

Rare but possible: clopidogrel-induced pancytopenia

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ABSTRACT

We present the case of an 84-year-old female patient admitted to the Internal Medicine Ward for atypical chest pain and laboratory findings of severe pancytopenia. Past medical history was remarkable for an episode of myocardial infarction approximately 4 weeks prior to the current hospitalization which had required angioplasty + drug-eluting stent and dual antiplatelet therapy with acetylsalicylic acid and clopidogrel. Some rare cases of clopidogrel-induced pancytopenia are described in scientific literature, therefore, after excluding infectious, vitamin deficiencies, and autoimmune causes, we modified the antiplatelet therapy by replacing clopidogrel with ticagrelor, obtaining complete leukocyte recovery within a few days. Since clopidogrel is an antiplatelet drug still used in clinical cardiological practice, the knowledge of this rare side effect may lead the clinician to suspect hematological toxicity which, if recognized promptly, may suggest modification of antiplatelet therapy and limit any possible infectious complications for the care of the patient.

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Key words: clopidogrel; neutropenia; myocardial infarction; adverse drug reaction.

Conflict of interest: the authors declare no potential conflict of interest.

Availability of data and materials: all data underlying the findings are fully available.

Consent for publication: the patient gave her written consent to use his personal data for the publication of this case report.

Received: 5 October 2023.

Accepted: 9 October 2023.

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Licensee PAGEPress, Italy
Italian Journal of Medicine 2023; 17:1660
doi:10.4081/ijm.2023.1660

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Clinical case

We present the case of an 84-year-old female patient, admitted to the Cardiology Ward for Acute coronary syndrome without persistent ST-segment elevation (NSTEMI) that was treated with percutaneous transluminal coronary angioplasty/drug-eluting stents on the right coronary artery, with residual total occlusion of the interventricular anterior artery. Dual antiplatelet therapy based on acetylsalicylic acid (ASA) and Ticagrelor was started, but the latter was quickly stopped due to the appearance of paroxysmal dyspnea and replaced with Clopidogrel. Given the clinical stability, she was discharged home in the following days.

About 4 weeks later she went to the local emergency department of our hospital for atypical chest pain lasting a few hours. She was admitted to the Internal Medicine ward for the necessary treatment.

Vital parameters and temperature were within limits, and the electrocardiogram was negative for ischemic/inflammatory changes of repolarization, with a negative troponins curve. Arterial blood gas analysis in a fraction of inspired oxygen of 21% was within the normal range. Chest x-ray was negative for pulmonary consolidations, effusions, or pneumothorax.

Blood chemistry revealed severe pancytopenia with severe neutropenia (white blood cells 720/uL, Neutrophils 10/uL), Hb 10 g/dl, platelets 106,000/uL. The peripheral blood smear didn't reveal immature forms.

Biomarkers of inflammation (C- reactive protein and erythrocyte sedimentation rate) were negative, creatinine 2.23 mg/dl in the context of chronic kidney disease; folate, vitamin B12 and electrolytes were within limits, as well as anti-nuclear antibodies (ANA). Serologies for herpes viruses (Herpes simplex virus, cytomegalovirus, Epstein Barr Virus) were negative for acute infection. Pharyngeal swab testing for SARS-CoV-2 was negative.

Since the complete blood count was almost normal in the past hospitalization, given the absence of signs, symptoms, or laboratory findings suggestive of sepsis or other causes, we presumed an iatrogenic etiology of pancytopenia, for which it was stopped clopidogrel, the only drug recently introduced, replacing it again with ticagrelor, that was well tolerated by the patient during this hospitalization; at the same time, granulocyte growth factors (G-CSF) were administered to enhance white blood cell production and, after 6 days, there was a rapid increase in the leukocyte count until normalization.

During the hospitalization, congestive heart failure developed which required continuous positive airway pressure and parenteral diuretic therapy, until complete weaning from oxygen therapy.

A high-resolution chest computed tomography scan excluded foci of pneumonia.

The transthoracic echocardiogram showed an ejection fraction of 45-50%, akinesia of the mid-basal interventricular septum and mid-distal antero-lateral wall hypokinesia; type II diastolic dysfunction, biatrial dilatation, slightly dilated and normokinetic right ventricle (tricuspid annular plane systolic excursion of 20 mm). Moderate mitral regurgitation, sclerotic aortic valve with normal antegrade gradients in the absence of regurgitation. The aortic root and tubular portion of the ascending aorta not dilated. Moderate tricuspid regurgitation (right ventricular assist device gradient of 42 mmHg) with increased pulmonary artery pressure (42+10 mmHg), mild circumferential pericardial effusion.

Upon discharge, the patient had normalization of the leukocyte and platelet counts, while moderate anemia remained (Hb 9.8 g/dl).

Discussion

In the current clinical case, the patient presented a reduction of all hematopoietic lines (red blood cells, white blood cells, and platelets), but especially the neutropenia stood out for its severity, which is defined as severe when the neutrophil count falls below 100/mm³.

The causes to be investigated in the differential diagnosis of hemocytopenia are mainly divided into: reduced bone marrow production (*e.g.*, aplastic

anemia, systemic infection/inflammation, drugs related, due to neoplastic infiltration, due to radio-chemotherapy, and nutritional deficiencies) and increased peripheral consumption (*e.g.*, autoimmune diseases, hypersplenism, direct damage from drugs or infectious agents).

