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Systematic Review

Kounis Syndrome Associated With the Use of Diclofenac

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Abstract

Background: Diclofenac is a widely used analgesic, anti-inflammatory, antipyretic drug. In several case reports, its use was associated with the occurrence of Kounis syndrome. The aim of this review was to investigate and summarize published cases of Kounis syndrome suspected to be associated with the use of diclofenac.

Methods: Electronic searches were conducted in PubMed/MEDLINE, Scopus, Web of Science, Google Scholar, and the Serbian Citation Index.

Results: Twenty publications describing the 20 patients who met inclusion criteria were included in the systematic review. Specified patient ages ranged from 34 to 81 years. Eighteen (90.0%) patients were male. Five patients (25.0%) reported a previous reaction to diclofenac. Reported time from the used dose of diclofenac to onset of the first reaction symptoms ranged from immediately to 5 hours. Diclofenac caused both type I and type II Kounis syndrome, with the presence of various cardiovascular, gastrointestinal, dermatologic, and respiratory signs and symptoms. Most patients experienced hypotension (n = 15 [75.0%]) and chest pain (n = 12 [60.0%]). The most frequently reported finding on electrocardiogram was ST-segment elevations (n = 17 [85.0%]). Coronary angiogram showed normal coronary vessels in 9 patients (45.0%), with some pathologic findings in 8 patients (40.0%).

Conclusion: Clinicians should be aware that Kounis syndrome may be an adverse effect of diclofenac. Prompt recognition and withdrawal of the drug, with treatment of both allergic and cardiac symptoms simultaneously, is important.

Keywords: Diclofenac; Kounis syndrome; acute coronary syndrome; anaphylaxis

Introduction

In 1991, Kounis and Zavras[1] described the "syndrome of allergic angina" and "allergic myocardial infarction," currently known as Kounis syndrome (KS). Kounis syndrome is the concurrence of acute coronary syndrome (ACS) (including coronary spasm, acute myocardial infarction [AMI], and stent thrombosis) with conditions associated with mast cell and platelet activation in the setting of allergic, hypersensitivity, anaphylactic, or anaphylactoid reactions.[2,3]

Three variants of KS have been described.[3,4] Type I occurs in patients with normal or nearly normal coronary arteries who have no predisposing factors for coronary artery disease and in whom the acute release of inflammatory mediators can lead to either coronary artery spasm without increase of cardiac enzymes or coronary artery spasm progressing to AMI.[3,4] Type II refers to patients with culprit but quiescent preexisting atheromatous disease in whom the acute release of inflammatory mediators can induce either coronary artery spasm with normal cardiac

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enzymes or coronary artery spasm with plaque erosion or rupture manifesting as AMI.[3,4] Type III includes patients with drug-eluting stent thrombosis with the presence of mast cells and eosinophils revealed with Giemsa and hematoxylin-eosin staining.[3,4] Kounis syndrome is not rare, but it is not well recognized, which leads to underdiagnosis and undertreatment.[5] To date, resources on KS are limited, and most of the information comes from clinical case reports and small case series.[6]

Kounis syndrome is caused by inflammatory mediators such as histamine, platelet activating factor, arachidonic acid products, neutral proteases, and a variety of cytokines and chemokines released during the allergic activation process.[3]

Diclofenac: Indications, Mechanism of Action, and Adverse Effects

Diclofenac is a phenylacetic acid–derivative nonsteroidal anti-inflammatory drug (NSAID).[7] These drugs act by inhibiting cyclooxygenase 1 (COX-1) and COX-2, consequently reducing the synthesis of prostaglandins, prostacyclins, and thromboxanes; in this way, they achieve anti-inflammatory, analgesic, and antipyretic effects.[8] Diclofenac, like other NSAIDs, is used in the treatment and management of acute and chronic pain associated with inflammatory conditions[9] as well as for the prevention and treatment of postoperative pain.[10] Diclofenac preparations pair the drug with a salt, such as sodium, potassium, or epolamine, which (depending on the formulation) can be administered through various routes (eg, oral, intramuscular [IM], intravenous [IV], transdermal, rectal).[9]

The most common adverse effects of diclofenac are gastrointestinal (GI) problems (erosive gastritis, gastric or duodenal ulcerations, hemorrhage, or perforations), kidney impairment, hypertension, MI, heart failure, stroke, impaired liver function, and increased transaminase levels.[9] As with other NSAIDs, allergic reactions, including anaphylactic and anaphylactoid reactions, can occur in rare cases with diclofenac, even without earlier exposure to the drug.[11] Hypersensitivity reactions can also progress to KS.[11] These NSAID hypersensitivity reactions can be compartmentalized into pharmacologic (secondary to COX-1 inhibition) or a specific (likely immunoglobulin E [IgE]–mediated effect).[12] All NSAIDs inhibit COX-1 and thus favor the lipoxygenase pathway of arachidonic acid metabolism, resulting in increased cysteine leukotriene synthesis release of inflammatory mediators, including histamine and tryptase, from mast cells, and eosinophils.[13]

Diclofenac is 1 of the most prescribed NSAIDs worldwide.[14] The goal of this systematic review was to investigate and summarize information about the characteristics of published cases of KS suspected to be associated with the use of diclofenac to provide a useful perspective for better recognition and management of this possible adverse effect of diclofenac.

Abbreviations and Acronyms

ACS	acute coronary syndrome
AMI	acute myocardial infarction
COX-1	cyclooxygenase 1
GI	gastrointestinal
IgE	immunoglobulin E
IM	intramuscular
IV	intravenous
KS	Kounis syndrome
MI	myocardial infarction
NSAID	nonsteroidal anti-inflammatory drug
SCIndeks	Serbian Citation Index

Patients and Methods

Our systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration No. CRD42021277053.

Two authors (A.V.P. and M.N.M.) searched the following electronic databases independently from the beginning of indexing to September 15, 2021, with no language or date restriction: PubMed/MEDLINE, Scopus, Web of Science, Google Scholar, and Serbian Citation Index (SCIndeks). Table I shows a detailed search strategy for each database. Case reports or case series that included detailed clinical descriptions of the patients diagnosed with KS (vasospastic allergic angina, allergic MI, or stent thrombosis with occluding thrombus infiltrated by eosinophils or mast cells) caused or suspected to be caused by diclofenac and that had available full text were included in the systematic review. Conference abstracts were included if they contained sufficient data for analysis and quality assessment. At a minimum, the following information had to be available for each patient to include a publication in the review: age group, sex, identification of suspected drug, manifestations of the reaction, clinical course, treatment, and outcome. Case reports or case series were excluded if they (1) did not include a detailed clinical description of each patient (ie, without all previously mentioned minimum required information), (2) reported on patients who received diclofenac with other drugs for whom the exact cause of KS could not be determined or in whom diclofenac was excluded as a possible cause, and (3) reported

other cardiac or hypersensitivity adverse effects associated with the use of diclofenac. The reference lists of the retrieved articles were also searched for additional relevant publications.

Initially, the eligibility of retrieved publications was screened based on the title and abstract by 2 authors (A.V.P., M.N.M.) independently. Where it was not possible to assess whether the publication fully corresponded to the research topic based on the title and information provided in the abstract, the full text of the publication was retrieved and analyzed. Publications were included in the systematic review if all authors agreed that eligibility criteria had been met. Disagreements between individual judgments were resolved by consensus.

