Kounis Syndrome and Vanadium allergy: heed your hunch

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N.G. Kounis and G.M. Zavras described in 1991 the "allergic angina syndrome" as coronary spasm progressed to allergic acute myocardial infarction in healthy arteries [1]. To date, there have been reported four variants of the so-called Kounis Syndrome (KS); it may occur in patients with normal or nearly normal coronary arteries (type I), with pre-existing atheromatous disease (type II), with stent thrombosis (subtype IIIa) or stent restenosis (subtype IIIb) and in patients with coronary grafts (type IV) [2]. Percutaneous coronary intervention (PCI) with coronary stent implantation has become the most frequently performed therapeutic procedure in acute coronary syndrome (ACS). Polymer coating, stent metallic platforms and the released drugs can act as strong antigenic complexes. So far, there are three stent generations; bare metal stents (BMS), first and second generation of drug-eluting stents (DES) and the bioresorbable-bioabsorbable stents. Coronary stents in use are almost exclusively drug-eluting stents as recommend current

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clinical practice guidelines in all clinical and anatomic scenarios, although many patients seen in clinical practice have prior procedures with old bare-metal stents or even bioresorbable platforms, they are not longer used in routine clinical practice.

We report a 52-year-old man with a medical history of diabetes mellitus, dyslipidemia and chronic ischemic heart disease with several episodes of ACS, leading to different revascularization procedures from 2016 to May 2021. He had undergone four PCI procedures outside our hospital: three with unknown stents and one with Orsiro® (Biotronik SE & Co KG, Berlin, Germany). Three more revascularizations were performed in our hospital since June 2019: two with Onyx® (Medtronic plc., MN, USA) and one with Synergy® (Boston Scientific Corp. S.A., MA, USA), for a total of seven stents implanted. He had no other cardiovascular risk factors than those described and they were all well controlled, with good persistence and adherence to optimal medical therapy including combined aspirin and ticagrelor long-term treatment, high-dose rosuvastatin and evolocumab. After admission for unstable angina, angiographic findings showed persistence of adequate results of previous PCI in left circumflex and right coronary artery and severe in-stent restenosis (ISR) of the left anterior descending artery (LAD). Optical-coherence tomography (OCT) showed important neointimal formation (Supplementary file 1). He then underwent coronary artery bypass surgery. Six months after surgery, another catheterization for recurrent severe angina revealed ISR of left circumflex and a second surgical revascularization procedure was performed. Due to the multiple cardiovascular events and the unusual OCT findings, he was referred to the Allergology Department.

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Patch tests with a baseline battery recommended by the European Contact Dermatitis Society (ECDS): T.R.U.E. Test, Marti Tor® (Barcelona, Spain), with an expanded metal battery including those described in the technical data sheet by the known stents manufacturers, with Everolimus 1%, Sirolimus 0.16% and using cut "actual stents": cobalt-chromium BMS (CoCr-BMS; Biotronik SE & Co), cobalt-chromium sirolimus eluting stent (CoCr-SES; Orsiro®), chromium-platinum everolimus eluting stent (CrPt-EES; Synergy®) and cobalt(shell)-platinum-iridium(core) zotarolimus eluting stent (Co-Pt-Ir-ZES; Onyx®) were performed (Table 1). Tests were read at 48 and 96 hours according to ESCD guidelines [3]. They were all negative except for a positive reaction (+++) to vanadium (III) chloride 1% pet. at 48 and 96 hours (Supplementary file 2) and for the Onyx® stent, which reported a doubtful reaction with a faint erythema only. Patch test with vanadium (III) chloride 1% was assessed in five asymptomatic controls with Onyx® stent and showed no reaction. The patient was re-interviewed on previous exposure to metals, and referred childhood contact with chrome-vanadium cars hand-tools in his father's workshop, without symptoms.

A semi-quantitative analysis of an Onyx® sample surface (theoretically "vanadium-free") was performed by scanning microscopy and energy dispersive spectrometer at 20°C and 20 kV. Chemical composition analysis was carried out on the missing areas of organic film around the sample filaments (directly analyzing the stent base material) by Metal-test, S.L. (Barcelona, Spain). The presence of the metals described in the data sheet was confirmed and it showed vanadium content of 0.1%. No other elements were detected. A lymphocyte

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transformation test (LTT) to detect T-cell proliferation against the metals present in the stent was then performed. Four different concentrations of the metals salts (ChemoTechnique MB Diagnostics AB©) and mTOR Inhibitors were used (Supplementary file 3) as a stimulus for six days. Cells were stimulated with Dynabeads CD3/CD28 (ThermoFisher Scientific®) as a positive control. Negative control comprised the cells without any stimulation. Lymphocyte proliferation in cultures was measured as described elsewhere [4]. A stimulation index (SI) ≥3 is considered as a positive response [4]. Our patient had a positive reading at all concentrations of vanadium (III) chloride and negative to the remaining allergens (Supplementary file 3). LTT in five controls with Onyx® stent showed no response to any component.

