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Tyrosine kinase inhibitor-induced carotid stenosis: A case report

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ABSTRACT

Tyrosine kinase inhibitors are considered as highly effective and relatively safe drugs for the treatment of chronic myeloid leukemia. If several side effects on short and long term are well known and described, their involvement in the development of carotid stenosis remains unclear. Here, we describe a case of carotid stenosis in a patient receiving tyrosine kinase inhibitors and discuss the current literature.

1. Introduction

Tyrosine kinase inhibitors (TKI), the mode-of-action of which is to inhibit the oncoprotein BCR-ABL, are highly effective for the treatment of chronic myeloid leukemia (CML) [1].

However, tyrosine kinase enzymes are expressed in multiple tissues and are involved in several signaling pathways. Thus, TKI have several off-target side effects. Although these side effects are well known in the short-time, long-term effects remain unclear. Particularly, some reports of cardiovascular toxicities caused by the second generation TKI nilotinib, dasatinib, and ponatinib have recently raised critical concerns [2,3,4]. Another tyrosine kinase, the Discoidin Domain Receptor 1, has been identified as a major secondary target of these TKI and is now considered one of the mechanisms responsible for the adverse cardiovascular effects observed in TKI-treated CML patients [5].

We report a case of a patient with CML who developed carotid stenosis while under TKI therapy.

2. Case report

A 61-years-old male diagnosed in May 2006 with a chronic phase CML firstly received imatinib (600 mg daily) for treatment of his malignancy. In the absence of a satisfactory molecular response associated with osteoarticular pain and digestive disorders, the treatment was changed on December 2008 to the second-generation TKI dasatinib (100 mg daily). In front of a loose of major molecular response associated with significant side effects, nilotinib (200 mg in the morning and 400 mg in the evening) was introduced in December 2010 as a third-line treatment.

The patient did not drink nor smoke, neither had a sedentary lifestyle nor a family history of premature cardiovascular disease, and his SCORE at 10 years was 3%. However, after three and a half years under nilotinib treatment, the patient presented an increase of lipid markers (total cholesterol: 2.7 g/l, norm < 2 g/l; low-density lipoprotein: 1.94 g/l, norm < 1.6 g/l), an hypertension (systolic blood pressure: 152 mmHg; diastolic blood pressure: 85 mmHg), and a weight gain (+5 kg). Taking into account these new cardiovascular risk factors and the possibility of cardiovascular side effects of nilotinib, a first supra-aortic trunks doppler ultrasonography was performed in August 2014 and the stenosis percentage of carotid arteries were estimated following the recommendations of the Society of Radiologists in Ultrasound Consensus [6]. This examination detected a hypoechogenous, homogenous, regular patch on the right intern carotid (estimated stenosis of about 10–30%), without hemodynamic effect (Fig. 1A and B).

A control examination by doppler ultrasonography performed in May 2015 objectified a stability of the carotid lesions. However, in front of this stenosis associated with non-controlled cardiovascular risk factors, an antiplatelet therapy (aspirin 75 mg daily) as well as an antihypertensive (ramipril 2.5 mg daily) therapy were settled in August 2015, and the CML treatment was shifted from nilotinib to bosutinib

