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Case Report

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Homozygous Factor V Leiden Complicated by Heparin-Induced Thrombocytopenia: A Case Report

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Abstract

Homozygous factor V Leiden (FVL) is a rare condition, occurring in 0.2% of the white population. This disease's rarity and aggressive pathophysiology can represent a challenge even to the most experienced clinicians. We report a case of a 35-year-old white man, who presented to the emergency department with a 1-week history of bilateral thigh swelling and pain. His past medical history included homozygous FVL mutation complicated by multiple venous thromboembolic events in the last decade, recent inferior vena cava (IVC) filter placement, diabetes mellitus type 2, and hypertension. Despite being trialed for different anticoagulation therapies over 10 years, including warfarin (international normalized ratio (INR) goal 2 - 3), rivaroxaban, and dalteparin, he continued to thrombose. On admission, while on a therapeutic dose of dalteparin, he was diagnosed with extensive acute deep vein thrombosis involving the bilateral femoral and iliac veins, extending proximally to his IVC filter to the renal veins, and pulmonary embolisms in the bilateral lower lobes and right middle lobe. A heparin drip was initiated, and he developed progressive thrombocytopenia over 96 h. Heparin was discontinued, and he was switched to argatroban. He was diagnosed with heparin-induced thrombocytopenia (HIT) with positive anti-platelet factor 4 (PF4)/heparin antibodies and a serotonin release assay. His platelets trended up to normal levels 5 days after heparin discontinuation. He underwent multiple thrombectomies, thrombolysis, and angioplasty of the abdominal and lower extremity veins. The IVC filter was removed. Secondary thrombophilia workup was remarkable for a positive lupus anticoagulant, which had been negative in the past. The patient was bridged to warfarin, discharged with a higher INR goal of 3 - 3.5, and continuously monitored factor II activity (goal 15-30%). This case illustrates a patient with recurrent episodes of thromboembolic events because of homozygous FVL. This condition's pathophysiology and therapeutic approach has been well studied in heterozygous carriers; however, homozygous individuals represent <1% of cases. Given the rareness of the disease, there are no well-established therapeutic guidelines, and long-term anticoagulation remains the therapeutic cornerstone. This case emphasizes the challenges in managing patients with homozygous FVL and complications that can occur due to this gap in the literature. We suggest further case reports and research studies to shed light on this serious condition and its lifetime complications.

Keywords: Homozygous factor V Leiden; Heparin-induced thrombocytopenia; Anticoagulation

Introduction

Factor V Leiden (FVL) is an autosomal dominant condition with incomplete penetrance [1]. Normally, factor V is synthesized in the liver and is activated by thrombin, and in turn, will activate prothrombin to thrombin [1]. Point mutations from G to A substitution in factor V gene in nucleotide position 1691 lead to an increased risk of developing thrombosis in one's lifetime, especially in homozygous mutations due to reduced factor V breakdown by activated protein C (APC) [1-3]. FVL is a point mutation that eliminates a critical cleavage site in factor V and factor Va, making activated factor V resistant to inactivation by APC, while inactivated factor V is less effective as a cofactor for APC cleavage of factor Va and factor VIIIa, overall increasing the risk of thrombosis due to these two changes in the coagulation cascade [4]. Specifically, factor Va is destroyed by APC by a series of cleavages, the first cleavage at Arg 506 allows for cleavage at Arg306 and Arg 679 [4]. However, the FVL mutation does not allow factor V to be cleaved at the first cleavage site of Arg 506, therefore no further cleavage occur on Arg 306 and Arg679, creating a 20-fold slower degradation process, allowing activated factor V to be present longer, resulting in thrombin to be continuously generated [4]. Since inactivated factor V cannot be cleaved at the first cleavage site of Arg 506, it is unable to act as a cofactor to degrade factors Va and VIIIa, causing reduced degradation of factors Va and VIIIa, thus reducing the anticoagulant role of factor V increasing risk of thrombosis [4]. Heterozygous mutations increase the lifetime risk of thrombosis by seven-fold, while homozygosity increases it 20- to 80-fold [1, 5]. Patients with FVL can develop venous thromboembolic events (VTEs), most commonly deep venous thrombosis (DVT) and pulmonary embolisms (PEs), but also can include increased risks for cerebral

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vein thrombosis and Budd-Chiari syndrome [1]. The current management for patients with FVL that develop VTE is the same as VTE management for the general population, which is oral anticoagulation, preferably warfarin, due to increased adherence [4].

