Case Report

A Severe Case of Neutropenia Secondary to Clopidogrel

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Abstract

An 83-year-old male patient presented with complaints of generalized body aches, fever, rhinorrhea, and worsening dyspnea for the past 5 days. Four weeks ago, he was started on clopidogrel after he underwent stent placement to his left leg. Current admission laboratory findings revealed a white blood cell (WBC) count of 1180, with no neutrophils corresponding to an absolute neutrophil count of zero. After an extensive negative infectious workup, clopidogrel was determined to be the offending agent. This medication was discontinued and the patient was placed on a leukocyte growth factor with significant improvement in his WBC and neutrophil counts. On discharge, clopidogrel was replaced with ticagrelor. During post-discharge follow-up visits scheduled at 2 weeks and at 6 months, the patient continues to remain stable with blood counts back to baseline.

Keywords: Clopidogrel, drug-induced neutropenia, leukopenia, neutropenia, pancytopenia, Plavix

Introduction

Clopidogrel-induced bone marrow suppression is a very rare adverse effect. Prior studies found a few rare cases of hematological abnormalities with the use of clopidogrel, which include 0.1% neutropenia and 0.2% thrombocytopenia.[1] There was also one case of aplastic anemia and two cases of febrile pancytopenia,[1] all of which should be considered in the differential diagnosis for a patient presenting with unexplained neutropenic sepsis who was recently started on clopidogrel therapy. In the clopidogrel versus aspirin in patients at risk of ischemic events study, only 0.1% of the patients in the clopidogrel group reported neutropenia,[2] which was consistent with other research.[3] Studies conducted with ticagrelor did not reveal hematological adverse effects such as neutropenia, leukopenia, thrombocytopenia, agranulocytosis or anemia, as outlined in the prescribing information, therefore it can be considered a safe alternative.[4]

Case Report

The patient is an 83-year-old male patient with a significant past medical history of hypertension, hyperlipidemia, coronary artery disease, aortic stenosis status-post (s/p) bioprosthetic aortic valve replacement, diastolic heart failure with an ejection fraction of 55%, peripheral arterial disease, chronic kidney disease stage 3 (CKD) not currently on dialysis, diabetes mellitus type 2, benign prostatic hyperplasia, and mild depression. He presents to the emergency room with complaints of generalized body aches, fever, rhinorrhea, and worsening dyspnea for the past 5 days. The patient denies any recent travels or sick contacts. His only new medication was clopidogrel (Plavix) 75 mg daily, which was started 1 month ago s/p left leg stent placement.

The patient is a former tobacco smoker (quit 20 years ago) with a 30 pack-year smoking history. He drinks 1 glass of wine with dinner. His family history was noncontributory.

Vitals revealed a blood pressure of 92/46 mm/Hg; heart rate of 68 bpm, regular rhythm; respiratory rate of 16 breaths/min, unlabored; temperature of 37.3°C (99.2°F); and oxygen saturation of 97% with 2 L of oxygen flow. He is 5 feet and 6 inches tall with a weight of 169 pounds (76.66 kg). On physical examination, the patient is in no acute distress with an otherwise unremarkable examination.

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Table 1: Complete blood count trend over time

Parameter	4 weeks prior to admission	On admission	On discharge (8 days after admission)	2 weeks postdischarge
WBC (103/uL)	9.83	1.18	11.4	7.7
Hgb (g/dL)	13.1	11.6	10.1	11.8
Hct (%)	42.6	34.7	30.7	35.6
Plt (uL)	202,000	168,000	165,000	315,000
Neutrophils (%)	68		64 + 3 bands	64
Lymphocytes (%)	27	70	16	22
Atypical lymphocytes (%)		3		
Monocytes (%)	4	27	14	9
Eosinophils (%)			2	4
Basophils (%)	1		1	1
Absolute neutrophils	6684	0	7638	4928

WBC: White blood cell, Hgb: Hemoglobin, Hct: Hematocrit, Plt: Platelet

Medications include – amlodipine 5 mg daily, aspirin 81 mg daily, atorvastatin 10 mg daily, carvedilol 12.5 mg twice a day, clopidogrel 75 mg daily, furosemide 40 mg daily, pantoprazole 40 mg daily, sertraline 50 mg daily, and terazosin 5 mg daily.

Initial laboratory findings revealed white blood cell count (WBC) of 1.18 × 10^3/uL; hemoglobin (Hgb) of 11.6 g/dL; hematocrit (Hct) of 34.7% and platelets (Plt) of 168, 000/uL. A manual WBC differential count was notable for lymphocytes 70%, atypical lymphocytes 3%, and monocytes 27%. There were no neutrophils in the differential corresponding to an absolute count (ANC) of zero. His renal function was at his baseline for his CKD, while his liver function tests, prothrombin time and partial thromboplastin time were normal.

A review of the complete blood count from 4 weeks ago showed WBC of 9.83 × 10^3/uL; Hgb of 13.1 g/dL; Hct of 42.6% and Plt of 202,000/uL. The WBC differential count revealed neutrophils of 68%, lymphocytes of 27%, monocytes of 4%, and basophils of 1%. Influenza screening and urinalysis were negative. A chest X-ray revealed a small right pleural effusion and mild cardiomegaly (which has not changed from prior X-rays), with no infiltrates.

Blood and urine cultures were collected, and the patient was started on IV fluids, antipyretics, broad-spectrum antibiotics, an antiviral and an anti-fungal agent as a result of the neutropenic fever and no current etiology. It was determined that clopidogrel was the offending agent; therefore, this medication was discontinued. The patient was also started on filgrastim 5 mcg/kg subcutaneous daily which was stopped after 3 days due to significant improvement in his WBC. All cultures were negative with no sources of infections identified. His antibiotics, antiviral, and antifungal medications were discontinued after 5 days. Clopidogrel was replaced with ticagrelor 90 mg twice daily on discharge (day #8). Two weeks postdischarge, the patient had no complaints and his blood count continued to remain stable, around his baseline [Table 1]. At 6 months postdischarge, the patient continues to remain stable with no significant change in his blood counts.

Discussion

Clopidogrel bisulfate (Plavix) is a widely used drug among cardiovascular patients. It is a thienopyridine class inhibitor of the $P2Y_{12}$ adenosine diphosphate Plt receptor that is indicated for the acute coronary syndrome, recent myocardial infarction, recent stroke, and established peripheral artery disease.[5] In addition to the increased risk of bleeding with the use of Clopidogrel, some of its additional rare but serious side effects include agranulocytosis, aplastic anemia/pancytopenia, thrombotic thrombocytopenic purpura, acquired hemophilia A,[5,6] and neutropenia.[3] Neutrophils make up a significant portion of the WBCs. A decrease in the ANC below 1500 cells/ml is considered neutropenia.[7] The severity of neutropenia can be categorized as mild, moderate, and severe with corresponding ANC of ≥1000 to <1500, ≥500 to <1000, and <500, respectively. It is important to accurately assess the severity of ANC since it is directly related to the risk of developing an infection. That is, the lower the ANC, the higher the chance of developing infections.[7]

The patient developed severe neutropenia within 4 weeks of starting clopidogrel, though it was found that neutropenia can occur up to 5 weeks following the initiation of clopidogrel.[1] Although not as common, drug-induced neutropenia is a very serious condition which can lead to potentially life-threatening adverse events.[8] Therefore, the prompt identification and removal of the offending drug are of utmost importance and a safe alternative should be selected. For the continued safety of our patients, they should be closely monitored while on the replacement medication.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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