The diagnostic process is structured through an objective examination of the patient which will reveal signs and symptoms indicative of a specific cellular deficiency: for example, in the case of severe neutropenia, we must look for the presence of mucosal aphthae and pay attention to the potential development of bacterial and fungal infections, even with atypical manifestations (*e.g.*, absence of fever or minimal temperature rise, absence of evident purulent foci).

It will be necessary to investigate whether there is a family predisposition to cytopenia, whether the problem is of recent onset or is chronic, whether there has been exposure to new or toxic drugs, and search for viral serologies (especially herpesviruses), general (ANA) or specific autoimmunity (anti-neutrophil antibodies in case of autoimmune neutropenia), serum levels of micronutrients (zinc, copper) and group B vitamins (folates and vitamin B12), and look for immature forms on peripheral blood smear that may suggest myelodysplasia/leukemia.

If diagnostic investigations are negative, in doubtful cases, it will be appropriate to proceed with bone marrow biopsy/aspiration.¹

Therapy is based on the correction of the triggering cause: in this case, we thought of an adverse effect from clopidogrel due to the temporal relationship between the recent introduction of the drug (about 4 weeks before) and the new finding of pancytopenia; otherwise, it would be difficult to explain after having excluded other causes such as sepsis, vitamin deficiencies, autoimmune diseases, and viral infections.

Clopidogrel is an antiplatelet drug belonging to the second-generation thienopyridine family. It carries out its action by irreversibly binding to the P2Y₁₂ platelet receptor and inducing the selective inhibition of adenosine diphosphate-induced platelet aggregation. The effect is dose-dependent and generally appears 4 days after taking it at a dosage of 75mg/day or after 3 hours at a loading dose of 600mg/day.

Currently, the appearance of adverse hematological disorders during the use of clopidogrel is extremely rare and there is no certain data in the literature regarding the incidence.²

In the CAPRIE study, which paved the way for the use of clopidogrel as an antiplatelet agent, severe neutropenia (<0.45'10⁹/l) was observed in 4 patients (0.04%) treated with clopidogrel and in 2 patients (0,02%) treated with ASA. In two of the 9,599 patients treated with clopidogrel and in none of the 9,586 patients treated with ASA the neutrophil count was

zero. Only one case of aplastic anemia occurred in the clopidogrel group. The incidence of severe thrombocytopenia ($<80 \times 10^9/l$) was 0.2% in the clopidogrel group and 0.1% in the ASA group.³

In the CURE study (which evaluated the efficacy of long-term treatment with clopidogrel in addition to standard treatment with ASA in patients with unstable angina and NSTEMI in reducing the incidence of an overall endpoint including cardiovascular mortality, non-fatal myocardial infarction and stroke) the number of patients with thrombocytopenia (19 clopidogrel + ASA vs. 24 placebo + ASA) or neutropenia (3 vs. 3) was similar for both groups.⁴

The appearance of hematological toxicity is reported in a small case series in the literature, 22 days on average after the introduction of clopidogrel, while blood count recovery occurs approximately 4-8 days after drug suspension, associated or not with the administration of G-CSF.⁵⁻⁷

Ticagrelor belongs to the pharmacological class of cyclopentyltriazolopyrimidines and is an oral, direct, selective, and reversible antagonist of the P2Y₁₂ receptor. Compared to clopidogrel, it exerts its action faster and has been shown to reduce the percentage of the combined endpoint of cardiovascular death, myocardial infarction, or stroke compared to clopidogrel. In patients undergoing percutaneous coronary intervention, it also reduces the rate of stent thrombosis.⁸

Our patient developed dyspnea after administration of ticagrelor, a side effect reported by 13.8% of patients treated with ticagrelor and 7.8% of patients treated with clopidogrel. Dyspnea, which appears to be linked to the increase in adenosine activity on bronchial nerve fibers, is mild to moderate and often resolves without requiring interruption of treatment.⁹

We decided to suspend clopidogrel, but, given that the continuation of the single anti-platelet with only ASA would have entailed a high risk of ischemic recurrence given the very recent (<4 weeks) myocardial infarction, the dual anti-platelet therapy was continued by introducing ticagrelor again, which was better tolerated by the patient during this hospitalization.

The few data available in scientific literature suggest suspending treatment with clopidogrel when adverse hematological disorders such as neutropenia or, more generally, pancytopenia arise, replacing it with other anti-aggregating drugs such as prasugrel and ticagrelor.

We also have chosen to restart ticagrelor due to the different chemical structure compared to prasugrel and clopidogrel which could explain the different incidence of side effects; furthermore, actually, there have been no reported cases of neutropenia induced by ticagrelor unlike prasugrel ($<0.1\%$ in the group of patients in the TRITON-TIMI 38 study).¹⁰

Conclusions

To conclude, in the case of a marked cytopenia of recent onset, the suspicion of an iatrogenic etiology must be considered earlier, since stopping the offending drug could bring a favorable response, allowing a rapid diagnosis and minimizing the use of invasive osteomedullary investigations.

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