Case Report

Investigations

A 35-year-old white man presented to the emergency department with complaints of worsening bilateral thigh swelling and pain for 1 week. His past medical history included homozygous FVL mutation complicated by recurrent VTE, followed by inferior vena cava (IVC) filter placement, diabetes mellitus type 2, and hypertension. His grandmother has a history of DVT.

He was first diagnosed with an unprovoked right popliteal DVT at age 25. Thrombophilia workup revealed homozygous FVL DNA gene mutation; the prothrombin (PT) gene mutation (PGM) *G20210A* was negative. The decision was to pursue indefinite anticoagulation with warfarin (international normalized ratio (INR) goal of 2 - 3). Despite reported medication adherence, at age 30, he developed chest pain and shortness of breath (SOB). Chest computed tomography angiography (CTA) revealed a saddle embolus and extensive bilateral acute PE; lower extremities (LE) duplex revealed indeterminate age bilateral occlusive DVT in the femoral veins. Warfarin was discontinued because the INR was found to be subtherapeutic on admission, and rivaroxaban was initiated with frequent anti-factor Xa monitoring given concerns of non-compliance by the primary hematologist. At age 33, a CTA performed given complaints of SOB showed resolution of prior PE. Eight months before presentation, while on uninterrupted anticoagulation with rivaroxaban, he was diagnosed with acute right posterior tibial DVT, and the decision was made to place an IVC filter. Eight weeks before admission, he developed abdominal pain while taking rivaroxaban. Imaging revealed distal IVC and bilateral common iliac vein thrombi. He underwent thrombolysis, and mechanical thrombectomy with balloon angioplasty of the left iliac vein and IVC; he was maintained on a heparin drip while hospitalized. He was then discharged on enoxaparin but complained of pruritus at the injection site. He was switched to dalteparin, which had been used and tolerated consistently until admission to our institution.

Diagnosis

Physical exam revealed blood pressure (BP) 122/88 mm Hg, heart rate (HR) 105 beats/min, respiratory rate (RR) 17/min, saturating 100% on room air; cardiovascular exam: tachycardic, normal S1 and S2, no S3, S4 murmurs, rubs or gallops; lungs were clear to auscultation bilaterally; the abdomen had normal bowel sounds, was mildly distended and nontender; bilateral lower extremity pitting edema up to the thighs. On admission, LE venous duplex revealed acute DVT involving the femoral veins bilaterally. Computed tomography (CT) venogram of the chest, abdomen, and pelvis revealed acute PE in the bilateral lower lobe pulmonary arteries, right middle lobe pulmonary arteries, and extensive acute DVT involving the femoral and iliac veins bilaterally, extending proximal to the IVC filter to the level of the renal veins. Laboratory workup showed a hemoglobin (Hb) 12.4 g/dL (normal range (NR) 12 - 16 g/dL), white blood cells (WBC) 8.12 × 10^3/µL (NR 4 - 10 × 10^3/µL), platelets 124 × 10^3/µL (NR 150 - 399 × 10^3/µL).

