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UNMASKING ACQUIRED HEMOPHILIA B DISGUISED IN AN ELDERLY MALE ON WARFARIN TREATMENT – A CASE REPORT AND LITERATURE REVIEW.

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Abstract

Acquired hemophilia B is a rare disorder of blood coagulation[1]. It is not uncommon for Acquired Hemophilia B to be disguised under the mask of Warfarin treatment overdose as the manifestations like easy bleeding and bruisibilty are similar[2]. Thus, a delayed diagnosis can be expected resulting in the consequent delay in effective management[2]. Here we want to present a case of a 51-year-old gentleman whose repeated hematomas were assumed to be due to Warfarin overdose, a diagnosis more commonly experienced. Suspicion arose when the patient's international normalized ratio was normal and a persistent abnormal activated partial thromboplastin time was noted. On further coagulation work up, the deficiency of Factor IX was noted which was due to the antagonistic actions of Warfarin on Vitamin K, which lead to the deficiency of Factor IX. Patient was thus diagnosed of Acquired Hemophilia B and management was shifted to the focus of not letting the levels of Factor IX fall below 5-10%, instead of targeting the conventional INR therapeutic range approach for patients on Warfarin.

The diagnosis of Hemophilia B could thus be easily masked in patients on Warfarin therapy, resulting in a dangerous delay in correct management approach and repeated bleeding episodes despite a normal INR[2]. The manifestations of Acquired Hemophilia B are easily disguised under Warfarin therapy, as the former being a very rare disorder compared to the more common Warfarin overdose associated bleeding[2]. Awareness of Acquired Hemophilia B is thus empirical for the timely diagnosis and correct management approach for patients under anti coagulation therapies.

Background:

Acquired hemophilia B is a rare disorder of blood coagulation[1]. Acquired Hemophilia B is caused by the deficiency of Factor IX due to causes not inherited[3]. It can be seen with the use of anti-coagulation treatment like Warfarin[4].

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The effect of Warfarin treatment on Factor IX activity started coming into the notice of health care practitioners in the 1970s when patients on anti-coagulant treatment started revealing disturbed factor IX activity[5], in the absence of any congenital or family history of any bleeding disorders[4]. A delay in diagnosis was noted because the symptoms of bleeding were falsely, but very expectedly, associated with Warfarin treatment[6].

We describe here the unmasking of a case of Acquired Hemophilia B disguised under Warfarin treatment and the change in the treatment approaches of the two mentioned disorders[7].

Case Presentation:

A 50-year-old gentleman presented in February 2018 in Shifa International Hospital, Islamabad, with known history of status post bileaflet mechanical Mitral Valve Replacement (MVR) on 16TH June 2017 with lifelong oral anticoagulation with Vitamin K antagonist (Warfarin) with target INR 2.5-3.5. The presenting complaint was severe left hip pain radiating towards leg with no history of any trauma.

On examination there was a left thigh hematoma of about 5x8 cm. Patient had a past medical history of rheumatic fever, rheumatic heart disease, transient ischemic attack and recent recurrent episodes of hematomas post warfarin therapy (since Oct. 2017) mostly managed conservatively and once large Psoas hematoma was Ct guided drained in Oct. 2017. Patient gives no previous pre Warfarin therapy history of easy bruisibility. He further added that all previous hematomas were seen while INR was in therapeutic range (2.5-3.5).

Vitally the patient was stable and was observed in CCU. The admitting physician suspected bleeding secondary to Warfarin therapy (Warfarin induced hematomas). Drug modification was advised by stopping Warfarin and starting sub-cutaneous Low Molecular Weight Heparin (LMWH) till detail work was done. Hematology was taken on board and tests for Von Willebrand Disease and coagulation work up for recurrent bleeding were done.

On admissions the bloods were Hb 11.4 g/dl, WBC count 11.2, Platelet count 281000 / UL, Serum Creatinine 0.66 mg/dl, Nucleosome antibodies < 0.1 AU, negative ANA and DsDNA Antibodies and < 0.1 AU Histones antibodies. Factor VIII, Von Willebrand's Factor and Ristocetin CoF all were within the normal range (124%,165% and 132% respectively).

APTT was prolonged (38-49.6 sec) and INR was 1.9. Patient was discharged with drug modification of s/c Clexane.

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On a repeat follow-up on 8th March 2018, no more bleeding episodes were reported since warfarin was withheld, the INR was within the therapeutic range but the aPTT was still prolonged.

