Prothrombin G20210A Gene Mutation-Induced Recurrent Deep Vein Thrombosis and Pulmonary Embolism: Case Report and Literature Review

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Abstract
Inherited thrombophilia is an important cause of venous thrombosis. The Factor V Leiden (FVL) is the most commonly encountered mutation, followed by the prothrombin G20210A gene mutation (PTM). The typical venous thrombotic events (VTEs) associated with PTM mutations are deep vein thrombosis (DVT) and pulmonary embolisms (PE). The PTM is inherited in an autosomal dominant pattern with variable penetrance. While heterozygous PTM mutations are more frequent and well documented in the literature, rare cases of homozygous PTM mutations are also reported. In this report, we discuss a 56-year-old male with a past medical history of homozygous prothrombin gene mutation (G20210A) who presented with an unprovoked DVT of the right lower extremity involving both the proximal and distal veins associated with multiple bilateral PEs. This case is unique in terms of the homozygous PTM inheritance, the age at which the patient presented (usually presentation is earlier in life), and the fact that he had a recurrence of both DVT and PE simultaneously.

Keywords
prothrombin mutation, pulmonary embolism, deep venous thrombosis

Introduction
The prothrombin G20210A gene mutation (PTM) is the second most commonly inherited thrombophilia after Factor V Leiden (FVL) and was first described by Poort and colleagues in 1996.1 Their paper identified a missense mutation in the 3' untranslated region of the prothrombin gene associated with thromboembolic events and an elevated level of serum prothrombin. The mutation results from a substitution of guanine for adenine at position 20210 of the prothrombin gene on chromosome 11.2 There is evidence that the hypercoagulable state is due to the increased efficiency of the polyadenylation site, leading to an increase in prothrombin mRNA and protein expression.3 Although hyperprothrombinemia may also be found among the normal population, Castoldi and colleagues demonstrated that the concurrent elevation of all liver-synthesized factors including protein S and antithrombin precludes a hypercoagulable state.4 PTM is accordingly classified as an autosomal dominant mutation with variable penetrance.

Estimates of the prevalence of PTM heterozygotes range between 1% and 6%, with an overall prevalence estimate of 2% of the general population.5,6 Prothrombin G20210A gene mutation homozygotes, such as our patient, are even less common, and indeed, there is a paucity of reports in the literature regarding homozygotes. As of 2006, only 70 cases of homozygous PTM were highlighted in the literature.7 The mutation also appears to have an ethnic predisposition. While there is a preponderance of the allele among persons of Southern European heritage, the allele frequency drops significantly among persons of African or Asian descent.6

Multiple studies have explored the relationship between PTM and the occurrence of venous thromboembolism (VTE). Decidedly, there is a 3 to 4-fold increased risk of thrombosis among PTM patients, with odds ratios in the range of 3.13 to 3.7 after excluding patients with coexisting

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When the co-occurrence of PTM with FVL is examined, a synergism is unveiled with odds ratios for VTE in the range of 11.8 to 58.6. The typical VTE events encountered among PTM patients are deep vein thrombosis (DVT) and pulmonary embolism (PE). However, there have been reports of thrombosis occurring at atypical sites, including portal, hepatic or cerebral veins.

The gold standard for the diagnosis of PTM remains genetic testing via polymerase chain reaction (PCR). Since there is a significant overlap between the distributions of serum prothrombin concentration within the normal population versus PTM patients, coagulation testing for the disorder is unreliable for the diagnosis of PTM. The mainstay of management remains anticoagulation for 3 to 6 months, with indefinite anticoagulation considered based on other factors such as sex, family history, homozygosity, or whether the index event was provoked or unprovoked.

Here, we present the case of a PTM homozygote who developed recurrent DVT/PE 4 years following a provoked VTE event in the setting of trauma.

