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THROMBOCYTOPENIA INDUCED BY CLOPIDOGREL: A RARE ADVERSE EFFECT

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ABSTRACT

Introduction: Immune thrombocytopenic purpura (ITP) can be induced by several drugs but there are few case reports of ITP induced by clopidogrel. Second-line treatment with thrombopoietin receptor agonists (TPO-RA) presents solid evidence and should be considered in patients in need of elective surgery who are poor responders to steroids.

Case description: We report the case of a 79-year-old male who developed severe immune thrombocytopenic purpura after initiating treatment with clopidogrel. Because he needed elective orthopaedic surgery and he did not respond to corticotherapy and immunoglobulin, second-line treatment with romiplostim was initiated with a significant increase in platelet count.

Discussion and conclusion: Clopidogrel can induce ITP and this diagnosis should be considered in patients who present with isolated thrombocytopenia. First-line therapy of ITP is not always successful; second-line treatment with TPO-RA has a high response rate and should be considered in patients in need of elective surgery who have failed to respond to first-line therapy.

KEYWORDS

Thrombocytopenia, ITP, clopidogrel, TPO-RA, romiplostim

LEARNING POINTS

- Clopidogrel can cause immune thrombocytopenic purpura (ITP); although there are some published cases in literature, it is a rare adverse effect.
- ITP induced by clopidogrel should be considered in the differential diagnosis of patients experiencing isolated thrombocytopenia.
- Second-line treatment of ITP with thrombopoietin receptor agonists (TPO-RA) presents solid evidence and should be considered in patients in need of elective surgery who are poor responders to steroids.

INTRODUCTION

Clopidogrel, in combination with aspirin, is used for the prevention of thrombosis in patients who have recently received coronary artery stents[1]. Thrombocytopenia is a rare adverse effect of clopidogrel. It can present as thrombotic thrombocytopenic purpura (TTP), isolated

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thrombocytopenia and immune thrombocytopenic purpura (ITP)[1]. ITP is an acquired autoimmune disease in which there is humoral and cellular dysregulation, leading to defects in platelet production and increased platelet destruction[2]. The traditional concept is that antibody-coated platelets are prematurely destroyed in the spleen, liver or both. However, antiplatelet antibodies are not detected in up to 50% of patients; this raises the possibility of alternative mechanisms of platelet destruction[3]. The lack of a sensitive or specific diagnostic test for ITP and the large number of other potential causes of thrombocytopenia also contribute to the challenges in diagnosing ITP.

We conducted a literature search through PubMed on 3 September 2023. Most of the case reports were of patients with thrombocytopenic thrombotic purpura; we found that ITP induced by clopidogrel is a rare adverse effect.

We report a case of an acute and severe drop in platelet count after initiation of clopidogrel.

CASE DESCRIPTION

Our patient was a 79-year-old male weighting 110 Kg, with a history of acute inferior myocardial infarction with coronary stenting 7 months before admission. He was on dual antiplatelet therapy (DAPT) with aspirin and ticagrelor. One month before admission he suffered a subcapital fracture of the right femur. Because he was on DAPT he was treated conservatively, and before discharge ticagrelor was replaced by clopidogrel, 75 mg daily. On that day he had a platelet blood count of 170 × 10^9/l.

Thirty-four days after discharge from the orthopaedics department he went to the emergency room with a two-week history of petechiae on his abdomen and limbs. *(Fig. 1 and 2)*. Laboratory studies were unremarkable except for a platelet count of 1 × 10^9/l.

He was haemodynamically stable, with no signs of active bleeding. He had no fever or other skin changes other than petechiae, and no neurological abnormality was noted. Cardiac and pulmonary observation were unremarkable and he did not have jaundice, hepatomegaly or splenomegaly.

Due to severe thrombocytopenia, clopidogrel and aspirin were discontinued. Two platelet transfusions were performed, without response. The patient was started on prednisolone 80 mg/day and intravenous immunoglobulin (IVIg) 0.4 mg/Kg/day for 5 days.

Severe isolated thrombocytopenia was confirmed with 0.4% of schistocytes on peripheral blood smear. Fibrinogen, haptoglobin, LDH and complement levels were within normal range. Antiplatelet antibody test results were negative, as were viral serology tests including HIV.

