

Metronidazole-Induced Kounis Syndrome Type III Presenting as Acute In-Stent Thrombosis: A Case Report

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Abstract

Kounis syndrome describes an acute coronary syndrome occurring in association with a hypersensitivity reaction and may present as stent thrombosis in its type III form. We report a 60-year-old man with a history of anterior myocardial infarction treated with percutaneous coronary intervention and stent implantation who developed an intensely pruritic urticarial rash 12 hours after starting oral metronidazole following surgical drainage of an ischiorectal abscess. Peripheral eosinophilia was documented. Forty-eight hours later, he presented with an anterior ST-segment elevation myocardial infarction. Urgent coronary angiography demonstrated critical proximal left anterior descending artery stenosis with grade IV in-stent thrombosis. Manual thromboaspiration followed by percutaneous coronary intervention restored normal epicardial flow. Subsequent immunological evaluation showed persistent eosinophilia and markedly elevated serum immunoglobulin E levels. The urticarial rash progressively resolved after definitive withdrawal of metronidazole. The temporal association between metronidazole exposure, the hypersensitivity reaction, and acute in-stent thrombosis supported the diagnosis of Kounis syndrome type III. This case highlights the importance of recognizing hypersensitivity as a potential contributor to acute stent thrombosis and of addressing both the allergic and coronary components of the syndrome.

Categories: Cardiology

Keywords: acute coronary syndrome, allergic myocardial infarction, drug hypersensitivity, in-stent thrombosis, kounis syndrome (ks)

Introduction

Kounis syndrome, described by Kounis and Zavras in 1991, comprises a spectrum of cardiovascular manifestations triggered by a hypersensitivity reaction presenting as an acute coronary syndrome. Its pathophysiology involves mast-cell activation and the release of inflammatory mediators that can induce coronary vasospasm, atherosclerotic plaque rupture, and coronary thrombosis. Three variants are recognized: type I, involving coronary vasospasm in patients without underlying coronary disease; type II, involving plaque disruption in patients with pre-existing atherosclerosis; and type III, characterized by stent thrombosis associated with hypersensitivity. Although probably underdiagnosed, recognition is essential because treatment must address both the acute coronary syndrome and the allergic reaction [1,2]. Metronidazole is a rarely reported trigger of Kounis syndrome. We report a case of metronidazole-associated hypersensitivity followed by ST-segment elevation myocardial infarction due to in-stent thrombosis.

Case Presentation

A 60-year-old man with a history of smoking and acute myocardial infarction five years earlier had undergone percutaneous coronary intervention with stent implantation in the left anterior descending artery. Detailed information regarding the type and dimensions of the previously implanted stent was not available. He remained on chronic aspirin therapy, with adherence documented during follow-up outpatient visits, and had experienced no further cardiovascular events.

Forty-eight hours after rash onset, he developed chest pain radiating to the left arm, diaphoresis, and nausea and presented to the emergency department. Diffuse urticarial lesions and positive dermographism persisted (Figure 1). He was hemodynamically stable (Killip-Kimball class I [3]), and serum troponin was markedly elevated at 8,742 pg/mL. Electrocardiography showed ST-segment elevation in V2-V6, consistent with anterior ST-segment elevation myocardial infarction (Figure 2).

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FIGURE 1: Cutaneous manifestations of the hypersensitivity reaction

(A) Urticaria and dermographism on the anterior thorax. (B) Urticarial lesions on the dorsal region. (C) Erythematous urticarial lesions on the dorsum of the foot.