Vanadium is a hard, ductile and malleable heavy metal with similar properties as titanium. It is used in different alloys, particularly in orthopaedic and dental implants, since it makes it more resistant to corrosion and strengthened, and it is also an essential trace element which may cause adverse reactions. Cases of failure metal implants with vanadium-containing ostial screws and metallic rods [5] and vanadium release from handheld tools [6] have been reported. The association between allergic reactions to stent components and the occurrence of ISR was first demonstrated with patch-test [7]. Furthermore, combination of techniques may enhance the outcomes. Thus, positive LTT to metals has demonstrated higher correlation to periprosthetic histology regarding patch testing [8].

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KS is a rare entity, and KS-III represents 5.1% of total KS reported [9]. This case report describes a case of KS associated with allergy to vanadium. One of the main lessons of this work is that it highlights the importance of the anamnesis in the clinical suspicion. The symptomatology and the initial findings (positive patch test to vanadium, theoretical not present in the stent) made it necessary to use all possible means to confirm the presence of this metal and its clinical relevance, which was later achieved. Since vanadium is frequently used in alloys with other metals, it cannot be ruled out that it may be also present in other stent alloys. This finding emphasizes the need to consider a correct labelling, describing all the possible components used in the manufacture of a product (as occurs with foodstuffs), in order to avoid potential problems and improve the quality of life of those who use them.

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Conflicts of interest

The authors have no conflict of interest to declare.

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Table I. Allergens tested, stent components and results.

Allergen tested	Onyx®†	Orsiro®†	Synergy®†	BMS† (Biotronik)	Result‡
True test					
Nickel sulfate 200 µg/cm2	x	x	x	x	-
Potassium dichromate 54 µg/cm2	x	x	x	x	-
Cobalt Chloride 20 µg/cm2	x	x		x	-
Others*					-
Expanded metal battery					
Copper sulfate 2%					-
Zinc chloride 2%					-
Cadmium chloride 1%					-
Titanium dioxide 10%					-
Palladium chloride 2%					-
Silver nitrate 1%					-
Vanadium chloride 1%					+++
Aluminum hydroxide 6.5%					-
Molybdenum chloride 5%	x		x		-
Zirconium chloride 0.2%					-
Niobium chloride 0.2%					-
Manganese chloride 0.5%		x	x	x	-
Cobalt chloride 1%	x	x		x	-
Nickel sulfate 5%		x	x	x	-
Potassium dichromate 2%	x	x	x	x	-
Ferric chloride 2%		x	x	x	
mTOR Inhibitors					
Everolimus 1%			x		-
Sirolimus 0.16%		x			-
Zotarolimus¼	x				
Cut "actual stent"					
Onyx®					?+
Orsiro®					-
Synergy®					-
BMS (Biotronik)					-

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[†]The x indicates the components present in the stent according to the data sheet.
[‡]Reading at 96h. (-): No Reaction. (?+): Faint erythema only. (+): Erythema, infiltration, possiblypapules. (++): Erythema, infiltration, papules, vesicles. (+++): Intense erythema, infiltrate, coalescing vesicles. (IR): Various morphologies, e.g. soapeffect, bulla, necrosis.

[*]Wool Alcohols, Neomycin Sulfate, Cainase Blend, Perfume Blend, Rosin, Paraben Blend, Empty Patch, Balsam of Peru, Ethylenediaminadihydrochloride, p-Tert-Butylphenol Formaldehyde Resin, Epoxy Resin, Carbamate Blend, Black Gum Blend, Cl+Me-Isothiazolinone, Quaternium-15, Methyldibromoglutaronitrile, P-tert-Butylphenol Formaldehyde Resin, Methyldibromoglutaronitrile, P-tert-Butylphenol Formaldehyde Blend, p-Phenylenediamine, Formaldehyde, Mercapto mixture, Thiomersal, Thiuram mixture, Diazolidinyl urea, Quinoline mixture, Thixocortol-21-pivalate, Sodium gold thiosulfate, Imidazolidinyl urea, Budesonide, Hydrocortisone-17-butyrate, Mercaptobenzothiazole, Bacitracin, Parthenolide, Disperse blue 106 and 2-bromo-2-nitropropane-1,3-diol.
[ǂ]Patch testing with Zotarolimus was no performed since its form of presentation is only as a drug-eluting agent in coronary stents.

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