After 5 days of corticotherapy and IVIg the platelet count rose to 66 × 10^9/l. At this time the patient was discharged with oral prednisolone 80 mg/day. The diagnosis of clopidogrel-associated thrombocytopenia was highly suspected and aspirin was subsequently resumed. Three days later his platelet count had dropped to 30 × 10^9/l. He was re-evaluated by his orthopaedic surgeon and surgery was proposed. He was then readmitted to the internal medicine ward to stabilise platelet counts before surgery. He developed transient leukopenia (3.39 × 10^9/l) so a myelogram was performed; it was unremarkable. During hospitalisation, the leukopenia resolved spontaneously.

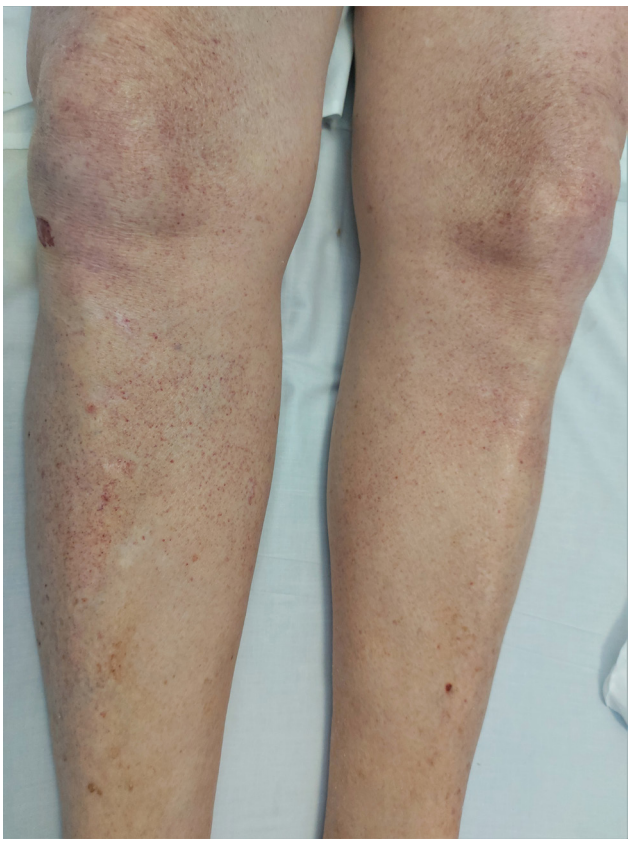

Figure 1. Lower limb petechiae

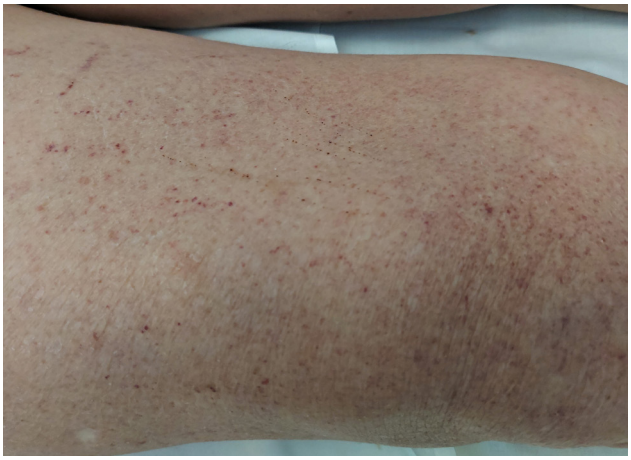

Figure 2. Abdomen petechieae

He completed another 5 days of IVIg but platelets remained below 50 × 10^9/l. Because of the lack of response to corticotherapy, tapering was started. We then started a second-line therapy with romiplostim 1 mcg/Kg with a substantial improvement in the levels of platelets after 5 days of therapy. He underwent a cementless bipolar hemiarthroplasty of the right hip without significant blood loss. At the time of discharge he had a platelet count of 100 × 10^9/l.