**Case Presentation**

A 56-year-old man with a history of underlying homozygous prothrombin gene mutation G20210A and prior provoked bilateral lower extremity DVTs and PE presented to the emergency department post-acute onset of palpitations in February 2020. His past medical history was notable for a motorcycle accident in 2017 for which he had shoulder surgery, after which he developed a DVT and PE and was discharged on rivaroxaban. Hypercoagulability workup including FVL, Prothrombin G20210A mutation, and deficiencies of antithrombin, protein C and protein S, only revealed homozygous prothrombin G20210A mutation. In June 2020 patient had a negative venous duplex, and a CT angiogram of the chest was negative for PE. He has been off anticoagulation for about 1 year after recommendations to be discontinued due to negative radiographic imaging. The patient reported that he is not on any current medications. Family history was negative for thrombosis or bleeding disorders. He was tachycardic with a heart rate of 120-130 beats per min, normotensive 139/78, hypoxic at 88% on room air upon initial presentation to the emergency department. Physical examination was otherwise unremarkable. Electrocardiogram showed sinus tachycardia, S1Q3T3, incomplete RBBB, right heart strain pattern evidenced by T wave inversions in V1-V3 as seen in Figure 1. Lab studies were as follows: Hb 15 g/dl (normal range 14-18 g/dl), platelets 190,000/ ul (normal range 130-400 x 10^3), troponin I 1.15 ng/ml (normal range < 0.5), Cr 1 mg/dl (0.5-1.2 mg/dl), BNP < 15 pg/ml (normal range <100), D-dimer (DDU) > 5000 ng/ml (normal range < 230), PT/INR 15.7/1.3 (PT normal range 12.6-14.6), PTT 30s (normal range 23-38). Chest x-ray was unremarkable, as seen in Figure 2. CT pulmonary angiogram showed extensive bilateral PEs with evidence of right heart strain (Figure 3-4). Echocardiogram confirmed...
right heart strain with moderate to severe enlargement of the right ventricle. The right ventricle was severely hypokinetic (positive McConnell sign), severe right ventricular pressure overload with a shift of interventricular septum to the left, and hyperdynamic left ventricle with an ejection fraction of 70-75%. Given the right heart strain and elevated troponin, PE was considered submassive intermediate-high risk PE. Interventional radiology (IR) consultation was obtained for catheter-directed thrombolysis. The patient was taken within 4 hours to IR, where he had catheter insertion followed by infusion of 0.5 mg of Alteplase (TPA) via 2 ports of both catheters for a total of 1 mg/hr for 24 hours and 700 unit/hr heparin. Coagulation profile and hemoglobin were monitored every 6-8 hours. Venous duplex scan demonstrated acute deep venous thrombosis of the right common femoral, femoral, popliteal, gastrocnemius, and peroneal veins and long-term DVT of the left posterior tibial vein. The patient had bleeding from the catheter site that resolved after the interventional radiologist removed the catheter after 24 hours. The patient had a significant drop in hemoglobin from 14 to 7.7 g/dl. The patient received a transfusion of 2 units of packed RBCs. No active source of bleeding was found. Hemolytic and DIC workup were negative as follows: serum LDH 200 u/l (normal range 98-192), reticulocyte count 2.6%, corrected for Hct is 1.2% (normal range 0.5-1.5%) and peripheral smear was normal, fibrinogen 305 mg/dl (normal range 270-500), Fibrin split products negative, PTT 27s, PT 15. Fecal occult blood was negative. CT scan of the chest, abdomen, and pelvis failed to show any evidence of internal bleeding. It was presumed that the drop in hemoglobin was due to the late equilibration of the blood loss that the patient had at the time of the catheter-directed thrombolysis. Physical therapy evaluated the patient as he was noted to become tachycardic up to 150 beats/min with ambulation and recommended subacute rehabilitation and cardiac rehabilitation. Therefore, the patient was discharged to subacute rehabilitation on rivaroxaban 20 mg daily with outpatient hematology and cardiology follow-up.