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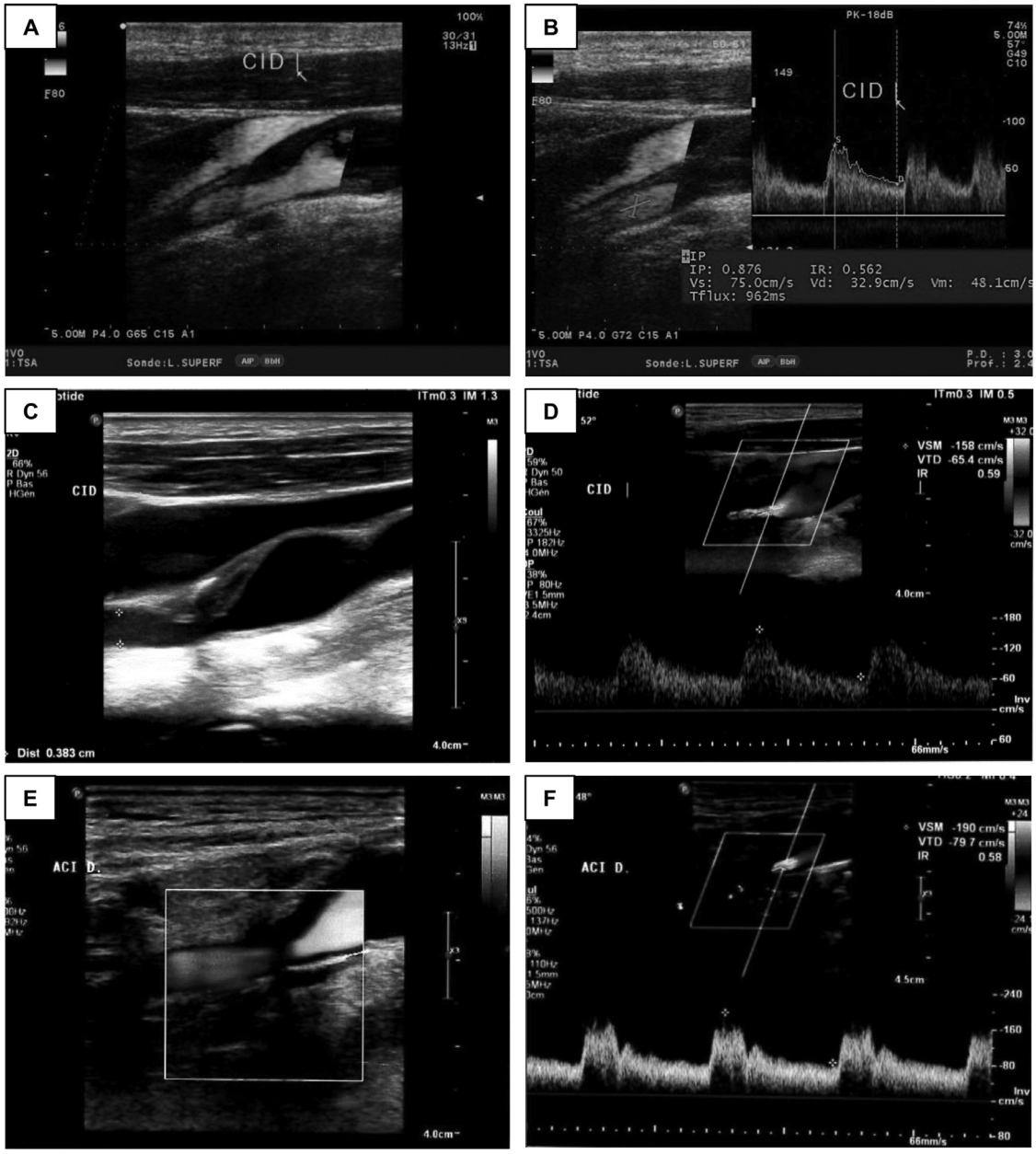

Fig. 1. Doppler ultrasonography pictures of the right intern carotid showing the evolution of stenosis at diagnosis (August 2014, A and B), after one year (May 2015, C and D) and before endarterectomy (February 2017, E and F). The thrombosis of right intern carotid was estimated at around 10–30% at first examination (A), evolved to almost 50% after one year (C), then progressed to 70% (E), which was the indication for a surgical intervention. If this stenosis had no consequences on flow velocity at first discovery (75 cm/s, B), it rapidly evolved to an increase of this parameter above the pathological threshold of 125 cm/s (158 cm/s at 50% stenosis, D, and 190 cm/s at 70% stenosis, F).

