

CASE REPORT

Tyrosine kinase inhibitor induced rapidly progressive vasculopathy after intracranial stent placement

Ching-Jen Chen,¹ Brian J Sorace,² Aria Shakeri,² Min S Park,¹ Andrew M Southerland,² Bradford B Worrall,² M Yashar S Kalani¹

¹Department of Neurological Surgery, University of Virginia, Charlottesville, Virginia, US

²Department of Neurology, University of Virginia, Charlottesville, Virginia, US

Correspondence to
Dr M Yashar S Kalani,
YK6Z@hscmail.mcc.virginia.edu

Accepted 15 March 2018

SUMMARY

Tyrosine kinase inhibitor (TKI) therapy for chronic myeloid leukemia (CML) has been associated with progressive peripheral arterial disease and, more recently, rare cases of intracranial vascular stenosis have been reported. We report the fourth case of TKI treatment associated intracranial vasculopathy and rapid progression of intracranial vascular stenosis following intracranial stent placement. This was a 49-year-old woman who developed right-sided weakness, paresthesias, numbness, and speech difficulties 7 years following TKI treatment for CML. Cerebral catheter angiography demonstrated 90% stenosis of the left supraclinoid internal carotid artery, for which the patient underwent intracranial stent placement with no residual stenosis and improved distal blood flow. Approximately 1 month following the procedure, the patient returned with similar symptoms. Catheter angiography demonstrated 70% and 50% stenosis just distal and proximal to the stent construct, respectively. Rapid disease progression and non-atherosclerotic vasculopathy may argue against endovascular therapy.

BACKGROUND

Tyrosine kinase inhibitors (TKIs), such as Imatinib, Nilotinib, and Bosutinib, have become the mainstay therapy in preventing the progression of chronic myeloid leukemia (CML) in its chronic phase. TKI therapy for CML has been associated with progressive peripheral arterial disease and, more recently, rare cases of intracranial vascular stenosis have been reported.^{1–4} Successful cases of intracranial stent placement and surgical revascularization have been

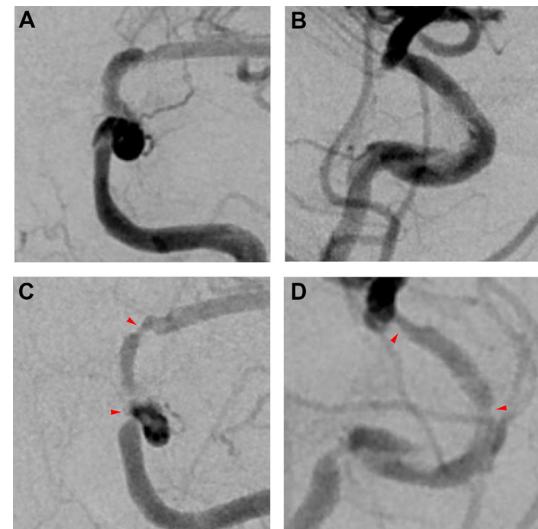


Figure 2 (A, B) Cerebral catheter angiograms in anteroposterior (AP) and lateral views, demonstrating improved left supraclinoid internal carotid artery segment with no residual stenosis after stent placement. (C, D) Cerebral catheter angiogram in AP and lateral views, demonstrating 70% and 50% stenosis just distal and proximal to the stent construct (red arrowheads), respectively.

reported.^{2,3} However, due to the paucity of these cases, the efficacy and safety of these interventions cannot be evaluated.

Here, we report the fourth case of TKI treatment associated intracranial vasculopathy, and rapidly progressive intracranial vascular stenosis following intracranial stent placement. This patient is also the first case of TKI induced concurrent transient ischemic attack (TIA) and myocardial infarction in the medical literature.

