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Case Report

Warfarin Hypersensitivity in a Patient with Mechanical Valve: A Real Challenge for the Management of Life-Long Anticoagulant Treatment

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ABSTRACT

Bleeding is the most common adverse effect of vitamin K antagonist (VKA) therapy. We describe the case of a patient who reported severe spontaneous bleeding episodes after starting treatment with warfarin-based anticoagulants following a mechanical mitral valve implant, although the international normalized ratio was within the therapeutic range. Exhaustive coagulation testing detected very low plasma factor IX (FIX) activity (FIX:C= 5 IU/dL) that increased to normal values(89 IU/dL) upon warfarin withdrawal. F9 gene sequencing revealed the presence of the p.Ala37Thr missense variation in the pro-peptide coding region. This substitution was previously associated with FIX hypersensitivity to warfarin. Patients with this variation are usually switched from VKA to direct oral anticoagulants or heparin. However, the current guidelines recommend warfarin for all patients with mechanical valves. Therefore, we determined the target plasma FIX levels in this patient to monitor warfarin therapy and allow effective anticoagulation without bleeding complications.

Keywords: Factor IX; Pro-peptide; Warfarin; Bleeding; Warfarin sensitivity

Abbreviations: ADP: Adenosine diphosphate; APTT: Activated partial thromboplastin time; DOAC: direct oral anticoagulants; F: factor; FIX C: factor IX activity; INR: International Normalized Ratio; MAF: Minor Allele Frequency; VKA: Vitamin K Antagonist; VWF: von Willebrand Factor

INTRODUCTION

Warfarin is the most widely used vitamin K antagonist (VKA) in the world [1-3]. Despite the recent introduction of direct oral anticoagulants (DOAC), warfarin is still taken by millions of patients worldwide. However, warfarin has a narrow therapeutic index, long half-life (40 hours), and large inter-patient variability; therefore regular international normalized ratio (INR) monitoring is required to guide dosing. In most clinical situations, the recommended INR therapeutic target ranges from 2.0 to 3.0. Bleeding events are the most frequent complication of warfarin therapy, and this drug was identified as one of the molecules most commonly implicated in adverse events in emergency departments. Bleeding complications attributable to warfarin are a global public health issue, because 1% of the population receives warfarin in Western countries [4], and the incidence of major bleeding events in patients receiving warfarin ranges from 0 to 16%. Although INR within the target range is usually associated with better clinical outcome and lower bleeding risk, approximately 50% of warfarin-related bleeding events occur in patients with INR between 2.0 and 3.0 [4].

We describe here a patient without personal history of bleeding, who reported multiple, severe, spontaneous bleeding episodes after starting oral anticoagulation with warfarin following cardiac valve replacement surgery.

CASE REPORT

The patient is a 52-year-old Pakistani man with a family history of hypertension and personal history of rheumatic mitral valve disease, without cardiovascular risk factors, such as hypertension, diabetes, obesity or hypercholesterolemia, but for occasional smoking. He previously underwent hernia surgery without any bleeding complication. The patient, his seven sisters and parents had no history of spontaneous or surgery- or trauma-induced bleeding. The patient reported no easy bruising, epistaxis, or gum bleeding. He had an ischemic stroke in 1997 at the age of 30, and received combined therapy with warfarin 2.5 mg and aspirin 100 mg once per day. Any attempt to increase warfarin dose resulted in large spontaneous hematomas. In 2017, the patient had a

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second ischemic stroke, while on antithrombotic treatment with fixed dose warfarin (2.5 mg) and aspirin. Mitral valve replacement surgery was advised and was performed in Islamabad in July 2017. Due to his young age, a mechanical valve (Cardiomedics®bileaflet mechanical heart valve, M7-029) was chosen, thus requiring life-long anticoagulation with VKA. There was no excessive bleeding during surgery or in the immediate postoperative period when he was treated with heparin. Warfarin (5 to 10 mg daily) was introduced during the first week after surgery (INR target between 2.5 and 3.5) in association with aspirin 75 mg and bisoprolol 2.5 mg, daily. No bleeding occurred during the first month of antithrombotic treatment. Four weeks later, the patient started to notice excessive bleeding tendency, despite INR values within the target range. During the first post-operative year, he had several emergency hospital admissions due to three sublingual hematomas, macroscopic hematuria, one spontaneous left ilio-psoas hematoma, one retroperitoneal hemorrhage, and two episodes of joint bleeds of the left knee and left hip. After the first severe bleeding episode (i.e. sublingual hematoma), aspirin was stopped and warfarin dose was reduced with a lower INR target (between 2 and 3) to reduce the risk of warfarin-related bleeding complications. However, INR target was difficult to achieve and maintain during this period. Therefore, the patient contacted our expert center of Clinical Hemostasis & Thrombosisby internet from Islamabad. Exhaustive hemostasis testing was advised. Blood cell and platelet count, platelet aggregation tests, activated partial thromboplastin time (APTT), plasma factor (F) II, FV, FVII, FX, FVIII, FIX, FXI, von Willebrand factor (VWF) antigen and ristocetin cofactor activity as well as FXIII levels were measured (Table 1).

