Kounis Syndrome and Vanadium Allergy: Heed Your Hunch

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In 1991, Kounis and Zavras [1] described allergic angina syndrome as a coronary spasm that progresses to allergic acute myocardial infarction in healthy arteries. To date, 4 variants of so-called Kounis syndrome have been reported. The syndrome may occur in patients with normal or nearly normal coronary arteries (type I), in patients with pre-existing atheromatous disease (type II), in patients 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. Polymer coating, stent metallic platforms, and the drugs released can act as strong antigenic complexes. Three stent generations have been developed to date, namely, bare metal stents (BMS), first- and second-generation drug-eluting stents, and bioresorbable-bioabsorbable stents. Currently used coronary stents are almost exclusively drug-eluting stents, as recommended in current clinical practice guidelines for all clinical and anatomic scenarios, although many patients seen in the clinic have previously undergone procedures with older BMS or even bioresorbable platforms, which are no longer used in routine clinical practice.

We report the case of a 52-year-old man with a medical history of diabetes mellitus, dyslipidemia, and chronic ischemic heart disease with several episodes of acute coronary syndrome. He underwent several revascularization procedures from 2016 to May 2021. He had undergone 4 PCI procedures outside our hospital: 3 with unknown stents and 1 with Orsiro (Biotronik SE & Co KG). Three further revascularization procedures have been performed at our hospital since June 2019: 2 with Onyx (Medtronic plc) and 1 with Synergy (Boston Scientific Corp.), giving a total of 7 stents implanted. He had no cardiovascular risk factors other than those described, and they were all well controlled, with good adherence to optimal medical therapy, including long-term treatment with combined aspirin and ticagrelor, high-dose rosuvastatin, and evolocumab. After admission for unstable angina, angiography showed persistence of adequate results for the previous PCI in the left circumflex and right coronary arteries and severe in-stent restenosis of the left anterior descending artery. Optical coherence tomography revealed important neointimal findings (Supplementary file 1). The patient then underwent coronary artery bypass surgery. Six months after surgery, further catheterization for recurrent severe angina revealed in-stent restenosis of the left circumflex artery, and a second surgical revascularization procedure was performed. Given the multiple cardiovascular events and the unusual optical coherence tomography findings, the patient was referred to the allergology department.

Patch tests were performed with the baseline series recommended by the European Contact Dermatitis Society (ECDS), namely, the T.R.U.E. Test (Marti Tor), with an expanded metal battery including those described in the technical data sheet by the stent manufacturers, with everolimus 1%, sirolimus 0.16%, and cut "actual stents" (cobalt-chromium BMS [Biotronik SE & Co], cobalt-chromium sirolimus eluting stent [Orsiro], chromium-platinum everolimus-eluting stent [Synergy]), and cobalt[shell]-platinum-iridium[core] zotarolimus–eluting stent [Onyx]) (Table). Tests were read at 48 and 96 hours according to ECDS 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 a doubtful reaction with faint erythema only in the case of the Onyx stent. Patch testing with vanadium (III) chloride 1% in 5 asymptomatic controls with the Onyx stent elicited no reaction. The patient was reinterviewed on previous exposure to metals and referred childhood contact with chrome-vanadium car hand-tools in his father's workshop, without symptoms.

A semiquantitative analysis of an Onyx sample surface (theoretically vanadium-free) was performed using scanning microscopy and energy dispersive spectrometry 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 using Metal-Test, S.L., Barcelona, Spain. The presence of the metals described in the data sheet was confirmed, showing a vanadium content of 0.1%. No other elements were detected. A lymphocyte transformation test (LTT) to detect T-cell proliferation against the metals present in the stent was then performed. Four different concentrations of the metal salts (ChemoTechnique, MB Diagnostics AB) and mTOR inhibitors were used (Supplementary file 3) as a stimulus for 6 days. Cells were stimulated with Dynabeads CD3/CD28 (Thermo Fisher Scientific) as a positive control. The negative control comprised nonstimulated cells. Lymphocyte proliferation in cultures was measured as described elsewhere [4]. A stimulation index ≥3 was considered a positive response [4]. The patient had a

positive reading at all concentrations of vanadium (III) chloride and a negative reading with the remaining allergens (Supplementary file 3). LTT in 5 controls with the Onyx stent showed no response to any component.

Vanadium is a hard, ductile, and malleable heavy metal with properties similar to those of titanium. It is used in various alloys, particularly in orthopedic and dental implants, since it makes them stronger and more resistant to corrosion, and is

Table. Allergens Tested, Stent Components, and Results.

Allergen tested	Onyx[a]	Orsiro[a]	Synergy[a]	BMS[a] (Biotronik)	Result[b]
True test					
Nickel sulfate 200 µg/cm^2	x	x	x	x	-
Potassium dichromate 54 µg/cm^2	x	x	x	x	-
Cobalt chloride 20 µg/cm^2	x	x		x	-
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			-
Zotarolimus[d]	x				
Cut "actual stent"					
Onyx					?+
Orsiro					-
Synergy					-
BMS (Biotronik)					-

[a]The x indicates the components present in the stent according to the data sheet.
[b]Reading at 96 hours. (–), no reaction; (?+), faint erythema only; (+), erythema, infiltration, possibly papules; (++), erythema, infiltration, papules, vesicles; (+++), intense erythema, infiltrate, coalescing vesicles. (IR), various morphologies (eg, soap effect, bulla, necrosis).
[c]Wool alcohols, neomycin sulfate, cainase blend, perfume blend, rosin, paraben blend, empty patch, balsam of Peru, ethylenediamine dihydrochloride, epoxy resin, carbamate blend, black gum blend, cl+me-isothiazolinone, quaternium-15, methyldibromoglutaronitrile, p-tert-butylphenol formaldehyde resin, p-phenylenediamine, formaldehyde, mercapto mixture, thiomersal, thiuram mixture, diazolidinyl urea, quinoline mixture, tixocortol-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.
[d]Patch testing with zotarolimus was not performed since its form of presentation is only as a drug-eluting agent in coronary stents.

also an essential trace element that may cause adverse reactions. Cases of failure with 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 in-stent restenosis was first demonstrated using patch testing [7]. Furthermore, combining techniques may enhance outcomes. Thus, a positive LTT result to metals correlates better with periprosthetic histology regarding patch testing [8].

Kounis syndrome is a rare entity, and type III accounts for 5.1% of all cases reported [9]. In the present study, we report a case of Kounis syndrome associated with allergy to vanadium. One of the main lessons of this work is that it highlights the importance of the medical history in clinical suspicion. The symptoms and initial findings (positive patch test result for vanadium, which is theoretically 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, we cannot rule out the possibility that it may also be present in other stent alloys. This finding emphasizes the need for correct labeling to ensure that all possible components used in the manufacture of a product are described (as occurs with foodstuffs) and thus avoid potential problems and improve the quality of life of those who use them.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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