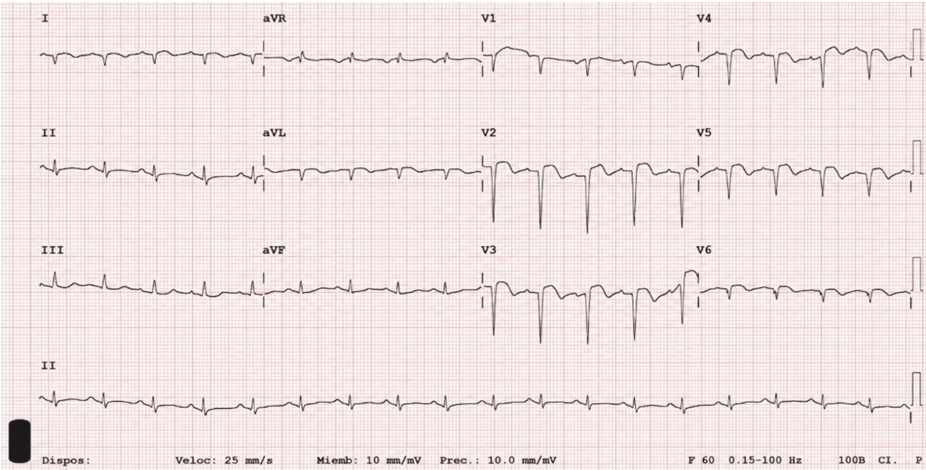


FIGURE 2: 12-lead electrocardiogram

ST-segment elevation in precordial leads V2-V6.

Urgent coronary angiography demonstrated a 95% ostioproximal left anterior descending artery stenosis immediately proximal to the prior stent, grade IV in-stent thrombus, and a 90% mid-distal stenosis. Manual thromboaspiration removed abundant thrombotic material. Percutaneous coronary intervention with an everolimus-eluting stent and balloon angioplasty of the first diagonal branch and circumflex ostium restored thrombolysis in myocardial infarction grade 3 flow (Figure 3).

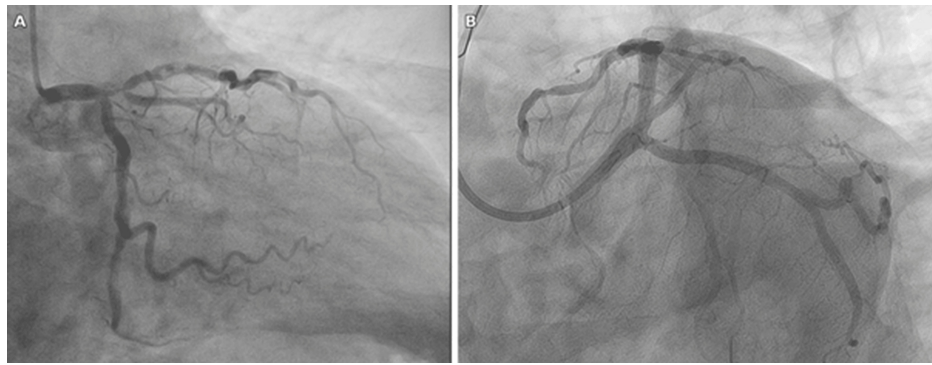


FIGURE 3: Left coronary angiography

(A) In-stent thrombosis in the left anterior descending artery with 95% critical stenosis and reduced coronary flow.
(B) Final angiographic control after percutaneous coronary intervention with restoration of grade 3 flow.

Because cutaneous hypersensitivity and acute coronary syndrome coexisted, immunological evaluation was expanded. Persistent eosinophilia and elevated total immunoglobulin E (775 IU/mL) were documented, with normal complement levels. The Immunoallergy Service considered the presentation compatible with a type B adverse drug reaction secondary to metronidazole. After definitive discontinuation of the antibiotic, the rash progressively resolved without recurrence during hospitalization.

Discussion

Kounis syndrome represents the interaction between the immune and cardiovascular systems, in which a hypersensitivity reaction is capable of triggering an acute coronary syndrome by massively activating mast cells and releasing inflammatory mediators. Although it is probably underdiagnosed, it is an entity of increasing clinical recognition whose real incidence remains unknown. A U.S. population-based study estimated that approximately 1.1% of patients hospitalized for allergic reactions develop Kounis syndrome [4,5].

Kounis syndrome is classified into three pathophysiological variants. Type I occurs in patients without atherosclerotic coronary artery disease, in whom inflammatory mediators induce coronary vasospasm with or without elevation of myocardial necrosis biomarkers. Type II occurs in patients with pre-existing atherosclerotic coronary artery disease, where the inflammatory response triggers plaque erosion or rupture, favouring the development of an acute coronary syndrome. Finally, type III corresponds to stent thrombosis secondary to a hypersensitivity reaction [6].

