities improved to MRC grade 4. The patient was discharged with a modified Rankin Scale score of 4. Lipid levels were improved at 1 month after admission (total cholesterol, 122 mg/dL; triglyceride, 134 mg/dL; HDL-C, 39 mg/dL; LDL-C, 59 mg/dL).

Our patient developed acute stroke due to intracranial atherosclerosis associated with lorlatinib-induced dyslipidemia. Dyslipidemia is the most common adverse event of lorlatinib and usually occurs after the first few weeks of treatment.[1] Persistent dyslipidemia can cause intracranial atherosclerosis. Furthermore, a significant number of lorlatinib users undergo radiation therapy since lorlatinib is used in patients with metastatic NSCLC. Since radiation therapy promotes atherosclerosis, lorlatinib-induced dyslipidemia may increase the risk of atherosclerotic stroke, especially in patients with a history of radiation therapy in the head and neck.

Monitoring and treatment targets differ between patients with lorlatinib-induced dyslipidemia and atherosclerotic stroke. The treatment for lorlatinib-induced dyslipidemia is determined by total cholesterol or triglyceride levels.[1] However, patients with atherosclerotic stroke should be monitored and managed with LDL-C at <70 mg/dL and >50% reduction from baseline based on guidelines.[3] We may therefore apply secondary prevention guidelines to patients with atherosclerotic stroke caused by lorlatinib-induced dyslipidemia.

Our patient had been treated using high-intensity statins and ezetimibe, but his dyslipidemia was not well controlled. The response rate to lipid-lowering treatments in patients who receive lorlatinib is unknown. In our case, the LDL-C level decreased dramatically after administering evolocumab, which is a monoclonal antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. PCSK9 inhibitors reduce LDL-C levels by preventing LDL receptor recycling.[4] If dyslipidemia persists after statin and ezetimibe therapy, an aggressive lipid-lowering strategy using PCSK9 inhibitors may be considered.

This case indicates that lorlatinib-induced dyslipidemia may be associated with severe intracranial atherosclerotic disease and acute ischemic stroke. Careful screening and strict management of lorlatinib-induced dyslipidemia may help to prevent atherosclerotic stroke in lorlatinib users.

Ethics Statement

This study was approved by the Institutional Review Board of Kyungpook National University Chilgok Hospital (IRB No. 2022-07-029) and exempted from informed consent.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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REFERENCES

1. Bauer TM, Felip E, Solomon BJ, Thurm H, Peltz G, Chioda MD, et al. Clinical management of adverse events associated with lorlatinib. *Oncologist* 2019;24:1103-1110.
2. Tsivgoulis G, Safouris A, Kim DE, Alexandrov AV. Recent advances in primary and secondary prevention of atherosclerotic stroke. *J Stroke* 2018;20:145-166.
3. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111-188.
4. Giugliano RP, Sabatine MS. Are PCSK9 inhibitors the next breakthrough in the cardiovascular field? *J Am Coll Cardiol* 2015;65:2638-2651.