Clinical Case Reports

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CASE REPORT

Extensive intracranial arterial stenoses in conjunction with the use of tyrosine kinase inhibitor Nilotinib

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Key Clinical Message

New-generation tyrosine kinase inhibitors (TKI) are promising agents for the treatment of chronic myeloid leukemia (CML), but the linkage to vascular diseases warrants a special attention from treating physicians, as it may carry major morbidity and mortality.

Keywords

Cerebrovascular disease, Moyamoya, Nilotinib, stroke, tyrosine kinase.

Introduction

Tyrosine kinase inhibitors (TKI) block the initiation of the pathway resulting from the aberrant Bcr/Abl fusion known as "Philadelphia chromosome" in chronic myeloid leukemia (CML). Imatinib mesylate was the first to be used in this family, but multiple other drugs with various potencies were released later, which carried different side effects including vascular arterial diseases. Here, we report a case of an extensive intracranial arterial disease in a patient treated with Nilotinib.

Case Report

We are reporting a fifty-year-old man from a Korean-American descent who presented with two transient episodes of right arm and leg weakness and numbness, associated with dysarthria, which occurred in the last 2 days prior to his presentation to our center. The symptoms lasted for <10 min and then completely resolved. He had not had any similar events in the past.

The patient was diagnosed with bone marrow biopsy-proven CML in 2007. He was maintained on imatinib mesylate for 4 years. In 2011, quantitative PCR revealed a gradual elevation of Bcr/Abl levels. Thus, he underwent repeat bone marrow biopsy and was switched to Nilotinib 400 mg twice daily, which succeeded in achieving remission. The patient had no identified vascular risk factors other than his age and mildly elevated low-density lipoprotein (LDL) cholesterol (132 mg/dL). He has no smoking or illicit drug abuse history. He drinks alcohol occasionally. His only medications were Nilotinib and Aspirin 81 mg daily.

His physical examination on arrival was normal including detailed cardiovascular and neurological examination. His blood pressure was 175/90, which resulted in an ABCD2 score of 3.

The patient underwent computed tomography angiogram (CTA) imaging of the head and neck which revealed severely narrowed bilateral middle cerebral arteries (MCA), with patent neck arteries (Fig. 1). These findings were confirmed with a conventional digital subtraction angiogram (DSA), which also gave an approximate "puff of smoke" appearance around the basal ganglia suggestive of moyamoya syndrome, but there was no involvement of the intracranial carotid arteries.

A complete serum workup for autoimmune diseases was negative, and the angiogram images did not reveal

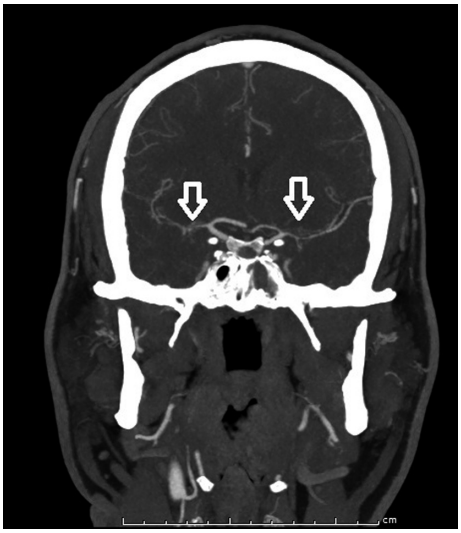

Figure 1. coronal head CT angiogram. CT head angiogram showing bilateral proximal MCAs stenoses.

the typical "beading pattern" of central nervous system (CNS) vasculitis.

The patient was placed on dual antiplatelet therapy and a high-potency statin. The episode of hypertension on admission was transient and did not require prolonged antihypertensive therapy. Nilotinib was replaced with another TKI agent. A bilateral direct revascularization (superficial-temporal-artery to middle-cerebral-artery bypass) was performed later, and the patient continues to be symptom-free 6 months following the initial presentation.

Discussion

New-generation TKI are promising agents for the treatment of CML, but the novelty of these agents comes with the uncertainty regarding long-term adverse effects. Nilotinib showed a superior outcome in newly diagnosed CML compared to imatinib [1]; however, a prospective review has described an increased rate of peripheral arterial disease 26% in patients treated with Nilotinib versus 6.3% of patients placed on Imatinib, with similar cardiovascular risk factors in both groups. The median duration of treatment was 30 months in the Nilotinib arm [2]. Similar results were reported by others [3].

There is a paucity of reports on the development of cerebrovascular disease in patients treated with newer TKI, but an FDA-issued black-box warning suggested that vascular complications, including peripheral and cerebral, occurred in up to 27% of subjects who were in phase I and II studies of a sister compound, Ponatinib [4]. A recent report described a rapid progression of intra- and extracranial atherosclerosis leading to stroke in a previously reported patient with Nilotinib-associated peripheral artery disease PAD. Interestingly, there was a diffuse intracranial arterial disease involving bilateral MCAs similar to our patient. Yet, our case lacked the extracranial involvement [5].

The mechanism by which Nilotinib affects the vasculature is not completely understood. However, in vivo studies suggested that Nilotinib reduces angiogenesis by impairing endothelial cell migration and promotes atherogenesis by increasing the transcription of adhesion molecules [6]. Moreover, animal studies have shown that Nilotinib inhibits discodin-domain receptor DDR, which plays a role in limiting proliferation and matrix formation in atherogenesis [7].

Conclusion

The tyrosine kinase inhibitor, Nilotinib, may pose a detrimental effect on the cerebrovascular tree, in addition to the peripheral vasculature. Knowledge of this effect may help neurologists and oncologists in treating and counseling their patients who have CML. Future well-designed studies are required to confirm the association between Nilotinib and intracranial stenoses.

Conflict of Interest

None declared.

Authorship

AZ and RA drafted the manuscript. CM revised the content.

References

1. Saglio, G., D.-W. Kim, S. Issaragrisil, P. Le Coutre, G. Etienne, C. Lobo, et al. 2010. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N. Engl. J. Med. 362:2251–2259.
2. Kim, T., D. Rea, M. Schwarz, P. Grille, F. Nicolini, G. Rosti, et al. 2013. Peripheral artery occlusive disease in chronic phase chronic myeloid leukemia patients treated with nilotinib or imatinib. Leukemia 27:1316–1321.
3. Aichberger, K. J., S. Herndlhofer, G. H. Schernthaner, M. Schillinger, G. Mitterbauer-Hohendanner, C. Sillaber, et al. 2011. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in CML. Am. J. Hematol. 86:533–539.
4. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm370971.htm
5. Coon, E. A., N. L. Zalewski, E. M. Hoffman, A. Tefferi, and K. D. Flemming. 2013. Nilotinib treatment-associated cerebrovascular disease and stroke. Am. J. Hematol. 88:534–535.
6. Albrecht-Schgoer, K., K. Huber, F. Grebien, G. Eisenwort, W. Schgoer, C. Kaun, et al. 2013. Nilotinib exerts direct pro-atherogenic and anti-angiogenic effects on vascular

endothelial cells: a potential explanation for drug-induced vasculopathy in CML. Blood 122:257.

7. Franco, C., P. J. Ahmad, G. Hou, E. Wong, and M. P. Bendeck. 2010. Increased cell and matrix accumulation during atherogenesis in mice with vessel wall-specific deletion of discoidin domain receptor 1. Circ. Res. 106:1775–1783.