Discussion

Since the description of PTM in 1996, many studies have explored the relationship between the mutation and the development of VTE. PTM heterozygosity increases the risk of VTE 3 to 4-fold.8-10 We postulate that the risk of VTE may be even greater for homozygotes on account of a further increase in serum prothrombin concentration. Our patient developed postoperative DVT/PE following a motorcycle accident. The patient’s status as a PTM homozygote naturally lends itself to the patient’s hypercoagulable state, but the patient’s VTE was provoked in the setting of trauma and postoperative immobility. Indeed, Stralen and colleagues determined that minor leg injuries, even those as innocuous as a sprain, can predispose to the development of venous thrombosis in the absence of other risk factors.16 Furthermore, they found that patients with leg trauma and FVL carry a 50-fold increased risk of thrombosis.16 Therefore, there may also be an underlying synergism between trauma and PTM.
Table 1. Prothrombin G20210A Homozygous Case Reports.

| Publication | Age/sex | Event | Acquired risk factors | Family history | Additional risk factors |
|-------------|---------|-------|-----------------------|----------------|-------------------------|
| Scott et al\(^{17}\) | 18, female | DVT, ileo-femoral | Pregnancy | Negative | Negative |
| Howard et al\(^{18}\) | 24, male | Myocardial infarction; subsequent DVT; PE | Smoking, surgery, and immobilization | Negative | FVL het |
| Kyrle et al\(^{19}\) | 56, male | DVT, right leg; phlebitis | Not reported | Positive | Negative |
| 52, female | Phlebitis, bilateral legs, recurrent | Pregnancy | Positive | Negative |
| González Ordóñez et al\(^{20}\) | 65, male | Thrombotic transient ischemic attacks; DVT, femoro-iliac | Surgery | Not reported | Negative |
| Zawadzki et al\(^{21}\) | 48, male | DVT; PE, mesenteric venous thrombosis | Not reported | Positive | MTHFR C677T het\(^*\) |
| 30, female | PE | Not reported | Positive | MTHFR C677T het\(^*\) |
| Howard et al\(^{22}\) | 44, male | DVT, left popliteal; PE | Not reported | Positive | MTHFR C677T het\(^*\) |
| 74, female | Asymptomatic | Preganancies | Positive | MTHFR C677T hom\(^\dagger\) |
| 33-43, female (3 cases) | Asymptomatic | Pregnancy, surgery | Positive | MTHFR C677T hom\(^*\) (2 hom, 1 het) |
| Alati et al\(^{23}\) | 72, male | Asymptomatic | Surgeries | Positive | Negative |
| Girolami et al\(^{24}\) | 29, male | Asymptomatic | Surgery | Negative | Not reported |
| 39, male | Asymptomatic | OC, pregnancies | Negative | Not reported |
| Girolami et al\(^{25}\) | 21, female | Asymptomatic | Surgery | Positive | Not reported |
| 15, female | Asymptomatic | Negative | Positive | Not reported |
| Giordano et al\(^{26}\) | 31, female | Phlebitis, left leg; TIAs; ischemic stroke | Negative | Negative | Anticardiolipin antibodies |
| Eikelboom et al\(^{27}\) | 66, female | DVT, left leg | Minor surgery | Positive | Negative |
| 68, male | Asymptomatic | Not reported | Positive | Not reported |
| Souto et al\(^{28}\) | 51, female | Asymptomatic | Negative | Positive | Negative |
| 19, female | Asymptomatic | Negative | Positive | Negative |
| Akar and Eğin\(^{29}\) | 73, male | Asymptomatic | Diabetes, carcinoma | Not reported | Not reported |
| Meinardi et al\(^{30}\) | 34, male | DVT | Negative | Negative | FVL hom |
| 26, female | PE | Surgery | Positive | FVL het |
| 20, female | Asymptomatic | Negative | Positive | FVL het |
| Kling et al\(^{31}\) | 44, male | Retinal vein and retinal artery occlusion | Lymphoma | Positive | Negative |
| Corral et al\(^{32}\) | 45, female | DVT | Surgery | Positive | FVL het |
| 43, male | DVT, PE | Trauma, vascular injury | Positive | FVL het |
| 34, female | DVT | Pregnancy | Positive | FVL het |
| Bauduer et al\(^{33}\) | 40, male | Mesenteric venous thrombosis | Obesity | Positive | Negative |
| Martlew et al\(^{34}\) | 31, female | Asymptomatic | Pregnancies | Negative | MTHFR C677T het\(^*\) |
| Acquila et al\(^{35}\) | 22, female | DVT, left leg | Pregnancy | Negative | Negative |
| Sivera et al\(^{36}\) | 28, female | DVT, femoral-iliac | OC, systemic lupus | Negative | Anticardiolipin antibodies |
| 2, male | Asymptomatic | Not reported | Positive | Negative |
| Soria et al\(^{37}\) | 9, male | DVT, right popliteal | Negative | Negative | FVL hom, MTHFR C677T hom\(^\dagger\) |
| Wulf et al\(^{38}\) | 18, male | Superficial thrombosis | Negative | Positive | FVL hom |
| 15, female | Asymptomatic | Not reported | Positive | Negative |
| Vayá et al\(^{39}\) | 19, female | DVT, recurrent | OC, smoker | Unknown | Negative |
| Kosch et al\(^{40}\) | 13, male | DVT, bilateral legs; PE, recurrent | Immobilization | Positive | Protein S deficiency |
| 19, male | Asymptomatic | Not reported | Positive | Protein S deficiency |
| Boinoc et al\(^{41}\) | 13, male | DVT, bilateral femoral; PE, bilateral | Immobilization | Positive | Protein C deficiency, Protein S deficiency |
| Kurkowska-Jastrzebska et al\(^{42}\) | 29, female | Cerebral venous thrombosis | OC | Negative | FVL het |
| Klein et al\(^{43}\) | 29, female | Eclampsia, HELLP syndrome | Pregnancy | Negative | Negative |
| WBH Klein et al\(^{44}\) | Neonate, female | Cerebral venous sinus thrombosis, PE | None | None noted | MTHFR C677T het\(^*\), low antithrombin |

