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CASE REPORT

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Cerebrovascular stenosis related to tyrosine kinase inhibitor for chronic myeloid leukemia: two illustrative cases

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Abstract

Background Tyrosine kinase inhibitors (TKIs) improve prognosis in chronic myeloid leukemia (CML). Nilotinib and ponatinib, second- and third-generation TKIs, respectively, have been reported to cause adverse vascular occlusive events such as myocardial infarction and peripheral arterial disease. However, little is known about the risk of cerebral infarction associated with severe cerebrovascular stenosis, which is a late complication of TKIs. Herein, we report two cases of cerebrovascular stenosis associated with TKIs for CML.

Case presentation A 53-year-old man with CML experienced transient right-sided hemiparesis and dysarthria. The patient had been treated with ponatinib for 5 years. Digital subtraction angiography revealed diffuse stenosis with luminal narrowing from the terminal portion of the internal carotid artery (ICA) to the entire M1 length of the middle cerebral artery (MCA). He was diagnosed with hemodynamic cerebral ischemia due to severe intracranial ICA stenosis and underwent superficial temporal artery (STA)-MCA bypass surgery. He had no atherosclerotic factors or immunological serum markers such as vasculitis. As a side effect of TKI therapy was suspected, ponatinib therapy was discontinued.

A 74-year-old man treated with nilotinib for CML presented with gait disturbances. Diffusion-weighted magnetic resonance imaging revealed multiple infarctions in the right cerebral hemisphere, and magnetic resonance angiography revealed severe bilateral intracranial ICA and MCA stenosis. The patient underwent a STA-MCA bypass surgery. We discontinued nilotinib treatment. The postoperative course was uneventful.

Conclusions CML prognosis has steadily improved with the advent of new TKIs. In the future, reports of cerebrovascular stenosis caused by TKIs for CML may increase and systemic complications may become a problem. We should be aware that some TKIs may cause cerebrovascular stenosis.

Keywords Cerebrovascular stenosis, Tyrosine kinase inhibitor, Chronic myeloid leukemia, Vascular endothelial cell

Background

The prognosis of patients with chronic myeloid leukemia (CML) has improved with the advent of tyrosine kinase inhibitors (TKIs). TKIs for CML are molecular-targeted drugs that induce apoptosis of leukemic cells by inhibiting BCR-ABL tyrosine kinase activity. There are cases in which existing TKIs are ineffective due to genetic mutations and some patients may have to discontinue TKIs

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owing to adverse events. Therefore, second- and third-generation TKIs are currently mainly administered. However, it has been reported that long-term administration of nilotinib, a second generation, and ponatinib, a third generation TKI cause vascular occlusive adverse events such as myocardial infarction, peripheral arterial disease, and cerebral infarction [1]. The 6-year vascular occlusive events with nilotinib have been reported to be 7.5–13.4%, while the 5-year vascular occlusive events with ponatinib have been reported to be 26% [2, 3]. Therefore, algorithms to monitor for vascular occlusive events during TKI treatments have been proposed, including blood pressure, ankle-brachial index (ABI) measurement, electrocardiography, and echocardiography [4]. However, in the field of neurosurgery, little is known about the risk of cerebral infarction associated with severe cerebrovascular stenosis as a late complication of TKIs. Herein, we report a case of severe intracranial internal carotid artery (ICA) stenosis while taking ponatinib, and a case of multiple severe cerebrovascular stenoses during nilotinib treatment with superficial temporal artery-middle cerebral artery (STA-MCA) bypass surgery.

