SCIENCEHOOD

Research Article

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Kounis Syndrome in Oncology: A Review of Triggers, Differential Diagnosis, and Clinical Management

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ABSTRACT

Kounis syndrome—an acute coronary syndrome precipitated by hypersensitivity reactions—is under-recognized in oncology despite the widespread use of allergenic antineoplastic agents and infusion biologics. We narratively reviewed the literature across PubMed/Medline, PMC, and major publishers to synthesize current knowledge on pathophysiology, oncologic triggers, differential diagnosis and management. We identified reported cases linked to platinum salts (notably oxaliplatin and carboplatin), taxanes (paclitaxel), and, more recently, immune checkpoint inhibitors. Oxaliplatin and paclitaxel are recurring culprits; notably, a 2025 case documents the first report of Kounis syndrome associated with atezolizumab, underscoring expanding immunotherapy-related cardiovascular hypersensitivity. Clinicians should differentiate Kounis from Takotsubo cardiomyopathy, vasospastic angina unrelated to allergy, and classic myocardial infarction. Prompt recognition, cessation of the culprit, and tailored anti-allergic and anti-ischemic therapy are key. Greater awareness of this syndrome in oncology practice is essential, as early identification may prevent adverse outcomes and guide future pharmacovigilance in cardio-oncology. (1–6).

KEYWORDS:

Kounis syndrome, chemotherapy, immunotherapy, Atezolizumab, cardiovascular toxicity

Abbreviations:

Kounis syndrome (KS), Pubmed Central (PMC), Acute coronary syndromes (ACS), Coronoary artery disease (CAD), Non-steroid anti-inflammatory drug (NSAID), Immune checkpoint inhibitor (ICI), Programmed Death-Ligand 1 (PD-L1), Human epidermal growth factor receptor - 2 (HER-2), Electrocardiogram (ECG), 5- Fluorouracil (5-FU), Magnetic Resonance Imaging (MRI).

INTRODUCTION

Kounis syndrome (KS) is defined as the concurrence of acute coronary syndromes (ACS)—ranging from coronary vasospasm to myocardial infarction or stent thrombosis—with mast-cell–driven hypersensitivity reactions. Three subtypes are recognized: Type I (vasospasm without underlying coronary disease), Type II (plaque destabilization/rupture on pre-existing CAD), and Type III (stent thrombosis or restenosis related to hypersensitivity). Although antibiotics and NSAIDs are the most frequently described precipitants, anticancer agents and infusion biologics are increasingly implicated, making KS a relevant but likely under-diagnosed emergency in oncology (7,8).

From an oncology perspective, several factors converge to elevate risk: high rates of drug hypersensitivity (e.g., with platinum salts and taxanes), repeated exposures, premedication complexity, and growth in immune checkpoint inhibitor (ICI) use with its unique spectrum of immune-related adverse events. Cardio-oncoimmunology literature emphasizes that cardiovascular hypersensitivity

bridges allergic mechanisms with ACS and myocarditis, putting KS on the cardio-oncology radar (8).

Kounis syndrome in Oncology. Reports span chemotherapy (platinum salts, taxanes), contrast media during cancer care pathways, monoclonal antibodies and, lately, immunotherapy. Early oncologic-drug–related cases involved oxaliplatin and carboplatin presenting with coronary spasm and transient ST-elevation with non-obstructive coronaries—classic KS. More recently, paclitaxel cases have been described (Type I in many), and in 2025 a case with atezolizumab (PD-L1 inhibitor) was published as the first immunotherapy-triggered KS. Together, these observations suggest KS should be part of the differential when cancer patients develop peri-infusion chest pain, hypotension, or ST-changes, even when angiography is "clean" (4–6,9,10).

Materials and Methods

This is a narrative (non-systematic) review. We searched PubMed/Medline, PubMed Central (PMC), and major publisher platforms (JACC, ASCO/Journal of Clinical Oncology, Karger, MDPI, Frontiers, Elsevier/ScienceDirect) using combinations of terms: *"Kounis syndrome," "allergic coronary syndrome," "oncology," "chemotherapy," "oxaliplatin," "carboplatin," "paclitaxel," "immune checkpoint inhibitor," "atezolizumab," "nivolumab," "pembrolizumab," "trastuzumab," "taxane"*. Stating the literature gap, we screened titles/abstracts for oncologic triggers and included case reports/series and reviews with enough clinical detail to attribute KS to an oncologic agent. The focus was to (i) catalog oncologic drug triggers, (ii) highlight the new ICI-associated case, and (iii) discuss differential diagnoses and management considerations for oncology practice. Because this was not a systematic review, no quantitative synthesis or risk-of-bias assessment was performed.

