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CASE REPORT
Coronary heart disease

A case report of Kounis syndrome presenting with a rash, very late stent thrombosis and coronary evaginations

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Background Very late stent thrombosis (ST) is a concern in the era of drug-eluting stents (DESs), and ST is associated with peri-DES coronary artery aneurysmal lesions or coronary evaginations. An increasing number of cases of concurrent systemic allergic reaction and ST have been reported as Kounis syndrome (KS) in the literature. The number of patients with very late ST caused by KS is small, and further investigation of the potential pathophysiology is required.

Case summary We report a case of KS that manifested as systemic urticaria followed by very late ST 14 years after placement of two sirolimus-eluting stents (SESs). Three months after the event of ST, coronary evaginations at the stented segments were detected on intravascular optical coherence tomography.

Discussion Coronary evaginations are associated with local hypersensitivity, stent malapposition, uncovered strut, and flow disturbance that may predispose to ST. Systemic allergic reactions are known to promote platelet adhesion and aggregation. This case of KS suggests a pathophysiology in which the synergic effects between the coronary evaginations and a systemic allergic reaction may contribute to very late ST. For patients with Type 3 KS, performing follow-up intracoronary imaging tests may be important to confirm potential coronary evaginations, especially in patients with SESs.

Keywords Very late stent thrombosis • Sirolimus-eluting stent • Optical coherence tomography • Evagination • Hypersensitivity • Kounis syndrome • Case report

Learning points

- The concurrence of a systemic allergic reaction and in-stent thrombosis is defined as Type 3 Kounis syndrome.
- Coronary evaginations are associated with the use of sirolimus-eluting stents, local hypersensitivity, flow disturbance, uncovered strut, stent malapposition, thrombosis, and target lesion revascularization.
- The synergic effects between coronary evaginations and activation of platelet adhesion and aggregation in a systemic allergic reaction may contribute to very late stent thrombosis.

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Introduction

Although percutaneous treatment of coronary artery disease has come to the era of newer-generation drug-eluting stents (DESs), very late stent thrombosis (ST) is still a concern especially in patients treated with first-generation sirolimus-eluting stents (SESs).[1,2] Some studies have shown that ST is associated with peri-SES coronary artery aneurysmal lesions or coronary evaginations.[3,4] Concurrence of allergic reactions and acute coronary syndrome has been reported as Kounis syndrome (KS).[5] The pathophysiology of KS involves coronary artery spasm (Type 1), atheromatous plaque erosion or rupture (Type 2), or ST (Type 3) during an anaphylactic process. The number of patients with very late ST caused by Type 3 KS is limited to those indicated in case reports, rendering it difficult to evaluate a possible link between very late ST caused by Type 3 KS and coronary evaginations. We report a case of Type 3 KS concurrent with coronary evaginations that occurred 14 years after placement of two SESs.

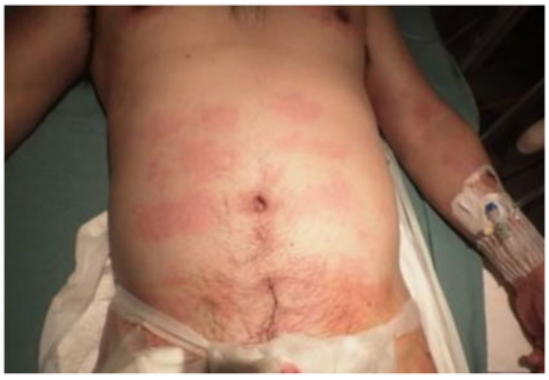

Figure 1 Erythematous, pruritic, and oedematous skin lesions on the trunk and extremities.

