Acquired Hemophilia A May Be Associated with Ticagrelor Therapy in a 52-Year-Old Man After a Recent Percutaneous Transluminal Coronary Angioplasty

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ABSTRACT: We present a case report of a 52-year-old man who was hospitalized for right leg pain due to a relevant hemorrhagic effusion. He was on dual antiplatelet therapy (DAPT): acetylsalicylic acid and ticagrelor, a reversible P2Y12 receptor antagonist. Signs, symptoms, and laboratory blood tests led to the diagnosis of acquired hemophilia A (AHA). Ticagrelor therapy-associated AHA was hypothesized due to the fact that, before adding this drug, all laboratory and clinical examinations were repeatedly normal. Prednisone and cyclophosphamide treatment was started without DAPT interruption due to the high risk of stent thrombosis. After 10 days, prolonged activated partial thromboplastin time dropped from 107 to 49 seconds, the patient's factor VIII (FVIII) levels gradually normalized over the following few weeks, and FVIII inhibitor titer was negative. Recently, some reports have established a link between the development of AHA and treatment with clopidogrel, an irreversible P2Y12 receptor antagonist. However, to the best of our knowledge, this is the first time that a link between AHA and ticagrelor has been reported.

KEYWORDS: acquired hemophilia A, factor VIII, platelet aggregation inhibitors, ticagrelor, percutaneous transluminal coronary angioplasty

Introduction

Acquired hemophilia A (AHA), a rare bleeding disorder triggered by autoantibodies against factor VIII (FVIII), occurs without a family history of hemophilia.[1] Bleeding is usually mucocutaneous, soft tissue, or gastrointestinal, and is often severe or even life threatening. There is a reported mortality rate of 9.7%–33%.[2] AHA invariably causes a prolonged activated partial thromboplastin time (APTT), and the laboratory diagnosis is confirmed by demonstrating a reduced FVIII level along with a detectable FVIII inhibitor.[1] Up to 85% of affected individuals are older adults (>60 years) of either sex.[1] To date, the underlying causes of AHA are still under debate. In more than 50% of AHA cases, FVIII autoantibodies are present in patients without any relevant concomitant diseases. The remaining cases may be associated with autoimmune diseases, the postpartum period, infections, vaccinations, underlying hematologic diseases, or solid cancer.[3] Moreover, an analysis of literature data showed several cases of drug-induced anti-FVIII autoantibodies, highlighting this finding as one of the most relevant causes of AHA.[4]

Recently, some cases of AHA associated with antiplatelet drug such as clopidogrel[5,6] and vitamin K antagonist, like warfarin,[7–10] have been reported. This makes the diagnosis of drug-associated autoantibodies against FVIII a complicated challenge, since the sudden onset of bleeding might be erroneously attributed to these drugs. Clopidogrel, prasugrel, or ticagrelor, plus aspirin, is the most commonly used treatment for patients with acute coronary syndrome: the so-called dual antiplatelet therapy (DAPT).[11] Ticagrelor is an orally administered direct-acting P2Y12 receptor antagonist that is not a prodrug and does not require metabolic activation for antiplatelet activity, unlike clopidogrel and prasugrel, that binds irreversibly to the receptor for the life of the platelet.[11] Pharmacodynamic studies have demonstrated that ticagrelor has a faster onset and inhibits platelet aggregation more strongly than does clopidogrel. These properties may well contribute to reduced rates of thrombotic outcomes compared to clopidogrel, as demonstrated in a phase III clinical trial (PLATO trial).[12] Ticagrelor represents an advancement in P2Y12 receptor inhibition therapy, and no distinctive adverse effects, other than bleeding, have been reported for this new chemical entity.

This report describes a patient, who has given consent for publication of all information about his clinical case, with AHA associated with ticagrelor therapy who showed complete remission after steroid and cyclophosphamide administration, in spite of DAPT continuation.

Case Report

A 52-year-old man, treated with acetylsalicylic acid (ASA) 100 mg/day and ticagrelor 180 mg/day (DAPT) for recent percutaneous transluminal coronary angioplasty with medicated coronary stents, arrived complaining of right leg pain due to a relevant hemorrhagic effusion.