(400 mg daily). A third doppler ultrasonography performed in July 2016 found an aggravation of the right intern carotid lesions. The stenosis was around 50% and had hemodynamic consequences, with a velocity of 158 cm/s, a value which is above the threshold of 125 cm/s defined by the European Society of Cardiology [7] (Fig. 1C and D). Although the patient remained asymptomatic, a control doppler ultrasonography of supra-aortic arteries performed in February 2017 found a right intern carotid stenosis of about 70% with a velocity of 190 cm/s (Fig. 1E and F). This observation was confirmed by an angioscanner in June 2017 which found a right intern carotid stenosis of 70% with a hypodensity patch. This constituted an indication for an endarterectomy which was performed in January 2018.

Since the surgical intervention, all control doppler ultrasonographies of the carotids objectified no significant stenosis, with good velocities. Besides, in front of a major molecular response with undetectable BCR-ABL transcript since late 2015, bosutinib has been discontinued in May 2018 and the patient is since closely monitored with a bimonthly quantification of the BCR-ABL transcript.

3. Discussion and conclusions

Tyrosine kinase inhibitors target the oncogene BCR-ABL and are the gold standard for the treatment of CML. However, tyrosine kinases are ubiquitous proteins and, as a consequence, TKI have several adverse effects that could be attributed to the inhibition of tyrosine kinases other than BCR-ABL. Especially, the Discoidin Domain Receptor 1, responsible for the activation of cellular processes such as adhesion, migration, differentiation or cytokine production in response to the

binding to extracellular collagen [8], has been demonstrated to be specifically inhibited by nilotinib, ponatinib, and to a lesser extent by dasatinib, but not by other TKI [5,9]. Accordingly, nilotinib is able to activate the vascular endothelium and to potentiate thrombus growth and stability over time [10]. These effects are not seen with imatinib and are reduced after exposure to dasatinib, suggesting a unique prothrombotic effect of nilotinib as compared to other TKI [10].

We report here the case of a CML patient treated for almost five years with nilotinib and diagnosed with a carotid stenosis which necessitated an endarterectomy. Very few descriptions of TKI-associated carotid stenosis are available and only few reports evaluated the incidence of supra-aortic vascular events in CML patients treated with nilotinib. For example, although it remains possible that the outcome of carotid stenosis was underestimated since the authors considered only severe lesions (stenosis > 70%), none of the cardiovascular events (overall incidence of 9%) reported in a follow-up study of 63 patients receiving nilotinib involved carotid or vertebral artery [3]. Likewise, a similar study following 73 patients receiving nilotinib reported an overall incidence of 15% of cardiovascular events, among which only two involved carotid arteries [4].

Nilotinib is not likely the single risk factor responsible for the development of carotid stenosis in our patient and we cannot exclude that pre-existing risk factors also contributed to this pathology. Indeed, it has already been shown that concomitant conventional cardiovascular risk factors increase the onset frequency of vascular events in TKI-treated patients [4,10,11]. On the opposite, the only presence of vascular risk factors cannot fully explain the development of these lesions. Especially, their aggravation despite the setup of an appropriate protective treatment (i.e. aspirin) is in favor of a nilotinib, and to a lesser extent dasatinib, involvement. Likewise, if previous reports evidenced that the incidence of cardiovascular adverse effects is reduced with bosutinib as compared to nilotinib or dasatinib [2], it remains possible that the aggravation of carotid stenosis in our patient originated in part from the use of this TKI for CML treatment.

In conclusion, the development of atheroma and carotid stenosis in our patient most probably originated from the combination of pre-existing cardiovascular risk factors and TKI therapy, suggesting it would be beneficial for these patients to perform a systematic and regular ultrasonography control of carotid arteries. The European LeukemiaNet network recently recommended a measurement of the ankle-brachial index or a duplex ultrasonography to assess asymptomatic peripheral arterial occlusive disease every 6–12 months in patients treated with nilotinib or ponatinib over 65 years or with cardiovascular risk factors [9]. Thus, if recommendations for preventive evaluation of cardiovascular events are emerging, carotid involvement remains insufficiently documented in this context and further long-term prospective studies of TKIs cardiovascular adverse effects are needed to validate these recommendations.