Our patient developed in-stent thrombosis preceded by a metronidazole-associated systemic hypersensitivity reaction, characterized by urticaria, dermographism, peripheral eosinophilia, and elevated serum IgE, followed by an acute ST-segment elevation myocardial infarction within 48 hours. Histopathological examination of the aspirated thrombus and serum tryptase measurement were unavailable, limiting diagnostic certainty. Nevertheless, the temporal association between drug exposure, systemic hypersensitivity, angiographically confirmed in-stent thrombosis, and clinical improvement after drug withdrawal supported the diagnosis of Kounis syndrome type III, although definitive causality cannot be established [7].

Other potential contributors to in-stent thrombosis should also be considered. The recent ischiorectal infection and surgery may have contributed to a transient prothrombotic state. No overt mechanical complication was identified angiographically; however, intracoronary imaging was not performed, so subtle stent-related abnormalities could not be excluded [8]. Adherence to chronic aspirin therapy was documented during follow-up, although platelet function testing was not performed. Despite these potential contributors, the close temporal association between metronidazole exposure, systemic hypersensitivity, and acute in-stent thrombosis supported type III Kounis syndrome as the unifying diagnosis.

In a systematic review of 214 patients with Kounis syndrome, medications were the most common trigger (38.3%), followed by animal stings or bites (26.2%), food, and contrast media. Among pharmacological triggers, antibiotics accounted for 42.7% of cases (6). In this context, the association with metronidazole continues to be exceptional, since only one pediatric case directly attributed to this drug and one additional case in an adult exposed simultaneously to ceftriaxone and metronidazole have been reported, without it being possible to establish with certainty the causative agent [9,10]. These findings highlight the rarity of the present case and expand the available evidence on metronidazole as a possible trigger for Kounis syndrome type III.

The pathophysiology of Kounis syndrome is based on the activation of mast cells by IgE-dependent and independent mechanisms. The release of histamine, tryptase, leukotrienes, prostaglandins, and platelet-activating factor generates an intensely proinflammatory and prothrombotic microenvironment that favours coronary vasoconstriction, endothelial dysfunction, and platelet activation. In patients with intracoronary devices, this inflammatory response can induce stent thrombosis and trigger an acute coronary syndrome, a pathophysiological mechanism that explains the clinical presentation observed in our patient [11,12].

The diagnosis of Kounis syndrome continues to be predominantly clinical and requires demonstrating a consistent temporal relationship between the hypersensitivity reaction and the acute coronary event. Assessment of cardiac biomarkers, electrocardiography, and coronary angiography confirms cardiovascular involvement. Although serum tryptase is the most specific biomarker of mast cell activation when available and obtained in a timely manner, elevated IgE and peripheral eosinophilia may provide complementary evidence to support diagnosis in the appropriate clinical setting. Due to the absence of standardized diagnostic criteria, a high index of suspicion continues to be essential to establish the diagnosis and initiate prompt treatment [13].

There are currently no specific guidelines for the management of Kounis syndrome, so treatment should be individualized according to the clinical subtype, severity of the hypersensitivity reaction, and presentation of acute coronary syndrome. Immediate suspension of the triggering agent is a key measure. Management requires a simultaneous approach to both processes, combining conventional treatment of acute coronary syndrome with control of the allergic response using H1 and H2 antihistamines and, in selected cases, systemic corticosteroids. Although the latter have raised concerns about a possible increased risk of myocardial rupture after acute myocardial infarction, the available clinical evidence does not contraindicate its use when there is a clear indication for a moderate or severe hypersensitivity reaction, so its administration should be individualized by carefully assessing the risk-benefit [14,15]. Drugs with the potential to exacerbate mast cell degranulation or perpetuate the allergic response should also be avoided whenever possible. In patients with Kounis syndrome type III, the reperfusion strategy should be individualized according to the clinical presentation and angiographic findings. Routine manual thromboaspiration is not recommended in STEMI; however, in this patient it was used as an individualized strategy because of the high thrombus burden and abundant intracoronary thrombotic material.

Conclusions

Kounis syndrome should be considered when acute coronary syndrome is preceded by manifestations of hypersensitivity. In this case, the temporal relationship with metronidazole exposure, systemic allergic findings, and angiographically confirmed in-stent thrombosis supported type III Kounis syndrome. Prompt identification and withdrawal of the trigger, together with simultaneous treatment of the allergic and coronary processes, are central to management.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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submitted work.