A disturbance in the early part of the intrinsic coagulation would display a prolonged aPTT with the PT returning to normal. Therefore, confirmatory factor assays were warranted. Mixing test was performed to check aPTT. The results of this test implied the deficiency of Factor IX in this patient responsible for the persistently prolonged aPTT despite the INR within the normal range.

Patient was diagnosed as acquired Hemophilia B and was restored on Warfarin therapy. Factor IX monitoring was advised instead of the conventional care to keep INR within the target range. Patient was advised to continue Warfarin with a target Factor IX around 8-10%.

As of November 2019, patient is doing fine. He gets his Factor IX checked every two months and if it is below 8%, he reduces his Warfarin dose for one day, and after that he returns to the normal dosage. The patient is now staying free of any bleeding or clotting complication since the new regime of bi-monthly monitoring of Factor IX (instead of INR) and Warfarin dose modification if it falls below 8%.

Discussion:

Given how rare Hemophilia is, it is not surprising to expect a delay in the diagnosis of its even more rare subtype, Acquired Hemophilia B. This delay could be more common in patients on Warfarin therapy, as the bleeding episodes in such patients could be easily but incorrectly explained by the more common Warfarin overdose[2], an endorsement of which is seen when the bleeding episodes stop after Warfarin cessation, as seen in this patient.

It is however, very important to keep the diagnosis of Acquired hemophilia B also in mind because the management approaches for the two closely related disorders differ and delay in diagnosis can have devastating consequences[3].

Acquired hemophilia B is a rare disorder of blood coagulation[1]. Acquired Hemophilia B is caused by the deficiency of Factor IX due to causes not inherited[2]. It can be seen with the use of anti-coagulation treatment like Warfarin[3].

Warfarin is a Vitamin K antagonist, and its regular use may therefore cause disturbances in the coagulation pathway[7]. Because the effect of warfarin is to inhibit the action of vitamin K, factor IX deficiency is also acquired as part of the therapeutic response to warfarin[7]. Factor IX deficiency can thus be acquired in patients who have vitamin K deficiency[8].

Most commonly, the INR is used to monitor patients on warfarin and a target range of usually 2.0-3.0 is given with a higher range for patients with mechanical heart valves[9]. A value below

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this therapeutic range can indicate risk of clot development while a higher value may suggest a greater risk of bleeding[9].

The prothrombin time (PT) and the International Normalized Ratio (INR) evaluate the extrinsic pathway and common pathway of coagulation[10]. They help to calculate the Warfarin dosage by showing the clotting tendency of blood and status of Vitamin K[10].

An accompanying test of activated partial thromboplastin time (aPTT) is used to measure the intrinsic pathway and common pathway of coagulation[10].

Physicians should keep in mind that both the situations (use of anti-coagulant or Hemophilia B) can give a prolonged aPTT[11]. Further workup is required where the mixing test will distinguish between the two disorders. Persistence of the abnormality indicates the presence of an anti-coagulant like Heparin or specific inhibitors of coagulation factors[12]. However, the disappearance of the abnormality indicates the increased likelihood of the deficiency of a factor including factors VIII, IX, XI and XII and von Willebrand factor[12].

Learning from this case, initial suspicion for the presence of Acquired Hemophilia B should rise in view of a prolonged Partial Thromboplastin Time (PTT) and a normal prothrombin time, despite the cessation of Warfarin therapy even if the bleeding has stopped. such scenarios warrant specific Factor IX levels to be obtained.

This case report gives us an awareness that for any patient presenting with unusual or unexplained bleeding, a full coagulation screening should be performed, and not just an INR reading, if the patient is on Warfarin. Clinicians should be mindful that a disproportionate prolongation of aPTT in patients on warfarin might not be automatically attributable to that treatment, but may in fact be caused by AH. A simple aPTT mixing study should be considered to aid accurate diagnosis.

Given the rare incidence of such cases, further observations would be welcomed to raise awareness of this rare but dangerous manifestation of Warfarin therapy.

Conclusion:

Acquired Hemophilia B can be caused be the therapeutic effects of anti-coagulant treatment like Warfarin, easily masking each other because of similar clinical manifestations and profile on routine coagulation screening. Factor specific tests are however warranted when an abnormally prolonged aPTT persists, despite the removal of the anticoagulant. In contrast to the management of Warfarin overdose where the focus is on targeting the INR range, the diagnosis of Acquired hemophilia B shifts the focus to maintain optimum Factor IX levels.

Refereances:

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