Timeline

Day	Events
2003	Two sirolimus-eluting stents (SESs) were placed in the left anterior descending artery for the treatment of angina pectoris
5 June 2018	Transient systemic urticaria presented without any known triggers
8 June 2018	The urticaria recurred, followed by acute chest pain a few hours later. The electrocardiography finding was remarkable for ST-segment elevation in the precordial leads. Coronary angiography (CAG) confirmed in-stent thrombi. Owing to the thrombosis, peri-stent contrast staining or coronary evaginations were not visualized. The subsequent treatments were thrombectomy and drug-coated balloon dilation, with recurrent in-stent thrombosis observed. Afterward, catheter-directed urokinase thrombolysis was performed
9 June 2018	The subsequent CAG images confirmed the shrinkage of the in-stent thrombosis
September 2018	Follow-up CAG and optical coherence tomography images demonstrated coronary evaginations at the site of the two SESs
2019	The patient was followed up, and no further events were reported

Case presentation

The patient was a 67-year-old man with a history of angina pectoris and placement of two SESs in the left anterior descending (LAD) artery in 2003. He had had no complications and had been taking aspirin until 2018, when he experienced transient urticaria on the trunk and extremities without any known underlying triggers. The allergic reaction subsided spontaneously within 24 h, but a similar reaction occurred 3 days later. A few hours after the onset of the recurrent urticaria, the patient experienced acute chest pain.

He was transferred to a cardiac centre. Physical examination findings demonstrated erythematous, pruritic, and oedematous skin lesions on the trunk and extremities (*Figure 1*). The electrocardiography showed ST-segment elevation in leads V1 through V5 with reciprocal changes (*Figure 2*). Steroids were administered for his allergic reaction, and he underwent emergent coronary angiography (CAG).

The imaging test revealed in-stent thrombi in the LAD artery (*Figure 3*). Thrombectomy and drug-coated balloon dilation were performed, which resulted in coronary artery flow of TIMI III, but in-stent thrombosis occurred immediately after the procedure. Afterward, catheter-directed urokinase thrombolysis was performed. Owing to the underlying thrombosis, coronary evaginations were not visualized on the optical coherence tomography (OCT). The subsequent CAG performed on the next day revealed in-stent thrombosis that had diminished. Three months later, we performed a follow-up CAG and confirmed contrast staining outside the stent contour. This is referred to as peri-stent contrast staining (PSS; *Figure 4*). OCT images confirmed that the PSS were in fact coronary evaginations around the two SESs (*Figure 5*).

The decision was taken to initiate lifelong dual-antiplatelet therapy, as patients with coronary evaginations are at increased risk for subsequent ST. The systemic allergic reaction was thought to be an element that promoted platelet activation and thrombus formation, but antihistamine medications were not prescribed per patient's preference. The patient was followed up for 1 year, and no further events were reported.

Discussion

Despite the era of newer-generation DESs, very late ST remains a problem, especially in patients treated with SESs.[1,2] Some of the proposed causes for ST include uncovered struts, stent malapposition, restenosis, neoatherosclerosis, and local hypersensitivity.[6–9] Further