The following data were extracted for each described case by 2 authors independently (A.V.P., M.N.M.): demographics (age, sex); country of study; patient medical history; drug dosage; indication; route of diclofenac administration; salt form of diclofenac; concomitant medications; diagnostic investigations (electrocardiography, echocardiography, coronary angiography, myocardial perfusion scintigraphy, laboratory analyses, etc); time to onset of the first symptoms (including symptoms of allergic, hypersensitivity, anaphylactic, or anaphylactoid reaction); setting in which the reaction occurred; KS variant (ie, type I, II, or III); clinical manifestations; complications; treatment; length of stay in hospital; outcome; and information about causality assessment by the authors, if reported (eg, Naranjo score). Another author (N.D.F.) collated the 2 tables and produced the final extraction table.

To evaluate the quality of the included cases, the "Guidelines for submitting adverse events reports for publication," endorsed by the International Society for Pharmacoepidemiology and the International Society of Pharmacovigilance, were used.[15] The authors evaluated the items that the guidelines reported as required information: title (consistency of the title with the content of the report), patient information (demographics, current health status, medical history, physical examination, patient disposition), suspected drug information (identification, dosage, drug-reaction interface, concomitant therapies), description of the adverse event, and discussion.[15] All items were rated as present (yes), partially present (partial), or absent (no), with descriptive statistics (median, range, proportions), narrative summation, and tabulation of the extracted data.

Results

Figure 1 shows the results of the literature search. Twenty publications (19 case reports[2,16-33] and 1 conference abstract[34]) describing a total of 20 patients who satisfied inclusion criteria were included in the systematic review. The quality assessment of the identified cases is shown in Figure 2. Most of the cases had all required information regarding title (n = 19 [95.0%]), patient demographics (n = 20 [100.0%]), current health status (n = 18 [90.0%]), medical history (n = 19 [95.0%]), physi-

TABLE I. Detailed Database Search Strategy

Database	Search strategy
PubMed/MEDLINE	("diclofenac"[MeSH Terms] OR "diclofenac"[All Fields]) AND ("kounis syndrome"[MeSH Terms] OR ("kounis"[All Fields] AND "syndrome"[All Fields]) OR "kounis syndrome"[All Fields] OR ("kounis syndrome"[MeSH Terms] OR ("kounis"[All Fields] AND "syndrome"[All Fields]) OR "kounis syndrome"[All Fields] OR ("allergic"[All Fields] AND "angina"[All Fields] AND "syndrome"[All Fields]) OR "allergic angina syndrome"[All Fields]) OR ("kounis syndrome"[MeSH Terms] OR ("kounis"[All Fields] AND "syndrome"[All Fields]) OR "kounis syndrome"[All Fields] OR ("allergic"[All Fields] AND "acute"[All Fields] AND "coronary"[All Fields] AND "syndrome"[All Fields]) OR "allergic acute coronary syndrome"[All Fields]) OR ("kounis syndrome"[MeSH Terms] OR ("kounis"[All Fields] AND "syndrome"[All Fields]) OR "kounis syndrome"[All Fields] OR ("allergic"[All Fields] AND "myocardial"[All Fields] AND "infarction"[All Fields]) OR "allergic myocardial infarction"[All Fields]))
Web of Science	All databases: TS=(diclofenac AND ((Kounis Syndrome) OR (Allergic Angina Syndrome) OR (Allergic Acute Coronary Syndrome) OR (Allergic Myocardial Infarction)))
Scopus	TITLE-ABS-KEY (diclofenac AND ((kounis AND syndrome) OR (allergic AND angina AND syndrome) OR (allergic AND acute AND coronary AND syndrome) OR (allergic AND myocardial AND infarction)))
SCIndeks	(ARTAK: diclofenac AND ((Kounis Syndrome) OR (Allergic Angina Syndrome) OR (Allergic Acute Coronary Syndrome) OR (Allergic Myocardial Infarction)))
Google Scholar	diclofenac AND ((Kounis Syndrome) OR (Allergic Angina Syndrome) OR (Allergic Acute Coronary Syndrome) OR (Allergic Myocardial Infarction))

SCIndeks, Serbian Citation Index.

cal examination (n = 20 [100.0%]), patient disposition (n = 20 [100.0%]), drug identification (n = 20 [100.0%]), drug-reaction interface (n = 18 [90.0%]), dosage (n = 12 [60.0%]), and adverse events (n = 14 [70.0%]). Only 5 cases (25.0%) had reported an assessment of potential contribution of concomitant therapies. Discussion was rated as partial in the majority of cases (n = 19 [95.0%]), mostly because they did not have specific discussion of the adverse event in relation to product labeling.

Table II summarizes the basic characteristics of included cases, whereas Table III provides an overview of each included case. Specified patient ages ranged from 34 to 81 years; for 1 patient, only age group was reported (middle age). The majority of the patients were male (n = 18 [90.0%]). Five patients (25.0%) had a history of previous reaction to diclofenac (anaphylaxis,[23] hypersensitivity,[22] allergic reaction,[31] ST-segment elevation MI,[27] or chest pain with ischemic ST-segment changes[26]). One patient (5.0%) had a history of an aspirin-induced asthma attack that required intubation and admission to an intensive care unit.[28] A history of diagnosed coronary artery disease and hypertension was reported in 5 patients (25.0%) each, whereas asthma and diabetes were reported in 3 (15.0%) and 2 patients (10.0%), respectively. Many of the cases occurred in Turkey (n = 9 [45.0%]).

The most frequently used diclofenac dosages that were specified were 50 and 75 mg in 4 cases (20.0%) each. Route of administration was IM in many cases (n = 9 [45.0%]); use of diclofenac with sodium salt was reported in half the patient group. The most frequently reported indication for diclofenac use was pain management (n = 17 [85.0%]). Information about concomitantly used medications is provided in Table III. For most patients, the authors did not specify whether they received concomitant medications (n = 13 [65.0%]).

The reported time from the dose of diclofenac used to onset of the first symptoms of the reaction ranged from immediately to 5 hours. Most reactions occurred in the outpatient setting (n = 13 [65.0%]). The diagnosis was based on clinical presentation and use of relevant diagnostic investigations. Patients generally had clinical symptoms and signs associated with allergic, hypersensitivity, or anaphylactic reactions (only 1 patient with recurrent KS had no sign of systemic allergic reactions, except coronary spasm[27]) accompanied by cardiac manifestations. In total, 15 (75.0%) patients experienced hypotension, and 12 (60.0%) had chest pain. Tachycardia and atrioventricular block were seen in 8 (40.0%) and 3 (15.0%) patients, respectively. Cardiac arrest, ventricular fibrillation, and cardiogenic shock complicated the clinical course in 3 (15.0%), 2 (10.0%), and 1 (5.0%) patients, respectively. Premature ventricular contractions, palpitations, raised jugular venous pres-

TABLE II. Summary of the Basic Characteristics of Included Cases (N = 20)

Characteristic	Value
Age, median (range), y (n = 19)	60.0 (34.0-81.0)
Sex, No. (%)	
Female	2 (10.0)
Male	18 (90.0)
Country, No. (%)	
Austria	1 (5.0)
Egypt	1 (5.0)
India	2 (10.0)
Japan	1 (5.0)
Malaysia	1 (5.0)
Portugal	1 (5.0)
Saudi Arabia	1 (5.0)
Serbia	1 (5.0)
Spain	1 (5.0)
The Netherlands	1 (5.0)
Turkey	9 (45.0)
Diclofenac dosage, No. (%), mg	
12.5	1 (5.0)
50	4 (20.0)
75	4 (20.0)
100	3 (15.0)
Not reported	8 (40.0)
Diclofenac salt, No. (%)	
Sodium	10 (50.0)
Potassium	4 (20.0)
Not reported	6 (30.0)
Route of administration, No. (%)	
IM	9 (45.0)
Oral	7 (35.0)
Rectal	2 (10.0)
IV	1 (5.0)
First time after oral, second time after IV	1 (5.0)
Concomitant medications, No. (%)	
Yes	5 (25.0)
No	2 (10.0)
Not specified	13 (65.0)
Setting in which reaction occurred, No. (%)	
Outpatient	13 (65.0)
Inpatient	6 (30.0)
First time outpatient, second time inpatient	1 (5.0)
Outcome, No. (%)	
Survived	20 (100.0)
Died	0 (0.0)

IM, intramuscular; IV, intravenous.

