



Allergic recurrent coronary stent thrombosis: A mini-review of Kounis syndrome ☆☆☆☆

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ABSTRACT

Kounis syndrome (KS) consists of an association between hypersensitivity reactions triggered by various environmental and pharmacological factors and acute coronary syndromes. Blood supply may be compromised by either vasospasm (type I), native plaque destabilization (type II) or stent thrombosis (type III). Although the prognosis is generally favorable, treatment should include aggressive anti-thrombotic and anti-allergic therapies. A case compatible with type III KS, manifested as a macular rash followed by two episodes of stent thrombosis after primary angioplasty (PCI) of the right coronary artery is presented, and complemented by a review on the topic.

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1. Introduction

Kounis syndrome (KS) consists of an association between hypersensitivity reactions triggered by various environmental and pharmacological factors and acute coronary syndromes. The pathophysiology involves mast cell degranulation and the release of inflammatory mediators that could induce coronary vasospasm (type I), native plaque destabilization (type II) or stent thrombosis (type III) [1]. Diagnosis relies essentially on the clinical identification of an allergic reaction

preceding the cardiac manifestations. Allergy-related peripheral blood markers are difficult to identify because of their generally short half-life. Standard treatment strategies only directed to the ongoing acute coronary syndrome may be insufficient to adequately control the associated inflammatory response. As such, the case description reports a patient with an episode compatible with type III KS, manifested as a new-onset macular rash followed by two occurrences of stent thrombosis after primary angioplasty (PCI) of the right coronary artery (RCA). Solely optimizing antithrombotic therapy without anti-allergic medications was insufficient to prevent the second event.

2. Case description

A previously asymptomatic 57 year-old man with hypertension and dyslipidemia presented to the emergency department of our institution after 2 h of ongoing acute-onset chest pain. Previous medications

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included only candesartan and atorvastatin, and there was no history of allergies. On admission, his vital signs were normal but the initial electrocardiogram (EKG) revealed a 2 mm ST-segment elevation in leads DII, DIII and aVF (Fig. 1A). Thereafter, 200 mg of aspirin and a 600 mg oral loading dose of clopidogrel were administered. The patient was immediately transferred to the catheterization laboratory and within 40 min of the first medical contact, primary PCI was performed through the right radial artery. The RCA was occluded with a substantial amount of thrombi before the bifurcation of the posterior descending and ventricular branches, and a significant obstructive lesion was identified in the proximal segment (Fig. 1B). All other arteries were free of any obstructions. Aspiration thrombectomy was performed and a total of 3 everolimus-eluting stents (Synergy®) were placed in the proximal segment and both the posterior descending and ventricular branches, with an angiographically successful outcome and resolution of the ST-segment deviation and chest pain (Fig. 1C and D). During the procedure, 5000 U of unfractionated heparin (UFH) and a total of 250 ml of a low-osmolar iodinated contrast medium were administered. In addition, both intracoronary and peripherally delivered abciximab were administered as two 5 mg loading doses, followed by a continuous infusion during the next 12 h, in the coronary intensive care unit (CICU).

On the next day, 19 h after the procedure and 1 h after receiving the 75 mg maintenance dose of clopidogrel and 100 mg of aspirin, the patient developed a macular, non-pruriginous rash, predominantly on the thorax and abdomen (Fig. 2). Shortly afterwards he complained of a low intensity left-sided chest discomfort, and a new EKG revealed recurrence of the ST-segment elevation in the inferior wall and depression in the lateral and anterior leads (Fig. 3A). An emergency coronary angiography was performed and demonstrated an occlusion of the middle segment of the RCA, once more with a considerable amount of thrombi (Fig. 3B). Although the occlusion initiated in a segment that had not been previously stented, proximal extension of a thrombotic process that began within the distal stents could not be excluded. Aspiration thrombectomy was then followed by placement of another



Fig. 2. Thoracic and abdominal macular, non-pruriginous rash identified 1 h after aspirin and clopidogrel administration.

everolimus-eluting stent in the middle segment of the RCA (Fig. 3C). Unfractionated heparin and intracoronary abciximab were once again administered and clopidogrel was replaced by prasugrel (60 mg periprocedural loading dose). Despite residual thrombi after the intervention, TIMI flow grade III was still achieved. The EKG no longer demonstrated an inferior wall ST-segment elevation and the patient returned to the CICU without symptoms (Fig. 3D).