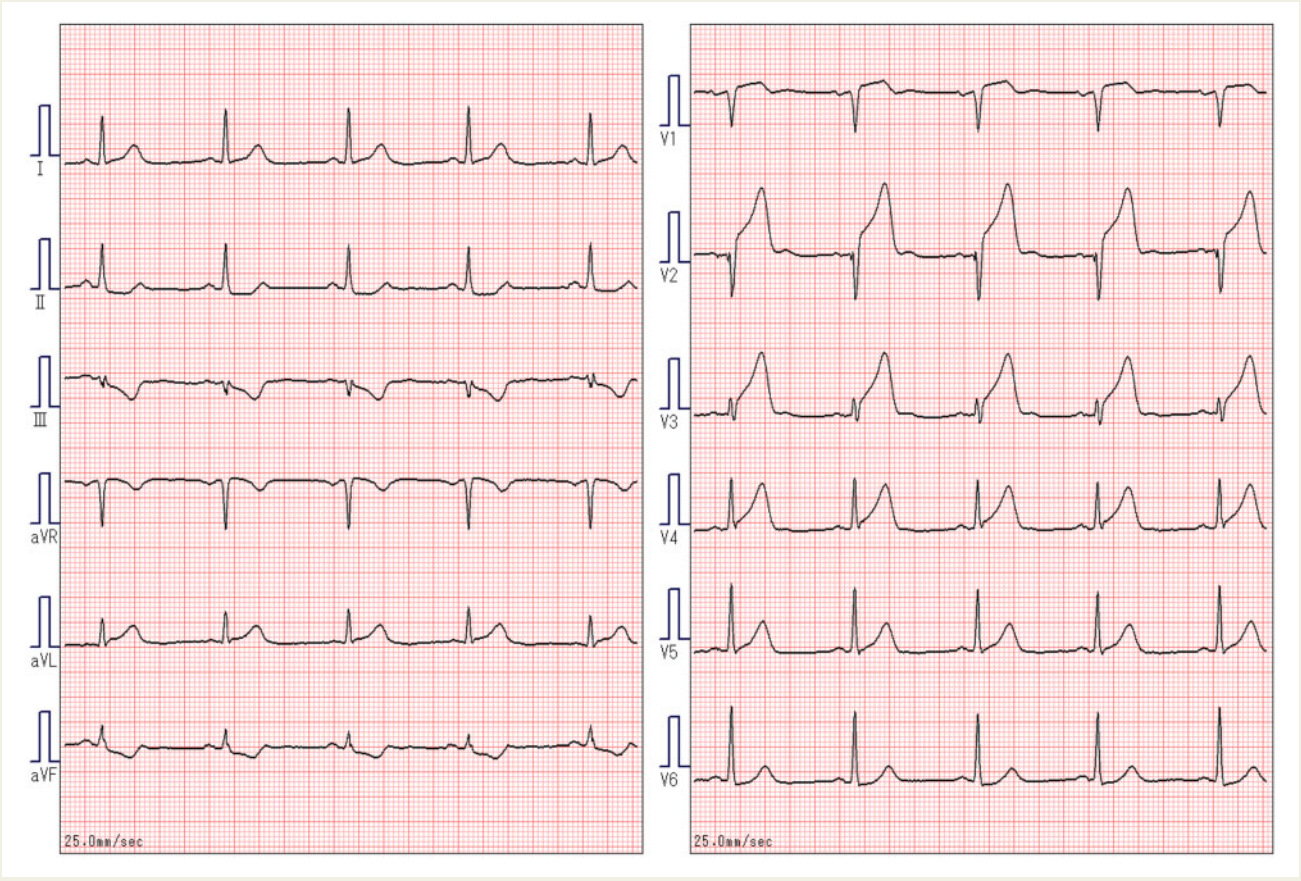

Figure 2 Electrocardiographic image significant for ST-segment elevation in leads V1 through V5 with reciprocal changes.

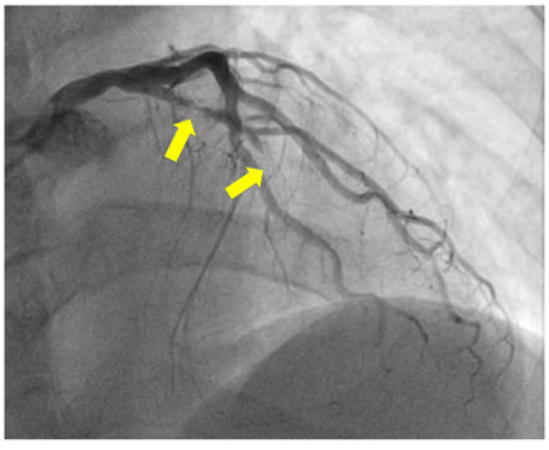

Figure 3 Emergent coronary angiogram showing some in-stent thrombi at the two sirolimus-eluting stents (arrows) in the left anterior descending artery.