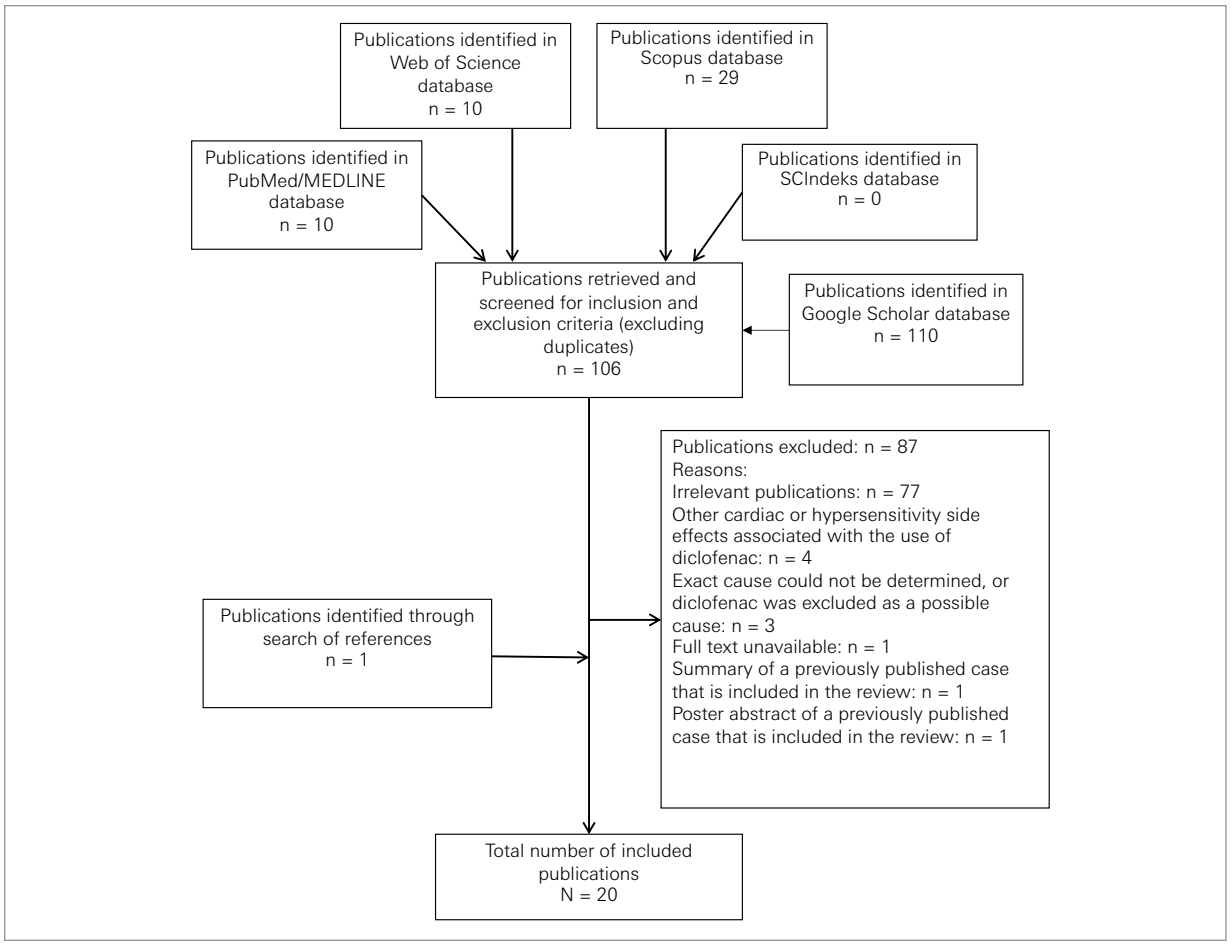

Fig. 1 Chart shows the selection of publications.

SCIndeks, Serbian Citation Index.

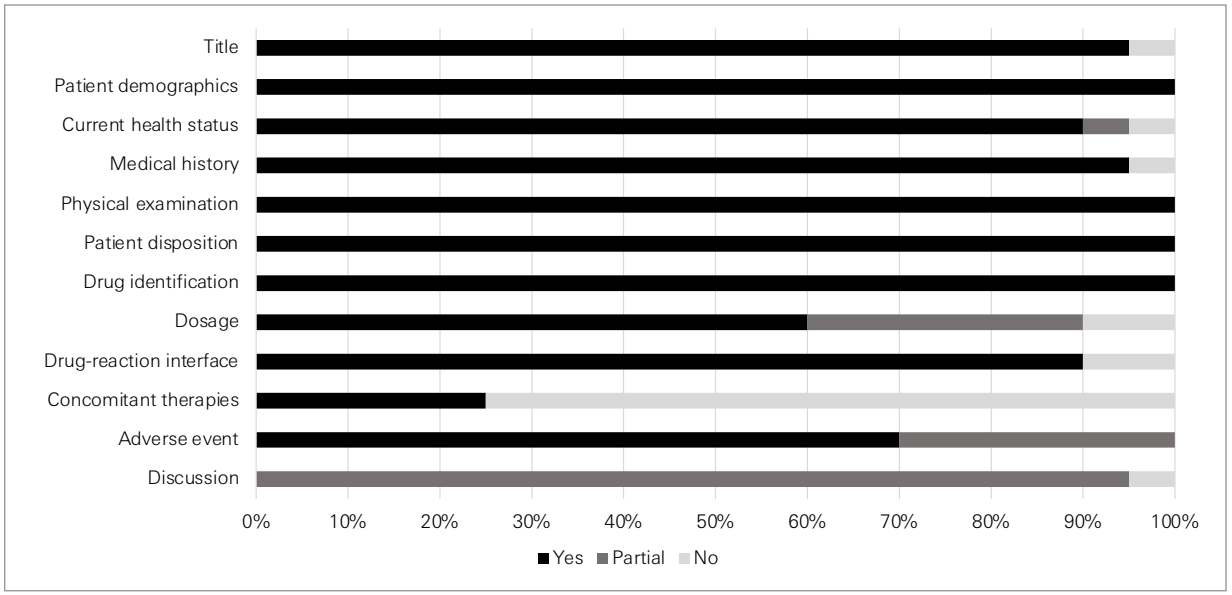

Fig. 2 Quality assessment of the identified cases.