Eighteen hours after the second intervention, the patient remained clinically stable and asymptomatic, although still with the same rash, as previously described. Nonetheless, continuous EKG monitoring revealed a reappearance of the ST-segment deviation in addition to a second degree atrioventricular block. A new 12 lead EKG confirmed a recurrence of the ST-segment elevation in the inferior leads (Fig. 4A). An immediate coronary angiography was performed once again,

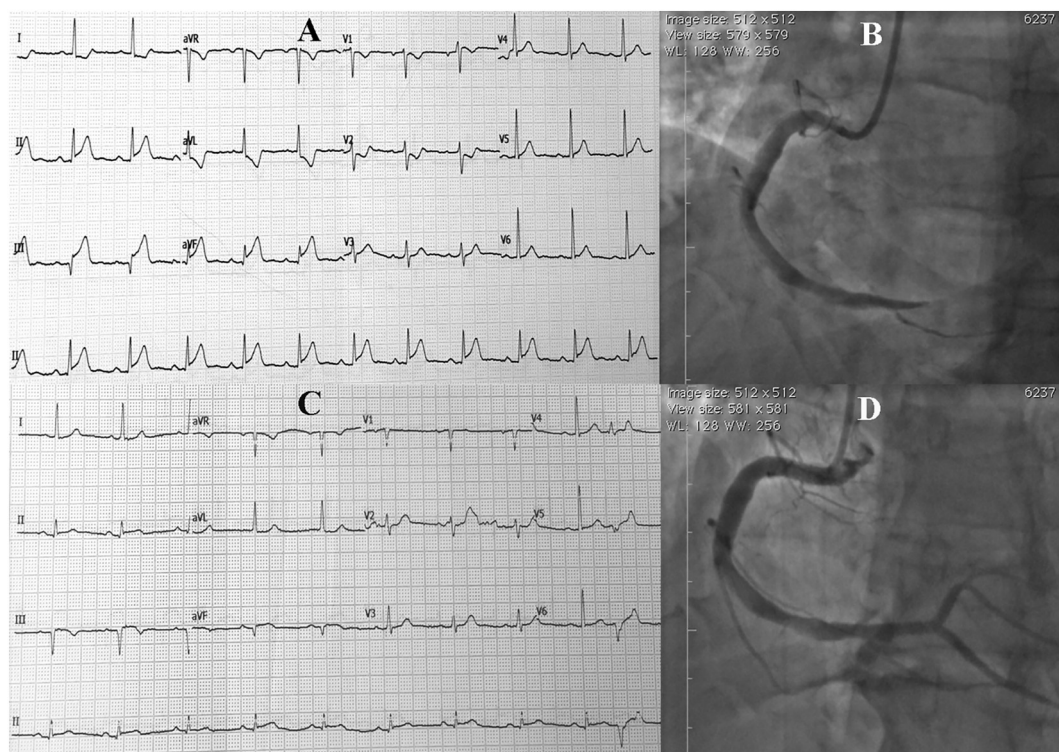


Fig. 1. (A) Admission electrocardiogram (EKG) with ST-segment elevation in the inferior leads and depression in DI, aVL, V1 and V2. (B) Coronary angiography performed 40 min after the first medical contact demonstrating distal occlusion of the right coronary artery (RCA), and an obstructive lesion in the proximal segment. (C) Post-procedural EKG demonstrating improvement of the ST-segment deviations. (D) Restoration of RCA patency after thrombectomy and deployment of 3 everolimus-eluting stents (Synergy®) in the proximal segment and both the posterior descending and ventricular branches.