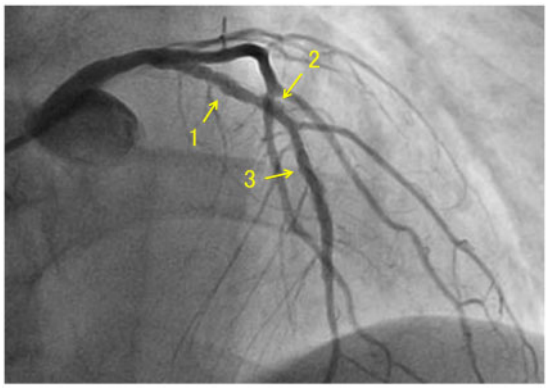

Figure 4 Coronary angiography obtained 3 months after the stent thrombosis developed, demonstrating some peri-stent contrast-staining lesions (arrows) at the sight of the two stents.

more, arterial aneurysmal lesions have been proposed as another cause of very late ST.[4] These lesions are detected as PSS on CAG or as coronary evaginations on OCT. Local hypersensitivity against DESs has been suspected as a cause of coronary evaginations.[7,9] These evaginations are frequently observed in patients with SESs, and they are associated with high incidence of uncovered struts, stent malapposition, and stent fractures.[3,4] Coronary evaginations can cause local coronary artery flow deceleration and disturbance.[10]