References

1. Kounis NG, Zavras GM: Histamine-induced coronary artery spasm: the concept of allergic angina. *Br J Clin Pract.* 1991, 45:121-8. [10.1111/j.1742-1241.1991.tb10251.x](#)
2. Rochel-Perez E, Santaularia-Tomas M, Martin-Dorantes M, et al.: Triggers, types, and treatments for Kounis syndrome: a systematic review. *Clin Pract.* 2025, 15: [10.3390/clinpract15050059](#)
3. Killip T 3rd, Kimball JT: Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *Am J Cardiol.* 1967, 20:457-64. [10.1016/0002-9149\(67\)90023-9](#)
4. Desai R, Parekh T, Patel U, et al.: Epidemiology of acute coronary syndrome co-existent with allergic/hypersensitivity/anaphylactic reactions (Kounis syndrome) in the United States: a nationwide inpatient analysis. *Int J Cardiol.* 2019, 292:35-8. [10.1016/j.ijcard.2019.06.002](#)
5. Douedi S, Odak M, Mararenko A, Ross J, Sealove B: Kounis syndrome: a review of an uncommon cause of acute coronary syndrome. *Cardiol Rev.* 2023, 31:230-2. [10.1097/CRD.0000000000000436](#)
6. Kounis NG: Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? . *Int J Cardiol.* 2006, 110:7-14. [10.1016/j.ijcard.2005.08.007](#)
7. Cahuapaza-Gutierrez NL, Calderon-Hernandez CC, Chambergo-Michilot D, De Arruda-Chaves E, Zamora A, Runzer-Colmenares FM: Clinical characteristics, management, diagnostic findings, and various etiologies of patients with Kounis syndrome. A systematic review. *Int J Cardiol.* 2025, 418:132606. [10.1016/j.ijcard.2024.132606](#)
8. Klein LW, Nathan S, Maehara A, et al.: SCAI expert consensus statement on management of in-stent restenosis and stent thrombosis. *J Soc Cardiovasc Angiogr Interv.* 2023, 2:100971. [10.1016/j.jscai.2023.100971](#)
9. Terlemez S, Eryılmaz U, Tokgöz Y, Uysal P, Coşan A, Bulut Y: Kounis syndrome caused by metronidazole—a case of 14 year-old boy. *Int J Cardiol.* 2015, 179:222-4. [10.1016/j.ijcard.2014.11.049](#)
10. Çakmak A, Keskin G: Kounis syndrome: is ceftriaxone or metronidazole responsible for acute myocardial infarction? A rare case. *Anatol J Cardiol.* 2021, 25:451-2. [10.5152/AnatolJCardiol.2020.36422](#)
11. Forzese E, Pitrone C, Cianci V, et al.: An insight into Kounis syndrome: bridging clinical knowledge with forensic perspectives. *Life (Basel).* 2024, 14: [10.3390/life14010091](#)
12. Giugliano GR, Giugliano RP, Gibson CM, Kuntz RE: Meta-analysis of corticosteroid treatment in acute myocardial infarction. *Am J Cardiol.* 2003, 91:1055-9. [10.1016/S0002-9149\(03\)00148-6](#)
13. Kounis NG: Kounis syndrome: an update on epidemiology, pathogenesis, diagnosis and therapeutic management. *Clin Chem Lab Med.* 2016, 54:1545-59. [10.1515/cclm-2016-0010](#)
14. Ollo-Morales P, Gutierrez-Niso M, De-la-Viuda-Camino E, Ruiz-de-Galarreta-Beristain M, Osaba-Ruiz-de-Alegria I, Martel-Martin C: Drug-induced Kounis syndrome: latest novelties . *Curr Treat Options Allergy.* 2023, 1-18. [10.1007/s40521-023-00342-9](#)
15. Kalambay JD, Tashli M, Zaman M, Elwidaa A, Shet V, Phillip M: Kounis syndrome: a systematic review and meta-analysis. *Am J Cardiol.* 2026, 268:25-31. [10.1016/j.amjcard.2026.03.019](#)