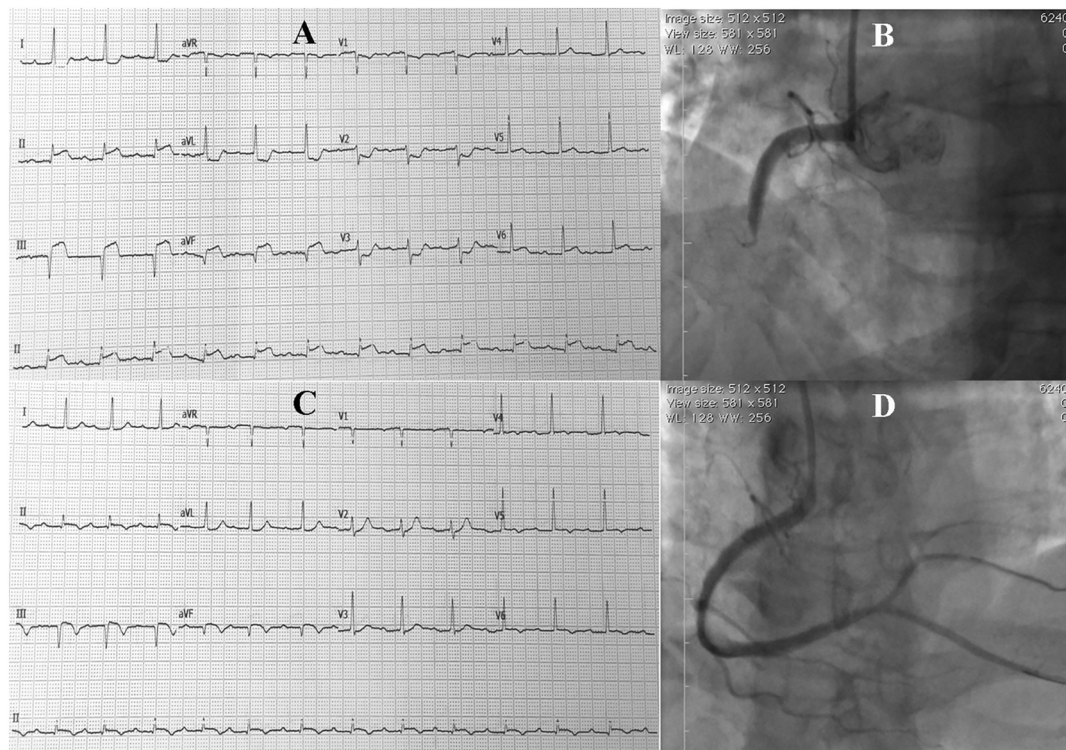


Fig. 3. (A) Electrocardiogram (ECG) with ST-segment elevation recurrence in the inferior leads and depression in DI, aVL, V1, V2 and V3, 1 h after aspirin and clopidogrel administration. (B) Mid-segment occlusion of the right coronary artery. (C) Post-procedural ECG demonstrating improvement of the ST-segment deviations. (D) Successful reperfusion of the RCA after thrombectomy and deployment of 1 everolimus-eluting stents (Synergy®) in the middle segment.

which demonstrated proximal in-stent thrombosis occluding the RCA (Fig. 4B). Subsequently, two additional everolimus-eluting stents were placed with a successful angiographic outcome, though a residual

ST-segment elevation remained in the inferior leads (Fig. 4C and D). A total of 6 everolimus-eluting stents were implanted throughout the 3 interventions, after which no other native segments were left to treat.