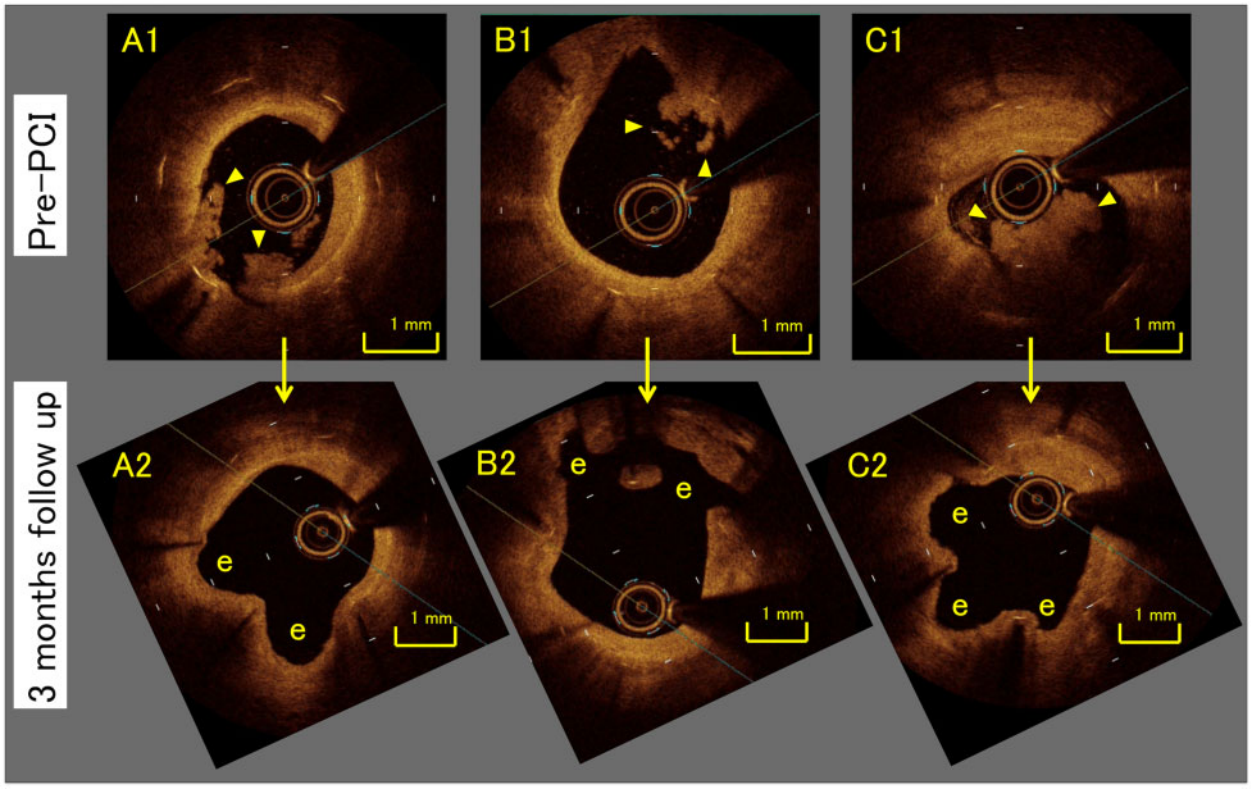

Figure 5 Respective optical coherence tomography images (*A1* and *A2*, *B1* and *B2*, and *C1* and *C2*) corresponding to the peri-stent contrast staining lesions in *Figure 4* (arrows 1, 2, and 3). The optical coherence tomography image obtained at 3-month follow-up confirmed some evaginations (*A2*, *B2*, and *C2*) that were covered with thrombi that were not fully visualized in the acute phase (*A1*, *B1*, and *C1*). The arrowheads signify thrombi, and 'e' indicates an evagination.

In this case, very late ST and coronary evaginations were confirmed 14 years after the placement of two SESs. OCT confirmed the evaginations without neoatherosclerosis at the site of the two SESs. Thus, an underlying peri-stent hypersensitivity and flow disturbance were considered as some of the predisposing factors to thrombus formation. To the best of our knowledge, the optimal therapeutic approach for evaginations is currently unknown.

Concurrence of acute coronary syndrome with hypersensitivity reactions has been reported as KS.[5] The pathophysiology of KS involves coronary artery spasm (Type 1), atheromatous plaque erosion or rupture (Type 2), or ST (Type 3) during an anaphylactic process. Augmentation of platelet adhesion and aggregation by inflammatory molecules such as histamine, trypsin, and platelet-activating factors secreted by mast cells secondary to allergen stimuli are proposed as the cardinal mechanism of the syndrome.[11,12]

In this case, an urticarial rash preceded the ST, and the manifestation was consistent with Type 3 KS. We are aware of no more than 10 case reports of very late ST secondary to KS, and only one case report addressed the relationship between coronary evaginations and KS.[13] Hoshi *et al.*[13] reported a case of very late ST that occurred 36 months after SES placement. They observed evaginations around the SES and an eosinophilic infiltration in in-stent thrombi. Regarding the recurrent in-stent thrombosis observed in our patient, a similar case of KS was previously reported for whom oral prednisone and fexofenadine were given after the third episode of ST, resulting in settlement of the ST.[14] A study showed that steroids and mast cell stabilizers reduce the incidence of inflammation-induced thrombotic events.[15] In our case, antihistamine drugs were not used in accordance with the patient's preference, and antiplatelet therapy and steroids were insufficient in controlling the recurrent in-stent thrombotic events in the acute phase. Aggressive anti-thrombotic and anti-allergic therapies may be necessary for patients with KS.

In summary, we report a case of Type 3 KS that manifested as a systemic allergic reaction and very late ST. The OCT performed 3 months after the ST confirmed evaginations around two SESs that were not visualized in the acute phase because of the underlying thrombosis. The findings suggest an underrecognized pathophysiology in which the synergic effects between the coronary evaginations and the systemic allergic reaction may have contributed to the development of very late ST. For patients with Type 3 KS, follow-up intracoronary imaging tests may be important to confirm potential coronary evaginations, especially in patients with SESs.

Lead author biography

Tomohiro Fujisaki was born in Kagoshima, Japan, in 1990. He received the MD degree from Kumamoto University School of Medicine, Kumamoto, Japan in 2016. He completed 2 years of Japanese general residency training. Since 2018, he had a brief period of interventional cardiology and echocardiography training at Makiminato Chuo Hospital and Kanoya Medical Center in Japan. Currently, he is working as an internal medicine resident physician at Mount Sinai St. Luke's and Wes, NY, USA. His research interest is mainly focused on ischemic heart diseases, heart failure, and palliative care.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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