TABLE III. Overview of the Included Cases

No.	Study	Age, y; sex	Medical history	Diclofenac salt, dose, administration route, indication	Concomitant medications	KS type	Onset	Summary of treatment	LOS	Outcome
1	Mori et al[26] (1997)	69; M	7 wk before admission, chest pain with ischemic ST-segment changes after diclofenac sodium (25 mg) suppository; no history of allergic factors or major CAD risk factors	Sodium, 12.5 mg, rectal, fever	NS	NR	5 min	Nitroglycerin and atropine sulfate IV; intracoronary isosorbide dinitrate after ergonovine provocation test; later diltiazem, long-acting nitrate, and nicorandil	NR	Survived
2	Blanco et al[17] (2003)	57; M	No history of coronary or vascular risk factors, previous allergies, or drug use	NR, 100 mg, rectal, acute lower back pain	No	NR	4 h	Methylprednisolone, rt-PA, parenteral nitroglycerin infusion	NR	Survived
3	Gluvic et al[22] (2007)	66; M	History of diclofenac sodium hypersensitivity, excessive smoking habit	Sodium, NR, IM, pain in left toe from foot injury	NS	NR	Several minutes	CPR (airway intubation, oxygen therapy, establishing IV access, precordial thump, crystalloid administration), oxygen, methylprednisolone, theophylline, IV nitrates (nitroglycerin)	NR	Survived
4	de Groot et al[20] (2009)	48; M	No history of allergies, eczema, or asthma; surgery for a herniated disc; father and grandfather had died of CV event; smoker; used diclofenac several years earlier without problems	NR, 50 mg, oral, back pain	No	NR	Within minutes	Initially IV fluid replacement, then adrenaline and clemastine IV; IV administration of fluids continued	NR	Survived
5	Cakar et al[19] (2011)	74; F	No history of allergy at first administration	First time: potassium, NR, oral, NR Second time: potassium, NR, IV, upper respiratory tract infection symptoms	NS	First time: II Second time: I and II	First time: 30 min Second time: NR	First time: IV antihistaminic and prednisolone, saline and dopamine infusions, successful coronary angioplasty with implantation of sequential 3.0- × 16-mm and 3.0- × 8-mm bare-metal stents Second time: IV antihistaminic and prednisolone	NR	Survived
6	Granitz et al[34] (2011)	60; M	Planned knee arthroscopy	NR, NR, IV, used during induction of anesthesia	NS	II	Immediately after	Resuscitation, clopidogrel	NR	Survived

Continued

TABLE III. Overview of the Included Cases (continued)

No.	Study	Age, y; sex	Medical history	Diclofenac salt, dose, administration route, indication	Concomitant medications	KS type	Onset	Summary of treatment	LOS	Outcome
7	Cagliyan et al[18] (2013)	49; M	CV risk factors (diabetes mellitus, hyperlipidemia, tobacco use), appendectomy before 9 y	Sodium, NR, IM, sore throat, and generalized pain	NS	II	5 min	Defibrillation, CPR, intracoronary nitroglycerin (no benefit), placement of a floppy guidewire in the LAD (grade 2-3 TIMI flow achieved), successful PPCI (direct stenting of the vessel)	5 d	Survived
8	Rodrigues et al[2] (2013)	62; M	Obesity; HTN; history of atopy, with frequent allergic conjunctivitis and rhinitis; food allergies (nut); bronchial asthma	NR, 75 mg, oral, shoulder pain	NS	I	10 min	Metoclopramide IV, morphine and aspirin IV, dopamine infusion, hydrocortisone, ranitidine IV	24 h after ICU admission	Survived
9	Tiwari et al[32] (2013)	64; M	Admitted for surgery after fracture; not a known smoker or alcoholic; no history of allergy, bronchial asthma, or previous surgeries; denied any previous episode of CAD	Sodium, 50 mg, IM, severe pain	NS	I	10 min	Adrenaline, chlorpheniramine IV, methylprednisolone, IV fluids	NR	Survived
10	Şahinkuş et al[30] (2016)	34; M	Smoker; no history of allergy or CAD	NR, NR, IM, NR	NS	NR	NR	Acetylsalicylic acid and clopidogrel peroral; discharged with medical therapy (desloratadine, isosorbid-5-mononitrate)	3 d	Survived
11	Akboğa et al[16] (2017)	51; M	Former smoker, no history of any allergic disease	Sodium, 100 mg, oral, knee pain	NS	I	45 min	Pheniramine, dexamethasone, enoxaparin, aspirin	NR	Survived
12	Gunes et al[23] (2017)	67; M	CAD, HTN, kidney failure, previous anaphylaxis after IM diclofenac potassium almost 1 y previously	Potassium, NR, oral, arthralgia	NS	II	NR	IM pheniramine and dexamethasone, IV infusion of 0.9% NaCl. The occlusion was opened through repeated balloon dilatation, but stenting of the lesion site could not be achieved because of ectasia of the artery	2d	Survived

Continued

TABLE III. Overview of the Included Cases (continued)

No.	Study	Age, y; sex	Medical history	Diclofenac salt, dose, administration route, indication	Concomitant medications	KS type	Onset	Summary of treatment	LOS	Outcome
13	Kerai et al[25] (2017)	47; M	Scheduled for the left parotid gland excision under general anesthesia; no history of asthma or drug or food allergy; no underlying cardiac disease	Sodium, 75 mg, IM, pain management (administered after parotid gland was excised and surgical closure started)	Midazolam, fentanyl, propofol, vecuronium, sevoflurane in an oxygen-nitrous mixture	I	10 min	IV fluids, sevoflurane was switched off, IV hydrocortisone, chlorpheniramine, ranitidine, dopamine infusion	NR	Survived
14	İbrahim et al[24] (2018)	54; M	CAD, HTN; no history of allergy to any drug	Sodium, 75 mg, IM, myalgia (severe back pain)	NS	II	Immediately after	IM adrenaline and pheniramine, methylprednisolone, IV fluids, vasopressors; emergency CV percutaneous intervention not deemed necessary; medically treated	36 h	Survived
15	Sarıoğlu et al[31] (2018)	64; M	History of allergic reaction to diclofenac potassium; sacroiliitis; no prior CAD; family history of CAD, diabetes, HTN, smoking, hyperlipidemia, and asthma	Potassium, 50 mg, oral, headache	Prednisolone	I	About 1 h	Nasal oxygen, IV isotonic saline, hydrocortisone, SC adrenaline	4 d	Survived
16	Rajh et al[28] (2019)	69; M	Type 2 diabetes, bronchial asthma, HTN, GERD, overweight, osteoarthritis, CAD, CABG 6 y before, aspirin-induced asthma attack 20 y before	NR, NR, IM, shoulder pain (osteoarthritis)	Albuterol, budesonide, formoterol	NR	10 min	Albuterol and ipratropium nebulization, IV methylprednisolone, magnesium sulfate	1 d	Survived
17	Yıldırım et al[33] (2019)	81; M	NR	Sodium, 100 mg, oral, knee pain	NS	I	30 min	IV antihistaminic, prednisolone`	2 d	Survived
18	Elsayed[21] (2020)	44; M	Reported no history of cardiac, thyroid, or other relevant diseases	Potassium, 50 mg, oral, recurrent kidney pain	NS	I	1 h	Oxygen, IM adrenaline, IV hydrocortisone, IV chlorpheniramine, IV 0.9% normal saline, IV Ringer solution; on discharge: IV hydrocortisone, oral chlorpheniramine for 3 d	No (3 h in outpatient clinic)	Survived

Continued

TABLE III. Overview of the Included Cases (continued)