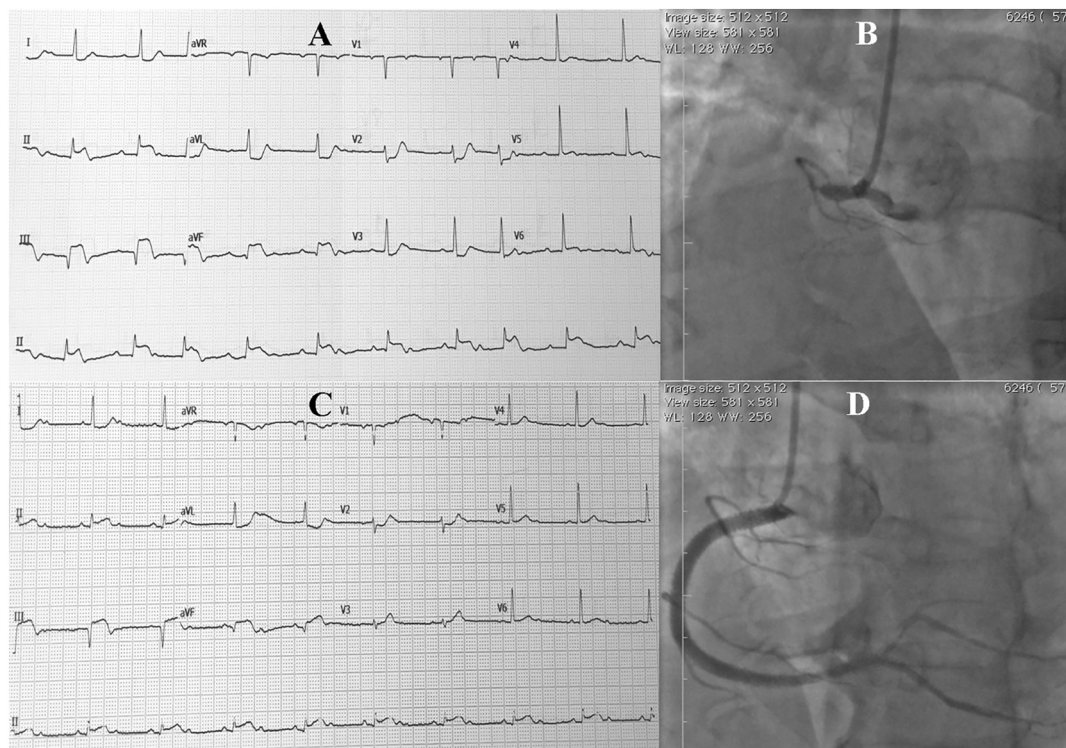


Fig. 4. (A) Electrocardiogram (ECG) with a second ST-segment elevation recurrence in the inferior leads and depression in DI, aVL, V1, V2 and V3, in addition to a new second degree atrioventricular (AV) block. (B) Proximal stent thrombosis of the right coronary artery (RCA). (C) Post-procedural ECG demonstrating residual ST-segment deviations and persistent 2:1 AV block. (D) Restoration of RCA patency and TIMI flow grade III following a third intervention, after which a total of 6 everolimus-eluting stents were deployed.

Besides 5000 U of intravenous UFH, no further periprocedural anti-thrombotic treatment was added to the dual antiplatelet therapy. However, full dose subcutaneous enoxaparin (80 mg bid) was subsequently initiated in the CICU.

Blood samples for both the VerifyNow™ P2Y₁₂ and aspirin platelet reactivity tests were collected during the last procedure. The results for the P2Y₁₂ assay were not interpretable due to interference by recent abciximab administration. However, aspirin platelet inhibition was within the therapeutic range (377 ARU; therapeutic inhibition <549 ARU). Since a suspicion of type III Kounis syndrome was raised, 40 mg of oral prednisone and 180 mg of fexofenadine were prescribed after the third intervention. An elevated total IgE level (217 KU/L; reference value <114 KU/L) further supported the hypothesis of a hypersensitivity-mediated stent thrombosis, although no peripheral eosinophilia was identified and coronary thrombi were not recovered for analysis.