Case presentation

Case 1

A 53-year-old man presented with high serum leukocyte and erythrocyte levels on medical examination 6 years prior and was diagnosed with CML after a detailed examination. The patient was treated with dasatinib, a second TKI; however, no molecular response was observed. Therefore, oral administration of 45 mg ponatinib was initiated 5 years ago and provided a molecular response. However, he experienced transient right hemiparesis and dysarthria for approximately 5 min while working, and was hospitalized. Diffusion-weighted magnetic resonance imaging (MRI) revealed only one high-intensity area on the medial side of the left temporal lobe, while magnetic resonance angiography (MRA) revealed poor visualization of the left intracranial ICA (Fig. 1). Digital subtraction angiography (DSA) revealed severe stenosis of the left ICA and delayed perfusion of the distal portion of the stenosis. The stenosis was diffuse, with the lumen narrowing from the terminal portion of the ICA to the entire M1 length, and exhibited a longitudinal pattern (Fig. 2). The collateral circulation of the left posterior cerebral artery was well developed. The patient was diagnosed with hemodynamic cerebral ischemia secondary to severe intracranial ICA stenosis. Antiplatelet therapy with 100 mg aspirin, 75 mg clopidogrel, and fluid replacement was initiated. However, his neurological symptoms reappeared 3 days later and gradually worsened. Re-examination of the head MRI revealed new acute infarcts in the deep white matter of the left frontal lobe (Fig. 3). The patient was resistant to medical therapy; therefore, we performed emergency left STA-MCA bypass surgery. Postoperatively, the right hemiparesis improved; however, dysarthria persisted. Although the patient had hypertension for 1 year, he had no history of smoking or alcohol consumption, no other atherosclerotic factors or immunological serum markers of vasculitis. As a side effect of TKI was suspected, we consulted a hematologist and decided to temporarily discontinue ponatinib therapy. The patient was discharged without any symptom recurrence. A follow-up at 1 year after surgery revealed no symptom recurrence. The patient is currently receiving ponatinib at a reduced dose of 15 mg/day.

Case 2

A 74-year-old man with diabetes mellitus had started receiving 800 mg of nilotinib for CML 12 years prior to presentation. Six years prior, he had a sporadic cerebral infarction in the cortical area of the left MCA territory. The left MCA had a 70% stenosis according to the Warfarin and Aspirin for Symptomatic Intracranial

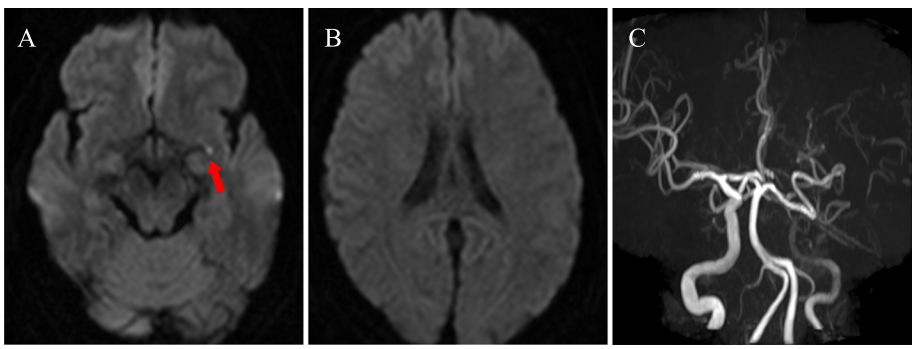

Fig. 1 DWI shows only one high-intensity area on the medial side of the left temporal lobe (**A**, **B**); however, MRA showed poor visualization of the left intracranial internal carotid artery (ICA) (**C**). Arrow indicates the high-intensity area. DWI, diffusion-weighted imaging; MRA, magnetic resonance angiography; ICA, internal carotid artery

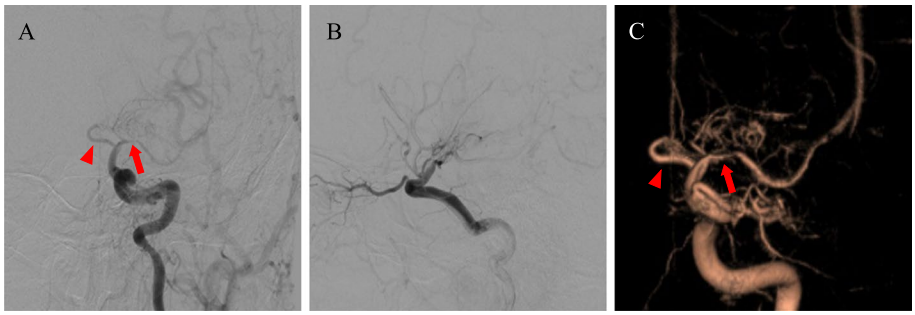

Fig. 2 DSA shows the left ICA severe stenosis and delayed perfusion in the distal portion of the stenosis (**A** anteroposterior view, **B** lateral view). Three dimensional-DSA shows diffuse stenosis with the lumen narrowing from the terminal portion of the ICA to the entire length of M1 (**C**). The arrows indicate stenosis proximal to the anterior choroidal artery. Arrowheads indicate posterior communicating artery. DSA, digital subtraction angiography; ICA, internal carotid artery