Excessive bleeding was not caused by thrombocytopenia or thrombopathy because platelet count and function tests with collagen, adenosine diphosphate (ADP), epinephrine and ristocetin were all normal. The coagulation factors FII, FVII and FX were within the expected range for patients taking VKAs with an INR between 2-3. Moreover, FV and fibrinogen levels were normal, suggesting no liver failure. However, APTT was significantly prolonged (51.1 seconds) and FIX activity was markedly reduced (5 IU/dL).

Table 1: Results of the standard coagulationtests performed during VKA therapy and platelet characteristics. *Factor IX activity measurement after VKA withdrawal.

Coagulation tests		
	PT	16.3 s
	INR	1.6
	APTT	51.1 s
	FII:C	51 IU/dL
	FV:C	75 IU/dL
	FX:C	34 IU/dL
	FVIII:C	124 IU/dL
	FIX:C	5 IU/dL (89 IU/dL*)
	FXI:C	86 IU/dL
	FXIII deficiency screening	No deficiency
	VWF:Rco	132 IU/dL
	VWF:Ag	165 IU/dL
Platelet characteristics		
	Platelet count	187 G/L
	Platelet agglutination with ristocetin	Normal response
	Platelet aggregation with ADP	Normal response
	Platelet aggregation with collagen	Normal response
	Platelet aggregation with epinephrine	Normal response

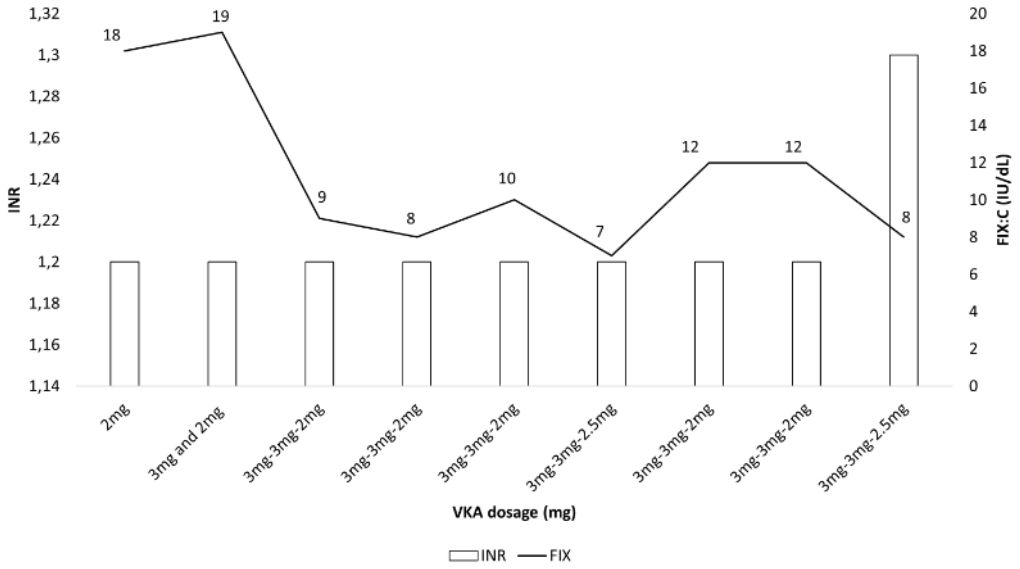

Figure 1: INR and FIX activity levels during the warfarin dose adjustment period. The X axis indicates the tested VKA dose regimens. INR underestimated the anticoagulation level in this patient with low FIX level. While FIX level does not affect the INR, there is evidence that it can influence the bleeding risk in patients on warfarin. Therefore, FIX level was used to monitor VKA therapy and to tailor the regimen in this patient. Based on our experience in patients with hemophilia B, the objective was to maintain FIX levels above 10 IU/dl to avoid spontaneous bleeding. First, coumarin (2 mg daily) reduced FIX to 18 IU/dl, then the 3 mg/day alternated with 2 mg/day regimen maintained FIX stable at 19 IU/dl. Therefore, the regimen was changed to 3 mg/day on day 1, 3 mg/day on day 2, and 2 mg/day on day 3 (and then repeated). This led to FIX activity levels between 8 and 10 IU/dl. A slightly higher dosage (3 mg/day-3 mg/day-2.5 mg/day) decreased FIX activity level to 7 IU/dl with epistaxis. The aim was to maintain FIX activity level between 10 and 15 IU/dl.