Prednisone and anti-histamines were maintained during three days, after which the rash subsided, no further dynamic EKG changes were identified and high-sensitivity troponin T levels progressively declined (Fig. 5). Five days after the third procedure, full dose enoxaparin was also withdrawn. Thereafter, the patient had an uneventful recovery, with a pre-discharge echocardiogram revealing inferior wall akinesis, although with preserved global right and left ventricular function. He was prescribed bisoprolol, atorvastatin, aspirin and prasugrel.

3. Discussion

Although a relationship between allergic clinical manifestations and acute coronary syndromes has been suspected for many decades, the “allergic angina syndrome” was only defined in 1991 by Kounis and Zavras. The report described how histamine-mediated vasospasm could result in myocardial infarction, when triggered by specific antigens [2]. However, since then this concept has expanded and the syndrome has been divided into three distinct types according to the mechanism of coronary obstruction. The type I variant represents the most common mechanism (72.6%), where coronary obstruction results from vasospasm, usually in younger patients without native atherosclerotic disease. In type II KS (22.3% of cases), myocardial infarction results from the rupture or erosion of an atherosclerotic coronary plaque, in addition to vasospasm. Finally, type III represents only 5.1% of all cases, and results from thrombosis adjacent to or within a coronary stent, as a consequence of a hypersensitivity reaction [1,3].

While KS is probably under-diagnosed in clinical practice, the disease has been described in a wide variety of patient profiles and age groups. Nonetheless, the annual incidence seems to vary according to geographical locations, and appears to be more common in southern Europe [4]. In parts of Greece, the annual incidence has been estimated

to be approximately 4 cases/100,000 inhabitants [5]. This could be a consequence of a greater awareness of the syndrome's existence or a greater exposure to environmental triggers in these areas. In contrast, emergency department studies have reported annual incidences as high as 19.4 cases/100,000 patients [6].

All three types have a common initial mechanism, where an allergic response induces a mast cell-mediated inflammatory cascade, which leads to the compromise of the coronary circulation, according to each clinical subtype. The degranulation of mast cells that results in the release of inflammatory mediators is initiated either by an antigen-antibody interaction on the surface of the mast cells and basophils, or through the activation of the complement system. The most important mediators include histamine, chemokines, chymase, tryptase, cathepsin-D, peptides, proteoglycans, cytokines, growth factors and arachidonic acid products [4]. This process tends to occur very rapidly after the exposure to the antigen, and many of these substances have significant effects on the cardiovascular system. These include coronary vasospasm, activation of the coagulation cascade and platelet aggregation, in addition to plaque rupture and erosion. As such, the majority of KS cases (80%) tend to manifest within 1 h after contact with the trigger [1].

Type III KS is a particularly dangerous event, because the mortality rate associated with stent thrombosis could be as high as 40%. Multiple factors are usually implicated in this complication, including angiographic, procedural and clinical variables, but an allergic response is often overseen. The thrombotic process in these cases results from platelet adhesion, activation and aggregation, all of which can be triggered by the inflammatory mediators released by mast cells after the exposure to specific antigens. Furthermore, drug-eluting stents appear to function as a favorable surface where the activation of both mast cells and platelets can occur [7]. This process could also manifest in the coronary intima adjacent to the stent [3]. A previous report has even described simultaneous multivessel drug-eluting stent thrombosis only 3 days after stent implantation, suggesting that the phenomenon is not restricted to a local reaction and could affect the entire coronary circulation as a more systemic event [8]. Future studies should focus on the development of short lasting stents composed by non-allergic material, although thrombotic events with bioresorbable scaffolds have been reported [3]. Whether these stents could minimize the risk of KS has yet to be determined, though this area of research represents a promising prospect.