Consent to participate and for publication

A detailed written informed consent was obtained from the patient prior to publication of this case report.

CRediT authorship contribution statement

Jeanne Hersant: Writing - original draft, Writing - review & editing, Investigation. **Martine Gardembas:** Resources. **Georges Leftheriotis:** Conceptualization, Supervision. **Patrick Vandeputte:** Writing - original draft, Writing - review & editing. **Pierre Abraham:** Conceptualization, Supervision. **Samir Henni:** Conceptualization, Supervision, Investigation.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

References

[1] B.J. Druker, N.B. Lydon, Lessons learned from the development of an abl tyrosine kinase inhibitor for chronic myelogenous leukemia, J. Clin. Invest. 105 (2000) 3–7.
[2] J.J. Moslehi, M. Deininger, Tyrosine kinase inhibitor-associated cardiovascular toxicity in chronic myeloid leukemia, J. Clin. Oncol. 33 (2015) 4210–4218.
[3] N. Aghel, J.H. Lipon, E.G. Atenzfu, D.D.H. Kim, D.H. Delgado, Cardiovascular events after exposure to nilotinib in chronic meloid leukemia : long-term follow-up, Clin. Lymphoma Myeloma Leuk. 17 (2017) 870–878.
[4] G. Gugliotta, F. Castagnetti, M. Breccia, L. Levato, M. D'Adda, F. Stagno, et al., Long-term outcome of a phase 2 trial with nilotinib 400 mg twice daily in first-line treatment of chronic myeloid leukemia, Haematologica 100 (2015) 1146–1150.
[5] U. Rix, O. Hantschel, G. Dürnberger, L.L. Remsing Rix, M. Planyavsky, N.V. Fernbach, et al., Chemical proteomic profiles of the BCR-ABL inhibitors imatinib, nilotinib, and dasatinib reveal novel kinase and nonkinase targets, Blood 110 (2007) 4055–4063.
[6] E.G. Grant, C.B. Benson, G.L. Moneta, A.V. Alexandrov, J.D. Baker, E.I. Bluth, et al., Carotid artery stenosis: gray-scale and Doppler US diagnosis–Society of Radiologists in Ultrasound Consensus Conference, Radiology. 229 (2003) 340–346.
[7] M. Sprynger, F. Rigo, M. Moonen, V. Aboyans, T. Edvardsen, M.L. de Alcantara, et al., Focus on echovascular imaging assessment of arterial disease: complement to the ESC guidelines (PARTIM 1) in collaboration with the Working Group on Aorta and Peripheral Vascular Diseases, Eu. Heart J. Cardiovasc. Imaging 19 (2018) 1195–1221.
[8] T. Yoshimura, W. Matsuyama, H. Kamohara, Discoidin domain receptor 1: a new class of receptor regulating leukocyte-collagen interaction, Immunol. Res. 31 (2005) 219–230.
[9] J.L. Steegmann, M. Baccarani, M. Breccia, L.F. Casado, V. García-Gutiérrez, A. Hochhaus, D.W. Kim, T.D. Kim, H.J. Khoury, P. Le Coutre, J. Mayer, D. Milojkovic, K. Porkka, D. Rea, G. Rosti, S. Saussele, R. Hehlmann, R.E. Clark, European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia, Leukemia 30 (2016) 1648–1671.
[10] N. Alhawiti, K.L. Burbury, F.A. Kwa, C.J. O'Malley, P. Shuttleworth, M. Alzard, et al., The tyrosine kinase inhibitor, nilotinib potentiates a prothrombotic state, Thromb. Res. 145 (2016) 54–64.
[11] E. Bondon-Guitton, S. Combret, M.C. Pérault-Pochat, M. Stève-Dumont, H. Bagheri, F. Huguet, F. Despas, et al., Cardiovascular risk profile of patients with peripheral arterial occlusive disease during nilotinib therapy, Target. Oncol. 11 (2016) 549–552.