CASE PRESENTATION

This was a 49-year-old woman with known type 2 diabetes mellitus and hyperlipidemia who was diagnosed with CML in 2010. She was initially treated with Imatinib but there was a slow increase in her BCR-ABL expression by 2016. Therefore, she was transitioned from Imatinib to Nilotinib, resulting in her BCR-ABL oncogene level becoming undetectable. In 2017, the patient presented to several emergency departments with episodes of transient right-sided weakness, paresthesias, numbness, and speech difficulties. She later presented

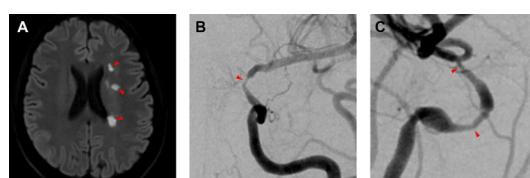


Figure 1 (A) Axial MRI in diffusion weighted imaging sequence, demonstrating multifocal acute infarcts (red arrowheads) within the left cerebral hemisphere in a watershed distribution. (B, C) Cerebral catheter angiograms in anteroposterior and lateral views, demonstrating findings suggestive of moyamoya syndrome, with 80% and 90% stenosis of the left cavernous internal carotid artery (ICA) and left supraclinoid ICA segments (red arrowheads), respectively.



To cite: Chen C-J, Sorace BJ, Shakeri A, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2018-013777

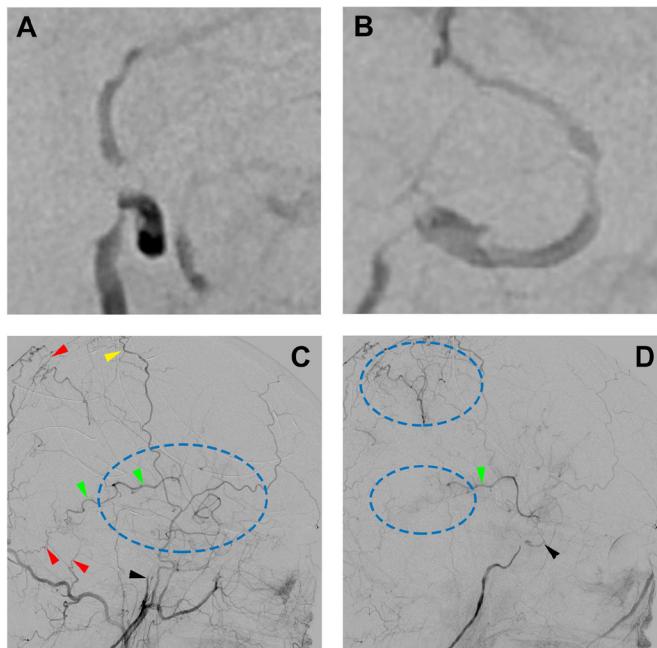


Figure 3 (A,B) Cerebral catheter angiograms in anteroposterior and lateral views, demonstrating interval near occlusion of the intracranial segments of the left internal carotid artery (ICA). (C) Cerebral catheter angiograms in lateral view in the early arterial phase, demonstrating contrast filling of the left ICA to the level of the petrous segment (black arrowhead), and external carotid artery (ECA) to pial collaterals via branches of the occipital artery (red arrowheads) and parietal branch of the superficial temporal artery (yellow arrowhead). There is retrograde filling of the distal left MCA branches via the ECA to pial collaterals (green arrowheads) and filling of the left MCA candelabra (blue circle) via collaterals. (D) Cerebral catheter angiograms in lateral view in the late arterial phase, demonstrating contrast filling of the left ICA to the level of the cavernous segment (black arrowhead), ECA to pial collaterals (blue circles), and retrograde filling of distal left MCA branches (green arrowhead).

with recurrent TIA symptoms and was found to be in the midst of a non-ST elevation myocardial infarction. This is believed to be the first report of concurrent TIA and myocardial infarction in TKI induced vasculopathy.

