CLINICAL VIGNETTE

Two Distinct Genetic Mutations Leading to Hypercoagulability In a Patient Presenting with Pulmonary Emboli

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A 56-year-old male with hypertension and hypercholesterolemia noticed occasional episodes of shortness of breath, and was given a short course of antibiotics. He initially felt slightly improved, but developed worsening acute dyspnea with sharp chest pain, and was directed to the emergency room. Initial evaluation included an elevated D-Dimer, venous Doppler showing clot in the left peroneal vein, and CT angiogram with bilateral filling defects, consistent with pulmonary emboli. He was clinically stable, and was started on apixiban, and discharged from the emergency room.

He was referred for hematologic evaluation. His main medical history is only as above, with prior orthopedic procedures, with no post-operative complications. He is up to date with recommended cancer screening. His family history is significant for his paternal grandmother with a deep venous thrombosis (DVT) in her 80's. His family tree is otherwise fairly limited, but he is unaware of any other clotting issues.

Given his fairly young age, and the family history, he was tested for an inherited hypercoagulable state. This included Protein C or S deficiency, Antithrombin deficiency, and genetic testing for the Factor V Leiden (FVL) or Prothrombin G20210A mutation. Interestingly, he was found to have a mutation in both the FVL gene and in the Prothrombin gene, indicating he is a compound heterozygote for two distinct genetic hypercoagulable conditions.

He clinically improved on apixiban, and our current plan is life-long anti-coagulation as the clot was unprovoked, with potentially life-threatening pulmonary emboli. We discussed screening family members. Although there are no clear data such screening will improve survival, he wanted his daughter tested as she is considering oral contraceptives.

Understanding of the clotting cascade, and its critical ability for self-regulation continues to expand. The hemophilias have long been defined given their well-known inheritance pattern, and dramatic clinical implications. On the other hand, defects in the clotting cascade that may lead to unchecked clotting can be less obvious clinically, and who to test remains an area of some controversy. Although the patient does not have a striking family history, and his age is not out of range for a spontaneous event, he has two separate genetic defects that predispose to hypercoagulability, as manifest by his unprovoked development of a DVT with embolization to the lungs.

It has been known for decades that deficiencies in Protein C, Protein S and antithrombin, proteins that limit the coagulation cascade, can lead to clinical hypercoagulability. However they are relatively rare in the general population, with an estimated prevalence of 0.02 to 0.2% for antithrombin deficiency and up to 0.5% for Protein C deficiency. In the last two decades, commercially available assays have become available for the FVL mutation and the prothrombin mutation. This has been a game-changer for hematologists tasked with looking for the cause of clotting in certain individuals, as these genes are relatively common. The prevalence of a FVL mutation in the United States is estimated at up to 5%, and the prothrombin gene at 2%. There are racial differences, with these genes being more common in Caucasians, and much less common in Asians, where the gene prevalence is 0.45%. Stated another way, one in twenty-three individuals may carry the FVL mutation and one in sixty-five the prothrombin gene, so the likelihood of being a compound heterozygote is roughly one in fifteen hundred, as in our patient.

The mechanism of action for these two inherited conditions has been elucidated, perhaps more clearly for FVL then for the prothrombin mutation carriers. Those who have the FVL mutation, have an aberrant protein due to a single amino acid change of arginine to glutamine at position 506. This leads to a factor V that is resistant to deactivation by activated protein C – hence the original papers describing the FVL mutation referred to it as Activated Protein resistance, and prior to assays for the gene, the diagnosis was based on demonstrating this resistance.[1] Patients with the prothrombin gene, which also is caused by a single amino acid substitution, have a roughly 30% higher circulating concentration of prothrombin, which is felt to be the main cause of their hypercoagulability.[2]

The acute management of a patient with a clot related to one of these genetic alterations is no different from that of a patient without such a mutation. That is, three to six months of anti-coagulation, with no known benefit amongst available options for such anti-coagulation. The main questions become that of duration of anti-coagulation, and handling of screening of family members. Interestingly, there is no clear data that

recurrent clotting is necessarily higher in carriers of FVL or the prothrombin gene, so their mere presence does not mandate life-long anti-coagulation. Rather, the decision for longer duration of therapy should be individualized, taking it to account whether or not the clot was provoked, the clinical severity of the clot, and if the clot arose in an unusual location.[3] Screening of family members is generally not recommended, unless there may be changes to the family member's ongoing management, as the presence of the gene in a family member does not dictate management. Our patient has both mutations with higher risk of recurrent clot and presented with pulmonary emboli, so longer-term therapy was recommended. We also recommended testing his daughter specifically, as it may effect her contraceptive choice, but did not advocate testing of his son or other family members.

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