The allergic reaction associated with KS can be triggered by any allergen, including drugs, insect bites, foods, contrast media, latex and even drug-eluting stents themselves. However, because of a wide array of clinical presentations, physicians must have a high level of suspicion in order to correctly diagnose the syndrome and treat the patient accordingly. The measurement of systemic specific inflammatory mediators released by mast cells, such as histamine and tryptase, has little diagnostic value in these cases, because of their short serum half-life. Nevertheless, the analysis of coronary thrombi could not only reveal the presence of these cells, but also eosinophils, which would support an allergy-mediated mechanism for the thrombosis. Similarly, elevated total and specific IgE levels could further suggest an ongoing allergic process, although normal values and the absence of peripheral eosinophilia do not exclude the diagnosis [1,4]. Skin testing for specific allergens could also be useful, but is not always available for all of the potential triggers. Conversely, an increase in cardiac biomarkers, such as troponin I and T, is common and reflects the degree of myocardial damage resulting from the allergic response. Table 1 describes the main clinical features associated with KS.

Treatment strategies should be concentrated on controlling the ongoing hypersensitivity reaction and minimizing myocardial damage. Since the allergic response is present in all three KS subtypes, patients may benefit from corticosteroids (i.e. hydrocortisone 1–2 mg/kg/day) and both H1 and H2 anti-histamines (i.e. diphenhydramine 1–2 mg/kg and ranitidine 1 mg/kg) [1,4]. Even so, steroid therapy should be



Fig. 5. Resolution of the rash after 3 days of prednisone and fexofenadine treatment.

Table 1

Potential triggers, clinical manifestations, laboratory findings and electrocardiographic signs associated with Kounis syndrome.

Potential triggers	Clinical manifestations	Laboratory findings	EKG signs
Drugs - NSAIDs (ibuprofen, diclofenac, naproxen) - Antibiotics (penicillins, cephalosporins, quinolones) - Anti-neoplastics (interferons, 5-Fluorouracil, paclitaxel) - Antithrombotics (aspirin, clopidogrel, heparin, streptokinase, alteplase) - Anesthetics (etomidate, propofol, midazolam) - Glucocorticoids (hydrocortisone, betamethasone) - Proton pump inhibitors (lansoprazole) - Others (enalapril, losartan, fluconazole, allopurinol, bupropion, oseltamivir, tramadol) Foods - Shell fish, tuna fish, anchovies, fruits, vegetables Environmental exposures - Grass cutting - Poison ivy - Poisonous snake bites - Insect bites (bee, wasp, Hymenoptera) - Arachnid stings (spiders, scorpions) - Jellyfish stings Others - Latex - Chlorhexidine - Iodine - Contrast media - Stents (bare metal, drug-eluting) - Nicotine - Exercise-induced anaphylaxis - Serum sickness	- Chest Pain - Dyspnea - Pulmonary edema - Syncope - Headache - Nausea - Pruritus - Vomiting - Palpitations - Arrhythmias - Diaphoresis - Skin rash - Wheezing - Anaphylaxis - Hypotension - Cardiac arrest - Cardiogenic shock - Sudden death	- Eosinophilia - High tryptase, chimase and/or histamine levels - Elevated total IgE - Elevated arachidonic acid products - High C-reactive protein - Increased TnI, TnT and CK-MB - Eosinophils and mast cells in coronary thrombi - SPECT: myocardial ischemia - Cardiac echo: regional motion abnormalities and/or global LV dysfunction - Coronary spasm or thrombosis on angiography	- AV block - Atrial fibrillation - Sinus bradycardia or tachycardia - ST-segment elevation or depression - T-wave inversion - QRS widening - QT-segment prolongation - PVCs - Ventricular tachycardia or fibrillation

AV – atrioventricular; CK-MB – creatine kinase-MB; Echo – echocardiogram; EKG – electrocardiogram; LV – left ventricular; NSAIDs – nonsteroidal anti-inflammatory drugs; PVCs – premature ventricular contractions; SPECT – single photon emission computed tomography; TnI – troponin I; TnT – troponin T.

administered with caution in the context of a recent myocardial infarction due to the risk of myocardial rupture, though a previous meta-analysis has suggested that these drugs appear to be safe in this scenario [9]. Mast cell stabilizers (e.g. sodium cromoglycate) have also been used in this context and may be considered as an additional treatment option [10].