No.	Study	Age, y; sex	Medical history	Diclofenac salt, dose, administration route, indication	Concomitant medications	KS type	Onset	Summary of treatment	LOS	Outcome
20	Rui et al[29] (2021)	55; M	CAD, for which stents were inserted into the LAD and RCA; active smoker; no known allergies; no history of atopy	Sodium, 75 mg, IM, lower back pain	Compliant to ACS treatment (drugs not specified)	II	Shortly after	IM adrenaline, IV hydrocortisone, IV chlorphenamine, fluid therapy, oral aspirin, oral clopidogrel, IV streptokinase; consequently had his regular medical therapy continued	Few days	Survived

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; CPR, cardiopulmonary resuscitation; CV, cardiovascular; F, female; GERD, gastroesophageal reflux disease; HTN, hypertension; ICU, intensive care unit; IM, intramuscular; IV, intravenous; KS, Kounis syndrome; LAD, left anterior descending coronary artery; LOS, length of stay; M, male; NR, not reported; NS, not specified whether the patient received any concomitant medications; PPCI, primary percutaneous coronary intervention; RCA, right coronary artery; rt-PA, recombinant tissue plasminogen activator; SC, subcutaneous; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.

sure, and apparent pathologic venous pulsations were sporadically reported (n = 1 [5.0%]). Nausea and vomiting were reported in 4 patients (20.0%). Dermatologic manifestations, including rash, erythema, and urticaria, were reported in 14 patients (70.0%). Itching (pruritus) was reported in 8 patients (40.0%), and edema (facial, mucous membrane, lips) was reported in 3 patients (15.0%). Sweating was described in 4 patients (20.0%), and eye lacrimation was seen in 1 patient (5.0%). Loss of consciousness, syncope, or collapse was reported in 8 patients (40.0%). Respiratory signs and symptoms, such as tachypnea, dyspnea, wheezing, sense of suffocation, irregular spontaneous respirations with cyanosis, and prolonged expiratory time, were described in 6 patients (30.0%). One patient (5.0%) experienced partial respiratory acidosis and hematuria; another patient (5.0%) developed pulmonary edema.

Detailed results of relevant cardiovascular diagnostic investigations for each patient are provided in Table IV. Electrocardiography, coronary angiography, echocardiography, and myocardial perfusion scintigraphy were performed in 20 (100.0%), 17 (85.0%), 12 (60.0%), and 1 (5.0%) patients, respectively. The most frequently reported finding on electrocardiograms were ST-segment elevations (n = 17 [85.0%]). Decreased heart wall motion (hypokinesia) was reported in 5 patients (25.0%), and an ejection fraction of less than 40% was reported in 3 patients (15.0%). Coronary angiogram showed normal coronary vessels in 9 patients (45.0%), with pathologic findings seen in 8 patients (40.0%). Dipyridamole myocardial perfusion scintigraphy showed no ischemic tissue of myocardium in 1 patient (5.0%).[19] Elevated cardiac enzyme levels were reported in 14 patients (70.0%). Eosinophilia was reported in 3 patients (15.0%). Elevated tryptase was reported in 2 patients (10.0%), whereas 2 patients (10.0%) had normal tryptase levels measured several hours after presentation. Elevated IgE levels were reported in 5 patients (25.0%), whereas 2 patients (10.0%) had normal IgE levels measured several hours after presentation. Hyperglycemia and hyperlipidemia were reported in 3 (15.0%) and 2 (10.0%) patients, respectively. Elevated white blood cell counts (neutrophilia) were reported in 4 patients (20.0%). The activities of protein C, protein S, antithrombin III, and activated protein C were within normal limits; antiphospholipid antibodies and factor V Leiden mutation were negative in 1 patient (5.0%).

The authors diagnosed KS type I and type II in 7 (35.0%) and 5 (25.0%) patients, respectively. The clinical situation for 1 patient (5.0%) was described to be between types I and II (the patient had coronary disease with elevated troponin I levels but no severe stenosis, plaque erosion, or rupture).[27] In another case (n = 1 [5.0%]),[19] the authors described a 74-year-old female patient who experienced an anaphylactic reaction after taking oral diclofenac potassium and type II KS (ST-segment elevations in inferior derivations resulting from coronary artery spasm and underlying coronary artery disease); 2 months later, after receiving IV diclofenac potassium, she felt chest pain, and her electrocardiograms showed the same findings as those observed during the previous application. Coronary angiography was not repeated because myocardial perfusion imaging showed no coronary ischemia; therefore, the authors concluded that this case is an example of both type I (at the second application because no coronary ischemia occurred after coronary stenting) and type II KS at the

TABLE IV. Results of Relevant Cardiovascular Diagnostic Investigations

No.	Study	ECG	Echocardiogram	Coronary angiogram	Cardiac enzymes	Diagnosis (KS type), as reported by the authors
1	Mori et al[26] (1997)	Significant STEs in leads II, III, aVF, V_5, and V_6, with 2:1 AV block	Normal	Normal coronary trees; ergonovine provocation test showed severe spasm at middle portion of RCA and LCA accompanied by chest pain and ischemic ST changes promptly resolved by 2.5 mg intracoronary isosorbide dinitrate	NR	Vasospastic angina associated with anaphylactic reaction
2	Blanco et al[17] (2003)	Elevation of the ST segment of leads V_1-V_4 indicative of anterior acute MI	Anterior hypokinesia with global EF of 49%	Normal, with no atherosclerotic organic lesions	Elevated total CK and troponin T	Anterior acute MI associated with anaphylactic reaction
3	Gluvic et al[22] (2007)	Up to 5-mm STE in inferior and entire precordial leads	No motility disorders of heart muscle (EF, 53%; trace mitral and tricuspid regurgitation)	Not performed (refused by patient)	Elevated CK, normal troponin I	ACS associated with type I hypersensitivity reaction
4	de Groot et al[20] (2009)	STEs in leads II, III, and aVF; acute inferolateral MI diagnosed	NR	No significant coronary stenosis	Elevated troponin T, whereas CK, and CK-MB remained normal	STEMI associated with anaphylaxis
5	Cakar et al[19] (2011)	First time: 1-mm STE in inferior derivations, reciprocal ST-segment depression up to 4 mm in entire precordial leads and third-degree AV block Second time: same as previously	NR	First time: 2 sequential 70% RCA lesions and noncritical lesion in LAD	Normal	ACS associated with anaphylaxis (first time: II; second time: I and II)
6	Granitz et al[34] (2011)	Transient STEs over inferior posterior wall	NR	Stenosing CAD could be ruled out angiographically, but ubiquitous plaques found	Elevated troponin, without CK deflection	ACS associated with anaphylactic reaction (II)
7	Cagliyan et al[18] (2013)	Emergent ECG compatible with acute anterior MI; fourth-hour control ECG showed resolution of STE	NR	LAD occluded just distal to the first diagonal branch	Marked elevation	Anterior acute MI triggered by allergic reaction (II)
8	Rodrigues et al[2] (2013)	STE in the inferior leads	No motility disorders of heart wall muscle or other abnormalities	No lesions on coronary vessels or contractility abnormalities	Elevated troponin I and CK-MB	ACS associated with anaphylaxis (I)
9	Tiwari et al[32] (2013)	STE in leads II, III, and aVF; STEMI of inferior wall diagnosed	NR	Normal coronary vessels	Elevated troponin T, normal CK, and CK-MB	STEMI associated with anaphylaxis (I)

Continued

TABLE IV. Results of Relevant Cardiovascular Diagnostic Investigations (continued)

