Amiodarone-induced Immune Thrombocytopenia: a Rare Hematologic Side effect of a Common Cardiac Drug

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Abstract

Amiodarone induced thrombocytopenia is a rare immune mediated hematologic complication of the drug. We describe a case of delayed onset amiodarone induced thrombocytopenia. We highlight the process adopted to arrive at a clinical diagnosis of the same in a 72-year-old male admitted to the hospital with competing causes of thrombocytopenia. Timely diagnosis of drug-induced immune thrombocytopenia is crucial in order to minimize unnecessary testing, avoid treatments with potential harm and prevent life-threatening hemorrhagic complications.

Introduction

Thrombocytopenia is defined as platelet count lower than 150 K/mm^3 and is commonly encountered in hospitalized patients[1]. Drug induced immune thrombocytopenia (DITP) is marked by severely reduced platelet count, often less than 20 K/mm^3 range where it could be associated with life-threatening bleeding. The underlying mechanism is understood to be immune mediated platelet destruction caused by drug-induced antibodies[2]. In 1985, US Food and Drug Administration approved amiodarone for prophylaxis and treatment of potentially fatal ventricular arrhythmias[3,4]. In practice it is widely used for the management of supraventricular tachyarrhythmias especially atrial fibrillation/atrial flutter, prevention, cardiac arrest from refractory ventricular arrhythmias, treatment of postoperative tachyarrhythmias and as an adjunct to implantable defibrillator[4]. Physicians are familiar with side effects of amiodarone including hypothyroidism, interstitial pneumonitis, and hepatotoxicity[3]. An idiosyncratic reaction such as amiodarone-induced immune thrombocytopenia (AITP) is a rare hematologic complication and has been described only a few times[5-8]. Bone marrow granulomas resulting from long term amiodarone use is a non immune-mediated cause of thrombocytopenia that is usually accompanied by other cytopenias[9,10].

Clinical Course

We present the case of a 71-year-old male who was admitted for hyperkalemia and symptomatic bradycardia from a missed hemodialysis session due to occlusion of his arteriovenous fistula. He was also diagnosed with Enterobacter bacteremia and started on Cefepime. Shortly before this, he was recently admitted for five days for atrial fibrillation with rapid ventricular rhythm and treated with intravenous amiodarone loading followed by oral maintenance dose. He was discharged three days before the aforementioned admission. On day 2 the labwork revealed worsening thrombocytopenia of 37 K/mm^3 was noted (compared to 62 K/mm^3 upon previous discharge) and was presumed to be in the context of sepsis. Amiodarone was restarted for atrial fibrillation, and anticoagulation was held due to thrombocytopenia. On day 3, blood culture showed no growth and all signs of sepsis resolved. Yet, the platelet count went down to 14 K/mm^3 at which point, 1 unit of platelet was transfused. Fortunately, there was no evidence of bleeding. Response to transfusion

was modest and temporary. Platelet count again decreased to 25 K/mm^3 at which point, the hematology team was consulted.

Pseudothrombocytopenia, alcohol abuse, nutritional deficiencies (Vitamin B12 deficiency, folate deficiency), HIV, HCV were ruled out. Heparin induced thrombocytopenia antibody testing by ELISA was negative (O.D. 0.112). Review of peripheral blood smear showed decreased platelet count, but no platelet clumping or schistocytes and few giant platelets were notable. The latter, in addition to mild reactive neutrophilia pointed against the possibility of bone marrow suppression from sepsis. Giant platelets on peripheral blood smear and elevated immature platelet fraction at 20.1% pointed at rapid bone marrow turnover of platelets in the peripheral circulation. Abdominal imaging with CT scan ruled out splenomegaly; liver echotexture supported a functioning liver. Given that platelet count dropped below 20 K/mm^3 despite resolution of sepsis, drug induced immune thrombocytopenia secondary to amiodarone was entertained as a working diagnosis. He was on chronic hemodialysis for end stage renal disease and was perceived to be at higher risk of bleeding due to functional coagulopathy from uremia[11]. Meanwhile, since AITP was a rare possibility, we were reluctant to stop amiodarone immediately for lack of better alternatives and risk of hemodynamic compromise. Hence, two doses of intravenous immunoglobulin (IVIG) 1mg/kg were administered on Day 11 followed by 1mg/kg oral prednisone maintenance. Amiodarone was eventually discontinued on Day 17 considering AITP as a working diagnosis when platelet nadir reached 14 K/mm^3. Platelet recovery occurred in parallel to a peak of 76 K/mm^3 on Day 26.