The very low FIX activity during warfarin therapy might be explained by two mechanisms: i) mild hemophilia B worsened by warfarin treatment, or ii) warfarin hypersensitivity. To distinguish between these diagnoses, warfarin was replaced by low molecular heparin (enoxaparin 6000 IU anti-Xa, twice per day) for 8 days, and FIX was measured at day 9 after warfarin withdrawal. FIX activity was normal (89 IU/dL), strongly suggesting FIX hypersensitivity to warfarin. To confirm this hypothesis, the physicians in charge of the patient in Pakistan and his family sent us a DNA sample from the patient after obtaining his informed consent for genetic testing. Sanger sequencing of the F9 gene, performed using the Big Dye Terminator kit (Applied Biosystems, Foster City, CAUSA) and an ABI 3130XL sequencer, revealed the presence of the c.109G>A(p.Ala37Thr) missense variation in exon 2 that encodes the FIX pro-peptide. This variant was found in the GnomAD database (GnomAD, https://gnomad.broadinstitute.org, May 2020) with a minor allele frequency (MAF) <1% in South Asian populations, and was previously detected in patients with warfarin hypersensitivity [5-9].

Therefore, several warfarin regimens were tested with the aim of identifying the target FIX activity for effective anticoagulation without bleeding complications. First, plasma FII and FIX levels were monitored to maintain FII activity between 30-35 IU/dL and FIX above 10 IU/dL. A dosing regimen that provided stable FIX levels between 10-15 IU/dL were established (Figure 1): warfarin 3 mg for two consecutive days followed by 2 mg on the third day and then repeated. Plasma FIX levels were measured every month and clinical symptoms, even minor bleeds, were closely monitored. In the last two years, FIX activity levels have been stable (between 8-20%) without bleeding complications and thrombosis.

DISCUSSION

This report highlights the difficulties encountered and the therapeutic challenge in patients with VKA hypersensitivity that requires long-term anticoagulation.

As bleeding is the most important complication of warfarin therapy, VKA hypersensitivity might be overlooked in some cases. In previous VKA hypersensitivity cases reported in the literature, bleeding events were of different severity, ranging from subcutaneous hematoma to life-threatening hemorrhage. In all patients with VKA hypersensitivity, the following pattern emerges: patients without history of bleeding who present bleeding episodes shortly after starting VKA therapy, despite therapeutic or even sub therapeutic INR levels. We previously showed that while FIX level does not affect INR; it can influence the risk of bleeding in patients on warfarin [4]. Thus, APTT can be a good screening test. In our patient, APTT was prolonged, and factor analysis revealed low FIX activity levels, whereas all other vitamin K-dependent coagulation factors were within the expected range. Our patient showed a similar pattern, confirming that the diagnosis of warfarin hypersensitivity should be considered whenever bleeding occurs shortly after initiating VKA therapy. In these cases, physicians should investigate APTT and FIX activity. These effects are quickly reversed by stopping VKA therapy or by administering vitamin K. Sequencing of the F9 gene are useful to confirm the diagnosis.

Two F9 variations in the highly conserved residue at position 37 (p.Ala37Thr and p.Ala37Val) have been described as warfarin hypersensitivity-causing variants [5-9]. These substitutions alterFIX affinity for gamma-glutamyl carboxylase, leading to hypersensitivity towards VKA8. Both are rare variants with a minor allele frequency (MAF)<1%. Thep.Ala37Thr variant seems to be more common in South Asian populations, while the p.Ala37Val mutation is mostly found in European populations [9].

No guideline exists for the management of patients with VKA hypersensitivity, but in the majority of reported cases, the authors suggested to use alternative anticoagulant drugs, such as DOAC or heparin [9]. However, alternative treatments are not always the best option for patients. Indeed, European and American cardiology guidelines recommend life-long warfarin therapy for patients with mechanical heart valves. Therefore, patients with warfarin hypersensitivity cannot be always switched to other anticoagulant agents, and VKA management becomes a real challenge because of their narrow therapeutic index.

To the best of our knowledge, this is the first case report describing how VKA therapy may be managed in patients with warfarin hypersensitivity. In these patients, INR monitoring does not accurately reflect the drug anticoagulant effect, and should be associated with regular FIX activity quantification. Laboratory monitoring associated with careful clinical follow-up are crucial to determine the personalized FIX or INR target that allows effective anticoagulation without bleeding complications in such patients.

CONCLUSION

Rare VKA hypersensitivity cases were reported in the literature with bleeding events despite INR between 2 and 3. Two F9 variations in the highly conserved residue at position 37 (p.Ala37Thr and p.Ala37Val) of exon 2 that encodes FIX pro-peptide are usually responsible for warfarin hypersensitivity. However, little is known about the clinical management of these patients. We report here that FIX level is a useful biomarker for monitoring anticoagulant therapy in these patients.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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