(continued)
Although our patient required shoulder surgery in the aftermath of his accident, he conceivably suffered minor trauma to the lower extremities.

Bosler and colleagues investigated the existing case reports of homozygotes and attempted to categorize each according to categories such as age, index event, and risk factors. In this article, we attempt to expand on the work undertaken by Bosler and colleagues to include individual cases reported in the literature between 2005 and 2021. Table 1 shows the reported cases of homozygous prothrombin G20210A patients during this time period. While many were asymptomatic, the most common VTE event was isolated DVT. In contrast, our patient suffered a concurrent DVT/PE during both the initial event and recurrence 4 years later. Intriguingly, while our patient had no other identifiable genetic coagulopathies, all except one of the previously reported patients with concurrent DVT/PE carried an additional inherited risk factor such as FVL, Protein S deficiency, Protein C deficiency, or antithrombin deficiency. Furthermore, our patient’s first VTE occurred at 52 years of age. Strikingly, the index event of only 12 of the 73 reported cases occurred over age 50 years. We believe that these aspects of the patient’s disease course align with the phenotypic heterogeneity among PTM homozygotes discussed by Bosler and colleagues.7

### Table 1. (continued)

| Publication      | Age/sex | Event                          | Acquired risk factors | Family history | Additional risk factors |
|------------------|---------|--------------------------------|-----------------------|----------------|-------------------------|
| Bosler et al7    | 33, female | DVT leg, PE                   | OC, former smoker     | Yes, father DVT | MTHFR A1298C het⁴      |
|                  | 63, male  | Recurrent DVTs arm,            |                       | Yes, mother PE | MTHFR C677T het⁴      |
|                  |          | subsequent DVT leg           |                       |                |                         |
|                  | 43, male  | DVT leg                       | Former smoker         | None noted     | Low antithrombin       |
|                  | 22, female | DVT                           | OC                    | Positive       | FVL hom                |
| Germanakis et al⁷ | 4, male   | Stroke                        | Glenn anastomosis for double inlet left | Positive       | MTHFR C677T hom⁴      |
|                  |          |                               | ventricle            |                |                         |
| Sogawa et al⁸⁷   | 16, male  | Stroke, DVT, PE               | Negative              | Positive       | FVL het                |
|                  | 30, female | DVT                           |                       | Positive       | FVL hom                |
|                  | 43, male  | Recurrent DVTs arm,           | Behcet’s disease, OC  | None noted     | Negative               |
|                  |          | subsequent DVT leg           |                       |                |                         |
|                  | 43, male  | DVT                           | Negative              | Negative       | Anticardiolipin        |
|                  |          |                               |                       |                | antibodies, MTHFR      |
|                  |          |                               |                       |                | C677T het⁴             |
|                  | 24, female | Asymptomatic                 | Negative              | Positive       | Negative               |
|                  | 40, female | Stroke                        | Negative              | Positive       | Negative               |
| Roman-Gonzalez et al⁵³ | 32, male      | DVT, PE                      | Sedentary             | Positive       | Not reported           |