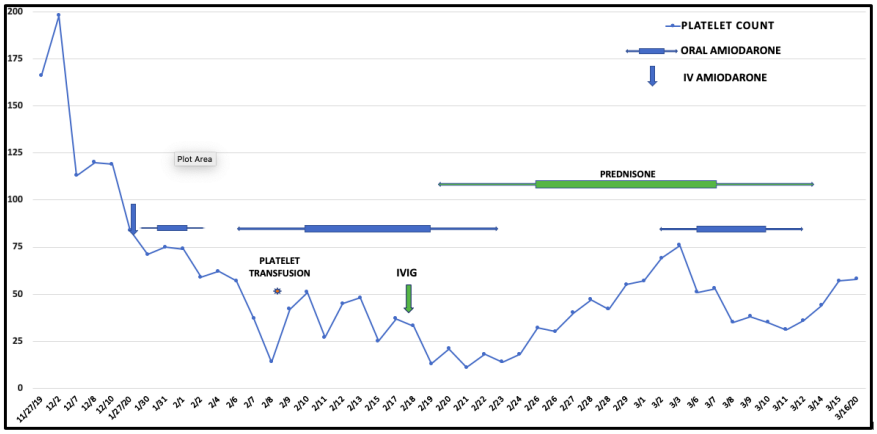
On Day 25, the patient experienced hemodynamic instability in the setting of tachyarrhythmias for which he was cautiously restarted on oral amiodarone due to lack of a better alternative. Two days later, platelet count started worsening and continued to do so until amiodarone was safely weaned off 11 days after restarting it. Thrombocytopenia started recovering the following day lending more credibility to earlier suspicion of an immune mediated amiodarone dependent platelet destruction process. Unfortunately, the patient succumbed to a cardiac arrest before his platelet count could recover fully.

Discussion

The incidence of AITP is unknown due to the rarity of this complication and paucity of documented cases. DITP has been associated with increased risk of in-hospital mortality[1]. A distinctive feature of one of the well-known examples of DITP such as quinine induced DITP involves a platelet reactive antibody that bind tightly to platelets only in the presence of quinidine leading to immune destruction of platelets after 5-7 days of continuous drug administration. In addition to the above, Aster and Bougie have summarized various mechanisms for DITP, some of which include hapten-dependent antibody (e.g. penicillin), autoantibodies which elicit immune response in the absence of drug (gold salt, procainamide) and immune complex formation (heparin)[2]. Weinberger et al was the first to postulate delayed hypersensitivity as a mechanism for AITP by performing a lymphocyte stimulation test[6]. Monitoring drop in platelet counts two weeks after starting amiodarone was recommended. Amiodarone-dependent antibodies causing platelet destruction cannot be identified using traditional serological methods owing to water insolubility of the drug. This issue was elucidated by Sahud et al who described a case series of three patients with AITP and employed elaborate laboratory techniques to demonstrate amiodarone-dependent antibodies specific for platelet glycoproteins GPIa/IIa and/or GPIIb/IIIa to explain thrombocytopenia in these patients[5].