Atherosclerotic Disease (WASID) criteria [5], and there was no reduction in cerebrovascular reactivity. At that time, the diagnosis was arteriosclerotic cerebral infarction, and the possibility of TKI side effects was not considered. Since then, he has continued to take 75 mg of clopidogrel; however, this year, he presented with gait disturbances. Diffusion-weighted MRI revealed multiple infarctions in the right cerebral hemisphere, and MRA revealed severe bilateral intracranial ICA and MCA stenoses that progressed gradually (Fig. 4). DSA revealed diffuse stenosis along the entire length of M1, and the stenosis had a serpiginous pattern (Fig. 5). Additionally, North American Symptomatic Carotid Endarterectomy Trial, 80% stenosis was observed in the left cervical ICA. Carotid artery ultrasonography revealed an increase in the peak systolic velocity in the left ICA; however, no intimal thickening was observed in the bilateral carotid arteries other than in the area of stenosis. N-isopropyl-^{123}I-p-iodoamphetamine-single photon emission computed tomography (IMP-SPECT) showed decreased bilateral cerebrovascular reactivity. We performed right STA-MCA bypass surgery. During surgery, the STA and MCA stumps were collected for pathological diagnosis. Although the intima of the STA was thickened during pathological diagnosis, no infiltration by inflammatory cells or macrophages was observed. In addition, the MCA slices were normal (Fig. 6). We consulted a hematologist and discontinued the nilotinib treatment. Two months after the bypass surgery, carotid artery stenting was performed for left cervical ICA stenosis (Fig. 7). The postoperative course was uneventful and the patient did not experience any further cerebral ischemia. A follow-up at 1 year after bypass surgery revealed no symptom recurrence. Because his leukemia was currently stable, nilotinib treatment was discontinued.

Discussion and conclusions

First-generation imatinib, second-generation dasatinib, bosutinib, nilotinib, and third-generation ponatinib are the TKIs used to treat CML. TKIs improve the prognosis of CML; however, their long-term use induces mutations such as T315I in the ABL region of BCR-ABL, resulting

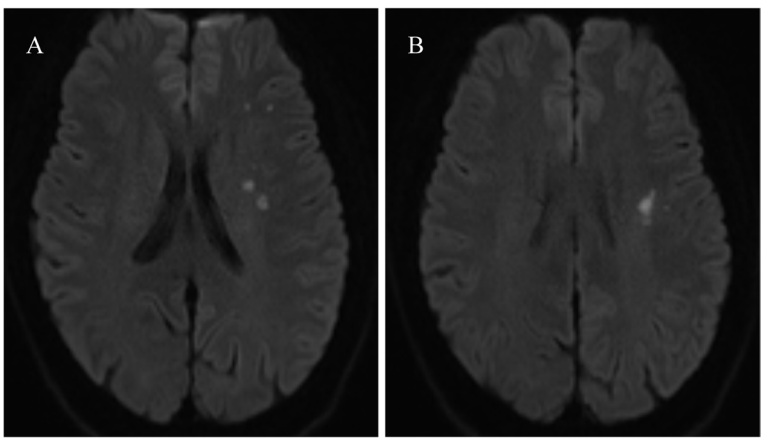

Fig. 3 Repeated MRI shows an increase in sporadic infarcts in the deep white matter of the left frontal lobe. MRI, magnetic resonance imaging