|                  | 33, female | Asymptomatic                 | OC, Pregnancy         | Positive       | Not reported           |
|                  | 31, female | DVT                           | Negative              | Positive       | Not reported           |
|                  | 31, female | Asymptomatic                 | OC, Pregnancy         | Positive       | Not reported           |
| Velarde-Félix et al⁵⁴ | 48, female | Budd-Chiari Syndrome; DVT, recurrent | Negative | Positive | FVL het, JAK-2 V617F mutation |
|                  | 25, male  | PE                            | Negative              | None noted     | Anticardiolipid        |
|                  | 24, female | Asymptomatic                 | Negative              | Positive       | syndrome               |
| Stoeva and Koleva⁵⁶ | 15, male   | Bilateral superficial femoral artery thrombosis | Negative | None noted |                      |
|                  | 25, male  | PE                            | Negative              | Positive       | PAI-1 4G/5G, MTHFR A1298C and C677T het⁴ |
|                  | 24, female | Asymptomatic                 | Negative              | Positive       | MTHFR A1298C and C677T het⁴ |
| George and Kent⁵⁷ | 15, female | DVT, PE                      | OC, Obesity           | Positive       | FVL het                |
| Costa et al⁵⁸    | 25, male  | PE                            | Not reported          | None noted     | FVL het                |
| Fiore et al⁵⁹    | 31, unknown | PE, Internal iliac vein thrombosis | Not reported | None noted | Anticardiolipid         |
| TRMC, not previously reported | 56, male | DVT, PE                      | Trauma, surgery, immobility | None noted | Negative               |

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; FVL, Factor V Leiden mutation; OC, oral contraceptive use; het, heterozygous; hom, homozygous; WBH, William Beaumont Hospital cases; TRMC, Trinitas Regional Medical Center.

⁴ Per AHA, MTHFR variants are no longer considered a risk factor for VTE.⁶⁰
colleagues. In addition, during the recurrent VTE episode, our patient suffered DVT of the common femoral, femoral, and popliteal veins. Thus, the patient’s presentation supports the findings of Dentali and colleagues, whose data suggest that there is a slight increase in the risk of proximal DVT versus distal DVT among PTM patients. Following our patient’s initial and recurrent DVT/PE, he was prophylactically prescribed rivaroxaban. While the management of VTE among PTM patients is infrequently reported in the literature, Costa and colleagues reported the case of a PTM homozygote with coexisting FVL who was prescribed enoxaparin in the acute setting and placed on apixaban for indefinite anticoagulation. The authors reported a favorable d-dimer response and suggested that this treatment option can be considered for unprovoked VTE in the context of inherited thrombophilia. Likewise, patients such as ours with elevated D-dimer levels >5000 mg/dL may be suitable candidates for trending the treatment response to anticoagulation with novel oral anticoagulants.

Conclusion

In summary, middle-aged or elderly patients may develop a provoked DVT/PE in the setting of isolated PTM homozygosity, despite being previously asymptomatic. This case is, therefore, worth reporting to expand upon the spectrum of presentations among PTM homozygotes encountered in practice. We urge our readers to conduct more research on the choice and duration of anticoagulation treatment needed to manage patients with prothrombotic mutations.

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Ethics approval

Ethics approval is not required for case reports in our institution.

Informed Consent

Verbal consent was obtained from the patient for their anonymised information to be published in this article.

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