No.	Study	ECG	Echocardiogram	Coronary angiogram	Cardiac enzymes	Diagnosis (KS type), as reported by the authors
10	Şahinkuş et al[30] (2016)	STE in leads D_2, D_3, aVF, V_4-V_6; reciprocal ST-segment depression in leads aVL, V_1, V_2; diagnosed with acute inferolateral wall MI	EF, 60%; left ventricle wall motion normal	No pathological changes, such as plaque rupture, thrombus, or dissection	Elevated troponin I	STEMI secondary to allergic reaction
11	Akboğa et al[16] (2017)	2- to 3-mm STE in D_2, D_3, and aVF leads; reciprocal changes in other leads	Normal	Normal coronary arteries without obstruction	Normal	ACS associated with anaphylaxis (I)
12	Gunes et al[23] (2017)	First ECG: slight STE in inferior leads (II, III, aVF) accompanied by slight ST-segment depression and negative T waves in leads V_2-V_5; Second ECG: prominent STE in inferior leads (II, III, aVF) accompanied by prominent ST-segment depression and biphasic T waves in leads V_2-V_5	Left ventricular EF, 25%	Total (100%) occlusion of RCA by thrombus material	NR	ACS associated with anaphylaxis (II)
13	Kerai et al[25] (2017)	ST depression and T-wave inversion in leads II and III; VF from V_2-V_5 suggestive of inferior and lateral wall MI	NR	Normal coronary vasculature	Elevated CK-MB and troponin I	Acute MI associated with anaphylaxis (I)
14	İbrahim et al[24] (2018)	Normal ECG—no changes	EF, 25%; global hypokinesia of left ventricle	Not performed—emergency cardiovascular percutaneous intervention not necessary	Elevated troponin and CK-MB	ACS associated with anaphylaxis (II)
15	Sarıoğlu et al[31] (2018)	Sinus tachycardia and STE in leads D_1 and aVL, with reciprocal ST depressions in leads D_3 and aVF	Lateral and anterolateral wall hypokinesis, with EF of 35%; no valve abnormality	Normal coronary arteries without significant lesions	Elevated troponin I, normal CK-MB	ACS associated with anaphylactic reaction (I)
16	Rajh et al[28] (2019)	STEs in leads III and aVF, with changes in leads V_4, V_5, V_6, I, and II	NR	No new occlusions, confirmation of preexisting 3-vessel disease (100% occluded LAD, 20%-30% of LCA, and 70% of RCA); graft study demonstrated patency through left internal mammary artery to left anterior ascending artery and saphenous vein graft to diagonal arteries	Elevated CK, normal troponin T	STEMI associated with allergic reaction

Continued

TABLE IV. Results of Relevant Cardiovascular Diagnostic Investigations (continued)

No.	Study	ECG	Echocardiogram	Coronary angiogram	Cardiac enzymes	Diagnosis (KS type), as reported by the authors
17	Yıldırım et al[33] (2019)	2- to 3-mm STE in leads D2-D3 and aVF; reciprocal changes in other leads	NR	Normal coronary arteries without obstruction	NR	MI (I)
18	Elsayed[21] (2020)	Sinus tachycardia (130/min), with a few univocal PVCs and ST-segment depression in the anterior (I, aVL, and V_6) and inferior (II and aVF) leads	No detected abnormalities; EF, 66%	NR	NR	ACS associated with anaphylaxis (I)
19	Özdemir et al[27] (2020)	Prominent STE in leads II, III, aVF, V_5, and V_6; ST-segment depression in leads aVL and V_1-V_3, with AV complete block	EF, 60%; mild hypokinesia in midsegment of inferior wall of left ventricle	Dominant LCX with nonsignificant plaque; LAD with normal appearance; RCA was nondominant without a fixed stenosis	Elevated troponin I	Recurrent allergic STEMI with no sign of systemic allergic reactions, except coronary spasm (between I and II)
20	Rui et al[29] (2021)	Significant STEs over V_2-V_4, with reciprocal ST-segment depressions over leads II, III, and aVF (anteroseptal STE with reciprocal changes)	Anterior wall hypokinesia	No acute culprit lesions in the LAD; mild in-stent restenosis in the LAD; no remnants to suggest a recent thrombus or plaque rupture	Elevated CK and troponin T	STEMI secondary to anaphylactic reaction (II)

ACS, acute coronary syndrome; AV, atrioventricular; CAD, coronary artery disease; CK, creatine kinase; CK-MB, creatine kinase myocardial band; ECG, electrocardiogram; EF, ejection fraction; KS, Kounis syndrome; LAD, left anterior descending coronary artery; LCA, left coronary artery; LCX, left circumflex coronary artery; MI, myocardial infarction; NR, not reported; PVC, premature ventricular contraction; RCA, right coronary artery; STE, ST-segment elevation; STEMI, ST-segment elevation myocardial infarction; VF, ventricular fibrillation.

same time.[19] The authors did not report KS type for 6 cases (30.0%).

Causality assessment findings using Naranjo score were reported in just 1 case.[21] The author calculated that the Naranjo score was +10, indicating a definite relationship between the adverse drug reaction and the culprit drug: oral diclofenac potassium.[21] Positive rechallenge of signs and symptoms associated with KS after diclofenac administration was described in 3 patients (15.0%)—1 each in Mori et al,[26] Cakar et al,[19] and Özdemir et al.[27]

Most patients (n = 19 [95.0%]) required hospitalization for treatment, although 1 patient (5.0%) was able to go home without issues 3 hours after treatment in an outpatient clinic.[21] Four patients (20.0%) were treated in an intensive care unit, and 3 patients (15.0%) were treated in a cardiac care unit. The specified total length of hospital stay for these 7 patients ranged from 1 to 5 days (median, 2 days). During management of the reaction, diclofenac was discontinued in all patients after they experienced first symptoms. The summary of treatment for each patient is provided in Table III. Corticosteroids (n = 14 [70.0%]), histamine receptor 1 (H_1) antihistamines (n = 11 [55.0%]), and IV fluids (n = 11 [55.0%]) were the most frequently prescribed treatments, followed by adrenaline (n = 6 [30.0%]), antiplatelet drugs (n = 6 [30.0%]), nitrates (n = 5 [25.0%]), vasopressors (n = 4 [20.0%]), bronchodilators (n = 3 [15.0%]), oxygen (n = 3 [15.0%]), the anticoagulant enoxaparin (n = 2 [10.0%]), morphine (n = 2 [10.0%]), the H_2 antihistamine ranitidine (n = 2 [10.0%]), atropine (n = 2 [10.0%]), the calcium channel blocker diltiazem (n = 2 [10.0%]), statins (n = 1 [5.0%]), nicorandil (n = 1 [5.0%]), ramipril (n = 1 [5.0%]), magnesium sulfate (n = 1 [5.0%]), and metoclopramide (n = 1 [5.0%]). Reperfusion therapy was performed in 4 patients (20.0%): 2 (10.0%) patients re-

ceived fibrinolytics, and the other 2 (10.0%) underwent stent placement. In 1 patient (5.0%), an occlusion was opened by repeated balloon dilatation, but a stent could not be placed at the lesion site because of ectasia of the artery. Resuscitation had to be performed in 3 patients (15.0%), and 1 patient (5.0%) required defibrillation. All patients survived.