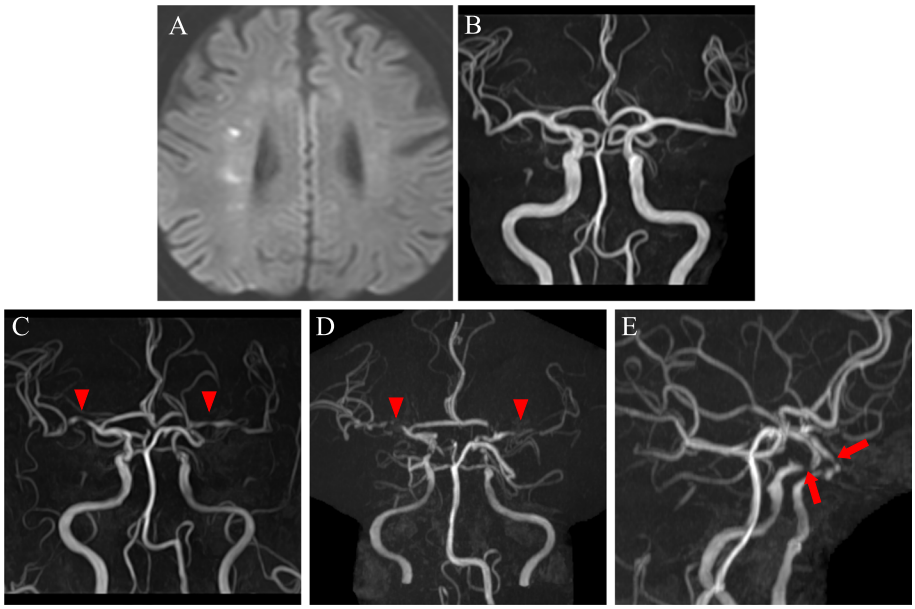

Fig. 4 DWI shows multiple infarctions on the right cerebral hemisphere (**A**). MRA shows bilateral intracranial severe stenosis of the ICA and MCA that progressed gradually (**B** 12 years ago, **C** 6 years ago, **D** current; anterior–posterior view, **E** current; oblique view). Arrows indicate the ICA stenoses. Arrowheads indicate the MCA stenoses. DSA, digital subtraction angiography; MRA, magnetic resonance angiography; ICA, internal carotid artery; MCA, middle cerebral artery

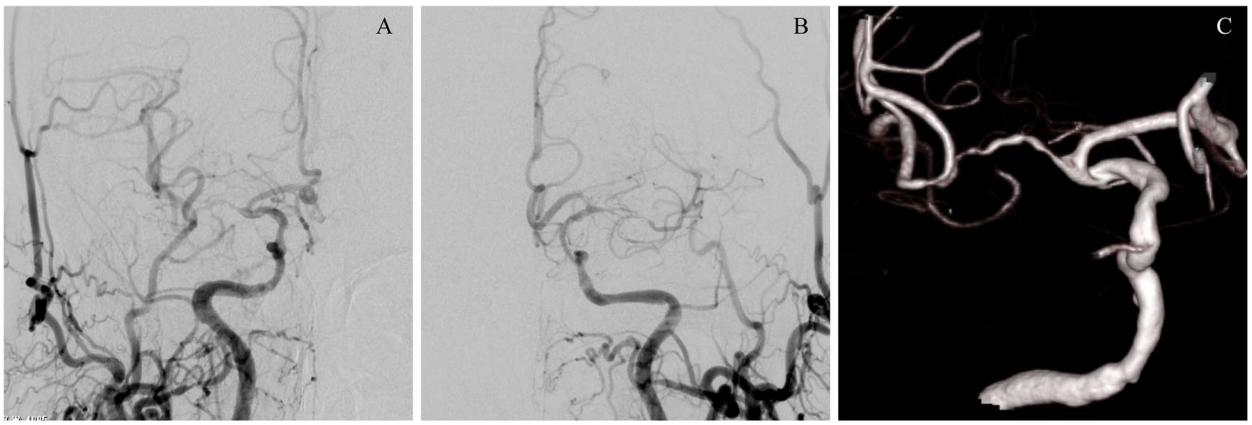

Fig. 5 DSA shows bilateral ICA and MCA stenosis (**A** right anteroposterior view, **B** left anteroposterior view). Three dimensional-DSA shows diffuse stenosis along the entire length of M1 (**C**). DSA, digital subtraction angiography; ICA, internal carotid artery; MCA, middle cerebral artery

in acquired resistance to treatment [6]. In recent years, third generation ponatinib has been increasingly selected for patients who have become treatment-resistant owing to genetic mutations or who cannot continue conventional treatment owing to adverse events (Table 1).

Nilotinib and ponatinib reportedly cause vascular occlusive adverse events [1, 7, 8]. A few reports have described the relationship between these drugs and peripheral arterial disease; however, there are few reports on myocardial and cerebral infarction. Cerebrovascular stenosis as an adverse event has received little attention in the field of neurosurgery. To our knowledge, only 15 cases of cerebrovascular stenosis caused by nilotinib or ponatinib have been reported to date (Table 2). In most cases, the stenosis affects multiple intracranial and extracranial cerebrovascular vessels. The average period from TKI administration to cerebral infarction was approximately 5 years. Damaged vascular endothelial cells are normally repaired. However, it is conceivable that the chronic accumulation of non-inflammatory