Treatment

The patient immediately began treatment with a heparin drip. On admission day (AD) 3, he underwent right femoral vein suction thrombectomy, and thrombolysis was initiated with tissue plasminogen activator (tPA). The daily platelets count decreased (AD 1 = 124, AD 2 = 93, AD 3 = 56, and AD 4 = 39); heparin-induced thrombocytopenia (HIT) type 2 was suspected. The 4Ts score = 6, based on the following criteria: platelets fall > 50% and platelets *nadir* ≥ 20,000 (2 points), platelets fall within 1 day after starting heparin if the patient had been exposed to heparin products in the last 30 days (2 points), no alternative explanation for platelets fall (2 points). On AD 4, the patient was switched to argatroban for therapeutic anticoagulation and anti-platelet factor 4 (PF4)/heparin immunoglobulin (Ig)G antibodies test was obtained. On AD 5, venogram demonstrated minimal improvement in the acute bilateral lower extremity venous clot burden despite treatment with tPA; the lack of improvement was attributed to possible HIT and its prothrombotic effects, thus mechanical thrombectomy was performed on the bilateral lower extremities yielding patent bilateral iliac, femoral, and central popliteal veins at completion. On AD 8, he underwent a venogram with suction thrombectomy of the IVC, bilateral common iliac, and external iliac veins; the IVC filter was removed, and bilateral common iliac vein stents were placed. Also, on AD8, the anti-PF4/heparin IgG antibodies returned positive with an optical density of 1.56, and a serotonin release assay was performed and returned positive with 44% and 82% serotonin release after low-dose unfractionated heparin exposure, and a decrease to 1% after exposure to the high dose of unfractionated heparin. Platelets slowly normalized with an uptrend to 154 × 10^3/µL on AD 9, 5 days after the initial discontinuation of heparin. Workup for alternative hypercoagulable states, including occult malignancy and paroxysmal nocturnal hemoglobinuria were negative. Protein C and protein S activities were within normal limits. There was no clinical evidence of Behcet syndrome. Interestingly, lupus anticoagulant (LAC) was positive with a PTT-LAC screen of 62 s (NR < 40), dilute Russell's viper venom time (DRVVT) screen of 36 s (NR < 45), and hexagonal phase was positive. Anti-B2 glycoprotein IgG/IgA/IgM and anticardiolipin IgG/IgM/IgA were negative. The patient had antiphospholipid antibody (APLA) screening 10 years prior that was negative, and there was a concern that LAC was a false positive result as it was obtained while the patient was receiving treatment with heparin infusion.

Follow-up and outcomes

He was later bridged to warfarin and discharged with a higher INR goal of 3 - 3.5 given concerns of prior thrombosis while on warfarin treatment with an INR goal of 2 - 3, and questionable falsely elevated INR due to LAC. Continuous monitoring of factor II activity (goal 15-30%) was recommended until antiphospholipid antibody testing was repeated 12 weeks apart.

Discussion

FVL is an autosomal dominant disease, and heterozygosity for the FVL mutation is the most common form of inherited thrombophilia in the white population, with a prevalence of about 1-5% [1]. Homozygous FVL is an even rarer condition, occurring only in 0.2% of the population [2]. Heterozygous mutations increase the lifetime risk of thrombosis by sevenfold, while homozygosity increases it 20- to 80-fold [1, 5]. Homozygous individuals also experience thrombotic events earlier in life than heterozygous individuals [6]. The median age at which individuals experience their first thrombotic event is 31 years in homozygous individuals, compared to 44 years in heterozygous individuals [6]. This case illustrates a patient with recurrent episodes of thromboembolic events because of this entity.

The current recommended management of recurrent VTE and its complications in patients with FVL is the same as of the general population of lifetime anticoagulation, and the decision of which kind of anticoagulation does not change based on FVL mutation, but patient preference, adherence, and the severity of VTE and its complications [1]. A case series that studied a total of 65 patients with homozygous PGM (prothrombin *G20210A*), homozygous FVL, and compound heterozygous FVL-PGM demonstrated that 90% of recurrent thrombotic events occurred during times where these patients were not treated with anticoagulation; while 6% occurred in patients treated with warfarin [7]. This study concluded that anticoagulation is an effective method for preventing recurrent thromboembolism and should be pursued in all patients with homozygous FVL and compound heterozygous PGM-FVL after the first diagnosis of unprovoked DVT [7]. Our patient exhibited thrombosis recurrence despite uninterrupted anticoagulation for 10 years.

On the other hand, HIT is an acquired immune complication after exposure to heparin products or low-molecular-weight heparin, resulting in thrombosis [8, 9]. HIT typically occurs 4 - 14 days following initiation of heparin therapy and is caused by the formation of heparin and platelet factor 4 complex, with IgG antibodies resulting in an immune reaction that leads to thrombocytopenia and an increased risk for thrombosis due to the activation of platelets and generation of thrombin [9, 10]. This patient exhibited extensive clot burden primarily from homozygous FVL mutation and worsened by HIT given failure to improve with thrombolytic therapy, which led to invasive procedures and removal of the IVC filter. The removal of the IVC filter may seem counterintuitive when looking at the indications for IVC filters: failure of anticoagulation, and thrombocytopenia, both of which our patients meet [10]. However, an IVC filter can increase the risk of thrombosis as it is a foreign body in a patient with a hypercoagulable state [10]. A study investigated the safety of IVC filters in patients with HIT, and they found that nine of 10 of the patients with IVC filters and HIT developed new thromboses related to IVC filters [10]. This demonstrates that removing the IVC filter was necessary and crucial in our patient's case.

