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Clopidogrel-associated small vessel vasculitis in acute coronary syndrome: a diagnostic and therapeutic challenge

Vasculitis de pequeño vaso asociado al uso de clopidogrel en síndrome coronario agudo: un reto diagnóstico y terapéutico

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ABSTRACT

The treatment of acute coronary syndrome includes the use of acetylsalicylic acid and a P2Y12 inhibitor, with clopidogrel being the most commonly used agent in clinical practice. Fortunately, hypersensitivity reactions to clopidogrel are uncommon; however, when they occur, they are typically type I reactions mediated by IgE (e.g., urticaria, angioedema, and cutaneous rash). Type III hypersensitivity reactions, such as small vessel vasculitis, are exceedingly rare and pose a therapeutic challenge, particularly in the setting of acute coronary syndrome (ACS). This case report shows an uncommon presentation that should be considered in patients receiving antiplatelet therapy.

RESUMEN

El tratamiento de síndrome coronario agudo incluye el uso de ácido acetil salicílico y un inhibidor de P2Y12, siendo el clopidogrel el más utilizado en la práctica clínica. Afortunadamente, las reacciones adversas por hipersensibilidad con el clopidogrel son inusuales, sin embargo, cuando ocurren, por lo general son tipo I mediadas por IgE (urticaria, angioedema y erupción cutánea). Las reacciones de hipersensibilidad tipo III como la vasculitis de pequeño vaso son extremadamente raras y suponen un reto terapéutico, sobre todo en el contexto de un síndrome coronario agudo (SCA). Este trabajo evidencia la presentación de una reacción infrecuente que debería tenerse presente en pacientes con terapia antiagregante.

Abbreviations:

ACS = Acute Coronary Syndrome
ADP = Adenosine DiPhosphate
AF = Atrial Fibrillation
ANCA = AntiNeutrophil Cytoplasmic Antibodies
DOAC = Direct Oral AntiCoagulant
LCV = LeukoCytoclastic Vasculitis
NSAIDs = Non-Steroidal Anti-Inflammatory Drugs
P2Y12 = P2Y12 receptor
PCI = Percutaneous Coronary Intervention

INTRODUCTION

Acute coronary syndrome (ACS) management relies on dual antiplatelet

therapy, typically consisting of acetylsalicylic acid and a P2Y12 receptor inhibitor, with clopidogrel being one of the most widely used agents in clinical practice.^{1,2} Although clopidogrel has a well-established safety profile, hypersensitivity reactions have been described, most commonly type I reactions mediated by immunoglobulin E, including urticaria, angioedema, and cutaneous rash.²

In contrast, type III hypersensitivity reactions, such as leukocytoclastic vasculitis (LCV),³ are extremely rare and may pose a diagnostic and therapeutic challenge, especially in patients with recent ACS who require antithrombotic

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therapy.² Drug-induced small vessel vasculitis is characterized by immune complex deposition within vessel walls, leading to complement activation and neutrophilic inflammation, manifested typically as palpable purpura with a predilection for the lower extremities.^{3,4}

We describe a case of clopidogrel-associated small vessel vasculitis following an ACS. This case highlights the importance of early recognition and the challenges involved in optimizing antithrombotic therapy in this context.

CASE PRESENTATION

An 87-year-old woman with preserved functional independence (Barthel Index: 100 points), a history of hypothyroidism, and atrial fibrillation (AF) receiving chronic oral anticoagulation with rivaroxaban 20 mg once daily was admitted with acute coronary syndrome consistent with unstable angina. She underwent percutaneous coronary intervention (PCI), during which a significant lesion in the circumflex artery was identified and treated with angioplasty and implantation of a drug-eluting stent. The patient had a favorable clinical course and was discharged on combined antithrombotic therapy with rivaroxaban and clopidogrel because of her concomitant AF.

One month later, she was readmitted because of generalized palpable purpuric lesions, non-

blanching with pressure, predominantly involving the lower extremities, lower abdomen, and periumbilical region (*Figure 1*).

An extensive diagnostic workup was performed to assess for systemic involvement. There was no evidence of renal, gastrointestinal, or neurological involvement based on laboratory tests, clinical assessment, and imaging studies. The morphology and distribution of the lesions raised the initial suspicion of cutaneous small-vessel vasculitis. The differential diagnosis included systemic and immune-mediated conditions such as ANCA-associated vasculitis, hepatitis virus-associated cryoglobulinemia, systemic lupus erythematosus, and rheumatoid arthritis. These conditions were considered unlikely after the corresponding laboratory investigations were negative.