Results and Discussion

3.1 Reported oncologic triggers

First author & year	Oncologic drug	Cancer type	Kounis type	Timing	Key diagnostics	Management	Outcome
Chang 2011	Oxaliplatin	Metastatic sigmoid colon cancer	Likely Type I (vasospasm)	During infusion (palliative chemotherapy)	ST changes; angiography without obstructive CAD	Supportive; cessation of drug	Clinical improvement
Baroni 2011	Carboplatin	NSCLC (lung adenocarcinoma)	Not specified (vasospastic ACS)	6th cycle of chemotherapy	Chest pain; ECG changes	Acute ACS care; withdrawal of culprit	Recovered
Wang 2018	Paclitaxel	NSCLC	Type I (reported)	During infusion	ST elevation; normal coronaries	Antihistamines/steroids; vasodilators	Recovered
Muñoz 2025	Paclitaxel	HER2+ early breast cancer	Type I	During administration	ST changes; no obstructive CAD	Steroids/antihistamines; nitrates	Recovered
Albanesi 2023	Oxaliplatin	Colorectal cancer	Reported as KS	4th cycle	ECG/troponin; angiography	Supportive; immunologic testing positive	Recovered
KSD 2024	Oxaliplatin (during desensitization)	Colorectal (not specified)	Type I	During desensitization protocol	Clinical + ECG	Protocol stopped; treated for KS	Recovered
Agostara 2025	Atezolizumab (ICI)	NSCLC	First immunotherapy-induced KS	After infusion	ACS during hypersensitivity; imaging/biomarkers	Stopped ICI; ACS + anti-allergic management	Recovered
Oneglia 2011	Chemotherapy (unspecified)	Ovarian cancer	Vasospastic angina/KS	During chemotherapy	Angina; allergy to contrast	Vasodilators and supportive care	Improved

Table 1. Reported cases of oncologic drug–triggered Kounis syndrome

Abbreviations: Immune checkpoint inhibitor (ICI), Non small cell lung cancer (NSCLC), Human epidermal growth factor receptor - 2 (HER-2), Acute coronary syndromes (ACS), Coronoary artery disease (CAD), Electrocardiogram (ECG), Kounis syndrome (KS)

3.1.1 Platinum salts

Oxaliplatin is the most frequently reported chemotherapy trigger for KS. Canonical presentations include chest pain and ST-segment deviation during infusion, with angiography showing no obstructive disease, consistent with vasospasm (Type I) or, less commonly, Type II. A widely cited early case from 2011 detailed oxaliplatin-induced coronary vasospasm manifesting as KS; subsequent reports, including a 2023 case with immunologic confirmation (oxaliplatin-specific B-cell proliferation) and a 2024 case during desensitization, reinforce oxaliplatin as a true allergenic cardiac trigger. Pharmacovigilance notes further cases (Type I) in colorectal settings (1,4,11,12).

Carboplatin has also been implicated. A 2011 report in a patient with lung adenocarcinoma developed KS during later cycles, highlighting that sensitization over multiple

exposures may precede the event—important for surveillance across treatment lines (10).

3.1.2 Taxanes

Paclitaxel hypersensitivity is well known; several KS cases have been reported, including a Type I KS during paclitaxel infusion in a young patient with HER2-positive early breast cancer (2025) and prior reports in lung cancer. Recognition matters because standard anaphylaxis algorithms often emphasize epinephrine, yet coronary spasm may complicate management in KS (5,9).

3.1.3 Immune checkpoint inhibitors (ICIs)

While ICIs have established cardiotoxicities—myocarditis, pericarditis, arrhythmias—KS has been largely theoretical until recently. In 2025, a peer-reviewed case detailed Kounis syndrome induced by atezolizumab in a patient with non-small cell lung cancer, reported as the first immunotherapy-triggered KS. This expands the spectrum of ICI cardiovascular hypersensitivity beyond classic myocarditis and underscores the need to consider allergic ACS mechanisms when chest pain and ischemic ECG changes occur during or soon after ICI infusion (6,13).

3.1.4 Other oncology-related contexts

Older literature describes vasospastic angina compatible with KS during chemotherapy for ovarian cancer, and 5-fluorouracil/capecitabine vasospasm sometimes framed as potential KS. Although not every 5-FU vasospasm represents KS (IgE-mediated), clinicians should keep it on the radar, particularly when hypersensitivity features (urticaria, bronchospasm, hypotension, flushing, or elevated tryptase) accompany ischemia (14–16).