In type I KS, the reversal of the inflammatory response may be sufficient to control coronary vasospasm, though in some cases calcium channel blockers and nitrates are also necessary. In type II and type III, the management should follow the treatment recommendations of ST and non-ST elevation coronary syndromes, with appropriate antithrombotic and reperfusion strategies. Besides aspirin and oral P2Y₁₂ inhibitors, aggressive intravenous antiplatelet therapy with periprocedural IIb/IIIa inhibitors should be considered, particularly when stent thrombosis is confirmed. Although these medications are potential antigens themselves, concomitant administration of corticosteroids and anti-histamines is vital to minimize the risk of perpetuating the allergic response. While the early use of corticosteroids may be a concern during an acute coronary syndrome, the benefits seem to justify the potential risks in the context of KS patients [9,10].

The case description is compatible with type III KS since it describes the association of systemic allergic manifestations and evidence of new onset myocardial ischemia after recent PCI, both of which only subsided after adequate anti-allergic therapy. Although coronary thrombi were not analyzed, any patient who presents with these clinical characteristics should be suspected as having the syndrome, and treated accordingly [4]. While clopidogrel may have been responsible for the allergic manifestations, the diagnosis was only presumed, since no specific tests were performed to confirm the association. However, all other medications were maintained and the rash still resolved. Additionally, only clopidogrel and aspirin had been administered within the 1 h time frame during which most cases manifest, and the latter was subsequently well tolerated and had been previously used without

complications. This time interval also reduced the probability of abciximab being implicated as the trigger, though this possibility cannot be completely excluded.

Even though clopidogrel has been previously implicated as a trigger in a patient with recurrent stent thrombosis and allergic manifestations, we describe a unique case of prasugrel treatment failure in a similar scenario [11]. The fact that prasugrel was not associated with the perpetuation of the allergic process in our case does not exclude clopidogrel as being the potential trigger, since cross-reactivity occurs in <20% of patients [12]. Prasugrel and ticagrelor are recommended as first line agents to replace clopidogrel in cases of confirmed or suspected stent thrombosis, due to their greater antiplatelet activity [13]. However, our report raises the question of whether more potent drugs are required when the thrombosis occurs in the context of an allergic reaction. Perhaps this would be a scenario where cangrelor could be utilized, although this consideration remains speculative.

Technical aspects associated with PCI and stent implantation are also important determinants of stent thrombosis, and probably have a role in the development of KS. Slow flow, inadequate post-procedural lumen dimensions, residual dissection, and tissue prolapse are important predictors with early thrombosis. In addition, stent underexpansion and malapposition are known determinants of this complication and should be considered in these circumstances [14]. Optical coherence tomography (OCT) and intravascular ultrasound (IVUS) have become important diagnostic tools in this context, especially when long and overlapping stents are deployed. In our report, despite optimal angiographic results after each procedure, OCT and IVUS could have been helpful to guarantee adequate stent implantation. Finally, though multiple stenting may in fact be deleterious during an ongoing case of suspected type III KS, the most effective strategy to balance successful reperfusion and minimal allergen exposure in this scenario has yet to be determined. Perhaps the development of stents with hypoallergenic material could be a possible solution in the future.

4. Conclusion

Kounis syndrome is a unique form of acute coronary syndrome where treatment should not be limited to the restoration of coronary blood flow, but also be directed to controlling the associated systemic allergic response. Such inflammation seems to perpetuate the process of coronary obstruction and myocardial damage, which conventional antithrombotic and reperfusion strategies may fail to control. Although the prognosis of patients with KS appears to be favorable, with a 2.9% estimated mortality rate, cardiologists should be aware of this diagnosis especially because of the large scale use of PCI with drug-eluting stents [1]. Prompt initiation of anti-allergic therapy seems safe and beneficial, though further research is needed to clarify the most effective diagnostic and therapeutic strategies.

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