The temporal relationship between clopidogrel initiation and the onset of the skin lesions was then considered. Clopidogrel was the only medication introduced shortly before the onset of the skin lesions. After multidisciplinary assessment by Dermatology, Cardiology and Toxicology, the clinical presentation was considered most consistent with drug-induced cutaneous small-vessel vasculitis, likely representing leukocytoclastic vasculitis. Although skin biopsy would have provided histopathological confirmation, it was deferred because the clinical diagnosis was considered sufficiently clear and the

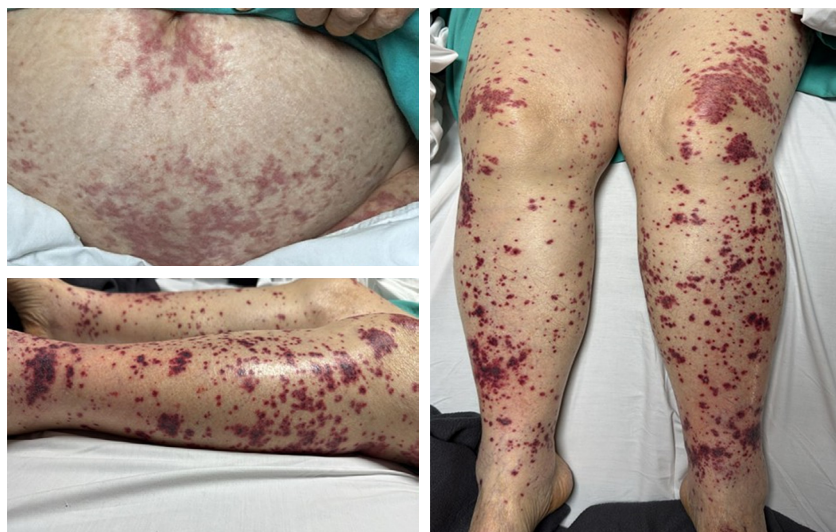


Figure 1: Initial palpable purpuric lesions, non-blanching on pressure, localized predominantly in the lower extremities, the lower half of the abdomen, and the periumbilical area. Source: authors' own work. Images published with patient consent.



Figure 2:

Evolution of purpuric lesions until resolution (20 days after onset).
Source: authors' own work. Images published with patient consent.

biopsy result was not expected to change the therapeutic approach.

Treatment with prednisolone was started at 0.5 mg/kg for two weeks, followed by a gradual reduction of 5 mg per week until discontinuation. Clopidogrel was withdrawn, as discontinuation of the suspected offending drug represents the main therapeutic measure in drug-induced vasculitis.

The main challenge, however, was how to modify the antithrombotic treatment after discontinuation of clopidogrel. The patient was only one month after PCI with implantation of a drug-eluting stent for an acute coronary syndrome, and antiplatelet therapy remained important to reduce the risk of stent thrombosis. An alternative P2Y₁₂ inhibitor was not considered because of the potential for cross-reactivity among structurally related agents. Therefore, after multidisciplinary discussion, the antithrombotic regimen

was changed to rivaroxaban 15 mg once daily plus acetylsalicylic acid 100 mg once daily, adapting an antithrombotic strategy evaluated in the PIONEER AF-PCI trial. This decision required balancing the need to discontinue the suspected offending drug against the risk of ischemic complications following recent PCI.

The patient was closely followed, with complete resolution of the cutaneous lesions and no apparent ischemic or thrombotic complications during the one-month follow-up (Figure 2).

Figure 3 presents the timeline of the patient's clinical course and the main diagnostic and therapeutic decisions.

DISCUSSION

Clopidogrel is an antiplatelet agent that works through irreversible inhibition of the adenosine diphosphate (ADP) P2Y₁₂ receptor,

thereby reducing platelet aggregation and preventing thrombotic events.^{1,2} It is generally well tolerated, and adverse events are rarely reported; among these, small vessel vasculitis is exceedingly uncommon.² This condition is defined as inflammation of small blood vessels and the skin, clinically characterized by palpable purpura predominantly affecting the lower extremities with a symmetric distribution.³ In the medical literature, only a limited number of cases have been reported, with a highly variable clinical course ranging from 24 hours to up to six weeks after treatment initiation.^{3,4}

Hypersensitivity reactions are immune-mediated responses triggered by exposure to an antigen. Hypersensitivity reactions associated with clopidogrel include urticaria, angioedema, and cutaneous rash.⁴ The pathophysiology of clopidogrel-induced small vessel vasculitis is most commonly associated with a type III hypersensitivity reaction, characterized by immune complex deposition within the walls of blood vessels.⁵ These deposits activate the complement cascade and lead to neutrophil infiltration, resulting in what is known as leukocytoclastic vasculitis

(LCV) with fibrinoid necrosis.^{1,3} Although skin biopsy remains the gold standard for confirming this condition, in cases with a clear temporal relationship to drug exposure, absence of systemic involvement, and clinical improvement following drug withdrawal, the possibility of an alternative etiology is low, making an alternative diagnosis unlikely.⁵⁻⁷