3.2 Clinical patterns and bedside clues

Across cases, a recurring pattern emerges: immediate or early per-infusion chest pain, hypotension or anaphylactic signs, ST-segment deviations, and normal or near-normal coronaries on emergent angiography. These are classic Type I KS hallmarks. Type II (plaque destabilization) is less common but possible in older patients with CAD, and Type III (stent thrombosis) remains rare in oncology reports to date. Awareness of subtype matters because it shapes the risk–benefit of vasoconstrictors and antithrombotics (3).

3.3 Differential diagnosis in oncology cardio-toxicity

Takotsubo (stress) cardiomyopathy. Both KS and Takotsubo can be precipitated by adrenergic or inflammatory surges. Takotsubo yields transient regional wall-motion abnormalities (often apical ballooning), modest troponin rise, and non-obstructive coronaries; KS additionally shows temporal linkage to a hypersensitivity reaction and may demonstrate coronary spasm. Case discussions in oncology frequently list Takotsubo as the principal differential—particularly with oxaliplatin and ICIs. Clues favoring KS: urticaria/bronchospasm/hypotension; elevated serum tryptase; improvement with anti-allergic therapy; provoked spasm or dynamic ischemic ECG changes (17,18).

ICI myocarditis. Presents with chest pain, troponin elevation, arrhythmias, heart block, and T-cell–mediated myocardial inflammation. Lack of hypersensitivity stigmata and MRI/biopsy findings help distinguish it. KS should be suspected with peri-infusion allergic features and angiographic spasm with clean coronaries—especially

in the atezolizumab case (13).

Non-allergic vasospastic angina or type 1 MI. Vasospasm unrelated to allergy and conventional plaque rupture MI must be considered; however, temporal coupling with a known allergenic infusion and resolution upon cessation + anti-allergic therapy lean toward KS (3).

3.4 Diagnostic approach

When KS is suspected in a cancer patient:

Immediate ACS protocol (ECG, troponin, hemodynamics), with parallel allergy work-up (serum tryptase within 1–2 hours, histamine if available). Tryptase can be crucial to support IgE-mediated mechanisms (18).

Coronary angiography to exclude obstructive disease; intracoronary nitrates may relieve spasm.

Document chronology relative to infusion start/stop and premedications; maintain high suspicion during desensitization protocols, where KS has been reported (17).

3.5 Management principles (and oncology-specific considerations)

Stop the suspected culprit immediately.

Treat both the allergic reaction and the ACS: H1/H2 blockers and corticosteroids for hypersensitivity; nitrates and calcium-channel blockers for spasm. Epinephrine can be lifesaving in anaphylaxis but may worsen spasm—use with caution (titrate, consider dilute IV infusion under monitoring) and cardiology support (3).

Antiplatelets/anticoagulation per ACS protocol if Type II/III suspected; avoid β-blockers in severe anaphylaxis (unopposed α-vasoconstriction).

Plan future therapy: switch class (e.g., to non-cross-reactive regimens), desensitization only with allergy/cardiology collaboration, and careful pre-medication—keeping in mind KS can occur even during desensitization (11).

For ICIs, weigh risks/benefits of rechallenge; if KS is confirmed, permanent discontinuation of the culprit ICI is often prudent, mirroring myocarditis guidance but individualized (13).

Conclusions

Kounis syndrome is a clinically meaningful, time-critical entity in oncology. Platinum salts (especially oxaliplatin) and paclitaxel are the most frequently reported chemotherapy triggers, and emerging evidence now includes immune checkpoint inhibitors, with atezolizumab recently reported as the first ICI-induced KS. Diagnostic success hinges on thinking of KS when peri-infusion ischemia coincides with allergic signs, and on integrating ACS care with allergy/immunology evaluation (including serum tryptase). Management balances anti-allergic and anti-ischemic strategies while minimizing interventions that may exacerbate spasm. Finally, treatment plans should avoid rechallenge with the culprit and consider alternative regimens; multidisciplinary cardio-oncology approaches and pharmacovigilance will be vital as immunotherapy use broadens (3,6,8).

Looking ahead, prospective studies and dedicated registries for drug-induced KS in oncology are warranted. Such efforts could clarify incidence rates, refine diagnostic algorithms, and better characterize outcomes across

different oncologic agents. Building structured pharmacovigilance and collaborative cardio-oncology registries will be key to advancing understanding and guiding safer therapeutic strategies.

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