Studies have recommended lifelong anticoagulation, and warfarin is typically used for patients with severe VTE with an INR goal at the upper end of the therapeutic range [1, 6]. However, this current recommendation does not come without limitations; while most episodes of recurrent VTE appear to be present while patients are not anticoagulated, warfarin is a drug with a narrow therapeutic window, minimal dietary changes, or missed doses can significantly alter the INR. Our patient, in this case, failed therapy with a direct oral anticoagulant (DOAC). Lastly, HIT further complicates medical management as he could no longer use heparin analogues as part of his anticoagulation regimen, limiting the options for anticoagulation and potentially medication adherence.

It is crucial to exclude multiple causes of thrombophilia in patients with recurrent VTE, as these can often coexist. This case posed a clinical dilemma when LAC testing returned positive, as the sample had been collected while the patient was on treatment with heparin infusion. Two screening tests commonly detect LAC: partial thromboplastin time (PTT)-LAC screen and DRVVT. The hexagonal phase is a confirmatory test that would validate the presence of LAC. LAC testing is discouraged in patients receiving anticoagulation with unfractionated heparin, given the potential for false positive results. Although most novel laboratory tests have reagents that neutralize heparin, false positives are possible [11]. On this patient, APLA had been performed in the past and yielded negative results. It has also been described transient LAC in the presence of endothelial injury, and thus the importance of repeat testing at least 12 weeks apart to confirm a diagnosis of antiphospholipid syndrome (APLS) when the clinical context is appropriate [12]. Decision was made to treat our patient with warfarin. It is the anticoagulant of choice in patients with APLS. It is also given contraindication for heparin products and recurrent thrombosis while on a DOAC; warfarin was also the drug that would allow for versatility when increasing the therapeutic dose. Given his history of thrombosis while on warfarin with an INR goal of 2 - 3, and the possibility of a falsely elevated INR due to LAC, his INR goal was increased to 3 - 3.5. Factor II activity and chromogenic assay for factor X are two studies used to measure anticoagulation in patients taking vitamin K antagonists with unreliable INR [13]. Therapeutic anticoagulation is described as an activity level between 15% and 30%, which is reliable when adjusting warfarin doses [13].

Anticoagulation still represents a challenge in patients with homozygous FVL, as recurrent thrombosis is common. This case illustrates the unique complexity of suffering from an inherited thrombophilia and developing an acquired thrombophilia such as HIT. It also describes challenges that might interfere with medication adherence and effectiveness. Finally, this case depicts the difficulties encountered when thrombophilia testing is performed in patients receiving therapeutic an-

ticoagulation, and how this could further complicate medical management. To the best of our knowledge, after revision of the literature, similar cases have not been previously described.

The limitations of this manuscript are that it is a particular case and does not represent all patients with homozygous FVL. This case demonstrates the need for further case reports and research studies to explore optimal management for patients with homozygous FVL with recurrent VTE while on anticoagulation therapy.

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Conflict of Interest

We declare that none of the authors have any conflict of interest regarding the manuscript.

Informed Consent

Verbal consent was obtained.

Author Contributions

Rocio Bautista Sanchez collected data, wrote part of the manuscript, and performed literacy research. Yumiko Gely wrote part of the manuscript and performed literacy research. Josune Iglesias collected data and wrote part of the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

FVL: factor V Leiden; VTEs: venous thromboembolic events; IVC: inferior vena cava; HIT: heparin-induced thrombocytopenia; INR: international normalized ratio; DVT: deep venous thrombosis; PE: pulmonary embolism; PGM: prothrombin gene mutation; SOB: shortness of breath; CTA: computed tomography angiography; BP: blood pressure; HR: heart rate; RR: respiratory rate; CT: computed tomography; Hb: hemoglobin; WBC: white blood cell; AD: admission day; tPA: tissue plasminogen activator; DOAC: direct oral anticoagulant; DRVVT: dilute Russell's viper venom time; LAC: lupus anticoagulant; APLA: antiphospholipid antibody; APLS: antiphospholipid syndrome; LE: lower extremity

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