Most cases of small vessel vasculitis are idiopathic or primary (approximately 44% to 55% of cases).^{5,6} Drug-induced vasculitis represents 10% to 24% of cases, with antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs) being the most commonly implicated agents.^{5,6} Other causes include infections (20%), autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis (15-20%), and, in less than 1% of cases, paraneoplastic processes.^{6,7}

Standard management reported in the literature primarily consists of immediate discontinuation of clopidogrel.² The general treatment of leukocytoclastic vasculitis follows a stepwise approach: conservative measures such as rest, lower limb elevation, and compression stockings are sufficient in mild cases.⁸ In

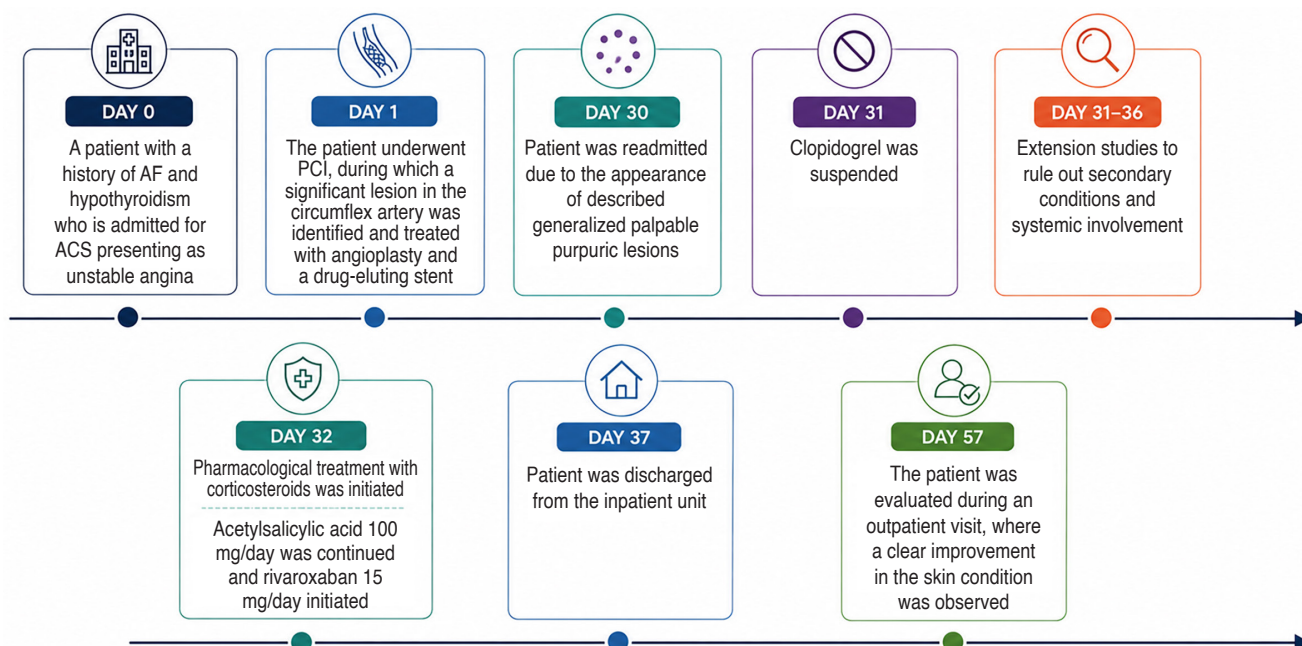


Figure 3: Timeline of the patient's clinical course from admission to resolution of symptoms.

ACS = acute coronary syndrome. AF = atrial fibrillation.

patients with significant or recurrent cutaneous involvement, the use of antihistamines, colchicine, dapsone, and topical or systemic corticosteroids has been described.^{1,3,9}

Cutaneous disease usually resolves within one to two weeks after the discontinuation of the causative drug, in this case, clopidogrel.^{1,2} However, complete remission is achieved only in approximately half of patients within 6-12 months. The remainder may develop a chronic or recurrent course, particularly in the presence of associated arthralgias or cryoglobulinemia.^{8,9} In our patient, skin lesions resolved after clopidogrel withdrawal and corticosteroid therapy, with no recurrence during follow-up.

The occurrence of leukocytoclastic vasculitis in the setting of recent acute coronary syndrome represents a significant therapeutic challenge, as it limits antiplatelet options required to prevent stent thrombosis.¹ Described alternatives include clopidogrel desensitization or switching to another P2Y₁₂ inhibitor such as ticlopidine or ticagrelor; however, the risk of cross-reactivity is well documented and increases the risk of severe adverse events.^{1,5} In our case, the pharmacological management was adjusted to account for the patient's comorbidities. Given her indication for chronic anticoagulation due to AF, antithrombotic therapy could be simplified. After completing one month of dual therapy following drug-eluting stent implantation, clopidogrel was discontinued, and treatment was continued with a combination of a direct oral anticoagulant (DOAC) and acetylsalicylic acid.