Our patient had severe anemia (Hb 6.9 g/dL), prolonged APTT of 80 seconds, and normal prothrombin time and platelet levels. The mixing test showed no normalization of the prolonged APTT after incubation with severe evident FVIII deficiency (1.1%), due to a detectable FVIII inhibitor (6.72 Bethesda units [BU]) confirming the diagnosis of AHA. Extensive radiological/hematological examinations, ie, computed tomography of the chest and abdomen with contrast medium, laboratory testing for antinuclear antibodies, anti-DNA antibodies, antiphospholipid antibodies, autoantibodies to extractable nuclear antigens, antineutrophil cytoplasmic antibodies, C- and S-reactive proteins, activated protein C resistance, and serum immunoglobulin tests were uneventful for any underlying disorders, such as connective tissue disorders, lymphoproliferative disease, or inflammatory bowel diseases. On the basis of the AHA diagnosis and in line with the standard guidelines for its management, prednisone at 100 mg and cyclophosphamide at 90 mg were administered daily.

In the present case, skin, muscle, and soft tissue bleeding, and APTT prolongation developed within one month after ticagrelor had been added to the ASA treatment, while APTT had been repeatedly normal before taking this drug. The diagnosis was made one month later when the patient arrived to our attention after we had dosed an FVIII inhibitor titer of 6.72 BU/mL. Because of the high risk of stent thrombosis, ticagrelor and ASA therapy was continued and treatment with prednisone at 100 mg and cyclophosphamide at 90 mg/day was promptly started. Following stabilization of the bleeding, the immunosuppressive therapy was continued until such time as there was eradication of the inhibitor.

After 10 days, APTT dropped from 107 to 49 seconds, the patient's FVIII levels gradually normalized over the following few weeks, and the inhibitor titer was negative. Therefore, the dosage of cyclophosphamide and prednisone was gradually reduced according to the inhibitor titer and the FVIII level, but the ticagrelor therapy was not stopped.

The patient was continuously monitored and his FVIII levels remained in the normal range. He was given DAPT antiplatelet therapy for one year as prescribed by his cardiologist because of the high risk of stent thrombosis, even though ticagrelor had most probably induced the disease.

Discussion

According to The European Acquired Haemophilia Registry (EACH2), AHA may be idiopathic even if an underlying disorder is identified in about 50% of the patients.[13] Although the drug-induced anti-FVIII antibodies have been reported to account for only 3%[4] of AHA, the real incidence could be underestimated. Moreover, drugs such as clopidogrel or warfarin might well mask the correct diagnosis of AHA.[5–10] Therefore, some authors suggest that for elderly patients on clopidogrel or warfarin therapy presenting with unusual/unexplained bleeding, not only the treatment but also the possibility of AHA should be carefully investigated.[7] Ticagrelor, the first reversible oral P2Y12 receptor antagonist, provides faster, greater, and more consistent adenosine diphosphate receptor inhibition, thus becoming an accepted option in several clinical situations, such as unstable angina, non-ST-segment elevation acute coronary syndrome, and percutaneous coronary intervention.[11,14,15]

In this case, we report a patient diagnosed as having developed ticagrelor-associated AHA. Even though, to the best of our knowledge, no other such cases have been reported, our hypothesis is supported by several factors.

One important point is that the patient developed a severe bleeding disorder associated with a significant blood titer of an inhibitor against FVIII one month after ticagrelor had been added to ASA therapy and after repeatedly dosing a normal APTT. The temporal relationship of the administration of the drug and the onset of the illness, the prompt clinical and laboratory response to corticosteroids, and the exclusion of causes other than drugs or confounding factors are in agreement with our hypothesis.