It has now been 4 months after clopidogrel was discontinued

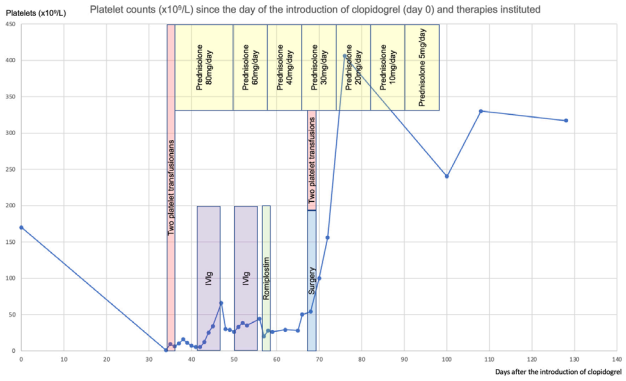

Figure 3. Evolution of platelet counts since the day of the introduction of clopidogrel (day 0) and the therapies instituted

and almost 3 months after treatment with romiplostim, and platelet levels remain in the normal range with no need for other administrations of romiplostim.

Figure 3 shows the evolution of platelet counts since the day of the introduction of clopidogrel (day 0) and the therapies instituted.

DISCUSSION

Thrombocytopenia is a rare but dangerous adverse effect of clopidogrel. Our patient was on DAPT with aspirin and ticagrelor after coronary stent implantation. One month before he was admitted to hospital, he switched from ticagrelor to clopidogrel. The time between drug intake and the beginning of thrombocytopenia, and the time between drug withdrawal and the recovery of platelet count, makes the diagnosis of thrombocytopenia induced by clopidogrel very likely. Hypersensitive reactions to clopidogrel often manifest as an erythematous, macular, morbilliform rash starting on the trunk and spreading to the extremities, and patients can also develop fever[4]. Our patient did not have any of these symptoms and the eosinophil counts were in the normal range, therefore this hypothesis would be less likely. But as it was questionable whether clopidogrel could be regarded as the origin of the thrombocytopenia, we applied a widely used adverse drug reaction (ADR) probability scale to systematically assess causality. Our assessment resulted in a score of 4, classified as a "possible ADR"[5].

In this case, we excluded causes of decreased production of platelets such as haematologic malignancies and other causes of increased destruction of platelets such as viral infections or TTP, or pseudothrombocytopenia.

Two known mechanisms for clopidogrel-induced thrombocytopenia have been reported in the literature: clopidogrel-induced thrombotic thrombocytopenic purpura, which was ruled out in our patient, and immune thrombocytopenic purpura, which occurs at a lower incidence[6].

Clopidogrel-induced ITP is treated by drug withdrawal, corticosteroids and IVIg. Medical therapies for patients with ITP who do not have an initial response to glucocorticoids include thrombopoietin receptor agonists (TPO-RAs) such as romiplostim[3]. TPO-RAs are also a good alternative for patients undergoing elective surgery[2]. Our patient was successfully treated with this regimen.

CONCLUSION

Clopidogrel has emerged as one of the cornerstone antiplatelet therapies in addition to aspirin in cardiovascular disease. Thrombocytopenia and bleeding are the most feared adverse effects of antithrombotic agents[6].

Patients treated with clopidogrel should be carefully monitored for haematologic adverse effects, especially in the first 2 to 3 months after initiation of therapy[6]. Early recognition and prompt initiation of treatment can be life-saving in patients who have haematologic adverse effects to clopidogrel. As our patient needs ongoing treatment for his stents, ticagrelor and prasugrel represent potential alternatives. However, since the patient was already approaching 1 year after the stenting, we decided to maintain monotherapy with acetylsalycilic acid.

This case highlights the importance of considering immune thrombocytopenic purpura induced by clopidogrel in the differential diagnosis of patients experiencing thrombocytopenia. It also highlights the need to measure platelet levels before and after initiating clopidogrel therapy. Older patients with ITP present a higher risk of bleeding, thrombosis and infection, and have more adverse reactions to therapy. First-line therapy is usually corticotherapy with or without IVIg. Due to their safety and efficacy profile, TPO-RAs became the main second-line therapy in this patient group. In patients who are poor responders to corticosteroids preparing for elective surgery, there is now a trend to replace the administration of IVIg with TPO-RAs.

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