Discussion

This review observed the clinical relevance of diclofenac preparations as a cause of KS. This life-threatening adverse effect occurred with therapeutic doses of diclofenac and was reported significantly more frequently in men than in women. Most patients included in this review did not have a history of cardiovascular disease or allergic reaction to diclofenac. The drug caused both type I and type II KS, with various cardiovascular, GI, dermatologic, and respiratory signs and symptoms. Although there were no fatal outcomes, severe cases with complications such as cardiac arrest, ventricular fibrillation, cardiogenic shock, and pulmonary edema were reported.

Etiology and Epidemiology of Kounis Syndrome

Many triggers of KS have been identified to date, such as different kinds of food, insect bites, various medications, environmental exposures, and several health conditions.[3] Among medications, antibiotics and NSAIDs are the most common triggers.[35,36] Kounis syndrome can occur in all age categories, but almost 70% of all reported cases to date have been in people between 40 and 70 years of age,[35] which is in accordance with the results

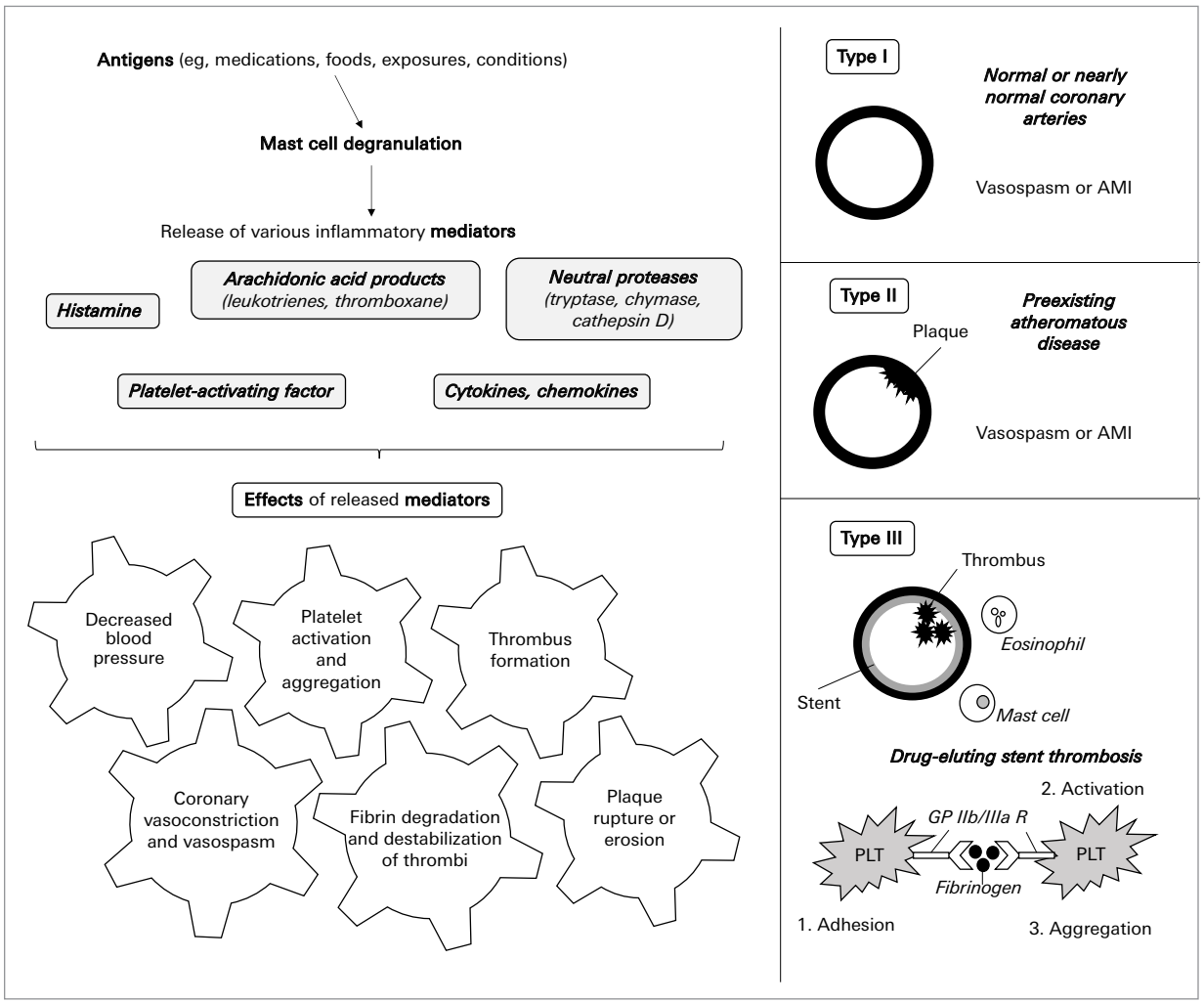

Fig. 3 An overview of Kounis syndrome pathophysiology.

AMI, acute myocardial infarction; PLT, platelet; GP IIb/IIIa R, glycoprotein IIb/IIIa receptor.

of this review. What is particularly interesting among the results presented here, however, is that diclofenac-induced KS occurred much more frequently in men than in women (90% vs 10%). Similarly, results of a systematic review conducted by Ridella et al[37] showed that 76% of patients with KS following β-lactam antibiotic use were men. Awareness and knowledge of KS are particularly high among physicians in southern Europe[4]; that finding was confirmed in the present study, with almost half of all reported cases of diclofenac-induced KS coming from Turkey. It is difficult to determine the precise prevalence and incidence of KS.[4] Many cases certainly remain unrecognized, misdiagnosed, or unreported by clinicians.[6,38] Although overall the number of identified cases of KS is low, it has grown exponentially over the past few years,[39] reflecting increasing awareness among physicians.[40]

Pathophysiology

Figure 3 provides an overview of the proposed pathophysiology of KS. Central in the pathogenesis is mast cell degranulation and the release of inflammatory mediators. Mast cell degranulation can occur either as a result of antigen binding to IgE antibodies on the mast cell surface or as a consequence of complement system activation.[41] Many mediators are released from mast cell granules, including histamine, platelet-activating factor, chemokines, cytokines, arachidonic acid products (eg, leukotrienes, thromboxane), and neutral proteases (eg, tryptase, chymase, cathepsin D).[42] These inflammatory mediators cause anaphylactic symptoms in patients with KS. Histamine induces coronary vasoconstriction, decreases diastolic blood pressure, and activates platelets.[3,35] Leukotrienes, chymase, and cathepsin D also have powerful vasoconstrictive effects.[43,44] Thromboxane stimulates platelet aggregation,[45] and tryptase caused fibrin degradation and thus contributes to the destabilization of thrombi.[46] Neutral proteases through metalloproteinase activation can cause plaque rupture or erosion.[47] Among medications, NSAIDs are frequently involved in allergic reactions, affecting 20% to 25% of all patients evaluated in allergy units.[48-50] These drugs may cause hypersensitive reactions by 2 different mechanisms. The first is mediated by drug-specific IgE antibodies when a patient is hypersensitive to 1 specific chemical group of NSAIDs but tolerant of NSAIDs that are not structurally similar.[51,52] The second mechanism is a consequence of the pharmacologic action of this group of drugs because they inhibit cyclooxygenase and stimulate the lipoxygenase pathway of arachidonic acid metabolism, increasing leukotriene production.[53] In this case, there is cross-reactive hypersensitivity toward NSAIDs from different chemical groups.[50] Anaphylactic reaction to diclofenac can appear in patients who have never been exposed to this drug before.[54] Severe allergic reactions are more common after IM and IV administration of diclofenac, although cases have been reported after oral, rectal, and subcutaneous administration, as well.[54] This finding is in accordance with the results in the current study, with almost half of reported cases of KS occurring after the IM administration of diclofenac, although this side effect also occurred after oral, rectal, and IV administration.