This approach is in line with the 2026 ACC Scientific Statement, which recommends limiting the duration of combined antithrombotic therapy in patients with atrial fibrillation undergoing PCI to reduce bleeding risk. In patients requiring long-term oral anticoagulation, a DOAC combined with a single antiplatelet agent is generally preferred after an initial period of triple therapy, with prolonged triple therapy avoided.¹⁰

In our patient, clopidogrel was discontinued after one month because of suspected drug-induced leukocytoclastic vasculitis, and therapy was continued with rivaroxaban and aspirin to provide ongoing antithrombotic protection while avoiding re-exposure to the suspected

culprit drug. The rivaroxaban dose was based on the regimen evaluated in the PIONEER AF-PCI trial in patients with atrial fibrillation undergoing PCI.¹¹ This treatment was chosen considering the need to prevent thrombotic complications while also minimizing the risk of recurrent vasculitis.

CONCLUSIONS

Clopidogrel-associated leukocytoclastic vasculitis should be suspected in any patient presenting with a purpuric rash following acute coronary syndrome treatment onset. Although this is a rare entity, early recognition is crucial to prevent systemic involvement and adjust the pharmacological management. In most cases, patients have a favorable clinical course after discontinuation of the offending agent and conservative management; however, some may require systemic therapy. Overall, these clinical presentations pose a therapeutic challenge and require adjustment of baseline antithrombotic therapy.

REFERENCES

- Shetty RK, Madken M, Naha K et al. Leucocytoclastic vasculitis as a late complication of clopidogrel therapy. *BMJ Case Rep.* 2013; 2013: bcr2012007861. doi: 10.1136/bcr-2012-007861.
- Erpolat S, Nazli Y, Colak N et al. Leucocytoclastic vasculitis associated with clopidogrel. *Cutan Ocul Toxicol.* 2012; 31 (2): 171-173. doi: 10.3109/15569527.2011.627578.
- Lehr S, Meiss F, Kiritsi D et al. Small-vessel vasculitis after ST-segment elevation myocardial infarction: clopidogrel or amiodarone? *JACC Case Rep.* 2022; 4 (15): 967-971. doi: 10.1016/j.jaccas.2022.05.008.
- Gutiérrez-Fernández D, Fuentes-Vallejo MS, Rueda-Yguera MD et al. Immediate hypersensitivity and delayed hypersensitivity to clopidogrel. *Allergol Immunopathol (Madr).* 2007; 35 (5): 213-215. doi: 10.1157/13110317.
- Jovanovic M, Sabovic M. Refractory drug-induced systemic small-vessel vasculitis with two varied extracutaneous manifestations: a case report and review of the literature. *J Med Case Rep.* 2023; 17 (1): 470. doi: 10.1186/s13256-023-04174-8.
- Gil-Ramos JM, Coronado-Magalhaes G, Martínez-Sánchez LM. Vasculitis leucocitoclástica, clasificación y abordaje diagnóstico. *Salutem Scientia Spiritus* 2024; 10 (1): 43-49.
- Chanussot-Deprez C, Vega-Memije ME, Flores-Suárez L et al. Etiología de las vasculitis cutáneas: utilidad de una aproximación sistémica. *Gac Med Mex.* 2018; 154 (1): 62-67. doi: 10.24875/GMM.17002773.

8. Gota CE, Calabrese LH. Diagnosis and treatment of cutaneous leukocytoclastic vasculitis. *Int J Clin Rheumatol*. 2013; 8 (1): 49-60. doi: 10.2217/ijr.12.79.
9. Jovaní-Casano V, Fernández-Carballido C, Ibero-Díaz I. Vasculitis leucocitoclásticas. En: Belmonte MA, Castellano JA, Román JA, Rosas JC, editores. *Enfermedades reumáticas: actualización SVR*. 2a ed. Valencia: Ibáñez & Plaza Asociados; 2013. p. 289-299.
10. Kumbhani DJ, Armbruster AL, Cheng RK et al. Direct oral anticoagulants in primary and secondary prevention of thrombotic events: 2026 ACC scientific statement: a report of the American College of Cardiology. *J Am Coll Cardiol*. 2026. doi: 10.1016/j.jacc.2026.05.033.
11. Gibson CM, Mehran R, Bode C et al. Prevention of bleeding in patients with atrial fibrillation undergoing

PCI. *N Engl J Med*. 2016; 375 (25): 2423-2434. doi: 10.1056/NEJMoa1611594.

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