Ticagrelor therapy was not suspended nor was it changed for other similar drugs such as clopidogrel. First, the patient's critical clinical situation made it unadvisable to change the dosage or interrupt the drug. Second, over time, the immunosuppressive therapy controlled the anti-FVIII antibodies. Third, clopidogrel may also induce AHA.[5,6]

The Naranjo algorithm[16] was used to evaluate the likelihood of adverse drug reaction. This questionnaire included 10 questions that rate adverse drug reactions using a numeric score that ranged from −4 to +13. The reaction is considered definite if the score is 9 or higher, probable if it is from 5 to 8, possible if it is from 1 to 4, and doubtful if it is 0 or less. AHA related to ticagrelol was scored as 5. There are previous similar conclusive reports on this reaction,[5,6] the adverse event appeared after the suspected drug had been administered, and there were no alternative causes (other than the drug) that could have been responsible for the reaction. Moreover, the fact that several publications have reported that AHA is an adverse event due to drug treatment is noteworthy, and recently, some reports have established a link between the development of AHA and clopidogrel.[5,6] This finding is in line with our hypothesis, since both ticagrelor and clopidogrel inhibit the P2Y12 receptors even though ticagrelor shows properties that distinguish it from clopidogrel.[11,14]

Conclusions

This case report indicates that ticagrelor might trigger AHA, even if an idiopathic form cannot be excluded. Although ticagrelor and clopidogrel differ from a chemical point of view,

they do share the same P2Y12 receptor action and have the same adverse effect.[5,6] A prompt response to prednisone and cyclophosphamide therapy was obtained in our patient, without suspending DAPT therapy.

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Author Contributions

Wrote the first draft of the manuscript: PP. Jointly developed the structure and arguments for the paper: RC. Contributed to the writing of the manuscript: TC, BD, LP. Agreed with manuscript results and conclusions: CM. Made critical revisions and approved: LS. All the authors reviewed and approved the final manuscript.

REFERENCES

1. Shetty S, Bhave M, Ghosh K. Acquired hemophilia A: diagnosis, aetiology, clinical spectrum and treatment options. *Autoimmun Rev*. 2011;10(6):311–6.
2. Collins P, Macartney N, Davies R, Lees S, Giddings J, Majer R. A population based, unselected, consecutive cohort of patients with acquired haemophilia A. *Br J Haematol*. 2004;124(1):86–90.
3. Collins PW, Chalmers E, Hart D, et al. Diagnosis and management of acquired coagulation inhibitors: a guideline from UKHCDO. *Br J Haematol*. 2013;162(6):758–73.
4. Franchini M, Capra F, Nicolini N, et al. Drug-induced anti-factor VIII antibodies: a systematic review. *Med Sci Monit*. 2007;13(4):RA55–61.
5. Haj M, Dasani H, Kundu S, Mohite U, Collins PW. Acquired haemophilia A may be associated with clopidogrel. *BMJ*. 2004;329(7461):323.
6. Hwang HW, Kong JH, Yu DW, Kim WT, Kim HS, Lee CI. A patient with acquired hemophilia A induced by clopidogrel. *Korean J Hematol*. 2012; 47(1):80–2.
7. Lawless S, Benson G. A 75-year-old woman with acquired haemophilia disguised by warfarin treatment. *BMJ Case Rep*. 2015;1–3.
8. Vadikolia CM, Riddell A, Brooks S, Yee TT, Brown S, Lee C. Acquired haemophilia masked by warfarin therapy. *Int J Lab Hematol*. 2007;29(1):64–8.
9. Uggla B, Linder O, Schulman S. Acquired hemophilia masked by warfarin therapy: report on two cases. *Blood Coagul Fibrinolysis*. 2003;14(8):769–72.
10. Kantor R, Mayan H, Puritz L, Varon D, Farfel Z. Acquired hemophilia masked by warfarin therapy. *Am J Med Sci*. 2000;319(3):197–201.
11. Dobesh PP, Oestreich JH. Ticagrelor: pharmacokinetics, pharmacodynamics, clinical efficacy, and safety. *Pharmacotherapy*. 2014;34(10):1077–90.
12. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–57.
13. Tiede A, Scharf RE, Dobbelstein C, Werwitzke S. Management of acquired haemophilia A. *Hamostaseologie*. 2015;35(4):311–8.
14. Cannon CP, Husted S, Harrington RA, et al. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. *J Am Coll Cardiol*. 2007;50(19):1844–51.
15. Norgard NB, DiNicolantonio JJ. P2Y12 antagonists in non-ST-segment elevation acute coronary syndromes: latest evidence and optimal use. *Ther Adv Chronic Dis*. 2015;6(4):204–18.
16. Naranjo CA, Busto U, Sellers EM, et al. A method of estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239–45.