Symptoms

Kounis syndrome can manifest with various symptoms, but the main clinical symptoms and signs are always associated with subclinical, clinical, acute, or chronic allergic reactions accompanied by cardiac symptomatology.[3] In 80% of cases, the symptoms appear within 1 hour after exposure to the trigger.[35] This study found that the reported time from the use of diclofenac to the onset of symptoms ranged from immediately to 5 hours; however, Ridella et al[37] showed that the time between β-lactam antibiotic administration and occurrence of symptoms in patients with KS is shorter, ranging from immediate to 2.5 hours. Except for 1 patient whose only symptom was coronary spasm,[27] all patients included in this review had symptoms and signs associated with allergic, hypersensitivity, or anaphylactic reactions. The most common cardiac symptoms were chest pain (60%) and hypotension (75%); dermatologic, respiratory, and GI symptoms were reported in 70%, 30%, and 20% of patients, respectively. There were no significant differences in the prevalence of symptoms among patients in whom the trigger for KS was β-lactam antibiotics, where chest pain was reported in 65% of patients; hypotension in approximately 71% of patients; and dermatologic, respiratory, and GI symptoms in approximately 77%, 41%, and 12% of patients, respectively.[37]

Diagnosis

The diagnosis of KS is based on reliable anamnestic data, clinical symptoms, and signs that emphasize multisystem involvement as well as on laboratory, electrocardiographic, echocardiographic, and angiographic evidence.[3,35,39] When KS is suspected, it is necessary first to determine whether the patient has a history of allergic reactions. It has been shown that 25% of patients have a known history of allergy, mostly to the trigger.[35] The results of this study are in accordance with these findings: 5 patients (25.0%) with diclofenac-induced KS had had a previous reaction to the culprit drug, and 1 patient had a history of an aspirin-induced asthma

attack and obviously had cross-reactive hypersensitivity to diclofenac. Regarding laboratory findings, measuring serum tryptase, histamine, cardiac enzyme, and cardiac troponin levels may be helpful.[3,35] Histamine has a half-life of 8 minutes,[53,55] however, so blood samples should be collected promptly after symptom onset.[56] Tryptase has a half-life of approximately 90 minutes,[57] so testing for tryptase may be more useful than for histamine. The role of IgE levels in diagnosis remains unclear,[55] although elevated IgE levels were reported in 20% of patients with diclofenac-induced KS and in approximately 24% of patients in whom β-lactam antibiotics were the trigger.[37] Cardiospecific enzymes, such as troponin I and T, creatine kinase, and creatine kinase myocardial band, are important indicators of myocardial injury associated with the allergic insult.[3,35,58] Abdelghany et al[35] found that approximately 60% of all patients with KS had elevated troponin levels, and elevated levels of various cardiac enzymes were observed in 70% of patients in this systematic review. Electrocardiography is also important in the diagnosis of KS.[6] In patients with diclofenac-induced KS, the most frequently reported finding was ST-segment elevation (85% of patients). An even higher proportion of electrocardiogram findings indicating ST elevation (95%) was observed in patients with KS resulting from the use of β-lactam antibiotics.[37] Transthoracic echocardiography may be useful for the differential diagnostic exclusion of pericarditis or aortic dissection as potential causes of chest pain,[6] and cardiac catheterization may show coronary vasospasm or stenosis.[35]

Abdelghany et al[35] showed that type I is the most common variant of KS, accounting for approximately 73% of cases, followed by the type II and type III variants, whose frequencies are approximately 22% and 5%, respectively. Type I was also the most common variant in KS cases resulting from β-lactam antibiotics (70.5%); the remaining 29.5% of cases were categorized as type II.[37] In contrast, this study found that among patients with diclofenac-induced KS, the difference in the frequency of the type I variant was not as drastically pronounced (35% in type I vs 25% in type II). It is important to emphasize, however, that in more than one-third of cases, the authors did not state or were unsure of the type of KS.

Treatment

No precise guidelines exist for the management of KS.[35] In patients with type II KS, it is necessary to treat both the allergic and the cardiac symptoms simultaneously; in patients with the type I variant, treatment of the allergic event alone can abolish symptoms.[3] For relief of allergic symptoms, hydrocortisone 1 to 2 mg/kg/day and H_1 and H_2 antihistamines such as diphenhydramine 1 to 2 mg/kg and ranitidine 1 mg/kg are considered adequate.[3,6] Because of increased vascular permeability during anaphylaxis, up to 50% of intravascular fluid volume may be transferred into the extravascular space within 10 minutes, so fluid replacement is advised.[6] Fluid replacement should be performed with caution in patients with left ventricular dysfunction, however, because of the increased risk of pulmonary edema.[6] Supplemental oxygen should be administered to all patients.[6] For treatment of coronary vasospasm, calcium channel blockers are recommended, whereas nitrates could be used in patients with normal blood pressure.[3]

Note that use of adrenaline in this setting is controversial: although adrenaline is life-saving in anaphylaxis, it may worsen vasospasm in patients with KS because it acts on α-adrenergic receptors.[3] In addition, adrenaline preparations contain sulfite as a preservative and antioxidant, which can cause allergic and anaphylactoid reactions.[59,60] Finally, adrenaline could be ineffective in patients with KS who previously used β-blockers.[3,6]

Fentanyl and its derivatives are the analgesics of choice for the treatment of chest pain in patients with KS.[3,6] Other opioids, such as morphine, codeine, and meperidine, should be avoided because they may worsen allergic reaction. Similarly, IV acetaminophen should be avoided because of the risk of hypotension.[3,36] In the type III variant, clinicians should follow the most recent guidelines for the treatment of ACS.[3,35]

Prognosis

Generally, ACS within KS has a better prognosis and lower mortality rate than for conventional types of ACS.[3] Complete resolution of contractile abnormalities and full recovery are usually seen.[6,35] Abdelghany et al[35] showed that the death rate in patients with KS is 2.9%, but patients hospitalized for KS experience higher all-cause in-hospital mortality, prolonged hospital length of stay, higher hospitalization charges, and more frequent transfers to other facilities than patients hospitalized for non-KS allergy, hypersensitivity, or anaphylactic reactions.[61]

Limitations

This systematic review has the following shortcomings: (1) it analyzed a relatively small number of reported cases with diclofenac-induced KS; (2) the completeness of the included cases varied, and important information was missing or incompletely presented (eg, dose of administered diclofenac, duration of treatment before symptom onset); (3) data on the type of KS were missing in several case reports; (4) in the vast majority of the case reports analyzed, assessment of the potential contribution of concomitant therapies was missing; and (5) even if cases contained all the essential information,

it was often not possible to establish definitive conclusions on causality.[15] Despite these limitations, the results of this review could help clinicians in various specialties better recognize and manage diclofenac-induced KS.

Conclusion

Diclofenac administered at therapeutic doses, regardless of route of administration, may cause KS, even in patients without a known history of hypersensitivity and allergic reactions. Clinicians should be aware that KS may be an adverse effect of diclofenac: prompt recognition and withdrawal of the culprit drug, with treatment of both allergic and cardiac symptoms simultaneously, are of the utmost importance.

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