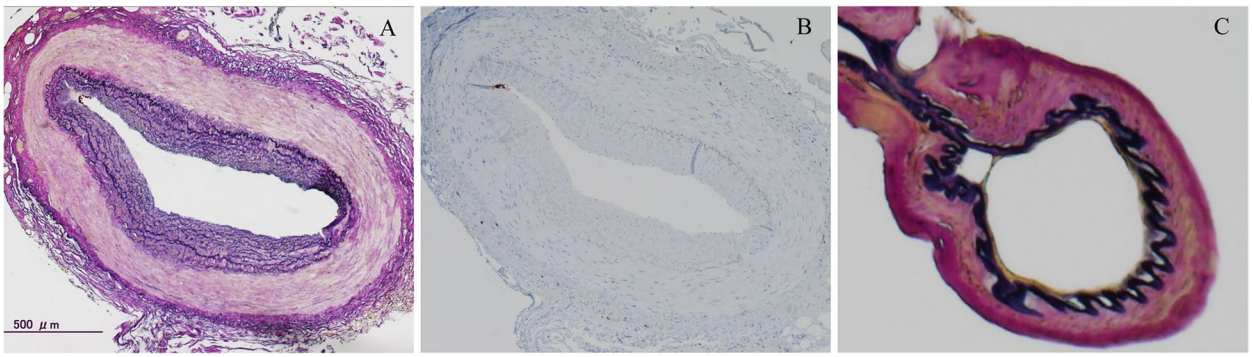

Fig. 6 The intima of STA is thickened (**A** Elastica van Gieson stain). No infiltration of macrophages was observed on STA (**B** CD163 stain). The MCA slice is not thickened (**C** Elastica van Gieson stain). STA, superficial temporal artery; MCA, middle cerebral artery

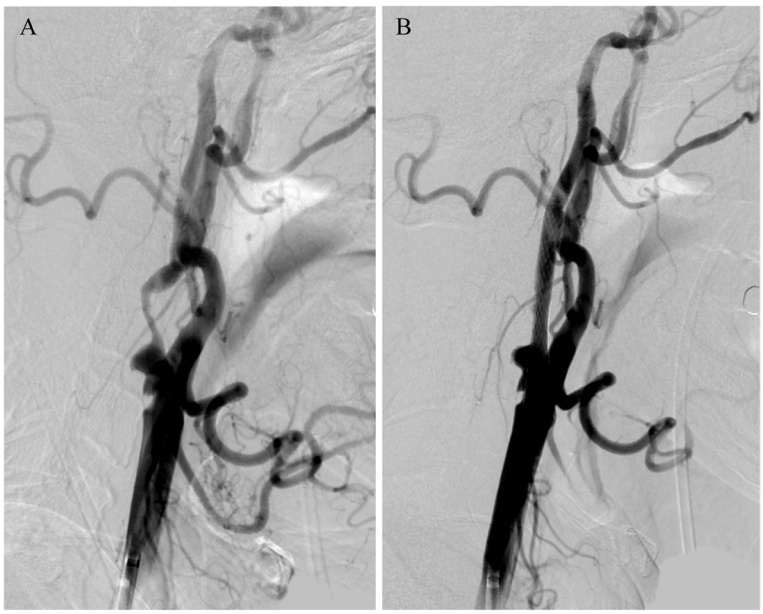

Fig. 7 Carotid artery stenting is performed for left cervical ICA stenosis (**A** pre, lateral view, **B** post, lateral view). ICA, internal cerebral artery

endothelial damage outpaces endothelial repair, leading to chronic vascular stenosis. In some cases, invasive interventions are required due to resistance to medical treatment. Although the postoperative course is favorable in most cases, long-term outcomes are unknown because of the short follow-up period. Case 1 is the first in which revascularization was performed for ponatinib-induced cerebrovascular stenosis. This patient had not undergone cerebral angiography before starting ponatinib treatment; however, he had no history of smoking or alcohol consumption, arteriosclerotic factors other than hypertension, or immunological serum markers such as vasculitis. In addition, ponatinib itself has the side effect of hypertension [9], and our patient exhibited hypertension after starting ponatinib treatment. The period from the onset of hypertension to the onset of cerebral infarction was shorter than that of general arteriosclerotic changes. Therefore, the patient was diagnosed with ponatinib-induced cerebrovascular disease.