INVESTIGATIONS

CT angiography of her head demonstrated severe multifocal vascular irregularity and stenoses, most significant in the left anterior intracranial circulation. MRI of her brain demonstrated chronic hypoperfusion ischemic changes in the left centrum semiovale and posterior periventricular region, without evidence of acute infarct. The patient subsequently underwent coronary catheter angiography with a drug eluting stent placed in her right coronary artery for severe stenosis. The patient was subsequently discharged on a high intensity statin (atorvastatin 80 mg daily) and dual antiplatelet therapy (aspirin 325 mg daily and clopidogrel 75 mg daily).

Within a month she represented to the emergency department with similar symptoms. MRI demonstrated multifocal acute infarcts within the left cerebral hemisphere in a watershed distribution (figure 1A). Subsequent cerebral catheter angiography demonstrated 80% and 90% stenosis of the left cavernous internal carotid artery (ICA) and left supraclinoid ICA, respectively

(figure 1B and C). Her Nilotinib was switched to Bosutinib due to concerns for progressive Nilotinib vasculopathy.

TREATMENT

The patient underwent intracranial stent placement (2.25 mm × 8 mm; Multi-link Vision, Abbott, Illinois, USA) over the stenotic left supraclinoid ICA segment with no residual stenosis (figure 2A, B), resulting in improved distal blood flow. There was also interval resolution of the previously noted narrowing of the left cavernous ICA, representing slow flow rather than true stenosis.

OUTCOME AND FOLLOW-UP

Approximately 1 month following placement of the intracranial stent, the patient returned to the emergency department with a transient episode of right-sided numbness. Cerebral catheter angiography demonstrated 70% and 50% stenosis just distal and proximal to the stent construct, respectively (figure 2C, D). Aspirin and P2Y assays demonstrated therapeutic levels. The risk of further endovascular or surgical intervention was deemed high due to the progressive vasculopathy and inability to withhold dual antiplatelet therapy. Hence the patient was maintained on dual antiplatelet therapy with permissive blood pressure parameters. Follow-up angiogram at 3 months demonstrated interval near occlusion of the intracranial segments of the left ICA (figure 3A, B), both within and outside of the stented segment, with development of extensive external carotid artery to pial collaterals (figure 3C, D).

DISCUSSION

Growing evidence suggests that TKIs may be associated with an increased risk of vasculopathy causing peripheral arterial disease, stroke, and ischemic heart disease.⁵ However, intracranial vascular stenosis is an extremely rare adverse effect associated with TKI treatment for CML. This was first described by Coon *et al.*⁴ They reported a 70-year-old woman who after approximately 11 years of starting treatment with TKIs for CML presented with left-sided weakness and dysarthria, with MR angiography demonstrating multifocal narrowing of the anterior and posterior circulations, and >95% narrowing of the right ICA on cerebral catheter angiography.⁴ That patient was managed conservatively due to the risks associated with endovascular or surgical intervention. More recently, Alshiekh-Nasany *et al* reported a case of bilateral middle cerebral artery narrowing in a 50-year-old man who presented with right-sided weakness and dysarthria after 10 years of TKI treatment for CML.³ This patient was successfully treated using surgical revascularization via superficial temporal artery to middle cerebral artery bypass. Subsequently, Ozaki *et al* reported a case of successful intracranial stent placement for symptomatic right ICA stenosis that developed in a 47-year-old man after 7 years of TKI treatment for CML.² Our report represents the fourth documented case in the literature of this extremely rare yet significant adverse effect of TKI treatment for CML.