Thrombocytopenia is one of the commonest reasons for inpatient hematology consultation. The differential diagnosis is long and sometimes multifactorial. Thrombocytopenia workup guidelines described by Arnold and Lim were useful to approach our case. They have described a handy 6 step approach to evaluate thrombocytopenia: exclude thrombocytopenic emergencies, peripheral blood smear examination, consider clinical context, degree timing and lastly assess for bleeding/thrombosis[12]. In the case discussed here, firstly a citrated platelet level ensured that severely low platelet count was not a lab error. Fatal etiologies of severe (sometimes referred as *significant*) thrombocytopenia like disseminated intravascular coagulation (no overt bleeding, normal hemolysis markers, normal fibrinogen), and thrombotic thrombocytopenic purpura (no schistocytes, no hemolysis), heparin-induced thrombocytopenia (negative HIT ELISA screen, typical platelet nadir is 60 K/mm^{3}in HIT) were ruled out. DITP as a possible cause of severe thrombocytopenia

was suspected given worsening thrombocytopenia to less than 20 K/mm^3 despite prompt resolution of sepsis with appropriate antibiotic, timing of onset at day 5 after starting amiodarone, and, presence of giant platelets on the blood smear, high immature platelet fraction (20.1%) both indicating an immune mediated phenomenon. Severe sepsis can sometimes cause severe thrombocytopenia but that is usually associated with severe leukopenia as a marker of severe bone marrow suppression. Amiodarone was listed as a possible cause of DITP in a commonly referred expanded online list of drugs and their level of association with thrombocytopenia at*https://www.ouhsc.edu/platelets/ditp.html*[13]. Later during the clinical course, recurrence of thrombocytopenia with amiodarone introduction and improvement after drug discontinuation lent more support to the diagnosis. It must be pointed that drug rechallenge is not required to diagnose any DITP. Platelet reactive antibodies were not tested since amiodarone-dependent platelet-responsive antibodies are not detectable by conventional methods[5]. It was not feasible to apply criteria laid out by George et al to establish causal relation of amiodarone to immune thrombocytopenia since the patient died prematurely before platelet count could return to normal[14]. Regardless, the clinical picture pointed to AITP and there was no alternate explanation. Although platelet recovery may be relatively prompt after drug discontinuation, complete recovery may take a few weeks owing to the long half-life of amiodarone from its large volume of distribution[3,7]. Antibodies can persist for years and hence re-exposure of the drug even months to years later can elicit a similar immune destruction of platelets[15]. Offending medication must be added to the allergy list in order to maximize safety.



Salient features of DITP
Acute life-threatening thrombocytopenia
Blood smear shows severe thrombocytopenia; giant platelets support the diagnosis
Degree of thrombocytopenia is usually severe: <20 K/mm^3
Timing of onset is typically 5-10 days are drug exposure*
Thrombocytopenia recovers typically within days after drug discontinuation**

* (sooner if previously sensitized with drug exposure) **(drugs with longer half-lives may have delayed recovery)

One of the most common indications of amiodarone is atrial fibrillation and this diagnosis requires anticoagulation for thromboembolic stroke prevention[16,17]. If a patient develops severe amiodarone induced thrombocytopenia in this setting, anticoagulation may require interruption for several days due to the long half-life of amiodarone. This can increase the risk of thromboembolic stroke with serious clinical consequences.

The role of both high dose steroids and IVIG in the management of DITP has not been well established

unlike immune thrombocytopenia (ITP) where both these drugs have a long track record of efficacy[18]. High dose steroids can have serious side effects including hypertension, poor glycemic control, gastric ulceration (thrombocytopenia compounds bleeding risk), edema, encephalopathy (especially intravenous administration in elderly patients), anxiety, restlessness, insomnia which contribute to patient morbidity and rarely mortality during hospitalization. IVIG therapy, other than being expensive, carries risk of serious allergic reactions. However, we believe that if there is a strong clinical suspicion of DITP and it is perceived that the patient is at risk of life-threatening hemorrhage from severe DITP despite discontinuation of the offending drug then a trial of corticosteroids/IVIG can be justified. Platelet transfusion carries risk of infection, allergic reaction, alloimmunization, fluid overload and hence its judicious use is advised. Platelet transfusion is recommended in case of active bleeding with a platelet count under 50,000[19].

Conclusion

DITP can present as an acute or delayed-onset complication of amiodarone. Given its frequent use in clinical practice, it is crucial to diagnose this entity in a timely manner in order to prevent hemorrhagic complications.

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