Diagnosing whether cerebrovascular stenosis is a side effect of TKIs, based on imaging alone, is difficult. In our cases, the angiographic patterns of intra- and extracranial stenosis were not so different from isolated atherosclerotic stenosis on DSA. Patients may also have concomitant atherosclerotic factors. In addition, inflammatory diseases such as vasculitis should be ruled out. In Case 2, no infiltration of inflammatory cells or macrophages was observed in the pathological diagnosis of the STA and

Table 1 Summarize of both cases

	Case 1	Case 2
Age	53	74
Sex	Male	Male
Hypertension	+	-
Diabetes	-	+
Leukemia	CML	CML
TKI	Ponatinib	Nilotinib
Site of lesion	Lt intracranial ICA	Bil intracranial ICA, Bil MCA, Lt cervical ICA
Pattern of stenosis	longitudinal	serpiginous
Period	5 Years	6 Years
Treatment	Medication → Bypass	Bypass, CAS
Follow-Up	12 Months	12 Months

TKI tyrosine kinase inhibitor, *CML* chronic myeloid leukemia, *Lt* left, *Bil* bilateral, *ICA* internal carotid artery, *MCA* middle cerebral artery, *CAS* carotid artery stenting

MCA; however, vasculitis could not be sufficiently ruled out using laboratory tests or other indicators. Due to incompletely excluding vasculitis, it could not be determined with certainly that cerebrovascular stenosis was TKI-induced, which is a shortcoming of Case 2. Ideally, a prospective study to understand the side effects should be conducted, particularly in terms of reducing the influence of confounding factors such as atherosclerotic factors and vasculitis. In cases with a high risk of atherosclerotic factors, it is important to select either a conventional first-generation TKI or another second-generation TKIs with fewer vascular occlusive events. Before starting nilotinib or ponatinib treatment, it is necessary to check for preexisting atherosclerotic factors. However, intracranial vascular stenosis cannot be detected using ABI or carotid ultrasonography. We believe that head MRA is necessary before and during the use of certain TKIs.

TKIs for CML primarily target BCR-ABL in leukemic cells. However, TKIs also inhibit various non-target molecules lead to endothelial damage [19]. Among TKIs, the likelihood of cardiovascular events varies depending on the differences in the target molecules. TKIs inhibit enzymes such as SRC kinase, fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor receptors (VEGFR) [20]. Particularly important for the development of cerebral ischemia, the inhibition of VEGFR induces vascular endothelial cell dysfunction and apoptosis [20]. Normal vascular endothelial cells exhibit anti-inflammatory, antithrombotic, and anticoagulant functions, and inhibit intimal thickening. VEGF signaling is important in endothelial cell function. The pro-thrombotic and pro-inflammatory effects are likely due to loss of endothelial integrity with subsequent activation of coagulation and loss of normal endothelial VEGFR-mediated antiplatelet activity which was mediated by nitric oxide and prostacyclin [21]. Therefore, the inhibition of VEGFR, which occurs as an off-target effect of TKIs, promotes vascular endothelial

Table 2 Cerebrovascular stenosis with TKIs for leukemia

Author	Case	Leukemia	Site of lesion	Period	Treatment	TKI	Follow-Up
Coon et al. 2013 [10]	70F	CML	Bil MCA, Bil PCA, Rt intracranical ICA, Rt ACA	8 Years	Medication	Nilotinib	NR
Alshiekh et al. 2016 [11]	50 M	CML	Bil MCA	NR	Bypass	Nilotinib	6 Months
Ozaki et al. 2017 [12]	74 M	CML	Lt intracranial ICA, BA	2.5 Years	Medication → stent	Nilotinib	3 Months
Chen et al. 2018 [13]	49F	CML	Lt intracranial ICA	1 Year	stent	Nilotinib	1 Month (re-stenosis)
Suzuki et al. 2019 [14]	55 M	CML	Rt intracranial ICA, Lt MCA	3 Years	Bypass	Nilotinib	11 Months
Nakaya et al. 2019 [15]	76 M	CML	Bil cervical ICA	7 Years	Medication → CAS	Nilotinib	4 Months
Uemura et al. 2020 [16]	62 M	CML	Rt MCA, Lt ACA, Lt PCA	9 Years	Medication	Nilotinib	24 Months
	59 M	CML	Lt MCA, BA	7.5 Years	Medication	Nilotinib	NR
Spina et al. 2020 [17]	62 M	CML	Bil cervical ICA	3 Months	Medication	Ponatinib	12 Months
Fujiwara et al. 2021 [4]	53F	CML	Bil cervical ICA, Bil subclavian A, Lt VA	5.5 Years	PTA	Nilotinib	42 Months
Hirayama et al. 2022 [3]	46F	CML	Bil cervical ICA	10 Years	CAS	Nilotinib	3 Months
	43F	CML	Bil intracranial ICA	3 Months	Medication	Ponatinib	3 Months
Rai & Hara. 2023 [18]	39F	ALL	Rt MCA, cervical ICA	3.5 Years	Bypass	Nilotinib	6 Months
Present Case1	53 M	CML	Lt intracranial ICA	5 Years	Medication → Bypass	Ponatinib	12 Months
Present Case2	74 M	CML	Bil intracranial ICA, Bil MCA, Lt cervical ICA	6 Years	Bypass, CAS	Nilotinib	12 Months

F female, *M* male, *CML* chronic myeloid leukemia, *Bil* bilateral, *Rt* right, *Lt* left, *MCA* middle cerebral artery, *PCA* posterior cerebral artery, *ACA* anterior cerebral artery, *ICA* internal carotid artery, *BA* basilar artery, *VA* vertebral artery, *PTA* percutaneous transluminal angioplasty, *CAS* carotid artery stenting, *TKI* tyrosine kinase inhibitor, *NR* not reported

cell damage, resulting in intimal thickening, thrombus formation, and platelet aggregation [19, 22]. Vascular endothelial cell damage is an important mechanism underlying TKI-induced cerebral infarction. Moreover, various factors such as the expression of inflammatory cytokines are involved. Some TKIs increase plasma levels of interleukin-6 and interleukin-1 beta, which may lead to atherosclerotic changes [23]. Elevated plasma levels of these inflammatory cytokines accelerate atherogenic pathways leading to plaque growth and instability [21]. A relationship between TKIs and the expression of adhesion factors such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 has also been suggested [24]. In vivo studies have reported that nilotinib and ponatinib increase the transcription of the intrinsic and extrinsic coagulation pathways and reactive oxygen species from vascular endothelial cells [25]. Furthermore, ponatinib has been shown to increase von Willebrand factor multimers and induce platelet adhesion [26]. TKI-induced cerebral infarction involves various mechanisms, including damage to vascular endothelial cells, inflammation, platelet adhesion, coagulation, and fibrinolysis.

Whether cerebrovascular stenosis caused by TKIs is reversible is unknown; however, it is irreversible in peripheral arterial diseases [27]. If cerebrovascular stenosis is irreversible, revascularization should be considered because discontinuation of TKIs alone does not improve the condition. Invasive intervention is unavoidable, especially in cases of resistance to medical treatment such as antithrombotic therapy. In the present case, the patient's prognosis after revascularization was good. However, the long-term prognosis after revascularization remains unknown, and further accumulation of cases is required. It is also unclear which patients taking TKIs are more likely to develop cerebrovascular stenosis. A previous report suggested the possibility that some genetic mutations such as RNF213 p.4810 K variant are associated with cerebrovascular stenosis under treatment with TKIs [16].

In conclusion, CML prognosis has steadily improved with the advent of new TKIs; however, systemic complications have become problematic. In the future, reports of cerebrovascular stenosis caused by TKIs in patients with CML may increase. Understanding the pathological mechanisms is important for selecting treatment when making decisions regarding invasive interventions.

Abbreviations

TKI	Tyrosine kinase inhibitor;
CML	Chronic myeloid leukemia
ABI	Ankle-brachial index
STA-MCA	Superficial temporal artery- middle cerebral artery
ICA	Internal carotid artery
DWI	Diffusion weighted imaging
MRI	Magnetic resonance imaging
MRA	Magnetic resonance angiography
DSA	Digital subtraction angiography
WASID	Warfarin and Aspirin for Symptomatic Intracranial Atherosclerotic Disease
NASCET	North American Symptomatic Carotid Endarterectomy Trial
IMP-SPECT	N-isopropyl-^{123}I-p-iodoamphetamine single photon emission computed tomography
VEGFR	Vascular endothelial growth factor receptor

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Informed consent
We obtained informed consent from the patients.

Authors' contributions
NS, TH, HM, and YEg examined the patient, obtained images, and diagnosed them. NS reviewed the literature and prepared the manuscript. YEn and TI revised the manuscript. All the authors contributed to the manuscript and approved the submitted version.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The patients provided informed consent for all procedures.

Consent for publication
Written informed consent was obtained from the patients.

Competing interests
The authors declare no competing interests.

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