Nilotinib has been increasingly implicated in the development of vascular events.^{1,6} While the exact etiology is unclear, various mechanisms of the pathophysiology underlying Nilotinib induced vasculopathy have been proposed. Nilotinib causes multiple metabolic derangements, increasing the risk of vascular disease. These include increased fasting glucose, type 2 diabetes mellitus, and increased total high density and low density lipoprotein cholesterol. Nilotinib also interferes with endothelial cell migration, cell proliferation, and promotes a pro-atherogenic

phenotype by increasing the expression of cell surface adhesion molecules.⁷ A recent paper revealed multiple pathways through which Nilotinib encourages a prothrombotic state.⁸ Nilotinib potentiates PAR1 mediated release of platelet alpha granules and also increases platelet thrombus volume. Furthermore, Nilotinib was associated with a phenotype of activated endothelium (increased plasma levels of soluble forms of E-selectin, P-selectin, and VCAM) and also promoted a proinflammatory state via increased serum tumor necrosis factor α and Interleukin 6 levels.⁷

Recently, surgical revascularization has gained acceptance as a primary treatment for moyamoya syndrome, given the documented safety profile of surgery in long term follow-up and the poor response to medical therapy.⁹ Given the unclear mechanism and natural history of TKI treatment associated intracranial vascular stenosis, optimal therapy is also unknown. Despite a previous report of successful stent placement for TKI treatment associated intracranial vascular stenosis, the rapid disease progression seen in our patient and the non-atherosclerotic vasculopathy demonstrated on angiography may argue against endovascular therapy.² The rapid development of stent adjacent stenosis may also indicate

Learning points

- Intracranial multifocal vascular stenosis is an extremely rare adverse effect of tyrosine kinase inhibitor (TKI) treatment for chronic myeloid leukemia (CML).
- The mechanism of vasculopathy is unknown; proposed mechanisms include induced atherosclerosis, impaired vascular repair, and metabolic drug effect.
- Rapid progression of vasculopathy can occur despite intracranial stent placement for TKI treatment associated intracranial vascular stenosis.
- Surgical revascularization may need to be considered in intracranial vascular stenosis associated with TKI treatment for CML.

a more widespread systemic vascular pathology for which targeted stent placement may not alter its natural history.

Contributors C-JC: conception of the project, data collection, drafting of the manuscript, critically revising the manuscript, and approval of the final manuscript. BJS and AS: drafting of the manuscript, critically revising the manuscript, and approval of the final manuscript. MSP, AMS, and BBW: critically revising the manuscript and approval of the final manuscript. MYSK conception of the project, critically revising the manuscript, and approval of the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Aichberger KJ, Herndlhofer S, Schernthaner GH, et al. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in CML. *Am J Hematol* 2011;86:533–9.
- 2 Ozaki T, Nakamura H, Izutsu N, et al. Intracranial stenting for nilotinib treatment-associated cerebrovascular stenosis in chronic myeloid leukemia. *Interv Neuroradiol* 2017;23:527–30.
- 3 Alshiekh-Nasany R, Zidan A, Martinez C. Extensive intracranial arterial stenoses in conjunction with the use of tyrosine kinase inhibitor Nilotinib. *Clin Case Rep* 2016;4:1184–6.
- 4 Coon EA, Zalewski NL, Hoffman EM, et al. Nilotinib treatment-associated cerebrovascular disease and stroke. *Am J Hematol* 2013;88:534–5.
- 5 Chai-Adisaksophia C, Lam W, Hillis C. Major arterial events in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors: a meta-analysis. *Leuk Lymphoma* 2016;57:1300–10.
- 6 Dahlén T, Edgren G, Lambe M, et al. Cardiovascular events associated with use of tyrosine kinase inhibitors in chronic myeloid leukemia: a population-based cohort study. *Ann Intern Med* 2016;165:161–6.
- 7 Hadzijusufovic E, Albrecht-Schgoer K, Huber K, et al. Nilotinib-induced vasculopathy: identification of vascular endothelial cells as a primary target site. *Leukemia* 2017;31:2388–97.
- 8 Alhawiti N, Burbury KL, Kwa FA, et al. The tyrosine kinase inhibitor, nilotinib potentiates a prothrombotic state. *Thromb Res* 2016;145:54–64.
- 9 Scott RM, Smith ER. Moyamoya disease and moyamoya syndrome. *N Engl J Med* 2009;360:1226–37.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow